Targeting Mechanisms of Emotion Regulation During Cognitive Behavior Therapy in Depression: Preliminary ERP Findings During Lateralized Presentations of Aversive Pictures

Jürgen Kayser [1,2], Yifan Gao [1,2], Tayler Wilson [3], Rocco Rinaldi-Rose [3], Christopher Aceto [3], Steven D. Hollon [4], Gerard E. Bruder [1], Ronit Kishon [1,3]

Columbia University, Department of Psychiatry, New York, NY, USA [1]; New York State Psychiatric Institute, Translational Epidemiology [2] & Depression Evaluation Service [3]; Vanderbilt University, Department of Psychology [4]

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Abstract

Introduction: This study aims to clarify the neurobiological mechanisms by which change occurs during cognitive behavior therapy (CBT) for major depressive disorder (MDD). Emotion regulation is deemed critical for CBT success (**Fig. 1**). Event-related potentials (ERPs) to salient affective pictures reflect different stages of motivated attention, ranging from automatic or stimulus-driven categorization (bottom-up) to cognitive appraisal (top-down) during emotion processing (**Fig. 4A**). Blunted ERPs to emotionally-arousing stimuli have been observed in MDD (**Fig. 4**). Building on prior event-related potential (ERP) findings, we examined whether abnormal early (preconscious) responsivity to negative arousing stimuli, which is indicative of right parietotemporal dysfunction in MDD patients, is moderated by or predictive of treatment response. **Methods:** Using highly-controlled negative/neutral picture pairs during an emotional hemifield paradigm, ERPs (72 sites) were recorded from 25 depressed patients (13 male, age 21-56 years) before and after 12 weeks of cognitive-behavioral (n = 11, 73% BDI-based responder) or nonspecific-supportive (n = 14, 64%) therapy. Reference-free current source density (CSD) transformations of ERPs were quantified by temporal principal components analysis (tPCA). The CSD-tPCA solution (**Fig. 5**) confirmed prior findings of three distinct stages of emotional processing comprising the late positive potential (negative-greater-than-neutral; **Fig. 6**): early N2 sink (peak latency 208 ms), P3 source (330 ms), and late centroparietal (CP) source (575 ms). **Results:** Repeated measures ANOVAs of corresponding component scores revealed divergent emotional effects for N2 sink: Whereas responders had greater emotional effects over left-than-right posterior sites at baseline, with this asymmetry reversed after treatment, nonresponders showed a right-greater-than-left asymmetry at both sessions, exhibiting no emotional effects over the left hemisphere before treatment (**Fig. 7, left panel**). These early effects were further differentially modulated by visual field, with responders showing amplitude enhancement with contralateral stimulation, whereas nonresponders did not (**Fig. 8**). By contrast, prominent late emotional content effects were seen for CP source for responders before and after treatment at both hemispheres, whereas nonresponders failed to show notable emotional effects for CP source at any testing session or hemisphere (**Fig. 7, right panel**). **Conclusions:** Although caution is warranted given the preliminary status of this ongoing clinical trial with its current limited sample size, findings are consistent with hypothesized differences in top-down regulation of bottom-up emotion processing that are linked to MDD treatment response (**Fig. 3**). Our findings suggest that the hierarchical activation of 'emotional' brain regions along the occipitotemporal ventral stream, ranging from preconscious stimulus categorization to conscious appraisal (**Fig. 2**), is aberrant in treatment nonresponders, which leads to inhibition of downstream emotional processing. An increased sample size will be required to differentiate placebo response from CBT success.

Introduction

- Dysfunction in ***emotion regulation*** **(ER)** is at the core of mood disorders
- Involves abnormal activations of specific brain regions[25] critical for emotion processing and self-awareness (**Fig. 1**).[20,23]
- Activity in these brain regions is modulated by **prefrontal regions** responsible for **up- and down-regulation of emotional processes**[4,23]
- An improved understanding of these processes will benefit the treatment of mood disorders
- In unipolar depression, CBT is effective for ~50% of patients: Identify mechanism and **biomarkers that predict CBT response**
- We developed an ***emotional hemifield task*** **(EHT)**[11] that targets the right temporoparietal and occipital cortex (ventral attention network[3]) involved in **bottom-up salience detection**[14]
- During this task, the ***late positive potential*** **(LPP)**, a prominent event-related potential (ERP) over parietal regions that is greater to negative vs. neutral stimuli, is **reduced** in ***major depressive disorder*** **(MDD)**[11]
- These emotional ERP effects reflect brain activations of the ventral visual pathway during stages of salience processing, with maximal activations in ***right occipitotemporal*** (212 ms; **N2**), ***bilateral posterior cingulate*** (385 ms; **P3**) and ***bilateral inferior temporal cortex*** (630 ms; **LPP**; **Fig. 4**)[14]
- These emotional effects were **reduced in** individuals at risk for or with a lifetime diagnosis of **MDD** (**Fig. 4**)[15]
- This suggests neuronal activation patterns indicative of dysfunctional emotion processing in a frontoparieto-temporal neural network are a **possible biomarker of treatment outcome, including CBT**[22]
- However, although fMRI evidence links conscious ER to CBT success[21], there are no longitudinal studies of **whether clinical response to CBT** is likewise **associated with normalization of ERPs to motivationally salient stimuli**

Objective:

- **measure ERPs during the EHT in MDD *before* and *after* *cognitive-behavioral*** **(CBT) or *nonspecific-supportive*** **therapy (placebo [PBO])**
- **evaluate if blunted emotional ERPs before treatment predict and/or change with treatment outcome**

Participants

Depressed Patients (MDD) (n = 25; 12 female, 48.0%)

Therapy, 12-week	Cognitive-behavioral (CBT) n = 11			Nonspecific-supportive (PBO), n = 14			p
Sex (m / f / f%)	6	5	45%	7	7	50%	*n.s.*
BDI responder	5	3	72%	4	5	64%	*n.s.*
Variable	**Mean**	**SD**	**Range**	**Mean**	**SD**	**Range**	p
Age (years)	37.9	9.1	33 - 56	33.6	8.6	21 - 45	*n.s.*
EHI LQ [a]	84.9	22.0	38 - 100	86.4	16.6	60 - 100	*n.s.*
Education (years)	15.2	4.7	3 - 18	15.3	4.0	4 - 21	*n.s.*
Parental SES [b]	45.0	12.1	24.5 - 66	49.1	11.9	19.5 - 61	*n.s.*
Baseline BDI [c]	28.9	6.1	19 - 38	26.8	9.3	13 - 43	*n.s.*
Baseline HAMD [d]	19.6	4.4	12 - 27	18.5	3.1	13 - 22	*n.s.*

Note. [a] *Edinburgh Handedness Inventory* (EHI)[18] laterality quotient (LQ) can vary between −100.0 (completely left-handed) and +100.0 (completely right-handed). [b] *Parental Socioeconomic Status* (SES)[6]. [c] *Beck Depression Inventory* (BDI)[1]. [d] *Hamilton Rating Scale for Depression* (HAMD)[5]. Race and ethnicity were Asian (5), Black/African American (1), White/Caucasian (17), and more than one race/unknown (2).

Treatment Response Stratification

BDI ≤ 50% baseline	Responder, n = 17			Nonresponder, n = 8			
Variable	**Mean**	**SD**	**Range**	**Mean**	**SD**	**Range**	p
Age (years)	32.6	7.2	21 - 46	41.8	9.4	24 - 56	.01
EHI LQ	91.3	16.4	38 - 100	73.9	18.9	50 - 100	.03
Education (years)	14.7	4.5	3 - 18	16.6	3.4	12 - 21	*n.s.*
Parental SES	47.2	12.4	19.5 - 66	47.5	11.6	24.5 - 58.5	*n.s.*
Baseline BDI	26.2	5.8	18 - 36	30.6	11.3	13 - 43	*n.s.*
Last BDI	6.6	4.2	0 - 13	22.5	8.8	12 - 34	<.001
Baseline HAMD	18.4	3.4	12 - 23	20.4	4.1	13 - 27	*n.s.*
Last HAMD	11.8	6.0	0 - 24	18.4	2.4	15 - 21	.007

Statistical Analysis

- 2-pronged analytical approach using permutation tests[12,17] and split-plot ANOVA
- Differences in emotional content were evaluated for factor scores via non-parametric randomization tests to probe the entire topography for each subgroup (**Fig. 6**)
- For each component, factor scores were pooled across selected parietooccipital sites over each hemisphere where emotional content effects were most robust[14]
- Emotional content, visual field, and group effects were evaluated with repeated measures ANOVA for mixed factorial designs

Emotion Regulation (ER)

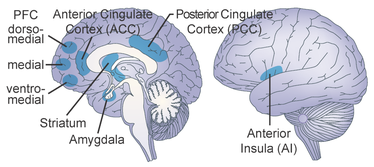


Fig. 1. Brain regions involved in emotion processing and regulation.[23] PFC: Prefrontal Cortex.

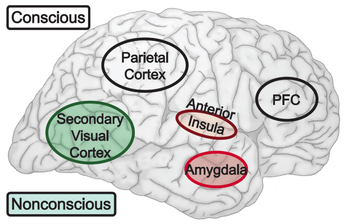


Fig. 2. Brain regions involved in conscious and nonconscious processing of visual stimuli.[16] PFC: Prefrontal Cortex.

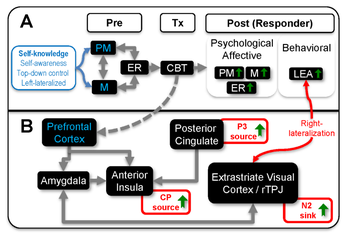
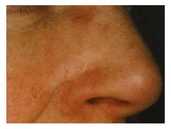


Fig. 3. Conceptual model. **A.** Meta-cognitive constructs and study design. **B.** Neural circuits and key brain regions/circuits with associated affective ERP components (red). Green up-arrows indicate predicted change after successful CBT.

Stimuli and Procedure

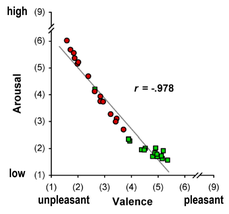
- 16 closely matched pairs of pictures depicting facial areas of patients with dermatological diseases before (negative) and after (neutral) surgical treatment (**example pair**):

Negative: Facial areas before or during surgical treatment (e.g., a cheek with a melanoma)

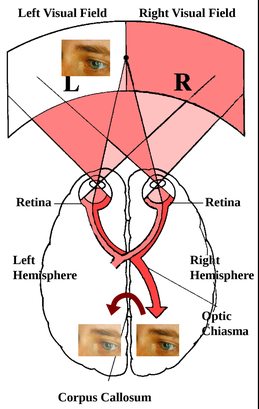


Neutral: Same facial areas healed after treatment (i.e., healthy skin or a scar)

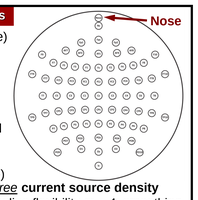
- SAM stimulus ratings[2] indicated that ***negative*** pictures were perceived as moderately unpleasant and mildly arousing, and ***neutral*** pictures as neither pleasant or unpleasant and not arousing[14]



- Stimuli presented for 250 ms to the left or right hemifield using a pseudo-randomized sequence (i.e., 4 blocks of 32 trials) with variable intertrial intervals (8 – 13 s)[14]
- Participants attended to stimuli while maintaining fixation
- No manual response



EEG/ERP Recording and Analysis



- 72-channel EEG (nose reference)
- Biosemi, 1024 samples/s
- **spatial SVD blink reduction** (continuous EEG)
- -200 to 1300 ms EEG epochs (baseline-corrected)
- ERPs for 4 conditions: emotional content [negative, neutral] x hemifield [left, right]
- 12.5 Hz low pass (-24 dB/octave)
- ERPs transformed to *reference-free* **current source density (CSD)** estimates (μV/cm² units; spline flexibility m = 4; smoothing constant $\lambda = 10^{-5}$): sharpen topographies, eliminate volume-conducted activity (spherical splines surface Laplacian)[9,19,24]
- CSDs submitted to ***unrestricted*** **temporal principal components analysis (tPCA)** to obtain data-driven summaries of radial current flow at scalp[7,8]
- Focus on CSD-tPCA component showing robust emotional effects (i.e., negative-minus-neutral)[14]

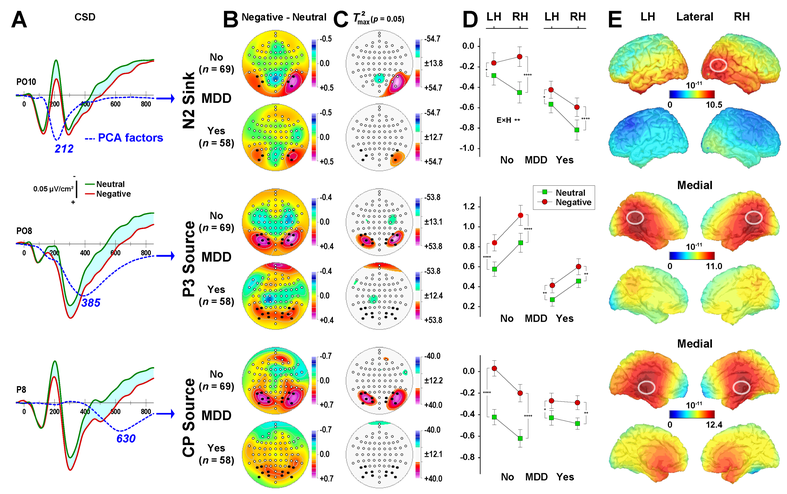


Fig. 4. Emotional effects for individuals with and without a lifetime history of MDD (prior findings)[15]. **A**: CSD waveforms and factor loadings. **B**: CSD topographies (negative-minus-neutral) corresponding to N2 sink, P3 source, and late centroparietal (CP) source. **C**: Significant differences (permutation tests). **D**: Means (±SEM) at representative sites (marked in B). **E**: Corresponding source inverses (sLORETA) reveal sequential activation of ventral visual pathway regions (i.e. from extrastriate to ventromedial cortex; cf. **Fig. 2**).

Temporal PCA (tPCA): Factor Loadings and Scores

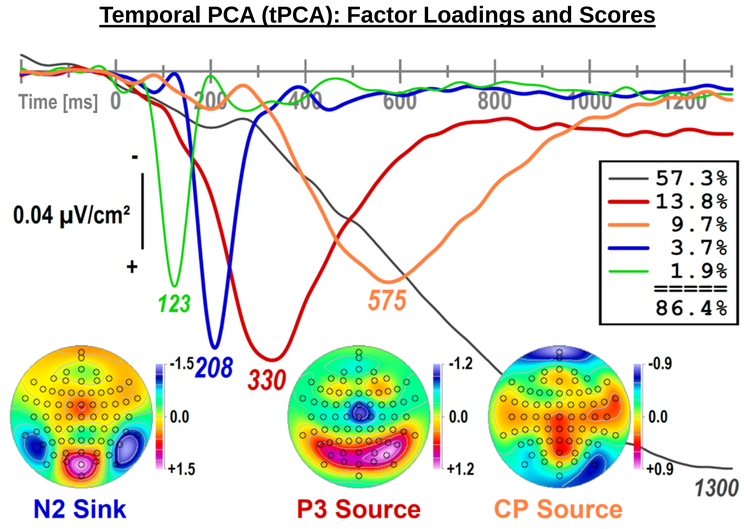


Fig. 5. Among the first five high-variance factors, three CSD factors closely replicated those previously identified as affect-sensitive LPP subcomponents (N2 sink, P3 source, centroparietal [CP] source).[14,15]

CSD Waveforms

Difference Topographies and Randomization Tests

Fig. 6A. Current source density (CSD) [μV/cm²] waveforms (–100 to 800 ms, 100 ms pre-stimulus baseline) for negative and neutral stimuli (pooled across hemifield) at selected left and right lateral-parietal sites (P7/8) for the full sample and subgroups stratified by BDI[1] treatment response. CSDs were reconstructed (filtered) by tPCA factors 2-5 (**Fig. 5**). Factor loadings of the targeted temporal PCA factors corresponding to N2 sink (208) P3 source (330) and CP source (575) are shown for comparison (dashed lines). Distinct CSD components (N2 sink, P3 source) are labeled in italics at P8.

Statistical evaluation of topographic emotional content effects for the corresponding CSD-tPCA factor scores using randomization tests for paired samples (10,000 repetitions) for each subgroup. Shown are negative-minus-neutral topographies and squared univariate (channel-specific) paired samples T statistics thresholded at the 95th quantile (p = 0.05) of the corresponding randomization distribution (maximum of all 72-channel squared univariate paired samples T statistics). To facilitate comparisons of the max(T^2) topographies with the underlying difference topographies, the sign of the difference at each site was applied to the respective T^2 value, which is otherwise always positive. Symmetric scales were optimized for score ranges across all subgroups. Sites marked as black dots were used in repeated measures ANOVA.

Fig. 6B. Emotional effects for **N2 sink** were prominent and right-lateralized over occipitotemporal regions.

Fig. 6C. Emotional effects for **P3 source** were weak and not significant.

Fig. 6D. Emotional effects for **CP source** were present over parietal-occipital regions for responders but not non-responders.

Fig. 7. Mean (±SEM) factor score amplitudes over parietooccipital regions (see Fig. 6B-D) for negative and neutral stimuli at each hemisphere (LH/RH) and session (A/B). Significant emotional content effects are marked as: (*) $p < 0.10$; * $p < 0.05$; ** $p < 0.01$.

Fig. 8. Hemifield modulations of emotional content effects (RVF/LVF: right/left visual field).

Summary and Conclusions

- **Early (preconscious) emotional content effects of N2 sink changed from pre- to post-treatment in responders (from left- to right-lateralized) but not in non-responders (right-lateralized)**
- **Moreover, responders showed 'normal' hemifield modulations (i.e., N2 sink enhancements with contralateral stimulation) that aligned with these asymmetries whereas nonresponders did not**
- **There were no emotional content effects of P3 source, consistent with prior findings in MDD**
- **Overall P3 source amplitude was greater in responders than nonresponders**
- **Emotional content effects during the late LPP (CP source) were observed in responders but not nonresponders**
- **This pattern of findings is – in part – consistent with hypothesized differences in top-down regulation of bottom-up emotion processing linked to MDD treatment response (Fig. 3)**
- **This suggests that the hierarchical activation of 'emotional' brain regions along the occipito-temporal ventral stream, ranging from pre-conscious stimulus categorization to conscious appraisal (Fig. 2), is aberrant in treatment non-responders, presumbably leading to inhibition of downstream emotional processing**
- **However, considerable caution is warranted given the limited sample size of this ongoing clinical trial**
- **Although treatment groups were matched in clinical and demographic variables, treatment response yielded subgroup differences in age and handedness**
- **An increased sample is required to distinguish placebo response from CBT success**

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