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RESEARCH ARTICLE

Abnormal visual scanning and impaired mental state recognition in pre-manifest Huntington disease

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Abstract

Huntington's disease (HD) is a genetic neurodegenerative disorder that affects not only the motor but also the cognitive and the neuropsychiatric domain. In particular, deficits in mental state recognition may emerge already at early pre-manifest stages of the disease. The aim of this research was to explore the relation between visual scanning behavior and complex mental state recognition in individuals with pre-manifest HD (preHD). Eighteen preHD and eighteen age- and gender-matched healthy controls took the revised "Reading the Mind in the Eyes" test while their eye-movements were tracked. In addition to the expected deficits in mental state recognition, preHD showed abnormalities concerning all three scanning variables we considered, namely the absolute number of fixations (FC), the average fixation duration (AFD), and the percentage of time spent fixating (FTR). In preHD, FC and FTR but not AFD predicted mental state recognition over and beyond general disease-related declines in cognition and motor functioning. Notably, preHD showed abnormal vertical and horizontal fixation patterns, and these patterns predicted mental state recognition, suggesting the involvement of mechanisms related to the embodied processing of emotional stimuli. Overall, our results suggest that impaired facial mental state recognition in pre-manifest HD is partly due to emotional-motivational factors affecting the visual scanning of facial expressions.

Keywords Huntington's disease · Mindreading · Theory-of-mind · Eye-tracking · Visual scanning · Embodied processing · Emotional-motivational factors

Introduction

Huntington's disease (HD) is a genetic neurodegenerative disorder that affects not only the motor, but also the cognitive and the neuropsychiatric domain (see Snowden 2017, for review). Though motor symptoms such as chorea, dystonia, bradykinesia, and limb rigidity are the most evident features of the disease, both cognitive symptoms such as cognitive slowing, impaired executive skills, and deficits in social cognition (Bora et al. 2016; Migliore et al. 2019; Stout et al. 2011), and neuropsychiatric symptoms such as apathy, irritability and depression (Craufurd et al. 2001; Martinez-Horta et al. 2016; Van Duijn et al. 2007), deserve particular attention because they may appear much earlier than the motor symptoms and have a considerable impact on the quality of life of patients and their families.

Among the most salient cognitive symptoms in HD are deficits in recognizing other individuals' expressions of basic emotions (see Bora et al. 2016, for a meta-analysis; Henley et al. 2012; Kordsachia et al. 2017; for reviews) and more complex mental states (e.g., Eddy and Rickards 2015; Olivetti Belardinelli et al. 2019). These deficits can emerge up to 10 years before the onset of motor abnormalities and worsen with disease progression (Tabrizi et al. 2009, 2012, 2013). While the conceptual understanding of mental states remains relatively intact in HD, the deficits in mental state recognition concern both facial and non-facial (e.g., vocal)

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stimulus domains, suggesting that they are due to some kind of domain-general mental state processing mechanism rather than to a specific facial or visual processing mechanism (see Kordsachia et al. 2017, for review). However, it is possible that domain-specific mechanisms contribute to the deficits, as it is unclear in how far the severity, patterns, and onset of the deficits are similar across domains.

The neural correlates of impaired mental state recognition in HD have so far been investigated only in a particular domain, i.e., facial expressions of basic emotions. In both manifest and pre-manifest HD, deficits in facial emotion recognition have been found to be associated with regional brain atrophy, altered brain activation, and changes in brain connectivity in a range of emotion-related regions, including striatal and extra-striatal regions, such as the insular, amygdala, and orbitofrontal cortex (see Kordsachia et al. 2017, for review). Furthermore, several researches provide evidence that can contribute to explain why impaired mental state recognition in HD appears to be associated with other cognitive as well as with neuropsychiatric symptoms. For example, deficits in facial emotion recognition have been found to be associated with alterations concerning the neural correlates of visual processing, suggesting an involvement of basic perceptual processes (Croft et al. 2014; Dogan et al. 2014; Harrington et al. 2014), with reduced activation in sensorimotor and somatosensory cortices, suggesting the involvement of neural mirroring mechanisms supporting emotion simulation (Dogan et al. 2014), and with structural changes in the orbitofrontal cortex and striatum, suggesting a shared neuropathology with apathy (see Osborne-Crowley et al. 2019, for review).

To better understand the mechanisms associated with impaired mental state recognition, it is promising to analyze the visual scanning of facial expressions because it affects the amount of information yielded for mental state recognition and may therefore be related to deficits in mental state recognition. So far, however, only two studies assessed the relation between visual scanning and mental state recognition in HD, and these two studies report quite different results and suggest very different explanatory hypotheses (Kordsachia et al. 2018; van Asselen et al. 2012). Using the Ekman 60 Faces Test (Ekman and Friesen 1976; Young et al. 2002) in a facial emotion recognition task, van Asselen et al. (2012) found evidence of impaired emotion recognition in participants with manifest HD, but no significant differences in the duration and frequency of fixations on three regions of interest (ROIs): the eyes, the nose, and the mouth. Van Asselen et al. (2012) therefore conclude that the observed deficits in emotion recognition are more likely due to higher order processing impairments than to abnormal visual scanning. By contrast, using the colored stimuli of the Amsterdam Dynamic Facial Expression Set (ADFES) (van der Schalk et al. 2011) in a valence rating task, Kordsachia et al. (2018) found that the dwell time ratio and the fixation count ratio for two ROIs (the eyes and the nose/mouth region) were significantly lower in participants with manifest or close-to-manifest HD than in healthy controls. Furthermore, visual scanning of the eyes region, but not the nose/mouth region, predicted emotion recognition performance in the HD group, over and beyond general disease-related decline. Kordsachia et al. (2018) therefore suggest that two different mechanisms contribute to impaired emotion recognition in HD, one mechanism that is associated with general declines in cognition and motor functioning and another mechanism that is associated with a social-emotional deficit resulting in reduced visual scanning to the eye region of faces.

Given this background, we wanted to explore the relation between visual scanning behavior and mental state recognition in individuals with pre-manifest HD. Unlike van Asselen et al. (2012) and Kordsachia et al. (2018), however, we assessed the recognition of more complex mental states rather than basic emotions. Furthermore, we did not define ROIs in terms of physiological features such as eyes, nose, mouth, partly because of the difficulties and ambiguities in defining the precise limits and extension of physiologically defined facial areas. Instead, we defined ROIs by taking into account two well-established facts concerning the embodied processing of emotion, namely (1) the fact that sadness is associated with downward inclination of head and gaze (Semyonov et al. 2019), and (2) the fact that emotional processing is a lateralized phenomenon, resulting in lateralized expression and perception of affective mental states (see Gainotti 2019, 2020, for review). Considering that emotion-related symptoms such as apathy and depression are frequently present already in pre-manifest HD (Epping et al. 2016; Thompson et al. 2012) and have been found to be associated with poorer cognitive performance (Baudic et al. 2006; Smith et al. 2012) and impaired emotion recognition (Osborne-Crowley et al. 2019; Kempnich et al. 2018), we therefore expected that individuals with pre-manifest HD might show vertical or lateral abnormalities in visual scanning associated with impaired mental state recognition.

Methods

Participants

The study sample consisted of 18 participants with pre-manifest HD (preHD) and 18 age- and gender-matched healthy controls (HC), recruited at the IRCCS Casa Sollievo della Sofferenza Research Hospital, CSS Mendel Institute in Rome. General inclusion criteria were normal or corrected to normal visual acuity, normal color vision, and right-handedness, as it is known to interfere with other phenomena of lateralization such as those considered in this study (e.g., Bourne 2008; Willems et al. 2010). General exclusion criteria were medical conditions that might influence cognition (e.g., a history of developmental disorder, psychotic disorder, or substance or alcohol dependence) and incomplete test performance. Specific inclusion criteria for preHD were a positive genetic test with a CAG expansion ≥ 40, a Unified Huntington's Disease Rating Scale Total Motor Score (UHDRS-TMS) ≤ 10 and a Diagnostic Confidence Level < 4. All preHD had a CAG/Age Product (CAP) score below 400 (Penney et al., 1997). A Mann–Whitney U test indicated that the age difference between preHD and HC was not statistically significant ($U = 135$, $Z = -0.59$, $p = 0.57$). All participants had a normal Total Functional Capacity ($TFC = 13$), but preHD differed from HC in their UHDRS-TMS, $F(1, 34) = 68.2$, $p < 0.001$, $\eta_p^2 = 0.67$. Basic demographic and clinical information on the two groups of participants is summarized in Table 1.

Instruments and measures

Revised adult version of the "Reading the Mind in the Eyes Test" (RMET)

The RMET (Baron-Cohen et al. 2001; Italian version: Vellante et al. 2013) is a well-established test of advanced mental state recognition, which has been frequently used with both clinical and non-clinical samples. It consists in 36 black-and-white photographs of the eye region of 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. Participants are requested to select the mental state descriptor that best describes the mental state expressed in the photograph.

For each RMET stimulus, we defined eight Regions of Interest (ROIs) by dividing each stimulus into four equal parts: upper left, upper right, lower left, lower right, and by distinguishing between the photo area, i.e., the area covered by the photograph, and the word area, i.e., the surrounding blank area containing the mental state descriptors (Fig. 1).

Table 1 Basic demographic and clinical characteristics of participants with pre-manifest HD (preHD) and healthy controls (HC)

	preHD	HC
Number (m/f)	18 (9/9)	18 (9/9)
Age (in years)		
Mean (± SD)	35.6 (± 7.2)	37.3 (± 9.6)
Range	26–47	22–53
UHDRS-TMS		
Mean (± SD)	5.8 (± 2.2)	0.7 (± 1.2)
Range	2–10	0–4

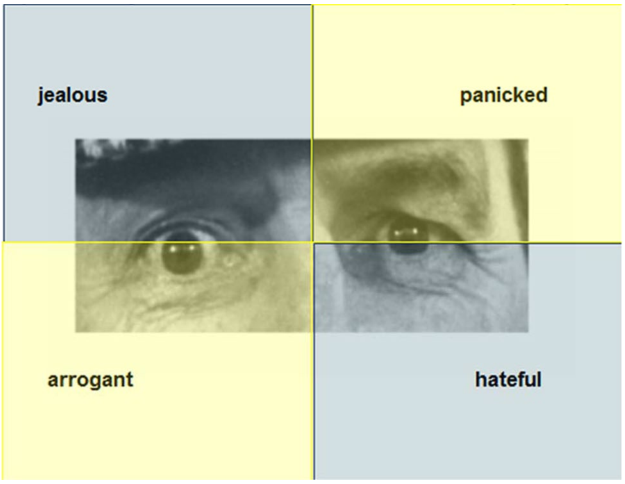


Fig. 1 Example of a RMET stimulus and its division into eight Regions of Interest (ROIs)

Though both the face section and the gaze direction differ strongly between the RMET stimuli, the expressors' left eye was always in the right half and the right eye in the left half of the photograph. However, both eyes, especially the right one, were located more often in the lower than in the upper half of the photographs (see Table 2 for details).

Eye-movement recording and processing

Eye movements were recorded with a remote eye-tracker (RED 500, SensoMotoric Instruments), with a frequency of sampling of 500 Hz and an accuracy of 1°. A 9-point calibration was performed before starting the experiment, followed by validation. Participants were seated at approximately 70 cm in front of a 22 inch LCD computer monitor (1680 × 1050 pixel).

The following eye-tracking variables were extracted per ROI:

- *Fixation Count (FC)* Number of fixations inside a ROI;
- *Average Fixation Duration (AFD)* Sum of the fixation durations inside a ROI (in ms) divided by the number of fixations inside the ROI.

Table 2 Position of the expressors' eye pupils in the 36 RMET stimuli

	Left half (expressors' right eye)	Right half (expressors' left eye)
Above the meridian line	3	9
On the meridian line	13	13
Below the meridian line	20	14

- *Fixation Time Ratio (FTR)* Sum of the fixation durations inside a ROI in percent of the total trial time, with “total trial time” referring to the total time a stimulus is presented.

Procedure

Having given their informed consent, the participants were introduced to the eye-tracking device and to the RMET. The RMET stimuli were presented on the computer monitor and participants were instructed to hit the spacebar as soon as they would have settled on an answer. Hitting the spacebar, the RMET stimulus was replaced by an answer slide showing only the four mental state terms of that stimulus, and the participants had time to select the correct answer. To go on, participants had to hit the spacebar again. The answer slide was then replaced by a blank slide for three seconds, followed by the next RMET stimulus. Following a test trial, the 36 RMET stimuli were administered. The research was approved by the Ethics Committee of the “Istituto Leonarda Vaccari”, Rome, on January 24, 2018.

Design and statistical analyses

In order to determine whether there were group differences between preHD and HC, we performed two types of ANOVA with Group (preHD; HC) as between-subjects factor: (1) a MANOVA on mindreading accuracy and response time, and (2) a repeated measures ANOVA with Content (word area; photo area), Verticality (upper half; lower half), and Laterality (left half; right half) as within-subject factors, on each of our three eye-tracking variables FC, AFD, and FTR. In addition to these group comparisons, we performed separate Pearson correlation analyses in each of the two groups, in order to assess how mindreading accuracy was related to visual scanning of our ROIs, as assessed by our three eye-tracking variables. Finally, we performed three hierarchical regression analyses predicting mindreading accuracy in the preHD group, in order to determine whether visual scanning of our ROIs, as assessed by our three eye-tracking variables, predicted mindreading accuracy over and above general disease-related decline. In the first step, we entered the UHDRS-TMS as a well-established measure of general disease-related declines in cognition and motor-functioning (Paulsen 2011; Tabrizi et al. 2013). In the second step, we entered either FC, or AFD, or FTR for each of our eight ROIs. All statistical analyses were performed using IBM SPSS Statistics 19.

Results

Effects of group on mindreading accuracy and response time

The MANOVA with mindreading accuracy and response time as dependent variables indicated a significant effect of Group on mindreading accuracy, $F(1,34)=4.4$, $p<0.05$, $\eta_p^2 = 0.12$, but not on response time, $F(1,34)=2.4$, $p=0.13$, $\eta_p^2 = 0.06$. In particular, mindreading accuracy was lower in preHD ($M=67.8$, $SE=1.8$) than in HC ($M=73.1$, $SE=1.8$).

Effects of group on our three eye-tracking variables

In the following, we will report the results of our three repeated measures ANOVA with Group (preHD vs. HC) as between-subject factor, and Content (word vs. photo area), Verticality (upper vs. lower half), and Laterality (left vs. right half) as within-subject factors, on our three eye-tracking variables FC, AFD, and FTR, respectively. Given the aim of this research, we will report only the main effects and interactions concerning Group.

Fixation count

The repeated measures ANOVA with the number of fixations as the dependent variable indicated a significant main effect of Group, a significant three-way interaction between Group, Content and Verticality, and a significant three-way interaction between Group, Content and Laterality, whereas the other interactions with Group were not statistically significant (see Table 3 for details).

As to the significant main effect of Group, the number of fixations per ROI was significantly smaller in preHD ($M=2.2$, $SE=0.2$) than in HC ($M=3.1$, $SE=0.2$).

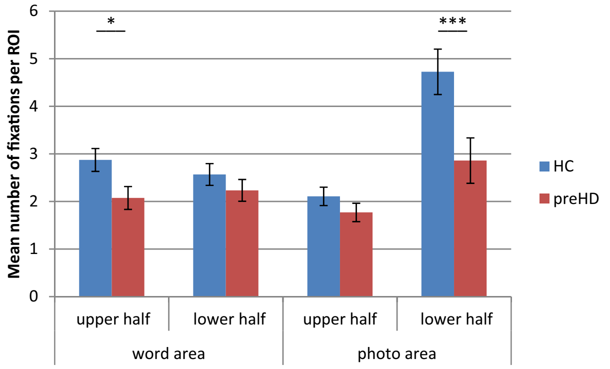
As to the significant three-way interaction between Group, Content and Verticality, follow-up analyses revealed that preHD fixated significantly less often than HC on the upper half of the word area ($p<0.05$) and on the lower half of the photo area ($p<0.01$), but did not differ significantly from HC in the number of fixations on the lower half of the word area ($p=0.31$) and on the upper half of the photo area ($p=0.22$) (see Fig. 2).

As to the significant three-way interaction between Group, Content and Laterality, follow-up analyses revealed that preHD fixated significantly less often than HC on the right half of the photo area ($p<0.01$), but did not differ significantly from HC in the number of fixations on the left photo area ($p=0.11$), on the left word area ($p=0.06$), and on the right word area ($p=0.14$) (see Fig. 3).

Table 3 Main effect and interactions of Group (G) with content (C), verticality (V), and laterality (L) on the number of fixations (FC), the average fixation duration (AFD), and the fixation time ratio (FTR)

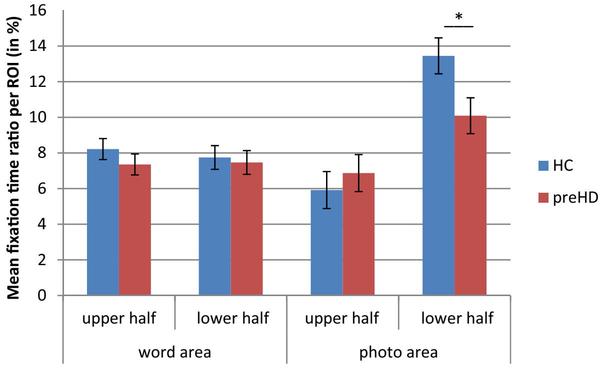
	FC		AFD		FTR	
	F	η_p^2	*F*	η_p^2	*F*	η_p^2
G	7.198*	0.175	5.224*	0.133	3.029	0.082
G·C	1.938	0.054	1.159	0.033	0.195	0.006
G·V	2.451	0.067	0.260	0.008	2.418	0.066
G·L	1.179	0.034	0.812	0.023	2.825	0.077
G·C•V	9.912**	0.226	0.026	0.001	4.893*	0.126
G·C·L	4.747*	0.123	2.779	0.076	2.789	0.076
G·V·L	0.046	0.001	0.026	0.001	0.003	0.000
G·C·V·L	0.974	0.028	0.458	0.503	1.729	0.048

df = 1, for all effects; *df* = 34, for all Errors; *$p < 0.05$, **$p < 0.01$



Note: *$p < .05$, ***$p < .001$.

Fig. 2 Mean number of fixations per ROI on the upper and lower half of the word and photo area in participants with pre-manifest HD (preHD) and healthy controls (HC). *$p < 0.05$, ***$p < 0.001$



Note: *$p < .05$.

Fig. 4 Fixation time ratio per ROI (in percent of the total trial time) on the upper and lower half of the word and photo area of the RMET stimuli in participants with pre-manifest HD (preHD) and healthy controls (HC). *$p < 0.05$

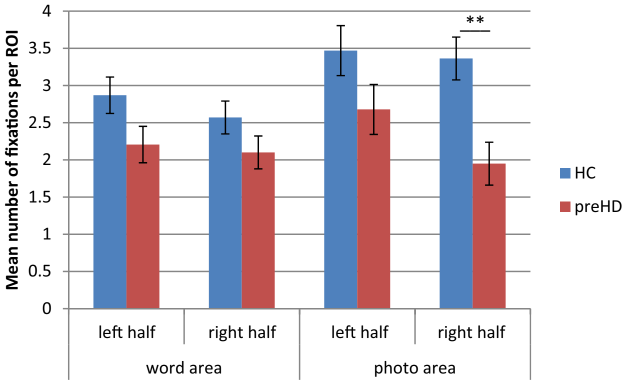


Fig. 3 Mean number of fixations per ROI on the left and right half of the word and photo area in participants with pre-manifest HD (preHD) and healthy controls (HC). **$p < 0.001$

Average fixation duration

The repeated measures ANOVA with the average fixation duration as dependent variable indicated a significant main effect of Group, whereas none of the interactions with Group was statistically significant (see Table 3 for details). In particular, the average fixation duration was significantly shorter in preHD ($M = 144.9$, $SE = 8.4$) than in HC ($M = 172.2$, $SE = 8.4$).

Fixation time ratio

The repeated measures ANOVA with the fixation time ratio per ROI (in percent of the total trial time) as the dependent variable indicated a significant three-way interaction between Group, Content, and Verticality, but no other significant effects concerning Group (see Table 3 for details). In particular, preHD spent a significantly smaller percentage of their trial time than HC fixating on the lower half of the photo area ($p < 0.05$), but they did not differ significantly from HC in their fixations on the upper half of the word area ($p = 0.31$), on the lower half of the word area ($p = 0.77$), and on the upper half of the photo area ($p = 0.52$) (see Fig. 4).

Correlations between mindreading accuracy and our three eye-tracking variables

The results of the Pearson correlation analyses between mindreading accuracy and our three eye-tracking variables for different ROIs are reported in Table 4.

In HC, there was only one significant correlation: mindreading accuracy decreased with increasing average duration of fixations on the upper left photo area ($r = -0.536$, $p < 0.05$). In preHD, by contrast, there were significant correlations concerning the upper right photo area and the lower left word area: the more often and the longer preHD fixated on the upper right photo area the higher were their mindreading scores ($r = 0.644$, $p < 0.01$, and $r = 0.588$, $p < 0.05$, respectively), and the more often they fixated on the lower left word area the lower were their mindreading scores ($r = -0.510$, $p < 0.05$). Accordingly, mindreading scores increased with increasing percentage of time spent fixating on the upper right photo area ($r = 0.663$, $p < 0.01$), whereas they decreased with increasing percentage of time spent fixating on the lower left word area ($r = -0.497$, $p < .05$).

Table 4 Correlations of mindreading accuracy (ACC) with Fixation Count (FC), Average Fixation Duration (AFD), and Fixation Time Ratio (FTR) concerning different ROIs in a) healthy controls (HC) and b) participants with pre-manifest HD (preHD)

	ACC correlated with:		
ROI	FC	AFD	FTR
(a) HC			
Word area			
Upper left	– 0.060	– 0.354	– 0.148
Upper right	– 0.046	– 0.211	– 0.150
Lower left	– 0.147	– 0.146	– 0.136
Lower right	– 0.133	– 0.165	– 0.175
Photo area			
Upper left	– 0.049	– 0.536*	– 0.174
Upper right	0.166	– 0.104	0.106
Lower left	0.127	– 0.261	0.007
Lower right	0.193	– 0.200	0.168
Total word area	– 0.098	– 0.235	– 0.165
Total photo area	0.170	– 0.398	0.113
Across all ROIs	0.070	– 0.336	– 0.097
(b) preHD			
Word area			
Upper left	0.071	– 0.111	0.002
Upper right	– 0.292	– 0.080	– 0.221
Lower left	– 0.510*	– 0.178	– 0.497*
Lower right	– 0.448	0.003	– 0.196
Photo area			
Upper left	0.057	0.352	0.322
Upper right	0.644**	0.588*	0.663**
Lower left	– 0.463	– 0.192	– 0.288
Lower right	– 0.314	– 0.254	– 0.189
Total word area	– 0.337	– 0.095	– 0.271
Total photo area	– 0.217	0.109	0.258
Across all ROIs	– 0.295	– 0.009	0.016

*$p < 0.05$, **$p < 0.01$, two-tailed

Eye-tracking variables predicting mindreading accuracy in preHD

The results of the three hierarchical regressions analyses predicting mindreading accuracy in preHD are reported in Table 5. In the first step, the UHDRS-TMS explained only 8.3% of the variance and did not significantly predict mindreading accuracy. In the second step, the inclusion of the numbers of fixations for the eight ROIs (Model 2a) explained 80.0% of the variance, strongly increasing the fit of the model ($p < 0.01$), whereas the inclusion of the average fixation duration (Model 2b) explained 53.0% of the variance without significantly increasing the fit of the model ($p = 0.33$). Finally, the inclusion of the fixation time ratio (in percent of the total trial time) in the second step (Model 2c) explained 77.8% of the variance, significantly increasing the fit of the model ($p < 0.05$). Thus, the number of fixations as well as the percentage of time spent fixating significantly predicted mindreading over and above general disease-related decline, whereas the average fixation duration did not.

As regards single ROIs, in the overall model with the number of fixations as the predictor variable (Model 2a) the only significant effect concerned the upper right photo area: a higher number of fixations on that area predicted higher mindreading accuracy ($p < 0.01$). In the overall model with the fixation time ratio (in percent of the total trial time) as predictor variable (Model 2c) there were significant effects concerning the upper left word area ($p < 0.05$), the upper left photo area ($p < 0.05$) and the upper right photo area ($p < 0.01$): a higher percentage of time spent fixating on the upper left word area or on the upper right photo predicted higher mindreading accuracy, whereas a higher percentage of time spent fixating on the upper left photo area predicted lower mindreading accuracy.

Discussion

The aim of this research was to explore the relation between visual scanning behavior and complex mental state recognition in individuals with pre-manifest HD. In addition to the expected deficits in mental state recognition accuracy, our results evidenced abnormalities concerning all three scanning variables we considered, namely (1) the number of fixations, (2) the average fixation duration, and (3) the

Table 5 Results of the three hierarchical regression analyses with (a) Fixation Count (FC), (b) Average Fixation Duration (AFD), and (c) Fixation Time Ratio, for each of the eight ROIs, as predictors of mindreading accuracy

	B	SE B	β	T	R^2	ΔR^2	ΔF
Model 1					0.083	0.083	1.447
(Intercept)	0.739	0.054		13.619***			
UHDRS-TMS	– 0.011	0.009	– 0.288	– 1.203			
Model 2a					0.883	0.800	6.865**
(Intercept)	0.635	0.061		10.492***			
UHDRS-TMS	0.000	0.006	0.001	0.006			
FC (upper left word area)	0.019	0.018	0.225	1.107			
FC (upper right word area)	0.018	0.021	0.243	0.860			
FC (lower left word area)	– 0.034	0.037	– 0.440	– 0.942			
FC (lower right word area)	– 0.055	0.032	– 0.607	– 1.731			
FC (upper left photo area)	– 0.003	0.012	– 0.048	– 0.265			
FC (upper right photo area)	0.101	0.025	0.726	3.999**			
FC (lower left photo area)	– 0.008	0.023	– 0.179	-0.347			
FC(lower right photo area)	0.021	0.022	0.337	0.893			
Model 2b					0.613	0.530	1.368
(Intercept)	0.675	0.101		6.667***			
UHDRS-TMS	– 0.009	0.011	– 0.234	– 0.755			
AFD (upper left word area)	0.001	0.001	0.566	1.008			
AFD (upper right word area)	0.000	0.001	– 0.321	– 0.514			
AFD (lower left word area)	– 0.001	0.001	– 0.655	– 0.776			
AFD (lower right word area)	0.000	0.001	0.289	0.434			
AFD (upper left photo area)	0.000	0.001	– 0.173	– 0.428			
AFD (upper right photo area)	0.001	0.001	0.716	1.410			
AFD (lower left photo area)	0.001	0.001	0.413	0.546			
AFD (lower right photo area)	– 0.001	0.001	– 0.727	– 1.141			
Model 2c					0.861	0.778	5.595*
(Intercept)	0.725	0.055		13.233***			
UHDRS-TMS	– 0.007	0.006	– 0.183	– 1.119			
FTR (upper left word area)	0.016	0.006	0.592	2.600*			
FTR (upper right word area)	– 0.006	0.007	– 0.251	– 0.832			
FTR (lower left word area)	– 0.011	0.008	– 0.485	– 1.500			
FTR (lower right word area)	– 0.004	0.009	– 0.145	– 0.461			
FTR (upper left photo area)	0.023	0.005	1.148	– 3.342*			
FTR (upper right photo area)	– 0.009	0.003	– 0.919	4.328**			
FTR (lower left photo area)	0.000	0.004	0.013	– 0.265			
FTR (lower right photo area)	– 0.001	0.005	– 0.066	0.060			

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

percentage of time spent fixating. As regards (1), the number of fixations was overall significantly smaller in preHD than in HC, mainly due to a significantly smaller number of fixations on the lower half and on the right half of the photo area. As regards (2), the average fixation time was overall significantly shorter in preHD than in HC. Finally, as regards (3), the percentage of time spent fixating on the lower half of the photo area, was significantly shorter in preHD than in HC.

These findings are in contrast with expectations based on van Asselen et al.'s (2012) hypothesis, whereas they are perfectly in line with expectations based on Kordsachia et al.'s (2018) hypothesis. In fact, on the ground of van Asselen et al.'s (2012) hypothesis, there is no reason to expect abnormal visual scanning behavior, because the known deficits in facial mental state recognition are supposed to be more likely due to higher-order impairments. On the ground of Kordsachia et al.'s (2018) hypothesis, by contrast, we did expect abnormal visual scanning behavior especially concerning the lower half of the photo area, i.e. concerning those ROIs which overall contained most of the eye region, because the known deficits in facial mental state recognition are supposed to be partly due to social-emotional deficits resulting in reduced visual scanning to the eye region of faces.

The involvement of social-emotional deficits in abnormal visual scanning in preHD is also suggested by our finding that preHD fixated significantly less often than HC on the right half of the photo area, corresponding to the left half of the face represented in the photos, but did not differ significantly from HC in the number of fixations on the left half of the photo area and on the left and right halves of the word area. In fact, the finding calls for an explanation in terms of lateralized emotion processing. Various models of lateralized emotion processing have been advanced over the last four or five decades, but recent research provides convergent evidence in favor of the "right hemisphere hypothesis" (see Gainotti 2019, 2020, for review). According to this hypothesis, the right hemisphere is specialized for the expression and perception of any kind of emotions, resulting in enhanced expression of emotion especially on the left half of the face and enhanced perception of emotional information especially on the left half of emotional stimuli, due to the contralateral organization of the brain. On the ground of the "right hemisphere hypothesis", the above finding that preHD fixated significantly less often than HC on the right half of the photo area, but did not differ significantly from HC in the number of fixations on the other ROIs might therefore be related to the fact that the right half of the photo area shows the eye region of that half of the face that is supposed to show more expression of emotion.

Kordsachia et al.'s (2018) hypothesis is further confirmed by the results of our regression analyses in the sample of preHD. In fact, both the number of fixations and the percentage of time spent fixating significantly predicted mental state recognition accuracy in preHD over and beyond general disease-related declines in cognition and motor functioning, as assessed by the UHDRS-TMS. Notably, different ROIs contributed differently to this effect, with the upper right photo area being particularly relevant. The particular relevance of the upper right photo area is also evident in the results of the correlation analyses which evidenced positive correlations between mental state recognition accuracy and all three of our scanning variables. These findings suggest that the social-emotional mechanism hypothesized by Kordsachia et al. (2018) involves two distinct mechanisms concerning the embodied processing of emotions: one mechanism underlying an effect of laterality and another mechanism underlying an effect of verticality, which together resulted in the particular relevance of the upper right photo area. The effect of laterality might again be explained in terms of the "right hemisphere hypothesis" by supposing that a higher number of fixations and a higher percentage of time spent fixating on the eye region of that half of faces that is supposed to show more expression of emotion result in overall more accurate mental state recognition. The effect of verticality, by contrast, might be explained in terms of a tendency towards the downward inclination of gaze associated with sadness (Semyonov et al. 2019). Supposing such a tendency, lower levels of sadness might be associated with a higher number of fixations and a higher percentage of time spent fixating on upper ROIs, resulting in overall more comprehensive information acquisition and more accurate mental state recognition.

Taken together, our results confirm Kordsachia et al.'s (2018) hypothesis that mental state recognition deficits in HD are partly due to a social-emotional mechanism, which is reflected in reduced visual scanning to the eye-region of faces. Our results furthermore suggest that this mechanism involves both lateral and vertical gaze tendencies that can be explained in terms of factors concerning the embodied processing of emotion. Notably, the fact that these gaze tendencies were evident both in the number of fixations and in the percentage of time spent fixating but not in the average fixation duration suggests that they are rather related to motivational factors than to cognitive factors. In fact, unlike cognitive factors such as basic executive functions, motivational factors may be expected to affect especially those fixation parameters that are under greater voluntary control. Considering that emotional-motivational symptoms such as apathy and depression are frequently present already in pre-manifest HD (Epping et al., 2016; Thompson et al., 2012), it seems therefore likely that the social-emotional mechanism hypothesized by Kordsachia et al. (2018) involves reduced motivation, or even avoidance, to process facial expressions of emotions, perhaps due to apathy or depression.

A limitation of our study is the small sample size, especially as regards the regression analysis within the group of preHD ($N = 18$). Furthermore, the test we used to assess mental state recognition consists of rather heterogeneous stimuli, not only in terms of the kind and emotional valence of the mental states expressed but also in terms of the face sections and gaze directions shown in the photos. Last not least, we did not assess specific cognitive factors such as basic executive functions, or specific emotional-motivational factors such as apathy and depression. Despite these limitations, our research provides important new insights into how emotional-motivational factors, in addition to cognitive and motor factors, may affect HD many years before the appearance of manifest symptoms. Future research should test whether analogous effects are obtained with other, possibly more homogeneous, measures of mental state recognition, and it should also control for the possible involvement of specific cognitive and motivational factors.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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