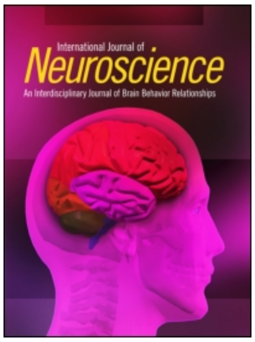

Taylor & Francis
Taylor & Francis Group

International Journal of Neuroscience

ISSN: 0020-7454 (Print) 1543-5245 (Online) Journal homepage: http://www.tandfonline.com/loi/ines20

Effects of stimulus-related variables on mental states recognition in Huntington's disease

Marta Olivetti Belardinelli, Thomas Huenefeldt, Sabrina Maffi, Ferdinando Squitieri & Simone Migliore

To cite this article: Marta Olivetti Belardinelli, Thomas Huenefeldt, Sabrina Maffi, Ferdinando Squitieri & Simone Migliore (2018): Effects of stimulus-related variables on mental states recognition in Huntington's disease, International Journal of Neuroscience, DOI: 10.1080/00207454.2018.1552691

To link to this article: https://doi.org/10.1080/00207454.2018.1552691

INTERNATIONAL JOURNAL OF NEUROSCIENCE
https://doi.org/10.1080/00207454.2018.1552691

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Check for updates

Effects of stimulus-related variables on mental states recognition in Huntington's disease

Marta Olivetti Belardinelli[a], Thomas Huenefeldt[a], Sabrina Maffi[b], Ferdinando Squitieri[b] and Simone Migliore[b]

[a]ECONA Interuniversity Centre for Research on Cognitive Processing in Natural and Artificial Systems, Sapienza University, Rome, Italy; [b]Huntington and Rare Diseases Unit, Fondazione IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy

ABSTRACT

Background: Cognitive abnormalities in Huntington's Disease (HD) can involve the specific impairment of the social perspective taking as well as difficulties in recognizing others' mental state many years before the onset of motor symptoms.

Aims: At the scope of assessing how the difficulties in mental state recognition might be an HD early sign before motor symptoms appear, our study was aimed to investigate how the recognition of others' mental states in HD subjects is moderated by different stimulus related features (gender, difficulty (low, medium, high), and valence (positive, negative, neutral) of the mental states that are to be recognized).

Methods: Subjects with premanifest ($n = 20$) and manifest ($n = 40$) HD performed the revised 'Reading the Mind in the Eyes Test' and were compared with age-matched healthy controls (HC, 40 subjects per cohort).

Results: Our results highlight an early impairment in mental state recognition preceding manifest HD symptoms and a deterioration of these abilities with HD progression. Moreover, we found in HD premanifest subjects an impairment concerning the recognition of negative and neutral mental states, as well as of mental states with moderate recognition difficulty. Finally, we found that participant gender did not influence the performance in recognizing others' mental states, while all participants recognized mental states displayed by females more accurately than those displayed by males.

Conclusions: We conclude that difficulties in the recognition of complex mental states can be considered as an early sign of HD, before evident behavioral manifestations, and peculiar features of the stimulus influence it.

ARTICLE HISTORY
Received 12 July 2018
Revised 2 November 2018
Accepted 20 November 2018

KEYWORDS
Mental state recognition in Huntington's disease; manifest and premanifest patients; early diagnosis; Reading the Mind in the Eyes test; emotional valence

1. Introduction

A renewed attention has recently been devoted to the cognitive and behavioral manifestations of Huntington's disease (HD), a neurodegenerative illness whose genetic cause is well known [1,2] although no resolving therapy has been found until now [3]. Besides the contemporary investigations for the cerebral modifications underlying the progressive cognitive degeneration (most of them based on animal models) [4–7], the reasons for this interest to shed light on overt behavioral HD symptoms are principally tied to the fact that the initial manifestations of the disease are different in different people, appearing at different ages, causing a difficulty and a delay for a correct diagnosis, so that when the symptoms are numerous and clearly manifest, the cognitive decline might be already advanced [8,9]. The most common and evident symptoms of HD and consequently the most studied ones are various involuntary movements that HD patients are unwillingly forced to perform [10]. Besides this, new growing evidence was recently collected for what concerns the cognitive domain that is involved in the disease progression, sometimes since before the appearance of any motor symptom [11].

The most interesting early cognitive alteration found in HD subjects is the difficulty in the recognition [11,12] and awareness of emotions [13]. Different

CONTACT Marta Olivetti Belardinelli marta.olivetti@uniroma1.it ECONA Interuniversity Centre for the Research on Cognitive Processing in Natural and Artificial Systems, Sapienza University of Rome, Via dei Marsi 78, 00185, Rome, Italy; Simone Migliore sim.migliore@gmail.com Huntington and Rare Diseases Unit, Fondazione IRCCS Casa Sollievo della Sofferenza and CSS-Mendel, Viale Regina Margherita, 261 00198, Rome, Italy

Supplemental data for this article can be accessed here.

studies highlighted that emotion recognition skills in premanifest HD subject are influenced by valence of the stimulus [12,14]. Particularly, they showed a specific and early impairment to negative emotions recognition (i.e. disgust, fear, anger) associated with fronto/subcortical brain alteration [14]. However, there is still a lot of discussion about the causes of this difficulty (i.e. related to general cognitive decline or to affective or motor impairment) [15], the specificity of the inputs (i.e. related to a verbal, visual, auditory stimulus, or to inanimate objects or to body acting in a context, to faces, or to eyes only). Moreover, considering that the worldwide construct of 'emotion' may include either affective or cognitive characteristics, instead of emotions, we will speak of 'mental states' as the inner fundament of every affective and/or cognitive manifestation. By adopting this terminology, we intend to limit possible different interpretations of the construct and theoretical speculations.

In recent literature, the capacity of appreciating mental states of other people is mostly referred to as Theory of Mind (ToM) [16]. Researchers tried different ways to assess ToM in adults either with implicit or explicit tasks, putting in evidence the complexity of the theory and related construct, ranging from the simple recognition by naming others' mental states that may also imply the ability to understand another person's thoughts (and is named first-order theory of mind) up to mental state reasoning in the second-order theory of mind, that is the ability to infer what one person thinks about another person's thoughts [17].

A more tuned interpretation could be found in the distinction between cognitive and affective aspects of ToM [18]. Regarding HD, Eddy and Rickards [19] specifically found an impairment of ToM and highlighted differences between premanifest HD subjects and healthy controls (HC) in empathy and everyday perspective taking, in spite of normal performances in a number of executive measures. However, the results on prodromal or manifest patients are discordant: on one side an impairment of social-cognitive functions increasing with the pathology progression seems to find confirmation [20] and on the other side no correlation was found between affective ToM impairment and global cognitive function [21]. The most probable explication of this discordance is tied to the interference of other variables, comparable to what happens in autistic spectrum disorders for which it was recently demonstrated that alexithymia and not autism predicts poor recognition of emotional facial expressions [22–24]. The discordance persists also in studies whose main scope is to find correlations between the HD disturbances and the alteration of the cerebral structures, in this case probably due to the multiplicity of the involved structures [25–27].

Although many studies attributed the social difficulties of HD patients to an eventual disturbance of the capacity of inferring mental states of other people [18], very few studies investigated the occurrence of this abnormality in subjects at a premanifest stage of the disease [19].

It is evident that the proved existence of an eventual deficit in the capacity of recognizing the mental states of other people by premanifest HD subjects could supply a useful indicator of the breakdown of a pathological process before any motor manifestation. According to our meaning however, the investigation of the possible decay of the capacity of detecting other people's mental states should be performed independently of the assessment of other potential cognitive dysfunctions. The eventual correlations between cognitive degeneration and affective impairment should be assessed only afterwards, when the exact measure of the social-affective difficulties in premanifest HD subjects is clearly established.

In this study, we focused on the ability of premanifest HD subjects to detect other people's mental states compared to HD symptomatic and healthy subjects.

As highlighted in healthy and HD subjects, as well as in other neurodegenerative disorders, the recognition of others' face expressions is influenced by various features of the stimulus [14,28,29]. Therefore, we investigated whether different features of the stimulus could influence these skills. Specifically, we took into account the gender (of the stimulus and of the participant) and two different characteristics of the stimulus, i.e. the valence (positive, negative, neutral), and the recognition difficulty (high, medium, low).

On the basis of what had been so far described in manifest HD people [19], we hypothesized that HD premanifest subjects' performances are worse than those by HC, although still better than the performances by manifest patients. Moreover, we expected to find an influence of the negative mental state valence of the stimulus on the recognition performance in premanifest subjects coherently to what described for emotion recognition tasks [11,12]; while a more comprehensive impairment including all affective valence was expected in manifest HD. Regarding the difficulties in the recognition of the mental state expressed by the gaze of the stimulus, we expected that premanifest HD subjects were more impaired than HC, although they might perform better than symptomatic subjects.

2. Material and methods

2.1. Participants

We recruited 140 participants belonging to four groups: 20 participants with premanifest HD (*10 Females,* Diagnostic Confidence Level—DCL <4) [30], compared with 40 age-matched HC subjects (*20 Females*) and 40 participants with manifest HD (*20 Females*, DCL =4), compared with 40 age-matched HC subjects (*20 Females*). The HC were neither biologically nor personally related to individuals with premanifest or manifest HD. Control groups were matched for age, gender, and education degree with the participants in the two HD groups.

Subjects' groups underwent a neurological examination and were assessed using the Unified Huntington's Disease Rating Scale (UHDRS) [30]. All premanifest HD subjects were free of medication when assessed; 25% of symptomatic patients took low doses of benzodiazepines and/or neuroleptics. We excluded HD subjects with a medical condition that might influence cognition (i.e. deafness, ipovisus), a history of a developmental disorder (e.g. attention-deficit hyperactivity disorder (ADHD), learning disability), a history of substance or alcohol dependence, or current abuse, a history of psychotic disorder. Basic demographic and clinical information on the four groups of participants is summarized in Table 1. The participants were recruited at LIRH Foundation and C.S.S. Mendel institute in Rome. HD was genetically confirmed in all cases (all with CAG expansion ≥40).

2.2. Measures

In order to assess HD subjects' ability to recognize mental states, we employed the revised version of the 'Reading the Mind in the Eyes Test' (RMET-R) [31]. Although the terminological and conceptual doubts that we presented in the introduction about the nature of the constructs used in social cognition assessment can be applied also to RMET-R [22], this is a well-established test of the cue-based recognition of mental states, which has been frequently used with both clinical and nonclinical samples. In particular, it has been repeatedly used in studies with HD subjects [18–21,25,27,32,33]. Moreover RMET-R is well suitable for our main scope that is looking for an early impairment of the capacity of detecting mental states of others by premanifest HD patients. In the present study, we used the Italian version of the RMET-R, which has been shown to have good internal consistency (Cronbach's α = .605) and test–retest stability (ICC = .833) [34]. The RMET-R consists of 36 photographs of the eye region from different actors displaying different kinds of rather complex mental states. Each photograph is presented together with four mental state descriptors: one target word and three foil words (see Figure S1 in supplementary information). Participants were requested to select the mental state descriptor that according to each one of them best described the mental state expressed in the photograph. We considered three different features of RMET-R items: 1) the gender (male vs. female) of the actors displaying mental states (henceforth called '*stimulus gender*', 2) the affective valence (negative vs. neutral vs. positive) of the mental states displayed (henceforth called '*stimulus valence*'), and 3) the recognition difficulty (high vs. moderate vs. low) of the mental states displayed (henceforth called '*stimulus difficulty*'). The gender and the stimulus valence of the RMET-R stimuli were defined following Baron-Cohen and colleagues [31] and Harkness and colleagues [35], respectively. The recognition difficulty was defined according to the mean recognition rate of each stimulus. In particular, those stimuli that in one sample *t*-tests ($df = 79$, $p < .05$, $t_{crit} = 1.99$) had mean recognition rates significantly below the overall mean recognition rate across all stimuli in the two control groups ($M = .694$), were considered stimuli with high recognition difficulty while those stimuli with mean recognition rates significantly above the overall mean, were considered stimuli with low recognition difficulty and,

Table 1. Demographic and clinical characteristics of the study sample.

		Premanifest HD	Control group 1	Manifest HD	Control group 2
Subjects (*N*)		20	40	40	40
Female (*N*)		10	20	20	20
Age	Mean ± SD	34.9 ± 8.9	31.7 ± 4.7	45.3 ± 10.1	47.2 ± 7.2
	Range	22–48	23–39	27–69	40–67
	U-test	$U = 331$, $Z = -1.07$, $p = .28$		$U = 704.5$, $Z = -.91$, $p = .36$	
TMS	Mean ± SD	5.3 ± 2.3	–	32.9 ± 12.4	–
	Range	1–9	–	11–57	–
TFC	Mean ± SD	13		9.8 ± 1.8	
	Range	13		7–13	

TMS: total motor score; TFC: total functioning capacity; SD: standard deviation.

finally, those stimuli with mean recognition rates that did not differ significantly from the overall mean, were considered stimuli with moderate recognition difficulty (see Table S1 in supplementary information).

2.3. Procedures

Participants were naïve to the purpose of the experiment and gave written informed consent after reading an information leaflet about the study. Informed consent was obtained according to a procedure approved by the local ethics committee and to the Declaration of Helsinki. The RMET-R stimuli were displayed on a large computer screen. Each stimulus was presented for 25 seconds and was followed by a blank slide for 5 seconds. Participants were asked to mark their answers on an answer sheet.

3. Results

3.1. Preliminary assessment of the effects of the participants' clinical condition and gender

A two-way univariate ANOVA with clinical condition (manifest HD, premanifest HD, and two HC groups) and participant gender (male, female) as between-subject variables evidenced a highly significant main effect of clinical condition, $F(3;132)=65.8$, $p < .001$, $\eta_p^2 = .60$, on the accuracy in detecting the exact descriptor, whereas the main effect of participant gender (p $\approx$ .08) and the effect of the interaction between clinical condition and participant gender ($p \approx .5$) were not statistically significant. A Tukey post-hoc test revealed that recognition accuracy was overall significantly lower in HD manifest participants and in HD premanifest participants than in their age-matched HC ($p < .001$ and $p < .01$, respectively) (see Figure 1). Furthermore, recognition accuracy was overall significantly lower in HD manifest participants than in HD premanifest participants ($p < .001$), whereas it did not differ significantly between their age-matched HC groups ($p \approx 1$).

3.2. Effects of stimulus gender

A two-way repeated measures ANOVA with clinical condition (manifest HD, premanifest HD, and two HC groups) and participant gender (male, female) as between-subject variables and stimulus gender (male, female) as within-subject variable evidenced, in addition to the above-mentioned significant main effect of clinical condition, a significant main effect of stimulus gender, $F(1;132) = 11.4$, $p < .01$, $\eta_p^2=.08$, on recognition accuracy, whereas none of the effects of

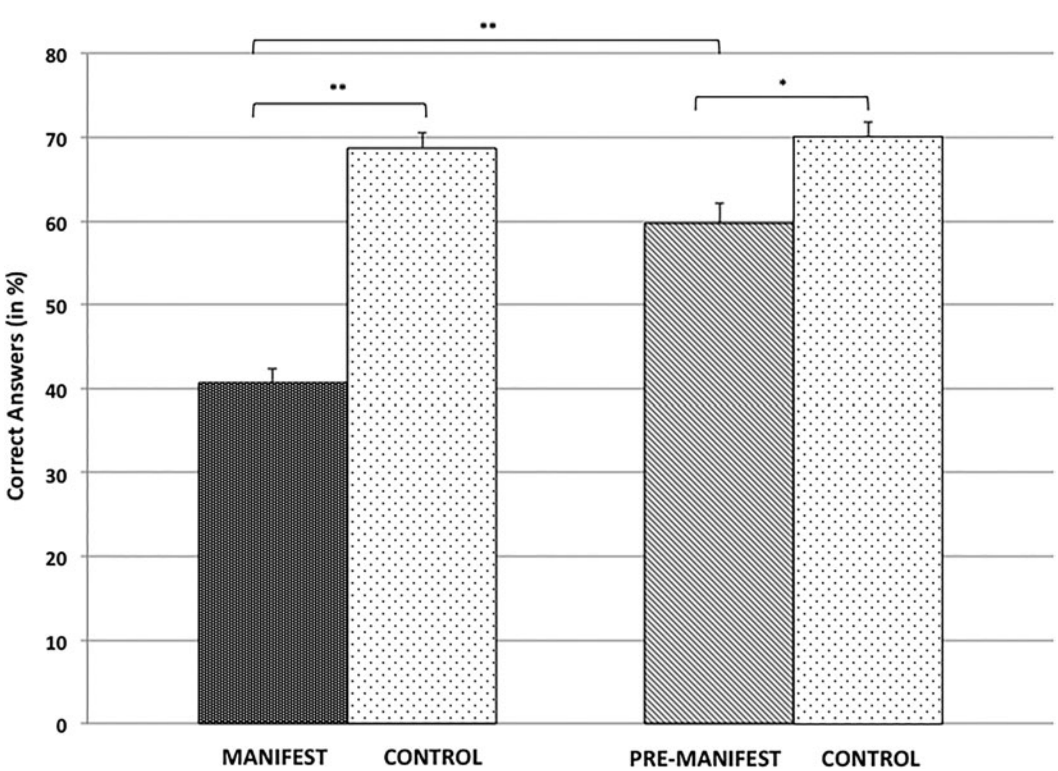

Figure 1. Overall mindreading accuracy of participants with manifest HD, participants with premanifest HD, and their age-matched controls (** $p < .001$, * $p < .01$).

interaction with the variable stimulus gender was statistically significant. Overall, participants correctly recognized 61.9% of the mental states displayed by female actors, but only 58.0% of the mental states displayed by male actors.

3.3. Effects of stimulus valence

A two-way repeated measures ANOVA with clinical condition (manifest HD, premanifest HD, and two HC groups) and participant gender (male, female) as between-subject variables and stimulus valence (negative, neutral, positive) as within-subject variable evidenced, in addition to the above-mentioned significant main effect of clinical condition, a significant main effect of stimulus valence, $F(2;264) = 26.5$, $p < .001$, $\eta_p^2 = .17$, and an effect of the interaction between clinical condition and stimulus valence, $F(6;264) = 4.3$, $p < .01$, $\eta_p^2 = .09$, on recognition accuracy. No other effects of interaction with the variable stimulus valence were statistically significant.

As to the main effect of stimulus valence, pairwise comparisons showed that the accuracy in detecting the correct gaze descriptor was overall significantly lower for neutral (56.9%) and negative (58.3%) mental states than for positive (68.0%) mental states ($p < .001$, respectively), but overall did not differ significantly between negative and neutral mental states.

As to the significant effect of the interaction between clinical condition and stimulus valence, pairwise comparisons showed that recognition accuracy was significantly lower in participants with manifest HD than in their HC for negative, neutral, and positive mental states ($p < .001$, respectively) (see Figure 2, panel A), whereas it was significantly lower in participants with premanifest HD than in their HC only for negative and neutral mental states ($p < .05$, respectively), but not for positive mental states (see Figure 2, panel B). Furthermore, the performance accuracy was significantly lower in participants with manifest HD than in participants with premanifest HD for negative, neutral, and positive mental states ($p < .001$, $p < .01$, and $p < .01$, respectively) (see Figure 2, panel C), whereas it did not differ significantly between the two HC groups neither for negative, nor for neutral, nor for positive mental states. Finally, both in participants with manifest HD and in participants with premanifest HD, but not in their HC, the accuracy in detecting the exact descriptor of the mental state was significantly lower for negative than for positive mental states ($p < .001$ and $p < .05$, respectively), and in participants with manifest HD but not in participants with premanifest HD the accuracy was also significantly lower for negative than for neutral mental states ($p < .01$).

3.4. Effects of stimulus difficulty

A two-way repeated measures ANOVA with clinical condition (manifest HD, premanifest HD, and two HC groups) and participant gender (male, female) as between-subject variables and stimulus difficulty (high, moderate, low) as within-subject variable evidenced, in addition to the above-mentioned significant main effect of clinical condition and apart from the obvious main effect of stimulus difficulty, $F(2;264) = 147.2$, $p <. 001$, $\eta_p^2 = .53$, a highly significant effect of the interaction between clinical condition and stimulus difficulty, $F(6;264) = 10.2$, $p < .001$, $\eta_p^2 = .19$, on mind-reading accuracy.

Pairwise comparisons showed that the accuracy in detecting the mental state expressed by the gaze was significantly lower in participants with manifest HD than in their HC for mental states with high, moderate, and low recognition difficulty ($p < .001$, respectively) (see Figure 3, panel A), whereas it was significantly lower in participants with premanifest HD than in their HC only for mental states with moderate recognition difficulty ($p < .05$) (see Figure 3, panel B), but not for mental states with high or low recognition difficulty. Furthermore, the accuracy was significantly lower in participants with manifest HD than in participants with premanifest HD for mental states with moderate and low recognition difficulty, but not for mental states with high recognition difficulty ($p < .001$, $p < .001$, and $p \approx 1$, respectively) (see Figure 3, panel C). Finally, in both HC groups and in participants with premanifest HD the accuracy differed significantly between mental states with different levels of recognition difficulty. In participants with manifest HD, by contrast, it differed only between mental states with low recognition difficulty, on the one hand, and mental states with moderate or high recognition difficulty ($p < .01$ and $p < .001$, respectively), on the other, but not between mental states with high and moderate recognition difficulty ($p \approx .4$).

4. Discussion

We tested the influence of stimulus features related to genre, valence, and difficulty on the recognitions of others' mental state in premanifest, manifest HD and HC subjects. At a preliminary level we noticed

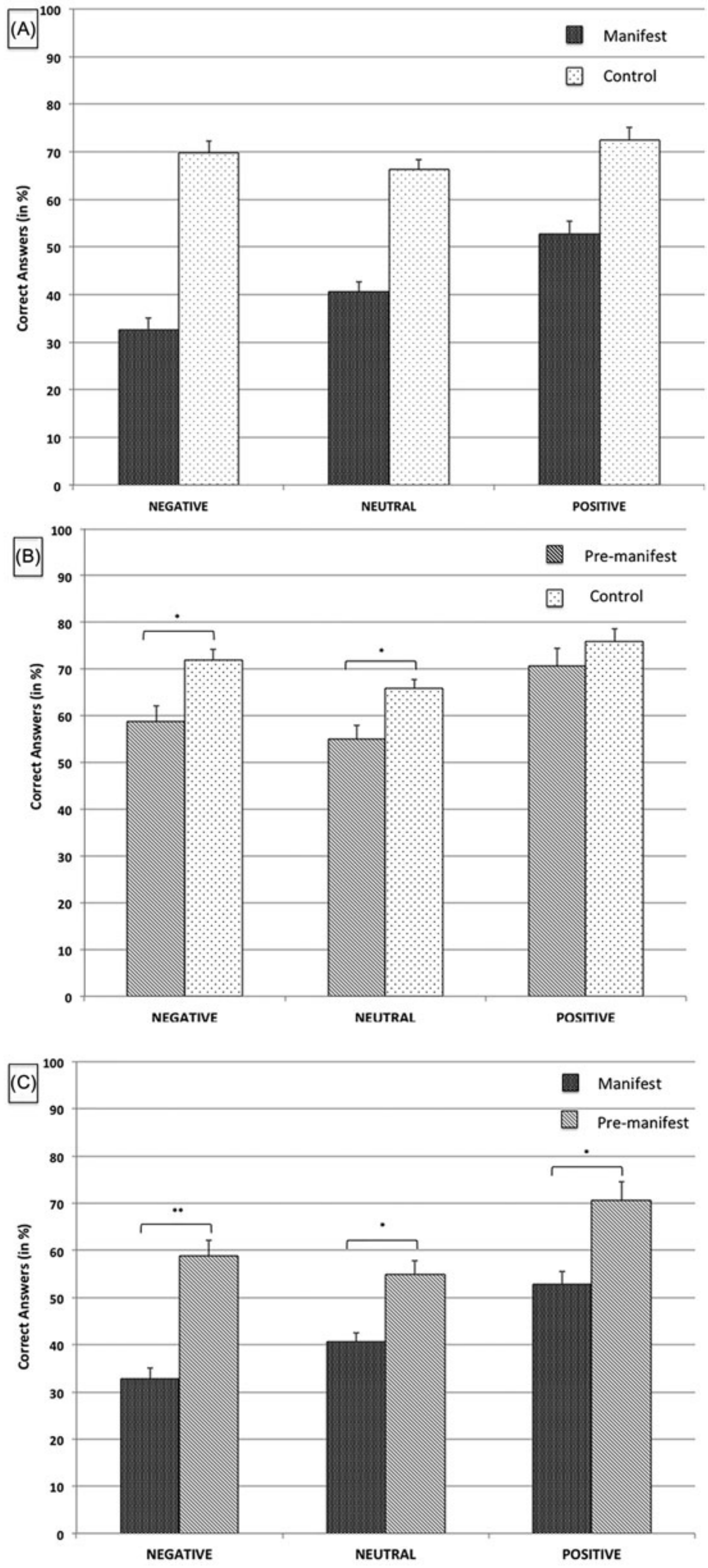

Figure 2. (a) Mindreading accuracy of participants with manifest HD and their respective age-matched controls, for negative, neutral, and positive mental states ($p < .001$, respectively). (b) Mindreading accuracy of participants with premanifest HD and their respective age-matched controls, for negative, neutral, and positive mental states ($^* p < .05$). (c) Mindreading accuracy of participants with premanifest HD and manifest HD, for negative, neutral, and positive mental states ($^{**} p < .001$, $^* p < .01$).

that there was no significant difference in the task performances between males and females, in all cohorts.

As expected, the recognition accuracy was overall significantly lower in the two clinical groups of gene positive subjects when compared with their respective

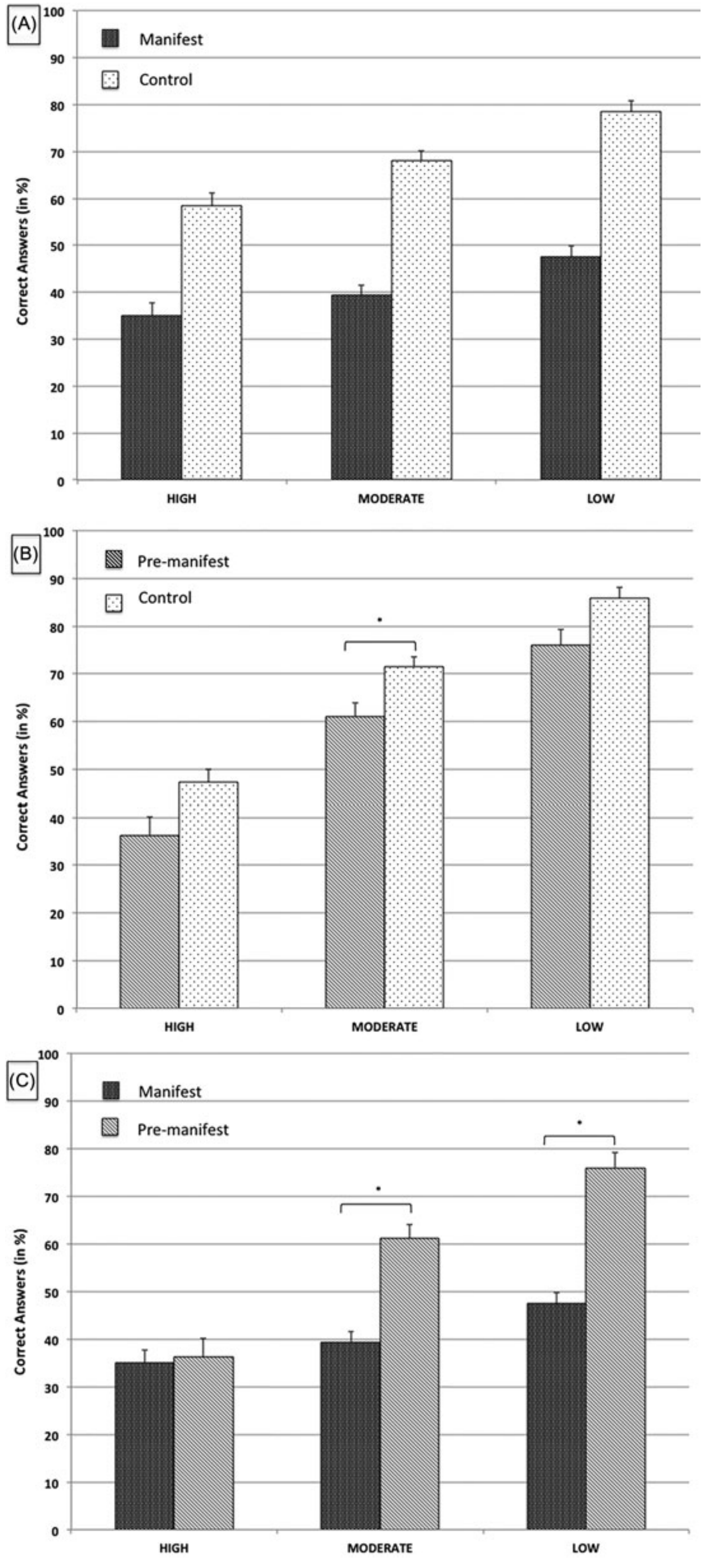

Figure 3. (a) Mindreading accuracy of participants with manifest HD and their respective age-matched controls, for mental states with high, moderate, and low recognition difficulty ($p < .001$, respectively). (b) Mindreading accuracy of participants with manifest HD and their respective age-matched controls, for mental states with high, moderate, and low recognition difficulty ($^*p < .05$). (c) Mindreading accuracy of participants with manifest HD and premanifest HD, for mental states with high, moderate, and low recognition difficulty ($^*p < .001$).

control groups and, overall, symptomatic participants showed a worsen performance than premanifest subjects. These results are in line with previous studies and confirm that the impairment of the skill of recognizing other people's mental states anticipates the onset of motor signs [19]. Such impairment could be potentially related to the early dysfunction of the striatum and to its impaired connection with prefrontal cortex [36,37].

Considering that the deficit in recognizing other people's mental states in HD is still controversial in premanifest stage of the disease [15], our data seem to support the hypothesis that abnormalities we found in such a task start very early, even before HD manifests.

Our study highlighted that participants with premanifest HD performed significantly better than participants with manifest HD, but their performance accuracy was significantly worse than their HC. Overall, the gender of the subjects did not apparently influence the skills of detecting other people's mental states.

Regarding the gender of the stimulus, we observed a significant tendency to better recognize mental states expressed by female stimuli than by male ones from all cohorts independently of the gender of the participants. An easy interpretation of this result may be found in the literature supporting the higher emotional expressiveness of women compared to men [38]. Moreover a recent study, while questioning about gender effect, showed that the eyes test is influenced more by the artistic inclination of the perceivers and less by their gender [39]. However, such abnormalities in the mental state recognition may eventually depend on other factors, e.g. brain functions, structure, development or culture-based differences of the individuals [40].

Regarding the valence of the stimulus, the premanifest HD subjects were less accurate in recognizing negative and neutral mental states compared with controls, while symptomatic patients always failed to recognize negative, neutral, and positive mental states. This result is in favor of a role of the emotional valence in the skills of HD subjects to detect the mental states of other people and is in line with previous studies [12,41], highlighting specific impairment in recognition of negative mental states (i.e. anger, fear, disgust) occurring since the premanifest HD stage.

The impairment of HD premanifest subjects in recognizing negative and neutral mental states that we found could be related to some structural and functional brain abnormalities such as the reduced activity in the right supramarginal gyrus and the increased activity in the anterior cingulate during mental state recognition in premanifest HD subjects [42]. Interestingly, such evidence would suggest that such possible neural correlate of the social cognition impairment in premanifest HD may anticipate the cognitive decline that will develop later, during more advanced HD stages and that in our results is evident in the failure of manifest HD in recognizing all types of mental state as expressed in other people's gaze.

Another possible intriguing explanation concerning the difficulty in recognizing negative mental states by premanifest subjects could be found in the intrinsic difficulty in recognizing a negative compared to a positive mental state, because negative states require greater demand on perceptual processing resources (i.e. different negative emotions share a number of configurational features) [43]. Similarly to negative mental states, neutral states are harder to recognize due to an obvious ambiguity of items that do not clearly allow a mental state classification [44]. A recent study [45] showed that healthy subjects perceived neutral faces as more smiling or scowling when paired with unconscious affective (positive or negative) stimuli. This finding demonstrates the role of affect in the perception of complex mental states and could open a new interesting line of research in HD.

Finally, an additional explanation may suggest that personal distressful experiences are a potential cause of the empathy refusal towards negative mental states that would explain the diminished recognition of neutral and negative mental states by our premanifest subjects [19]. A support to this interpretation can be found in the demonstration that information coming from the interior of the body modulates the processing of information incoming from outside [45].

Unexpectedly, premanifest subjects compared to controls showed impaired performances only in recognizing mental states of moderate difficulty and showed performances at the same level of manifest subjects for mental state of high difficulty, whereas the performances of symptomatic patients were always lower than their controls, independently of the difficulty of the stimulus. A possible but partial explanation of this result might be related to the fact that in the RMET-R the stimuli of moderate and low difficulty and of positive valence are mainly presented with female gazes, while the stimuli of male gazes mostly present neutral or negative mental states that, as stated before, are more difficult to detect than females gazes and positive mental states. As it was recently shown, the impairment of emotional awareness in HD patients is enhanced by the co-occurrence of depressive symptoms [13], and even if it is already controversial which one between cognitive impairment and depression is the cause of the other [46], we would like to underline that our results clearly show that the impairment in social cognition is an early HD symptom before any behavioral manifestation.

The relatively small sample size of our HD groups and the potential influence of pharmacological therapies on the cognitive performance of symptomatic patients, although they used very limited doses of benzodiazepines or neuroleptics, may be indicated among the limitations of our study.

Notwithstanding these limitations, our results unequivocally highlighted an early impairment in affective social cognition preceding manifest symptoms. This finding has the important clinical implication that the skills of detecting other people's mental state show abnormalities many years before the onset of motor manifestations affording a help for an early diagnosis. Our results, moreover, suggest that specific features of the stimulus, particularly for it concerns the negative and neutral mental states, may represent cues modifying the other's mental state recognition skills in subjects at the presymptomatic stage of HD. Further studies on larger cohorts may try to analyze whether these abnormalities may also represent potential clinical markers of onset or progression in the first stages of HD.

Acknowledgments

We thank Chiara Esposito for her support in data collection. Moreover, we thank Fondazione Cattolica Assicurazioni and CHDI for kindly supporting the observational research of LIRH Foundation (www.lirh.it) and the Italian Ministry of Health (RF-2016-02364123 and RC-2018 to FS, SaM and SiM). We also thank all HD patients and their families who contributed to this program.

Disclosure statement

No potential conflict of interest was reported by the authors.

ORCID

Marta Olivetti Belardinelli http://orcid.org/0000-0003-3169-3359

References

[1] Group HsdCR. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. Cell. 1993;26:971–983.

[2] Squitieri F. Neurodegenerative disease: 'Fifty shades of grey' in the Huntington disease gene. Nat Rev Neurol. 2013;9:421–422.

[3] Dorsey ER, Beck CA, Darwin K, et al. Natural history of Huntington disease. JAMA Neurol. 2013;70:1520–1530.

[4] Gasset-Rosa F, Chillon-Marinas C, Goginashvili A, et al. Polyglutamine-expanded huntingtin exacerbates age-related disruption of nuclear integrity and nucleocytoplasmic transport. Neuron. 2017;94:48–57. e4.

[5] Grima JC, Daigle JG, Arbez N, et al. Mutant Huntingtin disrupts the nuclear pore complex. Neuron. 2017;94:93–107. e6.

[6] Khakh BS, Beaumont V, Cachope R, et al. Unravelling and exploiting astrocyte dysfunction in Huntington's Disease. Trends Neurosci. 2017;7:422–437.

[7] Veldman MB, Yang XW. Huntington's disease: nuclear gatekeepers under attack. Neuron. 2017;94:1–4.

[8] Ross CA, Aylward EH, Wild EJ, et al. Huntington disease: natural history, biomarkers and prospects for therapeutics. Nat Rev Neurol. 2014;10:204–216.

[9] Squitieri F, Cannella M, Giallonardo P, et al. Onset and pre-onset studies to define the Huntington's disease natural history. Brain Res Bull. 2001;56:233–238.

[10] Bates GP, Dorsey R, Gusella JF, et al. Huntington's disease. Nat Rev Dis Primers. 2015;1:15005.

[11] Stout JC, Paulsen JS, Queller S, et al. Neurocognitive signs in prodromal Huntington disease. Neuropsychology. 2011;25:1–14.

[12] Henley SM, Novak MJ, Frost C, et al. Emotion recognition in Huntington's disease: a systematic review. Neurosci Biobehav Rev. 2012;36:237–253.

[13] Zarotti N, Simpson J, Fletcher I, et al. Exploring emotion regulation and emotion recognition in people with presymptomatic Huntington's disease: the role of emotional awareness. Neuropsychologia. 2018;112:1–9.

[14] Henley SM, Wild EJ, Hobbs NZ, et al. Defective emotion recognition in early HD is neuropsychologically and anatomically generic. Neuropsychologia. 2008;46:2152–2160.

[15] Bora E, Velakoulis D, Walterfang M. Social cognition in Huntington's disease: a meta-analysis. Behav Brain Res. 2016;297:131–140.

[16] Leslie AM. Pretense and representation: The origins of theory of mind. Psychol Rev. 1987;94:412–426.

[17] Carruthers P. Two systems for mindreading? Rev Phil Psych. 2016; 7:141–162.

[18] Allain P, Havet-Thomassin V, Verny C, et al. Evidence for deficits on different components of theory of mind in Huntington's disease. Neuropsychology. 2011;25:741–751.

[19] Eddy CM, Rickards HE. Theory of mind can be impaired prior to motor onset in Huntington's disease. Neuropsychology. 2015;29:792–798.

[20] Larsen IU, Vinther-Jensen T, Gade A, et al. Do I misconstrue? Sarcasm detection, emotion recognition, and theory of mind in Huntington disease. Neuropsychology. 2016;30:181–189.

[21] Lagravinese G, Avanzino L, De Ferrari AR, et al. Theory of mind is impaired in mild to moderate Huntington's disease independently from global cognitive functioning. Front Psychol. 2017;8:80.

[22] Oakley BF, Brewer R, Bird G, et al. Theory of mind is not theory of emotion: A cautionary note on the reading the mind in the eyes test. J Abnorm Psychol. 2016;125:818–823.

[23] Cook R, Brewer R, Shah P, et al. Alexithymia, not autism, predicts poor recognition of emotional facial expressions. Psychol Sci. 2013;24:723–732.
[24] Bird G, Cook R. Mixed emotions: the contribution of alexithymia to the emotional symptoms of autism. Transl Psychiatry. 2013;3:e285.
[25] Mason SL, Zhang J, Begeti F, et al. The role of the amygdala during emotional processing in Huntington's disease: from pre-manifest to late stage disease. Neuropsychologia. 2015;70:80–89.
[26] Misiura MB, Lourens S, Calhoun VD, et al. Cognitive control, learning, and clinical motor ratings are most highly associated with basal ganglia brain volumes in the premanifest Huntington's disease phenotype. J Int Neuropsychol Soc. 2017;23:159–170.
[27] Poletti M, Enrici I, Adenzato M. Cognitive and affective Theory of Mind in neurodegenerative diseases: neuropsychological, neuroanatomical and neurochemical levels. Neurosci Biobehav Rev. 2012;36:2147–2164.
[28] Hoffmann H, Kessler H, Eppel T, et al. Expression intensity, gender and facial emotion recognition: Women recognize only subtle facial emotions better than men. Acta Psychologica. 2010;135:278–283.
[29] Krause M, Wendt J, Dressel A, et al. Prefrontal function associated with impaired emotion recognition in patients with multiple sclerosis. Behav Brain Res. 2009;205:280–285.
[30] Huntington H. Unified Huntington's disease rating scale: reliability and consistency. Mov Disord. 1996;11: 136–142.
[31] Baron-Cohen S, Wheelwright S, Hill J, et al. The "Reading the Mind in the Eyes" Test revised version: a study with normal adults, and adults with Asperger syndrome or high-functioning autism. J Child Psychol Psychiatry. 2001;42:241–251.
[32] Adenzato M, Poletti M. Theory of Mind abilities in neurodegenerative diseases: an update and a call to introduce mentalizing tasks in standard neuropsychological assessments. Clin Neuropsychiatry. 2013;10: 226–234.
[33] Eddy CM, Mahalingappa SS, Rickards HE. Putting things into perspective: the nature and impact of theory of mind impairment in Huntington's disease. Eur Arch Psychiatry Clin Neurosci. 2014;264:697–705.
[34] Vellante M, Baron-Cohen S, Melis M, et al. The "Reading the Mind in the Eyes" test: systematic review of psychometric properties and a validation study in Italy. Cogn Neuropsychiatry. 2013;18: 326–354.
[35] Harkness K, Sabbagh M, Jacobson J, et al. Enhanced accuracy of mental state decoding in dysphoric college students. Cognit Emot. 2005;19:999–1025.
[36] Wolf RC, Klöppel S. Clinical significance of frontal cortex abnormalities in Huntington's disease. Exp Neurol. 2013;247:39–44.
[37] Tabrizi SJ, Reilmann R, Roos RA, et al. Potential endpoints for clinical trials in premanifest and early Huntington's disease in the TRACK-HD study: analysis of 24 month observational data. Lancet Neurol. 2012; 11:42–53.
[38] Gallois C. The language and communication of emotion: universal, interpersonal, or intergroup? Am Behav Sci. 1993;36:309–338.
[39] Guariglia P, Piccardi L, Giaimo F, et al. The eyes test is influenced more by artistic inclination and less by sex. Front Hum Neurosci. 2015; 9:292.
[40] Kret ME, De Gelder B. A review on sex differences in processing emotional signals. Neuropsychologia. 2012;50:1211–1221.
[41] Trinkler I, de Langavant LC, Bachoud-Lévi A-C. Joint recognition–expression impairment of facial emotions in Huntington's disease despite intact understanding of feelings. Cortex. 2013;49:549–558.
[42] Eddy CM, Rickards HE, Hansen PC. Through your eyes or mine? The neural correlates of mental state recognition in Huntington's disease. Hum Brain Mapp. 2018;39:1354–1366.
[43] Simon D, Craig KD, Gosselin F, et al. Recognition and discrimination of prototypical dynamic expressions of pain and emotions. PAIN®. 2008;135:55–64.
[44] Mattek AM, Wolford GL, Whalen PJ. A mathematical model captures the structure of subjective affect. Perspect Psychol Sci. 2017;12:508–526.
[45] Siegel EH, Wormwood JB, Quigley KS, et al. Seeing what you feel: affect drives visual perception of structurally neutral faces. Psychol Sci. 2018;29:496–503.
[46] Rabins PV, Pearlson GD. Depression induced cognitive impairment. In Burns A, Levy R, editors. Dementia. Boston, MA: Springer; 1994. pp. 667–679.