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Research Article

When Distress Becomes Somatic: Dementia Family Caregivers' Distress and Genetic Vulnerability to Pain and Sleep Problems

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Abstract

Background and Objectives: Stress can trigger physical pain and disturb sleep. Whether dementia family caregivers experience heightened pain is unknown. Cycles of unwanted thoughts about caregiving stressors and avoidance of these thoughts—that is, caregiving-related distress—may exacerbate both pain and sleep disturbances, and genetic susceptibility to stress may further modulate these associations.

Research Design and Methods: Dementia caregivers (72 spouses, 58 adult children, ages 34–89) rated the extent to which they experienced unintended thoughts about caregiving and tried to suppress such thoughts. They also reported their pain levels, sleep problems, and depressive symptoms. Peripheral blood leukocytes were genotyped for 5-HTTLPR (serotonin-transporter-linked polymorphic region) and 5-HT_{1A} receptor polymorphism rs6295 on the *5HTR1A* locus.

Results: Short-allele carriers for 5-HTTLPR experienced more pain and sleep problems in association with greater caregiving-related distress than those with other genotypes. For rs6295, C carriers also showed the strongest links between distress and sleep problems. Those who experienced more avoidance and intrusive thoughts about caregiving had more severe depressive symptoms, consistent with past work.

Discussion and Implications: Caregivers' genetic profiles helped to explain whether caregiving-related distress predicted worse pain and sleep problems. These data reveal new somatic risks of caregiver distress and provide targets for intervention. According to plasticity theories, caregivers genetically predisposed to greater stress reactivity may also respond particularly well to interventions, and many brief treatments may effectively address caregivers' intrusions and avoidance.

Keywords: Caregiving-related distress, Informal dementia caregivers, Serotonin genes, Intrusions/avoidance, Physical symptoms

Stress and Its Links to Pain and Sleep Problems: Relevance for Dementia Family Caregivers

Stress can ignite and exacerbate physical pain and sleep problems. In both chronic pain sufferers and healthy people, even a short-lived stressor such as a public-speaking task increases sensitivity to painful stimuli (Crettaz et al., 2013). Among the most demanding roles, family caregiving may heighten the risk for pain, but little is known about the pain cascade in this vulnerable population. Dementia family caregivers

may face particular risks given the often protracted nature of dementias, in addition to care recipients' gradual deterioration. Many dementia caregivers report sleep disturbances, and those who find caregiving more upsetting are more likely to experience disrupted sleep (Leggett, Polenick, Maust, & Kales, 2018). Moreover, pain and sleep problems can fuel each other: pain in its aversiveness heightens arousal and disturbs sleep; in turn, sleep loss magnifies pain sensitivity (Smith & Haythornthwaite, 2004). Because family caregivers' level of functioning affects their own well-being, as well as their self-care and care recipients' well-being, their suffering stands to amplify public health burden.

Caregiving-Related Distress and the Symptom Cluster of Pain, Sleep Problems, and Depression

Caregiving-related distress may increase caregivers' risks for pain and sleep problems in part by prolonging the noxious effects of caregivers' stress. According to social-cognitive theory, individuals who experience extreme stress can cycle between unwanted thoughts or feelings about the stressor and suppression of these thoughts and feelings (Lepore, 1997). Paradoxically, avoiding unwanted thoughts makes them more intrusive (Lepore, 1997). Caregivers' ability to minimize this avoidance-intrusion cycle may modulate its associated physical and psychological risks. Indeed, dementia family caregivers' intrusive thoughts were linked to greater depression (Schulz, Savla, Czaja, & Monin, 2017), a condition that shares close ties to pain and sleep problems (Smith & Quartana, 2010). Further, spousal dementia caregivers who slept more poorly reported greater denial and more avoidant behaviors, and expressed more negative emotions than did better sleepers (Taylor et al., 2015). Thus, preliminary evidence suggests that caregivers' intrusions and generalized avoidant coping may be associated with depression and sleep problems, but caregiving-specific avoidance and intrusive thoughts have not been examined in relation to a symptom cluster in a single study.

Likewise, intrusions and avoidance may exacerbate pain by increasing awareness and sensitivity to painful stimuli, and by amplifying negative thoughts and feelings about pain. For example, healthy participants asked to suppress, or avoid, their thoughts during a cold pressor task reported greater pain than those asked to record their thoughts; thought suppressors' heightened pain sensitivity was explained by their increased intrusive thoughts (Sullivan, Rouse, Bishop, & Johnston, 1997). This finding provides further evidence that avoiding unwanted thoughts likely leads to greater distress and also increased pain sensitivity. Whether this process extends to caregiving-related distress and caregivers' existing pain is unknown.

Moderating Role of Serotonin-Related Genes: A Gene–Environment Framework

Pain, sleep problems, and depression tend to co-occur, and the neurotransmitter serotonin plays a key role in all three (Smith & Quartana, 2010). Serotonin-related genes, including the well-characterized serotonin transporter polymorphic region 5-HTTLPR and the single nucleotide polymorphism rs6295 on the serotonin receptor *5HTR1A* gene, code for key serotonin proteins and, thus, influence serotonergic reuptake and function. These genes have also been implicated in diathesis–stress and differential susceptibility theories (e.g., Disner, McGeary, Wells, Ellis, & Beevers, 2014), which suggest that particular genetic variants increase vulnerability or susceptibility to stress (Belsky et al., 2009). In this way, 5-HTTLPR and rs6295 may help to govern links between caregiving-related distress and physical symptoms.

A large majority of 5-HTTLPR studies have focused on the association between stressful life events and syndromal depression, with mixed results across four meta-analyses (Culverhouse et al., 2017; Karg, Burmeister, Shedden, & Sen, 2011; Risch et al., 2009; Sharpley, Palanisamy, Glyde, Dillingham, & Agnew, 2014). The equivocal findings may be due to the focus on mere exposure to life stressors. Instead, effects may emerge when the cycle of intrusive thoughts and avoidance prolongs a stressful event, more potent than sheer exposure. Further, genetic vulnerability to stress has never been examined in relation to pain, despite its link to both stress and depression, and has rarely been studied in caregivers or with regard to sleep. In one exception, dementia family caregivers with two short alleles had poorer sleep compared to controls with the same genotype (Brummett et al., 2007). Examining the association between caregiving-related distress and pain, sleep problems, and depressive symptoms as a function of serotonin transporter genotype will determine whether a dose–response relationship exists between distress and a cluster of serotonin-linked symptoms among short-allele carriers—allowing for variation among more and less distressed caregivers.

In terms of the serotonin receptor *5HTR1A* gene and its SNP rs6295, most prior work has examined genetic differences in depression rates, and results have been mixed. Some have linked the G allele to higher depression rates (e.g., Lebe et al., 2013), whereas others have reported null relationships (e.g., Hettema et al., 2008) or greater depression risk with the C allele (Galvao-de Almeida et al., 2014). One gene–environment study found at a trend level that C/C adults with elevated life stress were more likely to commit suicide than other groups (Wang et al., 2017).

Far fewer studies have investigated links between rs6295, sleep, and pain. A pilot study of fewer than 20 participants found no differences in sleep disturbance by *5HTR1A* genotype (Biard, Douglass, Robillard, & De Koninck, 2016). No prior work has examined gene–environment associations between rs6295, sleep, and pain.

Current Study

Using a gene–environment framework, the current study sought to examine dementia family caregivers' risks for

heightened pain, sleep problems, and depressive symptoms, in relation to the cycles of intrusive thoughts and avoidance that characterize caregiving-related distress. Guided by prior empirical work (e.g., Brummett et al., 2007; Caspi, Hariri, Holmes, Uher, & Moffitt, 2010) and theory (Belsky et al., 2009), we hypothesized that 5-HTTLPR would moderate the links between caregiving distress and symptoms, such that those with the S/S genotype would have the strongest dose–response relationships between greater distress and more severe pain, sleep problems, and depressive symptoms (Hypothesis 1). We also predicted that links between caregiver distress and symptoms would differ by 5-HT_{1A} receptor polymorphism rs6295 (Hypothesis 2) (Belsky et al., 2009; Caspi et al., 2010; Disner et al., 2014), but did not establish directional hypotheses due to the smaller, mixed literature.

Method

Participants

Participants were recruited for a caregiving study through community and university newspapers, senior centers, a collaborating neurologist, and the local Alzheimer's Disease Association (Kiecolt-Glaser et al., 2011). Individuals with notable health problems, such as cancer or recent surgeries, were excluded.

The sample consisted of 130 adults caring for a spouse (55.4%) or parent (44.6%) with Alzheimer's disease or another progressive dementia. More than half were female (75%), consistent with national estimates. Their mean age was 65 (*SD* = 12.5, range = 35–90), and they had provided care for an average of 4.5 years (*SD* = 3.6). See Tables 1 and 2 for further description.

Table 1. Sample Description

Attribute	*N* (%)
Female caregiver	98 (75.4%)
Caregiver race	
White	107 (82.3%)
Black	19 (14.6%)
Multiracial	4 (3.1%)
Caregiver education	
High school or below	20 (15.4%)
Some college	26 (20.0%)
Graduated college	50 (38.5%)
Graduate or professional	34 (26.2%)
Caregiver employed	55 (42.3%)
Caregiver relation	
Spouse	72 (55.4%)
Child	58 (44.6%)
Care recipient diagnosis	
Alzheimer's disease	82 (63.1%)
Multi-infarct dementia (vascular dementia)	4 (3.1%)
Parkinson's disease	2 (1.5%)
Pick's disease (frontotemporal dementia)	1 (1.0%)
Other	39 (30.0%)
Care recipient location	
Caregiver's home	82 (63.1%)
Other family home	7 (5.4%)
Alone	10 (7.7%)
Nursing home	30 (23.1%)

Procedure

The Ohio State University Institutional Review Board approved the project; all subjects provided written informed consent before participation. Eligible individuals were scheduled for a laboratory or home appointment between 8 am and 10 am. Participants provided blood samples and completed self-report measures.

Self-Report Measures

The 15-item Impact of Events Scale (IES) assessed two related facets of caregiving-related distress: intrusive thoughts about caregiving and avoidance (Horowitz, Wilner, & Alvarez, 1979). Intrusion items assessed unintended thoughts, for example, "I thought about caregiving and my caregiving experiences when I didn't mean to." Avoidance items captured attempts to suppress thoughts about recent caregiving experiences, for example, "When I was not providing care for my spouse, I tried not to think about caregiving." Each subscale was highly correlated with the total sum score ($r_{Intrusion}$ = .86, p < .0001; $r_{Avoidance}$ = .87, p < .0001), and with each other (r = .51, p < .0001), consistent with the notion that intrusion and avoidance fuel a single vicious cycle (Lepore, 1997). To mirror this theory and minimize the number of statistical tests, we used the total score (Cronbach's α = 0.85).

The pain subscale of the 36-item RAND Health Survey provided data on bodily pain and its interference with activities (Ware & Sherbourne, 1992). Typically, higher scores indicate less pain, but we reverse-scored the scale to indicate greater pain, consistent with the study's other outcomes. The Center for Epidemiological Studies-Depression (CES-D) scale has been used extensively as a brief measure of depressive symptomatology (Radloff, 1977), where higher values reflect more severe symptoms. The Pittsburgh Sleep Quality Index (PSQI; Buysse, Reynolds, Monk, Berman, & Kupfer, 1989) assesses sleep quality and disturbances in the prior month; higher scores indicate greater sleep disturbance.

Comorbidities

The Older Adult Resources and Services Multidimensional Functional Assessment Questionnaire assessed the number of chronic conditions (Fillenbaum & Smyer, 1981). Because of their association with pain, sleep problems, and depression, comorbidities were included as a covariate in analyses.

Table 2. Description of Key Study Variables

	1	2	3	4	6	7	8	*M* (*SD*)
1. Caregiving-related distress								20.0 (12.8)
2. Pain	0.16+							27.8 (22.8)
3. Sleep problems	0.39*	0.39*						6.1 (3.3)
4. Depressive symptoms	0.50*	0.30*	0.62*					11.0 (8.4)
6. Age	0.06	−0.04	−0.24*	−0.21*				64.5 (12.5)
7. Body mass index	0.02	0.30*	0.13	0.20*	−0.26*			28.9 (7.5)
8. Comorbidities	0.16+	0.25*	0.16+	0.08	0.23*	0.18*		1.2 (1.0)
9. Physical activity	0.12	−0.13	0.05	−0.01	−0.01	−0.19*	0.01	18.1 (12.5)

Note: *$p < .05$. +$p < .08$.

Physical activity

The Community Healthy Activities Model Program for Seniors (CHAMPS) questionnaire assessed the weekly frequency and duration of various physical activities (Stewart et al., 2001). Physical activity was treated as a covariate in analyses due to its associations with pain, sleep, and depression.

Medication use

Use of relevant medications (i.e., opioids, steroids, or prescription anti-inflammatories) was treated as a covariate due to their effects on pain and sleep.

Genotyping

Using a candidate gene approach, 5-HTTLPR and rs6295 were selected given their support in prior studies and gene–environment interaction theory (e.g., Belsky et al., 2009; Birmingham et al., 2006; Disner et al., 2014).

5-HTTLPR

The 5-HTT genotype was determined from genomic DNA isolated from 1 ml of EDTA-treated peripheral blood leukocytes. Briefly, 50 ng of DNA was amplified using a sense primer from -1416 to -1397 (5′ GGCGTTGCCGCTCTGAATGC) and an antisense primer from -888 to -910 (5′ GAGGGACTGAGCTGGACAACCAC), relative to the transcriptional start site. The amplification conditions consisted of 2.5 mM dNTPs, 2 µM of each primer, 10 mM Tris–HCl (pH 8.3), 50 mM KCl, 1.5 mM $MgCl_2$, and 1 U *Taq* polymerase. The cycling conditions were 60°C annealing for 30 s, 720°C extension for 1 min, and 950°C denaturing for 30 s, for 35 cycles. The products were analyzed in 2.5% agarose and detected by ethidium bromide staining. The L allele was identified by the presence of a 528-bp band, and the S allele, by the presence of a 484-bp band.

5-HT_{1A} receptor polymorphism

The 5-HT_{1A} rs6295 genotype was determined by a *Fok* I restriction fragment length polymorphism of a polymerase chain reaction product, as described in prior work (Birmingham et al., 2006). In the results, C refers to the 1019C allele, and G refers to the 1019G allele.

Analytic Plan

We used regression models to evaluate hypotheses that the link between caregiving-related distress and pain, sleep problems, and depressive symptoms would depend on serotonin-based polymorphisms. To minimize the number of tests, we began by modeling this two-way interaction between caregiving-related distress and each polymorphism in separate models on the three focal outcomes: pain, sleep problems, and depressive symptoms. Covariates included age, race, sex, body mass index, relationship to the care recipient (spouse or adult child), physical activity, comorbidities, and medication use. For statistically significant interactions, estimates were generated for each genotype; nonsignificant interaction terms were removed in final models. Because evidence for the dominance structure of these polymorphisms is mixed, we reported all comparisons among the genotypes for each polymorphism (Caspi et al., 2010). Ancillary models tested whether effects held controlling for care recipients' residence and functioning (Blessed Dementia Scale; Erkinjuntti, Hokkanen, Sulkava, & Palo, 1988), as well as length of caregiving.

Results

Description

Genotype frequencies

The frequencies for 5-HTTLPR and rs6295 are displayed in Table 3. Analyses showed that both were in Hardy–Weinberg equilibrium (HW $coefficient_{5\text{-HTTLPR}} = 0.04$, 95% CI [−0.004, 0.077]; HW $coefficient_{rs6295} = 0.023$, 95% CI [−0.028, 0.061]); that is, the distribution of alleles did not significantly vary from population expectations. According to chi-square tests, white and non-white caregivers did not significantly differ in their genotype distributions ($p_{5\text{-HTTLPR}} = .080$, $p_{rs6295} = .627$).

Bivariate associations

As expected, caregivers with more caregiving-related distress had more sleep problems ($r = .39$, $p < .0001$) and greater depressive symptoms ($r = .50$, $p < .0001$); the link between higher distress and greater pain was marginally significant ($r = .16$, $p = .069$). Also, greater pain was significantly correlated with more sleep problems ($r = .39$, $p <$

.0001) and higher depressive symptoms (r = .30, p = .001); likewise, caregivers with more sleep problems had higher depressive symptoms (r = .62, p < .0001). Caregivers did not differ in their mean levels of caregiving-related distress, pain, sleep problems, or depressive symptoms as a function of either 5-HTTLPR or rs6295 genotypes (ps > .250).

The Moderating Role of 5-HTTLPR in Links Between Distress and Symptoms

Pain

Caregivers with two short alleles had a significantly stronger association between distress and pain than did caregivers with two long alleles (B = −0.82, SE = 0.38, p = .035, 95% CI [−1.58, −0.06]) and those with one short allele (B = −1.15, SE = 0.43, p = .009, 95% CI [−2.00, −0.30]). The difference between having one or two long alleles was not significant (p = .376, 95% CI [−0.41, 1.07]). As depicted in Figure 1, more distressed S/S caregivers also had greater pain (estimate = 0.85, SE = 0.32, p = .009, 95% CI [0.22, 1.48]); the effect was not significant among S/L or L/L caregivers (ps > .250).

Sleep

S/S caregivers had a significantly stronger association between distress and sleep problems than L/L counterparts (Figure 2, B = −0.16, SE = 0.05, p = .001, 95% CI [−0.25, −0.06]). There were no differences S/S and S/L caregivers (though the effect trended in the expected direction, B = −0.10, SE = 0.05, p = .077, 95% CI [−0.20, 0.01]) or between S/L and L/L caregivers (p = .184, 95% CI [−0.15, 0.03]). Among S/S caregivers (estimate = 0.20, SE = 0.04, p < .0001, 95% CI [0.13, 0.28]) and S/L caregivers (estimate = 0.11, SE = 0.04, p = .004, 95% CI [0.04, 0.18]), having more distress was associated with greater sleep problems; the effect was not significant among L/L caregivers (p = .104).

Depression

There were no significant differences in the association between distress and depressive symptoms between S/S caregivers and the others (ps > .116). With the interaction term removed, those with more caregiving-related distress had greater depressive symptoms than the less distressed, regardless of genotype (B = 0.33, SE = 0.06, p < .0001, 95% CI [0.22, 0.44]).

Table 3. Allele Frequencies

Genotype	Frequency
5-HTTLPR	
S/S	0.20
S/L	0.41
L/L	0.39
Rs6295 (*5HTR1A*)	
C/C	0.25
C/G	0.47
G/G	0.28

Note: N = 125 for 5-HTTLPR; N = 124 for rs6295.

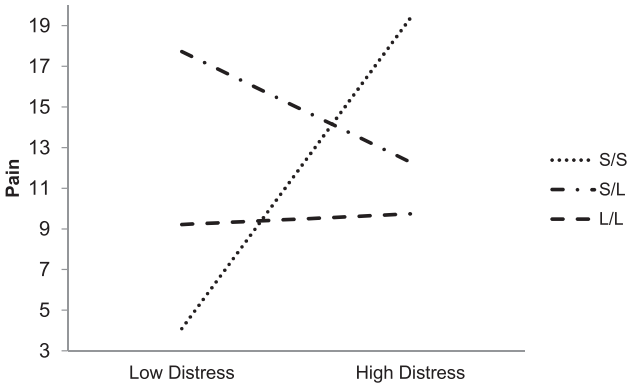

Figure 1. 5-HTTLPR genotype moderating the link between caregiving-related distress and pain. In the plot, *low distress* denotes subclinical caregiving-related distress with an Impact of Events Scale (IES) score of 8, approximately 1 *SD* below the sample mean. *High distress* signifies clinically elevated distress with an IES score of 26. As indicated by the dotted line, more distressed S/S caregivers also had greater pain (B = 0.85, SE = 0.32, p = .009, 95% CI [0.22, 1.48]); the effect was not significant among S/L (dashed-dotted line) or L/L (dashed line) caregivers (ps > .250).

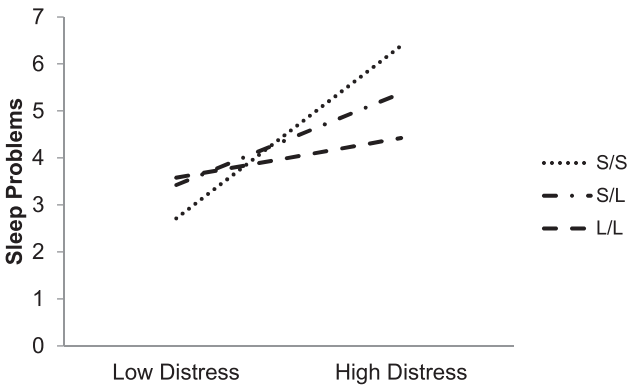

Figure 2. 5-HTTLPR genotype moderating the link between caregiving-related distress and sleep problems. In the plot, *low distress* denotes subclinical caregiving-related distress with an Impact of Events Scale (IES) score of 8, approximately 1 *SD* below the sample mean. *High distress* signifies clinically elevated distress with an IES score of 26. Among S/S caregivers (dotted line, B = 0.20, SE = 0.04, p < .0001, 95% CI [0.13, 0.28]) and S/L caregivers (dashed-dotted line, B = 0.11, SE = 0.04, p = .004, 95% CI [0.04, 0.18]), having more distress was associated with greater sleep problems; the effect was not significant among L/L caregivers (dashed line, p = .104).

The Moderating Role of rs6295 in Links Between Distress and Symptoms

Pain

The association between distress and pain did not differ by rs6295 genotype (ps > .250), nor was there a main effect of distress on pain in this model with the interaction term removed (p > .250).

Sleep

C/C caregivers evidenced a significantly stronger association between distress and sleep problems than G/G caregivers (Figure 3, $B = 0.17$, $SE = 0.06$, $p = .007$, 95% CI [0.05, 0.30]) and compared to heterozygotes ($B = 0.15$, $SE = 0.05$, $p = .004$, 95% CI [0.05, 0.26]). Heterozygotes did not differ from G/G caregivers in the magnitude of association between distress and sleep problems ($p > .250$). Simple effects revealed that among C/C caregivers (estimate = 0.21, $SE = 0.05$, $p < .0001$, 95% CI [0.12, 0.30]) and C/G caregivers (estimate = 0.06, $SE = 0.03$, $p = .032$, 95% CI [0.01, 0.11]), having more distress related to greater sleep problems; the effect was not significant among G/G caregivers ($p > .250$).

Depression

There were no significant genotypic differences in the link between distress and depressive symptoms ($ps > .117$). Again, more distress predicted greater depressive symptoms, regardless of rs6295 genotype ($B = 0.30$, $SE = 0.05$, $p < .0001$, 95% CI [0.20, 0.41]).

Ancillary Analyses

No results changed when ancillary covariates were included: care recipients' residence and functioning, and length of caregiving. Given potential genotypic and phenotypic variability of 5-HTTLPR across races, follow-up analyses restricted the sample to white participants, and results remained similar (see Supplementary Material). Refer to Supplementary Material for exploratory associations with the individual PSQI sleep subscales, which revealed some evidence of genotypic moderation in all seven components.

Discussion

Dementia family caregivers with more caregiving-related distress had more severe depressive symptoms, and caregivers' genetic profiles modulated whether caregiving-related distress was also linked to worse physical symptoms. In particular, short-allele carriers for 5-HTTLPR who had greater caregiving-related distress experienced more pain and sleep problems, and for the 5-HT_{1A} polymorphism, C carriers showed the strongest links between caregiving-related distress and sleep problems. Caregivers with greater pain also tended to report more sleep problems and higher depressive symptoms; similarly, sleep problems were associated with depressive symptoms. Mean levels of caregiving-related distress, pain, sleep problems, and depressive symptoms did not differ by genotype. These data reveal new somatic risks associated with caregiving-related distress and provide modifiable intervention targets for this at-risk population.

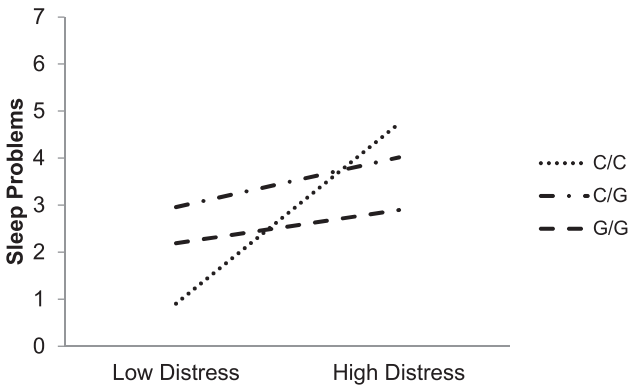

Figure 3. rs6295 polymorphism on the *5HTR1A* locus moderating the link between caregiving-related distress and sleep problems. Among C/C caregivers (dotted line, $B = 0.21$, $SE = 0.05$, $p < .0001$, 95% CI [0.12, 0.30]) and C/G caregivers (dashed-dotted line, $B = 0.06$, $SE = 0.03$, $p = .032$, 95% CI [0.01, 0.11]), having more distress related to greater sleep problems; the effect was not significant among G/G caregivers (dashed line, $p > .250$).

Consistent with prior work (Schulz et al., 2017), individuals with more caregiving-related intrusions and avoidance also had higher depressive symptoms, and this link did not differ by genotype. The cascade linking caregiving-related distress to depression likely follows a direct path that may not be interrupted or exacerbated by a particular genotype. Indeed, depressed individuals also struggle to disengage from negative, unwanted thoughts and emotions (Beck, 2008).

Greater caregiving-related distress also predicted more severe sleep problems. In related prior work using polysomnography assessment, spousal caregivers with more avoidant coping styles, which included behaviors such as denial, cognitive disengagement, and emotional venting, faced heightened risks for clinically significant sleep problems compared to others (Taylor et al., 2015). Our data suggest that the combination of caregiving-specific intrusive thoughts and avoidance of such thoughts may pose unique risks for sleep dysfunction, particularly among caregivers with the riskier serotonin genotypes.

Prior studies have reported effects of stressor-related intrusions and avoidance on sleep in other populations, including bereaved individuals and hurricane victims (Hall et al., 1997; Ironson et al., 1997). Building on studies of these time-limited stressors, our findings underscore the relevance of intrusions and avoidance for the sleep of genetically at-risk family caregivers. Indeed, the continuous stream of stressors that accompanies dementia caregiving provides a steady source for intrusions. Likewise, daily care activities may prompt unintended thoughts about prior caregiving difficulties, further hampering recovery from distress, disrupting sleep, and escalating caregivers' already elevated health risks. In fact, the average caregiver in our sample suffered from clinically significant sleep disturbances, which increase their future risks for developing chronic health conditions (Assari, Sonnega, Pepin, & Leggett, 2017).

Among caregivers with the riskiest 5-HTTLPR genotype (S/S), intrusive thoughts and avoidance also predicted more severe pain. To our knowledge, these findings offer some of the first data on caregivers' risks for pain, which have important functional implications for caregivers' quality of

life, their ability to provide care, and the overall burden on the healthcare system. Caregiving-related intrusions and avoidance may increase pain directly. For example, in women with fibromyalgia and their healthy counterparts, hot and cold pain sensitivity increased following a stressful lab task (Crettaz et al., 2013). Also, in daily diary work, people had greater pain on days after they had been in a worse mood (Charles & Almeida, 2006). This effect may arise in part due to the overlapping neural circuitry of pain and emotional experiences. Indeed, the anterior cingulate cortex responds to both stressful social exclusion tasks and painful stimuli (Eisenberger, Jarcho, Lieberman, & Naliboff, 2006). By this route, intrusions and avoidance would exacerbate pain by effectively prolonging the stressful experience and triggering affective pain regions.

Further, intrusions and avoidance likely bring attention to and amplify symptoms. For example, people asked to avoid their thoughts during a cold pressor task ultimately had more intrusive thoughts and reported greater pain than those in the other conditions (Sullivan et al., 1997). Among breast cancer survivors, a group at risk for persistent pain years after treatment, cancer-related intrusive thoughts predicted greater pain 1 year later (Dupont, Bower, Stanton, & Ganz, 2014). Together with these prior findings, our results suggest that caregiving-related distress is relevant to symptoms, beyond experimentally induced pain. Moreover, our findings were not specific to any one disease process, and thus may be relevant to all caregivers with the high-risk genotype.

In addition to these pathways, stress directly triggers proinflammatory cytokine signaling via the sympathetic nervous system (Miller, Maletic, & Raison, 2009). This signal induces pain sensitivity, a key sickness behavior evolved to promote rest and recovery following illness (Miller et al., 2009). Other sickness behaviors include negative mood and sleep alterations, suggesting that this inflammatory phenotype may partially underlie the similar associations we observed between intrusions/avoidance and pain, sleep problems, and depression—in addition to their shared serotonergic bases.

Once triggered, depression and sleep problems may fuel pain indirectly as well. Indeed, both sleep disruption and deprivation increased pain sensitivity to heat in healthy adults (e.g., Kundermann, Spernal, Huber, Krieg, & Lautenbacher, 2004). Depressed people report more pain symptoms than nondepressed counterparts (Hermesdorf et al., 2016). Depressed mood and sleep disruption may also act synergistically to escalate pain: depressed patients had increases in self-reported pain and increased pain sensitivity to hot and cold stimuli following sleep deprivation (Kundermann, Hemmeter-Spernal, Huber, Krieg, & Lautenbacher, 2008).

The current findings add clarity to the ongoing debate about the role of 5-HTTLPR in physical and mental health. According to Caspi and colleagues (2010), stressor-specific studies have been more likely to find gene–environment interaction effects on mental health problems than larger population-based studies, in part because they tend to characterize the stressor's severity or disruptiveness in a more nuanced way than the typical epidemiological assessment of general life event exposure. Consistent with this working hypothesis, we found genotypic differences in the dose–response relationship between caregivers' intrusions and avoidance and their physical symptoms. Indeed, caregiving-related intrusions and avoidance represent these stressors' potency, and S/S individuals with more caregiving-related distress also had the most severe physical symptoms.

Our findings also extend the relevance of 5-HTTLPR beyond depression to related physical symptoms, sleep problems and pain. To our knowledge, only one prior study has linked stress-related effects of 5-HTTLPR to sleep problems (Brummett et al., 2007), and none have yet shown associations with pain. The current results add credence to 5-HTTLPR as a meaningful modulator of the connection between stressful experiences and health by extending its reach to biologically plausible symptoms, related to depression through serotonergic and inflammatory pathways. This study also builds on the prior work that found sleep differences between caregivers and noncaregivers by 5-HTTLPR genotype (Brummett et al., 2007), by examining variations within a sample of family caregivers. Indeed, our results suggest that this genotype distinguishes caregivers' physical symptom severity associated with varying degrees of intrusions and avoidance.

We found a moderating pattern for the rs6295 polymorphism between intrusions/avoidance and sleep problems similar to that of 5-HTTLPR. However, we consider these findings preliminary due to the small number of studies that have examined this SNP in gene–environment interactions. Future work should attempt to replicate the pattern.

It would be interesting for future studies to examine the combined effects of 5-HTTLPR and rs6295; our sample size did not accommodate three-way interactions with both genotypes. A larger replication study should also recruit a greater proportion of African American and Asian caregivers due to potential genetic and cultural differences, as we could not compare racial groups directly. Also, the cross-sectional design prevents causal, directional conclusions. Multi-timescale longitudinal work will be best suited to assess exactly how the dynamics of caregiving-related distress, pain, sleep problems, and depression unfold over time among genetically predisposed caregivers.

Clinical Implications

The current findings stand to inform practice by uncovering dementia family caregivers' risks for physical symptoms, determining which caregivers may suffer most, and identifying a treatable target for intervention. Indeed, caregivers' stress-related risks for pain have not been extensively described, and although caregivers' sleep problems are better characterized,

prior work has not fully identified those at greatest risk. Our results show that caregivers with the greatest pain and sleep problems may have a genetic predisposition to stress-related symptoms. Furthermore, caregivers with two short alleles (5-HTTLPR) or the C/C genotype (rs6295) had not only the greatest distress-related pain and sleep problems, but also the strongest associations; that is, those with lower caregiving-related distress also had the *mildest* physical symptoms among caregivers with these genetic profiles. Indeed, according to the differential susceptibility hypothesis (Belsky et al., 2009), those at greatest genetic risk for stress reactivity may also respond most robustly to interventions.

Encouragingly, evidence-based treatments such as mindfulness-based stress reduction (MBSR) and cognitive-behavioral approaches can effectively address avoidance and intrusive thoughts. For instance, MBSR was superior to education and support conditions in reducing family caregivers' perceived stress (e.g., Whitebird et al., 2013). In a pilot study of 38 family caregivers, MBSR was also associated with significant decreases in avoidance (Brown, Coogle, & Wegelin, 2016). Scalable treatment options such as self-guided smartphone applications and professional telehealth services maximize feasibility for already-burdened family caregivers (e.g., Williams et al., 2010).

Primary care settings that serve either the caregiver or the care recipient would be ideal vehicles to widely disseminate information about caregivers' treatment options. Indeed, these simple steps may help to limit caregivers' physical symptoms, to stave off related long-term health consequences, and to support the well-being of both caregivers and care recipients.

Supplementary Material

Supplementary data are available at *The Gerontologist* online.

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Conflict of Interest

None reported.

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