Loneliness and social isolation

How can we protect our mental health and cognitive functions?

It is well known that social isolation can cause poor mental and physical health. Our recent global experience of compulsory social isolation during the COVID-19 pandemic has created a need to find new ways to prevent its devastating consequences, such as anxiety-induced cognitive decline, from manifesting. Dr Jing Liang and her team at the University of Southern California's Mann School of Pharmacy, USA, have extensive experience in studying and analysing the different biological and behavioural effects of social isolation on mice. They recently identified a promising therapeutic with the power to reverse these changes.

Loneliness and social isolation are known to cause mental health issues such as anxiety, insomnia, and suicidal tendencies. In the long run, these can lead to cognitive decline, an early sign of dementia, and Alzheimer's disease. This was evident during and after the COVID-19 pandemic which immensely affected the mental health of millions of people worldwide. We saw an increased number of cases of anxiety/depression and acute stress disorder in people that had to be socially isolated for several weeks.

Although previous studies have shown that anxiety can lead to cognitive decline, the mechanisms behind this connection have not yet been fully understood. Dr Jing Liang and her team at the University of Southern California's Mann School of Pharmacy, USA, have been working on improving our understanding of the impact social isolation has on the brain. Through their research, the team hopes to find new ways to prevent its catastrophic effects from happening.

HOW SOCIAL ISOLATION CHANGES THE BRAIN

Social isolation has been shown to cause changes to specific areas in the brain such as the hippocampus, a complex brain structure that is not only responsible for emotional control, including fear, anxiety, and depression, but also regulates long-term memory formation. The dysfunction of the hippocampus is believed to be associated with conditions such as anxiety, cognitive decline, and memory loss.

Another finding in the brain of cognitively impaired people is the loss of previously made connections between nerve cells (neurons). Neurons connect to each other and transfer signals through the tips of dendrites, called synapses. The dendrites can be thought of as the 'arms' of neurons, with synapses being the 'hands'. Healthy and well-functioning synapses are necessary for normal brain function, and their absence leads to cognitive decline and memory loss. Liang and her team have previously studied an Alzheimer's disease animal model. They showed that there is reduced activity of a specific type of synapses in the brain, called GABAergic (gamma-aminobutyric acid) synapses, which are responsible for regulating cognitive functions and emotions such as anxiety through special receptors (GABAARs).

Liang's team studied the impact of social isolation on mice brains.

Mice treated with DHM demonstrated improved object recognition abilities compared to their non-treated peers and fewer negative changes in their astrocytes.

But it's not only the neurons in the brain that get affected. Astrocytes are the star-shaped structural cells of the immune system in the brain. Their role is to support the neuro-synapses, form tri-synapses with the neuro-synapses, and keep them in an optimal functional state. Astrocytes also provide nutrients to neurons, protect neuro-synapses, and create an environment for optimal functioning of neuro-synapses. Therefore, any damage to the astrocytes can directly affect the function of the neuro-synapses. It has been shown before that in cognitively impaired brains such as those of patients with Alzheimer's disease, the astrocytes are fewer in number, smaller, and dysfunctional. The fact that similar changes were identified in the astrocytes of animals that had been socially isolated for the purpose of experimentation (social isolation model) suggests that cognitive decline associated with social isolation is caused by the damaged connections between astrocytes and the neurons (triple synapse theory).

THE IMPACT OF SOCIAL ISOLATION

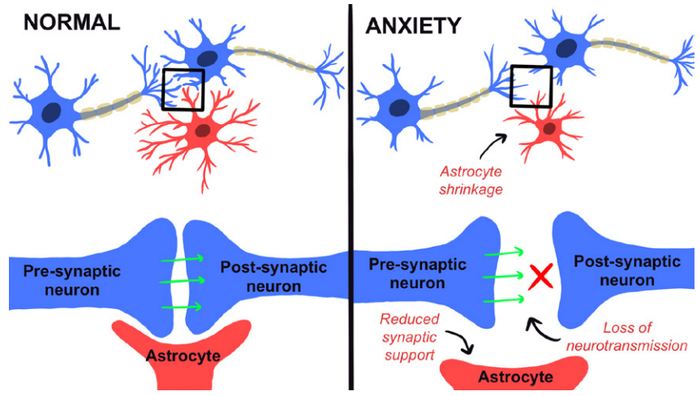
Liang's team decided to create a social isolation animal model and study its impact on mice brains. They found that socially isolated mice exhibited more anxious/aggressive behaviours compared to the ones that were housed in groups and had daily social interactions. Just like in previous experiments, they decided to examine the effects of a substance called dihydromyricetin (DHM) in mice. DHM is a natural compound extracted from the Japanese raisin tree with cell protective properties. Among others, DHM was previously shown to have great potential in improving alcohol-related behaviours and mental disorders. In addition, Liang and her team have previously demonstrated its role in improving social isolation-related cognitive impairment and memory loss in the same model of mice.

To better understand how social isolation affects the mammal brain, Liang and her team aimed to use their animal model to further investigate the mechanisms that lead to cognitive decline through stress and anxiety. They also identified the structural changes in the brain and examined whether these can be reversed using DHM.

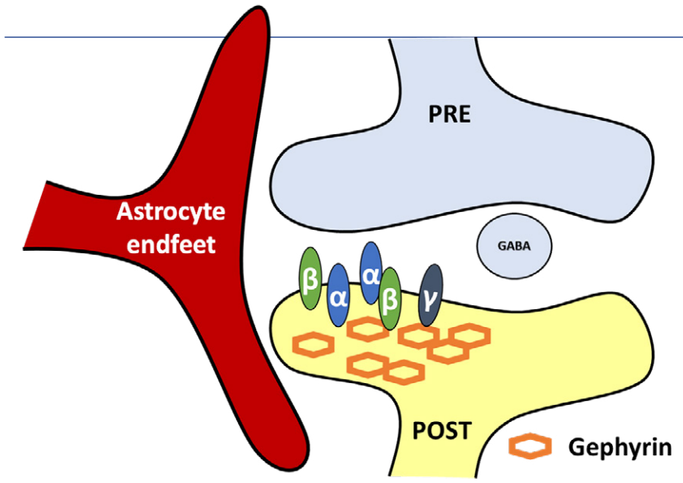
LOOKING INTO MICE BEHAVIOURS

For their experiment, Liang's team used 6-week-old (adult) mice that were exposed to a 12-hour light/dark cycle and had free access to bed, food, and water. The researchers then created different groups of mice, with some of them being housed in cages together in groups of two or three. The remaining mice – the social isolation group – were placed in an opaque cage, each mouse on their own to help completely isolate them from the others. All mice were housed under the above conditions for four weeks in total. Over the last two weeks of the experiment, the mice were either given a treatment with DHM or were given a dummy drug (vehicle) containing just agar to create a control group to which the treated group would be compared against. This created four groups of mice: the DHM social isolation group, the vehicle social isolation group, the DHM group housing group, and the vehicle group housing group.

Next, all mice underwent behavioural tests to evaluate their cognitive abilities. These included object recognition testing, where the mice were tested on whether they could tell the difference



In cognitively impaired brains, such as those of patients experiencing stress or anxiety, the astrocytes are fewer in number, smaller, and dysfunctional.



Triple synapse theory: cognitive decline associated with social isolation is caused by damaged connections between astrocytes and the neurons.

between familiar and new objects, and context recognition tests, where the animals were tested on their ability to remember the setting a specific object was initially found in and identify any changes that were implemented by the researchers. The latter is associated with relevant regulation centres on the hippocampus and is an indirect method to evaluate the structure's functionality and health.

Brain tissues from all four groups were extracted and treated with immunohistochemistry stains, a technique that enabled the researchers to identify specific proteins in the brain tissues. The proteins that they looked for were markers related to astrocyte function and health. Next, the team studied the stained tissues under the microscope and all results were analysed using statistical methods, with the results for each of the four teams compared to one another.

COULD DHM PREVENT BRAIN DAMAGE?

The researchers were surprised to find that even this short period of isolation caused significant changes in the mice's brain, resulting in memory deficits and impaired cognitive function. They also discovered that the isolated mice that hadn't received DHM treatment had atrophied astrocytes with smaller branches compared to the group housing mice, suggesting their functionality was impaired.

The results of this study showed that even two weeks of social isolation led to changes in the brain.

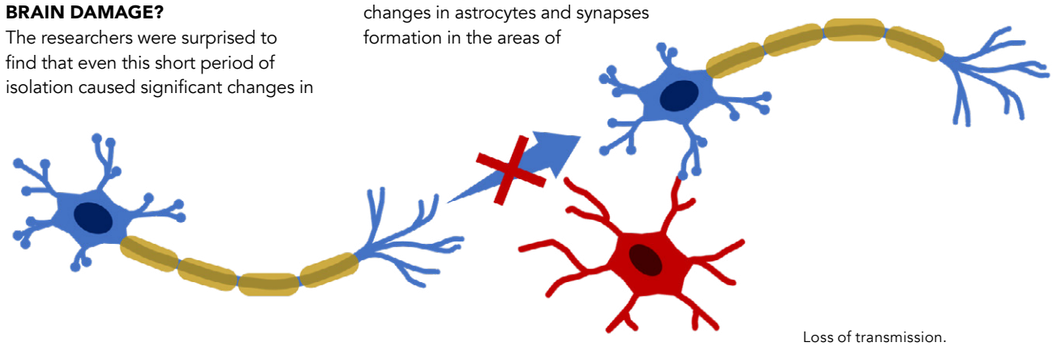
These findings were less evident in isolated mice treated with DHM, which demonstrated improved object recognition abilities compared to their non-treated peers and fewer negative changes in the structure and functionality of their astrocytes as well.

Liang's team confirmed with this latest study that social isolation made cognitive and memory abilities worse in mice. They also observed the relevant changes in astrocytes and synapses formation in the areas of the brain responsible for emotional regulation and long-term memory.

Dihydromyricetin, a herbal substance that had previously shown promising results in improving cognition and memory loss in mice, was able to reverse these effects. It improved memory, cognitive function, and induced regeneration of the damaged astrocytes.

The findings of Liang and her team are crucial, not only because they clearly demonstrate the impact of short-term social isolation on the brain, but because they also showcase a new potential preventative treatment for its consequences on mental health and brain function. These impressive results make the researchers hopeful that DHM could potentially be used in the future to prevent social isolation-related cognitive decline and permanent brain damage. DHM could also function as a component of new therapeutic strategies against dementia and Alzheimer's disease.

The results of this study showed that even two weeks of social isolation led to changes in the brain, which worsened after four weeks. Fortunately, these changes could be reversed with DHM treatment. This is why the team is already planning future studies with an aim to identify the maximum length of social isolation period that allows for timely intervention with DHM, before any permanent brain damage occurs.



Loss of transmission.

Behind the Research

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Research Objectives

Dr Jing Liang and her team studied the effects of dihydromyricetin on mice brains.

Detail

Bio

Dr Jing Liang, a professor at the USC Mann School of Pharmacy, focuses her research on the impacts of social isolation on the brain. Her team found that short-term social isolation in mice induces astrocyte shrinkage and triple-synapse, a basis of cognitive/memory formation, disintegration in hippocampus, while dihydromyricetin reverses these pathophysiological changes.

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Collaborators

- Saki Watanabe, PhD student
- Chen Xue, Master student
- Richard W Olsen, Distinguished Professor at the David Geffen School of Medicine at UCLA

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Personal Response

What are your plans for further testing DHM on animal models and how far away are we from studying the medication's effects on humans?

"During the COVID-19 pandemic, we conducted studies that aimed to investigate the impacts of social distance on human health, including stress and depressive symptoms, sleep, and mental health problems. The participants who voluntarily took DHM experienced fewer symptoms compared to the placebo group (Shao 2022; Watanabe 2023). We hope that, through our work, more people who experience anxiety and/or depression due to social isolation – or for any other reason – will benefit from the findings of our research."