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MIND OVER MATTER®

INSIDE THE LAB
OF THE WORLD'S FIRST RESEARCH CHAIR IN WOMEN'S BRAIN HEALTH & AGING

HOT & BOTHERED
PERIMENOPAUSE & DEPRESSION

WHAT IT FEELS LIKE TO HAVE ALZHEIMER'S

CAN YOUR LIFESTYLE AND ENVIRONMENT INFLUENCE YOUR GENES?

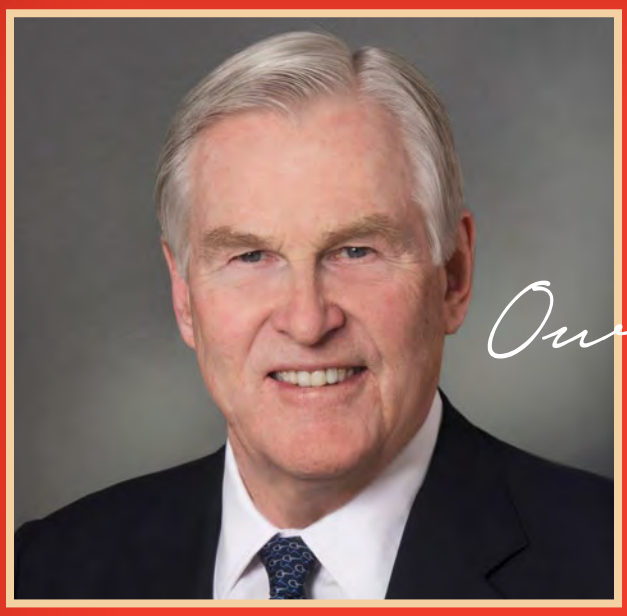
BRAIN BENEFITS OF BEING AN OPTIMIST

NEW FOCUSES FOR AN ALZHEIMER'S CURE

Insight into the latest research findings to combat brain-aging diseases and what you need to stay brain healthy longer.

Women's Brain Health Initiative

WBHI.ORG | VOLUME 8



Our Tribute

THIS EDITION OF MIND OVER MATTER® WAS MADE POSSIBLE THANKS TO THE GENEROUS AND ONGOING SUPPORT AND ENCOURAGEMENT OF OUR PARTNERS BRAIN CANADA FOUNDATION AND HEALTH CANADA.

As the Brain Canada Foundation celebrates our 20th anniversary, we are deeply saddened by the passing of one of our founders, the Hon. Michael H. Wilson, on February 10, 2019.

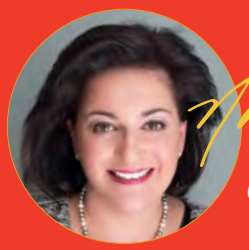
It is difficult to put into words the impact Michael had on our organization, as a past Chair and, along with Allan R. Taylor, our heart and soul. It was Michael's vision to create an organization that would support brain research — an area underserved for too long. Michael led us through our first fundraising campaign and made possible the partnership we established with the federal government. Brain Canada was a personal priority; he devoted the time, resources, and his network to ensure our success. He remained a passionate champion through the years.

But perhaps most important, Michael created a space for the conversation about mental health. Every person and organization working to reduce stigma, improve services, deepen our understanding of the causes, and accelerate the pace of our search for new or improved diagnostics and treatments — and ultimately cures — was in some way directly linked to Michael, or indirectly a beneficiary of a new public awareness about mental illness and its impact on individuals, families, society, and the economy.

Michael was the example of doing things with integrity and without ego, because that was the way to build a community and not a silo. Michael inspired our tagline "One brain. One community." He believed in the power of people coming together to address our greatest challenges. He always sought ways to create links and to find common ground. Partnerships were central to this vision, and Brain Canada is proud of the more than 100 partnerships we have established since our founding, including our partnership with Women's Brain Health Initiative, an organization Michael also supported. It has been a collective community effort to raise and disburse $250 million to support 300 research projects involving more than 1,000 researchers at 115 institutions across the country.

Canada has lost one of its greatest advocates for brain and mental health, and as Brain Canada's looks back on our history, we know that we stood on the shoulders of a giant to build something magical. Michael's vision for a brain research organization is as important and relevant as ever, and we honour his legacy as we write the next chapter.

At the time of this publication, we are pleased to share that the federal government has renewed its commitment by providing an additional $40 million in matching funding to Brain Canada over the next two years. This will boost our positive momentum, and enable us to continue our vital work with a range of valued partners.



Naomi Azrieli
Chair, Brain Canada Foundation

Inez Jabalpurwala
President and CEO,
Brain Canada Foundation

Brain Canada Foundation

EDITOR'S LETTER

I love what I do.

It is so rewarding to be promoting a cause in which I passionately believe, and to see the progress that we have made since we launched Women's Brain Health Initiative (WBHI) in 2012. Across the globe, more and more people are recognizing that Alzheimer's disease disproportionately impacts women, and that dementia affects men and women differently, both in terms of disease development and progression. Importantly, an ever-growing number of researchers now acknowledge the necessity of considering sex and gender differences when studying brain disease, and more funding agencies are demanding that sex and gender are taken into account throughout the research process. At the same time, the general public is learning about prevention and the ways in which we can make positive lifestyle changes to help preserve our brain health.

Happily, we are no longer alone in this campaign. As part of my role with WBHI, it is my great fortune to regularly meet visionary individuals who are changing the way that we look at the world. Recently, I had such an opportunity at the AccessCircles Health and Wellness Forum in Miami, Florida. AccessCircles was founded by Carolee Lee, and is a non-profit organization that describes itself as a global network for women, providing connectivity, knowledge, and access to thought leaders, resources, and experiences that transform our lives.

It was inspirational to listen to brilliant people making the case for a more nuanced, precise, and effective approach to research, and the importance of accelerating those projects that help us understand why women are exclusively, disproportionately, or differently affected by some diseases.

Among the speakers was Dr. Marjorie Jenkins, who is the Founding Director and Chief Scientific Officer for the Laura W. Bush Institute for Women's Health at Texas Tech University Health Sciences Center. She is a pioneer in the emerging scientific field of precision medicine (also referred to as personalized or individualized medicine), which explores the ways in which sex and gender are implicated in disease processes – an approach to disease prevention and treatment that is at the heart of WBHI's mission.

Dr. Jenkins has been a powerful and influential voice in calling for the elimination of gender-blind medical research. She was invited to AccessCircles to speak about the future of precision medicine for women. Part of being precise means recognizing that diseases affect men and women differently and structuring research projects accordingly.

"The thing about sex and gender medicine is that it's good for everyone," Dr. Jenkins said later in an interview with Mind Over Matter®. "When we do gender-blind research, nobody wins, not men, not women."

Dr. Jenkins noted that in neuroscience research, more than 75% of laboratory animals are male – an incomprehensible imbalance, given that dementia and many brain disorders affect women at a much higher rate than men.

While we are making progress, we need to do much, much more. To get precision medicine, we need precision research. That is why I am so proud that WBHI played a key role in the funding and creation of the world's first Research Chair in Women's Brain Health and Aging, awarded to Dr. Gillian Einstein at the University of Toronto. This initiative has helped make Canada a global leader in exploring the sex-gender divide.

In this edition of Mind Over Matter®, we bring you an inside look at Dr. Einstein's team – a group of remarkable researchers who are passionately devoted to righting past wrongs and to expanding our understanding of the workings of women's brains.

Before inviting you to learn more through the pages of Mind Over Matter®, I would like to share a few words of tribute to Michael Wilson, an extraordinary Canadian and treasured friend of WBHI. Michael had great success both in business and politics, and became a visionary campaigner for mental health. Michael served on the board of our partner, Brain Canada. He was someone who instinctively understood the value of promoting women's brain health and we were truly fortunate to have him as an Honorary Member of our board. We mourn Michael's passing, celebrate his memory, and offer our deepest condolences to his family.

I believe that Michael would be as impressed as we are of the work being done by the researchers at the Einstein lab. They are planting seeds of knowledge that will lead to better outcomes for our daughters and for future generations.

Lynn Posluns
Founder and President, Women's Brain Health Initiative

PHOTO: JAYLYN TODD

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CONTRIBUTORS

AMY CRYSTAL // CONTRIBUTING EDITOR

Amy is a real estate lawyer at DelZotto, Zorzi LLP, one of Canada's top real estate boutique law firms. "Although many people think of dementia as a disease that affects older adults, the disease begins to impact the brain decades before symptoms are even noticed. WBHI is inspiring a new generation of women to take care of our brain health today, since research now shows that the earlier you protect your brain health, the better the cognitive outcome."

VITINA BLUMENTHAL // CREATIVE DIRECTOR

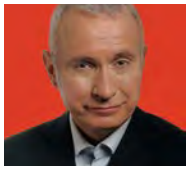
Vitina is creative to her core. An adventurous soul with a passion for travel, a healthy lifestyle (especially all things yoga), and sharing her love of mindfulness with others. She runs a self-discovery business, WanderfulSoul, which focuses on creating unforgettable, transformational experiences that promote mental and emotional well-being. Through WBHI's Young Person's Cabinet, she encourages millennials to start taking care of their mental and brain health.

STEPHANIE HAHN // WRITER

Stephanie is a writer and yoga instructor living in Waterloo Region, Ontario. It was through the "gift" of back pain that Stephanie learned to slow down, listen to her body, and rediscover the joys of moving. "Writing for this magancine allowed me to merge my love of writing with my love of spreading the word that stress relief is critical for health."

DILIA NARDUZZI // WRITER

Dilia is a writer and editor living in Hamilton, Ontario. She's been interested in healthy eating and a balanced lifestyle for almost twenty years. She studied gender dynamics while doing graduate work at McMaster University and was honoured to write for Mind Over Matter®. "I want the medical profession and all women to know that women's bodies require specialized medical care."



SEAN MALLEN // WRITER

Sean Mallen is a Toronto-based communications consultant, media trainer, and writer. Having seen close family members deal with dementia, he's a passionate supporter of WBHI's mission and he's inspired by telling the stories of researchers who are expanding our knowledge of women's health. Sean's first book, *Falling for London-A Cautionary Tale* from Dundurn Press, is widely available across Canada, the U.S., and the U.K.

SASHA & FELECIA EXETER // ON THE COVER

Sasha and Felecia share many passions in life, but what has helped create their unbreakable bond as mother and daughter is their love for staying active through exercise, wellness, and empowering women of all ages to create a life path based on authenticity and their own passions. Participating in this month's issue of Mind Over Matter® was a dream for these two women who love to encourage other women to be more knowledgeable and proactive when it comes to their brain and overall health and wellness.

COVER PHOTO: JAYLYN TODD

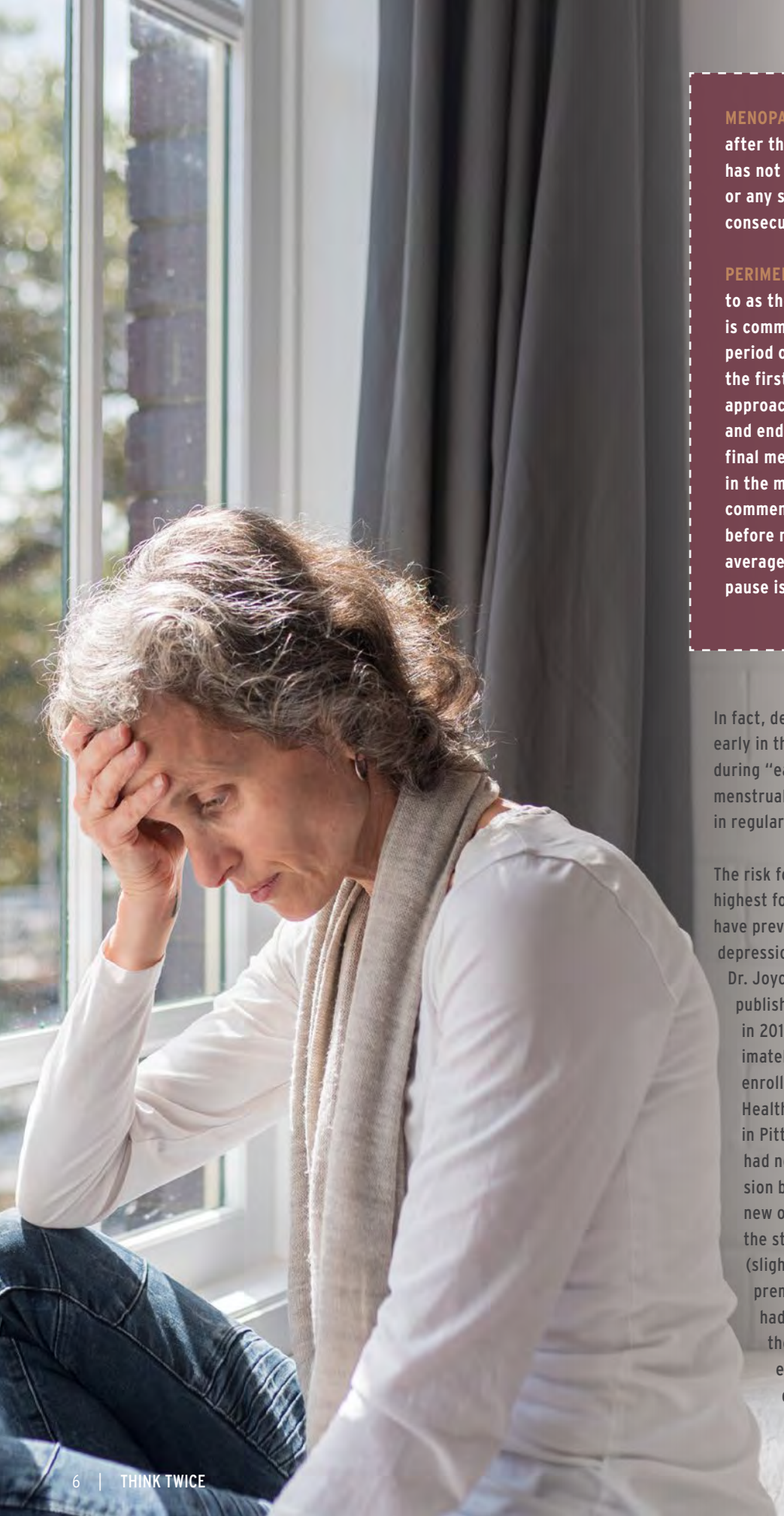
HOT & BOTHERED

Exploring Perimenopause & Depression

At midlife – roughly mid-forties to mid-sixties – many women juggle responsibilities at work (during the peak years of their careers) and at home (sometimes caring for both children and aging parents). At the same time, women in this cohort experience physical and emotional changes associated with aging and menopause. It can be a particularly stressful time for women – full of significant life changes, mood swings, and, in some cases, depression.

With all that women face during this phase in their lives, it is not surprising that research has shown that perimenopause is a time of increased vulnerability for depressive symptoms and clinical depression (formally called major depressive disorder).

WHILE BOTH PERI- AND POSTMENOPAUSAL WOMEN HAVE A CONSIDERABLY INCREASED RISK OF WORSENING DEPRESSIVE SYMPTOMS COMPARED TO PREMENOPAUSAL WOMEN, DEPRESSION RISK APPEARS TO BE HIGHER DURING PERIMENOPAUSE THAN AFTER MENOPAUSE. ⟶



MENOPAUSE is usually diagnosed after the fact, once a woman has not had a menstrual period or any spotting for 12 months consecutively.

PERIMENOPAUSE, also referred to as the menopause transition, is commonly defined as the period of time starting when the first changes related to approaching menopause begin, and ending one year after the final menstrual period. Changes in the menstrual cycle can commence four to eight years before menopause, but the average length of perimenopause is four years.

In fact, depression risk begins very early in the menopausal transition, during "early perimenopause" when the menstrual cycles first begin to change in regularity.

The risk for clinical depression is highest for middle-aged women who have previously experienced major depression. One study conducted by Dr. Joyce Bromberger and colleagues, published in *Psychological Medicine* in 2015, examined data of approximately 443 women, aged 42-52, enrolled in the Study of Women's Health Across the Nation (SWAN) in Pittsburgh. Among women who had never experienced depression before, the risk of developing new onset major depression during the study's 13-year span was 28% (slightly higher than the risk during premenopause). For women who had experienced depression in the past, the risk of experiencing an episode of major depression during the study period was 59%.

WHY ARE PERIMENOPAUSAL WOMEN MORE VULNERABLE TO DEPRESSION?

One factor that has been studied for its effect on women's depression throughout the life cycle is hormones. Estradiol, in particular, has received much attention from researchers because it is the predominant estrogen present during a woman's reproductive years. Among other things, estradiol affects levels of serotonin, a brain chemical that is involved in depression.

It was first suspected that low levels of estradiol might be the reason for increased risk of depression. However, estradiol does not just gradually taper off as a woman transitions to menopause. Rather, levels of estradiol fluctuate widely during the transition period, and it is now believed that these dramatic fluctuations are what influences mood disruption.

While all women experience fluctuations of estradiol during the menopause transition, only some experience depression. Despite the fact that hormone fluctuations are universal, the duration of exposure to estradiol throughout one's adult years varies substantially among women. Dr. Wendy Marsh and colleagues conducted a study examining patterns of estrogen exposure during the reproductive years and the risk of depression during the menopausal transition and early postmenopausal years.

They discovered that being exposed to estradiol for a longer period of time from the start of menstruation until the onset of menopause was significantly associated with a reduced risk of depression during the transition to menopause and for up to ten years postmenopause.

WOMEN WHO EXPERIENCED EARLIER MENOPAUSE OR WHO HAD FEWER MENSTRUAL CYCLES IN THEIR LIVES (AND THEREFORE HAD LESS ESTROGEN EXPOSURE) WERE AT HIGHER RISK FOR DEPRESSION.

Another interesting finding from this study was that longer duration of birth control use was associated with a decreased risk of depression, but the number of pregnancies or incidence of breastfeeding was not. These findings were published in *Menopause* in July 2017.

Changes in another hormone, progesterone, during perimenopause may also play an important role in depression. Allopregnanolone, a by-product of progesterone, is an important regulator of stress responsivity in women. Changes in this system may predispose women to depression. These findings were described in a research paper by Dr. Jennifer Gordon and colleagues, published in January 2015 in *The American Journal of Psychiatry*.

IT APPEARS THAT HORMONES PLAY A SIGNIFICANT ROLE IN A WOMAN'S VULNERABILITY TO DEPRESSION DURING MIDLIFE.

Other factors can certainly be involved, too. It is possible that hormones are interacting with a woman's biological vulnerability and life stress to affect her individual susceptibility to depression. There is still a lot to be learned about midlife depression in women, but enough is known at this point for women and health care providers to take proactive steps to identify and treat midlife depression.

TAKING ACTION ON PERIMENOPAUSAL DEPRESSION: NEW GUIDELINES FOR HEALTH PROFESSIONALS

In September 2018, the North American Menopause Society (NAMS) and the Women and Mood Disorders Task Force of the National Network of Depression Centers (NNDC) released guidelines to help health professionals better understand and address perimenopausal depression. These guidelines, the first of their kind, were developed by an 11-member expert panel that conducted a systematic review of the literature on depressive disorders and symptoms in perimenopausal and postmenopausal women.

The guidelines – published in both *Menopause* and *Journal of Women's Health* in September 2018 – summarize the latest information about depression during perimenopause and provide a comprehensive list of recommendations for the evaluation and treatment of depression during the menopause transition.

Highlights from the article by Dr. Pauline Maki and colleagues entitled "Guidelines for the Evaluation and Treatment of Perimenopausal Depression: Summary and Recommendations" include the following:

SYMPTOMS

- Women with depression during midlife experience the classic symptoms of depression (e.g., feeling constant and persistent sadness, feeling worthless, and loss of interest in favourite activities), often along with menopause-specific symptoms (e.g., hot flashes, night sweats, sleep, and sexual disturbances, and changes in cognitive function) and psychosocial challenges (e.g., stress). Some of the common menopause-specific symptoms complicate or overlap with the classic depression symptoms.

DIAGNOSIS

- "To determine whether a perimenopausal woman should →

be diagnosed and treated for major depression, a health provider should complete a comprehensive evaluation that considers: menopausal stage, co-occurring and overlapping menopause and psychiatric symptoms, and psychosocial risk factors," said Dr. Maki, a Professor of Psychiatry and Psychology at the University of Illinois at Chicago. "Although menopause-specific assessment tools do not yet exist, health professionals can use existing tools to help disentangle symptoms and distinguish diagnoses."

TREATMENT

"We recommend that the same drugs and psychotherapies used to treat depression in the general population should be used to treat major depressive episodes experienced during perimenopause," noted Dr. Maki. "Treatment for hot flashes and night sweats could also be helpful, especially if they are affecting sleep."

There is some evidence that estrogen therapy can help with depression in perimenopausal women, but it appears to be ineffective for helping depressed postmenopausal women. The expert team also reviewed the research evidence on alternative therapies. "If someone is experiencing depressive symptoms that don't reach the threshold for clinical depression, things like mindfulness-based stress reduction, yoga, and a good diet might help," continued Dr. Maki. "But for cases of clinical depression, we concluded that there is insufficient evidence at this time to recommend any herbal or complementary approaches, the one exception being exercise, which has been shown in research to help."

COMMON SYMPTOMS OF PERIMENOPAUSE

Although most women go through the transition into menopause without experiencing a major depressive episode, it is important that those who do experience depression receive the help that they need.

> **SOMETIMES A PERSON FEELS SAD OR DOWN FOR A BRIEF PERIOD OF TIME. THIS EXPERIENCE IS COMPLETELY NORMAL AND WOULD BE REFERRED TO AS A DEPRESSIVE SYMPTOM (WHICH LIKELY DOES NOT REQUIRE TREATMENT), RATHER THAN CLINICAL DEPRESSION (WHICH DOES REQUIRE TREATMENT).**

You might be suffering from clinical depression – and should consult with your doctor – if you experience any of the following symptoms for the majority of the day, almost every day, for at least two weeks consecutively:

- ***Feelings of sadness or irritation;***
- ***Loss of interest in favourite activities;***
- ***Feelings of worthlessness;***
- ***Thoughts of death or suicide;***
- ***Difficulty concentrating or making decisions;***
- ***Fatigue or lack of energy;***
- ***Sleeping too much or too little; and***
- ***Weight gain or loss.***

"We hope that these clinical guidelines will raise awareness about the link between the menopausal transition and mood," said Dr. Maki. "Our goals are to help more women recognize symptoms and seek medical advice as needed, and also help health professionals know how to identify depression in perimenopausal women and how best to help women who experience mood issues at this time in their lives." The guidelines are being promoted to doctors around the world, through media exposure after the launch and ongoing presentations by Dr. Maki.

UNDER PRESSURE

Millennials – The Most Stressed Demographic

It was a delicious antidote to a brutally cold winter night in downtown Toronto. A roomful of millennials (those born between the years 1984 and 2000) gathered to hear about fine food and healthy eating from one of the nation's most celebrated chefs and restaurateurs, Michael Bonacini. The occasion was one of Women's Brain Health Initiative's Engaging Millennial Minds® events, designed to raise awareness amongst those under the age of 40 about the value of making positive lifestyle choices that can significantly improve one's odds of staying brain healthy longer.

The subject matter was timely and pertinent. Numerous studies have found that millennials are more stressed, more anxious, and more prone to mental health problems than any other age cohort.

As the attendees mingled before the event, sipping wine and snacking on delectable hors d'oeuvres, several millennials told Mind Over Matter® that they believe the studies are true.

Laura, a neuroscience researcher, nodded her head when asked about millennial stress. "I think it's competition within your workplace, with job searches, with finances, and it's all heightened through social media," she said.

Aseel, a financial planner who is currently completing a master's degree in psychotherapy, said she feels it too. "Today's Thursday, and I haven't been home before 9 or 10 o'clock this week. I'm constantly doing activities after work and they're all in alignment with the quest of finding what I want to fully engage with," she said.

Erin, who works in sales, cited the omnipresence of technology and social media in our lives. →

"I think we're being inundated with a lot of information from a ton of different avenues and it can be stressful to break that down and figure out what you should be taking in and what you should be leaving behind," she said.

In its most recent Monitor survey on adult mental health and substance use (released in January 2019), Toronto's Centre for Addiction and Mental Health (CAMH) noted that

> **MILLENNIALS ARE MORE LIKELY THAN OTHER AGE GROUPS TO REPORT PROBLEMATIC USE OF ALCOHOL, CANNABIS USE, AND E-CIGARETTE USE, AS WELL AS TO HAVE SIGNIFICANTLY HIGHER REPORTS OF SUICIDAL IDEATION, FREQUENT MENTAL DISTRESS DAYS, AND PSYCHOLOGICAL DISTRESS.**

"These multiple indicators of problematic and high-risk behaviours occur at a time when these young people are charting their lives, finding careers, and starting families," said Dr. Sanjeev Sockalingam, Associate Professor of Psychiatry at the University of Toronto and Vice President of Education at CAMH. "These data point to the high levels of stress during this stage in life and the importance of recognizing these risks and responding to them in a timely manner."

In an interview with Mind Over Matter®, Dr. Sockalingam described millennials as a "high-risk group", citing several stressors such as transitioning from home to school to the work force.

"It's often a key time in developing identity, navigating whether they're leaving home, and relationships are often continuing to evolve during this time. We see that finances can be a concern, pressures related to education and changes in their peer groups with all of these transitions as well," he continued.

Dr. Sockalingam also commented on the role of social media, noting that an increasing number of individuals are attending crisis services complaining of distress because of online conversations that are shaming, intimidating, or full of conflict. Dr. Sockalingam was wary, however, of blaming the much-discussed "fear of missing out" (FOMO) phenomenon, in which individuals experience anxiety at the thought of not being included in an event or not being "in the know." FOMO is typically experienced by overly active social media users, and has been linked with degraded mood levels and decreased satisfaction with one's life. These feelings can then contribute to symptoms of depression. To date, though, there has been little clinical research on this phenomenon, and so its impacts remain primarily anecdotal.

The CAMH Monitor survey adds to the growing body of evidence of millennial stress. In 2017, an Ipsos poll for Global News found that 63% of Canadian millennials are at "high risk" for mental health issues, up from 56% in 2016 and 53% in 2015. Gen-Xers (those born between the mid 1960s and early 1980s) were the second most-stressed demographic, followed by the baby boomers (those born between 1946 and 1964).

There are similar findings in the United States. The American Psychiatric Association surveyed more than 1000 adults in 2018 and found that millennials were the most anxious of the demographic groups (although baby boomers had the largest year-over-year increase in anxiety levels).

THE RESEARCH ALSO INDICATES THAT, AMONGST MILLENNIALS, WOMEN ARE MORE STRESSED THAN MEN.

In a recent poll commissioned by Sanity & Self (a wellness app for women launched in July 2018), approximately 1,500 American men and women were asked to rate their stress on a scale of 1 to 5, with 5 being the most stressed. On average, the women reported their stress level was 3.03, compared with 2.66 for the men. Millennial women reported the highest levels of stress at 3.4, and were also more likely to experience insomnia multiple times a week due to stress, as well as more likely to feel alone and isolated (and to experience anxiety about those feelings of loneliness).

On a positive note, though, millennials are consistently more likely to seek help for their stress than any other demographic group, with women more willing to speak with a therapist than men.

Dr. Sockalingam of CAMH believes that society's improved awareness of mental health has not only reduced the stigma, but has also made individuals more willing to talk about their issues and seek care from health professionals.

At CAMH, employees are offered a variety of mental health-related activities to help combat stress and anxiety, including access to gyms, yoga, and mindfulness programs. "There are treatments available, as well as methods of self-care – sleep, good diet, exercise – all things that are more preventative in the long run," said Dr. Sockalingam.

Research has indicated that eating nutritious foods can go a long way toward achieving a mentally-healthy lifestyle. When asked about his favourite recipe, Michael Bonacini replied "a simple mushroom soup" – a low-stress, comforting concoction. On that cold winter night at the recent Engaging Millennial Minds® event, listening to Bonacini discuss his passion for food was a pleasant release for all present. Indeed, when he and his colleague, chef Jeremy Korten, demonstrated how to make a quiche and seasonal salad of root vegetables, the only anxiety felt in the room was the tension of waiting for the opportunity to taste their creations.

IN THE PALM OF YOUR HAND

Can Your Lifestyle and Environment Influence Your Genes?

There are two categories of genes that influence whether an individual will develop Alzheimer's disease (AD): risk genes and deterministic genes. **Risk genes** increase the likelihood of developing the disease, but do not guarantee that it will happen. Apolipoprotein E (APOE) is the gene most commonly associated with late-onset AD, and it has three variants (or alleles): →

- APOE e2 is the least common form of the APOE gene and may provide some protection against AD;
- APOE e4 is slightly more common than APOE e2 and appears to increase the risk of AD; and
- APOE e3 is the most common form of the APOE gene and does not seem to impact the risk of AD.

Deterministic genes, on the other hand, directly cause the disease, guaranteeing that anyone who inherits this type of gene will develop early-onset AD. Scientists have identified three rare deterministic genes that will result in AD: amyloid precursor protein (APP), presenilin-1 (PSEN1), and presenilin-2 (PSEN2). However, these genes are estimated to account for less than 1% of all cases of AD.

ASIDE FROM GENETICS, THEN, WHAT ELSE MIGHT BE INFLUENCING WHO DEVELOPS AD AND WHO DOES NOT?

Scientists believe that complex interactions between genetic and environmental factors are at play, and that epigenetics may be the underlying mechanism affecting those interactions. Epigenetics is an emerging field in science that studies the "additional layer of information" that controls when and where genes are expressed, without changing the DNA sequence.

What is particularly interesting is that while genes are fixed, gene expression (i.e. how a gene ultimately functions) is not. Instead, some epigenetic marks can change over time in response to external stressors and lifestyle choices.

OUTSIDE FACTORS THAT ARE KNOWN TO IMPACT HEALTH SUCH AS EXERCISE, DIET, AND EXPOSURE TO CHEMICALS HAVE BEEN SHOWN TO AFFECT THE EPIGENOME.

Neuroepigenetics is the term used to describe epigenetic changes specifically in the brain. To date, this field of study has provided insights into brain and mental health issues such as addiction, depression, post-traumatic stress disorder, and AD.

The investigation of how epigenetic marks impact genes in AD is a fairly new area of study, and there is still a tremendous amount to learn. Research to date has shown that epigenetic mechanisms are dysregulated during the progression of AD, starting early in the disease process. It is not clear, though, if the epigenetic changes that have been observed are a cause or consequence of AD.

All of the cells in a human body contain the same set of genetic instructions (DNA), yet there are different cells in the body with widely varying roles. The identical genetic code produces all of the different cell types thanks to an assortment of chemical markers and switches known as epigenetic marks (which are collectively referred to as the epigenome). These epigenetic marks, together with the transcription factors, control which genes are switched on or off, or fine-tune their activity. The epigenome provides instructions to the DNA about what to do, where, and when (i.e. instructions that influence gene expression).

One recent study conducted by a team of researchers from the Perelman School of Medicine at the University of Pennsylvania, published in *Nature Neuroscience* in April 2018, examined the epigenetic landscape in post-mortem brain tissue donated by individuals with AD, as well as younger and elderly cognitively-normal control subjects. The researchers discovered epigenetic differences between the AD brains and healthy-aging brains. In particular, they found differences in an epigenetic mechanism referred to as acetylation of lysine 16 on histone H4 (H4K16ac).

"H4K16ac is a key factor in human health because it regulates responses to stress and DNA damage," explained Dr. Shelley Berger, a professor at the Perelman School of Medicine and one of the study's authors. "In this study, we found that normal aging leads to increases in H4K16ac – in new positions along the genome, as well as in locations where it is already present. In contrast, AD brains showed losses of H4K16ac in locations close to certain genes that have been linked to aging in Alzheimer's disease."

THIS FINDING SUGGESTS THAT DURING THE HEALTHY AGING PROCESS, EPIGENETIC CHANGES OCCUR IN THE BRAIN THAT MAY PROTECT AGAINST AD, BUT WHEN THESE GO AWRY, A PERSON MAY BECOME PREDISPOSED TO DEVELOPING THE DISEASE.

Alzheimer's is a disease known to develop over a long period of time, with symptoms only becoming evident late in the process. Epigenetic alterations might be occurring early in the disease process, though, making them a potential biomarker that could aid in diagnosis and a possible target for new therapies.

"Our study findings do not suggest a cure for Alzheimer's disease," emphasized Dr. Berger. "However, they do suggest that H4K16ac could represent a potential target for future drug

development aimed at preventing AD progression early on."

Recently, a group of researchers from Drexel University in the U.S. conducted a study on fruit flies and successfully reversed symptoms of AD by restoring the balance between two epigenetic enzymes that regulate gene expression. The research focused on the balance between histone deacetylase 2 (HDAC2) – an enzyme known to help control the expression of genes linked to memory and learning – and Tip60 histone acetyltransferase (Tip60 HAT). It appears that when HDAC2 is more abundant than Tip60 HAT, gene expression is repressed, which leads to problems with neuroplasticity (the brain's ability to adapt to new stimuli or recall reactions to stimuli that it has already encountered).

The researchers discovered that if they added extra Tip60 HAT to the brains of flies with Alzheimer's-like symptoms, the balance between the two enzymes could be successfully restored. Moreover, when that balance was reinstated, the flies were able to re-learn and remember behaviours that the researchers previously taught the flies. These findings were published in *The Journal of Neuroscience* in May 2018.

"By studying fruit flies during an early stage of their development, our research team was able to look at what happens early in the neurodegeneration process," said Dr. Felice Elefant, associate professor at Drexel University and one of the authors of the study. "As a result, we were able to test an intervention aimed at correcting what is happening during those early stages. Our positive results warrant further research related to Tip60 HAT activators as a potential Alzheimer's treatment."

H4K16ac and the HDAC2/Tip60 HAT enzymes are not the only epigenetic mechanisms that have been found to have an association with Alzheimer's disease. They represent just two examples of potential epigenetic targets for treatment that have been discovered to date.

Research involving the study of neuroepigenetic mechanisms is an enormous undertaking. The mapping of genes (i.e. the human genome) has been extremely complex and it is just the basic infrastructure upon which epigenetic mechanisms operate. The study of epigenetics is so challenging because of the vast number of potential combinations of epigenetic marker type and location.

While this research continues, there is much that we can do to apply what is already known about epigenetics.

AN INDIVIDUAL'S EPIGENETIC LANDSCAPE CHANGES OVER TIME IN RESPONSE TO EXTERNAL INFLUENCES, SOME OF WHICH WE HAVE CONTROL OVER.

There is an abundance of research that points to the benefits of making healthy lifestyle choices for your brain (e.g., engaging in physical and mental exercise, staying socially engaged, consuming healthy foods, sleeping well, meditating, and participating in other activities for stress relief). Knowing that the decisions we make affect the epigenetic marks in our brains (and correspondingly influence our brain health) is a powerful motivator to start making brain-healthy choices today.

HALF FULL

Looking on the Bright Side

Are you a glass half-empty or glass half-full kind of person? Your answer to this question – which reflects your tendency to be either an optimist (half full) or a pessimist (half empty) – not only affects your overall life perspective, but also impacts your physical and mental well-being.

OPTIMISM IS GOOD FOR YOU

Research shows that optimism is good for your health in numerous ways, both psychologically and physically. For example, optimists tend to experience better recovery rates after surgery, improved cancer survival rates, better cardiovascular health, lower rates of depression, and longer life spans. They also tend to have lower stress levels and cope better with the amounts of stress that they do encounter.

Several studies have suggested that optimism may affect cognitive function as well.

1. The AARP Global Council on Brain Health (GCBH) published a report in 2018 that examined how mental well-being – comprised of seven elements including optimism – can impact brain health in adults aged 50 and older. After reviewing the existing research on the subject, the expert panel discovered that poor mental well-being (e.g., pessimism, not feeling useful) may negatively impact one's ability to think and reason, while greater mental well-being is associated with reduced dementia risk.

2. To complement the GCBH's report, the AARP conducted a survey of nearly 2,300 American adults, asking about their perceptions of their own mental well-being and brain health. Although the survey cannot establish cause and effect, it revealed that adults aged 50 and older who reported high levels of mental well-being tended to also report having better memory and thinking skills than those who reported lower levels of mental well-being.

3. In a recent study conducted by Katerina Gawronski and colleagues in the U.S., the researchers looked specifically at the association between optimism and cognitive impairment in older adults. Examining data from over 4,600 men and women aged 65 and older who were part of the Health and Retirement Study, the researchers found that higher levels of optimism were associated with reduced likelihood of becoming cognitively impaired. **The more optimistic a person was, the lower his or her risk of cognitive impairment**. These findings were published in the June 2016 issue of *Psychosomatic Medicine*.

Optimism is the quality of having hope or confidence about the successful outcome of a future occurrence. It refers to believing that something good will happen or emphasizing the positive aspects of a situation.

An individual who is pessimistic, on the other hand, expects the worst, blames him or herself for negative outcomes, and expects those outcomes to be permanent or unrealistically long-lasting.

ATTITUDES ABOUT AGING MATTER

Pessimism involves negative thinking about the future. One form of negative thinking that is prevalent in many Western cultures is regarding the aging process with dread. Dr. Becca Levy, an associate professor of epidemiology and psychology at the Yale School of Public Health, and her colleagues sought to examine the impact of negative age stereotypes on brain structure and pathology. To do so, the research team analyzed the data of 158 individuals who enrolled in the brain-neuroimaging program of the Baltimore Longitudinal Study of Aging. "We discovered that participants known to hold more negative age stereotypes earlier in life had significantly higher loss of volume in their hippocampal area and significantly greater accumulation of neurofibrillary tangles and amyloid plaques," explained Dr. Levy. "These are changes that tend to happen in the brains of people with Alzheimer's disease." These findings, which were published in *Psychology & Aging* in 2016, suggest a new pathway to identifying mechanisms and potential interventions related to the neuropathology of Alzheimer's disease.

More recently, Dr. Levy's team published additional research that demonstrated that positive attitudes about aging were linked with reduced risk of dementia in older adults. "We found the protective effect of positive beliefs about old age applied to all participants, even those carrying a gene that puts them at higher risk of developing dementia (APOE e4)," said Dr. Levy. **"Among APOE e4 carriers, those who held positive aging beliefs were 50% less likely to develop dementia than those who held negative aging beliefs."** (These findings appeared in the February 2018 issue of *PLOS ONE*.)

It is clear that we should all strive to adopt a more positive outlook on aging – both individually and collectively as a society. And, the good news is, previous research conducted by Dr. Levy and colleagues – published in *Psychological Science* in 2014 – has shown that it is possible to strengthen positive aging beliefs.

OPTIMISM'S IMPACT ON PEOPLE WHO ALREADY HAVE DEMENTIA

Dr. Linda Clare, a professor at the University of Exeter and Director of the Centre for Research in Ageing and Cognitive Health (REACH), and her colleagues recently examined what helps individuals with dementia "live well." The researchers asked 1,547 participants diagnosed with mild to moderate dementia to rate their quality of life, satisfaction with life, and well-being.

The findings were combined into one overall "living well" score. A variety of factors were analyzed to assess their impact on the living well score. "A wide range of factors were found to play a role in living well for people with dementia," explained Dr. Clare. "Psychological factors, including optimism, were found to be closely linked to the ability to optimize quality of life and well-being." The research suggests that being optimistic, even when facing dementia, has enormous benefit.

OPTIMISM'S EFFECT ON CAREGIVERS

In the same U.K. study conducted by Dr. Clare and colleagues, the researchers also surveyed 1,283 caregivers of individuals with dementia, asking the same questions in order to establish a "living well" score for each of them. **The researchers discovered that positive psychological states, including optimism, were also strongly related to living well amongst caregivers.**

"Our research sheds new light on what factors play a key role in maximizing quality of life and well-being for people with dementia and their caregivers, and optimism is one of the key factors on that list," said Dr. Clare. "We hope that our findings are used to inform the type of support provided to the millions of people facing dementia worldwide, as well as to those who care for them." (These findings were published in the December 2018 issue of *Alzheimer Disease & Associated Disorders*.)

A research team from Spain, led by Dr. Pablo Ruisoto from the University of Salamanca, also explored the association between optimism and quality of life amongst caregivers of individuals with dementia, and reached similar conclusions. The researchers worked with a sample of 130 participants with dementia and their informal caregivers, having each complete a comprehensive assessment. The analysis, published in *International Psychogeriatrics* in July 2018, revealed that optimism was consistently linked with better well-being and quality of life for the caregivers.

OPTIMISM CAN BE LEARNED

Experts believe that optimism is only partly determined by one's genetics, and therefore there is great potential for optimism to be learned at any point in life. In other words, **even if someone has tended to be extremely pessimistic his or her entire life, it is not too late to develop a more optimistic outlook.**

Shifting to a more optimistic way of thinking begins with setting the intention to do so. Then, you might focus on shifting your inner self-talk to be more positive; the Mayo Clinic describes this as an important technique for achieving a higher level of optimism.

Fortunately, there are numerous resources available (both online and on the shelves of your local library or bookstore) that can help you learn about optimism and how to integrate positive thinking into your life, including the following:

- *Learned Optimism: How to Change Your Mind and Your Life* by Martin Seligman;
- *Relentless Optimism: How a Commitment to Positive Thinking Changes Everything* by Darrin Donnelly; and
- *My Pocket Positivity: Anytime Exercises That Boost Optimism, Confidence, and Possibility* by Courtney Ackerman.

THE GERM OF AN IDEA

Infections Could Play a Role in Alzheimer's

The idea that infectious agents (such as viruses, bacteria, or fungi) may play a role in dementia is not new. Alois Alzheimer – the man who first described a "peculiar disease" in 1906 that would later become known as Alzheimer's disease – first proposed that infection might be involved in the disease process. Over the years, various researchers have uncovered findings that support potential links between different infectious agents and neurological disorders.

Recently, a wave of new research has been published related to herpes viruses in particular, and their role in dementia. This research adds to the existing evidence that

HERPES IS A STRONG RISK FACTOR FOR DEMENTIA,

outlines theories that might explain the relationship between herpes and dementia, and suggests potential directions for new dementia drug research.

LINKS BETWEEN HERPES VIRUSES AND DEMENTIA

Herpes simplex virus type 1 (HSV-1) is the infectious agent that has been most strongly linked to Alzheimer's disease to date. Over 150 research publications directly or indirectly support this association.

One study – conducted by Dr. Ruth Itzhaki and colleagues, published in *The Lancet* in 1997 – found that when HSV-1 is present in the brains of individuals with a particular gene variant, apolipoprotein E epsilon 4 (APOE e4), those individuals have a strong risk of developing Alzheimer's disease. "We estimate that the likelihood of APOE e4 carriers with HSV-1 in the brain developing Alzheimer's disease is 12 times greater than for people with neither factor," said Dr. Itzhaki, a professor at the University of Manchester in the U.K. "Our research suggests that it is the combination of these two factors together that are damaging the brain, not either factor on its own."

Later research conducted by Dr. Itzhaki's research team showed that infecting human cell cultures with the herpes simplex virus causes the accumulation of amyloid-beta and abnormal tau proteins – both characteristic traits of Alzheimer's disease.

In the April 2018 issue of *Neurotherapeutics*, Dr. Nian-Sheng Tzeng and colleagues shared findings from their study involving more than 33,000 people in Taiwan (8,362 of whom were diagnosed with severe herpes simplex virus – either HSV-1 or HSV-2 – and the rest randomly-selected controls). Utilizing data from the National Health Insurance Research Database, they found that the risk of developing dementia was 2.56-fold greater in the HSV-infected group than in the control group. However, when the researchers compared those in the HSV-infected group who had been treated with antiviral drugs versus those in the group who had not, they discovered a dramatic impact on incidence of dementia;

> **THE RELATIVE RISK OF DEVELOPING DEMENTIA WAS REDUCED BY A FACTOR OF 10 FOR THOSE TREATED WITH ANTIVIRALS.** ⟶

HERPES VIRUSES (HERPESVIRIDAE)

There are more than 100 known herpes viruses. Eight of these routinely infect only humans:

- **herpes simplex virus type 1;**
- **herpes simplex virus type 2;**
- **varicella-zoster virus (chicken pox, shingles);**
- **cytomegalovirus;**
- **Epstein-Barr virus;**
- **human herpesvirus 6 (variants a and b);**
- **human herpesvirus 7; and**
- **human herpesvirus 8 (Kaposi's sarcoma).**

Herpes simplex virus type 1 (HSV-1) usually causes sores around the mouth, commonly referred to as cold sores. HSV-1 can also cause genital herpes, resulting in sores around the genitals or rectum, although most cases of genital herpes are caused by herpes simplex virus 2 (HSV-2). Both HSV-1 and HSV-2 are common, lifelong infections that frequently have no symptoms. Many people acquire HSV-1 early in life, and it is estimated that more than 9 in 10 people have been exposed to the virus by the time that they reach old age. HSV-2 is thought to affect 1 in 6 U.S. adults.

Human herpesviruses 6 and 7 are common viruses best known for causing roseola, a skin rash experienced by children.

Herpesviridae are so common that infection in the general population of one type or more is estimated to be close to 100%. In other words, almost all people carry at least one type of herpes virus, irrespective of whether or not they have ever experienced symptoms.

This was not the first study to examine the impact of HSV-antiviral agents on Alzheimer's disease. Dr. Itzhaki's team conducted a study (published in *PLOS ONE* in October 2011) to examine the effects of antiviral drugs on cell cultures acutely infected with HSV-1. The researchers found that the antiviral agents acyclovir, penciclovir, and foscarnet reduced the accumulation of amyloid-beta and abnormal tau proteins in the cell cultures.

These findings suggest that antiviral drugs for herpes infections might be used for preventing or treating dementia, although more research is needed. It is important to note, though, that the aforementioned studies focused on *severe* herpes infections, which are rare. Additional research is needed to learn about the effects of antivirals on other populations – for instance, individuals without dementia who have the herpes virus but are only experiencing mild symptoms or are asymptomatic, and those who already have dementia.

While much research has focused on HSV-1 (as it appears to be the most abundant type of herpes virus present in the brains of elderly people), other herpes viruses have also been linked to dementia. In a recent study from the Icahn School of Medicine at Mount Sinai, researchers found that two strains of human herpes virus – human herpes viruses 6a and 7 (HHV-6a and HHV-7) – are present in the brains of individuals with Alzheimer's at levels up to twice as high as in the brains in those without the disaese. The researchers also identified previously unknown networks in which viruses operate and influence known Alzheimer's genes. Their findings could potentially translate to the identification of virus or virus-related biomarkers that could be used for improved diagnosis. The findings also suggest a potential new direction for the search for drugs to prevent or treat Alzheimer's disease. This research was published in *Neuron* in June 2018.

WHAT MIGHT EXPLAIN THE HERPES-DEMENTIA LINK?

In a 2018 review paper published in *Frontiers in Aging Neuroscience*, Dr. Itzhaki proposes a "viral concept of Alzheimer's disease" as a possible explanation for the herpes-dementia link. As our immune systems weaken with age, the herpes virus makes its way into the brain where it remains in a mostly dormant state. "The viral concept proposes that the dormant HSV-1 virus is reactivated intermittently and leads to direct viral damage in infected brain cells and to viral-induced inflammation," explained Dr. Itzhaki. "Repeated activation causes cumulative damage, leading eventually to Alzheimer's disease in people who carry the APOE e4 gene allele. Our theory is that in APOE e4 carriers, there is more herpes-induced formation of toxic products in the brain or less repair of the damage, compared to non-APOE e4 carriers."

> **AN IMMUNE RESPONSE TO INFECTIONS, INCLUDING ONES THAT ARE MILD AND DO NOT INDUCE SYMPTOMS, MAY BE AT THE ROOT OF THE FORMATION OF TOXIC PRODUCTS – THE PLAQUES AND TANGLES ASSOCIATED WITH ALZHEIMER'S DISEASE.**

Research has shown that amyloid-beta (Aβ) is a natural antimicrobial that works to protect the brain from infection, and is not just a functionless, abnormal substance that sometimes appears and accumulates with age, as previously thought. So, when an infectious agent makes its way into the brain, the body's defense system activates and uses Aβ to surround the invader, which subsequently dies inside the Aβ "cage." The cage – which is essentially the plaque associated with Alzheimer's disease – gets left behind. This process has been confirmed in brain cells growing in the laboratory, as well as in simple organisms and mice. More research is needed to determine if a similar process occurs in human brains.

A group of Harvard Medical School researchers at Massachusetts General Hospital have recently proposed that the role of Aβ starts out as protective but then, in cases of Alzheimer's disease, becomes overactivated, causing neuroinflammation and widespread death of neurons. They refer to their theory as the "antimicrobial response hypothesis." In their 2018 research paper published in *Neuron*, the research team (Eimer et al.) suggest that several factors might be involved in mediating a shift of Aβ from protective to pathological: strength and persistence of the infectious agent, genetics, and environmental factors. With respect to genetics, for instance, individuals with a gene variant called APOE e2 have brains that seem to be successful at removing Aβ plaque, and have a low risk of developing Alzheimer's disease. Conversely, individuals with the APOE e4 gene variant have brains that appear to be inefficient at sweeping out Aβ plaque.

NO NEED TO WORRY

Dr. James Pickett, Head of Research at the Alzheimer's Society in the U.K., emphasizes the need for more research, and urges the public not to be worried about the latest findings regarding a herpes-dementia link. "Herpes is a hot topic in dementia research right now. Our researchers are hard at work to understand more about the diseases of the brain that do cause dementia, but there is still a lot to learn.

> "IT'S IMPORTANT TO REMEMBER THAT MOST PEOPLE WHO CARRY THE HERPES VIRUS – WHICH IS MOST OF US BY THE TIME WE RETIRE – WILL NOT DEVELOP DEMENTIA,

said Dr. Pickett. "So, the link between herpes and dementia isn't something that we feel people should worry about, although it's sensible general advice to seek treatment for persistent cold sores. Dementia is not contagious and should not be thought of as an infectious disease."

PAST THE CALL OF DUTY

Military Veterans' Risk of Dementia

Traumatic brain injury (TBI), post-traumatic stress disorder (PTSD), and depression have been associated with an increased risk of developing dementia, either each on its own or in combination with one another. This is of particular concern for military veterans because they are more likely than civilians to experience any or all of these risk factors. This article reviews what is currently known about the relationship between dementia and TBI, PTSD, and depression in the veteran population. →

VETERANS & TBI

TBI is a severe or moderate trauma to the head, where physical portions of the brain are damaged and functioning is impaired. There is growing evidence that TBI is associated with a variety of short- and long-term adverse health outcomes.

In one study published in 2014 in *Neurology*, the researchers sought to determine whether TBI is independently associated with the risk of incident dementia in older veterans after accounting for the competing risk of mortality and adjusting for potential confounders. The researchers analyzed data from the medical records of over 188,000 U.S. veterans aged 55 years or older. None of the participants had a dementia diagnosis at baseline.

"We found that during the nine-year follow-up period, 16% of participants with TBI developed dementia compared with 10% of those without TBI," explained Dr. Kristine Yaffe, a professor of psychiatry, neurology, and epidemiology at the University of California, San Francisco, and one of the authors of the study. In other words,

> OLDER VETERANS WITH TBI WERE 60% MORE LIKELY TO DEVELOP DEMENTIA, AND THEIR AGE OF DEMENTIA ONSET WAS APPROXIMATELY TWO YEARS EARLIER THAN THOSE WITHOUT TBI.

VETERANS & PTSD

PTSD is a common psychiatric syndrome associated with high rates of morbidity and mortality, and is one of the most common conditions in veterans returning from combat. The prevalence of PTSD is much higher among veterans (12% to 31%) than it is among the general population (7%). Multiple studies have found that veterans with PTSD are nearly twice as likely to develop dementia than veterans without PTSD.

The first study to demonstrate a link between PTSD and risk of dementia in the veteran population was conducted by Dr. Yaffe and colleagues, and published in June 2010 in *Archives of General Psychiatry*. In this study, the researchers analyzed the medical records of over 181,000 U.S. veterans aged 55 years or older (96.5% men), none of whom had a dementia diagnosis at baseline. "We found that the cumulative incidence rates of dementia were significantly higher for veterans with PTSD than those without the condition," said Dr. Yaffe.

Dysthymia, also referred to as persistent depressive disorder, is less severe than major depression, but more chronic. The disorder is characterized by depressed mood, experienced for most of the day, for at least two years.

"Over an average follow-up period of 7.2 years, 10.6% of those with PTSD developed dementia, whereas 6.6% of those without PTSD did." After adjusting for important differences between those with and without PTSD (such as demographics, as well as medical and neuropsychiatric comorbidities), the researchers concluded that the

> VETERANS WITH PTSD HAD ALMOST DOUBLE THE RISK OF DEVELOPING DEMENTIA COMPARED TO THOSE WITHOUT PTSD.

"Given how much more common PTSD is among veterans than the rest of the population, this finding of increased risk of dementia is of particular concern," emphasized Dr. Yaffe. "It is important that those with PTSD are treated, and that they are screened for cognitive impairment as they age."

VETERANS & DEPRESSION

Dr. Yaffe and colleagues conducted another study to investigate how dysthymia and depression affect the risk of dementia and mortality among older U.S. veterans. They analyzed the medical records of over 281,500 veterans aged 55 years or older, predominantly men, all of whom did not have dementia at baseline. Approximately 10% of the participants had a diagnosis of depression at baseline and almost 1% had dysthymia.

"We found that, over the follow-up period of an average of 7.2 years, patients with dysthymia or depression were twice as likely to develop dementia compared to participants without either of these diagnoses," explained Dr. Yaffe.

> OUR FINDINGS DEMONSTRATE THAT EVEN A MILD FORM OF DEPRESSION IS LINKED WITH INCREASED RISK OF DEMENTIA.

These findings were published in the August 2012 issue of *American*

Journal of Geriatric Psychiatry.

MULTIPLE RISK FACTORS

It is not uncommon for veterans to have more than one of these three conditions.

Veterans who have been diagnosed with TBI are more likely to also be diagnosed with PTSD, and have an increased risk of developing depression. PTSD also commonly co-occurs with depression. A large meta-analysis published in 2013 reported that 52% of individuals with current PTSD also had major depressive disorder. That percentage was higher among the subset of participants from the military.

The presence of multiple risk factors appears to heighten the risk of dementia. Dr. Yaffe and colleagues, for instance, found that the risk of dementia increased in an additive manner when TBI was combined with other medical and psychiatric comorbidities, including PTSD and depression.

RESEARCH ON FEMALE VETERANS

To date, only a handful of studies about the relationship between dementia and TBI, PTSD, and/or depression in the veteran population have included female participants. Recently, Dr. Yaffe and colleagues sought to address this research gap by exploring the risk of dementia among female veterans specifically. Their findings were published in December 2018 in *Neurology*.

> WE FELT THAT IT WAS IMPORTANT TO LEARN ABOUT HOW THESE CONDITIONS AFFECT WOMEN IN PARTICULAR, AS WOMEN ARE JOINING THE MILITARY IN INCREASING NUMBERS AND MORE ARE TAKING ON COMBAT ROLES, AND BECAUSE WOMEN MAY BE AT GREATER RISK FOR SOME OF THESE CONDITIONS THAN MEN.

The researchers reviewed the medical records of over 109,140 female veterans aged 55 years or older to identify who had a diagnosis of TBI, PTSD, or depression at baseline. There were approximately 81,135 women who had none of the conditions; 20,410 who had depression only; 1,363 with PTSD only; 488 with TBI only; and 5,044 with more than one condition. None of the women had dementia when the study began.

Over an average four-year follow-up period, 4,125 of the participants (4% of the entire group) developed dementia. Consistent with previous findings from research on the general public and male veterans, the researchers found a relationship between TBI, PTSD, or depression and incidence of dementia in this group of women. "After adjusting for demographics and medical conditions, we found that women with TBI, PTSD, or depression had a significant increase in risk of developing dementia compared to women without these diagnoses," explained Dr. Yaffe. "Women with one of these military-related risk factors had between a 50% and 80% increase in risk of developing dementia, while women with multiple risk factors had double the risk."

It is important to note, however, that although the study shows an association between these three conditions and dementia risk, it does not prove that there is a cause-and-effect relationship.

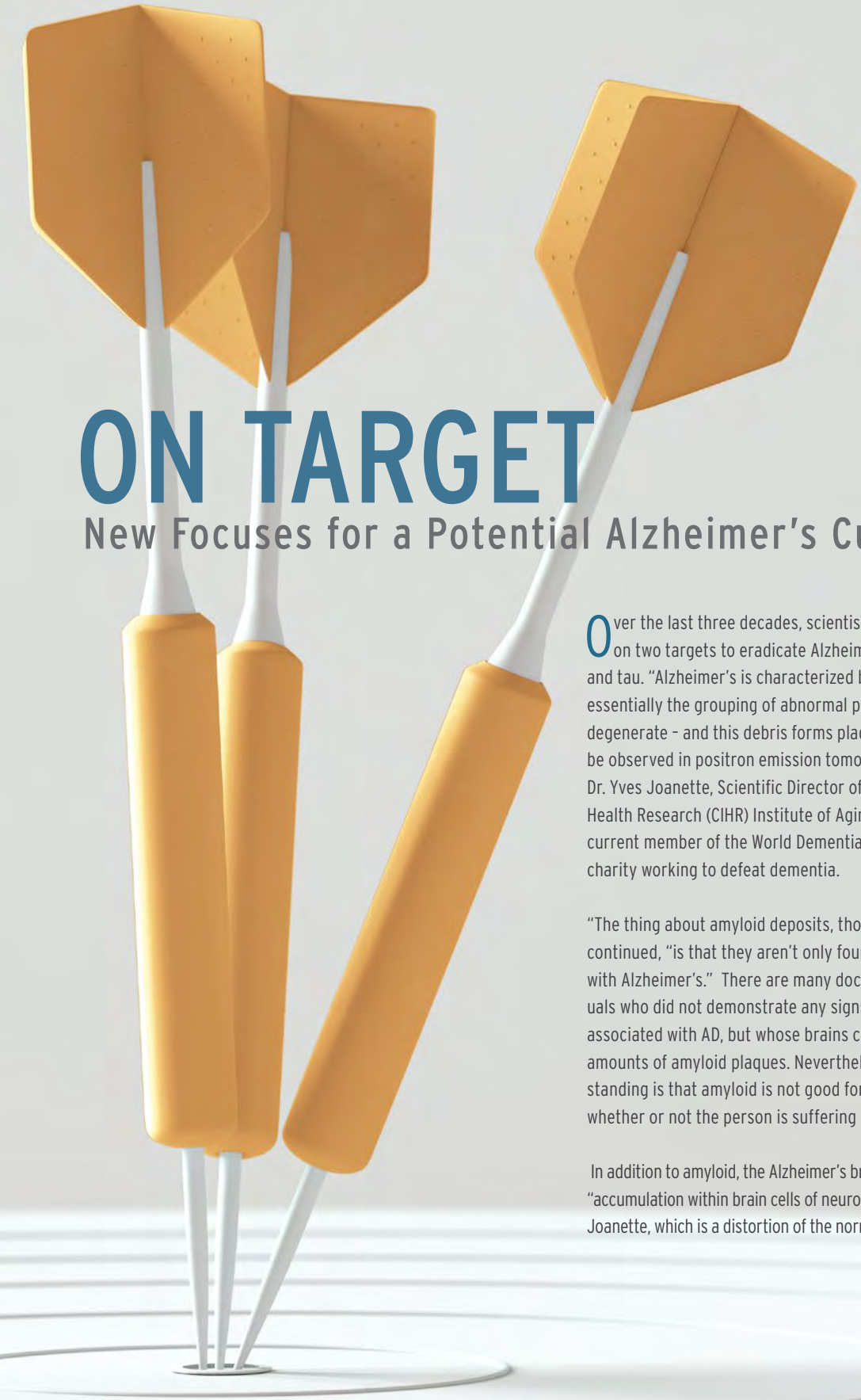
Additionally, the researchers used official diagnoses noted in the medical records in order to determine which participants had the various conditions. It is possible that there were additional women with these conditions, but had not been diagnosed because they exhibited less severe symptoms.

Finally, the overall risk for women veterans to develop dementia is low, even if TBI, PTSD, or depression is present. "Among the participants who had none of these conditions, 3.4% developed dementia, compared to between 3.9% and 5.7% for women who had any of the three conditions," explained Dr. Yaffe.

"I want to emphasize to female veterans that if they have one of these conditions, it is certainly not inevitable that they will develop dementia," Dr. Yaffe continued.

> THESE PERCENTAGES DEMONSTRATE THAT WHILE HAVING TBI, PTSD OR DEPRESSION DOES INCREASE RISK OF DEMENTIA, THE VAST MAJORITY OF FEMALE VETERANS – WITH OR WITHOUT THESE CONDITIONS – WILL NOT DEVELOP DEMENTIA.

"The findings from our various studies highlight the need for increased screening for TBI, PTSD, and depression among veterans, both female and male. Diagnosing and treating these conditions might help to reduce dementia risk."



ON TARGET

New Focuses for a Potential Alzheimer's Cure

Over the last three decades, scientists have focused primarily on two targets to eradicate Alzheimer's disease (AD): amyloid and tau. "Alzheimer's is characterized by deposits of amyloid – essentially the grouping of abnormal proteins that cause cells to degenerate – and this debris forms plaques in the brain," which can be observed in positron emission tomography (PET) scans, says Dr. Yves Joanette, Scientific Director of the Canadian Institutes of Health Research (CIHR) Institute of Aging, and former chair and current member of the World Dementia Council – an international charity working to defeat dementia.

"The thing about amyloid deposits, though," Dr. Joanette continued, "is that they aren't only found in the brains of people with Alzheimer's." There are many documented cases of individuals who did not demonstrate any signs or symptoms commonly associated with AD, but whose brains contained significant amounts of amyloid plaques. Nevertheless, scientific understanding is that amyloid is not good for the brain, irrespective of whether or not the person is suffering from AD.

In addition to amyloid, the Alzheimer's brain concurrently experiences "accumulation within brain cells of neurofibrillary tangles," explains Dr. Joanette, which is a distortion of the normal tau protein in the brain.

> THE MOST IMPORTANT DISCOVERY OVER THE LAST DECADE IS THAT THESE AMYLOID AND TAU TANGLE PHENOMENA ARE OCCURRING WELL BEFORE ANY CLINICAL SIGNS OF ALZHEIMER'S, SOMETIMES UPWARDS OF 25 TO 30 YEARS BEFORE.

The challenge, therefore, is to attack the abnormal build up of plaques and tangles early enough to prevent this mind-robbing disease from taking hold.

To date, much of the effort to prevent, slow, or reverse AD has focused on finding one drug that would eliminate the accumulation of amyloid and tau. "The area of dementia, for the pharmaceutical companies, has been the biggest nightmare in terms of negative results," says Dr. Joanette. While some possible drug options have shown promise in removing amyloid and tau deposits in animal studies, these treatments have failed in the critical "phase 3" human clinical trials. So far, experimental AD drugs have had a dismal track record, with more than 100 failures. Consequently, a one-size-fits-all solution to eliminate amyloid and tau build up may be too simplistic a target to find a cure for AD and other dementias.

In other diseases such as HIV, for instance, there are three to four drugs, well-balanced to each individual, that have been found to appropriately manage the disease, Dr. Joanette observes. And HIV is a single, simple virus, whereas AD and other diseases that cause dementia are now understood to be much more complex disease processes than initially thought, and therefore it makes sense that such diseases would also require multi-pronged approaches.

In fact, Dr. Howard Chertkow, the Scientific Director of the Canadian Consortium on Neurodegeneration and Aging (CCNA) and Senior Scientist at Baycrest's Rotman Research Institute in Toronto, says that we still do not even know what causes AD in the first place.

"JUST BECAUSE SOMETHING GOES ALONG WITH THE DISEASE (I.E. AMYLOID AND TAU), IT DOESN'T PROVE THAT IT CAUSES IT. ASSOCIATION IS NOT CAUSATION."

The difficulty in finding a treatment for AD arises, in part, from the lack of knowledge of the origin of the disease.

There has been nearly two decades of anti-amyloid therapy without convincing evidence of slowing Alzheimer's progression, says Dr. Chertkow. Amyloid and tau might be the result of having AD, rather than the initial cause, posits Dr. Joanette, which has propelled some researchers to query what causes the first changes in the brain that then leads to amyloid and tau tangles. Where amyloid and tau are concerned, there are still a few trials awaiting results. Dr. Chertkow warns, however, that if these clinical trials are not successful, then many members of the research community will likely declare the amyloid theory "if not dead, then at least on its deathbed."

In order to make a breakthrough in understanding and treating AD, scientists across the country and around the globe are beginning to look for "other approaches, other considerations, other things that might explain Alzheimer's disease," says Dr. Chertkow. The following is an overview of some of the latest trajectories of research.

OXIDATIVE STRESS AND FREE RADICALS

There is mounting evidence that free radical-induced oxidative damage may play a role in the pathogenesis of AD. Free radicals are created by unstable oxygen species in the brain, which in turn may attack and damage lipids, proteins, and DNA.

ALTHOUGH FREE RADICAL DAMAGE MAY BE A CONSEQUENCE OF NORMAL AGING, RESEARCHERS ARE INVESTIGATING HOW IT MIGHT AFFECT ABNORMAL AGING PROCESSES THAT OCCUR IN AD AS WELL.

Dr. Hyman Schipper, a Professor of Neurology and Medicine (Geriatrics) at McGill University in Montreal, has discovered an enzyme in the bloodstream that is related to oxidative stress – heme oxygenase-1 suppressor – that is nearly strong enough to be a diagnostic test for AD. There may be a genetic component to the free radical hypothesis since individuals who have the main risk gene associated with AD – Apolipoprotein E (APOE-4) – have been found "to be less protected from free radicals."

Those who have experienced head trauma, which is a known associated risk for AD also have more free radical damage, says Dr. Chertkow. Anti-oxidant therapy may be an approach to halt free radical damage, but more research is required to better understand this treatment option.

CHRONIC INFLAMMATION

Targeting specific elements of the inflammatory process could be useful in treating or preventing AD. Some researchers believe that there may be a "trigger that initiates the cascade of events that eventually causes neurodegenerative processes, which then causes amyloid deposits," observes Dr. Joanette.

"If you look at the plaques of Alzheimer's disease in the brain, you see inflammatory cells," says Dr. Chertkow. These cells could be a response to "some inflammatory agent we don't yet recognize, such as a virus or a fungus."

Researchers at McGill University are examining PET scans to →

observe the life cycle of inflammation in the brain.

EARLY ON, INFLAMMATION APPEARS TO BE A "PROTECTIVE" MECHANISM, BUT LATER BECOMES HARMFUL.

"It may not be a simple one-way story," says Dr. Chertkow. It could be that only some AD patients are highly affected by inflammation.

University of British Columbia's neuroscientist Dr. Patrick McGeer has suggested that a simple anti-inflammatory drug like Advil could work for AD, but there has been no research on this to date because the long-term use of ibuprofen can increase one's risk of other health problems, such as gastrointestinal issues.

GLUCOSE METABOLISM

PET scans of individuals with AD have shown that their brains do not absorb glucose in the same manner as healthy brains. In type 1 or 2 diabetes, not enough insulin (or no insulin) is produced to process glucose correctly or the body no longer responds to insulin, which affects the functioning of the entire body. In AD, it appears that a similar problem is occurring, but instead of causing problems in the body's functioning, the effects occur in the brain.

INDEED, SO CLOSE IS THE LINK BETWEEN AD AND DIABETES THAT SCIENTISTS HAVE OFTEN REFERRED TO THE DISEASE AS "TYPE 3 DIABETES."

There are currently trials underway in which researchers are administering intra-nasal insulin to participants in order to examine its effects on glucose activity, as well as research exploring the ways in which bypassing glucose altogether (for instance, through a ketogenic diet) might impact AD.

CASPASES

Dr. Andréa LeBlanc, a Professor of Neurology and Neurosurgery at McGill University and a researcher at the Bloomfield Center for Research in Aging in the Lady Davis Institute for Medical Research in Montreal, has been examining how changes in the levels of the caspases enzymes – those enzymes that play an essential role in regulating cell death – might be related to AD.

Dr. LeBlanc's research team detected changes in caspases levels very early on in individuals with AD, indicating that caspases may not only contribute to neurodegeneration, but also may promote the underlying pathology associated with the disease. Therefore, caspase inhibitors may prove to be an effective strategy for treating AD.

AMYLOID-PRECURSOR PROTEIN

The amyloid precursor protein (APP) has been investigated in connection with its role in AD due to its cleavage resulting in the production of the amyloid-beta protein that aggregates into the plaques characteristic of the disease. Clinical trials are underway to determine whether removing APP will cease amyloid production.

The problem, though, is that APP is thought to play a key role in neural growth and repair. One theory is that the fatty/lipid surface of the cells that this protein interacts with could be compromised in some way (interestingly, APOE-4 is involved in carrying fats/lipids). Omega fatty acids are therefore being considered in new research, as well as medications that could excise lipids that are "too thick" (i.e. those that would then go on to form amyloid deposits).

VASCULAR FACTORS

Recently, there has been keen interest in vascular factors that may increase the risk of developing AD. Diabetes, a high level of cholesterol, and tobacco smoking, for instance, have each been associated with a higher risk of AD.

THE TREATMENT OF ONE OF THE IMPORTANT ATHEROSCLEROTIC VASCULAR RISK FACTORS, HYPERTENSION, HAS BEEN SHOWN TO REDUCE THE RISK OF DEMENTIA, INCLUDING AD OR VASCULAR AND MIXED DEMENTIAS.

"There is clearly a strong interplay between vascular and brain health," says Dr. Chertkow. "Vascular changes are happening earlier and more frequently than we realize – not only when an individual has suffered a stroke, but even without clear events in individuals with diabetes, hypertension, and other vascular risk factors." Accordingly, controlling vascular factors may be an important mechanism for the prevention of AD.

COGNITIVE RESERVE

"If you look at the brains of people with Alzheimer's, it is now becoming clear that you don't just see amyloid, you see multiple forms of pathology, multiple abnormalities," says Dr. Chertkow. "There are dozens of combinations of pathologies. Maybe what we call Alzheimer's is a final common pathway for diseases that affect the cortical cells."

Defeating AD could be less about finding solutions to "this protein or that protein," says Dr. Chertkow, and more about focusing on strengthening what is referred to as "cognitive reserve," which describes the mind's resilience to damage of the brain.

RESEARCH HAS SUGGESTED THAT THE EXTENT OF SOMEONE'S COGNITIVE DECLINE DOES NOT CORRESPOND WITH THE AMOUNT OF BIOLOGICAL DAMAGE IN HIS OR HER BRAIN AS IT AGES.

Rather, certain life experiences determine someone's cognitive reserve and, therefore, his or her ability to avoid dementia

or memory loss. In this way, some people have better cognitive reserve than others, and are better at withstanding the effects of certain pathological proteins as they age.

Several studies have indicated that engaging in activities that stimulate cognition (such as learning a new language, completing crosswords, and having high levels of social interaction), as well as exercising regularly, can help improve one's cognitive reserve and thereby reduce the risk of developing dementia. Dr. David Bennett, the Director of the Rush Alzheimer's Disease Center in Chicago, is currently investigating the molecular basis of cognitive reserve in order to produce a drug that would boost it.

GEROSCIENCE

While we all know it, we often forgot that the main risk factor for AD and other forms of dementia is age, says Dr. Joanette. Researchers are therefore examining "the relationship between the biology of aging itself and what's going on to trigger neurodegenerative diseases and other chronic diseases."

Perhaps the biology of aging is interacting with other bodily systems and issues such as late-life diabetes or arthritis. More research is being conducted on these types of questions in a new area of research referred to as "GeroScience." Just last year, CIHR launched a call to support grants for researchers in this nascent field of study.

GUT MICROBIOME

The human body is host to trillions of microbes. In fact, slightly more than half of the cells found in our bodies are microbes – mostly bacteria, but also fungi, viruses, protozoa, archaea, and other microorganisms. The majority of these microbes reside in the gastrointestinal (GI) tract – commonly referred to as the "gut" – and the rest can be found in different parts of the body, including on the skin, in the urogenital tract, and in the nasal, oral, and otic (ear) cavities.

Microbes handle a variety of essential and beneficial functions in the human body. They play a fundamental role in digestion, nerve cell growth and survival, immunity, and inflammation.

EVIDENCE IS EMERGING THAT SUGGESTS THAT MICROBES AFFECT COGNITION, BEHAVIOUR, AND MENTAL HEALTH, PARTICULARLY THROUGH INTERACTIONS BETWEEN THE GUT MICROBES AND THE CENTRAL NERVOUS SYSTEM, COMMONLY REFERRED TO AS THE "GUT-BRAIN AXIS."

As such, researchers are now exploring the role of gut bacteria in the development and treatment of AD. The Wisconsin Alzheimer's Disease Research Center, for instance, found that individuals with AD have different gut microbiome compositions than those without the disease. It is an emerging area of research that might yield novel treatments for AD in the future – including using probiotics as a preventative measure and fecal transplants for those already afflicted with the disease.

PORPHYROMONAS GINGIVALIS

According to new research published in *Science Advances* in January 2019, there may be a relationship between a common bacterium known as Porphyromonas gingivalis (Pg) – which is found in our mouths and causes gum disease – and the development of AD. In addition to Pg itself, the research team detected the organism's toxic proteases (referred to as "gingipains") in the neurons of patients with AD.

The researchers posit that targeting gingipains may reduce neurodegeneration in AD. Human clinical studies are about to commence with small-molecule gingipain inhibitors that were found to protect neouronal cells against Pg in the animal studies.

IMPORTANTLY, RESEARCHERS ARE NOW MORE AWARE THAT GIVEN THE COMPLEXITIES OF AD, CONQUERING THE DISEASE WILL INVOLVE MULTI-PRONGED INTERVENTIONS.

Each of the new areas of research might in fact be part of the "initial triggering of the cascade of events that eventually turns into a neurodegenerative process, which then turns into the amyloid and tau changes," says Dr. Joanette.

Instead of a single drug, then, it is more likely that individuals with AD will be prescribed several medications at once, similar to the treatment of HIV. Moreover, a growing body of evidence suggests that interventions will not just involve pharmacological solutions, but also behavioural modifications, such as changing one's diet and sleep habits, and engaging in physical exercise.

It also means that collaboration between researchers, academia, and industry is more important now than ever. This is part of the reason why the Canadian Consortium on Neurodegeneration and Aging (CCNA) was created, which is a significant investment on the part of the Canadian government, and industry organizations like Women's Brain Health Initiative and the Alzheimer's Society. The consortium encourages data pooling, as well as national and international collaboration.

"I strongly believe that no country, no sector alone will crack the code – we need to work together here," says Dr. Joanette. Canadian researchers are already sharing data with U.S. and European collaborators in over 30 countries. "We should be more optimistic now than we were five years ago," says Dr. Joanette, "when the approach was same-old, same-old, and probably naïve in its search for a single solution."

DAZED & CONFUSED

Brain Fog During the Menopause Transition

It is common for women to experience cognitive difficulties, sometimes referred to as "brain fog," as they go through the menopause transition. They might be forgetful, or have trouble concentrating or thinking clearly. In one study, approximately 62% of midlife women self-reported an undesirable change in memory.

Objective measurements of cognitive function (i.e. using standardized neuropsychological tests) have shown that women's perceptions are accurate.

> PERIMENOPAUSAL WOMEN DO APPEAR TO EXPERIENCE A DOWNWARD SHIFT IN SOME ASPECTS OF COGNITIVE FUNCTION, DEMONSTRATED BY POORER PERFORMANCE ON NEUROPSYCHOLOGICAL TESTS, COMPARED TO PREMENOPAUSAL AND POSTMENOPAUSAL WOMEN.

In one longitudinal research study conducted by Dr. Gail Greendale and colleagues, over 2,300 participants from the U.S. Study of Women's Health Across the Nation (SWAN) completed multiple cognitive tests over a four-year period. Consistent with transitioning women's perceived memory difficulties, perimenopause was associated with a subtle reduction in cognitive performance, characterized by an absence of a learning effect with repeated testing. This effect, however, was only temporary, with the participants' performance rebounding to premenopausal levels in postmenopause. These findings – published in the May 2009 issue of *Neurology* – suggest that cognitive difficulties during the menopause transition may be time-limited.

In another large, longitudinal study conducted by Dr. C. Neill Epperson and colleagues, the researchers examined menopause →

In a **longitudinal study**, researchers collect data about the same participants over a period of time, sometimes many years. This allows researchers to examine changes over time within individuals, as well as across the entire group as a whole.

When individuals take cognitive tests repeatedly over time (as is the case in longitudinal studies), it is the norm that their scores will improve with each subsequent taking of the test because of practice/familiarity. This is referred to as a "**learning effect**" or "practice effect."

effects on verbal memory in particular, using various endocrine, behavioural, and cognitive assessments. The researchers wanted to determine whether there was an objectively-measured decline in cognition during the natural menopause transition that exceeded what would be expected with normal aging.

A total of 403 women who were enrolled in the Penn Ovarian Aging Study participated in this research, undergoing annual assessments over a 14-year period from pre- to postmenopause. The researchers discovered a decline in verbal memory performance during the natural menopause transition that was independent of the typical effects of aging.

They observed an actual worsening of performance on the cognitive tests over time, not just a failure to demonstrate practice-associated improvements. The overall decline in verbal memory was modest, but sufficient to validate women's self-reported experiences of memory decline during the menopause transition. These findings were published in the September 2013 issue of *The Journal of Clinical Endocrinology & Metabolism*.

POTENTIAL FACTORS INFLUENCING MENOPAUSAL BRAIN FOG

Historically, women's self-reported complaints about brain fog were often attributed to life stress commonly experienced during midlife, as opposed to actual changes in a woman's body as a result of menopause.

SCIENTISTS HAVE NOW DEMONSTRATED, THOUGH, THAT MENOPAUSE PLAYS A DIRECT ROLE IN THE COGNITIVE DEFICITS THAT WOMEN EXPERIENCE IN THEIR 40S AND 50S.

Although the factors contributing to menopause-associated alterations in cognitive function are not yet fully understood, there are two pathways thought to underlie these changes, independently or in combination: (1) direct effects of estrogen; and (2) symptoms associated with the menopause transition.

ESTROGEN'S POTENTIAL ROLE

Estrogen influences hippocampal and prefrontal cortex function, thereby affecting the cognitive functions associated with these brain regions, including verbal memory and executive function. A 2014 review of over 15 years of research found that, in women aged 60 years and older, higher estradiol levels were potentially associated with better memory performance across multiple domains. (This research was conducted by Dr. Lisa Boss and colleagues, and published in *Western Journal of Nursing Research*.)

A logical hypothesis, therefore, might be that as estrogen levels lower during the menopause transition, women experience cognitive challenges.

> HOWEVER, A PREDICTABLE, LINEAR RELATIONSHIP BETWEEN ESTROGEN LEVELS AND COGNITIVE FUNCTION HAS NOT BEEN FOUND.

For starters, while all women experience declines in estrogen levels during the menopause transition, not all women experience menopause-related cognitive difficulties. Moreover, the 2009 research conducted by Dr. Greendale and colleagues found that cognitive function rebounded after a woman passed from perimenopause (when estrogen levels fluctuate significantly) into postmenopause (when estrogen levels are at their lowest).

POTENTIAL IMPACT OF MENOPAUSE SYMPTOMS

Scientists have further hypothesized that symptoms commonly associated with the menopause transition, such as hot flashes, sleep disruption, and depression, may account, at least in part, for menopausal brain fog. The findings on this matter to date, however, have been inconsistent, perhaps because of differing research methodologies.

Some research has found that menopause symptoms do not appear to account for perimenopausal declines in cognitive function. For example, a longitudinal study conducted by Dr. Greendale and colleagues – published in the 2010 issue of *American Journal of Epidemiology* – examined 1,903 midlife U.S. women over a period of six years and considered two questions: (1) whether menopause-associated symptoms were related to cognitive function; and (2) whether such symptoms were responsible for the negative effect of perimenopause on cognitive performance.

The researchers investigated four common menopause-associated symptoms: depressive, anxiety, sleep disturbance, and vasomotor (e.g., night sweats and hot flashes). They found that although there was a link between depressive and anxiety symptoms and poorer cognitive performance, none of the four symptoms accounted for the temporary declines in memory, learning, and how fast the brain processes information during the menopause transition.

One small-scale study of 29 women – conducted by Dr. Pauline Maki and colleagues, and published in 2008 in *Menopause* – found that subjectively-measured (i.e. self-reported) hot flashes did not predict verbal memory performance. However, the researchers discovered that when moderate-to-severe hot flashes were objectively measured using a portable monitoring device, they were, in fact, related to declines in verbal memory.

> IN THIS STUDY, WE HAD PARTICIPANTS RECORD THE HOT FLASHES THEY NOTICED IN A DIARY WHILE WEARING A MONITOR AT THE SAME TIME,

explained Dr. Maki, a Professor of Psychiatry and Psychology at the University of Illinois at Chicago. "This research approach revealed a very interesting finding: that the women were experiencing quite a few more hot flashes than they were self-reporting. We discovered that on average, the women underreported the number of hot flashes they had by 43%."

"This study revealed that objective, but not subjective, hot flashes are indeed linked to poorer verbal memory in midlife women with moderate-to-severe vasomotor symptoms," continued Dr. Maki. The data suggested that this relationship was primarily due to nighttime rather than daytime hot flashes. The researchers therefore thought that perhaps it was sleep disruption caused by hot flashes that was negatively affecting cognitive function. When they analyzed the results in a way that allowed them to isolate the effects of sleep duration and nighttime hot flashes, though, each of those variables independently contributed to impaired verbal memory.

"This 2008 study suggested that interventions to address hot flashes might provide cognitive benefit to women who experience moderate-to-severe symptoms," said Dr. Maki. "We tested that theory in a later study – published in *Maturitas* in 2016 – and demonstrated that cognition does rebound when hot flashes are treated."

WHAT MIGHT EXPLAIN THE POSTMENOPAUSE BOUNCE BACK IN COGNITIVE PERFORMANCE?

> **RESEARCH SUGGESTS THAT PERIMENOPAUSAL BRAIN FOG IS USUALLY NOT PERMANENT, NOR A SIGN OF A MORE SERIOUS CONDITION LIKE DEMENTIA.**

Although many women experience a subtle decline in cognitive performance compared to premenopause, their performance bounces back to premenopausal levels once they reach postmenopause.

Interesting research involving brain scans has provided some insight into what is occurring in a woman's brain as she progresses through the various stages of menopause. "Women's brains appear to adapt as they progress through the menopause transition. Their brain circuitry actually changes," explained Dr. Maki.

"Neuroimaging studies have shown that during pre- and perimenopause, the left side of the brain is primarily engaged to accomplish memory tasks. Postmenopausal women use both sides of the brain, though. It seems that the lower the estrogen levels, the more the two hemispheres of the brain are functionally connected."

"There is still a lot more to learn about cognitive function during the menopause transition," continued Dr. Maki, "but women can take heart in the findings to date that indicate memory function appears to be most affected – and in only a subtle way – during perimenopause, but then rebounds."

MIND THE GAP

Sex and Gender Differences in Alzheimer's Disease

Approximately two-thirds of those diagnosed with Alzheimer's disease (AD) are women. However, research into sex and gender differences in AD is astonishingly limited. Because the greatest risk factor for dementia is age, the discrepancy between the sexes has historically been attributed to the longevity of women.

While it is true that women generally live longer than men, we also now know that Alzheimer's is a disease that begins years, or even decades, before the onset of overt symptoms. A growing body of research suggests that there may be unique biological reasons for these differences, as well as related genetic, lifestyle, and societal factors at play.

In recent years, due to the significant shift towards precision medicine, the scientific community has started to look further into why women are more likely to develop AD than men. In contrast to the "one-size-fits-all approach," precision medicine (also referred to as personalized or individualized medicine) aims to optimize the effectiveness of disease prevention and treatment, and minimize side effects for those less likely to respond to a particular therapeutic, by considering an individual's specific pattern of genetic variability, environment, and lifestyle factors.

The concept that a treatment option might work well in some patients and not as well in others is consistent with an emerging sense that AD may be several different diseases, as well as the idea that genetic factors predispose some individuals to AD while protecting others.

Although substantial advances in precision medicine have been made over the past years for some diseases (particularly in cancer care), for most other diseases – including AD – precision medicine is only in its beginning. Part of the customization of precision medicine includes examining the ways in which sex and gender are implicated in disease processes.

> **IN THE CONTEXT OF AD, PROGRESS TOWARDS SEX AND GENDER INTEGRATION IN RESEARCH HAS LAGGED BEHIND.**

To improve the diagnosis of the disease, and to accelerate the development of new treatments and interventions, sex and gender differences must be better understood and measured.

Since its launch in 2012, Women's Brain Health Initiative (WBHI) has worked incessantly to help transform the international conver- →

sation around dementia, and has quickly become an important, trusted voice across the globe for women's brain health.

WBHI has forged strategic alliances within the scientific and medical communities both in Canada and abroad. For instance, WBHI supports the Canadian Consortium on Neurodegeneration in Aging (CCNA), which includes approximately 340 researchers across the country, where sex and gender considerations are now being taken into account as part of research practice. In 2015, WBHI partnered with other esteemed organizations from the U.S., the U.K., and Canada to form the Global Alliance on Women's Brain Health, which advocates for gender-sensitive focus and investment.

More recently, WBHI was the driving force behind the funding and creation of the world's first Research Chair in Women's Brain Health and Aging, awarded to Dr. Gillian Einstein at the University of Toronto. This initiative has helped make Canada a world leader in exploring the sex-gender divide.

In the U.S., the Society for Women's Health Research (SWHR) has similarly worked towards correcting imbalances in health care for women by addressing unmet needs and research gaps in women's health. In 2016, the SWHR convened an expert panel of clinicians and scientists to review ongoing and published research related to sex and gender differences in AD. The results of that exploration were published in the June 2018 issue of *Alzheimer's & Dementia: The Journal of the Alzheimer's Association* in a groundbreaking paper entitled "Understanding the impact of sex and gender in Alzheimer's disease: A call to action."

"In the past, sex had initially been adjusted for," says Dr. Michelle Mielke, an Associate Professor in the Departments of Epidemiology and Neurology at the Mayo Clinic in Rochester, Minnesota, and one of the paper's authors. In other words, any differences noted in research inquiries were removed from the equation, rather than factored in.

> SEX AND GENDER HAS BEEN SEEN MORE AS A NUISANCE OR LABEL AND PEOPLE HAVE PREVIOUSLY UNDERSTOOD THAT THERE ARE DIFFERENCES, BUT IT WASN'T A FOCUS OF THE RESEARCH.

Much of what is known to date about sex and gender differences in disease formation has come from those innovative researchers who, as they were conducting analyses, "realized that there were differences in sex, and the more they looked at it, the more differences they saw," explains Dr. Mielke. Now, though, structural change is beginning to occur. The major Canadian, European, and U.S. funding agencies, since 2010, 2014, and 2015 respectively, have created and implemented policies that require researchers to include sex as a variable in research design and in the reporting of research findings. It is an important step in the long road ahead.

THE CANADIAN INSTITUTES OF HEALTH RESEARCH (CIHR) DEFINITIONS OF SEX AND GENDER:

SEX refers to the biological and physiological distinctions between men and women – for instance, differences in hormones that impact men and women on the cellular, organ, and systems levels.

GENDER, on the other hand, refers to the socially-constructed roles, expectations, behaviours, relationships, relative power, and other traits that societies ascribe to women, men, and people of diverse gender identities. These structural gendered differences can have real, tangible effects on an individual's bodily experience.

> **ONE OF THE MOST SIGNIFICANT SEX-BASED DIFFERENCES THAT HAVE BEEN DISCOVERED IS THAT WOMEN WITH THE APOE E4 GENE ARE AT GREATER RISK FOR DEVELOPING AD THAN MEN WITH THAT SAME GENE.**

"Although it's a genetic risk factor for both sexes, women are more vulnerable to that genetic risk factor than men," says Dr. Pauline Maki, a Professor of Psychiatry and Psychology and Associate Director of the Center for Research on Women and Gender at the University of Illinois at Chicago, and co-senior author on the paper. "Among persons aged 65 to 75 years with the APOE e3/e4 genotype, the risk of AD dementia is fourfold higher in women than that in men." Unfortunately, the reasons as to why this is the case remain elusive.

Another key sex-based difference between men and women is hormonal. For instance, a woman's brain undergoes a considerable change in function and structure during menopause and, according to Dr. Maki, researchers are just beginning to examine whether this critical female-specific life event might in some way set up, for at least a portion of women, AD later in life. Women who have their ovaries removed before a natural menopause are at a "70% increased risk in cognitive impairment or dementia," says Dr. Maki.

If women take estrogen until the age of 50, though, that risk factor is eliminated. "That tells us in a fundamental way that estrogen, created from the ovaries, protects our brains," says Dr. Maki. Of course, while all women go through menopause, not all women develop AD. It is therefore important not to "pathologize what's normal." Nevertheless, researchers still need to uncover why for certain women "this reproductive event is the perfect storm," notes Dr. Maki.

A further difference between the sexes is that "women have a lifelong advantage in verbal memory," says Dr. Rebecca Nebel, Director of Scientific Programs at the SWHR, and one of the paper's authors. While this advantage may benefit women by delaying verbal memory impairment until more advanced pathology, it may also delay diagnosis and treatment intervention. Many of the tests that are used to diagnose AD depend on verbal memory acuity.

Despite having an inherent advantage, women are assessed the same way as men, using the same cutoff score (which is an average of both men and women's scores).

> CONSEQUENTLY, WOMEN ARE OFTEN DIAGNOSED WITH THE DISEASE LATER THAN MEN, AND IT HAS BEEN HYPOTHESIZED THAT THIS DELAYED DETECTION COULD BE PART OF THE REASON WHY WOMEN DECLINE MORE RAPIDLY AFTER DIAGNOSIS.

In light of this difference between the sexes, researchers need to rethink how AD and other forms of dementia are initially recognized, and perhaps institute different testing mechanisms and/or use sex-specific cutoff scores, says Dr. Nebel.

With respect to gender-specific risk factors, it is important to note that while they are unique, they cannot be completely isolated from sex, says Dr. Mielke. These risk factors include exercise (women exercise less than men, and we know exercise is protective) and marital status (men who are not married or are widowed have a greater risk of developing AD, perhaps because single women are more likely to see a health-care provider and to engage in social activities). Women are more likely to be caregivers, which is associated with elevated levels of cortisol and impaired attention and executive functioning. Caregiver spouses may also be at a higher risk of developing dementia. Much more research is needed to understand these gender differences and to fill the knowledge gaps.

To promote future research, the paper's authors identified twelve "high-priority areas" that warrant further investigation:

- the extent to which differences in longevity, survival bias, and comorbidities impact sex and gender differences in AD;
- potential risk factors that affect only one sex, such as pregnancy and menopause for women and testosterone loss for men;
- the influence of estrogens and hormone therapy on brain function and disease risk;
- possible sex differences in genetic risk factors, such as in the case of APOE e4 carriers;
- how sex and gender may be differently implicated in AD in risk factors that both sexes experience, including cardiovascular disease, diabetes, education, and depression;
- sex differences in disease progression and change in cognitive function, neuroimaging, cerebrospinal fluid, and biomarkers;
- whether sex differences in brain development impact sex differences in brain aging and disease pathology;
- sex and gender differences in racial and ethnic subgroups;
- societal, political, and geographical changes in estimates of sex differences in AD;
- gender differences in caregiving and how the burden of caregiving influences AD risk for the caregiver;
- variances in the development of therapeutics in preclinical and clinical studies, as well as in designing clinical trials; and
- differences on clinical detection, diagnosis, management, and treatment of AD for men and women.

It is important to remember that focusing the conversation on sex and gender is beneficial for both men and women. "We're trying to find individualized approaches for both sexes and genders," says Dr. Mielke. The hope is that the call-to-action paper will motivate the industry, academia, and the government to change the ways in which research is conducted and, specifically, improve the integration of sex and gender at all stages of the research process.

INSIDE THE LAB

Your Best Interests in Mind

with Dr. Gillian Einstein

The centre of world-leading research into women's brain health and aging can be found in a windowless lab on the ground floor of the University of Toronto's Sidney Smith Hall – a communal, computer-filled workspace with adjacent testing rooms, which include a magnetic resonance imaging (MRI) scanner.

On a recent Tuesday afternoon, a handful of women and one man gathered and opened their laptops to commence their regular weekly meeting. On one computer screen was the face of a colleague joining via Skype from Montreal. The room was decorated with posters by the cartoonist Soglow and the sculptor Alexander Calder.

While their project may have profound implications, the atmosphere was casual, unassuming, and welcoming.

The team leader Dr. Gillian Einstein made a point of highlighting the accomplishments of a student who entered the room after the meeting started, named Elizabeth Baker-Sullivan. Dr. Einstein pointed out that she had helped them establish the participant database and flagged potential participants for eligibility. Of Baker-Sullivan's contributions, Dr. Einstein said, "You just see these talents emerge."

Dr. Einstein currently holds the Wilfred and Joyce Posluns Chair in Women's Brain Health and Aging,

THE FIRST RESEARCH CHAIR IN THE WORLD DEVOTED TO IMPACTING AND ENHANCING RESEARCH ON SEX AND GENDER DIFFERENCES IN BRAIN HEALTH.

When Dr. Einstein started this lab in 2006, it was just her and one or two associates. Now, she is enthusiastic to have more compatriots, students, and postdoctoral fellows joining her on the journey.

"It's great. I love it! They're so excited about the work and I love thinking that these guys will have their own labs someday and carry it forward," she said in an interview later in her office.

"You need a critical mass working on a project, and we've got that now."

The subject of the meeting was the challenging task of recruiting participants for their studies. The research team works in cooperation with various Toronto hospitals, as well as one in Sweden and one in Montreal, where they recruit patients who might be suitable for the project. They are focusing on women who have had their ovaries removed (ovariectomy or oophorectomy) in young and middle age (before the age of 50) as a precautionary measure because they carry a gene (BRCA1/2) that puts them at high risk of developing breast and ovarian cancer.

THE RESEARCHERS WANT TO DETERMINE HOW THE RESULTANT CHANGES IN ESTROGEN LEVELS AFFECT COGNITION, WHICH THEY FEEL MAY ULTIMATELY CONTRIBUTE TO UNDERSTANDING WHY WOMEN SUFFER FROM ALZHEIMER'S DISEASE MORE OFTEN THAN MEN.

To maintain appropriate scientific rigour for their study, the research team must ensure consistency in the medical histories of each

subject. At this meeting, they were considering whether two new potential recruits met the inclusion criteria for the control population. Dr. Einstein quizzed post-doctoral researcher Nicole Gervais about the women's ages and whether they had already gone through menopause naturally before ovarian removal (which might indicate other endocrine issues that would complicate the interpretation of their results).

They then moved onto a discussion of their research questionnaire for the second year of testing. Not wishing to overwhelm their participants, they had whittled 80 questions down to 30 and were now examining every word of every sentence in order to ensure clarity.

Concerned that the participants might overlook an important question about how long they had received hormone replacement therapy, Dr. Gervais recommended that they write the question in bold face type. Then they also decided to write the term out in full (as opposed to using the abbreviation "HRT"), so that there would be no confusion.

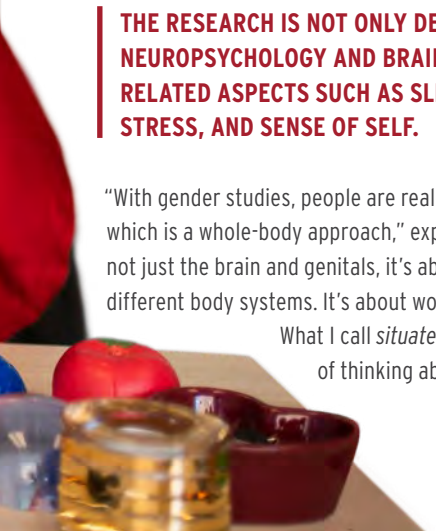
It is a painstaking, but essential process. When the time comes to have papers peer reviewed, the researchers can expect to be interrogated about whether they have sufficient numbers of participants, whether participant medical histories are consistent with the underlying research question, and whether the questionnaires are clear and pertinent. Details matter at this level of scientific research. There is a constant tension in the recruitment process – the researchers need to recruit enough women to get a valid sample, but they also need to ensure that the participants meet the study's criteria.

"That's why I like having these meetings," said Dr. Einstein. "We are strengthening the science." It is a project drawing interest across the globe, with Dr. Einstein asked regularly to speak about it.

She thinks people are intrigued by the depth and breadth of the work.

> **THE RESEARCH IS NOT ONLY DEALING WITH NEUROPSYCHOLOGY AND BRAIN IMAGING, BUT ALSO RELATED ASPECTS SUCH AS SLEEP, INFLAMMATION, STRESS, AND SENSE OF SELF.**

"With gender studies, people are really interested in the approach, which is a whole-body approach," explained Dr. Einstein. "It's not just the brain and genitals, it's about the interaction of the different body systems. It's about women's whole lives actually. What I call *situated neuroscience*, another way of thinking about the brain in context."



The mission statement on Dr. Einstein's website summarizes her work:

> THE EINSTEIN LAB EXPLORES HOW "THE WORLD WRITES ON THE BODY" ... BY STUDYING HOW HEALTH CONDITIONS MORE COMMON IN WOMEN AND GENDER-DIVERSE INDIVIDUALS AFFECT BRAIN FUNCTION AND COGNITION. OUR GOAL IS TO UNDERSTAND HOW SEX AND GENDER INFLUENCE BRAIN HEALTH, MEMORY, AND AGING.

It is an intriguing image: "how the world writes on the body." When asked to explain the concept, Dr. Einstein noted that she does not believe it is possible to think of one's life experiences as separate from biology. "The social becomes biological. You can think of people doing a certain kind of work that shapes the way their bodies are, literally. If people undergo certain types of surgery, then that shapes the way their bodies are. For instance, if women have their ovaries removed, that changes their brains."

It is through observing and testing their participants in Toronto, Montreal, and Sweden that Dr. Einstein's research team hopes to find answers. There are both written and verbal cognition tests, as well as MRI scans to look for physical changes in the participants' brains. It is suspected that lower estrogen levels might be related to the higher rates of dementia in women, although Dr. Einstein is reluctant to draw any definitive conclusions at this time. There are several papers coming close to publication, possibly within the year.

She hopes that her work will provide both doctors and patients with a fuller picture of the impact of ovarian removal surgery, giving women more information about the potential risks and ramifications so that they can make informed decisions.

Dr. Einstein is also interested in studying the trans population and, specifically, the impact of long-term hormone treatment. The aim of hormone treatment in transgender people is to adjust their secondary sex characteristics to be more congruent with their experienced gender. Dr. Einstein has already conducted studies with trans men, but would also like to conduct research with aging trans women, as there is very limited research in this area.

It all supports progress towards a broader goal. "I am interested in ultimately knowing why more women than men have Alzheimer's disease, and how estrogen loss plays a role in that," said Dr. Einstein.

A better understanding of the early signs of Alzheimer's disease and other forms of dementia could translate into earlier diagnosis and intervention – all raising the tantalizing prospect of reversing the devastating effects of these mind-robbing diseases.

INSIDE THE LAB

Hedging Your Bet

with researcher Dr. Anne Almey

For any researcher, the prospect of shedding light on an under-studied field is an intriguing opportunity. Dr. Anne Almey was drawn to explore the complex interaction between hormones and cognition in women – an area that has, until recently, garnered little attention.

"There's not a lot of research on female-specific conditions and the particular roles that hormones like estrogen and progesterone play in cognition. I feel that work fell at the wayside for a while. So, I get to contribute to righting that wrong," Dr. Almey said in a telephone interview from her office at the Douglas Mental Health Institute in Montreal.

Dr. Almey is the recipient of the Posluns Postdoctoral Fellowship in Women's Brain Health and Aging. Although based in Montreal with an affiliation with McGill University, she is also part of the research team at the Einstein Lab, which is centred at the University of Toronto.

Despite the fact that women suffer from dementia twice as much as men, and an astounding 70% of new Alzheimer's patients will be women, the majority of research for brain-aging diseases has focused primarily (if not entirely) on men. "It does represent some level of institutionalized sexism," she said.

DR. ALMEY HOPES TO CLARIFY THE ROLE THAT ESTROGEN PLAYS IN COGNITIVE AND NEUROBIOLOGICAL FUNCTIONING IN WOMEN, AND PERHAPS CONTRIBUTE TO TREATMENTS TO SLOW THE PROGRESSION OR PREVENT THE DEVELOPMENT OF ALZHEIMER'S DISEASE IN WOMEN.

Her interest in sex differences in cognition and behaviour began early in her career during her undergraduate thesis, which examined sex differences in social learning and aggression in rodent models, as well as the role that estrogen played in these sex differences. Her graduate studies examined the contribution of estrogen to numerous dopamine-dependent cognitive processes, including selective attention, reversal learning, and perseveration.

Now, as a postdoctoral researcher with the Einstein Lab, Dr. Almey has moved on to human subjects, studying women who have

had their ovaries removed as a precautionary measure because they carry a gene (BRCA1/2) that puts them at high risk of developing breast and ovarian cancer.

This research has a personal resonance for Dr. Almey. A few years ago, her mother was diagnosed with breast cancer. She recovered and was prescribed hormone-blocking medications in order to reduce the chances of a recurrence.

Dr. Almey now has an opportunity to study the impact of hormone loss on women, a real issue for her mother. "It became clear that we don't understand the side effects of those medications particularly well. So, this experience has really helped me to relate to the patients that we see in the study and has driven my interest in the topics that I'm studying in the Einstein Lab."

She joined Dr. Gillian Einstein's team in November 2017, with a mandate to recruit Montreal-area women willing to participate in the study. It was a means of broadening the base of test subjects beyond those already recruited in Toronto and at a site in Sweden. The larger the test group, the more credible the results.

As she started to build her pool of participants in Montreal, Dr. Almey was able to quickly commence her research, using data from the women already recruited at the other sites. At its heart, her research tries to understand the effect that hormones, specifically estrogen, have on cognition. She and her colleagues are comparing the experiences of three groups of women of a similar age: those who have had an oophorectomy (ovary removal surgery) and did not receive hormone replacement therapy; those who have had an oophorectomy, but have received hormone therapy; and those who still have their ovaries.

Dr. Almey and her colleague Dr. Nicole Gervais, another postdoctoral researcher in the Einstein Lab, already have made some important preliminary findings, which they recently presented at a conference in California.

FOR THE FIRST GROUP OF PARTICIPANTS (I.E. WOMEN WHO HAVE HAD THEIR OVARIES REMOVED AND DID NOT RECEIVE HORMONE REPLACEMENT THERAPY), THE RESEARCHERS OBSERVED BOTH A DECREASE IN WORKING MEMORY PERFORMANCE AND A DECREASE IN THE THICKNESS OF THE GREY MATTER IN THE CORTEX (KNOWN AS CORTICAL THICKNESS).

Interestingly enough, the researchers did not observe either of these changes in those participants who received hormone therapy after surgery, which seems to suggest that replacing hormones that are lost when one's ovaries are removed can help to reduce the negative effects on the brain and cognition.

"It's been really exciting," said Dr. Almey. "But we don't want to get ahead of ourselves." Dr. Almey emphasized that these results are preliminary, and further research is needed with additional subjects.

She hopes that through her test group in Montreal she will be able to also explore the relationship between hormone loss and mood changes.

THERE IS SOME EVIDENCE THAT WOMEN WHO HAVE HAD THEIR OVARIES REMOVED EXPERIENCE AN INCREASE IN ANXIETY AND DEPRESSION.

Dr. Almey's goal is to further our understanding of women's brain health and to help better inform women of the implications of an oophorectomy.

"The research means a lot to me," said Dr. Almey. "It makes you feel like you're actually making a contribution, and the knowledge that I'm generating might help people like my mother."

"It feels like women empowering other women."

INSIDE THE LAB

Tough Pill to Swallow

with researcher Laura Gravelsins

In the more than half a century since it was approved for use, the oral contraceptive pill (also known as the birth control pill) has been taken by millions of women across the globe – making it one of the world's most-prescribed medications. Despite its widespread use, though, there have only been a handful of studies to date that examine the cognitive effects of the pill.

When Laura Gravelsins started investigating the birth control pill and its effect on memory as part of her master's research at the University of Toronto, she was surprised to learn that the research in this area was incredibly limited.

"One of the very shocking things that we found through doing our literature searches was that no one had ever looked at whether the time at which you took the pill might have any consequences for cognition," said Gravelsins in an interview with Mind Over Matter®.

> **THE TIMING MATTERS BECAUSE THE CONCENTRATIONS OF HORMONES CONTAINED IN THE BIRTH CONTROL PILL VARY THROUGHOUT THE DAY IN WHICH IT IS TAKEN – SPIKING IN THE FIRST COUPLE OF HOURS, AND THEN GRADUALLY DIMINISHING AS THE BODY METABOLIZES IT.**

Gravelsins wanted to find out whether the differing hormone levels would affect a woman's cognition and queried whether the higher levels of hormones in the early hours of the day would lead

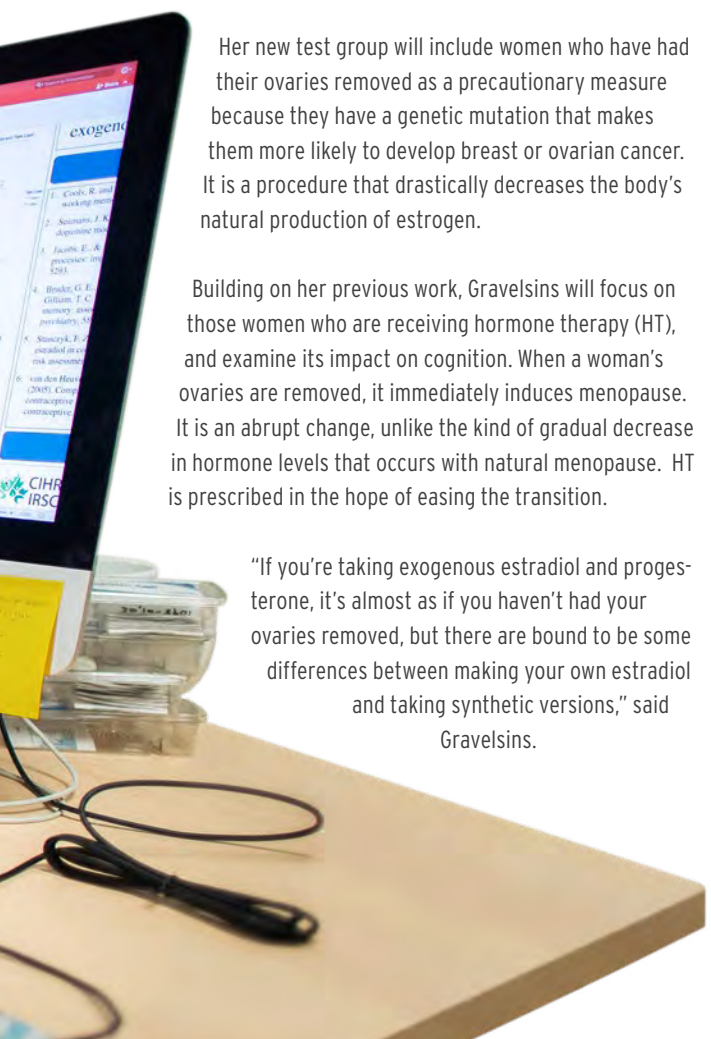
to lower performance on tests.

Filling this knowledge gap has been a powerful motivator for Gravelsins, inspiring not only her master's project, but also her current research at the Einstein Lab where she continues to explore the effect of hormones on women's cognition. "It's very rewarding to be able to do a study to uncover some of this knowledge, which is unknown, and which has implications for women's health," she said.

In her initial studies of the birth control pill, Gravelsins focused on young, healthy women (primarily between the ages of 18 and 22) and was relieved to discover that there was no difference in an individual's cognitive performance throughout the day, nor was there a difference between women with varied genetic makeups.

But now, as she launches her PhD work with the Einstein Lab, Gravelsins will be examining a much different cohort of women: those who have had their ovaries removed at a young age.

"When you're investigating memory in such a young, healthy, already high-functioning population, it's difficult to find differences between the groups. However, looking at other literature, it's common to see these differences emerge between genetic groups in older populations," she said.



Her new test group will include women who have had their ovaries removed as a precautionary measure because they have a genetic mutation that makes them more likely to develop breast or ovarian cancer. It is a procedure that drastically decreases the body's natural production of estrogen.

Building on her previous work, Gravelsins will focus on those women who are receiving hormone therapy (HT), and examine its impact on cognition. When a woman's ovaries are removed, it immediately induces menopause. It is an abrupt change, unlike the kind of gradual decrease in hormone levels that occurs with natural menopause. HT is prescribed in the hope of easing the transition.

"If you're taking exogenous estradiol and progesterone, it's almost as if you haven't had your ovaries removed, but there are bound to be some differences between making your own estradiol and taking synthetic versions," said Gravelsins.

ONE OF THE AREAS THAT GRAVELSINS IS INTERESTED IN EXPLORING IS WHETHER OR NOT HORMONE THERAPY RESTORES COGNITIVE FUNCTION IN WOMEN WHO HAVE UNDERGONE AN OOPHORECTOMY (THE SURGICAL REMOVAL OF ONE OR MORE OVARIES).

Gravelsins suspects that, consistent with previous research, HT will have a beneficial effect on memory, but notes that the existing studies have only covered the first few months after the surgery, whereas her project will observe the participants for several years.

"If you just had the surgery, you might not notice any differences, but they might appear at a later date. I think it's important to look at all of these components because humans are so complex, with different histories and different genetics, different hormone makeups."

Gravelsins is currently helping to recruit women who are prepared to share their life experiences to assist in the research. It is a multi-stage process that involves working with various hospitals and doctors to identify potential candidates, scheduling interviews, and having candidates complete a detailed demographic questionnaire to ensure that they fit the desired profile. "It's an amazing population to examine. And to be connected to the hospitals – to actually be able to recruit this population – is really fantastic too."

At times, recruiting research participants can be a delicate matter. The women in this cohort have often experienced considerable hardship and may have recently received bad news from their physician. "We always ask the doctor for permission to enter the room and sometimes he or she will say this is not a good candidate, or that this person is taking it very hard, they're not in a good mental or emotional state to be approached today and we do respect that because we do have to remember that we're dealing with people. These are their lives."

Gravelsins also has a personal motivation driving her research. Her aunt survived a bout with cervical cancer. Watching a close family member go through such a traumatic experience sparked a desire to advance knowledge of women's health.

"Having very strong, important women figures in my life has really made an impact and changed the way that I view things. It makes these issues all the more important."

As someone who is fascinated by the complex relationship between hormones, genes, and cognition, Gravelsins says that she feels very fortunate to be a member of a research team that shares her passion and whose collective work aspires to fill critical gaps in research.

INSIDE THE LAB

If Memory Serves

with researcher Alana Brown

Often taken for granted, the ability to find one's way is essential to autonomy, independence, and self-reliance. The process of finding one's way includes knowing where you are, knowing your desired destination, knowing (and following) the best path or route to the destination, recognizing the destination upon arrival, and finding the way back.

SPATIAL DISORIENTATION AND DECLINING "WAYFINDING" ABILITIES ARE AMONG THE EARLY SYMPTOMS OF DEMENTIA, LIMITING AN INDIVIDUAL'S ABILITY TO PERFORM ACTIVITIES OF DAILY LIVING INDEPENDENTLY (SUCH AS FEEDING ONESELF, BATHING, DRESSING, GROOMING, AND HOMEMAKING).

As someone who is passionate about exploring the city on foot, Alana Brown empathizes with individuals with dementia whose difficulties with spatial orientation can leave them unable to navigate their way home.

"I couldn't imagine that being taken from me. Places are so important to your memories, and so it's an emotional thing for me," she said in an interview with Mind Over Matter®.

Brown will be delving deeper into the mysteries of the brain as part of her work in the Einstein Lab at the University of Toronto. The first-year Masters student in psychology was already well acquainted with lab leader Dr. Gillian Einstein, having taken a memorable class with her as she pursued her undergraduate degree.

Brown volunteered in the lab for two years prior to joining as a graduate student. She is particularly interested in the impact of hormones, and specifically estrogen, on brain structure and function in the context of spatial abilities, navigation strategies, and wayfinding behaviours in humans. This is an area that resonates with any caregiver of an individual living with dementia, given the grave concerns about individuals getting confused, lost, or easily disoriented – in both familiar and unfamiliar environments – as the disease takes its toll. Surprisingly, there is very limited research on this subject, despite its practical implications.

Brown is currently working with the lab's research participants: women who have had their ovaries removed as a precautionary measure because they carry a genetic mutation that makes them more susceptible to developing breast or ovarian cancer. This procedure drastically decreases the body's natural production of estrogen.

INTERESTED IN CONTRIBUTING TO DR. EINSTEIN'S RESEARCH?

If you live in the GTA or Montreal, are a woman between the ages of 30 and 60, and DO (study group) or DO NOT (controls) have the BRCA1/2 mutation, please contact: **estrogens.cognition@utoronto.ca** or Dr. Gillian Einstein at **416-978-0896**.

BROWN IS EXAMINING THE PARTICIPANTS' ABILITY TO ASSOCIATE NAMES WITH FACES AND THE WAYS IN WHICH THEY REMEMBER THOSE ASSOCIATIONS.

In this study, the participants are first shown photographs of faces that are each accompanied by a name and are asked to subjectively rate whether they believe the name suits the face. This helps to ensure that the participants are processing each face-name pair and focusing on the task at hand.

Immediately thereafter, in what is called the "recognition phase," the participants are shown the photographs of the faces again, but this time they are provided with two names and are asked to recall which name was previously associated with a particular face. The researchers monitor brain activity, focusing on the hippocampus (a region of the brain that is associated primarily with memory, learning, and cognition) and the prefrontal cortex (a region of the brain that is involved in the regulation of behaviour and attention).

BROWN AND HER COLLEAGUES SUSPECT THAT THERE WILL BE DIFFERENCES IN BRAIN ACTIVITY WHEN THE PARTICIPANTS ARE LEARNING FACE-NAME PAIRS BETWEEN THOSE WHO HAVE HAD AN OOPHORECTOMY (OVARY REMOVAL SURGERY) AND THOSE WHO HAVE HAD NOT.

Decreased activity in the hippocampus and increased activity in the prefrontal cortex have been observed during encoding of new information in individuals with Alzheimer's disease.

Brown is careful to not describe the testing as any kind of early diagnostic tool for Alzheimer's disease, but says that it could be useful for identifying which parts of the brain are first affected, long before an individual shows any outward signs of cognitive decline.

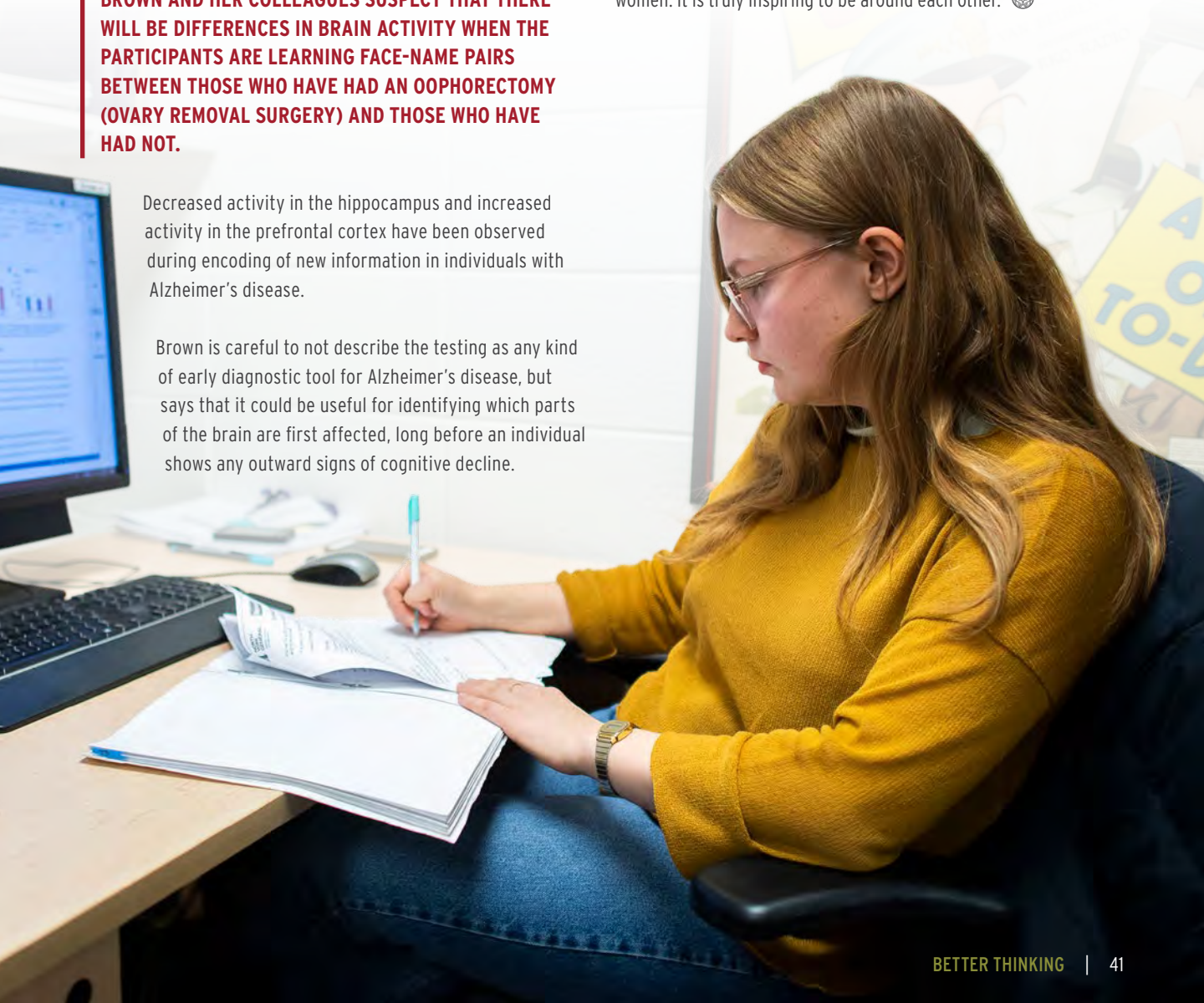
"This work could be helpful if there are therapies that emerge in the future to treat dementia. It's best to use them at the earliest point possible – it could result in more successful therapeutic treatment," she said.

Brown hopes to help track the entire trajectory of the disease, and to better understand the differences between the sexes – a subject that, historically, has been overlooked by the broader research community.

"While working on my own thesis, I've realized that it is exceedingly difficult to find information and statistics that are specific to Alzheimer's disease in women versus men. It takes a bit of digging."

All of which contributes to the personal significance of being a part of a research team whose central mission is to fill this knowledge gap.

"It's good to be working with other young women…women who are very intelligent and think about these issues that really impact women. It is truly inspiring to be around each other."



INSIDE THE LAB

Dream On

with researcher Dr. Nicole Gervais

When Nicole Gervais started her PhD research at Concordia University examining the effect of hormones on memory, she was surprised to learn that the test subjects were all male rodents – a discovery that was particularly concerning given that she was trying to better understand the causes of Alzheimer's disease, which strikes women far more than men.

Indeed, female mammals have historically been excluded from neuroscience and biomedical research, often on the assumption that results from males apply to females, or because of concerns that hormonal fluctuations confound effects of experimental manipulations.

With the support of her supervisor, Dr. Gervais's research project proceeded with female rodents, which allowed her to examine the impact of biological sex and the hormone estrogen on aging, with a specific focus on memory.

During her first post-doctoral project at the University of Massachusetts - Amherst, Dr. Gervais worked with both female and male common marmosets (small monkeys from Brazil) to explore the effect of the drug letrozole, which is administered to women after breast cancer surgery in an effort to reduce the risk of recurrence. Letrozole is one of a class of drugs referred to as aromatase inhibitors (AIs) that suppress the production of estrogen, which stimulates the growth of breast tumours expressing the estrogen receptor. Although side effects such as mood disturbances and memory issues have been reported in both humans and animals, little is known about how the drug impacts the brain and cognition.

Dr. Gervais and her colleagues administered letrozole to the marmosets for four weeks and observed many of the same behavioural changes in the female marmosets that are experienced by women receiving similar treatment, including hot flashes and increased anxiety. The researchers also found that letrozole compromised the function of neurons in the hippocampus and impaired spatial memory. Together, these findings – published in the January 2019 issue of the *Journal of Neuroscience* – suggest adverse effects of letrozole on the brain, and call for new therapies that effectively prevent breast cancer recurrence while minimizing side effects that further compromise quality of life.

In the two years since joining the Einstein Lab at the University of Toronto, Dr. Gervais has been working with female participants who have undergone a bilateral salpingo-oophorectomy (BSO) – a surgical procedure in which both of the ovaries and the fallopian tubes are removed. BSO is often recommended for women who have a gene mutation (BRCA1 or BRCA2) that puts them at a higher risk for developing breast or ovarian cancer. While BSO reduces cancer risk, it often induces premature or early menopause, and drastically decreases the body's natural production of estrogen.

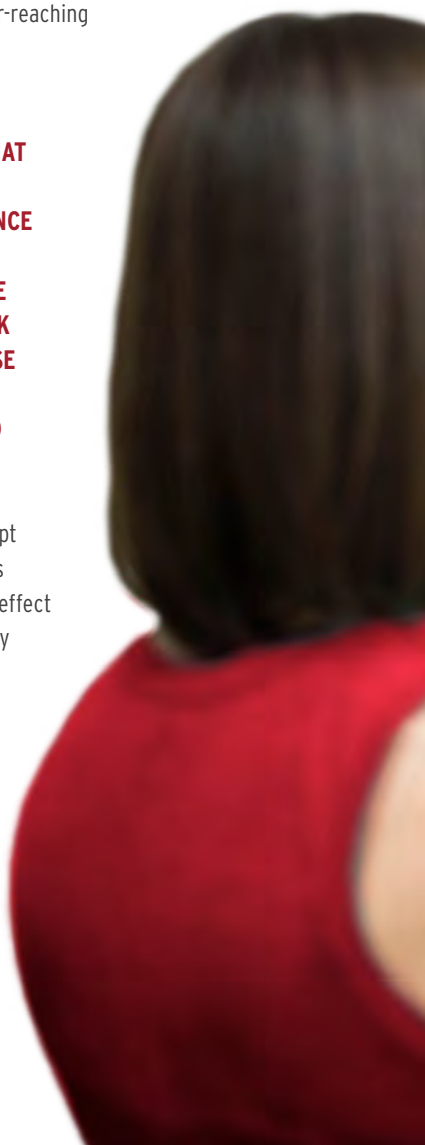
Dr. Gervais and her colleagues are exploring whether early menopause has an impact on memory.

The research has potentially far-reaching implications.

> **MANY WOMEN WHO HAVE UNDERGONE BSO FIND THAT THEIR QUALITY OF SLEEP DETERIORATES, EXPERIENCE MORE EPISODES OF WAKEFULNESS, AND HAVE DIFFICULTY FALLING BACK ASLEEP. OVER TIME, THESE EFFECTS MIGHT CAUSE PERMANENT CHANGES TO THE BRAIN.**

Estrogen loss is known to disrupt sleep patterns. The researchers are currently investigating the effect of sleep disturbance on memory and cognition. They measure objective sleep parameters using polysomnography – a test that records brain waves, the oxygen level in blood, heart rate, and breathing, as well as eye and leg movements.

In her office at the University of Toronto, Dr.



Gervais called up cross-sectional images of a participant's brain on her computer screen, which showed two small areas of the hippocampus highlighted in blue. She explained that this participant demonstrated signs of brain atrophy (the loss of neurons and the connections between them) in one region. That particular area was noticeably smaller in the female participants who had undergone BSO surgery when compared with the control participants of a similar age who still have their ovaries.

"This is an area important for memory, so this might indicate memory changes. And if it's not observable at this age, it might be a marker for changes later on," she said. "We do not know how the findings might relate to Alzheimer's disease, but they potentially could be an early sign of memory changes."

Observable differences in the shape and size of regions in the brain might occur before the individual actually shows functional changes in how his or her brain works.

After having spent so much time with non-human subjects, working with this group of women has been a particularly meaningful experience for Dr. Gervais, who is appreciative of the time that these participants have devoted to the research, which involves very personal health matters.

"Most are so warm and welcoming. I feel that even after two hours, I have developed a really close relationship, like having a chat with a good friend," she said in an interview with Mind Over Matter®.

The women in her test group are far from passive participants. They often conduct their own research through the Internet and are naturally anxious about their futures. "A lot of them are aware of their sleep problems, so they do report, and they are very frustrated by the lack of available knowledge about the impact of the surgery on sleep," said Dr. Gervais.

She hopes that her research will help fill the present knowledge gaps and assist women facing the BSO surgery, to better understand what lies ahead.

DR. GERVAIS'S WORK CONNECTS TO ONE OF THE CENTRAL GOALS OF THE EINSTEIN LAB – TO UNDERSTAND HOW SEX AND GENDER DIFFERENCES INFLUENCE BRAIN HEALTH, MEMORY, AND AGING.

"So much research attention is being focused on sleep and memory, but a lot of the studies in animals are focussed exclusively on males. That's extremely surprising and I'm still surprised today when speaking with colleagues, as they kind of roll their eyes when you talk about sex differences."

But there is no eye rolling amongst the members of the Einstein Lab. The researchers share a passion for exploring issues that have been neglected for too long. "I feel very privileged to be in this position, to be part of an amazing team addressing important questions."

INSIDE THE LAB

If Truth Be Told

with feminist scholar Nina Lykke

Nina Lykke is a renowned feminist scholar and a distinguished professor of gender studies at Linköping University in Sweden. She believes passionately in the importance of collaborating with academics from other disciplines, and is currently working with Dr. Gillian Einstein (leader of the Einstein Lab based at the University of Toronto) on a project called Cognition After Bilateral Salpingo-Oophorectomy (CABSOE), funded by the Swedish Cancer Society (Canderfonden).

The focus group consists of women who have undergone a bilateral salpingo-oophorectomy (BSO) – a surgical procedure in which both of the ovaries and the fallopian tubes are removed. BSO is often recommended for women who have a gene mutation (BRCA1 or BRCA2) that makes them more susceptible to developing breast or

ovarian cancer. While the procedure reduces cancer risk, it also leads to a sudden loss of estrogens and abruptly induces menopause.

The trans-Atlantic collaboration is making an important contribution to the Toronto team's research into the effects of hormone loss on cognition in women, with the broader goal of understanding why women develop Alzheimer's disease at a much higher rate than men.

The CABSOE project takes a "whole-body" approach to research, which involves exploring the ways in which the structure and function of the brain are influenced by the context of people's lives, including hormones and genes, as well as culture, social environment, and personal life experiences.

THE PROJECT LOOKS BEYOND THE PHYSICAL IMPACTS OF HORMONE LOSS TO DELVE DEEPER INTO THE FEELINGS, FEARS, AND CONCERNS OF WOMEN WHO ARE EXPERIENCING PROFOUND LIFE CHANGES.

"I really think that the project is enormously inspiring and very good at making people with different approaches team up and collaborate in very productive ways," said Lykke in an interview with Mind Over Matter® from her office in Linköping, a small city about 200 kilometres southwest of Stockholm.

"This project is examining what happens when we remove that part of the body," added Lea Skewes, a philosopher and psychologist who works with Lykke on Dr. Einstein's Swedish team. "It has this domino effect throughout the body. It's not a simple narrative."

Working with 13 participants, the researchers conduct detailed interviews – some lasting up to two hours – inquiring about the participants' experiences with the surgery and its effect on their quality of life, sexuality, identity, and memory. The process is often far more in depth than the average counselling session that patients might have with their doctors.

These types of interviews are referred to as qualitative or intensive interviews because they are designed to glean comprehensive insights into the quality of the experience from a relatively small group of individuals, as opposed to quantitative studies, which gather broader, but less-detailed information from larger groups.

The primary objective of these interviews is to hear from participants about what they think is important about the topic at hand and to hear it in their own words. The interviewers are sensitive to the experiences of the participants and are careful to give them space to share their stories in their own way.

"We give a lot of priority to people's narratives and it gives them the opportunity to come up with things that we hadn't thought about. And some unexpected things have come out," Lykke noted. For instance, the researchers were surprised to hear the women report overwhelmingly that the surgery was the right thing to do.

"It came out as a strong statement, stronger than we expected, that even though it might have influenced their sexuality in a negative sense, even though it may have impacted memory in a negative sense, they do not regret it because the cancer risk is really an overwhelming thing."

Most of the participants indicated that they had watched their mother, sisters, and/or aunts die of breast cancer. Those powerful, painful memories led them to the realization that they did not want their close relatives to have to go through a similar experience, which is one of the reasons why they wanted the surgery, despite the consequences.

"There were reflections on how their dying from cancer would influence their partners, but mostly their kids. Really, really strong stories about pain and suffering and co-suffering with close relatives," said Lykke.

"THEY'RE WILLING TO PAY A PRETTY HIGH PRICE IN TERMS OF LOSS OF SEXUAL DESIRE AND LOSS OF MEMORY, AND THEY REALLY WANTED THESE STORIES TO BE TOLD."

She believes that this kind of exploration of human experiences is an essential element of research and can yield important insights that will lead to more holistic treatment methods.

"The more in depth you go into people's lives, the better you can counsel them. Doctors can empathize with patients in different ways," observed Lykke. "It gives depth and individuality to understanding patients' perspectives and I think understanding patients' perspectives is really important."

Adding to the breadth of this international project, the researchers are also exploring the cultural differences between North America and Europe from the perspective of the female participants who are sharing their personal stories – all of which is being compiled and analyzed by researchers from various nations and different specialities, both in the humanities and medical science.

More and more women are being recruited to participate in this project, and to contribute their unique life experiences and perspectives. "It's important to have these kinds of connections, to do science in these different ways, to create more whole pictures, which is really needed," said Lykke.

Information gained from this study will be useful for women who are considering having preventive surgery in the future, as well as for women who have already elected to have this procedure.

IN SOMEONE ELSE'S SHOES

What Does It feel Like to Develop Alzheimer's?

Reprinted with permission from the author Michael Carley

Have you ever walked into a room and forgotten why you're there? You probably have. Most of us have at one time or another.

But what if, instead of this happening every once in a while, it happened a couple of times a day? Then, several times a day.

Maybe it starts with a missed appointment, or a few of them. You can never seem to keep your schedule straight. The things that you do every day at the same time pose no problem, but the haircut, the doctor, the dentist, the therapist, these are all irregular and somehow, you seem to be showing up at the wrong time or on the wrong day.

You find yourself losing things, your keys, phone, wallet, nothing seems to be where you put it. You try keeping things in the same place each time, but it never seems to work. Someone must be moving them.

People are starting to think you are a flake, unreliable. They get frustrated with you and you don't understand why. You get defensive and angry. You feel a lack of control of the ability to manage your own affairs.

So, you try to grasp for control.

YOU COME UP WITH TECHNIQUES TO MANAGE YOUR DIMINISHING SKILLS.

They take time and attention away from other things, but they give you a sense of purpose. You make lists, you lay out your clothes for the day ahead of time, you plan more than you ever had in your life.

You might use technology to help, putting things on the calendar, in your phone, or computer. But somehow, that backfires. The calendar in your phone never seems to match the one on the wall. Appointments change and you can never remember why.

People are looking at you funny for other reasons. "You just said that," they keep telling you. Somehow, you seem to have repeated the same thing twice within five minutes, though you have no memory of doing so.

On the other hand, you ask other people questions they claim to have already answered. Arguments ensue, putting a strain on your relationships. Increasingly, people are getting frustrated with you, yet you have no control of, memory of, or, in some cases, understanding of, the things they say you are doing wrong. If you could fix it, you would, but as often as not, you don't even remember it happening.

This is making you second-guess yourself and undermining your confidence.

YOU FEEL GUILT, PERHAPS WITHDRAW INTO YOURSELF, START APOLOGIZING, EVEN WHEN YOU HAVEN'T DONE ANYTHING WRONG. OR, WHEN WHAT YOU'VE DONE ISN'T SOMETHING YOU CAN DO ANYTHING ABOUT.

Someone is giving you driving directions, but there are too many steps. You can't possibly remember them. You adjust by writing more things down.

At work, people around you are getting annoyed. How can you get things done when you can't remember what has been requested of you? You can't keep asking others over and over. So, you guess, but sometimes, you guess wrong. Your bosses and coworkers are starting to think you can't be trusted with basic tasks.

You no longer keep track of the days of the week. You know that certain appointments occur on certain days, but when you wake up in the morning, which day it is, is a complete mystery.

Tasks are becoming more difficult. You have to ask how to spell simple words. Balancing your accounts and paying your bills is strenuous. The bills get lost and you get confused in math steps that once came easily.

Technology is starting to baffle you. Computers seem to be using a foreign language. The television remote has too many buttons. The functions on your cell phone have become confusing and they seem to be moving around. Manuals may as well be written in a foreign language. Lately, even light switches are causing you difficulty.

Going out to eat has become difficult. The menu is confusing and there's too much noise, which you can't filter out. People try to help you by asking do you want A, or B, or C? But by the time they get to C, you've forgotten what A was, and if anyone says a word, B is gone too. You end up getting C, even if reluctantly. When it arrives, you don't remember ordering it.

CONVERSATIONS, ESPECIALLY IN LARGE GROUPS, BECOME DIFFICULT TO FOLLOW.

People are speaking too fast and you cannot keep up. You try to contribute to the discussion, but when you make a comment, people stare in awkward silence. You must have said something wrong, but you cannot figure out what it is. Somehow, you seem to have derailed the conversation. It is making you nervous and reluctant to participate.

Nothing in your house is where it is supposed to be. The dishes are in different cabinets each time you go to find them. Now, you're guessing where to put things. You try to put laundry away, but you cannot remember which is your underwear drawer and which one is your sock drawer. You start putting things away randomly because that seems to be the easiest way to find them the next time.

You are running out of things at home all the time, coffee, salt, toiletries. Making lists doesn't work anymore, so there are nearly daily trips to the store.

The doctor wants you to take a driving test and reluctantly, you comply. You are tentative, but sure you have passed yet the DMV instructor says otherwise. You wonder what he has against you. Of course, you'd never want to hurt anyone.

But now, you have lost your license, your independence. You must rely on others for the simplest of things.

YOU FEEL TRAPPED, ISOLATED.

You can no longer work and now, you cannot run an errand by yourself.

Others though, are helpful. You find you have more friends, and

more loyal ones, than you ever thought. Some people drop away, too busy with their own lives, but others step up in ways you could never have imagined. They take you places, listen, and do not judge. You feel incredible gratitude, but also responsibility and guilt.

You miss important events. Birthdays, anniversaries. Your spouse gets you a present, but you forgot to get one, though it crossed your mind several times. You feel guilty, so you buy one for the next event, but you misplace it. It must be somewhere. You try to explain what it is and where it might be, but cannot seem to get the words right. Your spouse says it's OK; a present isn't necessary, but it's another loss. Your relationship has become one-sided in too many ways.

Those around you seem to keep things from you. You never know from one moment to another what you are supposed to be doing. You get in the car and eventually, you are at a location you hadn't realized you were going to.

> **NO ONE SEEMS TO INCLUDE YOU IN THE PLANNING OR DECISION-MAKING OR, IF THEY DID, YOU DON'T REMEMBER.**

You try to let things go and just show up where you are supposed to. Do what you are supposed to.

Relaxing and just going with the flow makes things easier, but it's harder than you'd think. Hovering over you is this pervasive sense that you are supposed to be somewhere, doing something, that you are missing some important task or appointment and letting someone down. When others try to reassure you, you calm for a moment, but the feeling never completely goes away.

This anxiety becomes a part of your everyday life. As your short-term memory has become less reliable, there are more instances when you don't know what you're supposed to be doing. You are in a store, looking for something, but you're not sure what. You pick something up off the shelf and put it into your cart, hoping it is the right thing.

Reading was a passion, but books no longer provide the joy they once did. You cannot seem to keep up with the story and find yourself reading the same paragraph over and over and not retaining it.

Television has the same problem. You watch a show, but the story seems incoherent, filled with disconnected scenes and characters. You see someone you think must be important, but cannot place them. You start watching the same shows over and over as they provide a comfort.

Someone takes you to the movies, but you cannot remember which film you are there to see, though you had been excited about it. You step out for the restroom and enter the one for the wrong gender, find yourself apologizing. Or, you return to the wrong theatre; the people you came with are not there.

> **IT'S GETTING HARDER TO MAKE YOURSELF UNDERSTOOD. YOU HAVE SOMETHING IMPORTANT TO SAY, BUT THE WORDS WON'T COME TO YOU.**

Sometimes, just one word, usually the noun, is missing. Sometimes, you get the sentence out, but see a blank look from whomever you are speaking to, as though you were speaking gibberish, or another language altogether.

Your nutrition is suffering. You are hungry, but you aren't sure if you ate breakfast. So, you get a snack. Sometimes, you're forgetting to get enough of the right foods or drink enough water and it affects your physical health and contributes to your mental fuzziness.

Fuzzy is what you feel; it's like there's a
constant fog in your brain, like you
are drunk or under the influ-
ence of some substance.
It takes you longer
to do anything
and you
start

several things without being able to finish them.

You find half-eaten sandwiches on the counter, but don't remember making them. Maybe someone else did. You pull out clothes to get dressed, but don't remember doing so. You pull out some more and they are piling up in your room. You don't remember which ones are clean, so you wash them all. Your spouse says you washed them the wrong way, but you don't understand why.

Things take longer. That sandwich took you fifteen minutes to make and it doesn't taste right. A cup of coffee takes twenty minutes, sometimes thirty. But it doesn't matter. Time is all you have.

It feels like people are talking behind your back.

CONVERSATIONS ARE DISCONNECTED AND OTHERS OFTEN FORGET TO INCLUDE YOU.

When they do speak to you, they are often condescending. Sometimes, they speak about you in the third person, even when you are right there in the room. Increasingly, they are making decisions for you. It has become infantilizing.

Not everything is bad. You find new outlets. Long dormant hobbies come to the forefront; the changes to your brain seem to have reduced mental blocks and barriers. You find talents you never knew you had. Artistic, creative. And as a consolation for your isolation, you now have the time to pursue them.

There may be children in your life, whom you love dearly. But, it's getting difficult to be around them. They speak too fast; they are unpredictable, and they seem to interrupt all the time. You find yourself getting impatient and abrupt with them and they don't understand why. They're getting reluctant to be around you and this is a painful loss.

Your temper is short with others as well. You are confused and people seem to be tricking you, moving things around, stealing from you, or lying about you. They are correcting you when you are sure you are right. You find yourself snapping at them and saying things you never would have said before.

Now, your longer-term memory is starting to be affected. You run into someone in the store and you only vaguely remember him or her and have no idea where you met.

PEOPLE AROUND YOU TALK ABOUT EVENTS YOU DON'T REMEMBER.

You find yourself filling in the blanks of the parts you aren't sure about. Only now, they don't correct you anymore, but just stare quietly or change the subject.

People are visiting less often and they're quiet when they do come. It seems they have little to say after a few minutes.

Worry increases. You should be doing something; you should be somewhere, but you're not sure what or where. You pace around the house, agitated. You wring your hands and develop other ticks and habits. Your brain is a fog, as though filled with cotton candy and stray, disconnected thoughts. You need to move, go somewhere, do ... something.

So, you leave. You wander. Whatever it is, wherever you should be, maybe you'll find it ... out there ...

WHEN PUSH COMES TO SHOVE

Managing Challenging Dementia-Related Behaviours Without Drugs

Dementia is commonly associated with cognitive impairment, particularly memory decline. However, dementia not only affects an individual's ability to think and remember, it also causes changes in personality, emotions, and behaviour. These non-cognitive changes are collectively referred to as behavioural and psychological symptoms of dementia (BPSD). Examples of BPSD include depression, anxiety, delusions, hallucinations, decreased

inhibition, and agitation, as well as physical and verbal aggression.

Nearly all individuals with dementia will experience at least one behavioural or psychological symptom at some point during the course of the disease. Which of these symptoms are experienced, when, and for how long varies for each person.

Often, the behavioural and psychological symptoms of dementia are more challenging for caregivers to handle than the cognitive decline. Agitation and aggression can be especially challenging and, in some cases, can result in dangerous situations for the person with dementia and/or his or her caregiver.

Antipsychotic drugs are commonly used to manage challenging BPSD. They are a tempting treatment option because it is relatively quick and easy to give someone medication, and the desire is understandably strong to find a solution that will curb challenging behaviours. However, research has consistently demonstrated that antipsychotics are not particularly effective for addressing BPSD, and their use comes with a high level of risk.

In fact, the risks are considered so significant that the United States Food and Drug Administration (FDA) requires that all types of antipsychotic drugs contain a black box warning, highlighting the higher risk of death if the drugs are used by individuals with dementia. This black box warning requirement has been in effect for atypical antipsychotics since 2005, and for conventional (or typical) antipsychotics since 2008.

RISK OF MORTALITY IS NOT THE ONLY SIGNIFICANT SIDE EFFECT EXPERIENCED BY INDIVIDUALS WITH DEMENTIA WHO USE ANTIPSYCHOTICS.

Other potential side effects include increased risk of falls, heart disease, pneumonia, diabetes, and movement disorders. Use of antipsychotics has also been associated with increased risk of cognitive decline.

Despite all of the evidence of little benefit and the great potential for harm, and despite recommendations that individuals with dementia should avoid antipsychotics, except in cases of severe aggression or agitation, these drugs continue to be widely prescribed for dementia patients. A recent review and meta-analysis conducted by Dr. Stephen Ralph and Dr. Anthony Espinet – published in *Journal of Alzheimer's Disease Reports* in 2018 – found that inappropriate prescribing of antipsychotics continues to be common, with some countries seeing little to no change in use over the past decade or, in many cases, usage has increased notwithstanding all warnings to the contrary.

TYPES OF ANTIPSYCHOTICS

Antipsychotic medications are classified into two sub-groups: (1) Conventional, or typical; and (2) atypical. Conventional/typical antipsychotics were the first generation of this type of drug, developed in the mid-1950s. Examples include Haldol and Loxitane. The second generation of antipsychotic medications – atypical – were developed in the 1980s. Examples include Abilify and Risperdal.

A black box warning is the most serious type of warning placed on medication, and is used when there is reasonable evidence of a serious hazard.

Ten years ago, the Banerjee report established that inappropriate prescribing of antipsychotics in the elderly was occurring in the U.K. and such patients had an 85% increased risk of adverse events and greater mortality. "The Banerjee report found that of the 180,000 antipsychotic prescriptions for people with dementia reviewed in the study, 140,000 were considered inappropriate," noted Dr. Ralph, associate professor at the School of Medical Science, Griffith University in Australia. "Our research revealed that many significant studies worldwide since the Banerjee Report have further contributed to the evidence of adverse impacts of use of antipsychotic drugs in dementia." According to Dr. Ralph and Dr. Espinet, the recent literature is consistent: there is an increased risk of all-cause mortality associated with dementia or other patients when prescribed the antipsychotic drugs. Accordingly, prescribing antipsychotic drugs for dementia or for other mental health care should be avoided and alternative means should be sought for handling behavioural disorders of such patients.

ALTERNATIVES FOR ADDRESSING BPSD

There are a multitude of non-drug interventions that may help with BPSD. So many, in fact, that it can be difficult for caregivers to figure out what to try, as well as to keep track of what does and does not work. One team of experts has developed an approach to help caregivers detect BPSD, consider possible →

The U.K.-based Banerjee Report provided international leadership on the topic of treatment and practices for dementia patients, with an aim to reduce prescribing antipsychotic drugs.

causes, and discover optimal treatments in a systematic way. They call the approach DICE – an acronym that captures the four steps of the process: describe, investigate, create, and evaluate.

"We designed DICE to be used by any health professional and, over the course of working with family caregivers over the past few years, we realized that the approach was easily adaptable for their use in the home, or for staff caregivers in facilities," explained Dr. Helen Kales, the lead researcher on the DICE Approach, and head of the University of Michigan Program for Positive Aging. "Family members are easily able to identify and describe new symptoms; look for what factors in the person with dementia, caregiver, or environment might be associated with BPSD; implement some of the interventions; and assess how well various interventions are working. In many cases, family caregivers may be the ones that make the health professionals aware of the DICE Approach, and encourage its use."

The DICE Approach, which aims to help caregivers manage BPSD, was developed in 2011 by experts from the University of Michigan Program for Positive Aging, the Johns Hopkins Alzheimer's Disease Research Center and Center for Innovative Care in Aging.

THE FOUR STEPS OF THE DICE APPROACH

1 STEP 1 DESCRIBE

The goal of the first step is to collect a thorough description of the problematic behaviour. For instance, in what context is the behaviour occurring (i.e. who, what, when, and where), what is the degree of distress to the patient and caregiver, and what is the social and physical environment. At this stage, caregivers should also think about possible triggers of the behaviour.

2 STEP 2 INVESTIGATE

In the second step, the health care provider searches for any potential underlying, modifiable causes for the challenging behaviour. "BPSD seem to be a consequence of multiple, interacting factors related to the patient, caregiver, and environment," explained Dr. Kales. "All three types of factors are considered in the investigate step." For instance, a challenging behaviour might be caused by undiagnosed medical conditions or untreated pain (factors related to the patient), ineffective communication style (caregiver factor), or overstimulation or lack of activity/structure (environmental factors).

3 STEP 3 CREATE

The third step involves the health care team, family caregivers, and the individual with dementia (if possible) collaborating to create and implement a treatment plan. The contents of this plan will depend on what was discovered in the previous steps. Of course, a top priority should be addressing any physical problems that were detected. For instance, this might involve treatment for a urinary tract infection, constipation, or dehydration. Other medical interventions might include stopping drugs with behavioural side effects, managing pain, and addressing any hearing and vision impairments.

Behavioural and environmental approaches should also be considered. While there are several strategies that may be effective depending on the particular situation, the following five generalized strategies are often a good place to start when seeking to address BPSD through non-pharmacological means:

- Providing caregiver education and support (for instance, learning about the various stages of dementia and what are realistic expectations at each stage);
- Enhancing communication between caregivers and the person with dementia (for instance, using reassuring and calming tones, as opposed to using negative or confrontational language);
- Creating meaningful activities for the person with dementia (for instance, if an individual enjoyed fishing but is no longer able to do so, then meaningful activities might include sorting a tackle box without hooks, watching a fishing video, or looking through a fishing magazine);
- Simplifying tasks and establishing structured routines; and
- Ensuring that the individual's surroundings are safe, and increasing or decreasing stimulation in the environment.

Antipsychotic medication may be part of a DICE treatment plan as well, but only when there is the potential for the individual with dementia or caregivers to be harmed by the behaviour, or as a last resort when other interventions have not worked.

4 STEP 4 EVALUATE

The fourth step involves assessing whether the treatment plan was implemented effectively, whether the target symptom improved, whether the caregiver's stress was reduced, and whether there were any unintended effects. "If antipsychotic drugs were used, it is important to consider reducing the dose or discontinuing use at this stage," emphasized Dr. Kales. "The drug may no longer be needed, given that behaviours change and fluctuate throughout the course of dementia."

Once a challenging symptom has been effectively addressed, caregivers will continue to look for new behaviours and use the DICE process again as needed.

RESEARCH HAS SHOWN THAT OVER TIME CAREGIVERS CAN LEARN WHAT TRIGGERS SYMPTOMS IN THE INDIVIDUAL WITH DEMENTIA AND OFTEN CAREGIVERS BECOME ADEPT AT NOTICING AND ADDRESSING THE TRIGGERS BEFORE SYMPTOMS FULLY DEVELOP.

"I'm really excited that the DICE Approach is now being promoted for widespread use through a new manual and training website," said Dr. Kales. "The more caregivers that discover and use DICE, the better, because our research has shown that the approach helps both the person with dementia and the caregivers themselves by helping to decrease their distress over BPSD. And when it comes to dealing with challenging behaviours associated with dementia, caregivers really need the help."

Another key resource that can help family caregivers deal with challenging BPSD is a book entitled *The 36-Hour Day: A Family Guide to Caring for People Who Have Alzheimer's Disease, Related Dementias, and Memory Loss*. This book, written by Nancy Pace and Dr. Peter Rabins, provides useful information about all aspects of caring for someone with dementia, including a section that describes the "six Rs" for managing challenging behaviours (restrict, reassess, reconsider, rechannel, reassure, and review).

THE SIX RS

Restrict:
If an individual with dementia is experiencing challenging behaviour, the first thing a caregiver should do is to attempt to calmly halt the behaviour, particularly if the behaviour is potentially harmful to the person or to others. Sometimes, however, trying to restrict or stop the behaviour may upset the person even more.

Reassess:
This strategy involves considering the underlying causes or triggers of a particular behaviour. For instance, it could be a medical issue, such as joint or gut pain, or it could be fatigue or a reaction to medicine.

A manual and training website about the DICE Approach launched earlier this year. The manual, *The DICE Approach: Guiding the Caregiver in Managing the Behavioral Symptoms of Dementia*, is available for US$29.99 on amazon.com. The DICE website (www.programforpositiveaging.org/dice-approach) is a training course, where caregivers learn in detail over a series of modules how to use the DICE Approach. The training course includes electronic simulations for caregivers to practice what they have learned with realistic cases. Access to the website costs US$69.99 for one year of access and includes the manual, as well as a downloadable DICE worksheet for caregivers to use. Group rates are available for facilities that want to train their staff using the website and manual. Interested facilities should contact the Program for Positive Aging for pricing.

Reconsider:
Caregivers are encouraged to imagine the situation from the point of view of the individual with dementia, which cultivates empathy and can ease the stress on both parties.

Rechannel:
This strategy involves directing or steering the individual with dementia away from challenging behaviours to safe, non-destructive activities.

Reassure:
The caregiver should take time to comfort and support the individual with dementia when he or she is upset, anxious, or afraid.

Review:
Once a challenging behaviour has transpired, and the individual has been redirected, the caregiver should consider the effectiveness of the various techniques applied (and what worked and what did not), and come up with strategies to try next time.

The book contains numerous scenarios to help caregivers apply the concepts described. One of the key messages in the book is that challenging behavioural and psychological symptoms are the result of damage to the brain. While it can be easy to accept that memory and thinking problems are caused by dementia, it can be difficult for caregivers to understand that their loved ones' outbursts, argumentativeness, and stubbornness are also because of the disease. These upsetting behaviours are rarely deliberate and, although challenging, it is important to not take the behaviour personally.

OUT OF SEASON

Do the Seasons Affect Cognition in Older Adults?

Seasonal rhythms are known to affect several aspects of human behaviour and physiology. For example, moods fluctuate throughout the year in individuals with Seasonal Affective Disorder (SAD), and seasonality seems to impact timing of onset in schizophrenia and brain responses to cognitive tasks, as seen with magnetic resonance imaging (MRI) technology. A group of researchers – Dr. Andrew Lim and colleagues – wondered if the seasons might also have an impact on cognitive function and its underlying neurobiological factors, specifically in older adults. They analyzed data from nearly 3,400 participants from five different study groups in the United States, Canada, and France to explore that possibility, and shared their findings in the September 2018 issue of *PLOS Medicine*. Their findings included the following:

COGNITIVE FUNCTION FLUCTUATED SEASONALLY IN HEALTHY OLDER ADULTS.

Healthy older adults who completed cognitive testing in the summer and fall performed better than those who were tested in the winter and spring. "Peak cognition occurred near the fall equinox," explained the lead author on the study, Dr. Lim of Sunnybrook Health Sciences Centre and the University of Toronto. **"THE DIFFERENCE IN PERFORMANCE BETWEEN THE FALL AND SPRING WAS QUITE LARGE, EQUIVALENT TO APPROXIMATELY FOUR YEARS OF AGING."** These findings were consistent even after the researchers accounted for potential confounding variables such as mood, amount of physical activity, and sleep quality.

OLDER ADULTS WITH ALZHEIMER'S DISEASE EXPERIENCED SEASONAL FLUCTUATIONS IN COGNITIVE FUNCTION, TOO.

When the researchers analyzed data from participants who had Alzheimer's disease, a seasonal pattern in cognition was found, similar to the pattern discovered in the healthy older adults. "This suggests that there is a seasonal component to cognition that is preserved during the progression of Alzheimer's disease," said Dr. Lim. Individuals with Alzheimer's disease do not appear to get steadily worse as time goes on; instead, their cognitive abilities seem to fluctuate throughout each year.

THE ODDS OF MEETING CRITERIA FOR MILD COGNITIVE IMPAIRMENT (MCI) OR DEMENTIA WERE HIGHER IN THE WINTER/SPRING.

The seasonal fluctuations observed in cognitive function appeared to translate into an effect on diagnosis of MCI and dementia.

> **"WE FOUND THAT THE ODDS OF MEETING DIAGNOSTIC CRITERIA FOR MILD COGNITIVE IMPAIRMENT OR DEMENTIA WERE 30% HIGHER IN THE WINTER AND SPRING, COMPARED TO THE SUMMER AND FALL," SAID DR. LIM.**

AMYLOID-BETA LEVELS ALSO FLUCTUATE FROM SEASON TO SEASON.

One of the hallmarks of Alzheimer's disease is the accumulation of amyloid-beta (Aβ) proteins in the brain. Data was available on Aβ levels in the cerebrospinal fluid from a subset of participants in the study – 321 individuals both with and without Alzheimer's disease. "When we examined the cerebrospinal fluid data, we discovered that Aβ levels fluctuated from season to season, in alignment with the shifts we found in memory and thinking," noted Dr. Lim.

GENE EXPRESSION SHOWED SEASONAL PATTERNS IN LINE WITH COGNITIVE FLUCTUATIONS.

After analyzing post-mortem brain tissue from a subset of deceased participants, the researchers found that season was also associated with the brain expression of four cognition-associated gene modules – yet another factor that seems to vary in rhythm with the seasonal cognitive changes that were discovered.

LIMITATIONS OF THE FINDINGS

While these findings are interesting and novel, they should be interpreted with a degree of caution, keeping in mind the limitations of the research. For starters, the data was "cross-sectional," which means that different sets of people took the cognitive tests in the different seasons (i.e. each participant was tested once each year at about the same time of year). Comparisons between seasons reflect the group of participants collectively and do not represent known shifts within individuals. In other words, participants were not tested multiple times per year with their own scores in different seasons compared directly – this type of research would be ideal to conduct in the future.

Another study limitation is that all of the participants were from countries located in the northern hemisphere, so it is not known whether these findings would apply in other parts of the world. It would be interesting for future research to examine the effects of time of year on cognition in the southern hemisphere and equatorial regions.

IMPLICATIONS OF THIS STUDY

HEALTH CARE IMPLICATIONS

The findings suggest potential wisdom in adjusting health care availability seasonally. "There may be value in increasing the level of dementia-related clinical resources available in the winter and early spring months," said Dr. Lim, "when symptoms are likely to be most pronounced."

Neuropsychologists and physicians should keep these findings in mind when diagnosing MCI and dementia. Repeated cognitive assessments, conducted at different times of year, would provide the most comprehensive data on cognitive performance, perhaps improving the accuracy of diagnosis.

Although Alzheimer's disease can only be definitively diagnosed after death, the presence of amyloid-beta proteins in cerebrospinal fluid – the clear liquid that cushions the brain and spinal cord – is one biomarker used, primarily by researchers, to point to the potential presence of the disease.

FUTURE RESEARCH IMPLICATIONS

There are a variety of theories about what factors might be behind these seasonal fluctuations related to cognition. Some of the theories suggest potential non-drug interventions. For example, if light or temperature influence the fluctuations, perhaps light therapy or temperature modification would work to sustain the summer-fall cognitive peak year-round. Vitamin D supplementation may help as well. Other factors that might play a role include seasonal variations in physical activity, sleep, diet, and psychological state – each of which would suggest different possible drug and/or non-drug interventions. More research is required to explore all of these options.

The seasonal differences found in this research are sizeable; in fact, they are as big as the effect researchers would look for in clinical trials assessing potential interventions and treatments. If these seasonal effects are not considered during research design for clinical trials, they could skew the results, either making a treatment look more effective or less effective than it truly is.

Your body produces vitamin D when your skin is exposed to sunlight without sunscreen on. Consequently, during the colder months of the year, it is more difficult for individuals to get enough vitamin D from the sun. (Vitamin D is also found in a small number of foods.)

CAREGIVER IMPLICATIONS

It will be helpful for family and professional caregivers to understand that the brain of an individual with Alzheimer's disease changes with the seasons. Cognition will probably fluctuate throughout each year, as opposed to steadily declining over time. Additional support likely will need to be provided during the winter and spring. Caregivers can reasonably hope that there may be some improvement each summer and fall.

ON THE MOVE

Tips for Caregiving Beyond the Everyday

Coping with dementia is not easy, for the individual with the disease or his or hers caregiver. There will be many challenges to face, losses to grieve, and, for caregivers in particular, many new skills to learn in order to provide effective support throughout the various stages of the disease.

There are many resources available that offer in-depth information and practical advice to help caregivers navigate through the complexities of providing for the everyday needs of someone with dementia, including tips for successful communication, safety, and administration of medications. Addressing individuals' basic needs is critical, of course, but it is also important to remember that there are additional ways to enrich the lives of those with dementia and to maximize their quality of life.

This article provides tips for two types of activities – dining out and travelling – that can each be quite enjoyable for individuals with dementia who are in the early-to-middle stages of the disease. While these activities may not be appropriate for everyone with dementia, with careful planning and preparation they are worth trying if you feel that your loved one could potentially benefit from the experience.

7 TIPS FOR DINING OUT

Mealtime is more than just about eating food. It physically brings people together and gives everyone an opportunity to relate socially and emotionally as they talk about their days and reminisce about the past. Dining with others can give the individual with dementia something to look forward to in his or hers day and reduce the potential for feeling socially isolated. Going out to eat offers a welcome change of scenery for both the person with dementia and his or her caregiver, and allows the person with dementia to continue to be part of his or hers community. Caregivers may be surprised by how much they enjoy the outing, too, and by the number of staff and strangers that are especially understanding and helpful.

WITH A LITTLE EXTRA PLANNING, DINING OUT WITH A LOVED ONE WITH DEMENTIA CAN BE A POSITIVE WAY TO SPEND TIME TOGETHER.

Here are a few tips to keep in mind:

1. **CONSIDER THE UNIQUE NEEDS OF THE PERSON WITH DEMENTIA WHEN CHOOSING THE RESTAURANT.** Individuals with dementia are more sensitive to their environment. Finding a restaurant that will not cause agitation, anxiety, or confusion helps individuals enjoy themselves and minimizes the chances of having a negative experience. If your loved one with dementia has a favourite restaurant already, that might be a good place to start because it is familiar. However, his or her favourite spot may or may not be the best choice, depending on whether the space itself is accessible and the staff is dementia-friendly.

You will want to select a restaurant that is not too formal, offers quick service, and is not chaotic and excessively noisy. The restaurant should be laid out in a way that is easy to move through – for instance, with a sufficient amount of space between tables. This will be important when you make your way to the table initially, as well as if a trip to the washroom is necessary. A restaurant with booths is ideal, as a booth offers a more private, quiet space with fewer distractions.

Once you find a suitable restaurant, you might consider making it your regular dining-out spot. Choosing one restaurant to frequent is a great strategy for those with dementia because routine is helpful for them and, over time, the staff is likely to get to know your loved one and be especially responsive to his or her needs.

2. **GO AT AN IDEAL TIME OF DAY.** What time of day is your loved one with dementia at his or her best (i.e. in the best mood, with the most energy, and the least likely to be triggered)? Many older adults, especially those with dementia, feel and behave better during the day than in the evening. If that is the case for your loved one, you might want to go out for lunch, an early dinner, or even breakfast.

Also consider what time of day is likely to be less busy at the restaurant. Try to go during non-peak hours when the space will be quieter and the staff will find it easier to provide any extra attention needed.

3. **BEFORE YOU HEAD OUT, CONSIDER WHAT ITEMS YOU MIGHT NEED AND TAKE THEM WITH YOU.** To make dining out easier, it is helpful to bring those items that your loved one typically uses during a meal. It is always better to be too prepared than to be caught by surprise. The items that might be helpful to have on hand will vary by individual and change over time as the disease progresses.

Some items that you might want to take with you include special utensils, dishware, or a cup, a sweater (in case it gets cold), a stylish covering/bib to keep clothes clean, towel or moist wipes, and a change of clothes. You may also want to take along something interactive to do while you wait for food such as a Sudoku or crossword puzzle, or a newspaper.

4. **COMMUNICATE WITH THE STAFF ABOUT THE SITUATION AND ANY SPECIAL REQUESTS.** You may want to discreetly inform →

the restaurant staff that your loved one has dementia. Some caregivers do this by handing the server a pre-prepared "awareness card" with a simple message on it, such as,

> **"MY MOTHER HAS DEMENTIA AND MAY BEHAVE IN UNEXPECTED WAYS. THANK YOU FOR YOUR PATIENCE AND UNDERSTANDING."**

Using such a card allows you to help others be more understanding without drawing too much attention or potentially embarrassing your loved one by talking aloud about his or her condition. Contacting the restaurant ahead of time for special accommodations, such as a particular table, extra napkins, or dietary restrictions, may also be helpful. It is important to communicate clearly with the server about your loved one's unique needs, and to ask for anything special that you might need.

5. HELP YOUR LOVED ONE WITH ORDERING.

Depending on the stage of dementia, it might be overwhelming or impossible for your loved one to read through a complex and/or lengthy menu. To help simplify things, but still allow for a sense of independence, you might help your loved one make a selection by suggesting one or two items that you know he or she likes, read certain sections of the menu to him or her, and/or point to photographs of the items, if any.

If possible, you may want to consider previewing the menu online and deciding what to eat beforehand, so that your loved one does not feel rushed or pressured to make a decision when he or her is at the restaurant. You should also ask the server for a written copy of the specials instead of having them listed verbally, which can be difficult to remember. You might also suggest ordering finger foods if your loved one is struggling to use utensils.

6. INTERACT THROUGHOUT THE MEAL.

One of the most enjoyable parts of the restaurant experience is the interaction and dialogue between people. Use this outing as an opportunity to connect with one another. You might share stories about your day and your past; individuals with dementia often enjoy reminiscing about childhood.

While some of what your loved one talks about might not be accurate, it is often best to simply go along with the story as though it is factual; the joy for him or her will be in the telling of the tale. If your loved one is not up for much conversation, you could bring out any interactive items that you brought along with you to provide stimulation and something to do as you wait for your food to arrive.

7. KEEP THE OUTING SHORT.

Older adults with dementia often tire easily, so you will want to plan for a shorter outing. Do not rush your loved one while he or she is eating, but do watch for signs he or she is getting tired so that you can take your loved one home before fatigue leads to any anxious or uncooperative behaviour. It might be wise to skip having appetizers and desserts, or order dessert to go, to help keep the outing to a reasonable length.

7 TIPS FOR TRAVEL

Like dining out, travel offers many potential benefits for both the person with dementia and his or her caregiver, such as opportunities for socialization and enriched quality of life. However, with the changes in routine, noise, and the occasional chaos that accompanies travel – all things that many people with dementia do not handle well – it can be challenging or overwhelming to travel together. Here are a few tips to help make travelling with someone who has dementia a safer, more enjoyable experience:

1. CONSIDER TAKING A TRIAL "STAYCATION."

It can be difficult to tell if someone with dementia will handle travel well or not. Even if your loved one is doing well at home, that could change when he or she is removed from his or her familiar environment and daily routine. It is possible that when your loved one gets out of his or her comfort zone, he or she might be agitated, angry, or wander.

> **TO HELP YOU DECIDE WHETHER TRAVELLING IS A GOOD IDEA FOR YOUR LOVED ONE WITH DEMENTIA, YOU MIGHT WANT TO TAKE A TEST TRIP NEARBY.**

This could be as simple as staying with friends or relatives overnight, or as complex as booking a couple of nights at a hotel not too far away. In either case, you will want to go for a lengthy drive and dine out as part of the experience, to observe your loved one's response to as many common aspects of the travel experience as possible. This will allow you to see how your loved one reacts to the changes in routine and environment, and if his or her behaviour or symptoms get unmanageable, then you can easily take him or her home.

2. PLAN YOUR TRIP WITH DEMENTIA NEEDS IN MIND.

If possible, select a destination that your loved one has already visited before the onset of dementia. Plan an itinerary that will allow as much of the daily routine to remain in place as possible, and one that is relatively simple and flexible (i.e. not overpacked with activities) so that you will have a sufficient amount of time to relax and can take each day slowly without rushing.

Just as the time of day can make a significant difference to how enjoyable it is to dine out with someone who has dementia, it matters when travelling too. Aim to schedule any of the more challenging parts of your itinerary during your loved one's "good" hours. It will be easier if you keep time spent travelling to your destination as short as possible, preferably no more than four hours – spreading long distance drives out over multiple days if you

can, and booking direct flights when available. Driving to your destination will allow the most flexibility and control, whereas air travel is likely to be more challenging because it is unpredictable, noisy, and hectic.

3. IDEALLY, PLAN A TRIP THAT WILL ALLOW FOR SHARED CAREGIVING RESPONSIBILITIES. Try to travel in a group that includes more than one caregiver. That way, there will always be someone available to assist the individual with dementia, even if one caregiver is in the shower or taking care of other tasks that require time alone. Another option is to make the journey on your own with the person with dementia, but choose a destination where you will get help once you arrive such as visiting family and friends.

4. TAKE NOISE-CANCELLING HEADPHONES. Noise-cancelling headphones can be used at any time throughout your trip when your loved one is getting overstimulated by his or her surroundings and needs some quiet space. They also come in handy for playing music, which provides comfort and enjoyment for the person with dementia.

5. CONSIDER TAKING "AWARENESS CARDS." As previously discussed, even a simple, pre-prepared "awareness card" can advise others about your loved one's illness in a discreet way. There may be several opportunities to use a tool like this throughout your trip.

6. TAKE STEPS TO KEEP YOUR LOVED ONE SAFE WHILE TRAVELLING. Make sure to bring necessary medications, most recent medical information, a list of emergency contacts, physician information, a list of any allergies, and copies of important legal documents.

Unfamiliar surroundings can cause confusion and wandering. Be especially careful to keep an eye on where your loved one is at all times and try not to leave him or her unattended. Bring along an identification bracelet or necklace, or enroll in a program such as MedicAlert® + Alzheimer's Association Safe Return® (a 24-hour nationwide emergency response service for individuals with dementia who wander or have a medical emergency).

In the absence of an identification bracelet or necklace, or as back-up option, place a note in your loved one's wallet or pocket that includes his or her name, medical condition(s), hotel address and phone number, and emergency contact information.

7. IF TRAVELLING BY AIR, TAKE ADVANTAGE OF SUPPORTS OFFERED. Flying with someone who has dementia can be especially challenging. Airports and airplanes are noisy, crowded, and filled with distractions – all of which can trigger someone with dementia. As you try to support your loved one's needs during air travel, you will also be the one responsible for keeping track of boarding passes and other important travel documents, navigating through the airport, checking in, and handing over luggage, amongst other things.

Consider informing the airline that you are travelling with a person with dementia. You may want to request a wheelchair and escort through the airport to your gate, early boarding, assistance getting on and off the plane, help with stowing carry-on baggage, and seating near washrooms. These services will help your vacation get off to a smooth start.

If your loved one with dementia is still able to travel, embrace the opportunity to spend time together and fully savour each moment. Although your loved one may not retain memories from the trip, you will. He or she will experience love and joy along the way, and may enjoy looking at photographs from your time together for years to come.

MY CUP OF TEA

Boost Your Brain with Green Tea

Green tea has been widely consumed and appreciated throughout Asia for centuries, and its popularity has been increasing rapidly in the West in recent decades as more and more people discover its potential for boosting physical and mental health.

A growing body of research suggests that the consumption of green tea provides a wide range of health benefits. For example, green tea has been linked with reduced risk of type 2 diabetes, cardiovascular disease, and certain types of cancer. Research also shows that green tea may improve bone mineral density, help reduce the symptoms of rheumatoid arthritis, prevent dental cavities, and reduce anxiety. It even appears to benefit cognition and brain function.

RESEARCH HIGHLIGHTS

Dr. Shinichi Kuriyama, a researcher and professor from the Tohoku University School of Public Policy in Japan, and his colleagues conducted cross-sectional research using data from 1,003 Japanese individuals aged 70 years and older. Each person completed a Comprehensive Geriatric Assessment that included questions about how frequently they consumed green tea.

> **THE RESEARCHERS FOUND THAT HIGHER CONSUMPTION OF GREEN TEA WAS ASSOCIATED WITH A LOWER PREVALENCE OF COGNITIVE IMPAIRMENT.**

These findings were published in 2006 in *The American Journal of Clinical Nutrition*.

In another study conducted by Dr. Lei Feng and colleagues (reported in June 2010 in *Journal of Nutrition, Health & Aging*), the researchers examined the relationship between self-reported tea consumption habits and cognitive function in over 700 Chinese adults aged 55 years and older. The researchers found that tea drinking was associated with better cognitive performance. This result was true for green tea, as well as black and oolong.

More recently, Dr. Moeko Noguchi-Shinohara and colleagues investigated the relationship between tea consumption and the incidence of dementia and mild cognitive impairment.

These researchers worked with residents from Nakajima, Japan who were over 60 years old. Each participant completed a cognitive function test, as well as provided blood samples and information about their consumption of green tea, coffee, and black tea.

Analysis of the data revealed that the consumption of green tea was significantly associated with reduced risk of cognitive decline, even after adjusting for potential confounding factors. The finding was specific to green tea. No such association was found for coffee or black tea consumption. This research was published in May 2014 in *PLOS ONE*.

In addition to preventing cognitive decline, research suggests that green tea may help improve cognitive function in individuals who already have cognitive deficits or dementia.

- One study published in 2011 in *Journal of Medicinal Food* examined the effect of LGNC-07 (a combination of green tea extract and l-theanine, an amino acid in green tea) on cognitive function in individuals with mild cognitive impairment. Findings from this study led the researchers to conclude that LGNC-07 has potential as an intervention for cognitive improvement.

- In another study conducted in 2012 at a nursing home in Japan, twelve elderly residents with cognitive dysfunction consumed green tea powder each day for three months, while continuing with any usual intake of home-brewed tea beverages. The concentration of bioactive compounds in the green tea powder consumed each day was the equivalent of what would be found in two to four cups of bottled or home-brewed green tea. The findings, published in 2014 in *Nutrients*, suggested that green tea consumption may be helpful in improving cognitive function or reducing the progression of cognitive dysfunction.

Recently, two comprehensive research reviews also concluded that green tea and its constituent ingredients provide cognitive performance benefits.

The first review, published in *Current Pharmaceutical Design* in May 2017, examined the findings from 49 human intervention studies and summarized the research on the effects of green tea phytochemicals – specifically caffeine, L-theanine, and epigallocatechin gallate (EGCG) – on cognitive performance and mood. Caffeine, even at low doses, improved performance on long-duration cognitive tasks and increased self-reported alertness, arousal, and vigor. L-theanine improved self-reported relaxation, tension, and calmness. When caffeine and L-theanine were combined, they improved performance in attention-switching tasks and alertness, although to a lesser extent than caffeine on its own. No conclusions could be reached about the effects of EGCG because of limited available research.

The second review, published in *Phytomedicine* in October 2017, summarized the findings from 21 human research studies of differing designs that investigated the effects of green tea in various forms. Each of the studies reviewed provided evidence that green tea influences cognition, in particular benefiting memory and attention. Green tea also appears to impact brain function, activating working memory, which could be observed in magnetic resonance imaging (MRI) scans.

There are many theories about the underlying mechanisms that might be at play in green tea's brain-boosting properties. For example, green tea catechins are thought to be neutralizing stress-induced free radicals and reducing inflammation.

MUCH MORE RESEARCH IS NEEDED TO FULLY UNDERSTAND HOW GREEN TEA PROVIDES THESE NEUROPROTECTIVE AND NEURORESTORATIVE BENEFITS.

In the meantime, though, there is enough evidence to recommend consuming green tea on a regular basis in order to boost one's brain health, as well as to obtain many other health benefits.

A NOTE ABOUT SAFETY

Many ready-to-drink green tea beverages and supplements have been launched in the market in recent years to capitalize on green tea's growing popularity. These processed products provide widely varying amounts of catechins, often in concentrated amounts that exceed what would be found in a home-brewed cup of tea.

Sometimes it is possible to have too much of a good thing – and the consumption of green tea is no exception.

After conducting an extensive review of the existing research, Dr. Jiang Hu et el. (2018) concluded that "green tea is safe across a wide range of intakes and preparations," under certain circumstances consumption can result in gastrointestinal irritation and liver injury (particularly when a product contains concentrated extracts with high levels of individual constituents such as EGCG). Consumption of green tea with contents that closely reflect what would be in a traditional cup of steeped tea is perfectly safe.

WHAT IS GREEN TEA?

Green tea is made from the leaves of the Camellia sinesis plant. White, black, and oolong tea are also made from the same species of plant, but each type of tea is processed differently to achieve different levels of oxidation. Green tea leaves are unoxidized, making green tea one of the least processed types of tea. As a result, it is especially rich in nutrients and antioxidants.

Green tea contains thousands of bioactive ingredients, including caffeine, amino acids (such as L-theanine), polyphenols (such as epigallocatechin gallate), and vitamin C. The polyphenols, which account for approximately one third of green tea's bioactive compounds, are thought to be responsible for many of the health benefits of green tea. Matcha tea is a special type of green tea that is made from ground whole green tea leaves mixed with boiled water (and then the entire mixture is consumed, tea leaves and all). This results in higher antioxidant and caffeine content than steeped green tea.

Quinoa Tabouli

SERVES 4 TIME: 30 MIN

INGREDIENTS

1/2 cup quinoa
1 cup water
2 cups finely-chopped, flat-leaf parsley
1/2 cup finely-chopped fresh mint
1 cup halved cherry tomatoes
1 cup finely-diced cucumber
1/2 cup fresh lemon juice
2 Tbsp extra-virgin olive oil
1/2 tsp sea salt
Pinch of pepper

TAHINI LEMON ZEST DRESSING

1 small garlic clove, minced
1/4 cup tahini
3 Tbsp extra-virgin olive oil
2 Tbsp fresh lemon juice
1/4 tsp sea salt
Water for thinning, if needed

INSTRUCTIONS

1. In a small pot, combine the quinoa and water. Bring to a boil and then reduce the heat to low. Cover and simmer for 15 minutes.

2. Meanwhile, toss the parsley, mint, tomatoes, and cucumber in a large bowl.

3. Once the quinoa is cooked, it should be fluffy and all of the water will be absorbed. Take it off the heat and let it cool. You can put it in the fridge for 5 minutes to cool it down quickly.

4. While the quinoa is cooling, whisk all the dressing ingredients (except the water) together until blended.

If the dressing is too thick, you can add a few spoonfuls of water until the mixture reaches your desired consistency.

5. Toss the quinoa with the vegetables, lemon juice, olive oil, salt, and pepper.

6. Drizzle 2–4 tablespoons of the dressing over each serving, or more if you prefer.

7. The leftovers will keep in an airtight container in the fridge for up to 4 days.

Quinoa

Gluten free, this pure protein is loaded with fiber, iron, and vitamin B2, to support brain health.

MEMORYMORSELS®

A WOMEN'S BRAIN HEALTH INITIATIVE

This edition's recipes are courtesy of Sarah Grossman, author, nutritionist, and the co-founder of Living Kitchen.

For more recipes, morsels, and the latest from our Featured Foodie, Sarah Grossman, visit memorymorsels.org.

Miso Sesame Glazed Cod

SERVES 4 TIME: 20 MIN

INGREDIENTS

4 pieces of cod (each 5 oz)
2 Tbsp miso
2 Tbsp toasted sesame oil
1.5 tsp grated peeled ginger root

Extra Boosts:
4 chives, finely chopped
2 tsp sesame seeds
Handful of sprouts (optional)

INSTRUCTIONS

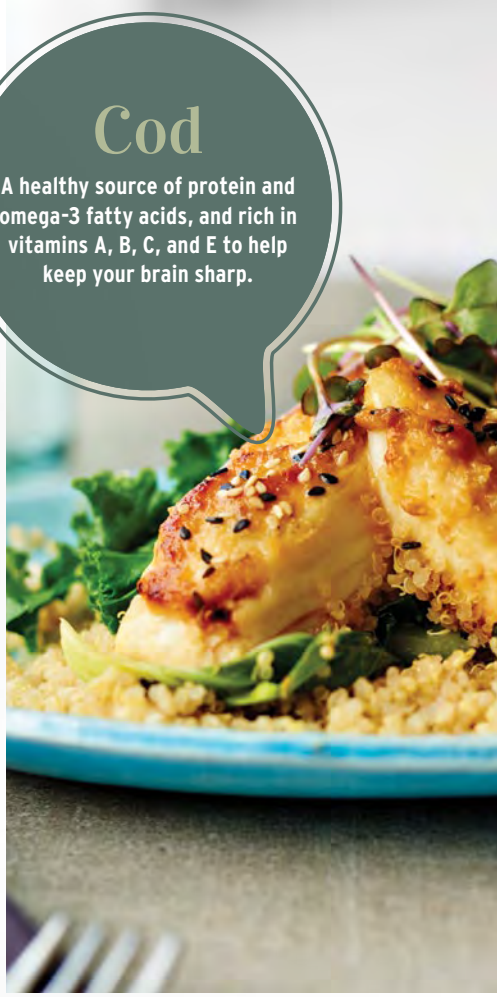
1. Preheat the oven to 350°F and line a baking sheet with parchment paper. Place the cod on the baking sheet.

2. Mix the miso, sesame oil, and ginger together in a small bowl. Spread some of the mixture over each piece of cod and bake in the oven for 15 minutes. You'll know it's ready when the flesh gently flakes with a fork.

3. Top the cod with chopped chives and sesame seeds and serve. You can keep leftovers in the fridge for up to 4 days and reheat them when you are ready to eat.

Cod

A healthy source of protein and omega-3 fatty acids, and rich in vitamins A, B, C, and E to help keep your brain sharp.



Your diet is crucial to the maintenance of a healthy brain and functional independence as you get older. Memory Morsels® is a website dedicated to delicious, brain-health recipes, brain health tips (our morsels), and great information to help keep your brain functioning the way you want.

Almonds

Decrease oxidative stress and are packed with vitamins and minerals to help enhance memory function and overall brain health.

Chocolate Tahini Cookies

MAKES 14 TIME: 18 MIN

INGREDIENTS

1 large egg
1/2 cup tahini
1/2 cup blanched almond flour
1/2 cup coconut sugar
1/2 tsp baking powder
1 dark chocolate bar (3.5 oz, 70% or higher), coarsely chopped
1/4 tsp coarse sea salt

INSTRUCTIONS

1. Preheat the oven to 350°F and line a baking sheet with parchment paper.

2. In a medium-sized bowl, mix together the egg, tahini, almond flour, coconut sugar, and baking powder. It will make a thick, sticky mixture.

3. Fold in the chopped chocolate.

4. Scoop about 1 tablespoon of batter and place it on the baking sheet. Continue to do this, spacing each cookie about 2.5 inches apart, until you have used all of the dough. If you prefer a larger cookie, scoop 2 tablespoons per cookie. Sprinkle cookies with the coarse salt.

5. Bake in the oven for 8–9 minutes, watching carefully because they can burn easily. They should be just lightly browned on top.

6. Let cool for 10 minutes on the baking sheet. Then transfer to a plate or container for storage.

7. These can be stored in a cool place in the pantry for 2 days or in the fridge for 1 week. You can freeze these for 3 to 4 months.

OCT 2018 |
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PRESENTED BY CIBC
TO OUR EARS
(L-R) Lynn Posluns, Marcia Gay Harden, Jeanne Beker

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Support for WBHI and women's brain health continues

JAN 2018 | PRESENTED BY RBC | ARCADIAN STUDIO
ENGAGING MILLENNIAL MINDS // COOKING FOR ME
(L-R) Dr. Elizabeth Chertkow, Carly Picov, Chef Jeremy Korten, Laura Best, Matteo Tino, Chef Michael Bonacini, Alvin Chauhan, Matthew Earl

NOV 2018 | CO-HOSTED WITH AGE-WELL AT AUTODESK

MIND MATTERS // DIABETES

(L-R) Dr. Joseph Cafazzo, Dr. Laura Rosella, Dr. Vivien Brown

DEC 2018 | CO-HOSTED WITH AGE-WELL AT AUTODESK

MIND MATTERS // STAYING INDEPENDENT

(L-R) Dr. Alex Mihailidis, Dr. Goldie Nejat, Nira Rittenberg, Dr. Vivien Brown

Domenico De Sole

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(L-R) Huma Abedin, Sylvana Ward Durrett

(L-R) Jamie Tisch, Lynn Posluns

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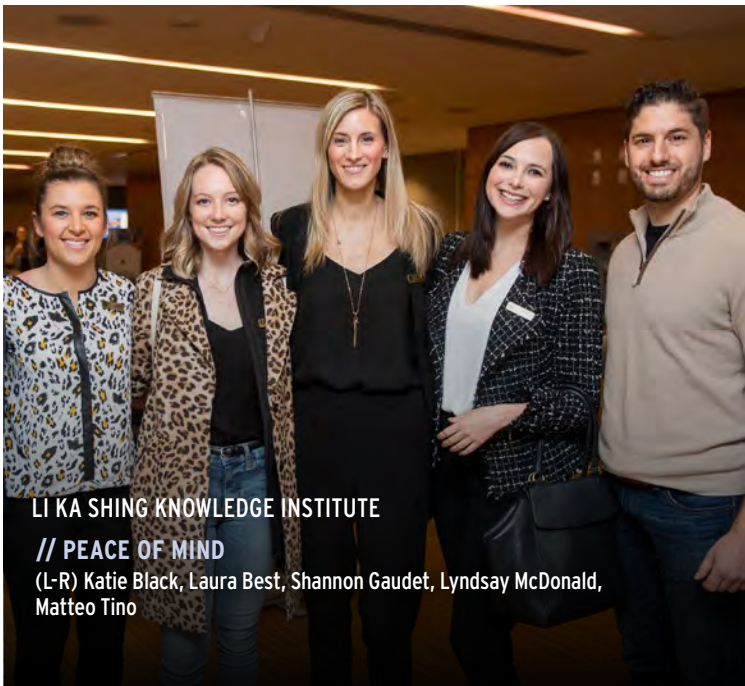
ENGAGING MILLENNIAL MINDS

(L-R) Julia Hamer, Martin Reader, Dr. Hayley Hamilton



LI KA SHING KNOWLEDGE INSTITUTE

// PEACE OF MIND

(L-R) Katie Black, Laura Best, Shannon Gaudet, Lyndsay McDonald, Matteo Tino

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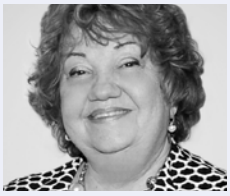

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