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Neural correlates associated with impaired disgust processing in pre-symptomatic Huntington's disease

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Summary

Disturbances in recognizing facial expressions of disgust have been reported previously in pre-symptomatic and manifest Huntington's disease. Given the substantial role of the insula and basal ganglia in the perception of disgust as revealed by functional imaging, lesion studies and intracerebral recordings, we propose dysfunction within the insula and/or basal ganglia as the underlying neural substrate. Using functional MRI (fMRI), we studied a group of nine pre-symptomatic Huntington's disease gene carriers and nine healthy controls, matched for age, gender, intelligence and years of education, while they were viewing disgusted facial expressions. As control conditions, surprised and neutral expressions were presented. Compared with healthy controls, Huntington's disease gene carriers showed reduced responses within the left dorsal anterior insula during processing of disgusted facial expressions. Moreover, processing of disgust was associated with significant activation of the left dorsal anterior insula and putamen in healthy controls, but not in Huntington's disease gene carriers. Furthermore, behavioural assessment revealed a selective impairment in recognizing facial expressions displaying disgust in Huntington's disease gene carriers. Our finding of dysfunctional decreased insula activation in pre-symptomatic Huntington's disease provides an explanation for the clinical deficit in recognizing facial expression of disgust. Furthermore, it underscores the role of the insula in the emotion of disgust.

Keywords: Huntington's disease; fMRI; disgust; facial expression; insula

Abbreviations: CI = caudate index; FDR = false discovery rate; fMRI = functional MRI; IQ = intelligence quotient; ROI = region of interest

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Introduction

Huntington's disease is a dominantly inherited neurodegenerative disorder primarily affecting the striatum with a generalized loss of medium-sized spiny neurons (Goto *et al.*, 1989). The clinical picture is characterized by involuntary choreiform movements and cognitive and emotional dysfunctions (Speedie *et al.*, 1990; Lawrence *et al.*, 1998) including impairments in the processing of faces and emotional facial expressions (Jacobs *et al.*, 1995). In a study using prototypical emotion expression stimuli and morphed emotional expressions produced from six basic emotions (happiness, surprise, fear, sadness, disgust and anger), patients with manifest Huntington's disease showed problems in recognizing several emotional expressions, but a disproportionately severe impairment in recognizing facial expressions of disgust (Sprengelmeyer *et al.*, 1996). The finding that Huntington's disease particularly affects recognition of disgust has been corroborated by a case study of two manifest Huntington's disease patients (Sprengelmeyer *et al.*, 1997*b*) and a study with Chinese patients suffering from Huntington's disease (Wang *et al.*, 2003). Furthermore, there is evidence for impaired recognition of facial disgust in the absence of manifest Huntington's disease symptomatology. Gray *et al.*

Table 1 *Characteristics of gene-positive participants*

Code	Sex	Age (years)	Education (years)	IQ	CAG	CI	Handedness
01	Female	42	9	118	43	1.9	Right
02	Male	42	10	118	43	2.0	Right
03	Male	33	9	100	46	2.7	Right
04	Female	36	13	118	45	2.1	Right
05	Male	46	14	124	42	1.7	Right
06	Male	36	10	130	45	2.1	Right
07	Male	36	9	100	41	2.4	Right
08	Female	38	12	104	45	1.8	Right
09	Female	28	10	104	43	2.4	Right

Handedness was measured with the Edinburgh inventory (Oldfield, 1971), IQ with the MWT-B (Lehrl, 1977).

(1997) investigated face processing in pre-symptomatic people at risk of carrying the gene mutation associated with Huntington's disease. Participants subsequently identified as gene carriers were compared with the non-gene carriers and a group of healthy controls. Compared with both groups, gene carriers showed a selective impairment in the recognition of disgusted faces, which could not be explained by basal visual and cognitive deficits.

Together with evidence from patients with amygdala lesions suffering from a selective deficit in recognizing facial expressions of fear (Adolphs *et al.*, 1994; Young *et al.*, 1995; Sprengelmeyer *et al.*, 1999), these findings support the notion of partly separable and specialized neural systems for recognizing different facial expressions. Furthermore, perception of disgusted but not fearful facial expressions has consistently been associated with activations of the insula and putamen, as revealed by means of functional imaging (Phillips *et al.*, 1997, 1998; Sprengelmeyer *et al.*, 1998). These findings converge with evidence for impaired disgust recognition in a case study of a patient with left hemisphere infarction involving the insula and putamen (Calder *et al.*, 2000; Calder, 2003). Moreover, Krolak-Salmon *et al.* (2003) demonstrated intracerebral event-related potentials to facial expressions of disgust from insular contacts in patients suffering from drug-refractory temporal lobe epilepsy.

However, the neural substrate underlying the deficit of recognizing disgust in Huntington's disease has not been investigated yet. Given the prominent interconnections between the striatum and insular cortex (Chikama *et al.*, 1997) and their implication in the perception of disgust (Phillips *et al.*, 1997, 1998; Sprengelmeyer *et al.*, 1998; Calder *et al.*, 2000; Krolak-Salmon *et al.*, 2003), we hypothesized that the selective impairment of processing disgusted facial expressions in pre-symptomatic Huntington's disease is associated with decreased activation of the insula and/or putamen. In the current study, we tested this hypothesis using blood oxygenation level-dependent (BOLD) functional MRI (fMRI) to compare the response of the insula and putamen during perception of disgusted facial expressions in pre-symptomatic Huntington's disease gene carriers with that in age-, gender-, education- and intelligence-matched healthy subjects.

Methods

Participants

Nine pre-symptomatic Huntington's disease gene carriers (mean number of CAG repeats: 43.7, SD = 1.7), four females and five males, took part in the study. The mean age of the gene carriers was 37.4 years (SD = 5.4 years), mean duration of schooling was 10.7 years (SD = 1.9 years) and mean intelligence quotient (IQ) was 112.9 (SD = 11.1) as measured with the MWT-B German vocabulary recognition test (Lehrl, 1977). All gene carriers were right-handed following the criteria of the Edinburgh Handedness Inventory (Oldfield, 1971) and showed no signs of manifest choreic movements (for individual data, see Table 1). For all gene carriers, T1-weighted anatomical MRIs were acquired. Subcortical and cortical atrophy in frontal, parietal and temporal lobes was evaluated by two experienced neuroradiologists, naive about the results of neuropsychological testing and functional MRI. Furthermore, the caudate index (CI) was determined as a measure for subcortical atrophy, defined as the ratio of maximum and minimum distance between both side ventricles at the level of the interventricular foramen. The CI of one gene carrier (Huntington's disease subject 05) was scored pathological (CI <1.8) (see Table 1). There were no signs of cortical atrophy within the insular cortex in all Huntington's disease gene carriers. In two gene carriers, minimal cortical atrophy was detected in parietal areas.

The control group consisted of nine healthy adults free of neurological and psychiatric disorders, matched to the Huntington's disease group according to age ($t = -1.20$, $P > 0.1$), education ($t = 1.79$, $P > 0.05$), IQ ($t = 1.52$, $P > 0.1$) and gender (four female, five males). All controls were right-handed according to the criteria of the Edinburgh Handedness Inventory (Oldfield, 1971). Informed written consent according to the Declaration of Helsinki was obtained from each subject. The local Ethics Committee of the Technische Universität München gave approval for this study.

Neuropsychological background assessment

To ensure that any problems in facial expression processing could not be explained by deficits in basal visual and cognitive functions, gene carriers were tested with a number of standard neuropsycho-

logical tasks. The Mini-Mental State Examination (MMSE) (Folstein *et al.*, 1975) was given for dementia screening. Global intellectual function was measured with a German short version of the Wechsler adult intelligence scale (WIP, Wechsler, 1987), consisting of the subtests 'Information', 'Similarities', 'Picture Completion' and 'Block Design'. The Vistech VCTS 6000 contrast sensitivity chart, measuring visual accuracy and contrast sensitivity, was applied to test for basic visual processing. To ensure that early processing stages of perception of faces were intact, the Benton Facial Recognition Test (Benton *et al.*, 1983) was used. In this test, subjects are asked to pick a photograph of a target face from amongst six simultaneously presented faces of the same person. Items include identical photographs, as well as transformations of orientation or lighting.

In summary, there were no signs of dementia (MMSE; mean = 28.8, SD = 1.2) or impairments in global intellectual function (WIP; mean = 103.4, SD = 7.2). Gene carriers showed normal contrast sensitivity and visual acuity for all spatial frequencies (Vistech VCTS 6000), and early stages of face processing were intact (Benton; mean = 45.8, SD = 4.7).

Recognition of facial expressions of emotion

Immediately after fMRI scanning, facial expression recognition abilities of gene carriers and controls were assessed. A set of morphed pictures showing faces of the actor J.J. taken from the Facial Expressions of Emotions: Stimuli and Test (FEEST) (Young *et al.*, 2002) was used. Each face shows two of the six basic emotions (happiness, surprise, fear, sadness, disgust and anger) with different degrees of intensity (e.g. 90% happiness/10% surprise; 70% happiness/30% surprise, 50% happiness/50% surprise, 30% happiness/70% surprise and 10% happiness/90% surprise; for a detailed description, please refer to the handbook of the FEEST) (Young *et al.*, 2002). A set of 30 morphed photographs, spanning the six basic emotions, was presented five times, adding up to a maximum score of 20 for each emotion. Subjects were instructed to categorize each morphed face according to one of the six basic emotions. Responses were made by pressing one of six buttons labelled with the names of the six possible emotions. To ensure their understanding of the meanings of verbal emotion terms used for responses, participants gave verbal examples for each emotion. There was no time restriction, and no feedback was given as to the appropriateness of any responses. Before statistical analysis, the data were screened for homogeneity of variance. Differences among group means for each emotion were assessed using Student's *t* tests. Welch's approximation to the *t* test for unequal variances was used when group variances were not homogeneous (Welch, 1947). Since we predicted impairment of recognizing disgusted faces, these comparisons were based on one-tailed probabilities.

fMRI stimuli and paradigm

Gene carriers and controls viewed grey-scale pictures of faces from the FEEST (Young *et al.*, 2002), displaying disgust, surprise or neutral expressions. As a neutral face, we used a morphed image with a slightly happy expression (25% happy, 75% neutral), produced by computer graphical manipulation, because 100% neutral faces appear slightly cold and threatening (Phillips *et al.*, 1997). Each picture was presented individually against a grey background for 3 s with an interstimulus interval of 0.76 s. Within one block, eight faces (three male/five female) of the same expressions were presented in randomized order. Ten blocks with alternating emotional (disgusted or surprised) and neutral faces constituted one session. Participants performed four separate sessions in a counterbalanced order, two sessions including disgusted and neutral and the other two surprised and neutral faces. In line with previous studies of emotion perception (Morris *et al.*, 1996; Phillips *et al.*, 1997, 1998; Sprengelmeyer *et al.*, 1998; Blair *et al.*, 1999), an implicit paradigm of facial expression perception was applied, with subjects pressing left or right response buttons in a gender decision task. To familiarize subjects with the stimuli, they viewed each picture once before fMRI scanning.

Image acquisition and analysis

Echoplanar brain MRIs were acquired using a 1.5 T Siemens Symphony Scanner (Erlangen, Germany) with a standard head coil. During each run, 110 T2*-weighted images were acquired at each of 33 slices (at 4 mm) parallel to the intercommissural line (AC–PC), covering the whole brain [repetition time (TR) = 3 s, echo time (TE) = 50 ms, flip angle = 90°, matrix = 64 × 64, field of view (FOV) = 200 mm]. The first five volumes of each session were discarded to allow time for the longitudinal magnetization to reach a steady state. High resolution T1-weighted anatomical images were also acquired for each subject at the end of the sessions.

Statistical analysis was performed using Statistical Parametric Mapping software (SPM99, Wellcome Department of Cognitive Neurology, London, UK) based on the general linear model (Friston, 1997). Images were realigned to the first scan of the session, stereotactically normalized into a standard space approximating that of Talairach and Tournoux (1988) and smoothed with an isotropic Gaussian kernel of 10 mm full-width at half-maximum (FWHM). Data analysis was performed by modelling the different conditions as reference waveforms, using box-car functions convolved with a canonical haemodynamic response function. For individual subject analyses, the four functional sessions were entered into an individual design matrix. Subject-specific low frequency confounds were removed by a high pass filter with individually adjusted cut-offs. Subjects of both groups (Huntington's disease gene carriers and controls) were analysed contrasting emotion conditions with the neutral face condition (disgust/neutral, surprise/neutral). Individual images for both contrasts subsequently were entered into separate second level (random effects) analyses. To study the involvement of the insula and putamen during disgust processing within groups, we conducted second level one-sample *t* tests for each group separately. A two-sample *t* test was applied for calculating differences in disgust responses between groups (controls versus Huntington's disease carriers). In order to establish the discriminant validity of our findings, i.e. to check if activation differences between both groups are specific for the processing of disgusted facial expressions, the same analyses were conducted for perception of surprise expressions. According to our *a priori* hypothesis, Huntington's disease gene carriers were expected to show significantly decreased activation within the insula and/or putamen only during perception of disgust expressions but not while processing a different emotion (surprise).

For the insula and the putamen, regions of interest (ROIs) were defined by spheres of 10 mm radius centred on mean coordinates derived from previous studies of disgust perception (Phillips *et al.*, 1997, 1998; Sprengelmeyer *et al.*, 1998) (see Table 2). Reported *P* values are corrected for the number of comparisons made within each *a priori* ROI. Significance was accepted for clusters of five or more contiguous voxels exceeding a statistical threshold of $P < 0.05$.

For non-predicted regions, significance was accepted for voxels surviving false discovery rate (FDR) correction ($q < 0.05$) for multiple spatial comparisons across the whole brain. All coordinates reported are based on the Talairach atlas and were transformed from Montreal Neurological Institute (MNI) space to Talairach stereotactic space applying procedures developed by Matthew Brett (http://www.mrc-cbu.cam.ac.uk/Imaging).

Results

Recognition of facial expressions of emotion

Results for identification of morphed facial expressions of emotion are presented in Fig. 1, showing mean identification rates and SEMs for each of the six basic emotions by Huntington's disease gene carriers and controls. Huntington's disease gene carriers performed significantly worse than controls in recognizing disgust ($t_{10.59} = 2.03$, $P < 0.05$, one-tailed). However, the groups did not differ significantly on recognition of any other emotion (happiness: $t_{16} = 0.00$, $P > 0.1$; surprise: $t_{16} = 1.40$, $P > 0.05$; fear: $t_{12.08} = 0.49$, $P > 0.1$; sadness: $t_{16} = –0.34$, $P > 0.1$; anger: $t_{16} = 1.72$, $P > 0.05$; all one-tailed).

fMRI results

Consistent with previous reports involving healthy subjects (Phillips *et al.*, 1997, 1998; Sprengelmeyer *et al.*, 1998), controls showed significant signal increases within the left dorsal (intermediate) anterior insula/opercular region and left putamen during processing of disgusted relative to neutral facial expressions, that were absent in Huntington's disease gene carriers (Table 3). More importantly, Huntington's disease gene carriers showed reduced responses within the left dorsal (intermediate) anterior insula and adjacent opercular region during processing of disgusted faces, as

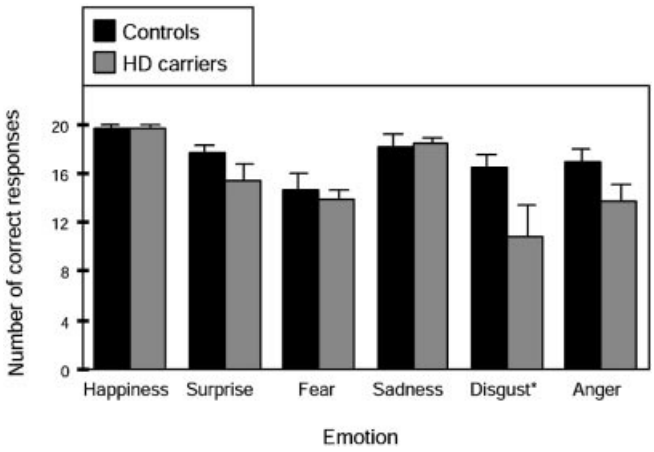

Fig. 1 Mean number of faces correctly labelled for each of the six emotions in the expression recognition task, in controls and Huntington's disease carriers. Error bars represent SEMs. *$P < 0.05$ (one-tailed).

Table 2 *Coordinates for a priori ROIs*

Region	Talairach coordinates		
	x	*y*	*z*
Insula			
Left	–35	8	8
Right	37	–3	7
Putamen			
Left	–26	–19	9
Right	23	–5	2

Mean coordinates for *a priori* ROIs (insula and putamen), based on previous fMRI studies contrasting disgusted with neutral face perception (Phillips *et al.*, 1997, 1998; Sprengelmeyer *et al.*, 1998). The coordinate for the left putamen is based on a single observation (Phillips *et al.*, 1998).

Table 3 *BOLD responses within ROIs (insula and putamen) to disgusted versus neutral expressions in within- and between-group comparisons*

Brain region/group	Talairach coordinates			*Z* score*
	x	*y*	*z*	
Insula				
Controls				
Left dorsal anterior mid-insula	–42	6	13	4.31
Huntington's disease gene carriers	–	–	–	NS
Controls versus Huntington's disease gene carriers				
Left dorsal anterior mid-insula	–44	5	13	4.21
	–40	1	11	3.43
Putamen				
Controls				
Left putamen	–28	–15	12	3.62
Huntington's disease gene carriers	–	–	–	NS
Controls versus Huntington's disease gene carriers	–	–	–	NS

x, *y*, *z* express the position of the voxel(s) with peak activation level within a cluster in mm relative to the anterior commissure (AC) in stereotactic space (Talairach, 1988), *x* = lateral distance from the midline (–right, +left), *y* = anteroposterior distance from the AC (+ anterior, – posterior), *z* = height relative to the AC line (+ above, – below). NS, not significant. *$P < 0.05$ corrected for multiple spatial comparisons across a small volume of interest.

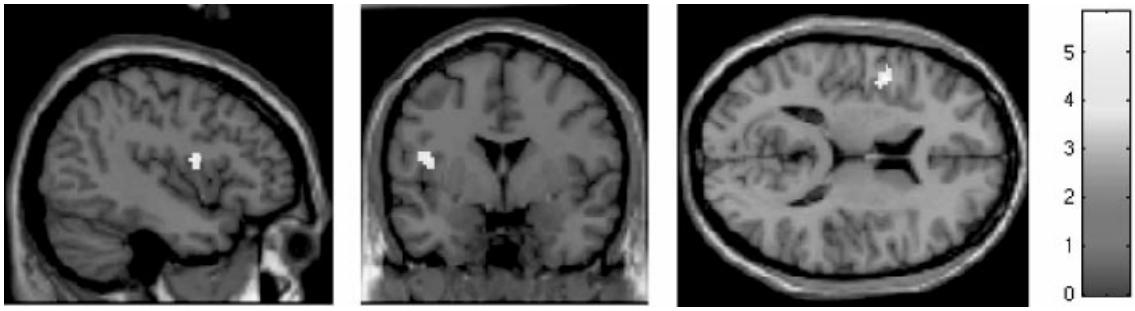

Fig. 2 Statistical parametric map illustrating differences in BOLD response between Huntington's disease gene carriers and controls during perception of disgusted facial expressions. Huntington's disease gene carriers show significantly decreased activation in the left dorsal anterior mid-insula and adjacent opercular region ($P < 0.05$, small volume corrected). Activation is displayed superimposed onto three orthogonal sections of the MNI brain.

revealed by a two-sample *t* test (see Fig. 2, Table 3). Note that all reported within- and between-group differences in activation for our ROIs were specific for the emotion of disgust, since they were not apparent for the surprise contrasts. Furthermore, between-group comparisons of the neural responses to the neutral face condition alone (Huntington's disease gene carriers versus controls, controls versus Huntington's disease gene carriers) revealed no significant differences between groups within ($P < 0.05$, small volume corrected) and outside our ROIs ($q < 0.05$, FDR-corrected across the whole brain). Thus, the observed between-group differences in neural response to disgusted versus neutral faces within the left anterior insula were clearly the result of signal decreases in this region to disgust expressions rather than increases to neutral expressions in the Huntington's disease gene carriers. Moreover, the exclusion of Huntington's disease subject 05 showing a CI that was scored pathological (CI = 1.7) had no influence on the results of our ROI analyses as revealed by *post hoc* between- and within-group comparisons for emotion (disgust/surprise) versus neutral expression contrasts.

To identify areas of significant activation for the disgust and surprise condition relative to the neutral face condition, independent of specific ROIs, an additional whole brain analysis ($q < 0.05$, FDR-corrected) was conducted. For the disgust versus neutral expression contrast, this analysis revealed further signal increases within the middle occipital gyrus bilaterally [Brodmann area (BA) 18/19], right middle temporal gyrus (BA 19) and right precentral gyrus (BA 4) in controls and within the right cerebellum in Huntington's disease gene carriers (see Table 4). There were no sites of activation that survived correction across the whole brain volume in the between-group comparison of the disgust versus neutral expression contrast or the within- and between-group comparisons of the surprise versus neutral expression contrast.

Table 4 *BOLD responses within non-predicted regions to disgusted versus neutral expressions in within- and between-group comparisons*

Brain region/group	Talairach coordinates			*Z* score*
	x	*y*	*z*	
Controls				
R middle occipital gyrus BA 18	38	–93	3	5.27
R middle occipital gyrus BA 19	44	–81	11	4.83
R middle temporal gyrus BA 19	46	–60	12	4.67
R precentral gyrus BA 4	46	–15	52	4.62
L middle occipital BA 19	–40	–79	15	4.55
Huntington's disease gene carriers				
R cerebellum	36	–36	–30	5.09
Controls versus Huntington's disease gene carriers	–	–	–	–

x, *y*, *z* express the position of the voxel(s) with peak activation level within a cluster in mm relative to the anterior commissure (AC) in stereotactic space (Talairach, 1988), *x* = lateral distance from the midline (–right, +left), *y* = anteroposterior distance from the AC (+anterior, –posterior), *z* = height relative to the AC line (+above, –below). *$P < 0.05$ FDR-corrected across the whole brain volume. R = right; L = left.

Discussion

This study aimed at investigating the neural correlate of the selective impairment of processing disgust in pre-symptomatic Huntington's disease. Using a hypothesis-driven ROI approach, we demonstrate for the first time that this deficit is associated with altered neural activity in a circumscribed brain region: compared with healthy controls, an age-, gender-, education- and intelligence-matched group of pre-symptomatic Huntington's disease gene carriers showed reduced activations within the left dorsal anterior mid-insula during perception of disgusted facial expressions, that were absent while processing a different emotion (surprise). Moreover, only in controls was perception of disgusted when compared with neutral faces associated with activations of the left dorsal anterior insula and putamen. In contrast, Huntington's disease gene carriers failed to show activations within our ROIs. These imaging data are consistent with the

results of the behavioural assessment revealing that Huntington's disease gene carriers were selectively impaired in recognizing facial expressions displaying disgust.

Our finding of reduced responses within the dorsal anterior insula during disgust processing in Huntington's disease gene carriers is well in line with findings from previous imaging studies reporting very similar regions for processing of disgusted expressions in healthy subjects (Phillips *et al.*, 1997, 1998; Sprengelmeyer *et al.*, 1998). Though there is converging evidence for a role for the insula in the emotion of disgust, findings concerning the laterality of insula responses are not consistent. Whereas some studies have demonstrated left-sided insula activation (Sprengelmeyer *et al.*, 1998; Wicker *et al.*, 2003), being well in line with our results, others have shown bilateral involvement of the insula (Phillips *et al.*, 1997, 1998). The left lateralized decreased activation in the posterior part of the anterior insula found in our study, however, is in agreement with evidence for impaired disgust recognition in a case study of a patient with left hemisphere infarction involving the posterior part of the left anterior insula (Calder *et al.*, 2000).

The insular cortex is divided into three cytoarchitectonic areas: an intermediate dysgranular compartment that is closely associated with gustatory functions; a rostroventral agranular part related to olfactory and autonomic processing; and a caudodorsal granular part linked to somatosensory, auditory and visual functions (Penfield and Faulk, 1955; Mesulam and Mufson, 1985; Friedman *et al.*, 1986; Schneider *et al.*, 1993). Processing of disgusted facial expressions previously has been linked to the intermediate 'gustatory' (Phillips *et al.*, 1997, 1998; Sprengelmeyer *et al.*, 1998) and rostroventral 'olfactory' insula (Krolak-Salmon *et al.*, 2003). The primary cortical gustatory area in the monkey is located in the anterior insulo-opercular (intermediate) region (Scott *et al.*, 1986; Yaxley *et al.*, 1990). In humans, functional imaging has revealed activations within the insular/opercular primary taste cortex during gustatory stimulation (Frey and Petrides, 1999) and perception of pleasant and unpleasant tastes (O'Doherty *et al.*, 2001). Our finding of impaired performance in disgust recognition and decreased activation within the 'gustatory' (intermediate) insula and adjacent opercular region is therefore consistent with the notion that perception of others' disgust and that of taste are closely linked (Rozin and Fallon, 1987) and share a similar neural substrate (Phillips *et al.*, 1997).

Given that the striatum shows pathological changes even in early Huntington's disease, interruption of basal ganglia–thalamocortical loops (Alexander *et al.*, 1986) at the level of the ventral striatum has been proposed as a possible explanation for the selective impairment in recognizing disgusted facial expressions (Gray *et al.*, 1997). A role for the striatum in this deficit is supported by the finding of impaired disgust recognition in people with Wilson's disease (Wang *et al.*, 2003), obsessive–compulsive disorder (Sprengelmeyer *et al.*, 1997*a*) and unmedicated Parkinson's disease (Sprengelmeyer *et al.*, 2002), since these disorders are also associated with abnormal metabolic activity in fronto-striatal regions (Tankanow, 1991; Saxena *et al.*, 1998; Ceballos-Baumann, 2003). In fact, lack of significant striatal activation during perception of disgusted faces in our group of Huntington's disease gene carriers, as revealed by separate within-group analyses, indicates that the basal ganglia might also play a role in impaired disgust recognition. Functional neuroimaging applied to other disorders characterized by a selective loss of disgust, such as obsessive–compulsive disorder, may help to clarify further the importance of the basal ganglia in this deficit.

However, pathological changes in Huntington's disease are not confined to the striatum, but also affect cortical regions (de la Monte *et al.*, 1988; Jernigan *et al.*, 1991). Recently, neural loss in the insular cortex detected by means of voxel-based morphometry in a pre-clinical sample of Huntington's disease gene carriers (Thieben *et al.*, 2002) has been considered a more plausible explanation for the selective impairment in recognizing disgust and might also explain dysfunctional insula activations found in later stages of Huntington's disease (Weeks *et al.*, 1997; Boecker *et al.*, 1999). Moreover, the insular cortex has also been implicated in other disorders associated with impaired performances in recognizing disgust, such as obsessive–compulsive disorder (Breiter *et al.*, 1996) and Wilson's disease (Duchen and Jacobs, 1992).

Recognition of facial expressions comprises multiple processes, including top-down modulatory projections from hetero- or transmodal regions onto the visual processing stream, that have been interpreted in terms of an allocation of attentional resources to the visual modality due to emotional significance (Vuilleumier *et al.*, 2001; Pessoa *et al.*, 2002). Consistent with this notion, an additional whole brain analysis, independent of specific ROIs, revealed signal increases within occipital/posterior temporal cortices during processing of disgusted compared with neutral faces in healthy controls. In contrast, Huntington's disease gene carriers yielded no significant signal increases within these regions, probably due to dysfunctional back-projections from higher order hetero- or transmodal regions (e.g. the insular cortex) on the visual processing stream. However, this finding has to be interpreted cautiously since the between-group comparison for the disgust versus neutral contrast did not reveal decreased activations within posterior occipital/temporal regions in Huntington's disease gene carriers.

In conclusion, the present study offers a neural substrate for impaired performances in recognizing disgust associated with pre-symptomatic Huntington's disease. Our findings provide evidence that this deficit is closely related to dorsal anterior insula dysfunction, as indicated by reduced activation of this area in Huntington's disease gene carriers only during perception of disgusted faces. Furthermore, they emphasize the role of the anterior insula in the processing of this emotion, supporting the concept of partly separate neural subsystems for perceiving different emotional facial expressions. The results of the current study may be limited by the

small sample size of our groups, given that the number of pre-symptomatic and genetically tested Huntington's disease gene carriers is generally small. However, they provide a fruitful basis for future studies with larger samples to elucidate further the neural networks implicated in this deficit.

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