Title

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Journal

The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry, 27(10)

ISSN

1064-7481

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Publication Date

2019-10-01

DOI

10.1016/j.jagp.2019.04.009

Peer reviewed

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Article *in* American Journal of Geriatric Psychiatry · April 2019

DOI: 10.1016/j.jagp.2019.04.009

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Am J Geriatr Psychiatry. Author manuscript; available in PMC 2019 October 01.

Published in final edited form as:

Am J Geriatr Psychiatry. 2019 October ; 27(10): 1046–1056. doi:10.1016/j.jagp.2019.04.009.

Neurodegenerative Disease Caregivers' 5-HTTLPR Genotype Moderates the Effect of Patients' Empathic Accuracy Deficits on Caregivers' Well-Being

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Abstract

Objective: To test the hypothesis that a functional polymorphism of the serotonin transporter gene (serotonin-transporter-linked polymorphic region [5-HTTLPR]), which is thought to be associated with differential environmental sensitivity, moderates the association between low levels of empathic accuracy (i.e., ability to recognize emotions in others) in patients with neurodegenerative disease and caregivers' well-being.

Methods: Participants were 54 patients with neurodegenerative disease and their caregivers. Patients' empathic accuracy was measured using a dynamic tracking task in which they continuously rated the emotions of a character in a film; accuracy was determined by comparing

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.jagp.2019.04.009.

patient ratings with those made by an expert panel. Caregivers provided a saliva sample for genotyping. Caregivers' well-being was measured as a latent construct indicated by validated measures of depression, anxiety, and negative affect.

Results: Lower levels of patients' empathic accuracy were associated with lower levels of caregivers' well-being. Importantly, caregivers' 5-HTTLPR genotype moderated this association such that lower empathic accuracy in patients predicted lower well-being for caregivers with the short/short genotype (standardized $\beta = 0.66$), but not for caregivers with the short/long (standardized $\beta = 0.66$) or long/long genotypes (standardized $\beta = 0.66$).

Conclusion: Consistent with previous findings that the short/short variant of 5-HTTLPR is associated with greater sensitivity to environmental influences, caregivers with the short/short variant manifest lower well-being when caring for a patient with low levels of empathic accuracy than caregivers with the other variants. This finding contributes to the authors' understanding of biological factors associated with individual differences in caregiver vulnerability and resilience.

Keywords

Caregiver; depression; anxiety; empathic accuracy; 5-HTTLPR; gene-environment interaction

INTRODUCTION

Neurodegenerative diseases are incurable, debilitating conditions that result in deficits in cognitive, emotional, and motor functioning. With increasing incidence of these diseases, the number of close loved ones serving as caregivers is rising dramatically.[1] Compared with non-caregiving adults and nondementia caregivers, caregivers of patients with dementia have considerably lower well-being.[2,3] Not all caregivers experience similar declines in well-being. Therefore, it is important to identify the factors accounting for caregivers' vulnerability and resilience.

Research implicates a number of factors associated with greater vulnerability to the adverse outcomes of caregiving: personality traits, such as neuroticism;[4] demographic or external factors, including inadequate financial or social support;[4] and patients' behavioral and psychological symptoms, such as a lack of empathy.[4] Indeed, emerging consensus from the literature suggests that patients' behavioral and psychological symptoms are even worse for caregiver burden and health than patients' cognitive or functional impairments.[5–7] In particular, deficits in empathy have emerged as an important source of caregiver vulnerability.

Empathy is critical for close relationships. Having a more empathically accurate close relational partner is associated with lower depression,[8] and patients with more empathic therapists and physicians often have better mental and physical health outcomes.[9,10] Empathy is particularly important for those in high stress contexts in which social support is needed (such as caregiving). For example, a study using caregiver report of patient empathy found that lower patient empathy was related to poor relationship quality between the patient and caregiver.[11] Moreover, patients with lower empathic accuracy (who are less able to track others' changing emotions) have caregivers who experience greater burden, strain,

loneliness, and depressive symptoms.[6] These findings suggest patients' inability to recognize and respond to others' changing emotions may be particularly devastating for caregivers.

Important individual differences may exist in the ways that caregivers respond to environmental risk factors. Caregivers with genetic variations associated with heightened sensitivity to environmental influences may be more impacted by patients' empathic accuracy deficits. A series of studies using a candidate gene approach has shown that short allele carriers of the serotonin-transporter-linked polymorphic region (5-HTTLPR) polymorphism manifest greater sensitivity to both positive and negative aspects of their environment. Examples include heightened amygdala reactivity to negative faces,[12] greater empathic responding to distressing stimuli,[13] and increased positive emotional expressions to amusing stimuli.[14]

Early studies on 5-HTTLPR demonstrated an association between the short allele and heightened risk for depression, anxiety, and suicide in the face of adversity.[15] Findings from this approach were met with controversy, as replication issues arose and meta-analyses concluded that the 5-HTTLPR by environment interaction did not predict depression.[16] However, more recent meta-analyses have found support for this prediction.[17] These findings support hypotheses that caregivers who are 5-HTTLPR short allele carriers would be more sensitive to the negative stresses of patients' empathic accuracy deficits, leading to worse outcomes for those caregivers.

The present study investigates whether caregivers' 5-HTTLPR genotypemoderates the association between patients' empathic accuracy and caregivers' well-being. We hypothesized that caregivers with two copies of the short allele of 5-HTTLPR would be at greater risk for lowest levels of well-being when caring for a patient with lower empathic accuracy, compared with caregivers with the other genotypes. To our knowledge, this study is the first to investigate this relationship.

METHODS

Participants

Patients with neurodegenerative disease and their caregivers (N dyads = 54) were recruited from the Memory and Aging Center at the University of California, San Francisco (UCSF). Patients were evaluated at UCSF and diagnosed based on current consensus criteria.[18–23] The sample included patients with frontotemporal dementia, Alzheimer disease, neurodegenerative diseases that impact motor functioning, and those at high risk for a neurodegenerative disease (e.g., mild cognitive impairment). Caregivers were predominantly spouses, and all self-identified as playing a primary role in providing care to the patient. Demographic characteristics of patients and caregivers are presented in Table 1.

Procedure

Patients underwent detailed neurologic, neuropsy-chological, and neuroimaging assessments at UCSF. Within 3 months of their UCSF visit, patients and caregivers came to the Berkeley Psychophysiology Laboratory at the University of California, Berkeley. Informed consent

was obtained from both patients and caregivers. All procedures were approved by the University of California, Berkeley Committee for Protection of Human Subjects. Patients completed emotional functioning tasks,[24] including an objective measure of empathic accuracy.[6,25] Caregivers completed questionnaires and provided a saliva sample for genetic testing.

Patient Empathic Accuracy

Apparatus and procedures—Patients sat in front of a television monitor with a rating dial located near their dominant hand. The dial consisted of a small metal box with a rotating pointer that traversed a 180° path. The path overlaid a 9-point scale anchored by the legends "very bad" on the left, "neutral" in the middle, and "very good" on the right. Patients moved the rating dial continuously to reflect the feelings of a target character in an 80-second film clip, which depicted an actress experiencing a range of positive and negative emotions. Patients demonstrated that they understood the instructions. During the task, a voltage was generated reflecting the dial position; a computer sampled the voltage every 3 milliseconds and computed the average dial position for every second.

Accuracy score calculation—Empathic accuracy was calculated using time-lagged cross-correlations between each patient's ratings and those obtained from an expert panel of healthy individuals. To allow for differences in information processing and motoric speed that is common in neurodegenerative disease, the maximum correlation coefficient was selected for lags between −10 and +10 seconds.

Clinical Measures for Patients and Caregivers

Patient disease severity—At UCSF, the Clinical Dementia Rating Scale was completed using a semi-structured interview by clinicians,[26] assessing functional performance in six domains: memory, orientation, judgment and problem-solving, community affairs, home and hobbies, and personal care. For each domain, a score was given ranging from 0 (none) to 3 (severe) based on a description of functioning. Scores were summed across domains to create a score (Clinical Dementia Rating Scale Box Score), ranging from 0–18. Higher scores indicated greater disease severity.

Caregiver well-being—Caregiver well-being was conceptualized as a latent variable indicated by low levels of depressive symptoms, anxiety symptoms, and negative affect.

Caregiver depression—Caregivers' depressive symptoms for the past week were assessed using the Center for Epidemiologic Studies Depression Scale[27] 20-item questionnaire. Caregivers rated themselves on a 4-point scale from 0 (rarely or none of the time) to 3 (most or all of the time) for each item (e.g., "I felt lonely"). Four items were reverse scored, then all items were summed. Higher scores indicated greater levels of depressive symptoms.

Caregiver anxiety—Caregivers' anxiety symptoms were assessed using the Beck Anxiety Inventory,[28] a 21-item questionnaire. Caregivers rated themselves on a 4-point scale from 0

(not at all) to 3 (severely) for each symptom (e.g., “unable to relax”). Scores were summed. Higher scores indicated greater levels of anxiety symptoms.

Caregiver affect—Caregivers’ trait positive and negative affect were assessed using the Positive and Negative Affect Schedule,[29] a 20-item questionnaire that evaluates levels of positive affect (e.g., enthusiastic, interested, determined) and negative affect (e.g., scared, afraid, upset). Caregivers rated the extent to which they experienced each of 20 emotions in the past month on a 5-point scale from 1 (very slightly or not at all) to 5 (extremely). Scores were summed, with higher scores indicating greater levels of affect. Four caregivers did not complete one item on the Positive and Negative Affect Schedule. For them, scores were imputed by taking the average of the nine completed items and multiplying that value by 10.

Caregiver 5-HTTLPR Genotyping

Caregivers were invited to participate in a DNA assessment during the laboratory session. DNA were collected and extracted from saliva using Oragene kits (DNA Genotek, Kanata, Ontario, Canada) according to manufacturer’s protocol. Anonymized DNA samples were extracted and purified by Creative Genomics (Port Jefferson Station, NY). The extracted DNA were genotyped at the University of California, Los Angeles. Amplification was performed using the AccuPrime Taq High Fidelity DNA Polymerase kit (Invitrogen, Carlsbad, California). The reaction contained a 6-FAM labeled forward primer (/56-FAM/ GGCGTTGCCGCTCTGAATGC) and a reverse primer (GAGGGACTGAGCTGGACAACCA).[30] The polymerase chain reactions were then sent for fragment analysis on an AB3730XL with a LIZ1200 size standard. Data quality was assessed by duplicating a sub-set of random DNA samples; genotype data reproducibility was 100%. The genotyping yielded three groups, individuals with two short alleles (S/S; n= 14), one short and one long allele (S/L; n = 26), or two long alleles (L/L; n= 14). This genotype distribution was consistent with previous studies and did not deviate from Hardy-Weinberg equilibrium: $\chi^2(1) = 0.07$; $p = 0.791$. The 5-HTTLPR genotype was coded using an additive coding scheme (1 = L/L, 2 = S/L, and 3 = S/S), as in previous studies.[13,15]

Analytic Plan

First, we conducted bivariate correlations to evaluate associations between patients’ empathic accuracy and dementia severity, and caregivers’ depression, anxiety, negative affect, and positive affect (Table 2). In addition, we evaluated internal consistency among the indicators of well-being and tested for main effects among the indicator variables as a function of caregiver genotype groups.

Structural equation modeling analyses proceeded in three steps. First, we used confirmatory factor analyses (CFA) to test a measurement model of caregiver wellbeing, a latent variable indicated by caregivers’ depressive symptoms, anxiety symptoms, and negative affect, using the lavaan package in R software version 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria). Next, we created a path model with patient empathic accuracy predicting caregiver well-being and used multi-group modeling to examine whether caregivers’ 5-HTTLPR genotype moderated this association. We report standardized β and z-statistic (similar to t-statistic in linear regression) for these associations, which are measures of effect

size. Finally, we probed the stability of the findings when controlling for patients' dementia severity and caregivers' age, sex, and race.

Nonsignificant χ^2 values (ps >0.05) indicated satisfactory model fit. We also inspected the comparative fit index (CFI) and standardized root mean square of residual (SRMR), following established guidelines.[31] For CFI, values greater than 0.90 indicated reasonable fit and values greater than 0.95 indicated good fit. For SRMR, values less than 0.08 indicated good fit.

To rule out the possibility that observed effects were driven by individuals at "high risk" for a neuro-degenerative disease, we repeated the structural equation modeling analyses, removing those with mild cognitive impairment diagnoses and primary relatives of patients with frontotemporal dementia (Supplementary Tables S1–S3).

RESULTS

Preliminary Analyses

The Pearson correlations revealed that lower patients' empathic accuracy was associated with greater caregivers' depression (r =−0.31; p = 0.021), anxiety (r =−0.29; p = 0.036), and negative affect (r =−0.26; p = 0.060). Patients' empathic accuracy was not associated with caregivers' positive affect (r = 0.11; p = 0.45), consistent with its exclusion from the well-being latent construct. As expected, patients' empathic accuracy and dementia severity were also correlated (r =−0.41; p = 0.002).

Next, we examined reliability among caregivers' depressive symptoms, anxiety symptoms, and negative affect. Reliability was high (Cronbach's α = 0.89), supporting the possibility that the observed scores for these variables are influenced by an underlying, latent construct.

We also tested whether there were significant differences in caregivers' levels of depression, anxiety, and negative affect across genotype groups. Using the Levene test, we found that there was inequality in the variances of caregivers' depressive symptoms (but not the other measures) across genotype groups. The Kruskal-Wallis one-way analysis of variance (a nonparametric method that allows for heteroskedasticity) revealed no differences in caregivers' depressive symptoms and one-way analysis of variance revealed no differences in caregivers' anxiety symptoms and negative affect across caregivers' genotype groups (Table 1).

Structural Equation Modeling

We used CFA to test a measurement model of caregiver well-being, indicated by caregivers' depressive symptoms, anxiety symptoms, and negative affect. For clarity of interpretation, we reversed the directions of the factor loadings (such that greater loadings of depression, anxiety, and negative affect reflect *lower* well-being). In the initial CFA, the residual variance for caregivers' negative affect was not significantly different from zero (δ = 0.079; p = 0.26). The χ^2 analyses comparing a measurement model with caregivers' negative affect residual variance fixed to zero to the initial measurement model (without negative affect residual variance fixed to zero) demonstrated that the models were not significantly different

($\Delta\chi^2(1) = 1.15$; p = 0.28). Therefore, we repeated the CFA, fixing the residual variance for caregivers' negative affect to zero. The CFA for caregiver well-being indicated excellent fit: $\chi^2(1) = 1.15$; p = 0.28; CFI = 1.00; SRMR= 0.02.

Subsequent analyses showed that a structural equation model (Fig. 1) with patient empathic accuracy as a predictor of caregiver well-being had excellent fit: $\chi^2(3) = 3.82$; p = 0.28; CFI = 0.99; SRMR = 0.05. Factor loadings and residual variances are reported in Table 3.

Multi-Group Modeling

Next, we examined whether the inclusion of 5-HTTLPR genotype groups improved model fit using multi-group modeling (i.e., by comparing a model in which the association between patients' empathic accuracy and caregivers' well-being was constrained to be equal across caregiver 5-HTTLPR genotype variants to a model in which this association was not constrained using $\Delta\chi^2$ tests). Results showed that including caregivers' 5-HTTLPR genotype group significantly improved model fit: $\Delta\chi^2(2) = 8.76$; p = 0.013. The multi-group model also indicated excellent fit, $\chi^2(9) = 9.30$; p = 0.41; CFI = 1.00; SRMR = 0.04.

Consistent with our hypothesis, 5-HTTLPR moderated the association between patient empathic accuracy and caregiver well-being. Specifically, lower patient empathic accuracy predicted lower caregiver well-being—*only* for those with the short/short genotype (β = 0.66; z = 2.81; p = 0.002)—but not for those with the short/long (β =0.05; z = 0.23; p = 0.82) or long/long (β = −0.21; z = −0.79; p = 0.44) genotypes. These associations are depicted in Figure 2, and the simple correlations for each genotype group show the same pattern of findings (Supplementary Table S4).

Finally, we probed the stability of the results by controlling for patients' dementia severity and caregivers' age, sex (coded 0 = female, 1 = male), and race (coded 0 = non-white, 1= white). Multi-group modeling revealed that including caregivers' 5-HTTLPR genotype significantly improved model fit: $\Delta\chi^2(2) = 7.96$; p = 0.019. Overall, the multi-group model with the addition of these covariates indicated suboptimal fit: $\chi^2(33) = 66.37$; p = 0.001; CFI = 0.80; SRMR = 0.08. Again, patient empathic accuracy was positively associated with caregiver well-being for those with the short/short genotype (β = 0.47; z = 2.21; p = 0.018), but not for those with the short/long (β = 0.07; z = 0.52; p = 0.61) or long/long (β = −0.28; z = −1.07; p = 0.30) genotypes.

DISCUSSION

The present study sought to increase understanding of individual differences in caregiver well-being by evaluating the influence of caregivers' 5-HTTLPR genotype on their vulnerability to patients' empathic accuracy deficits. We measured patients' empathic accuracy objectively through a dynamic tracking task and used this measure to predict caregivers' well-being as indicated by measures of depression, anxiety, and negative affect. We explored differences in this relationship across caregivers' 5-HTTLPR genotypes.

Findings revealed a significant positive relationship between patients' empathic accuracy and caregivers' well-being for caregivers with the short/short genotype (even after

controlling for caregivers' age, sex, and race and patients' dementia severity), but not for caregivers with the short/long and long/long genotypes. Given the study's relatively small sample size and the inclusion of multiple covariates in the model, independent replication will be necessary before these results can be considered conclusive. Nevertheless, these findings provide preliminary evidence that caregivers with the short/short genotype may be at heightened risk for low well-being when caring for a patient with neurodegenerative disease who has deficits in empathic accuracy. To our knowledge, this is the first study to identify a specific genetic polymorphism that may play a role in moderating the association between patient deficits and caregiver outcomes.

Our results are consistent with prior work suggesting that the short/short 5-HTTLPR genotype acts as a susceptibility factor to environmental stimuli, amplifying negative outcomes in negative contexts[12] (i.e., stressful caregiving environment) and positive outcomes in positive contexts.[14] Given this bidirectional sensitivity, one might expect caregivers with short/short to be particularly healthy (i.e., high well-being) when caring for a patient with high empathic accuracy. However, because neurodegenerative disease overwhelmingly produces declines in patient functioning, associated environmental effects will pre-dominately be reflected in negative outcomes.

Prior research has documented short allele carriers' heightened sensitivity both on distal or long-term measures (e.g., psychopathology and marital satisfaction)[15,32] as well as on more proximal measures (e.g., reactivity to an emotional stimulus).[13,14] Extending this model further, heightened emotional reactivity may be a proximal mechanism through which the short allele contributes to distal out-comes.[33] Longitudinal studies are needed to test whether caregivers' heightened negative emotional reactivity (a proximal mechanism), perhaps *in response to* patients' increasing empathic accuracy deficits, mediates the relationship between caregivers' genotype and changes in caregivers' well-being over time (a distal outcome).

It is also important to understand the biological basis of caregivers' vulnerability. The short allele is associated with lower levels of serotonin uptake and lower transcriptional efficiency of the serotonin transporter protein.[34] It has been argued that increased available synaptic serotonin in short allele carriers may result in increased amygdala excitability to external stimuli,[12] which may result in heightened emotional reactivity. The efficiency of the serotonin system has been shown to decline with age both in terms of central serotonin transporter availability and postsynaptic serotonin receptors.[35] Therefore, it is possible that the effects of serotonin-related genes such as 5-HTTLPR are magnified with age, which may shed light on how this single allele could have such a powerful effect in our sample of older adults. Although brain imaging data were not collected in this study, white matter pathology has been similarly implicated in the stress exposure-outcome pathway in caregivers.[36] Future studies that evaluate multiple pathways could disentangle the relative contributions of these mechanisms to caregivers' increased vulnerability.

Implications

Patients' empathic accuracy deficits may render them incapable of identifying and therefore responding to others' emotions. When patients' empathic accuracy declines and caregivers

lose a vital source of social support, caregivers with the short/short genotype might feel particularly lonely and isolated. If these findings replicate, they suggest that evaluating caregivers' genotype in conjunction with patient deficits may facilitate identification of caregivers at greatest risk for low well-being. These caregivers may be good candidates for preventative interventions and supportive resources, such as emotion regulation skills (to mitigate heightened emotional reactivity) or referrals to caregiver support groups (to address feelings of loneliness). There are also important implications for pharmacological interventions. Short allele carriers show promising response and remission rates for depression treatment using selective serotonin reuptake inhibitors.[37] Additional work is needed to clarify the specific biological pathways through which selective serotonin reuptake inhibitors may mitigate depressive symptoms for short allele carriers. In light of recent evidence showing that low levels of mental health in caregivers are associated with greater patient mortality,[38] the implications of these findings are important for patients and caregivers alike.

Strengths and Limitations

Strengths of this study include the dyadic design and a specific measure of stress. Previous research on 5-HTTLPR has typically studied individual participants and assessed overall levels of stress without regard to the particular contributing stressors (e.g., stressful life event checklist).[17] In addition, patients' empathic accuracy was measured objectively and separately from the caregiver; therefore, we reduced common method variance that could inflate found associations.

There are also important limitations to note. Our sample size (N = 54 dyads) was small by the standards of candidate gene studies.[39] Therefore, the results should be interpreted cautiously awaiting future replication in larger samples. A larger sample size would also have enabled us to detect possible codominant effects of the 5-HTTLPR alleles (i.e., differences between one and two long alleles). In addition, it will be important to evaluate the boundary conditions of these findings, such as whether they are generalizable across all types of caregiving relationships (e.g., professional caregivers, friends) and other types of patient deficits in emotional functioning (e.g., problems with emotion regulation).

In general, candidate gene approaches have been met with criticism.[16] Our decision to focus on 5-HTTLPR as a candidate genetic vulnerability factor in caregivers was based on documented biological pathways linking 5-HTTLPR and well-being (with 5-HTTLPR encoding a direct target for antidepressant medication)[37] and well-established links between 5-HTTLPR and heightened reactivity to emotional stimuli.[12–14,32] Other approaches (e.g., genome-wide association studies) have clear benefits, although we note that they typically do not assess tandem repeat genetic variants, such as 5-HTTLPR.[40]

CONCLUSION

Caregiving can exact a heavy toll, but there is huge variability in how caregivers react to the challenges of caregiving. As the number of older adults in the population rises, there is an urgent need to identify factors that contribute to individual differences in caregiver outcomes. Evaluating the role of specific patient deficits (e.g., empathic accuracy) in the

context of caregiver vulnerabilities (e.g., 5-HTTLPR polymorphism) provides valuable information regarding which caregivers are susceptible to a particular kind of environmental stressor. Future research should continue to examine the pathways through which genes interact with the social environment to alter caregivers' quality of life. Uncovering patient and caregiver factors that undermine caregiver well-being will be critical for developing effective interventions that promote the health of caregivers and the patients in their care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by NIA grants 2P01AG019724-11 and 1R01AG041762-01A1 awarded to Robert W. Levenson and NIMH Affective Science Training grant 5T32MH020006-20 awarded to Jenna L. Wells.

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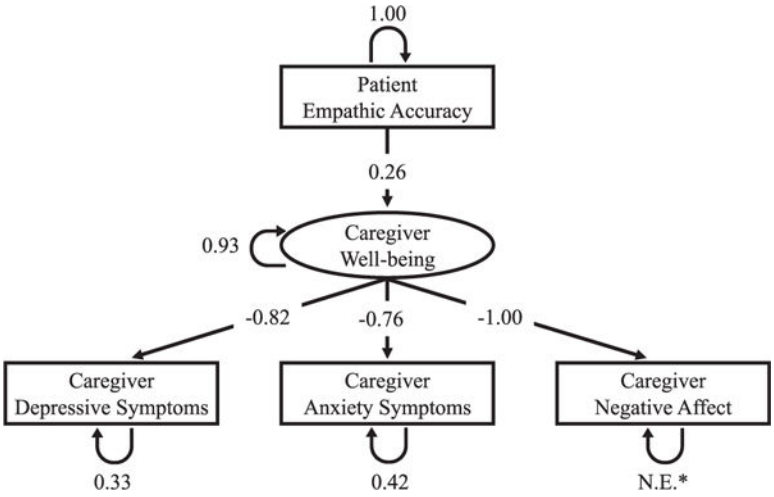

FIGURE 1.

Structural equation model with patient empathic accuracy predicting caregiver well-being.

* N.E. = not estimated; fixed to 0

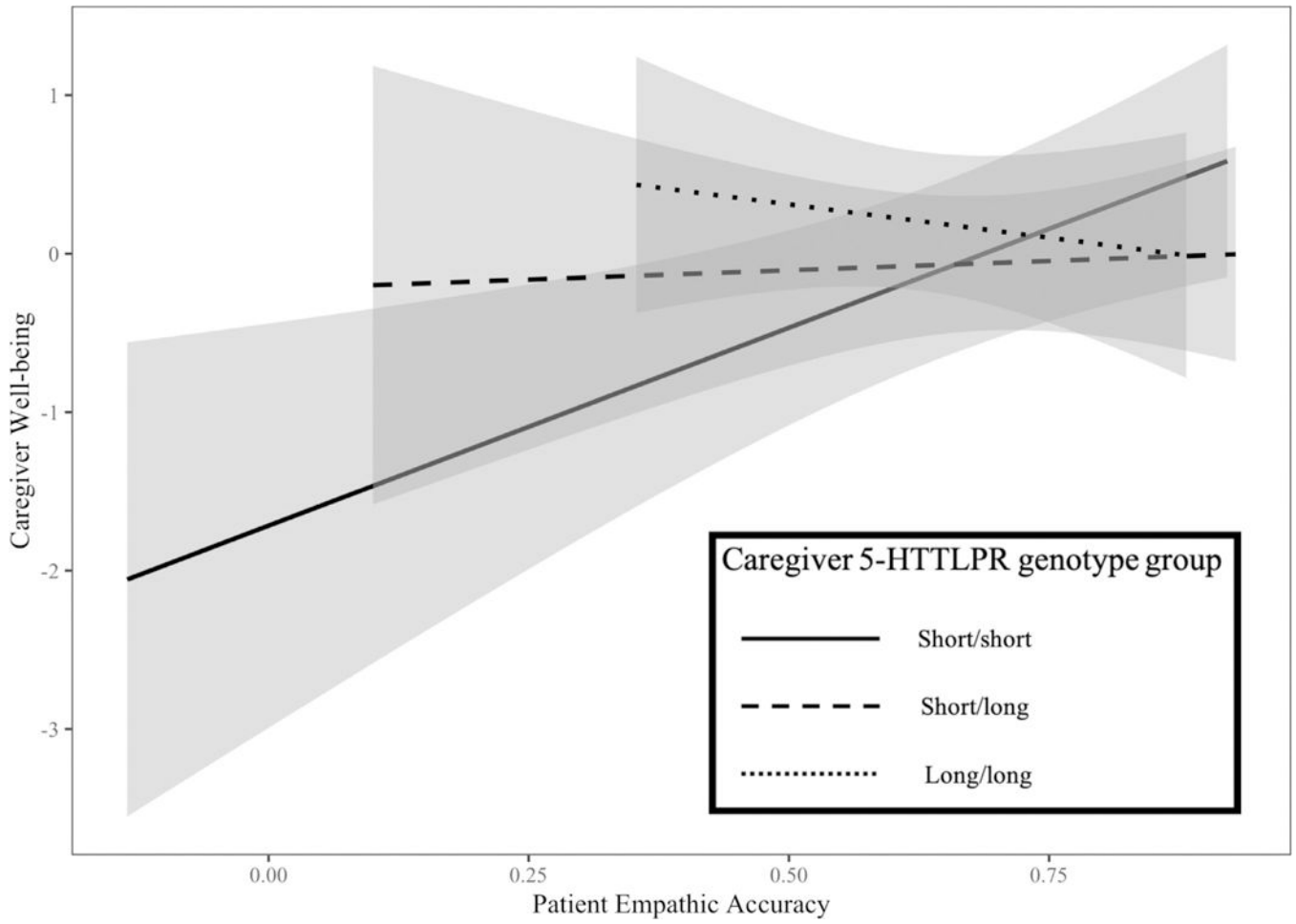

FIGURE 2.
Simple slopes and 95% confidence intervals by 5-HTTLPR genotype group.

TABLE 1.

Demographic Characteristics of Caregivers and Patients

	S/S (n = 14)	S/L (n = 26)	L/L (n = 14)	Test[a]	p
Caregiver					
Sex	8M; 6F	6M; 20F	7M; 7F	4.98	0.083
Age	61.44(8.25)	59.82 (10.40)	62.05 (11.96)	0.23	0.79
Race (n)				1.98	0.37
White/European American	10	23	12		
Non-white	4	3	2		
Caregiver type (n)				2.47	0.65
Friend	0	1	0		
Other relative	1	1	2		
Spouse	13	24	12		
Depressive symptoms (CES-D)	14.50 (12.08)	11.58(8.45)	7.14(3.35)	3.29[b]	0.19
Anxiety symptoms (BAI)	8.36 (10.09)	6.54(7.41)	5.36(4.27)	0.56	0.58
Negative affect (PANAS)	19.29(8.45)	19.04(7.11)	17.21 (5.10)	0.39	0.68
Positive affect (PANAS)	30.37 (7.72)	34.81 (8.60)	33.12(6.02)	1.48	0.24
Patient					
Sex	6M; 8F	18M; 8F	7M; 7F	4.53	0.10
Age	61.89(11.58)	62.98 (9.96)	64.41 (8.39)	0.22	0.80
Race (n)				4.02	0.13
White/European American	9	17	13		
Non-white	5	9	1		
Diagnosis (n)				11.80	0.30
Alzheimer disease	2	2	3		
Frontotemporal dementia (FTD)	3	11	6		
Mild cognitive impairment	2	0	2		
Motor neurodegenerative disease	4	10	2		
Other neurodegenerative disease	2	0	1		
Primary relative of FTD patient	1	3	0		

	S/S (n = 14)	S/L (n = 26)	L/L (n = 14)	Test[a]	p
Empathic accuracy	0.65 (0.33)	0.69(0.19)	0.63(0.18)	0.41	0.67
Disease severity (CDR-Box)	4.36(2.91)	3.65 (2.85)	2.64 (2.00)	1.46	0.24

Notes. Mean (with standard deviation in parentheses) for participant characteristics listed by caregiver 5-HTTLPR genotype group, unless otherwise noted. BAI: Beck Anxiety Inventory; CDR-Box: Clinical Dementia Rating Scale Box Score; CES-D: Center for Epidemiologic Studies Depression Scale; F: female; FTD: frontotemporal dementia; L/L: long/long; M: male; PANAS: Positive and Negative Affect Schedule; S/L: short/long; S/S: short/short.

[a]Reporting F-statistic from one-way analysis of variance for continuous variables and the Pearson χ^2 test for categorical variables to test for significant differences across the three genotype groups.

[b]Kruskal-Wallis one-way analysis of variance because of heteroskedasticity across genotype groups.

TABLE 2.

Zero-Order Correlations of Key Study Variables

	1	2	3	4	5
1. Caregiver depressive symptoms (CES-D)	–				
2. Caregiver anxiety symptoms (BAI)	0.68[d]	–			
3. Caregiver negative affect (PANAS)	0.82[d]	0.76[d]	–		
4. Caregiver positive affect (PANAS)	−0.41[c]	−0.17	−0.24[a]	–	
5. Patient empathic accuracy	−0.31[b]	−0.29[b]	−0.26[a]	0.11	–
6. Patient dementia severity (CDR-Box)	0.59[d]	0.31[b]	0.40[c]	−0.38[c]	−0.41[c]

Notes. BAI: Beck Anxiety Inventory; CDR-Box: Clinical Dementia Rating Scale Box Score; CES-D: Center for Epidemiologic Studies Depression Scale; PANAS: Positive and Negative Affect Schedule.

[a] p <0.10.

[b] p <0.05.

[c] p <0.01.

[d] p <0.001.

TABLE 3.

Caregiver Well-Being Factor Loadings and Residual Variances

Indicator	Measurement Model	Multi-Group Model			Multi-Group Model with Covariates[a]		
		S/S	S/L	L/L	S/S	S/L	L/L
Depressive symptoms (CES-D)	−0.82	−0.93	−0.79	−0.68	−0.93	−0.79	−0.68
	(0.33)	(0.13)	(0.37)	(0.54)	(0.13)	(0.36)	(0.54)
Anxiety symptoms (BAI)	−0.76	−0.86	−0.68	−0.81	−0.86	−0.68	−0.81
	(0.42)	(0.26)	(0.53)	(0.35)	(0.26)	(0.54)	(0.35)
Negative affect (PANAS)	−1.00	−1.00	−1.00	−1.00	−1.00	−1.00	−1.00
	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)

Notes. Factor loadings (with residual variances in parentheses). BAI: Beck Anxiety Inventory; CES-D: Center for Epidemiologic Studies Depression Scale; L/L: long/long; PANAS: Positive and Negative Affect Schedule; S/L: short/long; S/S: short/short.

[a]Covariates include caregiver age, sex, race, and patient dementia severity.

Am J Geriatr Psychiatry. Author manuscript; available in PMC 2019 October 01.