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Cerebellar Contribution to Anger Recognition Deficits in Huntington's Disease

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Abstract

Although there is increasing evidence that cerebellar loss of grey matter volume (GMV) is associated with affective deficits, this has not been tested for patients suffering from Huntington's disease (HD), who show a pronounced impairment in the recognition of anger. We assessed GMV in 18 symptomatic HD patients and 18 healthy controls using voxel-based morphometry. The GMV of cerebellar subregions was correlated with participants' intensity and accuracy ratings for facial expressions of basic emotions from the Karolinska Directed Emotional Faces (Lundqvist et al. 1998). The patients gave lower and less accurate anger ratings for angry faces than controls. This anger recognition deficit was correlated with atrophy of selected hemispheric and vermal regions of the cerebellum. Furthermore, cerebellar volume reductions of the HD patients were associated with longer disease duration and greater functional impairment. The data imply that anger recognition deficits could potentially serve as indicators of disease onset and progression in HD. Furthermore, the patients might profit from specific affect trainings.

Keywords

Huntington's disease; Cerebellum; Facial affect recognition; Voxel-based morphometry

Introduction

Huntington's disease (HD) is a neurodegenerative disorder characterized by involuntary hyperkinetic movements (chorea). The classical motor symptoms are often preceded by affective changes in the afflicted patients (e.g., irritability, aggression, and depression). These emotional dysfunctions are a very distressing part of the condition and thus a good understanding of these are crucial to good clinical practice [1].

The majority of conducted studies on affective processing in (pre)symptomatic HD points to an altered recognition of facial displays of emotions (for a summary, see [1]). Negative emotions (fear, anger, disgust, and sadness) are not especially accurately classified by HD patients. Henley et al. [1] conducted a review of 16 controlled studies on manifest HD.

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Evidence of reduced anger recognition was found consistently (in each experiment), although identification of the other negative emotions also tended to be impaired.

These deficits have been related to the specific atrophy pattern of HD, which in the beginning primarily targets basal ganglia regions that contribute to the recognition of human anger and disgust signals [2, 3]. However, localized atrophy in several other brain regions is correlated with affective deficits in HD. In a study by Ille et al. [4], the patients reported reduced emotion recognition intensity for disgust, anger, and sadness. These reductions were associated with smaller grey matter volume (GMV) of the insula (disgust and sadness), the orbitofrontal cortex (disgust and sadness), and the hippocampus (disgust and anger). Kipps et al. [5] showed that in preclinical HD disgust and happiness recognition correlated with insula and amygdala volume. Scahill et al. [6] observed an impaired recognition of negative emotions in patients with pre-manifest and early HD, which was associated with volumetric reductions of the (pre)cuneus.

Accordingly, a widespread neural network involved in affective processing is affected in HD. Interestingly, one region which is also implicated in emotion decoding has not been studied extensively: the cerebellum. This might be due to the fact that HD involves early neurodegeneration of the striatum, whereas the cerebellum is relatively spared [7, 8]. There is increasing evidence that the cerebellum contributes to the processing of basic emotions and that specific cerebellar regions are responsible for different affective functions [9, 10].

For the present study, we reanalyzed data from a published voxel-based morphometry (VBM) study on facial affect processing in HD [4]. We tested the hypothesis that the consistently found anger recognition deficit in HD correlates with volume reductions of cerebellar subregions. Additionally, by means of exploratory correlation analyses, we investigated the possible association of disease duration and disease severity with GMV of the cerebellum.

Materials and Methods

Participants

We studied 18 symptomatic and genetically tested HD patients (eight women and ten men; mean age, 51.9 ± 10.4 years). The average disease duration for motor symptoms was 47.9 ± 29.9 months (range, 6–109). Mean CAG repeat lengths was 45.1 ± 2.8 (range, 41–54). We also studied 18 healthy individuals (eight women and ten men) with a comparable mean age (49.2 ± 10.3 years). Written informed consent was obtained from each individual. The study was carried out in accordance with the Declaration of Helsinki and had been approved by the ethics committee of the Medical University of Graz.

Questionnaires

The patients answered the Unified Huntington Disease Rating Scale (UHDRS), which is a standardized clinical rating instrument for the assessment of motor, cognitive, behavioral symptoms, and functional capacity in HD [11]. The UHDRS motor scale ranges from 0 to 124, with higher scores indicating motor impairment. Eye movements, motor control, rigidity, bradykinesia, dystonia, chorea, and gait are assessed. The UHDRS functional

assessment scale consists of 25 questions referring to the performance of daily life activities (e.g., “Can the subject operate an automobile safely and independently”), ranging from 0 to 25. Using the UHDRS independence scale, the current level of a patient’s independence is estimated between 0 and 100 % (higher score=better function). The UHDRS functional capacity scale consists of five items assessing engagement in occupation, capacity to handle financial affairs, capacity to manage domestic responsibilities, and capacity to perform activities of daily living and the type of residential care provided. Scores range from 0 to 13, with higher scores indicative of better functioning and greater independence.

Both patients and controls answered the Beck Depression Inventory (BDI; [12]), and the Test for Early Detection of Dementia (TFDD; [13]). The BDI consists of 21 items rated on 4-point scales. A sum score of 18 or higher indicates clinical relevance. The TFDD allows the detection of early signs of cognitive impairment. The scores of this scale range between 0 and 50. A score below 35 indicates a tentative dementia diagnosis and therefore was considered an exclusion criterion.

Stimuli and Design

All participants viewed 42 pictures with emotional facial expressions depicting happiness (six), fear (six), sadness (six), anger (six), disgust (six), surprise (six), and a neutral affective state (six) from the Karolinska Directed Emotional Faces [14]. Half of the posers were female, and half were male. All pictures showed the faces from a frontal perspective. Each picture was presented once on a computer screen (15-in. diameter) for a maximum of 15 s. The participants could terminate the presentation early by pressing a button on a keyboard, which had been developed for the experiment. Then, the subjects were asked to rate the picture. For each facial expression, the subjects rated how intense the depicted person experienced the six basic emotions (e.g., “Please indicate how intense the depicted person experienced anger”: 1=very little; 9=very intense). After the last rating of a picture, the next picture was presented without any delay.

Image Acquisition

T1-weighted anatomical scans were acquired using a 3 T Siemens Tim Trio system (Siemens, Erlangen, Germany) by means of a 3D-MPRAGE sequence (0.8×0.8×2 mm; 104 transverse slices, TR=1,300 ms, TE=2.69 ms, and TI=900 ms; flip angle=9°; and overall duration, 4:48 min) using a 12-channel head coil.

VBM Analysis

Brain imaging data were analyzed using SPM8 (Wellcome Trust Centre for Neuroimaging) including the VBM8 toolbox (revision 343, <http://dbm.neuro.uni-jena.de/vbm>) for VBM in order to gain voxel-wise comparisons of GMV. Individual anatomical scans were segmented into grey matter, white matter, and cerebrospinal fluid partitions. An optimized blockwise nonlocal means de-noising filter, a hidden Markov random field approach, 33 partial volume estimates, and normalization to MNI space by high-dimensional warping (DARTTEL) with a standard template included in the VBM8-toolbox were used for pre-processing (final resolution, 1.5×1.5×1.5 mm). In order to preserve brain volume and to correct for individual head sizes already in the pre-processing steps of the data, Jacobian modulation was applied

to tissue class segments using non-linear normalization only. Finally, segments were smoothed with a FWHM=10 mm Gaussian kernel.

Afterwards, statistical analyses were carried out using random effects models. A two-sample *t* test was computed in order to assess volume differences between patients and control participants (comparisons, patients>controls and controls>patients). Age and gender were considered covariates. In order to be able to compare our results with the original analyses [4], the modulated grey matter images were explicitly masked by the same grey matter a priori template included in the SPM8 distribution (threshold>0.2). Statistical parametric maps were initially thresholded by an uncorrected $p<0.05$ for all analyses. Peaks for voxel intensity tests of region-of-interest (ROI) analyses are reported if significant ($p<0.05$ corrected for family-wise error and small volume correction). In order to take the precise organization of the cerebellar subregions into account, we used the cerebellar parcellation system suggested by Schmahmann et al. [15, 16]. The ROI masks for the cerebellum based on the automated anatomical labeling template [17] were created using the WFU Pickatlas (WFU Pickatlas v2.4; Wake Forest University School of Medicine). See Table 1 for a complete list of the used ROIs.

Furthermore, to assess correlations between GMV, affective ratings, and clinical data, simple regression analyses were carried out using the following predictors: affect recognition intensity, affect recognition accuracy, symptom severity (UHDRS scores), and symptom duration (in months). For all regression analyses, age and gender were considered covariates.

Results

Questionnaires

The patients obtained the following scores on the UHDRS scales ($M\pm SD$): motor=31.0±17.9, functional assessment= 20.1±5.0, independence=81.7±16.2, and total functional capacity=9.6±3.4. These scores indicate mild to moderate symptom severity. Patients (6.61±6.89) and controls (4.50±4.22) did not differ in their BDI scores ($t(34)=1.11$, $p=0.276$). The dementia screening was negative for both groups. However, patients had a lower TFDD score (38.2±4.3) than controls (46.3±2.3; $t(34)=-7.04$, $p<0.001$).

Ratings

The HD patients gave lower anger intensity ratings ($M\pm SD$) for angry faces than the control subjects (patients, 5.45±2.20 and controls, 7.31±1.17; $t(34)=3.15$, $p=0.003$). Recognition of the other three negative emotions tended to be impaired, but the group differences were non-significant when applying a Bonferroni correction (significance cut off, 0.05/3=0.017): disgust (patients, 5.61±2.44 and controls, 7.04±1.67; $t(34)=2.05$, $p=0.049$), fear (patients, 5.11±2.00 and controls, 6.21±1.18; $t(34)=2.08$, $p=0.045$), sadness (patients, 5.30±2.27 and controls, 6.57±1.37; $t(34)=2.05$, $p=0.049$), happiness (patients, 7.81±1.22 and controls, 8.27±0.68; $t(34)=1.4$, $p=0.17$), and surprise (patients, 6.72±2.16 and controls, 7.75±1.21; $t(34)=1.7$, $p=0.09$).

In order to follow-up the altered anger recognition in HD, we computed an anger classification accuracy score (ACA= difference between the perceived anger intensity for an angry face and the mean intensity for all nontarget emotions: disgust, fear, sadness, happiness, and surprise). The patients had a lower mean ACA (1.85 ± 2.30) than controls (4.26 ± 2.27 ; $t(34)=3.17$, $p=0.002$). Within-group t tests showed that for HD patients, the perceived anger and fear intensity did not differ for angry faces ($t(17)=1.7$, $p=0.21$), whereas the perceived intensity of sadness, disgust, surprise, and happiness in angry faces was lower than the target emotion (all $p<0.005$). The control group gave lower ratings for all nontarget emotions relative to the target emotion anger (all $p<0.001$).

Finally, in the HD group, the ACA correlated with the UHDRS independence score ($r=0.54$, $p=0.020$), the functional capacity score ($r=0.50$, $p=0.037$), and the functional assessment score ($r=0.52$, $p=0.027$) indicating that a higher rating accuracy was associated with better functioning.

VBM

First of all, we compared the total GMV ($M \pm SD$) of the cerebellum between patients and controls. The control group ($94.64 \text{ ml} \pm 7.53$) had more total GMV than the patients ($85.07 \text{ ml} \pm 13.30$; $t(34)=-2.66$; $p=0.012$). Several cerebellar subregions of HD patients showed a reduced GMV compared with controls (Fig. 1). The detailed results are displayed in Table 2. However, a few regions had a higher GMV in the clinical group, indicating a differential atrophy pattern.

More importantly, we correlated the GMV of the selected cerebellar subregions with the affect recognition intensity reported by the participants (Table 3; Figs. 2 and 3). In the patient group, lower anger ratings were correlated with reduced GMV in several vermal and lateral cerebellar areas. Also, the degree of anger misclassification was associated with reduced GMV of vermal lobule III and hemispheric lobule III. The intensity ratings for the other facial expressions showed no association with cerebellar volume in the patient group. For controls, only sadness recognition was associated with localized cerebellar volume (Table 3).

We also correlated measures of symptom severity (UHDRS scores) and symptom duration with GMV. We observed a positive correlation between the volume of vermal lobule VI and the UHDRS independence score (MNI (x , y , and z): 2, -75, and -11; $t=3.65$, $p=0.035$), indicating that patients with more GMV had a smaller impairment. The symptom duration (in months) showed a negative correlation with the GMV of hemispheric lobule X (MNI (32, -34, and -42; $t=3.35$, $p=0.033$)). Thus, the longer the clinical manifestation had lasted, the smaller the volume of this subregion.

Discussion

This VBM study focused on volumetric reductions of cerebellar subregions and their association with anger recognition deficits in patients suffering from HD. Our results showed that the decoding of human anger signals was most severely impaired in the patient group relative to other basic emotions. This finding is in good accordance with previous

research (e.g., [1, 18, 19]). As a new finding, we were able to demonstrate that HD patients not only perceived facial displays of anger as less intense, but that they additionally showed a lowered rating accuracy. HD patients gave similar intensity ratings of anger and fear for angry faces. They seemed to have mixed up the two emotions or were not able to differentiate between them. Moreover, the lowered anger identification accuracy correlated with disorder-related impairment (as indexed by the UHDRS independence, functional capacity, and functional assessment scores). Thus, the anger recognition deficit was associated with poorer social functioning in HD.

The observed anger recognition deficit (intensity and accuracy) was associated with cerebellar GMV loss in the HD group. Whereas the original study [4] had identified a correlation between hippocampal volume and anger recognition, the present analysis points to an additional cerebellar contribution to identification problems of this basic emotion. Patients' reduced anger rating intensity and recognition accuracy was mainly associated with bilateral GMV loss of the anterior lobe (lobes III–V) and vermal regions. The involvement of the vermis in anger processing is especially in line with previous studies (e.g., [10]). The vermis, together with other older cerebellar regions (e.g., the flocculonodular lobe), are referred to as limbic cerebellum [20]. Schmahmann [21] proposed that the vermis may be primarily responsible for “primitive” emotions such as fear of dangerous stimuli and anger towards aggressors.

It has to be noted that no other affect rating was correlated with GMV of the selected cerebellar subregions in the HD patients. Thus, there is a specific association which does not only mirror general atrophy of the cerebellum. This statement is also supported by the group comparison of GMV volume. Although HD patients showed volume reductions in several cerebellar subregions, there were also a few regions with greater GMV relative to the controls.

For the control group, the association between cerebellar volume and the chosen affective ratings was minor. This result can be traced back to the relatively small rating variance. Obviously, the task was not difficult for healthy individuals, which led to quite homogenous and accurate perceptions of displayed emotion intensities. The selective correlation between sadness ratings and GMV should only be discussed in the case of replication, as the peak was located at the border of the template.

Furthermore, we found a negative association between patients' disease duration and GMV of hemispheric lobule X (flocculonodular lobe). Our outcome confirms previous findings on HD that cerebellar neuronal loss occurs later in the clinical course of this disorder [22]. Possibly, in early HD specific cerebellar regions take over functions of earlier atrophied brain regions that are responsible for the decoding of facial emotions and associated functions. Our results also might suggest that within the cerebellum localized neuronal atrophy progresses at different speeds.

As a limitation of the present study, the small sample size has to be mentioned. Also, it seems unlikely that a volume reduction in circumscribed cerebellar areas is the cause of the observed anger recognition deficit. Rather, this loss of grey matter might influence the

information flow in a network concerned with affective processing. Therefore, it would be of interest for future studies to assess the structural connectivity (white matter pathways) of the cerebellum with other brain regions, e.g., with methods such as diffusion tensor imaging (DTI). Then, it would be possible to analyze whether differences in DTI indices between HD patients and healthy controls are correlated with the performance in the anger recognition task.

The asset of our study is the important clinical implication of our main finding. Anger recognition deficits could potentially serve as indicator of disease onset and progression in HD. Further, therapy programs should include affect training modules. For example, HD patients might profit from using additional strategies to decode the anger of other persons not only relying on their facial expressions but also on their gestures and affective prosody. It may be possible that such strategies help to compensate for the specific structural changes of the cerebellum by using alternative affective circuits of the brain.

Conclusions

The current study is, to the best of our knowledge, the first investigation assessing the specific association between cerebellar atrophy and deficient facial anger decoding in HD. Since the reduced intensity as well as accuracy of anger recognition was correlated with disease duration and functional impairment, affect training for HD patients is recommended.

Acknowledgments

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Fig. 1.
Cerebellar GMV differences between HD patients and controls

Fig. 2.
Positive correlation between GMV of cerebellar subregions and anger recognition intensity in HD patients

Fig. 3.

Scatterplot showing the correlation of anger recognition intensity scores and cerebellar volume of the hemispheric lobules IV and V

Table 1

Cerebellar regions of interest

Left/right anterior hemisphere	Left/right posterior hemisphere	Anterior vermis	Posterior vermis	Flocculonodular lobe
Lobule III	Lobule VI	Lobule I, II	Lobule VI	Left lobule X of cerebellar hemisphere (flocculus)
Lobules IV and V	Crus I	Lobule III	Lobule VII	Right lobule X of cerebellar hemisphere (flocculus)
	Crus II	Lobule IV and V	Lobule VIII	Lobule X of vermis (nodulus)
	Lobule VIIB		Lobule IX	
	Lobule VIII			
	Lobule IX

Table 2

Cerebellar grey matter volume differences between HD patients and controls

Region	<i>H</i>	<i>X</i>	<i>Y</i>	<i>Z</i>	<i>T</i>	<i>P</i> (FWE)	Cluster size
Patients<controls							
Hemispheric lobule III	L	-6	-36	-18	3.06	0.028	242
Hemispheric lobule III	R	8	-36	-18	3.54	0.013	303
Hemispheric lobules IV and V	L	-21	-52	-14	4.97	0.001	1,326
Hemispheric lobules IV and V	R	22	-49	-15	6.70	<0.001	1,303
Hemispheric lobule VI	L	-21	-55	-14	4.89	0.002	3,093
Hemispheric lobule VI	R	20	-66	-14	6.68	<0.001	3,081
Hemispheric lobule VIIIB	R	45	-60	-59	3.67	0.022	834
Hemispheric lobule VIII	L	-21	-57	-45	4.21	0.012	2,414
Hemispheric lobule VIII	R	22	-60	-47	4.04	0.021	3,271
Hemispheric lobule IX	L	-21	-52	-47	3.66	0.021	1,039
Hemispheric lobule IX	R	3	-54	-39	3.54	0.026	772
Vermal lobule X	L/R	0	-51	-35	3.28	0.013	58
Vermal lobules I and II	R	3	-36	-20	3.84	0.002	110
Vermal lobule III	R	6	-36	-17	3.69	0.007	247
Vermal lobule VIII	R	3	-60	-35	2.94	0.041	87
Vermal lobule IX	R	2	-54	-36	3.83	0.005	324
<i>Whole hemisphere</i>	L	-21	-52	-14	4.97	0.009	4,913
<i>Whole hemisphere</i>	R	22	-49	-15	6.7	<0.001	13,534
<i>Whole vermis</i>	R	3	-36	-20	3.84	0.032	357
Patients>controls							
Hemispheric lobule X	L	-22	-33	-41	4.66	0.001	317
Hemispheric lobule X	R	21	-34	-42	5.71	<0.001	280
Hemispheric lobule VIII	L	-26	-37	-44	4.18	0.013	100
Hemispheric lobule IX	L	-22	-42	-44	3.49	0.030	33
Vermal lobule VII	L/R	0	-79	-24	3.13	0.027	138
<i>Whole hemisphere</i>	L	-22	-33	-41	4.66	0.019	461
<i>Whole hemisphere</i>	R	21	-34	-42	5.71	0.002	366

Entries set in italics are exploratory tests; entries in normal text are region-of-interest tests

FWE family-wise error

Table 3

Positive correlations between grey matter volume of cerebellar subregions and affect recognition

Region	<i>H</i>	<i>X</i>	<i>Y</i>	<i>Z</i>	<i>T</i>	<i>P</i> (FWE)	Cluster size
Patients							
<i>Anger recognition/intensity</i>							
Hemispheric lobule III	L	-9	-34	-14	5.89	0.001	49
Hemispheric lobule III	R	12	-33	-12	5.19	0.002	96
Hemispheric lobules IV and V	L	-12	-31	-12	7.27	0.001	107
Hemispheric lobules IV and V	R	9	-40	-8	4.68	0.015	120
Hemispheric lobule IX	R	12	-40	-51	4.13	0.026	90
Vermal lobule X	R	4	-42	-39	3.47	0.021	11
Vermal lobule III	R	6	-39	-8	4.69	0.004	132
Vermal lobules IV and V	R	6	-42	-5	3.99	0.030	13
Vermal lobule VIII	L	-3	-64	-44	3.45	0.032	9
<i>Whole hemisphere</i>	L	-12	-31	-12	7.27	0.004	156
<i>Whole vermis</i>	R	6	-39	-8	4.69	0.028	145
<i>Anger recognition/accuracy</i>							
Hemispheric lobule III	L	-12	-30	-20	3.20	0.040	5
Hemispheric lobule III	R	12	-31	-20	3.72	0.023	48
Vermal lobule III	L	-3	-40	-3	3.14	0.047	4
Controls							
<i>Sadness recognition/intensity</i>							
Hemispheric crus I	R	57	-63	-26	6.91	0.002	568

Entries set in italics are exploratory tests; entries in normal text are region-of-interest tests

FWE family-wise error