Supplementary Results

Figure S1: All 21 symptom-response maps derived from the discovery BDI dataset

Figure S2: Clustering was significantly better for real data than for three control analyses. Left panels depict Fisher-transformed cross correlogram to show the spatial correlation between symptom-based circuit maps (diagonals are depicted in black). Middle panels depict a force-directed graph visualization produced in Gephi 0.9.2. In this algorithm, the correlation between nodes is treated as an attractive force, so highly correlated nodes are in close proximity to one another. Node sizes are proportional to the normalized PageRank score(2), a metric of the degree to which that node contributes to the solution. Distinct colors represent distinct clusters. Right panels represent variance explained by the clustering solution, as quantified by the gap statistic(4). **(a)** Individual symptom-based circuit maps were strongly correlated or anti-correlated with one another (left panel). Symptoms thus separated into two distinct clusters which explained 73% of the variance. **(b)** When repeating the analysis with baseline symptoms instead of symptom change, the cross-correlogram revealed a continuous pattern rather than two discrete clusters. A two-cluster solution explained only 25% of the variance. **(c)** Clustering is not evident based on symptom improvement alone. **(d)** Permutation testing showed that clusters generated by random chance are weaker than those generated from the actual data.

Figure S3: Distributions of cross-correlations between symptom maps. (a) Across 100 permutations, randomly-shuffled data showed cross-correlations that followed a normal distribution with a peak near zero. (b) The real data followed a skewed distribution with a trough near zero.

Figure S4: Force-directed graph visualizations depicting the clustering solutions for each dataset. Visualization follows the same parameters described in Fig. S1.

Figure S5: Cluster-response maps across different datasets (top: lateral view, bottom: medial view). Cluster-response maps were reproducible across different symptom scales and independent cohorts.

Figure S6: Regions of overlap between the two cluster maps.

Figure S7: Circuit maps for two-cluster solution generated when using a connectome database of 38 subjects with major depression rather than 1000 healthy controls.

Figure S8: Alignment of optimal targets with consensus cortical parcellation schemes.

Table S1: Dataset characteristics and patient demographics

Table S2: Clustering is not driven by baseline symptoms or overall clinical trajectory.
In the discovery dataset and the active arm of the replication dataset, clinical improvement was approximately equal between the two symptom clusters. In the sham dataset, dysphoric symptoms improved significantly more than anxiosomatic symptoms. Anxiosomatic symptom improvement was significantly greater in the active replication dataset than in the sham replication dataset. These results are consistent with the fact that the majority of patients in the replication dataset were stimulated at relatively anxiosomatic stimulation sites.
Clinical change in each cluster was not significantly correlated with baseline severity of that cluster in either the discovery dataset or the active arm of the replication dataset. In the sham dataset, clinical improvement was significantly related to baseline severity in the corresponding symptom cluster.

Table S3: Index of specific symptoms in figure 3a.

Table S4: Details of the studies included in the exploratory meta-analysis.

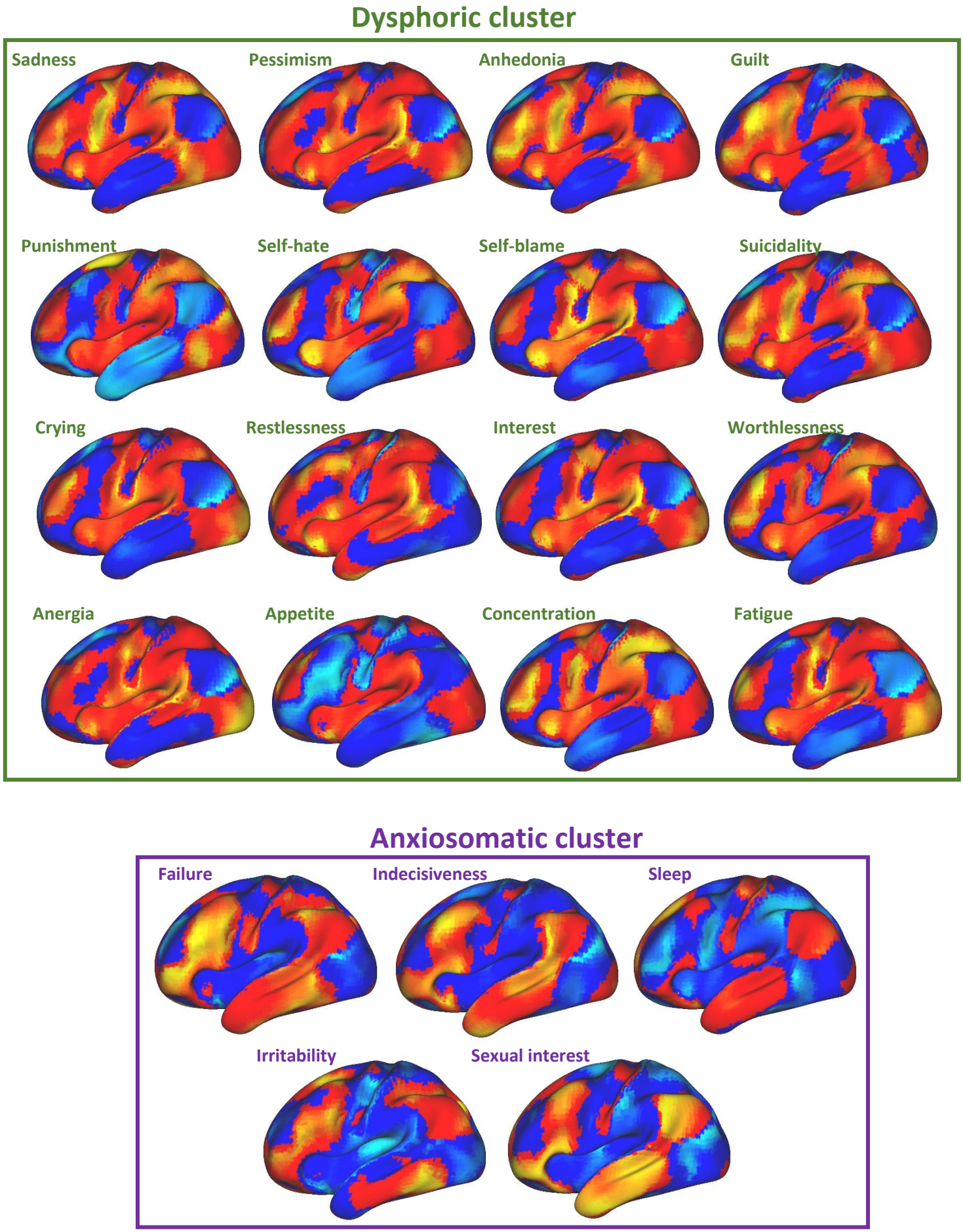
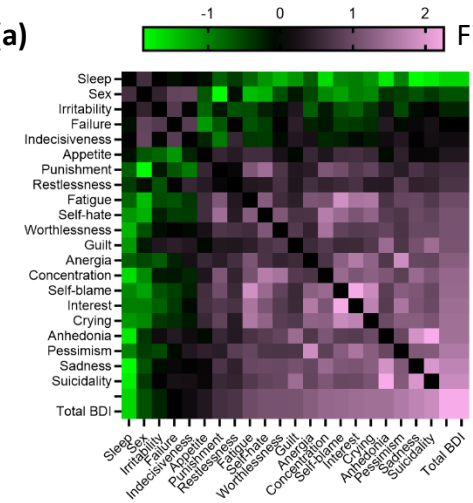
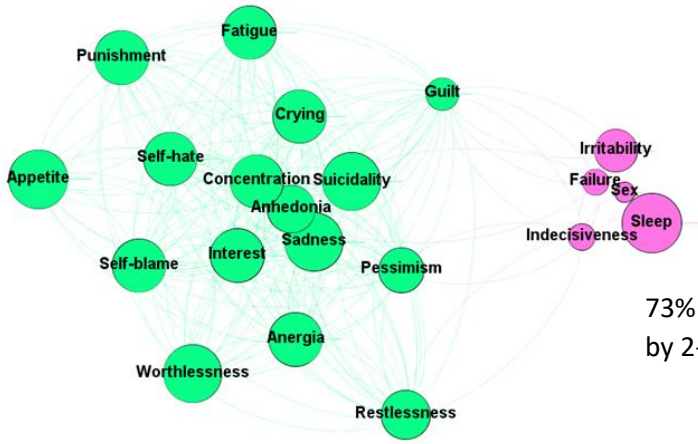


Figure S1: All 21 symptom-response maps derived from the discovery BDI dataset.

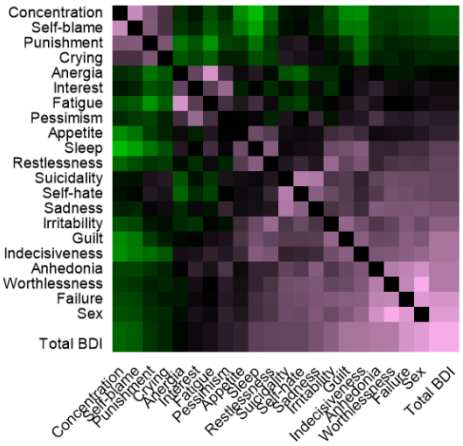
(a) Fisher *z*

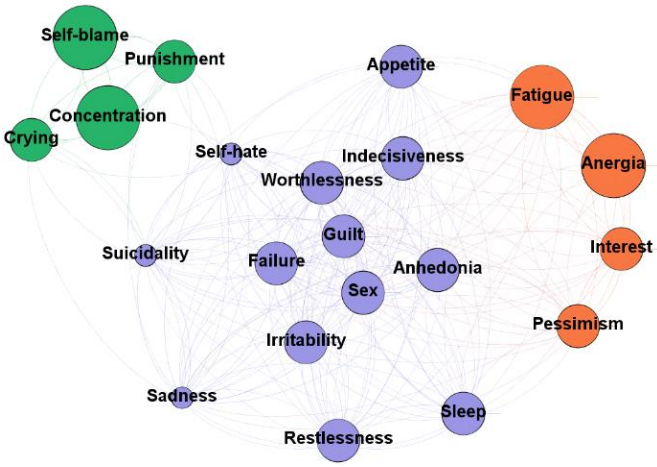




73% variance explained by 2-cluster solution

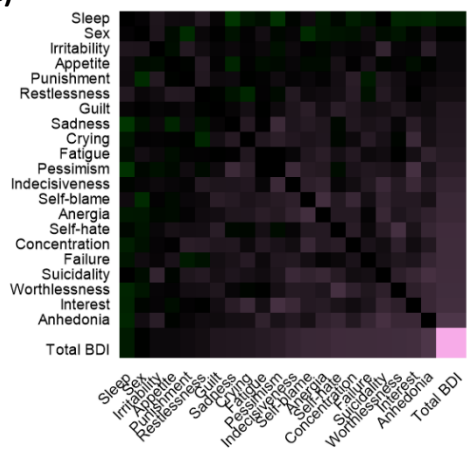
(b) Unpaired t-test: $p = 1.0 \times 10^{-12}$

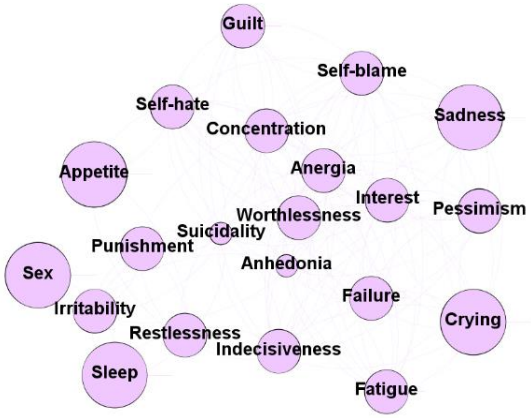




25% variance explained by 2-cluster solution

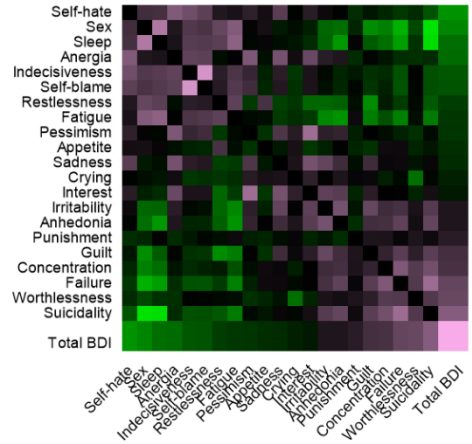
(c)

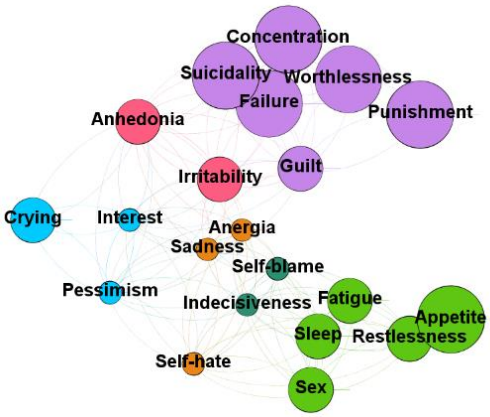




No clustering evident

(d) Permutation test for cluster maps: $p = 0.005$



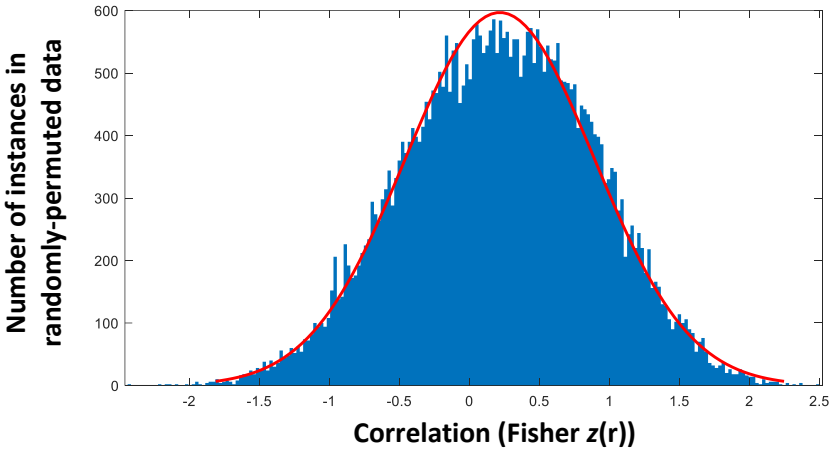


Mean 28% variance explained by 2-cluster solutions ($p = 0.02$)

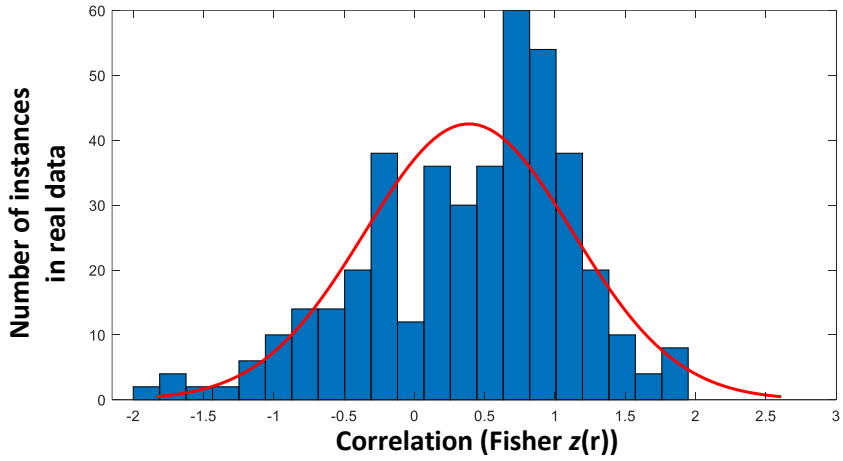
Mean 40% variance explained by "optimal" solutions ($p = 0.03$)

Figure S2

(a)



(b)



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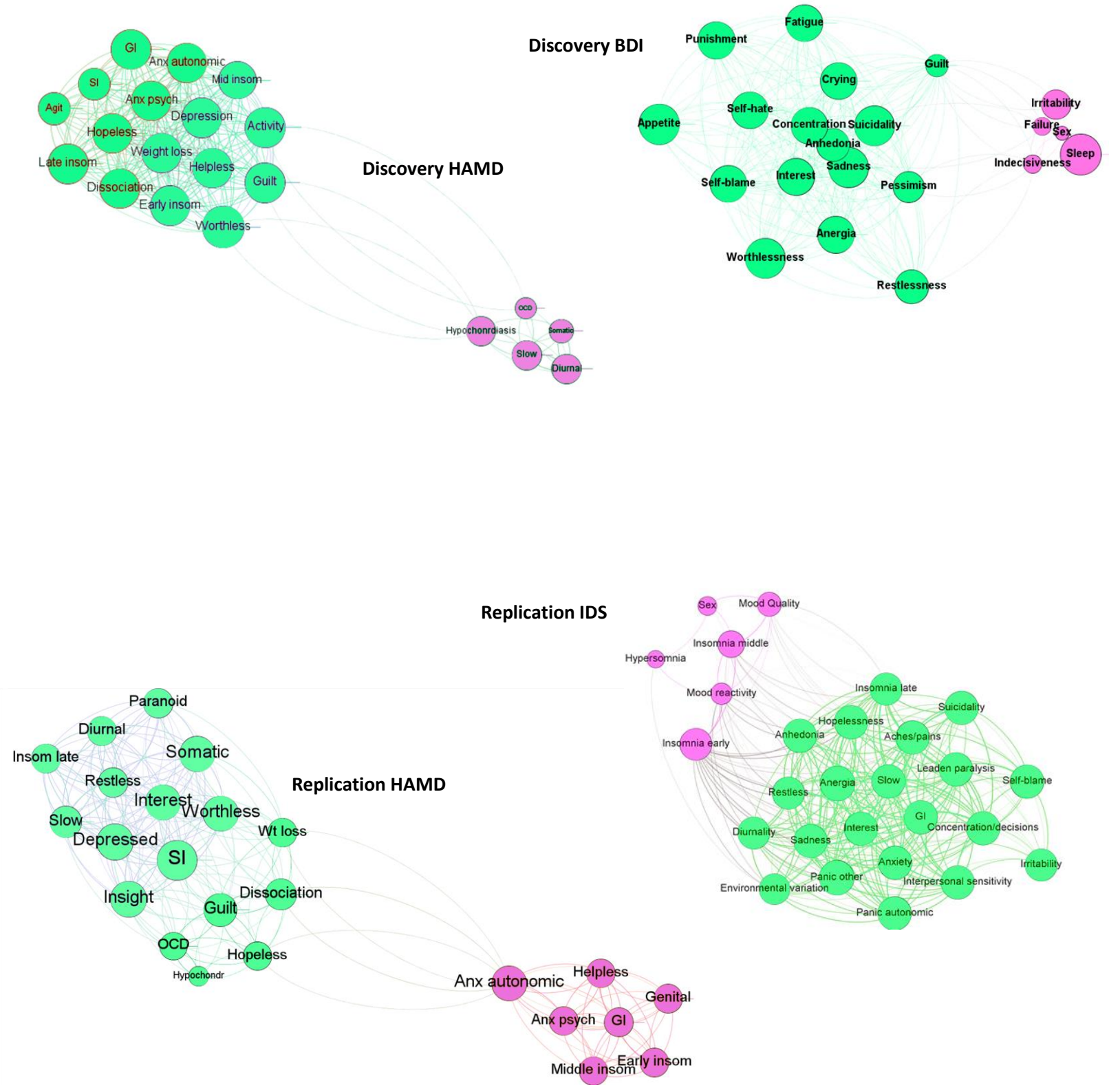
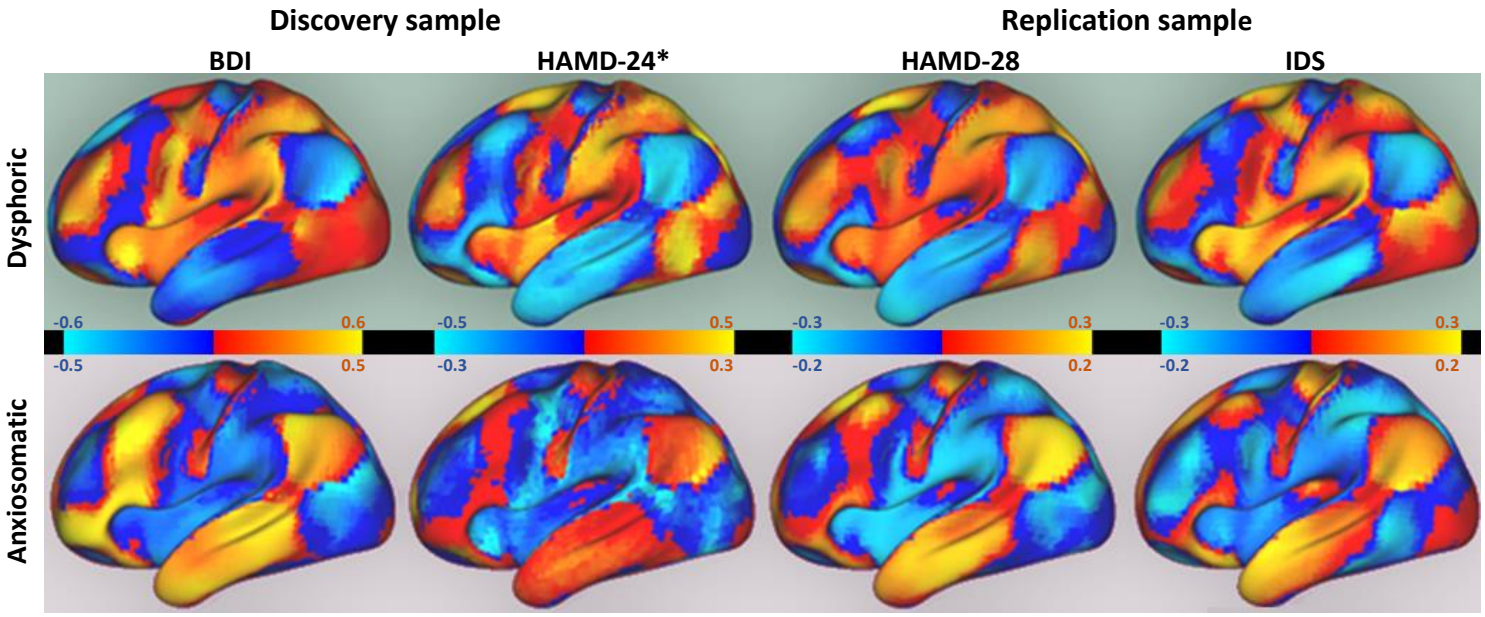


Figure S4: Force-directed graph visualizations depicting the clustering solutions for each dataset. Visualizations follow the same parameters described in Fig. S1.



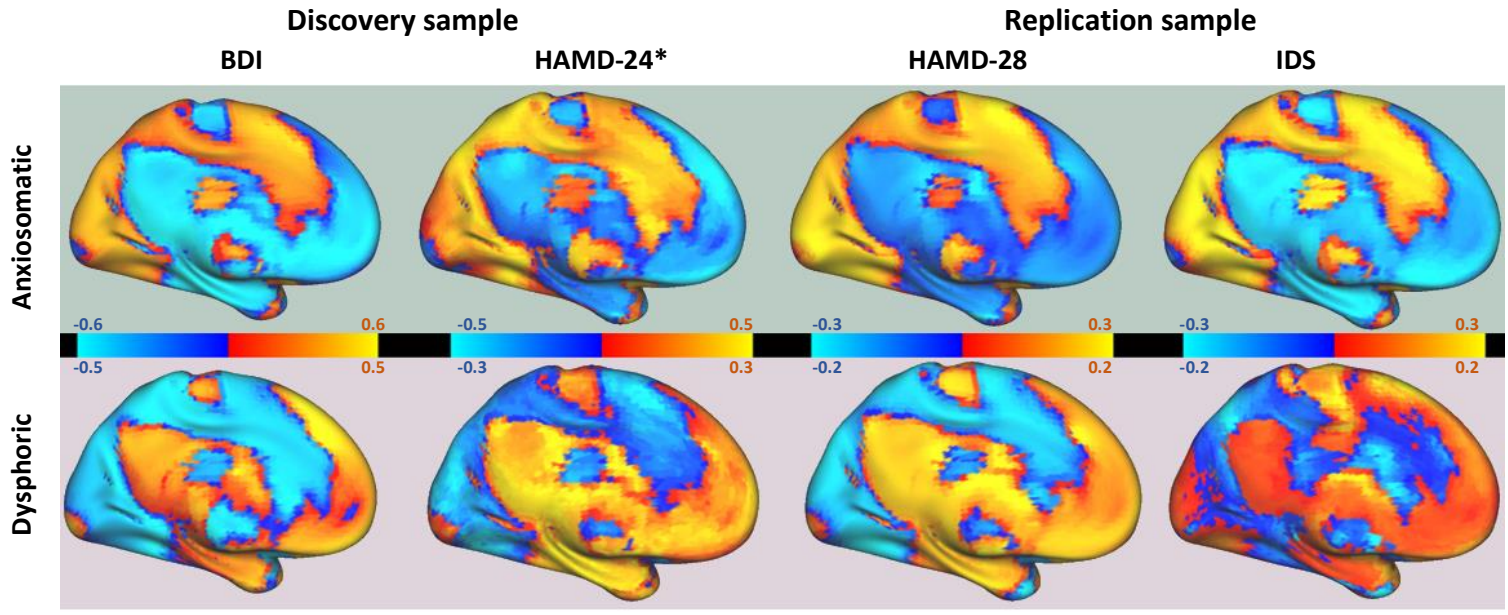


Figure S5: Cluster-response maps across different datasets (top: lateral view, bottom: medial view). Cluster-response maps were reproducible across different symptom scales and independent cohorts.

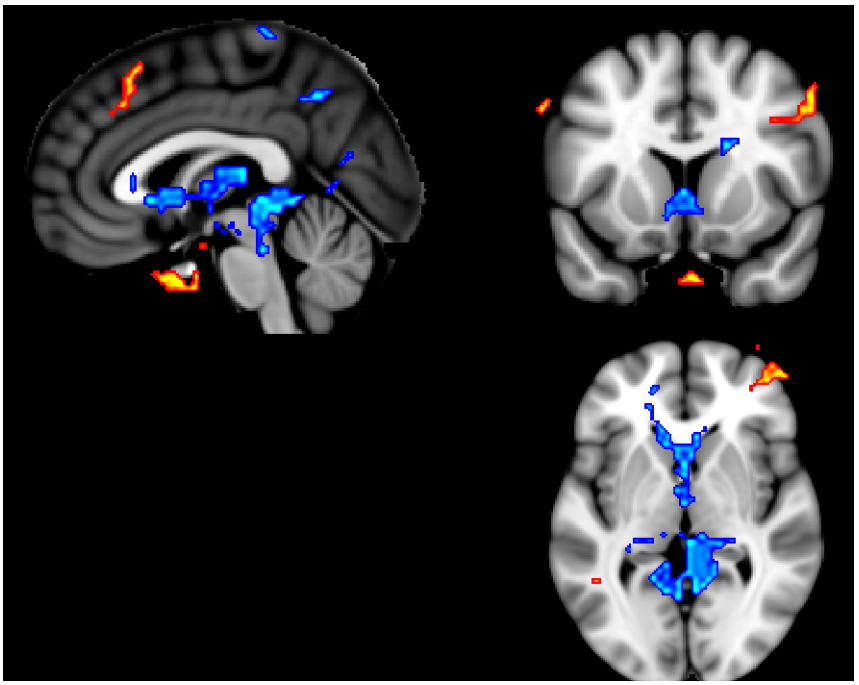
*Three items in the HAMD-24 (discovery sample, secondary analysis) were omitted from the standard clinical assessment due to clinician judgment. These included Item 14 (genital symptoms), item 17 (insight), and Item 20 (paranoia).

Positive peaks

Region	Coordinate
Right orbitofrontal cortex	(17, 48, -12)
Left DLPFC	(-47, 30, 36)
Left anterior insula	(-27, 21, -6)

Negative peaks

Region	Coordinate
Right fusiform gyrus	(22, -36, -18)
Right extrastriate cortex	(52, -60, 12)
Left extrastriate cortex	(-40, -60, 15)
Periaqueductal gray	(0, -32, -6)



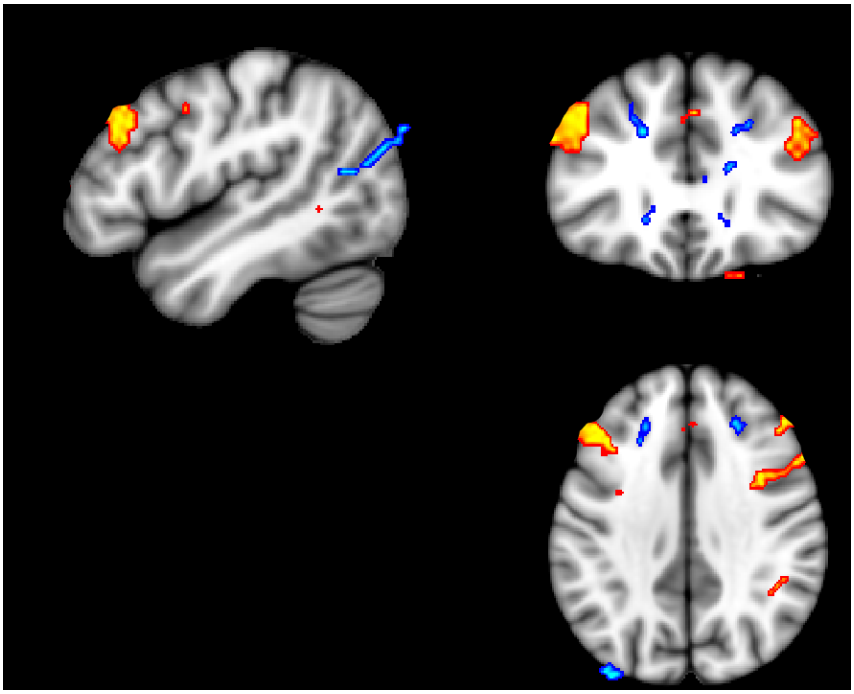


Figure S6: Regions of overlap between the two cluster maps.

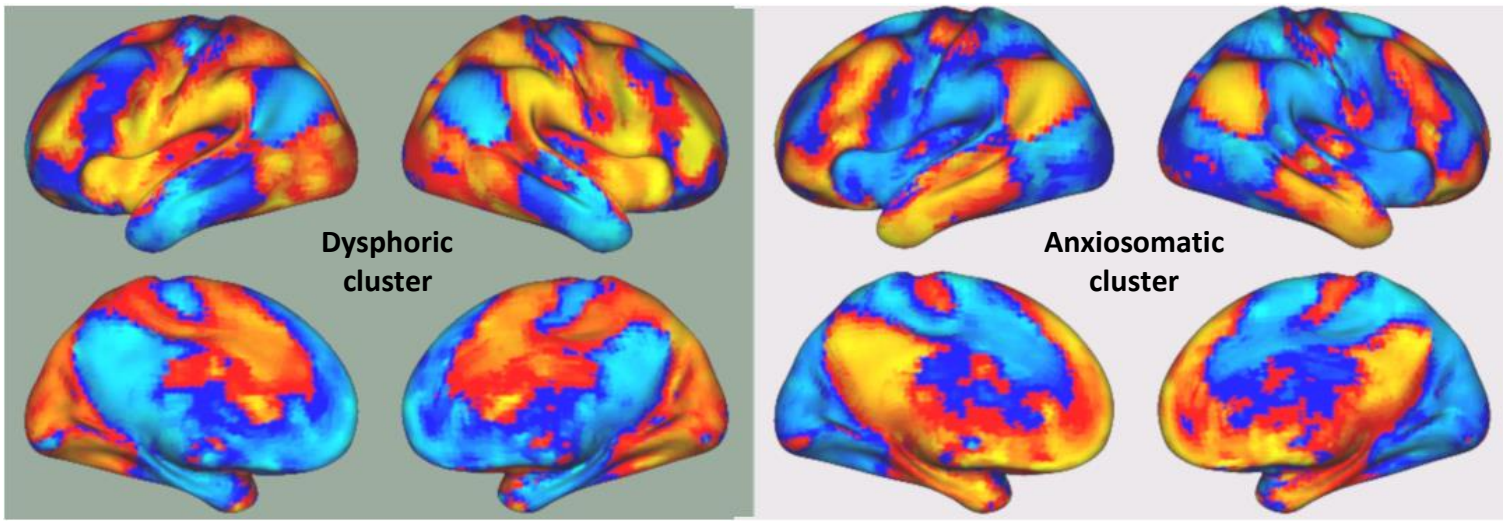


Figure S7: Two-cluster solution generated when using a connectome database of 38 subjects with major depression rather than 1000 healthy controls.

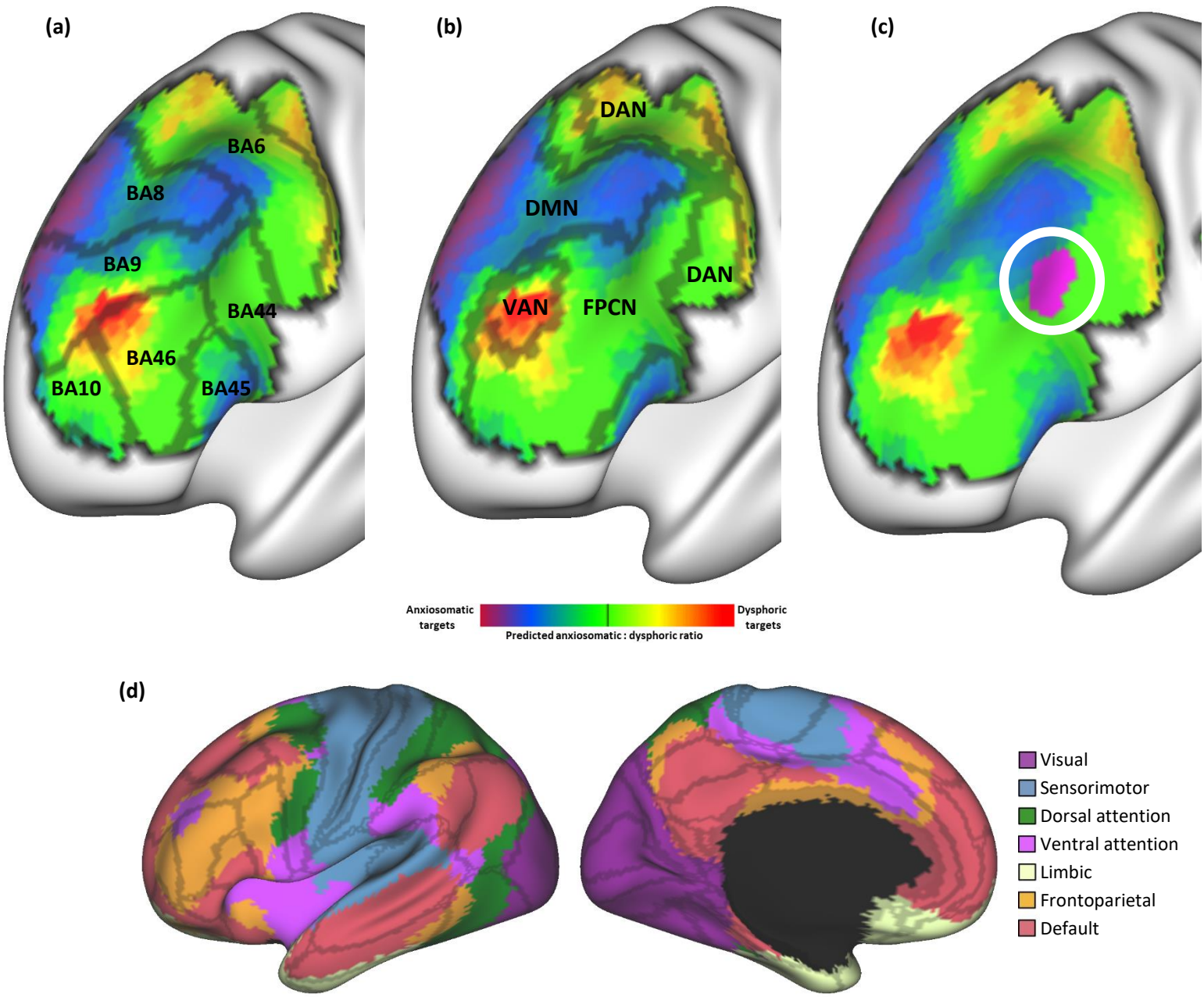


Figure S8: Alignment of optimal targets with consensus cortical parcellation schemes.
(a) Brodmann areas: The dysphoric target lies at the intersection of Brodmann areas 9, 10, and 46. The anxiosomatic targets lie in Brodmann area 8.
(b) Yeo parcels(5)**:** The dysphoric target aligns with the Ventral Attention Network (VAN) parcel, also known as the "cingulo-opercular network" or the "salience network." Other parts of the dysphoric network also align with the dorsal attention network (DAN). The anxiosomatic target aligns with the default mode network (DMN).
(c) Lesion network map of depression(6): A dorsolateral prefrontal site that has been shown to be connected to depression-causing lesions is depicted in magenta. This site was not preferentially connected to either symptom-specific circuit.
(d) Surface projection of Yeo parcellation (colors) and Brodmann parcellation (gray lines) for reference.

Table S1: Dataset characteristics and patient demographics

	Discovery	Replication
Sample size	30	81 active, 87 sham
Treatment device	47% Neuronetics, 53% Magstim	Neuronetics 2100
Setting	Naturalistic	Multi-site trial
Targeting method	"5.5 cm"	"5 cm"
Clinical outcomes	BDI (primary), HAMD	HAMD (primary), IDS
Stimulation site recording procedure	Stim sites recorded using neuronavigation	Stim site marked during MRI
Mean age (range)	53 (24-67)	47 (22-69)
Gender	67% female	57% female
Concomitant antidepressant use	100%	0%
Mean number of concomitant medications	3.0	0

		Dysphoric cluster	Anxiosomatic cluster
Clinical improvement (Mean ± SD)	**Discovery**	47% ± 24%	49% ± 28%
	Replication (active)	14% ± 36%	16% ± 52%*
	Replication (sham)	13% ± 26%**	-4% ± 77%**
Correlation between baseline and change (Spearman rho)	**Discovery**	0.07 (p = 0.75)	0.19 (p = 0.36)
	Replication (active)	0.02 (p = 0.84)	0.11 (p = 0.32)
	Replication (sham)	0.24 (p = 0.03)	0.25 (p = 0.02)

*p<0.05 in comparison with sham (unpaired t-test)
**p<0.05 in comparison with the other cluster (paired t-test)

Table S2: Clustering is not driven by differences in baseline symptoms or overall clinical trajectory of patients in each dataset.

In the discovery dataset and the active arm of the replication dataset, clinical improvement was approximately equal between the two symptom clusters. In the sham dataset, dysphoric symptoms improved significantly more than anxiosomatic symptoms. Anxiosomatic symptom improvement was significantly greater in the active replication dataset than in the sham replication dataset. These results are consistent with the fact that the majority of patients in the replication dataset were stimulated at relatively anxiosomatic stimulation sites.

Clinical change in each cluster was not significantly correlated with baseline severity of that cluster in either the discovery dataset or the active arm of the replication dataset. In the sham dataset, clinical improvement was significantly related to baseline severity in the corresponding symptom cluster.

Discovery cohort		Replication cohort	
1	BDI Sadness	43	IDS Insomnia early
2	BDI Pessimism	44	IDS Insomnia middle
3	BDI Failure	45	IDS Insomnia late
4	BDI Anhedonia	46	IDS Hypersomnia
5	BDI Guilt	47	IDS Sadness
6	BDI Punishment	48	IDS Irritability
7	BDI Self-hate	49	IDS Anxiety
8	BDI Self-blame	50	IDS Mood reactivity
9	BDI Suicidality	51	IDS Diurnality
10	BDI Crying	52	IDS Environmental variation
11	BDI Restlessness	53	IDS Mood Quality
12	BDI Interest	54	IDS Concentration/decisions
13	BDI Indecisiveness	55	IDS Self-blame
14	BDI Worthlessness	56	IDS Hopelessness
15	BDI Anergia	57	IDS Suicidality
16	BDI Sleep	58	IDS Interest
17	BDI Irritability	59	IDS Anergia
18	BDI Appetite	60	IDS Anhedonia
19	BDI Concentration	61	IDS Sex
20	BDI Fatigue	62	IDS Slow
21	BDI Sex	63	IDS Restless
22	HAMD Depression	64	IDS Aches/pains
23	HAMD guilt	65	IDS Panic autonomic
24	HAMD Suicide	66	IDS Panic other
25	HAMD Insomnia early	67	IDS GI
26	HAMD Insomnia middle	68	IDS Interpersonal sensitivity
27	HAMD Insomnia late	69	IDS Leaden paralysis
28	HAMD Activities	70	HAMD Depression
29	HAMD Slowing	71	HAMD Guilt
30	HAMD Restlessness	72	HAMD Suicide
31	HAMD Anxiety psychic	73	HAMD Insomnia early
32	HAMD Anxiety autonomic	74	HAMD Insomnia middle
33	HAMD Somatic GI	75	HAMD Insomnia late
34	HAMD Somatic general	76	HAMD Activities
35	HAMD Hypochondriasis	77	HAMD Slowing
36	HAMD Weight loss	78	HAMD Restlessness
37	HAMD Diurnal	79	HAMD Anxiety psychic
38	HAMD Dissociation	80	HAMD Anxiety autonomic
39	HAMD Obsessionality	81	HAMD Somatic GI
40	HAMD Helplessness	82	HAMD Somatic general
41	HAMD Hopelessness	83	HAMD Genital
42	HAMD Worthlessness	84	HAMD Hypochondriasis
		85	HAMD Weight loss
		86	HAMD Insight
		87	HAMD Diurnality
		88	HAMD Dissociation
		89	HAMD Paranoia
		90	HAMD Obsessionality
		91	HAMD Helplessness
		92	HAMD Hopelessness
		93	HAMD Worthlessness
		94	HAMD Anergia
		95	HAMD Hypersomnia
		96	HAMD Increased appetite
		97	HAMD Rejection sensitivity

Table S3: Index of specific symptoms in figure 3a. Green symptoms fell into the dysphoric cluster, while purple symptoms fell into the anxiosomatic cluster.

	Study	Target	Diagnosis/ population	*n*	Mood Scale	Anxiety Scale
Superficial TMS	Blumberger(7)	Anti-sgACC	MDD	177	HAMD	BSI-A
	Carpenter(8)	Beam F3	PTSD	35	IDS-SR	PSS
	Berlim(9)	EEG F3	MDD	15	HAMD	HAMA
	Taylor(10)	Functional	MDD	16	MADRS	GAD-7
	Leong(11)	Left 6cm	MDD	32	HAMD	GAD-7
	Downar(12)	dmPFC	MDD	47	BDI	BAI
	Dunlop 1(13)	dmPFC	AN/BN	28	BDI	BAI
	Dunlop 2(14)	dmPFC	OCD	20	BDI	BAI
	Yesavage(15)	Left 6cm	MDD	73	HAMD	PCL-M
	Discovery data	Left 5.5cm	MDD	30	Clusters	Clusters
	Replication data	Left 5cm	MDD	81	Clusters	Clusters
	Mansur(16)	Right 5cm	OCD	30	HAMD	HAMA
	Dilkov(17)	Right 5cm	GAD	15	HAMD	HAMA
	Tovar-Perdomo(18)	Beam F3	MDD	24	QIDS-C	BAI
Deep TMS	Levkovitz(19)	Left 5.5cm	MDD	65	HAMD	HAMA
	Tavares(20)	Left 6cm	BPAD	25	HAMD	HAMA
	Berlim(21)	Left 6cm	MDD	17	HAMD	HAMA
	Kaster(22)	Left 5.5cm	Geriatric MDD	27	HAMD	BSI-A
	Isserles(23)	mPFC	PTSD	9	HAMD	CAPS
	Rosenberg*(24, 25)	Left 5.5cm	MDD	8	HAMD	HAMA

Diagnoses:
MDD = Major Depressive Disorder
PTSD = Post-traumatic stress disorder
AN/BN = Anorexia nervosa and bulimia nervosa
OCD = Obsessive-compulsive disorder
GAD = Generalized Anxiety Disorder
BPAD = Bipolar affective disorder (current episode depressed)

Dysphoric scales:
HAMD = Hamilton Rating Scale for Depression
IDS-SR = Inventory of Depressive Symptoms (self-report)
MADRS = Montgomery-Asberg Depression Rating Scale
BDI = Beck Depression Inventory
Clusters = data-driven clustering
QIDS-C = Quick Inventory of Depressive Symptoms (clinician-report)

Anxiosomatic scales:
BSI-A = Brief Symptom Inventory for Anxiety
PSS = Perceived Stress Scale
PCL-M = PTSD Checklist for Military
CAPS = Clinician-Administered PTSD Scale
HAMA = Hamilton Rating Scale for Anxiety
BAI = Beck Anxiety Inventory
GAD-7 = Generalized Anxiety Disorder 7-item Scale

Treatment targets:
Anti-sgACC: MRI neuronavigated coordinate with maximal normative sgACC anti-correlation (Fox et al, 2012)(1)
"5cm": 5cm anterior to motor cotex
"5.5cm": 5.5cm anterior to motor cortex
"6cm": 6cm anterior to motor cortex
EEG F3: F3 coordinate on standard 10-20 EEG system
Beam F3: Scalp-based heuristic to estimate location of F3 (Beam et al, 2009)(3)
dmPFC: Neuronavigated dorsomedial prefrontal coordinate
mPFC: Scalp-based medial prefrontal target

*This dataset included two publications from the same center with the same treatment protocol. Data from individual subjects were reported in both publications. Due to the small sample sizes, the studies were combined into a single dataset. Subjects were included in this analysis if they completed the full 4-week treatment protocol.

Table S4: Details of the studies included in the exploratory meta-analysis.

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