Theory of mind and empathy in preclinical and clinical Huntington’s disease

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Abstract

We investigated cognitive and affective Theory of Mind (ToM) and empathy in patients with premanifest and manifest Huntington’s disease (HD). The relationship between ToM performance and executive skills was also examined. Sixteen preclinical and 23 clinical HD patients, and 39 healthy subjects divided into 2 control groups were given a French adaptation of the Yoni test (Shamay-Tsoory, S.G., Aharon-Peretz, J. (2007). Dissociable prefrontal networks for cognitive and affective theory of mind: a lesion study. Neuropsychologia, 45(3), 3054–67) that examines first- and second-order cognitive and affective ToM processing in separate conditions with a physical control condition. Participants were also given questionnaires of empathy and cognitive tests which mainly assessed executive functions (inhibition and mental flexibility). Clinical HD patients made significantly more errors than their controls in the first- and second-order cognitive and affective ToM conditions of the Yoni task, but exhibited no empathy deficits. However, there was no evidence that ToM impairment was related to cognitive deficits in these patients. Preclinical HD patients were unimpaired in ToM tasks and empathy measures compared with their controls. Our results are consistent with the idea that impaired affective and cognitive mentalizing emerges with the clinical manifestation of HD, but is not necessarily part of the preclinical stage. Furthermore, these impairments appear independent of executive dysfunction and empathy.

Key words: social cognition; Huntington’s disease; theory of mind; empathy

Introduction

Huntington’s disease (HD) is an inherited autosomal dominant neurodegenerative disorder caused by an unstable expansion of the trinucleotide repeat cytosine-adenine-guanine (CAG) of the gene IT-15, on the short arm of chromosome 4 that codes for the protein huntingtin. Intraneuronal inclusions of the aggregated mutant huntingtin lead to progressive cerebral degeneration starting in the striatum (Douaud et al., 2006; Bohanna et al., 2008). Until recently, it was thought that the striatum was selectively targeted in the early stages of the disease (Vonsattel et al., 1985; Aylward et al., 2000; Douaud et al., 2009), but there is increasing evidence showing that cortical areas are also affected (Rosas et al., 2002; Thieben et al., 2002; Kassubek et al., 2004; Douaud et al., 2006; Henley et al., 2008) suggesting that early HD patients have cortical and subcortical atrophy.

Clinically, HD is characterized by motor symptoms such as chorea, rigidity and abnormal posturing occurring in mid-adulthood. Although these symptoms are the most obvious manifestation of HD, there is often evidence for subtle cognitive and neuropsychiatric abnormalities ahead of the motor
symptoms (Lawrence et al., 1998; Snowden et al., 2002). Cognitive difficulties encompass several domains, mainly including executive functions (Watkins et al., 2000), memory (Solomon et al., 2007), attention, language and social cognition (Stout et al., 2011).

The notion of social cognition embraces several subdomains and refers to all the socio-emotional abilities and experiences regulating the relationships between individuals, and allowing explaining individual human behaviours or behaviours in groups (Allain et al., 2011). Some researchers showed that social cognition deficits are among the best predictors of impaired social functioning, both in neurological (Torralva et al., 2007) or psychiatric diseases (Couture et al., 2006). Social cognition includes the acquisition of social knowledge, emotion recognition from facial expressions, prosody or body posture, as well as an ability commonly called ‘Theory of Mind’ (ToM), which refers to the process of making inferences about the mental states of others in terms of knowledge, intentions, beliefs, desires or feelings. Recent social cognitive neuroscience has begun to define subcomponents of the complex concept of ToM. One important differentiation is that of ‘affective’ vs ‘cognitive’ ToM (overview in Dvash and Shamay-Tsoory, 2014). Although cognitive ToM involves thinking about thoughts, intentions or beliefs, affective ToM involves thinking about feelings (knowledge about emotions) and so may require an empathic appreciation of the listener’s emotional state. This distinction between cognitive and affective components of ToM also raises the question of the relationship between ToM and empathy, which is another aspect of social abilities. Empathy is defined as the ability to infer and share emotional experiences of others (Spinella, 2005) or to share and understand another person’s feelings (Decety and Jackson, 2004). Shamay-Tsoory et al. (2004) and Harari et al. (2010) recently suggested that empathy, like ToM, could be divided into cognitive and affective components. The definition of ‘cognitive empathy’ refers to the ability to engage in the cognitive process of adopting another’s psychological point of view, whereas the definition of ‘affective empathy’ emphasizes its affective facets and refers to the capacity to experience affective reactions to the observed experiences of others. In other words, the concepts of “affective ToM” and cognitive empathy refer to the same ability and may be used interchangeably, as the authors acknowledge (Dvash and Shamay-Tsoory, 2014).

ToM and empathy have received very little attention in patients suffering from HD. Concerning ToM, few studies are available in the literature. Snowden et al. (2003) have explored different mentalizing abilities (humour, deception, bluff and double bluff) in patients with behavioural variant of frontotemporal dementia (bvFTD), clinical HD and healthy controls. HD patients were much less impaired in their ability to attribute mental states to others than bvFTD patients. Qualitative differences in the nature of patients’ errors were observed between the studied groups: HD patients presented eccentric interpretations of situations, showing that they made wrong inferences about characters’ mental states. However, the authors concluded that there was little convincing evidence of ToM deficits and a relatively weak correlation between performance on social cognition and standard executive tests in HD patients.

More recently, Brüne et al. (2011) administered a series of six cartoon picture stories and related questionnaires to HD patients, schizophrenic patients and healthy controls. Three types of stories depicted a scenario where two characters cooperated, a scenario where one character deceived a second character and a scenario showing two characters cooperating to deceive a third. Clinical groups performed similarly and worse than healthy controls. ToM performance of HD patients correlated with intelligence quotient and two indices of executive tasks (perseverative errors in a card-sorting test and Zoo Map Test). Allain et al. (2011) administered a cognitive attribution of intentions ToM task taken from Brunet et al. (2000) and an affective ToM task (a revised version of ‘Reading the Mind in the Eyes’ taken from Baron-Cohen et al., 2001) to early HD patients and healthy controls. HD patients failed in both tasks compared with controls. In the cognitive ToM task, their performance correlated with one measure of executive functioning (Brixton test), whereas performance correlated with two executive measures (verbal fluency and Stroop) in the affective ToM task. Finally, Eddy and Rickards (2012) investigated whether individuals with manifest HD exhibit impairments in ToM compared with healthy controls. Two ToM tasks were given. One task involved recognizing socially inappropriate behaviour (faux pas task; Stone et al., 1998) and the other task required judgements of complex mental states from photographs of people’s eyes (Reading the Mind in the Eyes). Patients with HD made significantly more errors in ToM tasks than controls, exhibiting difficulties in judging the social appropriateness of story character’s behaviour and problems inferring complex mental states from photographs of people’s eyes. Patients with HD also exhibited executive dysfunction. However, there was little evidence that executive impairments were related to ToM deficits (measures of verbal fluency, working memory and inhibition). No significant correlation was apparent between behavioural problems (The Problem Behaviors Assessment—short form) and ToM errors.

Overall, the study of ToM ability in HD patients was mainly conducted in manifest HD. To the best of our knowledge, only one study examined this ability in premanifest HD (Saft et al., 2013) using cartoon stories. No significant difference between premanifest HD subjects and controls was found. Concerning empathy assessment, studies are even rarer. In the only study available in the literature, Trinkler et al. (2013) assessed alexithymia and empathy with questionnaires in HD patients, and reported that alexithymia and empathy scores were very similar to controls.

To sum up the literature, notwithstanding the importance of these results, no definitive conclusions can be made concerning ToM and empathy in HD, due to rather small groups of patients [13, 16 and 18 patients respectively in the studies by Trinkler et al. 2013; Eddy and Rickards 2012; Allain et al. 2011] and to within-subjects heterogeneity (in regards to disease duration and/or neuropsychological performance) in some of the aforementioned studies. Taken together, the studies showed that only patients with manifest HD may present difficulties in ToM abilities. These deficits can affect their ability to judge other people’s cognitive and affective mental states and recognize whether a behaviour is socially appropriate. In addition, there was not always adequate control condition in ToM tasks used, and the assessment of cognitive and affective ToM tasks may involve different demands. Ideally, both conditions should have been measured in one task with a control condition. Hence, further studies are needed on this topic to determine whether ToM difficulties may also occur in premanifest HD, and whether ToM difficulties could potentially serve as a neuropsychological marker of disease onset and progression.

Thus, the purpose of this study was to further examine ToM and empathy abilities in HD. In the same vein than in our previous work on ToM in HD (Allain et al., 2011), we were interested in assessing cognitive and affective components of ToM in clinical HD patients. In this study, preclinical HD patients were also included as well as empathy questionnaires. Another important difference between this work and the precedent is that we wish
to clearly assess first- and second-order cognitive and affective ToM with a task involving the same demands with adequate control conditions. In order to do so, we used a ToM task designed by Shamay-Tsoory and Aharon-Peretz (2007) to examine patients with premanifest and manifest HD. We think this task is of considerable interest to assess ToM abilities in HD patients because it has cognitive, affective and physical conditions, each requiring a first- and a second-order inference.

Our main research questions were the following: (i) Can ToM and empathy impairments be identified in patients with premanifest and manifest HD?; (ii) If ToM and empathy deficits can indeed be observed in these patients, which subcomponents of ToM and empathy are impaired?; (iii) If ToM and empathy deficits can indeed be observed in these patients, are these deficits associated both together? and (iv) Are impairments in ToM and empathy performance associated with executive disorders?

Methods
Participants
Twenty-three French speaking clinical HD patients with clinically diagnosed and genetically confirmed HD, 16 preclinical HD patients defined by a positive gene test with absence of specific HD symptom and 39 healthy control subjects took part in the study.

HD patients
The clinical HD group consisted of 11 men and 12 women with a mean age of 50.34 [standard deviation (SD) = 9.8, range 33–69] years at the time of assessment. Patients’ mean age at onset of symptoms was 37 years (range 33–63, SD = 16.93), and the average duration of illness was 4 years (range 2–13, SD = 3.17). The level of education ranged from 7 to 23 years of schooling (mean = 11.9, SD = 3.21). The mean CAG length was 44.3 (range 41–53, SD = 3). According to the Unified Huntington’s Disease Rating Scale (UHDRS), HD patients had a mean functional capacity of 10.2 (range 3–13, SD = 3.1) and a mean independence score of 89.1 (range 60–100, SD = 12.5). The UHDRS mean motor score was 33.7 (range 1–57, SD = 15.2). In regards with the norms issued from Henley et al. (2008), clinical HD patients performed below the normal range on the functional and motor measures of the UHDRS. Their scores indicated that they were in the mild to moderate stages of the disease. The mean cognitive score from the Mattis Dementia Rating Scale (MDRS; Mattis, 1976) was 134.43 (range 127–144, SD = 5.69), indicative of very mild general cognitive impairments. According to self-report, all clinical HD patients were right handed.

The preclinical HD group consisted of 6 men and 10 women. In this group, the mean age was 35.9 (range 24–54, SD = 9.6) years. The level of education ranged from 8 to 22 years of schooling (mean = 12, SD = 3.4). The mean CAG length was 44.3 (range 42–50, SD = 2.3). As per Tabrizi et al. (2009), inclusion in the preclinical HD group required a UHDRS total motor score of ≤5 (mean motor score = 2.81, range 0–5, SD = 3.52). According to the UHDRS, preclinical HD patients had a mean functional capacity of 13 (SD = 0) and a mean independence score of 100 (SD = 0). The mean cognitive score from the MDRS was 141.25 (range 132–144, SD = 3.27). Preclinical HD patients had normal scores on all these measures. According to self-report, two preclinical HD patients were left handed. Preclinical HD patients’ estimated probability of neurological symptom onset within 5 years was determined from data previously proposed by Langbehn et al. (2004). A table is provided for each CAG repeat between 36 and 56, and lists the probability of onset within certain time frames for current ages from 0 to 95 years, conditional on the individual being currently presymptomatic (Langbehn et al., 2004). Probability of onset within 5 years was determined for each gene carrier based on their CAG repeat and current age (in percentage: range 2–66, mean = 23.31, SD = 20).

HD patients were recruited from the Huntington’s patient population receiving annual medical and neuropsychological monitoring in the Department of Neurology of the University Hospital of Angers. All patients underwent neurological and psychiatric examination by experienced clinicians (neuropsychological examination: Christophe Verny, Adriana Prudean and Clarisse Scherer; psychiatric examination: Bénédicte Gohier).

The statistical comparisons of the two groups revealed that clinical HD patients were significantly older than preclinical HD patients (t = −4.53, P < 0.0001). The education level (t = 0.09, P = 0.92) and sex distribution (P² = 0.40, P = 0.52) were similar between clinical and preclinical HD patients. In addition, the mean number of CAG repeats did not significantly differ between the two groups of patients (t = 0.22, P = 0.82). Logically, clinical HD patients performed worse than preclinical HD patients on the motor (t = 7.49, P < 0.0001), functional (t = 2.72, P = 0.009) and independence (t = −3.44, P = 0.001) scales of the UHDRS.

Control groups
The clinical HD patients being older than the preclinical HD patients, healthy controls were divided into 2 subgroups on the basis of their age at testing: (i) a healthy control group for clinical HD patients that comprised 23 individuals (10 men and 13 women) with a mean age of 50.8 (range 30–67, SD = 9.8) years, a mean level of education of 8–16 years of schooling (mean = 11.6, SD = 2.5) and a mean cognitive score from the MDRS of 140.2 (range 130–144, SD = 3.5); (ii) a healthy control group (4 men and 12 women) for preclinical HD patients that comprised 16 individuals with a mean age of 35.2 (range 21–52, SD = 10.6) years, a mean level of education of 9–15 years of schooling (mean = 12.9, SD = 1.9) and a mean cognitive score from the MDRS of 140.1 (range 127–144, SD = 4.9). The healthy control subjects were right handed and had no brain damage or evidence of neurological or psychiatric antecedents.

There was no significant difference in age (t = 0.15, P = 0.88), educational level (t = −0.36, P = 0.72) and sex distribution (χ² = 0.08, P = 0.76) between clinical HD patients and their controls, and between preclinical HD patients and their controls (t-test for age: t = −0.21, P = 0.83; t-test for educational level: t = 0.82, P = 0.41; χ² for sex = 0.58, P = 0.44). None of the patients and healthy controls showed signs of depression. The study was approved by the local research ethics committee and all participants gave written informed consent in accordance with the Declaration of Helsinki.

Materials and methods
Background neuropsychological assessment
As seen before, all HD patients were screened for symptoms of HD using the motor and functional subscales derived from the UHDRS. The cognitive part of the UHDRS was also administered to all participants. It comprises a neuropsychological battery that measures spontaneous flexibility with a letter fluency test (Benton, 1989), inhibition with a Stroop test (Stroop, 1935) and selective attention and working memory with the Symbol Digit Modalities Test (Smith, 1973). Additional neuropsychological
tests were given to measure general cognitive function (MDRS), semantic fluency, reactive flexibility with a Trail Making Test (Reitan, 1958) and memory with a Hopkins Verbal Learning Test-Revised (Benedict et al., 1998). Our aim was to gather cognitive background information about the patients, and to complete executive processes assessment. Neuropsychological scores are shown in Table 1.

ToM tasks

HD patients and control subjects were given a modified French-language version of the Yoni task. This task was developed by Shamay-Tsoory and Aharon-Peretz (2007) on the basis of a test previously described by Baron-Cohen et al. (1985). The Yoni task assesses the ability to judge mental states based on verbal cues, eye gaze and facial expression. Our modified French-language version of the Yoni task included 60 trials, that is, 6 more than in the version by Shamay-Tsoory and Aharon-Peretz (2007). In fact, our French-language version also included some item modifications in order to propose the same numbers of ToM items (10 first-order affective items, 10 first-order cognitive items, 10 second-order affective items and 10 second-order cognitive items) and the same numbers of control items (10 first-order control items and 10 second-order control items). In each trial (Figure 1), a face named Yoni was shown in the middle of the screen with four coloured pictures of objects belonging to a single category (e.g. fruits) or faces, one in each corner of the computer screen. Subject were asked to point to the correct answer (the image to which Yoni is referring), based on an incomplete sentence that appears at the top of the screen and available cues, such as Yoni’s eye gaze, Yoni’s facial expression or the eye gaze and facial expression of the face to which Yoni is referring (Figure 1). As mentioned before, 3 categories of items were presented with 20 items each: control items, cognitive items and affective items. Although answers in the control condition only required analysis of physical attributes of the

| Table 1. Cognitive scores for HD patients and their healthy controls |
|-------------------|------------------|------------------|------------------|------------------|-----------|
|                   | Preclinical HD patients (n = 16) | Healthy controls for Pre-clinical HD (PHD) patients (n = 16) | P value comparisons between PHD and controls | Clinical HD patients (n = 23) | Healthy controls for HD patients (n = 23) | P value comparisons for HD and controls |
| MDRS (maximum score = 144) | 141.25 (3.27) | 140.1 (4.9) | 0.64 | 134.43 (5.7) | 140.2 (3.5) | 0.0002 |
| UHDRS cognitive scores/144 | 71.3 (13.4) | 76.9 (11.6) | 0.30 | 47.1 (13.1) | 79.6 (11.1) | <0.0001 |
| Colour Stroop (total correct in 45 s) | 91.5 (11.6) | 94.7 (8.5) | 0.87 | 60.6 (16.4) | 96.7 (4.4) | <0.0001 |
| Reading Stroop (total correct in 45 s) | 48. (11.9) | 43.8 (9.1) | 0.19 | 26.6(11.2) | 42.8(13.2) | <0.0001 |
| Interference Stroop (total correct in 45 s) | 69.9 (29.9) | 61.8 (18.1) | 0.79 | 39.6 (10.9) | 54.5 (20) | 0.002 |
| Lexical verbal fluency (Letters P, R and V total score in 2 min) | 55.4 (15.8) | 56.1 (13.6) | 0.91 | 27.6 (11.7) | 54.2 (10.7) | <0.0001 |
| Symbol Digit Modalities Test (total correct in 90 s) | 37.6 (8.8) | 34.4 (6.7) | 0.33 | 21.8 (6.4) | 34.3 (6.9) | 0.24 |
| Semantic verbal fluency (animals total correct in 2 min) | 44.7 (14) | 38.6 (14.2) | 0.20 | 68.4 (28.2) | 45.3 (16.2) | 0.003 |
| Trail making test part A (time in seconds) | 0 (0) | 0 (0) | >0.99 | 0 (0) | 0 (0) | 0.80 |
| Trail making test part A (number of errors) | 60.1 (37.5) | 61.5 (34.9) | 0.83 | 139.6 (66.9) | 64.2 (19.7) | <0.0001 |
| Trail making test part B (time in seconds) | 0.5 (0.2) | 0.2 (0.7) | 0.67 | 0.2 (0.8) | 0.1 (0.3) | 0.78 |
| Trail making test part B (number of errors) | 6.7 (2.0) | 6.2 (1.6) | 0.38 | 5.2 (2.4) | 5.3 (1.6) | 0.91 |
| Hopkins verbal learning test | 9.5 (1.8) | 9.3 (2.2) | 0.79 | 6.6 (2.0) | 7.9 (1.7) | 0.04 |
| First recall (number of words) | 10.3 (2.1) | 10.7 (1.4) | 0.97 | 7.5 (2.0) | 9.3 (2.1) | 0.006 |
| Second recall (number of words) | 10.1 (1.8) | 9.8 (2.1) | 0.75 | 5.7 (2.8) | 7.9 (2.2) | 0.007 |
| Delayed recall (number of words) | 11.6 (0.5) | 11.8 (0.5) | 0.47 | 10.3 (2.0) | 11.7 (0.5) | 0.002 |

Note. Values in brackets are standard deviations.
character, choices in the cognitive and affective ToM conditions required mental inferences based on verbal cues (contained in the incomplete sentences), eye gaze and/or facial expression. The control, cognitive and affective conditions required either a first-order (10 items each) or a second-order (10 trials each) inference. More specifically, in the first-order ToM stimuli, Yoni’s mental state about one of the four images in the corners has to be inferred: ‘Yoni is thinking of ...’ (cognitive first order) or ‘Yoni loves ...’ (affective first order). In the more complex second-order ToM stimuli, the four stimuli in the corners consisted of face images, and an inference regarding the interaction between Yoni’s and the other stimuli’s mental state was necessary for the choice of the correct answer ‘Yoni is thinking of the ... that ... wants’ (cognitive second order) vs ‘Yoni loves the ... that ... loves’ (affective second order). Following Shamay-Tsoory and Aharon-Peretz (2007), in the first- and second-order cognitive items, both the verbal and Yoni’s facial cues were emotionally neutral, whereas in the first- and second-order affective items both cues provided positive (‘Yoni loves ...’) and negative (‘Yoni does not love ...’) affective information. The item sets of all subcategories were comparable with regard to sentence complexity and visual complexity. All items were presented on a computer screen in a randomized order for a maximum of 10 s during which the subjects had to answer by pressing a touch of the numeric keypad of the keyboard. The position of the answer buttons (Thieben et al., 2002; Kassubek et al., 2004; Shamay-Tsoory and Aharon-Peretz, 2007; Bohanna et al., 2008) corresponded to the positions of the four stimuli in the corners of the screen. As soon as subjects answered, a plain white screen was shown until the end of the 10-s time interval. In this task, we measure the total number of errors for each condition.

Empathy questionnaires

Two measures of empathy were used: the Interpersonal Reactivity Index (IRI) (Davis, 1980) and the Basic Empathy Scale (BES) (Jolliffe and Farrington, 2006). The IRI was chosen for four main reasons: (i) it is the most developed scale psychometrically with scales rating both the cognitive and emotional components of empathy (Spinella, 2005); (ii) the IRI has demonstrated good intra-scale and test–retest reliability, and convergent validity is indicated by correlations with other established empathy scales; (iii) there is a validated French version of the IRI (Gilet et al., 2013) and (iv) the IRI has just been used once to assess empathy in HD patients (Trinkler et al., 2013). The BES was chosen because it is one of the first empathy scales with good psychometric qualities (internal, test–retest and discriminant validity) to be made available in French (D’Ambrosio et al., 2009). The BES measures both cognitive and affective
empathy. The confirmatory factorial analysis showed that the French scale has the same factorial structure as in the original version with 2 factors (cognitive and affective empathy).

We decided to use two validated French version of empathy scales in order to better assess the various dimensions of empathy. In addition, the use of the IRI with HD patients appearing little convincing in the study by Trinkler et al. (2013), it seemed to us methodologically relevant to use another empathy scale.

Test 1: the interpersonal reactivity index. The IRI is a 28-item self-report scale designed to measure both cognitive and emotional components of empathy. It consists of four subscales that tap different aspects of empathy: (i) perspective taking items address one’s tendency to spontaneously adopt the psychological point of view of others; (2) fantasy items address respondents’ tendencies to transpose themselves imaginatively into the feelings and actions of fictitious characters in books, movies and plays; (iii) empathic concern items relate to ‘other-oriented’ feelings of sympathy and concern for unfortunate others and (4) personal distress items address the tendency to experience distress in stressful situations. The IRI subscales 1 and 2 assess cognitive components of empathy, whereas the IRI subscales 3 and 4 assess affective components of empathy. Each subscale comprises seven items. All the items are assessed on a 5-point Likert scale ranging from 0 (‘Does not describe me well’) to 4 (‘Describe me very well’). The IRI yields scores for each subscale and an overall empathy score. The scores could range from 1 (deficit in empathy) to 100 (high level of empathy).

Test 2: the basic empathy scale. The French version of the BES (Jolliffe and Farrington, 2006) is a 20-item self-report scale designed to measure cognitive (9 items: 3, 6, 9, 10, 12, 14, 16, 19, 20) and affective empathy (11 items: 1, 2, 4, 5, 7, 8, 11, 13, 15, 17, 18). Each item is assessed on a 5-point Likert scale ranging from 0 (‘Not agree’) to 5 (‘Quite agree’). The BES yields scores for each subscale and an overall empathy score. The scores could range from 1 (deficit in empathy) to 100 (high level of empathy).

Results

Background clinical and neuropsychological assessment

Neuropsychological data are summarized in Table 1. The clinical HD patients differed significantly (all P’s < 0.005) from their controls in terms of global cognitive efficiency (as assessed by the MDRS), executive functions (flexibility as assessed by fluency tasks, inhibition as assessed by the Stroop, selective attention as assessed by the Symbol Digit Modalities Test) and episodic memory (as assessed by the Hopkins verbal learning test). There was no significant difference between preclinical HD patients and their controls (all P’s < 0.10).

ToM task

As shown in Figure 2, all groups committed errors on the Yoni task. Data were analysed separately for clinical HD patients and their controls and for preclinical HD patients and their controls with 2 × 2 ANOVAs with group (HD patients, healthy controls) as the between-subjects factor, and order (first, second) and condition (cognitive, affective, physical) as the within-subjects factors. Concerning the comparison between clinical HD patients and their controls, the main effect of group was highly significant [F(1, 44) = 136, P < 0.0001], indicating differences in Yoni error scores among the groups, with an overall number of errors significantly higher in the clinical HD group (mean = 8.7) than in the healthy control group (mean = 3.9). There was also a main effect of order [F(1, 44) = 34.87, P < 0.0001] due to higher errors for second-order inferences (mean = 8.8) than for first-order inferences (mean = 3.8). The main effect of condition was highly significant [F(2, 88) = 36.04, P < 0.0001], indicating that errors were significantly more frequent (P < 0.0001) for cognitive items (mean = 5.8) than for control items (mean = 0.8), and (P < 0.0001) for affective items (mean = 5.9) than for control items. On the other hand, the difference between cognitive and affective items did not reach significance (P = 0.98).

Additionally, the two-way interaction between group and order was highly significant [F(2, 88) = 8.38, P = 0.004], indicating that the mean difference for errors between first- and second-order inferences was greater for clinical HD patients (mean = 3.7) than for their controls (mean = 1.3), with significance for both groups (both P < 0.001 on paired t-tests). Additional comparisons using Student t-tests indicated that clinical HD patients made significantly more first- (t136 = 2.70, P < 0.007) and second-order (t136 = 3.94, P < 0.0001) errors of inferences than their controls.

The two-way interaction between group and condition was also highly significant [F(2, 88) = 5.15, P < 0.006]. This interaction reflected that the groups’ patterns of errors varied across inference conditions (cognitive, affective and physical). Both groups committed more inference errors for cognitive and affective items than for physical items (all P’s < 0.0002). In the clinical HD group, the number of errors was higher for cognitive inferences in comparison with affective inferences with both statistically significant difference (P = 0.73). In contrast, in healthy controls the number of errors was higher for affective inferences in comparison with cognitive inferences. However, this difference was not significant (P = 0.13). Additional paired comparisons using Student t-tests indicated that clinical HD patients made significantly more errors for cognitive (t136 = 3.78, P < 0.0003) and affective (t136 = 2.63, P < 0.01) inferences than their controls. The difference for physical inference errors did not reach significance (t136 = 1.81, P < 0.14).

The three-way interaction among group, order and condition approached significance [F(2, 88) = 2.47, P = 0.08], confirming that the pattern of performance differed across the two groups.

Concerning the comparison between preclinical HD patients and their controls, the factorial ANOVA indicated that order [F(1, 30) = 5.88, P = 0.01], condition [F(1, 30) = 21.59, P < 0.0001] and order × condition [F(2, 60) = 21.59, P < 0.0001] have significant effects on inference abilities. However, the difference between groups was not significant [F(1, 30) = 0.46, P = 0.49], indicating that preclinical HD patients were not impaired as compared with their control group.
In summary, statistical analysis of the Yoni data mainly indicated that clinical HD patients committed significantly more errors than their controls in the first- and second-order cognitive and affective ToM conditions. Preclinical HD patients were unimpaired in this ToM task.

The interpersonal reactivity index
As shown in Figure 3, clinical HD patients and their controls performed similarly on all empathy subscales of the IRI (all $P's > 0.21$). Similar results were found for preclinical HD patients compared with their controls (all $P's > 0.42$).

The basic empathy scale
The participant’s results on the BES are represented in Figure 4. The comparison of the clinical and preclinical HD patients and their controls using Student $t$-tests revealed no significant difference for all empathy scores (all $P's > 0.26$).

Correlations in the clinical and preclinical HD groups
We first calculated correlations among ToM performance, age and level of education and between ToM performance and disease variables such as the number of CAG sequences, disease duration and several scores from the UHDRS (total motor score, total functional capacity score). No significant correlations were found between these measures and ToM scores ($P > 0.14$), suggesting that these factors did not directly determine patients’ ToM performance. Similar results were found ($P > 0.54$) with the measures of general cognitive function (MDRS). We repeated these analyses for empathy measures. No significant correlations were found (all $P's > 0.21$).

In addition, no significant correlations (all $P's > 0.19$) were found among doses of medications, ToM, empathy and cognitive scores. Consistent with this finding, no significant difference was found (all $P's > 0.31$ in Student $t$-tests) between medicated and unmedicated conditions in the clinical HD group for the ToM, empathy and cognitive scores.

In the preclinical HD group, correlations were performed to investigate whether performance in the Yoni tasks varied as a function of their estimate probability of HD symptom onset within 5 years. Correlations were significant for second-order cognitive ToM condition ($\rho = 0.60, P = 0.01$) and approached significant level for first-order ($\rho = 0.49, P = 0.06$) and second-order ($\rho = 0.48, P = 0.06$) affective ToM. There was no correlation between estimate probability of HD symptom onset within 5 years and first-order cognitive ToM ($\rho = 0.34, P = 0.17$) or empathy measures (both $P's > 0.24$).

Correlation among cognitive measures, Yoni task, and empathy scales in the clinical and preclinical HD groups
The correlations between performance on the Yoni task (error scores for first- and second-order cognitive and affective inferences), empathy measures (cognitive, affective and total scores of the IRI and the BES) and all cognitive scores (Table 1) were examined in each group of patients. There were no significant correlations between these different measures in the two groups (all $\rho$’s $< 0.33$, all $P's > 0.17$). In addition, in the preclinical HD group, no significant correlation between IRI and BES scores was observed (IRI cognitive score vs BES cognitive score: $\rho = 0.21, P = 0.41$; IRI affective score vs BES affective score: $\rho = 0.08, P = 0.76$; IRI total score vs BES total score: $\rho = 0.26, P = 0.89$). Similar findings were found in the clinical HD group (IRI cognitive score vs BES cognitive score: $\rho = 0.30, P = 0.16$; IRI affective score vs BES affective score: $\rho = 0.02, P = 0.88$; IRI total score vs BES total score: $\rho = 0.26, P = 0.21$).

Discussion
This study was aimed at examining the ability of preclinical and clinical HD patients in attributing cognitive and affective mental states to others. Another aim was to examine empathy using questionnaires. As far as we know, this is the first study which explores ToM and empathy in Huntington patients before and after disease onset with the same tasks.

Clinical HD patients displayed difficulties in detecting first- and second-order cognitive and affective mental states. The fact that they had similar scores as control subjects on the physical...
control conditions of the Yoni task confirm that their poorer performances in mentalizing were due to difficulties in inferring cognitive and affective mental states and not to mistakes due to misunderstanding (verbal cues, etc.). The observation that only the HD patients showed important differences between conditions in the Yoni task is also consistent with the idea that both cognitive and affective aspects of ToM could be impaired in clinical HD patients (Allain et al., 2011; Eddy and Rickards, 2012). In this study, these patients also showed difficulties in the cognitive and affective first-order ToM conditions, indicating that ToM impairments in the clinical HD group are important and could be observed in simple and complex levels of ToM tasks. This is inconsistent with the proposition of Snowden et al. (2003) who suggested that manifest HD patients’ ability to attribute intentions to others is partially intact. The Yoni task may therefore be particularly sensitive to ToM impairment in HD, with the added advantage that a visual measure of mental states based on verbal cues, eye gaze and facial expression is likely to make fewer language, attention or memory demands than a verbal task. Similar to previous findings, our results also include a lack of significant correlations between ToM performance and executive measures remain relatively weak in previous studies (Snowden et al., 2003; Allain et al., 2011; Eddy and Rickards, 2012). In short, all these studies indicate that only some executive processes could be implicated in different ToM tasks, suggesting that ToM abilities could partially be dissociated from executive control processes. This study is consistent with this proposal and could be interpreted as evidence of the independence of ToM and executive functions. An alternative explanation could be that only few correlations were found between performance on the ToM tasks and the tests selected to assess executive functions because these latter involved cognitive abilities that were less closely related to specific processes of ToM assessed by the Yoni task.

From a neuroanatomical perspective, the model proposed by Abu-Akel and Shamay-Tsoory (2011) was one of the first to delineate the neuroanatomical systems that would subserve the representation of cognitive and affective mental states. The dorsomedial prefrontal cortex, the dorsal anterior cingulate cortex and the dorsal striatum are engaged in the cognitive ToM network, whereas the ventromedial and orbitofrontal cortices, the amygdala and the ventral striatum are supposed to subserve the affective ToM network. More precisely, it can be hypothesized that impairment of the fronto-striatal-limbic network may predominantly contribute to impairment in affective ToM, while dorsolateral-prefrontal-striatal circuitry dysfunctions may affect cognitive ToM abilities. As we mentioned
Previously, the terms affective ToM and cognitive empathy may be used interchangeably because they refer to the same concept. Consequently, it may be argued that the cognitive empathy network is identical to that of affective ToM system (see also Shayan-Tsorey, 2011). Concerning affective empathy, evidence from lesion studies suggests that patients with lesions in the inferior frontal gyrus, insula, amygdala or anterior cingulate cortex are impaired in this ability (Dvash and Shayan-Tsorey, 2014). Recent publications also showed that damage to the right hemisphere is more likely to induce impairments in affective empathy (Hillis, 2014; Herbet et al., 2015). Pathologically, HD is characterized by neuronal loss and cerebral atrophy thought to progress in a dorsolateral to ventral direction (Hedreen and Folstein, 1995). The dorsomedial striatum (a component of the dorsolateral prefrontal cortex loop circuitry) would be affected earlier than the ventral striatum (a component of the orbitofrontal cortex loop circuitry). In sum, it may be hypothesized that early clinical HD patients would be more impaired in cognitive than in affective ToM (cognitive empathy) and that affective empathy would be spared. Our results support partially these assumptions, given the fact that both cognitive and affective empathy assessed by self-report questionnaires seems not impaired, whereas affective ToM evaluated by the Yoni tasks was deficient. We will discuss below this unexpected result.

Data from empathy questionnaires mainly show that HD patients consider that they can correctly infer feelings of others, suggesting that they demonstrate appropriate empathic understanding, even though they are impaired in first- and second-order affective and cognitive ToM abilities. These results in IRI questionnaire are consistent with those of Trinkler et al. (2013), but they may also seem surprising in view of the conceptual closeness between empathy and ToM, and more precisely between cognitive empathy and affective ToM. In addition, no significant association was observed between subscales of IRI and BES that tap different aspects of cognitive and affective empathy and the ToM measures of the Yoni including affective and cognitive ToM processes. Two hypotheses can be raised to try to explain these unexpected results. The first refers to a methodological point: although cognitive and affective ToM was assessed using objective measures, cognitive and affective empathy was evaluated with self-report questionnaires. However, several studies have shown that HD patients may have impaired self-awareness of cognitive or emotional abilities (Hoth et al., 2007; Duff et al., 2010). So this difference in data collection may explain in particular why clinical HD patients reported no deficit in cognitive empathy, whereas objective measure highlighted affective ToM impairment. This is a significant limitation of our study, which helps indirectly to confirm that HD patients may show anosognosia and corroborate the results of some publications which demonstrated recently some differences between objective and subjective measures of empathy (Devlin et al., 2014; Johnstone et al., 2015). The second explanation refers to the conceptual difference between the Yoni task and self-report questionnaires of empathy. A recent literature review of Achim et al. (2013) highlighted that the majority of ToM tasks failed to include participants in an ‘online’ social interaction, but rather consist in observing others interacting via a video film (or reading cartoons, or vignettes, etc.) without being engaged directly in the interaction, from a ‘spectatorial’ perspective (see also Hutto, 2004 for a similar point of view). This is the case of the Yoni task. In contrast, questionnaires of empathy refer to daily-life situations and might assess more adequately patient’s perception of ecological social interaction. Interestingly, a recent publication of Pleiffer et al. (2014) demonstrated an increased activity of the ventral striatum during social interaction, so it may be argued that lesions associated with HD may impact the perception of social interaction and so the results in empathy questionnaires.

Since there is no other study to date in the literature, the other aim of this report was to assess cognitive and affective ToM abilities and empathy in patients with preclinical HD. Statistical analyses showed no significant differences between patients with preclinical HD and healthy controls. Our preclinical HD patients performed better than patients with clinical HD in the cognitive and affective second-order conditions of the Yoni task. To date, this study is the first to demonstrate unimpaired decoding of affective ToM in preclinical HD based on eye gaze and facial expression, because the task used in the other study with preclinical HD patients mainly focused on the cognitive aspects of mentalizing (Saft et al., 2013). However, it should be recalled that, in the group of gene carriers, second-order cognitive ToM score correlated with the probability of onset of HD within 5 years, and that the correlations between first- and second-order affective ToM scores and probability of onset of HD within 5 years approached significance. This suggest that ToM impairments appear very early in the course of the disease. This does not seem to be the case for empathy impairments, as the measures of the IRI and the BES do not correlate with probability of onset of HD within 5 years. The fact that we found no empathy impairment in clinical HD is in line with this proposition.

The unimpaired affective ToM in preclinical HD based on eye gaze and facial expression is not consistent with recent results showing that patients with preclinical HD are impaired in recognizing facial emotions (Novak et al., 2012). This could be due to the complexity of the stimuli used to test perception of facial expression. This also suggests that there may be no link between affective mentalizing and ability in processing facial emotions. This proposition is consistent with the literature suggesting that facial recognition of emotion and ToM ability may be dissociated (Phillips et al., 2002; Henry et al., 2006) but does not support the literature suggesting that ToM competence is related to the ability to identify facial emotions (Buitelaar et al., 1999; Henry et al., 2006). These contradictions should motivate further work in HD in order to clarify the nature of the relationship between perception of emotion and attribution of affective mental states.

Aside from these considerations, this study has several limitations. We have to mention first the relatively small sample size of the preclinical and clinical HD groups. Consequently, our study should be considered as exploratory and the assessment of ToM dimensions repeated with larger numbers of preclinical and clinical patients. Second, as mentioned previously, the fact that the IRI and the BES are self-questionnaires possibly limits our results on empathy, because HD patients may present anosognosia. We considered these questionnaires as appropriate given the aims of this study, but measures of empathy like skin conductance (Hein et al., 2011) could have shown different results and could be more suitable for an objective measure of empathy. Third, we used only one task which assesses some aspects of cognitive and affective ToM. In fact, previous authors have separated ToM reasoning in several component processes (Sabbagh et al., 2004; Tager-Flusberg et al., 2001) including detecting/decoding others’ mental states based on immediately available observable information and reasoning about those mental states to explain or predict others actions. Based on this division, it could be speculated that the Yoni visual task mainly assess decoding mechanism. In this light, in order to complete our data, it would also be of real interest to assess ToM reasoning mechanisms in patients with preclinical HD because finally the preservation of ToM performance in these patients may be due to the fact that the Yoni...
task may not be sufficiently sensitive since it assesses only decoding processes. Fourth, another methodological limitation from our study is the lack of measurement of the reaction time on the Yoni task. In fact, it is possible that subtle differences in this task could have been observed in the preclinical HD patients, which might have been slower to respond to the task in order to perform it accurately. Finally, we were unable to obtain measures of social functioning in the HD groups, an issue of potential relevance given the assertion of some authors (Snowden et al., 2003), who proposed that ToM impairment partly underlies the behavioural disturbances and breakdown in interpersonal relationships occurring after HD.

In conclusion, this study confirms that HD patients, early in the course of the disease, have impairments of simple and complex cognitive and affective ToM decoding abilities and that these functions are preserved in patients with preclinical HD. These impairments appear independent of executive functioning. From a clinical point of view, ToM tasks may be useful in determining the onset of cognitive involvement and in tracking disease progression in HD. A better understanding of the pattern of deficits might also have some implications for anticipating the everyday life difficulties encountered by HD patients.

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