Data Supplement for Young et al., Amygdala Activity During Autobiographical Memory Recall in Depressed and Vulnerable Individuals: Association With Symptom Severity and Autobiographical Overgenerality. Am J Psychiatry (doi: 10.1176/appi.ajp.2015.15010119)

S1. Consistency Across Samples

As the present study includes participants in a previously published study in which amygdala activation was not statistically significant, it is important to show that the two subsamples (previously included participants, new participants) did not differ significantly from each other on the variables of primary interest in the current study (amygdala activation during positive and negative AM recall). Therefore, we performed additional analyses to examine the consistency across these two subsamples. We performed the repeated measures ANOVA with the between subjects factors of Diagnosis (Controls, High-Risk, Remitted, Depressed) and the repeated measures Valence (Positive, Negative) and ROI (Left, Right amygdala), and the additional between subjects factor of whether the participant had been Previously Included in a study (Yes, No). There was no main effect of Previous Inclusion ($F(1,156 = 0.78$, $p=0.38$), nor did Previous Inclusion interact with any of the other variables ($Fs(1,156$ or $3,156 < 0.78$, $ps>0.38$). Additionally, we performed independent samples t-tests within groups to determine if those who had been included in previous analyses differed from those who had not within each diagnostic category (Controls $ts(58)<1.05$, $ps>0.30$; High-Risk $ts(28)<1.03$, $ps>0.32$; Remitted $ts(23)<1.01$, $ps>0.32$; Depressed $ts(43)<0.99$, $ps>0.33$; all groups combined $ts(158)<1.57$, $ps>0.12$). No results were significant, suggesting that the results are consistent across the two subsamples.

S2. Whole Brain Activity

Image preprocessing and analysis was performed as described in the Methods section of the manuscript. At the group level, 3dMVM was used to identify regional differences in the blood oxygen level–dependent (BOLD) signal for the interactions of Group, Specificity, and Valence. The significance criterion for detecting differences was set at $p_{corrected}<0.05$, determined using AFNI 3dClustSim (cluster size >28 voxels, thresholded at voxel $p<.005$).

The Group x Specificity x Valence interaction did not yield any significant results using the significance threshold set *a priori.* This negative result may reflect the relatively low number of trials for categorical autobiographical memories in the controls, since further dividing these memories into positive and negative categorical autobiographical memories reduced power to detect regional differences in BOLD activity for such a complex interaction. For example, as the average number of categorical autobiographical memories recalled by controls was 2, the analysis was severely underpowered.

The Group x Specificity interaction revealed several regions where activity differed between groups (Table S2). The majority of the differences were due to differences between groups during *specific* memory recall. Only one region differed between groups during categorical autobiographical memory recall – the left middle occipital gyrus. Currently depressed participants had significantly elevated activity in this region during categorical autobiographical memory recall than remitted participants, who had significantly elevated activity relative to the high-risk participants, who had significantly elevated activity relative to the control participants. This finding is consistent with our previous result that depressed participants had elevated activity in the left middle occipital gyrus relative to high-risk and control participants(SR1). For the prefrontal regions listed in Table S2, including bilateral pregenual anterior cingulate cortex and right orbitofrontal cortex / BA47, the pattern of results was such that both depressed groups (remitted and currently depressed) were very similar to each other and had significantly greater activity than the healthy groups (high-risks and controls). These prefrontal regions are involved in emotional processing (anterior cingulate cortex; (SR2)) and rumination (SR3). This is consistent with our previous findings that depressed participants had increased anterior cingulate cortex activity relative to both control and high-risk participants(SR1) and that remitted participants had increased activity relative to controls(SR4). That the groups with a history of a depressive episode have increased activity in these regions relative to the groups never having experienced a depressive episode suggests the hypothesis that the experience of depression results in increased rumination upon available specific autobiographical memories that is not present in healthy individuals, including those at a high familial risk for developing depression.

The remaining regions that were different between groups during specific autobiographical memory recall were in the temporal cortex (bilateral middle temporal gyrus, and right superior temporal gyrus). In these regions depressed participants had significantly less activity than any of the other participant groups, consistent with our previous findings of reduced activity in these regions in depressed relative to remitted and control participants (SR4, SR5). This reduced activity appears to be mood-state specific as the high-risk groups had increased activity relative to both the depressed and control participants. This increased activity in those at risk for a depressive episode suggests that these groups must work harder to overcome their cognitive bias to recall general autobiographical memories and successfully retrieve a specific memory. Overall, these results replicate our previous findings and indicate that during specific autobiographical memory recall depressed participants show abnormally reduced activity core temporal regions consistently recruited during autobiographical memory recall (SR6), while

remitted and high-risk participants recruit these regions to a greater extent, perhaps reflecting increased effort needed to recall a specific autobiographical memory.

In order to be consistent with and better relate the results of the current analysis to that of our previous work, we examined the Group x Valence interaction for Specific autobiographical memories only (Table S3). In bilateral dorsomedial prefrontal cortex depressed participants had greater BOLD activity than all the other groups during positive autobiographical memory recall, but had decreased BOLD activity relative to the other groups during negative autobiographical memory recall. This region is involved in executive function, and activity correlates with task difficulty (SR7) and with cognitive control processes that serve to regulate emotional responses (SR8). Our results suggest that depressed participants require more effort to recall positive autobiographical memories, while the other groups require more cognitive effort to recall negative autobiographical memories, and is consistent with our previous results (SR4, SR9). Furthermore, in the left hippocampus depressed participants had increased activity during positive autobiographical memory recall relative to all other participant groups while they had the lowest amount of activity during negative autobiographical memory recall. This is consistent with our previous analyses (SR4) and we hypothesize that this may also be related to effort, as the hippocampus is a core region consistently recruited during autobiographical memory recall(SR6). Research has shown that depressed participants have decreased volume in this region (SR10), and that volume correlates positively with the ability to recall specific autobiographical memories (regardless of valence) in depressed participants(SR11). In post mortem studies the reduction in hippocampal volume in depression has been associated with abnormal reductions in neuropil associated with dendritic atrophy(SR12). The fMRI data thus conceivably suggest that the pathophysiology affecting this region in depressed participants results in a requirement for greater energy utilization and afferent synaptic transmission in order to support the neural processing required for positive specific autobiographical memory recall, potentially providing a neural basis for the hypothesis that currently depressed individuals require more “effort” to recall positive specific autobiographical memories.

In bilateral superior temporal gyrus depressed participants had increased activity relative to all other groups studied, with the remitted group having the least activity during *positive* autobiographical memory recall. In contrast, depressed participants had the lowest BOLD activity in these regions during *negative* autobiographical memory recall, with high-risks having the greatest activity in this region. The opposite pattern of results was evident in the precuneus; depressed participants had greater activity than the other groups during negative autobiographical memory recall while depressed participants had the lowest amount of activity

relative to the other groups during positive autobiographical memory recall. Notably, both the precuneus and superior temporal regions have been implicated in self-referential processing, but in reciprocal capacities. In previous reports, BOLD activity in the superior temporal gyrus increased when attention was focused on others versus self(SR13), whereas precuneus activity increased during self-referential processing and first-person perspective taking (SR14). Our results therefore suggest the hypothesis that high-risk and remitted participants focus attention on themselves during positive autobiographical memory recall to a greater extent than the controls, but shift attention toward others during negative autobiographical memory recall, whereas depressed participants focus attention towards themselves during negative autobiographical memory recall and towards others during positive autobiographical memory recall. That the participants at elevated risk for experiencing a depressive episode (high-risk and remitted participants) had activity different from both the healthy controls and depressed participants suggests that this pattern might underlie a cognitive strategy during autobiographical memory recall that plays an adaptive role in maintaining euthymia.

Finally, as the focus of the current manuscript is amygdala activity during autobiographical memory recall, we explored *post hoc* whether the changes in BOLD activity in amygdala observed in the region-of-interest analysis may simply have been below the significance threshold applied in the whole brain analysis. This post hoc analysis showed that when the cluster threshold was lowered to 20 voxels, then the groups indeed differed in *left* amygdala activation in the Group x Valence for Specific autobiographical memories interaction. Thus difference simply had not survived the cluster-level correction in the conservative whole brain analysis. This reflects a limitation of the whole brain analysis approach, since BOLD activity changes in anatomically small regions, such as the amygdala, can be filtered out by the requirement that BOLD activity changes occur over a larger anatomical area in order to exceed the cluster-level significance threshold (i.e., resulting in Type II error).

Overall, this whole brain analysis including all subjects collected to date replicated the whole brain findings of analyses performed with smaller samples and subpopulations of the entire sample used herein. Groups differed in BOLD activity in prefrontal, temporal, and parietal regions previously reported by our group (SR1, SR4, SR5, SR9). There were, however, regions that contained significant BOLD changes in our smaller analyses that did not reach significance in the current analysis, including the anterior insula, inferior temporal gyrus, and ventrolateral prefrontal cortex. These regions tended to be implicated in one analysis but not all, whereas the BOLD changes in regions such as the dorsolateral prefrontal cortex, and hippocampus

appeared in many of our previous analyses. Therefore, we replicated the most robust and consistent results of the group differences during autobiographical recall.

Collectively, our results suggest the following:

A. During specific autobiographical memory recall, individuals with a history of depression (whether remitted or depressed) engage regions previously implicated in rumination to a greater extent than healthy individuals (even those at a high-familial risk for developing depression)
B. Individuals at elevated risk for experiencing a depressive episode (whether due to being at high familial risk or having remitted depression) recruit regions implicated in task difficulty to a greater extent than the depressed or control group, suggesting recalling a specific autobiographical memory is more difficult for these participants and they put more cognitive effort into specific autobiographical memory recall.
C. Depressed individuals have difficulty recruiting core regions consistently recruited during autobiographical memory recall in healthy individuals, and recruit regions during positive autobiographical memory recall that are implicated in effortful processing, suggesting recalling specific positive autobiographical memories requires more cognitive effort for depressed participants.
D. During positive autobiographical memory recall, elevated risk groups (high familial risk, remitted depressed) engage more in self-referential processing than the depressed group, while during negative autobiographical memory recall the elevated risk participants engage regions involved in attentional focus on others and recruit regions suggesting recalling these memories requires more effort. This conceivably suggests a protective mechanism promoting euthymia.

References

SR1. Young K, Bellgowan P, Bodurka J, Drevets WC. Behavioral and neurophysiological correlates of autobiographical memory deficits in patients With depression and individuals at high risk for depression. JAMA Psychiatry 2013; 70(7):698-708.
SR2. Bush G, Luu P, Posner MI. Cognitive and emotional influences in anterior cingulate cortex. Trends Cogn Sci 2000; 4(6):215-22.
SR3. Lemogne C, Gorwood P, Bergouignan L, Pelissolo A, Lehericy S, Fossati P. Negative affectivity, self-referential processing and the cortical midline structures. Soc Cogn Affect Neurosci 2011; 6(4):426-33.

SR4. Young K, Bellgowan P, Bodurka J, Drevets W. Neurophysiological correlates of autobiographical memory deficits in currently and formerly depressed subjects. Psychol Med 2014; 44(14):2951-63.
SR5. Young K, Erickson K, Nugent AC, Fromm SJ, Mallinger AG, Furey ML, et al. Functional anatomy of autobiographical memory recall deficits in depression. Psychol Med 2012; 42:345-57.
SR6. Svoboda E, McKinnon M, Levine B. The functional neuroanatomy of autobiographical memory: a meta-analysis. Neuropsychologia 2006; 44(12):2189-208.
SR7. Kalbfleisch ML, Van Meter JW, Zeffiro TA. The influences of task difficulty and response correctness on neural systems supporting fluid reasoning. Cogn Neurodyn 2007; 1(1):71-84.
SR8. Phillips M, Drevets W, Rauch S, Lane R. Neurobiology of emotion perception I: The neural basis of normal emotion perception. Biol Psychiatry 2003; 54(5):504-14.
SR9. Young K, Bellgowan P, Bodurka J, Drevets W. Functional neuroimaging correlates of autobiographical memory deficits in subjects at risk for depression. Brain Sci 2015; 5:144-64.
SR10. Sheline YI, Gado MH, Kraemer HC. Untreated depression and hippocampal volume loss. Am J Psychiatry 2003; 160(8):1516-8.
SR11. Young K, Bellgowan P, Bodurka J, Drevets W. Autobiographical Memory Deficits Correlate with Gray Matter Volume in Depressed and High Risk Participants. Soc Sogn Affect Neurosci In Press.
SR12. Stockmeier CA, Mahajan GJ, Konick LC, Overholser JC, Jurjus GJ, Meltzer HY, et al. Cellular changes in the postmortem hippocampus in major depression. Biol Psychiatry 2004; 56(9):640-50.
SR13. van der Heiden L, Scherpiet S, Konicar L, Birbaumer N, Veit R. Inter-individual differences in successful perspective taking during pain perception mediates emotional responsiveness in self and others: an fMRI study. Neuroimage 2013; 65:387-94.
SR14. Cavanna AE, Trimble MR. The precuneus: a review of its functional anatomy and behavioural correlates. Brain 2006; 129(Pt 3):564-83.

TABLE S1. Clinical Characteristics of the Currently Depressed and Remitted Depressed Groups.

Clinical Characteristics of the Depressed Participants		
	Depressed	**Remitted**
Comorbid Diagnosis		
None	46.7% [n=21]	56.0% [n=14]
Social Phobia	22.2% [n=10]	20.0% [n=5]
Post-Traumatic Stress Disorder	22.2% [n=10]	16.0% [n=4]
Generalized Anxiety Disorder	8.89% [n=4]	8.00% [n=2]
Number of Major Depressive Episodes		
1 Episode	15.6% [n=7]	24.0% [n=6]
2 Episodes	4.44% [n=2]	16.0% [n=4]
3+ Episodes	80.0% [n=36]	60.0% [n=15]
Average Length in months of current Episode	31.9 (45.9)	N/A
Past Antidepressant Use		
None	46.7% [n=21]	44.0% [n=11]
1-2 previous	28.9% [n=13]	28.0% [n=7]
3+ Previous	24.4% [n=11]	28.0% [n=7]
Average Time in months Since Last Antidepressant	67.2 (68.5)	73.5 (83.0)

Numbers in parentheses indicate one standard deviation of the mean. Numbers in brackets indicate the number of subjects for each characteristic.

TABLE S2. Group x Specificity Interaction: Regions Where BOLD Activity Differed Between Groups for Specific and Categorical Memory Recall

				β Weight								Direction of Effect	
				Control	High-Risk	Remitted	Depressed	Control	High-Risk	Remitted	Depressed		
x, y, z[a]	Area	Cluster Size[b]	F	**Specific Memories**				**Categorical Memories**				Specific	Categorical
31, 21, -16	R OFC / BA47	41	6.20	0.13 (0.06)	0.15 (0.04)	0.32 (0.15)	0.38 (0.10)	0.48 (0.05)	0.46 (0.19)	0.50 (0.18)	0.47 (0.06)	dMDD>rMDD>HR=HC	=
-23, 41, 4	L Pregenual ACC	34	5.71	0.07 (0.02)	0.07 (0.02)	0.15 (0.05)	0.13 (0.04)	0.16 (0.09)	0.18 (0.10)	0.14 (0.12)	0.15 (0.12)	dMDD=rMDD>HR=HC	=
11, 43, 2	R Pregenual ACC	33	5.31	0.03 (0.01)	0.05 (0.02)	0.21 (0.04)	0.21 (0.02)	0.15 (0.10)	0.15 (0.05)	0.14 (0.07)	0.16 (0.04)	dMDD=rMDD>HR=HC	=
53, -43, 14	R Superior Temporal G	43	6.80	0.05 (0.11)	0.79 (0.07)	0.12 (0.07)	-0.04 (0.06)	-0.15 (0.07)	-0.12 (0.07)	-0.12 (0.14)	-0.13 (0.12)	HR>rMDD>HC>dMDD	=
-45, -39, -4	L Middle Temporal G	34	5.20	0.05 (0.04)	0.16 (0.06)	0.11 (0.04)	-0.16 (0.04)	0.07 (0.04)	0.06 (0.03)	0.08 (0.06)	0.08 (0.06)	HR>rMDD>HC>dMDD	=
61, -43, 4	R Middle Temporal G	35	5.65	0.02 (0.08)	0.32 (0.14)	0.07 (0.11)	-0.12 (0.06)	0.12 (0.11)	0.11 (0.08)	0.14 (0.08)	0.15 (0.10)	HR>rMDD>HC>dMDD	=
-31, -75, 8	L Middle Occipital G	49	6.45	-0.23 (0.13)	-0.27 (0.11)	-0.25 (0.15)	-0.24 (0.12)	-0.10 (0.02)	-0.04 (0.04)	0.10 (0.02)	0.30 (0.02)	=	dMDD>rMDD>HR>HC

Abbreviations: ACC = anterior cingulate cortex; BA = Brodmann area; dMDD = currently depressed major depressive disorder; G = gyrus; HC = healthy control participants; HR = individuals at high familial risk for developing depression; L = left; OFC = orbitofrontal cortex; R = right; rMDD= remitted major depressive disorder

[a] Coordinates correspond to the stereotaxic array by Talairach and Tournoux.

[b] Cluster size refers to the number of contiguous voxels for which the voxel t statistic corresponds to corrected P<0.05.

TABLE S3. Group x Valence Interaction for Specific Memories: Regions Where BOLD Activity Differed Between Groups for Positive and Negative Specific Memory Recall

				β Weight								Direction of Effect	
				Control	High-Risk	Remitted	Depressed	Control	High-Risk	Remitted	Depressed		
x, y, z[a]	Area	Cluster size[b]	F	Positive				Negative				Positive	Negative
-5, 43, 26	L DMPFC	28	5.73	0.14 (0.06)	0.25 (0.08)	0.18 (0.11)	0.29 (0.09)	0.29 (0.17)	0.35 (0.20)	0.23 (0.13)	0.09 (0.07)	dMDD>HR>rMDD>HC	HR=HC=rMDD>dMDD
9, 51, 26	R DMPFC	39	5.34	0.07 (0.11)	0.05 (0.09)	0.20 (0.12)	0.28 (0.08)	0.12 (0.11)	0.21 (0.07)	0.08 (0.10)	-0.09 (0.10)	dMDD>rMDD>HR=HC	HR>HC=rMDD>dMDD
-61, -39 12	L Superior Temporal G	50	5.42	-0.08 (0.04)	0.01 (0.02)	-0.14 (0.07)	0.07 (0.05)	-0.05 (0.07)	0.10 (0.06)	0.01 (0.06)	-0.17 (0.04)	dMDD>HR>HC>rMDD	HR>rMDD>HC>dMDD
35, 19, -28	R Superior Temporal G	94	6.08	0.13 (0.09)	0.14 (0.08)	0.01 (0.06)	0.18 (0.06)	0.11 (0.08)	0.11 (0.07)	0.05 (0.09)	-0.04 (0.09)	dMDD>HR=HC>rMDD	HR=HC>rMDD>dMDD
-33, -35, -6	L Hippocampus	30	4.68	0.06 (0.05)	0.05 (0.08)	0.05 (0.02)	0.15 (0.02)	0.13 (0.02)	0.11 (.04)	0.13 (0.05)	0.05 (0.04)	dMDD>HC=HR=rMDD	HC=rMDD=HR>dMDD
-15, -43, 52	L Precuneus	29	5.98	0.03 (0.02)	0.12 (0.04)	0.08 (0.02)	-0.05 (0.02)	-0.03 (0.02)	0.02 (0.04)	0.10 (0.03)	0.12 (0.02)	HR>rMDD>HC>dMDD	dMDD>rMDD>HR>HC
15, -59, 40	R Precuneus	39	6.88	0.19 (0.05)	0.24 (0.05)	0.47 (0.12)	0.05 (0.02)	-0.17 (0.07)	-0.16 (0.08)	0.09 (0.07)	0.21 (0.15)	rMDD>HR>HC>dMDD	dMDD>rMDD>HR=HC
-23, -9, -16	L Amygdala	23	3.89										

Abbreviations: dMDD = currently depressed major depressive disorder; DMPFC = dorsomedial prefrontal cortex; G = gyrus; HC = healthy control participants; HR = individuals at high familial risk for developing depression; L = left; OFC = orbitofrontal cortex; R = right; rMDD= remitted major depressive disorder

[a] Coordinates correspond to the stereotaxic array by Talairach and Tournoux.

[b] Cluster size refers to the number of contiguous voxels for which the voxel t statistic corresponds to corrected P<0.05.