Modulation of Cortical-Limbic Pathways in Major Depression

Treatment-Specific Effects of Cognitive Behavior Therapy

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Background: Functional imaging studies of major depressive disorder demonstrate response-specific regional changes following various modes of antidepressant treatment.

Objective: To examine changes associated with cognitive behavior therapy (CBT).

Methods: Brain changes underlying response to CBT were examined using resting-state fluorine-18-labeled deoxyglucose positron emission tomography. Seventeen unmedicated, unipolar depressed outpatients (mean±SD age, 41±9 years; mean±SD initial 17-item Hamilton Depression Rating Scale score, 20±3) were scanned before and after a 15- to 20-session course of outpatient CBT. Whole-brain, voxel-based methods were used to assess response-specific CBT effects. A post hoc comparison to an independent group of 13 paroxetine-treated responders was also performed to interpret the specificity of identified CBT effects.

Results: A full course of CBT resulted in significant clinical improvement in the 14 study completers (mean±SD posttreatment Hamilton Depression Rating Scale score of 6.7±4). Treatment response was associated with significant metabolic changes: increases in hippocampus and dorsal cingulate (Brodmann area [BA] 24) and decreases in dorsal (BA 9/46), ventral (BA 47/11), and medial (BA 9/10/11) frontal cortex. This pattern is distinct from that seen with paroxetine-facilitated clinical recovery where prefrontal increases and hippocampal and subgenual cingulate decreases were seen.

Conclusions: Like other antidepressant treatments, CBT seems to affect clinical recovery by modulating the functioning of specific sites in limbic and cortical regions. Unique directional changes in frontal cortex, cingulate, and hippocampus with CBT relative to paroxetine may reflect modality-specific effects with implications for understanding mechanisms underlying different treatment strategies.
response to CBT for depression. The literature characterizing brain changes associated with CBT response is sparse and based largely on the treatment of obsessive-compulsive and anxiety disorders. Theoretical models of CBT action in the treatment of depression generally implicate top-down mechanisms, because the intervention focuses on modifying attention and memory functions involved in the mediation of depression-relevant cognitions, affective bias, and maladaptive information processing. The time course of symptom changes with CBT further supports an initial cortical site of action, as improvement in hopelessness and views of self and mood generally precede changes in vegetative and motivational symptoms—a timeline not seen in patients treated with pharmacotherapy. Brain correlates of this chronology are, however, untested. Recent functional imaging studies examining brain changes following interpersonal psychotherapy report a variety of regional effects, but there is no consistent pattern across the few published studies.

A critical question is whether disparate antidepressant treatments result in common or modality-specific neural effects. As a first step in addressing this issue, this study examined changes in regional glucose metabolism measured with positron emission tomography (PET) associated with depression remission following 15 to 20 sessions of CBT. Metabolic change patterns with CBT response were contrasted post hoc with those of a previous study of paroxetine treatment to further test the hypothesis that modulation of distinct neural targets by different interventions within a putative limbic-cortical depression “network” occurs with clinical remission, regardless of the specific treatment modality.

METHODS

PATIENT SELECTION

Seventeen unmedicated, depressed patients (6 men, 11 women; mean ± SD age, 41 ± 9 years; mean ± SD 17-item Hamilton Depression Rating Scale [HDRS] score, 20 ± 3) with symptoms that required treatment were recruited to the Mood and Anxiety Disorders Program at the Centre for Addiction and Mental Health in Toronto, Canada, through newspaper advertisement. The clinical diagnosis of a major depressive episode, unipolar type, was confirmed using the Structured Clinical Interview for DSM-III-R and DSM-IV criteria. By history, none of the enrolled patients were considered treatment refractory. Mean ± SD education was 16 ± 2 years, and 10 of 14 were unmarried. Exclusion criteria included history of neurological disease, head trauma, or other Axis I psychiatric diagnoses, as well as current psychotic symptoms, substance abuse, antidepressant treatment within the preceding month, and pregnancy. Six patients were completely drug naive, and none had been treated with CBT for depression in the past. One patient required antidepressant washout for 4 weeks. Written informed consent was obtained from all participants, and the study was conducted as approved by the Centre for Addiction and Mental Health Ethics Committee.

TREATMENT PROTOCOL

All patients received 15 to 20 individualized outpatient sessions of CBT. Treatment was conducted by 1 of 2 trained CBT therapists (M.L. and P.B.) with 10 and 8 years of experience, respectively, according to the treatment manual described by Beck et al. All CBT sessions were audiotaped to enable ratings of treatment fidelity, which were confirmed by the supervising psychologist (Z.S.). Patients undergoing CBT used a number of therapeutic strategies intended to reduce automatic reactivity to negative thoughts or attitudes and to combat dysphoric mood. Behavioral activation was used to address the disruption of routine often brought on by depression and focused on increasing the frequency of pleasant and masterful events in patients’ lives, especially in those areas where marked avoidance and withdrawal were noted. Cognitive monitoring taught patients how to dissemble seemingly complex chains of thinking and feeling into separate components that could then be evaluated for evidence of biased information processing. Between sessions, patients were asked to test their interpretations and beliefs through the use of behavioral experiments and to record their thinking using thought records. During the sessions, the therapists used collaborative inquiry to guide the patient to a more evidence-based and less reactive construal of their experience.

Clinical response was monitored weekly using the Beck Depression Inventory. The HDRS scores (17-item) were assessed at study onset, at study completion, and once midway through therapy (eighth session). Patients were classified as responders based on the criteria of at least a 50% reduction in HDRS or nonresponders for those with a decrease in HDRS score of less than 20%. Smaller changes in HDRS were assessed at the end of treatment using standard imaging methods and a previously published protocol. Both scans were acquired within 1 week of the first and last therapeutic session. For each scan, a 5-mCi (185-Mbq) dose of fluorine-18–labeled deoxyglucose (FDG) was injected intravenously, with image acquisition beginning after 40 minutes (PC 2048b; GE Medical Systems Inc, Sherborn, Mass). The data were first screened for document compliance. Presence of active random thoughts was not quantitatively assessed. Emission data was acquired during a 35-minute period (approximately 1 million counts per slice; 10-cm field of view). A customized, thermoplastic face mask was used to minimize head movement for the initial scan and for accurate repositioning at the second session. Raw images (13 parallel slices; 6.5-mm center-to-center interslice distance) were corrected for attenuation, reconstructed, and smoothed to a final in-plane resolution of 7.0 mm at full width at half maximum.

DATA ANALYSIS

Statistical analyses were performed using SPM99 statistical software (Wellcome Department of Cognitive Neurology, London, England) implemented in Matlab (version 5.3; Mathworks Inc, Sherborn, Mass). The data were first screened for
## RESULTS

### CLINICAL EFFECTS

Fourteen of the 17 patients completed the full treatment course (mean ± SD number of sessions, 17.7 ± 2 for 26±7 weeks). Three participants withdrew within the first...
2 weeks due to worsening of symptoms (2 patients) or inability to comply with CBT instructions (1 patient); no second scan was acquired for these patients. For the 14 completers, the mean±SD HDRS scores were 20±3 before treatment and 6.7±4 after treatment, with a decrease of 66%±22% \((t=9.66, P<.001)\). Of these 14 completers, 9 patients met the 50% decrease criteria for full response (final mean±SD HDRS score, 4.7±3.5; decrease of 78±17). The remaining 5 patients had no less than a 35% decrease in their HDRS scores (final mean±SD HDRS score, 10.4±0.7). Because of the small overall sample size and lack of a pure CBT nonresponder group, all patients were included in the pretreatment-to-posttreatment analysis. Patients in the paroxetine-treated comparison group had a similar severity of symptoms at baseline (mean±SD HDRS score, 22.8±3.6) and showed a comparable clinical response (posttreatment mean±SD HDRS score, 6.0±4.1; mean±SD decrease of 75%±14%; \(t=17.2, P<.001\)).

**REGIONAL METABOLIC CHANGE EFFECTS**

Treatment with CBT was associated with significant regional metabolic changes (Table, left; Figure 1, top). Areas of increased metabolism before to after treatment included the hippocampus and dorsal midcingulate (BA 24b/c). In addition, widespread decreases were observed in dorsolateral prefrontal (BA 9/46), ventrolateral prefrontal (BA 11/47), and superior and inferior medial frontal regions (BA 9/10/11), as well as posterior cingulate (BA 31), inferior parietal (BA 40), and inferior temporal cortex (BA 20). The same significant metabolic change pattern was seen when the 5 patients who showed less than the 50% response rate were excluded from the analysis. The findings seem specific for clinical response rather than solely the passage of time, because covarying for the HDRS score nullified the between-occasion effects.

**POST HOC ANALYSES**

The conjunctional analysis contrasting CBT response change to paroxetine response change identified significant differences between the 2 treatments in numerous cortical and limbic regions (Table): dorsolateral prefrontal (BA 9), ventromedial frontal (BA 10/11), and inferior parietal (BA 40) cortices, as well as insula, hippocampus, ventral subgenual cingulate (BA 25), anterior and dorsal midcingulate (BA 24), posterior cingulate (BA 31), insula, brainstem, and cerebellum. The separate analyses of the 2 change patterns were in fact necessary to determine which group drove these differences and in what direction (Table).

The dorsolateral prefrontal, inferior parietal, and hippocampal differences identified in this conjunctional analysis represented an inverse pattern for CBT and paroxetine. The between-treatment differences in dorsal midcingulate, ventromedial frontal, and posterior cingulate were related to unique changes with CBT treatment and were not seen with paroxetine at any statistical threshold (Table). Differences involving subgenual cingulate (BA 25), insula, brainstem, and cerebellum like-wise were due to unique paroxetine treatment effects (Table). Similar for the 2 treatments were decreases in ventral prefrontal cortex (BA 47).

Direct comparison of baseline scans for the CBT and paroxetine groups demonstrated no significant differences. There were also no significant correlations between metabolism and weeks of treatment across groups. Finally, covarying the pretreatment and posttreatment changes with the HDRS score nullified the changes in both groups, providing additional evidence that the divergent change patterns reflect treatment-specific response effects.

**COMMENT**

Reciprocal limbic increases (hippocampus, dorsal midcingulate) and cortical decreases (dorsolateral, ventrolateral, and medial orbital frontal; inferior temporal and parietal) were identified following successful treatment with CBT. These regional changes involve sites similar, and in some cases identical, to those seen previously with paroxetine and other pharmacotherapies, but the changes were in the opposite direction.
Figure 2. Schematic model illustrating relationships among regions mediating cognitive behavior therapy (CBT) and drug response. Regions with known anatomical and functional connections that also show significant metabolic changes following successful treatment are grouped into 3 compartments—cognitive, autonomic, and self-reference. Red regions designate areas of change seen with both treatments. Green regions designate changes unique to CBT. Blue regions designate changes unique to paroxetine. Solid black lines and arrows identify known corticobulbom, limbic-paralimbic, and cingulate-cingulate connections. Gray arrows indicate reciprocal changes with treatment. The model proposes that illness remission occurs when there is modulation of critical common targets (red regions), an effect facilitated by top-down (medial frontal, anterior cingulate) effects of CBT (green) or bottom-up (brainstem, striatal, subgenual cingulate) actions of paroxetine (blue). PFF indicates dorsolateral prefrontal; pA4, inferior parietal; pGC, posterior cingulate; mF9/10, medial frontal; aCq24, anterior cingulate; oF11, orbital frontal; bg, basal ganglia; thal, thalamus; Cg25, ventral subgenual cingulate; a-ins, anterior insula; am, amygdala; hth, hypothalamus; and bs, brainstem. Numbers are Brodmann area designations.

Interpreted in the context of an extensive PET and functional magnetic resonance imaging behavior mapping literature, the metabolic change pattern seen with resolution of depressive symptoms following CBT provides tentative neural correlates of the long-theorized psychological or top-down mechanisms that mediate CBT response. Examples of such parallels include localization of tasks involving directed attention, reward-based decision making, and monitoring of emotional salience to the anterior cingulate and orbital frontal cortex; memory encoding, retrieval, and consolidation to the hippocampus; and working memory, self-referential processing, and cognitive ruminations to dorsolateral, medial frontal, and ventral prefrontal cortex, respectively. Components of these behaviors have been implicated in the initiation and maintenance of the depressive state and seem to be specifically targeted in CBT. Although speculative, hippocampal and mid and anterior cingulate increases coupled with decreases in medial frontal, dorsolateral, and ventrolateral prefrontal activity with CBT treatment might be nonetheless interpreted as correlates of CBT-conditioned increases in attention to personally relevant emotional and environmental stimuli associated with a learned ability to reduce online cortical processes at the level of encoding and retrieval of maladaptive associative memories, as well as a reduction in both ruminations and the overprocessing of irrelevant information.

In further support of a critical role for medial frontal modulation with CBT response compared with medication are the unique changes in anterior and dorsal midcingulate (BA 24), medial frontal (BA 10), and orbital frontal (BA 11) with treatment response. Although both groups demonstrated hyperactivity in medial frontal regions before treatment, only CBT was associated with widespread changes. Activation of these regions has been previously associated with emotional processing tasks in nondepressed control participants, including the active rereading and reappraisal of emotional feelings. Exaggerated activity in this region has been similarly reported in depressed patients in response to sad words, supporting the previously recognized negative emotional bias in this patient population. These observations are consistent with nonimaging studies that demonstrate increased relapse risk in those remitted depressed patients with persistent mood-linked reactivity to negative emotional stimuli and increased sustained remission for patients in whom this reactivity is reduced. Referable to the patients in this study, selective changes with CBT in these regions may reflect a reduced bias toward the processing of negative information in the recovered state, with implications for future relapse risk.

The frontal decreases seen with CBT response are strikingly similar to those reported in a recent FDG-PET study of interpersonal psychotherapy for major depression. Regional changes with CBT treatment for other disorders also describe areas of overlap with those reported herein for depression. For instance, changes in the hippocampus are reported with CBT treatment for social phobia, although the changes are in the reverse direction. A third distinct pattern of caudate and posterior orbital cortex decreases has been shown with CBT treatment for obsessive-compulsive disorder. Together, these findings suggest that brain change pattern variations with CBT for various disorders likely reflect both fundamental differences in the underlying psycho-pathology (depression, obsessive-compulsive disorder, social phobia) and procedural differences inherent in the cognitive method used to treat each condition. Method in this context not only refers to the subtleties of the CBT procedures themselves but also includes patient expectation and conditioned learning facilitated by both the specific intervention and the individual physician-patient interaction.

These various elements, inherent in any specified therapy, likely also explain the differences between the pattern of response to CBT and that reported for placebo medication, a response considered by some to be an uncontrolled psychological form of treatment. In the case of fluoxetine treatment for depression, the change pattern for placebo fluoxetine overlapped that seen with response to the active medication to which it was experimentally linked (frontal, parietal increases, subgenual cingulate decreases) rather than the psychological intervention pattern seen here with CBT (frontal decreases, hippocampal increases). Brain changes with placebo response, in fact, directly shadowed the true drug-response pattern, similar to that shown with both an acute dose of a dopamine-agonist in patients with Parkinson disease (striatal dopamine changes) and an acute dose of an opiate analgesic (cingulate and brainstem blood flow changes), suggesting a complex interaction of the specific treatment and expected behavioral effects. Obvi-
ously, a placebo-controlled CBT trial will be necessary to fully test the hypothesis that placebo-response changes mirror the specific intervention to which they are paired, meaning that placebo CBT would be expected to overlap true CBT changes, not those seen with placebo medication. A wait-list control group will also be needed to address effects potentially attributable to spontaneous remission with either treatment.

There are other potential explanations for reported change-pattern differences across various psychological treatment studies for depression, including the type of cognitive intervention (CBT vs interpersonal psychotherapy), the imaging modality (PET vs single-photon emission computed tomography; glucose metabolism vs blood flow), and the point of the second scan within the treatment course (6-8 vs >15 weeks). Although it is possible that brain changes with an incomplete course of a nonpharmacologic treatment may be similar to those seen with full clinical response, this is clearly not the case with antidepressant medication, where analyses of time course (1 vs 6 weeks) and response effects (responders vs nonresponders at 6 weeks) show significantly different metabolic change patterns.37 This may also explain differences in the nonpharmacotherapy treatment change patterns reported across other published reports.34,35 Explicit studies of the time course of brain changes with various cognitive interventions, including a parallel assessment of both responders and nonresponders, are needed to further test these hypotheses. Examination of the time course of change in HDRS scores in this CBT responder group (without corresponding PET scans) would suggest that metabolic change effects might be reasonably seen after 8 sessions (eighth session mean ± SD HDRS score, 11.5 ± 6), perhaps providing an early indication of who is most likely to respond to a full treatment course.50

Despite the absence of a prospective, randomized study design and obvious differences in treatment duration, the post hoc paroxetine comparison performed herein provided several critical clues for further interpreting the identified CBT change effects. Most notably, the conjunctural analyses demonstrated a complex set of change pattern differences between CBT and paroxetine responders. Most significantly, in contrast to the CBT increases in hippocampus and decreases in frontal cortex, the independent paroxetine analyses demonstrated the reverse pattern—frontal increases and hippocampal decreases. The localization and pattern of changes seen in the paroxetine group, including the unique changes in subgenual cingulate (BA 25), insula, and brainstem, replicate previous human and animal metabolic studies of various pharmacotherapies, including other selective serotonin reuptake inhibitors and tricyclics.36-10,21,37

This divergent pattern of frontal decreases and hippocampal increases with CBT relative to paroxetine is not explained by pretreatment metabolic abnormalities, because the 2 groups show no significant differences when directly compared. The differential change patterns also appear not to be simply the result of differences in the mean duration of treatment between the 2 groups, because there were no significant correlations between brain metabolism and weeks of treatment. Interestingly, in both groups, there is considerable overlap between the regions of metabolic change and areas of reported glial cell loss in postmortem studies, notably, dorsolateral, ventrolateral, and medial frontal cortices.73 That said, neither group showed significant baseline hypometabolism in either frontal cortex or hippocampus, suggesting a more complex relationship among glial abnormalities, brain atrophy, and metabolic change patterns than previously suggested.74-76 Quantitative magnetic resonance imaging volumetric analyses, however, were not performed.

Taken together, the treatment-specific change patterns in CBT and paroxetine responders support our initial hypothesis that each treatment targets different primary sites with differential top-down and bottom-up effects—medial frontal and cingulate cortices with cognitive therapy (Figure 2, green) and limbic and subcortical regions with pharmacotherapy (brainstem, insula, subgenual cingulate; Figure 2, blue), both resulting in a net change in critical prefrontal–hippocampal pathways (Figure 2, red). The overall modulation of this complex system rather than any one focal regional change may be most critical for disease remission. As previously stated, definitive conclusions regarding treatment-specific effects will require a randomized design of depressed patients seeking either treatment.

It has been previously suggested that variations in scan patterns both at baseline and following treatment reflect such clinical factors as illness severity, cognitive impairment, anxiety, psychomotor retardation, and depressive subtypes.77-81 In this study, there were no significant differences in illness severity, demographics, HDRS factor scores, or any other depression-related variable that might alternatively explain the differential metabolic change patterns across the 2 treatment groups. Detailed neuropsychological testing, however, was not performed. Although the paroxetine comparison group was exclusively composed of men, no significant sex differences were seen in either the baseline scans or change patterns of the CBT group, although statistical power was inadequate to definitely exclude sex effects.

Another potential confounder is the ongoing behavior of each patient at the time of each scan, particularly since patients were studied in a relatively uncontrolled state (eyes-closed rest). Previous studies92,83 during a variety of cognitive tasks demonstrate that medial frontal regions show decreases relative to rest, suggesting an ongoing activation of these regions in the resting state. The medial frontal increases, seen at baseline in both the CBT and paroxetine patients relative to healthy controls, although possibly interpretable as a pretreatment marker of increased attention to self, do not appreciably change with treatment, despite clinical improvement. Furthermore, the localization of these reported self-directed resting state markers is considerably more causal to those demonstrated herein either at baseline or with CBT response, suggesting that these baseline and change effects reflect disease rather than a confounding of the short-term behavioral state.

Similarly, in test-retest studies94-96 that examined effects of test environment, novelty, and levels of anxiety, published reports demonstrate a pattern of hyperactivity in lateral frontal cortices associated with the first test condition. Again, neither group in this study showed this dor-
solateral prefrontal pattern at rest, although both groups showed significant changes in these regions following clinical recovery. Although neither group was tested explicitly for state anxiety at the time of the scan, anxiety subscales of the HDRS performed just before each scan session showed no differences between the groups at baseline. In addition, comorbid anxiety disorders were among protocol exclusion criteria. It is possible that the absence of prefrontal findings at baseline reflect a first-test effect in both groups, in essence, counteracting the expected frontal hy-pometabolism typical of many published studies of major depression.70 This, however, would not explain the differ-ential changes in frontal cortex seen following treatment where again both groups showed comparable anxiety sub-scale scores. In the absence of more subtle behavioral mea-sures, there is no evidence to support the conclusion that the disparate changes in frontal activity for one group rela-tional to other are a function of state anxiety. The poten-tial contributions of other uncontrolled individual vari-ables, such as family history, specific gene polymorphisms, temperament, early life abuse, or previous depressive epi-sodes, were not examined.97,98

Finally, although the 2 groups were studied as inde-pendent cohorts, met identical inclusion criteria, and were recruited through the same media outlets, the pos-sibility of a selection bias still exists. A trial with ran-dom assignment of patients to 1 of the 2 treatments of comparable duration is needed to fully address this concern and is the focus of an ongoing study. That said, it is wet-ten worth noting that the self-selection by patients of a spe-cific antidepressant intervention may reflect their proba-bilistic calculation of benefit, taking past treatment into account. Anecdotally, many of those in the CBT group who had previously been treated with medication ex-pressed strong disinterest in repeating pharma-cotherapy. In fact, many demonstrated considerable in-sight, believing that their negative thoughts and beliefs were causing and maintaining their depressive state. In addi-tion, those who had taken antidepressant medica-tions in the past tended to minimize their effectiveness due to associated adverse effects. These subjective re-port may provide important targets for future investi-gations of the predictive value of patient treatment prefer-ences and their neural correlates.97

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