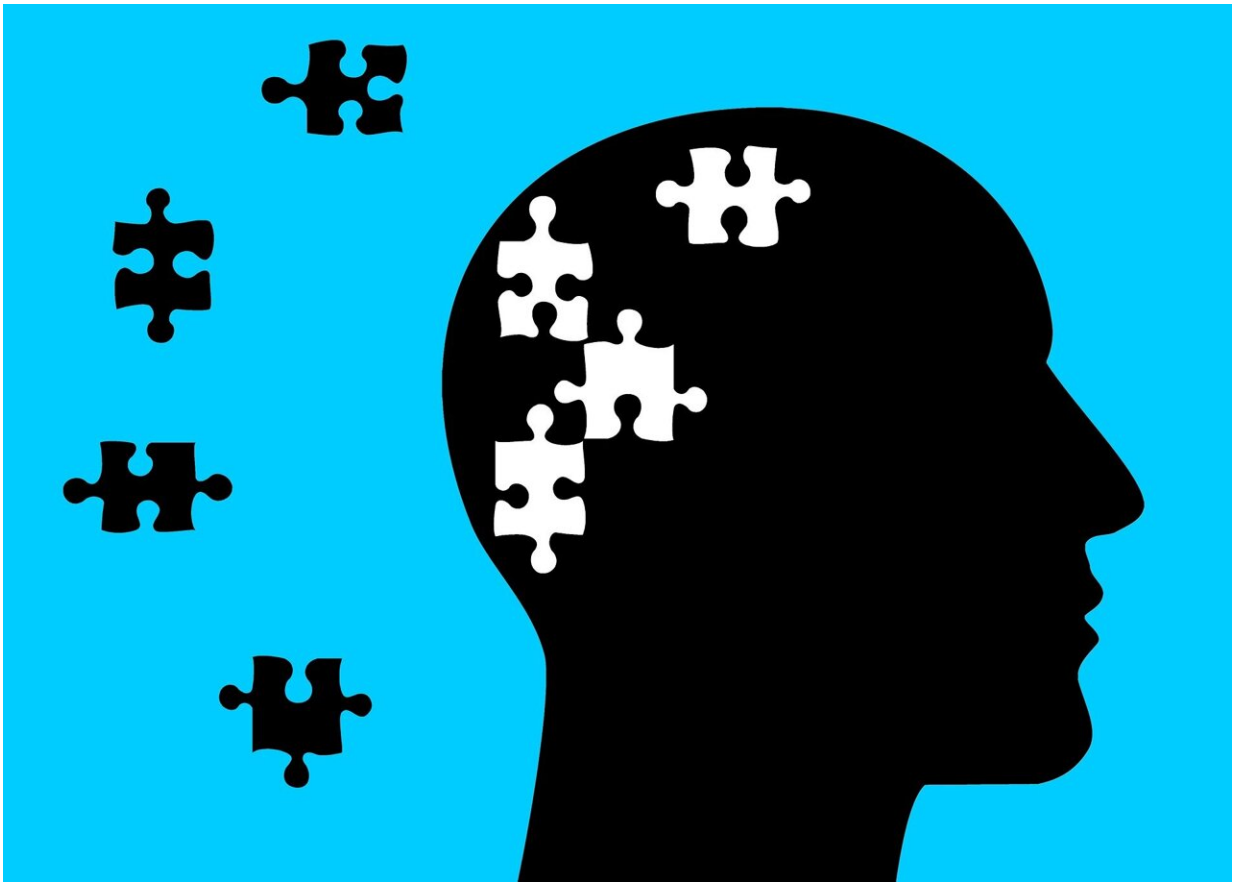
Moving beyond memory metrics for early identification of Alzheimer's risk

April 25 2022



Credit: Pixabay/CC0 Public Domain

Say the words "Alzheimer's disease," and the next word that most readily comes to mind is likely "memory." Indeed, one of the most devastating

effects of Alzheimer's disease is the toll that it takes on a person's memory. Long before declines in memory capabilities, however, brain changes happen as early as midlife, in some cases decades earlier than a diagnosis of dementia due to Alzheimer's. The work of cognitive neuroscientists to identify these midlife changes points the way to new diagnostics and interventions, as presented today at the annual meeting of the Cognitive Neuroscience Society (CNS) in San Francisco.

"The pathological process in Alzheimer's begins decades before the onset of dementia," says William Kremen of the University of California, San Diego. "The earlier we can identify people at risk, the better chance we will have of intervening to slow the disease process."

Kremen's work showing how a decline in executive function in midlife is predictive of Alzheimer's disease later in life is just one finding that is being presented at the CNS meeting today in a symposium on cognitive and brain aging. Anja Soldan and Corinne Pettigrew, both of Johns Hopkins University, organized the symposium to showcase research to better understand how to differentiate "normal" cognitive aging from disease-related cognitive aging.

"We now know that many age-related disorders, including Alzheimer's disease and cerebrovascular disease, have a so-called preclinical phase that precedes the emergence of clinical symptoms by many years," Soldan says. "This makes it really difficult to say whether age-related cognitive changes reflect 'normal' age-related changes, or early disease-related changes. Understanding cognitive aging really requires a lifecourse approach, but that's very difficult to accomplish."

New digital health technologies and biomarker work, coupled with large-scale longitudinal studies, however, are shedding more light on the brain changes associated with Alzheimer's and other neurodegenerative diseases earlier in life.

An eye toward executive function

Kremen first became interested in understanding the aging brain when conducting studies of cognition in twins. "One afternoon, a couple of colleagues and I were brainstorming about next steps in our research," he recalls. "We realized that if we studied this twin sample systematically over time, we could have a really interesting and valuable study of cognitive and brain aging. I am now very interested in the tremendous growth of genetics research so that we can better understand what genetic and environmental factors influence normal and pathological cognitive and brain aging."

In his latest work with Rongxiang Tang and Daniel Gustavson, Kremen sought to link cognition, brain, and genetics. Looking at genetic data from 1168 individuals and MRI data from 267 individuals ranging in age from 51 to 73 across 12 years, they found that executive function is a important area of study in understanding age-related brain change in those with Alzheimer's

"In Alzheimer's disease, the focus is predominantly on memory, but we wanted to highlight the fact that executive function is also important," he explains. "Executive function is important for many aspects of daily living since it involves planning and anticipation, organization, being able to shift appropriately from one task or topic to another, and inhibiting irrelevant thoughts or stimuli so that a person can focus on the task at hand."

In as-yet unpublished work, Tang and colleagues identified a "modal controllability network" that underlies both executive function in midlife as well as changes in executive function later in life. "Modal controllability refers to the ability of brain regions to facilitate distant and effortful transitions to difficult-to-reach states, which is kind of what executive function is about," Kremen explains. "Changes in

network controllability may be a key mechanism underlying aging-related decline in executive function."

They also found that poorer executive function was associated with higher genetic risk scores of Alzheimer's disease, which built on prior work showing that poorer executive function was associated with increased risk of progression to mild cognitive impairment (MCI), which can be a precursor to Alzheimer's. According to Kremen, this and prior work suggest that "executive function in midlife is predictive of progression" to Alzheimer's disease.

Kremen and his team want to continue to study the brain and genetic factors associated with Alzheimer's disease with the same cohort of participants as they continue to age. The goal, he says, is early identification, and he believes the combination of genetics and cognition research shows a promising path forward.

Identifying biomarkers for early detection

Corinne Pettigrew became interested in the aging brain when working with stroke patients in graduate school. She now works to understand cognitive changes and biomarkers in older adults who are at risk for Alzheimer's disease and other cognitive disorders.

At the CNS meeting, Pettigrew will be presenting results from the BIOCARD Study, a longitudinal study that began in 1995, enrolling some 350 primarily middle-aged adults. "Because the study is still ongoing, many of these generous volunteers have now been followed for more than 20 years," Pettigrew says. "Thanks to their dedication, we are in a relatively unique position to examine how midlife risk and protective factors and brain changes impact later life cognitive outcomes, including cognitive impairment and dementia."

One of the core findings from Pettigrew's research so far is that some of the brain changes underlying Alzheimer's disease begin in midlife. "Midlife may therefore be a very important time to intervene, for delaying or preventing the future cognitive decline or symptoms of dementia," she says.

In a 2020 study published in *Neurology*, for example, Pettigrew, Soldan, and colleagues reported on the how vascular risk scores (looking at factors such as hypertension, cholesterol levels, diabetes, and smoking, for example) and amyloid-β and tau protein biomarkers (associated with Alzheimer's disease) from midlife correlated with cognitive change. They found that the vascular risks and Alzheimer's biomarkers were each independently associated with cognitive decline over approximately 14 years.

"Our biomarker findings suggest that Azheimer's disease-related brain changes are evident in midlife or earlier, particularly among individuals at greatest risk of progressing to mild cognitive impairment or dementia," Pettigrew says. Although effective treatments do not yet exist for dementia, it is becoming increasingly clear, Pettigrew says, that protecting brain and vascular health throughout and lifespan, including by staying cognitively and physically active, are critical for reducing the risk of cognitive decline, even among those at increased genetic risk for dementia.

Soldan says, "I think this symposium very nicely illustrates the fact that cognitive aging trajectories are influenced by a large number of factors and that there might be things we can do—such as physical activity and managing vascular risks, like blood pressure and cholesterol—to stay on a more positive trajectory."

Soldan sees an exciting future for the integration of digital technology into the study of brain and cognitive aging. "This includes various smart

devices that people can wear at home while they go about their normal life that allows researchers to learn about their sleep-wake cycles, physical activity levels, heart rate, blood pressure, etc., which are related to brain and cognitive health," she says. "This may allow us to reach a wider and more diverse population."

She is also excited by the progress being made in developing blood-based biomarkers for Alzheimer's disease and other conditions. "In the not so far future, this might allow us to detect early Alzheimer's disease during routine clinical care, which could help with developing more effective interventions for cognitive decline."

Provided by Cognitive Neuroscience Society