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Archival Report

Impaired Recognition and Regulation of Disgust Is Associated with Distinct but Partially Overlapping Patterns of Decreased Gray Matter Volume in the Ventroanterior Insula

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ABSTRACT

BACKGROUND: The ventroanterior insula is implicated in the experience, expression, and recognition of disgust; however, whether this brain region is required for recognizing disgust or regulating disgusting behaviors remains unknown.

METHODS: We examined the brain correlates of the presence of disgusting behavior and impaired recognition of disgust using voxel-based morphometry in a sample of 305 patients with heterogeneous patterns of neurodegeneration. Permutation-based analyses were used to determine regions of decreased gray matter volume at a significance level $p <= .05$ corrected for family-wise error across the whole brain and within the insula.

RESULTS: Patients with behavioral variant frontotemporal dementia and semantic variant primary progressive aphasia were most likely to exhibit disgusting behaviors and were, on average, the most impaired at recognizing disgust in others. Imaging analysis revealed that patients who exhibited disgusting behaviors had significantly less gray matter volume bilaterally in the ventral anterior insula. A region of interest analysis restricted to behavioral variant frontotemporal dementia and semantic variant primary progressive aphasia patients alone confirmed this result. Moreover, impaired recognition of disgust was associated with decreased gray matter volume in the bilateral ventroanterior and ventral middle regions of the insula. There was an area of overlap in the bilateral anterior insula where decreased gray matter volume was associated with both the presence of disgusting behavior and impairments in recognizing disgust.

CONCLUSIONS: These findings suggest that regulating disgusting behaviors and recognizing disgust in others involve two partially overlapping neural systems within the insula. Moreover, the ventral anterior insula is required for both processes.

Keywords: Disgust, Emotion recognition, Frontotemporal dementia, Insula, Neurodegeneration, Voxel-based morphometry

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Disgust likely evolved from gustatory mechanisms that protect organisms from ingesting unsafe foods. Charles Darwin thought that disgust was elicited by "something revolting, primarily in relation to the sense of taste, as… perceived or imagined" (1). Disgust protects the body from infectious (e.g., fungi), inedible (e.g., rotten foods), unclean (e.g., feces), gory (e.g., body deformity), or morally offensive (e.g., incest) phenomena (2). Many sensory domains contribute to disgust, including gustation, olfaction, and interoception (3). The insula integrates information from these multiple sensory modalities and has been implicated in disgust processing (4). However, the functional and anatomical relationships between experiencing, expressing, and recognizing disgust remain unclear.

The anterior insula (AI) has been implicated in experiencing, expressing, and recognizing disgust. For example, the AI is activated in response to viewing disgusting scenes (e.g., cockroaches) (5,6) and smelling foul odorants (4). Furthermore, trait disgust sensitivity correlates with AI activation during viewing of disgusting images (6,7). Patients with obsessive-compulsive disorder who are preoccupied with contamination show abnormally increased AI activation when viewing disgusting scenes (8). When healthy subjects view disgusted faces, AI activity, as measured by functional magnetic resonance imaging and depth electrodes, increases significantly more than when viewing faces displaying other emotions (9–12). Additionally, a meta-analysis of 106 imaging studies found that the AI is significantly more activated in response to disgusting stimuli than to other emotional stimuli (13). Furthermore, direct electrical stimulation of the AI evokes unpleasant feelings in the throat (12), visceral changes associated with being sick (14), and

vomiting (15). Yet, prior studies have been limited to inter-rogation of healthy systems or investigations with epileptic patients, who have substantial neural reorganization that makes brain-behavior mapping problematic. Lesion studies offer a unique opportunity to delineate the clinical correlates of individuals in whom loss of disgust appears to drive behavioral abnormalities and to facilitate understanding of brain regions necessary for disgust processing.

Few studies have investigated the effects of insular lesions on disgust. One patient with a left-hemisphere infarction involving the insula had selective deficits in recognizing disgust in scenes and faces and decreased subjective reports of disgust, even though he could accurately recognize other emotions and could discuss the logical aspects of disgust without difficulty (16). Another patient with bilateral insular (but also temporal and frontal) lesions showed a general deficit in recognizing emotional facial expressions from static pictures, but when dynamic facial signals were used, he had selectively impaired disgust recognition (17). Both patients' lesions were not restricted to the insula, let alone the AI, allowing for the possibility that insular lesions were not solely responsible for their disgust-processing deficits. Selective disruption in disgust recognition has also been reported in patients with Huntington's disease, a neurodegenerative disease that affects the insula and striatum (18–20), and a single, small study of Huntington's disease patients directly linked these recognition deficits to AI atrophy (21). Additionally, selective deficits in recognition of disgust have been found in patients with Parkinson's disease (22). One large study found that vascular damage to right somatosensory cortices, including the insula, was associated with impaired ability to recognize emotions, though it did not investigate disgust specifically (23). Finally, we found that behavioral, physiological, and subjective responses were all reduced in behavioral variant frontotemporal dementia (bvFTD) patients compared with control subjects while watching a disgust-eliciting film (24). Although the AI is a common early target of neurodegeneration in bvFTD, this study did not report the anatomy of these deficits. In sum, existing links between insular lesions and disgust recognition deficits are imprecise, and there has been limited investigation into the effects of insular lesions on the experience of disgust or on the regulation of disgusting behavior.

We investigated the neural correlates of patients' increased tendencies to engage in disgusting behaviors and disrupted recognition of disgust in a large sample of patients with heterogeneous patterns of brain damage. We aimed to determine whether neurodegeneration of the insula results in loss of the experience of disgust as indexed by the emergence of behaviors that are typically prevented by feelings of disgust. We hypothesized that neurodegeneration of the insula, a key hub in visceromotor disgust reactivity and subjective emotional experience, would be associated with the presence of disgusting behaviors. We further hypothesized that the tendency to engage in disgusting behaviors and the inability to recognize disgust would correspond to distinct, but partially overlapping, patterns of AI atrophy.

METHODS AND MATERIALS

Assessment

We analyzed the charts of 305 consecutive patients in our research project between 1999 and 2010 diagnosed with one

of seven neurodegenerative diseases, as well as 25 asymptomatic first-degree relatives of bvFTD patients (FM). Patients were evaluated by a multidisciplinary team and had laboratory screening and brain magnetic resonance imaging. For neuropsychological analyses, data from a control group of 90 healthy older subjects (HS) (mean age: 69.4; SD: 7.0) were included for comparison. Neuropsychological testing was conducted on 287 of the 305 patients, all FM, and all HS and included the Clinical Dementia Rating Scale (CDR) and the Mini-Mental State Examination (MMSE), both measures of dementia severity (Table 1).

Disgusting Behaviors

Charts, including both patient and caregiver reports, as well as clinician observations, were reviewed by two raters for evidence of disgusting behaviors. Behaviors were recorded that fit into any of the categories of disgust derived from the Disgust Scale (25). Number or intensity of disgusting behaviors could not be accurately coded from retrospective chart review, so these variables were not quantified (i.e., a single episode of disgusting behavior was coded identically as multiple episodes). As not all patients with chart data had emotion recognition or neuroimaging data, subgroups with these data were analyzed to further explore the nature of these behavioral deficits. Studies of these rare neurodegenerative disorders are chronically underpowered. Therefore, we included all valid data to maximize power.

Emotion Recognition

One hundred forty-nine patients, 12 FM, and 90 HS were administered the Emotion Evaluation subtest of The Awareness of Social Inference Test (TASIT-EET) (26). Subjects watched 14 brief (20-second to 30-second) videos of actors displaying one of six emotions: disgust, happiness, sadness, fear, anger, surprise, or no emotion, using facial expressions, body language, and vocal tones. The perceived emotion was then selected from a list displayed on the screen without any time limit for responding. Importantly, patients with semantic variant primary progressive aphasia (svPPA) are not mute and are able to label basic emotions even late into the illness (27).

Behavioral Data Statistical Analysis

MMSE, CDR, and TASIT-EET score differences between patients with and without disgusting behaviors were analyzed using general linear models (Proc GLM) in SAS (SAS Institute Inc., Cary, North Carolina). To examine disgust-specific associations, we divided the TASIT-EET into two scores: the TASIT-EET disgust subscore and the sum of the subscores of the other emotions plus neutral.

Voxel-Based Morphometry

Magnetic resonance imaging scans of 231 of the 305 patients and all FM in the study were of sufficient quality for analysis within 6 months of disgust assessment. Voxel-based morphometry (VBM) is a technique for the detection of regional brain volume by voxel-wise comparison of combined gray and white matter volumes between groups of subjects. For the whole-brain analysis, the Anatomical Automatic Labeling atlas was used to name the regions with significantly less gray matter as

Table 1. Demographic and Clinical Parameters of Patients with Neurodegenerative Diseases and Healthy Subjects

	AD	bvFTD	bvFTD/ALS	ALS	CBS	nfPPA	PSP	svPPA	FM	HS	F Statistic (df)	p Value
	(n = 104)	(n = 79)	(n = 22)	(n = 6)	(n = 24)	(n = 18)	(n = 31)	(n = 21)	(n = 25)	(n = 90)		
Age	61.5 (8.1)[a]	60.7 (8.7)[a]	61.4 (8.5)[a]	52.5 (8.5)[a]	66.4 (7.3)[a]	67.7 (8.8)	66.9 (7.8)	62.8 (6.7)[a]	48.2 (12.4)[a]	69.4 (7.0)	18.8 (410,9)	<.001
Gender (M/F)	64/40	44/35	15/7	3/3	11/13	5/13	19/12	11/10	17/8	43/47	$\chi^2 = 13.7$	ns
MMSE	20.0 (7.3)[a]	20.7 (9.2)[a]	23.4 (7.6)[a]	29.4 (.9)	19.0 (8.4)[a]	23.1 (6.5)[a]	26.7 (2.4)	19.1 (8.2)[a]	29.4 (.7)	29.4 (.9)	18.5 (388,9)	<.001
CDR	1.0 (.5)[a]	1.6 (.8)[a]	1.3 (.9)[a]	.3 (.3)	1.0 (.8)[a]	.4 (.4)	1.0 (.6)[a]	.8 (.6)[a]	.1 (.3)	.0 (.1)	43.0 (375,9)	<.001
CDR-Box	5.4 (3.1)[a]	8.8 (3.8)[a]	7.1 (4.1)[a]	1.2 (1.7)	5.4 (4.0)[a]	2.8 (2.4)[a]	6.0 (3.3)[a]	4.6 (3.4)[a]	.4 (.9)	.0 (.2)	51.3 (375,9)	<.001
GDS	7.9 (5.6)[a]	6.4 (5.7)[a]	7.9 (4.9)[a]	6.5 (3.7)	6.9 (4.2)[a]	7.4 (6.5)[a]	13.3 (6.7)[a]	10.0 (5.9)[a]	5.1 (4.3)	2.4 (3.4)	13.0 (320,9)	<.001
With Disgusting Behavior	21.2%	68.4%[b]	22.7%	.0%	4.2%	22.2%	35.5%	42.9%[c]	4.0%	NA	$\chi^2 = 517.2$	<.001
TASIT	(n = 50)	(n = 41)	(n = 11)	(n = 0)	(n = 12)	(n = 9)	(n = 20)	(n = 6)	(n = 12)	(n = 90)		
Revolted (Maximum = 2)	1.1 (.1)[a]	.8 (.1)[a]	.6 (.2)[a]	NA	1.2 (.2)	1.0 (.2)	1.1 (.2)[a]	.7 (.3)[a]	1.2 (.2)	1.6 (.2)	8.8 (239,11)	<.001
Other Sum (Maximum = 2)	7.9 (.3)[a]	6.5 (.3)[a]	6.7 (.6)[a]	NA	8.7 (.6)	8.9 (.6)	8.1 (.4)[a]	7.2 (.8)[a]	8.5 (.6)	9.8 (.2)	12.4 (239,11)	<.001

For TASIT, the F statistic and p values are for overall diagnostic group differences controlling for age, gender, and MMSE. For other measures, no confounding covariates were included.

AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; bvFTD, behavioral variant frontotemporal dementia; CBS, corticobasal syndrome; CDR, Clinical Dementia Rating Scale; CDR-box, CDR-sum of boxes; F, female; FM, first-degree relatives of bvFTD patients; GDS, Geriatric Depression Scale; HS, healthy subjects; M, male; MMSE, Mini-Mental State Examination; NA, not applicable; nfPPA, nonfluent variant primary progressive aphasia; ns, nonsignificant; PSP, progressive supranuclear palsy; svPPA, semantic variant primary progressive aphasia; TASIT, The Awareness of Social Inference Test.

[a] Denotes p < .05 as compared with HS.

[b] Denotes a significantly (p < .05) higher proportion of patients with bvFTD have disgusting behaviors compared with patients with AD, bvFTD/ALS, ALS, CBS, nfPPA, PSP, and FM.

[c] Denotes a trend (p < .1) for a higher proportion of patients with svPPA having disgusting behaviors compared with FM.

determined by permutation-based thresholding ($p < .05$ familywise error rate [FWE]). For the region of interest (ROI) analysis, we generated masks of the bilateral insular cortices using MARINA (Bertram Walter Bender Institute of Neuro-imaging, University of Giessen, Germany) (28). The same permutation-based method was used to determine the $p < .05$ FWE threshold within these insular ROIs.

Main Effects Analyses

We performed three VBM analyses.

Analysis 1. To determine brain areas where less gray matter volume was associated with the presence of disgusting behavior, the presence of a disgusting behavior was the variable of interest. This whole-brain analysis across all subjects was followed by an ROI analysis only looking within two disorders with the highest number disgusting behaviors (bvFTD and svPPA) to investigate whether the same brain-behavior relationships also held true within diagnostic groups.

Analysis 2. To determine where decreased gray matter volume was associated with impaired disgust recognition, the Revolted subscore of TASIT-EET was the variable of interest.

Analysis 3. To determine where decreased gray matter volume was associated with impaired disgust recognition but not recognition of other emotions, we looked for voxel volumes that correlated with disgust recognition accuracy, controlling for recognition accuracy for all the other emotions plus neutral.

To account for the reduced power in this dysjunction analysis, we accepted a significance level at $p < .005$, uncorrected for FWE. Analyses 1 and 2 were considered significant only if they met a FWE threshold of $p < .05$. Age, gender, MMSE, total intracranial volume, and scanner type were entered as nuisance variables in all three analyses; scanner type was included, since a previous study showed that considering scanner type as a nuisance variable effectively accounted for variability introduced by multiple scanners in VBM (29).

Error Check-Linear Regression Comparison of Significant Peak Voxels

Regional atrophy in neurodegenerative disease is not randomly distributed across diagnostic categories. Instead, patterns of atrophy are similar within and, to some degree, across the categories, with groups of sometimes anatomically distant structures atrophying at a similar rate in each disease. As a result, main effects analyses using neurodegenerative disease patients are likely to demonstrate some degree of co-atrophy effects, in which areas of the brain unrelated to the behavior of interest will appear significant because they atrophy simultaneously with another region directly associated with the primary behavior of interest. Thus, to further isolate the independent contributions of each brain region identified in the main effects analyses, we performed linear regressions combining voxel values of each peak for each main effect analysis (for analysis 3, we only included significant peak voxels if they survived this error check in analysis 2). Voxel intensities were extracted from the smoothed, warped, modulated, gray plus white matter images of each subject at each peak voxel within the significant clusters in the main effects analysis. These voxel intensity values were then analyzed

together as predictors in linear regression analyses, including age, gender, MMSE, scanner type (1.5, 3, or 4T), and total intracranial volume as confounding covariates and the behavior of interest as the outcome variable (30).

Peak-Voxel Comparison

A meta-analysis by Kurth *et al.* (31) delineated 47 peak values in the insula involved in different domains such as emotion, empathy, interoception, and pain. To compare these peaks with peaks found in our study, we calculated the Euclidean distance of our insula peak voxels with the peak voxels reported in the meta-analysis. Kolmogorov-Smirnov tests at an alpha level of .05 revealed nonnormal distributions of the distances. As a result, we constructed kernel-smoothed density estimates for the 47 Euclidean distances to each peak voxel. Subsequently, we reported the smallest distances up to the fifth percentile.

For further methodological details, see Supplement 1.

RESULTS

Demographic and Behavioral Data

There were significant diagnostic group differences in age, CDR, CDR-sum of boxes, and Geriatric Depression Scale (32) scores (Table 1). Significantly more patients with bvFTD had disgusting behaviors (68.4%; Table 1) than other diagnostic groups except for svPPA. Furthermore, 42.9% of patients with svPPA and 21% of patients with Alzheimer's disease had disgusting behaviors. For examples of disgusting behaviors, see Supplement 1. For emotion recognition, bvFTD, svPPA, Alzheimer's disease, bvFTD/amyotrophic lateral sclerosis, and progressive supranuclear palsy patient groups were impaired at recognizing disgust and other emotions compared with HS. Subjects with disgusting behaviors were significantly more impaired at recognizing disgust and other emotions compared with patients without disgusting behaviors (Table 2). Subjects with disgusting behaviors were also more likely to have lower MMSE, CDR, and CDR-sum of boxes scores.

Main Effects Analyses

Analysis 1. Disgusting behaviors were associated with significantly less gray matter bilaterally in the ventral AI, left cingulate

cortex, and white matter tracts near the cingulate cortices ($p <$ .05, FWE) (Figure 1A; Table 3). To ensure that decreased gray matter volume was not simply due to the regional atrophy associated with bvFTD or svPPA, we performed ROI analyses of the insula with each group separately. We found that within both diagnostic groups, disgusting behaviors remained associated with reduced ventral AI volumes ($p <$ .05, FWE).

Analysis 2. Two clusters positively correlated with disgust recognition scores were identified in the left and right sides of the brain. Inside these clusters, there were peak voxels bilaterally in the ventral medial insula, amygdala, and temporal pole (Figure 1B).

Analysis 3. The clusters in the left and right ventral medial insula found in analysis 2 remained significant when controlling for the sum of the other TASIT-EET recognition scores. This highlights the importance of these regions in disgust recognition despite the decreased power obtained from controlling for recognition of several other emotions.

While comparing gray matter volumes related to disgusting behaviors and disgust recognition via a unified design matrix would be ideal, this was not possible due to the degree of nonoverlap between samples having the two data types. No HS had a chart review, as they did not have clinical charts available. Also, due to the expected high correlation between variance associated with disgusting behaviors and disgust recognition scores, this analysis would be underpowered given the smaller sample size. Thus, we represented each main effect in separate design matrices, making use of the fully powered datasets available to predict anatomic correlates and superimposed the resulting T-maps on a single template for interpretive purposes (Figure 1C).

Error Check

Linear regressions were performed on all peak values to remove variables with no independent relationship to the variable of interest. For analysis 1, peak voxels in the insula bilaterally remained significantly able to predict the presence of disgusting behaviors when entered into regression models with the other regions found to be significant in the main effect analysis. For analysis 2, the bilateral ventromedial insula and temporal poles remained significant independent predictors of disgust recognition (Table 3).

Table 2. Characteristics of Subjects with Neurodegenerative Diseases by Presence or Absence of Disgusting Behaviors

	Disgust ($n = 107$)	No Disgust ($n = 223$)	F Statistic (df)	p Value
Age	61.3 (9.1)	61.3 (9.9)	.0 (328,1)	ns
Gender (M/F)	66/41	123/100	$\chi^2 = 1.3$	ns
MMSE	19.6 (9.2)	23.1 (7.0)	14.1 (306,1)	<.001
CDR	1.5 (.7)	.8 (.7)	59.1 (294,1)	<.001
CDR-Box	8.3 (3.7)	4.6 (3.6)	64.7 (294,1)	<.001
GDS	8.0 (6.4)	7.8 (5.7)	.4 (239,1)	ns
TASIT	($n = 48$)	($n = 113$)		
Revolt (Maximum = 2)	.7 (.1)	1.0 (.1)	3.3 (156,4)	<.05
Other Sum (Maximum = 12)	6.5 (.3)	7.9 (.2)	5.02 (156,4)	<.001

CDR, Clinical Dementia Rating Scale; CDR-box, CDR-sum of boxes; F, female; GDS, Geriatric Depression Scale; M, male; MMSE, Mini-Mental State Examination; ns, nonsignificant; TASIT, The Awareness of Social Inference Test.
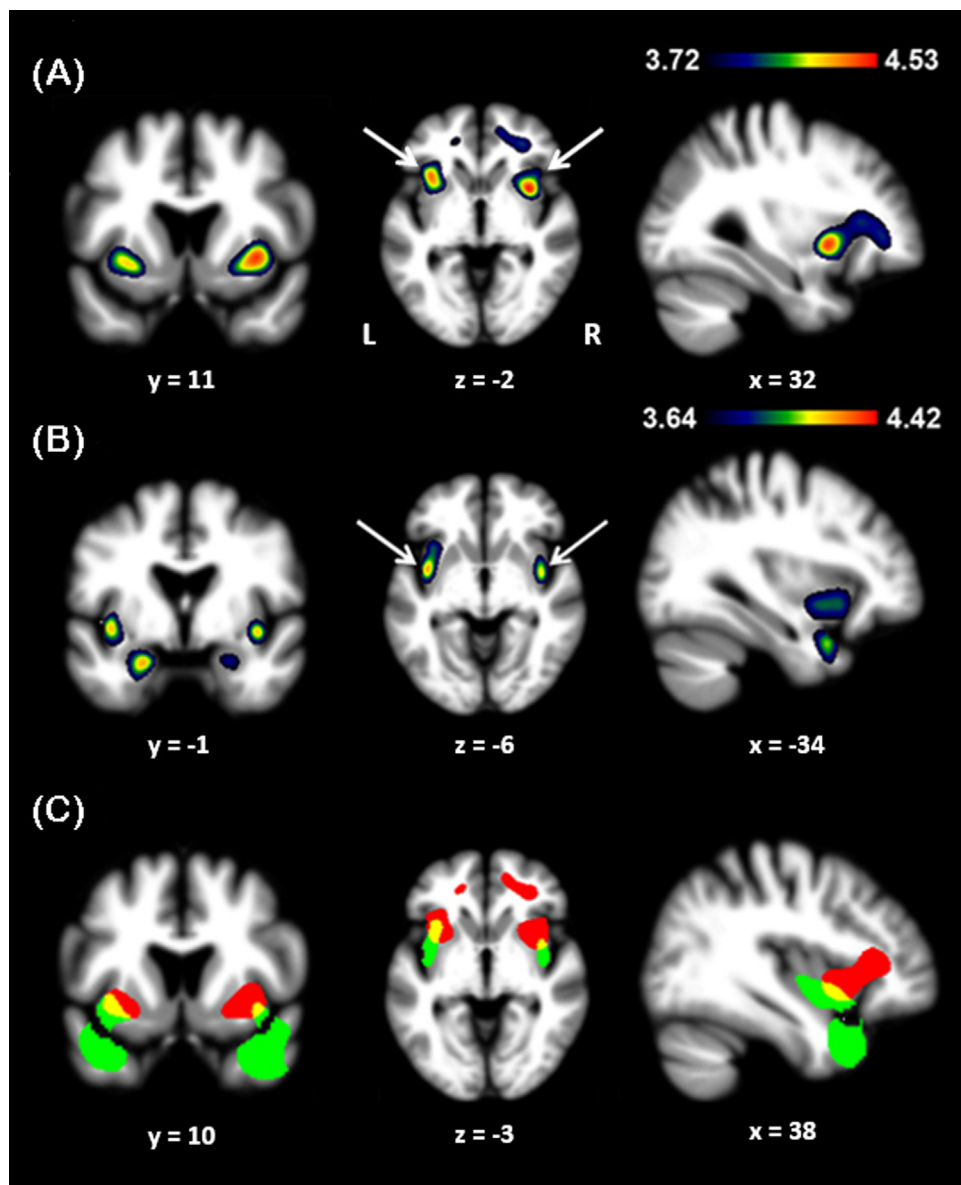
Figure 1. Sagittal, coronal, and axial sections representing the results of the main effects analyses, including **(A)** engagement in disgusting behaviors, **(B)** disgust recognition, and **(C)** the overlap in yellow between **(A)** in red and **(B)** in green. The regions indicated by the arrows in **(A)** also remained significant in a region of interest analysis of the insula restricted to patients with behavioral variant frontotemporal dementia and semantic variant primary progressive aphasia. The regions indicated by arrows in **(B)** remained significant after controlling for the recognition scores of the other emotions (happiness, sadness, fear, anger, surprise) and neutral. x, y, and z coordinates for each section are presented below the image, and the left-right orientation of the images is denoted by L and R.

Peak-Voxel Comparison

Peak voxels associated with disgusting behaviors were closer to areas associated with attention, gustation, and social functions as determined by the Kurth meta-analysis (31), while the voxels associated with deficits in disgust recognition were associated with insular areas associated with social and hedonic conditions (Table 4).

DISCUSSION

We found distinct patterns of decreased bilateral insula gray matter volume associated with an increased tendency to engage in disgusting behaviors and with impaired ability to recognize expressions of disgust in others. Decreased gray matter volume at the transition from frontal insula to the

dorsal AI, an area that is involved in integrating socioemotional with visceral information (31), was associated with both the presence of disgusting behaviors and impaired recognition of disgust. In addition to this shared region, the presence of disgusting behaviors was predominantly associated with decreased gray matter volume in more dorsal AI regions that have been previously associated with cognition (31). Furthermore, even when restricting our analysis to individuals with bvFTD or svPPA, this relationship remained significant. Deficits in recognizing disgust in others were predicted primarily by decreased gray matter volume in more ventral anterior and central insula regions involved in chemical sensory processing such as olfaction and gustation (31), as well as in bilateral amygdala and anterior temporal regions.

Table 3. VBM Summary of Main Effects and Regression Error Check

Anatomic Region	Cluster Size (mm^3)	x	y	z	t Score
(Presence of Disgusting Behaviors)					
R Ventroanterior Insula	11699	34	10	−2	4.44[a]
L Ventroanterior Insula	11699	−34	18	−6	4.50[a]
L Cingulate Cortex	11699	−12	42	4	3.79
R White Matter Tract	11699	30	42	0	4.06
R White Matter Tract	11699	38	30	10	4.03
(Disgust Recognition Scores)					
L Ventroanterior Insula	**5745**	**−38**	**2**	**−6**	**4.30[a]**
L Temporal Pole	5745	−42	12	−26	4.34[a]
L Amygdala	5745	−22	−2	−24	4.32
R Ventroanterior Insula	**3390**	**40**	**0**	**−6**	**4.28[a]**
R Temporal Pole	3390	40	16	−30	4.40[a]
R Amygdala	3390	24	−2	−20	3.84

Peak voxels are displayed where gray or white matter tissue density correlated with the presence of disgusting behaviors (analysis 1, lower t threshold −3.72 FWE, $p <$ .05) and disgust recognition scores as measured by the TASIT-EET revolted score (analysis 2, lower t threshold −3.64 FWE, $p <$ .05). The regions in bold remained significant after controlling for the recognition scores of the other emotions and neutral (analysis 3, lower t threshold −2.62, uncorrected $p <$ .005). NB. Given the nature of structural VBM, the output is typically comprised of large clusters of voxels above the correction threshold that encompass multiple neurologically distinct anatomical structures with multiple peaks. Our VBM results show that a single cluster extends through the frontal lobe, which is why cluster size refers to the same cluster across multiple structures.

FWE, familywise error rate; L, left; NB, nota bene; R, right; TASIT-EET, Emotion Evaluation subtest of The Awareness of Social Inference Test; VBM, voxel-based morphometry.

[a]Denotes regions that survived the error check.

While our study did not directly investigate the link between AI damage and alterations in the ability to experience disgust, this link can be logically inferred from patients' new willingness to spontaneously engage in behaviors that are considered disgusting and are seldom engaged in by healthy individuals. This link is also supported by our recent study demonstrating that FTD-spectrum patients have reduced subjective and physiological responses while watching disgusting videos (24). The overlapping anatomy between behavior and perception supports the hypothesis that the border area between the frontal and dorsal AI is required for disgust processing (31). This also suggests that the neural substrate allowing recognition of disgust expressions in others is partially involved in the prevention of behaving in ways others find disgusting. However, our results also suggest that additional, distinct,

nonoverlapping brain regions are required to successfully avoid engaging in disgusting behaviors oneself or to identify disgust in others.

The AI is implicated in both subjective feeling and recognition of emotion (33–35) and has been proposed as a neuroanatomic substrate for conscious awareness in general and for awareness of feeling disgusted in particular (36). The AI is activated when subjects inhale foul odorants or when they view others inhaling foul odorants (4). Similarly, when subjects view an actor becoming disgusted, read and imagine scenarios that involve disgust, or taste a bitter liquid and become disgusted themselves, the AI becomes activated (37). Furthermore, trait disgust sensitivity correlates with ventral AI activation in response to pictures of disgusting foods (6) and disgusting scenes (38). Taken together with the

Table 4. Relationships between Peak Voxels Identified in the Current Study and Those Identified by Kurth et al. (31) with Associated Domains

Peak Voxel	Kurth et al. (2010) Peak Voxel	Domain	Euclidean Distance
Disgusting Behavior			
(36, 10 ,0)	(39, 7 ,0)	Emotion	4.24
	(42, 13, −4)	Empathy	7.81
	(40, 12, −6)	Gustation	7.48
(−34, 18, −6)	(−33, 18, −5)	Attention	1.41
Impaired Recognition of Disgust			
(40, 0, −6)	(39, 7, 0)	Emotion	9.27
	(46, −6, −1)	Empathy	9.85
	(41, 2, 3)	Interoception	9.27
(−38, 2, −6)	(−39, 0, −4)	Somatosensation	3.00
	(−38, −4, 1)	Somatosensation	9.22

Peak voxels associated with disgusting behavior are closer to areas implicated in attention, gustation, and social functions, while the voxels associated with impaired recognition of disgust are associated with insular areas implicated in social and hedonic conditions.

electrophysiological and few lesion studies, these data support the hypothesis that the AI is involved in both subjective feelings and recognition of disgust.

Our results support the hypothesis that the AI underpins not only disgust perception but also the real-life behavioral response to disgusting stimuli. The insula is thought to be an integrative hub, receiving sensory, somesthetic, and interoceptive inputs from cortical areas including the medial temporal lobe and the amygdala, the basal ganglia, and the thalamus (39–43). The meta-analysis of 1768 functional neuroimaging experiments by Kurth et al. (31) revealed four functionally distinct regions in the human insula. Social-emotional tasks activated the anterior-ventral insula; sensorimotor tasks activated the mid-posterior insula; olfactogustatory stimuli activated the central insula; and cognitive tasks activated the anterior-dorsal insula. Furthermore, a conjunction analysis across these four domains revealed an area of functional overlap that includes the dorsal AI region identified in our study (Table 4). This convergence suggests that this dorsal AI region might provide functional integration between these systems and may explain why patients with damage to this region can neither recognize disgust in others nor properly regulate their own disgusting behavior, probably due to an inability to adequately feel disgusted. Additionally, because our results are derived from lesion-behavior mapping rather than patterns of functional activation in healthy individuals, our study suggests that this AI integrative region is not only functionally involved in, but is actually required for, normal disgust processing.

Outside of the key region of functional overlap in the insula, we found additional regions that correlated with either diminished perception of disgust or engagement in disgusting behavior. First, our patients' ability to recognize and correctly name a disgusted emotional expression correlated with decreased gray matter volume in the central and anterior insula, as well as in the amygdala and temporal poles bilaterally. The central insula peaks in our study were most near regions associated with somatosensory and chemical perception (taste and smell) according to the Kurth et al. (31) meta-analysis, suggesting that access to representations of sensory experiences may have played a role in the ability to discriminate among emotions and specifically to discern disgusted expressions in others. The role of the amygdala in emotional signal detection is well established (44,45), and the temporal regions found in our study have been widely associated with both socioemotional (right > left) and object-related (left > right) semantic knowledge (46,47), as well as the ability to access the lexical names of emotions (48–51).

Regional decreased gray matter volumes associated with patients' tendency to engage in disgusting behaviors were more dorsal and anterior to regions associated with impaired recognition of disgust, extending rostrally into the frontal lobe and including the anterior cingulate cortex (ACC). The functional domain determined by the Kurth et al. (31) meta-analysis most closely related to these AI peaks was attention, particularly on the left, followed by other aspects of cognitive processing (top-down error monitoring, working memory, speech, and language) and emotion processing (i.e., imagining or recalling emotion) on

the right. These findings are consistent with the known anterior to posterior functional gradient within the brain in which more posterior structures generally are involved in processing sensory inputs, while anterior structures, such as the ACC, are involved in behavioral response initiation and maintenance of task set (36,52). Functionally, the ACC is downstream of the sensory representations generated in the insula; thus, our patients' behavioral responses to disgusting stimuli were likely predicated upon their visceroceptive experience of the stimuli. Additionally, the ACC is the primary effector of autonomic response, and diminished output from this region may have dampened the individual's ability to stimulate the visceral responses associated with disgust.

Our analysis demonstrated that decreased gray matter volume in the central insula correlated with accuracy of disgust recognition over and above the recognition of other emotions. There is disagreement in the literature over whether there are dedicated neural circuits for specific emotions (e.g., fear or disgust) (45,53–59). Because the AI is involved in disgust, pain, and other emotion-related processes, a disgust-specific functional hypothesis for this brain region is untenable. This has led to the hypothesis that the AI may play a broader role in emotion processing by translating what we perceive into visceral responses that color our subjective feelings and that any disgust-specific relationships are due to disgust's relatively greater dependence on visceral feelings (60). This explanation is consistent with our findings that patients who exhibited disgusting behaviors had a deficit in recognizing disgust as a group, but not every subject who exhibited disgusting behaviors had a deficit in disgust recognition. One possible interpretation is that being able to translate disgusted faces into visceral feelings of disgust is helpful but not required for recognition of disgust in others. Indeed, our imaging and behavioral results suggest that some subjects may be able to recognize disgust in others using purely cognitive strategies without feeling the emotion themselves.

Clinical Implications

Patients with bvFTD and to a lesser extent svPPA were more likely to demonstrate disgusting behaviors than other diagnostic groups. BvFTD and svPPA are associated with dramatic behavioral symptoms including disinhibition, loss of insight and empathy, and socially inappropriate behavior (61,62). In bvFTD, these symptoms often are the first and sole symptoms leading to frequent diagnostic confusion with primary psychiatric disorders (63). While disgusting behaviors have frequently been described in bvFTD and svPPA (64) and decreased sensitivity to disgusting stimuli has been found in patients with bvFTD (24), this association has not previously been systematically quantified or localized to a specific anatomic substrate.

In the earliest clinical phases of bvFTD, atrophy can be seen within the AI, the ACC, and a network of subcortical and thalamic regions (65), a spatial pattern similar to the intrinsically connected salience network that processes diverse homeostatically relevant stimuli (64,66,67). In svPPA, initial symptoms are typically loss of knowledge of semantic meaning (68) and behavioral changes akin to those seen in bvFTD, depending upon the degree to which the disease has

advanced into the right hemisphere (27,68,69). This symptom progression pattern correlates well with the pattern of neural atrophy spread from temporal to frontal regions in svPPA (70). Thus, bvFTD and svPPA are associated with damage to the AI and the salience network, which likely explains the high prevalence of disgusting behaviors in these disorders (for further discussion, see Supplement 1).

Limitations

Our initial sample consisted of all patients with high-quality chart-based data. Only a subset of this sample had neuro-imaging or emotion recognition data, requiring us to perform subsample analyses to maximize power. Furthermore, there were discrepancies in cognitive impairment between diagnostic groups and between individuals with and without disgusting behaviors. This is a standard limitation in such observational studies of heterogeneous patient groups, and as a precaution, we have covaried all analyses using a measure of disease severity (MMSE). Disgusting behaviors were determined by chart review, raising the question of the reliability of the data. For example, disgusting behaviors might have been present that were unreported and subtle clinician bias may have been present. Furthermore, severity and frequency of disgusting behaviors could not be adequately assessed by chart review, raising the possibility of significant differences in severity between patient groups that went unmeasured. Cultural factors can also contribute to what is classified as disgusting, raising concern for cultural relativism. However, all of the behaviors classified as disgusting were new and distressing to the patient's family, suggesting that cultural factors could not solely explain our findings.

Additionally, because patients' sensory or subjective experiences of disgust were not directly measured, we do not have direct evidence that the disgusting behaviors demonstrated by our patients represent a failure to appropriately feel disgusted. Alternatively, disgusting behaviors may be due to more general disinhibition or impulsivity in spite of experiencing normal feelings of disgust. However, this explanation appears inadequate because disinhibition and impulsivity are common in multiple disorders, including Williams disease, suicidality, obesity, and substance abuse (71–76). Despite this, disgusting behaviors such as those found in the current study are rare in these other conditions and thus are unlikely to be simply due to general disinhibition or impulsivity. Additionally, we could not elucidate the factors that might contribute to disgusting behaviors. For example, loss of awareness of social conventions or of response inhibition could both contribute to disgusting behavior and these contributing factors could be disease-specific. Future studies should investigate whether AI lesions lead to decreased subjective and physiological responses to disgusting stimuli and should also investigate the specificity between AI lesions and disgust.

Conclusion

Ours is the first large-scale lesion study to demonstrate that disruption of partially overlapping neural circuits within the AI are associated with increased tendency to engage in disgusting behaviors and impaired ability to recognize disgust in others. These findings complement the extant literature linking disgust processing with the insula that have primarily used functional imaging techniques.

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