Data Supplement for Young et al., Randomized Clinical Trial of Real-Time fMRI Amygdala Neurofeedback for Major Depressive Disorder: Effects on Symptoms and Autobiographical Memory Recall. Am J Psychiatry (doi: 10.1176/appi.ajp.2017.16060637)

Contents

Supplementary Methods

Autobiographical Memory Test

Subjects were presented with three practice words and given examples of correct and incorrect memories. If a subject recalled a memory, the response time was recorded with a stopwatch and was defined as the latency to the first word of each response (a standard measure of response time used in studies examining autobiographical memory)(1). If a participant did not recall a memory within 60s a response of No Memory was recorded. Participants also reported the valence of the recalled memory. Two different cue word sets for the test were administered randomly on Visits 1 and 4 using words equivalent in valence and salience.

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Memories were coded according to their level of specificity using conventional definitions for coding autobiographical memories(2). A specific memory was defined as memory for a single event that took place at an identified place and did not last longer than one day. A categorical memory was defined as a memory referring to a category of events containing a number of specific episodes, without reference to one specific event. An extended memory was defined as a memory that referred to an extended period of time without reference to a specific event within the time period (e.g., a week-long vacation). A semantic memory was defined as a statement of fact without an associated event.

Real-Time fMRI Neurofeedback Paradigm

The rtfMRI-nf amygdala emotional training protocol has been previously implemented(3, 4). The amygdala and intraparietal regions were defined as spheres of 7mm radius in the stereotaxic array of Talairach and Tournoux(5) (Figure S2a). Participants were informed that they would be assigned to receive neurofeedback from one of two brain regions; one region involved in emotional processing or another region independent of emotional processing which may be difficult to regulate. They were informed to maintain the strategy of positive memory recall even if they felt it was ineffective at raising their brain activity, though they could change the positive memories utilized or the aspects of the memories focused on. Upon completion of Visit 4, participants were informed as to which condition they were assigned, and participants in the intraparietal rtfMRI-nf condition were offered the opportunity to return to the lab to repeat the rtfMRI-nf experiment with the amygdala as the target region-of-interest.

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The selection of a control task for rtfMRI-nf experiments is challenging, and no consensus has yet been reached as to the optimal approach. Studies utilizing out of scanner control conditions(6), control conditions in which the neurofeedback bar remains static(7), or no control condition (examining only within-subject changes; (8, 9) run the substantial risk of false positives as control participants know they are not receiving feedback, and experimenter blinding is impossible. Therefore improvements evident in the active relative to the control group may be due to experimenter bias or the appeal of a novel, technology-based intervention and not to gaining control over the target region. Sham control conditions in which the neurofeedback signal is either artificially created or derived from other participants' data(10) run the risk of participants detecting the non-contingency between their efforts and the resulting neurofeedback signal thereby discouraging performance. Control conditions using neurofeedback from a different region are best suited to determine a) specificity of the procedure; whether feedback from the target region is necessary for enhanced control of that region and b) whether changes in mood ratings are due to feedback from the target region or due to a placebo effect. Therefore, for our rtfMRI-nf protocol, we employed a control condition in which subjects received rtfMRI-nf from the horizontal segment of the intraparietal sulcus, a region implicated in number and not in emotional processing and which is independent of amygdala activity(11-14).

For each of the Rest, Happy, and Count blocks within a run, cues were presented on the screen using both text and color icons to indicate each condition. During the Happy Memory Condition (Figure S2b), the cue "Happy" and two color bars (red, blue) were displayed on the screen. The red bar represented the actual

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neurofeedback signal, which was updated continuously by changing the height of the bar either upwards or downward based on the corresponding level of BOLD activity. This neurofeedback signal was also indicated by a number shown above the red bar representing the percent signal change within the target region. During this condition, participants were instructed to retrieve and contemplate positive autobiographical memories while also attempting to increase the level of the red bar to the fixed target level displayed by the blue bar. Because the Happy Memories condition required memory recall and rumination on those memories could potentially not be stopped quickly(15), two control conditions were implemented to distract participants' attention from contemplating positive memories and to dampen the activation of the emotion regulation network. During the Count condition, the participants were shown the cue "Count" with the specific instruction to count backwards from 300 by subtracting a specified integer (9, 3, 4, 6, 7, and 9 for Baseline, Practice, Run 1, Run 2, Run 3, and the Transfer run, respectively). During the Rest condition, participants were presented with the cue "Rest" and were asked to relax and breathe regularly while looking at the display screen. No bars were displayed during the Count and Rest conditions.

The rtfMRI-nf procedure consisted of eight fMRI runs each lasting 8 minutes and 40 seconds (Figure S2c); a resting run, a baseline run in which no neurofeedback information was provided, a practice run, three training runs, a final transfer run in which no neurofeedback information was provided, and a final Rest run. During the Rest runs, a resting-state paradigm was employed and participants were instructed to clear their minds and not think of anything in particular while fixating on the display screen. All subsequent runs consisted of alternating blocks of Rest (5 blocks lasting 40 seconds

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each), Count (4 blocks lasting 40 seconds each), and Happy (4 blocks lasting 40 seconds each). The Baseline run served as a measure of amygdala activity during positive memory recall prior to rtfMRI-nf training. Participants were instructed simply to recall positive memories when the cue “Happy” appeared. No bars were presented. During the Practice run, participants were given an opportunity to become comfortable with the neurofeedback procedure. For the first three Happy Memory blocks participants were instructed to recall and contemplate positive memories prepared with help from the experimenter prior to entering the fMRI environment, and then, for the last Happy condition block, to use the one memory that elevated their mood to the greatest extent. Thus, the Practice run allowed participants to accommodate to the neurofeedback task and evaluate the emotional impact of the prepared happy memories within the experimental setting. During the subsequent three Training runs participants were encouraged to use various memories and to switch memories in order to help them raise the red bar. Because our preliminary experiments indicated that the activation level of the left amygdala could be as high as a 2% BOLD signal change, the target level of the blue bar was set to 0.5%, 1.0%, 1.5% and 2.0% for PR, R1, R2, and R3, respectively. During the Transfer Run, participants were instructed to perform the same task as during neurofeedback training, but rtfMRI-nf information was not provided. The transfer run was performed to assess the transfer of the learned control and to check whether the training effect generalized to situations where no neurofeedback was available. The procedure on Visit 3 was identical to that on Visit 2.

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Data Acquisition and On-line Analysis

A standard 8-channel receive-only head coil array was used for fMRI data collection. A single-shot gradient-recalled EPI sequence with Sensitivity Encoding (SENSE) was employed for fMRI. The following EPI imaging parameters were used: field-of-view/slice=240/2.9mm, axial slices per volume=34, acquisition matrix=96x96, repetition/echo time=2000/30 ms, SENSE acceleration factor R=2 in the phase encoding (anterior-posterior) direction, flip angle=90°, sampling bandwidth=250 kHz, number of volumes=263. Three EPI volumes (6 sec) were added at the beginning of each fMRI run to allow the fMRI signal to reach steady state, and were excluded from data analysis. The EPI images were reconstructed into a 128x128 matrix, in which the resulting fMRI voxel volume was 1.875x1.875x2.9mm^3. Additionally, simultaneous pulseoximetry and respiration waveforms were recorded (with 50 Hz sampling) for each fMRI run. A T1-weighted magnetization-prepared rapid gradient-echo (MPRAGE) sequence with SENSE was used to provide an anatomical reference for the fMRI analysis. It had the following parameters: field-of-view=240mm, axial slices per slab=128, slice thickness=1.2 mm, image matrix=256x256, repetition/echo time=5/1.9ms, acceleration factor R=2, flip angle=10°, delay/inversion time=1400/725 ms, sampling bandwidth=31.2 kHz.

The image data analyses were performed using Analysis of Functional NeuroImages (AFNI, http://afni.nimh.nih.gov/). The neurofeedback was implemented using the custom real- time fMRI system utilizing the real-time features of AFNI(16) and a custom developed graphic user interface (GUI) software. The regions-of-interest, defined as described above, were transformed to the EPI image space using each

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subject's high-resolution MPRAGE structural data. The resulting regions-of-interest in the EPI space contained approximately 140 voxels each. We performed a visual inspection of the regions-of-interest (both the intraparietal and amygdala regions in all participants to maintain the blind) prior to the start of neurofeedback.

Whole-Brain Analysis

Pre-processing of single-subject fMRI data included correction of cardiorespiratory artifacts using AFNI implementation of the RETROICOR method (17). The cardiac and respiratory waveforms recorded simultaneously during each fMRI run were used to generate the cardiac and respiratory phase time series for the RETROICOR. Further fMRI pre-processing included volume registration and slice timing correction for all EPI volumes in a given exam. Standard GLM analysis was then applied separately for each of the fMRI runs. The following regressors were included in the GLM model: two block stimulus conditions (Happy, Count), six motion parameters as nuisance covariates to take into account possible artifacts caused by head motion, and five polynomial terms for modeling the baseline. Hemodynamic response amplitudes were estimated using the standard regressors, constructed by convolving a boxcar function (representing the block duration) with the canonical hemodynamic response function using standard AFNI parameters. The GLM ß coefficients were computed for each voxel using the 3dDeconvolve AFNI program and then converted to percent signal changes for Happy versus Rest, Count versus Rest, and Happy versus Count contrasts. The resulting fMRI percent signal change maps for each run were spatially transformed to the stereotaxic array of Talairach and Tournoux (5) and re-sampled to 2x2x2 mm^3 isotropic voxel size. The spatially-normalized fMRI percent

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signal change maps were spatially smoothed using a Gaussian kernel with full width at half maximum (FWHM) of 5 mm.

For each group, statistical activation maps (t-tests comparing percent signal change from the initial baseline run to the final transfer run) were computed for the Happy versus Rest contrast. A group t-test examined statistical differences between the change scores obtained for each group. The significance criterion for detecting activation was set at $p_{corrected}<0.05$ determined using the AFNI program 3dClustSim (cluster size>25 voxels, thresholded at voxel $p<0.005$, and the Spatial AutoCorrelation Function to address recent criticisms of the cluster method(18)).

Supplementary Results and Discussion

Regional Temporal Signal-to-Noise Ratio

When selecting a control region for neurofeedback studies, it is important that the regions be independent from each other in function, but also that the temporal signal-to-noise ratio (tSNR) of the control region be at least as good in ability to detect BOLD fMRI activity as that of the experimental target region(19). Therefore, we computed tSNR maps for the amygdala and intraparietal regions in each participant. The tSNR was higher in the intraparietal region (tSNR=77+/-24) than the amygdala (tSNR=47+/-12) affording the control region a better signal quality by a factor of 1.7. This difference in tSNR was significant between regions ($t(66=12.6, p<0.001$), but not between groups (group t-test on amygdala tSNR $t(65)=1.48, p=0.15$; group t-test on intraparietal tSNR $t(65)=0.36, p=0.72$).

Because the tSNR values for the two regions of interest were not equivalent we

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performed an additional analysis to ensure the F values in our analysis were not inflated by the tSNR values. We repeated the linear mixed model including regional tSNR as a covariate. The ROI x Group effect went from ($F(1,120)=4.97$, $p=0.03$) to ($F(1,123)=4.44$, $p=0.04$), and the ROI x Group x Run x Day effect actually became more significant, going from ($F(5,517)=2.37$, $p=0.04$) to ($F(5,455)=2.52$, $p=0.03$). Therefore, we are confident our results were not influenced by heterogeneity in the tSNR across brain regions.

Association between Memory Recall, Neurofeedback Success, and Score Change

Residual HAM-D-21 score at follow-up was significantly associated with residual amygdala activity during the final transfer run ($\beta=-12.7$, $t=3.93$, $p<0.001$; adjusted $R^2=0.31$), as were residual BDI scores ($\beta=-20.0$, $t=3.39$, $p=0.002$; adjusted $R^2=0.25$), but not HAM-A ($\beta=-2.64$, $t=0.72$, $p=0.48$; adjusted $R^2=0.02$) or SHAPS ($\beta=-1.99$, $t=0.41$, $p=0.68$; adjusted $R^2=0.03$) scores.

A similar pattern was seen when examining the relationship between the other residualized clinical scores and residual memory performance at follow-up. Residual HAM-D-21 score at follow-up was significantly associated with residual specific positive memory recall at follow-up ($\beta=-0.12$, $t=1.97$, $p=0.05$; adjusted $R^2=0.08$), as were residual BDI-II scores ($\beta=-0.38$, $t=4.81$, $p<0.001$; adjusted $R^2=0.40$), but not HAM-A ($\beta=-0.02$, $t=0.28$, $p=0.78$; adjusted $R^2=0.03$) or SHAPS ($\beta=-0.05$, $t=0.69$, $p=0.50$; adjusted $R^2=0.02$) scores.

The Sobel test was significant for HAM-D-21($z=2.01$, $p=0.04$) and BDI-II ($z=2.20$, $p=0.03$) scores supporting the hypothesis that residual amygdala activity was a

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mediator of the association between residual positive specific memory recall and residual score change.

Whole-Brain Analysis

Results from the whole-brain analysis (Table S2) showed that the experimental group had increased activity from the pre-neurofeedback baseline run to the final transfer run, which was greater than the change observed in the control group, in bilateral dorsal anterior cingulate cortex, left insula, precuneus, amygdala/parahippocampal complex (encompassing the amygdala region-of-interest), right middle frontal gyrus, putamen and superior temporal gyrus. Decreased activity in the experimental group from baseline to transfer, which was greater than the change observed in the control group, was observed in the left dorsolateral prefrontal cortex and middle occipital gyrus.

The whole-brain voxel-wise analysis showed the ability to maintain elevated amygdala activity during positive memory recall following rtfMRI-nf training engaged a prefrontal-temporal cortical-limbic network implicated in emotion processing and memory recall(20, 21) relative to the baseline run prior to neurofeedback training. Many of these regions share extensive anatomical and functional connections with the amygdala and are recruited during emotional learning (including the medial prefrontal cortex; (20)), in the modulation of emotional processes (including the anterior cingulate; (22)), and in the processing of salient emotional stimuli (including the insula, dorsal anterior cingulate, and amygdala; (23)). These regions also form part of the core network recruited during AM recall(21). This pattern suggests that rtfMRI-nf from the amygdala is not dependent on a single brain region, but upon a network. Future studies

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investigating rtfMRI-nf may benefit from using a network as opposed to a signal region-of-interest. Therefore, the increased activity in these regions in depressed patients during experimental but not control neurofeedback suggests our neurofeedback procedure effectively recruits other regions important in emotional regulation which show abnormal BOLD responses in MDD, further suggesting potential for rtfMRI-nf in MDD treatment.

Detailed Methods for Preserving the Study Blind and Evidence for Effectiveness of the Participant and Rater Blind

Participants and all clinicians and research staff who interacted with participants were blind to assignment. We included clinician-administered and self-report depression rating scales as one check of whether the blind was maintained in the clinicians. If clinicians were unblinded to assignment and biased with the expectation that the experimental group would improve to a greater extent than the control group, we would expect the self-report BDI-II scores to show different results from the clinician-administered MADRS and HAM-D-21scores. This was not the case; the BDI-II, MADRS, and HAM-D-21 scores all decreased by a similar magnitude from baseline to follow-up, and there were strong and significant correlations between the final scores on these measures (BDI-II and MADRS $r=0.73$, $p<0.001$, BDI-II and HAM-D-21 $r=0.73$, $p<0.001$; MADRS and HAM-D-21 $r=0.89$, $p<0.001$). The consistency between self-report and clinician-administered scores argues against penetration of the blind in the clinicians who conducted the depression severity ratings for the primary outcome measure.

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To examine whether the blind was maintained in the participants we included a question asking them to rate on a 10-point scale how much control they felt they had over their brain activity at the end of the study. In the experimental group, the mean control rating was 6.06 (SD=2.08) and the mean control rating in the control group was 5.47 (SD=1.88). The difference between groups in control ratings was not significant ($t(32)=0.92$, $p=0.36$), suggesting that participants felt similarly in control of the region they were assigned to regulate, whether it was the amygdala or the intraparietal region. Furthermore, there was no significant correlation between residualized MADRS scores at follow-up and the control rating ($r=0.21$, $p=0.24$), suggesting that it is the actual control over amygdala activity that results in the clinical changes, and not perceived control. While we did not ask participants directly what group they believed they were assigned to, the lack of difference in perceived control provides support that the blind was maintained, as the main risk in blind penetration in this design comes from detecting a non-contingency between cognitive strategy/effort and the resulting neurofeedback signal(24). All other elements of the design were identical between the experimental and control group. Therefore, we are confident that the blind was maintained throughout the study and that the clinical results were not artificially inflated due to a placebo response.

Supplementary References

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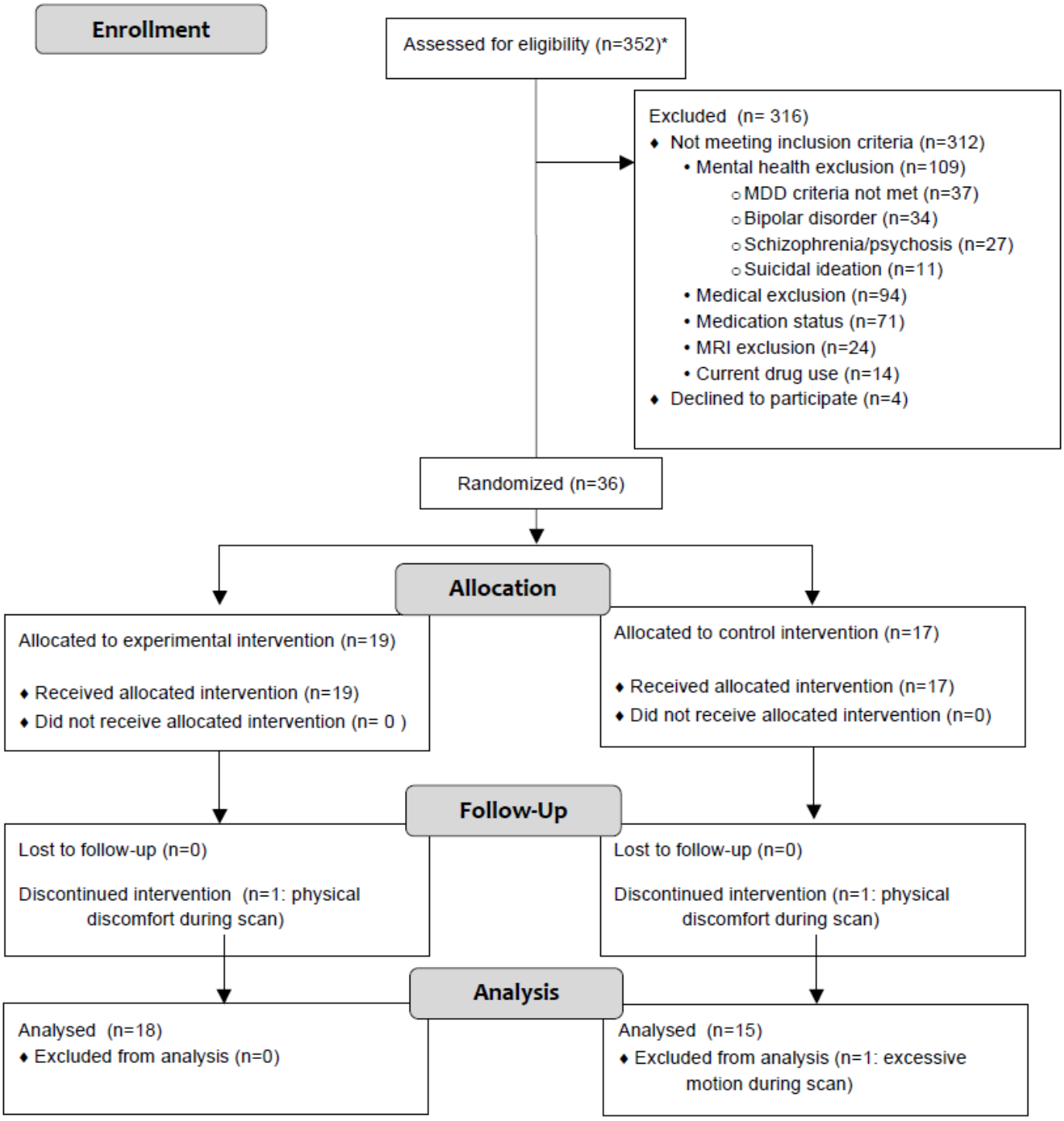
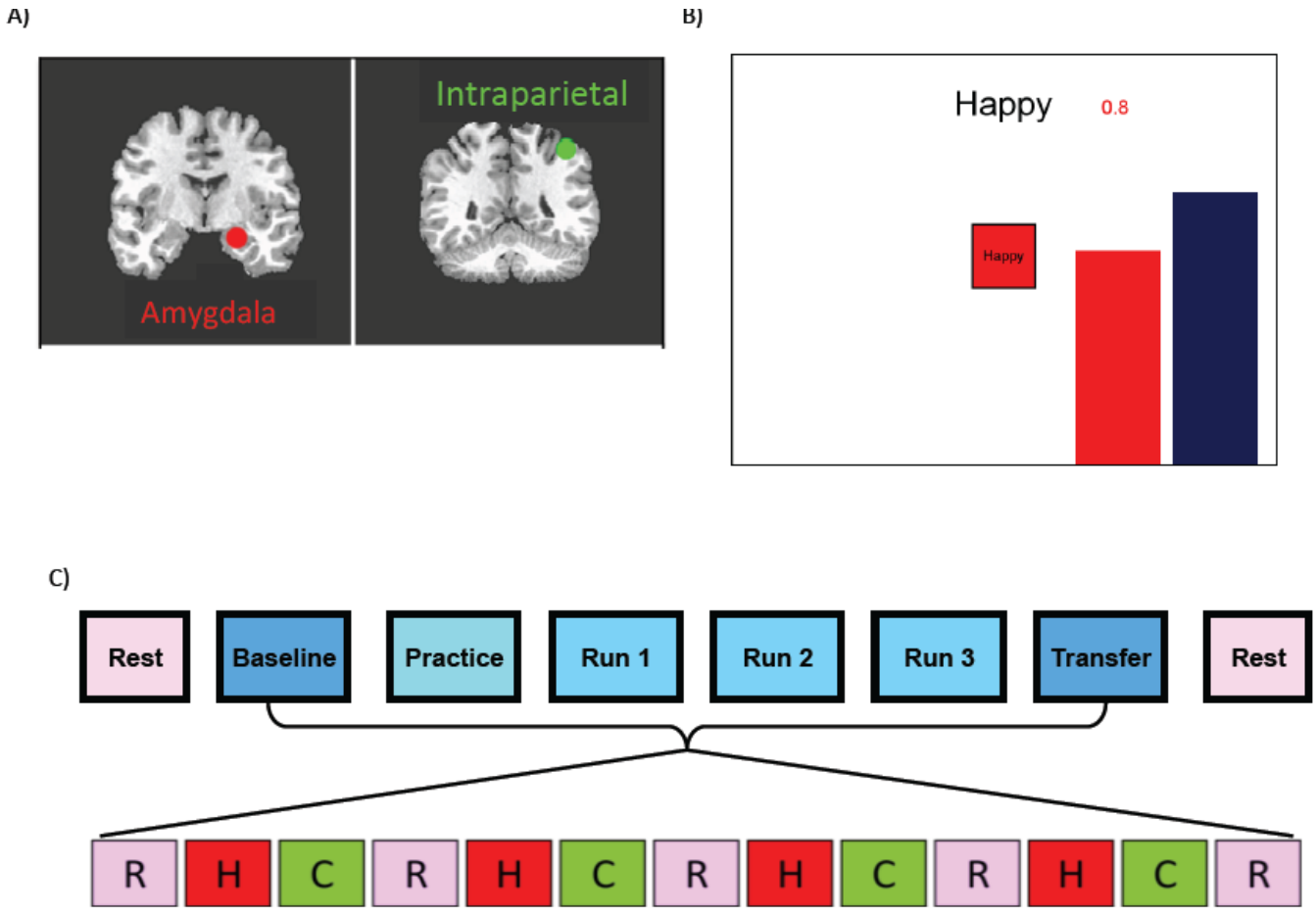
FIGURE S1. CONSORT Flow Diagram: Flow diagram of the progress through the phases of the parallel randomized clinical trial of two groups, including enrollment, intervention, allocation, follow-up, and data analysis



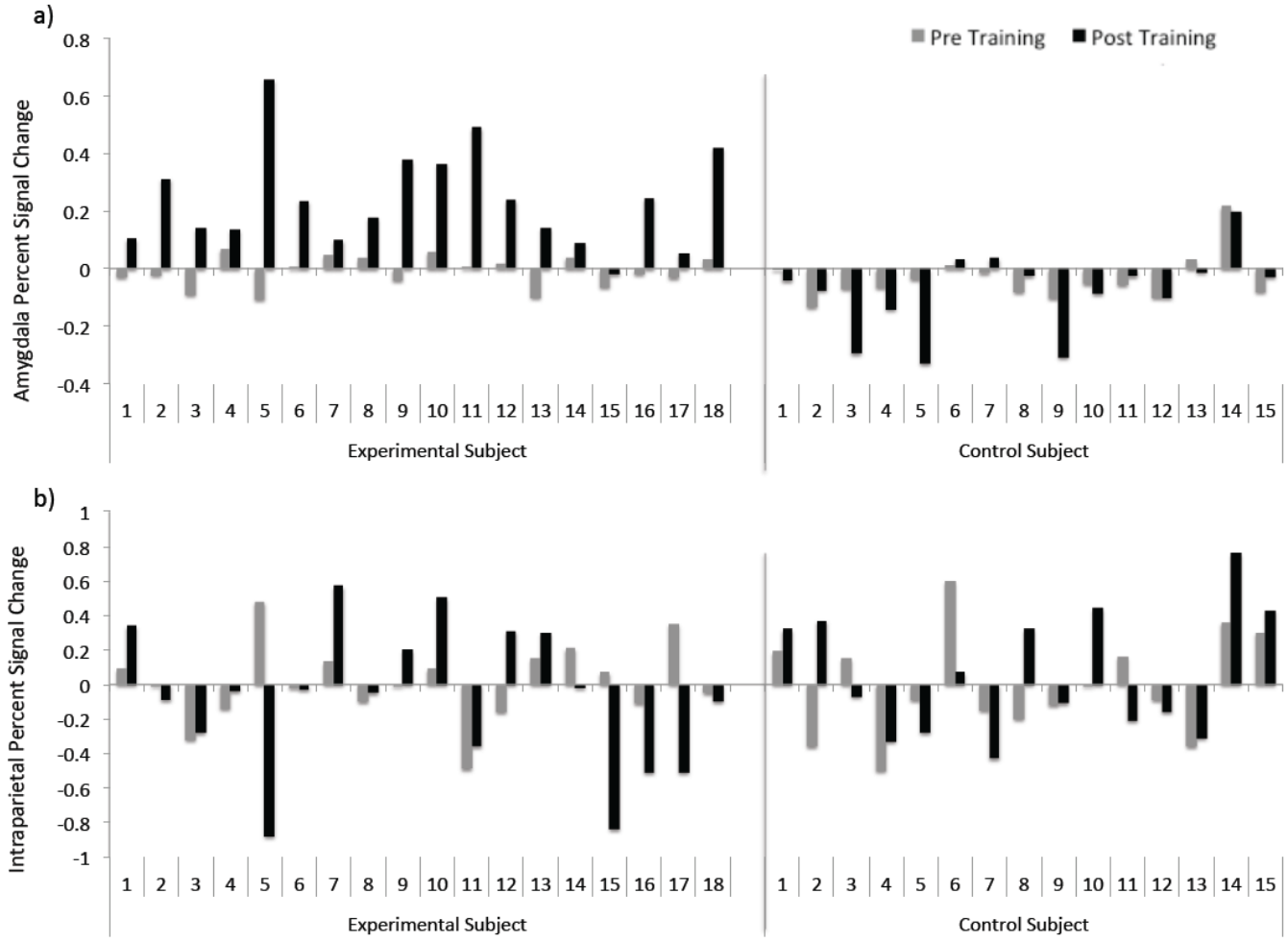
* Participants were screened as part of the general Laureate Institute for Brain Research recruitment for a wide range of studies with varying inclusion/exclusion criteria, and not specifically for this trial.

FIGURE S2. Design of the rtfMRI neurofeedback experiment



a) Regions-of-interest for the rtfMRI neurofeedback procedure: left amygdala (red, centered at -21,-5,-16) and left horizontal segment of the intraparietal sulcus (green, centered at -42,-48,48). Placements are illustrated on T1-weighted coronal human brain sections in Talairach space[48]. Following radiological notation, the left side (L) of the brain is shown on the right, and the right side (R) of the brain on the left. b) Real-time display screen for the rtfMRI neurofeedback procedure. During the Happy condition, the word “Happy,” two color bars, and a number indicating the neurofeedback signal were displayed on the screen. Participants were instructed to recall happy autobiographical memories to make themselves feel happy while trying to increase the level of the red bar representing the feedback signal from the target region to a given target level indicated by the fixed height of the blue bar. c) Protocol for the rtfMRI neurofeedback experiment. The experimental protocol consisted of eight runs each lasting 8min 40sec. Neurofeedback training consisted of alternating blocs of Rest (R, pink block), Happy (H, red block), and Count (C, green block, instructed to count backwards from 300 by a given integer), each lasting 40sec.

FIGURE S3. Individual Participants' Region-of-Interest Signal Change



The percent signal observed in (a) the amygdala and (b) the intraparietal region during the baseline run prior to rtfMRI-nf training and the final transfer run after undergoing 2 rtfMRI-nf sessions.

TABLE S1. Clinical and Demographic Characteristics for Each Group

Sample Characteristics				
	Experimental Group		**Control Group**	
	Mean	*N female*	*Mean*	*N Female*
n [n female]	19	13	17	13
	Mean	*SD*	*Mean*	*SD*
Age	32	12	31	9
MDE length in months	30	56	34	49
Time since Last Antidepressant (months)	33	34	31	35
	Number	*Percent*	*Number*	*Percent*
Number of Episodes				
1	5	26%	2	12%
2	2	11%	2	12%
3 or more	12	63%	13	76%
Previous number of antidepressants				
None	8	42%	4	24%
1-2	6	32%	7	41%
3 or more	5	26%	6	35%
Co-Morbid Diagnosis				
None	7	39%	7	41%
PTSD	6	32%	3	18%
GAD	5	26%	7	41%
Social Phobia	3	16%	6	25%

Abbreviations: GAD = generalized anxiety disorder; MDE = major depressive episode; PTSD = post-traumatic stress disorder

TABLE S2. Regions Where Hemodynamic Activity Differed between Groups in the Change from Baseline to Follow-up during the Happy versus Rest Contrast

				Experimental Group		Control Group	
Area	x, y, z[a]	Cluster Size[b]	t value	Mean	SD	Mean	SD
Increased Activity in the Experimental vs. Control Group Following Neurofeedback							
R Middle frontal G	53, 13, 36	122	2.85	0.39	0.07	0.11	0.09
L dACC	-9, -5, 33	45	3.27	0.18	0.05	0.02	0.08
R dACC	1, -7, 34	41	2.64	0.20	0.09	0.01	0.09
L Insula	-37, 1, 2	144	2.98	0.23	0.06	0.04	0.08
L Precuneus	-1, -59, 54	30	3.00	0.51	0.17	0.12	0.17
R Putamen	27, -3, 10	45	3.10	0.27	0.05	0.08	0.07
R Superior Temporal G	65, -35, 12	144	3.48	0.26	0.03	-0.04	0.06
L Amygdala	-21, -6, -14	35	2.81	0.24	0.07	0.09	0.11
Decreased Activity in the Experimental vs. Control Group Following Neurofeedback							
L DLPFC / BA 9	-3, 61, 30	165	2.50	-0.34	0.12	-0.17	0.2
L DLPFC / BA 9	-21, 35, 32	26	2.98	-0.24	0.06	-0.07	0.07
L Middle Occipital G	-33, -89, 2	93	2.77	-0.35	0.09	0.04	0.03

[a] Coordinates correspond to the stereotaxic array by Talairach and Tournoux(5).

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

Abbreviations: dACC = dorsal anterior cingulate cortex; BA = Brodmann area; DLPFC = dorsolateral prefrontal cortex; G = gyrus; L= left; R= right