Archival Report

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Coping Strategies, Neural Structure, and Depression and Anxiety During the COVID-19 Pandemic: A Longitudinal Study in a Naturalistic Sample Spanning Clinical Diagnoses and Subclinical Symptoms

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ABSTRACT

BACKGROUND: Although the COVID-19 pandemic has been shown to worsen anxiety and depression symptoms, we do not understand which behavioral and neural factors may mitigate this impact. To address this gap, we assessed whether adaptive and maladaptive coping strategies affect symptom trajectory during the pandemic. We also examined whether pre-pandemic integrity of brain regions implicated in depression and anxiety affect pandemic symptoms.

METHODS: In a naturalistic sample of 169 adults (66.9% female; age 19–74 years) spanning psychiatric diagnoses and subclinical symptoms, we assessed anhedonia, tension, and anxious arousal symptoms using validated components (21-item Depression, Anxiety, and Stress Scale), coping strategies (Brief–Coping Orientation to Problems Experienced), and gray matter volume (amygdala) and cortical thickness (hippocampus, insula, anterior cingulate cortex) from magnetic resonance imaging T1-weighted scans. We conducted general linear mixed-effects models to test preregistered hypotheses that 1) maladaptive coping pre-pandemic and 2) lower structural integrity pre-pandemic would predict more severe pandemic symptoms; and 3) coping would interact with neural structure to predict pandemic symptoms.

RESULTS: Greater use of maladaptive coping strategies was associated with more severe anxious arousal symptoms during the pandemic (p = .011, false discovery rate–corrected p [p_{FDR}] = .035), specifically less self-distraction (p = .014, p_{FDR} = .042) and greater self-blame (p = .002, p_{FDR} = .012). Reduced insula thickness pre-pandemic predicted more severe anxious arousal symptoms (p = .001, p_{FDR} = .027). Self-distraction interacted with amygdala volume to predict anhedonia symptoms (p = .005, p_{FDR} = .020).

CONCLUSIONS: Maladaptive coping strategies and structural variation in brain regions may influence clinical symptoms during a prolonged stressful event (e.g., COVID-19 pandemic). Future studies that identify behavioral and neural factors implicated in responses to global health crises are warranted for fostering resilience.

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The COVID-19 global pandemic is an ongoing stressful life event that has resulted in more than 3 million deaths as of May 2021 (1) and substantial increases in rates of depression and anxiety (2). This is a particularly unique stressful event given that it occurred across the world during the same time span, is perceived as being outside of one's control, and represents a prolonged stressor that affects multiple domains of functioning. For example, the mandatory shelter-in-place order implemented in the first few months, along with ongoing social distancing policies, involves a significant amount of social isolation, exacerbating mental health problems (3). Although stress is considered to be a healthy response in numerous contexts, an extensive body of work has shown that chronic stress can increase the risk of developing mood and anxiety symptoms and/or exacerbate current symptoms (4–12). Depression and anxiety have been conceptualized as maladaptive responses to chronic stress (5,13), consistent with prior work indicating that maladaptive coping strategies in response to stressful events are associated with poorer mental health (14–18). To date, only one study has identified specific coping strategies in response to stress that were associated with a worsening of anxiety and depression symptoms during the pandemic (19), which showed that self-blame, venting, behavioral disengagement, and self-distraction were related to more severe symptoms. Thus, the present study aimed to identify coping strategies and brain regions that predict anxiety

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and depression symptoms during the COVID-19 pandemic, specifically in the first few months (May–July 2020).

The ability to cope adaptively with stressful events is related to the capacity to regulate emotions (20), which in turn influences the development of anxiety and depression symptoms (14). Structural integrity of the brain regions involved in emotional processing of stressful events has been demonstrated to play a role in the development of symptoms. For example, studies have reported altered gray matter volume and cortical thickness in the amygdala, anterior cingulate cortex (ACC), insula, and hippocampus of individuals with symptoms of anxiety and depression (21–34). Specifically, there is evidence of amygdala gray matter volume reductions (21,23–25) and increases (27), as well as gray matter reductions in the hippocampus (21–23,29,32). In addition, reduced cortical thickness of the insula (21,23,32–34) and ACC (21,23,25,26,32) have been implicated in depression and anxiety. Structural variation in these regions has also predicted responses to stressful adverse events; reduced amygdala (35,36), insula (36), and hippocampal volume (35), and thinner ACC (35,37) have been linked to trauma. There is also evidence that early-life stress is related to lower hippocampal volume (38) and reduced insula thickness (38), although these findings are mixed (35). Discrepancies in the literature may be due to methodological features (e.g., sample sizes, imaging methods, and symptom heterogeneity) and/or differences in the impact of external life stressors. Nevertheless, existing research suggests that structural alterations within these regions may influence the risk of developing depression and anxiety symptoms in response to the pandemic. It is imperative to elucidate the impact of pre-pandemic brain structure on pandemic symptoms because this research could contribute to the identification of biomarkers that help to identify individuals at high risk for developing symptoms during highly stressful events and may also serve as neural targets for preventive interventions.

No study has investigated whether coping strategies and brain structure assessed pre-pandemic can predict the severity of anxiety and depression symptoms during the pandemic. In this study, we leveraged a sample of adult participants with varying levels of depression and anxiety symptoms prior to the pandemic and tested whether adaptive or maladaptive coping strategies would predict pandemic symptoms. We tested three preregistered hypotheses. First, we hypothesized that individuals who reported using maladaptive coping strategies pre-pandemic would develop more severe depression and anxiety symptoms during the pandemic. Second, we hypothesized that lower gray matter volume and smaller cortical thickness (as compared with other participants) of regions implicated in emotion processing assessed pre-pandemic would predict more severe symptoms during the pandemic. Third, we hypothesized that coping strategies would interact with neural structure to predict pandemic symptoms. We conducted exploratory analyses to identify which specific coping strategies would relate to pandemic symptoms and which strategies would interact with neural structure to predict pandemic symptoms. Identifying which coping strategies and brain regions contribute to more severe anxiety and depression during stressful events is critical for mitigating the negative psychological effects of the current and future global pandemics.

METHODS AND MATERIALS

Preregistration

The analysis plan was preregistered on September 24, 2020, on the Open Science Framework (https://doi.org/10.17605/OSF.IO/XPRT7) before any statistical analyses were conducted and after data collection. Prior to preregistration, the structural imaging data had not been viewed, but the experimenters visualized the distribution of coping and symptom measures. There were no deviations from the analysis plan.

Study Design and Participants

For this longitudinal investigation, baseline data (pre-pandemic) were collected at Stanford University, Stanford, California, between September 11, 2014, and December 3, 2019. Data were acquired as part of the primary sample for the Research Domain Criteria Anxiety and Depression (RAD) project (39) and a subsequent extension of this project designed to assess neural circuit dimensions and their relationship with clinical phenotypes of depression and anxiety. The extension included participants from the Human Connectome Project for Disordered Emotional States (40). Participants were recruited from community sources including the Gronowski Center and Crossover Health clinics, flyers posted in the surrounding community, and social media advertisements (Facebook and Instagram advertisements). Inclusion criteria were scanning eligibility (e.g., no metal embedded in the body), age $\geq$18 years, and self-reported anxiety and/or depression symptoms sufficient to cause distress in daily life. We also included a subsample of healthy individuals recruited on the basis of reporting no distress from anxiety or depression symptoms. Exclusion criteria for all participants included a current or past experience of psychosis and/or mania as well as any contraindication to neuroimaging. Details about the rationale, study design, and measures can be found in the RAD protocol paper (39). Only measures relevant to this analysis are presented.

During the pandemic (at the peak of the shelter-in-place orders in the San Francisco Bay Area), follow-up surveys were collected remotely between May 18, 2020, and July 8, 2020. Participants who completed baseline visits were sent questionnaires assessing coping strategies and symptoms as well as a survey developed in-house to assess the impact of the pandemic. This survey consisted of questions regarding changes in psychological, physical, social, and environmental health domains during the pandemic. Measures from this survey relevant to this study are summarized in Table 1.

The final sample was composed of 169 adult participants who had complete baseline survey data. At baseline, 81.66% (n = 138) were self-reported symptomatic participants (defined as those who reported significant distress from depression and/or anxiety symptoms at initial screen), while 18.34% (n = 31) were self-reported asymptomatic participants (defined as those who reported a lack of depression or anxiety symptom presence at initial screen). While 160 participants (80% symptomatic) had complete baseline and follow-up survey data, 155 (81% symptomatic) had complete baseline survey, baseline imaging, and follow-up survey data.

Table 1. Demographic and Clinical Features and Coping Stategies of the Sample for Baseline to Pandemic Follow-up Data

Demographic, Clinical, and Coping Stategies Information	Value
Demographic Information (*N* = 169)	
Biological Sex, *n* (%)	
Female	113 (66.9)
Male	56 (33.1)
Race, *n* (%)	
American Indian, Alaska Native, or Pacific Islander	3 (1.8)
Asian	36 (21.3)
Black/African American	2 (1.2)
White	107 (63.3)
Biracial or Other	21 (12.4)
Ethnicity, *n* (%)	
Hispanic or Latino	20 (11.8)
Not Hispanic or Latino	149 (88.2)
Pandemic Age, Years, Mean (±SD)	39.8 (±15.5)
Pandemic Student Status, *n* (%)	
In school onsite or in school remotely not due to pandemic	10 (5.9)
In school remotely due to pandemic or not in school due to pandemic	40 (23.7)
Not in school not due to pandemic	119 (70.4)
Pandemic Employment Status, *n* (%)	
Employed with usual hours onsite	21 (12.4)
Employed with usual hours remotely due to pandemic	65 (38.5)
Employed with usual hours remotely not due to pandemic	8 (4.7)
Employed but with significant reduction in hours due to pandemic	23 (13.6)
Unemployed due to pandemic	18 (10.7)
Unemployed but not due to pandemic	34 (20.1)
Time Between Baseline Visit and Pandemic Follow-up, Years, Mean (±SD)	3.2 (±1.6)
Clinical Information	
Self-report Symptoms[a], Mean (±SD)	
Baseline anhedonia	−0.04 (±1.0)
Pandemic anhedonia	−0.04 (±0.9)
Baseline anxious arousal	−0.14 (±0.8)
Pandemic anxious arousal	−0.37 (±0.8)
Baseline tension	0.12 (±1.0)
Pandemic tension	0.52 (±0.9)
Baseline Clinical Diagnoses[b], *n* (%)	
MDD	26 (15.4)
MDD past	72 (42.6)
Bipolar disorder	5 (3.0)
Bipolar disorder past	13 (7.7)
GAD	47 (27.8)
Panic disorder	10 (5.9)
Panic disorder past	30 (17.8)
Agoraphobia	28 (16.6)
SAD	25 (14.8)
OCD	14 (8.3)
PTSD	10 (5.9)
Current or past clinical diagnosis	110 (65.1)
Coping Strategies Information, Mean (±SD)	
Maladaptive Coping Score	23.0 (±5.0)
Self-distraction	5.5 (±1.7)
Denial	2.5 (±0.9)
Venting	4.1 (±1.4)
Substance use	2.6 (±1.1)
Behavioral disengagement	3.1 (±1.2)
Self-blame	5.2 (±1.9)
Adaptive Coping Score	39.6 (±8.5)
Active coping	5.5 (±1.6)
Planning	5.8 (±1.7)
Positive reframing	5.3 (±1.8)
Acceptance	5.4 (±1.4)
Humor	4.2 (±1.9)
Religion	3.5 (±1.9)
Emotional support	4.9 (±1.8)
Instrumental support	4.9 (±1.8)

This table describes demographic characteristics (sex, race, ethnicity, pandemic age, pandemic student status, pandemic employment status), years between baseline and pandemic follow-up, clinical characteristics (self-reported symptoms and clinical diagnoses), and coping strategies information. Percentages for diagnoses do not sum to 100% due to comorbidities. Diagnostic labels are for current disorders unless otherwise noted.

GAD, generalized anxiety disorder; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; PTSD, posttraumatic stress disorder; SAD, social anxiety disorder.

[a]Self-reported symptoms represent principal components from the 21-item Depression, Anxiety, and Stress Scale.

[b]Clinical diagnoses were assessed using the Mini-International Neuropsychiatric Interview (MINI-Plus), administered by trained interviewers.

Anxiety and Depression Symptoms

At baseline and pandemic follow-up, symptoms were assessed with the 21-item Depression, Anxiety, and Stress Scale (41). We used three principal components of the 21-item Depression, Anxiety, and Stress Scale based on a previous data-driven principal component analysis generated in an independent dataset and replicated in the primary RAD sample (42). These components, based on the 21-item Depression, Anxiety, and Stress Scale loading most strongly on each component, reflect anhedonia (loss of pleasure/interest, hopelessness, depressed mood), anxious arousal (autonomic anxiety symptoms such as heart racing, trembling, feelings of faintness or dizziness), and tension (cognitively oriented symptoms of generalized worry and stress about the future). Cronbach's α for anhedonia, anxious arousal, and tension was 0.93, 0.86, and 0.83, respectively, demonstrating high internal consistency.

Coping Strategies

At baseline and pandemic follow-up, coping strategies were assessed using the 28-item Brief–Coping Orientation to Problems Experienced (Brief-COPE) (43). The Brief-COPE consists of 14 subscales of two items each: active coping, planning, positive

reframing, acceptance, humor, religion, emotional support, instrumental support, self-distraction, denial, venting, substance use, behavioral disengagement, and self-blame. Given evidence that these strategies tend to be either generally adaptive or maladaptive (14–18), we used the adaptive and maladaptive subscales (43). The adaptive subscale includes 16 items with scores ranging from 0 to 48 and includes active coping, planning, positive reframing, acceptance, humor, religion, emotional support, and instrumental support. The maladaptive subscale includes 12 items with scores ranging from 0 to 36 and includes self-distraction, denial, venting, substance use, behavioral disengagement, and self-blame. The Brief-COPE has demonstrated good reliability and validity (43,44) and has been used to assess coping strategies during prior infectious disease outbreaks (45). For this study, Cronbach's α for the maladaptive COPE and adaptive subscales was 0.60 (acceptable) and 0.76 (good), respectively. See Table S1 for item-level questions, subscales, and psychometric properties.

Imaging Acquisition and Preprocessing

At baseline, images were acquired at the Stanford Center for Cognitive and Neurobiological Imaging on a GE Discovery MR750 3T scanner using a Nova Medical 32-channel head coil (GE Healthcare). For the RAD dataset, structural T1-weighted magnetic resonance imaging brain scans were acquired with a repetition time = 8.656 ms, echo time = 3.42 ms, voxel size = 1 mm, number of slices = 176, field of view = 256 × 256 mm, and flip angle = 11°. For the RAD extension dataset, structural T1-weighted magnetic resonance imaging brain scans were similarly acquired with a repetition time = 8.096 ms, echo time = 3.548 ms, voxel size = 0.8 mm, flip angle = 8°, acquisition time =8:33, field of view = 256 × 256 mm, 3D matrix size = 320 × 320 × 230, slice orientation = sagittal, angulation to anterior commissure–posterior commissure line, receiver bandwidth = 31.25 kHz, fat suppression = no, and motion correction = real-time prospective motion correction. To account for any T1 sequence differences between the RAD and RAD extension samples, the dataset was used as a covariate in the statistical models.

Structural scans were analyzed using FreeSurfer version 6.0 (46) (http://surfer.nmr.mgh.harvard.edu/) as implemented in fMRIPrep (47) (see the Supplement for details). Total intracranial volume and gray matter volumes of subcortical structures (amygdala), as well as thickness of cortical structures (hippocampus, insula, caudal ACC, rostral ACC [rACC]) were extracted. Cortical reconstruction and segmentation, motion correction, nonbrain tissue elimination, Talairach transformation, and intensity normalization were executed in FreeSurfer. All regions of interest (ROIs) were averaged across hemispheres and then each brain measure was scaled between 0 and 1 across subjects.

Primary Analyses

Analyses were conducted using R studio version 3.6.1.

Hypothesis 1: Maladaptive Coping Strategies at Baseline Predict More Severe Symptoms During the Pandemic. We conducted general linear mixed-effects models to assess associations between coping strategies (adaptive and maladaptive) used prior to the pandemic (baseline) and symptoms during the pandemic (follow-up). Separate models were conducted for each of the three dependent variables (anhedonia, anxious arousal, and tension symptoms). The three comparisons (number of symptom measures) were controlled for using false discovery rate (FDR) (48). Baseline maladaptive coping score and adaptive coping score were the independent variables. The following covariates were included: sex (fixed effect), pandemic age (fixed effect), race (fixed effect), pandemic student status (random effect), pandemic employment (random effect), time between baseline visit and pandemic (fixed effect), and baseline anhedonia/anxious arousal/tension symptoms (fixed effect). Of the 169 participants, 9 did not have complete baseline and follow-up survey data, thus 160 participants were used in this analysis.

Hypothesis 2: Reduced Gray Matter Volume and/or Reduced Cortical Thickness at Baseline Predict More Severe Symptoms During the Pandemic. We conducted general linear mixed-effects models to examine associations between neural circuit structure (amygdala, hippocampus, insula, caudal ACC, rACC) prior to the pandemic (baseline) and symptoms during the pandemic. We conducted separate models for each of the three dependent variables (anhedonia, anxious arousal, and tension symptoms). Each baseline brain ROI was an independent variable in separate models. Thus, 15 comparisons (three symptom measures × five brain regions) were controlled for using FDR (48). The following covariates were included: sex (fixed effect), pandemic age (fixed effect), race (fixed effect), pandemic student status (random effect), pandemic employment (random effect), time between baseline visit and pandemic (fixed effect), baseline anhedonia/anxious arousal/tension symptoms (fixed effect), baseline total intracranial volume (fixed effect), and dataset (fixed effect). Of the 169 participants, 14 did not have complete baseline survey, baseline imaging, and follow-up survey data; thus, 155 participants were used in this analysis.

Hypothesis 3: Maladaptive Coping Strategies Interact With Neural Structures at Baseline to Predict Symptoms During the Pandemic. We conducted general linear mixed-effects models to examine whether coping strategies (adaptive and maladaptive) interacted with neural circuit structures (amygdala, hippocampus, insula, caudal ACC, rACC) prior to the pandemic (baseline) to predict symptoms during the pandemic. We conducted separate models for each of the three dependent variables (anhedonia, anxious arousal, and tension symptoms). The interaction between baseline coping strategies (adaptive and maladaptive) and each baseline brain ROI was an independent variable in separate models. The main effects of coping and brain ROI were also included. Thus, 15 comparisons (three symptom measures × five brain regions) were controlled for using FDR (48). The following covariates were included: sex (fixed effect), pandemic age (fixed effect), race (fixed effect), pandemic student status (random effect), pandemic employment (random effect), time between baseline visit and pandemic (fixed effect), baseline anhedonia/anxious arousal/tension symptoms (fixed effect), baseline total intracranial volume (fixed effect), and dataset (fixed effect). Of the 169 participants, 14 did not have

complete baseline survey, baseline imaging, and follow-up survey data; thus, 155 participants were used in this analysis.

Exploratory Analyses

We conducted exploratory analyses using general linear mixed-effect models to examine which specific type(s) of coping strategies were associated with pandemic symptoms (follow-up analysis to hypothesis 1). We also conducted general linear mixed-effect models to examine whether specific type(s) of coping strategies (found to significantly predict worse symptom outcomes) interact with baseline neural circuit structure to predict pandemic symptoms (follow-up analyses to hypothesis 3). Four comparisons (two strategies found to be significant for each of the two models) were controlled for using FDR (48).

RESULTS

Demographic and Clinical Characteristics

Demographic and clinical characteristics of 169 participants (66.9% female) at baseline and pandemic follow-up are reported in Table 1. Participant characteristics summarized separately for each group (symptomatic and asymptomatic) are reported in Table S2. Self-reports of clinical symptom presence immediately before the pandemic, in addition to the subjective impact of the pandemic on symptoms, are reported in Table S3. Baseline measure differences between individuals who completed the pandemic follow-up and those who did not are summarized in Table S4. A correlation matrix of variables of interest is presented in Figure S1.

Anhedonia symptoms did not differ from baseline (mean = −0.04, SD = 1.0) to follow-up (mean = −0.04, SD = 0.9) (t_{159} = −0.21, p = .84), but anxious arousal symptoms were unexpectedly higher at baseline (mean = −0.14, SD = 0.8) than at follow-up (mean = −0.37, SD = 0.8) (t_{159} = −3.10, p = .002). In contrast, tension symptoms were higher at follow-up (mean = 0.52, SD = 0.90) than at baseline (mean = 0.12, SD = 1.0) (t_{159} = −4.63, p < .001). A comparison of pre-pandemic and pandemic symptoms within each symptomatic and asymptomatic group are described in the Supplement.

Primary Analyses

Hypothesis 1: Maladaptive Coping Strategies at Baseline Predict More Severe Symptoms During the Pandemic. Maladaptive coping strategies at baseline were associated with anxious arousal symptoms during the pandemic (β = 0.18, p = .011, FDR-corrected p [p_{FDR}] = .035) such that increased use of maladaptive coping strategies were associated with more severe anxious arousal symptoms (Figure 1A and Table 2).

Hypothesis 2: Reduced Gray Matter Volume and/or Reduced Cortical Thickness at Baseline Predict More Severe Symptoms During the Pandemic. Cortical thickness of the insula was associated with anxious arousal symptoms during the pandemic (β = −0.30, p = .001, p_{FDR} = .027) such that lower insula thickness was associated with more severe anxious arousal symptoms (Figure 1D and Table 3).

Hypothesis 3: Maladaptive Coping Strategies Interact With Neural Structure at Baseline To Predict Symptoms During the Pandemic. None of the uncorrected significant interactions survived FDR correction. We found an uncorrected significant interaction between maladaptive coping and amygdala volume (β = −0.14, p = .023,

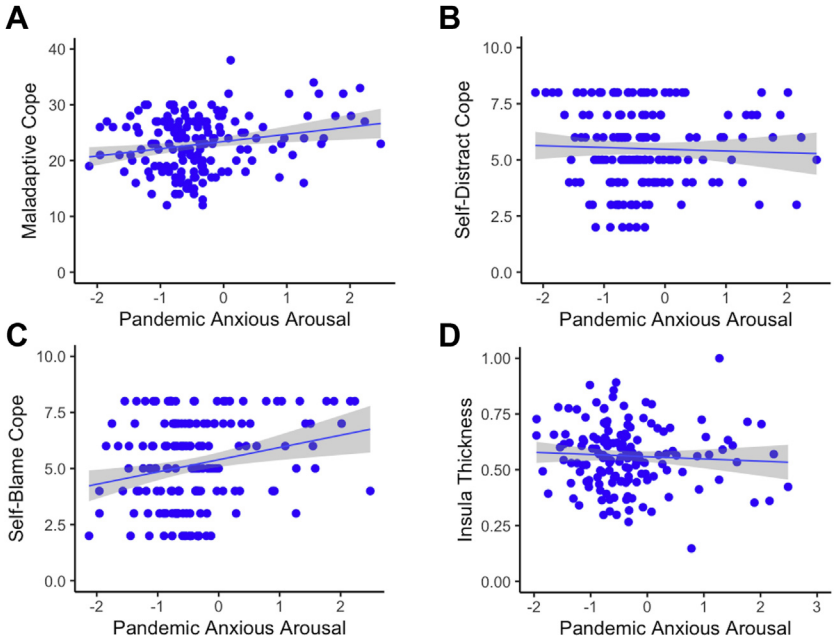

Figure 1. Associations between baseline coping strategies, baseline brain structure, and pandemic symptoms. **(A)** Maladaptive coping strategies at baseline were associated with anxious arousal symptoms during the pandemic. **(B)** Self-distraction coping was associated with anxious arousal symptoms during the pandemic. **(C)** Self-blame coping was associated with anxious arousal symptoms during the pandemic. **(D)** Cortical thickness of the insula was associated with anxious arousal symptoms during the pandemic.

Table 2. Associations Between Baseline Coping Strategies and Pandemic Anxious Arousal Symptoms

Independent Variables	β (95% CI)	SE	t_{159}	*p* Value
Primary Analysis				
Intercept	0.07 (−1.67 to −0.06)	0.41	−2.11	.035
Baseline Maladaptive Cope	0.18 (0.01 to 0.06)[a]	0.01[a]	2.55[a]	.011[a,b]
Baseline Adaptive Cope	0.06 (−0.01 to 0.02)	0.01	0.84	.402
Pandemic Age	−0.02 (−0.01 to 0.01)	0	−0.24	.807
Baseline Sex	−0.10 (−0.34 to 0.16)	0.13	−0.70	.486
Baseline Anxious Arousal Symptoms	0.40 (0.29 to 0.59)[a]	0.08[a]	5.65[a]	<.001[a]
Time Between Baseline and Pandemic	−0.17 (−0.18 to 0.00)[a]	0.04[a]	−2.04[a]	.041[a]
Exploratory Analysis				
Intercept	0.07 (−1.02 to 0.33)	0.34	−1.00	.318
Baseline Self-distraction Cope	−0.18 (−0.17 to −0.02)[a]	0.04[a]	−2.45[a]	.014[a,b]
Baseline Denial Cope	−0.02 (−0.15 to 0.11)	0.07	−0.29	.771
Baseline Substance Use Cope	0.02 (−0.10 to 0.13)	0.06	0.30	.764
Baseline Behavioral Disengagement Cope	0.09 (−0.04 to 0.17)	0.05	1.16	.246
Baseline Venting Cope	0.09 (−0.03 to 0.14)	0.04	1.17	.244
Baseline Self-blame Cope	0.25 (0.04 to 0.18)[a]	0.03	3.15[a]	.002[a,b]
Pandemic Age	−0.02 (−0.01 to 0.01)	0	−0.22	.826
Baseline Sex	−0.16 (−0.38 to 0.11)	0.13	−1.07	.284
Baseline Anxious Arousal Symptoms	0.42 (0.31 to 0.61)[a]	0.08	6.01[a]	<.001[a]
Time Between Baseline and Pandemic	−0.18 (−0.18 to −0.01)	0.04	−2.24	.025

This table describes significant associations between coping strategies at baseline and anxious arousal symptoms during the pandemic. Random effects of race, pandemic student status, and pandemic employment status were included in all models. All independent variables listed in the table are fixed. See the Supplement for random effects variables statistics.

β, standardized beta.

[a]Indicates significant difference ($p < .05$ uncorrected).

[b]Predictor of interest that survived false discovery rate correction.

p_{FDR} = .254) (Figure 2A and Table 4) when predicting anhedonia symptoms during the pandemic; for individuals with high maladaptive coping, there was a negative correlation between amygdala volume and anhedonia symptoms. In addition, there was an uncorrected significant interaction between maladaptive coping and rACC thickness (β = −0.14, p = .039, p_{FDR} = .254) (Figure 2B and Table 4) when predicting tension symptoms during the pandemic; for individuals with low maladaptive coping, there was a positive correlation between rACC thickness and tension symptoms.

Exploratory Analyses

We conducted exploratory analyses to identify which specific type of coping strategies were implicated in the associations found in hypotheses 1 and 3.

We found that maladaptive coping predicted anxious arousal symptoms in hypothesis 1: thus, we explored whether this effect was driven by a specific type of maladaptive coping strategy. We found that individuals with lower self-distraction (β = −0.18, p = .014, p_{FDR} = .042) (Figure 1B and Table 2) and higher self-blame (β = 0.25, p = .002, p_{FDR} = .012)

Table 3. Associations Between Baseline Neural Structure and Pandemic Anxious Arousal Symptoms

Independent Variables	β (95% CI)	SE	t_{154}	*p* Value
Intercept	0.28 (0.34 to 2.32)	0.50	2.64	.008
Baseline Insula	−0.30 (−2.94 to −0.74)[a]	0.56[a]	−3.28[a]	.001[a,b]
Pandemic Age	−0.22 (−0.02 to −0.00)[a]	0.01[a]	−2.24[a]	.025[a]
Baseline Sex	−0.13 (−0.43 to 0.21)	0.16	−0.69	.490
Baseline Anxious Arousal Symptoms	0.46 (0.34 to 0.64)[a]	0.08[a]	6.44[a]	<.001[a]
Time Between Baseline and Pandemic	0.00 (−0.19 to 0.19)	0.10	0.02	.987
Baseline Total Intracranial Volume	0.08 (−0.52 to 1.26)	0.45	0.82	.415
Dataset	−0.34 (−0.92 to 0.33)	0.32	−0.92	.359

The table describes significant associations between neural structure at baseline and anxious arousal symptoms during the pandemic. Random effects of race, pandemic student status, and pandemic employment status were included in all models. All independent variables listed in the table are fixed. See the Supplement for random effects variables statistics.

β, standardized beta.

[a]Indicates significant difference ($p < .05$ uncorrected).

[b]Predictor of interest that survived false discovery rate correction.

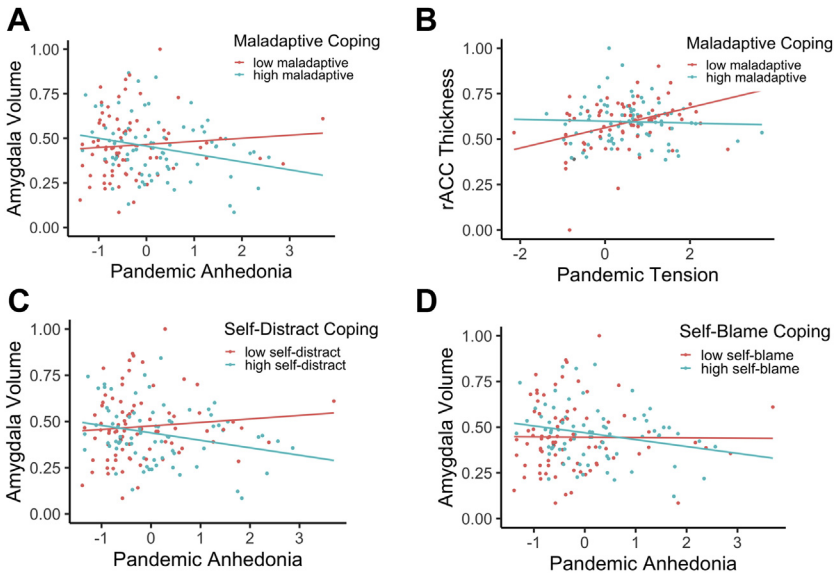

Figure 2. Coping strategies and neural structure interactions for predicting pandemic symptoms. **(A)** There was a significant (uncorrected) interaction between maladaptive coping and amygdala volume when predicting anhedonia symptoms during the pandemic. **(B)** There was a significant (uncorrected) interaction between maladaptive coping and rostral anterior cingulate cortex (rACC) thickness when predicting tension symptoms during the pandemic. **(C)** There was a significant (false discovery rate corrected) interaction between self-distraction coping and amygdala volume when predicting anhedonia symptoms during the pandemic. **(D)** There was a significant (uncorrected) interaction between self-blame coping and amygdala volume when predicting anhedonia symptoms.

(Figure 1C and Table 2) exhibited more severe anxious arousal symptoms during the pandemic.

In hypothesis 3, we found that there was a significant (uncorrected) interaction between maladaptive coping and amygdala volume in relation to anhedonia symptoms, in addition to a significant (uncorrected) interaction between maladaptive coping and rACC thickness in relation to tension symptoms. Therefore, we tested whether these effects were driven by self-distraction and/or self-blame strategies. We found a significant interaction between self-distraction coping and amygdala volume ($\beta = -0.16$, $p = .005$, $p_{FDR} = .020$) (Figure 2C and Table 4) when predicting anhedonia symptoms during the pandemic: for individuals with a self-distraction coping style, there was a significant negative correlation between amygdala volume and anhedonia symptoms. Similarly, there was a significant (uncorrected) interaction between self-blame coping and amygdala volume ($\beta = -0.13$, $p = .046$, $p_{FDR} = .090$) (Figure 2D and Table 4) when predicting anhedonia symptoms.

We conducted additional analyses to explore 1) the relationship between baseline clinical diagnoses and pandemic symptoms, 2) whether findings hold after removing participants with high pandemic symptom scores, 3) whether findings hold after removing outliers, and 4) pandemic coping strategy relationships (see the Supplement).

DISCUSSION

This study contributes new knowledge about how coping strategies and neural structure prior to the COVID-19 pandemic predict the severity of anxiety and depression symptoms during the pandemic. Our first key finding was that pre-pandemic maladaptive coping strategies (driven by self-distraction and self-blame strategies) predicted the severity of anxious arousal symptoms during the pandemic. Our second key finding was that cortical thickness of the insula pre-pandemic predicted the severity of anxious arousal symptoms during the pandemic. Third, we found that self-distraction coping and amygdala volume interact to predict the severity of anhedonia symptoms during the pandemic. These findings suggest that specific maladaptive coping strategies and reduced brain structure integrity in regions implicated in emotion processing before global stressful events are related to more severe clinical symptoms during the event.

Pre-pandemic maladaptive coping strategies—specifically self-distraction and self-blame—predicted anxious arousal symptoms during the pandemic. In particular, greater self-blame was related to more severe anxious arousal symptoms, which is consistent with prior research indicating that the use of maladaptive coping strategies is more strongly related to clinical symptom severity than the use of adaptive coping strategies, both cross-sectionally and longitudinally (15–18). Thus, it may be more beneficial for individuals to decrease their use of maladaptive coping strategies (e.g., self-blame) than to increase their use of adaptive strategies (e.g., positive reframing) in the face of stressful events to improve psychological outcomes. We also found, in contrast, that less self-distraction was related to more severe anxious arousal symptoms, indicating that while self-distraction is generally perceived as maladaptive (14), it may actually alleviate symptoms experienced during a global pandemic. It is possible that individuals who attempted to maintain normal routines (e.g., reading, working, exercising) during an unprecedented time when routines were disrupted were able to use these activities as healthy distractors, which in turn reduced anxious arousal symptoms. It is also possible that self-distraction is an adequate coping strategy in the short term, but not in the long-term; future studies should investigate whether self-distraction can improve symptoms over a longer period in response to a prolonged stressor. These findings underscore the importance of recognizing that specific coping styles are not

Table 4. Coping Strategies and Neural Structure Interactions for Predicting Pandemic Symptoms

Dependent Variable	Independent Variables	β (95% CI)	SE	*t*	*p* Value
Primary Analysis					
Anhedonia Symptoms During the Pandemic	Intercept	−0.40 (−3.41 to 0.87)	1.09	−1.16	.246
	Baseline amygdala × baseline maladaptive cope	−0.14 (−0.29 to −0.02)[a]	0.07[a]	−2.28[a]	.023[a]
	Baseline amygdala × baseline adaptive cope	0.01 (−0.08 to 0.09)	0.04	0.15	.878
	Baseline amygdala	−0.12 (−1.87 to 7.23)	2.32	1.16	.247
	Baseline maladaptive cope	0.12 (0.03 to 0.16)[a]	0.03[a]	2.81[a]	.005[a]
	Baseline adaptive cope	−0.05 (−0.05 to 0.03)	0.02	−0.38	.702
	Pandemic age	−0.11 (−0.02 to 0.00)	0.00	−1.37	.171
	Baseline sex	0.52 (0.17 to 0.82)[a]	0.16[a]	2.99[a]	.003[a]
	Baseline anhedonia symptoms	0.53 (0.35 to 0.60)[a]	0.06[a]	7.49[a]	<.001[a]
	Time between baseline and pandemic	−0.04 (−0.21 to 0.16)	0.10	−0.25	.801
	Baseline total intracranial volume	−0.16 (−1.86 to 0.19)	0.52	−1.59	.112
	Dataset	0.34 (−0.30 to 0.94)	0.32	1.01	.310
Tension Symptoms During the Pandemic	Intercept	−0.06 (−7.20 to 0.43)	1.95	−1.74	.082
	Baseline rostral ACC × baseline maladaptive cope	−0.14 (−0.39 to −0.01)[a]	0.10[a]	−2.06[a]	.039[a]
	Baseline rostral ACC × baseline adaptive cope	−0.07 (−0.18 to 0.07)	0.06	−0.90	.371
	Baseline rostral ACC	0.04 (0.95 to 13.30)[a]	3.15[a]	2.26[a]	.024[a]
	Baseline maladaptive cope	−0.01 (0.00 to 0.23)[a]	0.06[a]	1.99[a]	.047[a]
	Baseline adaptive cope	0.08 (−0.03 to 0.12)	0.04	1.13	.256
	Pandemic age	−0.18 (−0.02 to 0.00)	0.01	−1.86	.062
	Baseline sex	0.34 (−0.05 to 0.70)	0.19	1.70	.089
	Baseline tension symptoms	0.30 (0.13 to 0.42)[a]	0.08[a]	3.70[a]	<.001[a]
	Time between baseline and pandemic	0.09 (−0.17 to 0.28)	0.11	0.47	.636
	Baseline total intracranial volume	−0.23 (−2.27 to −0.17)[a]	0.54[a]	−2.28[a]	.023[a]
	Dataset	−0.07 (−0.80 to 0.67)	0.38	−0.17	.864
Exploratory Analysis					
Anhedonia Symptoms During the Pandemic	Intercept	−0.42 (−2.24 to −0.18)	0.53	−2.30	.021
	Baseline amygdala × baseline self-distraction cope	−0.16 (−0.89 to −0.15)[a]	0.19[a]	−2.78[a]	.005[a,b]
	Baseline amygdala	−0.13 (0.07 to 4.29)[a]	1.08[a]	2.02[a]	.043[a]
	Baseline self-distraction cope	0.15 (0.14 to 0.50)[a]	0.09[a]	3.57[a]	<.001[a]
	Pandemic age	−0.13 (−0.02 to 0.00)	0.00	−1.70	.090
	Baseline sex	0.53 (0.18 to 0.81)[a]	0.16[a]	3.11[a]	.002[a]
	Baseline anhedonia symptoms	0.56 (0.40 to 0.62)[a]	0.06[a]	9.04[a]	<.001[a]
	Time between baseline and pandemic	−0.03 (−0.20 to 0.17)	0.09	−0.17	.868
	Baseline total intracranial volume	−0.15 (−1.76 to 0.23)	0.51	−1.51	.132
	Dataset	0.38 (−0.25 to 0.97)	0.31	1.17	.244
Anhedonia Symptoms During the Pandemic[c]	Intercept	−0.36 (−1.33 to 0.56)	0.48	−0.81	.420
	Baseline amygdala × baseline self-blame cope	−0.13 (−0.71 to −0.01)[a]	0.18[a]	−1.99[a]	.046[a]
	Baseline amygdala	−0.13 (−0.79 to 3.09)	0.99	1.16	.246
	Baseline self-blame cope	0.05 (0.02 to 0.35)[a]	0.09[a]	2.13[a]	.033[a]
	Pandemic age	−0.12 (−0.02 to 0.00)	0.00	−1.59	.112
	Baseline sex	0.52 (0.16 to 0.82)	0.17	2.94	.003[a]
	Baseline anhedonia symptoms	0.57 (0.39 to 0.63)[a]	0.06[a]	8.48[a]	<.001[a]
	Time between baseline and pandemic	−0.00 (−0.19 to 0.19)	0.10	−0.00	.999
	Baseline total intracranial volume	−0.15 (−1.82 to 0.24)	0.52	−1.51	.131
	Dataset	0.31 (−0.33 to 0.91)	0.32	0.91	.360

The table describes significant interactions between coping strategies and neural structure in predicting symptoms during the pandemic. Random effects of race, pandemic student status, and pandemic employment status were included in all models. All independent variables listed in the table are fixed. See the Supplement for random effects variables statistics.

ACC, anterior cingulate cortex; β, standardized beta.

[a]Indicates significant difference ($p < .05$ uncorrected).

[b]Predictor of interest that survived false discovery rate correction.

[c]Anhedonia symptoms are listed twice because the exploratory analyses revealed significant results with anhedonia symptoms as the dependent variable, for two different specific types of coping strategies as independent variables in two different predictive models.

necessarily always adaptive or maladaptive, but instead depend on the context (49). Our findings indicate that the combination of strategies including self-distraction, denial, venting, substance use, behavioral disengagement, and self-blame may lead to higher levels of anxious arousal symptoms during the pandemic, although self-distraction on its own may improve symptoms. Notably, maladaptive coping strategies predicted anxious arousal symptoms, but not anhedonia or tension symptoms. Anxious arousal is characterized by hypervigilance and hyperarousal of the sympathetic nervous system, including physical symptoms of anxiety (e.g., racing heart, trembling hands). Thus, our data suggest that the pandemic stressor may require greater engagement in activities (e.g., work or leisure related) and reduced self-blame to manage anxious arousal symptoms that are exacerbated by ambiguity and a sense of uncontrollability.

We confirmed our hypothesis that preexisting cortical thickness of the insula predicted anxious arousal symptoms during the pandemic. These findings are consistent with prior research showing that reduced insula cortical thickness is implicated in anxiety (23,33,34) and responses to early-life stress (38). The insula plays a role in vigilance in the face of unexpected threat (50), cognitive and affective processing of negative stimuli (51), and emotional stimuli awareness (52). Our data suggest that the insula plays a role in the process by which physiological and autonomic arousal signs of anxiety develop during a salient stressful event such as the global pandemic.

We found that maladaptive coping and amygdala volume interact to predict anhedonia symptoms during the pandemic. Specifically, for individuals with a high maladaptive coping style (including high self-distraction and self-blame), smaller amygdala volume related to more severe anhedonia symptoms, although only the findings related to self-distraction coping survived FDR correction. These results support previous findings that demonstrate smaller amygdala volume in depression (21,23,24). Greater amygdala volume has been associated with an enhanced capacity for positive social processing and less interference from negative inputs (53). Anhedonia is defined by the lack of capacity to process positive affect in addition to interference from negative stimuli (54). Therefore, individuals with lower amygdala volume may have less inherent capacity for positive social processing, and if they use self-distraction coping instead of improving this capacity in the face of pandemic challenges that exacerbate social interaction difficulties, anhedonia symptoms may worsen.

Findings should be interpreted in light of the observation that as a group, only tension symptoms worsened during the pandemic (compared with baseline), while anhedonia symptoms did not differ and anxious arousal symptoms unexpectedly improved. This suggests that people differ in the extent to which their mental health is affected by the pandemic, in addition to the types of symptoms that the pandemic may influence. Nonetheless, approximately 80% of participants subjectively reported that their clinical symptoms worsened as a result of the pandemic, suggesting that the pandemic negatively contributed to mental health for most participants, despite varying impacts between individuals on symptom scores. Furthermore, we found that individuals who completed the follow-up exhibited less severe baseline anxious arousal symptoms compared with those who did not, indicating that individuals whose symptoms likely worsened during the pandemic did not complete the follow-up.

We note several limitations. This investigation focused primarily on depression and anxiety; future studies should examine whether our findings generalize to other types of clinical symptoms. Second, only a subset of participants from baseline completed the pandemic follow-up survey (approximately 28%), and the group who did not complete the follow-up demonstrated more severe anxious arousal symptoms, higher rates of posttraumatic stress disorder, and greater use of maladaptive coping strategies at baseline compared with the group who completed the follow-up. This suggests that individuals who made time to complete these surveys during the pandemic likely experienced less external stress and/or symptoms during the pandemic, thereby reducing the generalizability of our sample. Relatedly, our findings also may not generalize because our sample primarily consisted of symptomatic individuals. Despite this limitation, our study importantly examines a sample who may be at higher risk for worsening of clinical symptoms during the pandemic. In addition, although we covaried for time between baseline and follow-up, there was a large range (0.5–5.7 years), which was a significant covariate for our hypothesis 1 finding (i.e., maladaptive coping predicting anxious arousal symptoms). To maximize the number of participants in this analysis, we included some participants whose baseline visit was several years ago. Findings should be interpreted in light of this limitation. Finally, we selected specific ROIs that have been implicated in emotional processing of stressful events. However, it is possible that other effects exist in the brain outside of our preregistered hypothesized ROIs; future studies should investigate the role of other regions.

In summary, we provide novel insights into the identification of specific coping strategies and alterations in brain structure in individuals pre-pandemic that predict clinical symptoms during the pandemic. We found that self-distraction and self-blame coping strategies, in addition to the structure of brain regions involved in emotion processing, including the insula and amygdala, are involved in emotional responses to the pandemic. These findings elucidate some of the behavioral and neural correlates of poor psychological health during highly stressful events. Future studies that identify coping strategies and brain regions implicated in depression and anxiety symptoms experienced in response to stressful events are critical for promoting resilience in the face of future global health crises.

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LMW conceptualized the design of the primary RAD study and the RAD extension, obtained the funding, and oversaw the scientific implementation of the study. BH-G, LT, IHG, and LMW conceptualized the analytic plan presented in this manuscript. CAR preprocessed the imaging data. BH-G undertook the statistical analysis of the quantified data and generated the figures. BH-G, LT, IHG, and LMW wrote the manuscript. All authors approve the final version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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LMW declares patents 62/589,452 and 15/820,338 Systems and Methods for Detecting Complex Networks in MRI Image Data. All other authors report no biomedical financial interests or potential conflicts of interest.

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