**SUPPLEMENTARY MATERIAL**

**SUPPLEMENTAL METHODS AND ANALYSES**

**Study Design**

The present study combined data collected as part of two larger clinical trials focused on identifying whether neuroimaging and behavioral indices related to approach-avoidance behavior were predictive of treatment response in (1) a non-randomized, unblinded clinical trial in which all enrolled participants had clinically-significant depression and completed BA therapy (registered at the US National Institutes of Health; ClinicalTrials.gov: #NCT02602340) and (2) a randomized, parallel-group, unblinded clinical trial in which enrolled participants had clinically-significant generalized anxiety disorder symptoms and were randomized to complete either BA or exposure-based therapy (Santiago et al., 2020) (ClinicalTrials.gov: # NCT02807480). From the latter study, we only included individuals in the present analysis if they reported elevated depression symptoms as determined by the first study (Patient Health Questionnaire-9 [PHQ-9] scores > 9) and if they were randomized to complete BA. Both studies were ongoing at the time in which blood samples were processed for the purposes of the present study and thus only focused on individuals who had enrolled in the study as of 02/02/2018. Other than symptom severity requirements relating to GAD and depression, the inclusion/exclusion criteria and assessment measures were identical across studies. All participants completed baseline clinical, behavioral, and neurobiological assessments followed by 10 weeks of group-based BA therapy, and then repeated clinical, behavioral, and neurobiological assessments. The CONSORT diagram for each study (figure 1) shows participants approached/enrolled as of 02/02/2018, with added information concerning the number who completed the blood draw and reasons for not completing the blood draw. Notably, participants were contacted about this study if they were identified as potentially meeting study criteria from an institute-wide screening database. This screening study recruited participants from recruited through community advertisement (e.g., Facebook, radio advertisements) and referral from partnering clinical institutions (e.g., Laureate Psychiatric Clinic and Hospitals; Family and Children’s Services). On the CONSORT diagram, the number “approached” refers to the number of participants contacted who had already completed the LIBR Screening study and were identified as potentially eligible.

**Intervention**

Due to the non-randomized nature of the study, and the nature of the intervention (as a behavioral intervention), participants and clinicians were not blinded to treatment condition. Each BA group intervention was delivered by two co-therapists, each a licensed doctoral- or master’s-level clinician or a therapist-in-training (i.e., clinical psychology postdoctoral fellow or graduate student). Each therapist completed an in-person or online workshop on BA led by CM (e.g., Centre for Research on Eating Disorders at Oxford, <https://credo-oxford.com>), read articles and manuals related to BA (S. Dimidjian et al., 2006; Martell, Dimidjian, & Herman-Dunn, 2010) and watched videos of previous therapy sessions. Each therapy session was video and audio recorded, and weekly consultation and supervision were provided by RLA and CM. Group sessions were usually conducted in the evening (e.g., after 5pm) to reduce conflicts with work or other responsibilities. Participants were sent text or voicemail reminders prior to each session. If a subject did not attend a group session, a therapist contacted the subject via phone to check in briefly and summarize the content of the session and assigned homework. Participants who did not attend sessions were sent a link via email to complete their weekly surveys. Treatment could be discontinued for a participant due to participant request, or if they missed more than two of the ten group therapy sessions. A structured, group-based BA manual was developed by co-authors RLA and CM (with edits and revisions provided by AC), informed by previously published BA treatment guides (Martell et al., 2010). The content of each session is summarized in Supplementary Table 1. Fidelity ratings were provided for 34% of the sessions (24 of the 70 sessions conducted across 7 groups) by an independent expert (Dr. Ruth Hermann Dunn), using the Quality of Behavioral Activation Scale (Q-BAS; (Sona Dimidjian et al., 2017). The Q-BAS consists of fourteen items, each rated using a 7-point Likert-type scale (higher scores reflect higher quality; 3 = satisfactory). Average fidelity ratings across items and groups (M = 3.92, SD = 0.28) exceeded the “satisfactory” threshold and meets or exceeds what has been reported for the Q-BAS in previous work using the Q-BAS (Sona Dimidjian et al., 2017).

**Supplementary Table 1. Primary goals for of each session involved in behavioral activation therapy.**

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| Session | Behavioral Activation Content |
|  Pre | Brief pre-group individual check-in session: provide a summary of the format and focus of Behavioral Activation. |
| 1 | Session Content: Provide a brief overview of anxiety and depression and the rationale behavioral activation. Homework: Initiate self-monitoring.  |
| 2 | Session content: Homework review, introduce concept of working from the “outside in” and discuss values as a way of identifying potential behaviors that may improve mood.Homework: Continue self-monitoring, complete values worksheet. |
| 3 | Session content: Homework review, discuss goal-dependent versus mood-dependent behavior and “acting as if”, discuss initial activity scheduling.Homework: Continue self-monitoring, engage in planned value/goal- driven activities. |
| 4 | Session content: Homework review, introduce concept of function versus form and the tracking of antecedent, behavior, and consequences (ABC) to examine function of behavior.Homework: Continue self-monitoring, use “ABC” sheets to examine function of behaviors, engage in planned value/goal- driven activities. |
| 5 | Session content: Homework review, introduce concept of avoidance as it relates to mood, values, and value/goal-motivated behaviors. Homework: Continue self-monitoring, use “ABC” or “TRAP/TRAC” worksheets to examine function of avoidance behavior, engage in planned value/goal- driven activities. |
| 6 | Session content: Homework review, discuss how to integrate behavioral activation into their lives using “ACTION”. Homework: Continue self-monitoring, use “ABC” or “TRAP/TRAC” worksheets to examine function of behavior, engage in planned value/goal- driven activities |
| 7 | Session content: Homework review, discuss strategies to reduce the behavior of rumination, including “cueing action” and “attending to experiences”.Homework: Continue self-monitoring, use “ABC” or “TRAP/TRAC” worksheets to examine function of behavior, engage in planned value/goal- driven activities including those targeting rumination. |
| 8 | Session content: Homework review, discuss using behavioral activation to build the meaningful life that you want. Homework: Continue self-monitoring, use “ABC” or “TRAP/TRAC” worksheets to examine function of behavior, engage in planned value/goal- driven activities. |
| 9 | Session content: Homework review, discuss troubleshooting techniques to counteract activation barriers.Homework: Continue self-monitoring, use “ABC” or “TRAP/TRAC” worksheets to examine function of behavior, engage in planned value/goal- driven activities. |
| 10 | Session content: Homework review, reflect upon and review previously learned techniques, discuss relapse prevention strategies.Homework: Continue to engage in self-monitoring as needed, engage in value/goal- driven activities planned for the next 2-3 weeks and ongoing. |
|  Post | Brief post-group individual wrap-up session: Discuss observed trajectory of self-reported behaviors and symptoms through treatment, discuss treatment referrals as needed. |

Abbreviations: ABC = Antecedent, Behavior, and Consequence; TRAP = Trigger, Response, Avoidance Pattern; TRAC = Trigger, Response, Alternative Coping; ACTION = Assess behavior/mood, Choose alternate responses, Try out alternate responses, Integrate these alternatives, Observe results, Now evaluate.

**Supplementary Figure Legends**

**Figure S1.** Simplified representation of the kynurenine pathway (KP). Inflammatory mediators increase the breakdown of tryptophan into kynurenine via the enzyme, indoleamine de-oxygenase (IDO). Inflammation also drives metabolism of kynurenine down the quinolinic acid (QA) pathway, ultimately resulting in the formation of NAD+, an energy source for cells. QA is an NMDA receptor agonist that can have neurotoxic effects at high-enough concentrations. Alternatively, kynurenine can be broken down by the kynurenine acetyltransferase enzymes (KATs 1-3) into kynurenic acid (KynA), an NMDA receptor antagonist that may be neuroprotective in the context of an inflammatory environment.

**Figure S2.** Plots showing the magnitude and direction of the inter-correlations between the KP metabolites, cytokines, and clinical rating scales. The blue color indicates a positive correlation coefficient and the red color, a negative correlations coefficient.

**References**

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