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Behavioral interventions produce robust beneficial biological alterations

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Irwin and his colleagues¹ demonstrate in a randomized controlled trial that both cognitive behavior therapy for insomnia (CBT-I) and Tai Chi Chih (TCC), a Westernized variant of Tai Chi, both produce robust reductions of inflammatory markers in participants >55 years of age who suffer from insomnia. Though the temporal persistence of the effects vary and the specific molecular outcome measures differed to some extent, both interventions show beneficial biological changes immediately after the four month intervention and persistence of some of these effects up to one year following the completion of the intervention.

These findings are important for several reasons. The trial was a randomized three-arm design in which patients were randomized 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. Second, 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 rapidly². Third, by including a semi-active 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 group³ has highlighted the importance of using active comparison conditions with meditation intervention studies since these studies cannot be conducted using double-blind placebo-controlled methods for obvious reasons⁴. While the SS condition is clearly an important addition to this study, the instructors who teach this clearly know that it is a “control” intervention and thus their expectations for effects produced by this condition are different than the expectations for the active treatment interventions. Ultimately studies are required that truly match the experimental treatment with active comparison treatments taught by instructors who hold comparable expectations as those held by the instructors of the experimental interventions. While this is a high bar, it is an essential standard if we ultimately 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.

In a recent study, Rosenkranz and colleagues reported that Mindfulness-based Stress Reduction (MBSR) produced a significantly reduced post-intervention inflammatory response compared with a rigorously matched active comparison treatment using an experimental inflammatory provocation⁵. While there were some outcome measures that did

not differentiate between MBSR and the active comparison treatment, the fact that the post-treatment inflammatory response did differ significantly suggests, in this case, that the active ingredient of mindfulness was essential in producing this decrease in inflammatory mediators.

The Irwin et al article¹ raises many important questions that require further study in future research. The patterns produced by CBT-I and TCC were not identical. Precisely why these differences occur and what produces them needs to be disentangled in future work. Also critical will be to determine if the specific bioinformational pathways identified in the TELiS promoter-based analyses are replicable since many pathways are tested and some are clearly only of borderline significance.

The persistence of effects following the completion of the interventions is clearly of both practical and theoretical import. 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 in order to ascertain whether the persistence of effects is associated with the type and duration of daily practice. Some previous studies of meditation find that alterations in brain function in expert practitioners are predicted by the number of lifetime hours of practice⁶.

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 clearly are transduced by the brain and it is through their effects on the brain that the alterations in inflammatory processes occur. Precisely which neural circuits are implicated is not known. Other research, some of it conducted by Irwin and colleagues at UCLA, demonstrate that the interactions between the brain and inflammatory processes are bidirectional. For example, following low-dose exposure to an endotoxin (vs. placebo), Inagaki and colleagues⁷ found that amygdala reactivity to social threatening stimuli was significantly elevated. 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 discovered in our studies on brain function associated with inflammatory processes in the lung in asthmatics^{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. There have been precious few studies that have combined these methods in the same participants at the same points in time. However, the data presented in this report by Irwin and his colleagues¹ underscore the need for these types of studies in the future.

In addition to simply examining the neural circuitry of emotion in relation to inflammation, the time course of such activations may turn out to be a very significant feature that should be examined in future research. For example, we have 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 it is the extent to which such activation persists following the offset of negative emotional stimuli. We have reported that it is the magnitude of amygdala recovery (i.e., the MR signal in the amygdala during a period *after* the offset of a negative

emotional stimulus) that 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 in order to understand the dynamic neural circuits that modulate inflammation.

Finally the clinical importance of effects such as those reported by Irwin and his colleagues will be extended by conducting studies in patients with specific diseases for which inflammation is a significant contributing factor. Of course, such studies will require that the form of cognitive behavior 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 as well as inflammatory mediators can be jointly measured to determine the extent to which modulation of inflammation is associated with reductions in disease-related symptoms.

The study of Irwin and colleagues¹ presages a new era for behavioral interventions. It may well be the case that some behavioral interventions may produce more specific biological changes than any pharmacological 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 well represent the future of how we can effect specific alterations in behaviorally-relevant neural circuits and systemic biological processes.

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