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Data-driven, connectome-wide analysis identifies psychosis-specific brain correlates of fear and anxiety

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Abstract

Decades of psychosis research highlight the prevalence and the clinical significance of negative emotions, such as fear and anxiety. Translational evidence demonstrates the pivotal role of the amygdala in fear and anxiety. However, most of these approaches have used hypothesis-driven analyses with predefined regions of interest. A data-driven analysis may provide a complimentary, unbiased approach to identifying brain correlates of fear and anxiety. The aim of the current study

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AUTHOR CONTRIBUTIONS

BF, MC, SB, DH, KL, DO, AB, MS, RB, JB, and HW initiated and designed the research. BF, AB, KF, and HBW performed data analysis. BF, SH, RB, JB, and HBW interpreted the results. BF, JB, and HBW wrote the manuscript. BF and HBW prepared the figures. All authors edited the manuscript and approved the final submission.

COMPETING INTERESTS

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was to identify the brain basis of fear and anxiety in early psychosis and controls using a data-driven approach. We analyzed data from the Human Connectome Project for Early Psychosis, a multi-site study of 125 people with psychosis and 58 controls with resting-state fMRI and clinical characterization. Multivariate pattern analysis of whole-connectome data was used to identify shared and psychosis-specific brain correlates of fear and anxiety using the NIH Toolbox Fear-Affect and Fear-Somatic Arousal scales. We then examined clinical correlations of Fear-Affect scores and connectivity patterns. Individuals with psychosis had higher levels of Fear-Affect scores than controls ($p < 0.05$). The data-driven analysis identified a cluster encompassing the amygdala and hippocampus where connectivity was correlated with Fear-Affect score ($p < 0.005$) in the entire sample. The strongest correlate of Fear-Affect was between this cluster and the anterior insula and stronger connectivity was associated with higher Fear-Affect scores ($r = 0.31$, $p = 0.0003$). The multivariate pattern analysis also identified a psychosis-specific correlate of Fear-Affect score between the amygdala/hippocampus cluster and a cluster in the ventromedial prefrontal cortex (VMPFC). Higher Fear-Affect scores were correlated with stronger amygdala/hippocampal-VMPFC connectivity in the early psychosis group ($r = 0.33$, $p = 0.002$), but not in controls ($r = -0.15$, $p = 0.28$). The current study provides evidence for the transdiagnostic role of the amygdala, hippocampus, and anterior insula in the neural basis of fear and anxiety and suggests a psychosis-specific relationship between fear and anxiety symptoms and amygdala/hippocampal-VMPFC connectivity. Our novel data-driven approach identifies novel, psychosis-specific treatment targets for fear and anxiety symptoms and provides complimentary evidence to decades of hypothesis-driven approaches examining the brain basis of threat processing.

INTRODUCTION

Psychotic disorders are common and cause significant challenges for individuals and their families [1, 2]. Psychotic disorders impact functioning in multiple domains such as cognition, emotion, and function [3–6]. While the presence and clinical significance of altered emotional processes in psychosis have been acknowledged since the early accounts of psychosis [3, 7], our understanding of the role of emotions in psychosis remains limited. Importantly, alterations of emotions are tied to numerous negative outcomes in individuals with psychosis including increased rates of suicide, increased risk of alcohol and substance abuse, poorer social functioning, and lower quality of life [8–10]. A novel approach to examining the neural basis of disruptions in emotional processes in psychosis may increase our understanding of the mechanisms driving psychosis, as well as inform current interventions and identify new treatment targets.

Exploring the neural mechanisms underlying negative emotions in psychosis is crucial for advancing our understanding of the disorder and developing effective interventions. Alterations in negative emotions, such as fear and anxiety, are prominent in psychosis [11–13]. An accumulation of translational evidence has identified the amygdala as a central brain region involved in fear and anxiety related responses and threat processing, with human neuroimaging studies showing increased amygdala activation to aversive images [14–19]. Later work led to the identification of a larger group of brain regions involved with fear and anxiety-related processes that includes the amygdala, hippocampus, insula,

ventromedial prefrontal cortex (VMPFC), dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), and thalamus [20, 21].

People with psychosis have altered fear and anxiety related processes and amygdala function. They also experience increased levels of fear, anxiety, and stress [11, 13, 22]. For example, 38% of individuals with schizophrenia have a comorbid anxiety disorder and even more report anxiety symptoms [11, 12]. Neuroimaging studies have provided further evidence of amygdala alterations in psychosis. Individuals with psychosis display increased amygdala activation in response to neutral stimuli [23, 24] but have similar activation to emotional/threatening stimuli as controls [25, 26]. Individuals with psychosis also display alterations in amygdala connectivity, including decreased amygdala connectivity with regulatory prefrontal regions at rest and during emotional tasks [27–32]. Together this research provides consistent evidence of amygdala alterations in psychosis. However, much of this work relies on hypothesis-driven approaches using the amygdala as a pre-specified region of interest (ROI). A data-driven analysis may provide a novel, complementary, and unbiased approach to identify the neural correlates of fear and anxiety in psychosis and could identify additional brain regions that are not observed using ROI-based approaches.

The current study aimed to identify the brain basis of fear and anxiety in psychosis using the Human Connectome Project for Early Psychosis (HCP-EP) [33], a large, multisite, transdiagnostic dataset of individuals in the early phase of psychosis. Using the HCP-EP data, we performed an agnostic, data-driven analysis of the entire connectome to identify the neural basis of fear and anxiety across individuals with psychosis and controls. Our analysis aimed to use a data-driven approach to identify future treatment targets for fear and anxiety for individuals with psychotic disorders. Critically, the early phase of psychosis provides a unique window into the identification of the underlying mechanisms and long-term outcomes of the illness [34, 35].

In HCP-EP, fear and anxiety were assessed using the NIH Toolbox Fear-Affect and Fear-Somatic Arousal measures. Although the overlap and distinction of the brain basis of fear and anxiety is an ongoing research question [18, 36–42], the two self-report measures of fear and anxiety included in the HCP-EP dataset do not separate fear and anxiety. Instead, the measures separately assess affect and somatic symptoms of both fear and anxiety. Therefore, we examined the brain basis of fear and anxiety together. Our data-driven approach consisted of two steps: in the first, a multivariate distance matrix regression (MDMR) [43] was used to identify brain regions where global connectivity correlates with level of fear and anxiety, using the NIH Toolbox Fear-Affect and Fear-Somatic Arousal measures. Then in the second step, the identified region was used as a seed to determine how connectivity to this region varied with self-reported fear and anxiety symptoms.

METHODS

Participants

Data from 125 people with early psychosis and 58 matched healthy controls enrolled in the HCP-EP were included in the study (See Supplemental Methods for inclusion and exclusion criteria). Early psychosis participants were defined as being within the first 5 years of

illness onset and were categorized into non-affective or affective psychotic disorders (see Supplemental Methods for details). Prior to participation, all participants provided written informed consent in accordance with the institutional review boards of Indiana University, Indianapolis, Indiana or the Partners Institutional Review Board Committee (now MGB sIRB), which served as the single IRB of record for Boston sites. A total of 162 HCP-EP participants had complete neuroimaging and behavioral data. After completing quality control analyses, there were 138 HCP-EP participants with data available for analysis, including 86 individuals with early psychosis and 52 healthy controls (See Supplemental Table 1).

Behavioral assessments

Fear and anxiety.—Two measures of fear and anxiety symptoms were used from the NIH Toolbox: Fear-Affect and Fear-Somatic Arousal [44]. The two fear and anxiety measures were created for the NIH Toolbox using 55 individual items from three fear and anxiety questionnaires including the Generalized Anxiety Disorder 7 (GAD-7); [45], Mood and Anxiety Symptom Questionnaire (MASQ); [46] and Patient-Reported Outcomes Measurement Information System (PROMIS); [47, 48]. Exploratory factor analyses were conducted on the items, and the best solution was a two-factor solution with factor one capturing the affective and cognitive aspects (Fear-Affect) and the second factor captured the somatic aspects of fear and anxiety (Fear-Somatic); [44]. The two scales provide measures of fear and anxiety symptoms in the past seven days. The Fear-Affect scale is a 21 item self-report measure of perceptions of threat and autonomic arousal using a 5-item Likert scale ranging from “Never” to “Always”. The Fear-Somatic Arousal scale is a 7-item self-report measure of somatic and physiological symptoms of fear/anxiety on a 5-point Likert scale ranging from “Not at all” to “Extremely”. The summed scores were calculated for each measure and transformed into standardized scores (T values), which were used for analysis.

Psychotic symptoms.—The Positive and Negative Symptoms Scale (PANSS) was used to assess the severity of symptoms of psychosis [49]. A five-factor model was used to create PANSS factors for Negative, Positive, Disorganized, Excitement and Distress symptoms [50, 51].

MRI acquisition

All participants underwent a 5.6 min eyes-open resting-state scan (420 whole-brain volumes) where subjects were instructed to remain still during scanning, and deformable foam cushioning was used to stabilize the head. Real time image reconstruction and processing were used for quality assurance at the time of scanning. If there were any detectable problem, the scan was repeated. Data were acquired from three Siemens MAGNETOM Prisma 3 T scanners at Brigham & Women’s Hospital (BWH), McLean Hospital, and Indiana University (IU). BWH and IU used a 32-channel head coil. McLean used a 64-channel head and neck coil, with the neck channels turned off. All protocols were based on the 2016 CCF template protocol. Functional images were collected using the following parameters: 2 mm isotropic resolution, multiband acceleration factor of 8, TR 800 ms, TE 37 ms, 52-degree flip angle, 72 2-mm slices, 208-mm FOV acquired twice: one with

AP and once with PA phase encoding. For this analysis, the PA phase-encoded direction was used. In addition, high-resolution T1-weighted images were acquired for each participant with the following parameters: 0.8 mm isotropic resolution, 256 mm FOV, TR 2400 ms, TE 2.22 ms, 8-degree flip angle.

MRI data processing

All analyses were preprocessed using the DPABI toolbox (Data Processing and Analysis for Brain Imaging, <http://rfmri.org/dpabi>) [52]. For quality control, we removed individual time points with framewise displacement > 0.2 mm via scrubbing [53] and discarded scans that either exceeded motion thresholds (> 3 mm translation or >3 degrees rotation) or had > 50% of volumes removed for framewise displacement. A total of 45 scans were excluded (39 early psychosis, 6 healthy controls). All data were preprocessed to remove motion (24-parameter), CSF signals, white matter signals, global signal, and overall linear trend. A bandpass filter was applied (0.01–0.08 Hz). Data were normalized using the DARTEL toolbox (<http://www.neurometrika.org/node/34>) into Montreal Neurological Institute (MNI) space and smoothed with an 8-mm full-width half-maximum kernel. Voxels within a pre-defined (MNI) gray matter mask were used for further analysis. Data were resampled into 4 mm isotropic resolution prior to MDMR.

Multivariate distance matrix regression (MDMR)

We conducted an assessment across all participants (early psychosis and healthy control) to identify shared and diagnosis-specific circuits of fear/anxiety symptoms. We performed the multivariate pattern analysis of whole-connectome data (MDMR) to identify the strongest links between fear/anxiety and functional connectivity [43]. Briefly, this analysis occurs in two steps: the first step identifies any regions where fear/anxiety symptoms correlate with functional connectivity, and the second step involves seed-based analysis of the identified region (see Seed-Based Connectivity Analysis) to determine the spatial pattern of connectivity it represents [43, 54–56].

After preprocessing, resting-state fMRI data were analyzed with MDMR (Fig. 1) [43]. This method allows for an unbiased, data-driven approach to identifying phenotype-connectivity relationships. MDMR allows quantification of how a variable of interest (Fear-Affect score, Fear-Somatic Arousal score) is reflected in the distributed connectivity of individual voxels to the whole brain (i.e., at the finest resolution possible) without parcellating the brain into regions defined a priori (Fig. 1). In brief, MDMR tests every voxel to determine if whole-brain connectivity to that voxel is more similar in individuals with similar values on an independent measure (Fear-Affect score, Fear-Somatic Arousal score) than in individuals with dissimilar values.

We conducted the MDMR analysis twice to identify anatomical regions where connectivity significantly varied with (1) the Fear-Affect score and (2) the Fear-Somatic Arousal score. We modeled the effect of fear/anxiety symptoms (Fear-Affect or Fear-Somatic Arousal) on functional connectivity while covarying for effects of age, sex, and scanner site. After identifying any MDMR regions, we then conducted seed-based connectivity (see Seed-Based Connectivity Analysis) analysis to examine the spatial distribution of these

connectivity differences regressed against the variable of interest (fear/anxiety score) as in prior MDMR analyses [43, 57–59]. See Supplemental Methods for additional detail.

Seed-based connectivity analysis

The first step of MDMR identifies regions where connectivity correlates to a phenotype (e.g., fear/anxiety), but this initial analysis does not identify the direction of the correlation or its spatial pattern. Therefore, the second step of MDMR (Seed-Based Connectivity Analysis) is performed to reveal the spatial distribution of the results driving MDMR. To visualize spatial patterns of connectivity driving the results of MDMR, maps of connectivity to the region identified in MDMR were generated. This step identifies the spatial pattern of connectivity to the region identified in the MDMR analysis regressed against the variable of interest (fear/anxiety score) [43, 57–59]. The time course of the BOLD signals from rsfMRI scans in the region identified in the MDMR process was extracted and whole brain connectivity maps were generated using DPABI. Using SPM12 (SPM – Statistical Parametric Mapping, <http://www.fil.ion.ucl.ac.uk/spm>) we regressed the z-transformed Pearson’s correlation coefficient connectivity maps against fear/anxiety score, using age, sex, and scanner site as covariates, to generate spatial maps of how whole functional brain connectivity to the region varies with fear/anxiety score. We then measured region to seed connectivity at this step by measuring BOLD correlation between the MDMR-identified region and a 6 mm sphere (seed) placed at the location of maximal connectivity-fear/anxiety association. We then correlated connectivity between the MDMR-identified region and the seeds placed at maximal connectivity-fear/anxiety association with fear/anxiety score. See Supplemental Methods for additional detail.

Statistical approach

Pearson’s correlation coefficients were used to determine the relationships between functional connectivity and behavioral measures. Correlation coefficients were compared using a Fisher’s z test. T-tests were used to compare continuous outcomes based on dichotomous variables. ANOVAs were used to compare continuous outcomes based on three or more groups. All analyses were conducted in RStudio (Version 2023.03.1 + 446) using $\alpha < 0.05$.

RESULTS

Demographics

The psychosis and control groups significantly differed on age ($p < 0.0001$) and race ($p < 0.001$; Supplemental Table 1). See Supplemental Results for analyses of psychosis subgroups (non-affective vs. affective).

Individuals with early psychosis report higher levels of fear/anxiety

Individuals in the early psychosis group had higher scores compared to healthy controls on the Fear-Affect (56.44 vs. 49.7, $p = 0.0004$, Fig. 2) and Fear-Somatic Arousal scales (55.12 vs. 44.35, $p < 0.000001$, Fig. 2). The Fear-Affect score was correlated with the Fear-Somatic Arousal score ($r = 0.52$, $p = 5.9e-11$) in the full sample. Neither fear/anxiety measure differed by race (Fear-Affect $p = 0.75$; Fear-Somatic Arousal $p = 0.14$), and there was no

interaction between diagnostic group and race on either fear/anxiety score (Fear-Affect $p = 0.57$, Fear-Somatic Arousal $p = 0.41$). See Supplemental Results for analyses of psychosis subgroups.

Fear/anxiety scores are related to amygdala/hippocampal connectivity to the anterior insula

The data-driven analysis using MDMR revealed significant relationships between functional connectivity and NIH Fear-Affect t-score in the full sample (early psychosis and healthy controls, $N = 138$). We identified a single region (Cluster $k = 86$, $x = 18$, $y = 12$, $z = 23$), primarily encompassing the left amygdala and hippocampus (with extension into the temporal lobe, brainstem, and cerebellum), where functional connectivity correlated with Fear-Affect score ($p < 0.005$) (Fig. 3). The MDMR analysis also revealed a significant relationship between the Fear-Somatic Arousal score, with a 40-voxel cluster also centered around the left amygdala/hippocampus, but this cluster did not reach brain-wide significance ($p > 0.005$).

Next, we determined the spatial pattern of connectivity of this brain cluster related to Fear-Affect score. To obtain greater anatomical specificity in the connectivity patterns related to the regions within the significant Fear-Affect cluster [19], we identified the boundaries of the significant cluster that overlapped with the left amygdala/hippocampus using amygdala and hippocampus masks from the Harvard-Oxford atlas thresholded at a 50% probability [60]. Whole-brain connectivity maps were recalculated from this amygdala/hippocampal cluster, regressing connectivity against NIH Fear-Affect t-score; then the spatial pattern of connectivity of this amygdala/hippocampal cluster was examined (Fig. 3). We observed that higher Fear-Affect t-scores were associated with higher amygdala/hippocampus connectivity with multiple regions previously associated with fear processing: ACC, bilateral insula, hippocampus, amygdala, and multiple prefrontal regions (DLPFC, VMPFC). To confirm that our segmentation of the original cluster to obtain greater anatomical specificity did not alter the connectivity pattern of the cluster, we also generated maps from (1) the original MDMR cluster (Supplemental Fig. 1) and (2) the individual amygdala and hippocampus segmentations from the original cluster (Supplemental Fig. 2), all regressed against Fear-Affect score. These maps all showed connectivity to the same regions (i.e. VMPFC, bilateral amygdala/hippocampus, and bilateral insula).

To identify the strongest connectivity correlation with Fear-Affect score we performed a seed to voxel analysis using the amygdala/hippocampus cluster as a seed and regressed connectivity against Fear-Affect score. The strongest correlation was between the left amygdala/hippocampus cluster and a cluster in the right anterior insula ($x = 28$, $y = 20$, $z = -12$) in the full sample ($r = 0.31$, $p = 0.0003$) (Fig. 4). Amygdala/hippocampal-anterior insula connectivity was also associated with the Fear-Somatic Arousal score ($r = 0.22$, $p = 0.01$) in the full sample. To test if the relationship between fear/anxiety and amygdala/hippocampal-anterior insula connectivity might be explained by shared variability in the Fear-Affect and Fear-Somatic Arousal measures, rather than unique contributions from each scale, we included both Fear-Affect and Fear-Somatic Arousal in a model predicting amygdala/hippocampal-anterior insula connectivity. In this model, only Fear-Affect was a significant predictor ($p = 0.006$).

A post-hoc test between groups showed that there was no group difference (psychosis vs. control) in amygdala/hippocampal-insula connectivity ($p = 0.63$). There was also no group difference in the correlation between amygdala/hippocampal-insula connectivity and Fear-Affect score ($p = 0.57$). In the psychosis group, the connectivity-fear/anxiety correlation was not affected by antipsychotic medication ($p = 0.84$).

Amygdala/hippocampus-VMPFC connectivity is related to fear/anxiety only in the early psychosis group

To identify psychosis-specific brain correlates of fear/anxiety, we performed seed to voxel analyses using the amygdala/hippocampus cluster in the early psychosis and healthy control groups separately (Fig. 5). In the psychosis group, the strongest correlate of Fear-Affect scores was connectivity between the amygdala/hippocampal cluster and the VMPFC (Fig. 6; $x = 8, y = 56, z = 0, r = 0.33, p = 0.002$). This association between amygdala/hippocampal-VMPFC connectivity and Fear-Affect was specific to the psychosis group and not observed in the control group ($r = -0.15, p = 0.28$). Further, there was a significant group difference in the correlations between amygdala/hippocampal-VMPFC connectivity and Fear-Affect score ($p = 0.006$).

In psychosis, sex is a predictor of fear

Due to evidence of sex differences in the brain networks involved in the threat processing [61–63], we conducted exploratory analyses of sex differences in the fear/anxiety scores and connectivity measures. When we used included group, sex, and their interaction in a model, we did not observe any sex differences for Fear-Affect, Fear-Somatic Arousal, or amygdala/hippocampus-insula connectivity. In the entire sample, the relationship between amygdala/hippocampal-insula connectivity and Fear-Affect score was present in women ($r = 0.40, p = 0.004$) and men ($r = 0.28, p = 0.008$) and did not differ by sex ($p = 0.46$).

In the psychosis group, using a model predicting amygdala/hippocampus-VMPFC connectivity, sex was a significant predictor ($p = 0.0007$). In the psychosis group, women had lower amygdala/hippocampus-VMPFC connectivity than men (-0.0041 vs. $0.13, p = 0.0003$). The relationship between amygdala/hippocampal-VMPFC connectivity and Fear-Affect score was present in women ($r = 0.45, p = 0.01$) and men ($r = 0.41, p = 0.002$) and did not differ by sex ($p = 0.41$, Supplemental Fig. 3).

Fear/anxiety symptoms are correlated with psychosis symptoms

Using the PANSS five-factor model in the early psychosis group, the Distress Factor (anxiety, depression, guilt, tension) was strongly correlated with Fear-Affect ($r = 0.52, p < 0.000001$) but not related to Fear-Somatic Arousal ($r = 0.18, p = 0.10$). The PANSS Distress Factor was not correlated with amygdala/hippocampus-insula connectivity ($r = 0.18, p = 0.11$) nor with amygdala/hippocampus-VMPFC connectivity ($r = 0.12, p = 0.29$). The other PANSS factors were not related to the measures of fear and anxiety or connectivity.

DISCUSSION

The current study aimed to identify the brain basis of fear and anxiety in psychosis using an agnostic, data-driven analysis of the Human Connectome Project for Early Psychosis. The first aim was to determine if our data-driven approach would identify the traditional fear and anxiety network across the whole sample or if additional brain regions tied to fear and anxiety would be discovered. The second aim was to determine the specific brain basis of fear and anxiety in individuals with early psychosis using a data-driven approach. Our study identified both shared and psychosis-specific brain connectivity correlates of fear and anxiety symptoms in individuals with psychotic disorders and matched controls. Importantly, we identified a novel, psychosis-specific pattern of increased amygdala/hippocampus-VMPFC connectivity related to fear and anxiety. In addition, the shared brain basis of fear and anxiety across the psychosis and control groups aligned with existing literature identifying the amygdala, hippocampus, and anterior insula as central brain regions in a canonical fear and anxiety circuits. Together, this data-driven study provides novel, strong evidence for a psychosis specific connection between the VMPFC and amygdala/hippocampus and for the transdiagnostic roles of the amygdala, hippocampus, and insula in fear and anxiety processes in individuals with and without psychotic disorders.

Our data-driven approach provides evidence for crucial role of the amygdala and hippocampus in fear and anxiety across psychosis and control groups. Decades of translational evidence demonstrates that the amygdala is central to fear and anxiety processing and mediates a broader network that includes the hippocampus [20, 21]. In our study, we found additional evidence of the central role of the amygdala and hippocampus, using a novel, agnostic, data-driven approach. Given the challenges the field faces in replication of findings especially across studies [64], the alignment of hypothesis driven region-based approaches and data driven approaches is critical, novel, and important. The amygdala/hippocampal connectivity edge most significantly related to fear/anxiety was its connection to the anterior insula, aligning with previous work demonstrating the role of the anterior insula in fear and anxiety [19, 21, 36]. Further validating our results, self-reported fear/anxiety was also associated with amygdala/hippocampus connectivity with multiple regions known to be associated with fear and anxiety and intrinsically connected to the amygdala including with the dorsal anterior cingulate cortex (dACC), prefrontal regions (DLPFC, VMPFC) and bilateral insula [65–70]. Together our findings highlight that the amygdala, hippocampus, and insula have a central role in fear and anxiety processes both in people with and without psychosis. Of note, the MDMR cluster of the amygdala/hippocampus was on the right side, but at a lower threshold this cluster was apparent bilaterally (as shown in Fig. 3) and therefore may not suggest specific laterality findings. However, this should be explored by future studies.

Importantly, our study identified a novel psychosis-specific association between the amygdala/hippocampus and VMPFC that was associated with fear and anxiety symptoms. The VMPFC is involved in regulating fear and anxiety. Task activation studies show that the VMPFC is also crucial for fear extinction, a process that involves learning that certain contexts are safe versus threatening [19, 71–73]. In healthy individuals, increased hippocampus-VMPFC connectivity is associated with better fear extinction recall [72]. Our

findings of heightened connectivity of the fear and anxiety network at rest align with previous studies in schizophrenia showing heightened limbic responses during baseline conditions including neutral or safe stimuli, but intact fear processing. For example, fear conditioning and extinction studies in psychosis demonstrate that differences are driven by a heightened response to the baseline condition (CS-) and safety cues rather than the fear extinction process [74–76]. On the other hand, there is some evidence for lower VMPFC-amygdala connectivity at rest in individuals with anxiety disorders [77] and people with schizophrenia [78]. The opposing amygdala connectivity findings may be due to our novel data driven approach capturing different regions of the VMPFC and amygdala compared to studies using priori defined masks of the regions. Therefore, our study suggests the unique pattern of higher VMPFC-amygdala/hippocampus connectivity in early psychosis may reflect the sustained increase in the fear and anxiety networks at baseline in individuals with early psychosis with high levels of fear and anxiety.

Although the early psychosis group demonstrated higher levels of fear and anxiety than controls, but there was also significant variability in the fear/anxiety scores. This may suggest that a specific subgroup of individuals of psychosis are experiencing heightened levels of anxiety. Sex was also a significant psychosis-specific predictor of fear/anxiety scores. Previous theories of an affective pathway to psychosis propose a subgroup of individuals with psychosis that are more likely to be women and demonstrate elevated negative emotions, increased stress sensitivity, and increased distress [13]. Therefore, future research should aim to examine further and to classify this variability in negative emotions to identify potential subgroups of individuals with early psychosis.

Strengths of our analysis are its data-driven methodology and transdiagnostic sample that includes both psychosis and control groups. Specifically, our early psychosis population allows us to study underlying brain mechanisms without the confounding of the effects of age-related degeneration, chronic illness, and/or long-term antipsychotic treatment [34, 35]. However, this study had limitations. First, the HCP-EP used the NIH Toolbox, which only includes two self-reported measures of fear and anxiety that do not separately assess fear and anxiety. In the future it will be important for studies to use both subjective and objective (i.e. tasks, physiological) measures that distinctly assess both fear and anxiety. Second, the current study used resting state fMRI. Although resting state connectivity provides measures of altered intrinsic connectivity, it is important to also examine task-based connectivity during tasks that induce negative emotions. Future studies should also aim to use behavioral tasks in the MRI to induce states of fear and anxiety to determine how brain activity and connectivity may differ when negative emotions are evoked. Third, the current MDMR approach is a rigorous, data-driven analytic method with the ability to identify brain circuitry previously undiscovered by hypothesis-driven designs. However, with the current sample size, the initial step of this approach is less likely to capture smaller brain regions. Although a broad, whole-brain approach is helpful, there may be smaller brain regions that are missed with this method and are better examined using an ROI-based approach, such as the bed nucleus of the stria terminalis [30, 79]. Therefore, future studies should continue to use both the whole brain and ROI-based approaches depending on the research question. Fourth, the resting state scan used for the analyses is short (5 min) compared to current standards, as studies suggest that longer resting state scans may more

accurately represent resting state networks [80]. However, the subject group of our study (i.e., symptomatic individuals with early psychosis) is unique, difficult to identify, and challenging to image. Moreover, extended resting-state scans are at risk of greater movement artifact, especially with clinical populations. Therefore, our findings are an important first step for understanding the networks underlying fear and anxiety in early psychosis, but future studies should aim to replicate our findings with longer resting state scans. Fifth, the HCP-EP early psychosis group includes both affective and non-affective psychosis. Although we did not find significant differences between the two groups, the psychosis group was predominantly non-affective. Previous studies have shown differences between affective and nonaffective psychosis [81, 82] and future studies should further examine the differences between the two groups in a larger sample. Finally, our analysis identified a psychosis-specific brain correlate of fear symptoms; however, alterations in VMPFC connectivity are observed in other clinical populations [83, 84]. Therefore, future studies should test the associations between amygdala/hippocampus-VMPFC connectivity and fear and anxiety symptoms in several transdiagnostic samples.

The current study examined the brain basis of fear and anxiety by utilizing a data-driven analysis of the entire connectome. Our findings highlight the central role of the amygdala, hippocampus, anterior insula, and VMPFC in fear and anxiety and provide complimentary evidence from a novel data-driven approach to decades of hypothesis driven approaches. Our findings further our knowledge of the brain basis of fear and anxiety in normative populations as well as individuals with psychosis and identify a psychosis-specific brain correlate of fear and anxiety symptoms. These results have important treatment implications for both populations. For example, individuals with psychosis experience higher levels of fear and anxiety, which contribute to increased risk for negative outcomes and lower quality of life [8–10]. Therefore, the fear and anxiety circuit we have identified could serve as a biomarker or treatment target. Specifically, the VMPFC may provide a psychosis-specific target for modulation of fear and anxiety. Noninvasive neuromodulation, such as repetitive transcranial magnetic stimulation, should be used to probe fear and anxiety circuitry to modulate connectivity in this network and responses [85]. Future research should continue to examine the utility of novel treatment approaches targeting fear and anxiety networks.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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DATA AVAILABILITY

Data presented in the present work was collected and minimally processed by the Human Connectome Project, specifically the early psychosis subgroup and sites. Statistics, analysis scripts, and figures are available from the corresponding author upon reasonable request.

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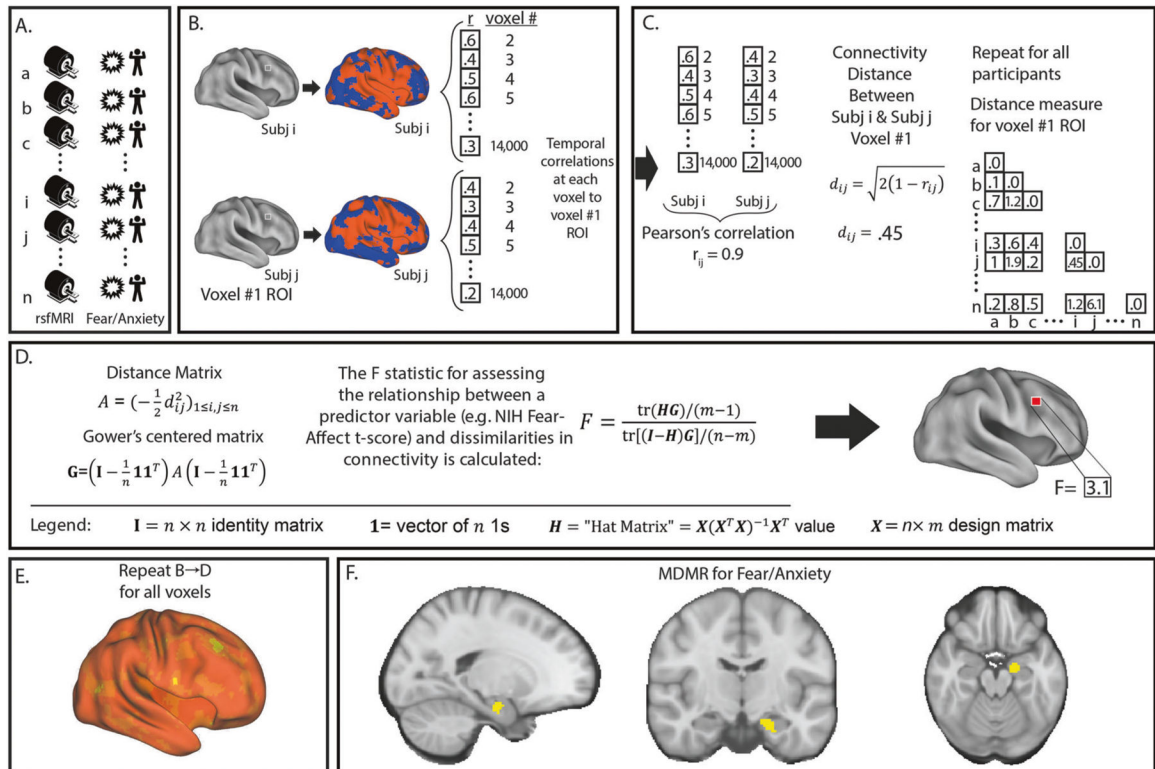


Fig. 1. Multivariate distance matrix regression (MDMR).

NIH Toolbox t-score measures of fear and anxiety (Fear-Affect, Fear-Somatic Arousal) and resting-state functional MRI (rsfMRI) data were collected for each participant **A**. For each voxel in the brain, the voxel was used as a seed region to create a connectivity map for each participant **B**. These maps were compared with each other to create a subject-wise similarity matrix **C**. Fear/anxiety scores for each participant were then combined with the connectivity similarity matrix to produce a pseudo-F statistic, which characterizes how individual variation in fear/anxiety scores explains individual variation in functional connectivity **D**. This is repeated for all voxels **E**. Each MDMR voxel-wise result was then combined to produce a map of the ability of the connectivity pattern to predict a fear/anxiety score in each voxel **F**. A permutation test of the study subjects' labels is used to test the significance of this pseudo-F statistic.

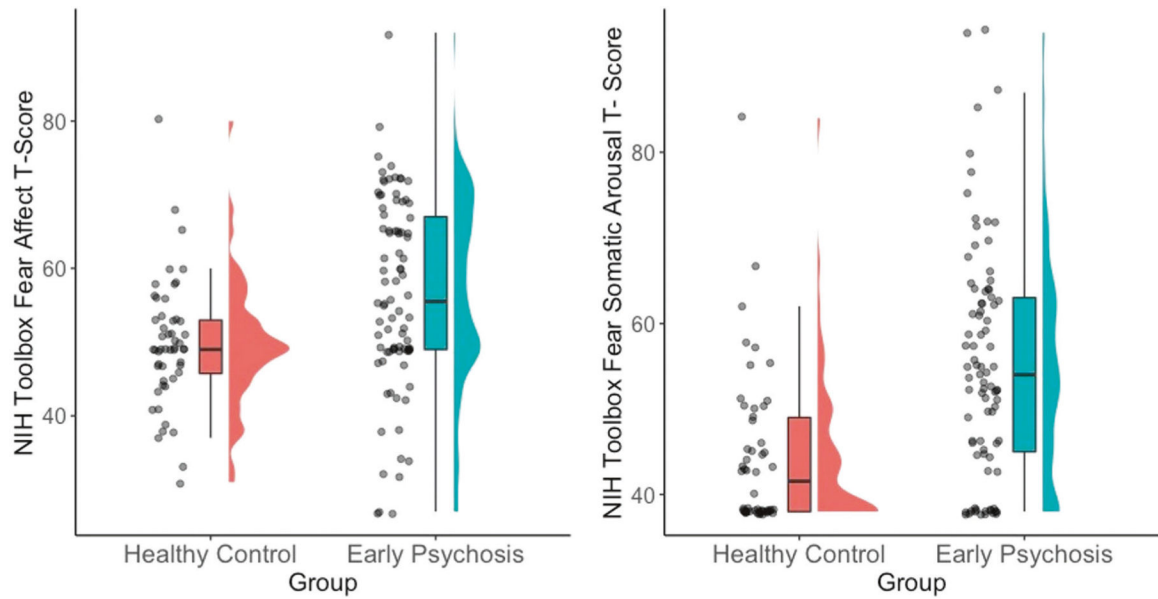
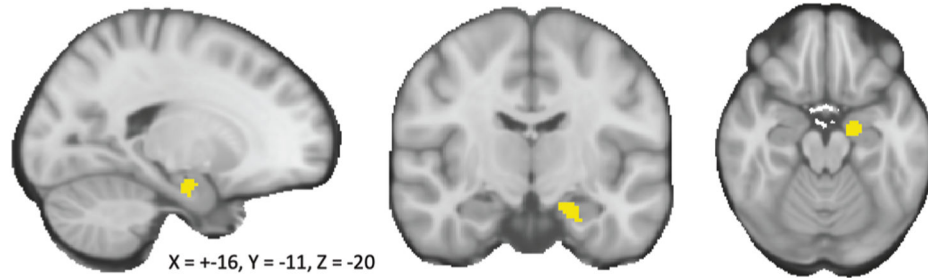


Fig. 2. Individuals in the early psychosis group ($n = 86$) had higher fear and anxiety scores than healthy controls ($n = 52$).

Individuals in the early psychosis group had higher scores compared to healthy controls on the Fear-Affect score (56.44 vs. 49.7, $p = 0.0004$) and on the Fear-Somatic Arousal score (55.12 vs. 44.35, $p < 0.000001$).

A. Entire Sample: Amygdala/Hippocampus MDMR Result

n=138



B. Entire Sample: Amygdala/Hippocampus Cluster Maps Regressed Against Fear-Affect Score

n=138

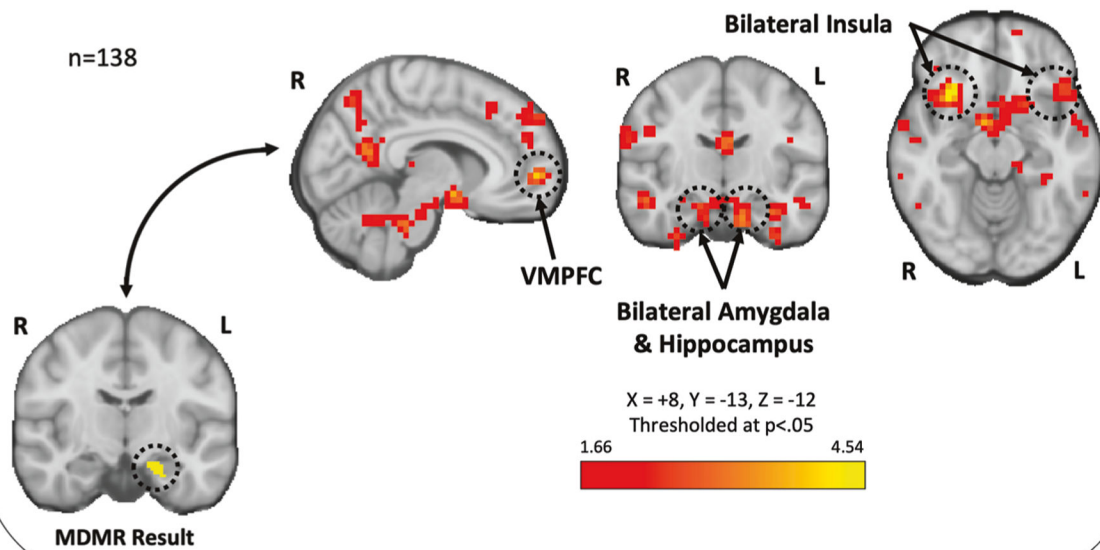


Fig. 3. Amygdala/hippocampal connectivity to broader network.

Our data-driven analysis identified a significant relationship between functional connectivity and Fear-Affect score ($p < 0.005$) in the entire sample between a region encompassing the amygdala and hippocampus (MDMR Result, Cluster $k = 86$, $x = 18$, $y = 12$, $z = 23$). To obtain greater anatomical specificity in the connectivity patterns related to the regions within the significant Fear-Affect cluster [19–21], we identified the boundaries of the significant cluster that overlapped with the left amygdala/hippocampus using amygdala and hippocampus masks from the Harvard-Oxford atlas thresholded at a 50% probability (Fig. 3A). Whole-brain connectivity maps were calculated from this amygdala/hippocampal cluster, regressing connectivity against NIH Fear-Affect t-score; then the spatial pattern of connectivity of this amygdala/hippocampal cluster was examined. Higher Fear-Affect scores were associated with stronger connectivity with multiple regions in a canonical fear network (Fig. 3B): the dACC, bilateral insula, hippocampus, amygdala, and multiple prefrontal regions (DLPFC, VMPFC). Color bar displays T-statistic. Displayed map is thresholded at $p < 0.05$.

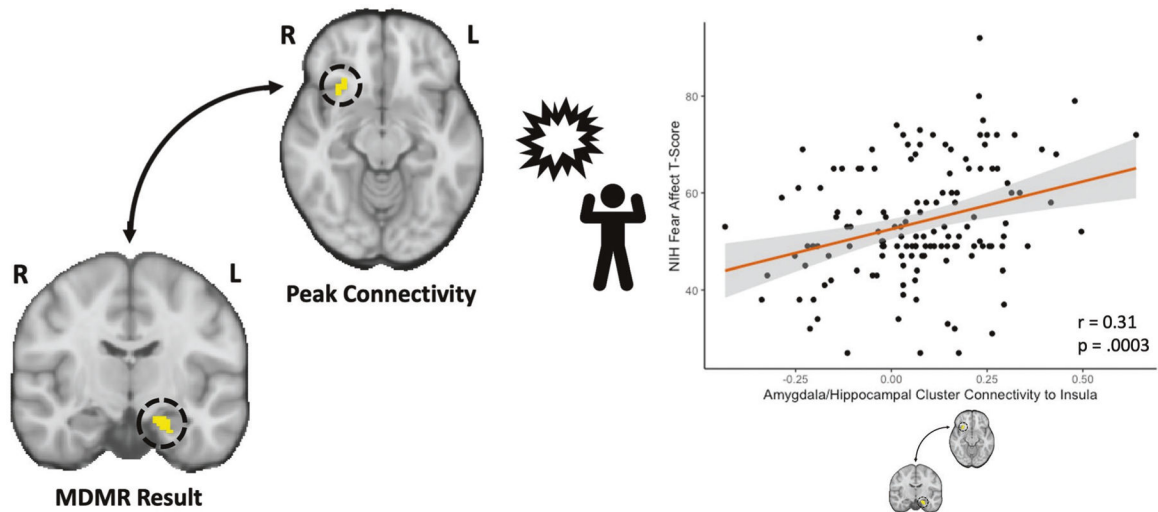


Fig. 4. Amygdala/hippocampal-insula connectivity is related to fear-affect scores in early psychosis and healthy controls.

Fear-Affect scores were correlated with connectivity between the amygdala/hippocampal cluster (MDMR result) and a cluster in the right anterior insula (Peak Connectivity; MNI $x = 28$, $y = 20$, $z = -12$, $r = 0.31$, $p = 0.0003$).

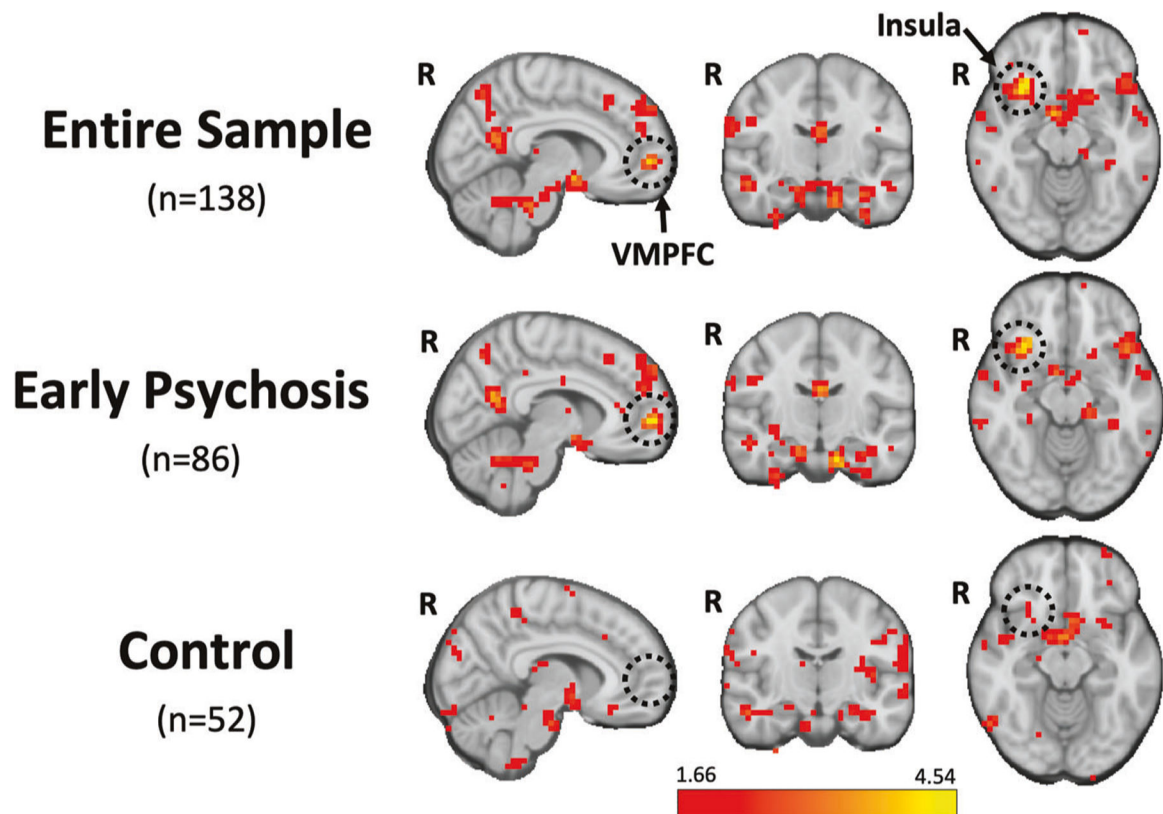


Fig. 5. Group-specific differences in amygdala/hippocampal cluster connectivity regressed against fear-affect score.

All three groups showed significant connectivity between the amygdala/hippocampus and right anterior insula. Connectivity with the VMPFC was only observed in the entire sample and early psychosis groups. Color bar displays T-statistic. Displayed map is thresholded at $p < 0.05$.

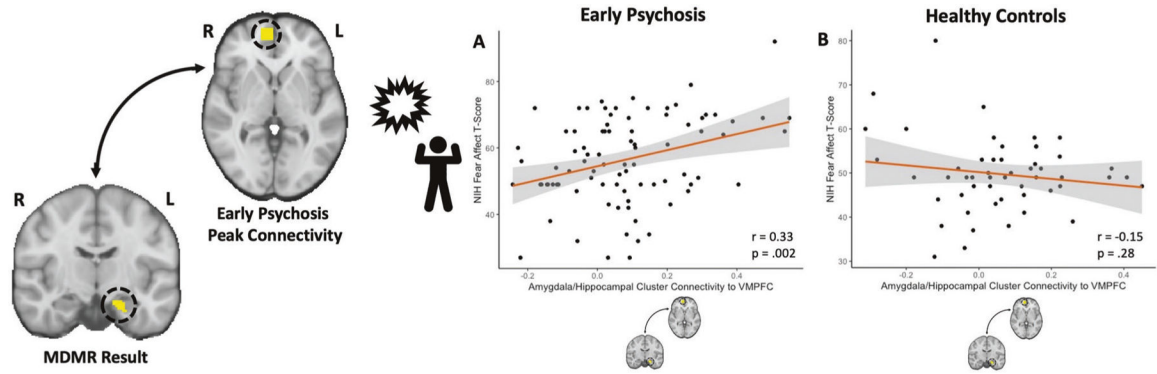


Fig. 6. Amygdala/hippocampal-VMPFC connectivity is related to fear-affect scores in early psychosis but not in healthy controls.

The left image shows the psychosis-specific finding where the strongest correlate of Fear-Affect was connectivity between the amygdala/hippocampal cluster (MDMR Result) and the VMPFC (Early Psychosis Peak Connectivity, $x = 8$, $y = 56$, $z = 0$). **A** Amygdala/hippocampal-VMPFC connectivity was significantly related to Fear-Affect score in the early psychosis group ($r = 0.33$, $p = 0.002$). **B** There was not a significant correlation between Amygdala/hippocampal-VMPFC connectivity and Fear-Affect in controls ($r = -0.15$, $p = 0.28$). There was a significant group difference between the correlations ($p = 0.006$).