Insomnia and inflammation as drivers of depression

Depression in older adults is common, and treatment with antidepressants is not always effective. Key driving factors of depression are insomnia and inflammation, which affect each other as well as driving disease. Dr Michael Irwin and his team at the Norman Cousins Center for Psychoneuroimmunology at UCLA, in the US, have been researching the associations between depression, insomnia, and inflammation in order to develop new targets for therapies.

Depression is a very common disease in older adults and severely impacts quality of life in terms of morbidity and mortality. Some treatments exist, but currently, antidepressants are only effective for a third of older adults suffering from depression. To develop new therapies, further research needs to be done to identify the risk factors associated with depression. This might not only result in new treatment methods but even prevent the disease from presenting itself in the first place.

KEY RISK FACTORS FOR DEPRESSION

Two significant risk factors associated with the development of depression are insomnia and inflammation. Previous studies have delved into the link between inflammation and depression, showing that increased immune activation leads to a depressed mood and that specific inflammatory factors can be used as predictors for depression. The link between insomnia and depression, however, is less well characterised. Both factors can contribute to the disease separately and in combination, as they have been shown to be linked.

Sleep is usually a recovery time for the body, which allows for the production of inflammatory cytokines that help fight any virus or bacteria we may encounter during the daytime. The sleep cycle is effective when working properly but can lead to disarray for both sleep and immunity when disrupted. It is also incredibly well regulated, so minor differences in sleep can have significant impacts on the body. Stress can cause increases in inflammation as well as changes in the sleep cycle, both of which affect and exacerbate each other. Disruptions to sleep lead to changes in inflammation; these changes in inflammation can increase disruptions to sleep, producing a vicious cycle that is difficult to break.

This interplay between insomnia and inflammation contributes to biological and cognitive ageing and the development of depression. Since inflammation can lead to depression and sleep can cause inflammation, it's clear that insomnia needs to be studied more closely – especially since one-third of older adults suffer from this sleep disorder. Learning more about how insomnia and inflammation lead to depression would help with preventing and treating the disease.

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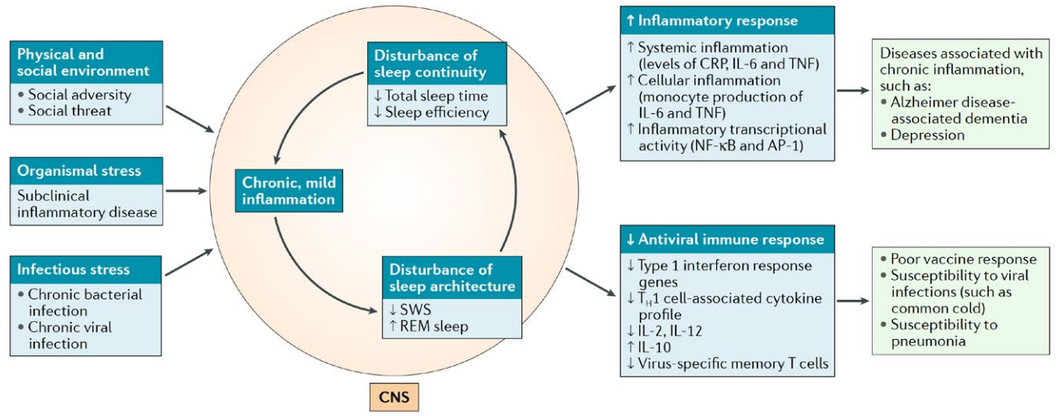

Putative pathways linking chronic stress or inflammatory exposure to sleep disturbance and adverse outcomes.

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REDUCED MOTIVATION

To better understand the relationship between sleep, inflammation, and depression, Dr Michael Irwin and his team, at the Norman Cousins Center for Psychoneuroimmunology at UCLA, have undertaken two research studies. The first investigates the effects of insomnia on motivation and sensitivity to monetary reward. Anhedonia, or a lack of pleasure, is a symptom of depression and can present itself in reward processing as a reduction in 'wanting' (motivation) or 'liking' (sensitivity) a reward. In this study, older adults were assessed for insomnia and depression before undergoing a behavioural reward task. This task involved different trials of varying levels of effort with associated monetary rewards.

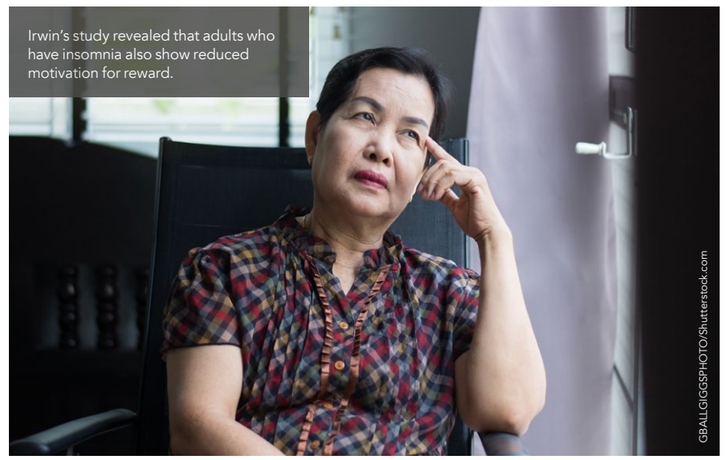
As predicted, results from the study revealed that adults who have insomnia showed reduced motivation as they were more likely to select a low-effort task with a lower reward. On the other hand, adults who didn't suffer from insomnia were more likely to choose a high-effort task with a higher reward. Insomnia was also revealed to be associated with reduced sensitivity to reward, as persons with insomnia were less responsive to increases in monetary reward.

The link to inflammation was also assessed in the study. This was done by measuring the levels of an inflammatory marker called CRP from blood samples provided by the participants. It was seen that CRP was elevated in patients with insomnia, once again highlighting the relationship between these two factors. Interestingly, the increase in CRP levels was particularly associated with a reduction in motivation in men, showing that some depression risk factors are sex-specific – this could point to more targeted treatments and preventions in the future.

Stress can cause increases in inflammation as well as changes in the sleep cycle, both of which affect and exacerbate each other.

EMOTION PROCESSING

The second study carried out by Irwin and his team focused on emotion perception and processing. Facial emotion perception is a complex neurological process that allows us to understand facial emotional expressions and their intensity. This is something that can be impaired in patients with depression; notably, they are less able to recognise sad facial expressions. In order to assess this, participants underwent a sleep study during which the time spent awake after initial sleep onset was measured. After the sleep study, the participants did an emotion recognition task and an emotion intensity task to



Irwin's study revealed that adults who have insomnia also show reduced motivation for reward.

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The combination of disturbed sleep and inflammation with advancing age increases the risk of depression.

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assess facial emotion perception. Blood samples were also taken, this time measuring levels of the inflammatory markers IL-6 and TNF-α.

In the emotion recognition task, subjects were shown a series of photos of a neutral face gradually progressing to a face expressing sadness, happiness, or anger. The participants had to identify the emotion being expressed. It was found that the participants who were awake longer in the night took longer to identify sadness than participants who had slept better. There was no change between the two groups in identifying happiness or anger. Higher levels of TNF-α but not IL-6 were also associated with this delay in recognising sadness.

In the emotion intensity task, subjects were shown photos of different emotional intensities, this time in random order. They then had to give a rating from 1 to 4 on the intensity of the expressed emotion. Again, it was found that participants who had disrupted sleep gave lower intensity ratings to sad faces compared to participants who had slept well. Higher levels of IL-6 but not TNF-α were associated with lower intensity ratings. The results of this study show that even small disturbances to sleep are associated with disturbance in how a person responds to facial emotions, which is a risk factor for depression. This lack of sleep is once again associated with increases in inflammatory markers, showing the connection between these two factors. These results are key for understanding the connection between insomnia, inflammation, and depression, and for developing future therapies.

Treating the inflammation or insomnia is to prevent and alleviate symptoms of depression.

TARGETING INSOMNIA AND INFLAMMATION TO PREVENT DEPRESSION

The results gained from these studies highlight the importance of insomnia in driving depression in older adults. The combination of disturbed sleep and inflammation with advancing age is clearly increasing the risk of depression. Understanding how insomnia and inflammation affect depression is important, not only to develop treatments but also as a way of preventing depression. Indeed, Irwin has recently found that the treatment of insomnia prevents incident and recurrent depression over 36 months in 291 older adults with insomnia disorder but without depression at entry. Specific markers of inflammation as well as sleep-cycle analysis could be used to monitor and predict disease in a targeted way. Perhaps treating the inflammation or insomnia would be a way to prevent and alleviate these symptoms of depression. Mind–body interventions that can reduce insomnia, such as meditation, are effective in reducing depression.

Equally, there has already been success using anti-inflammatory medications rather than antidepressants as treatment in some cases. Analysing the specific inflammatory cytokines at play would make this treatment even more effective. Understanding the roles of all these factors is yet another step towards reducing depression and increasing the quality of life of people who suffer from it.


In the emotion intensity task, the participants were shown photos of different emotional intensities.

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Behind the Research

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Research Objectives

Dr Irwin studies risk factors associated with depression.

Detail

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Bio
Dr Michael Irwin holds the Norman Cousins Distinguished Professorship in the Department of Psychiatry and Biobehavioral Science at the UCLA Geffen School of Medicine for his lifetime contributions to understanding the reciprocal interactions between the central nervous system, the immune system and health; and for pioneering mindfulness meditation and tai chi for reversing and treating insomnia, and preventing depression.

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- Chloe Boyle
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Personal Response

How can we use these results for targeted approaches to treating and preventing depression?

"We have recently demonstrated that the treatment of insomnia with cognitive behavioural therapy for insomnia (CBT-I) reduces the likelihood of incident and recurrent depression by over 50% as compared to a comparator control, sleep education therapy, in 291 older adults with insomnia disorder but no depression. Furthermore, when CBT-I leads to a sustained remission of insomnia, the likelihood of depression is reduced by over 83%. Given that inflammatory activation induces depressive symptoms and durable remission of insomnia reverses genomic, cellular, and systemic markers of inflammation, further secondary analysis is needed to examine whether mitigation of inflammation contributes to prevention of depression. Similarly, additional research will examine if insomnia remission leads to improvement in emotion regulation and reward processing, which may mediate the benefits of insomnia treatment in the prevention of depression. Together, a better understanding of the contributions of inflammation and mechanisms of reward and emotion processing will provide insight toward the development of more refined and precision-based strategies to prevent depression in those with insomnia, or to augment treatment outcomes in patients who are co-morbid for depression and insomnia disorder."