Response to Psychosocial Treatment in Poststroke Depression Is Associated With Serotonin Transporter Polymorphisms

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Background and Purpose—The Living Well With Stroke study has demonstrated effectiveness of a brief psychosocial treatment in reducing depressive symptoms after stroke. The purpose of this analysis was to determine whether key variables associated with prevalence of poststroke depression also predicted treatment response.

Methods—Response to a brief psychosocial/behavioral intervention for poststroke depression was measured with the Hamilton Rating Scale for Depression. Analysis of covariance models tested for interaction of potential predictor variables with treatment group on percent change in Hamilton Rating Scale for Depression from pre- to post-treatment as an outcome.

Results—Initial depression severity, hemispheric location, level of social support, age, gender, and antidepressant adherence did not interact with the treatment with respect to percent change in Hamilton Rating Scale for Depression when considered 1 at a time. Participants who carried 1 or 2 s-alleles at the 5-HTTLPR serotonin transporter polymorphism or 1 or 2 9- or 12-repeats of the STin2 VNTR polymorphism had significantly better response to psychosocial treatment than those with no s-alleles or no 9- or 12-repeats.

Conclusions—Opposite to the effects of antidepressant drug treatment with selective serotonin reuptake inhibitors, the Living Well With Stroke psychotherapy intervention was most effective in 5-HTTLPR s-allele carriers and STin2 VNTR 9- or 12-repeat carriers.

Clinical Trial Registration—URL: www.clinicaltrials.gov/ct/show/NCT00194454?order_1. Unique identifier: NCT00194454.

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Key Words: behavioral genetics ■ behavioral therapy ■ depression ■ stroke

Over 30% of stroke survivors experience poststroke depression. There is evidence that factors such as female gender, history of depression, younger age, and serotonin transporter (SERT) genotype are predictive of poststroke depression, but there are no published reports about factors influencing the response to any form of treatment for this condition. We therefore queried data from our recent successful randomized controlled trial of a psychosocial treatment adjuvant to antidepressants (Living Well With Stroke [LWWS]) to determine whether subsets of patients with poststroke depression respond better to treatment.

Methods

This analysis was a planned, exploratory aim from LWWS in which 101 clinically depressed patients with ischemic stroke were randomly assigned to a 9-session brief pleasant events, problem-solving intervention delivered by an advanced practice nurse therapist, plus antidepressant (intervention, n=48), or to usual care plus antidepressants (control, n=53). Investigated variables, chosen from those noted in prior literature to be predictive of poststroke depression or predictive of response to pharmacotherapy in primary depression, were: age, gender, stroke severity as measured by the initial National Institutes of Health Stroke Scale, stroke hemisphere location, baseline Hamilton Rating Scale for Depression, depression history from the Diagnostic Interview and Structured Hamilton, level of social support measured by the ENRICHD Social Support Inventory, antidepressant adherence, measured by a self-report medication log, and the 5-HTTLPR and STin2 VNTR polymorphisms of the SERT transporter. The 17-item Hamilton Rating Scale for Depression score using individual analysis of covariance.

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Details of the parent study design, participant characteristics, and measures are found in previous reports.3,6

**Results**

There were no significant main effects or interactions with treatment group for gender, stroke severity, hemispheric location, baseline Hamilton Rating Scale for Depression, history of depression, level of social support, or antidepressant adherence (Table 1). We saw a significant main effect for age but no significant interaction with age; younger subjects had better mean percent improvement in Hamilton Rating Scale for Depression in both intervention and control groups. There was a trend toward better treatment response in subjects with smaller strokes and those who were more adherent to antidepressant drug treatment. Because the SERT polymorphisms showed close to significant main and interaction effects, we further examined their impact on treatment outcome (Table 2). Among patients with the 5-HTTLPR s/s genotype or the STin2 VNTR 9/12 and 12/12 genotypes, behavioral treatment had a large effect; there was no evidence of an effect of LWWS among l/L homozygotes (Figure). These results did not change substantially when the analysis was controlled for race as white versus nonwhite (not shown).

**Discussion**

5-HTTLPR and STin2 VNTR are functional length polymorphisms of the SERT gene located in the promoter region (5-HTTLPR) and second intron (STin2 VNTR) where they act as regulators of SERT expression.7 The short (s) variant of 5-HTTLPR and the 9- or 12-repeat alleles of STin2 VNTR have previously been associated with comorbid depression in...
medically ill populations. In addition, the s-allele of 5-HTTLPR has been associated with lower remission and response rates and a higher number of medication side effects in depressed patients treated with selective serotonin reuptake inhibitors. Our observation that the SERT genotype is related to better treatment outcome with psychotherapy, in contrast with response to selective serotonin reuptake inhibitors, suggests the possibility of personalizing and tailoring both pharmacological and psychosocial treatments for poststroke depression. However, our study is limited by its small, ethnically heterogeneous sample, which allowed only for a limited detection of gene × treatment interactions. Our findings relate to reports in the literature showing 5-HTTLPR s-allele carriers to be more likely to view environmental stimuli with a negative bias, have heightened emotional reactivity, and develop negative information processing at an early age. Because the s/s genotype may confer an increased sensitivity to the social environment, subjects with this genotype could possibly derive particular benefit from an intervention like ours, which aims to supply tools to enhance personal psychological resources.

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Disclosures
None.

References
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