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New evidence for a biological pathway to mental health problems in dementia caregivers:

Invited commentary on the article by Wells et al. (AMGP-1247)

Stephen F. Smagula, PhD[1,2]

[1]Department of Psychiatry, School of Medicine, University of Pittsburgh

[2]Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh

Consider the case of a 62-year-old woman, Linda, whose spouse was recently diagnosed with frontotemporal dementia. In addition to the regular challenges of adjusting to post-retirement life, Linda faces a myriad of potentially stressful caregiving-related exposures. She now oversees an increasingly complex medical regime for her husband, yet only sees his decline; she often experiences intrusive thoughts about his health; she is woken at night due to her husband's problems sleeping; her relationship is strained due to his inability to recognize her emotional states; she fears he will walk off during the day and get lost; and as a result, she withdraws from her usual social activities.

As this case illustrates, family caregivers for people with dementia can be chronically exposed to a wide range of potentially stressful exposures. It is not surprising that, much like other stressful exposures (1), dementia caregivers are at very high risk of developing mental health symptoms and disorders (2–6). For example, one study found that 25% of dementia caregivers developed new clinically significant depression symptoms over 18 months (2).

Why do some, but not all, dementia caregivers develop mental health problems? If we understood why dementia caregivers develop mental health symptoms, we could identify vulnerability earlier on, and target these sources of vulnerability with new prevention approaches. In this issue of the *Journal*, Wells et al. presents some of the first biological evidence regarding why some dementia caregivers respond differently to an important potential stressor.

In brief, Wells et al. found that empathetic accuracy deficits in care recipients were related to worse mental health in caregivers - but only if the caregiver carried the s/s allele of the serotonin transporter polymorphism (5-HTTLPR). The demographic characteristics of the case described above are those of the average caregiver in the sample studied by Wells et al. The work by Wells et al. follows logically from decades of 5-HTTLPR gene by stressor research summarized in a meta-analysis confirming past findings (7); specifically, people with the s/s allele of 5-HTTLRP appear to be more sensitive to the effect of environmental stress on mental health.

Corresponding author: Stephen F. Smagula, PhD, 3811 O'Hara Street, Pittsburgh, Pennsylvania 15213.

The article by Wells et al. now demonstrates these effects in dementia caregivers. Strengths of the article include: the use of a sophisticated latent modeling approach; studying a composite outcome variable that integrates common mental health symptoms; objectively assaying empathic accuracy deficits in care recipients; and examining a biological moderator of the effects of this stressor on caregivers' mental health. However, like most compelling new scientific evidence, this work's limitations highlight several questions for future research.

First, from a screening/risk stratification perspective, it is not clear whether genotyping will improve the ability to identify vulnerable caregivers. The initial study by Wells et al. had a relatively small sample size and did not aim to evaluate the predictive utility of the s/s 5-HTTLRP allele in terms of detecting risk for clinically meaningful mental health outcomes. It is not known whether measuring the 5-HTTLRP allele improves risk stratification.

Second, the mechanisms linking the s/s 5-HTTLRP allele to vulnerability in dementia caregivers are not known. With support from past work (8), the authors propose that the effect of s/s allele status may be through heighted emotional reactivity, e.g., in the amygdala. Not only does this provide a plausible proximal mechanism, it could also provide a unifying pathway that multiple vulnerability mechanisms converge upon. Specifically, my own recent work in the *Journal* found that cerebrovascular disease in caregivers moderated the relationship of caregiving intensity and stress. In caregivers without significant cerebrovascular disease, greater caregiving intensity correlated with a greater probability of reporting stress; in contrast, regardless of caregiving intensity, almost all the caregivers who had significant cerebrovascular disease reported stress. Cerebrovascular disease has also been associated with an exaggerated brain response to an emotional reactivity task (9). Therefore, both the s/s allele and cerebrovascular disease may induce vulnerability in caregivers by influencing affective circuits in the brain.

Finally, and perhaps most critically, future studies are needed to determine what can be done to modify the downstream impact of these relatively-distal vulnerabilities (5-HTTLR allele status and cerebrovascular disease). Even if measuring biomarkers improves our ability to detect vulnerability, the task of interrupting these pathways stands tall. Prospective studies are needed to identify modifiable factors related to better outcomes in caregivers with biological vulnerability, e.g., studies that identify psychosocial and behavioral factors related to better mental health outcomes in s/s allele carriers.

In conclusion, the study by Wells et al. brings us one step closer to understanding the complex pathways which determine how dementia caregivers will respond to potentially stressful exposures. Future studies are needed to link genetic vulnerability to the proximal neurobiology of mental health in dementia caregivers, and to understand what can be done to modify these pathways to caregiver burnout, anxiety, and depression.

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