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Dissociating emotional and cognitive empathy in pre-clinical and clinical Huntington's disease

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ABSTRACT

Huntington's disease (HD) is centrally characterized by motor, neurocognitive and psychiatric symptoms, but impaired emotional decoding abilities have also been reported. However, more complex affective abilities are still to be explored, and particularly empathy, which is essential for social relations and is impaired in various psychiatric conditions. This study evaluates empathic abilities and social skills in pre-clinical and clinical HD, and explores the distinction between two empathy sub-components (emotional-cognitive). Thirty-six HD patients (17 pre-clinical) and 36 matched controls filled in the Empathy Quotient Scale, while controlling for psychopathological comorbidities. At the clinical stage of HD, no global empathy impairment was observed but rather a specific deficit for the cognitive sub-component, while emotional empathy was preserved. A deficit was also observed for social skills. Pre-clinical HD was not associated with any empathy deficit. Emotional deficits in clinical HD are thus not limited to basic emotion decoding but extend towards complex interpersonal abilities. The dissociation between impaired cognitive and preserved emotional empathy in clinical HD reinforces the proposal that empathy subtypes are sustained by distinct processes. Finally, these results underline the extent of distinct affective and social impairments in HD and the need to grasp them in clinical contexts.

1. Introduction

Huntington's disease (HD) is a genetically inherited neurodegenerative disease classically associated with a triad of motor, neurocognitive and psychiatric symptoms (Roos, 2010). Beyond these well-established impairments, other deficits have been documented, particularly the presence of emotional disturbances as HD is characterized by impaired ability to identify the six classically described (Darwin 1872; Ekman, 1993; Ekman and Friesen, 1971) basic facial emotional expressions: several studies have initially evidenced a specific deficit for the identification of disgust (Sprengelmeyer, 2007), but more recent works have shown that this deficit is generalized to other negative emotions like anger, fear or sadness (Johnson et al., 2007). Critically, this deficit is present at the clinical stage of the disease (i.e. among symptomatic patients presenting motor impairments) but might already exist at the pre-clinical stage [i.e. among non-symptomatic persons carrying HD's gene (Johnson et al., 2007)]. Moreover, as this impairment appears specific to emotional processing (Sprengelmeyer, 2007) and is also present for emotional prosody (Snowden et al., 2008) as well as for facial expression of emotions (Trinkler et al., 2013), HD appears associated with a generalized impairment in the detection and expression of emotions (Henley et al., 2012).

Efficient emotional processing is a crucial skill to maintain adapted interpersonal relations, and these emotional deficits thus negatively impact social life in HD as they are correlated with reduced functional capacity in everyday life (Craufurd and Snowden 2002). It is now clearly established that emotional

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impairments have deleterious consequences on personal and professional life in HD (Ille et al., 2011a). Moreover, at a clinical level, it has been shown in several psychiatric and medical conditions that the quality of social support and interpersonal environment has a crucial impact on treatment compliance (Dour et al., 2014), underlining the role of affective and social factors on treatment response. In view of these arguments, it appears crucial to further explore the extent of these emotional deficits and their links with interpersonal impairments in HD. Indeed, despite the exploration of basic emotional decoding and the proposal that higher-level affective abilities could also be impaired, these more complex emotional abilities involved in social interactions have been little explored in HD, hampering to obtain an exhaustive view of the emotional impairments.

Among the emotional competences that should be more thoroughly investigated, empathy occupies a core position as it is an essential ability to build and maintain affective bonds between mother and child, partners, and then larger social groups (Singer, 2006). Empathy is globally defined as the aptitude to understand and respond to other's feelings, thoughts, or emotions by imagining oneself in another individual's position (Decety and Jackson, 2006). Empathy is not a unitary concept but rather a multifaceted construct involving at least two distinct components (Lawrence et al., 2004), namely: (1) an emotional component linked to the ability of experiencing others' emotional states, and (2) a cognitive component related to perspective-taking ability allowing to understand others' mental states (e.g., thoughts, goals). The validity of this emotional-cognitive distinction has been experimentally explored by the observation of specific deficits in psychiatric states: autism (Smith, 2009) and euthymic bipolar disorder (Shamay-Tsoory et al., 2009) are associated with marked cognitive empathy deficit but preserved emotional empathy. Conversely, alcohol-dependence leads to impaired emotional empathy with preserved cognitive empathy (Maurage et al., 2011). These results clearly call for completing the classical exploration of global empathy by a separate exploration of its two sub-components.

Empathic abilities have also been recently explored in a wide-range of neuropsychiatric conditions, notably showing a general empathy deficit in Parkinson's disease (Narme et al., 2013), and a dissociation between preserved emotional and impaired cognitive empathy in Alzheimer's disease (Nash et al., 2007). These results underline the critical role played by empathy deficits in neurodegenerative states and lead to crucial theoretical and clinical implications (Kemp et al., 2012). Surprisingly however, there is currently a striking scarcity of knowledge on empathy abilities in HD. Indeed, on the one hand, some studies have explored cognitive processes that are related to empathy, showing deficits for social cognition (Snowden et al., 2008), perspective taking (Brüne et al., 2011) or intention attribution (Baez et al., 2015) in clinical HD. Nevertheless, the use of cognitive-demanding tasks do not allow to exclude that these deficits are partly related to more general cognitive impairments (e.g., working memory), and these studies did not directly measure empathy. On the other hand, only one study has explored empathy in HD (Trinkler et al., 2013), describing preserved empathic abilities in clinical HD. Although constituting a valuable first exploration, these preliminary results presented three main shortcomings: First, the evaluation of empathy relied on highly criticized questionnaires (Baron-Cohen and Wheelwright, 2004) unable to dissociate emotional and cognitive sub-components. Second, while clinical psychiatric diagnoses constituted exclusion criteria, sub-clinical anxiety and depression were not controlled for and might have influenced empathy scores (Grynberg et al., 2010). Third, the experimental sample was exclusively constituted of clinical HD patients presenting motor and cognitive impairments, preventing any conclusion concerning the presence of empathy deficits in pre-clinical HD and their evolution across the successive stages of HD.

To overcome these limitations, the present study explored empathy in pre-clinical and clinical HD, with a strict control of psychopathological variables and by means of a validated questionnaire [Empathy Quotient questionnaire, EQ (Baron-Cohen and Wheelwright, 2004)] allowing the separate exploration of emotional and cognitive empathy. As earlier results have suggested significant perspective taking and social cognition impairments in clinical HD (Baez et al., 2015; Brüne et al., 2011; Snowden et al., 2008), we hypothesized that this group would show massive deficits for cognitive empathy. Conversely, as interpersonal and emotional functions have been repeatedly described as preserved in pre-clinical HD (Kipps et al., 2007; Sprengelmeyer et al., 1996), it can be hypothesized that this group will present unaltered empathic abilities. Finally, a "social skills" subscale was included in the EQ, allowing to explore the global ability to behave appropriately in interpersonal situations (Lawrence et al., 2004). A last hypothesis was thus that clinical HD participants would, in view of their reduced capacity to maintain efficient social interactions, be impaired on this subscale compared to healthy controls and pre-clinical HD.

2. Methods

2.1. Subjects

Thirty-six adults (16 women) with a genetically confirmed HD diagnosis (Huntington's Disease Participants, HDP) were recruited in the HD care units of four Belgian hospitals. Participants were first contacted by their general practitioner or neurologist who explained the aims of the study, and were then referred to the principal investigator. All participants had a family history of HD and completed a genetic blood test assessing the HD's cytosine-adenine-guanine (CAG) expansion. HD is characterized by elongated CAG repeat on at least one allele of the chromosome 4 on the Huntingtin gene. All participants presented an expansion of at least 36 CAG repeats (Roos, 2010). Among them, 17 were at pre-clinical phase (carrying the HD's gene but non-symptomatic, HDP-) while 19 were at clinical phase (symptomatic participants with motor impairments, HDP+). The disease stage was assessed by their neurologist, their nurse, and a psychologist with expertise in HD, according to Roos' criteria (Roos, 2010): among HDP−, 14 were at the A2 stage (i.e. gene carrier, premanifest stage) and three were at the A3 stage (i.e. transition phase, ongoing changes at behavioural and motor levels); among HDP+, 12 were at the B1 stage (i.e. clinical stage I, with initial neurological, cognitive and psychiatric symptoms, chorea being the most prominent symptom) and seven were at the B2 stage (i.e. clinical stage II, with generalized motor disturbance and increased cognitive-psychiatric symptoms). The mean illness duration among HDP+ was 6.87 years ($SD=5.41$). The mean number of CAG repeats of the longer allele was 42.82 ($SD=3.81$) in HDP− and 42.84 ($SD=3.30$) in HDP+. Moreover, HD participants' global functioning was assessed by a neurologist through the Clinical Global Impression Scale (CGI), a widely-used clinical tool evaluating the psychological, social and occupational abilities on a scale ranging from 1 (normal) to 7 (among the most ill patients). In HDP−, CGI scores were between 1 (normal) and 2 (borderline) ($M=1.24$, $SD=0.44$). In HDP+, CGI scores were between 3 (mildly ill) and 5 (markedly ill) ($M=4.26$, $SD=0.65$).

HD participants were matched for age, gender, and education with 36 control participants (CP). Two subgroups of CP were determined (CP−, CP+) respectively matched with HDP− and HDP+. Groups' characteristics appear in Table 1. Exclusion criteria for both groups included major medical problems, neurological disease (except HD for the HD groups), psychiatric disorder and

Table 1
Demographic and psychopathological measures for clinical (HDP+) and pre-clinical (HDP−) Huntington's disease patients, and matched controls (CP+ and CP−): Mean(*SD*)

	HDP			CP		
	HDP+ (*N*=19)	**HDP− (*N*=17)**	**HDP (*N*=36)**	**CP+ (*N*=19)**	**CP− (*N*=17)**	**CP (*N*=36)**
Demographic measures						
Age	51.58 (12.3)	38.94 (13.3)	45.61 (14.1)	49.63 (16.3)	38.53 (13.1)	44.39 (15.7)
Gender ratio (F/M)	10/9	6/11	16/20	9/10	5/12	14/22
Educational level (in years)	11.63 (3.4)	13.06 (2.7)	12.31 (3.1)	12.37 (2.5)	11.47 (4.5)	11.94 (3.5)
Psychopathological measures						
Beck Depression Inventory	14.53 (9.9)	11.53 (8.8)	13.11 (9.4)	12.74 (6.4)	11.59 (7.6)	12.19 (6.9)
Trait Anxiety Inventory	44.74 (12.1)	44.53 (11.3)	44.64 (11.5)	39.42 (8.9)	44.59 (8.8)	41.86 (9.1)

substance abuse, assessed through the Mini International Neuropsychiatric Interview. While CP participants were free of any medication, four HDP− and 12 HDP+ participants were under stabilized psychotropic medication, namely benzodiazepines (lorazepam, alprazolam or zolpidem, one HDP−, eight HDP+), antidepressants (escitalopram or paroxetine, one HDP−, 10 HDP+) and/or antipsychotic (olanzapine or aripiprazole, two HDP−, one HDP+) drugs. Moreover, four HDP+ participants were treated with medication to limit choreatic symptoms (Tetrabenazine). Education level was assessed according to the number of years of education completed since starting primary school. Participants were provided with full details regarding the aims of the study and gave their written informed consent. The study was approved by the Ethical Committee of the Medical School (Université catholique de Louvain) and carried out according to the Declaration of Helsinki. Participants were paid 25 euros for their participation. This experiment was part of a larger project investigating cognitive and emotional impairments in HD.

2.2. Procedure and measures

2.2.1. Control measures

Validated self-completion questionnaires were used to assess depression [Beck Depression Inventory (Beck and Steer, 1987)] and trait anxiety [Spielberger Trait Anxiety Inventory (Spielberger et al., 1983)] in both groups.

2.2.2. Empathy measure

The evaluation of empathy was based on the EQ (Baron-Cohen and Wheelwright, 2004), a self-administered questionnaire comprising 60 items (40 empathy related, 20 fillers), each scored on a 4-point Likert scale (from *"totally agree"* to *"totally disagree"*). Each empathy item was scored (0–2), leading to a total empathy score (0–80). Three subscales were also computed, each comprising 5 items [0–10 (Lawrence et al., 2004; Muncer and Ling, 2006)]: (i) "Cognitive empathy" (e.g., *"I can tune into how someone else feels rapidly and intuitively"*), (ii) "Emotional reactivity-empathy" (e.g., *"I tend to get emotionally involved with a friend's problems"*) and (iii) "Social skills" (e.g., *"I do not tend to find social situations confusing"*). The EQ shows good test-retest reliability (Lawrence et al., 2004), and internal consistency for both global and subscales scores (Muncer and Ling, 2006).

2.3. Data analytic plan

Statistical analyses were performed using the SPSS software package. Group and subgroup comparisons were based on Student *t*-tests. *P*-values were adjusted for multiple comparisons using Benjamini & Hochberg's correction.

3. Results

3.1. Control measures

3.1.1. General group comparison

As described in Table 1, HDP and CP did not significantly differ in terms of age [$t(70)=.35$, $p=.73$], gender [$\chi^2(1,n=72)=.23$, $p=.63$], education [$t(70)=.46$, $p=.65$], depression [$t(70)=.47$, $p=.64$] and anxiety [$t(70)=1.13$, $p=.26$].

3.1.2. Subgroups comparisons

A similar absence of significant group differences was obtained for the comparison between: (1) HDP− and CP−, for age [$t(32)=.09$, $p=.93$], gender [$\chi^2(1,n=34)=.13$, $p=.71$], education [$t(32)=1.25$, $p=.22$], depression [$t(32)=.02$, $p=.98$] and anxiety [$t(32)=.02$, $p=.99$], and (2) HDP+ and CP+, for age [$t(36)=.42$, $p=.68$], gender [$\chi^2(1,n=38)=.11$, $p=.75$], education [$t(36)=.77$, $p=.45$], depression [$t(36)=.66$, $p=.51$] and anxiety [$t(36)=1.55$, $p=.13$].

3.2. Empathy measure

3.2.1. General group comparison

As shown in Fig. 1 (part A), HDP and CP did not significantly differ for the total empathy quotient [$t(70)=1.69$, $p=.10$], emotional reactivity [$t(70)=.21$, $p=.83$] and social skills [$t(70)=1.02$, $p=.31$]. However, HDP presented lower scores than CP for cognitive empathy [$t(70)=2.16$, $p=.03$, $d=.51$].

3.2.2. Subgroups comparisons

As shown in Fig. 1 (part B), (1) HDP- and CP- did not significantly differ on any experimental data: total empathy quotient [$t(32)=.88$, $p=.38$], cognitive empathy [$t(32)=1.00$, $p=.32$], emotional reactivity [$t(32)=.15$, $p=.88$] and social skills [$t(32)=1.04$, $p=.31$]; (2) HDP+ and CP+ did not significantly differ for total empathy quotient [$t(36)=1.56$, $p=.13$] and emotional reactivity [$t(36)=.15$, $p=.89$], but HDP+ presented lower scores than CP+ for cognitive empathy [$t(36)=2.03$, $p=.04$, $d=.67$] and social skills [$t(36)=2.78$, $p=.01$, $d=.91$], indexing reduced cognitive empathy and social skills in clinical HD.

3.3. Complementary analyses

Complementary analyses were performed to test:

- *The biasing effect of medication*: Pearson's correlations were conducted in HDP− and HDP+ groups between psychotropic medication (i.e. benzodiazepines and antidepressant) and experimental results (i.e. total score and subscales). No significant correlation was observed ($p > .05$ for every correlation);
- *The* biasing *effect of psychopathological variables*: Pearson's

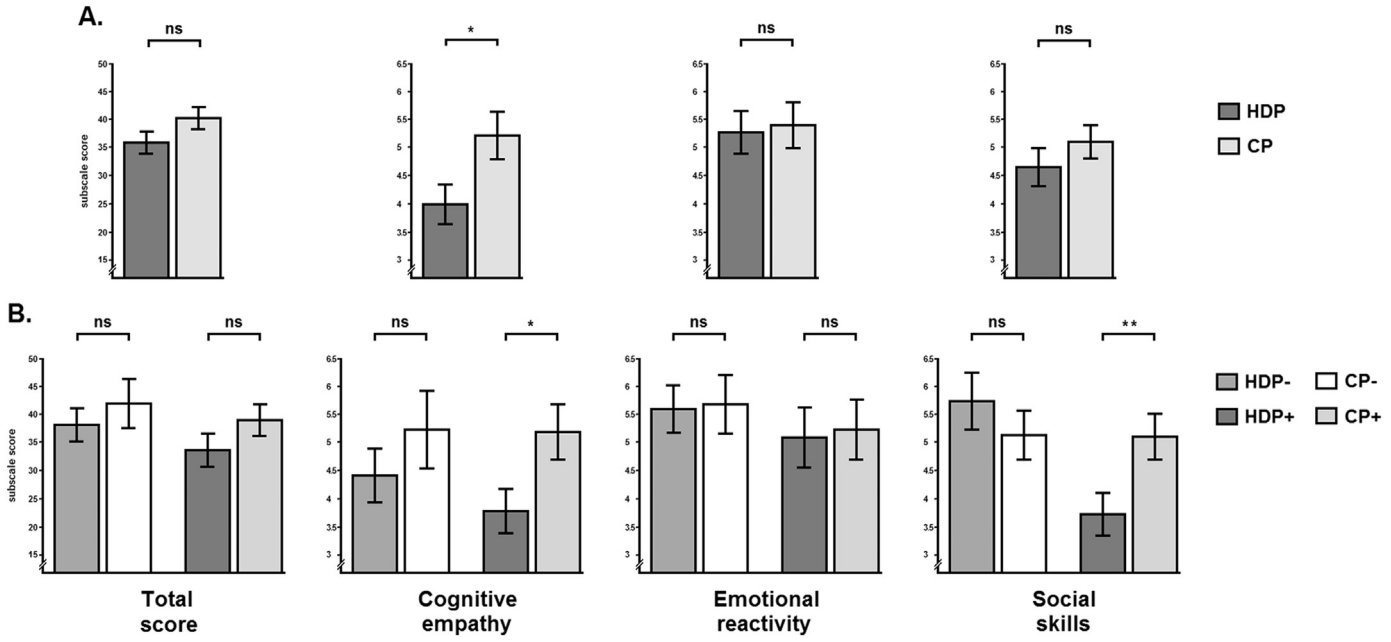

Fig. 1. Global group results (Part A) and subgroups results (Part B) for EQ total score and subscales. NS, Non-significant; $^{*}p < .05$; $^{**}p < .01$. Error bars represent standard errors of the mean.

correlations were conducted in the whole sample and in each group between psychopathological variables (i.e. depression and anxiety) and empathy measures (i.e. total score and subscales). No significant correlation was observed ($p > .05$ for every correlation).

– *The* links *between empathy subscales*: Pearson's correlations were conducted in the whole sample between empathy subscales (i.e. cognitive empathy, emotional reactivity, social skills). Significant correlations were found between cognitive empathy and emotional reactivity ($r = .274$, $p = .02$), cognitive empathy and social skills ($r = .271$, $p = .02$), as well as between emotional reactivity and social skills ($r = .25$, $p = .03$).

4. Discussion

This study was the first to investigate (1) empathy abilities in HD with a strict control of potentially biasing comorbidities, (2) the possible differential impairment between emotional and cognitive empathy in HD, (3) the specific empathy deficits related to the pre-clinical and clinical stages of the disease, and (4) the relations between empathy abilities and social functioning in HD. It should first be noted that no global deficit was observed in HD when empathy was considered as a unitary construct. This result is in line with earlier ones (Trinkler et al., 2013), and thus reinforces, with a more validated empathy scale and a better group matching on psychopathological variables, the proposal that HD does not lead to a reduction of global empathy scores. However, as mentioned above, this unitary approach of empathy is now outdated and the absence of deficit for general empathy might thus mask actual deficits for specific sub-components, this hypothesis being investigated here by exploring group differences on EQ subscales.

This disjointed exploration of emotional and cognitive empathy led to the major result of this study, namely the dissociation between impaired cognitive and preserved emotional empathy subcomponents in clinical HD. This impairment is specifically present in clinical HD, pre-clinical HD patients showing preserved empathy on both subscales. Noteworthy, as psychopathological comorbidities were controlled for and as no correlation was found between empathy measures and depression-anxiety scores, this deficit cannot be attributed to the presence of comorbid depressive or anxious symptomatology. As cognitive empathy is part of social cognition abilities, the observed impairment reinforces earlier studies showing alterations in this ability among clinical HD by means of various experimental tasks [social story sequencing (Brüne et al., 2011), faux-pas detection, complex mental states decoding (Baez et al., 2015)]. However, as these earlier results were based on complex tasks, the deficits observed might have been partly due to more general cognitive impairments and not to social cognition deficits *per se*. The present results, showing a deficit for cognitive empathy in HD by means of a measure requiring limited cognitive resources, are unlikely to result from cognitive demands. Conversely, the absence of deficits for emotional empathy might appear surprising in view of the widely described impairment for emotional abilities (Johnson et al., 2007) and of the extent of emotional alterations in this pathology (Henley et al., 2012). However, this result is coherent with the proposal (Trinkler et al., 2013) that clinical HD might be associated with a generalized dysfunction of the brain structures underlying identification and expression of emotions but with a preservation of the cerebral network related to semantic emotional processing and emotional concepts' understanding, as examined by the EQ emotional subscale.

Interestingly, similar empathy pattern had already been reported in psychiatric disorders [autism (Smith, 2009), bipolar disorder (Shamay-Tsoory et al., 2009)], but also in neurological states like Alzheimer's disease (Nash et al., 2007). The description of a dissociation between preserved emotional and altered cognitive empathy in HD thus suggests that different psychopathological and neurodegenerative states might be associated with similar dissociation in empathy deficits. Such dissociation further reinforces recent models postulating that cognitive and affective empathy, while sharing a common basis (as illustrated by the correlations observed in the present study), are different abilities underlaid by distinct cerebral networks (Singer, 2006). Moreover, as cognitive empathy appears to strongly rely on ventromedial-orbitofrontal cortices (Shamay-Tsoory et al., 2003), and as ventromedial-orbitofrontal impairments have been described in HD

(Ille et al., 2011b), these brain structures might play a crucial role in the cognitive empathy impairment observed in neurodegenerative diseases.

Beyond the dissociation between emotional and cognitive empathy, results also showed that clinical HD is associated with a reduction on the social skills subscale. This factor is considered as reflecting the ability to intuitively understand the social rules and norms involved in social situations and to behave appropriately in interpersonal relationships (Muncer and Ling, 2006). While this social skills subscale has been shown to be separated from other empathy sub-components, it appears to partly rely on cognitive empathy (Lawrence et al., 2004). The observation of a joint deficit for these two subscales in clinical HD is thus coherent and indexes a global impairment in the identification and response to others' mental states in social situations.

A last central result is the difference observed between pre-clinical and clinical HD groups. HD is a progressive neurological disorder and these populations thus strongly vary in terms of age, clinical HD groups being systematically older than pre-clinical ones. As empathy is influenced by age (Bailey et al., 2008), a direct group comparison on empathy would have been strongly biased by age difference. To avoid this age bias, the present study has thus been based on the comparison between each HD group and a control group matched for gender, age and education. Results clearly showed that pre-clinical HD is not related to any empathy deficit and that cognitive empathy-social skills impairments only appear at the clinical stage of HD. Pre-clinical HD's results are not in line with earlier ones showing impaired emotion decoding in a large sample (Johnson et al., 2007). This discrepancy might index that empathy abilities and emotional recognition rely on distinct cognitive processes and cerebral correlates, as it has been suggested by the similar dissociation observed in other populations (Nash et al., 2007). More globally, this clear distinction between pre-clinical and clinical HD leads to the proposal that empathy impairment is not a mere consequence of carrying HD's gene but rather appears at the clinical stage of the disease. Further studies are needed to determine the precise cerebral correlates of this deficit, but it might be related to the progressive neurodegeneration of brain structures involved in cognitive empathy (particularly orbitofrontal-ventromedial areas).

Although our results appear sound in view of the large effect sizes observed, the present data should be replicated and extended on larger samples as the current study was based on small groups in comparison with several earlier ones focusing on emotional processes (e.g., Johnson et al., 2007). Centrally, the self-report nature of the questionnaire might have influenced the results, as clinical HD patients might present reduced insight or self-evaluation abilities (Callaghan et al., 2010). While self-report questionnaires are the most widely used and validated way to measure empathy abilities, these abilities should be further investigated by directly comparing self-reported measures with more direct empathy and social skills measures in HD. Finally, clinical HD patients are characterized by globally reduced cognitive abilities and, while the experimental approach used in the present study did not require complex cognitive processing, these reduced abilities may have influenced the results. Future studies exploring empathy in HD should thus take cognitive functioning into account.

Despite these limitations, the present results have crucial implications at experimental and clinical levels. They centrally show that, beyond the global preservation of empathy indexed by the EQ total score and explored earlier (Trinkler et al., 2013), clinical HD is characterized, independently of comorbid depressive and anxious symptoms, by a dissociation between impaired cognitive empathy-social skills and preserved emotional empathy. Moreover, no deficit is present in sub-clinical HD, suggesting that empathy impairments are progressively appearing during HD's evolution and developing jointly with motor-cognitive deficits. At the therapeutic level, these results claim for taking emotional and interpersonal deficits into account in clinical HD and for applying rehabilitation programs focused on empathy abilities in this population, as such programs have been validated in other clinical contexts and as improving interpersonal abilities might increase treatment compliance (Riess and Kraft-Todd, 2014). In view of the wide-range psychological and cognitive deficits presented by clinical HD patients, these empathy rehabilitation tools should nevertheless be adapted to fit with patients' abilities. Moreover, another treatment avenue would be to inform and educate patients' relatives and caretakers about the actual consequences of empathy deficit on everyday life and interpersonal relations, in order to help them adapting and improving their social interactions with patients.

Contributors

(1) *Research project*: Conception (PM, ML, EC), Organization (PM, ML, DG, AH, JB, EC), Execution (ML, AJ, LG, CVD, SH)
(2) Data processing and Statistical Analysis: Design (PM, ML, DG, AH, JB, EC), Execution (PM, ML), Review and Critique (DG, AJ, LG, CVD, SH, AH, JB, EC)
(3) *Manuscript*: Writing of the first draft (PM), Review and Critique (ML, DG, AJ, LG, CVD, SH, AH, JB, EC)

Conflict of interest

All authors report no competing financial interests or potential conflicts of interest (related or non-related to the research covered in this paper) and no connection with pharmaceutical industries.

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