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The Alzheimer's Disease Down Syndrome Connection

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Down syndrome is a condition in which a person is born with extra genetic material from chromosome 21, one of the 23 human chromosomes. Most people with Down syndrome have a full extra copy of chromosome 21, so they have three copies instead of the usual two. In ways that we don't yet fully understand, the extra copies of genes present in Down syndrome cause developmental problems and specific health issues.

As with all adults, advancing age also increases the chances a person with Down syndrome will develop Alzheimer's disease. Autopsy studies show that by age 40, the brains of almost all individuals with Down syndrome have significant levels of Beta-amyloid plaques and Tau neurofibrillary tangles, which are considered hallmarks of Alzheimer's disease. But despite the presence of these brain changes, not everyone with the syndrome develops Alzheimer's dementia.

One of the genes that resides on the 21st chromosome, and is therefore present as an extra copy, is the amyloid precursor protein (APP) gene. This extra copy of APP leads to excess production of beta-amyloid and is thought to be the reason people with Down syndrome get Alzheimer's disease. The APP gene is also linked to Alzheimer's through small variations or mutations in the gene's chemical code that cause rare, inherited forms of early-onset Alzheimer's disease. In this case, there is overproduction of beta-amyloid. Last summer, it was discovered that other variations in the APP gene can lead to a decreased chance of developing Alzheimer's disease. Those variations actually cause less beta-amyloid to be produced than in normal aged brains. Moreover, the apolipoprotein E (ε4) genotype is associated with a higher risk of AD and an earlier onset of dementia in people with Down syndrome, in the same way as in the general population. Together, this makes a compelling case that learning about AD in DS will not only benefit older adults with DS, but also the general population as well.

This also raises the question of whether individuals with Down syndrome could benefit from the ongoing efforts to develop pharmacological treatment interventions for sporadic AD. Making this a reality will require the establishment of a large-scale, prospective, 5-year longitudinal natural history study in ~1,000 adults with Down syndrome using a standardized approach for assessment, similar to the Alzheimer's Disease Neuroimaging Initiative (ADNI).

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Sex differences in grey matter atrophy patterns among AD and aMCI patients

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This newsletter is prepared monthly by the Alzheimer's Disease Cooperative Study at the University of California, San Diego. Content is intended to educate the public about AD research endeavors and other AD issues.

Questions or comments?

Please email: brainlink@ucsd.edu

The Alzheimer's Disease Down Syndrome Connection continued...

The ADCS, in collaboration with Janssen Pharmaceuticals, has launched a 3-year pilot of such a study, called the 'Down Syndrome Biomarker Initiative' (DSBI). The cornerstones of this study involve specialized cognitive testing, retinal amyloid imaging, brain PET amyloid imaging and volumetric magnetic resonance imaging (MRI), as well as promising blood biomarkers. Over the next year, the ADCS, in collaboration with industry and philanthropic partners, will be planning the infrastructure to conduct the much larger DSBI study.

Number of People with Alzheimer's Disease May Triple by 2050

Findings by Researchers from the Rush Institute for Health Aging Published in Neurology

(CHICAGO) – The number of people with Alzheimer's disease is expected to triple in the next 40 years, according to a new study by researchers from Rush University Medical Center published in the February 6, 2013, online issue of *Neurology*, the medical journal of the American Academy of Neurology.

"This increase is due to an aging baby boom generation. It will place a huge burden on society, disabling more people who develop the disease, challenging their caregivers, and straining medical and social safety nets," said co-author, Jennifer Weuve, MPH, ScD, assistant professor of medicine, Rush Institute for Healthy Aging at Rush University Medical Center in Chicago. "Our study draws attention to an urgent need for more research, treatments and preventive strategies to reduce the impact of this epidemic."

For the study, researchers analyzed information from 10,802 African-American and Caucasian people living in Chicago, ages 65 and older between 1993 and 2011. Participants were interviewed and assessed for dementia every three years. Age, race and level of education were factored into the research.

The data was combined with U.S. death rates, education and current and future population estimates from the U.S. Census Bureau.

The study found that the total number of people with Alzheimer's dementia in 2050 is projected to be 13.8 million, up from 4.7 million in 2010. About 7 million of those with the disease would be age 85 or older in 2050.

"Our projections use sophisticated methods and the most up-to-date data, but they echo projections made years and decades ago. All of these projections anticipate a future with a dramatic increase in the number of people with Alzheimer's and should compel us to prepare for it," said Weuve.

Liesi Hebert, ScD, assistant professor at Rush University Medical Center, is lead author of the study.

The study was supported by the Alzheimer's Association and the National Institute on Aging of the National Institutes of Health.

Damaged Blood Vessels Loaded With Amyloid Worsen Cognitive Impairment In Alzheimer's Disease

February 4, 2013— A team of researchers at Weill Cornell Medical College has discovered that amyloid peptides are harmful to the blood vessels that supply the brain with blood in Alzheimer's disease — thus accelerating cognitive decline by limiting oxygen-rich blood and nutrients. In their animal studies, the investigators reveal how amyloid-ß accumulates in blood vessels and how such accumulation and damage might be ultimately prevented.

Their study, published in the Feb. 4 online edition of the Proceedings of the National Academy of Sciences (PNAS), is the first to identify the role that the innate immunity receptor CD36 plays in damaging cerebral blood vessels and promoting the accumulation of amyloid deposits in these vessels, a condition known as cerebral amyloid angiopathy (CAA).

Importantly, the study provides the rational bases for targeting CD36 to slow or reverse some of the cognitive deficits in Alzheimer's disease by preventing CAA.

"Our findings strongly suggest that amyloid, in addition to damaging neurons, also threatens the cerebral blood supply and increases the brain's susceptibility to damage through oxygen deprivation," says the study's senior investigator, Dr. Costantino Iadecola, the Anne Parrish Titzell Professor of Neurology at Weill Cornell Medical College and director of the Brain and Mind Research Institute at Weill Cornell Medical College and NewYork-Presbyterian Hospital. "If we can stop accumulation of amyloid in these blood vessels, we might be able to significantly improve cognitive function in Alzheimer's disease patients. Furthermore, we might be able to improve the effectiveness of amyloid immunotherapy, which is in clinical trials but has been hampered by the accumulation of amyloid in cerebral blood vessels."

Mounting scientific evidence shows that changes in the structure and function of cerebral blood vessels contribute to brain dysfunction underlying Alzheimer's disease, but no one has truly understood how this happens until now.

In the study, the research team — which also includes investigators from the Mayo Clinic in Florida, the McLaughlin Research Institute in Montana and The Rockefeller University — used mice that were genetically modified to develop amyloid in their brain and blood vessels, but in which the CD36 receptor was eliminated. They demonstrated that mice lacking CD36 have less buildup of amyloid in cerebral arteries (CAA) even if they have massive amyloid buildup in their brain tissue (amyloid plaques).

"Remarkably, mice lacking CD36, in which only CAA is reduced, perform significantly better in cognitive tests than do mice with intact CD36," says the study's first author, Dr. Laibaik Park, an assistant professor of neuroscience in the Brain and Mind Research Institute.

"In essence, reduced amyloid burden in cerebral blood vessels, or CAA, was able to preserve cognitive function despite the buildup of amyloid plaques in the brain tissue," says Dr. Iadecola, who is also a neurologist at NewYork-Presbyterian Hospital/Weill Cornell Medical Center. "These findings indicate that clearing the amyloid from cerebral blood vessels might be of tremendous benefit to patients with Alzheimer's disease. These conclusions are based on mice studies, and mice are not humans, of course, but we have a very exciting new direction to explore in our search for Alzheimer's disease therapies."

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Damaged Blood Vessels continued...

Scavenger Molecule Response Damages Blood Vessels

CAA is already known to be a major cause of brain dysfunction and hemorrhage from weak, damaged brain arteries in some elderly patients, but no one has identified how it occurs. It is also not clear how many older adults suffer from CAA because there is no way to make a clear diagnosis of the condition, unless sophisticated brain imaging studies are performed. But it is believed that this condition is widespread and that CAA, either in association with Alzheimer's disease or independent of it, is a major cause of cognitive decline in the elderly.

The human brain normally produces the amyloid-β peptide as part of neuronal function, but these peptides are routinely cleared from the brain, in large part, through the blood vessels. However, in most Alzheimer's patients, the brain's ability to clear amyloid-β is impaired and, consequently, one type of amyloid-β (Aβ42) accumulates in amyloid plaques and another type (Aβ40) collects in brain arteries, resulting in CAA.

The research team found that CD36, a protein located on the surface of immune cells and in blood vessels, is key to the buildup of Aβ40 in blood vessels. The protein is part of the innate immune system; its function is to act as a sensor to detect molecules that represent a danger to the host. Some of these molecules are derived from invading organisms, such as infectious agents, but some are produced by the body, such as amyloid peptides that, in excess amounts, could become toxic.

"CD36 is a scavenger protein that binds threatening molecules and activates a host of cellular responses designed to get rid of the threat," Dr. Iadecola says. "Such responses include ramping up inflammation and producing free radicals, both aimed at neutralizing the offenders. However, in the case of amyloid-β, inflammation and free radicals damage brain blood vessels and prevent the efficient clearance of the peptide through these vessels. This, in turn, sets up a vicious circle that favors the vascular accumulation of the amyloid-β peptide and promotes CAA."

Dr. Iadecola and his colleagues say it may be possible to design new drugs that bind to CD36 on the precise site on the protein's structure that amyloid-β sticks to, thus blocking the deleterious effects of receptor activation. "We now know how it occurs, and so now we have a new target," he says.

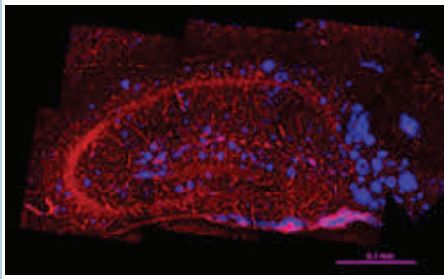

Image shows close relationship between amyloid plaques (blue) in the cerebral microvessels of a mouse's hippocampus.

This research study was funded by grants from the National Institutes of Health, the American Heart Association, and the Alzheimer's Association.

Study co-authors include, Dr. Laibaik Park, Joan Zhou, Dr. Ping Zhou, Dr. Sleiman El Jamal, Dr. Joseph Pierce, Andrea Arreguin, and Dr. Josef Anrather from Weill Cornell Medical College; Rose Pistick and Dr. George A. Carlson from McLaughlin Research Institute in Great Falls, Montana; Linda Younkin and Dr. Steven G. Younkin from the Mayo Clinic in Jacksonville, Florida; and Dr. Bruce S. McEwen from The Rockefeller University.

For more information, visit weill.cornell.edu.

Good Mood Helps Boost Brain Power In Older Adults

By Jeff Grabmeier
Senior Director, Research and Innovation Communications
Ohio State University

COLUMBUS, Ohio -- Older adults can improve their decision making and working memory simply by putting on a happy face, a new study suggests.

Researchers found that easy mood-boosters -- like giving people a small bag of candy -- helped seniors do significantly better on tests of decision-making and working memory.

This is the first study to show the power of positive moods in helping older people with these brain tasks.

“There has been lots of research showing that younger adults are more creative and cognitively flexible when they are in a good mood. But because of the cognitive declines that come with aging, we weren’t sure that a good mood would be able to help older adults,” said Ellen Peters, co-author of the study and professor of psychology at Ohio State University.

“So these results are good news. There are ways for older adults to overcome some of the cognitive declines that come with aging.”

The study was done with Stephanie Carpenter of the University of Michigan; David Västfjäll of Linköping University in Sweden; and the late Alice Isen, of Cornell University. It appears in the current issue of the journal Cognition and Emotion.

The study involved 46 adults aged 63 to 85. Half of them were put into a good mood by receiving a thank-you card and two small bags of candy, tied with a red ribbon, when they arrived at the lab for the experiment. The other “neutral mood” participants did not receive a card or candy.

The participants completed the study on a computer. Those who were induced into the positive mood had a background screen that was designed to help keep them feeling positive -- it featured smiling suns on a sky-blue background. The neutral-mood participants had a similar background, but with neutral round images with no face.

In the decision-making task, the participants were given $3 in quarters and presented with eight virtual decks of cards over the course of experiment. Each of the decks had a different pattern on its back so that participants could identify them. Four of the decks were “gain” decks, meaning that the participants won a quarter 75 percent of the time if they chose a card from that deck, while the other 25 percent they did not win or lose. The other four decks were “loss” decks, meaning they lost a quarter 75 percent of the time that they chose a card from the deck.

Participants could choose to accept or reject the top card of each deck that was offered to them. They were told the goal of the experiment was to win as much money as possible.

The researchers wanted to see how quickly and accurately the participants would learn which decks generally won them money, and which decks lost them money.

The findings were clear: older adults who were put into a good mood chose significantly better than those who were in the neutral mood.

These results are significant because this decision-making task was experiential, meaning that the participants knew nothing about the card values at the beginning of the experiment and had to learn through trial and error.

“We used an experiential task because real life is experiential,” Peters said.

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Good Mood Helps Boost Brain Power In Older Adults continued...

“For example, you meet a new person and she is like one of these decks of cards. You don’t know anything about her and you have to learn if she is someone you can trust. What this study suggests is that people who are in a good mood are going to learn faster and make better decisions.”

Later in the experiment, the researchers tested working memory -- how much information people can hold in their mind at any one time. Researchers read aloud a group of intermixed letters and numbers (such as T9A3) and participants were to repeat the group back in numeric and then alphabetic order (in this case, 39AT). The participants received groups with increasingly more letters and numbers.

Results showed that the older adults who were induced into a good mood scored better on this test of working memory.

“Working memory is important in decision making,” Peters said.

“If you’re working your way through different options, how much you can remember of each option -- and can therefore compare and contrast in your head -- has a big impact on how well you can make a decision.”

A positive mood did not help these older adults on some cognitive measures, such as speed of processing or vocabulary.

Still, Peters said the results provide some good news for a fast-growing population segment in the United States.

“Given the current concern about cognitive declines in the aged, our findings are important for showing how simple methods to improve mood can help improve cognitive functioning and decision performance in older adults, just like they do in younger people.”

The study was supported by a grant from the National Science Foundation to Peters.

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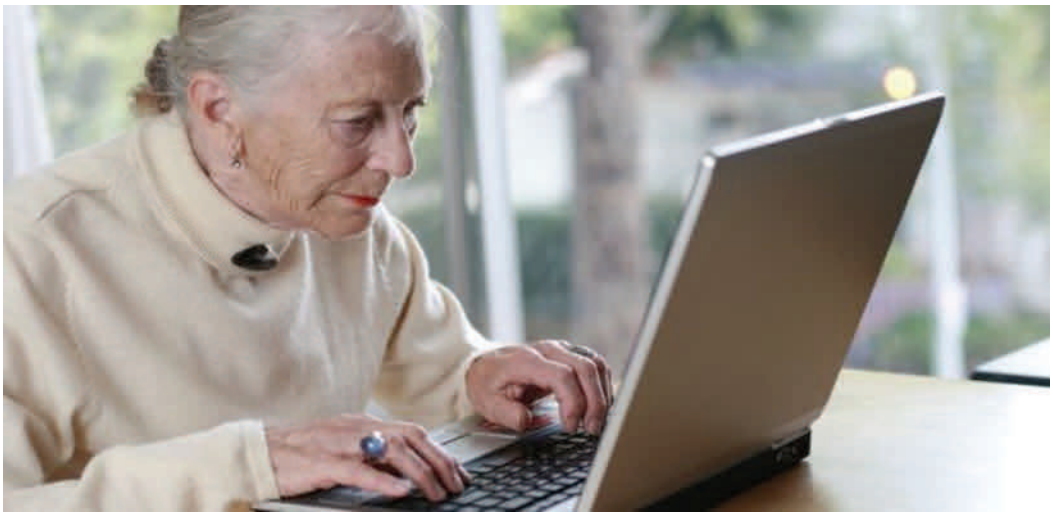
Should Grandma Join Facebook? It May Give Her A Cognitive Boost, Study Finds

By Alexis Blue
Office of University Communications
The University of Arizona

February 18, 2013

Preliminary research findings suggest that learning to use Facebook may help give adults older than 65 a cognitive boost.



For older adults looking to sharpen their mental abilities, it might be time to log on to Facebook.

Preliminary research findings from the University of Arizona suggest that men and women older than 65 who learn to use Facebook could see a boost in cognitive function.

Janelle Wohltmann, a graduate student in the UA department of psychology, set out to see whether teaching older adults to use the popular social networking site could help improve their cognitive performance and make them feel more socially connected.

Her preliminary findings, which she shared this month at the International Neuropsychological Society Annual Meeting in Hawaii, show that older adults, after learning to use Facebook, performed about 25 percent better on tasks designed to measure their ability to continuously monitor and to quickly add or delete the contents of their working memory – a function known in the psychology world as "updating."

Wohltmann, whose research is ongoing as part of her dissertation work, facilitated Facebook training for 14 older adults who had either never used the site or used it less than once a month. They were instructed to become Facebook friends only with those in their training group and were asked to post on the site at least once a day.

A second group of 14 non-Facebook using seniors instead was taught to use an online diary site, Penzu.com, in which entries are kept private, with no social sharing component. They were asked to make at least one entry a day, of no more than three to five sentences to emulate the shortness of messages that Facebook users typically post.

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Should Grandma Join Facebook? It May Give Her A Cognitive Boost, Study Finds continued...

The study's third group of 14 was told they were on a "wait-list" for Facebook training, which they never actually completed.

Prior to learning any new technologies, study participants, who ranged in age from 68 to 91, completed a series of questionnaires and neuropsychological tests measuring social variables, such as their levels loneliness and social support, as well as their cognitive abilities. The assessments were done again at the end of the study, eight weeks later.

In the follow-ups, those who had learned to use Facebook performed about 25 percent better than they did at the start of the study on tasks designed to measure their mental updating abilities. Participants in the other groups saw no significant change in performance.

Wohltmann conducted the study with help from her research adviser Betty Glisky, professor and head of the department of psychology, and a team of undergraduate and graduate research assistants. It was based on existing evidence about how learning new tasks can help older adults with overall cognitive function, as well as research suggesting a possible link between social connectedness and cognitive performance.

"The idea evolved from two bodies of research," she said. "One, there is evidence to suggest that staying more cognitively engaged – learning new skills, not just becoming a couch potato when you retire but staying active – leads to better cognitive performing. It's kind of this 'use it or lose it' hypothesis."

"There's also a large body of literature showing that people who are more socially engaged, are less lonely, have more social support and are more socially integrated are also doing better cognitively in older age," she said.

In Wohltmann's research, further analysis is needed to determine whether using Facebook made participants feel less lonely or more socially connected, she said.

Likewise, further analysis is needed to determine whether, or by how much, Facebook's social aspect contributed to improvements in cognitive performance. However, Wohltmann suspects that the complex nature of the Facebook interface, compared to the online diary site, was largely responsible for Facebook users' improved performance.

"The Facebook interface is actually quite complex. The big difference between the online diary and Facebook is that when you create a diary entry, you create the entry, you save it and that's all you see, versus if you're on Facebook, several people are posting new things, so new information is constantly getting posted," she said.

"You're seeing this new information coming in, and you need to focus on the new information and get rid of the old information, or keep it in mind if you want to go back and reference it later, so you have to constantly update what's there in your attention," she said.

Participants in the study, who had an average age of 79, represent a demographic whose social media behavior has not been closely examined.

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Should Grandma Join Facebook? It May Give Her A Cognitive Boost, Study Finds continued...

"Facebook is obviously a huge phenomenon in our culture," Wohltmann said. "There's starting to be more research coming out about how younger adults use Facebook and online social networking, but we really don't know very much at all about older adults, and they actually are quite a large growing demographic on Facebook, so I think it's really important to do the research to find out."

One in three online seniors use a social networking site like Facebook, according to the Pew Internet & American Life Project.

Wohltmann says she also sees Facebook as a potential alternative to some online games marketed to seniors to help boost mental acuity.

"Those games can boring after a while, and this might be a new activity for people to learn that's more interesting and keeps them socially engaged," she said, adding that it can also help older adults stay connected with grandchildren and other family and friends.

Yet, Wohltmann cautions it may not be for everyone.

"One of the take-home messages could be that learning how to use Facebook is a way to build what we call cognitive reserve, to help protect against and stave off cognitive decline due to normal age-related changes in brain function. But there certainly are other ways to do this as well," she said.

"It's also important to understand and know about some of the aspects of Facebook that people have concerns about, like how to keep your profile secure," she said. "So I wouldn't suggest to anyone to get out and get Granny online right away, unless you or somebody else can provide the proper education and support to that person, so that they can use it in a safe way."

Janelle Wohltmann, UA psychology graduate student

ADCS Trials Enrolling…

ADNI II Study

The goal of the Alzheimer's Disease Neuroimaging Initiative Study is to learn how to stop the progression of mild cognitive impairment (MCI) and Alzheimer's disease in future generations. Information from the study might, in the future, lead to new treatments. http://adcs.org/Studies/ImagineADNI.aspx.

imagine
stopping the progression of Alzheimer's disease
ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE

DIAN
Dominantly Inherited Alzheimer Network

The Dominantly Inherited Alzheimer Network (DIAN). DIAN is an international research partnership of leading scientists determined to understand a rare form of Alzheimer's disease that is caused by a gene mutation. Understanding of this form of Alzheimer's disease may provide clues to decoding other dementias and developing dementia treatments.

Funded by a multiple-year research grant from the National Institute on Aging, DIAN currently involves thirteen outstanding research institutions in the United States, United Kingdom, Germany and Australia. John C. Morris, M.D., Friedman Distinguished Professor of Neurology at Washington University School of Medicine in St. Louis, is the project's principal investigator.

DIAN is currently enrolling study participants who are biological adult children of a parent with a mutated gene known to cause dominantly inherited Alzheimer's disease. Such individuals may or may not carry the gene themselves and may or may not have disease symptoms (click here for information about genetic testing).

To register for DIAN drug trials or DIAN, visit www.DIANExpandedRegistry.org.

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