




Association Between Insulin-Like Growth Factor-1 and Social Cognition in Huntington's Disease

Cecilia Gil-Polo, MD, PhD,¹ Saul-Indra Martinez-Horta, PhD,²  Frederic Sampedro Santalo, MD, PhD,²  María Martín-Palencia, MD,³ Simón Gundín-Menéndez, MD,³ Pilar Alvarez-Baños, MD,⁴ Laura Maza-Pereg, MD,⁴ Sara Calvo, PhD,⁵ Carla Collazo, PhD,⁵ Esther Alonso-García, MD,⁶ Esther Riñones-Mena, MD,⁶ Angela Arrabal-Alonso, MD,³ Juan Núñez Rodríguez, MD,³ Miriam Saiz-Rodríguez, PhD,⁵ Laura Aguado, MD,¹ Natividad Mariscal, Rn,¹ Ignacio Muñoz-Siscart, MD,⁷ Dolores Piñero, MD,⁷ Jessica Rivadeneyra, PhD,⁵ Monica Díez-Fairen, PhD,⁸ Irene Miguel-Pérez, Rn,¹ and Esther Cubo, MD, PhD^{1,9,*} 

Abstract: Background: Insulin-like growth factor 1 (IGF-1) seems to be involved in the neural circuits associated with social cognition and brain structure.

Objectives: To investigate the association of IGF-1 levels with social cognition and brain structure in Huntington's disease (HD).

Methods: We evaluated social cognition using the Ekman test in 22 HD patients and 19 matched controls. Brain structure was assessed using standard volume-based voxel-based morphometry and surface-based cortical thickness pipeline. We analyzed the association of IGF-1 levels with social cognition and brain structure using adjusted regression analysis.

Results: Social cognition was worse in HD patients ($P < 0.001$), on antidopaminergic drugs ($P = 0.02$), and with lower IGF-1 levels ($P = 0.04$). In neuroimaging analyses, lower IGF-1 levels were associated with social cognition impairment and atrophy mainly in frontotemporal regions ($P < 0.05$ corrected).

Conclusions: In HD, abnormal IGF-1 function seems to be associated with brain atrophy leading to clinical deficits in social cognition.

Previous literature has proposed a relationship between hypothalamic dysfunction and the limbic system with the development of non-motor symptoms (NMS) in Huntington's disease (HD).¹ In this regard, several studies have found a range of neuroendocrine disturbances in HD, including higher vasopressin concentration levels and a trend for disturbed regulation of the oxytocin, corticotropic, thyrotropic, and lactotropic axes.^{2–4} Among these neuroendocrine disturbances, there is a growing interest in the protective role of insulin-like growth factor 1 (IGF-1) on metabolic and mitochondrial function in HD.⁵ Moreover, IGF-I receptors have

been discovered in the amygdala and prefrontal cortex, which contributes to the neural circuits known as the "social brain."⁶

Based on the data mentioned above, we hypothesized that IGF-1 dysfunction would be associated with social cognition impairment and brain structural changes. Therefore, we aimed to investigate the IGF-I function and its association with social cognition and brain structure in patients with HD versus controls. A secondary objective was to understand the role of the global hypothalamic function in social cognition, motor, and other NMS in HD.

¹Neurology Department, Hospital Universitario Burgos, Burgos, Spain; ²Movement Disorders Unit, Neurology Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; ³Biochemistry Analysis Department, Hospital Universitario Burgos, Burgos, Spain; ⁴Endocrinology Department, Hospital Universitario Burgos, Burgos, Spain; ⁵Research Unit, Hospital Universitario Burgos, Burgos, Spain; ⁶Radiology Department, Hospital Universitario Burgos, Burgos, Spain; ⁷Psychiatry Department, Hospital Universitario Burgos, Burgos, Spain; ⁸Genetic Department, Hospital Mutua de Terrassa, Burgos, Spain; ⁹University of Burgos, Burgos, Spain

*Correspondence to: Dr. Esther Cubo, Neurology Department, Hospital Universitario Burgos, 09006, Burgos, Spain; E-mail: mcubo@saludcastillayleon.es

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Methods

Design

This was a multicenter, cross-sectional, observational, case-control study. The research procedure was conducted using the RECORD guidelines.⁷

Sample characteristics and ethics

This study was approved by the Institutional Review Board of the Complejo Universitario Burgos and Soria (Spain) (Ceim 1973). Data were collected for ambulatory participants who signed the informed consent after a full explanation of the procedure, following the International Conference on Harmonization-Good Clinical Practice (ICH-GCP) guidelines, stored on file, and available on request.⁸ We included a consecutive sample of symptomatic HD patients with the larger allele ≥ 36 CAG repeats within the huntingtin gene, with a Unified Huntington's Disease Rating Scale (UHDRS) total motor (TMS) score >4 ,⁹ and age, gender-matched controls. We excluded participants with prosopagnosia, defined as Benton Facial Recognition Test score <40 ,¹⁰ relevant psychiatric illness with a short Problem Behaviors Assessment for HD (PBA) score ≥ 2 ,¹¹ visual or auditory interference, moderate-severe cognitive impairment (Mini-Mental State Examination score <25),¹² a pre-existent endocrine disease, central nervous system disorder disturbances other than HD, history of alcohol or drug abuse, treatment with corticosteroids, pregnant and breastfeeding women, delivery within the last 6 months, treatment with contraceptives, night shift working and weight change in the preceding 6 months. Controls were recruited principally from the HD group's partners, spouses, or caregivers with no clinical evidence or family history of HD, and the same exclusion criteria was applied.

Assessments

We collected information on demographics, education, smoking history, and use of antidopaminergic drugs, antidepressants (selective serotonin and serotonin/norepinephrine, tricyclic, bupropion, and trazodone), and benzodiazepines. The disease burden score, an indicator of the severity of neuropathology of HD, was calculated for each HD gene carrier using the formula $(\text{CAG repeat length} - 35.5) \times \text{age}$.¹³ Motor symptoms severity was assessed using the UHDRS-TMS,⁹ with higher scores indicating worse motor impairment. Disease stage was obtained from the Total Functional Capacity (TFC) scores, with higher scores indicating lower severity status.¹⁴ Social cognition and theory of mind (TOM) were evaluated using the Ekman 60 faces test,¹⁵ and the Reading the Mind in the Eyes test (eyes test), respectively,¹⁶ with higher scores indicating better social cognition performance. Other NMS disturbances were assessed, including apathy and social

behavior, using the Apathy Evaluation Scale-Clinician (AES), with higher scores indicating greater apathy.¹⁷ In addition, in HD participants, cognition was assessed using the cognitive UHDRS composite subscore (UHDRS-Cog), by adding the total correct scores for symbol digit modality test and Stroop subscore for word reading, with lower scores indicating worse performance.¹⁸

Hypothalamic-pituitary function

The following early morning, fasting hormones were assayed: IGF-1, vasopressin, oxytocin, corticotropin-axis hormones (adrenocorticotrophic hormone [ACTH], and cortisol), somatotropin-axis hormones (growth hormone [GH]), gonadotropin axis hormones (luteinizing hormone [LH]; follicle-stimulating hormone [FSH]; progesterone; 17β estradiol and testosterone), thyrotropin axis hormones (thyroid-stimulating hormone [TSH], and free thyroxine [fT4]), and lactotropin axis hormone (prolactin). Measuring range and hormone assays and general biochemistry determinations are described in Supplemental File S1.

Neuroimaging acquisition and processing

In a subset of 19 participants (9 HD and 10 age and sex-matched controls) for whom a 3 T magnetic resonance imaging (MRI) study was available, an additional exploratory analysis was performed to address the possible relationship between the IGF-1 levels and brain structure. Neuroimaging procedures, including volume-based voxel-based morphometry (VBM), gray matter volume (GMV), and surface-based cortical thickness (Cth) are described in Supplemental File S2.

Outcome measures

We included the Ekman 60 faces total score, the eyes test (social cognition outcome measures), and IGF-1 concentration levels as the first outcome measures. Secondary outcome measures included CAG repeats length, TFC, UHDRS-TMS, UHDRS-Cog, and AES scores, and other hypothalamic hormone concentration levels.

Sample size calculation

Based on previous literature using the Ekman test mean differences as the first outcome,¹⁹ assuming a pooled standard deviation of 20 units and 20% dropout rate, the study would require a sample size of 20 subjects for each group to achieve a power of 80% and a level of significance of 5% (two-sided), for detecting a true difference in means between the test and the reference group of 20 units.²⁰

Statistical analysis

Analyses were done using the software IBM-SPSS 28. We conducted group comparisons between HD and control participants, and all tests were two-tailed with a significance level set at $P < 0.05$. We conducted exploratory analyses, and there was no formal adjustment for multiple testing because all hypotheses tested are interesting in their own right.²¹ Post hoc bivariate correlations were performed between hypothalamic-pituitary hormone levels with clinical rating scales in untreated HD subjects. In addition, we conducted a multivariate linear regression analysis, Ekman 60 faces test as the dependent variable, the IGF-1 levels as the independent variable, and age, gender, group of participants (HD vs. controls), and intake of antidopaminergic and antidepressant drugs as the covariates.

To confirm whether the structural brain correlates of IGF-1 levels in HD, where related to the inherent neurodegeneration occurring in this population, we performed a group comparison of VBM-GMV and Cth data between HD and controls. Voxel-wise VBM-GMV and vertex-wise Cth metrics were introduced into a general linear model (GLM) to explore the structural brain relationship with IGF-1 levels, with age and CAG repeat length as nuisance covariates given their impact on brain structure. We considered significant clusters surviving $P < 0.05$ and family-wise error (FWE)

correction for multiple comparisons using random field theory for VBM and a Monte-Carlo simulation with 10,000 repeats for Cth. In addition, we analyzed the possible relationship between IGF-1 levels with Ekman test scores, GMV, and Cth in the various brain-level clusters using a correlation model in the HD group.

Results

We identified 30 HD candidates of those 22 met inclusion and exclusion criteria: 9 males (41%), 13 females (59%), with a mean age of 58.09 ± 9.72 years, 19 controls (9 [47%] males and 10 [53%] females), with a mean age of 52.00 ± 9.69 years (Table 1). Demographics and treatments were not significantly different between both groups, except for higher frequency of postmenopausal women ($P = 0.02$) and higher intake of antidopaminergic and antidepressant drugs in the HD group compared to controls ($P = 0.002$, $P = 0.01$, respectively) (Table 1). Higher concentrations of vasopressin with higher plasma and urine osmolality, lower 17 β estradiol, a trend for higher prolactin, LH, cortisol, GH and IGF-1, and lower oxytocin levels were found in the HD group compared to controls (Table 1, Supplemental tables S1, and S2).

TABLE 1 Clinical characteristics comparison between HD patients and controls

	Controls (n)	HD patients (n)	P value
Males/females (%)	9/10 (19)	9/13 (22)	0.68
Age (yr)	52.00 \pm 9.69 (19)	58.09 \pm 9.73 (22)	0.052
Postmenopausal women (%)	6 (60) (10)	13 (100) (13)	0.02
Education (>high school) (%)	17 (89.5) (19)	18 (81.8) (22)	0.67
Current smoking (%)	6 (31.58) (19)	6 (27.27) (22)	0.763
Antidopaminergics, yes (%)	0 (19)	9 (40.91) (22)	0.002
Antidepressants, yes (%)	2 (10.53) (19)	10 (45.45) (22)	0.014
Benzodiazepines, yes (%)	1 (5.26) (19)	6 (27.27) (22)	0.09
Ekman total score	52.79 \pm 4.23 (19)	37.68 \pm 7.59 (22)	<0.0001
Untreated subjects	53.41 \pm 2.47 (17)	40 \pm 8.60 (9)	NA
Eyes test	35.00 (35.00; 36.00) (19)	34.50 (32.75; 35.00) (22)	0.008
Untreated subjects	35.00 (34.50; 36.00) (17)	34.00 (31.50; 35.00) (9)	NA
Apathy evaluation scale	20.00 (18.00; 25.00) (19)	33.50 (28.00; 41.25) (22)	0.0001
Untreated subjects	20.00 (18.00; 24.00) (17)	35.00 (29.50; 36.50) (9)	NA
IGF-1 (ng/mL)	90.10 (67.90; 108.00) (17)	96.65 (88.57; 116.25) (9)	0.11
Male	68.00 (60.40; 116.55) (9)	106.00 (74.70; 136.50) (9)	NA
Female	94.80 (78.30; 118.75) (10)	96.00 (91.80; 111.00) (13)	NA
Untreated subjects	92.20 (67.95; 125.50) (17)	95.90 (81.30; 133.50) (9)	NA

Note: Data are expressed in means \pm standard deviation or median (interquartile range). Few variables were stratified based on taking antidopaminergic or antidepressant drugs (untreated subjects).

Abbreviations: HD, Huntington's disease; NA, not applied; IGF-1, insulin-like growth factor-1.

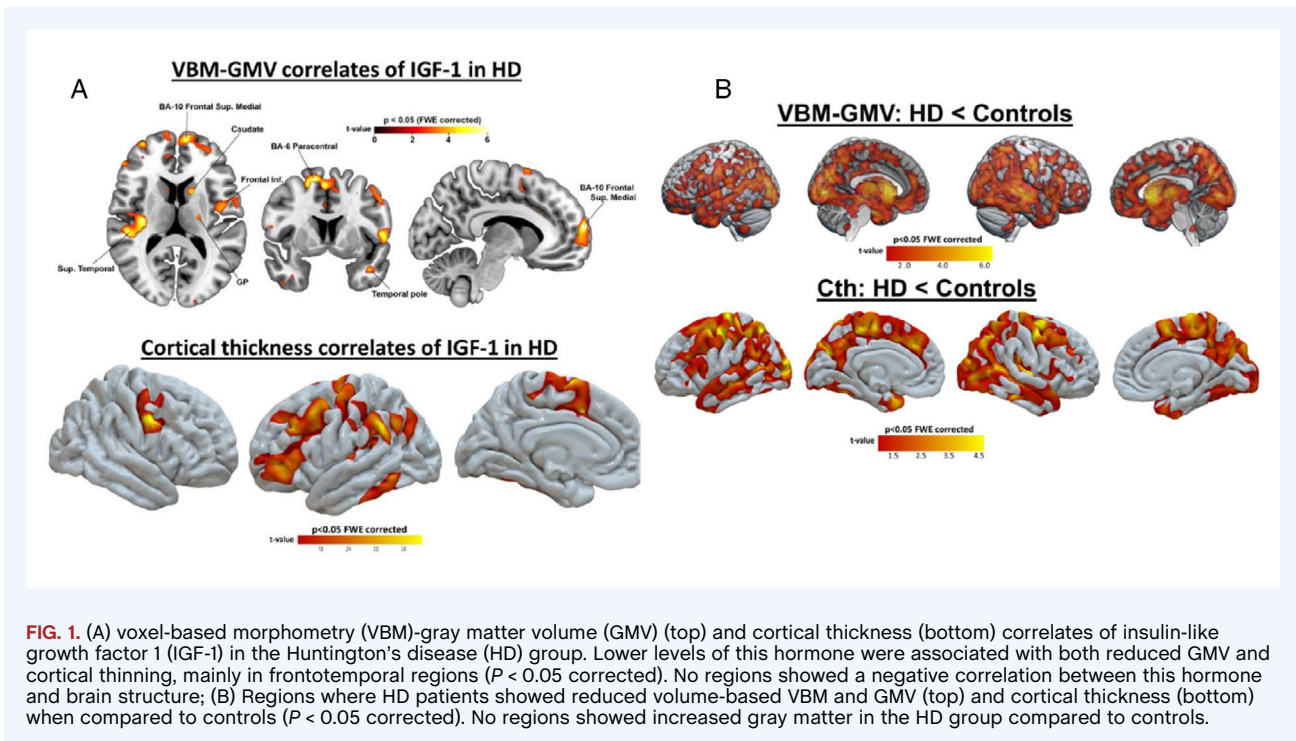


FIG. 1. (A) voxel-based morphometry (VBM)-gray matter volume (GMV) (top) and cortical thickness (bottom) correlates of insulin-like growth factor 1 (IGF-1) in the Huntington's disease (HD) group. Lower levels of this hormone were associated with both reduced GMV and cortical thinning, mainly in frontotemporal regions ($P < 0.05$ corrected). No regions showed a negative correlation between this hormone and brain structure; (B) Regions where HD patients showed reduced volume-based VBM and GMV (top) and cortical thickness (bottom) when compared to controls ($P < 0.05$ corrected). No regions showed increased gray matter in the HD group compared to controls.

Higher AES scores were found in the HD group compared to controls ($P < 0.001$) and in participants on antidepressants ($P = 0.002$) and antidopaminergic drugs ($P < 0.001$) compared to untreated subjects (Table 1). Similar findings were found with higher IGF-1 levels (Table 1) and lower Ekman scores in the HD group compared to controls (Figs. S1). Moreover, in untreated HD subjects, Ekman scores were highly correlated with IGF-1 levels ($r_s = 0.81$) and moderately with oxytocin levels ($r_s = 0.45$); AES scores were negatively correlated with oxytocin levels ($r_s = -0.44$); and higher UHDRS-TMS scores with lower IGF-1 levels ($r_s = -0.78$) (Supplemental File S3). In multivariate regression analysis, lower Ekman scores were more likely in HD patients ($\beta = -12.25$, 95% CI = 16.51; -7.98, $P < 0.001$), and on antidopaminergic drugs ($\beta = -5.91$, 95% CI = -11.11; -0.11, $P = 0.02$). In contrast, higher Ekman total scores were associated with higher IGF-1 levels ($\beta = 0.06$, 95% CI = 0.001; 0.12, $P = 0.04$) (Supplemental Table S3). According to this model, with 1-unit IGF-1 increase, the Ekman total scores increased 0.06 (95% CI = 0.003–0.13, $P = 0.04$). This model explained 69% of the variability of the Ekman total scores.

As expected, HD patients showed widespread cortical and subcortical atrophy with respect to controls, including the set of regions showing a significant association with IGF-1 levels in the HD group (Fig. 1A) and reduced VBM and GMV (top) and cortical thickness (bottom) when compared to controls ($P < 0.05$ corrected) (Fig. 1B). Lower IGF-1 levels correlated with lower GMV and cortical thinning in the HD group (Supplemental Tables S4 and S5). No significant neuroimaging correlates were obtained when testing for a negative correlation between IGF-1

levels and brain atrophy in the HD group, nor increased GMV/Cth in the HD group compared to controls.

Discussion

Based on these preliminary findings obtained from a small sample, otherwise well clinically characterized HD cohort, our study suggests a hormonal-clinical-brain structure framework, where abnormal IGF-1 function is associated with brain atrophy leading to impaired social cognition in HD. According to our results, IGF-1 seems to be the most robust peptide associated with social cognition impairment in HD.²² In post hoc analysis, higher IGF-1 and oxytocin levels were positively correlated with better social cognition function, and lower oxytocin and IGF-1 levels with higher apathy and motor impairment, respectively. Similarly, other authors have found an association between lower oxytocin plasmatic and cerebrospinal fluid levels with impaired social cognition in HD.^{23,24}

The association between IGF-1 and social cognition might be explained by its hypothetical neuroprotective role. According to previous literature, IGF-1 activates the enzyme serine/threonine kinase Akt, which phosphorylates the mutant huntingtin protein at serine 421,²² promoting neuronal survival and reducing tau phosphorylation in animal models.^{22,25,26} However, it is intriguing why the IGF-1 was associated with social cognition impairment in HD, when in both groups of participants, the IGF-1 concentration levels were within the age/gender normal range, with a trend for higher concentrations in the HD group. A hypothetical explanation could be the lack of IGF-1 function,

and the elevation of IGF-1 level might reflect a resistant state,²⁷ theoretically secondary to a loss of sensitivity to GH in HD.

Of note, we found a relationship between IGF-1 levels and the structural integrity in a set of brain regions involved in social cognition,²⁸ and particularly vulnerable to HD neuropathology. One possibility to explore in future studies would be that IGF-1 abnormalities present at birth contribute to brain structure during neurodevelopment in HD.²⁹ A second possibility would be that IGF-1 abnormalities occur at the receptor level or later in life, promoting damaging effects and consequently aggravating brain atrophy in certain areas of GMV.³⁰ A third possibility would be that peripheral IGF-1 concentration levels might not be correlated with central IGF-1 concentration levels.

We are aware of the main limitations of this study, and it is not possible to develop any causal model around this relationship with the present data. The exclusion of HD patients on medication in some analyses may result in selection bias, excluding more severely affected HD patients. In addition, we collected samples at a one-time point in the morning, excluding the possibility of analyzing the circadian rhythmicity in our sample. In contrast, we have reported preliminary novel results by integrating the HD clinical phenotype, endocrine function, and neuroimaging findings, which deserve more profound analysis.

In conclusion, our results suggest the clinical implication of IGF-1 in social cognition and brain structure. These data may serve other authors to generate new hypotheses for understanding the pathophysiology and conduct larger sample size studies to confirm these preliminary findings.

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Author Roles

(1) Research project: A. Conception; B. Organization; C. Execution. (2) Analysis: A. Design; B. Execution; C. Review and Critique. (3) Manuscript Preparation: A. Writing of the First Draft; B. Review and Critique.

C.G.P.: 1A, 1B, 1C, 2A, 2B, 2C, 3A, 3B.

S.I.M.H.: 1C, 2C, 3B.

F.S.S.: 1C, 2C, 3B.

M.M.P.: 1C, 3B.

S.G.M.: 1C, 3B.

P.A.B.: 1C, 3B.

L.M.P.: 1C, 3B.

S.C.: 1C, 2B, 3B.

C.C.: 1C, 3B.

E.A.G.: 1C, 3B.

E.R.M.: 1C, 3B.

A.A.A.: 1C, 3B.

J.N.R.: 1C, 3B.

M.S.R.: 1C, 3B.

N.M.: 1C, 3B.

L.A.: 1C, 3B.

I.M.S.: 1C, 3B.

D.P.: 1C, 3B.

J.R.: 1C, 3B.

M.D.F.: 1C, 2B, 3B.

I.M.P.: 1C, 3B.

E.C.: 1A, 1B, 1C, 2A, 2B, 2C, 3A, 3B.

Disclosures

Ethical Compliance Statement: We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines. This study was approved by the Institutional Review Board of the Complejo Universitario Burgos and Soria (Spain) (Ceim 1973), and all subjects signed the informed consent form before participating.

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Data Sharing Statement: We will provide data sharing information on reasonable request. ■

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Supporting Information

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

Supplemental S1. Supplemental file.

Figure S1. Ekman-60 face scores in relation to insulin-like growth factor-1 levels in patients with Huntington's disease.

Figure S2. Ekman-60 face scores in relation to insulin-like growth factor-1 levels in the control group.