Commentary

Biological Psychiatry

Behavioral Interventions Produce Robust Beneficial Biological Alterations

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Irwin *et al.* (1) demonstrate in a randomized controlled trial that cognitive-behavioral therapy for insomnia and tai chi chih, a westernized variant of tai chi, produce robust reductions of inflammatory markers in participants >55 years old with insomnia. Although the temporal persistence of the effects varies, and the specific molecular outcome measures differ to some extent, both interventions show beneficial biological changes immediately after the 4-month intervention and persistence of some of these effects up to 1 year after completion of the intervention.

These findings are important for several reasons. The trial was a randomized three-arm design in which patients were randomly assigned to one of the two active treatment conditions or to a sleep seminar (SS) education control condition. The impact of the active treatments was found in comparison to the SS control condition. In addition to measures of proinflammatory cytokines, the study included measures of proinflammatory gene expression. This study adds to a growing body of literature that indicates that "mind-body" interventions, including various forms of meditation, can produce alterations in gene expression, particularly for genes that regulate inflammation, and such alterations can occur very rapidly (2). Finally, by including a semiactive comparison condition (SS), the authors were able to demonstrate that the effects were produced by processes other than simple expectation, which they attempted to match across groups.

In other research, our group (3) highlighted the importance of using active comparison conditions with meditation intervention studies because these studies cannot be conducted using double-blind, placebo-controlled methods (4). Although the SS condition is an important addition to this study, the instructors who teach this know that it is a "control" intervention, and their expectations for effects produced by this condition are different than the expectations for the active treatment interventions. Ultimately studies are needed that truly match the experimental treatment with active comparison treatments taught by instructors who hold expectations comparable to the expectations held by the instructors of the experimental interventions. Although this is a high bar, it is an essential standard if we wish to assign the active ingredient to something specific about the practice or technique taught and not simply to the positive expectations that are held by the instructors.

Rosenkranz *et al.* (5) reported that mindfulness-based stress reduction produced a significantly reduced postintervention inflammatory response compared with a rigorously matched active comparison treatment using an experimental inflammatory provocation. Although some outcome measures did not differentiate between mindfulness-based stress reduction and the active comparison treatment, the fact that the posttreatment inflammatory response did differ significantly suggests, in this case, that the active ingredient of mindfulness was essential in producing the decrease in inflammatory mediators.

The article by Irwin *et al.* (1) raises many important questions that require further study in future research. The patterns produced by cognitive-behavioral therapy for insomnia and tai chi chih were not identical. Precisely why these differences occur and what produces them need to be determined in future work. It will also be critical to determine if the specific bioinformational pathways identified in the Transcription Element Listening System promoter–based analyses are replicable because many pathways are tested, and some are of only borderline significance.

The persistence of effects after the completion of the interventions is of practical and theoretical importance. Some forms of mind-body intervention provide participants with simple daily practices that they can use to maintain the effects that may be produced in the original intervention. It is important to obtain measures of practice history to ascertain whether the persistence of effects is associated with the type and duration of daily practice. Some previous studies of meditation found that alterations in brain function in expert practitioners are predicted by the number of lifetime hours of practice (6).

One of the most exciting and important extensions of this work will focus on the mechanisms through which these effects arise. The interventions that were taught in this study are transduced by the brain, and it is through their effects on the brain that the alterations in inflammatory processes occur. It is unknown precisely which neural circuits are implicated. Other research, some of it conducted by Irwin *et al.* at University of California, Los Angeles, demonstrates that the interactions between the brain and inflammatory processes are bidirectional. For example, Inagaki *et al.* (7) found that amygdala reactivity to socially threatening stimuli was significantly elevated after low-dose exposure to an endotoxin (vs. placebo). These data highlight the potential importance of affective circuitry—particularly activations in the anterior cingulate cortex and insula—in the modulation of inflammation, a general pattern we found in our studies on brain function associated with inflammatory processes in the lung in patients with asthma (8,9). By combining brain imaging with measures of inflammatory markers before and after mind-body interventions, systematic associations between alterations in brain function and modulation of inflammatory processes can be discovered. Very few studies have combined these methods in the same participants at the same points in time. However, the

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http://dx.doi.org/10.1016/j.biopsych.2015.09.001
Biological Psychiatry November 15, 2015; 78:668–669 www.sobp.org/journal
ISSN: 0006-3223

data presented in the study by Irwin *et al.* (1) underscore the need for these types of studies in the future.

In addition to examining the neural circuitry of emotion in relation to inflammation, the time course of such activations may turn out to be a significant feature that should be examined in future research. For example, we found that it is not the absolute magnitude of activation in the amygdala that is associated with negative affective traits such as neuroticism, but rather the extent to which such activation persists after the offset of negative emotional stimuli. We reported that the magnitude of amygdala recovery (i.e., the magnetic resonance imaging signal in the amygdala during a period after the offset of a negative emotional stimulus) predicts individual differences in neuroticism and not amygdala reactivity (the magnitude of the amygdala signal in response to a negative stimulus) (10). These findings highlight the need to characterize the dynamic time course of recovery and not simply reactivity to emotional stimuli to understand the dynamic neural circuits that modulate inflammation.

Finally, the clinical importance of effects such as those reported by Irwin *et al.* (1) will be extended by conducting studies in patients with specific diseases for which inflammation is a significant contributing factor. Such studies will require that the form of cognitive-behavioral therapy be adapted to the particular disease in question. The tai chi intervention may be generally applicable across disease contexts, and other mindfulness-based interventions may be similarly applicable across disease contexts. In such studies, disease-specific symptoms and inflammatory mediators can be measured jointly to determine the extent to which modulation of inflammation is associated with reductions in disease-related symptoms.

In conclusion, the study by Irwin *et al.* (1) presages a new era for behavioral interventions. Some behavioral interventions may be found to produce more specific biological changes than any pharmacologic intervention, given that the latter is a much more blunt procedure that will likely have many systemic side effects. An opportunity for the future will be to combine the ancient wisdom of some of the contemplative traditions that give rise to many mind-body interventions commonly used today with strategies that emerge directly from a deep understanding of the brain. Such "neurally inspired" behavioral interventions may represent the future of how we can effect specific alterations in behaviorally relevant neural circuits and systemic biological processes.

Acknowledgments and Disclosures

This work was supported by the National Institutes of Health National Center for Complementary and Integrative Health Grant No. P01AT004952 and National Institute of Mental Health Grant Nos. P50-MH84051 and MH43454 and several gifts to the Center for Investigating Healthy Minds at the University of Wisconsin-Madison.

RJD serves on the board of directors for the nonprofit organizations the Mind and Life Institute and the Center for Investigating Healthy Minds, Inc. No donors, either anonymous or identified, have participated in the design, conduct, or reporting of research results in this article.

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Received Aug 31, 2015; accepted Sep 1, 2015.

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