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Resilience Predicts Remission in Antidepressant Treatment of Geriatric Depression

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Abstract

Objectives.—With the world population rapidly aging, it is increasingly important to identify sociodemographic, cognitive, and clinical features that predict poor outcome in late-life depression. Self-report measures of resilience – i.e., the ability to adapt and thrive in the face of adversity – may identify those depressed older adults with more favorable prognoses.

Methods.—We investigated the utility of baseline variables including four factors of resilience (grit, active coping self-efficacy, accommodative coping self-efficacy, and spirituality) for predicting treatment response and remission in a 16-week randomized controlled trial of methylphenidate, citalopram, or their combination in 143 adults over the age of 60 with MDD.

Results.—Final logistic regression models revealed that greater total baseline resilience (Wald $\chi^2 = 3.8$, $p = 0.05$) significantly predicted both treatment response and remission. Specifically, a 20% increase in total resilience predicted nearly 2 times greater likelihood of remission (OR = 1.98, 95% CI = [1.01, 3.91]. Examining the individual factors of resilience, only accommodative coping self-efficacy (Wald $\chi^2 = 3.7$, $p = 0.05$; OR = 1.41 [1.00–2.01]) was significantly associated with remission. We found no relation between baseline sociodemographic factors (age, sex, race, education level) or measures of cognitive performance and post-treatment depressive symptoms.

Conclusions.—Self-reported resilience may predict greater responsivity to antidepressant medication in older adults with MDD. Future research should investigate the potential for resilience training – and in particular, interventions designed to increase accommodative coping – to promote sustained remission of geriatric depression.

Keywords

Elderly; geriatrics; psychiatry; resilient; individual differences; SSRI; remit; acceptance; problem-solving therapy; moderator

Late-life depression is a common and debilitating disorder, with roughly 9% of geriatric primary care patients meeting criteria for MDD[1]. Geriatric depression has a poorer

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prognosis compared to depression experienced earlier in life, with lower rates of remission and higher rates of recurrence following first-line antidepressant treatment[2–8]. With the world population rapidly aging, it is increasingly important to identify sociodemographic, cognitive, and clinical features that predict poor outcome in late-life depression to facilitate more targeted and effective interventions.

Studies investigating the relation between demographic variables and remission in geriatric samples have reported inconsistent findings. For example, a study of 215 depressed adults over the age of 60 found no effect of any demographic variable (age, gender, race, or education) on remission occurrence[9]. By contrast, other studies of the same age group have found that African American participants are less likely to respond with escitalopram treatment [10] and males are less likely to remit with venlafaxine[11]. However, a patient-level meta-analysis of seven placebo-controlled trials of second-generation antidepressants for geriatric depression found that sex did not moderate treatment response[5].

Research investigating age of depression onset as a predictor of treatment response have also reported contradictory results[12]. For example, several studies have found that early-onset depression is associated with poorer treatment response[13], slower remission[14], and higher rates of recurrence[15,16] compared to late-onset depression. By contrast, other studies have found that late-onset depression predicts poorer response to treatment[17] and more frequent and earlier relapse[18], while yet other research has reported no effect[19]. One possible explanation is that greater number of previous episodes (rather than earlier onset per say) predicts poorer treatment response. Partial evidence for this hypothesis comes from a study of 210 depressed adults ages 69 and older, which found that among those with late-onset depression, recurrent depression predicted delayed response to pharmacotherapy compared to single-episode depression[20]. Additionally, those with recurrent depression were more likely to require pharmacotherapy augmentation, regardless of age of onset. Reynolds and colleagues propose that late onset be considered a proxy for other variables (neuropsychological impairment, structural brain abnormalities, less family history of mood disorders, and fewer previous episodes) that can affect treatment response[14].

Multiple studies have found that executive dysfunction predicts poor and slow response to antidepressants in geriatric depression[21–26]. In particular, cognitive interference and impaired semantic organization have repeatedly been linked to poor rates of remission[27]. Other research has focused on clinical and social factors that predict treatment response in geriatric samples. Hopelessness[10], external locus of control[28], loneliness[10,29], neuroticism[30], poor health-related quality of life[10], comorbid medical conditions[28], functional limitations[28,31], and higher baseline severity of depression and anxiety symptoms[10,28] have each been associated with poor treatment response.

Self-report tools for assessing resilience – i.e., the ability to adapt and thrive in the face of adversity – may help identify those older adults who are less likely to respond to first-line antidepressant treatment. Preliminary evidence for this hypothesis comes from an exploratory factor analysis (EFA)[32] of the Connor-Davidson Resilience Scale (CD-RISC)[33], which a systematic review identified as having the best psychometric properties out of the 17 resilience scales identified[34]. EFA of data collected from 337 older adults with MDD yielded

four factors: 1) “Grit”, reflecting perseverance and passion for long-term goals; 2) “Active Coping Self-efficacy”, reflecting self-efficacy for coping with stress via problem-focused strategies; 3) “Accommodative Coping Self-efficacy”, reflecting self-efficacy for adapting to sources of stress; and 4) “Spirituality”, reflecting endorsement of spiritual beliefs. Each factor was significantly associated with lower severity of depressive symptoms and apathy[32]. Other studies have similarly found that spirituality[35,36], greater meaning/ purpose[37–39], greater coping self-efficacy[40], and self-reported use of active[41] and accommodative coping strategies[42] are associated with lower severity of late-life depression. Because accommodative coping is thought to increase over the life span[43,44], this aspect of resilience may be particularly relevant to geriatric depression.

Whether self-reported resilience predicts remission or treatment response in older adults with MDD is unknown. The current study investigates baseline demographic, cognitive, clinical, and psychosocial variables including resilience as possible predictors of antidepressant treatment response in sample of 143 adults with late-life depression.

Methods

Participants

Data were from a 16-week randomized controlled trial (RCT) evaluating the potential of methylphenidate to improve antidepressant response to citalopram[45](NCT00602290) conducted with depressed adults ≥60 years at UCLA. Participants were assigned to one of three arms, each of which included at least one active treatment (citalopram plus placebo; methylphenidate plus placebo; citalopram plus methylphenidate). Data were collected between 2008–2012. Inclusion criteria were: 1) current episode of unipolar MDD according to DSM-IV-TR[46]; 2) HAM-D score ≥14[47]; and 3) Mini-Mental State Exam (MMSE)[48] score ≥26. Exclusion criteria were: 1) history of any other psychiatric disorder (with the exception of stable anxiety or stable insomnia, which were permitted); 2) severe or acute unstable medical illness; 3) acute suicidal or violent behavior; or 4) any other central nervous system disease. Participants were free of psychotropic medications for at least two weeks prior to enrollment.

Measures

Resilience.—Resilience was assessed via the 25-item Connor-Davidson Resilience Scale (CD-RISC)[33] using a one-month recall period. Completion time is roughly 5–10 minutes. Respondents indicate their level of agreement on a 5-point Likert scale (0 = “Not true at all”; 1 = “Rarely true”; 2 = “Sometimes true”; 3 = “Often true”; and 4 = “True nearly all of the time”). Responses are summed with possible total scores ranging from 0–100; higher scores indicate greater resilience. Resilience factors identified in the above-mentioned EFA[32] (with example items) are: 1) Grit (e.g., “I have a strong sense of purpose”); 2) Active coping self-efficacy (e.g., “I am in control of my life”); 3) Accommodative coping self-efficacy (e.g., “I am able to adapt to change”); and 4) Spirituality (e.g., “I believe things happen for a reason”). A reliability analysis (with each item included only in the factor on which it loaded most strongly) using data from the larger EFA sample (N=337) yielded the following

Cronbach's α estimates: Total CD-RISC: 0.92, Factor 1: 0.89, Factor 2: 0.91, Factor 3: 0.90, Factor 4: 0.71.

Depression and apathy.—Severity of depressive symptoms was assessed with the self-report Geriatric Depression Scale (GDS)[49,50] and the 24-item clinician-rated HAM-D[47,51–53]. Apathy was evaluated using the clinician-rated Apathy Evaluation Scale (AES)[54]. AES total scores range from 18–72 with lower scores indicating greater apathy.

Physical Health.—Medical comorbidity was quantified using the clinician-rated Cumulative Illness Rating Scale for Geriatrics (CIRS[55]); higher scores indicate greater illness severity. Cerebrovascular risk (CVRF) was assessed via the 'Stroke Risk Factor Prediction Chart' from the Framingham Study to calculate 10-year risk of stroke [56].

Cognition.—Cognitive functioning was assessed via the MMSE[48,57]. In addition, a comprehensive neuropsychological test battery assessed five cognitive domains: memory (measured with the California Verbal Learning Test–II [long delayed free recall] and the Rey-Osterrieth Complex Figure Test [30-minute delayed recall]), language (the Boston Naming Test, FAS Verbal Fluency Task, and animal naming test), attention/processing speed (WAIS-III digit span task, Trail Making Test Part A, and Stroop Color Trial [Golden version]), executive functioning (Trail Making Test Part B and Stroop Interference [Golden version]), and visuospatial functioning (WAIS-III block design, Rey-Osterrieth Complex Figure Test [copy condition]). Raw scores were transformed to z-scores using published normative data for each test. Z-scores were reversed for tests in which lower values indicate better performance so that higher z-scores represented better performance for all measures. Z-scores were averaged within each neuropsychological domain to produce composite scores and then averaged over all tests to calculate a global neurocognitive performance score.

Analyses

Prior to analyses, data were inspected for outliers, skewness, and homogeneity of variance to ensure appropriateness of parametric statistical tests. The primary outcome variable was remission from depression, defined as a score ≤6 on the HAM-D post-treatment (at 16 weeks). Participants who met this criterion are hence referred to as "remitters". Treatment response, defined as a 50% or greater reduction from baseline depression (HAM-D) score, was examined as a secondary outcome. Participants who met this criterion are hence referred to as "responders". Predictive variables were: demographic variables (age, sex, race, years of education), cognitive variables (MMSE, global neurocognitive score, and each of the above-listed cognitive domains), clinical variables (age of onset, number of depressive episodes, physical health [CIRS, CVRF], baseline symptoms of depression [HAM-D, GDS] and apathy [AES]), and psychosocial variables (resilience [CD-RISC] and resilience factors).

First, a series of logistic regression models were estimated with remission as the dependent variable and each of the above predictive variables as the independent variable. Since the aim of these preliminary analyses was to select relevant variables for further multivariable analyses, all variables found to be significant at a level of $p < 0.1$ were retained. We also

used the stepwise selection method, with an inclusion cut-off of α=0.05, to identify possible predictors since some variables may affect the outcome differently when they are in a model simultaneously. We then estimated a multivariable logistic regression model including the aforementioned predictor variables. This was followed by pruning nonsignificant predictors and comparing model fit by using the Akaike information criterion, which estimates the relative quality of statistical models for a given data set. An a priori decision was made that if total resilience was obtained as a predictor, exploratory analyses would be conducted to determine whether any of the four resilience factors were also predictive of remission. The same procedure was employed to determine which of the demographic, cognitive, clinical and psychosocial variables significantly predicted our secondary outcome, treatment response. Finally, we examined whether the treatment group to which the participant was randomized significantly moderated any of the observed associations. Significance was set at $p<.05$ for all inferences.

Results

Sample Characteristics

Characteristics of the sample at baseline are summarized in Table 1. The average age of participants was 70 (range = 60–89 years). The majority of participants were White (75.5%), female (54.6%), and highly educated, with an average of nearly 16 years of education. At post-treatment, depression had remitted in 63 (44.1% of) participants, while 77 (53.9% of) participants had responded to treatment (100% of remitters responded; 81.8% of responders remitted).

Modeling of Remission

Univariate analyses using remission as the outcome (Table 2) identified higher baseline total resilience and lower baseline depression (HAM-D score) as significant predictors using $p<0.1$ criterion, and the stepwise logistic regression model identified only baseline total resilience as the significant predictor. The final multivariable logistic regression model, including baseline CD-RISC and HAM-D scores as predictors, yielded only greater baseline resilience (Wald $\chi^2 = 3.8$, $p = 0.05$) as a significant predictor of remission. Specifically, a 20-point (i.e., 20%) higher baseline resilience score was associated with a nearly 2 times greater likelihood of remission (Odds ratio, OR = 1.98, 95% CI = [1.01, 3.91]. Baseline HAM-D score was no longer significantly associated with remission (Wald $\chi 2 = 1.7$, $p = 0.2$). Examining the individual resilience factors, only accommodative coping self-efficacy (Wald $\chi^2 = 3.7$, p = 0.05, OR = 1.41 [1.00–2.01]) was significantly associated with remission.

Modeling of Treatment Response

The univariate analyses (see Supplementary Appendix) identified total resilience and apathy as predictors of treatment response, and the stepwise logistic regression model identified only baseline total resilience as significant. Including total resilience and apathy as predictors in the final logistic regression model, only total resilience (Wald $\chi 2 = 4.2$, $p = 0.04$) was obtained as a significant predictor; apathy did not reach significance (Wald $\chi 2 = 1.2$, $p = 0.3$). A 20-point (20%) higher CD-RISC score at baseline was associated with a

1.63 times greater likelihood of treatment response (OR = 1.63, 95% CI = [1.03, 2.59]. Examining the individual resilience factors, only accommodative coping self-efficacy (Wald $\chi 2 = 3.8$, $p = 0.05$; OR = 1.43 [1.03–2.03]) was significantly associated with treatment response.

Moderation by Treatment Group

Treatment group did not significantly moderate the effect of baseline resilience on either remission (interaction term of treatment group x resilience Wald $\chi 2 = 0.4$, $p = 0.5$) or treatment response (Wald $\chi 2 = 0.9$, $p = 0.4$).

Discussion

The current study evaluated the utility of baseline demographic, cognitive, clinical, and psychosocial factors in predicting responsivity to antidepressant treatment in a sample of 143 older adults with MDD. We found that participants with greater self-reported baseline resilience were more likely to experience improvement or remission from depression with antidepressant treatment. This finding is consistent with conceptualizations of resilience as "the ability to adapt to and recover from stress"[58], and supports the predictive validity of the CD-RISC in geriatric depression. Treatment group did not moderate the effect of resilience on treatment response or remission, suggesting that individuals with higher baseline resilience were more likely to improve regardless of the antidepressant medication(s) to which they were randomized.

Although no other studies to our knowledge have investigated self-reported resilience as a predictor of remission in individuals with MDD, our findings are highly similar to the results of a study of 92 adults receiving pharmacotherapy for posttraumatic stress disorder (PTSD) (60% of whom also met criteria for MDD)[59]. In that study, baseline self-reported resilience significantly predicted treatment response. Specifically, a one-unit (i.e., 1%) increase in baseline CD-RISC score was associated with a 4% increase in the odds of PTSD improvement and a 3–4% increase in the odds of PTSD remission. In our study, a one-unit increase in baseline resilience was associated with a 3% increase in the odds of MDD improvement and a 3.5% increase in the odds of MDD remission. Furthermore, the authors found that a one-unit (25% increase) on an item indicating use of cognitive restructuring (i.e., "I try to see the humorous side of things when I am faced with problems") was associated with a 125% increase in the odds of PTSD improvement. As this item loaded most strongly on the accommodative coping self-efficacy factor in our recent EFA[32], this is consistent with our finding that accommodative coping self-efficacy was uniquely predictive of treatment response in our sample.

Consistent with previous studies of antidepressant treatment of geriatric depression, we found no relation between sex[5] or education[9,10] and post-treatment depressive symptoms in our sample. Consistent with one previous study[9], but in contrast to another[10], we found no association of race with treatment outcome.

In contrast to previous research[27], we found no effect of executive functioning on treatment response or remission in our sample. Because we screened out individuals with an MMSE

score <26, it is possible our sample contained insufficient variability in neurocognitive performance to detect an effect. Although univariate analyses identified lower baseline severity of depressive symptoms and apathy as predictors of remission and response (respectively) at the $p<.10$ level, these associations were not significant in the multivariable logistic regression which included baseline resilience. Larger and more inclusive studies with cognitive cohorts are needed to replicate these findings.

Of the four previously-identified resilience factors, accommodative coping self-efficacy uniquely predicted treatment response and remission. While active (problem-focused) attempts to "solve" a source of stress are adaptive when facing a controllable stressor, the ability to accommodate is associated with better mental health outcomes in the face of uncontrollable stress[42,60–64]. Older adults may encounter uncontrollable stress more frequently than younger adults (e.g., sleep changes, chronic pain, declining cognitive abilities)[65], which could make accommodative coping especially essential in geriatric populations[66]. Consistent with this notion, older adults appear to engage in more accommodative coping[43] and less instrumental action coping[66] compared to younger adults.

Further support for the important role of acceptance in geriatric depression comes from recent meta-analyses of third wave cognitive behavioral therapies (i.e., Acceptance and Commitment Therapy, Mindfulness-Based Cognitive Therapy)[67] and Problem-Solving Therapy (PST) in geriatric depression[68]. These analyses found a moderate-sized effect (g = 0.55) of third wave cognitive behavioral therapies[67] and a large effect (Cohen's d = 1.15) of PST[69]. The large average effect observed for PST is especially promising given that the majority of trials employed active control conditions such as supportive therapy. PST may target multiple aspects of resilience such as behavioral activation, (which may facilitate grit), teaching problem-solving skills (which may increase active-focused coping) and accepting unsolvable problems (which may enhance accommodative coping). Future research is needed to investigate these factors as possible process variables accounting for PST's therapeutic effects.

One explanation for why resilience predicts treatment response in geriatric depression lies in a possibly shared neurobiological etiology. We recently determined that the resilience factor "grit" was associated with fractional anisotropy (FA) in the cingulum fibers and the callosal region connecting prefrontal cortex of depressed older adults[70]. Similarly, resilience in adolescence has been associated with higher FA in an anterior cingulate region projecting to frontal areas subserving cognitive processes[71]. Correspondingly, several studies have identified neural differences between those who achieve remission with treatment and those who fail to remit. For example, a study of 62 depressed older adults found that those who remitted with escitalopram had greater FA in the rostral and dorsal anterior cingulate cortex (ACC), the dorsolateral prefrontal cortex (DLPFC), the genu of the corpus callosum, white matter adjacent to the hippocampus, multiple posterior cingulate cortex regions, and insular white matter relative to those who failed to remit[72]. Another study found greater resting functional connectivity in the bilateral dorsal ACC, right DLPFC, and bilateral inferior parietal cortices in older adult remitters compared to nonremitters following escitalopram treatment[73]. Microstructural abnormalities in the corpus callosum, left superior corona radiate, and right inferior longitudinal fasciculum have also been associated with lower rates

of remission in geriatric depression[74]. Additional research is needed to further investigate psychosocial, cognitive, and neural indicators of resilience (including greater capacity for treatment response) as well as to identify the most effective therapies for depressed older adults with differing resilience "signatures".

Several limitations of the current study should be noted. First, as our study did not include a placebo-only or no-treatment control condition, the degree to which resilience predicts remission from geriatric depression in the absence of antidepressant treatment is unknown. The greater subsequent improvement observed in those with greater baseline resilience may be due to the combination of resilience and antidepressant medication, resilience and non-specific factors, or resilience alone. Presumably, resilience also predicts remission from late-life depression in the absence of treatment[58,75]; future placebo-controlled trials are needed in order to determine whether this effect is stronger or weaker among those receiving antidepressant treatment.

Second, resilience was assessed via self-report and as such is susceptible to issues of impression management, introspective ability, and degree of understanding. Possible future directions include the use of neural, physiological and behavioral (i.e., laboratory or field) measures of resilience to corroborate these findings. Such methods have been validated in individuals without psychopathology[58], and researchers have begun investigating the neural signature of resilience in individuals in remission from MDD[76]. However, few studies have attempted to identify the predictive validity of such an index (e.g., a laboratory attention task) in individuals currently experiencing a depressive episode[77]. Future research in this area would be useful.

A third limitation is that our sample was relatively homogenous with regard to demographic features such as age, race and education. Recruitment of more racially and socioeconomically diverse samples will allow for tests of group differences in the value of resilience for predicting treatment response. Additionally, because our recruitment criteria excluded participants with significant psychiatric comorbidity, whether our results generalize to depressed older adults with co-occurring cognitive impairment or psychiatric conditions (e.g., substance use disorder, PTSD) is unknown.

Our study contributes uniquely to the literature by investigating sociodemographic and clinical factors predicting response to antidepressant treatment in older adults with MDD. Our study further extends the literature by focusing on resilience, a construct that has been largely neglected in geriatric depression research. Interpretation of our finding that resilience uniquely predicts remission of geriatric depression depends upon one's conceptualization of resilience as malleable vs. a stable, trait-like characteristic. Our view, informed by recent research demonstrating the changeability of resilience across the lifespan[58,78], is that resilience is a dynamic capacity that is influenced by both internal and environmental resources [79]. As such, we believe our findings point to the potential utility of resilience training in geriatric depression. In particular, those patients with low accommodative coping self-efficacy may benefit from psychotherapies that include components designed to increase acceptance (e.g., PST). The potential for such therapies to facilitate sustained remission with

and without pharmacological treatment is an important area for future research that will help optimize treatment of geriatric depression.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key points:

1) Greater baseline resilience predicted treatment response and remission in depressed older adults receiving antidepressant treatment.

2) The resilience factor accommodative coping self-efficacy uniquely predicted treatment response and remission.

3) Future research should evaluate the potential for resilience training – and in particular, interventions designed to increase accommodative coping – to promote sustained remission of geriatric depression.

Table 1

Sample Characteristics

	Mean(SD)/ N(%)
Sex	
Female	78 (54.55%)
Male	65 (45.45%)
Race	
White	108 (75.52%)
Hispanic	14 (9.79%)
Black	15 (10.49%)
Asian	6 (4.20%)
Age	70.10 (7.26)
Years education	15.66 (2.75)
MMSE	28.66 (1.30)
GDS	18.78 (5.81)
HAM-D	18.94 (3.03)
AES	30.76 (9.73)
Late life onset (≥50)	70 (48.95%)
Number of episodes	3.67 (4.16)
More than 2 episodes	69 (48.26)
CD-RISC	55.75 (14.81)
Cerebrovascular risk	10.94 (5.18)
CIRS	5.08 (3.85)

Note. Total sample N = 143. MMSE = Mini-Mental State Exam; GDS = Geriatric Depression Scale; HAM-D = Hamilton Depression Rating Scale; HAM-A = Hamilton Anxiety Rating Scale; AES = Apathy Evaluation Scale; CD-RISC = Connor-Davidson Resilience Scale; CIRS = Cumulative Illness Rating Scale for Geriatrics. “Onset” refers to onset of Major Depressive Disorder. “Episodes” refers to depressive episodes that the participant endorsed experiencing in his or her lifetime.

Table 2

Univariate Analysis of Patient Characteristics Predicting Remission

Patient characteristic	OR	95% CI	P-value
Female sex	1.52	0.78–2.97	0.22
White race	0.79	0.37–1.69	0.54
Age	0.99	0.94–1.03	0.52
Years education	1.01	0.90–1.14	0.87
MMSE	1.06	0.82–1.37	0.64
Memory	1.25	0.81–1.94	0.32
Language	1.03	0.75–1.40	0.87
Attention	0.98	0.70–1.37	0.91
Executive functioning	0.98	0.67–1.42	0.90
Visuospatial functioning	0.94	0.64–1.40	0.78
GDS	0.96	0.90–1.01	0.12
HAM-D	0.90	0.80–1.01	0.08
AES	1.02	0.99–1.06	0.18
Late life onset (≥50)	0.65	0.33–1.26	0.20
More than 2 episodes	1.20	0.62–2.32	0.59
CD-RISC	1.04	1.00–1.07	0.05
Cerebrovascular risk	0.96	0.90–1.02	0.21
CIRS	0.94	0.86–1.03	0.18

Note. For continuous variables, odds ratios were calculated with regard to a one unit increase in the total measure score. OR = Odds ratio; CI = Confidence interval. MMSE = Mini-Mental State Exam; GDS = Geriatric Depression Scale; HAM-D = Hamilton Depression Rating Scale; HAM-A = Hamilton Anxiety Rating Scale; AES = Apathy Evaluation Scale; CD-RISC = Connor-Davidson Resilience Scale; CIRS = Cumulative Illness Rating Scale for Geriatrics. “Onset” refers to onset of Major Depressive Disorder