

Supplementary Online Content

Victor TA, Furey ML, Fromm SJ, Öhman A, Drevets WC. Relationship Between Amygdala Responses to Masked Faces and Mood State and Treatment in Major Depressive Disorder. *Arch Gen Psych*. 2010;67(11):1128-1138.

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This supplementary material has been provided by the authors to give readers additional information about their work.

METHODS

PARTICIPANTS

Participant Selection for Experiment 3

Following an interim analysis for experiment 1, which provided preliminary evidence suggesting that our experimental paradigm was revealing a differential response between participants with MDD and HCs, we initiated experiment 3 to evaluate the effects of antidepressant treatment on the emotional-processing bias in MDD. The depressed people enrolled in the study from this point forward were asked to complete 8 weeks of treatment, after which they would participate in additional follow-up fMRI. Participation in the antidepressant treatment was voluntary and did not affect the individual's eligibility to participate in the baseline portion of this study. If the individual declined treatment but was still eligible to participate, he or she was still enrolled as a depressed participant, and the data were included in the analysis for experiment 1. This was the case for 2 participants in experiment 1 who declined pharmacotherapy owing to their aversion to potential adverse effects. All of the participants who entered the treatment arm underwent subsequent fMRI after the 8-week period.

RESULTS

EFFECTS OF PSYCHIATRIC COMORBIDITY ON AMYGDALA RESPONSE TO MASKED FACES

To assess the effects of having comorbid conditions (ie, anxiety disorders) on emotional-processing biases in MDD, the mean BOLD response in the amygdala was compared for participants with vs without comorbid anxiety disorders (13 MDD cases without comorbid anxiety disorders vs 9 MDD cases with comorbid anxiety disorders). Independent *t* tests were used to assess the significance of differences across subgroups for the hemodynamic data obtained from the amygdala locus, where the entire MDD sample had differed from controls in experiment I. The results indicated a nonsignificant trend toward greater left amygdala response in participants without comorbid anxiety disorders to both HN-NN ($t_{20}=1.87$; $P=.08$)

and SN-NN ($t_{20}=1.91$; $P=.07$) and a nonsignificant trend toward greater right amygdala response in participants with comorbid anxiety disorders to SN-HN ($t_{20}=1.93$; $P=.07$).

COMPARISON OF dMDD PARTICIPANTS WHO UNDERWENT SUBSEQUENT fMRI AFTER TREATMENT vs PARTICIPANTS WHO HAD fMRI ONLY AT BASELINE

The mean demographic and clinical ratings for the 10 MDD participants who received treatment and the 12 MDD participants who did not receive treatment were compared using independent t tests to assess the significance of potential differences between subgroups. No significant difference was identified between subgroups in sex ratio, age, intelligence (WASI), depression severity (HAM-D, IDS-SR), negative ideation (ATQ), state or trait anxiety levels (STAI-S, STAI-T), or TCQ overall score or subscale scores.

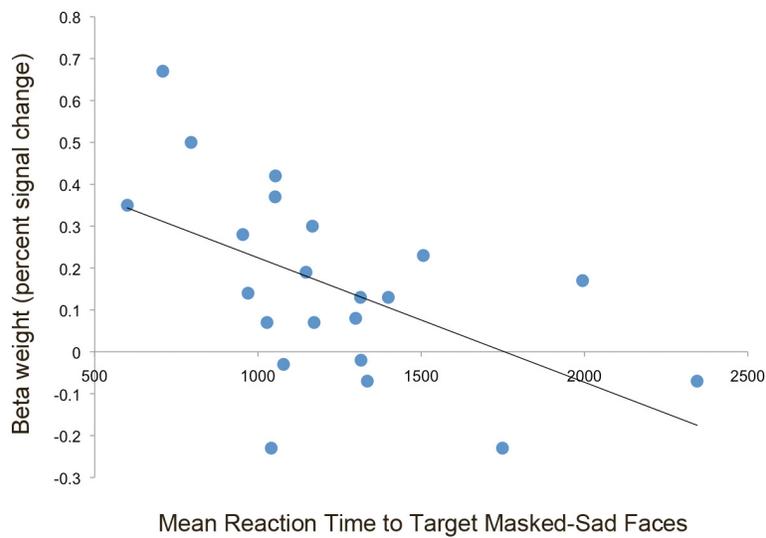
For the baseline neurophysiological data, the mean BOLD response in the amygdala to masked sad vs masked happy face stimuli (SN-HN) was compared between subgroups using independent t tests. The BOLD data were extracted from the locus where the entire MDD group had differed from the control group in experiment 1. No significant difference (ie, $P>.05$) in the mean BOLD response to SN-HN at baseline was identified in the MDD group that received treatment vs the MDD group that did not receive treatment.

For the behavioral data, the mean performance accuracy for detecting a target stimulus in the first face (masked) position was compared between subgroups using independent t tests. No significant difference was found ($t_{20}=0.09$; $P=.93$) in the mean accuracy across subgroups. For the reaction time data, a 2 (group) \times 5 (stimulus type) ANOVA revealed a significant main effect of group ($F_{1,4}= 7.32$; $P<.01$). This effect was attributable to the dMDD participants who entered treatment responding faster overall than the dMDD participants who did not enter treatment.

RELATIONSHIPS BETWEEN REACTION TIME AND AMYGDALA RESPONSE

To assess the relationship in dMDD participants between reaction time and amygdala response to masked emotional faces, the mean reaction time to masked sad faces was correlated with the amygdala response to masked sad vs masked happy faces. As referred to in the main article, eFigure 1 shows a significant inverse correlation between mean reaction time to masked sad faces and the right amygdala response to masked sad vs masked happy faces in the currently depressed participants from experiment 1 (n=22). Similarly, in the subgroup of depressed participants who entered treatment (n=10), a trend was also evident toward faster reaction time to masked sad faces and greater right amygdala response to these faces ($r=-0.63$; $P=.05$). The right amygdala data were obtained at the locus where the dMDD participants and controls differed most in experiment 1 (x=26, y=-1, z=-12). After treatment, the correlation between the reaction time to masked sad faces and the amygdala response in the MDD participants (n=10) from experiment 3 was not significant ($r=0.34$; $P=.35$). The treatment effect attenuated the relationship between reaction time and amygdala response to sad faces that had existed in the depressed participants before treatment. Future treatment studies with a larger sample size are needed to address the hypothesis that depressed people who show faster reaction time to masked sad faces show greater amygdala activity that subsequently reverses after treatment. Finally, no significant parallel correlation was found between reaction time to target masked happy faces and the amygdala response to masked happy faces in HCs or depressed participants ($P>.10$).

eFigure 1. Relationship between reaction time to target masked sad faces and amygdala response. In currently depressed participants (n=22), the mean reaction time when a target face was presented as a masked sad face was inversely correlated ($r = -0.53$; $P < .05$) with the hemodynamic response to masked sad faces vs masked happy faces (shown as the β -weight value) for this contrast for each participant, obtained at the right amygdala locus (26, -1, -12), where participants with depression and controls differed most significantly in experiment 1.



eTable 1. Course of Illness and Psychiatric Comorbidity for Currently Depressed Participants

Subject No.	Sex	Age at Onset, y	Course of Illness	Psychiatric Diagnoses	Treatment Naïve	Participation in Treatment Study
1	M	14	Chronic, single episode	MDD, PD	X	
2	F	22	Chronic, single episode	MDD, SAD	X	X
3	M	16	Chronic, single episode	MDD, SAD	X	
4	M	12	Chronic, single episode	MDD, SAD		
5	F	12	Recurrent	MDD, SAD	X	
6	F	22	Recurrent	MDD, PD	X	
7	M	10	Recurrent	MDD, PD		
8	M	14	Recurrent	MDD, PTSD, snake phobia	X	X
9	F	10	Recurrent	MDD, DD, SAD	X	
10	M	11	Recurrent	MDD	X	
11	M	25	Recurrent	MDD	X	X
12	F	15	Recurrent	MDD		X
13	M	12	Recurrent	MDD	X	
14	F	12	Recurrent	MDD		
15	F	14	Recurrent	MDD		X
16	F	28	Recurrent	MDD		X
17	F	15	Recurrent	MDD		X
18	M	21	Recurrent	MDD		X
19	F	30	Recurrent	MDD	X	
20	F	21	Recurrent	MDD	X	X
21	F	20	Recurrent	MDD	X	
22	M	10	Recurrent	MDD		X

Abbreviations: DD, dysthymic disorder; MDD, major depressive disorder; PD, panic disorder; PTSD, posttraumatic stress disorder; SAD, social anxiety disorder.

eTable 2. Course of Illness and Psychiatric Comorbidity for Depressed Participants in Remission

Subject No.	Sex	Age at Onset, y	Course of Illness	Past Psychiatric Diagnoses	Treatment Naïve
1	F	17	Episodic, Single	rMDD	
2	F	21	Episodic, Single	rMDD	
3	M	21	Episodic, Single	rMDD	
4	F	15	Episodic, Single	rMDD	X
5	M	17	Episodic, Single	rMDD	
6	F	17	Recurrent	rMDD	
7	F	30	Recurrent	rMDD	
8	M	14	Recurrent	rMDD	
9	F	21	Recurrent	rMDD	
10	F	18	Recurrent	rMDD	
11	M	24	Recurrent	rMDD	
12	F	17	Recurrent	rMDD	
13	F	13	Recurrent	rMDD	
14	M	17	Recurrent	rMDD, rSAD, alcohol abuse*	X
15	F	16	Recurrent	rMDD, alcohol abuse*	
16	F	14	Recurrent	rMDD, rPTSD	X

Abbreviations: rMDD, major depressive disorder in remission; rPTSD, posttraumatic stress disorder in remission; rSAD, social anxiety disorder in remission.

* Participants had not met *DSM-IV* criteria for alcohol abuse within the 1 year preceding functional magnetic resonance imaging.

eTable 3. Differences in the Hemodynamic Response to Masked Sad vs Masked Happy Faces in Currently Depressed Participants vs HCs in Regions Located Outside the Amygdala*

	Region	Stereotaxic Coordinates			Cluster Size	z Value
		x	y	z		
dMDD > HC	Left Hippocampus	-28	-18	-14	46	3.61
HC > dMDD	Left Thalamus	-8	-29	5	10	3.29

Abbreviations: dMDD, currently depressed participants with major depressive disorder; HCs, healthy controls;

* These data were generated using an exploratory voxelwise analysis of the entire brain conducted post hoc using SPM5 statistical software to compare the blood oxygen level–dependent data for this contrast between the dMDD participants (n=22) and HCs (n=25) from experiment 1. The significance threshold for reporting regional differences in this SPM analysis was set at a cluster size of 10 or more contiguous voxels, for which the voxel was set at $P < .001$. Note that the region-of-interest analysis, limited to the vicinity of the amygdala, applied a less conservative significance threshold because it involved fewer independent comparisons. Consequently, the independent results in the amygdala, which had peak voxel t values of $P < .005$, were significant in the region-of-interest analysis conducted to test the a priori hypothesis but are not included in this table. dMDD > HC designates where the regional hemodynamic response to the contrast of implicitly presented sad faces vs implicitly presented happy faces in the dMDD participants exceeds that of the controls; HC > dMDD designates where the regional hemodynamic response to the contrast of implicitly presented sad faces vs implicitly presented happy faces in the controls exceeds that of the dMDD participants.

eTable 4. Differences in the Regional BOLD Response to Unmasked Sad vs Unmasked Happy Faces in Currently Depressed Participants vs HCs*

	Region	Stereotaxic Coordinates			Cluster Size	z Value
		x	y	z		
dMDD > HC	Left Temporopolar C	-38	13	-21	29	3.99
HC > dMDD	Superior Frontal G	4	-17	49	159	4.38
	Right Precentral G	38	-13	47	137	3.97
	Right Precentral G	50	-15	49	...	3.52
	Right Precentral G	26	-23	53	14	3.32
	Left Precentral G	-44	-5	48	34	3.65
	Left Precentral G	-51	-4	41	...	3.15
	Postcentral G	61	-9	10	37	3.87
	Middle Temporal G	58	-10	-15	43	3.81
	Parietal Operculum	50	-21	16	26	3.53

Abbreviations: BOLD, blood oxygen level–dependent; C, cortex; dMDD, currently depressed participants with major depressive disorder; G, gyrus; HC, healthy controls.

*Data were obtained from an exploratory whole brain analysis performed post hoc using SPM5 statistical software to assess the specificity of the regional BOLD responses found using the backward masking technique. The analysis compared the functional magnetic resonance imaging data for the 22 dMDD participants and 25 HCs from experiment 1. The significance threshold for reporting regional differences in this SPM analysis was set at a cluster size of 10 or more contiguous voxels, for which the voxel was set at $P < .001$. dMDD > HC designates where the regional hemodynamic response to the contrast of explicitly presented sad faces vs explicitly presented happy faces in the dMDD participants exceeds that of the controls; HC > dMDD designates where the regional hemodynamic response to the contrast of explicitly presented sad faces vs explicitly presented happy faces in the controls exceeds that of the dMDD participants.