Published in final edited form as:

Nat Rev Rheumatol. 2013 October ; 9(10): 569–570. doi:10.1038/nrrheum.2013.139.

Stress affects rheumatoid arthritis, but via what mechanisms?

Patrick H. Finan and

Department of Psychiatry and Behavioural Sciences, Johns Hopkins University School of Medicine, 5510 Nathan Shock Drive, Suite 100, Baltimore, MD 21224, USA

Alex J. Zautra

Department of Psychology, Arizona State University, PO Box 1104, Tempe, AZ 85287-1104, USA

Abstract

The mind and body are thought to interact in a manner that influences health, but modelling the right aspects of each so as to best inform treatment is a tricky proposition. A new study discusses how stress can affect rheumatoid arthritis symptoms.

Even before Engel's¹ call for a new medical model, clinicians and scientists were alerted to Descartes' error² in separating mind from body, but science progresses only when such big ideas are followed by well-designed inquiries into the specific details. How exactly mind and body are related is the question that must be answered. In studies of embodied cognition, for instance, cognitive scientists have begun to specify the ways in which the mind is 'in' the body, rather than independent of it. In their new study, Evers *et al.*³ wrestle with the other side of this question, asking how the body responds to the mind.

Armed with 6 months of data on anxious worries and monthly exposure to stressful life events of patients with rheumatoid arthritis (RA; $n = 80$), the authors tested whether psychological factors (that is, worry) and social factors (that is, daily stressors) in one month would lead to exacerbations in RA symptoms (as measured by disease activity score in 28 joints and RA disease activity index, as well as reports of pain and fatigue) the next month. Furthermore, they tested whether a pathway to such influences could be charted through changes in immune and endocrine activation by measuring, among others, levels of cortisol and inflammatory markers such as TNF, IL-6 and IFN- γ . Indeed, the researchers found that worrying was a leading indicator of next-month RA disease activity and pain, and higher stress counts increased the likelihood of fatigue. However, they did not find any physiological markers to account for those mind–body interactions: neither cytokines nor cortisol levels changed in concert with psychosocial factors.³

The study builds upon evidence from prior investigations (including some of our own work), connecting both stress exposure and maladaptive cognitive styles with elevations in RA disease activity.^{4,5} Commendably, the authors required evidence of temporal precedence before interpreting associations between states of mind and body as supportive of causal

Correspondence to: A. J. Zautra, atajz@asu.edu.

Competing interests

The authors declare no competing interests.

connections. Even with these methodological constraints, they found support for the proposition that the mind influenced RA symptoms. Nonetheless, in our opinion, the null results were the most intriguing presented in this study. The tests for mechanisms of causal connections between worry and disease status came up short: proinflammatory cytokines and cortisol were not found to mediate the effects of worrying and daily stressors on RA symptoms.

At least three alternative explanations exist for their findings: the study was underpowered to detect subtle biopsychosocial effects, which tend to be quite modest; the methods for measuring and analysing the immune and endocrine effects were insufficient; or an alternative model might better fit the data. The first two potential explanations are interdependent; power is determined both by the size of the effect sought and by the amount of error associated with its measurement. A monthly timescale was used, but immune and endocrine markers have been shown to vary on a daily or even momentary basis.⁶ Thus, repeated observations of stress and/or distress and levels of immune markers over a shorter time frame might better detect the temporal dynamics of mechanisms underlying the mind–body relationships observed in this study.

The third potential explanation might be resolved by inserting another known stress-reactive biological mediator (such as C-reactive protein or nuclear factor κ B) into the authors' existing biopsychosocial framework. Each investigator will have a favourite yet unmeasured variable, but the authors did include sensible choices, and still came up empty-handed. We suspect a more fundamental lesson can be taken from their study; different biopsychosocial path ways of disease progression need to be charted. On the surface, the Evers *et al.*³ findings might be interpreted to imply that the mind and body work separately to influence the disease course of patients with rheumatic and other chronic pain disorders, but the model could be incomplete. Our work and that of others suggests that biopsychosocial effects are not confined to harmful factors such as chronic worry and stress exposure. Adaptive processes, such as the experience of positive emotions, self-efficacy and optimism, seem to have beneficial effects on both subjective perceptions and clinical indicators of pain-related illness. For example, Steptoe and colleagues⁷ have demonstrated that positive emotions are associated with reduced daily cortisol output, attenuated plasma fibrinogen response to induced stress and reduced circulating levels of proinflammatory cytokines.

Neurobiological systems other than the neuroimmune and neuroendocrine systems might additionally be relevant for understanding the disease course of rheumatic conditions. In a study published in 2013 of patients with osteoarthritis, Finan *et al.*⁸ demonstrated that short-term positive affective states were correlated not only with reduced daily clinical pain, but also with reduced mechanical temporal summation, a putative marker for central sensitization and enhanced glutamatergic activity in the spinothalamic tract.

Our work on patients with fibromyalgia also indicates that genetic factors might explain individual differences in the extent to which individuals regulate positive affect in the face of pain.⁹ Specifically, catechol-*O*-methyltransferase (*COMT*) genotype moderated patients' daily positive affective responses to elevations in pain. Given that *COMT* regulates dopamine metabolism, this finding implicates dopaminergic activity, particularly within the

mesolimbic reward system, as a potential mechanism of the association of positive affect and chronic pain.

Importantly, Engel's¹ message reminds us that social relations should not be overlooked. The strongest of our positive and negative states of mind arise from our social relationships. The stressors identified in Evers *et al.*,³ for instance, are social in nature. Positive relational events not measured in the study, such as an intimate embrace or a compassionate one, give rise to positive emotions. Parasympathetic balance is sustained through strong secure social ties, and lost in loneliness, with consequences on immune processes.¹⁰ Not only is the body subject to the mind, but this mind–body nexus is also subject to influences outside itself.

Moving forward, it will be necessary to test models that make explicit, theory-based predictions about both the positive and negative psychosocial antecedents and sequelae of rheumatic illness. Such an effort would advance the existing cognitive–behavioural paradigm of psychotherapeutic care for patients with rheumatic diseases and chronic pain, which focuses primarily on reducing negative affect and cognition, and which lacks empirically validated strategies to enhance positive affect through better relationships both with oneself and with others. As the Evers *et al.*³ study findings indicate, the biopsychosocial model is critical to our understanding of individual differences in the trajectory of rheumatic disease.

Acknowledgments

A. J. Zautra is supported by NIH/National Institute of Aging grant RO1 AG 026,006. P. H. Finan is supported by NIH/National Institute of Nursing Research/National Institute of Neurological Disorders and Stroke grant T32 NS070201, and NIH/National Institute of Nursing Research grant 1P30 NR014131.

References

1. Engel GL. The need for a new medical model: a challenge for biomedicine. *Science*. 1977; 196:129–136. [PubMed: 847460]
2. Damasio, A. *Descartes' Error: Emotion, Reason, and the Human Brain*. Putnam Publishing; New York: 1994.
3. Evers, AW., et al. Does stress affect the joints? Daily stressors, stress vulnerability, immune and HPA axis activity, and short-term disease and symptom fluctuations in rheumatoid arthritis. *Ann Rheum Dis*. <http://dx.doi.org/10.1136/annrheumdis-2012-203143>.
4. Zautra AJ, et al. Immune activation and depression in women with rheumatoid arthritis. *J Rheumatol*. 2004; 31:457–463. [PubMed: 14994388]
5. Davis MC, et al. Chronic stress and regulation of cellular markers of inflammation in rheumatoid arthritis: implications for fatigue. *Brain Behav Immun*. 2008; 22:24–32. [PubMed: 17706915]
6. Haack M, Sanchez E, Mullington JM. Elevated inflammatory markers in response to prolonged sleep restriction are associated with increased pain experience in healthy volunteers. *Sleep*. 2007; 30:1145–1152. [PubMed: 17910386]
7. Steptoe A, Dockray S, Wardle J. Positive affect and psychobiological processes relevant to health. *J Pers*. 2009; 77:1747–1776. [PubMed: 19796062]
8. Finan PH, Quartana PJ, Smith MT. Positive and negative affect dimensions in chronic knee osteoarthritis: effects on clinical and laboratory pain. *Psychosom Med*. 2013; 75:463–470. [PubMed: 23697467]
9. Finan PH, et al. Genetic influences on the dynamics of pain and affect in fibromyalgia. *Health Psychol*. 2010; 29:134–142. [PubMed: 20230086]

10. Jaremka LM, et al. Loneliness promotes inflammation during acute stress. *Psychol Sci.* 2013; 24:1089–1097. [PubMed: 23630220]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

iStockphoto/Thinkstock