Relationships between Interoceptive Sensibility and Resting-state Functional Connectivity of the Insula in Obsessive-Compulsive Disorder

Supplemental Information

Supplemental Figures and Tables

Supplemental Methods and Materials

Subjects and Procedure

Subjects were recruited at the Icahn School of Medicine at Mount Sinai (ISMMS), Nathan Kline Institute for Psychiatric Research (NKI), and New York University School of Medicine (NYUSoM) between May 2014 and March 2020. Ninety patients with OCD participated within that time frame (17 were recruited at ISMMS, 19 at NKI, and 54 at NYUSoM). Fifty-four healthy controls also completed the study (39 were recruited at ISMMS, 7 at NKI, and 8 at NYUSoM). ISMMS-recruited subjects were scanned at ISMMS, and NYUSoM- and NKI-recruited participants were scanned at NKI. Data from 13 OCD patients and 1 control were excluded (8 patients and 1 control were excluded as outliers for having scores that exceeded 1.5 times of the interquartile range (IQR) below the 25th percentile (i.e. lower than 25th percentile - 1.5*IQR) or above the 75th percentile (i.e. higher than 75th percentile + 1.5*IQR) on any subscale of the MAIA (Tukey 1977); 1 patient met study exclusion criteria after questionnaire completion; 4 patients were excluded for having high motion requiring censoring (see below for detail) (Yan et al. 2013). Final data were analyzed from 77 OCD patients (15 were recruited at ISMMS, 17 at NKI, and 45 at NYUSoM) and 53 controls (38 were recruited at ISMMS, 7 at NKI, and 8 at NYUSoM).

Twenty-four out of 77 patients (31%) had no Axis 1 comorbidities; the remaining 53 patients (69%) had at least one current comorbid Axis I disorder including generalized anxiety disorder (n=29), panic disorder (n=16), excoriation disorder (n=11), social anxiety disorder (n=10), attention deficit hyperactivity disorder (n=9), body dysmorphic disorder (n=9), and agoraphobia (n=8). Less frequent current comorbidities included illness anxiety disorder (n=5), alcohol use disorder (mild, n=5), trichotillomania (n=4), hoarding disorder (n=4), Tourette's disorder (n=3), substance use disorder (mild, n=3), binge eating disorder (mild, n=3), post-traumatic stress disorder (n=3), major depressive disorder (n=2), persistent tic disorder (n=2), somatic symptom disorder (n=2), anorexia nervosa (n=1), and bulimia nervosa (mild, n=1). Thirty-six of the 77 patients (47%) were not taking psychotropic medications; the remaining 41 patients (53%) were taking antidepressants targeting monoaminergic neurotransmission (including serotonin reuptake inhibitors, serotonin modulator and stimulators, and tricyclic antidepressants) (n=36), benzodiazepines as needed (n=8), atypical

antipsychotics (n=5), anticonvulsants (n=4), stimulants (n=3), bupropion (n=3) and psychoactive antihypertensives (n=2). More detailed breakdown of medications is provided in Figure S1.

Behavioral and clinical assessments – Dimensional Obsessive-Compulsive Scale (DOCS)

The Dimensional Obsessive-Compulsive Scale (DOCS) assesses severity of OCD symptoms in four categories: 1) concerns about germs and contamination; 2) concerns about responsibility for harm, injury, or bad luck; 3) unacceptable or taboo thoughts (e.g. about sex, immorality, or violence); and 4) concerns about symmetry, completeness, and the need for things to be "just right".

Supplemental Data Analyses and Results

Group comparisons of MAIA subscales

We have already reported group differences in MAIA subscale scores that included many of the same subjects (68 OCD patients and 47 controls from the present sample) (Eng et al. 2020), and describe the findings here again using the current data in order to provide context for the new PCA and neuroimaging analyses that are presented in the main text. Shapiro-Wilk tests of normality conducted on the residuals from the ANOVAs indicated that all subscales except *not-noticing*, *not-worrying*, and *attentional control* exhibited a non-normal error distribution. Although the ANOVA framework is typically considered appropriate when sample sizes are sufficiently large (e.g., $n > 50$) even when errors are non-normal (Pek et al. 2017), we also report replications from the non-parametric Mann-Whitney *U* tests.

ANOVAs comparing OCD patients with controls showed group differences on 5 of the 8 subscales (Table 1 in main text). Compared to controls, OCD patients reported increased *noticing*, *distracting* (lower scores on *not*-distracting), *worrying* (lower scores on *not*-worrying), *emotional awareness*, as well as reduced *trusting* (all $p < .001$; data distributions in Figure S2). No group differences were observed in the *attentional control*, *self-regulation*, and *listening* subscales (Figure S3). Mann-Whitney *U* tests confirmed these differences using non-parametric analyses ($p \leq .001$ for all subscales) and revealed an additional group difference in *self-regulation* ($p = .036$) – a finding that was not observed using parametric ANOVA.

Component structure of MAIA subscales

To examine the factor structure of IS, principal component analysis (PCA) with orthogonal rotation (quartimax) was applied on the 8 MAIA subscales for the patient and control groups separately. The quartimax rotation method simplifies the complexity of items (subscales) to minimize the number of components needed to explain each variable (Tabachnick and Fidell 2007). Components with eigenvalues greater > 1 were retained (Kaiser 1960). Bartlett's Test of Sphericity was significant in both groups (Controls: χ^2 ($df = 28$) = 218.45; Patients: χ^2 ($df = 28$) = 190.80, all $p < .05$), i.e. rejecting the null hypothesis of no relationships among the MAIA subscales, therefore justifying the PCA procedure (Bartlett 1950). The overall average Measure of Sample Adequacy

(MSA) was 0.81 for the controls group, and 0.75 for patients, and MSA of most items were above 0.60 (Tabachnick and Fidell 2013), again indicating a level of multi-collinearity among items that are sufficient for the PCA procedure (Table 2 in main text). MSA for the *not-worrying* (in controls: 0.42) and *not-distracting* (in patients: 0.37) subscales are lower than the suggested 0.60 cut-off (Tabachnick and Fidell 2013), however, we retained these subscales in the analysis due to the significant group differences in those subscales between patients with OCD and controls. To check that the latent solution is approximately orthogonal, we evaluated the correlation matrix of components by performing PCA with oblimin rotation with the number of desired components specified based on the quartimax rotated solutions (Tabachnick and Fidell 2007). Results from PCA with oblimin rotation revealed low correlations among components in control (r_{1_2} = .17), and patient groups (r_{1_2} = -.03, r_{1_3} = .17, r_{2_3} = -.09), indicating that the orthogonal rotation we used was appropriate for the dataset.

Structure congruence using Procrustes rotation

Although the current study revealed different components from the PCAs conducted for the patient and control groups, we statistically compared the component structures between OCD patients and controls using Procrustes rotation, which evaluates the similarity between two component structures ("target" VS "validation") by rotating the components to maximum agreement and computing congruence coefficients for each component (Cliff 1966; Schönemann 1966; Van de Vijver and Leung 2001; van de Vijver 2001). We first set the 2-components structure obtained from healthy controls as the "target" structure, and ran a separate PCA on the OCD group, specifying a 2-component solution without rotation ("validation" structure). This two-component structure for the patient sample ("validation" structure) was computed to perform Procrustes rotation by rotating the components to match the "target" structure (obtained from controls) to evaluate whether the patient group has a similar component structure as the controls ("target"). Congruence coefficient values of Tucker's $\phi > 0.95$ indicate good component structure similarity between the "target" and "validation" structures (Lorenzo-Seva and Berge 2006; Lovik et al. 2020), and values below 0.90 indicate non-negligible differences (Bentler and Bonett 1980; Vijver and Poortinga 1994; Van de Vijver and Leung 2001).

Results from Procrustes rotation indicate good similarity for patients with OCD and controls for Component 1, $\phi = 0.98$, but non-negligible differences between the groups for Component 2, $\phi = 0.86$. It should be noted that this analysis requires forcing the two structures being compared to have the same number of components. The three-component structure reported in Table 1 was only found in the OCD group and thus could not be compared with controls. Our results indicate that patients with OCD exhibit a different overall component structure for interoceptive sensibility than controls, that is mostly driven by differences in the second (*noticing, not-worrying, emotional awareness*) and third (*not-distracting*) components.

Potential confounds of medication, comorbidities, and clinical symptoms on reported findings

In the current study, among the 41 medicated OCD patients, 32 had at least one Axis 1 comorbidity and 9 did not. Among the 36 unmedicated OCD patients, 21 had at least one comorbidity and 15 did not. We first examined whether medications and presence of Axis 1 comorbidity were separately associated with component scores. ANOVAs revealed that patients with at least one Axis I comorbidity had reduced component 2 scores (i.e. more general noticing of sensations, more worry about uncomfortable sensations, less awareness of the link between emotion and the body) than those without a comorbidity ($F(1,73) = 4.92$, $p = .030$). There were no significant effects of medication and no interactions between medication and component scores.

Next, given the high proportion of OCD patients who had Axis I comorbidities (which is to be expected in a representative sample of OCD patients drawn from the community) and that other clinical variables such as symptom severity (Y-BOCS score), sensory phenomena severity (SPS score), and state anxiety severity (BAI score) were significantly related to component scores (see results in manuscript), we sought to determine whether observed associations between IS components and insula seed-to-voxel functional connectivity remained after separately accounting for variance related to the presence of a DSM Axis I comorbidity (yes/no), OCD symptom severity, sensory phenomena, and state anxiety. Fisher-transformed correlation coefficients were extracted from significant clusters (reported in Figures 2 and 3), then submitted to separate regression analyses specifying IS component score as predictor of FC with sex, site, and clinical variable (Axis I comorbidity [yes/no], Y-BOCS score, SPS score, or BAI score) as regressors-of-no-interest. We

found that all associations between IS component scores and insula functional connectivity reported in the main text and Figures 2 and 3 remained significant even after separately accounting for the effects of having a DSM Axis I comorbidity, overall OCD severity, sensory phenomena, and state anxiety severity, all FDR-adjusted $p \leq 3.60 * 10^{-5}$.

Appendix 1. Component structure of MAIA subscales and insula functional connectivity in controls [Analyses for Control Group Only]

As component solutions of MAIA subscales were derived within each patient and control group separately and were non-comparable, the current study could not directly contrast OCD and healthy controls on functional connectivity relationships with component scores. However, for completeness, we examined the relationship between component scores and functional connectivity with insula seeds in the healthy control group and presented the findings in this section.

Neuroimaging data acquisition and preprocessing (Controls only)

Out of the 53 controls that were included in the final dataset, 38 were recruited at ISMMS, 7 at NKI, and 8 at NYUSoM. As with the patient group, ISMMS-recruited controls were scanned on the MAGNETOM Skyra and NYUSoM- and NKI-recruited controls were scanned on the MAGNETOM TrioTim. MRI acquisition parameters for the 15 controls who were scanned on the MAGNETOM TrioTim and 11 (out of 38) controls on the MAGNETOM Skyra were the same as those used in the patient group (described in earlier sections). The remaining 27 ISMMS-recruited controls were also scanned on the same MAGNETOM Skyra but had a slightly different set of scanning parameters. The orientation of acquisition for structural data, as well as acceleration factor, number of slices, and TE for resting-state data were different between the 27 ISMMS-recruited controls and the other 11 ISMMS-recruited controls). (For structural data – 11 controls: transverse acquisition; 27 controls: oblique acquisition of T>C-20.0; for resting-state data – 11 controls: acceleration factor=6, 72 slices, and TE=25 ms; 27 controls: acceleration factor=7, 70 slices, and TE=35 ms). The first ten volumes were discarded to allow magnetization to reach equilibrium.

Data preprocessing for controls were similar to the patients (main text). To evaluate for the relationship between IS component scores and FC with the insula seeds in controls, an additional dummy variable for scan site was included as a covariate-of-no-interest. Therefore, in the regression analysis for the control group, component scores were treated as covariates-of-interest, controlling for sex and scan site (2 dummy variables for 3-level variable of scan site) as covariates-of-no-interest.

Results

Component structure of MAIA subscales

Similar to the patient group, controls showed an 'adaptive' Component 1 (original) that included *noticing* body sensations, *controlling attention* to sensation, being *aware of the link* between emotion and body sensations, *regulating* emotions, *listening* to the body for insights and guidance, and trusting the body, and a 'maladaptive' Component 2 (original) that included increased *focusing* on uncomfortable sensations (reduced *distracting*), increased *worrying*, and reduced *trusting* of the body (Table 1 in main text). As the *not-worrying* subscale had a low MSA of 0.42, we repeated PCA after removing the *not-worrying* subscale. While Component 1 (revised) has a similar component composition as Component 1 (original), Component 2 (revised) included a single loading of the *not-distracting* subscale (Table S1).

Functional Connectivity

We performed regression analyses examining the relationships between component scores (original and revised) and functional connectivity with insula seeds in the healthy control group.

Neuroimaging Results and Discussion

Correlations with component scores (original) in the control group

Higher Component 1 (original) scores were associated with less functional connectivity of the right ventral anterior seed with the left precentral gyrus and left medial frontal gyrus. There were no significant associations between Component 2 (original) scores with insula functional connectivity.

Correlations with component scores (revised) in the control group

Connectivity findings for Component 1 (revised) in controls were similar to the connectivity findings for Component 1 (original) (Table S2, Figure S5A). Lower Component 2 (revised) scores (more distracting) were associated with greater functional connectivity involving the right posterior insula seed with cerebellar lobule VI, vermis IX and the putamen (Table S2, Figure S5B).

Qualitatively, there was no overlap of insula functional connectivity patterns related to component scores between controls and OCD patients. Even though the functional connectivity findings were not directly comparable between the groups, our results suggest that patients with OCD may process interoceptive signals differently than the controls.

Medications		n
Antidepressants targeting monoaminergic neurotransmission		**36**
Selective serotonin reuptake inhibitors (SSRIs)		
	Paroxetine	1
	Sertraline	11
	Escitalopram	5
	Fluoxetine	7
	Fluvoxamine	5
Serotonin and norepinephrine reuptake inhibitor (SNRIs)		
	Desvenlafaxine	1
	Venlafaxine	4
Tricyclic antidepressants		
	Nortriptyline	1
	Clomipramine	1
Others		
	Trazodone	4
	Vortioxetine	1
Benzodiazepines (as needed)		**8**
	Clonazepam	4
	Alprazolam	2
	Lorazepam	2
Atypical antipsychotics		**5**
	Aripiprazole	2
	Quetiapine	1
	Risperidone	2
Anti-Convulsants		**4**
	Lamotrigine	2
	Topiramate	2
Stimulants		**3**
	Lisdexamfetamine	2
	Amphetamine Salts	2
Psychoactive Antihypertensives		**2**
	Clonidine	1
	Propanolol	1
Others		
	Bupropion	3

Figure S1: Breakdown of medication use in the patient sample. 41 out of 77 (53%) patients with OCD were taking psychotropic medications at the point of assessment. Note that some patients reported being on more than one type of medication.

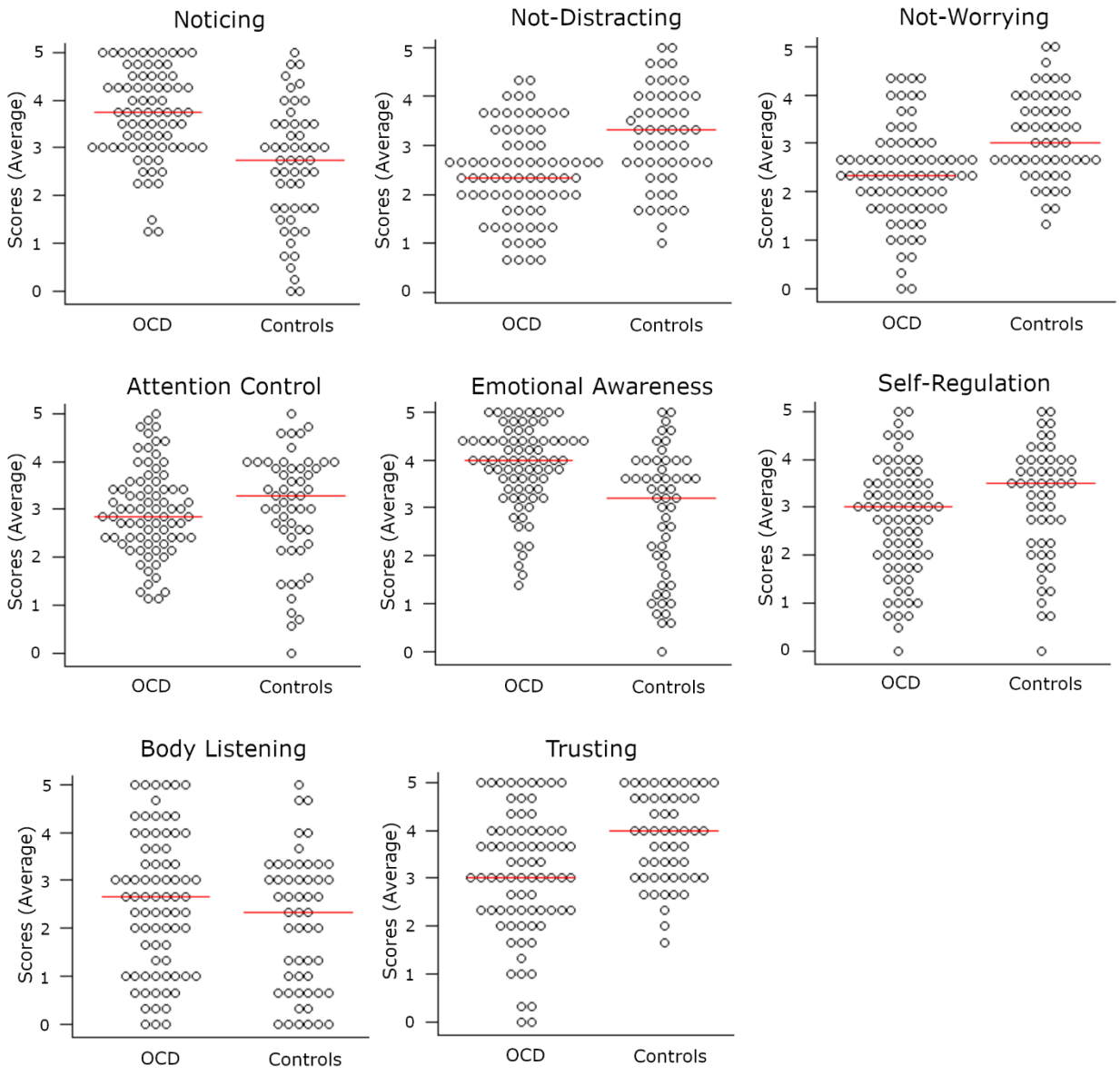

Figure S2: Distributions of average scores on all eight subscales of the MAIA in 53 healthy controls and 77 patients with OCD. Red line indicates the median score.

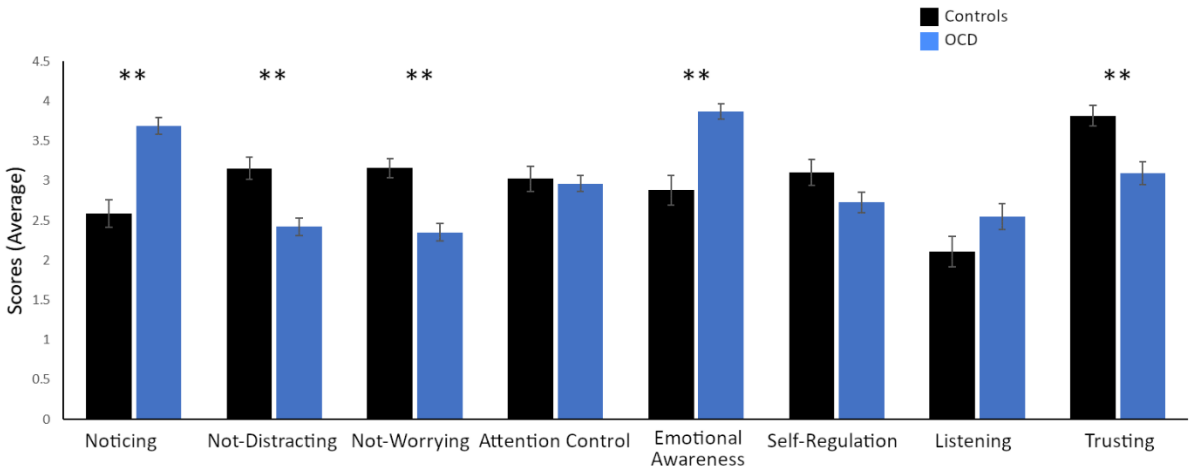

Figure S3: Average scores on all eight subscales of the MAIA in 53 healthy controls and 77 patients with OCD. Significant group differences are indicated with asterisks.

$^{**}p < .001$

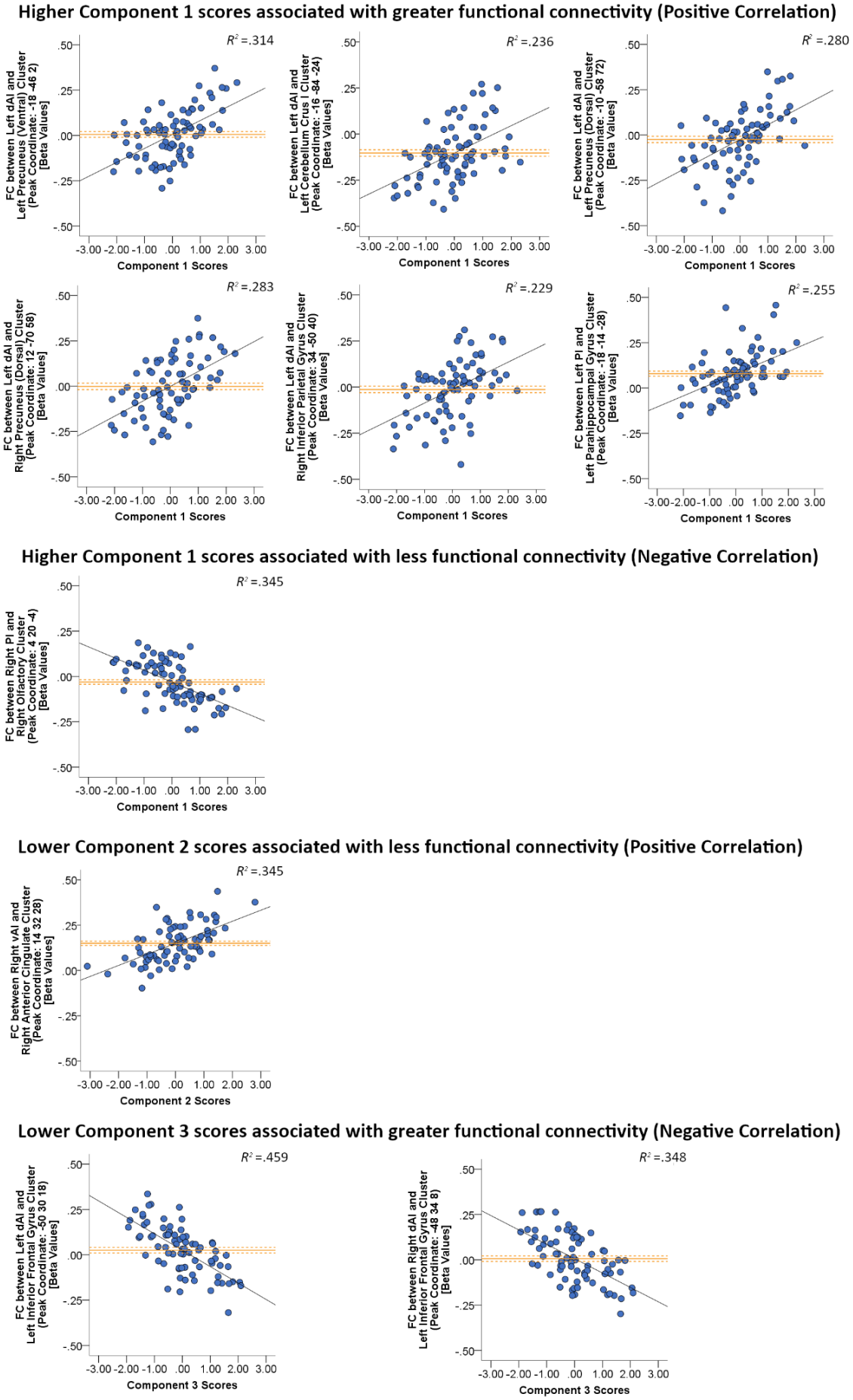

Figure S4: Scatterplots showing associations between component scores and insula functional connectivity in OCD patients (n = 77). Orange solid lines indicate mean values; dotted lines indicate standard errors.

Note: Please refer to Table 3 in main text for the entire list of regions within each specified cluster.

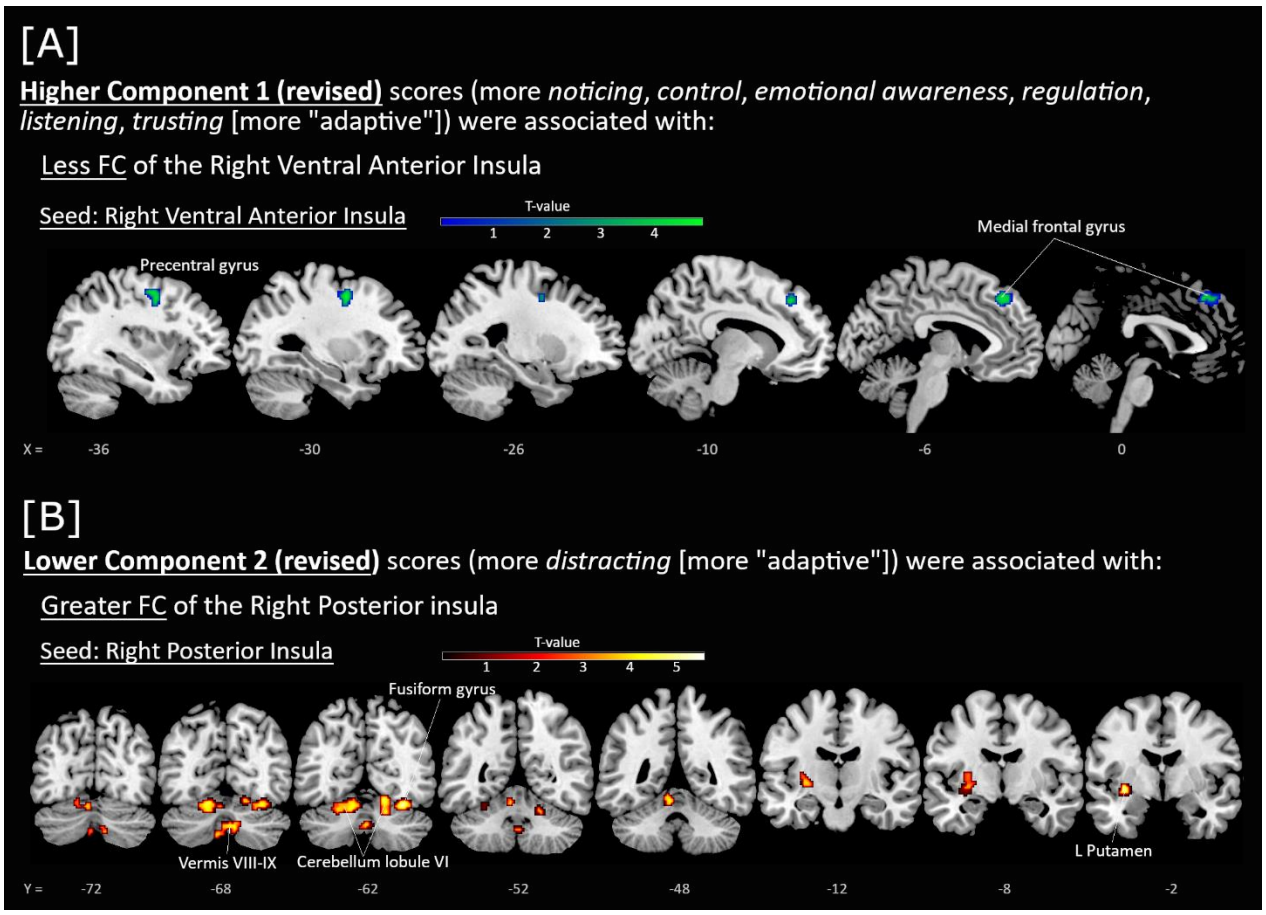

Figure S5: Associations between functional connectivity (FC) of insula seeds with revised IS components in controls (n = 53; sex and scan site included as covariates-of-no-interest).

[A] Higher Component 1 (revised) scores (more noticing, control, emotional awareness, regulation, listening, and trusting of the body [more "adaptive"]) were associated with less FC (blue-green) of the right ventral anterior insula seed.

[B] Lower Component 2 (revised) scores (more distracting [more "maladaptive"]) were associated with greater FC (red-yellow) of the right posterior insula seed.

All $p < .001$ voxelwise (uncorrected) with FWE < .05 clusterwise correction.

Table S1: Revised component structure and loadings of MAIA in controls after removing not-worrying subscale.

	Controls (n = 53)		
		Revised Component	
MAIA Subscale	Communalities	1	2
Noticing	0.58	0.75	
Not-distracting	0.91		0.95
Attention control	0.68	0.82	
Emotional awareness	0.89	0.94	
Self-regulation	0.82	0.90	
Listening	0.77	0.87	
Trusting	0.33	0.48	
Cumulative Variance (%)		56.53	71.14

Note: Loadings of absolute values < 0.32 were not presented.

Table S2: Significant correlations between revised component scores and insula-to-whole-brain functional connectivity in Controls (n = 53).

Higher Component 1 (revised) scores were associated with less functional connectivity in:	Peak Coordinates						Other Regions Included Within Cluster (> 30 voxels)	
	BA	k	x	y	z	T	BA	Regions [aal labels / *TD labels*]
Seed: Right Ventral Anterior Insula (32 10 -6)								
L Precentral gyrus	-	143	-30	-2	46	4.88	6	*Middle frontal gyrus*
L Precentral gyrus	-		-38	-4	40	3.58		
L Superior frontal gyrus, medial	-	141	-10	34	42	4.56	8	*Medial frontal gyrus*
L Superior frontal gyrus, medial	8		-4	38	46	4.46		

Lower Component 2 (revised) scores were associated with greater functional connectivity in:	Peak Coordinates						Other Regions Included Within Cluster (> 30 voxels)	
	BA	k	x	y	z	T	BA	Regions [aal labels / *TD labels*]
Seed: Right Posterior Insula (35 -11 6)								
R Cerebellum lobule VI	-	286	32	-64	-18	5.56		
R Cerebellum lobule VI	-		18	-60	-26	4.91	-	R Fusiform gyrus
R Cerebellum lobule VI	-		16	-64	-14	4.87		
L Putamen	-	132	-34	-4	-6	5.11	-	*Lentiform nucleus*
L Putamen	-		-30	-10	6	4.13		
R Cerebellum lobule VI	-	346	-14	-66	-18	4.57		
L Cerebellum lobule IV-V	-		-6	-50	-16	4.43	-	
L Cerebellum lobule VI	-		-28	-58	-18	4.37		
R Cerebellum lobule VIII	-	150	8	-68	-38	4.49		
L Cerebellum lobule VIII	-		-4	-70	-42	4.32	-	Vermis VIII
Vermis IX	-		0	-58	-38	4.15		

Note: Clusters significant at $p < .001$ voxelwise (uncorrected) with FDR < .05 clusterwise correction. Sex and scan site were included as covariates-of-no-interest. Coordinates are in MNI space.

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