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Changes in Positive and Negative Affect During Pharmacological Treatment and Cognitive Therapy for Major Depressive Disorder: A Secondary Analysis of Two Randomized Controlled Trials

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Abstract

The cardinal symptoms of major depressive disorder (MDD) are heightened depressed mood (negative affectivity, or NA) and diminished interest or pleasure (positive affectivity, or PA). It is unknown how well treatments for MDD repair either symptom. Two secondary analyses of randomized controlled trials were therefore conducted. In Study 1, 180 adult outpatients with MDD received 16 weeks of antidepressant medication (ADM; $n = 120$) or cognitive therapy (CT; $n = 60$). In Study 2, adult outpatients with MDD were treated until remission with ADM ($n = 225$) or ADM and CT ($n = 227$). Across trials and treatments, intake disturbances were more marked in PA than NA, there was smaller repair of PA than NA during treatment, and disturbances remained more pronounced for PA than NA after treatment. Greater change in PA and NA were independently associated with depression symptom change. These findings suggest that depression treatments more effectively repair NA than PA and that outcomes may be improved with more effective targeting of the latter.

Keywords

depression, emotion, evidence-based treatments

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Major depressive disorder (MDD) is a functionally debilitating and chronically recurrent condition that leads to substantial societal and economic costs (Kessler et al., 2003; Üstün, Ayuso-Mateos, Chatterji, Mathers, & Murray, 2004). Current pharmacological and psychological treatments are partly but not fully effective at treating MDD. At best, only two thirds of patients respond (show at least a 50% drop in symptoms), and only about a third remit (show a complete normalization of symptoms; Cuijpers et al., 2014; Rush, Kraemer, et al., 2006). Functional impairment often lags behind symptomatic improvements (Rush, 2015; Sheehan et al., 2011; Sheehan, Nakagome, Asami, Pappadopulos, & Boucher, 2017). Of those who no longer meet diagnostic criteria for MDD at the end of treatment, over half will relapse within 2 years even if continued on maintenance antidepressant medication (Anderson et al., 2008; Cuijpers, van Straten, Andersson, & van Oppen, 2008; Rush, Trivedi, et al., 2006; Vittengl, Clark, Dunn, & Jarrett, 2007). There is a pressing need to enhance treatment outcomes.

One way forward is to view MDD as a heterogeneous diagnostic construct and consider it in terms of distinct underlying functional domains that may require different intervention strategies (see Research Domains Criteria,

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or RDoC, approach; Insel et al., 2010). Likewise, proponents of network analysis accounts would argue that it is beneficial to view the depressed state as an emergent property of patterns of interrelationships among specific symptoms that become self-reinforcing (Borsboom, 2017; Fried et al., 2017; Hofmann, Curtiss, & McNally, 2016). Systematically targeting central nodes in the network may optimize depression treatment outcomes. Different nodes may need different intervention approaches.

An MDD diagnosis requires either a pervasive depressive mood (distress) or a loss of pleasure and interest in all or most activities (anhedonia). These symptoms result from disruptions to two underlying and partly dissociable neurobiological dimensions: up-regulation of a negative valence system that promotes withdrawal from punishing stimuli and drives negative affect (NA) and down-regulation of a positive valence system that guides approach to rewarding stimuli and shapes positive affect (PA; Gray, 1987; Paulus et al., 2017; Watson, Wiese, Vaidya, & Tellegen, 1999). This framework reflects the distinction drawn between the positive and negative valence systems in the RDoC approach (Insel et al., 2010).

Client definitions of recovery from depression emphasize the importance of repairing PA as well as NA disturbances (Demyttenaere et al., 2015; Zimmerman et al., 2006) to allow clients to function to the best of their ability in valued life domains (Slade, 2010). Network analyses consistently identify depressed mood (increased NA) and anhedonia (reduced PA) as central nodes in the networks maintaining a major depressive episode (Fried, Epskamp, Nesse, Tuerlinckx, & Borsboom, 2016; van Borkulo et al., 2015). These depressed mood and anhedonic symptoms (along with low energy and fatigue) are the strongest concurrent predictors of functional impairment in depression (Fried & Nesse, 2014). Both PA and NA disturbances predict a suboptimal treatment response and a poor future depression prognosis (McMakin et al., 2012; Spijker, Bijl, De Graaf, & Nolen, 2001; Uher et al., 2012).

The above analysis suggests that to effectively treat depression, improve functioning, and lead to sustained long-term recovery, treatments should simultaneously target both PA and NA disturbances. However, it has been proposed that existing depression psychological and pharmacological treatments place a greater emphasis on lowering NA than increasing PA (Dunn, 2012, 2019; Dunn & Roberts, 2016; Treadway & Zald, 2011). The failure to target PA deficits may contribute to suboptimal treatment outcomes.

This argument is based on a conceptual analysis of what the interventions target. Mainstream pharmacological treatments for depression predominantly target neurotransmitters linked to NA—for example, selective serotonin-reuptake inhibitors (SSRIs), selective noradrenaline-reuptake inhibitors (SNRIs), and tricyclic antidepressants (TCAs)—rather than neurotransmitters linked to PA (e.g., dopamine and opioids; see Argyropoulos & Nutt, 2013; Dunlop & Nemeroff, 2007; Shelton & Tomarken, 2001; Tomarken, Shelton, & Hollon, 2007). Likewise, mainstream psychological therapies focus on NA and neglect PA. For example, in cognitive therapy (CT; A. T. Beck, Rush, Shaw, & Emery, 1979), there is an initial emphasis on graded scheduling of positive activities to build a sense of mastery and pleasure. However, what is absent is a detailed theoretical model outlining the psychological mechanisms that drive reduced pleasure when engaging in positive activities and instructions about how to target these mechanisms in therapy (Dunn, 2019; Dunn & Roberts, 2016). Subsequent sessions predominantly focus on identifying and challenging negative thoughts and beliefs that maintain a negative view of the self, world, and future (the negative triad) and drive heightened NA, with little explicit focus on PA. CT represents one of a number of evidence-based therapies for depression (including emerging third-wave cognitive treatments), all of which show equivalently suboptimal treatment outcomes (Cuijpers et al., 2013; Hunot et al., 2013) and focus on NA to a greater extent than PA. However, conceptual analyses of this kind are subjective, and empirical evaluation is required.

As far as we are aware, there are few if any researchers who have empirically examined how well current treatments repair PA relative to NA. In three observational studies of treatment-seeking samples, greater changes in NA (relative to PA) over time have been reported (Brown, 2007; Kring, Persons, & Thomas, 2007; Naragon-Gainey, Gallagher, & Brown, 2013). Interpretation of these findings is hindered by the heterogeneity of treatments offered, absence of randomized comparison conditions, lack of treatment fidelity assessment, and use of indices of positive and negative temperament that combine data from both affect and personality measures.

A recent systematic review and meta-analysis examined the extent to which psychotherapeutic interventions repair PA versus NA (Boumparis, Karyotaki, Kleiboer, Hofmann, & Cuijpers, 2016). The mean (Hedges's *g*) effect size across the 10 randomized controlled trials identified was 0.41 for PA (95% confidence interval, or CI = [0.16, 0.66]) and 0.46 for NA (95% CI = [0.10, 0.59]; Boumparis et al., 2016), both small to medium effect sizes according to rules of thumb (Cohen, 1988). Taken at face value, this finding suggests that existing treatments are equally (partially) effective at repairing PA and NA. However, inspection of the studies included in this meta-analysis indicates that this conclusion is premature because of issues of study quality and scope.

Of the trials included, none delivered an adequate dose of a mainstream, evidence-based therapy to a diagnosed depressed population and evaluated outcomes using a well-validated and clearly described measure of PA and NA (see Table S1 in the Supplemental Material available online). Moreover, this meta-analysis focused solely on psychotherapeutic interventions and did not consider pharmacological treatments.

A parallel literature has examined the extent to which interventions alter extraversion and neuroticism. Given that there is some overlap of PA with extraversion and NA with neuroticism, these findings may indirectly cast light on how well existing treatments repair PA versus NA. Across presenting problems and treatments, there is consistently greater repair of neuroticism than extraversion (see meta-analysis by Roberts et al., 2017), perhaps suggesting treatments repair NA better than PA. However, whether this pattern of findings held in MDD specifically was not assessed in this meta-analysis. This is problematic because PA disturbances are relatively unique to depression (Watson & Naragon-Gainey, 2014) and a different pattern of PA change may be found in depression relative to other conditions as a result. Although personality has some overlap with affect, there are important conceptual differences. Positive emotionality makes up only one component of extraversion (alongside experience seeking and sociability). These facets are only weakly correlated and show distinct (and sometimes diametrically opposed relationships) with psychopathology (Watson, Stasik, Ellickson-Larew, & Stanton, 2015). Likewise, neuroticism consists of multiple facets, not all of which directly overlap with NA and which can have distinct relationships with psychopathology (Schimmack, Oishi, Furr, & Funder, 2004). If different facets have different criterion validities, they can cancel each other out when combined into domain level scores (Paunonen, 2003). Therefore, it is potentially misleading to use global extraversion and neuroticism scores as a proxy for PA and NA, respectively.

Overall, this means it is premature to conclude that mainstream depression treatments are better able to repair NA than PA, and further examination of this topic is required. To gain traction on this issue, we conducted secondary analyses of existing trials that have collected but have yet not published PA and NA outcomes. In Study 1, we analyzed self-reported changes in PA and NA from a previously published randomized control trial (RCT) of treatment for outpatients with moderate to severe MDD in which ADM and CT were each superior to pill-placebo and not different from one another in reducing depression symptoms (cognitive pharmacotherapy 2, or CPT2, trial; DeRubeis et al., 2005). In Study 2, we analyzed self-reported change in PA and NA in a previously published RCT for outpatients with chronic or recurrent depression in which combined (ADM + CT) treatment was superior to ADM alone in treating depression to remission (CPT3 trial; Hollon et al., 2014). Both of these were post hoc secondary analyses planned after the data were collected.

Some thought is required about how to best measure repair of PA and NA in these analyses. When using symptom-focused measures such as the Hamilton Depression Rating Scale (HDRS; Hamilton, 1960), the objective is to eliminate depression symptoms and ensure individuals fall under some cutoff that indicates remission (ideally as close to zero as possible). Response is typically defined as showing a 50% reduction in depression symptom severity during treatment (Rush, Kraemer, et al., 2006). However, for PA and NA, it is less clear what counts as sufficient or optimal response and what cutoffs should be used to indicate remission. A state devoid of any NA and with a total maximum possible of PA is unlikely to be adaptive to the individual.

One approach is to examine where an individual falls in the general population distribution of PA and NA, expressing these as *z* scores (0 indicates a general population average score, and a score of ±1 indicates a score 1 *SD* above or below the general population average). An additional advantage of this *z*-score approach is that PA and NA are on a common scaling (with the same mean, standard deviation, and theoretical maxima and minima), making it possible to directly compare PA and NA repair in analyses. Response can be defined as at least a 50% shift back toward the population mean (e.g., moving from 2 *SD* to 1 *SD* below the mean during treatment). Remission can be defined as being no more than 0.5 *SD* from the general population mean at treatment end (i.e., for PA, ≥ -0.5 and for NA, ≤ 0.5), based on claims that 0.5 *SD* is a useful proxy universal measure of minimum important difference for measures of health-related quality of life (Norman, Sloan, & Wyrwich, 2003). We will use this *z*-score method to evaluate the extent to which PA and NA are repaired in the CPT2 and CPT3 trials. We will also examine whether greater repair of PA and NA during treatment is associated with greater depression symptom reduction.

Study 1: Secondary Analysis of CPT2 Trial

Method

Participants and trial design. Four hundred and thirty-seven adult participants were screened, and 240 participants meeting criteria for the trial were recruited (59% female; mean age = 40 years, *SD* = 12;

mean HDRS = 23.4, *SD* = 2.9) from sites at Vanderbilt University and the University of Pennsylvania. The primary inclusion criterion was currently meeting diagnostic criteria for MDD with an HDRS score greater than 20 (indicating moderate to severe depression) at both the screening and baseline visits. The vast majority of patients in the recruited sample met criteria for recurrent depression, and a sizable minority had chronic depression. Institutional review boards at both sites approved the study, and all participants gave written informed consent. Participants were stratified by gender and number of prior depressive episodes and then randomized to 16 weeks of CT (n = 60), 16 weeks of ADM (n = 120), or 8 weeks of pill-placebo (n = 60); an equal number of people participated in each condition at the Vanderbilt and Pennsylvania sites. ADM consisted of up to 50 mg of paroxetine daily, augmented by lithium hydrochloride or desipramine hydrochloride if necessary. CT followed established procedures outlined in standard texts to treat depression (A. T. Beck et al., 1979; J. S. Beck, 1995) and comorbid personality disorders (A. T. Beck & Freeman, 1990).

Patients and prescribing physicians were blind to pill-placebo versus ADM condition for the first 8 weeks of the trial, and independent assessors were blind to condition throughout. There was 15% attrition in the CT arm and 16% attrition in the ADM arm across the 16 weeks of treatment. This RCT predated trial registration, so trial registration details cannot be provided. For a full summary of inclusion and exclusion criteria, the consolidated standards of reporting trials (CONSORT) diagram, sample characteristics, treatment conditions, and fidelity assessments, see DeRubeis et al. (2005). The present secondary analysis focused on changes in NA and PA in the two active arms at 16 weeks and how this related to concurrent change in depression symptoms during treatment (pill-placebo findings are not considered here).

Measures. The Positive and Negative Affect Schedule (PANAS; Watson, Clark, & Tellegen, 1988) was used to assess PA (10 items; e.g., "excited"; Cronbach's α = .84) and NA (10 items; e.g., "distressed"; α = .85) over the past week. The PANAS was administered at intake, at midtreatment (8 weeks), and after treatment (16 weeks). We concentrated on the intake and posttreatment data. To benchmark individuals' PA and NA scores against general population scores, PA and NA were z-transformed relative to data collected from a U.S. general population sample (328 adults from the Dallas area; Watson & Clark, 1999). This comparison sample had a PA mean of 31.1 (*SD* = 7.5) and an NA mean of 18.0 (*SD* = 7.1). All subsequent analyses were conducted on these z scores.

Depression severity was measured using the 17-item HDRS (Hamilton, 1960), a clinician-administered interview that is frequently seen as the "gold standard" outcome measure in depression clinical trials.

Results

α was set at .05, and all tests were two-tailed. Analyses were conducted in IBM SPSS (Version 25). Intake data were available for 117 of 120 of the ADM participants (98%) and 59 of 60 of the CT participants (98%); there was no significant difference in the availability of data between the conditions ($\chi^2 < 1$). Data were available at 16 weeks for 102 of 120 (85%) of those in the ADM arm and 52 of 60 (87%) of those in the CT arm; again, there was no significant difference in proportion of missing data between arms ($\chi^2 < 1$). There were no significant differences in intake PA, intake NA, and HDRS severity between those who had and did not have 16-week PANAS data (independent-sample t test ps > .326).

Figure 1 plots PA (Fig. 1a) and NA (Fig. 1b) z scores for each condition at intake and after 16 weeks of treatment. Clinical improvement is represented by an increase in PA and a decrease in NA. To aid visual comparison of the magnitude of PA and NA deficits, the y-axis of the PA graph has been reversed.

We used multiple imputation to simulate missing values before statistical analysis. Guidance recommends that the number of imputations should exceed the percentage of data missing (White, Royston, & Wood, 2011), so we used 20 imputation runs given that we had a maximum of 15% of missing data. We included all variables used in subsequent analysis models (intake and 16-week PA, NA, and HDRS; group) and also variables that might predict variables with missing data (age, gender, site, condition, number of previous episodes, and first age of onset). Imputation was conducted using a Markov Chain Monte Carlo (MCMC) algorithm. All subsequent analyses (run on an intent-to-treat basis) use pooled data across these 20 imputations.

Intake analyses. PA and NA levels were not significantly associated with one another at intake (simple Pearson's correlation r = −.084, p = .272; attenuated correlation = −.099), which indicates they are dissociable constructs. HDRS depression severity at intake was significantly positively associated with NA (r = .235, p = .002) and negatively associated with PA at the level of a nonsignificant trend (r = −.126, p = .099). In all subsequent analyses, we reverse-scored PA to make it possible to compare the magnitude of the deviation from general population averages for NA and PA. The magnitude of the NA and PA (reverse-scored) associations with HDRS did not significantly differ (z = 1.110, p = .272).

A repeated measures analysis of variance (ANOVA) was run with emotion (PA reverse-scored, NA) as the

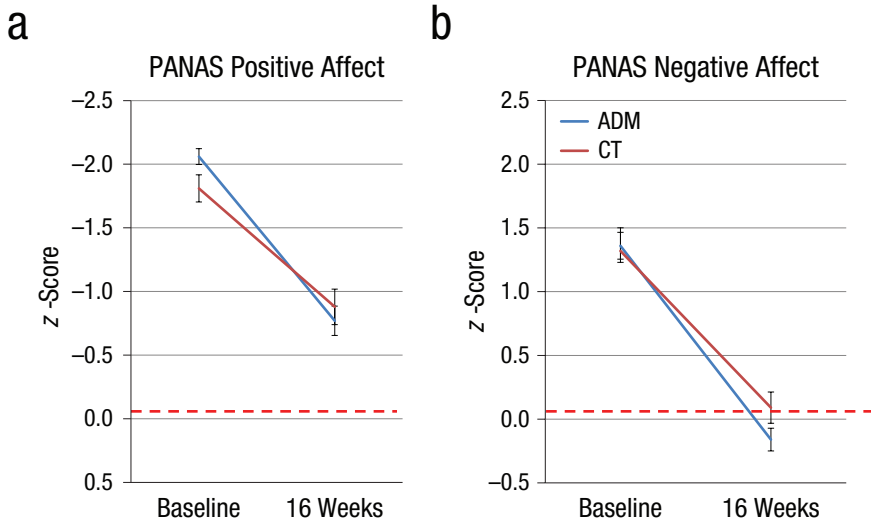

Fig. 1. Positive and negative affect. Positive affect (a) and negative affect (b) at intake and end of treatment (16 weeks) in the antidepressant medication (ADM) and cognitive therapy (CT) arms of the CPT2 trial. Data are mean (1 *SEM*) *z*-score values. To allow visual comparison with negative affect, the positive affect axis is reverse-scored. Therefore, moving downward represents clinical improvement for both negative affect and positive affect. Zero on each vertical axis (highlighted with bold dotted line) represents U.S. adult general population mean levels; −1 and +1 represent 1 *SD* below and above this mean, respectively.

within-subjects factor and condition (CT, ADM) as the between-subjects factor. The ANOVA revealed a main effect of emotion, $F(1, 178) = 33.643$, $p < .001$, $\eta_p^2 = .159$; PA deficits (z mean = −1.981, $SD = 0.736$) were more marked than NA elevations (z mean = 1.360, $SD = 1.110$) at intake. There was no significant main effect of condition, $F(1, 178) = 2.140$, $p = .151$, $\eta_p^2 = .001$, and no significant condition by emotion interaction, $F(1, 178) = 1.027$, $p = .322$, $\eta_p^2 = .006$.

At intake, on average, 132.4 participants met clinical criteria for both PA (z score < −0.5) and NA (z score > 0.5). Five participants did not meet clinical criteria for either NA or PA, 37.6 met the clinical criterion only for PA, and 5.1 met the clinical criterion just for NA. In total, 170 met the clinical criterion for PA, and 137.4 met the clinical criterion for NA; there was a significantly greater proportion for PA relative to NA (McNemar $p < .001$).

Sixteen-week analyses. To compare the magnitude of PA relative to NA change brought about by treatment, we calculated a simple difference score between z scores at intake and week 16 for NA and PA. Change scores are seen as a valid way to achieve this measurement goal (see Jamieson, 2004). Similar to analyses of intake data, a repeated measures ANOVA was conducted that specified emotion (reverse-scored ΔPA, ΔNA) as the within-subjects factor and condition (CT, ADM) as the between-subjects factor. A significant main effect of emotion emerged, $F(1, 178) = 5.362$, $p = .032$, $\eta_p^2 = .029$. There was no significant main effect of condition, $F(1, 178) = 3.096$, $p = .105$, $\eta_p^2 = .017$, and no interaction between emotion and condition, $F < 1$. There was a greater reduction in NA (Δz mean = −1.442, $SD = 1.310$) than there was an increase in PA (Δz mean = 1.209, $SD = 1.237$).

We analyzed absolute levels of NA and PA at week 16, again running a repeated measures ANOVA specifying emotion (reverse-scored PA, NA) as the within-subjects factor and condition (CT, ADM) as the between-subjects factor. Analysis found a significant main effect of emotion, $F(1, 178) = 70.931$, $p < .001$, $\eta_p^2 = .284$. PA deficits still remained, and mean PA levels continued to fall below general population averages (z mean = −0.772, $SD = 1.97$). NA elevations had now normalized, and mean NA now fell below general population average (z mean = −0.082, $SD = 0.987$). There was no significant main effect of condition, $F(1, 178) = 1.046$, $p = .375$, $\eta_p^2 = .006$, and no significant condition by emotion interaction, $F < 1$.

Next, response rates (> 50% z-score repair) and remission rates (z score ≥ −0.5 for PA; z score ≤ 0.5 for NA) were examined; we collapsed the two across treatments given that there were no significant differences between the CT and ADM arm at 16 weeks. For response, on average, 82.8 individuals responded for both NA and PA, 56.4 individuals responded for NA only, 14.1 individuals responded for PA only, and 26.7 individuals responded for neither NA nor PA. In total, 139.2 individuals met the NA response criterion, and only 96.9 individuals met the PA response criterion;

these proportions significantly differed (McNemar $p < .001$).

For remission, on average, 68.9 participants met remission criteria for both NA and PA, 67.0 participants met the remission criterion for NA only, 7.2 participants met the remission criterion for PA only, and 37.0 participants met remission criteria for neither PA nor NA. In total, 135.9 participants met the NA criterion for remission, whereas only 76.0 participants met the PA criterion for remission; these proportions significantly differed (McNemar, $p < .001$).

Furthermore, the number of participants showing reliable and clinically significant change (Jacobson & Truax, 1991) was computed. The threshold used to indicate clinically significant change was that posttreatment scores were closer to the general population average than to the clinical population average (criterion c). On average, 54.0 individuals failed to improve for either NA or PA, 65.5 individuals improved for both PA and NA, 22.5 individuals improved only for PA, and 38.0 individuals improved only for NA. This calculation resulted in 87.9 individuals in total improving on PA and 103.5 individuals improving in total on NA; this proportion differed at the level of a nonsignificant trend (McNemar $p = .074$).[1]

Are changes in NA and PA related to depression outcomes? To assess whether changes in NA and PA related to acute depression outcomes, we computed standardized residual change scores from intake to 16 weeks for the HDRS, NA, and PA scales. We examined whether NA change and PA change correlated with HDRS change. Greater HDRS reduction was associated with greater PA increase ($r = -.440$, $p < .001$) and greater NA decrease ($r = .559$, $p < .001$). There was a difference in the magnitude of these associations at the level of a nonsignificant trend ($z = 1.832$, $p = .067$; first reverse-coding PA residual change score). We also simultaneously entered PA change and NA change into a regression model. Greater NA decrease ($r_p = .452$, $p < .001$) and greater PA increase ($r_p = -.255$, $p < .010$) were independently associated with greater reduction in HDRS.

Additional analyses. To examine whether the response and remission findings would vary using a different general population comparison sample, we reran key analyses compared with a Scottish general-population sample (1,441 adults from the Aberdeen area; Crawford et al., 2009). The same pattern of findings emerged, although a smaller proportion of participants met response and remission criteria for PA relative to NA. It is also possible that the remission findings might be different if we used a percentile cutoff to define remission (e.g., < 75% for NA and > 25% for PA) because these do not make any assumptions about an underlying normal distribution. Individual participant data were available for the Crawford et al. (2009) normative sample, allowing us to compute the interquartile range for these norms. Using this revised definition of remission, an identical pattern of findings emerged.

Discussion

A secondary analysis of the CPT2 trial established that PA deficits were more marked than NA elevations at intake, that NA elevations were repaired to a greater extent than PA reductions during treatment, and that PA deficits remain more marked than NA elevations at the end of treatment. A greater proportion of the sample met response and remission criteria at posttreatment for NA than PA. There was also a nonsignificant trend for a greater number of participants to show reliable and clinically significant change for NA than PA. These findings support the claim that ADM and CT do a better job of repairing NA than PA in depressed individuals. Increase in PA and reductions in NA during acute treatment were both uniquely associated with concurrent reduction in depression symptoms during acute treatment (although the association tended to be more marked for NA than PA).

Study 1 had a number of limitations that mean these findings should be considered preliminary. The sample size was limited, which means that estimates of differences between conditions and changes in positive versus negative affect may have wide confidence intervals. The dose and duration given of both ADM and CT may not have been sufficient to fully repair PA and NA. Combination treatment (giving individuals both CT and ADM together) may be more effective than either treatment alone, but this possibility was not examined. Finally, it is potentially circular logic to examine whether affect change relates to depression change given that affective symptoms are core components of depression. An alternative approach could be to examine whether affect change relates to measures of functional improvement because functional measures have no direct content overlap with affect measures.

In addition to these limitations, it is important to replicate findings to have confidence in the conclusions reached, particularly when analyses are post hoc. An independent replication is required on a trial with a larger sample size in which there is a sufficient dose of treatment given (ideally including a combined treatment arm) and functional as well as symptom severity outcomes are measured.

Therefore, we next examined whether the same findings emerged in the CPT3 trial, in which 452 individuals with chronic or recurrent depression were randomized

to either ADM alone versus combined ADM and CT (Hollon et al., 2014). The CPT3 trial also included the Global Assessment of Functioning (GAF; American Psychiatric Association, 2000) as a measure of functional impairment. On the basis of the findings of Study 1, we hypothesized that intake levels of PA would be more impaired than intake levels of NA, that both treatments would lead to a greater change in NA relative to PA, and that levels of PA would remain more impaired than levels of NA at the end of treatment. We predicted that PA and NA change would be independently associated with improvement in depression symptoms and functional outcomes. We had no a priori predictions about differential effects of ADM alone versus combined treatment on PA versus NA.

Study 2: Secondary Analysis of CPT3 Trial

Method

Participants and trial design. Four hundred and fifty-two treatment-seeking adult outpatients with MDD were recruited (59% female; mean age = 43.16 years, *SD* = 13.10; mean HDRS = 22.08, *SD* = 4.21) from outpatient clinics run at the University of Vanderbilt, Nashville, Tennessee; the University of Pennsylvania, Philadelphia; and Rush Medical Centre, Chicago, Illinois. The primary inclusion criteria were meeting the diagnostic criterion for recurrent or chronic (episode duration ≥ 2 years) depression and a 17-item HDRS score of 14 or more. Institutional review boards at both sites approved the study, and all participants gave written informed consent.

Participants were randomly assigned in a 1:1 ratio to antidepressant medication treatment alone (ADM group; n = 225) or combined ADM and CT (COM group; n = 227); allocation was stratified by sex, marital status, symptom severity, history of recurrence, chronicity, and comorbid Axis II disorders. In the acute phase of treatment, participants were treated until they met the criterion for remission (4 consecutive weeks of minimal symptoms, assessed at least monthly during the trial by interviewers blind to condition). Median time to remission was 39 weeks in the ADM arm and 31 weeks in the combined arm. Pharmacotherapy followed a principle-based algorithm to deliver personalized antidepressant therapy. The algorithm allowed for up to four different classes of ADM (SSRIs, SNRIs, TCAs, and monoamine oxidase inhibitors) and the use of any of the augmenting agents commonly used in clinical practice. The first-line treatment was typically an SSRI or SNRI. Cognitive therapy followed the treatment manual for CT for depression (A. T. Beck et al., 1979), augmented as necessary for patients with comorbid personality disorders (A. T. Beck & Freeman, 1990). For a full summary of inclusion and exclusion criteria, sample characteristics, treatment conditions, fidelity assessments, trial registration, and the trial CONSORT diagram, see Hollon et al. (2014).

Measurements. The Mood and Anxiety Symptom Questionnaire (MASQ; Watson & Clark, 1991) measured affect change during treatment. Participants were asked to judge, for each of 90 items, how much they had felt the way described over the past week, ranging from 1 (*not at all*) to 5 (*extremely*). The general distress (GD) subscale served as a measure of NA, and the anhedonic depression subscale served as a measure of PA. The MASQ was administered at each assessment point during the trial (at least monthly). We focused on the MASQ taken at the end of acute treatment (remission for those whose illness remitted and termination for those whose illness did not remit within 18 months).[2]

The factor structure of the MASQ proposed by Watson and Clark (1991) has not been replicated in recent studies; many of the negatively keyed loss of interest items originally included in the anhedonia subscale load more clearly on general distress (Bedford, 1997; Kendall et al., 2016; Keogh & Reidy, 2000). Therefore, we used the revised factor structure proposed by Keogh and Reidy (2000), in which the anhedonic depression (AD) scale consists solely of positively keyed high-positive-affect items. Reliability in the present sample was high (intake: GD α = .937; AD α = .938). As in Study 1, AD and GD scores were z-transformed relative to a general population sample (534 United Kingdom undergraduate students; Keogh & Reidy, 2000). This sample had a GD mean of 40.92 (*SD* = 16.26) and an AD mean of 66.02 (*SD* = 17.99). All subsequent analyses were conducted on these z scores.

As in Study 1, the 17-item HDRS (Hamilton, 1960) was administered to assess depression severity. In addition, the GAF (American Psychiatric Association, 2000) was used to assess day-to-day functioning (in psychological, social, and occupational functioning domains) over the past week.

Results

α was set at .05, all tests were two-tailed, and analyses were conducted in IBM SPSS 25 except where otherwise stated. Intake MASQ data were available for 215 of 225 participants (96%) in the ADM arm and 221 of 225 participants (98%) in the combined arm; the proportion of complete data did not differ between arms ($\chi^2 < 1$). There were MASQ data for 210 of 225 participants (93%) in the ADM arm and 216 of 227 participants (95%) in the combined arm at the end of acute treatment assessment;

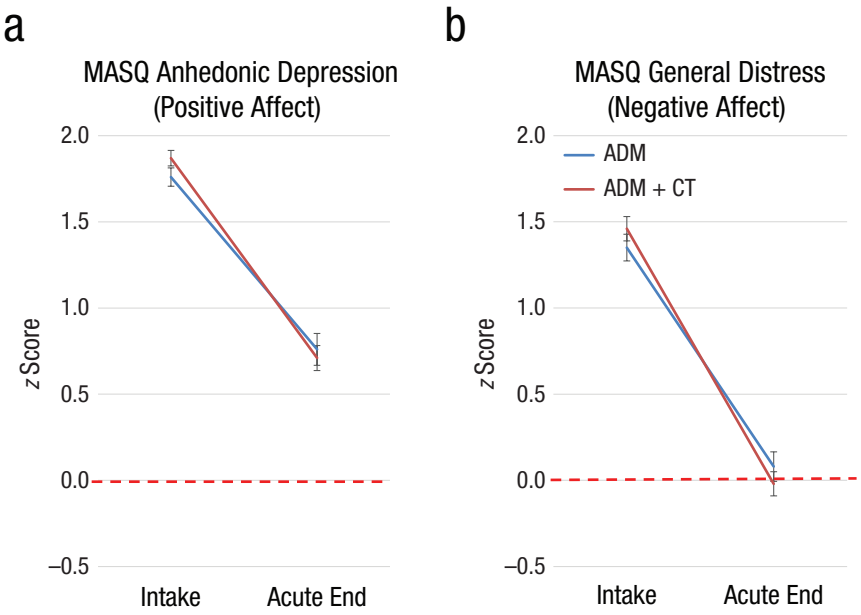

Fig. 2. Mood and Anxiety Symptom Questionnaire. Anhedonic depression (a) and general distress (b) at intake and acute treatment end in the antidepressant-medication-only (ADM) and the antidepressant and cognitive therapy combined (ADM + CT) arms of the CPT3 trial. Data are mean (1 *SEM*) *z* score values. Moving downward represents clinical improvement for both anhedonic depression and general distress. Zero on each vertical axis (highlighted with bold dotted line) represents United Kingdom adult general population mean levels; −1 and +1 represent 1 *SD* below and above this mean, respectively.

again, the proportion of complete data did not differing between arms ($\chi^2 < 1$). There were no significant differences in intake depression severity, intake AD, or intake GD between those included in the intake analyses with and without complete data at the acute end follow-up (*p*s > .094). Figure 2 plots GD and AD scores for participants in each arm at intake and the end of acute treatment.

As in Study 1, multiple imputation (implemented via a MCMC algorithm, entering all variables used in the analyses and also age, gender, site, condition, number of previous episodes, and intake depression severity) was used to simulate missing data, and the data were analyzed on an intent-to-treat basis. This time, 10 imputation runs were used because the maximum level of missingness was 7%. All subsequent analyses average across these 10 imputation runs.

Intake analyses. GD and AD were significantly positively correlated ($r = .423$, $p < .001$, correction for attenuation $r = .451$; a medium effect; Cohen, 1988). This finding indicates that AD and GD are less clearly orthogonal than PANAS PA and NA used in Study 1 but nevertheless are still dissociable. Greater AD ($r = .219$, $p < .001$) and GD ($r = .382$, $p < .001$) were significantly associated with greater HDRS score at intake; the magnitude of this association was significantly greater for GD than AD ($z = 3.395$, $p < .001$). When both were entered into the same regression, greater levels of GD ($r_p = .327$, $p < .001$) but not AD ($r_p = .069$, $p = .151$) were uniquely associated with greater levels of depression.

Mean functioning score at intake was 56.003 (*SD* = 7.370; moderate difficulty). Lower functioning was significantly related to greater intake AD ($r = -.215$, $p < .001$) and GD ($r = -.243$, $p < .001$); there was no difference in the magnitude of the associations ($z < 1$). When both were entered into the same regression, greater levels of AD ($r_p = -.128$, $p = .009$) and GD ($r_p = -.172$, $p < .001$) were each uniquely associated with lower levels of functioning.

A repeated measures ANOVA was run on the *z*-transformed intake scores, with MASQ-factor (AD, GD) as the within-subjects factor and condition (ADM, COM) as the between-subjects factor. This test found a main effect of MASQ-factor, $F(1, 450) = 72.292$, $p < .001$, $\eta^2_p = .138$. Replicating the pattern of findings from Study 1, AD symptoms (*z* mean = 1.816, *SD* = 0.731) were more marked than GD symptoms (*z* mean = 1.406, *SD* = 1.092) at intake. There was no significant main, $F(1, 450) = 2.357$, $p = .134$, $\eta_p^2 = .005$, or interactive ($F < 1$) effect of condition.

We also determined the proportion of the sample showing clinical levels of AD and GD at intake (*z* scores > 0.5). On average, 346.9 participants met clinical criteria

for AD and GD, 80.3 participants met the clinical criteria only for AD, 6.5 participants met the clinical criteria only for GD, and 18.3 participants met clinical criteria for neither AD nor GD. In total, 427.2 participants met clinical criteria for AD, and 353.4 participants met clinical criteria for GD at intake; a significantly greater proportion met criteria for AD than GD (McNemar $p < .001$).

End of acute treatment analysis. A repeated measures ANOVA examined simple change in AD and GD during treatment, specifying MASQ-factor (ΔAD, ΔGD) as the within-subjects factor and condition (ADM, COM) as the between-subjects factor. A significant main effect of MASQ-factor emerged, $F(1, 450) = 26.556$, $p < .001$, $\eta_p^2 = .056$. Mirroring findings from Study 1, there was a greater repair of GD (Δz mean = −1.350, $SD = 1.299$) than AD (Δz mean = −1.057, $SD = 1.228$). There was a greater repair of overall symptoms in the COM arm (relative to the ADM arm) at the level of a weak, nonsignificant trend, $F(1, 450) = 2.894$, $p = .097$, $\eta_p^2 = .006$. There was no significant interaction between condition and MASQ-factor ($F < 1$).

We also analyzed absolute levels of AD and GD at acute treatment end. Repeated-measures ANOVA found a significant main effect of MASQ-factor, $F(1, 450) = 201.400$, $p < .001$, $\eta_p^2 = .309$. There were no significant main or interactive effects of condition (Fs < 1). Again replicating Study 1, AD symptoms (z mean = 0.759, $SD = 1.213$) were more marked than GD symptoms (z mean = 0.056, $SD = 1.146$) at the end of treatment.

Next, we collapsed across conditions and looked at the proportion of individuals meeting response (> 50% z score change), remission (z score ≤ 0.5), and reliable and clinically significant change criteria. For response, on average, 189.5 participants met criteria for both GD and AD, 109.0 participants met criteria only for GD, 41.7 participants met criteria only for AD, and 111.8 participants failed to meet either criterion. In total, 298.5 participants met the response criterion for GD, and 231.2 participants met the response criterion for AD; the proportion was greater for GD than AD (McNemar $p < .001$).

For remission, 183.9 participants met criteria for both GD and AD, 7.5 participants met criteria only for AD, 151.9 participants met criteria only for GD, and 108.7 participants met neither remission criteria. In total, 335.8 participants met remission criteria for GD, and 191.4 participants met remission criteria for AD; the proportion was greater for GD than AD (McNemar $p < .001$).

For reliable and clinically significant change (Jacobson & Truax, 1991; criterion c), on average 200 participants met criteria for both AD and GD, 121.9 participants failed to meet criteria for either AD or GD, 26.9 participants met criteria only for AD, and 103.2 participants met criteria only for GD. In total, 226.9 individuals met criteria for AD, and 303.2 individuals met criteria for GD; the proportion was greater for GD than AD (McNemar $p < .001$).[3]

Are changes in AD and GD related to depression and functional outcomes? As in Study 1, we computed standardized residual change scores for the HDRS, AD, and GD scales (in this case from intake to the end of acute treatment) and examined the associations between these change scores. Greater repair in HDRS depression severity was significantly associated with greater AD reduction (Pearson's $r = .454$, $p < .001$) and greater GD reduction ($r = .544$, $p < .001$). The correlation with depression severity was significantly stronger for GD than AD ($z = 2.625$, $p = .004$). Both AD residual change ($r_p = .180$, $p = .001$) and GD residual change ($r_p = .379$, $p < .001$) continued to predict depression change when entered simultaneously into a regression model.

We also examined the associations between residual change in affective and functional outcomes. Greater reduction in AD ($r = -.506$, $p < .001$) and GD ($r = -.489$, $p < .001$) were both associated with a greater increase in functioning. There was no significant difference in the strength of these associations ($z < 1$). When the two were entered in the same regression, greater reductions in both AD ($r_p = -.299$, $p < .001$) and GD ($r_p = -.262$, $p < .001$) uniquely predicted greater increases in functioning.

Additional analyses. Because participants were treated until remission, acute treatment end varied among participants. We repeated key analyses when looking at the MASQ assessment point closest to 6 months after acute treatment started (excluding cases in which that assessment point was not within plus or minus 30 days of 6 months). We chose 6 months because this is often a standard treatment period in depression psychotherapy trials (e.g., Richards et al., 2016; Wiles et al., 2013). An identical pattern of findings emerged. Unlike in Study 1, we were not able to repeat the response and remission analysis using a different normative data set because we are not aware of other published normative data on the MASQ factor structure put forward by Keogh and Reidy (2000). Likewise, we could not replicate remissions findings using percentile cutoffs because we did not have individual item data from Keogh and Reidy (2000) to allow us to calculate the interquartile range in this sample.

The MASQ was administered over repeated occasions in the CPT3 trial, which made it possible to examine whether the slope of change over time differed for GD and AD. A hierarchical linear model was run using the mixed command in Stata (Version 15) with affect (z-transformed AD, GD), nested within time (each point

at which MASQ was administered), nested within individual participant. We modeled random slopes for time and participant, only including MASQ data collected during the intake and acute treatment phases of the trial. Affect was binary coded (0 for AD; 1 for GD). We person-mean-centered the time variable as is generally recommended in longitudinal models of this kind (Wang & Maxwell, 2015), particularly when there is significant heterogeneity in the number and timings of assessments between participants (Blozis & Cho, 2008). Preliminary analyses found that model fit (based on the Akaike and Bayesian information criteria) was best when time was log transformed to reflect the fact that change in MASQ symptoms was more marked earlier than later in treatment. Therefore, we report results from this log transformed model. Data were available for 442 participants, with 2,696 observations for AD and GD (5,392 in total). There was a significant main effect of time ($\beta = -0.193$, $SE = .012$; $z = -16.21$, $p < .001$) and affect ($\beta = 0.083$, $SE = .026$; $z = -3.15$, $p = .002$), which was qualified by a significant time by affect interaction ($\beta = -0.037$, $SE = .011$; $z = -3.49$, $p < .001$). There was a reduction in symptoms over time, which was more marked for GD than AD.

Discussion

Study 2 fully replicated the findings of Study 1 in a different sample. AD deficits were more marked than GD deficits at intake, AD deficits changed to a lesser degree than did GD deficits during treatment and, as a result, posttreatment AD deficits were more marked than GD deficits. Improvements in AD and GD were uniquely associated with concurrent improvement in depression symptoms and functioning outcomes.

General Discussion

We examined the extent to which current mainstream MDD treatments repair elevations in NA and deficits in PA across two different randomized controlled trials. The CPT2 trial compared 16 weeks of CT and ADM for moderate to severe depression (DeRubeis et al., 2005) using the PANAS as a measure of affect. The CPT3 trial compared ADM to combined ADM and CT (treating to remission) for chronic or recurrent depression (Hollon et al., 2014) using the MASQ to measure affect.

In both trials, PA deficits were more marked than NA deficits at intake relative to comparison sample averages. This finding is consistent with the view that disturbances to the PA system are particularly prominent in MDD and therefore should be an explicit intervention target (Argyropoulos & Nutt, 2013; Dunn, 2012; Treadway & Zald, 2011). PA and NA improved during treatment in both trials with no difference between treatment arms. However, the magnitude of PA repair was significantly smaller than the magnitude of NA repair. In Study 2, hierarchical liner modeling analyses showed a slower repair of AD relative to GD over time. This is despite the fact that in both studies, PA was more disturbed than NA at intake, meaning that regression to the mean should have favored greater change in PA than in NA. At the end of acute treatment, PA disturbances remained significantly more pronounced relative to NA disturbances in both studies. As a result, PA levels continued to fall below general population average levels at these time points. That is, PA improved but never fully normalized. In contrast, NA levels largely normalized in both trials (with average NA scores falling close to general population averages). In both trials, a greater proportion of participants met response (50% reduction in symptoms) and remission (falling within 0.5 *SD* of the general population mean) criterion for NA than PA. A greater proportion of participants also showed reliable and clinically significant change for NA rather than PA (although the Study 1 findings were only a nonsignificant trend in that direction). Overall, these results suggest that none of the treatment examined (ADM alone, CT alone, or ADM and CT combined) was satisfactorily effective in repairing PA deficits in depression.

The present results are the first to delineate the absolute levels of PA and NA disturbance in depression (relative to general population averages), showing that PA deficits are more marked than NA deficits at both intake and posttreatment assessments. The treatment outcome findings parallel the results of Roberts et al. (2017), who found that treatments are more effective at repairing neuroticism than extraversion, extending these earlier findings into the affective domain, and focusing specifically on mainstream treatments of MDD. The results deviate from the meta-analytic results of Boumparis et al. (2016), who found that depression interventions produced comparably small to medium effects on both PA and NA. However, none of the studies included in Boumparis et al. were of current mainstream treatments delivered with an optimal dose and format to a diagnosed depressed population. Therefore, the conclusions in Boumparis et al. that depression therapies are similarly ineffective at repairing PA and NA should now be revised on the basis of the current results.

In both trials, greater repair of PA and NA was significantly associated with greater repair of depression. Although depression change was more strongly related to NA than PA in both trials (a trend toward significant difference in Study 1 and a fully significant difference in Study 2), when both PA and NA change were entered into the same analyses, each was independently

associated with depression repair. Causal conclusions cannot be drawn from association data of this kind (i.e., change in PA and NA is concurrent with change in depression symptoms, so temporal precedence is not established). Therefore, future studies should conduct mediation or cross-lagged analyses—in particular examining whether early change in PA or NA predicts subsequent change in depression—to more robustly test this hypothesis.

Another potential criticism of these association analyses is that they are based on circular logic given that anhedonia (PA) and depressed mood (NA) form central components of the depression construct. One way to evaluate this critique is to consider the overlap of individual items of the HDRS with PA and NA. Two items in the HDRS directly measure NA (Item 1 indexing depressed mood and Item 10 measuring psychic anxiety), whereas one item indirectly measures PA (Item 7 on work and activities mentions loss of interest in the scoring key). Therefore, there is moderate but not high item content overlap. Another way to evaluate this issue is to examine the strength of the association of individual depression symptoms with PA and NA. In the present samples, the associations between affect scores and individual depression items were generally nonsignificant and of small magnitude (see Table S2 in the Supplemental Material). Although this finding differs from the relationships of at least moderate strength reported in some previous studies (e.g., Watson, Clark, & Carey, 1988), it does not suggest a high degree of overlap within the CPT2 and CPT3 data sets. Moreover, in Study 2, it is encouraging that change in PA and NA both independently predicted functional improvement because this outcome measure has no direct overlap with affect. Therefore, in our view, the present association results are not substantially undermined by problems of circular logic.

The key implication of these findings is that better outcomes may result if treatments can target PA as effectively as they do NA given that anhedonia symptoms predict future prognosis, functional impairments, and suicide completion rates (Fawcett, Scheftner, Fogg, Clark, & Young, 1990; Fried & Nesse, 2014; Geschwind et al., 2011; McMakin et al., 2012; Spijker et al., 2001; Uher et al., 2012). Moreover, studies suggest that in the eyes of patients, repair of PA is at least as important as reduction in NA in recovery from depression (Demyttenaere et al., 2015; Zimmerman et al., 2006). This perspective resonates with a broader recovery literature arguing that mental-health treatments should place a greater emphasis on patient-defined recovery goals relating to positive functioning (Slade, 2010) and that a complete state of positive mental health involves both an alleviation of symptoms of mental illness and the cultivation of well-being (Provencher & Keyes, 2011). The fact that existing mainstream treatments fail to normalize PA to general population levels therefore indicates there is significant room for improvement.

It is conceivable that PA, relative to NA, is inherently less amenable to change (Brown, 2007; Naragon-Gainey et al., 2013) and therefore that treatment efficacy is already at ceiling. However, promising treatment advances indicate that improving PA outcomes may be achievable. There is preliminary evidence that drugs that act primarily on the dopamine system (e.g., bupropion and ketamine) can be effective in alleviating anhedonia in mood disorders (Jamerson, Krishnan, Roberts, Krishen, & Modell, 2003; Lally et al., 2015; Tomarken, Dichter, Freid, Addington, & Shelton, 2004). Adapted forms of psychotherapy targeting PA and broader well-being are emerging, including positive cognitive-behavioral therapy (Geschwind, Arntz, Bannink, & Peeters, 2019), positive-affect treatment (Craske et al., 2019), well-being therapy (Ruini & Fava, 2012), augmented depression therapy (Dunn et al., 2019), and adaptations of positive psychology interventions (e.g., Chaves, Lopez-Gomez, Hervas, & Vazquez, 2017). These novel treatments are informed by a better understanding of the underlying psychological mechanisms driving PA deficits, including elevated use of dampening appraisals and reduced experiential processing (e.g., Burr, Javaid, Jell, & Werner-Seidler, 2017; Dunn et al., 2018; Gadeikis, Bos, Schweizer, Murphy, & Dunn, 2017), opening up new avenues for intervention (see Dunn, 2017).

Given that most depressed clients present with impairments in both affective systems, optimal depression outcomes are likely to emerge from universal treatment protocols that are able to simultaneously target both PA and NA (rather than a proliferation of separate treatments for NA and PA). These universal treatment protocols should be flexible enough to tailor the relative focus on PA and NA based on the presentation of each individual client.

The present findings highlight the explanatory benefits of fractionating depression into underlying dimensions or symptom clusters, as recommended both by the RDoC approach (Insel et al., 2010) and network models of psychopathology (Borsboom, 2017; Fried et al., 2017; Hofmann et al., 2016). This perspective also fits with recent recommendations that the field should move to a "process-based therapy" perspective, whereby treatments should aim to target theoretically derived and empirically validated core processes that maintain key symptoms using empirically tested treatment procedures (see Hofmann & Hayes, 2019).

A concern voiced by patients regarding antidepressants that target serotonin is that such drugs numb their experience of positive emotion, thereby exacerbating

anhedonia (Price, Cole, & Goodwin, 2009). The present findings are not consistent with this viewpoint. In both trials, ADM treatment did improve levels of PA but failed to normalize them to general population average levels. Very few participants showed clinically significant deterioration in PA when using antidepressants in either trial. It is plausible that blunted levels of PA are interpreted by patients as a side effect of ADM treatment rather than as a residual feature of their condition that persists after only partially successful treatment.

The use of a benchmarking approach (expressing measures in *z*-score units relative to comparison sample distributions) is novel in that it makes it possible to test degree of normalization of the outcome variable. This benchmarking approach could be used when analyzing other RCT outcome data in situations in which adequate normative data are available.

That an identical pattern of findings emerged across two different trials and using different measures of positive and negative affect (and in Study 1 across different comparison samples) suggests that this is a robust, replicable result that is unlikely to be an artifact of the outcome measures or comparison sample chosen.

There are various limitations of the present analyses. First, CT reflects only one example of an evidence-based psychological treatment for depression, and we cannot rule out that this is a class effect. It is conceivable that other psychological therapies (e.g., behavioral activation; Martell, Dimidjian, & Herman-Dunn, 2010) may be more successful at repairing PA. However, given that the initial positive activity scheduling of CT has substantial overlap with behavioral activation, this seems unlikely. Second, the criteria used for remission (falling within 0.5 *SD* of general population averages), despite having a precedent in the broader literature (Norman et al., 2003), are as arbitrary as any other choice of cutoff point. It is reassuring in this regard that an identical pattern of findings emerged if using percentile rather than standard deviation definitions of remission in Study 1. Third, the 50% *z*-score response criterion could be seen as more stringent for PA than NA given that PA disturbances were more marked at intake. However, this finding mirrors the 50% response criterion routinely used to determine depression response (Rush, Trivedi, et al., 2006). Further supporting the use of percentage change criterion, some evidence suggests that in cases in which baseline impairments are more marked, depressed participants report needing to change a greater amount to feel they have reliably improved (e.g., Button et al., 2015).

Fourth, the validity of the present findings depends on the underlying tools used to measure PA and NA being robust and replicable. Although the PANAS factor structure has been extensively validated, the optimal MASQ factor structure remains open to debate. However, that results were identical for Study 1 using the PANAS and Study 2 using the MASQ is encouraging in this regard. Fifth, both the PANAS and MASQ are measures of dispositional positive and negative mood rather than an index of positive and negative reactivity to stimuli. A different pattern of results may emerge if looking at reactivity, for example, using the Snaith Hamilton Pleasure Scale (Snaith et al., 1995) as a measure of positive reactivity. Finally, PA can be fractionated into motivational (wanting), consummatory (liking), and cognitive (learning) elements (Berridge & Kringlebach, 2008; Treadway & Zald, 2011), and here we have focused on the consummatory aspect only. Future studies should measure how treatments repair these various components of PA.

In summary, individuals with MDD show more marked abnormalities in PA than in NA, and existing depression treatment such as antidepressants and cognitive therapy repair NA more effectively than PA. As a result, depressed individuals are left with residual deficits in PA after treatment. There is potential to improve depression outcomes by targeting PA more systematically in pharmacological and psychological treatment approaches.

Action Editor

Stefan G. Hofmann served as action editor for this article.

Author Contributions

B. D. Dunn had full access to all of the data in the studies and takes responsibility for the integrity of the data and the accuracy of the data analysis. The study was conceived and designed by B. D. Dunn, R. J. DeRubeis, G. Khazanov, and S. D. Hollon. R. J. DeRubeis and S. D. Hollon obtained funding. B. D. Dunn, R. E. German, C. Xu, R. J. DeRubeis, and S. D. Hollon were involved in acquisition, analysis, or interpretation of the data and drafted the manuscript. B. D. Dunn performed the statistical analysis. All of the authors approved the final manuscript for submission.

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Supplemental Material

Additional supporting information can be found at http://journals.sagepub.com/doi/suppl/10.1177/2167702619863427

Notes

1. We also examined reliable and clinically significant deterioration for PA and NA. Very few people deteriorated (on average 4.6 participants for PA only, 3.5 participants for NA only, and 1.2 participants for both PA and NA), with no significant difference between NA and PA (McNemar, n.s.).
2. The CPT3 trial did not include the PANAS as an additional outcome measure, precluding a direct replication of the Study 1 results.
3. As in Study 1, we examined reliable and clinically significant deterioration for AD and GD. Very few people deteriorated (on average 4.7 participants for AD only, 3.5 participants for GD only, and 4.1 participants for both AD and GD), with no significant difference between AD and GD (McNemar, n.s.).

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