Symposium at the 20th Meeting of the Norwegian Neuropsychological Association. September 7th (2:30 pm-4:00 pm) 2016 at Quality Hotel Expo, Fornebu.

Challenges in diagnosis of people with mild cognitive impairment (MCI).

1. The MCI concept and the relevance of neuropsychology for diagnosis and prognosis. (Prof. Erik Hessen, Dept. of Neurology, Akershus University Hospital/Dept. of Psychology, University of Oslo)

2. Mild cognitive impairment due to Alzheimer’s Disease. Biological markers, cognitive findings and prognosis (Prof. Tormod Fladby, Dept. of Neurology, Akershus University Hospital/Faculty of Medicine, University of Oslo).

3. Mild cognitive impairment due to Parkinson’s Disease. Biological markers, cognitive findings and prognosis (Prof. Kolbjørn Brønnick, Faculty for Social Sciences, University of Stavanger).

4. The Gothenburg MCI study and predictors for longitudinal outcomes (Dr. Arto Nordlund, PhD, Institute of Neuroscience and Physiology, University of Gothenburg).

5. Memory training and MRI in normal aging and SCI (Prof. Kristine Walhovd, Research Group for Lifespan Changes in Brain and Cognition (LCBC), University of Oslo)
The MCI concept and the relevance of neuropsychology for diagnosis and prognosis.

Prof. Erik Hessen
University of Oslo/Dept. of Psychology
Akershus University Hospital/Dept. of Neurology
What is MCI?

• Intermediate stage between the expected cognitive decline of normal aging and the more-serious decline of dementia.

• Can involve problems with memory, language, thinking and judgment.

• **Not meant to reflect lifelong low cognitive functioning (normal variation) - meant to reflect a change for this individual person!!**

• Changes usually not severe enough to interfere with ordinary activities.

• May increase risk of later progression to dementia, caused by Alzheimer's disease or other neurological conditions.

• Some people with MCI never get worse, and a few eventually get better.
Dementia forms

NIH, 2013

- Alzheimer's: 47%
- Mixed Alzheimer's: 28%
- Vascular: 9%
- Frontotemporal: 5%
- Parkinson's: 2%
- Mixed & Others: 9%

Total: 100%
Proposed disease development Alzheimer’s disease (AD)

- A prevailing (not undisputed) model suggest AD to start with deposition Amyloid b (Ab) protein in cortex - leading to:
  1. synaptic dysfunction
  2. neurodegeneration
  3. cognitive changes (MCI)
  4. and functional decline associated with early dementia (Jack et al., 2010, Sperling et al., 2011).

- Suggested time span from detectable amyloid pathology until dementia 10-15 years or more (Perrin et al., 2009).

Theoretical model for manifestation of risk factors for development of AD (Sperling et al., 2011).

Neuropsychology mostly relevant in the clinical disease stage.
Massive problem today:

- **5.4 million in the US have AD**  
  (Alzheimer’s Association 2016, alz.org)
- About 5.2 million above 65 years
- Approximately 200,000 below 65 (younger-onset AD).
- **One in nine people age 65 and older has AD**
- Increased longevity - larger problem tomorrow: **Risk of AD doubles every 5 years between 65 and 85**

- Early identification considered important as preventive measures and disease modifying treatments may be developed

---

**Mild Cognitive Impairment (MCI) - Why is it important?**

Concern regarding a change in cognition

• Compared to prior level. Obtained from patient, close informant or skilled clinician

Impairment in 1 or more cognitive domains

• More than expected from age/education.
• If repeated assessments, decline should be evident. Change can occur in several cognitive domains recommended to be tested (according to Key Symposium criteria): memory, executive, attention, language or visuospatial skills.
• Impairment in episodic memory most common in MCI patients who subsequently progress to AD
• Common impairment criterion: 1.5 SD or more below normative mean

Preservation of independence in functional abilities

• Only mild problems performing complex functional tasks: paying bills, preparing meals, shopping

Not demented

• No evidence of significant impairment in social or occupational function
Key Symposium criteria (still in use) (Stockholm 2003).

- First Key Symposium criteria demonstrate the syndromic phenotypes and how they can be paired with possible etiologies to assist the clinician in making a diagnosis.

<table>
<thead>
<tr>
<th>Etiology</th>
<th>AD</th>
<th>AD</th>
<th>FTD</th>
<th>DLB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degenerative</td>
<td>Alzheimer</td>
<td>Alzheimer</td>
<td>Frontotemporal dementia, MCI = mild cognitive impairment, VCI = vascular cognitive impairment.</td>
<td></td>
</tr>
</tbody>
</table>
MCI subtype and conversion to AD

- Studies find different risk profiles depending on broad/short test batteries/different algorithms/cut offs
- Amnestic, multiple domain – highest conversion rates
- Amnestic only - intermediate rate
- Single non-memory impairment - lowest conversion rates

Longitudinal outcomes from the Gothenburg – Oslo (Ahus) MCI study

Old samples in the large and dominating MCI studies:

- **70-89 years** in Mayo Clinic Study of Aging

- **Mean 75 years (SD=7.5)** in Alzheimer’s Disease Neuroimaging Initiative

The Gothenburg-Oslo MCI study much younger (mean 63 years, SD=7.5) and much lower risk for dementia.

Our question: Are the same cognitive progression factors known for older MCI also relevant in young MCI?

Inclusion criteria:

- Subjective and objective (verified by an informant) evidence for progressive cognitive impairment for more than 6 months.
- Mild objective cognitive symptoms according to screening procedures (Cognistat, MMSE 25-30)

Exclusion criteria:

- Major depressive and other severe psychiatric disorders
- Neurological disease
- History of TBI
- Cardiovascular accident
- Other severe somatic illness or current substance abuse
- Dementia: significant impairment in social or occupational function and/or a score below 25 on MMSE

(Hessen et al. 2014)

Prognosis og cognitive function in a relatively young cohort of patients characterized by neuropsychological criteria:

1. Single domain amnestic MCI
2. Single domain dysexecutive MCI
3. Multidomain deficit MCI (amnestic MCI + dysexecutive MCI)

We hypothesized that combined executive dysfunction and amnestic problems at baseline would increase the risk of conversion to dementia.
To achieve high n we included the tests of executive function and memory that were most frequently used at both sites – only four tests- a very brief test battery:

- **Two memory tests:**
  1. Delayed verbal memory: RAVLT
  2. Delayed visual memory: RCFT

- **Two executive measures:**
  1. Divided attention: TMT-B
  2. Verbal fluency: COWAT (FAS)

- **Cut off set to T=37, a criterion employed in several MCI studies**
  (Chao et al. 2009, Grambaite et al. 2011 etc).
MCI algorithm

Dysexecutive, amnestic and multidomain MCI defined by neuropsychological scores:

- A score below cut off on at least 1 executive or 1 memory test and no scores below cut-off in the other domain were characterized as either dysexecutive MCI or amnestic MCI.

- Patients scoring below the cut off on at least 1 test from both domains defined as multidomain MCI.

- The rate of conversion to dementia after 2 years (GDS 4 or higher) was analyzed for each of the MCI subtypes.
### Baseline characteristics study patients – Gothenburg-Oslo MCI Study (Hessen et al. 2014)

<table>
<thead>
<tr>
<th>Demographic and clinical variables</th>
<th>All patients (n=302)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD)</td>
<td>62.7 (7.5)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>166 (54.9)</td>
</tr>
<tr>
<td>Education (SD)</td>
<td>12.2 (3.4)</td>
</tr>
<tr>
<td>GDS (SD)</td>
<td>2.7 (0.5)</td>
</tr>
<tr>
<td>MMSE (SD)</td>
<td>28.4 (1.3)</td>
</tr>
<tr>
<td>RAVLT, delayed recall, T-score (SD)</td>
<td>44.2 (13.4)</td>
</tr>
<tr>
<td>RCFT, delayed reproduction, T-score (SD)</td>
<td>43.8 (15.4)</td>
</tr>
<tr>
<td>COWAT, T-score (SD)</td>
<td>49.7 (10.9)</td>
</tr>
<tr>
<td>TMT-B, T-score (SD)</td>
<td>47.3 (10.1)</td>
</tr>
</tbody>
</table>

*Group scores as normally expected regarding education and cognition*
## Development of MCI subtypes over 2-years - Gothenburg - Oslo MCI Study

<table>
<thead>
<tr>
<th>Baseline diagnosis</th>
<th>Follow-up after 2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>noMCI</td>
</tr>
<tr>
<td>noMCI (%)</td>
<td>140 (46.4)</td>
</tr>
<tr>
<td>Executive MCI (%)</td>
<td>19 (6.3)</td>
</tr>
<tr>
<td>Amnestic MCI (%)</td>
<td>96 (31.8)</td>
</tr>
<tr>
<td>Multidomain MCI (%)</td>
<td>47 (15.6)</td>
</tr>
<tr>
<td>Total (%)</td>
<td>302 (100)</td>
</tr>
</tbody>
</table>
 Development of MCI subtypes over 2-years - Gothenburg - Oslo MCI Study

• Only 4 % of patients with normal test results at baseline converted to dementia over 2 years- similar to expected for the normal population (Bruscoli & Lovestone 2004) – can be given a good prognosis.

• **Dysexecutive symptoms increased risk for dementia in a multidomain context, suggesting dysexecutive and amnestic symptoms combined represent a development of MCI, and is a strong risk factor for dementia in young MCI patients.**

• Pure amnestic impairment also significantly associated with development of dementia, but to a lesser degree than multidomain impairment.

• **Findings similar to older cohorts** (Petersen et al. 2009. Mild cognitive impairment: ten years later. *Archives of Neurology*. 66, 2, 1447–1455)
Hippocampal Subfield Atrophy in Multi-Domain but Not Amnestic Mild Cognitive Impairment
Eliassen C.F., Selnes P., Selseth Almdahl I., Reinvang I., Fladby T., Hessen E.
*Dement Geriatr Cogn Disord* 2015;40:44-53

- **Employing a comprehensive MCI criterion** (Jak. et al. 2009) we found atrophy in perirhinal and entorhinal cortices in amnestic MCI (aMCI) and significantly more affection of the hippocampal subfields in multiple domain MCI (mdMCI), probably representing a clinical progression relative to amnestic MCI coupled with hippocampal subfield affection.
SCI is frequent but is it a valid pre-dementia marker?

Approximately prevalence of subjective cognitive impairment (SCI), MCI and dementia 60-80 years


- Examined whether subjective memory impairment (SMI) predicts all-cause dementia or Alzheimer's disease (AD) in a population-based study with long-term follow-up.

- A total of 2043 initially dementia-free participants (≥ 60 years) made three memory ratings ("compared with others", "compared with five years ago", and "complaints from family/friends") at baseline. During follow-up (median = 10 years), 372 participants developed dementia (208 with AD).

- Cox regression revealed that subjective memory impairment ratings predicted:
  1. all-cause dementia in models adjusting for age and sex (Hazard ratio or HR from 2.04 to 3.94)
  2. even higher values for AD (HR from 2.29 to 5.74).

- The result persisted in models including other covariates, including baseline episodic memory performance, and in analyses restricted to participants with long time to dementia diagnosis (≥ 5 years).

- The findings underscore the usefulness of subjective memory assessment in combination with other factors in identifying individuals at risk for developing dementia.

- Similar findings in other studies, e.g.:
Cognitive disorders **underestimate** memory complaints (MCI)

Affective, adjustment and anxiety disorders **overestimate** memory complaints (SCI)

• Mean discrepancy scores (self-rating minus informant-rating) for all 39 items on the Ecog (Questionnaire about cognitive function.)

• A positive score indicates one is **overestimating** their cognitive decline relative to their study-partner’s report, while a negative score indicates one is **underestimating** their cognitive decline.

Effect of amyloid on memory and non-memory decline from preclinical to clinical Alzheimer’s disease
Yen Ying Lim et al., Brain Jan 2014, 137 (1) 221-231

• Healthy individuals, MCI and AD underwent PET imaging for beta-amyloid.

• Cognitive assessments at baseline, and 18- and 36-month follow-ups.

• Compared with amyloid-negative healthy - amyloid-positive healthy, and amyloid-positive MCI and AD showed moderate and equivalent decline in verbal and visual episodic memory over 36 months (Effect sizes = 0.47–0.51).

• Amyloid negative with MCI did not show any cognitive decline over 36 months.

Thus, a subgroup of normals/SCI (amyloid-positive) may be of particular interest
What happened to our noMCI/SCI patients after 6 years:

<table>
<thead>
<tr>
<th>Baseline diagnosis</th>
<th>After 2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>noMCI (%)</td>
<td>140 (46.4)</td>
</tr>
<tr>
<td>noMCI</td>
<td>110 (78.6)</td>
</tr>
<tr>
<td>Executive MCI</td>
<td>6 (4.2)</td>
</tr>
<tr>
<td>Amnestic MCI</td>
<td>15 (10.7)</td>
</tr>
<tr>
<td>Multidomain MCI</td>
<td>3 (2.1)</td>
</tr>
<tr>
<td>Dementia</td>
<td>6 (4.3)</td>
</tr>
</tbody>
</table>

- So far observed 81 of the noMCI/SCI (normal cognitive function at baseline) and followed them for 6 years (Submitted).

- Hypothesis:

  1. that the majority of the patients would remain cognitively stable.

  2. low Aβ42 at baseline would be the most powerful predictor of dementia development. We also assumed that other baseline CFS biomarkers would be more pathological in patients that developed dementia after 6 years.

  3. patients with memory decline during the first 2 years of observation would be at higher risk of both further cognitive decline and development of dementia after 6 years.
Two year follow up of 122 SCI patients find indication of neurodegenerative cause for memory decline: Memory decline > 0,5 SD (but within the normal range) associated with significantly higher T-tau at baseline than the group with improved memory (T-tau 341 vs 260, p=0.04).

The baseline memory score of those who declined was significantly better than the baseline score of those who improved over two years (T-score 56 vs T-score 52, p=0.02).

Thus, a memory cut-off indicating low baseline memory, would not would have identified the declining group!
Baseline neuropsychological scores for SCI patients that were followed for six years – all T-scores above 37 and normal group level

<table>
<thead>
<tr>
<th>Tests</th>
<th>All patients (n=81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAVLT, delayed recall, T-score (range)(SD)</td>
<td>53.9 (37-81) (9.0)</td>
</tr>
<tr>
<td>RAVLT, delayed recall, raw-score (range)(SD)</td>
<td>9.9 (5-15) (2.4)</td>
</tr>
<tr>
<td>RCFT, delayed reproduction, T-score (range)(SD)</td>
<td>55.2 (38-80) (10.4)</td>
</tr>
<tr>
<td>RCFT, delayed reproduction, raw-score (range)(SD)</td>
<td>18.9 (9-30) (4.9)</td>
</tr>
<tr>
<td>COWAT, T-score (range)(SD)</td>
<td>54.6 (38-75)(9.4)</td>
</tr>
<tr>
<td>COWAT, raw-score (range)(SD)</td>
<td>45.0 (22-88) (12.7)</td>
</tr>
<tr>
<td>TMT-B, T-score (range)(SD)</td>
<td>51.6 (37-72)(7.8)</td>
</tr>
<tr>
<td>TMT-B, raw-score (range)(SD)</td>
<td>81.7 (41-195) (27.6)</td>
</tr>
<tr>
<td>Average Memory T-score (range)(SD)</td>
<td>54.5 (40-70)(7.4)</td>
</tr>
<tr>
<td>Average Executive T-score (range)(SD)</td>
<td>53.1 (40-71)(6.2)</td>
</tr>
</tbody>
</table>
Results:

• Only 4 (5%) converted to dementia, 95% remained cognitively stable.
• Low Aβ42 at baseline and memory decline the first 2 years predicted dementia. Combined these variables associated with 50% risk of conversion to dementia.

Conclusions:

• The SCI group mainly consisted of cognitively healthy persons.
• Support the notion that low Aβ42 in CSF is a sensitive marker for development of dementia. Studies with more converters needed for stronger analysis of etiological mechanisms.

• Future studies should employ more stringent SCI criteria to avoid long term follow up of healthy persons.
Neuropsychological factors clearly useful in prediction of cognitive development: (Based on premises in Gothenburg-Oslo MCI study: inclusion/exclusion criteria, age group and short test battery, employed cut-off score)

• Neuropsychological defined SCI imply minimal risk for dementia after 6 years (about 5%), similar to the normal population

• Neuropsychological defined multidomain MCI (amnestic and executive deficit) found to be a strong risk factor for conversion to dementia in young MCI patients in a 2 year perspective (about 60%)

• Neuropsychological defined amnestic MCI also significantly associated with development of dementia in a 2 year perspective (about 29%)
Thank you for your attention!