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The specificity of neuropsychological impairment in predicting antidepressant non-response in the very old depressed

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SUMMARY

Objective In an earlier report, response inhibition predict antidepressant non-response in late-life depression (Sneed *et al*., 2007). The purpose of this study was to ascertain whether this effect is specific to response inhibition or whether impairment in other cognitive domains also predicts non-response.

Method Older depressed patients ($n = 84$) enrolled in an 8-week trial of citalopram were classified as impaired or non-impaired relative to the sample on mental status, psychomotor speed, reaction time, spatial judgment, and memory, and contrasted with regard to antidepressant response.

Results Patients who were impaired relative to the sample on digit symbol performance did not respond as quickly to citalopram as those who were unimpaired. By the end of the 8-week trial, however, both groups reached the same level of response. Impairment in other domains had no impact on antidepressant response.

Conclusions Non-response was not attributable to impairment on any of the neuropsychological tests suggesting that antidepressant non-response is specific to impaired response inhibition. Copyright © 2007 John Wiley & Sons, Ltd.

KEY WORDS — late-life depression; geriatric depression; neuropsychology; cognitive impairment; antidepressant response

INTRODUCTION

Patients classified as having impaired response inhibition (RI), a fundamental component of the executive functions, have been shown to respond less well to antidepressant treatment compared to patients without deficits in RI (Sneed *et al*., 2007). These findings converge with an emerging literature documenting the impact of response inhibition on antidepressant treatment response in late-life depression (Kalayam and Alexopoulos, 1999; Alexopoulos *et al*., 2005; Murphy and Alexopoulos, 2006).

Research suggests that psychomotor speed may independently predict antidepressant non-response (Taylor *et al*., 2006) raising the possibility that the effect of response inhibition on antidepressant response may be mediated by slowed information processing (Butters *et al*., 2004; Taylor *et al*., 2006). Although we observed differences in reaction time on complex tasks between those with and without RI impairment, including measures of reaction time did not diminish the effect of RI on antidepressant response (Sneed *et al*., 2007). This finding suggests that antidepressant non-response is not attributable to deficits in reaction time. However, our previous study did not address whether slowed information processing speed is an independent predictor of non-response or whether impairment in other neuropsychological domains predicts antidepressant non-response.

The purpose of this study was to address the possibility that other aspects of cognition besides RI predict poor treatment response in late-life depression. Using neuropsychological data collected as part of a

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large, double-blind, randomized clinical trial of citalopram in older patients with major depression, we examined whether impairment relative to the sample in gross cognitive ability (mental status), psychomotor speed, reaction time, visual perception, and memory predicted differences in antidepressant response.

METHOD

Sample

Eighty-four of 174 community dwelling men and women 75 years or older meeting DSM-IV criteria (based on SCID interview) for non-psychotic unipolar depression (single or recurrent) were randomized to citalopram in an 8-week, multi-site, placebo-controlled trial that has been previously described (Roose *et al*., 2004; Sneed *et al*., 2007). The sample consisted of 54% women, the mean age of the sample was 79, and the mean baseline score on the 24-item Hamilton Rating Scale for Depression (HRSD) was 24.4 (SD = 4.33). The remission rate (HRSD < 10) for citalopram in this sample was 35% and this was not different from the 33% remission rate in the placebo cell (Roose *et al*., 2004).

Neuropsychological test battery

The neuropsychological test battery was designed to assess a number of cognitive functions pertinent to aging and major depression, including mental status, psychomotor speed, reaction time, spatial judgment, and memory.

Mental status was assessed using the Folstein Mini-Mental State Exam (MMSE) (Folstein *et al*., 1975), a brief, structured 30-item mental status examination. The total score possible on the 30-item MMSE is 30; the mean MMSE score in this sample was 28.42 (SD = 1.56).

Processing speed was assessed using the WAIS-III Digit Symbol Subtest (DS) (Wechsler, 1997), which requires subjects to transcribe number-coded figures on to a blank number-coded grid. The total DS score corresponds to the total number of items completed correctly within 120 sec. The mean performance score for the sample was 45.38 (SD = 16.88).

Reaction time was assessed using the Choice Reaction Time (CRT) adapted from Thorne *et al*. (1985). In this task, subjects are instructed to 'catch the X' that is presented on successive trials in different areas of the screen by hitting the correct corresponding key. A total of 60 items are presented and median RT is computed from all correct individual responses. The mean reaction time (log transformed) for the sample was 6.73 (SD = 0.29)

Spatial judgment was assessed using the Judgement of Line Orientation (JOLO), which requires subjects to characterize the orientation of isolated line segments (Benton *et al*., 1983). The total score on this measure is the number of correct responses out of 30. The mean for this sample was 19.96 (SD = 5.28).

Memory was using the Buschke Selective Reminding Test (SRT) (Buscke and Fuld, 1974). The SRT is a list learning task that requires subjects to learn a list of words while being 'selectively reminded' of only those words that they fail to recall on successive trials. Scores for immediate memory were based on the total number of items recalled after six reminding trials. The mean for this sample was 36.46 (SD = 8.78). A forgetting score was also computed by taking the difference between the immediate recall score and the number of items recall after a 30 min delay. The mean for this sample was 2.11 (SD = 2.87).

Data analysis

The participants' performance on each of the six neuropsychological tests was defined as impaired if their score fell within the lowest quartile of performance relative to the sample at baseline. Treatment response was defined dichotomously, as a 50% reduction in HRSD scores over the 8-week treatment period, and continuously, based on change in HRSD scores.

First, the relationship between non-responder status and impaired performance on the neuropsychological tests was assessed by conducting a series of unadjusted χ^2 tests of independence and adjusted (for gender, age, and site of study) logistic regression analyses.

Next, we fit a series of growth curve models using the Mixed Models procedure in SPSS (version 14) to examine the relationship between change in HRSD scores and impairment on the neuropsychological tests. Separate growth curve models were fit for each of the tests in order to determine their prognostic significance in predicting change in HRSD scores. For each test, we used a 'top-down' approach in which the highest order term was removed on each successive run starting with the fullest model until a baseline model was reached indicating that impairment was not related to HRSD scores. The fullest model contained an intercept, the main effects of time and time^2, a dichotomous variable indicating cognitive impairment

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status, and its interaction with time and time^2. Because we were interested in endpoint scores, we 'centered' the time variables so that the intercept in the models corresponded to the endpoint of the study. All models adjusted (covaried) for baseline depression severity, site of study, age, and gender (all centered at their respective means). Significance was tested at the 5% level.

RESULTS

There was no association between antidepressant response and impairment relative to the sample on any of the neuropsychological tests, including MMSE [$\chi^2(1) = 0.18, p = 0.67$], DS [$\chi^2(1) = 0.029, p = 0.86$], CRT [$\chi^2(1) = 0.18$, $p = 0.67$], JOLO [χ^2 $(1) = 0.47$, $p = 0.49$], SRT immediate recall [$\chi^2(1) = 0.55$, $p = 0.46$], or SRT forgetting [$\chi^2(1) = 0.12$, $p = 0.73$]. Repeating the analyses adjusting for gender, age, and site of study in a logistic regression framework did not change the results.

In the growth curve models, impairment relative to the sample on the MMSE, CRT, JOLO, or SRT forgetting also did not effect change in HRSD scores over time. Impairment on the DS, however, did effect change in HRSD scores over time. Specifically, the full interaction model yielded a significant DS $\times$ Time^2 interaction indicating that depression scores for those with DS impairment did not decrease as fast as depression scores in those without DS impairment (see Table 1). Despite starting at approximately equivalent levels, depression scores at week 4 for those with impairment were 3.3 points higher than depression scores for those without DS impairment. As can be seen in Figure 1, however, by the end of the study, the difference between the two groups was less than one point and not statistically significant [B = 0.83, SE = 2.36, t (73.098) = 0.35, $p = 0.73$, 95% Confidence Intervals -3.87, 5.53].

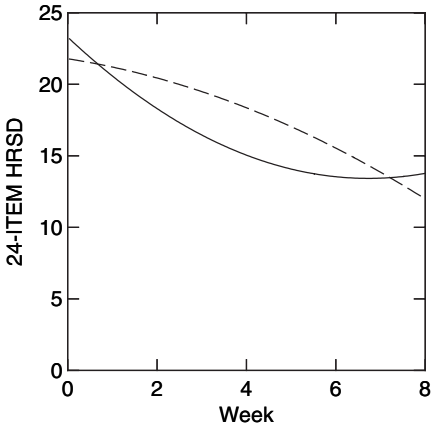

Figure 1. Change in HRSD scores over the 8-week citalopram trial for patients with (dashed line) and without (solid line) impairment relative to the sample on the digit symbol test.

DISCUSSION

Antidepressant response was not affected by cognitive impairment (relative to the sample) on any of the neuropsychological tests administered at baseline. Although impairment on the Digit Symbol test resulted in slower antidepressant response, there were no differences between the impaired and unimpaired DS patients at the end of the trial. These findings, taken together with those previously reported (Sneed *et al*., 2007), suggest that antidepressant non-response in late-life depression is specific to impairment in

Table 1. Final growth curve model estimates of impaired digit symbol functioning on change in Hamilton Rating Scale for Depression scores

Parameter	Citalopram					
	B	SE(B)	t	df	p	95% CI
Intercept	13.40	0.99	13.54	66.28	0.0001	11.41, 15.36
Time	0.12	0.44	0.28	64.06	0.78	−77, 1.01
Time^2	0.22	0.065	3.37	69.59	0.001	0.089, 0.35
Digit Symbol	0.83	2.36	0.35	73.10	0.73	−3.87, 5.53
Digit Symbol $\times$ Time	−1.91	1.02	−1.87	64.22	0.066	−0.77, 0.70
Digit Symbol $\times$ Time^2	−0.31	0.15	−2.10	68.83	0.039	−0.61, −0.016

Dependent variable is endpoint Hamilton Rating Scale for Depression score. All models covary for baseline HRSD, site, age, and gender centered at their means (not tabled).
B = Unstandardized Regression Weight; CI = Confidence Interval; SE = Standard Error. Coefficients for random effects are not tabled.

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response inhibition, a fundamental component of executive functioning.

The findings emphasize the potential specificity of executive dysfunction in treatment outcome of older adults with depression. The Depression with Executive Dysfunction Syndrome (Alexopoulos *et al*., 2002) has been proposed to describe a subset of older adults with depression that is characterized by depression with impairment in executive abilities. That impairment in no other neurocognitive domain predicted non-response except the executive ability of response inhibition (Sneed *et al*., 2007) is consistent with this syndrome and suggests heterogeneity in etiology of depression among older adults with depression. Those with predominant executive dysfunction may be particularly resistant to pharmacological intervention because of pathophysiological differences in the nature of their depression such as disruption of dorsolateral-prefrontal circuitry, which is critical to executive function and higher-order control of the limbic system. Because subclinical or overt vascular disease may underlie these functional deficits, it may account for a proposed subtype of late-life depression referred to as vascular depression (Sneed *et al*., 2006).

The causal relationships among geriatric depression, treatment response, vascular disease, and executive dysfunction clearly require further investigation. Prospectively designed treatment studies that include depressed patients with and without executive dysfunction and incorporate high-resolution neuroimaging modalities would help clarify these associations. Further, causal statistical models, such as structural equation modeling, may be incorporated in to this line of research to test specific theories about geriatric depression. For example, it may be possible that both executive dysfunction and poor treatment response are attributable to corticostriatal white matter pathology, or, alternatively, that white matter pathology causes executive function, which in turn causes poor treatment response.

Throughout the life span age has a marked effect on neuropsychological performance, but a non-linear one. It is greatest during childhood and adolescence—in terms of improvement in performance—and tends to decline during the adult years into old age. In the oldest old, however, it has been difficult to characterize consistent age trends because cognitive functioning is strongly dependent on overall physical health and rates of dementia increase exponentially as individuals reach their 90s and beyond. We adjusted for age in our regression analyses to account for systematic effects in our sample, which consisted of subjects with major depression. A parallel normative sample would have been useful, but prohibitive for this study.

Strengths of the current study include the use of data from a prospectively designed multi-site treatment trial of antidepressant treatment among elderly patients with depression, which may be generalizable to other elderly patients with depression. Potential weaknesses include the use of a somewhat limited neuropsychological battery. While the findings suggest that executive dysfunction is specifically related to treatment response, only one aspect of executive function (i.e. response inhibition) was evaluated in the trial. Further, although the MMSE contains aspects of attentional function, no formal test of attention was included in the battery. Nonetheless, data from the current study support the importance and specificity of response inhibition in treatment outcome in geriatric depression.

CONFLICT OF INTEREST

None.

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