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Running head: Predictor of BA Response

The Negativity Bias Predicts Response Rate to Behavioral Activation for Depression

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Abstract

Background and Objectives: This treatment study investigated the extent to which asymmetric dimensions of affective responding, specifically the positivity offset and the negativity bias, at pretreatment altered the rate of response to Behavioral Activation treatment for depression.

Method: Forty-one depressed participants were enrolled into 16 weekly sessions of BA. An additional 36 lifetime healthy participants were evaluated prospectively for 16 weeks to compare affective responding between healthy and remitted patients at post-treatment. All participants were assessed at Weeks 0, 8 and 16 using repeated measures, involving a structured clinical interview for DSM-IV Axis I disorders, questionnaires, and a computerized task designed to measure affective responses to unpleasant, neutral, and pleasant images.

Results: The negativity bias at pre-treatment predicted the rate of response to BA, while the positivity offset did not.

Limitations: Only one treatment condition was used in this study and untreated depressed participants were not enrolled, limiting our ability to compare the effect of BA.

Conclusions: Baseline negativity bias may serve as a signal for patients to engage in and benefit from the goal-directed BA strategies, thereby accelerating rate of response.

Keywords: major depression, IAPS, negativity bias, positivity offset, Behavioral Activation.

The Negativity Bias Predicts Response Rate to Behavioral Activation for Depression

An essential function of the affect system is to detect and accurately interpret the emotional salience of stimuli encountered in social and physical environments (Phaf et al., 2014). Evaluating emotional information is crucial for guiding individuals toward or away from scenarios that influence health, survival, and well-being. Evaluating an image as positive should, theoretically, potentiate an individual to approach and explore it, while viewing an image as negative should theoretically activate avoidance. An individual diagnosed with depression, however, may consistently alter their evaluation of the image reporting it to be more or less positive (or negative) than its actual valence. As found in the research, depressed relative to healthy participants show lower valence ratings of emotional images (Bylsma, Morris, & Rottenberg, 2008), as well as higher valence ratings to unpleasant stimuli (Roiser et al., 2012). Minimal research, however, has investigated how a depressed individual's evaluation of emotional images when entering treatment may potentiate or hamper treatment response (Harmer et al., 2008). Further, examining how remitted depressed individuals compare with healthy individuals at the end of treatment when evaluating emotional information may have implications for identifying factors that potentiate recovery.

Behavioral Activation (BA) treatment is an evidence-based intervention for major depression, effective for up to 75% of patients (Cuijpers, van Straten, & Warmerdam, 2007b; Dichter, Felder, & Smoski, 2010; Dimidjian et al., 2006; Ekers, Richards, & Gilbody, 2008; Hopko et al., 2011; Jacobson et al., 1996; Lejuez, Hopko, & Hopko, 2001; Lejuez, Hopko, Acierno, Daughters, & Pagoto, 2011, O'Mahen et al., 2014, O'Mahen et al., 2013; Sheldon et al., 2014). The BA model proposes that the patient's exposure to aversive situations, lost or

disrupted routines, and decreased access to positive activities produce and maintain depressive symptoms. The aims of BA are, therefore, to increase the individual's access to sources of positive reinforcement, to recognize routine disruptions and depressogenic avoidance patterns, and to modify skill deficits (Martell, Addis, & Jacobson, 2001). Both the patient and clinician aim to identify antecedent and consequential behaviors associated with depressed mood, monitor the link between activity and mood with the goal of decreasing activities associated with a negative mood or emotion, and increase activities that evoke positive emotion or a sense of mastery following goal-directed behaviors. Notably, BA teaches the patient how to engage in positively reinforcing contingencies even when these activities are unpleasant. Seeking job opportunities, actively developing friendships, and pursuing regular exercise may be perceived as aversive, but BA strategies assist patients to schedule and engage in these activities regardless of how they feel. Depressed patients who evaluate unpleasant information may not employ treatment strategies and experience little benefit from BA. Others may use their evaluation of unpleasant information as a cue to employ goal-directed BA strategies.

Patient predictors of positive treatment response for BA include a lower endorsement of existential reasons for depression (Addis & Jacobson, 1996); higher depressive severity (Dimidjian et al., 2006), limited comorbidity, being married (Colman et al., 2009), and diminished hostility (Gollan, Gortner, & Dobson, 2006). BA responders show an increased activation of a brain region involved with affective responses to positive and negative stimuli (paracingulate gyrus) and with cognitive flexibility (Dichter et al., 2010; Dichter, Felder & Smolski, 2009). Differentially, Cognitive Behavioral Therapy responders show: (i) increased affective responses to positive memories (Siegle et al, 2006; Mayberg et al., 1997; Fu et al., 2008); (ii) increased activation of the left anterior temporal lobe/ventral lateral prefrontal cortex,

which are associated with semantic elaboration of affective stimuli (Ritchey et al., 2011); and (iii) greater cognitive control of negative stimuli (Fitzgerald et al., 2008; Ritchey et al., 2011; see opposite findings: Drevets et al., 1997; Elliott et al., 2002).

Research on the affect system, guided by the Evaluative Space Model (ESM; Cacioppo, Berntson, Larsen, Poehlmann, Ito, 2000; Cacioppo & Berntson, 1994; Cacioppo, Gardner, Bernston, 1997, Cacioppo, Gardner, Bernston, 1999), suggests that when humans evaluate pleasant and unpleasant stimuli simultaneously, they show heightened response to, and reduced response latency to, unpleasant relative to pleasant stimuli, controlling for arousal and intensity of the stimuli (Cacioppo et al., 1997; Delplanque, Silvert, Hot, & Sequeira, 2005; Huang & Luo, 2006; Kisley, Wood, & Burrows, 2007). The '*negativity bias*' (Ito & Cacioppo, 2005; Ito, Larsen, Smith, & Cacioppo, 1998; Smith et al., 2006) is associated with increased muscular activity (corrugator supercilii) (Neta, Norris, & Whalen, 2009) and neural activity of the inferior frontal gyrus, suggesting semantic activation (Jung et al., 2006; Gollan et al., 2015). The negativity bias is generalizable across visual and auditory modalities and visual stimuli (e.g., pictures, words; Norris et al., 2011; Larsen, Norris, McGraw, Hawkley, & Cacioppo, 2009). Additionally, humans evaluate neutral information with positivity, or with a '*positivity offset*' (Cacioppo et al., 1997). The positivity offset is stable across time and regained quickly after unpleasant events (Diener & Diener, 1996; Gilbert, Pinel, Wilson, Blumberg, & Wheatley, 1998).

Applying the ESM model, it logically follows that depressed patients with a relatively weaker positivity offset may perceive less opportunity for pleasure and reduce exploratory behavior in neutral scenarios. If the positivity offset is higher, depressed persons may be still prompted towards exploratory behavior, consistent with BA's goal directed strategy, and they

may benefit from positively reinforcing contingencies. Likewise, depressed patients with a relatively lower negativity bias may not experience aversive reactions and see little reason to use BA to alter their depressogenic context. In comparison, those individuals with stronger negativity bias may experience stronger aversive reactions and engage and benefit from BA. Simply, BA may not be the best treatment for depressed persons with lower negativity bias as these individuals are not as reactive to unpleasant information as for those for whom BA works (Gollan et al., 2015).

The objective of this study was to investigate the extent to which the strength of the negativity bias and the positivity offset at pre-treatment predicted the rate of treatment response, controlling for the patient's severity of depression at pre-treatment. We hypothesized that controlling for severity of depression, negativity bias and positivity offset, all measured at pre-treatment, will independently predict the rate of response to BA. Further, we enrolled a healthy group of participants and tracked them over the course of 16 weeks to compare healthy and remitted patients at post-treatment on affective responding in an effort to measure the extent to which negativity bias and positivity offset 'normalize' among those participants who responded to BA treatment.

Method

Participants

Forty-one participants with a primary diagnosis of major depression using the *Diagnostic and Statistical Manual of Mental Disorders* (4^{th} ed.; DSM-IV) and scores $\geq$ 24 on the Inventory of Depressive Symptomatology-Clinician Rated (IDS-C; Rush et al., 1986) were enrolled into a treatment study at Northwestern University's Feinberg School of Medicine in Chicago, Illinois.

Another 36 participants with no lifetime psychiatric symptoms and scores ≤ 11 on the IDS-C were enrolled for assessment over 16 weeks. This study was approved by the ethics committees and informed consent was retrieved from all participants. Data collection occurred between 5/2009 and 7/2011.

The sample was primarily female (*n* = 46, 59.7%), in their mid-thirties (M = 35 years, *SD* = 13y, range = 19 - 49y), and college educated (*n* = 40, 52%). A few endorsed Hispanic or Latino ethnicity (*n* = 6, 8%). Over half of participants endorsed the racial category of Caucasian (*n* = 42, 54.5%), one third endorsed the category of African American (*n* = 24, 31.2%), and a small group endorsed Other (Indian) (*n* = 5, 6.5%). No other ethnicities were reported.

Inclusion criteria specified participants between ages 18 and 65 years, medically healthy, medication-free, and with no medication washout. Exclusion criteria included lifetime bipolar disorder, psychosis, obsessive-compulsive disorder, substance abuse/dependence, and several personality disorders (i.e., borderline, schizoid, schizotypal, antisocial).

Enrollment numbers are presented in Figure 1.[1] Treatment completers were defined as having attended ≥ 12 of 16 treatment sessions; treatment partial completers were defined as having attended 5-11 of 16 sessions; and, treatment noncompleters were defined as having completed less than five sessions).

INSERT FIGURE 1 ABOUT HERE

Intervention

[1] Sample size was adequate as a priori power analyses using GPower indicated that sufficient power was available to detect a medium effect size for differences in slopes.

Treatment included up to 16 weekly 50 minute psychotherapy sessions using BA (Addis & Martell, 2004; Martell et al., 2001, 2010). Techniques included functional analyses to identify the antecedent and consequential aspects of low mood, and interventions such as monitoring daily activities, assessing pleasure/satisfaction and competence achieved via activities, assigning tasks that induce mastery or pleasure, and reducing skill deficits. Clinicians included postdoctoral fellows in clinical psychology (n = 2) or licensed clinical psychologists (n = 2).

Treatment Integrity

Sessions were audiotaped and discussed in weekly supervision with JG, during which clinicians reviewed principles and techniques, homework, and treatment plans. Ten randomly selected audiotapes of each clinician were evaluated by BA experts for competence. These reviewers, Drs. Christopher Martell and Ruth Herman-Dunn, reviewed tapes of early, middle, and late sessions (selected at random among completer tapes) and clinician competency was rated using a competency manual, the Behavioral Activation Treatment Scale (BATS, Jacobson et al., 1996). The BATS is a 16-item measure completed by BA experts that assess clinician competency. Each items has a 6 point Likert scale (1 = *Poor* to 6 = *Excellent)*, permitting the expert to review the study clinicians' structural and stylistic strategies, conceptualization, and application of BA techniques. Our clinicians were evaluated and were issued competency score (M = 68.26, SD = 5.21, Range = 63-75) that surpassed the threshold score of 60, which shows basic clinical competency.

Adherence. Adherence was rated high for BA by trained evaluators (KHF, DH) using the BA items from the Collaborative Study Psychotherapy Rating Scale (CSPRS; Hollon et al., 1998) using early, middle, and late sessions from cases selected at random. The adherence measure

outlined 28 items using a 7 point Likert scale (1 = *behavior not present* to 7 = *behavior present*). After establishing inter-rater reliability (0.86), ratings were generating of 20% of the completer sample. Our clinicians were evaluated and issued adherence ratings (M = 4.96, SD =.37) that show adherence with the BA approach.

Measures

The clinical interviews and self-reports were issued before, during and after treatment. In addition, the IDS-SR was issued prior to each of the treatment sessions.

The *Structured Clinical Interview for the DSM-IV Axis I Disorders, Outpatient Version* (SCID, First, Spitzer, Gibbon, & Williams, 1997) is a semi-structured intake interview designed to assess *DSM-IV* diagnoses. The SCID has adequate inter-rater reliability with kappa values for modules reported to be between .70 and 1.00 (First et al., 1995, 1997). Our evaluators underwent a training program with SCID training tapes (Spitzer, Williams, Gibbon, & First, 1989), formal training, observing and demonstrating SCID competency, and co-rating and reviewing SCID interviews. Our reliability checks of three separate tapes yielded kappa coefficients of .83 for the Mood module and .93 for the Anxiety module.

The *Structured Clinical Interview for DSM-IV Axis II Disorders Questionnaire* (SCID-II; First et al., 1997) is a 47-item self-report screen used to exclude participants who endorsed symptoms of borderline, schizoid, schizotypal, antisocial personality disorders.

The *Longitudinal Follow-up Evaluation* (LIFE, Keller, Lavori, Friedman, Nielsen, & Endicott, 1987) is a semi-structured follow-up interview that measures weekly changes of *DSM-IV* depressive symptoms using a Psychiatric Status Rating (PSR) to represent severity of illness per week. PSR ratings are on a scale from 1-6 (1-2 = *no or minimal symptoms*; 3-6 = *moderate to*

severe symptoms). We used this measure to describe the sample, defining remission as LIFE PSR ≤ 2 (minimal or no DSM symptoms) and IDS-C ≤ 11 at post-treatment (Frank et al., 1991).

The *Inventory of Depressive Symptomatology – Clinician-Rated* (IDS-C; Rush, Giles, Schlesser, Fulton, Weissenburger, Burns, 1986; Rush, Carmody, & Reimitz, 2000; Rush, Trivedi, Ibrahim, Carmody, Arnow, Klein, et al., 2003) is a 30 item measure that assesses *DSM-IV* symptoms of depression. The inter-rater reliability estimate from this study's sample at pre-treatment was .874. We chose the IDS rather than other clinician scales because of its strong psychometric data and accessibility (Rush et al., 1986, 2003). We used this measure to provide a description of the sample, defining response as a ≥ 50% reduction of the IDS-C score from pre- to post-treatment and remission was defined as the IDS-C ≤ 11 at post-treatment.

The *Inventory of Depressive Symptomatology – Self-Rated* (IDS-SR; Rush et al., 1986, 2003) is a 30-item measure of depression severity. Convergent validity with the IDS-C in our sample was strong with correlations of .964 at pre-treatment and .910 at post-treatment. As this measure was administered before each treatment session, it was used to define the outcome variable (rate of response).

The *Implicit Affective Task* (Norris et al., 2011) is a computer-based task that presents color pictures from the International Affective Picture System (IAPS; CSEA-NIMH, 1999; Lang et al., 1999), during which participants rate their positive and negative reactions to each image. Images were equally split into three categories based on their normative valence ratings: pleasant, neutral, and unpleasant. Each group consisted of 80 images, yielding a total of 240 images.[2] Participants were informed that they would see pictures of varied emotional content and that they should attend to each picture for the entire time it was presented. Images were presented in one

[2] The picture numbers for IAPS stimuli are available upon request.

of two pre-determined pseudo-random orders (counterbalanced across participants) during both assessments. Each trial consisted of a 0.5 second baseline period, 4 second image presentation period, and a self-paced rating period. A fixation point appeared at the center of the screen during the baseline period, which was replaced by the image centered on the screen during the image presentation period. Participants indicated their positive and negative responses to each picture using the Evaluative Space Grid (ESG), a 5 (0 = *not at all*, 4 = *extremely positive*) x 5 (0 = *not at all* to 4 = *extremely negative*) matrix (Larsen et al., 2009), with positive valence reflected on the horizontal axis and negative valence on the vertical axis. Participants were instructed to move the mouse to one of the 25 cells in the 5 x 5 matrix to indicate the intensity of their positive and negative feelings. The positivity offset was calculated as the difference between the mean positive ratings and mean negative ratings of neutral images. Negativity bias was calculated as the difference in the mean negative ratings of very unpleasant images minus the positive ratings of very pleasant images (Norris et al., 2011). Analyses of temporal stability in our sample showed that negativity bias was significant in the depressed (r =.43, p< 0.05), but not in the healthy group (r = .35, *ns*). Positivity offset was significant for depressed (r = .58, p < 0.05) and healthy groups (r = .63, p < 0.05).[3]

Procedure

Participants were recruited from the same community locations via advertisements and the

[3] Chi-square and t-test analyses were conducted to examine the extent to which there were significant group differences on demographic, clinical, and affective response bias data between the treatment completers and non-completers. The results revealed no significant group differences on demographic and symptom severity characteristics. In addition, ANOVAs comparing affective response bias indicated no group differences in pre-treatment negativity bias between depressed participants who completed treatment from those depressed participants who dropped out, $F(1, 40)= 1.96$, $p > 0.05$. Also, there were no group differences in negativity bias between healthy participants who completed the 16 week assessment from those who dropped out before Week 16, $F(1, 35) = 1.31$, $p > 0.05$. Similarly, there were no group differences in positivity offset between depressed completers and non-completers, $F(1, 40) = 0.44$, $p > 0.05$, and healthy completers and non-completers, $F(1; 35)= 0.00$, $p > 0.05$.

internet. Participants were screened by phone to ensure eligibility, and then invited to the laboratory for two assessments separated by one week. During the first assessment, participants provided informed consent, passed a toxicology urine screen, and completed the clinical interview and self-report questionnaires. During the second assessment, participants were asked to sign another consent form, take a second toxicology urine screen, and undergo a 25 minute psychophysiology assessment (Gollan et al., 2014). Thereafter, depressed participants were scheduled for their first of 16 treatment sessions to start the following week, and healthy participants were evaluated prospectively for 16 weeks. Participants returned at Week 8 and 16 to complete the assessment battery again. In addition, participants completed the *Inventory of Depressive Symptomatology – Self-Rated* (IDS-SR; Rush et al., 1986, 2003) before each treatment session. At the end of the project, all patients were compensated and debriefed.

Analytic Plan

The primary outcome variable was the participant's change of the weekly IDS-SR scores over the course of treatment. We conducted tests of pre-treatment differences of demographic and clinical characteristics using Analysis of Variance (ANOVA) for continuous variables and Chi-square tests of independence for categorical variables. In the presence of small or empty cells in the tests of categorical variables, the Chi-square test was replaced by Fisher's exact test. Percentages were used to describe response and remission status at post-treatment.

The first analysis used an ANOVA to test group difference between negativity bias and positivity offset at pre-treatment. Analyses were 2-tailed at the .05 level of significance. The second analysis used Multilevel Linear Modeling (MLM) analyses (SPSS 20.0; Snijders & Baker, 1999; Tabachnick & Fidell, 2000; Singer & Willett, 2003) to investigate treatment response for the intent-to-treat sample (Raudenbush & Bryk, 2002). MLM is a method for

examining longitudinal treatment data that involves weekly assessment of clinical status, in this case, up to 16 (repeated) observations of depressive symptoms (IDS-SR) nested within each of the participants with two levels. Level 1 (within-subject) shows how the outcome varies within participants over time as a function of the person-specific growth curve. Level 2 (between-subjects) shows how the person-specific change parameters are observed as varying randomly across participants related to their treatment. The person-specific parameters correspond to a random intercept and random slope per subject. The rate of change in clinical severity, positivity offset, and negativity bias were entered as Level 1 within-subject variables.

Change was represented by slope of the regression lines for observed positivity offset and negativity bias for each participant, with pre-treatment (baseline) measurement. Positive slope indicated an increase of positivity offset and negativity bias, while a negative slope reflected a decrease in positivity offset and negativity bias. The variation of slopes among participants for each variable were calculated and tested for significance with .05. If significant, the second level of analysis, focused on predictors of the variation, was conducted. Slopes were regressed on the predictor variable, using treatment outcome to assess whether the relationship between outcome and the slopes were significant.

Results

Demographic and Clinical Characteristics

We enrolled 77 participants, of whom 40.3% (n = 31) were male, 7.8% (n = 6) were Hispanic, 54.5% (n = 42) were Caucasian, 52% (n = 40) were university or graduate school educated, 67.5% (n = 52) were employed or a full-time student, 71.4% (n = 55) were married. Chi-square analyses showed the depressed group was more likely to be Hispanic [9.8% vs. 5.6%]

and showed a trend towards greater unemployment [36.6% vs. 16.7%]. No other demographic variables varied as a function of diagnostic group (all p > .25). See Gollan et al., 2015 for more detailed demographic information. Table 1 presents the clinical characteristics by group (depressed and healthy controls) across the pre-, mid- and post-treatment assessments and the *F* tests to examine group differences. As expected, significant differences on pre-treatment depression severity were evident.

Treatment completers (*n* = 28) and partial completers (*n* = 4) attended on average 13.43 (*SD* = 1.68), or 84%, of the 16 available sessions. Treatment noncompleters (*n* = 9) attended an average of 2.54 (*SD* = 2.21) sessions.

Results on response rates indicated that for the intent to treatment sample (n = 41), only 11 (26.8%) participants remitted, another six (14.6%) participants responded, 17 (41.5%) showed no response or remission, and seven (17.1%) participants had missing data (i.e., did not complete the post-treatment assessment). Among completers (n = 28), 10 (35.7%) remitted, five (17.9%) responded, 13 (46.4%) showed no response or remission.

Table 2 summarizes the predictor characteristics at pre-, mid- and post-treatment with the total sample. To assess the extent to which negativity bias might normalize among treatment completers and partial completers to be comparable to healthy participants, results from an analysis of variance showed no significant group difference for either negativity bias at the 16 week assessment, $F(1, 57) = .703$, $p = .41$, or for positivity offset at the 16 week assessment, $F(1, 57) = .083$, $p = .77$.

INSERT TABLES 1 AND 2 HERE

Multilevel Linear Modeling

A two-level hierarchical model assessed the effects of negativity bias and positivity offset at pre-treatment on the rate of depression severity (IDS-SR) over 16 weeks of treatment (time). First level units were 'weeks in BA treatment', with participants limited to those who attended five or more therapy sessions, resulting in a total of 421 treatment weeks for analysis. Second-level units were the 'subjects entering treatment' (n = 41). Multilevel modeling was implemented using SPSS MIXED MODELS, Version 20.

A linear transformation of treatment time was used based on the linear progression of treatment improvement exhibited in the data (plot representing a straight line representing the inverse relationship between weeks of treatment and depression scores). The l*n* time transformation is linear base zero of weeks in treatment + 1. This transformation makes l*n* treatment = 0 refer to the pre-treatment time point, and 1 l*n* treatment unit beyond baseline corresponds to week one of treatment. Thus, the transformation yields intercept effects (referring to pre-treatment status), and "treatment" effects (i.e., interaction effects of negativity bias and positivity predictors with l*n*-treatment or time) referring to the rate or amount of change over each one week of treatment. The l*n*-treatment variable was treated as a random effect in our model, reflecting individual differences in the association between treatment and depression symptom severity. The intercept was also a random component reflecting individual differences in pre-treatment status. All predictors were standardized using z scores. Notably, depression severity was uncorrelated with negativity bias and positivity offset; and, negativity bias and positivity offset were inversely correlated (r = -.539, p < .01), posing no threat to MLM analyses.

Our first step was to model the effect of treatment, estimating an intercept value for all depressed participants of 36.09 on the IDS-SR, SE = 1.87, t(36.9) = 19.32, p < .001. The linear

change at pretreatment was estimated to be 0.40 point reduction on the IDS-SR per treatment week, SE = .76, t(31.18) = -8.38, p < .001, contributing a 6.38 point decrease in self-reported depression from pre- to post-treatment.

Our next step was to estimate the effect of depressive symptom severity at Week 1 (IDS-SR). Holding the effect of treatment constant, depression severity predicted rate of linear change, contributing an 8.28 point decrease in IDS-SR scores from pre-treatment/intercept to post-treatment, SE = 1.19, t(31.56) = 6.91, p < .001. However, the interaction term between treatment over time and depressive symptom severity was not significant, suggesting no effect of baseline depression severity over time, SE = 0.68, t(29.24) = -1.54, p = 0.13. The interaction effect from this result does not provide information on slopes for depression severity as a predictor of depressive symptoms at the end of treatment. Based on the finding of non-significant interaction effect, depressive severity was excluded from subsequent models.

The third step was to estimate the effect of negativity bias as a predictor. Holding the effect of treatment constant, the model showed that for every unit increase in negativity bias at pretreatment, there was an attenuated decrease of IDS-SR per week, SE = 2.01, t(37) = 1.76, p = .08, contributing a 3.6 point change in IDS-SR scores across treatment. As predicted, there was a significant interaction effect between treatment and negativity bias (SE = 0.75, t(31) =- 3.43, p = .002), indicating a change of 2.58 in depression scores when examining the interaction between negativity bias and BA treatment. The fourth step was to estimate the effect of positivity offset as a predictor. Results were not significant when examining the effect of positivity offset, SE = 1.84, t(35) = -0.75, p = .45, and interaction between BA treatment and positivity offset was not significant, SE = 0.74, t(30) = 1.49, p = .14. Table 3 summarizes the results of the proposed

multilevel linear models. [4,5] Finally, we conducted a post hoc analysis comparing participants in the highest quartile of negativity bias at pretreatment (75th percentile) with the remaining sample: The highest quartile showed a 20 point decrease in depression scores (See Figure 2).

INSERT TABLE 3 AND FIGURE 2 ABOUT HERE

Discussion

Considering that unipolar depression is a chronic disease with significant disability, BA treatment can favorably alter depressive illness for a subset of patients. In our study, 54% of the sample with an adequate dose of BA responded with a fifty percent reduction of depression and or experienced remission. These depression response rates are less than other large studies testing BA with unipolar depression, including one of the largest trials of BA, which reported a 60% response rate for participants who were classified as "very severe" (Dimidjian et al., 2006). A large group of participants remained symptomatic at study completion, suggesting that (a) the current version of BA was not sufficient to alter the depressogenic context or the participant's interaction with their environment or (b) the provision of the relatively short course of BA for moderately ill patients needed to be extended to facilitate patient recovery, if indeed BA could ultimately modify depressive symptoms. Further, as most of our patients were classified as

[4] As the negativity bias reflects a difference score of unidimensional ratings of positive and negative information, we evaluated the separate effects of valence on symptom reduction. Results showed that the mean negative ratings of very unpleasant images did not change significantly from pre- to post-treatment, respectively (M = -2.17, SD = .73; M = -2.05, SD = .87) and positive ratings of pleasant images did not change from pre- to post-treatment (M = 1.61, SD = .70, M = 1.65, SD = .86). This suggests that neither component measure independently predicted treatment response, and that the asymmetrical responses (i.e., the negativity bias) predicted rate of response.

[5] We ran post-hoc regression analyses to examine whether depressive symptoms, negativity bias, and positivity offset at pre-treatment predicted depressive symptoms at post-treatment. Regression analyses showed that predictors did not significantly predict depressive symptoms at post-treatment: R^2 = 0.09, R^2 Change = 0.09, F Change (3, 30) = 1.09, p = 0.36.

moderately depressed, our results suggest that baseline disease characteristics, like clinical severity, did not inform clinicians about the variability of response.

A more promising aspect of this study was that the strength of asymmetry of evaluative responding did expand our understanding about the rate of response to BA. Specifically, a stronger negativity bias predicted a faster rate of response. This finding is consistent with the observation that higher reactivity to intense negative affective imagery has predicted response to BA treatment (Dichter et al., 2009). The rate of response may be due to the patient's ability to identify negative relative to positive information and use adaptive, goal-directed responses (Mayberg et al., 1997; Pizzagalli et al., 2001). Stronger affective evaluations of negative relative to positive stimuli may evoke a 'mode of response' or a 'signal' that heightens attention, cognition, and behavioral resources to defend against the negative context. BA patients may use their strategies to modify the negative context, thereby recovering more quickly. Finally, replication is needed to confirm our results of group differences between treatment completers and healthy completers on affective response bias to explore the effect that BA has on normalizing response biases.

Our findings may help clinicians to teach patients that (a) their response to BA may be explained by the way they process information, and (b) they may use their affective responding to negative information as a 'cue' to approach the aversive context. Finally, negativity bias might be added to the dashboard of predictors towards the goal of identifying a 'responder endophenotype'.

There are several limitations including the attrition over the course of treatment and the smaller sample size, which may account for the lack of an effect for positivity offset and potential instability of effects (Leon, David, Kraemer, 2011). Additionally, there were no

measures that would permit a test the magnitude of change of reinforcement value as a result of BA (Manos, Kanter, & Busch, 2010), which we would recommend in order to identify mechanisms of action. Finally, the study enrolled adults who were medication-free, which may limit the generalizability of these results to those individuals who rely on pharmacotherapy and somatic therapies. There are strengths of the study, however, including a greater internal validity by using a medication-free sample whose task performance was unlikely to be hindered by medication and health disorders (Erickson, Drevets, Clark, Connon, Bain, et al., 2005; Harmer et al., 2008), the use of stimuli of natural scenes that varied across intensity and scenarios (Sabatinelli, Fortune, Qinglyang, Siddiqui, Krafft, et al., 2011), and our test of a well-developed model of emotion that has a task that measures concurrent evaluation of pleasant and unpleasant stimuli.

BA has been shown to be efficacious as a psychological treatment for MDD when individuals engage in treatment (Jacobson et al., 2006; Dimidjian et al., 2006), though the rates of attrition and nonresponse highlight the need for additional investigation of improving patient participation. Though the results from this open trial suggest that pre-treatment negativity bias may differentially predict the rate of response, there is a need for a future large randomized clinical trial (versus an open trial) to evaluate the predictive validity of negativity bias and positivity offset using a control group and, further, combining BA with pharmacotherapy and novel therapies (TMS) to increase the effects of BA. Moreover, there is the need to characterize the role of negativity bias and positivity offset in subpopulations that have been excluded from prior trials, including women who are pregnant or who use substances, bipolar spectrum illnesses, and post-traumatic disorder. Finally, these findings more generally highlight the

importance of using affective science to identify endophenotypes of response and nonresponse to BA.

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Table 1

Clinical Characteristics at Pre-, Mid- and Post-Treatment

	MDD (n = 41)		HV (n = 36)				
Measure	*M*	SD	*M*	SD	F(df)	*p*	*N2*
IDS-C							
Baseline	33.83	7.63	2.19	2.57	F (1, 75) = 562.58	$p < .01$	.88
8 weeks	20.97	11.06	2.83	3.36	F (1, 66) = 85.88	$p < .01$	.57
16 weeks	14.05	10.11	2.18	2.76	F (1, 66) = 43.70	$p < .01$	.40
IDS-SR							
Baseline	33.93	9.06	3.11	2.94	F (1, 75) = 380.88	$p < .01$	.84
8 weeks	23.73	11.20	3.80	4.57	F (1,66) = 94.63	$p < .01$	.59
16 weeks	16.88	13.37	2.97	4.58	F (1, 66) = 32.93	$p < .01$	.33

Note: IDS-C = Inventory of Depressive Symptomatology, Clinician Rated; IDS-SR = Inventory of Depressive Symptomatology, Self-Rated.

Table 2

Predictor Characteristics at Pre-, Mid-, and Post-Treatment

	MDD (n = 41)[a]		HV (n = 36)[b]			
Measure	*M*	SD	*M*	SD	*F*(*df*)	*p*
NB						
Baseline	.45	.45	.18	.55	F (1, 75) = 5.42	$p < .01$
8 weeks	.40	.50	.18	.71		
16 weeks	.38	.57	.19	.75		
PO						
Baseline	.30	.41	.61	.55	F (1, 75) = 7.69	$p < .01$
8 weeks	.31	.40	.46	.44		
16 weeks	.34	.38	.40	.40		

Note: NB = Negativity Bias; PO = Positivity Offset.

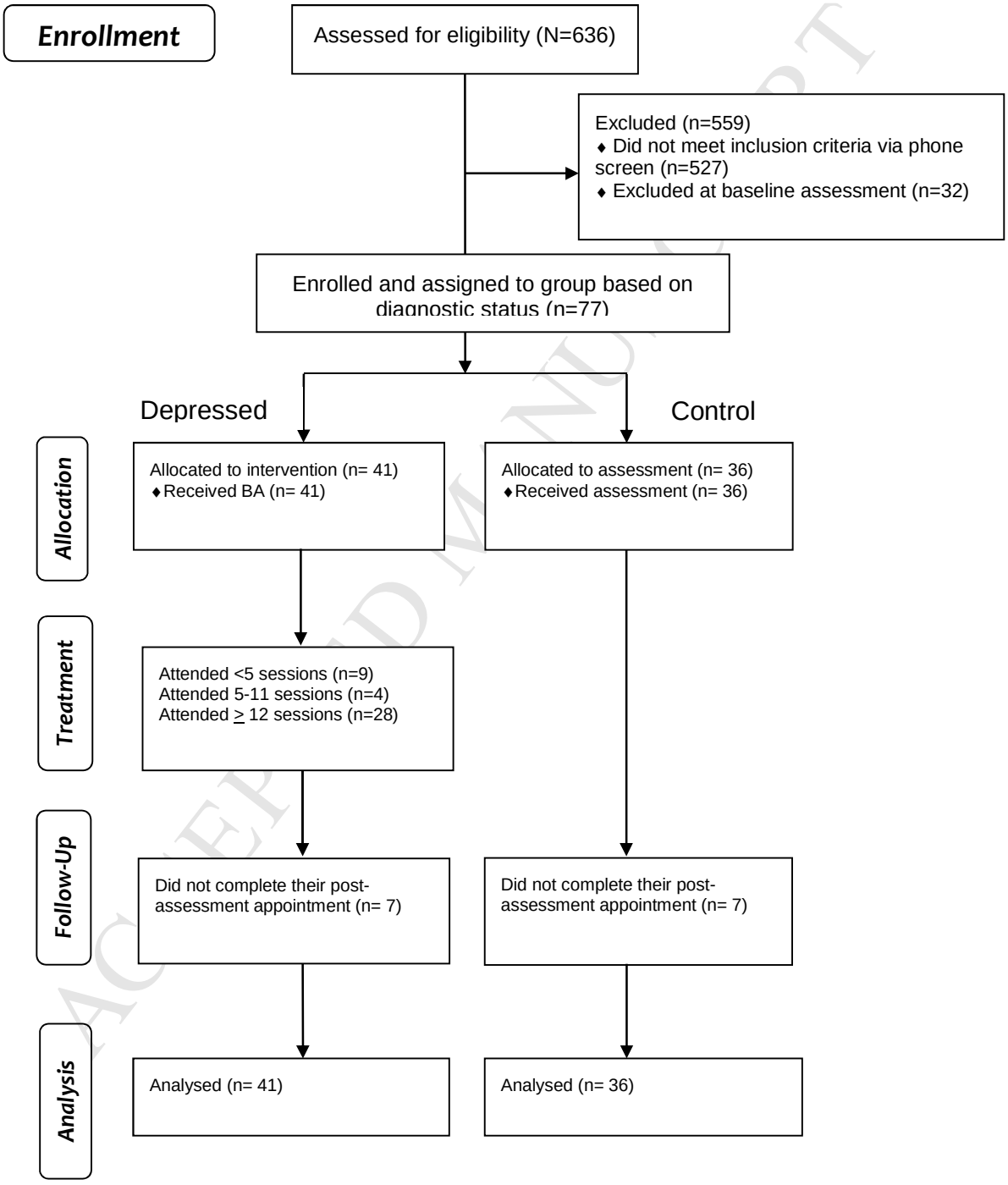
Table 3

Models With Clinical and Affective Reactivity Variables to Predict Rate of Response

Predictor	*Estimate*	*SE*	*t(df)*	*P*
Intercept	36.09	1.87	19.32 (36)	.000
Treatment	-6.38	0.76	-8.38 (31)	.000
Depression Severity	8.28	1.19	6.9 (31)	.000
Treatment * Depression Severity	-1.06	0.68	-1.54 (29)	.132
Negativity Bias	3.55	2.01	-1.76 (37)	.086
Treatment * Negativity Bias	-2.58	0.75	-3.43 (31)	.002
Positivity Offset	-1.39	1.84	-.75 (35)	.454
Treatment * Positivity Offset	1.11	0.74	1.49 (30)	.144

Estimate values represent unstandardized beta coefficients predicting IDS-SR scores from Weeks 0-16. Negative values represent reductions in IDS-SR scores from Weeks 0-16.

1


Enrollment
Assessed for eligibility (N=636)
Excluded (n=559)
♦ Did not meet inclusion criteria via phone screen (n=527)
♦ Excluded at baseline assessment (n=32)
Enrolled and assigned to group based on diagnostic status (n=77)
Depressed
Control
Allocation
Allocated to intervention (n= 41)
♦Received BA (n= 41)
Allocated to assessment (n= 36)
♦Received assessment (n= 36)
Treatment
Attended <5 sessions (n=9)
Attended 5-11 sessions (n=4)
Attended ≥ 12 sessions (n=28)
Follow-Up
Did not complete their post-assessment appointment (n= 7)
Did not complete their post-assessment appointment (n= 7)
Analysis
Analysed (n= 41)
Analysed (n= 36)

Legend.

Low = Participant scores reflected below 75% on negativity bias score at pre-treatment.

High = Participants scores reflected 75% or higher on negativity bias score at pre-treatment.

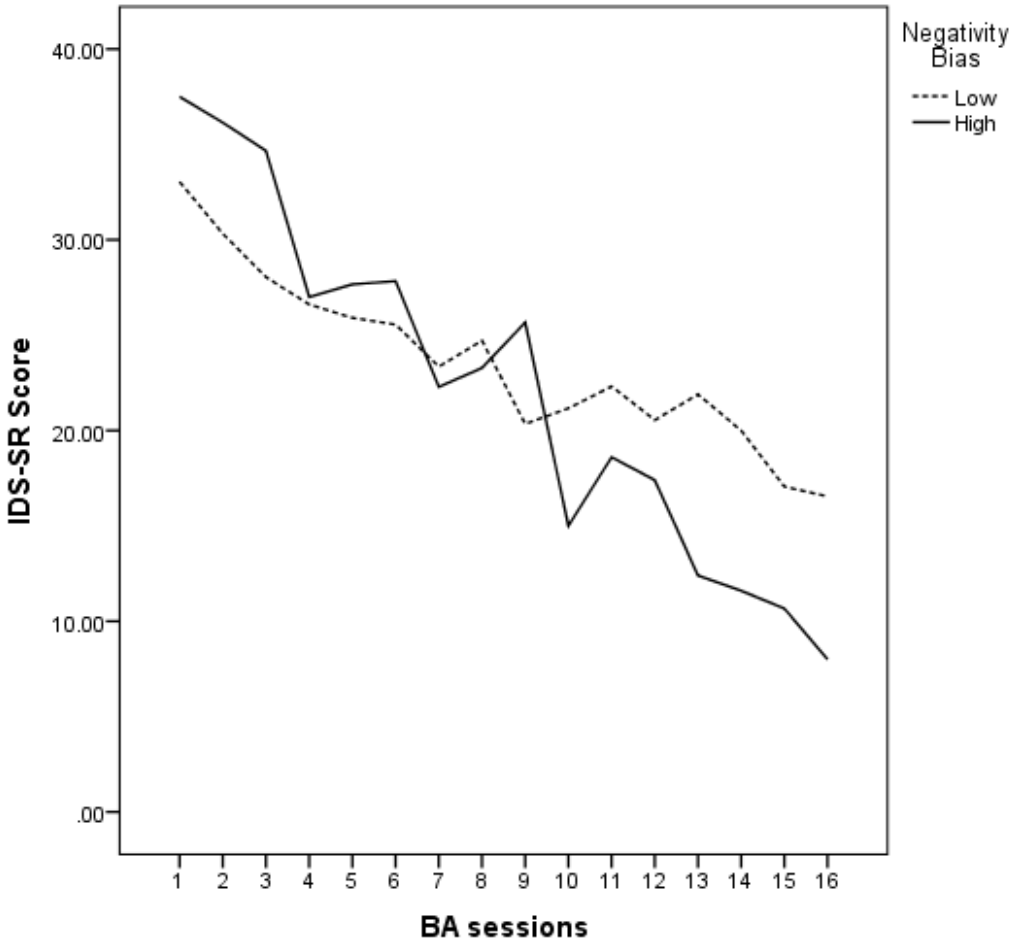


Figure Caption

Figure 1. Enrollment Chart

Figure 2. Faster rate of response among participants whose negativity bias score was in the top quartile (High) compared with the rest of the sample (Low).

Highlights

1. This study investigated the extent to which affective responses to unpleasant and pleasant stimuli at pre-treatment predicted rate of response to Behavioral Activation treatment for depression.
2. Negativity bias at pre-treatment predicted rate of response. Specifically, depressed participants with a stronger relative to weaker negativity bias at pre-treatment showed a significantly faster rate of response to treatment.
3. Pretreatment negativity bias may serve as a signal for patients to engage and benefit from BA strategies.