Heightened emotional contagion in mild cognitive impairment and Alzheimer's disease is associated with temporal lobe degeneration

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Emotional changes are common in mild cognitive impairment (MCI) and Alzheimer's disease (AD). Intrinsic connectivity imaging studies suggest that default mode network degradation in AD is accompanied by the release of an emotion-relevant salience network. We investigated whether emotional contagion, an evolutionarily conserved affect-sharing mechanism, is higher in MCI and AD secondary to biological alterations in neural networks that support emotion. We measured emotional contagion in 237 participants (111 healthy controls, 62 patients with MCI, and 64 patients with AD) with the Interpersonal Reactivity Index Personal Distress subscale. Depressive symptoms were evaluated with the Geriatric Depression Scale. Participants underwent structural MRI, and voxel-based morphometry was used to relate whole-brain maps to emotional contagion. Analyses of covariance found significantly higher emotional contagion at each stage of disease progression [controls < MCI ($P < 0.01$) and MCI < AD ($P < 0.001$)]. Depressive symptoms were also higher in patients compared with controls [controls < MCI ($P < 0.01$) and controls < AD ($P < 0.0001$)]. Higher emotional contagion (but not depressive symptoms) was associated with smaller volume in right inferior, middle, and superior temporal gyri ($P_{FWE} < 0.05$); right temporal pole, anterior hippocampus, parahippocampal gyrus; and left middle temporal gyrus (all $P < 0.001$, uncorrected). These findings suggest that in MCI and AD, neurodegeneration of temporal lobe structures important for affective signal detection and emotion inhibition are associated with up-regulation of emotion-generating mechanisms. Emotional contagion, a quantifiable index of empathic reactivity that is present in other species, may be a useful tool with which to study emotional alterations in animal models of AD.

empathy | social behavior | simulation | affective resonance

Progressive deterioration of memory and other cognitive functions characterizes Alzheimer's disease (AD) (1) and its prodromal stage, mild cognitive impairment (MCI) (2). Deposition of beta-amyloid plaques and neurofibrillary tangles, the hallmark pathological changes in AD (3), is hypothesized to begin decades before the emergence of cognitive symptoms and subsequent functional decline (4). Emotional symptoms are also common and have been found in 35–85% of patients with MCI (5–7) and up to 75% of patients with AD (8), with depression and anxiety the most frequent symptoms seen. Individuals with MCI who have comorbid emotional complaints are more likely to progress to dementia than those without such symptoms (9–13). Taken together, these studies suggest that a clinical presentation that includes both cognitive decline and emotion dysregulation may point to an underlying AD process and that emotional symptoms themselves may portend or even exacerbate disease progression (9, 11, 14).

The medial temporal lobe is among the earliest sites of disease in MCI and AD (2, 15), and hippocampal atrophy is associated with worse episodic memory performance on standardized neuropsychological testing (16) and predicts conversion from MCI to AD (17). Similarly, functional imaging studies reveal diminished intrinsic connectivity, the degree to which distributed brain structures fluctuate in synchrony in the absence of a structured task, in the default mode network in MCI and AD (18, 19). The default mode network, which includes the medial temporal lobe, posterior cingulate cortex, precuneus, medial prefrontal cortex, and lateral temporoparietal cortex, supports various cognitive processes including episodic memory (20, 21), a cognitive function that is particularly vulnerable in AD. The hippocampus, although most prominently known for its role in cognitive processes such as episodic memory and spatial navigation (22, 23), is also implicated in emotion. The anterior hippocampus, in particular, has rich connections with the hypothalamus and amygdala (24, 25), which are structures important for emotion reactivity (26), and plays an inhibitory role in affective behavior via its projections to autonomic and endocrine emotion generation systems (24, 27, 28). As default mode network integrity deteriorates in AD, there is a concomitant connectivity increase within an emotion-relevant salience network (14). The salience network, with hubs in pregenual anterior cingulate cortex and frontoinsula and connections to emotion generators including the amygdala, hypothalamus, and brainstem (26), is hypothesized to be essential for survival-relevant affective stimuli detection and visceromotor emotion generation (29). Heightened salience network connectivity in healthy individuals has been associated with negative emotional reactivity and glucocorticoid levels (e.g., cortisol), a neuroendocrine index of the stress response (30). In AD, increased salience network connectivity relates to neuropsychiatric hyperactivity symptoms (e.g., agitation, irritability, aberrant motor behavior, disinhibition, and euphoria) (31). Neurodegeneration of medial temporal structures that support emotion inhibition (27, 28) and lateral temporal structures that promote socioemotional processes, including evaluation of faces (32), prosody (33), intention (34), and trustworthiness (35), may alter affective physiology, behavior, and experience in MCI and AD.

Emotional contagion is a basic affective mechanism by which an organism automatically synchronizes its physiological and behavioral states with those of another to promote affective simulation and altruistic behavior (e.g., helping) (36, 37). Via salience network structures and emotion generators (26), emotions can unfold without conscious awareness (36) and travel rapidly from organism to organism through the activation of visceromotor mirroring mechanisms (36–38). With deep ontogenetic and phylogenetic roots, emotional contagion is present in human infants, birds, rodents, and nonhuman primates, among others (38, 39). Human neonates display this rudimentary form of empathy and, from the first days of life, mimic facial expressions (40) and share others' distress, as demonstrated by studies in which

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infants cry more after hearing the cries of other infants (but not after hearing recordings of their own cries) (41). Rats are also attuned to the affective cues of others and exhibit emotional contagion via empathic distress vocalizations, physiological reactivity, and activity in emotion-relevant brain structures (e.g., anterior cingulate cortex and amygdala) when in the presence of another rat in distress. These reactions motivate prosocial helping behavior (42, 43). Thus, emotional contagion is a simple form of affect sharing that is at the core of more sophisticated forms of empathy and is not dependent on higher-order cognitive processing. An ecologically valid index of empathic reactivity, emotional contagion can be examined across species and in laboratory settings (39) and can be used to investigate the integrity of neurobiological systems that support emotion.

In the present study, we used the Personal Distress subscale of the Interpersonal Reactivity Index (IRI), a measure of emotional empathy that indexes the degree to which an individual experiences self-oriented feelings of anxiety and discomfort in negative social situations (44), to investigate whether there are gains in emotional contagion in individuals with MCI and AD (compared with healthy controls) and whether emotional contagion enhancement is associated with brain atrophy in temporal lobe structures with established roles in emotion. We conducted whole-brain voxel-based morphometry analyses using structural magnetic resonance images to relate emotional contagion to regions of brain atrophy in a large sample that included individuals with MCI, those with AD, and healthy controls. Our primary hypothesis was that neurodegeneration of the hippocampus in MCI and AD may lead to higher emotional contagion secondary to less efficient emotion inhibition and salience network release. Given that AD also affects lateral temporal lobe structures with known roles in socioemotional stimulus detection and comprehension (32, 34), we examined whether atrophy in these structures may interfere with affective signal detection and may also be associated with emotional contagion. We contrasted our results with levels of self-reported depressive symptoms to determine whether changes in emotional contagion reflected broader mood dysregulation.

Results

Emotional Measures. We found a main effect of diagnosis on emotional contagion [$F(2, 229) = 29.0$, $P < 0.001$] (Fig. 1). There was no main effect of sex [$F(2, 229) = 3.0$; $P < 0.09$], and the sex × diagnosis interaction was not significant [$F(2, 229) = 0.9$; $P = 0.42$]. Because there was no main effect or interaction with sex, we conducted the post hoc analyses after removing sex from the model. Tukey-Kramer pairwise comparisons revealed significantly higher emotional contagion in MCI compared with healthy controls ($P < 0.01$), in AD compared with MCI ($P < 0.001$), and in AD compared with healthy controls ($P < 0.0001$). Table 1 presents the clinical and demographic data for each diagnostic group.

We found a main effect of diagnosis on depressive symptoms [$F(2, 206) = 14.5$; $P < 0.001$] (Fig. 1). There was no main effect of sex [$F(2, 206) = 0.8$; $P = 0.39$], the sex × diagnosis interaction was not significant [$F(2, 206) = 2.2$; $P = 0.12$], and none of the covariates was significant. Because there was no main effect or interaction with sex, we again conducted the post hoc analyses after removing sex from the model. Tukey-Kramer pairwise comparisons found significantly higher depressive symptoms in MCI compared with healthy controls ($P < 0.01$) and in AD compared with healthy controls ($P < 0.0001$), but not in MCI compared with AD ($P = 0.10$).

Emotional contagion and depressive symptoms were significantly but very weakly correlated [$r(214) = 0.15$; $P < 0.05$], which suggests that these measures evaluate possibly related, yet largely distinct, aspects of emotional functioning.

Neuroimaging. Whole-brain voxel-based morphometry (VBM) analyses revealed that higher levels of emotional contagion were associated with smaller volume in bilateral middle temporal gyri and right inferior temporal gyrus, superior temporal gyrus, temporal pole, anterior hippocampus, and parahippocampal gyrus ($P < 0.001$, uncorrected). The only cluster that survived correction for multiple comparisons was one that included right inferior, middle, and superior temporal gyri ($P_{FWE} < 0.05$). See Table 2 for the T scores and significance levels for each region; Fig. 2 displays the statistical maps. Higher emotional contagion was not associated with larger volume in any brain regions. A follow-up region of interest analysis of bilateral amygdala revealed a small cluster in the right amygdala for which smaller volume was associated with higher emotional contagion [$T = 3.25$; Montreal Neurological Institute (MNI) peak, 26, −4, −24 ($P < 0.001$); cluster size, 80 mm^3 ($P < 0.001$, uncorrected)].

When we repeated the whole-brain analysis and also included depressive symptoms as an additional nuisance covariate, the results were largely the same as those from the first analysis. Smaller volume in a cluster that included right inferior, middle, and superior temporal gyri ($T = 5.12$; MNI peak, 70, −14, −8; cluster size, 4,152 mm^3; $P_{FWE} < 0.05$) and smaller volume in right temporal pole ($T = 3.81$; MNI peak, 50, 22, −28; cluster size, 1,408 mm^3; $P < 0.001$, uncorrected) and left middle temporal gyrus ($T = 4.22$; MNI peak, −58, −6, −16; size, 1,632 mm^3; $P < 0.001$, uncorrected) continued to be associated with higher emotional contagion. Two additional clusters in right angular gyrus ($T = 3.63$; MNI peak, −58, −6, −16; size, 576 mm^3; $P < 0.001$, uncorrected) and left inferior frontal gyrus ($T = 3.65$; MNI peak, −52, 30, 18; size, 232 mm^3; $P < 0.001$, uncorrected) were also associated with higher emotional contagion in this analysis. A small cluster in right anterior hippocampus continued to be associated with higher emotional contagion ($T = 3.2$; MNI peak, 26, −8, −16; cluster volume, 56 mm^3; $P < 0.001$, uncorrected).

In a whole-brain analysis that examined whether smaller brain volume was also associated with higher levels of depressive

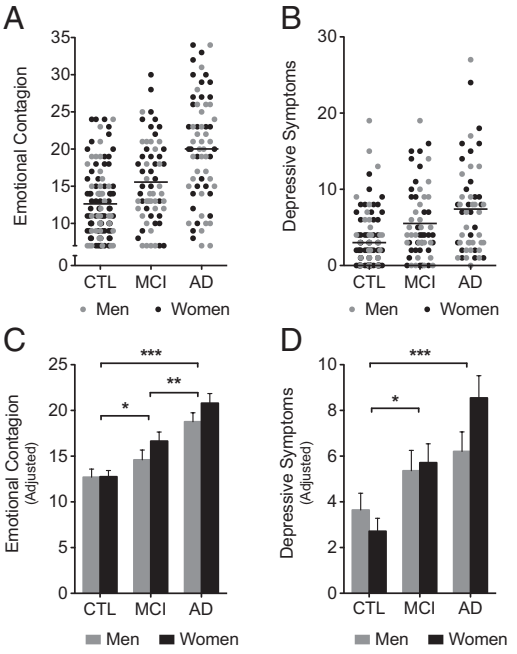

Fig. 1. Emotional contagion and depressive symptoms in MCI and AD are higher than in healthy controls (CTL). (*A*) Raw emotional contagion (IRI Personal Distress subscale) and (*B*) depressive symptom (GDS) scores for the CTL (n = 111), MCI (n = 62), and AD (n= 64) groups. Komogorov-Smirnov tests of normalcy indicated that there was a normal distribution of emotional contagion scores in MCI ($P > 0.05$) and AD ($P > 0.05$). (*C*) Emotional contagion and (*D*) depressive symptoms, adjusted for age and education and stratified by sex, were higher in patients than in healthy controls. Significant main effects of diagnosis are denoted by *$P < 0.01$, **$P < 0.001$, and ***$P < 0.0001$. Error bars represent SEMs.

Table 1. Demographic information for each diagnostic group

Clinical and demographic information	Controls	MCI	AD	Total
n	111	62	64	237
Sex, % female	63.1	53.2	46.9	56.1
Age, mean (SD)	69.1 (8.1)	69.4* (10.6)	64.4* (11.3)	67.9 (9.9)
Education, mean (SD)	16.9 (2.4)	17.0 (2.5)	15.9* (3.0)	16.7 (2.6)
Mini-Mental State Examination, mean (SD)	29.4 (0.7)	28.6 (1.5)	20.7*,† (5.2)	26.9 (4.7)
IRI Personal Distress, mean (SD)	12.6 (4.6)	15.6* (5.6)	20.0*,† (7.2)	15.4 (6.4)
GDS,‡ mean (SD)	3.0 (3.6)	5.5* (4.7)	7.4* (6.0)	4.8 (4.9)

Mini-Mental State Examination total scores, IRI Personal Distress subscale scores, and GDS total scores are presented for each diagnostic group.
*Different from controls at $P < 0.05$.
†Different from MCI at $P < 0.05$.
‡104 controls, 58 individuals with MCI, and 52 individuals with AD had available GDS data.

symptoms, no regions emerged as being significantly associated ($P < 0.001$, uncorrected).

Discussion

Emotional contagion, a basic affective mechanism by which emotions spread across individuals (37, 38), increased linearly in MCI and AD. There were significant gains in emotional contagion at each stage of disease progression (i.e., controls vs. MCI and MCI vs. AD). Sex did not influence emotional contagion in any diagnostic group. Consistent with previous studies, depressive symptoms were also higher in the patients, with the most notable escalation occurring between the control and MCI stages. Despite these gains, in all groups the mean level of endorsed mood symptoms remained in the range of minimal to mild depression. As expected, there was a weak correlation between emotional contagion and depressive symptoms, which suggests these measures primarily assess nonoverlapping components of emotional behavior. Thus, our findings of heightened emotional contagion in MCI and AD cannot be fully attributed to a more general mood disorder but, rather, likely reflect a more specific change in interpersonal emotional reactivity. Whole-brain structural MRI analyses revealed that smaller volume in primarily right-hemisphere temporal lobe structures was associated with greater emotional contagion. Tissue loss in these regions was not associated with higher depressive symptomatology.

Alteration in the neural systems that support emotion detection and emotion generation may accentuate emotional contagion in MCI and AD. At the most rigorous statistical thresholds, smaller right inferior, middle, and superior temporal gyri volume was associated with higher emotional contagion. At less stringent statistical thresholds, smaller volume in other predominantly right-hemisphere temporal lobe regions, including right temporal pole, right anterior hippocampus, and right parahippocampal gyrus, in addition to left middle temporal gyrus, was also associated with higher emotional contagion. These regions are important for a number of critical socioemotional abilities including processing of intention, theory of mind, faces, gaze, emotion, speech, sarcasm, and prosody (32–35, 45, 46). Atrophy in these areas in MCI and AD may interfere with comprehension of social nuances, especially in situations in which cognitive demands are high.

The association we found between hippocampal atrophy and higher emotional contagion is consistent with previous animal and human studies that have found an inhibitory role of the hippocampus in emotion. Smaller hippocampal volume has been associated with emotional reactivity and amygdala hyperactivity (28, 47) not only in AD (16, 48) but also in various neuropsychiatric disorders including major depressive disorder (49, 50), bipolar disorder (51, 52), and posttraumatic stress disorder (53, 54), among others. The hippocampus, which is densely populated with glucocorticoid receptors, is hypothesized to inhibit emotional responses to stressful stimuli via negative feedback of the hypothalamic-pituitary-adrenal axis (55). Chronic negative emotional reactivity and its accompanying autonomic-neuroendocrine cascade potentiate amygdala-dependent behavior [e.g., anxiety-like behavior (56), aggression (57), and fear conditioning (58)] by inducing reorganization of medial temporal circuitry (i.e., increased dendritic branching in the amygdala and simplification of dendritic branching in the hippocampus) (56, 59, 60). Although most studies suggest that heightened emotional reactivity causes hippocampal simplification and amygdalar elaboration at the neuronal level (59), there is evidence from human (61) and animal (62, 63) studies that smaller hippocampal volume at baseline and laboratory-induced hippocampal lesions can precede the behavioral manifestations of hyperemotionality. Rats with hippocampal lesions, for example, exhibit behavioral changes suggestive of hyper-reactivity; are more responsive to mild stressors, including foot-shock (63) and cage relocation (62); and have increased glucocorticoid responding to aversive events (64, 65). In humans harboring an underlying AD process, heightened emotional reactivity may exacerbate disease progression

Table 2. Volume loss in predominantly right-hemisphere temporal regions is associated with higher levels of emotional contagion (cluster volume >150 mm^3)

Anatomical region	Cluster volume (mm^3)	*x*	*y*	*z*	Maximum *T*-score
Right middle temporal gyrus	6,472	68	−12	−10	5.10*
Right inferior temporal gyrus	†				
Right superior temporal gyrus	†				
Left middle temporal gyrus	2,360	−58	−6	−16	4.38
Right temporal pole	1,608	50	22	−28	3.81
Right anterior hippocampus	296	26	−8	−18	3.36
Right parahippocampal gyrus	†				

Montreal Neurological Institute coordinates (*x*, *y*, *z*) given for maximum *T*-score for each cluster. All results are significant at $P < 0.001$, uncorrected.
*Results significant at $P_{FWE} < 0.05$.
†Regions that were included in the cluster immediately above.

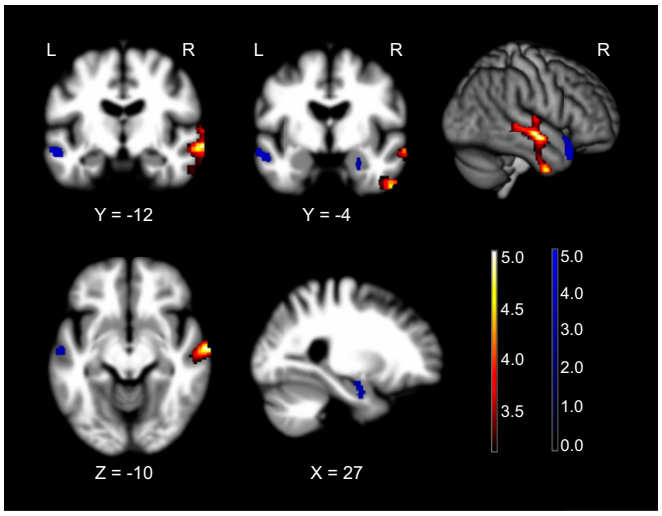

Fig. 2. *T*-score maps of brain areas for which smaller volume is associated with higher emotional contagion (IRI Personal Distress subscale score) when controlling for age, education, sex, diagnosis, field strength, and total intracranial volume (n = 237). Smaller volume in right inferior, middle temporal, and superior temporal gyri was associated with higher emotional contagion after correction for type 1 error ($P_{FWE} < 0.05$). At less stringent statistical thresholds, smaller volume in left middle temporal gyrus, right temporal pole, right anterior hippocampus, and right parahippocampal gyrus were also associated with higher emotional contagion ($P < 0.001$, uncorrected). Color bars represent T scores (hot, $P_{FWE} < 0.05$ according to study-specific permutation analysis; blue, $P < 0.001$, uncorrected; $T > 3.13$ and cluster size > 150 mm^3). Results are overlaid on a DARTEL-derived template of 50 older healthy controls.

through a positive feedback loop in which the autonomic-neuroendocrine cascade further potentiates hippocampal degeneration and salience network hyperexcitability in some individuals.

Volume change in predominantly right-hemisphere temporal lobe regions was associated with emotional contagion, a finding that is consistent with theories that emphasize the role of the right hemisphere in emotion (66). However, our results suggest that neurodegeneration of distinct right temporal lobe regions may have different influences on emotion. In MCI and AD, early neurodegeneration of the right hippocampus may result in dysregulation of emotional contagion through loss of negative feedback of emotional reactivity secondary to release of emotion-generating structures in the salience network (14) or loss of glucocorticoid receptors (55) or interneurons (65, 67) that help to regulate visceromotor affective responsivity. As atrophy progresses to temporal structures that are important for socioemotional stimulus detection (e.g., temporal pole and lateral superior, middle, and inferior temporal cortex) (68), degradation of social-cognitive resources may increase anxiety because patients are less accurate in their appraisal of socioemotional stimuli. Although formal studies of emotion recognition have found both preservation (69, 70) and impairment (71, 72) in AD, performance seems to be dependent, in part, on task difficulty and severity of cognitive impairment (71). Similar to theories of emotion that propose that affective stimuli can activate the amygdala via direct (i.e., a rapid pathway by which stimuli activate the amygdala via projections from the thalamus) or indirect (i.e., a slower pathway by which stimuli are first processed by cortex before activating the amygdala) routes (73), individuals with MCI and AD may retain their social graces and interpersonal relationships by relying on preserved automatic emotion-sharing mechanisms (i.e., direct pathway) despite degeneration of cortical systems important for more sophisticated socioemotional stimulus processing (i.e., indirect pathway).

In this study, we used the Personal Distress subscale of the IRI, a valid index of emotional contagion (74). Although emotional contagion may motivate prosocial behaviors that are essential for survival in social groups (36), if too strong, contagion may overwhelm the observer and interfere with helping and consolation (44). Although Personal Distress scores are a proxy measure of emotional contagion, and higher scores may in part reflect generally heightened anxiety and lack of emotional control (75) in the patient groups, our findings suggest that in MCI and AD there may be particular dysregulation of emotional reactivity in social contexts. Other psychological factors, including decreased self-efficacy and waning autonomy, may also contribute to patients' hyper-reactivity in stressful social situations.

There are some limitations to this study that should be considered. First, MCI is a heterogeneous syndrome, and although most individuals with MCI show neuropathological changes that are consistent with an underlying AD process (76), not all will progress to develop dementia, and some may have a neurodegenerative disease other than AD. Thus, our assumption that the MCI group represents an intermediate stage between the cognitive health and AD may be flawed, although it is likely that a subset, if not the majority, of patients in the MCI group have AD pathology.

Second, we found higher levels of depressive symptoms in MCI and AD than in healthy controls, a finding that is consistent with previous studies (5–7). Given that the mean level of endorsed mood symptoms was in the range of minimal depression for all diagnostic groups, this may have affected our ability to detect a relationship between brain volume loss and depressive symptomatology. It is also possible that by using a more specific measure of affective functioning (emotional contagion, which was based on informant observation rather than participants' self-reported symptoms), we were able to detect associations with specific patterns of brain atrophy.

Third, by using a structural neuroimaging technique, we did not detect positive associations (which here would reflect either less tissue loss or even possible growth) between emotional contagion and brain volume in our sample. We did not find evidence that larger volume in any salience network structures (e.g., anterior cingulate cortex or frontoinsula) was associated with higher emotional contagion. Rather, in a region of interest analysis, we found evidence that smaller volume in the right amygdala, a structure important for emotional reactivity, was also associated with higher emotional contagion. Although atrophy in salience network structures, including the amygdala, is common even early in AD, relative amygdala preservation has been associated with higher levels of anxiety and irritability (77), and there is heightened amygdala activation to faces in AD even when controlling for volume loss (48). Our findings, together with previous studies, suggest that higher salience network activation levels and stronger connectivity strength, rather than increased volume, may be a more sensitive indicator of emotional upregulation in this disease. Future work that uses other methods, such as functional neuroimaging, will be important to better understanding how specific network enhancement relates to heightened emotional contagion.

Heightened emotional contagion in MCI and AD reflects a biological change in the neural systems that support and inhibit emotion. We found a linear increase in emotional contagion, an evolutionarily conserved affect mechanism by which others' emotions resonate in an observer, in MCI and AD that was associated with atrophy in predominantly right-hemisphere temporal lobe regions with known roles in emotion detection and generation. In MCI and AD, relative preservation (or hyperconnectivity) (14) among salience network and emotion-generating systems may result in intensification of automatic affect-sharing, and gains in emotional contagion may lead to enhanced interpersonal connections and warmth despite deterioration of regions that support higher-order social-cognitive appraisal processes. Emotional contagion may be a useful mechanism by which to measure affective change in animal models of AD because it is an ecologically valid index of empathic reactivity that presents in other species and can be elicited in laboratory settings.

Materials and Methods

Participants. Two hundred thirty-seven participants (111 healthy controls, 62 individuals with MCI, and 64 individuals with AD) participated in the present study. All participants gave their informed consent for participation in the study. All procedures were approved by the Committee on Human Research at the University of California, San Francisco. All participants underwent a multidisciplinary diagnostic evaluation that included a neurological examination, neuropsychological testing, laboratory studies, and structural MRI. Healthy controls were recruited from advertisements and were free of current or previous neurological or psychiatric disorders. MCI was diagnosed according to modified diagnostic criteria (78) and included amnestic, executive, and multidomain MCI because individuals who are younger and are in the early stages of AD may have primary deficits in cognitive domains other than memory (79). AD was diagnosed according to standard research criteria (1). The Mini-Mental State Examination (80) was given to all participants to screen for cognitive dysfunction. See *SI Materials and Methods* for more details about the diagnostic criteria.

Emotional Measures. ***Emotional contagion.*** Informants completed the IRI and rated participants on their current behavior. Informant ratings of personality and behavior in patients with dementia have been demonstrated to be a reliable measure of functioning (81). The IRI is a psychometrically robust, multidimensional measure that is composed of four subscales that evaluate distinct components of empathy (44, 75). Our measure of emotional contagion was the Personal Distress subscale (scores range from 7 to 35, with higher scores reflecting greater emotional contagion), which measures the degree to which individuals experience anxiety and discomfort when they are exposed to the negative emotions of others (e.g., "Being in a tense emotional situation scares him/her"). Informants rated participants on each item on a scale of 1 (does not describe participant well) to 5 (describes participant very well).

Depressive symptoms. As a comparison measure, participants completed the Geriatric Depression Scale (GDS) (82). Participants were asked to report on their mood over the last 2 wk by responding yes or no to a series of questions (scores from 0 to 30, with higher scores reflecting greater levels of depression). The GDS classifies depressive symptoms as mild (0–10 points), moderate (11–20 points), or severe (21–30 points).

Analyses. The groups differed significantly in age [$F(2,237) = 5.74$; $P < 0.01$] and education [$F(2,237) = 3.91$; $P < 0.05$]. Thus, we adjusted for these variables in all analyses. The groups did not differ in their proportions of men and women [$\chi^2(2, n = 237) = 4.61$; $P = 0.10$]. However, because sex can influence emotion and empathy (83–85), we examined sex as a factor in our analyses. See Table 1 for means and SDs of these demographic variables.

We conducted separate 2 (sex: men, women) × 3 (diagnosis: control, MCI, AD) analyses of covariance (controlling for age and education) on emotional contagion and depressive symptoms. Post hoc Tukey-Kramer analyses were run to examine pairwise differences while correcting for multiple comparisons. To determine the degree to which emotional contagion and depressive symptoms measured the same underlying construct, we also conducted bivariate correlations between these two measures.

Neuroimaging. Participants underwent 1.5-T, 3-T, or 4-T research-quality structural MRI within 5 mo of completing the IRI, as described in *SI Materials and Methods*. Structural neuroimaging analyses using images collected across different modes of hardware have shown that the downstream effects of using images collected across different modes of hardware are minimal (86) and, thus, are unlikely to cause artifacts at the level of strict statistical thresholds.

Preprocessing. Structural T1 images were visually inspected for movement artifact; corrected for bias field; segmented into gray matter, white matter, and cerebrospinal fluid; and spatially normalized to MNI space (87), using statistical parametric mapping (SPM)5 (88). The diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL) toolbox was used to warp each participant's image to a template created from 50 additional older healthy control participants to optimize intersubject registration (89). Gray and white matter maps were then summed, and these images were smoothed with an 8-mm full-width at half-maximum Gaussian kernel. See *SI Materials and Methods* for more details about the preprocessing.

Analyses. We conducted whole-brain VBM analyses to correlate emotional contagion with combined gray/white matter structural maps. Results were considered significant at $P < 0.001$, uncorrected. One thousand permutation analyses using combined peak and extent thresholds were run to derive a study-specific error distribution to determine the one-tailed T threshold for multiple comparisons correction at $P_{FWE} < 0.05$ (90). Permutation analysis is a resampling approach to significance testing by which a test statistic is compared with the null distribution derived from the present study's data set, and thus is an accurate representation of type 1 error at $P < 0.05$ across the entire brain (91). In the VBM analyses, we included age, education, sex, diagnosis (0 = control, 1 = MCI, and 2 = AD to account for disease progression), field strength, and total intracranial volume (to account for individual differences in head size). We next performed two follow-up analyses to further explore the neural correlates of emotional contagion. First, we repeated our first analysis but restricted our search to bilateral amygdala to determine whether we could detect an association between emotional contagion and amygdala volume. Second, we conducted an additional whole-brain analysis of emotional contagion, but here also included GDS total score as a covariate (age, education, sex, diagnosis, field strength, and total intracranial volume were also included, as in the first analysis). Finally, we conducted a whole-brain analysis using depressive symptoms (i.e., GDS total score) as our independent variable of interest (age, education, sex, diagnosis, field strength, and total intracranial volume were included as nuisance covariates as described earlier) to determine whether emotional contagion and depressive symptoms were related to atrophy in overlapping neural systems.

Images were overlaid with MRIcron (http://www.mccauslandcenter.sc.edu/CRNL/) on an average brain based on the gray and white matter templates used for DARTEL warping.

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