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Impairments in negative emotion recognition and empathy for pain in Huntington's disease families

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ABSTRACT

Lack of empathy and emotional disturbances are prominent clinical features of Huntington's disease (HD). While emotion recognition impairments in HD patients are well established, there are no experimental designs assessing empathy in this population. The present study seeks to cover such a gap in the literature. Eighteen manifest HD patients, 19 first-degree asymptomatic relatives, and 36 healthy control participants completed two emotion-recognition tasks with different levels of contextual dependence. They were also evaluated with an empathy-for-pain task tapping the perception of intentional and accidental harm. Moreover, we explored potential associations among empathy, emotion recognition, and other relevant factors – e.g., executive functions (EF). The results showed that both HD patients and asymptomatic relatives are impaired in the recognition of negative emotions from isolated faces. However, their performance in emotion recognition was normal in the presence of contextual cues. HD patients also showed subtle empathy impairments. There were no significant correlations between EF, empathy, and emotion recognition measures in either HD patients or relatives. In controls, EF was positively correlated with emotion recognition. Furthermore, emotion recognition was positively correlated with the performance in the empathy task. Our findings highlight the preserved cognitive abilities in HD families when using more ecological tasks displaying emotional expressions in the context in which they typically appear. Moreover, our results suggest that emotion recognition impairments may constitute a potential biomarker of HD onset and progression. These results contribute to the understanding of emotion recognition and empathy deficits observed in HD and have important theoretical and clinical implications.

1. Introduction

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder caused by an expanded CAG repeat on chromosome 4 (Conneally, 1984), classically characterized by a triad of symptoms including cognitive, motor, and behavioral abnormalities, and associated with neuronal loss within corticostriatal circuits (Lawrence et al., 1998). Neuropathological and neuroimaging studies (Della Nave et al., 2010; Muhlau et al., 2007; Nopoulos et al., 2010) have revealed selective gray matter atrophy in HD, with the earliest changes progressing from the dorsolateral

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to the ventromedial portions of the neostriatum. Furthermore, the cerebral cortex is selectively affected with early involvement of the operculum. Subsequently, progressive atrophy involves the insula, primary sensory, motor, and visual cortices, and then the primary auditory cortex. Finally, atrophy extends to the entorhinal cortex and higher order cortical regions. Importantly, structural and functional abnormalities in the basal ganglia and the insula (Hennenlotter et al., 2004; Ille et al., 2011; Kipps et al., 2007) as well as in the frontostriatal pathways (Joel, 2001) have been associated with social cognition impairments in HD.

HD patients are typically impaired in their social functioning, partly due to emotional disturbances and lack of empathy (Kirkwood et al., 2001; Snowden et al., 2003). While emotion recognition impairments are well documented in HD patients (Henley et al., 2012; Johnson et al., 2007; Mitchell et al., 2005; Trinkler et al., 2013), only one study (Trinkler et al., 2013) has assessed empathy in these individuals and none has assessed this domain in first-degree relatives. This comes as a surprise, since lack of empathy is a prominent clinical feature of HD (Bodden et al., 2010; Kirkwood et al., 2001; Williams et al., 2009).

To cover such a gap, this study evaluated the performance of HD patients and first-degree asymptomatic relatives on empathy and emotion recognition tasks with different levels of contextual dependence. Moreover, we explored potential associations among empathy, emotion recognition, and other relevant factors – e.g., executive functions (EF).

Emotion recognition is essential for successful social interaction. Neuroanatomically, this process has been linked to regions in the temporal lobe, such as the fusiform gyrus, together with a network involving amygdala, orbitofrontal cortex, and cingulate structures (Adolphs, 2001). However, dissociations in the recognition of different facial expressions (e.g. Blair et al., 1999; Lawrence et al., 2007; Williams et al., 2009) suggest that different neural systems are specialized, at least in part, for the recognition of particular emotions. For instance, the amygdala appears to link perceptual representations to cognition and behavior on the basis of the emotional value of the stimuli (Adolphs, 2001). Thus, it appears to be involved in processing the emotional salience of both positive and negative stimuli, with a special role in coding signals of fear (Adolphs, 2001; Britton et al., 2006). The recognition of sadness expressions has been particularly associated with the right inferior and middle temporal gyrus (Blair et al., 1999; Rosen et al., 2006), while disgust recognition has been linked to the insula and the basal ganglia (Adolphs, 2002; Calder et al., 2000; Couto et al., 2013; Ibanez et al., 2010; Wang et al., 2003).

Emotion recognition has been systematically studied in HD. In manifest HD patients, anger recognition appears to be most consistently impaired, closely followed by recognition of disgust and fear (Aviezer et al., 2009; Henley et al., 2012; Milders et al., 2003; Montagne et al., 2006; Snowden et al., 2008). On the contrary, recognition of other emotions, such as happiness, sadness, or surprise, is rarely affected (Calder et al., 2010; Hayes et al., 2009). Some studies on pre-manifest HD (Gray et al., 1997; Hennenlotter et al., 2004; Sprengelmeyer et al., 2006) have reported a selective deficit in disgust recognition, whereas others (Johnson et al., 2007; Tabrizi et al., 2009) have found impairments across negative emotions. These findings and those of large longitudinal studies (Paulsen et al., 2006; Tabrizi et al., 2009) suggest that emotion recognition might be a sensitive biomarker of disease onset and progression in HD.

Most of the studies investigating facial emotion recognition in HD have relied on tasks involving isolated faces. However, real-life facial expressions are typically embedded in a rich, informative context. Recent reports (Barrett and Kensinger, 2010; Barrett et al., 2007; Van den Stock et al., 2007) have shown that facial expression recognition is a context-sensitive process. Visual scenes, voices, bodies, other faces, and even words influence how an emotion is perceived in a face (Barrett et al., 2011). Indeed, under certain conditions, context can modify the emotional category recognized in basic facial expressions (Aviezer et al., 2008). These findings notwithstanding, only one study (Aviezer et al., 2009) has assessed the recognition of facial expressions embedded within an emotional body and scene context in HD mutation carriers. This study showed that HD patients display relatively preserved processing of facial expressions when these are embedded in a given context. However, one limitation of this work concerns the employment of static, as opposed to dynamic stimuli. In this sense, the use of dynamic stimuli to assess facial emotion recognition in HD may provide a more realistic and sensitive measure, as these more closely resemble the moving faces encountered in everyday life (Mendoza et al., 2011; Russell et al., 2007; Schaefer et al., 2010).

Unlike emotion recognition, empathy has been scarcely studied in patients with HD. Empathy comprises the capacity to share and understand the subjective experience of others in reference to oneself (Decety, 2011). This complex construct involves (1) affective components: sharing and responding to the emotional experience of others (Decety and Jackson, 2004), which facilitates somatic, sensory, and motor representation of other people's mental states (Nummenmaa et al., 2008); (2) cognitive components: understanding the intentions and internal mental states of others (Blair, 2005); and (3) aspects related to the moral evaluation: judging the actions of a perpetrator or the punishment deserved (Decety and Jackson, 2004; Decety et al., 2012).

Only one study in HD patients (Trinkler et al., 2013) has assessed empathy, evidencing normal scores in self-report questionnaires. Here we implemented a novel paradigm with naturalistic stimuli that measures empathy for others' physical pain. This type of paradigm has been widely used due to the robustness of pain in inducing empathic responses (Bernhardt and Singer, 2012), and the well characterized neural circuit of empathy (Akitsuki and Decety, 2009). Neuroimaging studies on empathy for pain have systematically evidenced a neural network that is implicated in the experience of physical pain, and involved in the perception or imagination of another individual in pain (Jackson et al., 2006; Melloni et al., 2014). This neural network includes the supplementary motor area, the anterior cingulate cortex, the amygdala, and the anterior insula extending into the inferior frontal gyrus (Bernhardt and Singer, 2012; Decety et al., 2012; Singer and Lamm, 2009).

We employed an adaptation of an empathy for pain task (EPT) previously validated with behavioral measures, eye-tracking and fMRI (Decety et al., 2012). This adapted version has been used in the assessment of other neuropsychiatric populations (Baez et al., 2012, 2013, 2014; Baez and Ibanez, 2014; Sedeno et al., 2014). The task evaluates empathy in the context of intentional/accidental harms, and consists of three different scenarios: (1) intentional or (2) accidental harms in which one person is in a painful situation intentionally or accidentally caused by another, and (3) neutral or control situations. The EPT evaluates the following components: (A) comprehension of the accidental or deliberate nature of the action and the intention of the perpetrator to hurt (cognitive components); (B) the empathic concern, the degree of discomfort for the victim, and the valence behavior of the active performer (affective components); and (C) the correctness of the action and the punishment for the perpetrator (moral aspects). Note that the cognitive components of empathy assessed in this study have been associated to theory of mind (ToM) (Blair, 2005; Zaki and Ochsner, 2012; Ibanez et al., 2013), a fundamental ability to empathize with others by considering their mental states. Impairments in this ability have also been reported in HD patients. These individuals show a tendency to draw faulty inferences from social situations,

and are impaired in both affective and cognitive aspects of ToM (Brüne et al., 2011; Eddy et al., 2012; Snowden et al., 2003).

Emotion processing and empathy are two interrelated phenomena (Schipper and Petermann, 2013; Singer, 2006). Empathy and ToM are positively correlated with recognition of facial emotion expressions (Besel and Yuille, 2010; Ibanez et al., 2014). Furthermore, neuroimaging studies (Hooker et al., 2008; Singer, 2006) have shown that these different domains share similar processes and depend on the activation of common brain regions. Nevertheless, the relationship between emotion recognition and empathy has not yet been explored in HD patients or relatives.

In sum, emotion recognition and empathy are two important social cognition domains affected in HD (Kirkwood et al., 2001; Snowden et al., 2003). Both are highly context-dependent phenomena (Ibanez and Manes, 2012; Melloni et al., 2014), but none of them has been extensively studied through context-rich tasks. Moreover, there are no studies exploring the relationship between emotion recognition and empathy in HD.

Based on existing information, the present study assessed the performance of manifest HD patients as well as first-degree asymptomatic relatives on emotion recognition and empathy tasks. We included two emotion recognition tasks with different levels of contextual dependence and involvement of real-life scenarios. We also used an ecologically valid task tapping empathy for pain. Furthermore, we examined the relationship between emotion recognition and empathy. Finally, since social cognition skills have been linked to EF (Decety, 2011; Pessoa, 2011), we explored the association between executive processing and empathy/emotion recognition measures. Two main hypotheses guided this study. Given that emotion recognition may be a sensitive marker of HD (Henley et al., 2012), we hypothesized that emotion recognition would be impaired in both HD patients and asymptomatic relatives, though these deficits would not be related to the contextual cues processing. As an open hypothesis, we investigated whether different empathy aspects are affected in HD patients and relatives, and whether lack of empathy may also constitute a marker of HD vulnerability.

2. Materials and methods

2.1. Participants

Seventy-three subjects participated in the present study. The first group consisted of 18 symptomatic patients genetically and clinically diagnosed with HD. A second group consisted of 19 relatives (descendants or siblings) of individuals in the HD group. They did not present any HD symptoms, and had not been diagnosed with HD or other neuropsychiatric diseases. This sample of relatives did not receive genetic testing.

Both groups underwent a neurological examination and were assessed using the Unified Huntington's Disease Rating Scale (UHDRS) (Siesling et al., 1998). In addition, HD patients were assessed with the Total Functional Capacity Scale (HDFCS) (Shoulson and Fahn, 1979) (see Table 1). Patients and relatives live in the small rural town of Juan de Acosta, Colombia, a region characterized by having the second largest concentration of individuals with HD worldwide (Kargieman et al., 2014). This population also features a large number of families with individuals affected by HD with complete penetrance, and also displays high levels of anticipation.

Thirteen of the patients (72.23%) received no pharmacologic treatment. Five patients (27.77%) were taken antidepressants antipsychotics or/and Tetrabenzine. Patients and relatives had no history of other major neurological illness, psychiatric disorders, or alcohol/drug abuse.

Two control groups were recruited from the same geographical region. Each group consisted of 18 healthy participants matched

Table 1
Demographic, clinical and executive functions assessments.

	HDPs ($n=18$) Mean (SD)	HDPs CTR ($n=18$) Mean (SD)	HDPs vs CTR Mean (SD)	ARs ($n=19$) Mean (SD)	ARs CTR ($n=18$) Mean (SD)	ARs vs CTR Mean (SD)
Demographics						
Age (years)	43.8 (10.3)	43.2 (10.5)	NS	29.2 (9.6)	29.5 (10.2)	NS
Gender (F:M)	6:12	7:11	NS	13:6	12:6	NS
Education (years)	9.5 (5.0)	10.1 (4.2)	NS	11.5 (2.6)	11.4 (2.6)	NS
Intellectual level	89.1 (8.4)	90.2 (11.4)	NS	89.5 (11.1)	92.9 (8.6)	NS
Clinical assessment						
UHDRS	20.5 (8.6)			0.2 (0.4)		
HDFCS	11.8 (1.5)					
BDI-II	11.7 (8.4)	4.3 (2.0)	0.001	4.05 (3.0)	4.2 (1.6)	NS
HAM-A	7.2 (3.3)	1.8 (1.2)	0.00	3.3 (1.6)	1.5 (1.2)	0.003
Cognitive assessment						
MOCA total score	24.9 (2.6)	27.7 (1.4)	0.003	27.7 (1.4)	29.2 (1.2)	0.001
IFS total score	19.6 (4.6)	23.6 (1.5)	0.001	23.9 (1.9)	26.0 (2.0)	0.003
Motor series	2.5 (0.7)	2.8 (0.3)	NS	2.8 (0.3)	3.0 (0.0)	NS
Conflicting instructions	2.1 (1.1)	2.8 (0.3)	0.01	2.8 (0.3)	2.9 (0.2)	NS
Go-no go	1.7 (1.0)	2.6 (0.6)	0.006	2.6 (0.5)	2.7 (0.4)	NS
Backward digits span	2.9 (0.8)	3.1 (0.7)	NS	3.2 (0.8)	4.0 (1.1)	0.01
Verbal working memory	1.7 (0.5)	2.0 (0.0)	0.04	2.0 (0.0)	1.9 (0.2)	NS
Spatial working memory	1.3 (1.3)	2.0 (0.5)	NS	2.1 (0.6)	3.1 (0.8)	0.003
Abstraction capacity	2.1 (0.9)	2.6 (0.4)	0.03	2.6 (0.4)	2.6 (0.4)	NS
Verbal inhibitory control	5.1 (1.3)	5.5 (0.7)	NS	5.5 (0.7)	5.4 (0.9)	NS
Stroop test (W)	65.3 (24.5)	84.0 (15.3)	0.01	84.3 (14.9)	91.8 (7.9)	NS
Stroop test (C)	48.0 (23.5)	63.0 (10.4)	0.01	62.6 (10.2)	62.9 (12.5)	NS
Stroop test (W/C)	24.6 (17.8)	31.7(12.1)	NS	31.5 (11.8)	38.7 (14.2)	NS
Similarities subtest	18.0 (2.7)	18.2 (4.4)	NS	18.1 (4.3)	19.3 (3.2)	NS

HDPs=Huntington's disease patients; ARs=asymptomatic relatives; UHDRS=unified Huntington's Disease Rating Scale; HDFCS=total functional capacity scale; BDI-II=Beck Depression Inventory-II; HAM-A=Hamilton anxiety rating scale; IFS=INECO frontal screening; W=word; C=color, W/C=word/color.

by age, gender, years of education and intellectual level with the HD patients and the relatives. Control subjects did not have a history of alcohol/drug abuse or history of neurodegenerative or psychiatric disorders. All participants provided written informed consent in agreement with the Helsinki declaration. The Ethics Committees of the Institute of Cognitive Neurology and the Caribbean Autonomous University approved this study (resolution 59-A).

2.2. Instruments

2.2.1. Emotion recognition

2.2.1.1. Emotional morphing. Emotional morphing is a facial expression recognition task featuring six basic emotions (happiness, surprise, sadness, fear, anger, and disgust) taken from the Pictures of Affect Series (Ekman and Friesen, 1976). The pictures have been morphed for each prototype emotion and for a neutral state (Young et al., 1997). Facial morphing is generated by taking a variable percentage of the shape and texture differences between the two standard images: 0% (neutral) and 100% (full emotion) in 5% steps (500 ms for each image). The 48 morphed facial stimuli were randomly presented on a computer screen until the patient indicated a response on the keyboard. Participants were asked to respond as soon as they recognized the facial expression, and then to identify the facial expression from a forced choice-list of six options. This task measures the accuracy of emotion recognition and reaction times (RTs).

2.2.1.2. The Awareness of Social Inference Test (TASIT). TASIT is a sensitive test of social perception developed for studies on neuropsychiatry and comprises videotaped vignettes of everyday social interactions (Kipps et al., 2009; McDonald et al., 2006, 2003). We considered only part 1, called the Emotion Evaluation Test (EET), which assesses recognition of spontaneous emotional expression (fearful, surprised, sad, angry, and disgusted). In the EET, emotional meaning is indicated by speaker demeanor (voice, facial expression, and gesture) together with the social situation. This task introduces contextual cues (e.g., prosody, facial movement, and gestures) and additional processing demands (e.g., adequate speed of information processing, selective attention, and social reasoning) which are absent when viewing static displays. The brief EET comprises a series of 20 short (15–60 s) videotaped vignettes of trained professional actors interacting in everyday situations. In some scenes, there is only one actor talking, who is either on the telephone or talking directly to the camera. Other scenes depict two actors and instructions are given to focus on one of them. All scripts are neutral in content and do not lend themselves to any particular emotion. After viewing each scene, the participant is instructed to choose from a forced-choice list the emotion expressed by the focused actor.

2.2.2. Empathy

2.2.2.1. Empathy for Pain Task (EPT). We used an EPT previously employed in assessing other neuropsychiatric populations (Baez et al., 2012, 2013, 2014; Sedeno et al., 2014). This task evaluates empathy for pain in the context of intentional and accidental harm, as well as control situations and consists of a successive presentation of 24 animated situations with two persons (Decety et al., 2012). Three kinds of situations are depicted: (a) intentional pain, in which a passive performer is in a painful situation because of an active performer's deliberate action – e.g., stepping purposely on someone's toe; (b) accidental pain, where one person is in a painful situation accidentally caused by another one; and (c) control or neutral situations – e.g., one person receiving a flower from another. Importantly, participants were not shown the protagonists' faces or their emotional reactions.

Participants were instructed to press a button as soon as they understood the situation. We assessed replies to 7 questions about the following qualities: *intentionality* (the accidental or deliberate nature of the action); *empathic concern* (how sad participants feel for the passive performer); degree of *discomfort* (for the passive performer); *intention to hurt* (how bad the active performer's intent was); the *valence behavior* (happiness) of the active performer (how much positive emotion he/she felt in performing the action); *correctness* of the action (moral judgment); and, finally, *punishment* (how much penalty this action deserves). Each question was answered using a computer-based visual analog scale giving 7 different pain ratings by trial. Accuracy, RTs, and ratings were measured.

2.2.3. Clinical and cognitive assessments

All participants completed a series of psychiatric questionnaires to establish a clinical symptom profile. Depression rates were obtained through the Beck Depression Inventory-II (Beck et al., 1996), while anxiety symptoms were assessed with the Hamilton anxiety rating scale (HAM-A) (Hamilton, 1959).

Additionally, participants were evaluated with the Wechsler Abbreviated Scale of Intelligence (WASI). This test includes vocabulary and similarities subtests and provides a verbal estimated IQ (Weschler, 1999). The participants' general cognitive state was assessed using the Montreal Cognitive Assessment (MOCA) (Nasreddine et al., 2005).

All participants were also evaluated with the INECO Frontal Screening (IFS) (Torralva et al., 2009), which has been shown to successfully detect executive dysfunction (Gleichgerrcht et al., 2011; Torralva et al., 2009). This test includes the following eight subtests: (1) motor programming (Luria series, "fist, edge, palm"); (2) conflicting instructions (subjects are asked to hit the table once when the administrator hits it twice, or vice versa); (3) motor inhibitory control; (4) numerical working memory (backward digit span); (5) verbal working memory (months backwards); (6) spatial working memory (modified Corsi tapping test); (7) abstraction capacity (inferring the meaning of proverbs), and (8) verbal inhibitory control (modified Hayling test). The maximum possible score on the IFS is 30 points. In addition, the WAIS-III similarities subtest (Wechsler, 1997) was used to evaluate abstract thinking, and the Stroop test (Treisman and Fearnley, 1969) provided further data on the participants' mental speed, selective attention, and inhibitory control.

2.3. Data analysis

All statistical analyses compared the HD patients and relatives groups with their respective control groups. Demographic and neuropsychological data were compared between groups using ANOVA and Tukey's HSD post-hoc tests. Chi square tests were applied to analyze categorical variables (gender). Emotion recognition data were analyzed using repeated-measures ANOVA, considering group and emotion as factors. We used Tukey's HSD post-hoc tests (when appropriate) to examine group differences within each emotion. The ratings and RTs for each question of the EPT were analyzed using a 2×3 repeated-measures ANOVA comprising the factors of group and condition (intentional, accidental, neutral). Tukey's HSD post-hoc tests were used (when appropriate) to examine group differences within each condition.

To control for the influence of clinical symptoms (depression and anxiety) or cognitive state on social cognition tasks, we applied ANCOVA tests adjusted for BDI-II, HAM-A, and total MOCA scores. We report only effects that were still significant after covariation. In addition, we performed Pearson's correlations to examine the associations between (a) emotion recognition and empathy, and (b) EF scores and emotion recognition/empathy

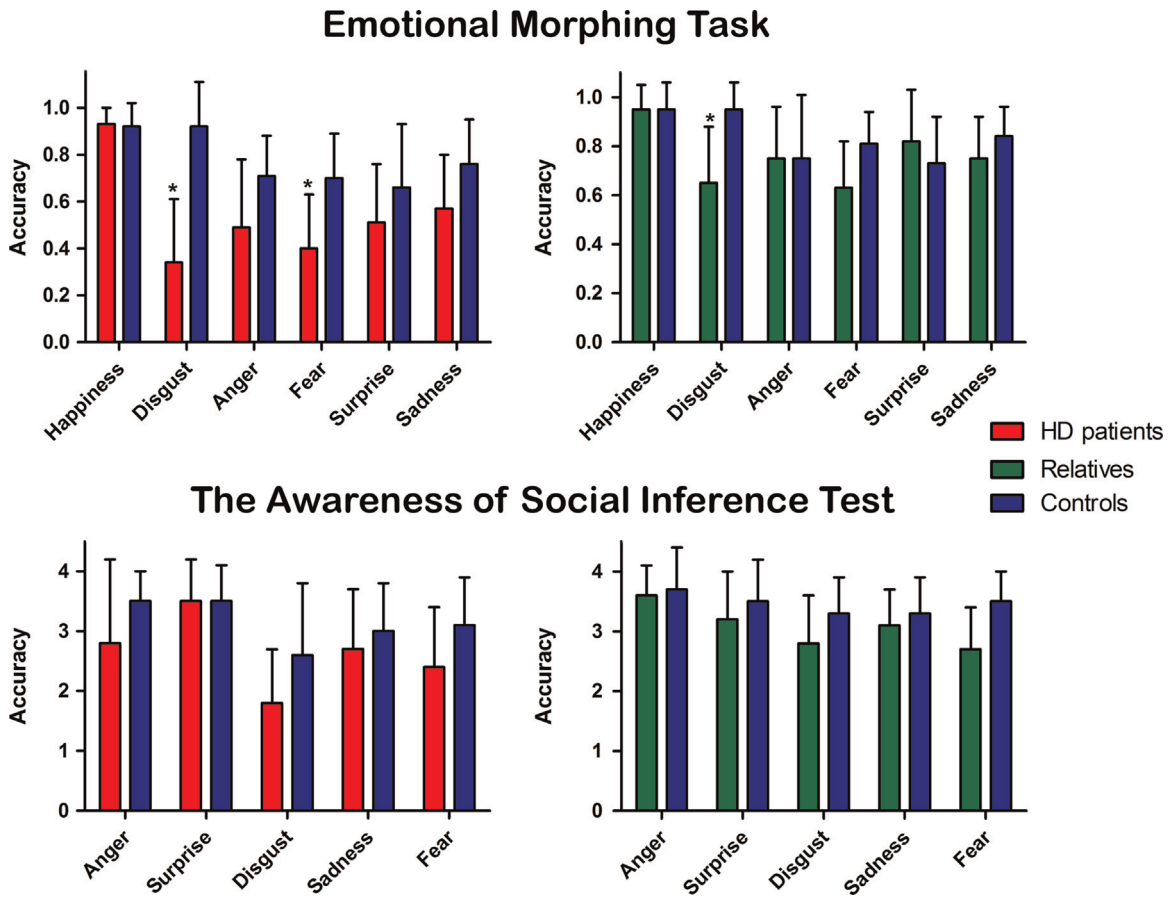

Fig. 1. Comparisons between groups on emotional processing tasks. Asterisk (*) indicates significant differences.

tasks. For correlation analyses, both control groups were pooled together. The significance of all correlations has been corrected for multiple comparisons using the Sidak method. The adjusted α level after correction was set at 0.001 for emotion recognition and empathy correlations, and 0.003 for the other correlations. The α value for all other statistical tests was set at 0.05.

3. Results

3.1. Demographic data

There were no significant differences between HD patients and controls in terms of age ($F(1,34)=0.030$, $p=0.86$), education level ($F(1,34)=0.15$, $p=0.69$), gender ($X^2(1)=0.00$, $p=1.00$), or intellectual level ($F(1,34)=0.004$, $p=0.94$). Similarly, relatives and their controls presented no significant differences in age ($F(1,35)=0.005$, $p=0.94$), education level ($F(1,35)=0.008$, $p=0.94$), gender ($X^2(1)=0.012$, $p=0.90$), or intellectual level ($F(1,35=1.80)$, $p=0.18$). Descriptive data are provided in Table 1.

3.2. Emotion recognition

Fig. 1 shows comparisons between groups on emotional processing tasks. All results are reported after covariation with relevant variables (see Section 2.3).

3.2.1. Emotional morphing

3.2.1.1. HD patients. The analysis of the accuracy on the emotional morphing task revealed a significant interaction between group and emotion ($F(5,170)=10.71$, $p<0.0000001$). A post-hoc analysis (Tukey HSD, MS=0.05, df=119.32) revealed that HD patients were less accurate than controls in recognizing emotions of disgust ($p=0.0001$) and fear ($p=0.006$).

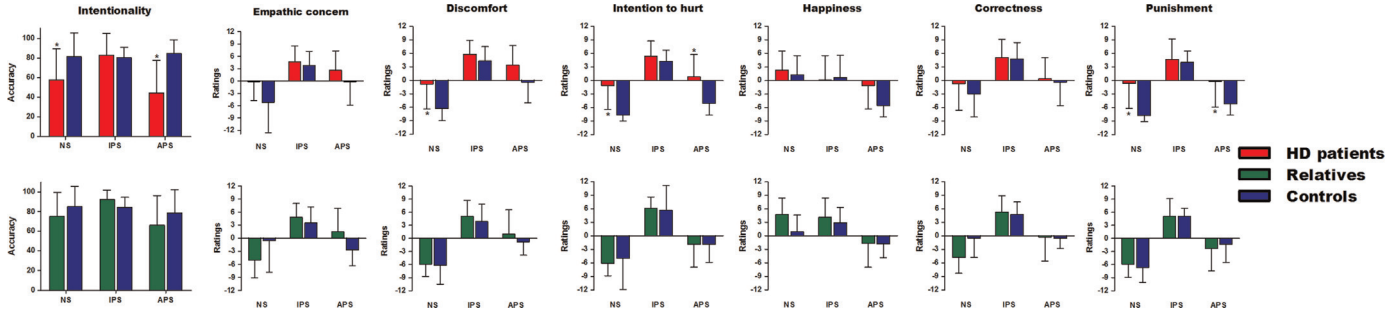

Fig. 2. Comparisons between groups on the empathy for pain task. NS=neutral situations, IPS=intentional pain situations, APS=accidental pain situations. Asterisk (*) indicates significant differences.

In addition, the analysis of the RT showed a significant interaction between group and emotion ($F(5,170=23.12)$, $p<0.0000001$). A post-hoc analysis (Tukey HSD, MS=1394, df=43.70) showed that HD patients had significantly slower RTs than controls for the emotions of disgust ($p=0.0003$), anger ($p=0.004$), surprise ($p=0.004$), and sadness ($p=0.0003$).

3.2.1.2. Relatives. The analysis of the accuracy revealed a significant interaction between group and emotion ($F(5,175)=5.23$, $p=0.0001$). A post-hoc analysis (Tukey HSD, MS=0.03, df=205.01) evidenced that relatives had difficulties in recognizing expressions of disgust ($p=0.00003$). No RT significant differences were observed between the groups.

3.2.2. TASIT

3.2.2.1. HD patients. No differences between HD patients and controls were observed on the TASIT total score ($F(1,31)=2.01$, $p=0.16$). The per-category analysis did not reveal a significant interaction between group and emotion ($F(4,136)=1.53$, $p=0.19$).

3.2.2.2. Relatives. No differences between relatives and controls were observed on the TASIT total score ($F(1,32)=1.54$, $p=0.22$). The per-category analysis showed no significant interaction ($F(4,140)=1.46$, $p=0.21$) between group and emotion.

3.3. Empathy

Fig. 2 shows comparisons between groups on the EPT.

3.3.1. HD patients

Regarding intentionality comprehension, a significant interaction between group and condition ($F(2,68)=7.03$, $p=0.001$) were observed. A post-hoc analysis (Tukey HSD, MS=574.84, df=101.60) revealed that HD patients had significantly poorer comprehension of neutral ($p=0.03$) and accidental ($p=0.001$) situations. Moreover, a significant interaction between group and condition was observed in discomfort ratings ($F(2,68)=4.12$, $p=0.02$). A post-hoc analysis (Tukey HSD, MS=16.79, df=68.33) showed that HD patients ($p=0.02$) had higher ratings than controls for neutral situations. A significant interaction between group and condition was also found in ratings of intention to hurt ($F(2,68)=8.40$, $p=0.0005$). According to the post-hoc analysis (Tukey HSD, MS=13.25, df=79.91), HD patients rated neutral ($p=0.0001$) and accidental ($p=0.0001$) situations significantly higher than controls. Finally, a significant interaction between group and condition was observed in punishment ratings ($F(2,68)=9.53$, $p=0.0002$). A post-hoc analysis (Tukey HSD, MS=17.14, df=77.75) showed that HD patients rated neutral ($p=0.0001$) and accidental ($p=0.006$) pain situations higher than controls.

Regarding RTs, a significant interaction between group and condition was found in terms of intentionality inference ($F(2,68)=6.83$, $p=0.001$). A post-hoc analysis (Tukey HSD, MS=252E4, df=83.82) revealed that HD patients took significantly longer to infer the intentionality of neutral situations ($p=0.0001$).

3.3.2. Relatives

No differences between relatives and controls were observed in empathy ratings or RTs.

3.4. Clinical and neuropsychological assessments

3.4.1. HD patients

HD patients had higher levels of anxiety than controls ($F(1,34)=40.13$, $p<0.0000001$), as measured by the HAM-A. In addition, HD patients showed higher levels of depression symptoms ($F(1,34)=12.73$, $p=0.001$).

Also, relative to controls, HD patients had significantly lower total scores on the MOCA ($F(1,34)=15.94$, $p=0.0003$) and the IFS ($F(1,34)=12.05$, $p=0.001$). A detailed comparison of performance on the eight IFS subtests indicated that HD patients exhibited deficits in verbal working memory ($F(1,34)=4.20$, $p=0.04$), conflictive instructions ($F(1,34)=6.57$, $p=0.01$), motor inhibitory control ($F(1,34)=8.36$, $p=0.006$), and abstraction capacity ($F(1,34)=4.77$, $p=0.03$). In addition, HD patients obtained lower scores than controls in the word ($F(1,34)=7.42$, $p=0.01$) and color naming ($F(1,34)=6.09$, $p=0.01$) conditions of the Stroop test. However, no differences were observed in the word/color condition ($F(1,34)=1.9$, $p=0.16$) or the similarities subtest ($F(1,34)=0.01$, $p=0.89$). See Table 1 for further details.

3.4.2. Relatives

Relatives showed higher levels of anxiety than their controls ($F(1,35)=15.92$, $p=0.0003$). However, the groups had comparable BDI-II total scores ($F(1,35)=0.84$, $p=0.77$).

Relative to controls, relatives obtained lower total scores on the MOCA ($F(1,35)=11.36$, $p=0.001$) and the IFS ($F(1,35)=9.67$, $p=0.003$). A detailed analysis of performance on the eight IFS subtests revealed impaired verbal working memory in relatives ($F(1,35)=6.39$, $p=0.01$). No differences between groups were observed in the word ($F(1,35)=3.61$, $p=0.06$), color ($F(1,35)=0.06$, $p=0.93$) or word/color ($F(1,35)=2.80$, $p=0.10$) conditions of the Stroop test. Both groups also performed similarly on the similarities subtest ($F(1,35)=1.02$, $p=0.31$). See Table 1 for further details.

3.5. The relationship between emotion recognition and empathy

No significant correlations between emotion recognition and empathy were found in either HD patients or relatives. In controls, anger recognition (TASIT) was positively correlated with the inference of the intentionality of accidental pain situations ($r=0.55$, $p<0.0000001$), and negatively correlated with discomfort ratings for neutral situations ($r=-0.57$, $p<0.0000001$).

3.6. Associations between EF, emotion recognition, and empathy measures

EF, emotion recognition, and empathy measures were not significantly correlated in either HD patients or relatives. In controls, executive functioning (IFS total score) was positively correlated with recognition of spontaneous emotional expression (TASIT total score) ($r=0.58$, $p<0.0000001$) and with fear recognition in the emotional morphing task ($r=0.52$, $p=0.001$). Also, the controls' performance on the similarities subtest showed a positive correlation with the TASIT total score ($r=0.51$, $p=0.002$).

4. Discussion

This is the first study on emotion recognition and empathy in HD patients and relatives. We included two emotion recognition tasks with different levels of contextual dependence and involvement of real-life scenarios. We also used an empathy for pain paradigm which requires contextual appraisal to infer intentions and provide empathy responses. Furthermore, we examined the relationship between EF, empathy, and emotion recognition measures.

Overall, our results showed that both HD patients and relatives were impaired in recognizing negative emotions, as assessed only by decontextualized tasks (faces alone). Regarding empathy, comprehension of the intentionality of others' actions was

compromised only in HD patients. Likewise, discomfort, intention to hurt, and punishment ratings for neutral and accidental pain situations were abnormal only in HD patients. Moreover, there were no significant correlations between EF, empathy, and emotion recognition measures in HD patients or relatives. These findings highlight the preserved cognitive abilities in HD families when using more ecological tasks displaying emotional expressions in the context in which they typically appear. Empathy deficits (related to intentionality identification) seem to be evident only after the disease is manifest. Finally, our results suggest that specific emotion recognition impairments may be considered a potential biomarker in HD.

4.1. The performance of HD patients and relatives on emotion recognition and empathy tasks

Using the (decontextualized) emotional morphing task, we replicated well-documented (Aviezer et al., 2009; Henley et al., 2012; Milders et al., 2003; Montagne et al., 2006; Snowden et al., 2008) fear and disgust recognition impairments in patients with manifest HD. For their own part, relatives exhibited a selective impairment in disgust recognition, which is in line with previous reports of individuals with pre-manifest HD (Gray et al., 1997; Hennenlotter et al., 2004; Sprengelmeyer et al., 2006).

Both HD patients and relatives showed a normal performance on the TASIT. This context-rich test taps inference of emotional states through the integration of face, prosody, gesture, and social context cues (Kipps et al., 2009; McDonald et al., 2006, 2003; Sparks et al., 2010). Previous studies (Baez et al., 2013; McDonald et al., 2003) showed that contextual cues in the TASIT normally assist healthy individuals to more accurately identify emotional expressions. Our findings suggest that these contextual cues also improve emotion recognition in HD patients and relatives. These results are consistent with those of the only study assessing context-based face recognition in HD mutation carriers (Aviezer et al., 2009). Taken together, the evidence suggests that HD patients and relatives are impaired in recognizing negative emotions from isolated faces, but that, as is the case with healthy subjects, the presence of contextual information improves their performance.

Regarding empathy, only HD patients exhibited deficits in distinguishing accidental and neutral from intentional pain situations. This finding may be related to two factors. First, empathy for pain is a contextual phenomenon affected by stimulus ambiguity (Melloni et al., 2014). Accidental and neutral situations, in particular, are less clear and explicit than intentional ones, increasing the level of ambiguity and the cognitive demands to interpret the action's intentionality. Second, previous studies have shown that HD patients (Bodden et al., 2010; Brüne et al., 2011; Eddy et al., 2012) exhibited deficits in ToM, the ability to infer the beliefs, intentions, and emotions of others (Baron-Cohen et al., 1985). ToM impairments may affect the capacity of HD patients to accurately infer the intentionality of others' actions in the context of more ambiguous scenarios. Furthermore, our results are consistent with those of a fMRI study (Saft et al., 2013) showing no differences between pre-manifest mutation carriers and healthy controls regarding the behavioral performance on a ToM task and the activation of the mentalizing network. This suggest that ToM impairments emerge with the clinical manifestation of the disease, but is not necessarily part of the pre-manifest stage.

In addition, relative to controls, HD patients gave higher discomfort, intention to hurt, and punishment ratings for neutral and accidental pain situations. Intentionality detection is crucial to determine how wrong an action is and how severe a punishment the perpetrator deserves (Decety et al., 2012). Previous results (Akitsuki and Decety, 2009; Decety et al., 2012) showed that empathic ratings of healthy participants are higher for intentional than accidental pain. Nonetheless, HD patients presented the exact opposite pattern, which suggests that their empathic ratings reflect their difficulties to distinguish accidental and neutral situations from intentional ones.

In brief, our results showed that more fundamental aspects of empathy, such as empathic concern, are preserved in both patients and relatives. However, some aspects of empathy related with intentionality detection are affected in the former group. These results suggest that individuals with HD do not exhibit a primary loss of empathic concern, but rather subtle impairments that may be explained by the tendency to misinterpret the intentionality of others' actions. These findings are consistent with previous evidence (Trinkler et al., 2013) showing that HD patients perform normally in affective or core dimensions of empathy, as measured by self-report questionnaires. Further studies should address the qualitative characteristics of performance in experimental and real-life social situations to better characterize the basis of empathy impairments in HD.

4.2. Emotion recognition as a potential biomarker of HD

Both HD patients and relatives evidenced impairments in recognizing negative facial expressions. However, only HD patients exhibited empathy deficits. Thus, although both emotion recognition difficulties and lack of empathy are evident in the daily life of HD patients (Kirkwood et al., 2001; Snowden et al., 2003), only facial expression recognition deficits might be a potentially useful biomarker of HD onset and vulnerability due to two main reasons. First, unlike empathy, emotion recognition is systematically impaired in both HD manifest patients (Aviezer et al., 2009; Henley et al., 2012; Milders et al., 2003; Montagne et al., 2006; Snowden et al., 2008) and pre-manifest mutation carriers (Henley et al., 2008; Johnson et al., 2007; Tabrizi et al., 2009). Second, large longitudinal studies in pre-manifest mutation carriers and patients with the disease (Langbehn et al., 2010; Tabrizi et al., 2009) have shown that emotion recognition is a sensitive measure in distinguishing individuals according to time to predicted disease onset.

Specifically, our results showed that HD patients had deficits in recognizing fear and disgust expressions, whereas relatives showed deficits in disgust recognition only. Dissociations in the recognition of different facial expressions (e.g. Blair et al., 1999; Lawrence et al., 2007) suggest that different neural systems are (partly) specialized for the recognition of particular emotions. For instance, the recognition of fearful expressions has been critically associated with the amygdala (Adolphs, 2001; Britton et al., 2006) as well as the insula and the striatum (Phillips et al., 1997; Weniger and Irle, 2002; Whalen et al., 1998). Disgust recognition has also been linked to the insula and the basal ganglia (Adolphs, 2002; Calder et al., 2000; Couto et al., 2013; Ibanez et al., 2010; Wang et al., 2003). These structures are compromised in individuals with manifest (Fennema-Notestine et al., 2004; Kassubek et al., 2004) and pre-manifest HD (Kipps et al., 2007; van den Bogaard et al., 2011). Indeed, previous structural imaging studies in HD patients show that the identification of disgust (Ille et al., 2011) and fear (Henley et al., 2008) is associated with atrophy of the insula and the striatum. Disgust recognition is also related to gray matter volume of the insula in pre-manifest HD patients (Kipps et al., 2007). In line with this evidence, our results suggest that HD particularly compromises the recognition of negative emotions, such as disgust and fear, which may be related to damage to the insula and basal ganglia. In addition, our findings support the notion that emotion-specific recognition deficits may vary across disease stages, with a selective deficit for disgust in asymptomatic stages and an expansion to other negative emotions as the disease progresses (Johnson et al., 2007).

These differential patterns of emotion recognition and empathy impairments in HD patients and relatives may be explained by the development of atrophy and brain dysfunction in HD. Brain structures associated with disgust and fear recognition are damaged very early in HD, several years before the onset of symptoms (Nopoulos et al., 2010; Thieben et al., 2002). However, regions implicated in empathy for pain – e.g., supplementary motor area, anterior cingulate cortex, and amygdala (Decety et al., 2012; Singer and Lamm, 2009) – are compromised later or even preserved (except the insula) (Della Nave et al., 2010; Fennema-Notestine et al., 2004; Muhlau et al., 2007). Thus, early involvement of the basal ganglia and insula may account for the disgust recognition impairments observed in relatives. The more subtle deficits in empathy could be related to early involvement of the insula, subsequent atrophy of the motor cortices, and better preservation of the anterior cingulate cortex and the amygdala (Aylward et al., 2011; Della Nave et al., 2010). This explanation should be tested in longitudinal studies including genetic, neuroimaging, and behavioral measures of emotion recognition, and empathy.

Our results support the previous suggestion (Paulsen et al., 2006; Tabrizi et al., 2009) that deficits in emotion recognition might be a biomarker of disease onset and progression in HD. The relatives assessed here represent a group with vulnerability to HD or some unspecific related deficits (Panegyres and Goh, 2011). Although this group would include both HD gene carriers and non-carriers, its performance in recognizing disgust facial expressions was significantly lower than controls, which suggests that even non-carriers may have selective emotion recognition impairments. Our data are consistent with previous studies in HD reporting emotion recognition deficits without clinical motor signs (Henley et al., 2008; Tabrizi et al., 2009), and with findings of familial vulnerability factors even in the absence of HD mutation (Dorsey, 2012; Kargieman et al., 2014; Markianos et al., 2008). Although the probability of being a non-manifest carrier is 50%, all participants of this group were subclinical and even non-carriers can present vulnerability factors. Thus, two levels of vulnerability (one represented by gene carrier relatives with subclinical manifestations, and other by non-carrier relatives with diffuse vulnerability factors), seem to explain these impairments.

4.3. Dissociation between EF, emotion recognition, and empathy in HD

In line with a previous report (Besel and Yuille, 2010), our healthy controls showed a correlation between emotion recognition accuracy (TASIT total score) and performance on the empathy task. However, no significant associations were found in HD patients or relatives. In HD, then, emotion recognition and empathy may be differentially affected in a relatively independent way.

Also, our results are consistent with previous reports of executive deficits in HD patients (Lawrence et al., 1998; Lemiere et al., 2004) and pre-symptomatic individuals (Lemiere et al., 2004; O'Rourke et al., 2011). In controls, EFs were positively correlated with the TASIT total score and fear recognition in the emotional morphing task. This supports previous descriptions of relationships between EFs and emotion processing (Pessoa, 2011; Singer, 2006). However, EFs were not related to emotion recognition in HD patients or relatives. In sum, this pattern reinforces the claim that although both domains are affected in these populations, they are mutually independent.

4.4. Limitations and further directions

Some limitations must be acknowledged in this explorative study. First, the relatives assessed here did not receive genetic testing. Thus, it may have included both genetic pre-symptomatic individuals and healthy relatives without HD genetic heredity. Nevertheless, biological (Markianos et al., 2008), clinical (Dorsey, 2012; Robins Wahlin et al., 2000), and cognitive (Giordani et al., 1995; Kargieman et al., 2014) factors of familial vulnerability have been reported irrespective of whether the first-degree relatives are HD mutation carriers or not. Moreover, it has been shown (Giordani et al., 1995) that healthy individuals at risk for HD, regardless of their HD gene status, have a low performance in some neuropsychological measures compared to normal controls. Consistent with recent work (Kargieman et al., 2014), our results showed that although the relatives group assessed here might include both HD gene carriers and non-carriers, its performance in some neuropsychological and emotion recognition tests was significantly poorer than that of controls. The relatives who participated in this study represent a vulnerability group at risk of developing HD. Assessing these individuals is important to understand the nature of HD and identify potential biomarkers. Future studies should further assess the empathy and emotion recognition abilities of first-degree relatives with and without the HD mutation.

In addition, our results suggest that emotion recognition impairments may be considered as a potential biomarker of HD onset and progression. However, to establish whether this marker is truly associated with linear progression, large-scale longitudinal studies are required (Weir et al., 2011). Moreover, some of our HD patients received medication, which might potentially influence cognitive and social cognition performance.

5. Conclusions

Our results showed that HD patients and relatives were impaired in recognizing isolated face emotions but performed similar to controls in emotional tasks including contextual information. From a theoretical perspective, such a pattern supports the recently proposed social context network model (SCNM) (Ibanez and Manes, 2012). For the SCNM, contextual effects on social cognitive processing depend on a fronto-temporal cortical network which (1) updates contextual cues and uses them to make predictions (frontal areas, such as the orbitofrontal cortex, lateral prefrontal cortex, and superior orbital sulcus), and (2) consolidates context-social target associative learning (temporal regions, namely amygdala, hippocampus, perirhinal and parahippocampal cortices). In HD, brain damage is most severe in the striatum and its cortico-subcortical connections (Nopoulos et al., 2010), whereas the prefrontal and medial temporal cortices remain largely unchanged (Della Nave et al., 2010; Muhlau et al., 2007; Nopoulos et al., 2010). In SCNM terms, normal performance in HD patients and relatives during cued face emotion recognition may result from the relative preservation of this cortical fronto-temporal network, at least in early-middle stages. In addition, our HD patients showed subtle impairments in aspects of empathy related with the inference of the intentionality of others' actions.

From a clinical perspective, our results highlight the importance of identifying changes that occur before the appearance of motor symptoms in order to develop early intervention strategies. In addition, the finding that emotion recognition improves with the use of contextual cues opens new possibilities for HD treatment. The challenge for intervention programs is to develop strategies for improving emotion recognition through verbal, bodily, and contextual cues rather than isolated facial expressions. It is necessary to increase our understanding of the genetic, neuroanatomical, and cognitive mechanisms for impaired emotion recognition and empathy in HD patients and pre-symptomatic individuals. Further research may lead to better clinical predictions and tools to compensate for the prevalent social functioning deficits of these populations.

Conflict of interest

Authors declare no conflict of interest.

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