Supplementary Methods

Subject Screening

Medical history and physical examination were performed by an experienced physician. Standardized psychiatric screening was performed using the Mini International Neuropsychiatric Interview Plus to assess for a psychiatric disorder (eg, depression, dysthymia, anxiety, panic disorder, disorder of mania or bipolar disorder, phobia, post-traumatic stress disorder, substance abuse, eating disorder). Lactose intolerance, chronic gastrointestinal symptoms, chronic or acute pain disorder, psychiatric disorder, or other active medical condition were exclusionary. Only nonobese women were eligible for the study (ie, body mass index 18–30).

Diary and Symptom Data

Symptoms of anxiety and depression were assessed using the Hospital Anxiety and Depression scale at the pre and post-intervention visits. Analysis of variance was implemented in SPSS using the baseline Hospital Anxiety and Depression score as a covariate to determine group effects on anxiety and depression. Daily diary data for abdominal bloating, rumbling or gurgling stomach, gas or flatulence, abdominal pain or discomfort, and bowel movement satisfaction were recorded by the subjects in an automatic phone diary using a verbal descriptor anchored a 0 to 20-point scale for no symptoms to "extremely bothersome" symptoms, expect for bowel movement satisfaction, which was a −10 to +10 scale anchored by "extremely dissatisfied" to "extremely satisfied." Change in these measures was assessed using general linear mixed model for repeated measures data in SPSS using weekly means for each variable. Threshold of significance was set at $P < .05$.

Results

Response to the Emotional Faces Attention Task

To confirm adequate task performance, a group analysis was performed at baseline. The emotional attention task resulted in activation of brain regions associated with emotion regulation, including the pregenual cingulate and medial prefrontal cortices (Supplementary Table 1). As reported previously, variability in amygdala activation by the paradigm was seen, with some subjects displaying activation and some deactivation of the amygdala, resulting in a nonsignificant task-induced mean change in amygdala activity. Regions showing activation during the task at baseline are shown in Table 1.

FMPP Reduces Reactivity of a Widely Distributed Network of Brain Regions to an Emotional Attention Task

Regions in the network shown in Figure 1 are detailed in Supplementary Table 2.

Ingestion of FMPP Is Associated With Altered Reactivity of Interoceptive and Somatosensory Regions to an Emotional Attention Task

Regional differences between groups are detailed in Supplementary Table 3.

Ingestion of FMPP Is Associated With Alterations in a PAG-Seeded Resting-State Network

Regions shown in Supplementary Figure 3 are detailed in Supplementary Tables 4*A* and *B*.

Symptom Reports

No differences was observed in anxiety and depression scores between groups at baseline (anxiety F = 1.34; *df* 2; $P = .275$; depression F = .239, *df* 2; $P = .798$). Overall mean baseline scores were low and none met criteria for likely clinical case (mean anxiety, 2.66; standard deviation, 2.5; mean depression, 1.26; standard deviation, 1.8). No effect of intervention group was observed on anxiety (F = 1.47, *df* 2; $P = .245$) or depression symptoms (F = .408, *df* 2; $P = .668$). Baseline gastrointestinal symptoms were low and there were no group differences. Mean (standard deviation) for the gastrointestinal symptoms during the run in period were: bloating = .30 (.44), rumbling .39 (.58), gas/flatulence = .97 (.98), abdominal pain/discomfort = .18 (.29), bowel movement satisfaction = 6.8 (2.8). No effect of intervention group was seen for any of the gastrointestinal variables during the course of the study period: bloating (F = .18, *df* 2; $P = .84$) rumbling (F = .98, *df* 2; $P = .39$), gas/flatulence (F = .93, *df* 2; $P = .40$), abdominal pain/discomfort (F = .41, *df* 2; $P = .67$), bowel movement satisfaction (F = .24, *df* 2; $p = .80$).

Safety

The main emergent adverse events were similar between groups and are reported by number of subjects in the FMPP and Control groups, respectively: gastrointestinal (1 event, 2 events), nervous system disorders (1 event, 2 events), and pharyngolaryngeal pain (2 events, 0 events). The FMPP and Control products were safe and well tolerated.

Supplementary Table 1. Regions Showing Greater BOLD Activity During the Match Emotions Conditions Compared With Match Forms Condition

Brain region	X	Y	Z	Cluster extent	Z score	*P* (fwe)
Whole-brain analysis						
Anterior cingulate, BA 32	−2	52	−12	261	4.89	.003
Precuneus	6	−52	46	160	3.76	.030
Dorsomedial PFC	4	62	22	250	4.09	.004
Dorsolateral PFC	−30	60	14	125	4.56	.074
Cerebellum	−16	−90	−20	270	4.33	.002
Region of interest analysis[a]						
Pregenual cingulate	−2	52	−12	182	4.89	<.001
Subgenual cingulate	−6	34	−10	22	3.93	.012
Dorsolateral PFC	−30	60	14	96	4.56	.008
	24	34	46	224	4.62	<.001

BA, Brodmann area; fwe, cluster correction using family-wise error; PFC, prefrontal cortex.
[a]No significant findings for amygdala, insula, and somatosensory cortex.

SupplementaryTable 2. Brain Regions From an Emotional Reactivity Network With Decreased Activity in the FMPP Group Compared With No-Intervention and Control Groups

Brain region	X	Y	Z	Bootstrap ratio	Approximate *P* value	Cluster size
Insula						
Mid	50	2	0	−5.3239	<.0001	247
Posterior	−42	−18	−2	−3.6909	.0002	40
	−48	−2	14	−3.5396	.0004	57
Primary somatosensory and association						
BA 2	56	−20	38	−7.4125	<.0001	2168
	−60	−20	32	−6.5169	<.0001	1519
BA 6	28	0	68	−3.9636	.0001	34
	20	20	52	−3.741	.0002	55
	−8	10	54	−5.5904	<.0001	1629
Cerebellum						
Declive	−20	−68	−18	−8.5886	<.0001	6998
Culmen	34	−62	−22	−5.6182	<.0001	869
Midbrain						
PAG	−4	−26	−6	−5.3583	<.0001	94
Parahippocampal gyrus						
BA 35	20	−24	−20	−3.8944	.0001	59
BA 27	−10	−38	0	−4.1351	<.0001	41
Basal ganglia						
Putamen	32	−10	0	−3.0066	.0026	22
	34	−6	−10	−5.1755	<.0001	58
Frontal cortex						
BA 44	−54	10	16	−3.9533	.0001	38
BA 8	26	14	46	−4.4712	<.0001	59
	−22	24	48	−3.1785	.0015	88
BA 9/10	38	44	22	−3.453	.0006	73
BA 11	32	46	−16	−3.7562	.0002	30
Temporal lobe						
BA 38	38	8	−24	−3.9417	.0001	51
BA 22	54	−14	−6	−6.1559	<.0001	114
	−60	−14	4	−3.9333	.0001	39
Claustrum	−36	−10	−12	−3.482	.0005	20
Precuneus						
BA 31	−12	−42	42	−4.2555	<.0001	145

BA, Brodmann area.

Supplementary Table 3. Regions Identified Using Small Volume Correction Showing Significantly Less Activity in the FMPP Group During Reactivity Are Listed

Brain region	X	Y	Z	Cluster extent	*Z* score	*P* value (fwe)[a]
No intervention > FMPP						
Insula−mid	46	2	4	30	4.614	.004
Insula−posterior	40	−16	12	12	3.731	.020
Somatosensory cortex−BA2/3	−56	−20	36	78	3.922	.005
	60	−26	42	171	4.856	<.001
Control > FMPP						
Insula−mid	46	2	0	1	3.155	.032
Insula−posterior	34	−18	20	4	3.504	.039
Somatosensory cortex−BA2/3	−56	−24	34	7	3.291	.142
	62	−20	38	48	4.509	.016

BA, Brodmann area; few, family-wise error correction.

Supplementary Table 4A. The Resting-State Network Regions That Were Positively Correlated to Midbrain Reactivity in the No-Intervention Group Are Shown

Brain region	X	Y	Z	Bootstrap ratio	*P* value	Cluster size
Limbic regions						
Amygdala	26	0	−22	4.5239	<.0001	21
Cingulate gyrus	−8	−24	32	5.268	<.0001	99
	−8	−28	42	3.7114	.0002	27
Hippocampus	−36	−14	−18	6.3626	<.0001	67
Parahippocampal gyrus	18	−38	−6	6.9908	<.0001	214
	30	−34	−10	3.7757	.0002	22
Basal ganglia						
Caudate	−10	16	−6	4.8236	<.0001	20
Putamen	−34	−18	6	4.0582	<.0001	25
	36	−14	−2	5.1452	<.0001	123
Medial globus pallidus	22	−8	−8	3.6033	.0003	24
Somatosensory and association regions						
Insula (post/mid)	42	8	12	5.4835	<.0001	50
	32	−6	14	8.3758	<.0001	183
Primary somatosensory	40	−24	38	6.592	<.0001	31
	−22	−30	70	8.021	<.0001	890
	60	−12	40	3.3716	<.0007	22
Supplementary motor area	12	22	54	5.1483	<.0001	49
	−40	−12	36	5.0524	<.0001	134
Occipital/Brodmann 18/19	−12	−78	38	7.838	<.0001	2742
	20	−88	34	6.4068	<.0001	508
Midbrain	8	−30	−8	4.0335	.0001	25
	8	−16	−8	3.7286	.0002	43
Thalamus medial dorsal nucleus	−10	−18	12	5.3802	<.0001	50
Cerebellum						
Vermis/culmen	6	−56	−12	5.5832	<.0001	65
	−6	−68	−26	5.5087	<.0001	60
Cognitive and attentional regions						
Brodmann area 40	−60	−30	28	5.4903	<.0001	56
	−54	−34	24	4.8573	<.0001	72
Prefrontal cortex	12	58	0	6.9269	<.0001	21
	40	54	−2	5.1201	<.0001	21

NOTE. This network was negatively correlated with midbrain reactivity in the FMPP group (see Figure 2). In regions with more than one significant cluster only the largest is shown.

Table 4B. Resting-State Network Regions That Correlate Positively With Midbrain Reactivity in the FMPP Group Are Shown

Brain region	X	Y	Z	Bootstrap ratio	Approximate *P* value	Cluster size
Dorsolateral prefrontal cortex	−44	26	42	−6.1804	<.0001	21
	26	12	58	−5.3489	<.0001	21
	40	22	32	−4.9707	<.0001	22
Medial prefrontal cortex	−10	42	26	−4.0408	.0001	39