Biological Psychiatry

Archival Report

The Temporal Dynamics of Emotion Regulation in Subjects With Major Depression and Healthy Control Subjects

Noam Schneck, Sarah Herzog, Jun Lu, Ashley Yttredahl, R. Todd Ogden, Hanga Galfalvy, Ainsley Burke, Barbara Stanley, J. John Mann, and Kevin N. Ochsner

ABSTRACT

BACKGROUND: Emotion regulation (ER) processes help support well-being, but ineffective ER is implicated in several psychiatric disorders. Engaging ER flexibly by going online and offline as needs and capacities shift may be more effective than engaging ER rigidly across time. Here, we sought to observe the neural temporal dynamics of an ER process, reappraisal, during regulation of responses to negative memories in healthy control subjects (n = 33) and subjects with major depressive disorder (n = 36).

METHODS: To track the temporal dynamics of reappraisal neural systems, we used a functional magnetic resonance imaging neural decoding approach. In task 1, subjects explicitly engaged reappraisal on instruction in response to aversive images, and we used this task to develop the decoder for detecting reappraisal. In task 2, subjects experienced negative autobiographical memories from a distant (third person, ER condition) or immersed (first person, control condition) perspective.

RESULTS: The neural decoder, trained to detect reappraisal in task 1, predicted greater reappraisal occurring during the task 2 distance versus immerse trials and was engaged more intensely during memories that were rated as being more negative. Across time, decoder output manifested a temporal dynamic of early engagement followed by disengagement. These results were replicated in an independent subject dataset (n = 59). Relative to healthy control subjects, subjects with major depressive disorder had a comparable initial increase in decoder engagement at the beginning of the trial but an attenuated decrease at the end.

CONCLUSIONS: Subjects with major depressive disorder evidenced a more rigid neural dynamic of reappraisal compared with healthy control subjects. Rigid ER may indicate diminished ability to flexibly and effectively regulate emotion.

https://doi.org/10.1016/j.biopsych.2022.09.002

Emotion regulation (ER) processes play a key role in down-regulating negative affect and maintaining well-being. When applied effectively, ER processes can help balance responses to negative emotions and maintain emotional equilibrium (1). However, ineffective ER is implicated as a transdiagnostic factor in a range of psychiatric disorders (1). We have previously shown that subjects with major depressive disorder (MDD) and healthy control subjects (HCs) are similarly able to engage ER when instructed to do so (2). However, it is likely that subjects with MDD engage ER in a less effective way.

Self-report studies show that patient groups rely rigidly on one ER strategy as opposed to flexibly switching between types of ER (3–10). Prior work has used self-report to measure ER flexibility from the perspective of switching between types of ER. However, to date, no studies have measured ER flexibility using biological or objective measurements. Behavioral and physiological studies have measured the product of ER, i.e., reduced negative affect (11–15), but not flexibility in the ER process itself. Here, we sought to use a biological measure to test whether subjects with MDD engage a given ER process more rigidly than HCs. We focused on the ER process of reappraisal (i.e., reinterpreting the meaning of a situation) because it is a highly effective form of ER (1).

To identify the degree of flexibility with which reappraisal was engaged, we relied on temporal dynamics, i.e., fluctuations in the engagement of reappraisal during a period of regulation. When reappraisal is being engaged flexibly, it may come online or go offline as needs and capacities shift (11,16–19). The temporal dynamics of reappraisal may therefore indicate the flexibility with which it is being applied, with greater fluctuation indicating greater flexibility.

Reappraisal is a behavior whose access to conscious awareness is limited (20), making its temporal dynamics difficult to observe. We therefore used a neural decoding methodology to observe the dynamics of the neural systems supporting reappraisal. Neural decoding is a machine learning–based technique that allows moment-to-moment brain activity to be decoded to continuously assess the engagement of

 ISSN: 0006-3223

neural systems supporting specific psychological operations (21–23). Prior neuroimaging studies have investigated static neural components of ER or the temporal features of the initiation of ER (2,11,24–27). However, the ongoing temporal dynamics of reappraisal and whether these dynamics are implicated in MDD remain unknown.

To implement a decoder to track reappraisal system engagement, we conducted a functional magnetic resonance imaging (fMRI) study with 4 hierarchical steps. In step 1, we trained a neural decoder capable of detecting reappraisal using a task where subjects were instructed to either look at or to reappraise their emotional responses to aversive images. In step 2, we tested whether the decoder trained on the aversive images task could detect reappraisal system engagement during regulation of responses to negative autobiographical memories (2,13,28). Specifically, we tested whether the decoder would identify greater reappraisal system engagement during attempted regulation of responses compared with control trials. In step 3, we used the decoder to track temporal dynamics of reappraisal systems over the course of each of the 12-second distance trials during the autobiographical memory task. In step 4, we investigated differences in the temporal dynamics of reappraisal system engagement between MDD and HC groups.

METHODS AND MATERIALS

Sample

Seventy-seven subjects completed the fMRI tasks, including subjects with MDD (n = 36), HCs (n = 33), and individuals with high familial risk (healthy volunteers despite a first-or second-degree relative with depression) (n = 8). For the sake of increasing power, individuals with high familial risk were included in analyses grouping the entire sample together but not in analyses comparing groups to each other.

Subject Description

MDD and HC groups did not differ in age, gender, or education level. Mean depression levels for the MDD group were 26.3 (7.4) on the Beck Depression Inventory (29) and 18.5 (4.7) on the 17-item Hamilton Depression Rating Scale (30). Table 1 displays the clinical characteristics of this sample.

Clinical Assessments

Psychiatric diagnoses were established using the Structured Clinical Interview for DSM-IV (31), conducted by doctoral- or masters'-level psychologists trained to a criterion level in diagnostic reliability and accuracy. Depression severity was quantified with the 17-tem Hamilton Depression Rating Scale (30). Full inclusion and exclusion criteria are included in the Supplement.

fMRI Tasks

To identify a neural pattern underlying reappraisal, we used a multistep fMRI procedure involving 2 separate tasks (Figure 1). Task 1 was used to train a neural decoder to identify a pattern associated with reappraisal, and task 2 was used to observe fluctuations in the decoder's activity during a naturalistic task (recalling autobiographical memories). All stimuli were presented with E-Prime version 1.2.

Table 1. Demographic and Clinical Characteristics of the Sample

Characteristics	MDD, n = 36	HC, n = 33	Group Difference[a]
Age, Years, Mean (SD)	32.3 (9.4)	33.3 (8.6)	p = .55
Education, Years, Mean (SD)	15.2 (2.3)	15.4 (3.3)	p = .73
Gender, Male, n	18	12	p = .26
BDI, Mean (SD)	26.3 (7.4)	1.2 (2.4)	$p < .001$[b]
HDRS-17, Mean (SD)	18.5 (4.7)	1.03 (1.4)	$p < .001$[b]
Prior Depressive Episodes, n			
0	10	N/A	–
1	5	N/A	–
2	5	N/A	–
3	2	N/A	–
4	3	N/A	–
>5	11	N/A	–
Length of Current Episode, Days			
Range	1–780	–	–
Median	52	–	–
Current Anxiety Disorder, n	5	N/A	–
Medication Naïve, n	12	33	–
Days Off Medication			
Range	21–1296	–	–
Median	52	–	–

BDI, Beck Depression Inventory; HC, healthy control; HDRS-17, 17-item Hamilton Depression Rating Scale; MDD, major depressive disorder; N/A, not applicable.

[a]Assessed by independent samples t test.

[b]$p < .001$.

Task 1: Image-Based ER. Participants underwent 3 runs of fMRI on a GE 3T scanner while being presented with negative and neutral images from the International Affective Picture System (32). Subjects provided ratings of negative affect following each picture on a 5-point scale (1 "weak" to 5 "strong"). Negative and neutral images were selected on the basis of the normative ratings included within the International Affective Picture System. Each trial comprised an instruction cue (2 seconds), the presentation of a picture for 8 seconds, followed by a jittered fixation of 2 to 4 seconds, a negative affect rating period, and finally, a jittered intertrial fixation interval of 2 to 4 seconds (average = 3 seconds). Participants completed 15 trials per run, comprising 5 negative and 5 neutral images, in which the instruction was to look at the images, and 5 negative images, with an instruction to reappraise the images. Other task-related nuisance regressors included instruction periods, 6 degrees of freedom motion, and probe periods.

Task 2: Autobiographical Memory Task. In a prescan session, subjects provided 8 negative experiences that had occurred within the past 6 months and generated 2- to 4-word cues that could be used to elicit the memories of those experiences. In the scanner session, each trial began with a 10-second presentation of a memory cue, and participants were

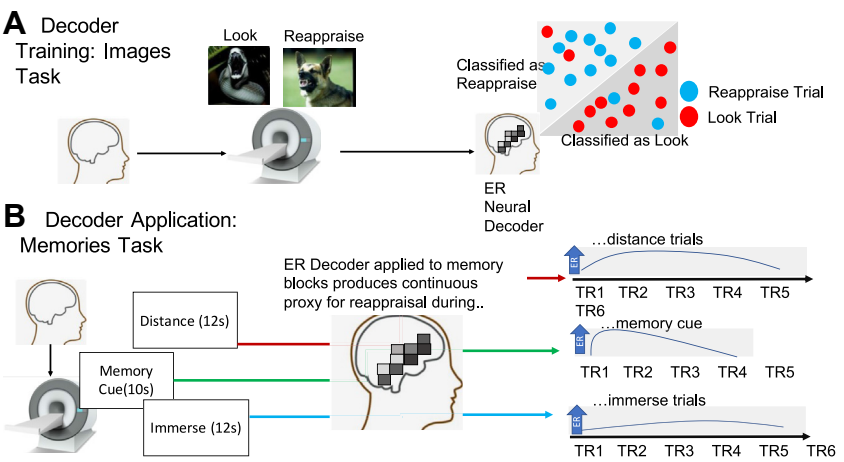

Figure 1. Decoder methodology. **(A)** The decoder was trained using data from a functional magnetic resonance imaging (fMRI) task in which negative photographs were presented with an instruction to either look and respond naturally or reappraise the photograph (left corner). Reappraisal is a form of emotion regulation (ER) that involves reinterpreting the meaning of a situation/stimulus (24). A binary classifier was trained using fMRI data to predict when a reappraisal vs. look trial was occurring (right corner). **(B)** This classifier was then applied to the 4 trial types in the memory task: memory cue exposure, distancing, immersion, and the nonemotional arrows task (not pictured, left corner). This produced a moment-to-moment proxy for the engagement of neural systems supporting reappraisal occurring throughout the memory task (right corner). TR, repetition time.

instructed to use the cue to bring the specific memory to mind. This was followed by a 12-second period in which participants were instructed to re-experience the memory from either a distanced third-person perspective ("as if watching events unfold from the viewpoint of a camera. . .") or an immersed first-person perspective ("as if reliving the event through your own eyes….") (Figure 1B, bottom left corner). In prior work, distance trials have been shown to be associated with diminished reports of negative affect (2), making this the ER condition. In addition to these conditions, a 20-second active perceptual task requiring subjects to indicate the direction that arrows were pointing on screen separated each memory. Details of task presentation are provided in the Supplement (2).

Step 1: Neural Decoder Training

Overview. Using fMRI data collected from the tasks described above, we developed a neural decoder based on task 1 data that could be used to produce a neural proxy of moment-to-moment ER occurring during the distance/immerse trials of task 2.

Neural Decoder Training: Feature Selection. In training the neural decoder, we sought to identify a pattern of activity that could successfully discriminate reappraise and look trials from task 1. We conducted a standard mixed-effects model conducted in FSL identifying voxel clusters significantly activated for reappraise versus look trials (voxel $p < .01$, cluster $p < .05$). Six directions of motion regressors were included as covariates. To maximize the generalizability of the derived decoder, we selected clusters only in the ventral-frontal and limbic regions, thereby excluding the dorsal visual processing stream and broader associative regions that may play general roles in stimulus perception and representation but are not thought to be essential for ER, per se (24).

Neural Decoder Training: Classification. We then conducted a multivariate elastic net logistic regression using the prespecified decoder mask as input to predict whether a given trial was a reappraise or look trial. Although this approach creates a circularity problem because the selected features have already been selected by the univariate analysis, our primary goal in this study was to observe naturalistic fluctuations in decoder output during the autobiographical memory task rather than simply train a decoder to discriminate reappraise versus look trials in the images task. Full details of this multivariate pattern analysis approach are described in the Supplement.

Step 2: Neural Decoder Application

The trained decoder was next applied to the neural data produced during the memories task. We applied the decoder to 3 separate trial types within the memory task: 1) the cued memory recall itself (10 seconds), 2) the distance trials (12 seconds), and 3) the immerse trials (12 seconds).

fMRI data from the memory task was preprocessed and registered to the standard template as described above. All data were standardized and residualized for the 6 degrees of freedom motion regressors. Application of the decoder produces a prediction for each repetition time (TR) of the degree to which neural data at each TR resemble either a reappraise trial from the images task or a look trial. Fluctuations in general blood oxygen level–dependent signals over the course of time can also influence decoder output though they may have little to do with the mental processes targeted by the decoder. We therefore incorporated average blood oxygen level–dependent signal in the decoder mask at each time point as a nuisance regressor. These steps resulted in a 10-second time course corresponding to each memory cue (16 per subject) and a 12-second time course corresponding to each immerse/distance trial (8 immerse/distance per subject).

Prediction of ER on Novel Data in Different Task Context

We next sought to determine whether the decoder could detect engagement of reappraisal systems when applied to both the fMRI and behavioral data from task 2 (the memory task). Starting with the fMRI data, we compared decoder output produced during the distance versus immerse trials, and we expected higher decoder output (indicating more ER) during distance trials. This was assessed using a mixed-effects

model with fixed effects for trial (distance vs. immerse) time (1–6, continuous, polynomial accounting for TR, TR^2, and TR^3), group (HC, subjects with MDD, individuals with high familial risk, categorical coded 1, 2, 3, with HC as reference group), average blood oxygen level–dependent signal (mean centered) in decoder mask and random effects for subject and run number. We considered linear, quadratic, and cubic effects of time in the model to reflect the nonlinear relation between time and the decoder output. A subsequent model was conducted, including affect rating (1–5, mean centered) as a fixed effect as well.

Step 3: Temporal Dynamics of ER

To identify the temporal dynamics of reappraisal system engagement during the 12-second distance/immerse trials, we calculated the Bonferroni-Holm–corrected comparison of TR-by-TR fixed effects on predicted decoder output based on the model described in the prior step. This compared decoder output at each TR with the output at other TRs and allowed us to identify the temporal dynamics of reappraisal system engagement as it evolved during the distance/immerse trials.

Step 4: MDD Versus HC

To test whether the temporal dynamics of reappraisal system engagement were different in the MDD versus HC groups, we ran a 2-way mixed-effect interaction model predicting decoder output from an interaction of time and group status. This analysis was applied to distance trials specifically because we expected to have highest signal-to-noise ratio in these trials. Critically, we did not initially run a 3-way model across all trials, including an interaction effect for trial type. Such a model addresses a separate question. A 3-way interaction tests whether the effect of group on the temporal dynamics of reappraisal systems changes across instruction conditions. Because we had no hypothesis regarding a shift in the effect of group on temporal dynamics across instruction types, we did not compute this analysis initially. However, because this is an important question, we conducted an exploratory analysis using this 3-way interaction. We also conducted a parallel exploratory analysis using the immerse trials and report these results in the Supplement.

These 2-way and 3-way interaction models included the same fixed and random effects as described above. Many trials were missing affect ratings, so we did not incorporate this into the main analyses. However, to ensure consistency, we also reran these models incorporating affect ratings subsequent to our initial tests.

RESULTS

Behavioral Data

Posttrial affective ratings during both the aversive image and autobiographical memory tasks indicated successful deployment of ER. In the aversive images task, posttrial affective ratings indicated less negative affect following reappraisal compared with look trials (look: mean [SD] = 3.59 [0.76], reappraise: mean [SD] = 2.83 [0.77], $t_{76} = 8.68$, $p < .001$). As previously reported, affect ratings during the autobiographical memories task were lower in distance versus immerse trials (2).

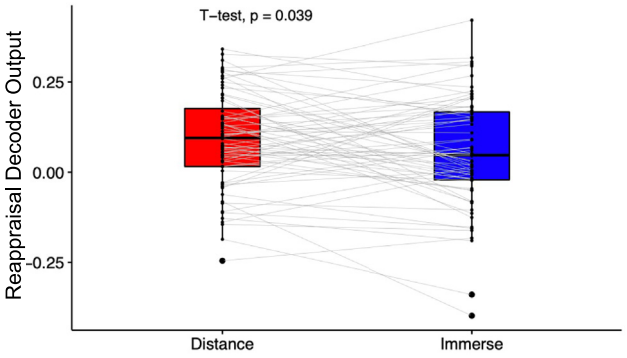

Figure 2. Predicting emotion regulation in a novel task. Pairwise subject averages of emotion regulation decoder output when applied to distance vs. immerse blocks of the memories task.

Step 1: Neural Decoder Training: Feature Selection and Classification

The general linear model analysis of the aversive pictures task identified a large set of voxel clusters associated with the reappraise versus look contrast. These clusters spanned the occipital, parietal, superior, and ventral-frontal lobes as well as the basal ganglia (Table S1 and Figure S1). Elastic net regression within this mask significantly classified reappraise versus look trials on the basis of neural data (area under the curve = 0.63, 1000-permutation p value $< .001$).

Step 2: Prediction of ER on Novel Data in Different Task Context

Our findings validated the decoder's ability to identify reappraisal system engagement occurring in a separate context in 3 ways: 1) trials with more negative affect ratings showed higher decoder output ($t_{4776} = 2.023$, $p = .04$) (Table S2), 2) the decoder generated higher output (indicating greater regulation) during distance blocks compared with immerse blocks (Figure 2 and Table 2), and 3) when applied to the autobiographical memory cue (before immerse or distance instructions was presented), there was no difference in decoder output between immerse and distance ($b_{5925} = -0.01$, $t = -0.52$, $p = .6$, 95% CI: −0.02 to 0.009). This means that the difference in output observed during the distance versus immerse trials arose only after the distance instruction cue was presented.

Step 3: Temporal Dynamics of ER

There was a significant main effect of time in predicting decoder output (Table 2) but no interaction between time and trial type ($F_{6343} = 2.4$, $p = .06$). As such, temporal dynamics of decoder output are presented across all trial types. The decoder showed a temporal dynamic in which the output built to a peak at TRs 2 to 4 and dropped off sharply afterward (Figure 3). Post hoc Bonferroni-Holm–corrected comparisons comparing each TR with every other TR showed that TRs 2 to 4 had higher output than TR1, TR5, and TR6 (corrected $p < .05$) (Table S3). TRs 3 to 6 showed a sequential decrease from one TR to the next, indicating a steep TR-by-TR dropoff in decoder output over time (Table S3).

Table 2. Predicting Reappraisal Decoder Output in a Novel Task Dataset I

ANOVA	Sum Square	Mean Square	NumDF	DenDF	*F* Value	*p* Value
Distance > Immerse	1.42	1.42	1	6366.4	17.7133	<.0000
3-Way Polynomial (TR, TR^2, TR^3)	7.91	2.64	3	6346.6	32.9512	<.0000
Group	0.01	0.01	1	67.2	0.1787	.6738
BOLD Average	739.54	739.54	1	6412.9	9244.1288	<.0001
Parameter Estimates	**Estimate**	**SE**	***df***	***t***	***p* Value**	**95% CI**
Intercept	−0.083	0.032	2190.916	−2.588	.010	−0.146 to −0.020
Distance > Immerse	0.031	0.007	7164.106	4.661	.000	0.018 to 0.044
TR	0.147	0.033	7164.037	4.424	.000	0.082 to 0.213
TR^2	−0.039	0.011	7164.035	−3.635	.000	−0.060 to −0.018
TR^3	0.003	0.001	7164.059	2.651	.008	0.001 to 0.005
HFRI > HC	0.028	0.029	73.473	0.971	.335	−0.030 to 0.086
MDD > HC	−0.010	0.018	74.012	−0.538	.592	−0.045 to 0.026
BOLD Average	0.000	0.000	7237.931	103.845	.000	0.000 to 0.000

Parameter estimates of fixed effects from linear mixed-effect model predicting decoder output applied to the autobiographical memory task. Decoder output is higher during distance trials than immerse trials. TR (1–6, continuous variable including TR, TR^2, and TR^3). BOLD average indicates average BOLD signal in decoder mask (scaled mean centered).

ANOVA, analysis of variance; BOLD, blood oxygen level–dependent; DenDF, denominator degrees of freedom; HC, healthy control; HFRI, high familial risk individual; MDD, major depressive disorder; NumDF, numerator degrees of freedom; TR, repetition time.

The decoder showed markedly different temporal dynamics during the 20-second arrow trials, which involved making simple perceptual judgments about the direction in which arrows were pointing. Specifically, during TR3 to TR9, output was higher than during TR1, TR2, and TR10, which indicated that the decoder rose to a plateau that remained consistent during most of the trial and tapered off at the end (Figure S2 and Table S4). However, differences in output between the distance and arrow trials may arise from differences in the timing of the arrow trials (20 seconds and without memory cue) compared with the distance trials.

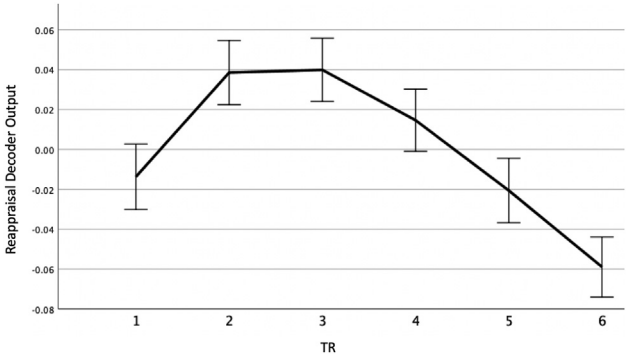

Figure 3. Temporal dynamics of emotion regulation. Emotion regulation decoder output levels across repetition times (TRs) (TR = 2 seconds) during both distance and immerse trials of the autobiographical memory task. Decoder output was residualized for average blood oxygen level–dependent activity within the decoder mask. Decoder output built to a peak in TR2 to TR4 vs. TR1 and then dropped off in TR5 to TR6.

Step 4: Using the Decoder to Test for MDD Versus HC Differences

The temporal dynamics of reappraisal system engagement, as indicated by the decoder, differed across MDD and control groups. The analysis of variance indicated a significant interaction between the diagnostic group variable and the polynomial time variable in predicting decoder output (Figure 4; Table S5). To determine the nature of this interaction, a set of post hoc mixed-effects models were run, comparing decoder output between MDD and HC groups at each TR. This analysis showed that the difference between MDD and HC groups was the greatest during TR6, during which the HC group had lower output than the MDD group (Table 3). There was no interaction between diagnosis and time when predicting decoder output during immerse trials (Table S6). The 3-way interaction assessing the effect of diagnostic group, time, and trial type showed no significant difference between groups regarding the interaction of trial type and time (p = .2236) (Table S7). When accounting for affect rating, the 3-way interaction of group, time, and trial type was not significant (p = .078) (Tables S8–S10), while the 2-way interaction effects remained the same.

Replication

We sought to replicate the present findings in a novel convenience sample of subjects with borderline personality disorder (BPD) (n = 59) who had completed a similar version of the autobiographical memories task (though with 20-second trials instead of 12); full details of this sample are provided elsewhere (28). Due to the longer trials, time was modeled as a quartic polynomial as indicated by analysis of variance best fit.

We replicated 3 key findings from this study. First, there was no difference in decoder output across trial types during memory cuing periods, i.e., before the trial instruction was provided (b_{4849} = 0.001, t = 0.14, p = .89, 95% CI: −0.02 to

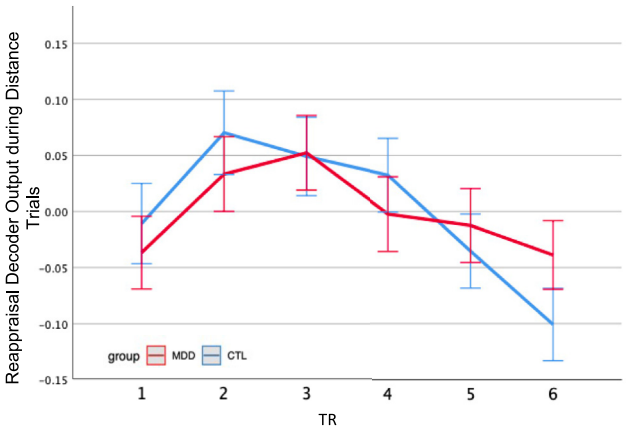

Figure 4. Temporal dynamics of emotion regulation in major depressive disorder (MDD) vs. healthy control (CTL) groups. During distance trials, the MDD group showed an altered temporal dynamic of emotion regulation compared with the healthy control group. The temporal dynamic of emotion regulation in the MDD group showed a less steep reduction during the second half. Decoder output has been residualized for average blood oxygen level–dependent activity in the decoder mask. TR, repetition time.

0.02). Second, once the cue was provided, distance trials showed higher output compared with immerse trials (b_{9695} = 0.02, t = 3.54, $p < .001$, 95% CI: 0.009 to 0.03) (Figure S3). Third, as in the first dataset, time was a significant predictor of decoder output (Table S11), but there was no time-by-trial type interaction (F_{9323} = 2.03, p = .11). Furthermore, we observed a similar temporal dynamic, showing an initial peak followed by a dropoff. Specifically, decoder output peaked from TRs 2 to 4, which showed higher output than TR1 and TRs 7 to 10. Notably, the height of the peak (TRs 3–4) showed higher output than TRs 5 to 10, indicating an immediate dropoff as seen in the first dataset (Table S12 and Figure S3).

DISCUSSION

We tracked a neural decoder trained to detect reappraisal system engagement during a 12-second period of ER in response to negative autobiographical memories. Decoder output from 2 independent datasets indicated that reappraisal system engagement rose to a peak in about 8 seconds and then dropped off immediately afterward. Critically, this pattern of rising to a peak and then dropping off was altered in the MDD group. In this group, decoder output did rise to a peak during the first 8 seconds but then failed to drop off as steeply as it did in the control group.

Temporal Dynamics of ER

The MDD group did engage the reappraisal systems to the same level as the HC group during the first 8 seconds of the trial but did not disengage to the same degree. By flexibly coming online and offline, reappraisal can modulate emotional responses without entirely shutting out emotional expression (33,34). This flexibility may assist in promoting a balance between facing and experiencing painful memories while still maintaining homeostasis (35,36). The MDD group may have approached the memory in a more rigid, invariant manner so as to maintain constant ER. However, this interpretation is made with the caveat that the MDD group may have engaged the decoder for longer because they were regulating more negative memories.

Interpreting Decoder Output

Central to our interpretation is the assumption that the decoder identifies reappraisal system engagement during the autobiographical memory task. Three points of evidence support this interpretation. First, the decoder produced higher output during more effectively negative memories. Second, the decoder produced higher output during the distance versus immerse trials. Third, the difference between distance and immerse trials was observed only after the instruction cue was presented but not during the memory cue. Hence, the decoder was engaged by the instruction to use distancing regulation and showed higher output during more negative memories, suggesting that it did indeed track an ER-related processes during the memories task (though some caveats apply, see Limitations and Future Directions).

Temporal Dynamics of Reappraisal Across Trial Types

The data summarized above suggest that the decoder did measure the neural systems supporting reappraisal and that the temporal dynamics in the engagement of these systems differed across MDD and HC groups. However, this conclusion may be tempered depending on how one expects MDD-related perturbations in ER systems to manifest across trial types (i.e., distance vs. immerse trials). If one expects that MDD-related differences in the temporal dynamics of ER systems would be specifically emphasized in the distance trials (i.e., the ER condition), then enthusiasm for these findings would be diminished. We tested for this group × trial type × TR interaction and did not find a significant 3-way interaction. The absence of this interaction may suggest that the 1) decoder does not adequately measure the regulatory processes engaged during distancing, 2) difference in temporal dynamics between MDD and HC is not very robust, or 3) effect of MDD on the temporal dynamics of regulatory processing is consistent across both trial types. While we favor the last interpretation, when focusing, we found no group difference in temporal dynamics during immerse trials (Table S6), though this may be a function of a lower signal-to-noise ratio.

Table 3. Post Hoc Analyses

	95% CI	HC-MDD	SE	*p* Value
TR1	−0.032 to 0.091	0.03	0.03	.337
TR2	−0.021 to 0.104	0.041	0.031	.192
TR3	−0.067 to 0.07	0.00	0.035	.963
TR4	−0.025 to 0.101	0.038	0.031	.229
TR5	−0.068 to 0.033	−0.017	0.025	.493
TR6	−0.104 to −0.012	−0.058	0.023	.015

Comparison of decoder output during distance trials for the HC vs. MDD groups for each TR separately. Analyses computed using mixed-effect models.

HC, healthy control; MDD, major depressive disorder; TR, repetition time.

Stronger validation of this decoder as a neural proxy for reappraisal would help clarify how to interpret these conflicting results. We have therefore made it publicly available: (https://github.com/mfschmidt/schneck_2021_temporal_emotion_regulation). By using this decoder in larger datasets with more varied approaches to measuring negative affect, we hope to provide greater validation of this decoder and further understanding of the relation between this decoder and behavioral measures of reappraisal. Furthermore, we have made available a version of the decoder that incorporates a broader mask, including clusters within the associative cortex. A clearer understanding of the cognitive process measured by this decoder will assist in interpreting the results yielded in this and future studies.

Neurobiology of Reappraisal in BPD

In subjects with BPD, as in the combined HC and MDD group, the decoder produced higher output during distance versus immerse trials and showed a similar temporal dynamic. This finding suggests that subjects with BPD engaged similar neural systems as that seen in the HC and MDD groups. However, direct comparison of the BPD and MDD or HC groups was impossible because of the different timescales of the memories task used for BPD (20 seconds) and MDD/HC (10 seconds) groups.

Development of a Generalizable Reappraisal Neural Decoder

This study begins the process of identifying a generalizable reappraisal neural decoder. The reappraisal decoder was trained on one set of data, i.e., the aversive images task, and then applied to a separate task, i.e., the autobiographical memories task. The decoder transferred successfully in both the same subjects and in a novel set of subjects. This finding provides evidence for the existence of a stimulus-independent set of neural systems supporting reappraisal (24).

An alternative approach would have been to train the classifier in the memories task and then apply the classifier to the same task to delineate moment-to-moment fluctuations. However, by using a classifier trained on separate data, we were able to ensure a more abstract representation of reappraisal less likely to be influenced by random biases or fluctuations in the memories data.

Limitations and Future Directions

One caveat to our interpretation of the decoder as a measure of reappraisal system engagement is that it was trained on the reappraise versus look trials of the images task. This opens the possibility that the decoder simply discriminated cognitive demand or effort. Countering this view is the fact that the decoder generated higher output during memory trials that were rated as being more effectively negative, indicating that it tracked an emotional process, i.e., reappraisal. Nevertheless, further independent validation of this decoder as a neural proxy for reappraisal is required. We also note that the study sample was not recruited specifically to assess this research question. Rather this was a secondary analysis on available data, which was collected primarily to investigate group differences between MDD and HC using positron emission tomography scanning. These findings are therefore presented as a first point of evidence about the temporal dynamics of reappraisal in MDD, which need to be confirmed in future studies using multimethod approaches. Furthermore, the study sample included a wide range of time-off of medication ranging from medication naïve to just over 21 days off to 1296 days off.

Conclusions

We observed the temporal dynamics of a neural decoder trained to detect reappraisal system engagement during attempted regulation of responses to negative autobiographical memories. In 2 datasets, the temporal dynamics of the decoder showed an initial peak in the first 8 seconds, which dropped off steeply. Subjects with MDD differed from HCs in that they did not show the same degree of reduction in decoder activation at the end of the trial. The dynamic of an initial peak followed by a subsequent dropoff may support a flexible process of ER that trades between modulating emotions and encountering painful memories that is lacking in MDD.

ACKNOWLEDGMENTS AND DISCLOSURES

This work was funded by National Institute of Mental Health grants (Grant Nos. PO1MH090964 [to JJM] and R01MH61017 [to BS]).

JJM receives royalties for commercial use of the Columbia Suicide Severity Rating Scale from the Research Foundation for Mental Hygiene and has stock options in Qualitas Health, a start-up developing a polyunsaturated fatty acids supplement. All other authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

From the Department of Psychiatry, Vagelos College of Physicians and Surgeons, Columbia University, New York, New York (NS, SH, AY, RTO, HG, AB, BS, JJM); Department of Biostatistics, Mailman School of Public Health, Columbia University, New York, New York (RTO, HG); Department of Psychology, Columbia University, New York, New York (KNO); Molecular Imaging and Neuropathology Division, The New York State Psychiatric Institute, New York, New York (NS, SH, AY, RTO, AB, BS, JJM); and the Division of Epidemiology and Biostatistics, School of Public Health, University of Illinois at Chicago, Chicago, Illinois (JL).

Address correspondence to Noam Schneck, Ph.D., at schneck@nyspi.columbia.edu.

Received Aug 2, 2021; revised Jul 28, 2022; accepted Sep 1, 2022.

Supplementary material cited in this article is available online at https://doi.org/10.1016/j.biopsych.2022.09.002.

REFERENCES

1. Sloan E, Hall K, Moulding R, Bryce S, Mildred H, Staiger PK (2017): Emotion regulation as a transdiagnostic treatment construct across anxiety, depression, substance, eating and borderline personality disorders: A systematic review. Clin Psychol Rev 57:141–163.
2. Doré BP, Rodrik O, Boccagno C, Hubbard A, Weber J, Stanley B, *et al.* (2018): Negative autobiographical memory in depression reflects elevated amygdala-hippocampal reactivity and hippocampally associated emotion regulation. Biol Psychiatry Cogn Neurosci Neuroimaging 3:358–366.
3. Bonanno GA, Burton CL (2013): Regulatory flexibility: An individual differences perspective on coping and emotion regulation. Perspect Psychol Sci 8:591–612.
4. Zimmer-Gembeck MJ (2021): Coping flexibility: Variability, fit and associations with efficacy, emotion regulation, decentering and responses to stress. Stress Health 37:848–861.

5. Myruski S, Dennis-Tiwary T (2021): Biological signatures of emotion regulation flexibility in children: Parenting context and links with child adjustment. Cogn Affect Behav Neurosci 21:805–821.
6. Dougherty EN, Murphy J, Hamlett S, George R, Badillo K, Johnson NK, Haedt-Matt AA (2020): Emotion regulation flexibility and disordered eating. Eat Behav 39:101428.
7. Westphal M, Seivert NH, Bonanno GA (2010): Expressive flexibility. Emotion 10:92–100.
8. Gupta S, Bonanno GA (2011): Complicated grief and deficits in emotional expressive flexibility. J Abnorm Psychol 120:635–643.
9. Aldao A, Sheppes G, Gross JJ (2015): Emotion regulation flexibility. Cognit Ther Res 39:263–278.
10. Conroy K, Curtiss JE, Barthel AL, Lubin R, Wieman S, Bui E, *et al.* (2020): Emotion regulation flexibility in generalized anxiety disorder. J Psychopathol Behav Assess 42:93–100.
11. Reinecke A, Filippini N, Berna C, Western DG, Hanson B, Cooper MJ, *et al.* (2015): Effective emotion regulation strategies improve fMRI and ECG markers of psychopathology in panic disorder: Implications for psychological treatment action. Transl Psychiatry 5:e673.
12. McRae K, Gross JJ, Weber J, Robertson ER, Sokol-Hessner P, Ray RD, *et al.* (2012): The development of emotion regulation: An fMRI study of cognitive reappraisal in children, adolescents and young adults. Soc Cogn Affect Neurosci 7:11–22.
13. Kross E, Davidson M, Weber J, Ochsner K (2009): Coping with emotions past: The neural bases of regulating affect associated with negative autobiographical memories. Biol Psychiatry 65:361–366.
14. Lang PJ, Bradley MM, Fitzsimmons JR, Cuthbert BN, Scott JD, Moulder B, *et al.* (1998): Emotional arousal and activation of the visual cortex: An fMRI analysis. Psychophysiology 35:199–210.
15. Zhang J, Lipp OV, Hu P (2017): Individual differences in automatic emotion regulation interact with primed emotion regulation during an anger provocation. Front Psychol 8:614.
16. Kashdan TB, Rottenberg J (2010): Psychological flexibility as a fundamental aspect of health. Clin Psychol Rev 30:865–878.
17. Levin ME, MacLane C, Daflos S, Seeley J, Hayes SC, Biglan A, *et al.* (2014): Examining psychological inflexibility as a transdiagnostic process across psychological disorders. J Contextual Behav Sci 3:155–163.
18. Levin ME, Luoma JB, Vilardaga R, Lillis J, Nobles R, Hayes SC (2016): Examining the role of psychological inflexibility, perspective taking, and empathic concern in generalized prejudice. J Appl Soc Psychol 46:180–191.
19. Krafft J, Hicks ET, Mack SA, Levin ME (2019): Psychological inflexibility predicts suicidality over time in college students. Suicide Life Threat Behav 49:1488–1496.
20. Braunstein LM, Gross JJ, Ochsner KN (2017): Explicit and implicit emotion regulation: A multi-level framework. Soc Cogn Affect Neurosci 12:1545–1557.
21. Schneck N, Haufe S, Tu T, Bonanno GA, Ochsner K, Sajda P, *et al.* (2017): Tracking deceased-related thinking with neural pattern decoding of a cortical-basal ganglia circuit. Biol Psychiatry Cogn Neurosci Neuroimaging 2:421–429.
22. Pereira F, Mitchell T, Botvinick M (2009): Machine learning classifiers and fMRI: A tutorial overview. Neuroimage 45(1 suppl):S199–S209.
23. Norman KA, Polyn SM, Detre GJ, Haxby JV (2006): Beyond mind-reading: Multi-voxel pattern analysis of fMRI data. Trends Cogn Sci 10:424–430.
24. Ochsner KN, Silvers JA, Buhle JT (2012): Functional imaging studies of emotion regulation: A synthetic review and evolving model of the cognitive control of emotion. Ann N Y Acad Sci 1251:E1–E24.
25. Thiruchselvam R, Blechert J, Sheppes G, Rydstrom A, Gross JJ (2011): The temporal dynamics of emotion regulation: An EEG study of distraction and reappraisal. Biol Psychol 87:84–92.
26. Sheppes G, Meiran N (2008): Divergent cognitive costs for online forms of reappraisal and distraction. Emotion 8:870–874.
27. Sheppes G, Meiran N (2007): Better late than never? On the dynamics of online regulation of sadness using distraction and cognitive reappraisal. Pers Soc Psychol Bull 33:1518–1532.
28. Silvers JA, Hubbard AD, Biggs E, Shu J, Fertuck E, Chaudhury S, *et al.* (2016): Affective lability and difficulties with regulation are differentially associated with amygdala and prefrontal response in women with borderline personality disorder. Psychiatry Res Neuroimaging 254:74–82.
29. Beck AT, Steer RA (1984): Internal consistencies of the original and revised Beck Depression Inventory. J Clin Psychol 40:1365–1367.
30. Hamilton M (1960): A rating scale for depression. J Neurol Neurosurg Psychiatry 23:56–62.
31. First M, Spitzer R, Gibbon M, Williams J (1995): Structured Clinical Interview for DSM-IV Axis I Disorders-Patient edition (SCID-I/P, Version 2.0). New York: Biometrics Research Department, New York State Psychiatric Institute.
32. Lang PJ, Bradley MM, Cuthbert BN (2008): International Affective Picture System (IAPS): Affective Ratings of Pictures and Instruction Manual (Technical Report A-8). Gainseville, FL: University of Florida.
33. Kobylińska D, Kusev P (2019): Flexible emotion regulation: How situational demands and individual differences influence the effectiveness of regulatory strategies. Front Psychol 10:72.
34. Southward MW, Altenburger EM, Moss SA, Cregg DR, Cheavens JS (2018): Flexible, yet firm: A model of healthy emotion regulation. J Soc Clin Psychol 37:231–251.
35. Bonanno GA, Papa A, Lalande K, Westphal M, Coifman K (2004): The importance of being flexible: The ability to both enhance and suppress emotional expression predicts long-term adjustment. Psychol Sci 15:482–487.
36. Gross JJ, Barrett LF (2011): Emotion generation and emotion regulation: One or two depends on your point of view. Emot Rev 3:8–16.