INTRODUCTION

Many patients with depression respond poorly to treatment and manifest continuous depressive symptoms. These patients with treatment-resistant depression (TRD) are at the greatest risk for disability, morbidity, and mortality.

Neuropsychological (NP) deficits are common in depression, especially during the major depressive episode; however, essentially nothing is known about the severity of cognitive impairment experienced by TRD patients compared to nonresistant controls.

Because cognitive impairment is a major determinant of disability, understanding its role in TRD, including the profile and severity of associated impairments, is clinically important.

While use of normative standards using regression analysis is an established methodology, this is the first study of cognitive impairment in TRD patients, comparing performance to that of age, gender, and education matched healthy controls.

ABSTRACT

A NORMATIVE STUDY OF NEUROPSYCHOLOGICAL PERFORMANCE IN TREATMENT RESISTANT DEPRESSION

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REFERENCES

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STUDY DESIGN

A large sample of patients with TRD (N = 497) was evaluated using a computerized battery of 21 tests designed to identify a clinical trial of an atypical antipsychotic agent, as augmentation to a selective serotonin reuptake inhibitor. A demographically similar sample of healthy control patients was examined to standardize scores, controlling for age, education, and gender. Standardized scores were then applied to the performance of the TRD sample, in order to determine the overall level of impairment. Patients clinically resistant to treatment were defined using criteria for major depressive disorder (MDD) and included single or recurrent episodes with or without psychotic features, and a score of ≥22 on the 17-item Hamilton Rating Scale for Depression (HAM-D) at screening and baseline. Included patients had failed to respond to the current antidepressive episode to at least 1 but <3 antidepressants (other than cholinesterase or escitalopram), given at adequate doses for ≥6 weeks. Healthy controls were collected from different research sites and had no history of lifetime major depression, bipolar disorder, or psychosis. Subjects in both groups were excluded if the following conditions were present: current substance dependence, seizure disorder, mental retardation, or head injury with loss of consciousness. The current analysis examines only patients ≥55 years old (n = 297) and similar controls.

The following cognitive assessment battery (COGTEST) was utilized:

- Auditory Number Sequencing (attention, working memory): patients repeated a series of numbers (minimum number of digits = 2; maximum = 8) in order, from lowest to highest.

- Continuous Performance Test (CPT) Flanker Version (executive attention-distractability): patients viewed an arrow centered on the screen pointing right or left, and were asked to respond as rapidly as possible with a corresponding (right or left) key press during “neutral” (no flankers), “congruent” (flanking arrows pointing in the same direction), and “incongruent” (flanking arrows pointing opposite directions) conditions. Performance of each condition was analyzed. Maximum scores are 50 items correct.

- Face Memory Test (secondary memory): subjects were presented with a series of 80 face-computer-generated face pairs (2-second exposure each) and asked to discriminate target faces from distractors in 40 forced-choice trials. Data are presented in terms of the percentage of correct responses.

- Set-Shifting Test (flexibility, executive function, processing speed): subjects viewed colored squares on either the right or left side of the screen accompanied by tones, signaling them to respond as rapidly as possible by pressing a right or left key. Faster response time (RT) at the end of each fixed sequence related to choice RT indexes procedural learning, and slower RT after the rule switches indexes set-shifting cost.

- Tapping Speed Test (TST) (simple motor speed): subjects pressed a key as fast as possible with their index finger for 10 seconds (5 trials/each).

Analyses

The data analytic approach was based on previous studies designed to generate demographically corrected performance scores.

Regression analysis was performed using the healthy control scores on each of the tests in the COGTEST battery as the dependent variable.

Age, education, and gender were regressed on each raw score dependent variable, resulting in a residual score with a mean of 0 and a standard deviation of 1.0. The regression coefficients and the intercept were then applied to the raw data in the TRD sample, resulting in a z-score profile of performance that was corrected for the effects of age, education, and gender.

RESULTS

Patient Demographics

Demographic variables were similar for TRD patients and healthy controls (Table 1).

Table 1. Summary of Patient Demographics and Clinical Characteristics

<table>
<thead>
<tr>
<th>Measure</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (in years)</td>
<td>42.3 (8.6)</td>
</tr>
<tr>
<td>Education level, n (%)</td>
<td>243 (89.3)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>3 (1.1)</td>
</tr>
<tr>
<td>Black</td>
<td>10 (3.7)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>211 (71.4)</td>
</tr>
<tr>
<td>Other</td>
<td>45 (14.3)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>248 (89.5)</td>
</tr>
<tr>
<td>Male</td>
<td>32 (10.5)</td>
</tr>
<tr>
<td>Citalopram or Escitalopram, given at adequate doses for ≥6 weeks</td>
<td>44.9 (9.1)</td>
</tr>
<tr>
<td>Whereas escitalopram (n = 63)</td>
<td>34.5 (5.5)</td>
</tr>
</tbody>
</table>

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CONCLUSIONS

- Patients with TRD performed consistently more poorly than healthy controls. All differences in performance (other than two of the reaction time variables) were significant. All P values other than incongruent CPT performance would also have met Bonferroni corrected criteria for significance.

- Z-score profiles for the COGTEST battery in TRD patients are presented in Figure 1.

Figure 1. 2 scores with demographics for the COGTEST battery in TRD patients.

The impairment was less substantial than those seen in depression, but more substantial than those expected in patients with major depression currently experiencing remission of symptoms.

- Evaluating the severity and profile of cognitive impairment in TRD patients is a substantial step in understanding the determinants of disability in this condition.

This information will be useful for interpreting the results of future studies of TRD.

- Later research will need to address the functional relevance of these cognitive deficits and their response to various forms of treatment.

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