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The Neural Bases of Interoceptive Encoding and Recall in Healthy and Depressed Adults.

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Abstract

Background—Theoretical models assert that the brain's interoceptive network links external stimuli with their interoceptive consequences, thereby supporting later recall of these associations to guide the selection of healthy behaviors. If these accounts are correct, previously reported interoceptive abnormalities in major depressive disorder (MDD) should lead to altered recall of associations between external stimuli and their interoceptive (somatic) consequences. To date, the processes underlying interoceptive recall have never been experimentally investigated.

Methods—We designed and implemented the Interoceptive Encoding and Recall (IER) task to compare interoceptive and exteroceptive recall among MDD (n=24) and healthy comparison subjects (n=21). During the encoding phase, subjects learned to pair neutral visual cues (geometric shapes) with aversive interoceptive and exteroceptive stimuli. Later, while undergoing fMRI, subjects were prompted to recall the stimulus associated with each shape.

Results—Interoceptive recall, relative to exteroceptive recall, was associated with bilateral mid-to-posterior insula activation. Relative to the healthy controls, depressed participants exhibited marked hypo-activation of the right dorsal mid-insula during interoceptive recall.

Conclusions—In non-depressed subjects, simply recalling a stimulus associated with a previous interoceptive challenge activated a key region in the brain's interoceptive network. Although previous research has linked MDD with aberrant processing of interoceptive stimuli, the current study is the first to demonstrate that individuals with MDD exhibit decreased insula activity while recalling interoceptive *memories*. It is possible that insula hypo-activation during interoceptive

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recall may affect the representation of prior interoceptive experiences in ways that contribute to depressive symptomatology and the relationship between depression and systemic health.

Keywords

Interoception; insula; memory; learning; depression; fMRI

Introduction

Major depressive disorder (MDD) affects more than 300 million individuals worldwide and is the leading cause of years lost to disability in the United States (1). The increasing prevalence of MDD results in marked economic and societal loss, with MDD-related work absence and health care utilization costing in excess of 200 billion dollars per year (2). This impact is driven in great part by the detrimental effect of depression on systemic health. In recent years, it has become clear that an important construct linking depression with systemic body functions is *interoception* – the perception and integration by the brain of primarily vagal visceral autonomic, metabolic, and immune signals from the body.

Although a host of regions in the brainstem and cortex are implicated in interoception, the insula has emerged as a key hub in the neurocircuitry underlying perceptual representations of body signals (3), as well as the synthesis of this information with other aspects of emotion and cognition represented in brain regions to which the insula is strongly connected (4–7). This is significant, as there exists a growing body of literature demonstrating that depression is associated with both underlying insula pathology (8–15), and altered interoception (12, 14, 16–22). Neuroimaging research on depression and interoception has demonstrated aberrant activity in the dorsal mid-insular cortex (12, 14), a region involved in the primary representation of visceral autonomic, metabolic, and immune signals, as well as the integration of these homeostatic signals with emotion and cognition (5, 23–25). For example, individuals with MDD demonstrate altered insula activity during thermal pain (26). Likewise, individuals with MDD exhibit decreased activity in the dorsal mid-insula during interoceptive attention to naturally-occurring sensations from the heart, bladder, and stomach (12), and the activity of this region during attention to the heart is negatively correlated with depression severity (12). Relatedly, depression severity is positively correlated with resting state functional connectivity between the insula and other regions that have been implicated in depression, including the amygdala, subgenual anterior cingulate, and striatum (12). All of these lines of evidence point to altered interoceptive processing in individuals with MDD.

Although impairments of interoceptive attention and perception may contribute to the decreased physical and mental health of depressed individuals, the findings described above may also have significant implications for how depressed individuals remember and represent previous experiences, and particularly, how these memories inform their ongoing decisions. Various theoretical accounts (e.g., (27, 28) have proposed that the brain's interoceptive circuitry actively monitors the state of the body, associating external stimuli with their attendant autonomic and endocrine consequences. Later, these associations can be recalled to help the selection of behaviors that minimize interoceptive distress and maintain

homeostasis (27). By these accounts, the insula serves not only an ongoing afferent monitoring function, but a mnemonic one.

Based on the evidence of altered brain-body signaling in MDD, it has been asserted that depression is associated with ‘noisy’ interoceptive representations (29), possibly resulting from a progressive decoupling of afferent interoceptive input from the body and the brain’s predictions about the body’s expected state (leading to interoceptive prediction error signals; for example see (27). If this is correct, then the pairing of external stimuli with their somatic consequences may also become impaired. This may have significant clinical implications: the pairing of external stimuli with unreliable interoceptive representations may cause a person with MDD to both perceive and conceive of the world as an unpredictable place. This in turn may motivate withdrawal behaviors (29), including symptoms such as appetite loss (30), social isolation (31), and anhedonia (32).

Unfortunately, to date, scholarship on interoceptive memory has been largely theoretical. There exists virtually no experimental research on the neural basis of acquiring and recollecting interoceptive associations with exteroceptive stimuli. To this end, we designed a novel paradigm and examined the process by which interoceptive associations are learned and later recalled in individuals with MDD and healthy comparison subjects. Our research participants completed a task we call the Interoceptive Encoding and Recall (IER) paradigm, during which they formed associations between neutral external stimuli (abstract geometric shapes) and either aversive exteroceptive stimuli (unpleasant screams) or aversive interoceptive stimuli (inspiratory breathing loads). Later, while undergoing fMRI scanning, participants performed an incidental (i.e., unexpected) recall task, during which they were presented with the geometric symbols used during encoding and prompted to recall the intensity of the associated interoceptive or exteroceptive stimulus (breathing load or scream).

If previously offered theoretical accounts of interoception are correct (27–29), then cued recollection of the breathing loads in the IER task, prompted by the presentation of the abstract geometric symbols that had previously been paired with breathing loads, should result in insular cortex activation in healthy control subjects. In contrast, because depression is associated with altered interoceptive perception and thus (according to theory) corrupted formation of interoceptive associations, we expect that depressed subjects will exhibit decreased insula activity during interoceptive recall, and that this will likely affect their recalled perceptions of the interoceptive stimuli.

Methods and Materials

Subject Recruitment and Assessment

Twenty-three healthy control (HC) subjects and 29 unmedicated subjects with a primary diagnosis of major depressive disorder (MDD) were recruited from the community and found to be eligible for the study. Two HC subjects and five MDD subjects were excluded from the study due to motion, an excess of censored imaging data, and/or imaging artifact. A resulting 21 HC (12 female) subjects and 24 MDD (15 female) subjects between the ages of 18 and 51 completed the IER paradigm. All participants provided informed consent, and all procedures were approved by the Western Institutional Review Board. None of the

participants in either the HC or MDD groups were taking any psychotropic medications at the time of the study. Exclusion criteria included a history of cardiac or respiratory conditions, use of psychotropic medication in the past six weeks, current pregnancy or breast-feeding, left-handedness, body mass index less than 18.5 kg/m² or greater than 40 kg/m², inability to tolerate MRI, or the presence of psychotic or substance use disorders.

All subjects were assessed for psychopathology by a research assistant trained in use of the Mini Interview for Neuropsychiatric Disorders (M.I.N.I). Subjects identified as meeting diagnostic criteria for MDD per the M.I.N.I were also assessed by a psychiatrist to confirm the diagnosis. Indices of depression and anxiety severity [e.g., scores on the clinician-administered Hamilton Rating Scale for Depression (33) and Hamilton Rating Scale for Anxiety (34)] were obtained on the day of scanning. Subjects also completed self-report measures, including the Snaith-Hamilton Assessment of Pleasure Scale, Toronto Alexithymia Index, and the Anxiety Sensitivity Index, which assessed subjective experiences of anhedonia, alexithymia, and anxiety sensitivity. All clinical and self-report measure are described in Table 1.

Interoceptive Encoding and Recall (IER) Paradigm

Encoding.—The IER paradigm was separated into three phases, as depicted in Figure 2. During phase one (encoding phase), subjects were situated in front of a computer screen, fitted with a nose-clip, and instructed to breathe through their mouths via a non-rebreathing valve (Hans Rudolph), as shown in Figure 1. They then completed a paired-associates task, in which they learned to associate certain simple (i.e., fewer than six edges) geometric shapes with the delivery of an inspiratory breathing load lasting 25 seconds. The breathing loads varied across three levels of intensity (10, 30 and 50 cmH₂O/L/sec). Inspiratory breathing loads have been used in several previous studies to induce an unpleasant interoceptive state (35–37).

There were two control conditions: an aversive exteroceptive condition, during which geometric symbols were paired with the onset of a loud female scream played for 850 milliseconds through headphones (Sennheiser HD 429) at low, moderate, and high intensities (80, 89, and 98 dB), and an unpaired condition, during which the geometric symbol appeared and no stimulus followed. Each trial lasted 30 seconds, with the onset of the geometric shape marking the beginning of the trial. Administration of the breathing load or scream occurred 5 seconds after the onset of the geometric shape. The geometric shape appeared on the screen throughout the duration of the entire trial.

All shapes (and their associated low, moderate, and high breathing load or screams) were presented 6 times, totaling 18 interoceptive and 18 exteroceptive learning trials. There were 2 shapes with no associated stimulus (i.e., unpaired shapes), each presented 3 times. In sum, there were 42 learning trials presented during the encoding phase. After each stimulus presentation, subjects were asked to separately rate the intensity and unpleasantness of the stimulus that followed the geometric shape on a visual analogue scale (VAS) ranging from 0–100, with a rating of 100 corresponding to an extremely intense or unpleasant stimulus.

Recall.—In phase two of the IER paradigm, subjects performed an unexpected recall task while undergoing fMRI. During the recall task, subjects were presented with the geometric symbols they previously learned to associate with the administration of a breathing load, the sound of a loud scream, or no paired stimulus. Subjects were instructed to recall the intensity of the stimulus (i.e., breathing load or scream) previously associated with each symbol when it appeared on the screen. Following approximately half of the trials, subjects were prompted to rate the recalled intensity and unpleasantness of the stimuli associated with the geometric symbol. These ratings were made on the same visual analogue scales presented to the subjects in the encoding phase. The recall task occurred during three scanning runs, each lasting seven minutes (420 seconds). Stimuli were separated by a variable-duration interstimulus interval lasting between 2.5 and 10 seconds, during which participants saw a black fixation mark against a white background. In each of the three fMRI scanning runs, the stimuli were presented in a pseudo-random order optimized for fMRI analysis by Optseq2 (<http://surfer.nmr.mgh.harvard.edu/optseq>).

Recognition.—Immediately after the recall task and while still in the scanner, subjects performed a recognition task to obtain an objective measure of memory accuracy. They were presented with several pairs of geometric symbols that had each previously been paired with a low, moderate, or high intensity breathing load or scream. Both symbols in each pair were associated with the same type of stimulus (either breathing load or scream). When the pair of symbols appeared on the screen, subjects were instructed to select the symbol that was associated with a more intense breathing load or scream. The subjects' veridical memory of the paired associations was represented by their score on the recognition task, which could range from 0% accuracy to 100% accuracy (for 100% accuracy, the symbol with greater intensity was correctly identified for all pairs shown to the participant).

Imaging Details

fMRI Data Acquisition.—A 3T GE MR-750 scanner with 3D MPRAGE sequence was used to obtain high-resolution anatomical images (FOV = 240mm, slices/volume (axial) = 176, slice thickness = 0.9mm, image matrix = 256×256, voxel volume = 0.938×0.938×0.9mm³, TR/TE = 5/2.02ms, acceleration factor R = 2, flip angle = 8°, inversion/delay time TI/TD = 725/1400ms, scan time = 372s). Functional data were collected as echo-planar image (EPI) volumes depicting BOLD contrast (220 EPI volumes, voxel size = 1.9×1.9×2.9mm, TR = 2500ms, TE = 22ms, 6mm FWHM spatial smoothing flip angle = 70°, axial-oblique slices with whole-brain coverage, 44 slices per volume) using a 32-channel transmit-receive head coil (Nova Medical), with a sensitivity encoding (SENSE) factor of 2 to minimize EPI distortions while also increasing the number of slices collected per TR.

Data pre-processing.—AFNI (<https://afni.nimh.nih.gov>) was used for preprocessing of fMRI data and subsequent statistical analyses. AFNI's anatomical-to-ePI alignment procedure registered the anatomical scan to the first volume of the EPI data, followed by spatial transformation to the stereotaxic array of Talairach and Tournoux (38) using AFNI's automated algorithm. In order to allow the fMRI signal to reach steady state, the first 4 volumes were excluded from analysis and a slice time correction was applied to all EPI

volumes. Spatial transformation and motion correction were both implemented in a single image transformation. The EPI data were resampled to a 1.75mm^3 grid and smoothed with a 6mm full-width at half-maximum Gaussian kernel. The signal value for each EPI volume was normalized to percent signal change using each voxel's average signal across the time course.

Statistical Analyses

Behavioral and self-report data analysis.—A 2×2 mixed ANOVA was used to assess for mean differences in recognition accuracy by group (depressed or healthy subjects) and stimulus type (interoceptive or exteroceptive) conditions. Additionally, the effects of group and stimulus type on subject's VAS ratings of perceived intensity and unpleasantness during encoding and recall were assessed using two 2×2 mixed ANOVAs.

Neuroimaging data analysis.—The imaging data were analyzed at the subject-level using a multiple linear regression model with regressors for each task condition (i.e., breathing load recall, scream recall, recall of the unpaired/control stimulus, and response periods). To adjust the model for the shape and delay of the BOLD function, task regressors were constructed by convolution of a gamma-variate function and a box-car function having a 5-second width beginning at the onset of occurrence of each condition. Nuisance regressors included each run's signal, mean, linear, quadratic, and cubic signal trends, as well as motion parameters (3 translations, 3 rotations).

In order to examine normative processes of interoceptive recall, the AFNI program 3dANOVA3 was used to evaluate the within-subjects effects of stimulus type (interoceptive or exteroceptive) and stimulus intensity (low, moderate, or high) in the healthy control sample. The AFNI program 3dMVM was then used for the entire sample to evaluate the main effect of group (MDD vs HC; between-subjects factor) and its interactions with stimulus type and stimulus intensity (within-subjects factors).

Masks of the insula in each hemisphere were anatomically defined using the TT-N27 brain atlas within AFNI. Given the prior evidence linking the insula to interoception, a small volume correction of $p < 0.005$ was applied within the insula, and a voxel-wise threshold of $p < 0.0005$ was set for the rest of the brain. Results were then corrected using the cluster-size threshold of $p < 0.05$. To accurately estimate the cluster sizes necessary to achieve familywise error correction, we used versions of AFNI's 3dFWHMx and 3dClustsim that employ a spherical non-Gaussian spatial autocorrelation function to generate smoothness and cluster-size estimates.

Results

Behavioral ratings

Recognition.—Due to a mechanical error recognition data were not obtained for two healthy control subjects; thus, recognition data were analyzed for 19 HC and 24 MDD subjects. There was a significant difference in recognition accuracy between MDD and HC subjects, as indicated by a significant main effect of group ($F(1,41)=7.89$, $p=.007$, $\eta^2G=.09$), such that MDD subjects had lower recognition accuracy on average. There was no

significant effect of stimulus type on recognition accuracy, nor was there an interaction between group and stimulus type.

Intensity and Unpleasantness Ratings.—MDD subjects did not differ from healthy controls in their assessment of stimulus intensity ($F(1,43)=.08$, $p=.78$, $\eta^2G=.002$), or unpleasantness ($F(1,43)=.02$, $p=.89$, $\eta^2G<.001$), during the encoding phase of the IER task. There were no differences in intensity ratings for the two types of stimuli during the encoding phase ($F(1,43)=.89$, $p=.35$, $\eta^2G=.007$). However, both groups rated the breathing loads as being more unpleasant than screams during the encoding phase, as indicated by a significant effect of stimulus type ($F(1,43)=11.9$, $p=.001$, $\eta^2G=.05$). We did not observe an interaction between subject group and stimulus type affecting intensity ($F(1,43)=.75$, $p=.39$, $\eta^2G=.005$) or unpleasantness ratings ($F(1,43)=1.8$, $p=.19$, $\eta^2G=.015$) during encoding.

MDD subjects did not differ from HC subjects in their ratings of recalled intensity ($F(1,43)=1.08$, $p=.30$, $\eta^2G=.01$) or unpleasantness ($F(1,43)=.44$, $p=.51$, $\eta^2G=.004$), during the scanning phase of the IER task. Although both groups assessed breathing loads as being more unpleasant during the encoding phase, during recall subjects rated breathings loads and screams to be of comparable unpleasantness ($F(1,43)=.15$, $p=.69$, $\eta^2G=.002$) and intensity ($F(1,43)=.32$, $p=.56$, $\eta^2G<.001$). There were no significant interactions between stimulus type and group affecting recalled ratings of intensity ($F(1,43)=.96$, $p=.33$, $\eta^2G=.005$) or unpleasantness ($F(1,43)=2.67$, $p=.11$, $\eta^2G=.02$) during the scanning phase of the IER task. These findings are depicted in Figure 3.

We also assessed the correlation between the subjects' VAS ratings of the interoceptive stimuli and their clinical self-report data. Although there were no significant correlations between depression severity and VAS ratings, we did observe correlations between breathing load unpleasantness ratings during encoding and subjects' cardiac and respiratory anxiety sensitivity on the Anxiety Sensitivity Index ($r=.42$, $p=.04$ and $r=.43$ and $p=.03$, respectively). Additional discussion and analyses related to anxiety sensitivity are detailed in Supplemental Materials.

Neuroimaging Results.

Effects of stimulus type and intensity in healthy controls.—Results in the HC sample revealed that subjects exhibited increased hemodynamic response within the bilateral insula during recall of interoceptive stimuli relative to activity during recall of exteroceptive stimuli. Specifically, three clusters within the insula were identified, all of which were arrayed along the longitudinal axis of the mid-to-posterior insula, from approximately the posterior short insular gyrus to the anterior long insular gyrus. Outside of the insula, greater BOLD activity during interoceptive recall was observed within the right parahippocampal gyrus. These findings are reported in Figure 4 and Table 2.

Significant group by stimulus interaction.—Results of the voxel-wise comparison revealed a significant group (MDD vs. HC) by stimulus (interoceptive recall vs. exteroceptive recall) interaction in the right dorsal mid-insula, as illustrated in Figure 5. Consistent with our hypotheses, post-hoc analyses revealed MDD subjects had decreased activation within this region during interoceptive recall. While it is evident from the

behavioral data (i.e., VAS ratings of intensity and unpleasantness) that the MDD subjects performed the task and provided ratings consistent with those given by healthy controls, they exhibited reduced activity in the dorsal mid-insula during recall of the interoceptive stimuli. We also conducted exploratory correlations between the MDD subjects' BOLD signal change in this region during interoceptive recall, relative to exteroceptive recall, and their behavioral data (i.e., VAS ratings), and found no significant correlations.

Discussion

Scientific assessment of interoceptive dysfunction in major depressive disorder has focused largely on bottom-up processes in which interoceptive signals are relayed via afferent projections from the viscera to the posterior and mid-insula for integration with information from emotional, cognitive, and motor regions. The ability to learn and recall associations between external cues (e.g., sights and sounds) and related interoceptive consequences (e.g., changes in the ability to breathe) is an important function of any organism, and yet remarkably little is known about the neural computations underlying this process in interoception. This is certainly not to say that researchers have not extensively studied associative memory using interoceptive stimuli (39–43), but rather that most studies do not compare these exteroceptive-interoceptive associations to exteroceptive-exteroceptive associations, and so little can be said about interoceptive associations specifically, as compared to domain-general associative memory processes. Additionally, to our knowledge, no studies have previously examined interoceptive learning in individuals affected by MDD, a condition associated with interoceptive disturbances and aberrant insula function.

Consistent with our initial hypothesis, we found that interoceptive recall, relative to exteroceptive recall, elicited activation within the bilateral mid-to-posterior insula in psychiatrically healthy subjects. A large body of previous research has demonstrated involvement of this region in response to afferent viscerosensory stimulation (44–47) as well as interoceptive attention (5, 48). The critical difference between these previous studies and the present work, however, is that participants performing the IER task were not receiving experimental interoceptive stimulation during the fMRI scan, nor did the task direct them to attend to their present interoceptive experience. Rather, in the present study the *recall* of a previous interoceptive experience, relative to that of an exteroceptive stimulus, was sufficient to activate viscerosensory regions of the insula. One interpretation of this finding is that the insula's involvement in interoception is not limited to the initial perception and integration of visceral sensations, but is also involved in interoceptive memory and the recall of interoceptive associations.

In the healthy control group, we also observed greater BOLD response in the right parahippocampal gyrus (PHC) during interoceptive recall. This region is thought to play a significant role in a broad range of cognitive functions, including contextual associative representation and episodic memory (49, 50). Greater activation in the PHC occurs in response to stimuli with stronger contextual associations (51). Although extant literature has demonstrated the importance of the PHC in the recollection of stimuli grounded in an exteroceptive (i.e., visuospatial) context (52), we found that PHC activation was greater for stimuli grounded in an interoceptive context. The use of breathing loads in our interoceptive

condition presented a relatively novel, unique sensation for our subjects. Thus, the parahippocampal contextual associations formed between the abstract geometric shapes paired with breathing loads may have been stronger than the associations between shapes paired with screams.

Depressed individuals exhibited reduced hemodynamic response in the right dorsal mid-insula during interoceptive recall when compared to healthy controls. Evidence suggests that this region of the insula is homeostatically sensitive, with activation in this region to food cues varying as a function of peripheral circulating markers of energy availability (53–55). Additionally, decreased activity in this region has been associated with somatic symptom severity (12) and appetite loss (30) among individuals with depression. Consistent with previous theoretical accounts (27–29), it is possible that recruitment of this region of the insula during interoceptive recall is involved in the integration of information about the recalled stimulus with information about the body's current homeostatic state, enabling the selection of behaviors that maintain or modify the state of the internal milieu. If so, when confronted with an external stimulus, a decreased response within the dorsal mid-insula may reflect an inability to integrate information related to the current homeostatic state of the body with the recalled interoceptive consequences of the external stimulus.

Contrary to expectation, subjects with MDD did not significantly differ from healthy controls in their behavioral ratings of intensity or unpleasantness for interoceptive and exteroceptive stimuli, and although MDD subjects' veridical memory was lower overall, there was no difference in memory ability between interoceptive and exteroceptive stimuli.

An interpretation of the behavioral findings, taken in conjunction with the group insula activity differences, could be that MDD is associated with an interoceptive meta-cognitive deficit. MDD subjects exhibit a discrepancy between their self-reported experience and what can be observed in the brain (i.e., neural activation associated with recollection of the experience). In other words, although there appears to be a processing deficit during interoceptive recall in MDD, no deficit is perceived. This could have important implications for psychotherapy approaches that may depend relatively more on depressed patients' awareness of their deficits.

Limitations.

Given that the recall task was completed shortly (i.e., 30 minutes) after the encoding phase, we are unable to draw conclusions about the fidelity of interoceptive memory over longer periods of time. This may be an interesting area of investigation for future research. Additionally, consideration should be given to the difference in perceived unpleasantness between the interoceptive and exteroceptive stimulus during the encoding phase; however, given that these effects were no longer present during the recall phase (i.e., during fMRI scanning), it is not certain that the rating differences measured at encoding influenced the neuroimaging findings at recall.

Findings from the current study indicate that MDD is associated not only with aberrant insula processing of interoceptive signals, as documented in previous research, but also with aberrant activation of the insula during the recollection of previously learned interoceptive

associations (i.e., interoceptive memories). Although the findings reported here demonstrate that MDD is associated with a relative inability to recruit the dorsal mid-insula during interoceptive recall, the current study is unable to elucidate the functional and/or clinical *causes* of aberrant insula activation during interoceptive memory. Consideration of the previous theoretical and empirical literature on the insula and interoception may suggest that aberrant insula activity during recall of breathing loads reflects an underlying interoceptive deficit, as we have argued here. Alternative explanations exist however. For example, it is possible that abnormal patterns of insula activity during interoceptive recall reflect broader processing deficits in MDD, such as diminished stimulus salience.

Further research into the possible relationship between insula recruitment during interoceptive recall and health behavior selection among depressed individuals may elucidate the role of brain-body communication in MDD symptomology. For example, weight gain in depression could be related to underutilization of the insula to evaluate both the current internal state (i.e., not physically hungry) and predictions about the interoceptive consequences of food consumption (i.e., feeling overly satiated). As the first study of the neural bases of interoceptive recall, this research furthers the understanding of the relationships between interoception and behaviors important for homeostasis. Additionally, as the first study of these processes in MDD, these results lend support to influential theoretical accounts of depression that propose impaired associations between external stimuli and interoceptive sensations as a core component in depression. Future research on interoceptive learning and memory in MDD may inform novel clinical interventions that improve the accuracy of interoceptive predictions made by depressed individuals in response to external stimuli, which could in turn promote healthier behavior.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Subjects were seated in front of a computer and fitted with headphones and a nose clip. Throughout the encoding phase, they breathed through a non-rebreathing valve attached to a hose. A research assistant seated at a computer on the opposite side of the desk (i.e., out of the participant's sight) applied the appropriate breathing loads when cued by inserting an air filter into the other end of the hose.

Figure 2.

Visual representation of the IER paradigm. Task instructions, encoding, and scan instructions occur outside of the MRI scanner, and recall and recognition tasks are performed inside of the scanner.

Figure 3.

Intensity and unpleasantness ratings. There were no significant differences between healthy control (HC) and depressed (MDD) subjects' ratings of intensity or unpleasantness. Both groups rated breathing loads as significantly more unpleasant than screams during the encoding phase ($*p < .05$, $\eta^2 G = 0.05$). Error bars represent ± 1 standard error.

Figure 4.

Main effect of stimulus type for healthy control subjects ($N=21$). A small volume correction of $p < 0.005$ was applied within the insula, and a voxel-wise threshold of $p < 0.0005$ was set for the rest of the brain. Results were then corrected using the cluster-size threshold of $p < 0.05$. For the clusters illustrated above, BOLD response was greater during recollection of breathing loads than recollection of screams. Recollection of aversive interoceptive stimuli, relative to that of aversive exteroceptive stimuli, results in greater activation in the bilateral dorsal mid-to-posterior insula and the right parahippocampal gyrus for HC subjects.

Figure 5.

Significant stimulus by group interaction in the right dorsal mid-insula (Talairach coordinates: $x = +32$, $y = +1$, $z = +13$; peak $F = 11.40$; voxels = 22). A small volume correction of $p < 0.005$ was applied within the insula, and a voxel-wise threshold of $p < 0.0005$ was set for the rest of the brain. Results were then corrected using the cluster-size threshold of $p < 0.05$. Percent signal change (i.e., beta values) represents the interoceptive condition relative to the exteroceptive condition (i.e., breath - sound). A total of 21 healthy control and 24 depressed subjects were included in this analysis.

Table 1.

Subject characteristics and clinical data

	Mean (SD)		Welch's <i>t</i>	<i>df</i>
	HC (<i>n</i> = 21)	MDD (<i>n</i> = 24)		
Demographics				
Age, years	30.8 (10)	29.3 (8)	0.6	38.1
BMI	27.5 (5.57)	29.71 (6.4)	−1.2	43
Clinical Measures				
HAM-D 25	2.89 (3.07)	22.5 (6.59)	−13.01***	33.6
HAM-A	1.86 (1.8)	18.08 (5.62)	−13.35***	28.39
STAI - State	24.29 (5.82)	50.9 (12.27)	−9.48***	33.78
STAI - Trait	26.8 (6.06)	58.6 (8.49)	−14.65***	41.50
TAS	38.7 (2.5)	57.6 (14.3)	−26***	39.16
ASI	15.42 (13.6)	54.5 (31.6)	−5.49***	32.11
SHAPS	20.52	29.29	−4.72***	41.98
Recognition Accuracy				
Interoceptive	83% (18)	73% (24)	1.43	40.9
Exteroceptive	85% (18)	65% (29)	2.72**	39.7

Note:

**
 $p < .01$ ***
 $p < .001$;

HAM-D = Hamilton Depression Severity Rating Scale, HAM-A = Hamilton Anxiety Rating Scale, STAI = State and Trait Anxiety Inventory, TAS = Toronto Alexithymia Index - 20, ASI = Anxiety Sensitivity Index – Revised 36, SHAPS = Snaith-Hamilton Assessment of Pleasure Scale. For all clinical measures, higher numbers indicate greater endorsement of the construct assessed.

Table 2.

Regions exhibiting significant activation during interoceptive recall relative to exteroceptive recall

Side/Location	Talairach Coordinates			Peak <i>t</i>	Cluster size (voxels)
	x	y	z		
R dorsal mid-insula	+48	-2	+6	5.47	208
R parahippocampal gyrus	-22	+36	-12	5.30	195
L posterior insula	-34	-11	+9	4.55	98
L dorsal mid-insula	-29	+6	+12	5.33	65

A voxel-wise threshold of $p < .005$ was set for the insula, and a voxel-wise threshold of $p < .0005$ for the rest of the brain; all significant activations passed a cluster-size correction for multiple comparisons of $p < .05$. For all significant clusters listed above, BOLD activation during breathing recall was significantly greater than BOLD activation during scream recall.