Henry Brodaty

Depression, Dementia, Pseudodementia, Pseudodepression.

- Centre for Healthy Brain Ageing
  www.cheba.unsw.edu.au
  University of New South Wales (UNSW Australia)
Depression & cognition

Depression

Cognitive impairment
Cognition during episode of depression

- Deficits = core feature at all ages
  - Memory, executive function, processing speed
- More in older people, if depression more severe

Airaksinen E Psycholog Medicine 2010; 34, 83–91
Cognitive deficits persist after recovery from depression

- Related to underlying neurobiological changes (atrophy, DWMH)
- More in elderly, late onset depression

1 Kohler S et al Psychological Medicine 2010;40:591-602
Older person with cognitive impairment and depression

- Is cognitive impairment secondary to depression?
- Is depression secondary to underlying brain pathology such as dementia?
Depression: risk factor for dementia

- Is it prodrome?
  - 30 year build up of AD pathology
- Is it secondary to depression?
  - Dep \( ^n \) \( \rightarrow \) cortisol \( \uparrow \) \( \rightarrow \) temporal lobe atrophy
- Is it secondary to treatment of depression?
  - Unlikely
- Mid-life depression associated with (\(?\uparrow\)) risk
- Late-life depression associated with \( \uparrow\uparrow \) risk
25-year follow-up of depression

• 71 depressed in-pts (10 deceased) and 50 surgical controls assessed 25 years later
• No signif. differences between depressed pts and controls on any neuropsychological test
• 10 depressed patients, no controls had dementia at follow-up \( P<0.01 \)
• Dementia predicted by older age at baseline
• Vascular dementia was most common type

Dementia: risk factor for depression

- Dementia associated with depression
  - $\approx 20\text{-}50\%$ people with dementia have depression
- Not associated with recency of diagnosis
  - Suggesting unlikely to be reaction
- Associated with type of dementia
  - More in subcortical dementia (PDD, VaD)
  - Suggesting likely linked to brain pathology
Risk factors common to both Depression and Dementia include brain pathology, such as CVD.
Vascular depression

- CVD predisposes, precipitates or perpetuates depressive syndrome
- MRI: > WMHs esp frontal-subcortical
- Cognitive ↓, psychomotor retardation/slowing, apathy, executive dysfunction
- Poorer response to treatment
- Worse prognosis: depression, dementia, death

Krishnan 1988, 1997; Coffey 1990; Alexopoulos 1997; Hickie 1997
Apo Eε4 & depression

• Late onset depression 43% vs EO 8% (Krishnan, 1996)
• HAAS - ApoEε4 modulates effect of depression on dementia risk in men (Irie F, 2006)
  – nondepressed w ApoEε4 ns
  – depressed w/out ApoEε4, 1.6x risk (0.8-3.0)
  – depressed men w ApoEε4, 7.1x risk (3.0-16.7)
• Cache County – no effect of ApoEε4 on LO depression, except those >80 (Steffens DC, 2003)
Depression & dementia

Clinical features overlap

Depression

Cognitive impairment
Symptoms common to both

- Hamilton Depression Rating Scale-21
  - total possible score of 64
  - Sleep disturbance, agitation, retardation, loss of interest, loss of weight/appetite, loss of libido, loss of energy, lack of insight, paranoid delusions, hallucinations $\rightarrow \leq 34$
Bedside Dx: depⁿ v dementia

Depression

• Onset recent, course > rapid
• Family always aware
• PPH, FH of dep >likely to be +ve
• > cognitive Sx, > specific
• Pt highlights failures
• Affect pervasive
• Behaviour incongruent with cognitive Sx eg social skills ↓
• O/E – “don’t know” answers, memory loss, past = recent; memory gaps often

Dementia

• Longer duration, >gradual
• Family often not aware
• FH of dementia may exist
• Pt. complains less
• Pt. highlights success
• Affect labile, shallow
• Behaviour compatible with cognitive Sx
• O/E recent memory<<past, memory gaps unusual

Wells CE, Am J Psychiatry, 1979 (n = 10, 33-69yo, 9 in-pts, 1 out-pt)
Depression* \( (n = 14) \)

- DMV: worse in morning
- >EMW, > anxiety, > libido↓

Dementia \( (n = 28) \)

- DMV: Worse in evening
- > disorientation to time
  > difficulty finding their way
  > impairment with dressing


*Pts in larger research on sleep and ageing, 35/42 in-pts.
Pseudodementia
Pseudodementia case

First episode:

- 74yo man with depression resistant to TCA Rx; MMSE 19/30
- Depression treated as inpatient with MAOI
- Recovery from depression; MMSE 30/30
- A case of pseudodementia

One year later, recurrence:

- cognitive impairment, longer time to recover, ECT; cognition did not fully recover
Pseudo-dementia case ctd

Two years later

• Third episode – only partially responsive to ECT, cognitive deficits more pronounced
• MRI reveals multiple DWMH

Three years later

• Dementia, now needs help with ADLs
Pseudodementia

• Wernicke (1934) chronic hysterical state mimicking mental weakness\(^1\)

• Madden (JAMA, 1952): 10% of 300 cases

• Kiloh (Acta Psych Scandanavica1961) put term “on the map”\(^1\)
  – Dementia very closely mimicked by psychiatric condition
  – Many patients misdiagnosed with depression which was untreated
  – Cures with ECT and antidepressants

\(^1\) Snowdon J, Australasian Psychiatry, 2011
Pseudodementia

- **Def**: Dx confirmed if cognition recovers when psychiatric condition resolves
- **Psychiatric conditions → Pseudodementia**¹
  - Depression
  - Schizophrenia, paraphrenia
  - Mania and bipolar
  - Hysteria
  - Malingering, Ganser syndrome

¹Kiloh LG, Acta Psych Scandanavica 1961
Pseudodementia

- Intellectual impairment in patients with primary psychiatric disorder in which the features of intellectual abnormality resemble … those of a neuropathologically induced cognitive deficit.

- This neuropsychological impairment is reversible and there is no apparent primary neuropathological process.

Caine ED. Arch Gen Psych 1981; 38:1359-1364
Number of 'pseudodementia' publications in Medline per year

Number of publications
The myth of pseudodementia

- Single case, 85yo ♂
- Lifelong history of unipolar depression
- With Rx his verbal IQ 86 → 99, tho’ deficits
- Stressed importance of treating pts with potential reversible depression even if cognitive impairment
- Used term pseudo-pseudodementia

Depression + ‘reversible dementia’

- Alexopoulos GS (1993) followed up 23 in-pts with depression and criteria for dementia vs 34 with depression and no dementia
- Age ≈74 ± 6.7; follow-up ≈33 months
- HRSD O/A 36.6 vs 27.3 **
- MMSE O/A 18.6 vs 27.3 ***
- MMSE D/C 26.4 vs 27.6 (p<0.09)
- Dementia by follow-up 43% vs 12% **; OR 4.69
- Mortality – 35% vs 24% (ns)
Pseudo-pseudodementia

- Cognitive deficits do not completely recover
- Persistent executive dysfunction, visuo-spatial and amnestic deficits
- Neurological Sg → > progression to dementia
- Longer follow-up many of pseudodementia pts. → true dementia

Kral 1983; Kral & Emery 1989; Reding 1985; Copeland 1992; Alexopoulos 1993
Kiloh’s pseudodementia patients

- Sachdev (1990) followed up 19/21 Kiloh’s PD pts 2-14 yrs later; two not as did not meet PD
- Pts 26-63 yo at baseline; 6 Sz, 13 Affective △
- All those alive followed for ≥ 12 yrs.
- 1 pt Dx changed to dementia; 1 pt possible dementia
- Conclusion: study validates clinical utility of pseudodementia
An observation: Pseudo or pseudo-pseudo

- All cases of pseudodementia were <65 and most had long term psychiatric illness
- All cases of pseudo-pseudo were > 65 and often had late onset psychiatric illness
What is apathy?
What is apathy?

The apathy spectrum includes reduced:

- initiative
- interest
- motivation
- spontaneity
- affection
- energy
- enthusiasm
- emotion
- persistence

+ blunted affect

Apathy components

• Behavioural: ↓ motivation, initiative
• Cognitive: ↓ drive, ↓ interest
• Affect: ↓ emotional responsiveness
WORLD RECORD ATTEMPT AT APATHY.
Frequency of apathy

• Apathy associated with neurological, psychiatric, medical, drug-induced & socioenvironmental conditions

• Frequency in neurological disease $\leq 92\%$

• Dementia & schizophrenia commonest

1 Marin Seminars of Clinical Neuropsychiatry 1996;1:304-314
Frequency of apathy

• Highest prevalences of apathy in
  – progressive supranuclear palsy\(^1\)
  – frontotemporal dementia\(^2\)
  – severe AD\(^3\)
• Apathy following stroke \(\sim 25 \%\)^4

\(^1\) Litvan et al *J Neurol Neurosurg Psychiatry* 1998;65:717-721
\(^2\) Hodges *Neurology* 2001; 56:S6-S10
\(^3\) Mega et al *Neurology* 1996;46:130-135
\(^4\) Brodaty et al *Psychol Med* 2005;35:1707-1716
Apathy & cognition

Cognitive impairment

Apathy
Apathy is most common BPSD in dementia?
BPSD prevalence (%)  Robert s et al, 2005
Frequency of apathy in dementia

• One of the most challenging, prevalent & persistent behavioural symptoms of dementia

• Occurs in up to 70% of those with AD

• A major clinical feature of dementia with subcortical & frontal pathology
  – Dementia with Lewy bodies
  – Huntington’s disease
  – Vascular dementia
  – Binswanger’s disease

1Starkstein et al European Journal of Psychiatry 2006;20:96-106
2Galvin et al Alzheimer Dis Assoc Disord 2010;24:177-181
3Baudic et al Dementia & Geriatric Cognitive Disorders 2006; 21:316-321
4Staekenborg et al J Neurol Neurosurg Psychiatry 2010;81:547-551
5Caplan Neurology 1995;45:626-633
Apathy in MCI

- In 11.1-39.8% of cases\(^1\)
- Intermediate between older normal controls & AD\(^2\)
- Predicts a higher rate of conversion to AD\(^3\)

\(^1\)Lyketsos et al *JAMA* 2002;288:1475-83
\(^2\)Crocco & Lowenstein *Current Psychiatry Reports* 2005;7:32-36
\(^3\)Robert et al *Clin Neurol Neurosurg* 2006;108:733-736
Apathy & dementia

Apathy increases with severity and duration of dementia
Diagnosis

• Lack of standardised diagnostic criteria¹
• Difficult for family caregivers to identify & quantify ➞ under-reporting²
• Differentiate lack of motivation rather than cognitive impairment ³

¹Starkstein et al European J Psychiatry 2006;20:96-106
³Marin Am J Psychiatry 1990; 147:22-30
Depression & apathy & cognition

- Related to but distinct from depression & dysphoria
- Symptoms overlap

Depression $\rightarrow$ apathy?

- Apathy common in depression
- 3 items in GDS, 2 items in Hamilton
- When depression lifts apathy improves

BUT …

- Apathy can occur independently of depression
- Depression can occur without apathy
Depression & apathy & cognition

- Apathy > associated with right frontal subcortical circuits
- Depression with left
- After stroke as > CVD
  - overlap between apathy & depression increases
  - overlap between apathy & cognition increases

Withall A, Brodaty H... Sachdev P *Int Psychoger*, 2011;23:264-273,
Distinct from depression

- Related to but distinct from depression & dysphoria\(^1\)
- Symptoms overlap
- Association between apathy & cognitive impairment (esp. executive function) stronger in apathy than depression\(^2\)

\(^1\) Marin et al J Nerv Ment Dis 1994;182:235-239
Apathy vs depression

**Apathy**
- Lack emotion
- Don’t care
- Not suicidal
- Not usually anxious
- Vegetative Sx absent usually except lose interest in food/ sex

**Depression**
- Sad, tearful
- No point to life
- May be suicidal/ “rather be dead”
- May be anxious
- Vegetative symptoms
  - Sleep, appetite, weight, libido
Symptoms in common

- Lack interest
- Lack initiative
- Lack motivation
- Decreased libido
- Decreased concentration
Secondary apathy

- Quiet delirium – infection
- Medication side effects can initiate, maintain or imitate apathy\(^1,2\)
  - antipsychotics
  - antidepressants
  - neuroleptics

\(^1\) Colling *J Gerontol Nurs* 1999;25:27-32
\(^2\) Barnhart et al *Journal of Psychiatric Practice* 2004;10:196-199
APOE ε4 & apathy

• In pts with probable AD, apathy has been associated with APOE ε4 independent of age, sex, cognitive ability and disease duration (1,2)
• Other cross-sectional studies no association 3-6

2. D’Onofrio G. IJGP 2011;26:1062–70.
Pseudodepression

- Apathy misdiagnosed as depression
- Wife: *My husband is depressed, doctor*
- Dr: “How do you know he is depressed?”
- Wife: “He just sits all day and does nothing”
- Dr: “Is he sad, does he cry, does he say life has no meaning?”
- Wife: “No he does not say anything unless I ask him. He just sits!”
Pseudodepression

- Apathy often misdiagnosed as depression
- Apathy is common in depression
- Apathy is unresponsive to antidepressants
- Apathy may respond to ChE inhibitors
- Apathy and depression may be comorbid

1Brodaty and Burns
Am J Ger Psychiatry
2012; 20(7):549–564

Frontal – subcortical pathology
Pseudo-depression case

- 67 yo man hit by a car → closed head injury
- “Dep^d” → Multiple antidepressants, group and individual therapy – no better
- Five years later, referred w TRD
- His P/Sx: I’ve lost the need to talk
- CT brain scan normal, MMSE 30/30
- MRI – frontal pathology
- Neuropsych – frontal executive dysfunction
Pseudo- vs pseudo-pseudodementia

- Older age
- Poorer memory performance on delayed word list recall
- Imaging - cortical atrophy, ↑ VBR, ↓ pre-frontal cerebral blood flow, DWMH, CVD

Visser 2000;
Conclusions

- Overlapping syndromes
- Overlapping symptoms
- Common pathologies
- Underlying brain chemistry, pathology differ
- Treatments/management strategies differ

www.cheba.unsw.edu.au
h.brodaty@unsw.edu.au