A NORMATIVE STUDY OF NEUROPSYCHOLOGICAL PERFORMANCE IN TREATMENT RESISTANT DEPRESSION

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ABSTRACT

Background: Treatment-resistant depression (TRD) is a significant mental health problem leading to substantial morbidity and mortality. Despite the disability associated with this condition, there is little information available about the determinants of this disability, and essentially no information available about the cognitive impairments seen in TRD. As cognitive impairment is a major determinant of disability across neuropsychiatric conditions, understanding the role of cognitive impairments in TRD, including both the profile and severity of these impairments, is clinically important.

Methods: In a large, multinational study of atypical antipsychotic treatment of TRD, a structured baseline cognitive assessment was performed on 297 of 489 patients. This computerized assessment measured multiple cognitive domains, including processing speed, working and episodic memory, and executive functioning. Normative data for healthy comparison subjects matched to the TRD population in age, education, and gender were also collected using the same assessment methodology.

Results: The profile and severity of performance relative to the healthy comparison sample will be described. Using regression-based techniques, standard scores will be calculated for each of the performance domains and for the overall composite score. These results will be used to examine the previously presented data on cognitive response following antipsychotic treatment.

Conclusions: Evaluating the severity and profile of cognitive impairment in TRD will be a substantial step in understanding the determinants of disability in this condition. This information will also be useful for interpreting the results of later, probably smaller, studies of TRD.

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 a major depressive episode; however, essentially nothing is known about the severity of cognitive impairment experienced by TRD patients compared to normative standards.
- It has been reported that people with nonrefractory major depression have a performance profile that falls approximately between those of people with schizophrenia and healthy individuals.[1,2]
- 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,[3] this is the first study of cognitive impairment in TRD patients, comparing performance to that of age, gender, and education matched healthy controls.

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METHODS

Study Design

- A large sample of patients with TRD (N = 497) was evaluated using a computerized NP assessment upon entry into 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 in the overall study met *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DSM-IV) criteria for major depressive disorder (MDD), had single or recurrent episodes with or without psychotic features, and a score of ≥20 on the 17-item Hamilton Rating Scale for Depression (HAM-D) at screening and baseline. Included patients had also failed to respond in the current depressive episode to at least 1 but ≤3 antidepressants (other than citalopram 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 samples 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-distractibility): 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 distractors), "congruent" (flanking arrows pointing in the same direction), and "incongruent" (flanking arrows pointing opposite the target arrow) conditions. Accuracy in each condition was analyzed. Maximum scores are 50 items correct.
  - Face Memory Test (secondary memory): subjects were presented with a series of 40 computer-generated faces (3-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 (SST) (procedural learning, 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 relative to choice RT indexes procedural learning, and slower RT after the rule switches indexes set-shift 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/hand).

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.
- These 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

	TRD (n = 272)	HC (n = 63)
Female, n (%)	193 (71.0)	33 (52.4)
Age, years [mean (±SD)]	42.3 (8.6)	35.8 (9.1)
Education level, n (%)		
Elementary/primary school	9 (3.3)	2 (3.2)
High school	91 (33.6)	29 (46.0)
College	171 (63.1)	32 (50.8)
Race		
Caucasian	243 (89.3)	45 (71.4)
Hispanic	13 (4.8)	9 (14.3)
Black/African-American	10 (3.7)	9 (14.3)
Asian	3 (1.1)	0 (0.0)
Other	3 (1.1)	0 (0.0)

TRD = treatment-resistant depression; HC = healthy controls.

- **Table 2** shows the results of important clinical variables from each cognitive assessment, including the mean raw scores (±SD) for the TRD subjects and healthy controls. The corrected scores reflect the z-score of the TRD patients, after correcting for expected normative performance based upon age, gender, and education matched controls (mean = 0, SD = 1 where positive scores reflect performance better than normative comparison and negative scores reflect worse performance). The comparison with HC reflects the significance of the difference between TRD subjects and healthy controls.

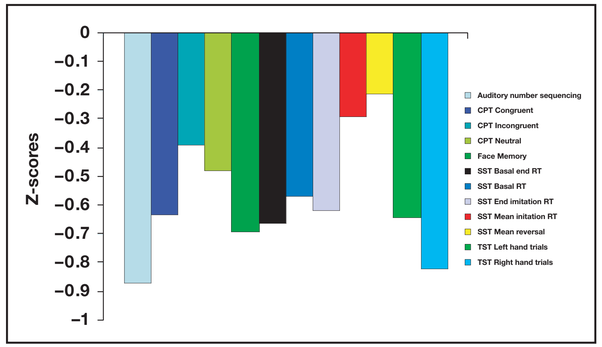
Table 2. Performance on COGTEST Battery at Baseline: TRD Group vs Healthy Controls

Test	TRD Patients Raw Scores (n = 272)		HC Patients Raw Scores (n = 63)		Difference in Corrected Scores (z)	Comparison with HC
	Mean	±SD	Mean	±SD		*P* value*
Auditory Number Sequencing, number correct	9.0	3.0	11.0	2.3	–0.87	.001
Continuous Performance Test						
Congruent	42.2	6.6	44.9	4.3	–0.63	.002
Incongruent	37.8	8.7	40.7	7.4	–0.39	.015
Neutral	42.0	6.5	44.3	4.8	–0.48	.009
Face Memory Test, % correct	72.7	13.9	79.5	9.8	–0.69	.003
Set-Shifting Test	381.7	183.4	349.6	48.4	0.66*	.003
Basal end RT	365.1	131.4	345.3	34.5	0.57*	.004
Basal RT	379.0	211.0	344.6	55.8	0.62*	.002
End imitation RT	369.4	184.9	355.0	50.0	0.29*	.552
Mean imitation RT	341.4	124.3	352.5	52.2	0.21*	.454
Mean reversal RT						
Tapping Speed Test						
Left hand trials	242.6	51.8	266.3	37.3	–0.64	.002
Right hand trials	248.0	58.3	282.7	42.2	–0.82	.001

**P* values are based on demographically corrected scores. Higher scores reflect worse performance on these items. TRD = treatment-resistant depression; HC = healthy controls; RT = response time; SD = standard deviation.

- TRD patients 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-scores with demographics for the COGTEST battery in TRD patients are presented in **Figure 1**.

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



Reaction time effect sizes are adjusted so that negative scores reflect impairment.

CONCLUSIONS

- Patients with TRD performed consistently more poorly than healthy control subjects across the different tests administered. Their level of performance is consistent with that seen previously in nonresistant patients who were depressed at the time of assessment.
- The impairments were 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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