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

Supplemental Information

Supplementary Methods and Materials

Subjects and Clinical Assessment

A total of 305 patients and 25 asymptomatic family members (FM) were recruited from the University of California, San Francisco, Memory and Aging Center, a tertiary care dementia clinic and research program. Clinical diagnosis in both patients and FM was determined after a detailed clinical history and neurologic examination by a neurologist, a 1-hour neuropsychological battery by a neuropsychologist, laboratory screening, and 1.5 T brain MRI.

As part of this evaluation, all patients received semi-structured clinical interview with a neurologist trained to identify symptoms relevant to frontotemporal dementia (FTD). Caregivers underwent a semi-structured interview by a nurse focused on the patient's symptoms and behavior. Together, the patient and caregiver evaluations included screening for several disgust-related domains including specific questions regarding alterations in hygiene such as changes in attention to bathing, grooming, personal care, and excretion functions, changes in eating habits, presence of socially inappropriate behaviors such as loss of decorum, general behavioral disinhibition, changes in personality, and unusual collecting behavior. Clinical diagnosis was made after the interviews during a multidisciplinary consensus meeting. The Clinical Dementia Rating Scale (CDR), a measure of dementia severity, was completed for patients based upon interviews with their primary caregiver. Face-to-face neuropsychological testing included the Mini-Mental State Examination (MMSE) and the Geriatric Depression Scale REF. Sample characteristics are described in Table 1. Patients diagnosed with behavioral variant FTD (bvFTD) and semantic variant primary progressive aphasia (svPPA) met Neary criteria (1; 2), patients with Alzheimer disease (AD) met AD probable National Institute of Neurological and Communication Disorders/Alzheimer's Disease and Related Disorders Association criteria (3), and patients with MCI met the American Academy of Neurology criteria (4). All patients and family members signed an institutional review board-approved research consent form. An attempt was made to recruit all consecutively available patients for this study.

Ninety healthy control subjects were recruited through advertisements in local newspapers and recruitment talks at local senior community centers. Healthy subjects were required to have had a normal neurological examination, a CDR score of 0, and an MMSE score equal to or greater than 28/30. All subjects and, when applicable, their caregivers signed an institutional review board-approved research consent form to participate in this study.

Emotion Recognition

The “disgust face” has often been narrowly defined as engagement of the two muscle units, lip raise and nose wrinkle (AU9 and AU10). However, other facial movements including the gape are also important aspects of some forms of disgust and the lip raise and the nose wrinkle are not specific to only disgust (5; 6). The videos used in the current study avoid many of these issues because they show actors engaging both AU9 and 10 as well as other associated facial movements including the gape and expressions occur over time (~15 seconds) thus both muscle units engage variably over the course of stimuli presentation. Furthermore, emotional communication is also not limited to the face as the actors communicate their emotion with tone of voice and body movements.

MRI Scanning

MRI scans were obtained on a 1.5 T, 3 T, or 4 T Magnetom VISION system (Siemens, Iselin, NJ) equipped with a standard quadrature head coil. Structural MRI sequences included a volumetric magnetization prepared rapid gradient echo MRI (repetition time/echotime/inversion time = 10/4/300 milliseconds) to obtain T1-weighted images of the entire brain, 15° flip angle, coronal orientation perpendicular to the double spin echo sequence, 1.0 × 1.0 mm^2 in-plane resolution, and 1.5-mm slab thickness. Each MRI image was visually inspected and scans with significant motion artifact were excluded. Of the 248 patients and FM who received an MRI scan, 231 of the patients had a scan of sufficient quality to be used for the voxel-based morphometry (VBM) analysis.

Voxel-based Morphometry

The technique comprises an image processing step (spatial normalization, segmentation, modulation, and smoothing) followed by statistical analysis. Both stages were implemented in the SPM5 software package (www.fil.ion.ucl.ac.uk/spm) and DARTEL toolbox using standard procedures, with the exception that light clean-up was performed to remove voxels outside of the brain. The images were smoothed using an 8 mm full-width at half-maximum Gaussian

kernel. Regionally specific differences in gray and white matter volumes were assessed using the general linear model on the whole brain and the significance of each effect was determined by using the theory of Gaussian fields. After segmentation, scans with outlying intracranial, white or gray matter volumes were visually inspected, and those with significant motion artifact were excluded.

Statistical parametric maps were displayed as overlays on a control template, created by warping 50 native space whole-brain images of neurologically healthy older controls to the final DARTEL template and calculating the average of the warped brain images. For the whole brain analysis, the Anatomical Automatic Labeling atlas was used to name the regions with significantly less gray matter at a level of significance $p < 0.05$ corrected for family-wise error across the whole brain, as determined by permutation-based thresholding of the exact T-distribution of error with 1000 iterations (7).

Error Check-Linear Regression Comparison of Significant Peak Voxels

Due to, 1) the large number of inter-correlated predictors which reduced statistical power, and 2) the inability to take into account local cluster variance in this analysis, we used a conservative approach in which variables were considered significant at an inclusion threshold of $p < 0.10$ to ensure that brain regions showing at least a modest independent relationship to the outcome variable remained in the model. Because the regression relied on excluding variables of no value rather than including variables meeting a predetermined threshold, the $p < 0.10$ alpha value is actually more conservative, and is the preferred approach in Allen-Cady backwards regression analyses (8). Given that volume on one side of the brain is highly correlated with volume on the contralateral side, peak voxels located in the same brain region bilaterally were modeled separately by hemisphere. Any bilaterally represented brain region was considered to significantly predict behavior if it was significant in either unilateral regression model, and no further determination of laterality was attempted due to the high collinearity between bilateral brain structures.

Statistics

X^2 analyses followed by logistic regression were conducted to determine differences in the proportions of disgusting behaviors across neurodegenerative disease groups.

Disgusting Behaviors

Behaviors were recorded that fit into any of the categories of disgust derived from the Disgust Scale (9), including the following: (a) hygiene (e.g., does not wash for weeks), (b) food (e.g., eats rotten foods), (c) sex/interpersonal contact (e.g., incest), (d) body products (e.g., lack of concern regarding feces on clothing), and (e) animal (e.g., pets dead animals) (10). Behaviors were considered disgusting only if the behavior did not occur in healthy subjects and was of sufficient degree or frequency to be considered unusual (e.g., "leaves dirty dishes in the sink" was not considered disgusting). Behaviors that appeared to result from impulsivity or general social insensitivity without a disgusting element were not included (e.g., compulsive masturbation). Reviewers were blind to patients' final diagnosis and reviewed charts independently. The initial reviewers (JW and ES) independently agreed on the presence or absence of disgusting behaviors in all subjects except for six. For these six individuals, a third reviewer (KR), blinded to final diagnosis, independently reviewed the behaviors and the majority opinion was used.

For bvFTD, examples of disgusting behaviors include: "brings home rancid food", "soils himself with urine and feces", "he will pick up an unfinished bottle on the sidewalk and drink from it", "would pet dead animals", "she has taken to urinating on the carpet near her bed or occasionally in her bed or recliner", and "uses cloth shower curtain as toiler paper". For svPPA, examples of disgusting behaviors include: "his wife has to prompt him through an argument to change clothes", "he has also taken to urinating in a bottle and pouring it out in the front yard", and "he picked a cigarette off the floor of a public garage and smoked it". For AD, examples of disgusting behaviors include: "He will oftentimes eat moldy lemons and apple cores and drink sodas left by strangers", and "difficult to convince to take a shower", "stopped using toilet paper", and "made a physical advance towards his daughter".

Clinical Implications

A substantial number of patients with AD also exhibited disgusting behaviors, although proportionally less so than in bvFTD and svPPA. Patients with AD who exhibited disgusting behaviors had higher CDR and CDR-box scores than patients with AD without disgusting behaviors (data not shown). Given that these measures are less reliant on intact memory functions than the MMSE and instead are more sensitive in predicting functional decline in bvFTD (11–16), this suggests that patients with AD who exhibited disgusting behaviors demonstrated more severe behavioral abnormalities than other patients with AD. Taken together with our VBM finding that the presence of disgusting behaviors was associated with

decreased gray matter volume in the anterior insula, these results suggest that disgusting behaviors likely occur in some patients with AD in whom atrophy has spread frontally into the anterior insula beyond the more characteristic parieto-temporal cortices. Alternatively, general AD-related cognitive deficits could be associated with some behaviors that can be described as disgusting such as poor hygiene. Future studies should investigate these possibilities.

Supplemental References

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