

# Neuroscience in service to society

Research has linked obesity with cognitive impairments at later stages of life, but the specific biological underpinnings of this association are yet to be ascertained. **Dr Andreeana Haley**, from the University of Texas at Austin, has been studying the biological mechanisms behind cognitive impairments typically associated with aging and dementia. Over the past decade, she has tried to identify neuroimaging markers of brain vulnerabilities, while assessing interventions that could improve cognitive functions at later stages of life.

memory, attention and planning. Studying biological mechanisms that might affect cognition in middle-aged individuals with obesity can be really challenging, as effects tend to be subtle, with more prominent cognitive impairments appearing later in life.

“When we talk about an effect that is very subtle in mid-life, we are sort of out of luck with the statistical procedures,” explains Dr Haley in an episode of the Psychosomatic Medicine Podcast. “So, we turned to recent recommendations by scientists and statisticians who are proponents of examining the direct and indirect effects of different variables separately. These methods allow us to look for mechanisms without requiring that obesity is related to cognitive dysfunction at the point when we are looking for the mechanisms.”

Dr Haley and her colleagues looked at certain neuro-chemical changes that have been observed in early stages of cognitive disorders, including Alzheimer’s Disease, Traumatic Brain Injury, and Multiple Sclerosis (MS). Using magnetic resonance spectroscopy, a type of imaging that uses the same scanner as functional MRI, they

**O**besity is known to be a risk factor for numerous medical conditions, including hypertension, cardiovascular disease, diabetes, and certain forms of cancer. Over the past decade however, a growing number of studies have also highlighted the detrimental effects of obesity on brain structure and function, which can ultimately result in poorer cognitive performance. Researchers are investigating the possible biological mechanisms that link obesity to serious cognitive problems at later stages of life, trying to identify effective ways to reduce the risk of brain deterioration in the elderly.

the next 50 years. As there is no existing cure for dementia and other conditions associated with a decline in brain function, preventing or delaying their onset remains of crucial importance. Researchers have hence been investigating the biological underpinnings of cognitive impairments in older age, trying to better understand the factors that might link them to obesity in earlier years.

## EXPLORING THE LINKS BETWEEN OBESITY AND THE BRAIN

Studies have linked high BMI to deterioration and changes within several different brain areas, particularly those associated with

## HEALTH BEHAVIOURS AND COGNITIVE FUNCTION

Over the past twenty years, the number of individuals classified as either overweight or obese has increased substantially, currently representing almost two-thirds of the adult population of both the US and the UK. In recent years, research linked mid-life obesity with higher incidence of dementia and cognitive issues in old age; middle-aged obese individuals being five times more likely to be diagnosed with vascular dementia and three times more likely to develop Alzheimer’s disease later in life.

Higher Body Mass Index (BMI) in middle age was found to increase the risk of developing dementia 18 to 27 years later, independent of other risk factors such as higher blood pressure, total cholesterol levels, and smoking. The number of elderly people who require assistance due to severe cognitive impairment is expected to quadruple over



Dr Andreeana Haley and her graduate students (left to right: Evan Pasha, Carolyn Cassill, Stephanie Oleson, Andreeana Haley, Alex Birdsill).

The aim is to identify effective ways to reduce the risk of brain deterioration in the elderly

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extracted information about the neuro-chemical composition of tissue samples taken from a group of 40-to 60-year-old adults with varying BMIs. Although the cognitive effects of higher BMI at mid-life were indeed very subtle, when the statistical model included the indirect effects of obesity on cognitive function, through the neuro-chemical markers they were measuring, the relationship was significant. "The relationship that we detected gives us a reasonable hypothesis that obesity might be impacting cognitive functions through early changes in neuro-chemical composition, possibly related to neuro-inflammation," explains Dr Harley.

#### TRANSCRANIAL LASER THERAPY AND OTHER EARLY INTERVENTIONS

In addition to exploring the biological mechanisms that could link mid-life obesity with cognitive impairments in old age, Dr Haley has also been assessing the benefits of early interventions in reducing these effects. Her studies suggest that transcranial infrared laser stimulation (TILS), also known as transcranial low-level light/laser therapy (LLLT), pictured right, might be a safe and effective method of improving neuro-cognitive functions in older people, with the potential of combating ageing-related and vascular disease-related cognitive decline.

Transcranial laser stimulation is a non-invasive form of brain stimulation that can increase brain energy production. It is currently being tested on individuals with a broad range of medical and psychiatric conditions and has so far achieved many promising results. This method involves the absorption of photons, particles that represent a quantum of light or other electromagnetic radiation, prompting the modulation of metabolic processes in cells.

Sedentary lifestyles and a diet rich in saturated and trans-fat in middle-age have been found to result in increases in visceral adiposity and vascular stiffness, consequently causing early brain vulnerability to cognitive impairments. Changes in diet and lifestyle could hence also improve chances of healthy cognitive ageing. Studies found that regular exercise alone can decrease the odds of acquiring dementia by as much as 55%.

#### PREVENTING COGNITIVE IMPAIRMENT

Dr Haley's research focuses on detecting early brain vulnerability and implementing early interventions that could ensure



Transcranial infrared laser stimulation.

## Changes in neuro-chemical composition is one possible biological mechanism linking mid-life obesity to cognitive impairments

successful cognitive ageing, by reducing risk factors associated with cognitive impairment. Her findings identified changes in neuro-chemical composition as one possible biological mechanism linking mid-life obesity to cognitive impairments. Yet the biological underpinnings of the association between obesity and brain function appear to be far more complex. "I believe that this process is going on at multiple levels," she explains. "I think that obesity is contributing to many different changes in the brain and they are not all of the same aetiology."

Dr Haley is currently collecting data to test if non-invasive transcranial laser stimulation therapies could help to enhance cognitive functioning in middle-aged individuals, reducing the risks of cognitive impairment in old age. Further studies and clinical trials are needed to ascertain their efficacy and benefits. According to Dr Haley, future research should try and identify ideal combinations of both surgical and non-surgical approaches, which could ultimately help to sustain positive health outcomes over time and preserve brain integrity throughout the lifespan. "I would

## Q&A

#### When and how did you first start investigating late-life cognitive impairments?

My first job after college was a Research Assistant for a study examining the effects of blood glucose and insulin levels on cognitive function in Alzheimer's disease. The principal investigator was Dr Suzanne Craft. I loved the work, but really wanted to dive into the brain mechanisms that link metabolic dysfunction to cognitive impairment, so I went on to graduate school, where I started learning neuroimaging. I am grateful to Drs Jack Knight-Scott and Lawrence Sweet for patiently teaching me what magnetic resonance imaging can do, and Drs Carol Manning and Ron Cohen, for encouraging the obsession. Women were not very common in brain imaging in the late '90s, and their support and mentorship were crucial.

#### After carrying out substantial research on the topic, what do you believe to be some of the primary biological mechanisms that link mid-life obesity to cognitive impairments later in life?

I think we have evidence of several potential mechanisms. Cellular damage due to inflammation, decreased neurogenesis due to oxidative stress, and brain hypoperfusion due to vascular dysfunction are prominent among them. However, peripheral markers of inflammation, neurogenesis, and vascular function do not seem to account for all the variance in cognitive function associated with obesity. The search continues... In all likelihood, different mechanisms are at play for different people, depending on individual combinations of genetic and environmental risk factors.

#### What do you feel have been your most interesting findings so far and why?

I love our findings pertaining to

mechanisms, such as insulin sensitivity and dyslipidemia driving the links between various markers of brain function and obesity, because they establish potential intervention points and help guide what those interventions might look like. I also find our work on gene/diet interactions pretty fascinating, because it may lead to better individualised medicine. In the end, however, I also love the unknowns, the variance unaccounted for, because that is how the new directions are charted.

#### Could dementia and other late-life cognitive impairments be prevented and if yes, what might be the most effective way to do that?

If I were not hopeful that we can at least delay cognitive impairment, I would not be working in this area. While complete prevention for everyone seems hard to imagine without genetic engineering, I firmly believe that any expansion of health span within the life span is a worthy goal. At this point, without genetic engineering, we have only the environmental risk factors to work with, so the most effective ways to delay cognitive impairment at present have to do with proper diet, maintaining cardiovascular fitness, and building brain reserve through new learning.

#### What are your plans for further research and investigation?

My most immediate plans are to pursue the brain mechanisms of transcranial laser stimulation in human participants using neuroimaging. Next, I'd like to look further into the mechanisms connecting mid-life obesity to late-life cognitive impairment, and pursue explanations for some of the variance not accounted for by inflammation and vascular dysfunction.

love to see a longitudinal study that could show us whether these changes that we're characterising at mid-life are going to track people on different cognitive trajectories," she says. "Can we identify who is going to

go down the successful ageing path and who is likely to go down the dementia road, and can we then intervene early on, switching them from one trajectory to the other? That is where I would love to go next."

## Detail

#### RESEARCH OBJECTIVES

Dr Haley is an Associate Professor of Psychology at the University of Texas at Austin. Her research examines the biological underpinnings of cognitive impairment associated with ageing and dementia. Dr Haley's goal is to bridge knowledge from basic and clinical neuroscience with the aim of improving how we understand, predict, and treat age-and disease-related cognitive impairment.

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#### COLLABORATORS

- Dr Francisco Gonzalez-Lima and Dr Hirofumi Tanaka, co-investigators
- Dr Jack Knight-Scott, Dr David Tucker and Dr Martha Pyron, consultants

#### BIO

After completing a pre-doctoral internship in Neuropsychology and Rehabilitation Medicine at Eastern Virginia Medical School, Dr Haley received her PhD in Clinical Psychology from the University of Virginia in 2005. She spent two years as a Dementia Research Fellow at Brown University, and a visiting Research Fellow at the Center for Neurological Imaging at the Brigham and Women's Hospital in Boston. She is currently Associate Professor of Clinical Psychology at UT Austin.

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