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Memory Performance Predicts Response to Psychotherapy for Depression in Bipolar Disorder: A Pilot Randomized Controlled Trial with Exploratory Functional Magnetic Resonance Imaging

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Abstract

Objective—This pilot randomized controlled trial compared Cognitive Behavior Therapy (CBT) and Supportive Psychotherapy (SP) for the treatment of depression in bipolar I disorder. We also examined whether exploratory verbal memory, executive functioning, and neural correlates of verbal memory during functional magnetic resonance imaging (fMRI) predicted change in depression severity.

Methods—Thirty-two adults (ages 18–65) with DSM-IV bipolar I disorder meeting current criteria for a major depressive episode were randomized to 18 weeks of CBT or SP. Symptom severity was assessed before, at the mid-point, and after the 18-week intervention. All participants completed a brief pre-treatment neuropsychological testing battery (including the California

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Conflicts of Interest

Amy T. Peters, Conor Shea, Aishwarya Gosai, Jonathan P. Stange, Andrew D. Peckham, and Kristen K. Ellard report no financial interests.

Contributors

TD was responsible for oversight of all aspects of the study, including study design, conduct, analysis, and write-up and revision. ATP assisted with execution of the clinical trial, data entry, data analysis, and drafting the manuscript. CS and AG were responsible for the analysis and interpretation of the fMRI data. JPS and ADP assisted with execution of the clinical trial, data entry, data analysis, and provided revisions to the manuscript. KKE assisted with fMRI data analysis and provided revisions to the manuscript. MWO, SLR, DDD, and AAN assisted with overall design of the study, interpretation of the results, and provided revisions to the manuscript.

Verbal Learning Test-2nd Edition, Delis Kaplan Executive Functioning System [DKEFS] Trail-making Test, and DKEFS Sorting Test), and a sub-set of 17 participants provided usable fMRI data while completing a verbal learning paradigm that consisted of encoding word lists.

Results—CBT and SP yielded comparable improvement in depressive symptoms from pre- to post-treatment. Better retention of learned information (CVLT-II long delay free recall vs. Trial 5) and recognition (CVLT-II hits) were associated with greater improvement in depression in both treatments. Increased activation in the left dorsolateral prefrontal cortex and right hippocampus during encoding was also related to depressive symptom improvement.

Limitations—Sample size precluded tests of clinical factors that may interact with cognitive/neural function to predict treatment outcome.

Conclusion—Neuropsychological assessment and fMRI offer additive information regarding who is most likely to benefit from psychotherapy for bipolar depression.

Keywords

bipolar depression; memory; executive function; fMRI; CBT

Introduction

Bipolar disorder, characterized by episodes of mania and most often also depression, is a chronic and debilitating psychiatric illness. Although mania is the hallmark symptom, depression constitutes one of the major unresolved problems (1), as patients spend approximately one-third of time depressed (2). Pharmacotherapy is the first-line of treatment, but often fails to bring patients to full, sustained remission (3). Hence, adjunctive psychotherapy has been investigated as an additional treatment option (4).

Psychotherapy adjunctive to mood stabilizing medication has demonstrated benefits for increasing medication adherence (5), relapse prevention (6), and more recently acute depression (7). For treating depression, the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) evaluated the efficacy of intensive psychotherapy (Cognitive Behavior Therapy [CBT], Family Focused Therapy [FFT], and Interpersonal Social Rhythm Therapy [IPSRT]), compared to collaborative care (a supportive, psychoeducational control) (7). The intensive psychotherapies yielded greater and faster improvements in depression compared to a brief 3-session psychoeducation comparison condition. (8). To date, it has not been tested whether intensive psychotherapy (e.g., CBT) for bipolar depression is superior to generic supportive psychotherapy, which is more widely available in the community.

For patients to benefit from psychotherapy, they need to attend to, remember, and apply information discussed in a therapy session. From this perspective, psychotherapy relies on patients' memory to exert its therapeutic effects (9). For instance, in unipolar depression, deficits in memory (10, 11) and executive function (12) have been linked with poorer CBT treatment outcome. There is similar evidence for elderly adults with generalized anxiety disorder treated with CBT (13, 14). In bipolar disorder, memory for the content of therapy sessions is strikingly low (15). Moreover, neuropsychological studies show that patients with bipolar disorder exhibit a number of cognitive difficulties, including impairments in

attention, learning and memory and executive functioning (e.g., planning, problem-solving, and set shifting (16)). These impairments are present during the acute phases of illness (e.g., depression) but tend to persist into periods of relative wellness (17). Impairments in learning and memory in bipolar disorder appear to be related to patients' difficulties in mentally organizing the study material during learning, which leads to subsequent difficulties in delayed recall (18–20).

Cognitive difficulties in bipolar disorder have also been linked to functional difficulties in daily life, including educational under-attainment and vocational underperformance (21, 22). For example, poorer verbal memory performance has been associated with decreased likelihood of being employed (23), and poorer executive functioning has been associated with occupational absenteeism and poor work quality (24). A recent study of relapse prevention with CBT and a supportive psychotherapy (SP) control in euthymic bipolar disorder found that patients with poorer verbal free recall during a list learning task were more likely to relapse in SP (25). However, whether cognitive performance (in particular memory and the ability to organize information during learning) predicts response to psychotherapy in bipolar depression has not yet been evaluated.

It is also important to understand whether these neuropsychological deficits are associated with disruption to the functional integrity of brain regions supporting learning, memory, and executive functioning. The prefrontal cortex (PFC) in particular, is thought to play a critical role in both the top-down attentional processes required to encode new information, as well as the maintenance processes involved in retaining that information within working memory. Moreover, limbic structures, such as the hippocampus, are well known for involvement in verbal encoding and retention (26). Indeed, neuroimaging studies in bipolar disorder have consistently shown that abnormalities in the prefrontal cortex (e.g., dorsolateral) (27) and temporal lobe (e.g., hippocampus) (28, 29) associated with difficulties in learning and memory and executive functioning. Findings by our group using positron emission tomography (PET) suggest that abnormalities in dorsolateral prefrontal cortex and hippocampus are associated with difficulties organizing verbal information during memorization (18).

The purpose of the present study was three-fold: (1) To compare the efficacy of CBT with that of supportive psychotherapy for depression in patients with bipolar I disorder; (2) to investigate whether the ability to organize information during verbal learning and memory or executive functioning predicts response to psychotherapy, and (3) to investigate the neural basis of difficulties in verbal organization and memory in bipolar disorder and whether this predicts treatment response. We hypothesized that CBT would yield more improvements in depressive symptoms relative to SP. We expected that participants with bipolar disorder with better verbal organization during learning, subsequent recall, and executive function would be more likely to benefit from CBT relative to supportive psychotherapy, and that impaired recruitment of the dorsolateral PFC and hippocampus, during an fMRI verbal learning paradigm would be associated with poorer response to CBT.

Methods

Participants

Participants were recruited as part of a pilot randomized controlled trial comparing 18 sessions of CBT and SP. They underwent diagnostic evaluation using the Mini International Neuropsychiatric Interview (MINI (30)), conducted by trained and reliably certified independent evaluators. Eligible participants were English speakers, 18–65 years old, who met DSM-IV criteria for bipolar I disorder, in a current major depressive episode, stable pharmacotherapy (no dose change within the past 8 weeks). Exclusion criteria included previous treatment with CBT for depression, diagnosis of rapid cycling bipolar disorder subtype or current mixed episode, as well as standard fMRI contraindications (e.g., pregnancy, claustrophobia, non-removable metallic objects), serious medical conditions, neurological disorder, or moderate to severe head trauma, lifetime schizophrenia spectrum disorder, substance/alcohol use disorder within the year prior to study enrollment, and IQ estimate <80 based on the Wechsler Adult Reading Test (31).

Figure 1 illustrates the CONSORT diagram for the randomized controlled trial. 32 participants met basic eligibility criteria and were randomized to CBT ($n = 17$) or SP ($n = 15$). Randomization was generated using Research Randomizer (32). Participants were informed of their randomization after the baseline fMRI scan. Of the $n = 32$ randomized participants, $n = 24$ completed the post treatment assessment. No patients were withdrawn for adverse clinical status. Eight patients were lost to follow-up (could not be reached) after the initial treatment phase. Demographic and clinical characteristics regarding the intent to treat study sample are provided in Table 1, separately by treatment group.

A subset of the randomized participants ($n = 27$) completed a verbal learning paradigm while undergoing fMRI scanning. Seven participants provided unusable fMRI data (e.g., excessive head motion). An additional $n = 3$ participants were excluded from the fMRI analysis because they dropped out of treatment before the post-treatment assessment and therefore did not have HDRS post-treatment score, resulting in group of $n = 17$ participants with fMRI data available for predicting treatment outcome. They were compared to a group of $n = 34$ age-, sex-, and education-matched healthy control (HC) participants who met the same eligibility criteria but had no history of psychopathology and completed the same memory paradigm during fMRI scanning but did not receive treatment.

Assessment and Intervention Procedures

After signing consent, participants underwent a clinical, neuropsychological, and fMRI baseline assessment (see assessment details below). Once randomized to CBT or SP, participants attended 18 50-minute sessions of either treatment. The first 16 sessions occurred on a weekly basis and the final two treatment sessions were scheduled biweekly. The clinical assessment battery was repeated by an independent evaluator mid-treatment (week 9) and post-treatment (week 20). Participants were invited to complete a follow-up assessment four-months after completing the intervention phase (week 36), during which time they were permitted to receive up to 3 booster therapy sessions.

Clinical Assessments

MINI—The MINI (30) is a well-established structured diagnostic interview for determining DSM-IV diagnoses. The full evaluation was completed by the IE at baseline.

Hamilton Depression Rating Scale – 17 Item (HDRS)—The HDRS (33) is a well-validated 17-item clinician-rated depression severity measure. The reliability, validity, and sensitivity to change are well documented. Scores range from 0 to 54, with higher score denoting greater depressive symptoms. The HDRS is the primary outcome measure of the study and was completed at all clinical assessment points (e.g., baseline, week 9, week 30, week 36).

Young Mania Rating Scale (YMRS)—The YMRS (34) is a reliable and well-validated 11-item clinician-rated manic symptom severity measure. Scores range from 0 to 56, with higher scores indicating greater symptoms of (hypo)mania. The YMRS was completed at all clinical assessment points.

Longitudinal Interval Follow-Up Evaluation - Range of Impaired Functioning Tool (LIFE-RIFT)—The LIFE-RIFT (35) is a clinician-rated scale that assesses psychosocial functioning in four functional domains. These 5 point rater-completed scales provide information about work, interpersonal relations with family and friends, recreation, and overall life satisfaction.

Neuropsychological Assessment

California Verbal Learning Test – 2nd Edition (CVLT-II)—The CVLT-II (36) measures verbal organization during learning and memory in an auditory-verbal modality. It was designed not only to measure how much a participant learned, but also show the strategies they used during learning. Specifically, semantic clustering refers to how much participants group words into their semantic categories during learning (e.g., animals, means of transportation, etc.). The CVLT-II provides indices of verbal organization during learning (semantic clustering), total learning (Trials 1–5), free recall after short and long delays, retention of learned material (long delay free recall vs. trial 5), and recognition.

Delis Kaplan Executive Functioning System (DKEFS)—The DKEFS (37) assesses a variety of executive functions. We administered the Trail Making Test (measures thinking flexibly on a visual-motor sequencing task), Color Word Interference Test (measures ability to inhibit a dominant and automatic verbal response), and Sorting Test (measures concept-formation skills, modality-specific problem-solving skills (verbal/nonverbal), and the ability to explain sorting concepts abstractly). Executive functioning variables of interest included visual-motor switching (Trail Making Test – Number Letter Switching), inhibition (Color Word Interference Test – Inhibition, Inhibition Switching), and conceptual reasoning (Sorting Test – Free Correct Sorts).

Treatment

Cognitive Behavior Therapy (CBT)—This treatment protocol was modeled after the CBT for acute bipolar depression that was also used in the NIMH STEP-BD psychosocial

treatment trial. It is a fully manualized treatment (4, 8). The first-half of the treatment model includes the classic elements of Beck's cognitive therapy (38), including thought records, cognitive restructuring, and activity scheduling. It includes a depression focus phase (9 weekly sessions psychoeducation and basic interventions). Consistent with state of the art CBT treatments, it also includes a flexible modular phase, which focuses on individual problem areas of the greatest concern (7 weekly sessions). Modules of choice for this trial included treatment of comorbid anxiety (39), ADHD skills (40), or emotion regulation (41). Treatment concluded with two sessions of relapse prevention (42).

Supportive Psychotherapy (SP)—SP was chosen as the comparison treatment because it provides nonspecific treatment factors (empathy, support, etc.) but, unlike CBT, it does not provide systematic training in skills to counteract depression (activity scheduling cognitive restructuring, problem solving) (43). The focus of SP is on reflecting and expressing feelings about current life issues. Patients are supported and comforted when coping with difficult situations, depression, mood swings, or anger. The general treatment techniques used are described in detail by Winston, Rosenthal & Pinsker (44). Briefly, for this study, SP included psychoeducation and mood charting to make it more similar to CBT in demand characteristics.

fMRI Memory Paradigm

The verbal learning fMRI paradigm was modeled after the California Verbal Learning Test (CVLT; see Neuropsychological Assessment, (36)). Participants were presented with words on a screen or a Fixation condition. In the 30-second *Fixation* condition, subjects looked at a black fixation cross on a gray screen, and were told to rest their minds. There were 2 word-related conditions: (1) Unrelated, and (2) Directed. In the 36-second *Unrelated* condition, subjects were asked to memorize words that were semantically dissimilar. In each 36 second block, a total of 12 words were presented, each word every 3 seconds in black letters on a gray screen. The words were visible on the screen for 2.5 seconds, followed by 0.5 seconds of blank screen. Subjects were informed that the words are unrelated to each other, and that they should memorize the words in any order. To investigate the effect of verbal organization (semantic clustering), in the 36-second *Directed* iteration, subjects were presented words in black letters on a gray screen that were linked semantically (could be grouped into different categories; e.g., fruits, clothes, etc.). Subjects were informed that the words could be grouped by category and were instructed to use this information to memorize them. A word from a given category was never followed by a word from the same category. Therefore, subjects had to reorder the words in working memory. Subjects completed four runs of the memory paradigm. Each run consisted of 2 Fixation conditions (at the beginning and end), 2 Directed blocks, and 2 Unrelated blocks. The order of the directed and unrelated condition blocks were counterbalanced. Following scanning, participant completed a long delay free recall and recognition tests. The behavioral measures were then computed using: 1) Number of correctly recalled words, and 2) Semantic clustering. Semantic clustering measured the subjects' tendency to group words together as per their shared semantic features. Clustering scores were calculated to reflect the proportion of clustered responses out of the total possible clusters for that condition. Thus, the semantic clustering score was defined as: [clusters/(words recalled–categories recalled)].

fMRI Data Acquisition and Analyses

Functional magnetic resonance imaging (fMRI) data were acquired using a Siemens TrioTim 3.0T whole body high-speed imaging device equipped for echo planar imaging (EPI) (Siemens Medical Systems, Iselin NJ) with a 3-axis gradient head coil, using a gradient echo T2*-weighted sequence (TR = 1.5sec, TE = 30msec). SPM8 (Wellcome Department of Cognitive Neurology, London, UK) software was used for image processing. FMRI images were motion corrected, spatially normalized to the standardized space established by the Montreal Neurologic Institute (MNI; www.bic.mni.mcgill.ca), resampled to 2mm³ voxels, and smoothed with a three-dimensional Gaussian kernel of 6 mm width (FWHM). All collected data had minimal head motion (< 3 mm linear movement in the orthogonal planes; <0.5 degrees radians of angular movement).

The general linear model was applied to the time series, convolved with the canonical hemodynamic response (45) function and a 128s high-pass filter. For each subject, condition effects were modeled with box-car regressors representing the occurrence of each block type (Fixation, Unrelated, Directed). For each subject (first-level analysis, individual subjects' analysis), condition effects were estimated at each voxel, and statistical parametric maps (SPMs; i.e. contrast images) were produced reflecting a linear increase in BOLD signal from the Fixation to Unrelated to the Directed condition (i.e. fixation < unrelated < directed). These contrast images (SPMs) from the individual subjects analysis were entered into a second-level analysis using a *t*-test with group (bipolar vs. controls) as the between subjects factor. For the a priori specified regions of interest (dorsolateral PFC and hippocampus) we adopted a statistical threshold of $p < .05$, uncorrected (46) followed by a whole-brain analyses with a Family-wise Error (FWE) corrected statistical threshold of $p < .05$.

For the predictor analysis, change in HDRS score (from pre- to post- treatment) we conducted a regression analysis for the bipolar participants ($n = 17$) who completed treatment and had usable fMRI data. HDRS change scores were regressed against the linear contrast image (Fixation<Unrelated<Directed; F<U<D), with baseline HDRS scores included as a covariate in the model. Correlations in a priori regions (dorsolateral PFC and hippocampus) were tested for significance at a value of $p < .05$ (one-tailed, uncorrected), and subsequent whole-brain correlations were evaluated at $p < .001$. The $p < .001$ was used instead of the FWE $p < .05$ in order to minimize the risk of Type II Errors, given that the correlation analysis only included $n = 17$ bipolar subjects (41).

Clinical and Neuropsychological Data Analyses

First, mixed-effects regression models (MRMs) were conducted on the Intent-to-Treat (ITT) sample via SPSS MIXED, comparing change in depression, mania, and functioning between CBT and SP. MRMs allow for the dependencies inherent in repeated assessments, are robust to missing data, and can be used to estimate scores using group trajectories. MRMs were used to assess the effects of treatment condition, and treatment condition-by-time, on the HDRS, YMRS, and LIFE-RIFT, in the thirty-six week combined treatment and follow-up phase. Based on previous studies (7, 8), we anticipated a large effect size for the comparison between CBT and Supportive Psychotherapy that could be detected with a sample between 20–30 participants at >90% power. This level of power also enables detection of differences

in HDRS change scores across the two groups of >3 points at post-treatment; a group difference of 3 points between conditions has previously been reported in CBT/antidepressant vs. placebo studies for mood disorders, as meaningful.

Baseline impairments on neuropsychological tests were evaluated using one-sample t-tests compared to the population mean. We also investigated whether pre-treatment cognitive performance predicted change in depressive symptoms among participants who completed post-treatment assessment. Pre-post difference scores were then calculated for change in HDRS scores between baseline and post-treatment and Pearson's bivariate correlations were used to assess the association with baseline cognitive performance. Linear regression models, including an interaction term for baseline cognitive performance by treatment group, evaluated whether the impact of cognitive performance on depression symptom improvement differed by treatment modality.

Results

Descriptive Statistics

Participants were an average of 40.21 years old ($SD = 13.13$), with a mean of 15.19 years of education ($SD = 1.59$). Average HDRS score was 20.93 ($SD = 3.19$), indicative of severe current depressive symptoms. Residual symptoms of mania were low ($M = 3.87$, $SD = 3.36$). There were no significant differences between groups on demographic or clinical measurements, indicating that randomization was successful. These descriptive statistics, including fMRI behavioral data, are reported in Table 1. Additionally, treatment completers ($n = 24$) did not differ from patients who were lost to follow-up ($n = 8$) on baseline clinical severity or memory performance (all p 's $> .08$). Patients whose data was used for the fMRI analysis had lower baseline HDRS scores ($M = 19.76$, $SD = 2.70$) compared to participants with unusable fMRI data ($M = 22.07$, $SD = 3.34$), but otherwise did not differ in mania severity or memory performance (all p 's $> .09$).

Clinical Results

Figure 2 illustrates the MRM results for the ITT sample including main and interaction effects for all primary outcome variables (depression, mania, functioning). Patients in both treatment groups demonstrated significant improvements in depressive symptoms ($F = 39.40$, $df = 82.66$, $p < .001$) and functioning ($F = 8.31$, $df = 75.93$, $p = .005$) between baseline and follow-up. Manic symptoms did not change significantly over time in both treatment groups ($F = 1.98$, $df = 84.07$, $p = .163$). There were no treatment group $\times$ time interactions for any outcome variable, indicating that CBT and SP yielded comparable improvement in depression and functioning. The average HDRS change scores for CBT ($M = 9.28$, $SD = 6.11$) and SP ($M = 10.60$, $SD = 5.10$), corresponded to a small effect size (Cohen's $d = .23$), which would have required a sample of 598 participants to detect any difference at 80% power. Additional statistical parameters for the model covariates are reported in Table 2.

Neuropsychological Results

Table 1 displays average scores for the CVLT-II and DKEFS subtests in the full sample and across treatment conditions. Participants randomized to SP and CBT performed comparably on all CVLT-II and DKEFS measurements (see Table 1). Participants in CBT were characterized by a higher IQ estimated based upon the WTAR Word Reading Standard Score (see Table 1); this difference was not associated with change in HDRS over treatment ($r = -.13$, $p = .55$). Bipolar patients clustered between one-half and one standard deviation below average on CVLT-II memory interference (Trial B), short delay free recall, long delay free recall, and recognition hits. In contrast, learning (Trials 1–5), retention (long delay free recall vs. Trial 5), semantic clustering, and executive functioning (number-letter switching, inhibition, inhibition-switching, free sorting) did not differ from the norm.

Baseline neuropsychological scores were used to predict HDRS symptom change in a sample of $N = 24$ treatment completers. Better retention of learned information (long delay free recall vs. Trial 5) was associated with greater improvement in depression ($r = .46$, $p = .02$). Similarly, better recognition (recognition hits) was associated with greater improvement in depression ($r = .41$, $p = .04$). These correlations are displayed in Figure 3, panels A (retention) and B (recognition). These associations remained significant after controlling for WTAR Word Reading Scores (CVLT-II Retention: $p = .023$; CVLT-II Recognition: $p = .046$). If a Bonferroni correction is applied, neither correlation remains significant; the correlation with CVLT-II retention does survive using 95% confidence intervals with iterative bootstrapping. Change in HDRS from pre- to post-treatment was not associated with CVLT-II semantic clustering ($r = .11$, $p = .61$), CVLT-II Trials 1–5 ($r = .05$, $p = .82$), CVLT-II Trial B ($r = .06$, $p = .79$), CVLT-II Short Delay Free Recall ($r = .14$, $p = .51$), CVLT-II Long Delay Free Recall ($r = .25$, $p = .24$). Nor was change in HDRS associated with performance on the DKEFS Trails Number Letter Switching ($r = -.22$, $p = .31$), Color Word Inhibition ($r = -.32$, $p = .13$), Color Word Inhibition-Switching ($r = -.30$, $p = .15$), or Free Sorting ($r = -.19$, $p = .40$). None of the interaction terms in linear regression models testing whether the relationship between baseline cognitive performance and HDRS change differed between treatment groups were significant (all p 's $> .08$).

fMRI Memory Paradigm

Performances by group on the fMRI memory paradigm are reported in Table 1. Both bipolar and HC subjects used semantic clustering strategies to learn words in the Directed condition ($M_{BP} = .59$, $M_{NC} = .55$). There were no differences between bipolar and HC groups in the use of semantic clustering ($t(49) = 0.43$, $p = .66$) or in correctly recalled words for the unrelated ($t(49) = 1.68$, $p = .10$) and directed conditions ($t(49) = 1.05$, $p = .30$). There were also no significant differences between bipolar and HC free recall scores ($t(49) = -1.40$, $p = .17$). Semantic clustering scores were positively correlated with the free recall score in the Directed condition ($r = 0.38$, $p < .01$).

BOLD Response During Encoding in Bipolar and Healthy Control Subjects

The a-priori region of interest analyses demonstrated no group differences in activation in either the dorsolateral PFC or the hippocampus ($p > .05$, uncorrected). Both groups demonstrated significant bilateral linear increases in the dorsolateral PFC and hippocampus

(Figure 4, Panels a.1– b.2). Whole brain analyses demonstrated no significant group differences in BOLD activity across task conditions, though both the bipolar and HC groups showed robust linear increases in many regions, including the bilateral posterior parietal cortex (BA 7) and right ventrolateral prefrontal cortex (BA 44).

BOLD Response During Learning in Bipolar Disorder and Depressive Symptom Improvement in Psychotherapy

Figure 4 shows voxels in bipolar subjects whose activity in the linear contrast ($F < U < D$) was significantly positively correlated with HDRS change scores, adjusted for baseline HDRS. There were a-priori positive associations between improvement in HDRS scores and activation in the left dorsolateral PFC (BA 9, $p < 0.01$) and the right hippocampus ($p < 0.001$). Whole-brain uncorrected analysis also indicated that depression improvement was associated with activation in the right inferior parietal lobule/supramarginal gyrus (BA 40, $p < 0.001$) and right ventrolateral PFC (BA 44; $p < 0.001$). Coordinates of significant clusters in the whole brain regression are included in Supplemental Table 1.

Discussion

We set out to investigate the impact of neuropsychological performance and neural functioning on response to psychotherapy for depression. In this pilot study, CBT and SP showed no difference in their benefit for depressive symptoms. However, across the treatment conditions, better memory performance predicted better treatment outcome; specifically, patients with better verbal memory retention and recognition were more likely to improve, regardless of treatment type. Dorsolateral PFC and hippocampus activation in bipolar participants predicted improvement in depressive symptoms from pre- to post-treatment.

The finding that patients with better verbal retention and recognition showed greater improvement in depressive symptoms in CBT and SP is consistent with findings in major depression (10). Of note, poor verbal recall has also been linked to recurrence of mania following supportive psychotherapy for relapse prevention in bipolar disorder (47). We had anticipated that verbal organization during encoding would also predict treatment response, given that difficulties in learning and impaired organization have been linked to impaired long-delayed recall in multiple studies (19, 48, 49). In our study, these indices were unrelated to response to psychotherapy. Rather, the ability to retain information predicted outcome. There is evidence that memory support strategies are commonly used in CBT, and that this use is linked to better memory and treatment outcome (11). Therefore, patients with poorer memory for session content or recognition of strategies and skills may respond more poorly to CBT where these skills are important. Moreover, if you are unable to recognize the material from either treatment modality, it is unlikely that any change makes it into daily life. As verbal recognition is a proxy for the verbal content discussed in session, an inability to recognize this material will preclude patients from applying anything in real life and restrict illness improvement. Nevertheless, it is possible that across both treatments, the learning environment in session (e.g., specific topics during a given session, time spent on topic, elaboration through discussion with the therapist) may well have compensated for any

initial learning difficulties, leaving impaired recall and recognition as the only predictor of outcome in our study; difficulties retaining information once learned may play out once the session is over and the new knowledge is not sufficiently consolidated over time. Formal mediation analyses in larger samples could test these hypotheses.

Bipolar patients and HCs did not differ in activation of the dorsolateral PFC, hippocampus, or any other brain regions during encoding. Yet, the degree to which patients activated these structures, in addition to other fronto-parietal areas, predicted treatment response. The dorsolateral PFC plays an important role for learning new information, including the ability to monitor, manipulate, and update the contents of working memory (26). Likewise, the hippocampus is well known for its role in encoding and retention of new information (26). Therefore, what differentiates patients from controls is not the recruitment of these structures during encoding overall, but if individuals with bipolar disorder are impaired in their ability to recruit these structures during encoding, it seems to have an impact on the success of psychotherapy.

Although novel, our study must also be interpreted in light of some limitations. First, the sample size of this study is relatively small, limiting our power to detect possible moderating effects of the neuropsychological and neuroimaging markers between each treatment modality. Moreover, the correlations between CVLT-II retention and recognition should be interpreted cautiously, seeing as how they did not survive a stringent Bonferroni correction. Nevertheless, the correlations were of a medium effect size, which is noteworthy within this pilot study. The neuroimaging findings, in particular, should also be interpreted cautiously, as the analyses involved an even smaller subset of participants. Second, we were only able to assess predictors of treatment outcome in the sub-sample of treatment completers and cannot comment on whether neuropsychological functioning or baseline neural circuitry might relate to attrition. Third, we evaluated neural correlates of encoding but did not assess the neural substrates of retention and recognition. Finally, as is typical in most psychotherapy studies for bipolar disorder (51), participants were taking at least one psychiatric medication. We are not able to dissociate the extent to which psychiatric medications had an effect on cognitive functioning or the neural circuitry sub-serving cognitive functions (52, 53).

In summary, our pilot study showed that better verbal retention and recognition predict better response to psychotherapy for bipolar depression. We also demonstrated that improvement in treatment is related to the degree to which patients engage frontal and medial limbic regions when encoding new information. These findings offer possible clinical utility, pending replication: patients with strengths in verbal retention and recognition may be especially good candidates for psychotherapy. This is also the first study to show that improvement in depression is, in part, related to recruitment of brain regions supporting encoding and learning new information, which requires further investigation in larger samples. Future research can test whether therapeutic modulation of neural networks during encoding (54), as well as cognitive remediation of retentive memory problems, enhances benefit from psychotherapy for bipolar depression. One promising meta-analysis in patients with heterogeneous psychotic and mood disorders supports that cognitive remediation interventions are associated with neuropsychological improvement (55). Although a direct comparison of in-person vs. computerized methods is needed, provisional integration of

cognitive remediation strategies (organization, planning, time management) could help augment traditional psychological treatments for patients with cognitive sequelae.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- This trial compared CBT and Supportive Psychotherapy for bipolar depression.
- CBT and SP yielded comparable improvement in depressive symptoms from pre- to post-treatment.
- Better retention and recognition of learned information predicted improvement in treatment.
- Activation of the DLPFC and hippocampus during encoding predicted depression improvement.

Figure 1.
Consort Diagram for Bipolar I Disorder Participants Enrolled in Randomized Trial of CBT
vs. SP

Figure 2. Changes in Depression, Mania, and Functioning in Bipolar Disorder Type I Depressed Participants Receiving CBT vs. SP.

Panel A. CVLT-II Retention & HDRS Change

Panel B. CVLT Recognition Hits & HDRS Change

Figure 3.
Association between Verbal Retention, Recognition, and Change in Depression

Figure 4.

Foci of significant activation for linear contrast $F < U < D$ (Panels a.1– b.2) and in HDRS treatment change regression (c.1–d.2)

Panel a.1: DLPFC activation in healthy control subjects ($p < .001$); Panel a.2: Hippocampus activation in healthy control subjects ($p < .05$); Panel b.1: DLPFC activation in bipolar subjects ($p < .001$); Panel b.2: Hippocampus activation in bipolar subjects ($p < .05$); Panel c.1: DLPFC cluster associated with HDRS change ($p < .001$); Panel c.2: Hippocampus cluster associated with HDRS change ($p < .05$); Panel d.1: DLPFC contrast weights and HDRS change; Panel d.2: Hippocampus contrast weights and HDRS change

Demographic, Clinical, and Neuropsychological Characteristics of Bipolar Patients and Healthy Controls in Intent-to-Treat and Neuroimaging Subsamples

Table 1

Demographic & Clinical	Intent to Treat Bipolar Sample				fMRI Sub-Sample					
	Overall (N = 32)		CBT (n = 17)		SP (n = 15)		HC (n = 34)		Bipolar (n = 17)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age	40.21	13.13	38.76	13.8	42.00	13.52	33.20	11.93	37.80	14.18
Sex (% Female)	50%	n=16	52.90%	n=9	46.70%	n=7	44.10%	n=15	64.71%	n=11
Years of Education	15.00	1.59	15.20	1.23	14.93	1.94	15.70	1.83	15.90	0.99
HDRS	20.93	3.19	20.88	3.98	20.80	2.11	1.34	1.75	19.81	2.72
YMRS	3.87	3.36	4.23	4.02	3.46	2.64	0.66	1.26	3.47	2.37
LIFE-RIFT	14.60	3.70	14.35	3.72	14.86	3.91	--	--	14.71	3.33
Neuropsychological	Mean	SD	Mean	SD	Mean	SD	t	p	--	--
WTAR Word Reading	110.94	10.50	115.06	7.94	106.27	11.31	2.57	.02	--	--
CVLT-II										
Trials 1-5	-0.20	12.74	51.12	12.37	45.67	12.95	1.22	.23	--	--
Trial B *	-0.70	1.14	-0.62	0.88	-0.80	1.40	0.45	.66	--	--
Short Delay Free Recall *	-0.42	1.40	-0.15	1.48	-0.73	1.28	1.19	.25	--	--
Long Delay Free Recall *	-0.53	1.37	-0.44	1.41	-0.63	1.36	0.39	.70	--	--
Retention	-0.47	0.67	-0.24	0.68	0.17	0.62	-1.73	.09	--	--
Recognition Hits *	-0.80	1.51	-0.47	1.35	-1.17	1.63	1.32	.20	--	--
Semantic Clustering	-0.05	1.12	-0.03	1.10	-0.07	1.19	-0.09	.93	--	--
DKEFS										
Trail Making Test	9.37	2.80	10.23	2.08	8.23	3.26	1.93	.07	--	--
Number-										
Letter Switching										
Color-Word Inhibition	9.71	2.65	10.41	2.00	8.86	3.13	1.68	.11	--	--
Color-Word Inhibition-Switching	9.06	3.01	9.71	2.62	8.29	3.36	1.32	.20	--	--
Sorting Test Free Sorting Description	9.93	3.43	10.25	3.00	9.54	3.99	0.55	.59	--	--
fMRI Memory Paradigm	--	--	--	--	--	--	Mean	SD	Mean	SD

Demographic & Clinical	Intent to Treat Bipolar Sample				fMRI Sub-Sample			
	Overall (N = 32)	CBT (n = 17)	SP (n = 15)	HC (n = 34)	Bipolar (n = 17)	Mean	SD	SD
Total Words Recalled	--	--	--	19.00	14.47	11.66	8.89	
Directed List Words	--	--	--	14.85	12.17	8.53	8.61	
Unrelated List Words	--	--	--	4.14	2.29	4.29	1.99	
Semantic Clustering	--	--	--	0.55	0.59	0.31	0.34	

* Denotes significant difference in one-sample t-test between overall sample mean from population mean

Table 2

Estimates of Fixed Effects of Group, Time, and their Interaction on Depression, Mania, and Functioning.

Parameter	Estimate	Std. Error	df	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
HDRS						
Intercept	19.82	1.21	83.24	0.00	17.42	22.22
Treatment	-1.18	1.65	83.16	0.48	-4.47	2.11
Time	-3.96	0.63	82.66	0.00	-5.22	-2.71
Treatment $\times$ Time	0.17	0.87	81.53	0.84	-1.56	1.91
YMRS						
Intercept	4.11	1.30	86.36	0.00	1.52	6.70
Treatment	0.03	1.79	86.27	0.99	-3.52	3.59
Time	0.97	0.69	84.07	0.16	-0.40	2.35
Treatment $\times$ Time	-0.47	0.96	83.04	0.63	-2.37	1.44
LIFE-RIFT						
Intercept	14.61	0.84	57.95	0.00	12.93	16.30
Treatment	-1.13	1.15	57.91	0.33	-3.44	1.19
Time	-1.08	0.37	75.93	0.01	-1.83	-0.33
Treatment $\times$ Time	0.04	0.52	74.52	0.94	-0.99	1.07