

Appendix 1 to Hilland E, Landrø NI, Harmer CJ. Attentional bias modification is association with fMRI response towards negative stimuli in individuals with residual depression: a randomized controlled trial. *J Psychiatry Neurosci* 2019.

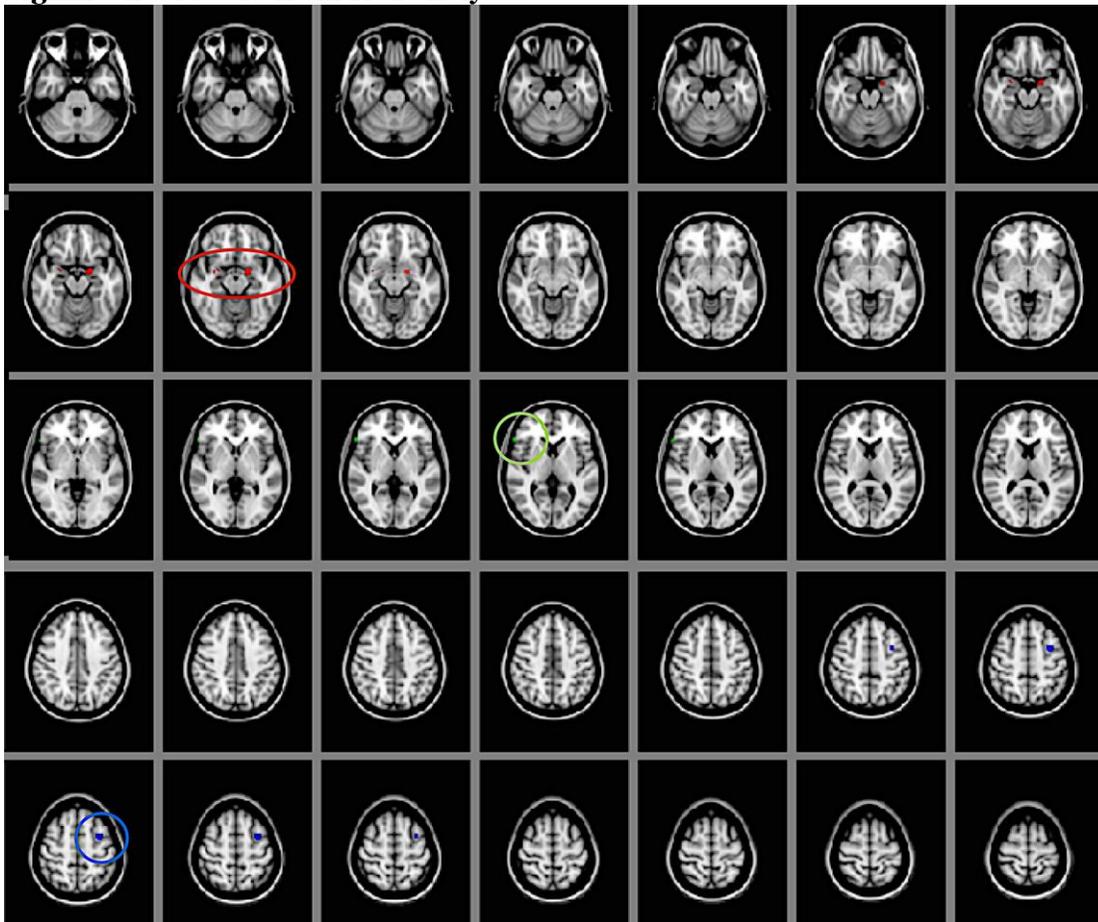
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Supplemental material

Significant clusters from ROI analyses



Supplemental Figure 1 shows activation map and cluster index from ROI's based on the contrasts AttendNegative > RegulateNegative that revealed bilateral amygdala response (red), and RegulateNegative > AttendNegative showing right and left middle frontal gyrus (green and blue).

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Supplemental Table 1: MNI coordinates ROI analysis

Contrast	Coordinates			Anatomical labels
	X	y	z	
RegulateNegative>AttendNegative	60	24	3	Middle frontal gyrus R
	51	15	48	Inferior frontal gyrus R
	9	30	39	Medial frontal gyrus R
	-33	3	54	Middle frontal gyrus L
	63	-51	39	Superior parietal lobule R
	-42	-66	42	Superior parietal lobule L
	-51	-39	3	Middle temporal gyrus L
AttendNegative>RegulateNegative	30	-3	-15	Amygdala L
	18	-3	-15	Amygdala R

Regions - and contrasts of interest for the ROI analysis based on Buhle (2014). We present the MNI coordinates for each region, and anatomical labels, L, left; R, right. All spheres had a size of 5 mm radius.

Supplemental table 2: MNI coordinates of activation clusters from whole brain analyses

Contrast	Volume (cm3)	Z	Coordinates			Anatomical labels
			x	y	z	
Negative>Neutral Placebo>ABM	1202	3.86	-16	36	-10	Frontal Medial Cortex (L) , Cingulate Gyrus, anterior division (L,R), Frontal Pole (R), Paracingulate Gyrus (L), Frontal Medial Cortex (L)
Negative>Neutral Intervention x AB	1061	4.05	54	-24	8	Planum temporale (R) , Insular cortex (L,R), Planum temporale (L), Central opercular cortex (L,R), Heschls Gyrus (L)
Negative>Neutral Intervention x HRSD	872	5.28	50	-10	18	Central opercular cortex (R) , Insular cortex (R), postcentral gyrus(R), precentral gyrus(R)

Clusters of activation for contrasts of interest. We present the volume of the cluster (thresholded at voxelwise $p < 0.01$, uncorrected), the peak voxel (maximum "intensity" z-statistic), MNI coordinates of peak (Z-max) activations within each cluster) and the anatomical extent of the cluster (based on local maxima cluster index and Harvard_ Oxford Cortical Structural Atlas in FSL). Anatomical labels in bold correspond to the MNI coordinates of peak activations. L, left; R, right.

Post-hoc assessment of potential outliers

Exclusion of 19 potential outliers that could cause differences in symptom degree and brain activity was conducted using the cut-off for moderate depression (BDI-II>21), ABM (M=11.1(6,75)) and placebo (M=9.7(5,81)) and did not influence the AttendNegative > AttendNeutral contrast (Figure 1.) [F(1,102)=14.933, $p < .001$] or the amygdala contrast (Figure 2.) [F(1,102)=8.403, $p = .005$]. **The potential single outlier outside 1.5 interquartile range (Figure 1.) had a BDI-II score of 23 and was also excluded during this assessment.**

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Picture characteristics fMRI experiment

In the current experiment 179 items were chosen from IAPS and 37 items from EmoPics. Stimuli were chosen by including the following categories *social, sadness, death, loss*, and excluding the following categories *no people, primarily shocking and gory*. An univariate ANOVA revealed statistically significantly higher arousal for the EmoPics as to IAPS stimuli [$F(1,209)=32.736$, $p<.001$]. Differences between stimulus conditions (AttendNeutral, AttendNegative, RegulateNegative) was statistically significant [$F(2,208)=123.615$, $p<.001$]. Arousal scores for AttendNeutral: $M=3.46(.66)$, AttendNegative: $M=5.63(.91)$, RegulateNegative: $M=5.64(.94)$. The interaction between condition and stimulus set was not statistically significant [$F(1,209)=.458$, $p=.50$]. Valence scores revealed no statistically differences between EmoPics and IAPS stimuli [$F(1,209)=.017$, $p=.89$]. Differences between stimulus conditions (AttendNeutral, AttendNegative, RegulateNegative) was statistically significant [$F(2,208)=582.282$, $p<.001$]. Valence scores for AttendNeutral: $M=5.48(.40)$, AttendNegative: $M=2.49(.61)$, RegulateNegative: $M=2.50(.62)$. The interaction between condition and stimulus set was not statistically significant [$F(1,209)=.039$, $p=.84$].

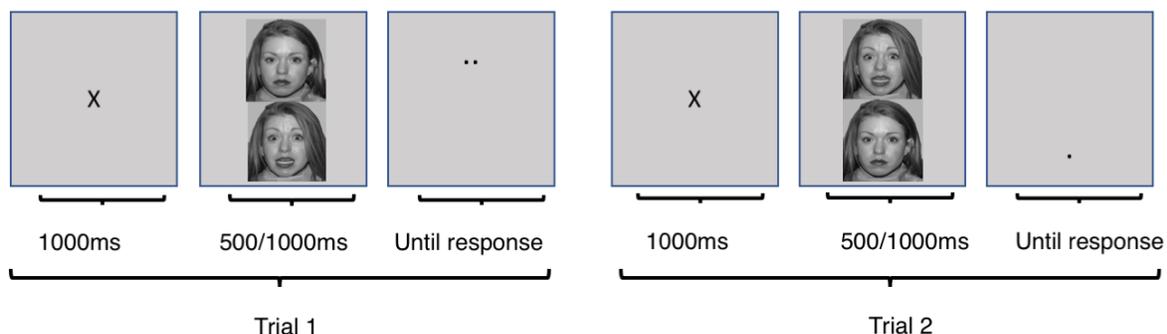
Instructions for fMRI experiment

Participants were viewing a series of negative and neutral images. The instructions that were given throughout the fMRI experiment were simply a screen with the instruction to “ATTEND” or “REGULATE” before each image was displayed. More detailed explanations on strategies for downregulating negative affect and responding naturally to negative and neutral stimuli were given prior to the experiment. Instructions were read out loud from a written protocol for all participants.

Picture characteristics ABM task

The training procedure consisted of 479 pictures (negative, neutral and positive faces) from four different databases. 219 images were taken from the Karolinska Directed Emotional Faces (KDEF)¹, 168 images were from NimStim², 44 from Matsumoto and Ekman's Japanese and Caucasian Facial Expressions of Emotion (JACFEE)³ and 48 from Ekman's Pictures of Facial Affect⁴. The following emotional expressions were used for the three categories, negative = angry and fearful, neutral = neutral, positive = happy. In the current study we chose a task that had been used and shown to produce an ABM effect in previous studies^{5,6}. The task was originally developed by Browning and coworkers⁶

Trial structure ABM task



Supplemental figure 2 shows two example trials from the ABM task. Adapted from Browning et al. (2012).

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Instructions for ABM task

The following instructions were given prior to every training session:

Your task is to determine how many dots you see on the screen. Each trial starts with a fixation cross. Focus on this cross. Immediately when the cross disappears, you will see two faces, one at the bottom and one at the top of the screen. As soon as the faces disappear you will see either one or two dots. The dots may appear at the top or at the bottom of the screen. When you see the dots, please indicate how many you see by pushing the button with one (.) or two (..) dots, as fast and correct as you can. Both accuracy and response time is important in this task. Press OK to start.

Attentional Bias measure

The attentional bias for each participant was calculated as the difference in reaction time (RT) between trials in which the probe replaced the relatively more negative face vs. the more positive face. Thus, a more positive score reflects a greater bias towards the more positive stimuli. The AB change score was derived as the difference in reaction time from pre- to post training, indicating the effect of the training procedure.

The clinical trial

The current pre-registered clinical trial (NCT02931487) is based on a subsample of a larger double-blinded randomized clinical trial (NCT02658682) including 321 patients with a history of depression. A total of 136 eligible participants between 18-65 years old were enrolled from the larger RCT to the neuroimaging trial after ABM training. Screening, inclusion, assessment of psychiatric history and symptom measurements as well as ABM training was conducted under the larger RCT. The scanning protocol post-training was done in the current RCT. All participants were asked whether they would be willing to participate in the MRI study. The protocol included structural MRI (T1, FLAIR, DTI), resting state-fMRI and an fMRI experiment. Inclusion to the neuroimaging RCT study stopped after reaching the minimum required number of participants according to the a-priori power analysis. All participants in this study were recruited from the main RCT (NCT02658682).

Randomization strategy

Block randomization was performed every week when new participants were included and started their training program. Every week there was a new list of confirmed participants, e.g. 5, 7 or 10 individuals, which were allocated to a study ID, and the list was randomized (0 and 1 for placebo and ABM) using the RAND function in excel. The randomization procedure was performed by a research assistant (RA) before the experimenter and the participant arrived at the lab. The same RA set up the training procedure (active or placebo condition) on the computers that were given to the participants for their two week training program. This RA did not meet or interact with the participants. All laptops were identical with the exact same software setup for both training conditions.

Power analysis

Brain activation and brain structure was assumed to be predicted by the ABM approach and indicators of habitual emotion regulation styles (4-6 predictor variables). In this project we used the A-priori Sample Size Calculator for Multiple Regression⁷. Anticipated effect size was set to .15, desired statistical power was set to .80, number of predictors was set to 6 and probability level was set to .01. Minimum required sample size was estimated to 134.

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Analysis site

fMRI analyses were performed on the Abel super cluster, owned by the University of Oslo and the Norwegian metacenter for High Performance Computing (NOTUR), and operated by the Department for Research Computing at USIT, the University of Oslo IT-department. <http://www.hpc.uio.no/>

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