As a reader of Mind Over Matter®, you are likely aware of mild cognitive impairment (MCI), an early stage of memory loss and thinking problems associated with a greater risk of developing Alzheimer's disease (AD) and other forms of dementia. But have you heard about mild behavioural impairment (MBI)?

MBI is a neurological syndrome that describes the emergence of new and persistent mood, behaviour, or personality disturbances after age 50. Individuals with MBI have a higher risk of developing AD and dementia.

"Traditionally, we treat individuals experiencing neuropsychiatric symptoms like anxiety and depression with psychiatric medications. However, if their symptoms meet the criteria for MBI, we should also be evaluating these people for underlying, emergent dementias," said Dr. Zahinoor Ismail, clinician scientist and Professor of Psychiatry, Neurology, Epidemiology, and Pathology at the Hotchkiss Brain Institute and O'Brien Institute for Public Health at the University of Calgary, Alberta.

> **"RECOGNIZING MBI AS A RISK SYNDROME FOR DEMENTIA WILL ALLOW MORE PEOPLE TO ACCESS NEW TREATMENT OPTIONS FOR PREVENTING OR DELAYING DEMENTIA AND MAKE EARLIER CARE PLANS WITH PHYSICIANS AND FAMILY MEMBERS AS SOON AS POSSIBLE.**

Dr. Ismail's work has focused on MBI for more than a decade. He led the international panel that created and validated the accepted criteria for diagnosing MBI, and a measurement tool called the MBI Checklist, which is now used in clinical trials of new drugs for preventing AD.

Mild Behavioural Impairment

WHAT YOU NEED TO KNOW ABOUT NON-COGNITIVE MARKERS OF DEMENTIA

You, a care partner, or your physician can download a copy of the MBI Checklist, which has been validated for completion in person, online, or by telephone. Canadian adults can also access it by participating in the CAN-PROTECT study, an online longitudinal study of brain aging detailed later in this story.

This article summarizes what you need to know about MBI from our interview with Dr. Ismail.

NEUROPSYCHIATRIC SYMPTOMS OF DEMENTIA

Neuropsychiatric symptoms of dementia (NPS) are sometimes referred to as non-cognitive dementia symptoms. Common NPS include anxiety, depression, irritability, agitation, apathy or indifference, delusions, and hallucinations.

NPS in AD have been known for more than 100 years. Dr. Alois Alzheimer's first case, Auguste Deter, presented with emotional distress and delusions of infidelity *before* she experienced memory loss and vision and language problems. After she passed away, autopsy results of her brain revealed plaques, tangles, and neuronal loss, later known as classic manifestations of AD.

NPS are associated with faster cognitive decline and an accelerated timeline to severe dementia and death from dementia. They are also associated with higher institutionalization rates, greater functional impairment, worse quality of life, a higher burden of other markers of dementia, and an increased burden of care partner stress.

WHAT'S SURPRISING, THOUGH, IS THAT NPS OCCUR BEFORE DEMENTIA IN *MORE THAN HALF* OF THE PEOPLE WHO DEVELOP AD, FRONTOTEMPORAL DEMENTIA, AND OTHER DEMENTIAS.

According to a large study by researchers at Johns Hopkins University, NPS were present before dementia for about two-thirds of cognitively normal individuals who later developed dementia without MCI, and for 55% of people who had MCI and went on to develop dementia. The study findings were published in *Alzheimer's & Dementia (Amsterdam)* in 2019.

"We tend to be 'cogno-centric' – thinking only cognitive assessments can provide early warning signs of impending dementia," said Dr. Ismail. "But the brain does lots of other work, controlling moods, behaviours, and personality. Disruptions in these areas can also indicate individuals might be on their way to developing dementia."

"Identifying NPS in cognitively normal individuals represents an important window of opportunity for preventing, delaying or reducing the severity and impact of dementia in individuals at risk."

SEX DIFFERENCES IN NPS LINKED TO AD

Recently, researchers at Johns Hopkins University and the University of Thessaly in Greece found that the associations between NPS and the incidence of AD were different for women and men. Their paper was published in the *Journal of Neurology* in 2023. Highlights of the findings were as follows:

For individuals who were cognitively unimpaired at the beginning of the study:

- **moderate to severe apathy was a strong predictor of future AD in men but significantly less predictive in women;**
- **mild depression and agitation were predictors of AD in women but less so in men; and**
- **moderate to severe depression was linked to a higher risk of AD for both sexes, but the risk was significantly higher for men than women.**

MBI CRITERIA

To define and capture the broad range of NPS associated with dementia risk, an international team of researchers developed and published the diagnostic criteria for MBI in 2016. Dr. Ismail was Academic Co-Chair of the research team, the U.S. Alzheimer's Association-International Society to Advance Alzheimer's Research and Treatment (ISTAART) Neuropsychiatric Syndromes Professional Interest Area, and led the development of the MBI concept.

An MBI diagnosis requires evidence that a change has occurred in symptoms falling under one of these five neuropsychiatric domains:

1. **decreased motivation:** decreased motivation or drive, loss of interest
2. **emotional dysregulation:** mood (depression) or anxiety symptoms, dysphoria (dissatisfaction with life), euphoria (intense elation)
3. **impulse dyscontrol:** agitation, irritability, poor frustration tolerance, impulsivity

4. **social inappropriateness:** lack of empathy, loss of insight, loss of social graces or tact

5. **abnormal perception or thoughts:** delusions or hallucinations

IF NPS IN THESE DOMAINS APPEAR FOR THE FIRST TIME AFTER THE AGE OF 50, PERSIST FOR AT LEAST SIX MONTHS, AND REPRESENT CHANGES IN AN INDIVIDUAL'S USUAL PERSONALITY OR BEHAVIOUR, AND ARE NOT EXPLAINED BY ANOTHER DISORDER OR A PRE-EXISTING DEMENTIA DIAGNOSIS, THEY MEET THE CRITERIA FOR MBI.

THE MBI CHECKLIST

To make the MBI Criteria actionable, Dr. Ismail and colleagues created an instrument called the MBI Checklist. Their paper describing the handy tool was published in *Journal of Alzheimer's Disease* in 2017.

Today, the MBI Checklist is available in 30 languages and used worldwide in dementia research, including by the U.S. National Alzheimer's Coordinating Center, the central hub for coordinating the National Institute of Aging's Alzheimer's Disease and Research Centers Program. Dr. Ismail was lead author of the national guidelines published in *Alzheimer's & Dementia* following the 5th Canadian Consensus Conference on the Diagnosis and Treatment of Dementia.

The MBI Checklist is an easy-to-use, two-page questionnaire that covers 34 items across the five MBI domains. Since even subtle changes in NPS in advance of cognitive impairment can predict dementia, there are checkboxes for indicating whether the symptoms are mild, moderate, or severe in intensity.

Dr. Ismail pointed out that researchers interpret MBI Checklist results carefully and in context. "The cut-off score for identifying MBI depends on an individual's baseline cognitive status," he said. "For example, eight points or more would be concerning for a cognitively normal individual, indicating they should see a clinician for a neurological evaluation. For someone with a pre-existing MCI diagnosis, a score of six or more would raise concern."

DIFFERENT TYPES OF BRAIN IMPAIRMENT

MILD COGNITIVE IMPAIRMENT (MCI)

MCI is an early stage of memory loss and thinking problems that do not affect a person's ability to carry out usual daily activities but are serious enough to be noticed by others.

The incidence of MCI increases with aging, but it is not part of the typical aging process, the Alzheimer's Association says.

Studies estimate that 10 to 15% of individuals with MCI go on to develop dementia each year, and about one-third of people with MCI develop Alzheimer's disease (AD) within five years. Also, some people diagnosed with MCI do not experience further cognitive decline, and some revert to normal cognition, according to the Alzheimer's Association.

Neuropsychiatric symptoms (NPS) are common in MCI and are consistently associated with a higher risk of dementia and poorer cognitive and psychosocial function, according to several population and clinic-based studies. The estimated annual rate of progression to dementia for individuals with MCI and NPS is 25%. For MCI without NPS, the annual rate of progression to dementia is estimated at 10 to 15%.

MILD BEHAVIOURAL IMPAIRMENT (MBI)

MBI is a neurological syndrome defined by mood, behaviour, or personality disturbances occurring for the first time after the age of 50 and persisting for six months or longer.

The NPS of MBI are sometimes called non-cognitive dementia symptoms. They stand out as distinct changes from an individual's usual mental, behavioural, and emotional health and are noticeable by the individual or their care partner, friend, or physician.

There is growing evidence that shows that MBI symptoms in cognitively normal individuals and those with MCI are linked with known AD markers. These markers include amyloid, tau, neurodegeneration, and AD risk genes.

MBI can emerge at any point on the dementia development continuum, from normal cognition to subjective cognitive decline to MCI, and signifies greater risk in all three groups compared to those without MBI.

“I MUST ALSO EMPHASIZE THAT ONLY NEWLY EMERGENT SYMPTOMS SHOULD BE SCORED – NOT MOOD, BEHAVIOUR, OR PERSONALITY SYMPTOMS THAT HAVE EXISTED OVER A LIFETIME. SYMPTOMS MUST ALSO BE PRESENT FOR SIX MONTHS OR MORE. FOR EXAMPLE, SHORT-TERM ANXIETY AFTER A BIG DISAGREEMENT WITH YOUR SPOUSE IS NOT LIKELY TO BE RELATED TO AN UNDERLYING DEMENTIA.

Individuals with symptoms that meet the MBI Criteria should also have a complete medical check-up to rule out other conditions that may be causing NPS, such as untreated hypothyroidism, Dr. Ismail said.

The MBI Checklist has been validated for completion by individuals, care partners, or physicians. However, it’s essential for a physician or clinician to interpret the results in context with an individual’s overall medical and psychiatric history. You can download a free copy by visiting mbitest.org after agreeing to some conditions and terms of use.

RESEARCH IN PROGRESS TODAY

Researchers are currently using the MBI Checklist in clinical trials of new drugs for preventing AD in cognitively normal individuals with amyloid beta deposits, which indicate a higher risk of developing AD. For example, investigators are using the tool in the Phase 3 TRAILBLAZER-ALZ 3 study to see if the medication donanemab reduces the likelihood of developing dementia.

Dr. Ismail has seen that effect in one of his patients who participated in one of the original clinical trials for aducanumab (Aduhelm®), the anti-amyloid antibody approved by the U.S. Food and Drug Administration in June 2021 but not yet approved in Canada. The patient had been taking the drug over the past seven years. When the study ended, and he had to stop taking the drug, his cognition declined. However, after going back on the drug in an extension of the trial, his cognition improved with every dose.

“HIS WIFE SAID HE WAS NOT JUST COGNITIVELY BETTER, HE WAS NO LONGER IRRITABLE, ILLUSTRATING THERE IS A NEUROBIOLOGY TO BEHAVIOUR DISRUPTION RELATED TO ALZHEIMER’S THAT IS DISTINCT FROM WHAT WE USUALLY THINK ABOUT PSYCHIATRIC CONDITIONS.

The CAN-PROTECT Study (www.CAN-PROTECT.ca), a nationwide study for evaluating risk factors and resilience in brain health as Canadian adults age, includes the MBI Checklist. Dr. Ismail is leading the study in partnership with colleagues at the University of Exeter in the United Kingdom.

Individuals 18 and older located anywhere in Canada with access to a computer or touchscreen device can participate. Once yearly, they complete a set of brain health assessments, including cognitive function tests, brain training games, daily function assessments, questionnaires about diet, activity, lifestyle, medical history, and a mental health assessment.

Each assessment takes about an hour, so the annual commitment to participate is about three to seven hours at the participant’s leisure, depending on how many assessments individuals choose and those required. The researchers hope to recruit 10,000 participants and plan to collect data for 20 years.

“We are tracking changes over time,” Dr. Ismail said. “Participants can opt in to be notified if their cognitive test scores drop over time and receive a suggestion to get checked out by their healthcare provider.”

“We are also enrolling caregivers of people living with dementia for caregiver-specific assessments. Informal caregivers, including partners, friends, family members, and formal caregivers, such as long-term care nurses, personal care aides, occupational and recreation therapists, and physicians, are eligible to take part in the study,” said Dr. Ismail. “Our goal is to learn more about the burden of dementia caregiving so that we may develop better supports.”

At the time of our interview, the CAN-PROTECT study had enrolled more than 2,000 participants. While the original cut-off age was 40, Dr. Ismail said they dropped it recently to 18.

“BRAIN AGING AND RESILIENCE DON’T MAGICALLY START AT 40,” DR. ISMAIL SAID. “BY OPENING UP THE STUDY TO CANADIANS 18 AND UP, WE CAN TRACK MORE PEOPLE OVER TIME AND ASSESS RISK AND RESILIENCE ACROSS THE LIFESPAN. WE HOPE OUR FINDINGS WILL OFFER A ROBUST LOOK AT BRAIN HEALTH AS PEOPLE AGE.

Being aware that NPS of dementia are core to the dementia process and recognizing MBI as a neurological syndrome that predicts future dementia is essential, especially given the rapid anticipated growth in the number of individuals living with AD and other dementias. The MBI Checklist will make it easier for individuals, care partners, and physicians to spot MBI, helping more individuals at risk access new treatment options for preventing or slowing AD and dementia.