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Lateralization for speech predicts therapeutic response to cognitive behavioral therapy for depression

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ABSTRACT

A prior study (Bruder, G.E., Stewart, J.W., Mercier, M.A., Agosti, V., Leite, P., Donovan, S., Quitkin, F.M., 1997. Outcome of cognitive-behavioral therapy for depression: relation of hemispheric dominance for verbal processing. *Journal of Abnormal Psychology* 106, 138–144.) found left hemisphere advantage for verbal dichotic listening was predictive of clinical response to cognitive behavioral therapy (CBT) for depression. This study aimed to confirm this finding and to examine the value of neuropsychological tests, which have shown promise for predicting antidepressant response. Twenty depressed patients who subsequently completed 14 weeks of CBT and 74 healthy adults were tested on a Dichotic Fused Words Test (DFWT). Patients were also tested on the National Adult Reading Test to estimate IQ, and word fluency, choice RT, and Stroop neuropsychological tests. Left hemisphere advantage on the DFWT was more than twice as large in CBT responders as in non-responders, and was associated with improvement in depression following treatment. There was no difference between responders and non-responders on neuropsychological tests. The results support the hypothesis that the ability of individuals with strong left hemisphere dominance to recruit frontal and temporal cortical regions involved in verbal dichotic listening predicts CBT response. The large effect size, sensitivity and specificity of DFWT predictions suggest the potential value of this brief and inexpensive test as an indicator of whether a patient will benefit from CBT for depression.

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1. Introduction

Cognitive behavioral therapy (CBT) is an evidence-based treatment for depression but, like medication, it is effective in only 40% to 60% of patients having a major depressive disorder (MDD) (DeRubeis et al., 2005; Siegle et al., 2011). This has led to research to identify predictors to aid in selecting a treatment that will benefit a patient. Although there are encouraging findings for potential neuroimaging biomarkers (Siegle et al., 2012; McGrath et al., 2013), these tests are expensive and may be difficult to implement in clinical settings. Although studies have raised the possibility of developing inexpensive behavioral tests for predicting response to CBT, the findings of early studies using self-report measures of beliefs or attitudes were conflicting (Rude and Rehm, 1991; Sotsky et al., 1991). There has, however, been less research

on whether performance on neuropsychological tests of cognitive abilities might predict CBT response. Studies using self-administered tests as estimates of IQ have reported conflicting findings. Haaga et al. (1991) measured vocabulary and abstraction scales in depressed patients, but found no relationship between IQ estimates and CBT outcome. More recently, Fournier et al. (2009) derived IQ scores from the Shipley–Hartford Living Scale and found higher estimates of intelligence before CBT or antidepressant medications were associated with lower depression ratings at end of treatment.

Cognitive therapies are highly verbal treatments that involve self-monitoring and re-evaluation of negative thoughts, emotions and cognitive distortions, which may be mediated by cognitive skills in which verbal abilities play an important role. Treatment success may therefore depend on verbal skills and activation of the left hemisphere, which is dominant for language processing in most right-handed individuals (Otto et al., 1987). In our initial study (Bruder et al., 1997), we found that clinical response to CBT for depression was related to left-hemisphere advantage for verbal dichotic listening. Different consonant–vowel syllables were simultaneously presented to the left

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and right ears, and the difference in accuracy of performance between ears provided an index of perceptual asymmetry (PA). Depressed patients who responded to 16 weekly CBT sessions ($n=15$) had more than twice the right ear advantage than non-responders ($n=12$). Patients with right ear accuracy greater than healthy controls had a 75% response rate, whereas those with less than normal right ear accuracy had only a 20% response rate. Given the largely contralateral projections between each ear and hemisphere, this is consistent with the hypothesis that patients with greater left-hemisphere advantage for verbal processing benefit more from CBT than other depressed patients. In contrast, there was no difference between CBT responders and non-responders in PA for a non-verbal dichotic listening test, which further supports left hemisphere dominance for verbal processing as a key predictor of response to CBT for depression. It is, however, important to demonstrate that this predictor is reliable and the findings replicable.

The main purpose of the present study was to attempt to replicate our findings in a new sample of depressed patients using a Dichotic Fused Words Test (DFWT), which yields a robust left hemisphere advantage in healthy adults (Wexler and Halwes, 1983). In this test, words that rhyme (e.g., coat and goat), are simultaneously presented to right and left ear. These words fuse into a single percept and accuracy for reporting the word in the right or left ear provides a measure of PA. This test has been shown to yield valid estimates of hemispheric lateralization for speech as determined by intracarotid amobarbital injections (Zatorre, 1989; Fernandez and Smith, 2000), and has high test–retest reliability ($r=0.85$; Wexler and Halwes, 1983). Patients having a depressive disorder were tested on the DFWT prior to receiving CBT, and healthy adults were tested to provide normative data. We previously found that depressed patients who respond to an antidepressant had a larger left hemisphere advantage than non-responders on the DFWT, and the mean PA for healthy adults can serve as a meaningful criterion for predicting treatment response (Bruder et al., 1996, 2004, 2007). Based on our prior findings, we hypothesized that CBT responders would have stronger left hemisphere advantage than non-responders, and patients with nominally above average left hemisphere advantage would be predicted to respond to CBT.

A secondary purpose was to examine performance on selected neuropsychological tests that have shown promise for predicting therapeutic response to antidepressants. Specifically, we used word fluency, psychomotor speed, and Stroop tests, which have been associated with response to antidepressants (Dunkin et al., 2000; Taylor et al., 2006; Gorlyn et al., 2008; Bruder et al., 2014). The National Adult Reading Test (NART) was also administered to provide estimates of premorbid intelligence (Bright et al., 2002). We examined whether or not these tests would also predict response to CBT, and in particular, evaluated the hypothesis that response to CBT depends on general verbal skills or cognitive abilities assessed by these tests.

2. Methods

2.1. Participants

Outpatients at the Depression Evaluation Service of the New York State Psychiatric Institute were recruited for this study before beginning a clinical trial of CBT and healthy controls were recruited from the New York metropolitan area. The patients met the DSM-IV-TR criteria for MDD ($n=16$) or dysthymia ($n=4$), and one of the dysthymic patients had comorbid anxiety disorders (panic disorder and social phobia),¹ as determined by the Structured Clinical Interview for DSM-IV Axis

I Disorders (SCID-I; First et al., 1995). Additionally, patients scored at least a 13 or higher at baseline on the Beck Depression Inventory (BDI-II; Beck et al., 1996). Exclusion criteria for patients were lifetime or current diagnoses of schizophrenia or any other psychotic disorder, major depressive disorder with psychotic or catatonic features, bipolar disorder, organic mental disease, or current substance abuse or dependence in the last 6 months (except nicotine or caffeine dependence). Patients with a prior history of treatment failure with CBT or who were currently receiving any form of psychotherapy or counseling were also excluded. Three patients (two who subsequently responded to CBT and one non-responder) were permitted to participate in the study while on concurrent antidepressant medication, but their doses were stabilized for a minimum of three months prior to study entry. Patients who clinically worsened during treatment could also be considered for medication. One patient (a non-responder) began an antidepressant after the 8th week of CBT.² All participants were required to be in good general medical and neurological health. This was established in patients via physical examination as part of the initial screening. Participants were excluded if they had an unstable medical or neurological condition or a hearing loss greater than 30 dB at 500, 1000 or 2000 Hz. The healthy controls were tested on the DFWT as part of a separate study in our laboratory over the same time frame as the patients and were screened using the Structured Clinical Interview for DSM-IV Axis I Disorders, Nonpatient Edition (First et al., 1996) to exclude those with Axis I disorders, except for nicotine dependence. All participants were right-handed and fluent in English. The New York State Psychiatric Institute Institutional Review Board (IRB) approved the protocol. All patients provided informed consent prior to enrolling in the study.

2.2. Treatment protocol

Twenty patients completed 14 weekly 50 min sessions of CBT free of charge. Therapy sessions used a CBT manual protocol for depression (Emery, 2000). The study author (RK) is a CBT therapist who has been in clinical practice for 25 years, and has been providing CBT sessions in different studies at New York State Psychiatric Institute (NYSPI) for the past 8 years. Her sessions are rated by the Beck Institute in Philadelphia on a regular basis and have reached adherence. CBT was provided by 3 graduate students of Clinical Psychology who were at the last phase of their PhD program and had extensive clinical experience in externships before joining the study. They were selected and screened by the study author (RK) and the head psychologist of NYSPI (L. Mufson). Before seeing patients in the study, all therapists received a treatment manual and training consisting of a short theoretical course and role playing in a clinical setting. Under the supervision of the study author (RK), they were assigned at least 3 training cases to ensure their clinical skills before working with study participants. During the study, the therapists received weekly individual supervision from the study author who evaluated their sessions based on their reports and audiotape of their sessions to ensure adherence to the treatment manual.

2.3. Assessment of treatment response

Clinical response was based on ratings from the 17-item Hamilton Depression Rating Scale (HAM-D₁₇; Hamilton, 1960) by an independent evaluator who was blind to the dichotic listening and neurocognitive test data, but who knew the treatment being given. The evaluator has a master degree in clinical and counseling psychology and was specifically trained for this role. Patients showing a reduction in HAM-D₁₇ $\geq 50\%$ from baseline to completion of CBT were considered to be treatment responders. Of 20 patients who completed the 14 weeks of CBT, 11 (55%) were responders and 9 were non-responders. As shown in Table 1, the responders and non-responder groups did not significantly differ in gender, age, or education, and all were right-handed as indicated by laterality quotient (LQ) scores on the Edinburgh Inventory (Oldfield, 1971). There was no difference between responders and non-responders in pre-treatment ratings on the HAM-D₁₇ or BDI-II, and responders showed significantly lower post-treatment depression ratings than non-responders.

(footnote continued)

CBT response in 3 of these 4 cases. Also, predictions of CBT response remained essentially the same when only the 16 patients having a MDD were included. Of the patients having a MDD, 7 of 8 with PA scores above the mean for HC responded to CBT, whereas only 2 of 8 with PA scores below the mean for HC responded to treatment. This is a positive predictive value of 88% and a negative predictive value of 75%, which agrees with the results for the total sample, including patients having dysthymia.

² The PA scores for the 4 patients who received medication during the course of CBT were well within the range of scores for the other patients and correctly predicted their response to CBT. The 2 medicated patients who responded had PA scores above the mean for HC (14.0 and 29.9), while the 2 medicated non-responders were below the mean for HC (0.87 and 9.2). Inclusion of these medicated patients did not adversely affect the findings of the study.

¹ We have not found a difference in DFWT performance between patients having a MDD and those having “pure dysthymia” (Bruder et al., 2012). In agreement with the overall results, the 2 dysthymic patients who were responders had a larger left hemisphere advantage (PA=8.0 and 28.6) than the 2 dysthymic patients who were non-responders (PA=1.7 and -0.8), with correct prediction of

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