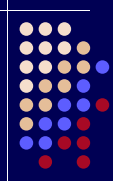


Sydney Memory and Ageing Study


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Prevention of dementia

- Universal strategy
 - eg reduce salt in food to lower BP
 - ? folate fortification of food
 - ?poly pill
 - ? regular mind exercises
- Targeted strategy
 - eg use of safe & effective vaccine for those at risk



Targeted dementia prevention

- Need to identify persons at risk
 - Biomarker – PET PIB, CSF, blood
 - Genotype eg ApoE ε4
 - **Clinical phenotype eg MCI**
 - **Gene * Environment interaction**



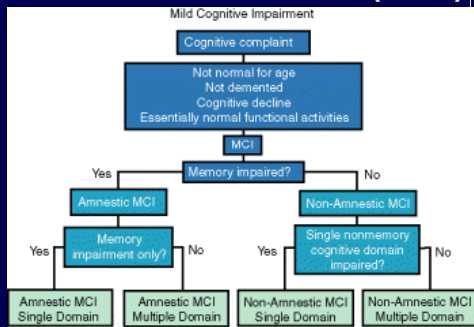
MCI: Dominant phenotype

- Petersen criteria revised ^{1, 2}
 - Not normal, not dementia
 - Self and/or informant report
 - Impairment on objective cognitive tasks and/or
 - Evidence of decline over time on objective cognitive tasks
 - Preserved basic ADLs and minimal impairment of complex function
 - Generally intact global cognition

¹ Petersen et al, Arch Neurol 1999;56:303-308 ² Winblad et al J Intern Med 2004;256:240-246



Revised Petersen Criteria (2004)



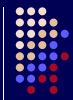
Petersen RC (2004) Journal of Internal Medicine 256 (3), 183-194



Controversies about MCI

- Definitional criteria
 - Mainly threshold questions
- Stability and predictability
 - Progression to dementia rates vary between 0 and 34% p.a.

Visser PJ, Brodaty H. For debate: MCI is not a clinically useful concept, *International Psychogeriatrics*, 2006;18(3)402-409.



MCI criteria: controversy 1

- Self and/or informant report of cognitive decline
- What is Subjective Cognitive Complaint?¹
 - From person or informant?
 - In response to question, spontaneous or seeking help?
 - Does it have to be in cognitive domain corresponding to objective impairment?
- Is SCC important in defining pre-dementia?^{1,2}

¹ Brodaty et al, 2008; ² Fisk et al, 2003



Link between Subjective Memory Complaints and Objective Performance

- | | |
|-------------------------|---------------------------|
| • Association ✓ | • No association ✗ |
| • Mol et al, 2006 | - Jungwirth et al, 2004) |
| • Lam et al, 2005 | - Frerichs & Tuokko, 2006 |
| • Cook & Marsiske, 2006 | - Luck et al 2007 |
| • Crooks et al, 2005 | |

SMCs have been associated with depression, personality variables



Limitations of Previous Studies

- Limited measurement of SMCs (1 yes/no question)
- Non-memory complaints not measured
- Objective cognitive impairment measured not at all or inadequately (eg only MMSE)
- Small group numbers



Other Cognitive Domains

- We asked similar questions about decline in last 5 years in other domains
- Language (eg word finding, tip of tongue, explaining things)
- Executive Fn - organisation/planning (eg following recipe), problem solving, interest in activities
- Visuo-spatial (eg finding way in familiar/unfamiliar places, dressing)

Brody, Slavin et al, ICAD, Chicago, July 2009



Sydney Memory and Ageing Study

- Little relationship between measures of SCC and objective impairment
- Participant more likely to have SCC than informant (for memory and non-memory)
- Subjective complaint is related to mood and personality
- No good evidence for a particular method of measuring subjective complaint

Brody, Slavin et al, ICAD, Chicago, July 2009



MCI criteria: controversy 2

Operationalizing "Preserved basic ADLs and minimal impairment of complex function" – what is threshold?

- Basic ADLs intact ✓
- Lower order IADLs intact: managing medications, finances, driving ✓
- Threshold for higher order IADLs ?

Brody, Slavin et al, ICAD, Chicago, July 2009



MCI criteria: controversy 3

Operationalizing “generally intact global cognition”

- MMSE score > 24?
 - Adjust for education?
 - Adjust for language/culture of administration
- Rely on informants?



MCI stability/ predictability

- Rates of progression to dementia vary from 0 – 19.5% pa depending on:
 - Criteria
 - Threshold for impairment/ decline
 - Population being studied
 - Setting - clinic, community
 - Age

Petersen RC et al 1999, Ritchie K et al 2003, Wahlund 2001; Fischer P 2007



The best MCI definition to predict progression?

- Aims of Memory and Ageing Study
 - to examine effects of different definitions of criteria on rates and types of MCI
 - to examine which set of criteria best predicts progression to dementia



Sydney Memory and Ageing Study

- Population based study
- Electoral roll 70-90 yo, eastern Sydney
 - 8914 mailed → 1772 responded
 - 1037 eligible (incl^u MMSE > 24)
- Exclude those with dementia, psychiatric disorders, neurological disorders, developmental disability, active malignancy, insufficient English competency for testing



Sydney Memory and Ageing Study

- Comprehensive assessment of 1037 Ss and informants including
 - detailed neuropsychological tests
 - MRI (52.3%)
 - bloods, genetics (>90%)
- This analysis focus on 718 Ss “native” English speakers with full data sets
- Follow up: at 12 months by telephone and at 2 yrs with comprehensive assessment



Rating Subjective Cognitive Complaint

- Participant
 - Changes in Thinking: 3 Qs each rated as
 - 1= a lot better,
 - 2 = a bit better,
 - 3 = a bit worse
 - 4 = a lot worse
 - memory
 - language
 - visuo-spatial
 - executive function
- Participant
 - MAC-Q = 5 specific questions and 1 global
- Informant
 - IQCODE \geq 3.3



Defining SCC – 6 methods

1. MAC-Q ≥ 25
2. IQCODE ≥ 3.3
3. Participant SCC (liberal) ie any complaint on MAC-Q or CIT (ie \geq a bit worse)
4. Participant SCC (strict) ie $>$ stringent ie "a lot worse" on MAC-Q or CIT
5. Informant SCC (liberal) ie any complaint on IQCODE (ie \geq a little more than usual)
6. Informant SCC (strict) ie complaint on IQCODE \geq much more than usual



Rating IADLs

- Bayer IADL scale
 - more sensitive to higher order IADLs
 - eg understanding financial affairs; doing two things at same time
- 25 items, scores 1 – 10
- Two thresholds for normal based on
 - strict = within 6.68% of mean
 - liberal = within 15.86% of mean



Objective Cognitive Impairment

Cognitive domain	Test measure
Premorbid IQ*	1. National Adult Reading Test - R
Attention/ Processing speed	1. Trail Making Test A 2. WAIS-III Digit Symbol
Memory	1. Logical Memory: delayed recall 2. Rey Auditory Verbal Learning Test: total learning; immediate & delayed recall 3. Benton Visual Retention Test
Language	1. Boston Naming Test 2. Semantic fluency (animals)
Visuo-spatial *	1. WAIS-R Block Design
Executive	1. Trail Making Test B 2. Controlled Oral Word Association test (FAS)

* Test not used in this analysis

Objective Cognitive Impairment

- Four conditions for any of four domains:
- Memory
- Speed
- Language
- Executive

Threshold Def of Impaired	<1 SD (16%)	< 1.5 SDs (<6%)
1 test impaired in a domain		
2 tests impaired in a domain		



Summary of MCI definitions

- 6 SCC x 2 IADL x 4 Objective Cognitive Impairment = 48 definitions
- Excluding variation in MMSE



Ranges of MCI rates (N = 718)

- amnesic single domain = 0.4% - 29.8%
- non-amnesic single domain = 0.1% - 12.3%
- amnesic multiple domain = 0.1% - 23.8%
- non-amnesic multiple domain = 0.1% - 7.9%
- TOTAL MCI = 1.5% - 55.8%



Category Conundrums



1. No SCC + no OCI + normal function = **Normal**
2. SCC + no OCI + normal function = **Worried Well**
3. SCC + OCI + normal function = **MCI**
4. No SCC + OCI + normal fntn = **no complaint MCI**
5. SCC + no OCI + impaired function = **c MFI**
6. No SCC + no OCI + impaired function = **nc MFI**
7. SCC + OCI (1 domain) + impaired fntn = **MCI + MFI**
8. No SCC + OCI (1 domain) + impaired function = **non-complaining MCI + MFI**
9. \pm SCC + OCI (≥ 2 domains) + imp^d fntn = **Dementia**

Category Conundrums



1. **Normal** = 3.1 – 70.1%
2. **Worried Well** = 0.4 – 58.8%
3. **MCI** = 1.5 – 55.8%
4. **No complaint MCI** = 1.9 – 57.5%
5. **Complaint MFI** = 0.4 – 10.6%
6. **No complaint MFI** = 0.3 – 7.5%
7. **MCI + MFI + SCC** = 0.4 – 10.6%
8. **MCI + MFI + no complaint** = 0.1 – 9.3%
9. **Dementia** – excluded from sample



Worried Well, MAC-Q ≥ 25



- 9.9% not below 1 SDs on one test and within 15.86% of mean on IADL
- 19.9% not below 1.5 SDs on one test and within 15.86% of mean on IADL



Stricter criteria predict progression to dementia better*

- **Classifying a domain impaired:** 2 tests better than one test per domain
- **Classifying a test impaired:** 1 SD > 1.5 SD, but only if 2-tests-per-domain rule
- **Classifying functional impairment:** IADL 15.86%+ better than 6.68%+ above mean
- **Classifying SCC:**
 - IQCODE (≥ 3.3) better than MACQ (≥ 25)
 - informants' evaluations > participants'

* Preliminary results; using certainty coefficient; 10 cases of dementia to date.



Using this algorithm: IQCODE >3.3 + 2 tests/1 SD per domain + >fntnl imp

- | | | |
|-----------------------|---------|--------|
| 1. Normal | = 45.4% | |
| 2. Worried Well | = 6.1% | |
| 3. MCI | = 9.1% | |
| 4. No complaint MCI | = 33.2% | |
| 5. Complaint MFI | = 1.8% | } 2.9% |
| 6. No complaint MFI | = 1.1% | |
| 7. MCI + MFI + SCC | = 1.5% | } 2.9% |
| 8. MCI + MFI + no SCC | = 1.4% | |



Improving the phenotype 1

- Which algorithm works best
- Defining or omitting SCC?¹
- Effects of personality, depression
- Defining impaired function : separating physical from cognitive aetiology
- Longitudinal testing of cognition

¹Fisk et al, 2003



Improving the phenotype 2

- Proxy longitudinal testing – informant + cog test eg GPCOG²
- Defining reliability of informant³
- Adding known risk factors to algorithm
 - Family history
 - Life long life-style
 - Eg LEQ⁴
 - Biological marker⁵
 - Genetic marker

²Brody et al, 2002; ³Kemp et al, 2002;



Targeted prevention – the future

- Which phenotype is best yet to be determined
- But we already know that ApoE ε4 is predictor – can this guide prevention?



Prevention if pre-dementia diagnosed

- Routine ApoE predictive testing not recommended
- But could ApoE testing help tailor life style modifications?
- E.g. epidemiological studies found that moderate alcohol is protective
- BUT only if ApoE4+ (Finland)
- AND not if ApoE4+ (Netherlands)



Will testing for ApoE assist in tailoring dementia risk reduction?

- Systematic review of 94 articles
- Influence of ApoE on effects of risk factors for dementia such as
 - CVD, stroke, blood pressure
 - Diabetes, cholesterol, BMI, diet, homocystine
 - Use of antihypertensives, NSAIDs, HRT, lipid lowering agents, other meds
 - Smoking, alcohol, physical/mental activity, overall lifestyle

L-F Low, M H Yap, H Brodaty (2009) Neuroscience and Biobehavioural Reviews (in press)



Current smoking?



- Review shows only increases risk if ApoE negative
- 4 out of 4 papers

L-F Low, M H Yap, H Brodaty (2009) Neuroscience and Biobehavioural Reviews (in press)



Consumption of high amounts of fat (esp saturated fats)?

- Review shows only increases risk if ApoE positive
- 3 out of 4 papers



L-F Low, M H Yap, H Brodaty (2009) Neuroscience and Biobehavioural Reviews (in press)

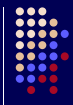


Hormone Replacement Therapy?



- If ApoE e4 positive → increases *protective effect*
- 3 out of 5 articles (+ 1 showing trend)

L-F Low, M H Yap, H Brodaty (2009).
Neuroscience and Biobehavioural Reviews (in press)



Inconclusive results...

- ApoE doesn't modify risk of dementia for:
 - CVD measures and treatments
 - Dietary factors
 - Estradiol levels
- Inconsistent or contradictory evidence:
 - other environmental factors

L-F Low, M H Yap, H Brodaty (2009).
Neuroscience and Biobehavioural Reviews (in press)



Conclusions

- Great variability in diagnosis of pre-dementia syndromes depending on criteria and thresholds
- Phenotypes alone unlikely to guide targeted prevention
- Limited evidence that ApoE genotype is useful to guide lifestyle prevention
- Future: determine best phenotype and combine with biomarkers

L-F Low, M H Yap, H Brodaty (2009).
Neuroscience and Biobehavioural Reviews (in press)



Thank you

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Thanks to Memory and Ageing Study
participants and team, Kristan Kang,
John Crawford, Lee-Fay Low, Katrin
Seeher