

# Specific Patterns of Endogenous Functional Connectivity Are Associated With Harm Avoidance in Obsessive-Compulsive Disorder

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## ABSTRACT

**BACKGROUND:** Individuals with obsessive-compulsive disorder (OCD) show persistent avoidance behaviors, often in the absence of actual threat. Quality-of-life costs and heterogeneity support the need for novel brain-behavior intervention targets. Informed by mechanistic and anatomical studies of persistent avoidance in rodents and nonhuman primates, our goal was to test whether connections within a hypothesized persistent avoidance-related network predicted OCD-related harm avoidance (HA), a trait measure of persistent avoidance. We hypothesized that 1) HA, not an OCD diagnosis, would be associated with altered endogenous connectivity in at least one connection in the network; 2) HA-specific findings would be robust to comorbid symptoms; and 3) reliable findings would replicate in a holdout testing subsample.

**METHODS:** Using resting-state functional connectivity magnetic resonance imaging, cross-validated elastic net for feature selection, and Poisson generalized linear models, we tested which connections significantly predicted HA in our training subsample ( $n = 73$ ; 71.8% female; healthy control group  $n = 36$ , OCD group  $n = 37$ ); robustness to comorbidities; and replicability in a testing subsample ( $n = 30$ ; 56.7% female; healthy control group  $n = 15$ , OCD group  $n = 15$ ).

**RESULTS:** Stronger inverse connectivity between the right dorsal anterior cingulate cortex and right basolateral amygdala and stronger positive connectivity between the right ventral anterior insula and left ventral striatum were associated with greater HA across groups. Network connections did not discriminate OCD diagnostic status or predict HA-correlated traits, suggesting sensitivity to trait HA. The dorsal anterior cingulate cortex-basolateral amygdala relationship was robust to controlling for comorbidities and medication in individuals with OCD and was also predictive of HA in our testing subsample.

**CONCLUSIONS:** Stronger inverse dorsal anterior cingulate cortex-basolateral amygdala connectivity was robustly and reliably associated with HA across groups and in OCD. Results support the relevance of a cross-species persistent avoidance-related network to OCD, with implications for precision-based approaches and treatment.

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Persistent active avoidance, which is continued safety seeking in the absence of threat, is a characteristic feature of obsessive-compulsive disorder (OCD) that significantly impacts patients' quality of life. Because many individuals with OCD do not fully respond to or tolerate conventional treatments (1–3), it is critical to develop new interventions. Elucidating the neural network abnormalities that are associated with persistent avoidance can provide objective markers that reflect underlying pathophysiological processes in OCD as targets to guide the development of novel and precision-based treatment approaches.

Extensive rodent model work suggests a causal link between altered connectivity within a cortico-amygdala-striatal network and persistent avoidance. These studies showed

that neurons in the basolateral amygdala (BLA) and prelimbic cortex (PL) [circuit-level similarities to primate dorsal anterior cingulate cortex (dACC) (4,5)] play a major role in the detection and selection of salient predictive cues and behavioral responses under decision uncertainty and learning (6,7). These regions, along with the ventral striatum (VS), support the expression of persistent avoidance in rodents (8). Specifically, while neurons in the PL help guide behavior under uncertain threat/reward, activation of glutamatergic PL neurons during conditioned threat/reward uncertainty was causally linked to greater avoidance behavior in rats, while their inhibition increased approach (9). Furthermore, activation of PL-BLA or BLA-VS and silencing PL-VS projections facilitated avoidance behavior, while the opposite reduced avoidance behavior (6).

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Thus, opposing PL and BLA projections to the VS may reflect competing behavioral control mechanisms, with PL–BLA projections being necessary for avoidance modulation when uncertainty/conflict is high. Further extending this cortico-amygdala-striatal network, the anterior insula (alns) and lateral orbital cortex have excitatory projections to the rostral PL, and inhibiting these cortico-cortical projections facilitated persistent avoidance following extinction with response prevention training (10).

The anatomical and functional organization of this cortico-amygdala-striatal network in nonhuman primates (NHPs) and humans largely overlaps with the rodent literature (11), making it a solid mechanistic starting point for increasing understanding of the neural mechanisms that underlie persistent avoidance in individuals with OCD. Neurons in the NHP dACC (similar circuitry to rodent PL) respond to available threat and reward information that guide behavioral control in the context of uncertainty (12). In NHPs, there are projections between subregions of the NHP caudal ventrolateral prefrontal cortex (vlPFC) (Brodmann area 42/11, similarity to rodent alns/lateral orbital cortex and human vlPFC/lateral orbitofrontal cortex [lOFC] [Brodmann area 47/45/44]) and the BLA (11,13), and vlPFC neurons respond to preferences for resolving uncertainty related to threat versus reward (12) and value discrimination (14). Lesions to the vlPFC in NHPs impair learning under uncertainty and reduce the ability to respond appropriately to learned contingency changes (15). This suggests key roles for the vlPFC and dACC in combining existing/prior beliefs and attitudes with currently available information to optimize value-driven choice. Consistent with this, the caudal vlPFC (Brodmann area 47/12) is a key integrative region that signals switches in attentional control between the canonical ventral and dorsal attention networks (16–18). These networks signal the salience of new or unexpected information (signaled by the alns and its connections with the BLA and VS) (19,20) relative to voluntary/goal-directed attentional control, respectively (21,22).

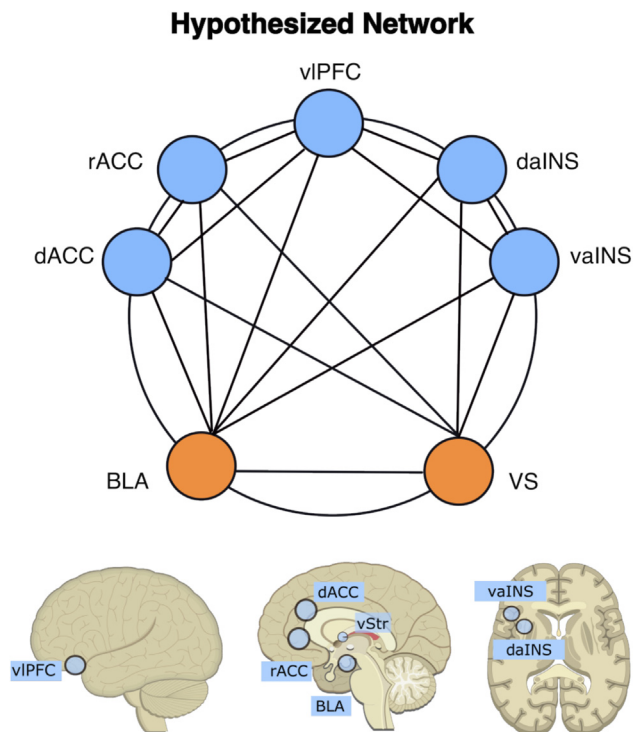
The BLA and VS in NHPs also signal different associative relationships and behavioral responses in uncertain (probabilistic) learning contexts (11,23,24). BLA lesions in NHPs impact choice behavior and reinforcement learning in reward and loss contexts and in probabilistic and deterministic learning contexts (25,26). Conversely, VS lesions result in higher response urgency and more errors, but only during probabilistic learning (25). Single-neuron recordings in NHPs suggest that stronger inverse synchrony between BLA and dACC activity during probabilistic learning leads to persistence of fear-related memories, greater synchrony during threat recall, and greater resistance to fear extinction (27,28). Additionally, BLA deactivation that is driven by dACC excitation while learning new associations, but not during testing, impairs devaluation task performance (27). Thus, both rodent and NHP research support causal links between persistent avoidance and impairments in an anatomically constrained network. Findings in both species suggest that behavioral inflexibility may emerge from inflexible attentional control that results from aberrant connectivity between vlPFC/alns and dACC. Alternatively, inflexible behavioral control may be due to aberrant connectivity between vlPFC/dACC and BLA, BLA and VS, dACC and VS, and/or alns connectivity with the BLA and VS given

their potential role in persistent avoidance, especially under conditions of uncertain or perceived threat.

Compared to the extensive animal work on persistent avoidance and expansive literature on affective processing and executive function in individuals with OCD (29), fewer studies have focused specifically on neural networks that underlie persistent avoidance in this population. Using a region of interest (ROI)-based functional connectivity magnetic resonance imaging (fcMRI) approach, Gillan *et al.* (30) reported that persistent avoidance in OCD was associated with hyperactivation of the caudate compared with healthy control (HC) participants. Greater caudate activation was also positively associated with self-reported urge to engage in habit-based actions (30). While hyperactivation of the OFC was observed with threat avoidance learning in OCD, it was not linked to persistent avoidance following threat removal (30). Focusing on prefrontal regions, we (31) reported that, compared with individuals with OCD and those with intact devaluation, individuals who failed to devalue behaviorally irrelevant cues showed reduced premotor cortex and vlPFC activity. These studies also suggest that neural substrates that underlie variability in persistent avoidance may not be observable using group comparisons alone, especially given that associated tendencies are observed at lower severity but similar variance in HC participants (32).

Resting-state fcMRI (rs-fcMRI) has been used to examine the endogenous organization of neural networks in participants with OCD compared with HC participants more broadly (33). rs-fcMRI has been consistently and reliably linked to trait-like tendencies and behavioral performance across multiple tasks in healthy and clinical populations, reflecting stable endophenotypes that can be used to understand individual differences (34–36). There are reports of hypoconnectivity between some hypothesized persistent avoidance network regions in OCD, including among inferior VS–dACC and OFC–VS (37) and between the alns and regions of the cortico-thalamic pathway more broadly, including the lateral PFC (38). Moreover, hyperconnectivity was reported between the VS–OFC and VS–ACC and between dorsal striatal regions and the lateral PFC (39–41). These inconsistent whole-brain rs-fcMRI findings in OCD are likely due to differences in seed/network selection (37), differences in age and symptom duration between samples (31,42), medication status (37,39,40), or overall symptom heterogeneity (40).

However, while existing studies inform heuristic-based hypotheses around neural network organization in OCD and overlap with causal networks that impact threat-related recall and learning in rodents and NHPs, they are not grounded in a translationally informed mechanistic understanding of neural networks associated with persistent avoidance. Using a constrained network (Figure 1) can facilitate the identification of a mechanistic model to guide understanding of the neural network abnormalities associated with persistent avoidance in individuals with OCD. Furthermore, while the above studies examining neural correlates of OCD indicate impairments in cortico-striato-thalamo-cortical networks, there are distinct networks involved in continuous trait-level OCD-related behaviors that contribute to persistent avoidance specifically. For example, reduced extinction to anxiety-provoking stimuli in HC participants has been associated with reduced connectivity



**Figure 1.** Illustration of hypothesized persistent avoidance-related network and associated regions included in this study. BLA, basolateral amygdala; dACC, dorsal anterior cingulate cortex; daINS, dorsal anterior insula; rACC, rostral anterior cingulate cortex; vaINS, ventral anterior insula; vIPFC, ventrolateral prefrontal cortex; VS/vStr, ventral striatum.

between the left amygdala and ACC, while OCD-related traits such as harm avoidance (HA) in HC participants show associations with altered activity including greater fronto-amygdala connectivity [see (32) for review].

Informed by mechanistic studies of persistent avoidance in rodents and NHPs, the aims of this study were to 1) identify measures of endogenous functional connectivity in the hypothesized persistent avoidance-related neural network that are associated specifically with HA, a trait-level measure associated with persistent avoidance, as opposed to the broader diagnostic category of OCD; 2) test the extent to which these associations remain after accounting for other OCD symptoms and comorbid depression and anxiety; and 3) test whether findings would replicate in a holdout testing subsample. We used established methods for feature selection that are appropriate given the high dimensionality of our feature space relative to sample size and to avoid redundancies in the final model. Given the findings mentioned above that have linked specific regional connections within our neural network of interest and persistent avoidance, we hypothesized that 1) HA would be associated with significant alterations in endogenous connectivity in one or more of the following known direct connections in the network: vIPFC–dACC, vIPFC–alns, vIPFC–BLA, alns–dACC, dACC–BLA, BLA–VS, dACC–VS, alns–VS, and alns–BLA; 2) these associations would remain significant after controlling for other OCD and comorbid symptoms in individuals with OCD; and 3)

findings would replicate in a feature selection-naïve holdout testing subsample.

## METHODS AND MATERIALS

### Participants

We recruited 106 right-handed participants (ages 18–35 years; OCD  $n = 54$ ; HC  $n = 52$ ) from community and outpatient settings. The sample was randomly split into training (70%) and holdout testing (30%) subsamples with equal proportions of HC participants and participants with OCD in each subsample.

### Procedures

Individuals were phone screened for MRI contraindications and handedness. If eligible, participants signed informed consent (protocol approved by the University of Pittsburgh Institutional Review Board) and completed a clinical evaluation. Participants who continued to meet eligibility criteria were scheduled for their functional MRI session at the University of Pittsburgh Magnetic Resonance Research Center, where they completed structural resting-state scans [viewing a fixation cross; scan procedures and parameters have been published previously (43)] (Supplement).

### Clinical Evaluation

The research study clinician, a licensed clinical social worker, conducted diagnostic evaluations using the Structured Clinical Interview for DSM-5. Measures used to test hypotheses were the Obsessive-Compulsive Trait Core Dimensions Questionnaire (OC-TCDDQ) [HA and incompleteness (INC) subscales (44)]; Yale-Brown Obsessive Compulsive Scale (Y-BOCS) (45); Hamilton Depression Rating Scale (46); and the Hamilton Anxiety Rating Scale (47) (see the Supplement for additional measures). Participants also completed the National Adult Reading Test (48) to measure premorbid verbal IQ and provided demographic information (Tables 1 and 2).

Participants with OCD met Structured Clinical Interview for DSM-5 OCD criteria and had a Y-BOCS score  $> 16$ . Individuals who predominantly reported hoarding-associated symptoms were excluded (49). HC participants had no personal history of psychiatric or substance abuse/use disorder and were excluded if they had any first- or second-degree relatives with a history of OCD (see the Supplement for additional prescreening and inclusion/exclusion criteria). Two participants with OCD were excluded for incidental radiological findings. An additional HC participant was excluded due to excessive motion (framewise displacement  $> 0.5$  mm). The final sample included 52 participants with OCD and 51 HC participants.

Data were randomly split into group-stratified training (70% of data; HC  $n = 36$ , OCD  $n = 37$ ) (Table 1) and testing (30% of data; HC  $n = 15$ , OCD  $n = 15$ ) (Table 2) subsamples. Subsamples did not differ significantly on clinical measures of interest, age, estimated IQ, sex distribution, medication status (selective serotonin reuptake inhibitor [SSRI] monotherapy; 17/37 in training and 3/15 in testing subsamples), or motion (all  $ps > .05$ ) (Tables S1 and S2). Continuous measures were analyzed using independent sample  $t$  tests, while categorical measures were analyzed using Pearson's  $\chi^2$  tests. Degrees of

**Table 1. Training Subsample (n = 73): Demographic and Clinical Measures**

Measure	Healthy Control, n = 36	OCD, n = 37	Statistic
Age, Years	23.70 (4.13)	23.28 (3.94)	$t_{71} = 0.443, p = .659$
Sex, Female/Male	26/10	25/12	$\chi^2_1 = 0.188, p = .665$
NART	110.12 (7.54)	112.37 (6.78)	$t_{71} = -1.34, p = .184$
Y-BOCS	0.14 (0.83)	21.16 (3.73)	$t_{45.95} = -39.42, p < .001$
HDRS-17	1.33 (1.07)	10.41 (5.40)	$t_{38.89} = -10.01, p < .001$
HAM-A	0.97 (1.18)	11.03 (6.33)	$t_{38.6} = -9.49, p < .001$
OC-TCDQ Harm Avoidance	2.75 (4.15)	22.16 (9.07)	$t_{50.7} = -11.81, p < .001$
OC-TCDQ Incompleteness	3.50 (4.09)	22.05 (10.36)	$t_{47.2} = -10.12, p < .001$
Motion, Framewise Displacement, mm	0.224 (0.096)	0.231 (0.073)	$t_{71} = -0.303, p = .762$
Antidepressant Medication, Yes/No	0/36	17/20	-

Values are presented as mean (SD) or *n*.

HAM-A, Hamilton Anxiety Rating Scale; HDRS-17, 17-item Hamilton Depression Rating Scale; NART, National Adult Reading Test; OCD, obsessive-compulsive disorder; OC-TCDQ, Obsessive-Compulsive Trait Core Dimensions Questionnaire; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.

freedom were adjusted when variances differed significantly between datasets or groups.

### Imaging Data Preprocessing

Preprocessing was completed using *fMRIPrep* version 20.2.6 (50,51), based on *Nipype* version 1.7.0 (52) (Supplement).

### rs-fcMRI Methods

ROIs were selected based on human and NHP cytoarchitectonic homologies (53) and previous NHP anatomical tracing work (5,17,54–56). Canonical dorsal alns and ventral alns (valns) coordinates were selected from Deen *et al.* (57). Spherical 4-mm ROIs were drawn for left and right hemispheres separately using standard Montreal Neurological Institute template coordinates (Table 3), and raw time series were extracted (averaged across voxels) using NiLearn's NiftiSphereMaster (version 0.10.1). Extracted signals were smoothed (6-mm full width at half maximum), denoised using the 24-confound regressors (Supplement), bandpass filtered (0.01–0.1 Hz), and standardized (NiLearn; signal\_clean). Subject-level pairwise Pearson correlations (*r*-z' transformed) were run (MATLAB version 2019a; The MathWorks, Inc.) between regions with known direct anatomical projections based on NHP tracing and human tractography data with mechanistic implications in persistent avoidance. We had

no specific hypotheses about laterality and kept left and right ROIs separate (87 total functional connections).

### Analyses to Test Hypotheses

**Training Subsample.** We used elastic net regression (lassoglm; MATLAB version 2019a) for HA-relevant feature selection (not regularization). To determine which connections or demographic variables were reliably and nonredundantly predictive of HA, we ran a 10-fold cross-validated elastic net model with a Poisson distribution across 9 levels of alpha (0.1–0.9). Each cross-validation fold was stratified to ensure similar proportions of OCD and HC participants. The alpha level determines the balance between lambda 1 (shrinkage in the number of predictors) versus lambda 2 (penalization of regression coefficients). The OC-TCDQ HA score was the dependent variable, and potential predictors included all relevant pairwise connections as well as age, motion, sex, and National Adult Reading Test scores. We used the minimum lambda threshold to reduce parameter space and identify which connections to include in our multiple regression analysis.

To determine whether findings from this first step were specific to HA and not to group membership, we ran a second 10-fold cross-validated elastic net model predicting group status in a logistic regression analysis.

**Table 2. Testing Subsample (n = 30): Demographic and Clinical Measures**

Measure	Healthy Control, n = 15	OCD, n = 15	Statistic
Age, Years	23.65 (3.99)	24.95 (5.66)	$t_{28} = 0.443, p = .659$
Sex, Female/Male	7/8	10/5	$\chi^2_1 = 1.22, p = .269$
NART	111.94 (5.66)	111.62 (4.73)	$t_{28} = 0.165, p = .435$
Y-BOCS	0 (0)	20.67 (3.64)	$t_{14} = -21.99, p < .001$
HDRS-17	1.20 (1.37)	9.73 (5.39)	$t_{15.81} = -5.94, p < .001$
HAM-A	0.80 (1.08)	11.47 (6.70)	$t_{14.73} = -6.09, p < .001$
OC-TCDQ Harm Avoidance	3.73 (6.22)	23.07 (7.08)	$t_{28} = -7.95, p < .001$
OC-TCDQ Incompleteness	6.13 (5.78)	21.80 (7.89)	$t_{28} = -6.09, p < .001$
Motion, Framewise Displacement, mm	0.217 (0.063)	0.256 (0.074)	$t_{28} = -1.53, p = .138$
Antidepressant Medication, Yes/No	0/15	3/12	-

Values are presented as mean (SD) or *n*.

HAM-A, Hamilton Anxiety Rating Scale; HDRS-17, 17-item Hamilton Depression Rating Scale; NART, National Adult Reading Test; OCD, obsessive-compulsive disorder; OC-TCDQ, Obsessive-Compulsive Trait Core Dimensions Questionnaire; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.

**Table 3. Region-of-Interest Coordinates**

Region Number	Region Name	Left Hemisphere,	Right Hemisphere,
		MNI x, y, z	MNI x, y, z
1	Ventrolateral PFC (caudal 47/12) <sub>2,3,4,5,6</sub>	-44, 20, -13	44, 22, 10
2	Rostral ACC (rostral area 24) <sub>1,3,4,5,6,7</sub>	-8, 39, 23	7, 34, 23
3	Dorsal ACC (dorsal area 24) <sub>1,2,4,5,6,7</sub>	-7, 21, 30	6, 16, 36
4	Ventral Anterior Insula <sub>1,2,3,5,6,7</sub>	-33, 13, -7	32, 10, -6
5	Dorsal Anterior Insula <sub>1,2,3,4,6,7</sub>	-38, 6, 2	35, 7, 3
6	BLA <sub>1,2,3,4,5,7</sub>	-24, -5, -20	25, -3, -20
7	Ventral Striatum <sub>2,3,4,5,6</sub>	-11, 9, -11	9, 10, -11

Subscripts correspond to regions with direct projections between them and known mechanistic roles in persistent avoidance. Intra- and internetwork connections were included in the original feature selection step.

ACC, anterior cingulate cortex; BLA, basolateral amygdala; MNI, Montreal Neurological Institute; PFC, prefrontal cortex.

Nonzero rs-fcMRI features and demographic variables from the feature selection step were entered as independent variables in a Poisson generalized linear model (GLM) (fitglm; MATLAB 2019a) with HA as the dependent variable to determine overall model fit and test for the statistical significance of the nonzero features. A conservative Bonferroni-corrected threshold based on the number of nonzero features corrected for multiple nonzero feature–HA relationship tests.

**Robustness of Predictors in OCD.** To test the robustness of these features after controlling for potential covariates in the OCD group, we ran a second Poisson GLM controlling for anxiety (Hamilton Anxiety Rating Scale), depression (Hamilton Depression Rating Scale), OC-TCDQ INC, OCD symptoms (Y-BOCS), and antidepressant medication status.

**Testing Subsample.** A GLM using the resulting nonzero features from the training subsample in the testing subsample tested whether the same connections selected using rs-fcMRI generalized to a feature selection-naïve holdout subsample. Given the limited degrees of freedom in this subsample, we did not test for robustness against all potential covariates. Instead, we tested whether network features were robust after accounting for SSRI status and motion. All models were Bonferroni-corrected for multiple comparisons based on the final number of nonzero predictors.

**Secondary Analyses.** As an alternative feature selection method, we used forward selection stepwise regression to predict HA in the training subsample and tested the selected features in the testing subsample.

## RESULTS

### Feature Selection and Model in Training Subsample

The Poisson elastic net model predicting OC-TCDQ HA symptoms converged at 6/9 levels of alpha (0.3, 0.4, 0.6, 0.7, 0.8, and 0.9). Three of the 6 models converged on a 2-feature model (right [R]\_dACC–R\_BLA, R\_valns–left [L]\_VS), and the other 3

converged on a single-feature model (R\_dACC–R\_BLA) (Figure 2). No demographic variables were selected.

Given that dACC–BLA and valns–VS connections were hypothesized to be related to HA a priori, we proceeded with the 2-feature solution (cross-hemispheric connections are addressed in the Supplement). Nonzero connections (unregularized) were entered into a Poisson GLM. The fit of the overall 2-feature model compared with the constant model was significant ( $\chi^2_{70} = 132, p < .0001$ ; deviance of fit = 0.14). A stronger inverse relationship between R\_dACC–R\_BLA connectivity ( $\beta = -1.78, SE = 0.182, t_{70} = -9.78, p < .0001$ ) and a stronger positive relationship between R\_valns–L\_VS connectivity ( $\beta = 1.49, SE = 0.199, t_{70} = 7.49, p < .0001$ ) were associated with greater HA across the entire subsample.

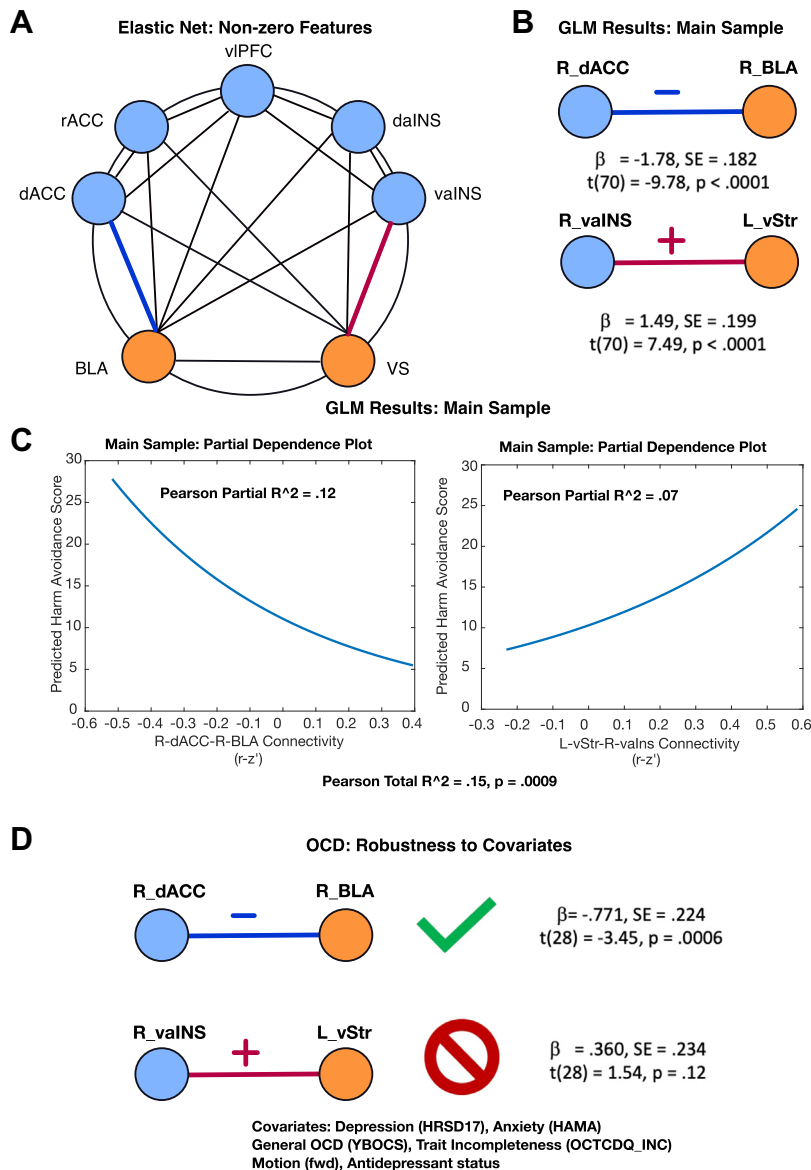
The binomial elastic net model predicting group status did not converge at any of the 9 alpha levels.

### Robustness of rs-fcMRI Predictors of HA in OCD

Within the OCD group, the relationship between R\_dACC–R\_BLA ( $\beta = -0.771, SE = 0.224, t_{28} = -3.45, p = .0006$ ) connectivity and HA was robust to covarying for depression severity (17-item Hamilton Depression Rating Scale), anxiety severity (Hamilton Anxiety Rating Scale), trait incompleteness (OC-TCDQ INC), general OCD symptom severity (Y-BOCS), antidepressant status (yes/no), and motion (framewise displacement). The R\_valns–L\_VS ( $\beta = 0.360, SE = 0.224, t_{28} = 1.54, p = .123$ ) connectivity–HA relationship was no longer significant after controlling for these variables. Both connections were robust to the inclusion of potential covariates across the full training subsample (all covariates included except for Y-BOCS and antidepressant status, which were present only in participants with OCD) (Tables S3–S5). The relationships between both connections and HA were also present within the HC group but were not robust to the inclusion of shared covariates (see the Supplement for results within the HC and OCD groups before and after inclusion of shared covariates).

### Replication in Testing Subsample

We used the same 2 nonzero connections identified using elastic net regression in the training subsample to test whether they significantly predicted HA in a holdout testing subsample (Figure 3). Training subsample results were partially replicated. Endogeneous connectivity between R\_dACC and R\_BLA was a reliable predictor of HA ( $\beta = -1.08, SE = 0.279, t_{27} = -4.02, p < .0001$ ) in the testing subsample. The relationship between trait HA and R\_valns–L\_VS connectivity was not significant in this subsample ( $\beta = -0.205, SE = 0.266, t_{27} = -0.770, p = .441$ ). The fit of the overall 2-feature model relative to the constant model was also significant in this subsample ( $\chi^2 = 17.7, p = .0001$ ; deviance of fit = 0.086). Due to the smaller size of the testing subsample, we did not plan to test for robustness for all potential confounds within the OCD group or across the whole testing subsample. Across the whole subsample after excluding the 3 individuals taking antidepressant medication and controlling for motion, the relationship between R\_dACC–R\_BLA connectivity and HA was still significant ( $\beta = -1.36, SE = 0.293, t_{23} = -4.64, p < .0001$ ). The effect of R\_valns–L\_VS connectivity remained nonsignificant, although the



**Figure 2.** (A) Illustration of nonzero connections selected as reliable predictors of harm avoidance using elastic net and displayed on the original model. (B) Specific connection estimates (dependent variable = harm avoidance) in main training subsample Poisson generalized linear model (GLM). (C) Partial dependence plots showing the relationship between the model predicting harm avoidance and each connection, keeping the other connection constant. (D) Illustration and coefficient estimates for each connection after controlling for potential covariates. BLA, basolateral amygdala; dACC, dorsal anterior cingulate cortex; daINS, dorsal anterior insula; fwd, framewise displacement; HAMA, Hamilton Anxiety Rating Scale; HDRS17, 17-item Hamilton Depression Rating Scale; L, left; OCD, obsessive-compulsive disorder; OC-TCDQ, Obsessive-Compulsive Trait Core Dimensions Questionnaire; R, right; rACC, rostral anterior cingulate cortex; vaINS, ventral anterior insula; vIPFC, ventrolateral prefrontal cortex; VS/vStr, ventral striatum; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.

direction of the effect was similar to that in the training subsample ( $\beta = 0.166, SE = 0.323, t_{23} = 0.514, p = .607$ ) (see Tables S6 and S7 for estimated coefficients and statistics for all analyses).

**Secondary Analyses**

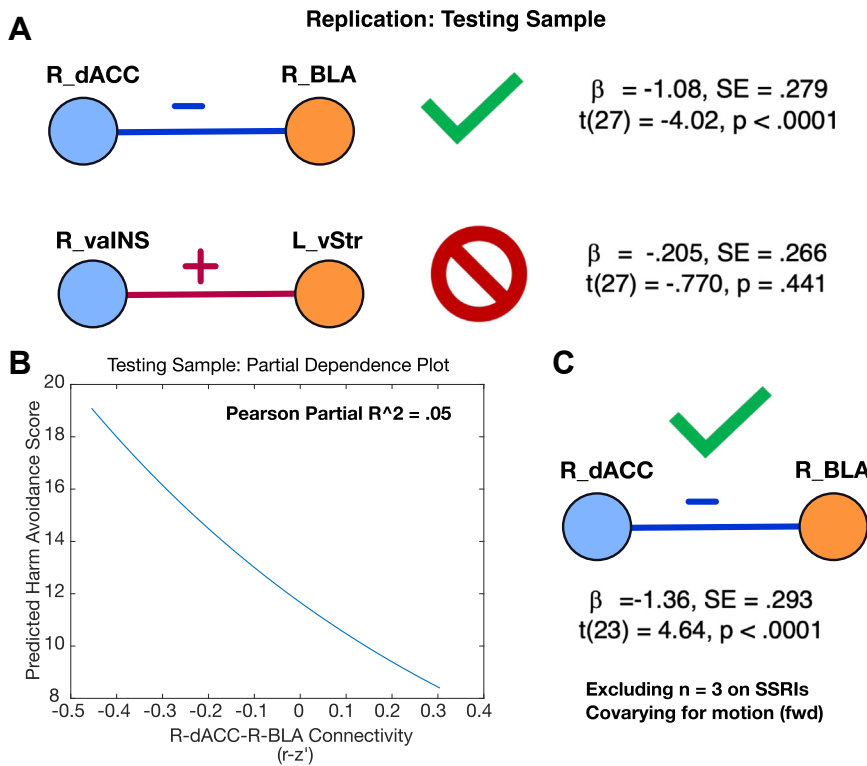
Results were consistent with those presented above (Supplement).

**DISCUSSION**

Our goal was to better understand how an anatomically constrained and mechanistic network model of persistent avoidance identified in rodents and NHPs could elucidate neural mechanisms that underlie trait HA in individuals with and without OCD. We used rs-fcMRI, a reliable measure of

endogenous network capacity, combined with theory and data-driven methods. Results supported our hypothesis that specific connections, stronger inverse connectivity between the R\_dACC and R\_BLA and stronger positive connectivity between the R\_valns and L\_VS would be associated with greater HA rather than with an OCD diagnosis. The dACC–BLA connection was robust to controlling for potential comorbid symptoms or medication status in participants with OCD in our training subsample and was similarly related to HA in our testing subsample. Understanding the endogenous neural network substrates of trait-level HA using this paradigm will provide neural markers to guide risk detection and neural targets for behavioral and neuromodulatory interventions.

The most replicable and robust finding of this study, stronger inverse dACC–BLA connectivity, is consistent with findings in rodent and NHP work on persistent avoidance and



**Figure 3.** (A) Illustration and coefficients for generalized linear model testing replication of findings from the training subsample to a separate testing subsample. (B) Partial deviance plot for model-predicted harm avoidance and right dorsal anterior cingulate cortex (R\_dACC)–R\_basolateral amygdala (R\_BLA) connectivity in the testing subsample, controlling for the other connection in the model. (C) Illustration of replicated effect and associated coefficient after excluding participants who were taking medication and controlling for motion. fwd, framewise displacement; L, left; SSRI, selective serotonin reuptake inhibitor; valNS, ventral anterior insula; vStr, ventral striatum.

adds to a more mechanistically guided understanding of this network in humans. Specifically, in NHPs, greater inverse coupling (synchrony) in neuronal firing between the dACC and BLA during extinction learning led to a persistence of fear-related memories and greater resistance to extinction, often associated with greater persistent avoidance. This synchrony was led by excitation of the dACC, which was considerably higher during learning under uncertainty (e.g., probabilistic reinforcement), and in turn inhibited BLA activity (27,28). Similar effects have been observed in rodent models, where activation of excitatory dACC (PL) projections that inhibit the BLA increase persistent avoidance, while silencing these projections reduces it (6,9). The BLA is necessary for fear and extinction learning, with disinhibition of this region necessary for assigning salience to conditioned stimuli and forming new associations (58). Inhibition of this region impacts the control of fear-/safety-related behavior (58), thought to be signaled by the dACC. In these contexts, uncertainty about stimulus-outcome associations and potential risk associated with possible negative outcomes appear to be major drivers of both dACC excitation and subsequent BLA inhibition (27,58). In humans, dACC activity parametrically increases with greater perceived stimulus-outcome uncertainty and greater choice difficulty (59,60). Greater activity in this region has also been associated with individual differences in risk aversion in humans and a tendency to avoid or pursue safer, but less valuable, options (61).

In our training subsample, we also showed a positive association between greater valns–VS connectivity and HA. This

association was not robust to covariates in the OCD group and did not replicate in our testing subsample, which was critical to the validity of our findings given our initial high predictor dimensionality ( $p > n$ ). There is no obvious reason for this difference in findings between subsamples given that the subsamples did not differ on demographic, symptom severity, or motion variables. Symptom heterogeneity might have contributed to this observed difference (62–64), and future research should explore this possibility in a larger sample. Additionally, our testing subsample was smaller, and we might have been underpowered to detect this effect. In exploratory follow-up analyses, we used a 2-sample  $t$  test to determine whether there were significant differences in valns–VS connectivity between training and testing subsamples and observed no statistically significant difference (Supplement). There is evidence that differences in alns activity and connectivity may be associated with the therapeutic effect of SSRIs (65,66). Our training subsample had a qualitatively larger proportion of medicated individuals; however, the difference in proportions was not statistically significant (Supplement). Thus, while medication may be associated with alns–VS connectivity and the relationship between alns–VS connectivity and HA, there was no conclusive evidence of this in our study. We will limit further discussion of this effect given our failure to replicate it in our testing and the lack of robustness in our training subsamples.

While our main results were not causal, the dACC–BLA connectivity finding was replicable, observed in both the HC and OCD groups, and robust to covariates (the latter is true in

the OCD group only), indicating a specific relationship with HA (Supplemental Results). Our findings overlap with some existing findings and theoretical models in OCD (67,68) but is the first to provide specificity by linking them to HA within OCD and to mechanistic neural network models of persistent avoidance more broadly. In fact, most rs-fcMRI studies in OCD have not implicated the dACC–BLA connection, with emphasis being placed on frontostriatal circuits (39,41). Our methods suggest that for behavioral tendencies/traits/symptoms that have similar variability (but perhaps different magnitudes) across healthy and clinical populations, dimensional rather than diagnostic approaches may be more useful for understanding brain-behavior relationships and the associated specificity of network contributions. As a further test of specificity, we also ran an exploratory elastic net feature selection step to determine whether any of the connections in the hypothesized persistent avoidance-related network reliably predicted OC-TCDQ INC. There were no connections that reliably predicted INC at the minimum lambda threshold, suggesting that the connections reported here are more reliably associated with HA and not OCD diagnosis or other highly correlated traits (e.g., INC). A transdiagnostic meta-analysis (69) reported that disrupted connectivity between the dACC and amygdala (frequently the BLA) was a consistent finding across anxiety/depressive disorders; however, they did not explore relationships with HA. Given that avoidance is a common behavioral response to distressing or feared situations, our findings indicate that this consistent shared feature may reflect how individuals perceive their environment more broadly (apprehensively and with amplified uncertainty) and how they cope with perceived risk (by engaging in safety behaviors or avoiding). Future research should test whether OC-TCDQ HA tendencies in transdiagnostic samples are in fact associated with inverse dACC–BLA connectivity and how differentiable these effects are from other behavioral/symptom dimensions.

There are limitations to our study. While our sample size was limited, we addressed this by replicating our initial findings in a holdout testing subsample. However, power limitations could have resulted in a failure to detect HA-relevant connections with smaller effect sizes. Furthermore, if larger sample sizes were required to observe effects, we would not expect any training subsample findings to replicate in the smaller testing subsample, which was less than half the size. Thus, replication of the dACC–BLA–HA relationship in the testing subsample increases confidence in the robustness of the finding. While lack of power in the testing subsample could explain nonreplication of the valns–VS connectivity–HA relationship, connectivity between these regions may be sensitive to the effects of other co-occurring symptoms, treatment, or demographic factors, given that it was not robust to controlling for covariates in the training subsample OCD group but was in the overall training subsample. We controlled for medication status rather than recruiting primarily nonmedicated individuals to ensure that findings generalized to the broader population of individuals with OCD, who are commonly treated with SSRIs. The dACC–BLA connectivity finding was robust to controlling for medication status in the training subsample, and results in the testing subsample were robust to removing participants taking medication. Sex was not a reliable predictor of OCD diagnosis or HA in the elastic net step (see Table S8 for

exploratory post hoc analyses by sex). Additionally, our study did not use a persistent avoidance task but instead examined the relationship between endogenous avoidance network connectivity and trait behavioral measures, for which rs-fcMRI is well-suited. Future work should test how modulation of dACC–BLA connectivity impacts task-related persistent avoidance, as well as how it influences real-world avoidance behavior and learning in clinical intervention contexts. Studies should also examine the extent to which the dACC–BLA connectivity relationship with HA replicates in larger OCD samples. Larger samples may also facilitate the detection of smaller brain-behavior effects.

## Conclusions

Our findings bring together cross-species work on functional and structural neuroanatomy to provide a deeper mechanistic understanding of neural risk and pathology in the context of persistent avoidance. The reliable and robust link between stronger inverse R\_dACC–R\_BLA connectivity and trait HA has important implications for clinical and neuromodulatory interventions for OCD and may extend to individuals with other diagnoses who show poorer devaluation and/or extinction learning. Given the role of the dACC in detecting risk/uncertainty, our findings and work by others point to this region as a potential neuromodulatory target to treat persistent avoidance and reduce perceived risk during new learning. Augmenting cognitive behavioral treatments with neuromodulation may also enhance treatment effects given that inhibition of the dACC and excitation of the BLA are crucial for new learning (24,70,71), potentially by inhibiting the influence of prior learning or previously held beliefs associated with cues (72). Future work should systematically test how mechanistically targeted clinical (73) and neuromodulatory treatments separately or together may influence HA-related behavior and quality of life in individuals with OCD.

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