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Tricky diagnoses:

when dementia is not dementia and depression is not depression

Never Stand Still | Medicine

- Centre for Healthy Brain Ageing

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University of New South Wales (UNSW Australia)

DCRC Dementia Collaborative Research Centres

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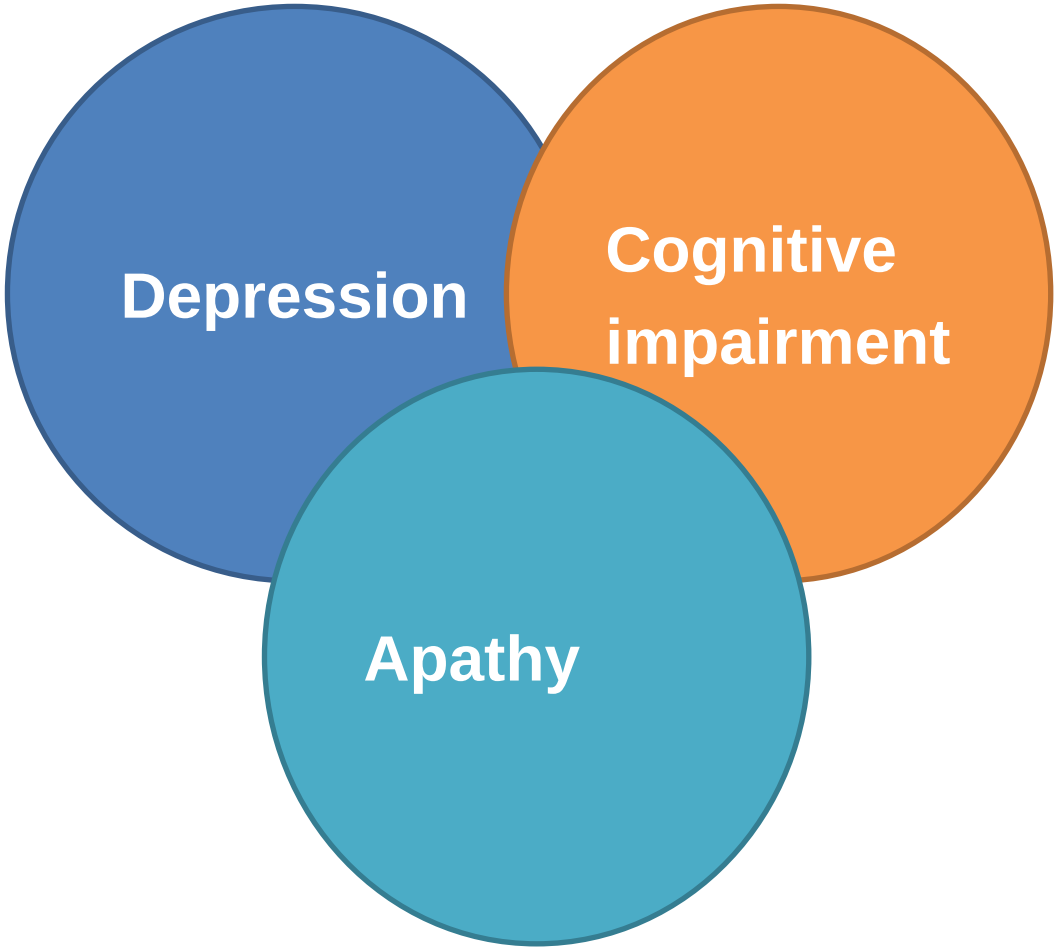
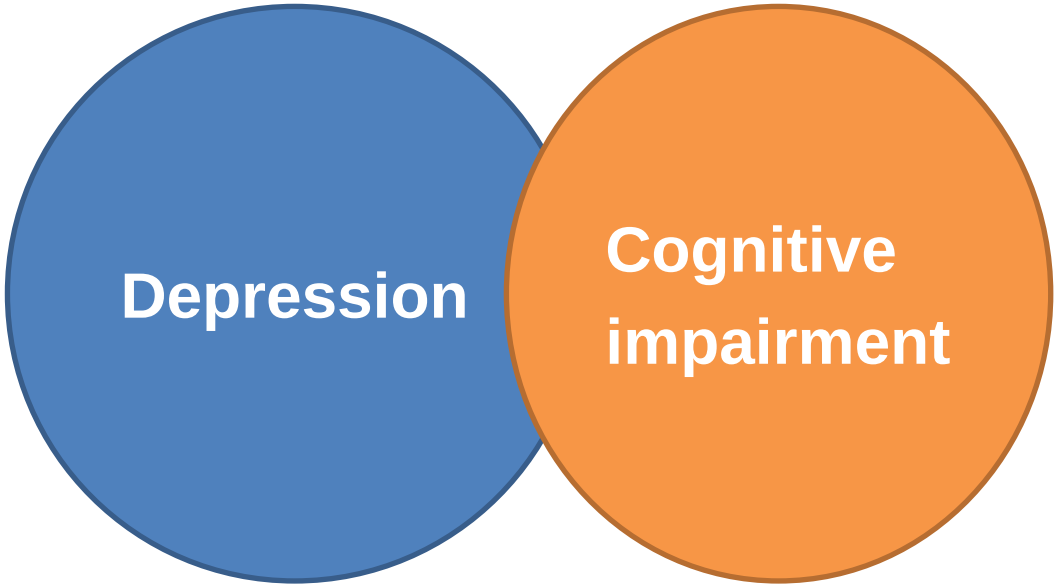
When dementia is not dementia

- **Definition of dementia**
  - **Cognitive decline → functional decline**
- **Not exclusively delirium**
- **Not an Axis 1 diagnosis such as**
  - **Depression**
  - **Schizophrenia (*Dementia Praecox)***
  - **Mania**
  - **Malingering**

Depression, apathy & cognition



Depression & cognition



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]**

[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?**
  - **25 year build up of AD pathology**
- **Is it secondary to depression?**
  - **Dep^{n} → cortisol↑ → temporal lobe atrophy**
- **Is it secondary to treatment of depression?**
  - **Unlikely**
- **Mid-life depression associated with (?↑) risk**
- **Late-life depression associated with ↑↑ risk**

25-year follow-up of depression

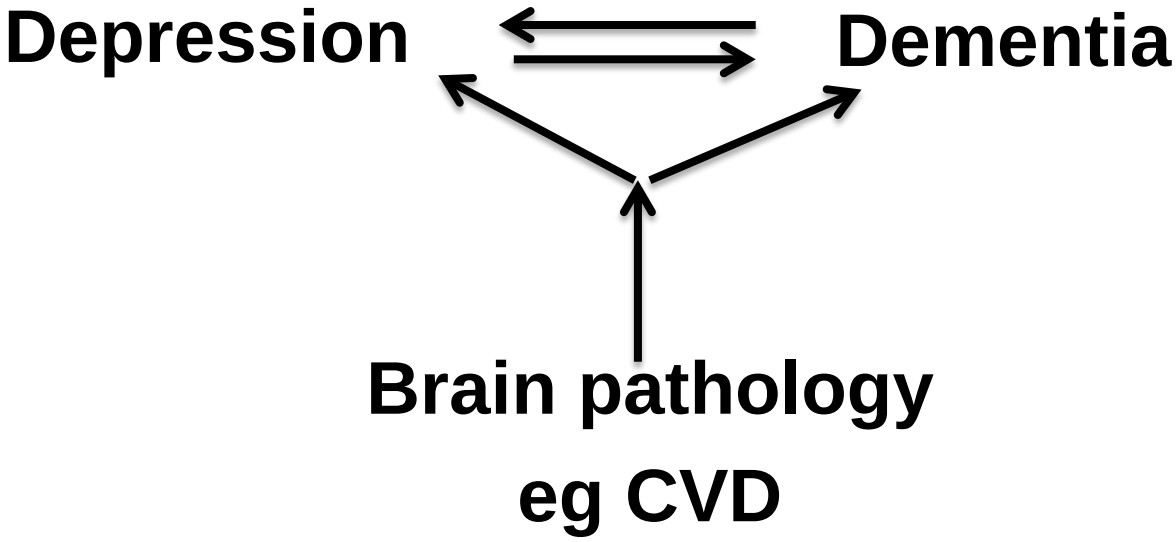
- **71 depressed in-pts (10 deceased) and 50 surgical controls assessed 25 years later**
- **No signif. differences between depressed pts and controls on any neuropsychological test**
- **10 depressed patients, no controls had dementia at follow-up *P*<0·01)**
- **Dementia predicted by older age at baseline**
- **Vascular dementia was most common type**

Brodaty H et al. *Psychological Medicine* 2003;33(7)1263-1275.

Dementia: risk factor for depression

- **Dementia associated with depression**
  - **≈ 20-50% people with dementia have dep^{n}**
- **Not associated with recency of diagnosis**
  - **Suggesting unlikely to be a reaction to Dx**
- **Associated with type of dementia**
  - **More in subcortical dementia (eg Parkinson's disease dementia, vascular dementia)**
  - **Suggesting likely link to brain pathology**

Risk factors common to both



Vascular dementia with deep white matter hyperintensities (DWMH) +++

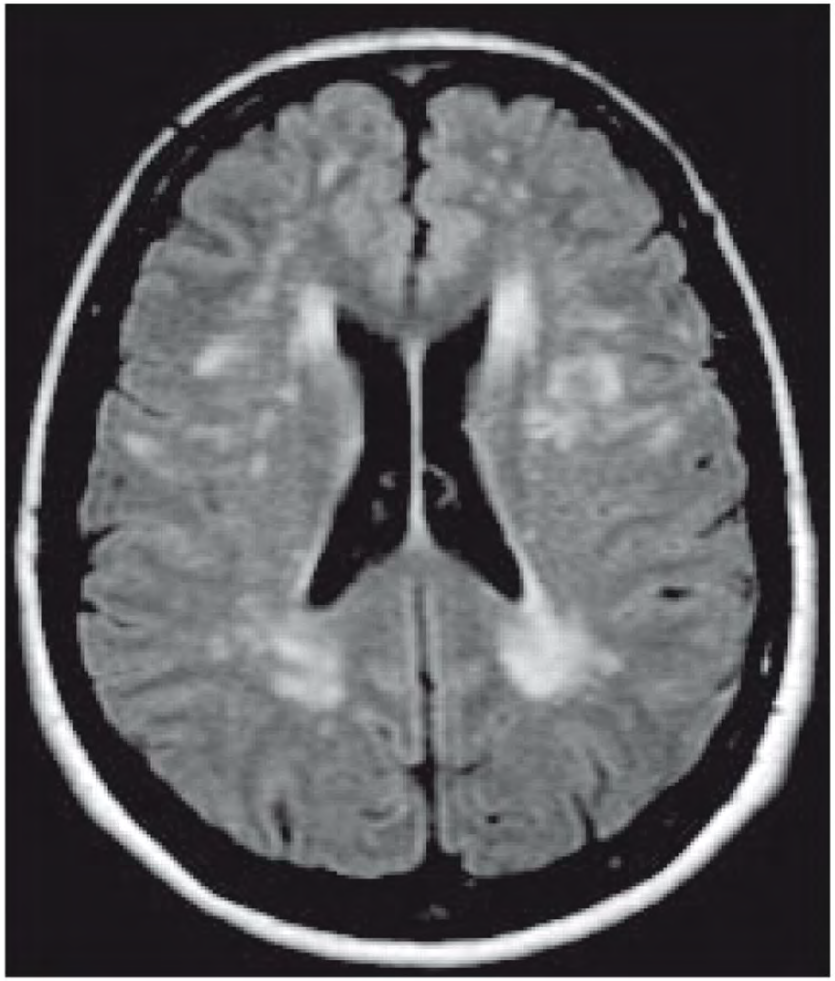


FIG 4 MRI scan of CADASIL.

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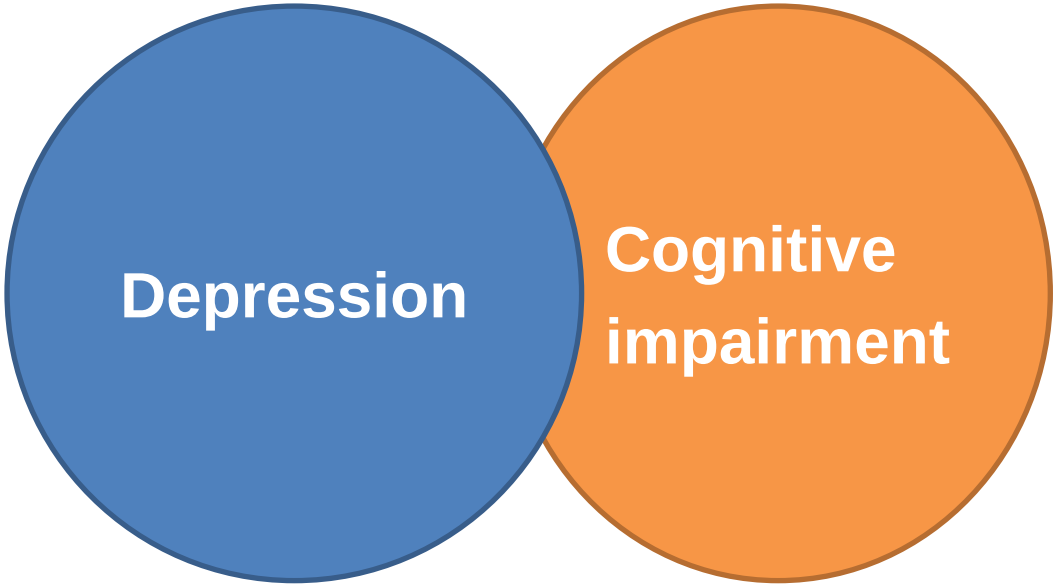
Vascular depression

- **Cerebro-Vascular disease predisposes, precipitates or perpetuates depression**
- **MRI: > DWMHs 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

Depression & dementia

Clinical features overlap



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 → ≤ 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 with pseudodementia)

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**

[1] **Snowdon J, Australasian Psychiatry, 2011**

Pseudodementia

- Kiloh 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] Kiloh L, 1961 Acta Psych Scandanavica

Pseudodementia

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

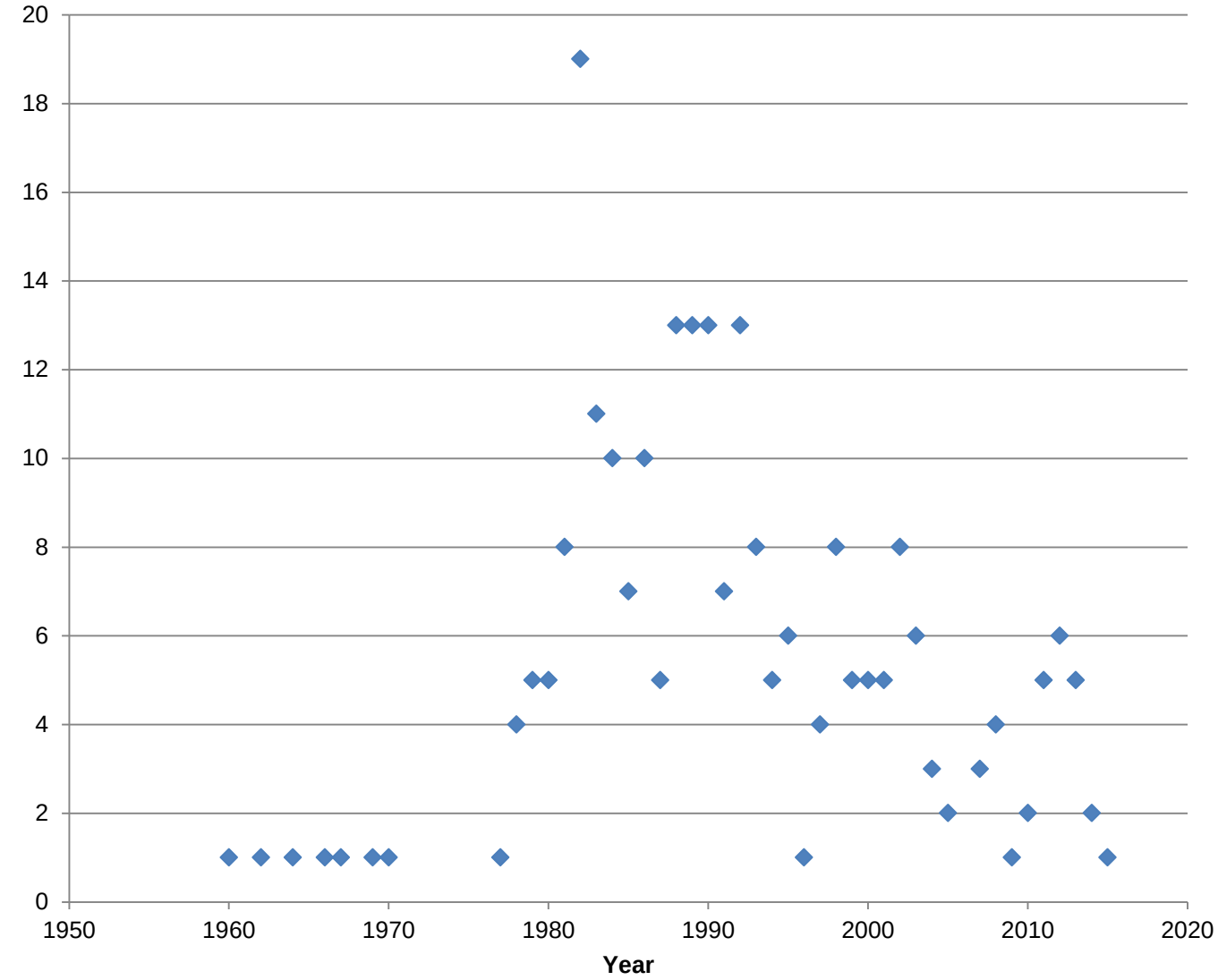
[1]Kiloh LG, Acta Psych Scandanavica 1961

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: Medline per year



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**

Shraberg D, Am J Psychiatry 1978:135:601-2

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 On Admission 36.6 vs 27.3 ****
- **MMSE On Admission 18.6 vs 27.3 *****
- **MMSE Discharge 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 signs → > progress 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

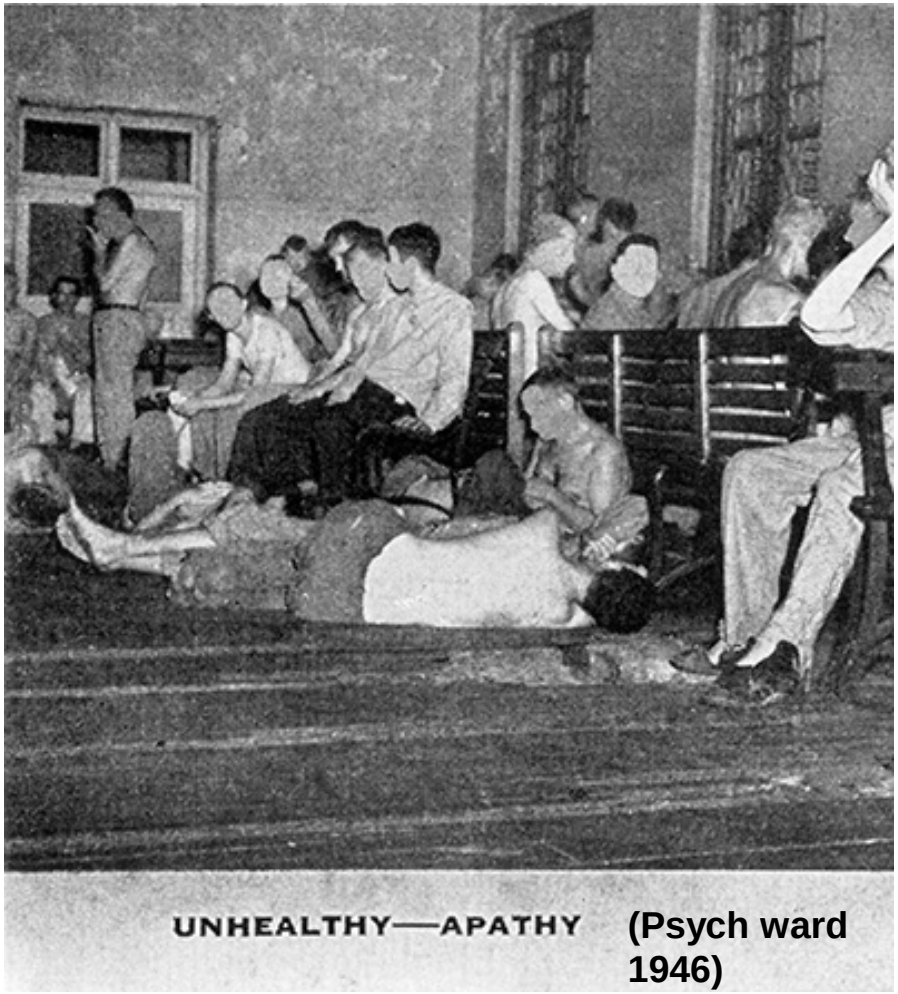
- **Sachdev (1990) followed up 19/21 Kiloh's PD pts 2-14 yrs later; two not as did not meet PD**
- **Pts 26-63 yo at baseline; 6 Sz, 13 Affective Δ**
- **All those alive followed for ≥ 12 yrs.**
- **1 pt's Dx changed to dementia; 1 pt possible dementia**
- **Conclusion: study validates clinical utility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

Pseudo or pseudo-pseudodementia

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

Visser 2000

What is apathy?



(Psych ward 1946)

Apathy components

- **Behavioural: ↓ motivation, initiative**
- **Cognitive: ↓ drive, ↓ interest**
- **Affect: ↓ emotional responsiveness**

What is apathy?

The apathy spectrum includes reduced:

- initiative
- interest
- motivation
- spontaneity

- affection
- energy
- enthusiasm
- emotion
- persistence

+ blunted affect

Levy et al *J Neuropsychiatry Clin Neurosci* 1998;10:314-9
Overshott et al *Expert Review of Neurotherapeutics* 2004;4:809-821


LOCAL ELECTIONS
LIB DEM
CON
LAB
APATHY
PUGH


APATHY
SUPPORT
GROUP
7:00 PM
search ID: rhan320


WORLD RECORD
ATTEMPT
AT
APATHY

Frequency of apathy

- **Apathy associated with neurological, psychiatric, medical, drug-induced & socioenvironmental conditions[1]**
- **Frequency in neurological disease ≤ 92%[2]**
- **Dementia & schizophrenia commonest [2]**

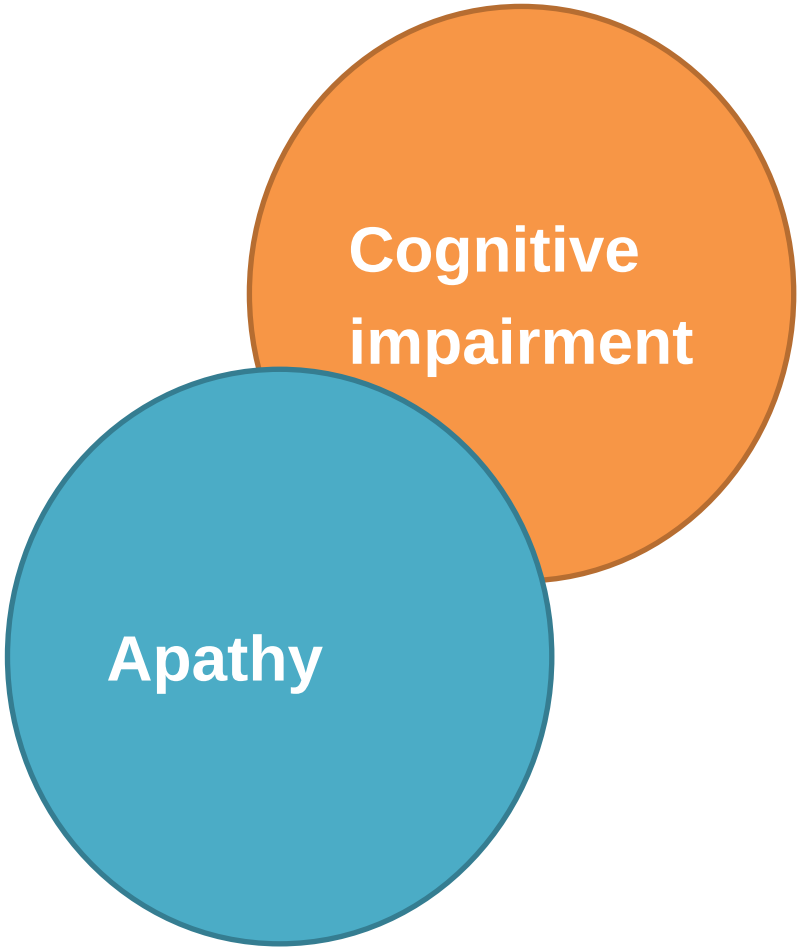
[1]Marin *Seminars of Clinical Neuropsychiatry* 1996;1:304-314
[2]Pluck & Brown *Journal of Neurol Neurosurg Psychiatry* 2002;73:636-642

Frequency of apathy

- **Highest prevalences of apathy in**
  - **Progressive supranuclear palsy[1]**
  - **Fronto-temporal dementia[2]**
  - **Severe AD[3]**
- **Apathy following stroke ~ 25 %[4]**

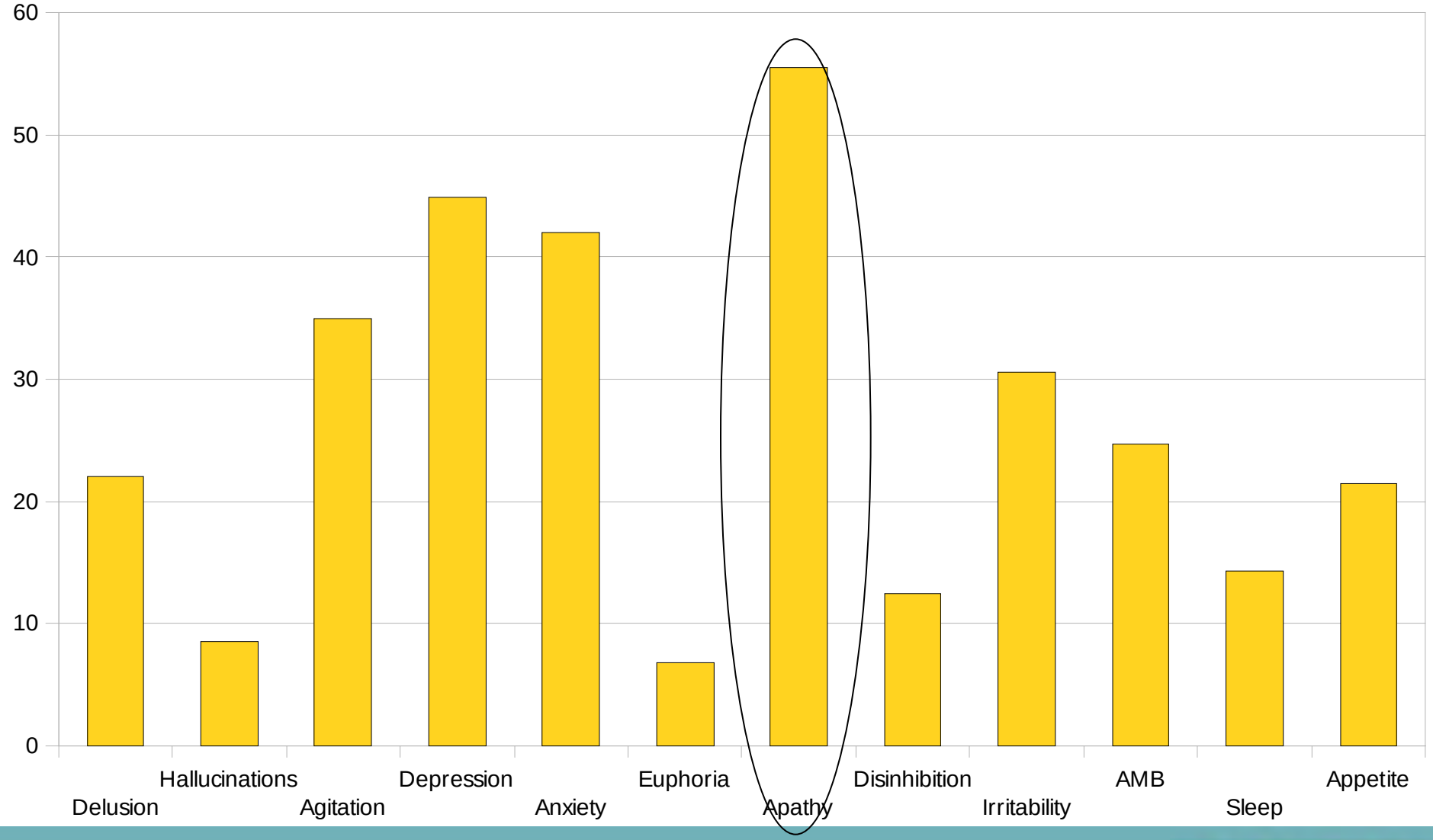
[1]Litvan et al *J Neurol Neurosur Psychiatry* 1998;65:717-721
[2]Hodges *Neurology* 2001; 56:S6-S10
[3]Mega et al *Neurology* 1996;46:130-135
[4]Brodaty et al Psychol Med 2005;35:1707-1716

Apathy & cognition



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[1]**
- **A major clinical feature of dementia with subcortical & frontal pathology**
  - **Dementia with Lewy bodies[2]**
  - **Huntington's disease[3]**
  - **Vascular dementia[4]**
  - **Binswanger's disease[5]**

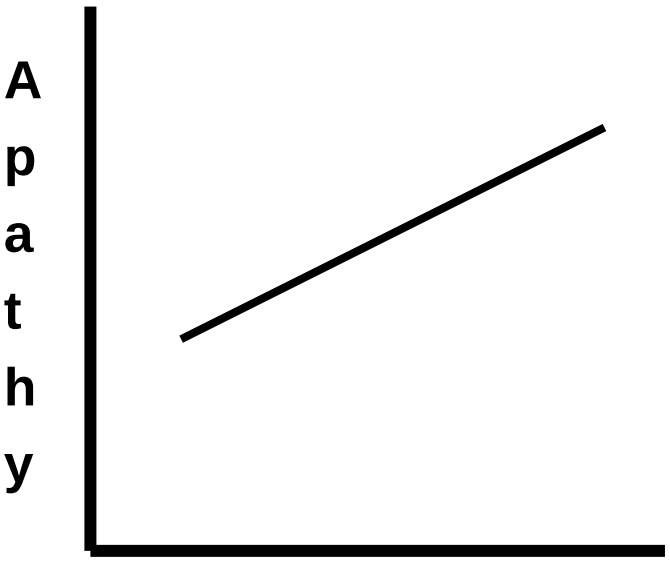
[1]Starkstein et al *European Journal of Psychiatry* 2006;20:96-106
[2]Galvin et al *Alzheimer Dis Assoc Disord* 2010;24:177-181
[3]Baudic et al Dementia & Geriatric Cognitive Disorders 2006; 21:316-321
[4]Staekenborg et al *J Neurol Neurosurg Psychiatry* 2010;81:547-551
[5]Caplan *Neurology* 1995;45:626-633

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 criteria[1]**
- **Difficult for family caregivers to identify & quantify ➔ under-reporting[2]**
- **Differentiate lack of motivation rather than cognitive impairment [3]**

[1]Starkstein et al *European JPsychiatry* 2006;20:96-106
[2]Landes et al *J Am Geriatr Soc* 2001; 49:1700-07
[3]Marin *Am J Psychiatry* 1990; 147:22-30
[4] Lanctot K et al, Alz & Dementia, 2016 in press

How do we diagnosis apathy?

- History
- Clinical impression
- Apathy rating tools
  - Apathy Evaluation Scale (AES) [1]
  - Apathy Index[2]
  - Apathy Inventory[3]
  - Apathy Scale[4]
  - Structured Clinical Interview for Apathy (SCIA)[5]
  - Dementia Apathy Interview and Rating (DAIR) [5]
  - Lille Apathy Rating Scale (LARS)[5]

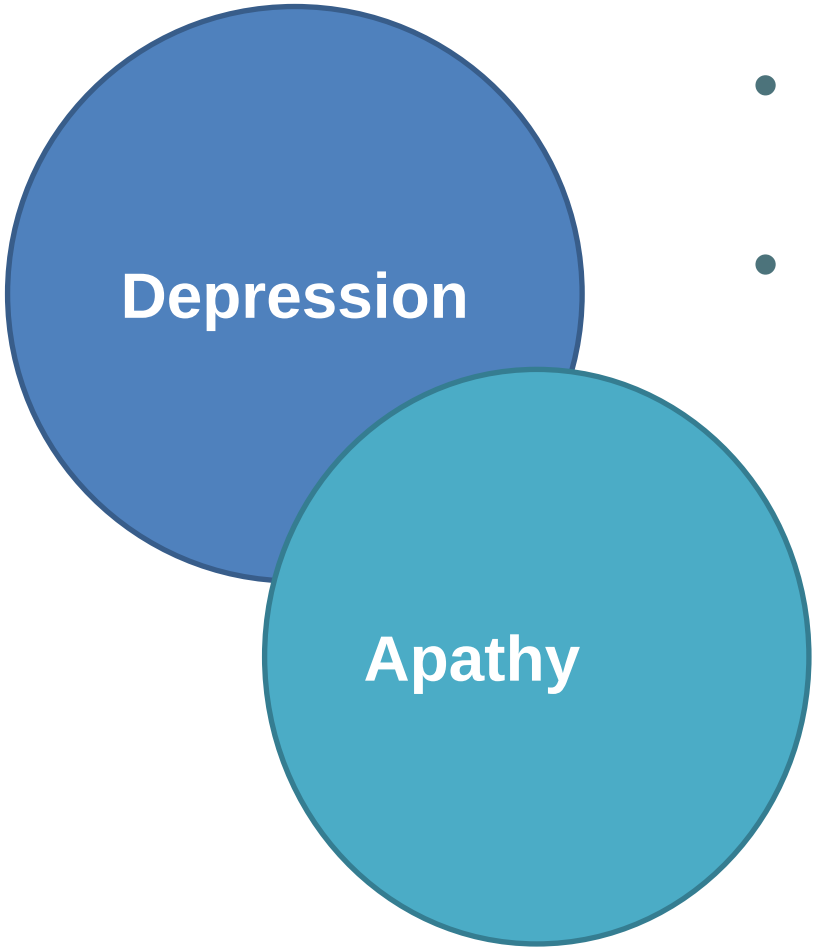
[1]Marin RS et al *Psychiatry Res* 1991;38:143-162
[2]Mayo et al *Stroke* 2009;40:3299-3307
[3]Robert et al *IJGP* 2002;17:1099-1105
[4]Starkstein et al *Euro J Psych* 2006;20:96-106
[5] Lanctot KS *Alz & Dementia 2016, in press*

How do we diagnosis apathy?

- **Apathy items in behavioural scales**
  - **NPI[5]**
  - **Behaviour and Mood disturbance Scale[6]**
  - **Clifton Assessment Procedures for the Elderly[7]**
  - **Frontal Behavioural Inventory**

[5]Cummings et al *Neurology* 1994;44:2308-14
[6]Neville & Byrne *Collegian: J Royal College of Nursing, Aust* 2001;20:166-172
[7]Pattie *Br J Clin Psychol* 1981;20:173-178

Depression & apathy & cognition



- **Related to but distinct from depression & dysphoria[1]**
- **Symptoms overlap**

[1]Marin et al *J Nerv Ment Dis* 1994;182:235-39

Depression → apathy?

- **Apathy common in depression**
- **3 items in Geriatric Depression Scale:**
  - **Have you dropped many of your activities or interests?**
  - **Do you prefer to stay at home, rather than go out and do things?**
  - **Do you feel full of energy?**

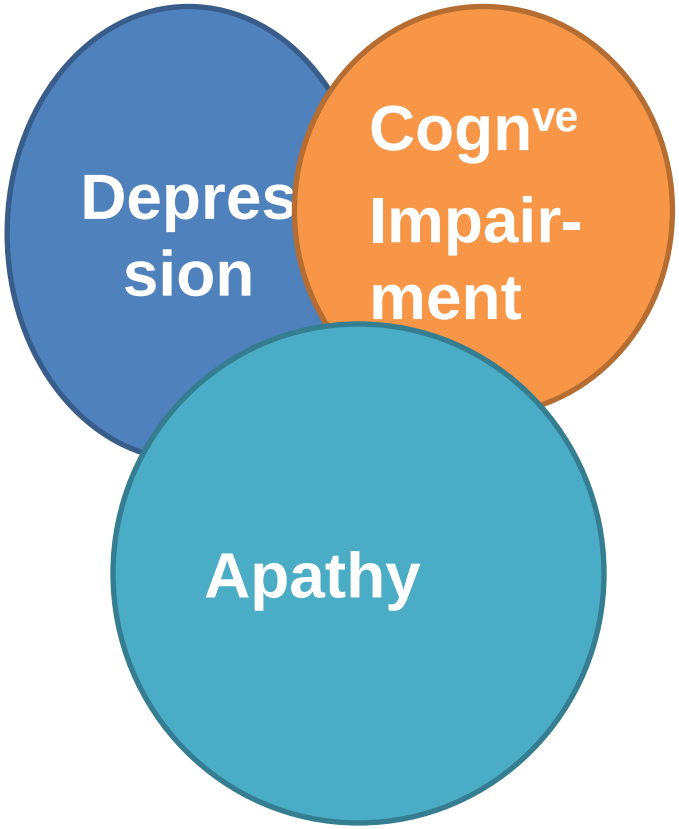
Depression → apathy?

- **2 items in Hamilton**
  - **Loss of interest, lack of activity in work or hobbies**
  - **Decreased energy**
- **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
[2]Brown & Pluck *Trends Neurosci* 2000;23:412-417

Apathy vs depression

Apathy

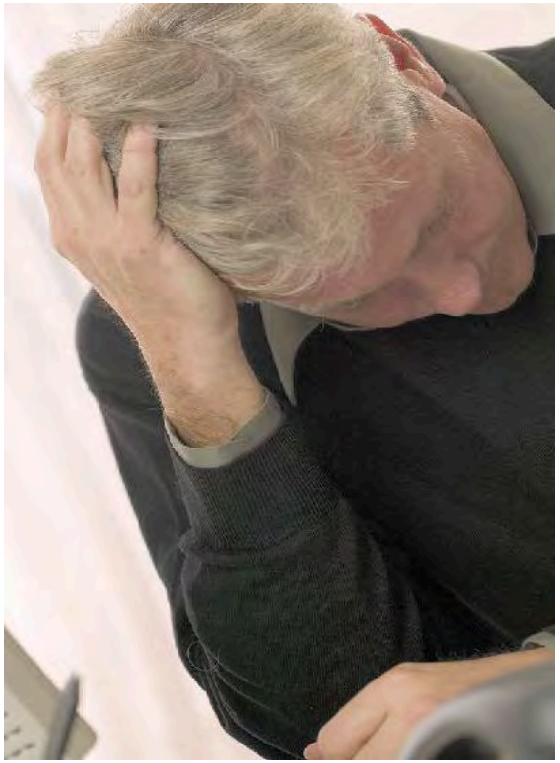
- Lack emotion
- Don't care
- Not suicidal

- Not usually anxious
- Vegetative Sx absent usually except lose interest in food/ sex
- No sadness 'transmits'
- AD Rx: Poor response

Depression

- Sad, tearful
- No point to life
- May be suicidal/ "rather be dead"
- May be anxious
- Vegetative symptoms
  - Sleep, appetite, weight, libido
- Clinician 'feels' sadness
- Rx: Moderate response

Symptoms in common



- Lack interest
- Lack initiative
- Lack motivation
- Decreased libido
- Decreased concentration
- Less energy

Secondary apathy

- **Quiet delirium**
- **Medical Δ - 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

When depression is not depression
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!*"**

Pseudo-depression case

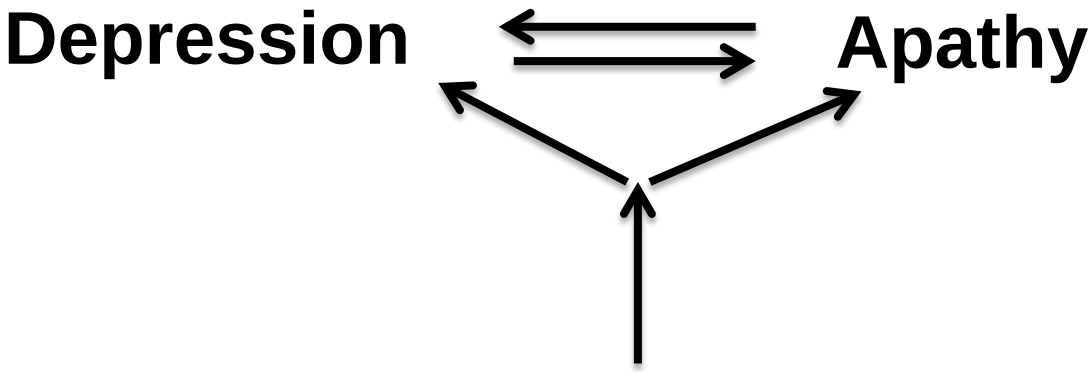
- **67 yo man hit by a car → closed head injury**
- **"Dep^{d}" → Multiple antidepressants, group and individual therapy, ECT – no better**
- **Five years later, referred w Treatment Resistant Depression**
- **His P/Sx: *I've lost the need to talk***
- **CT brain scan normal, MMSE 29/30**
- **MRI – frontal pathology**
- **Neuropsych – frontal executive dysfunction**

Pseudodepression

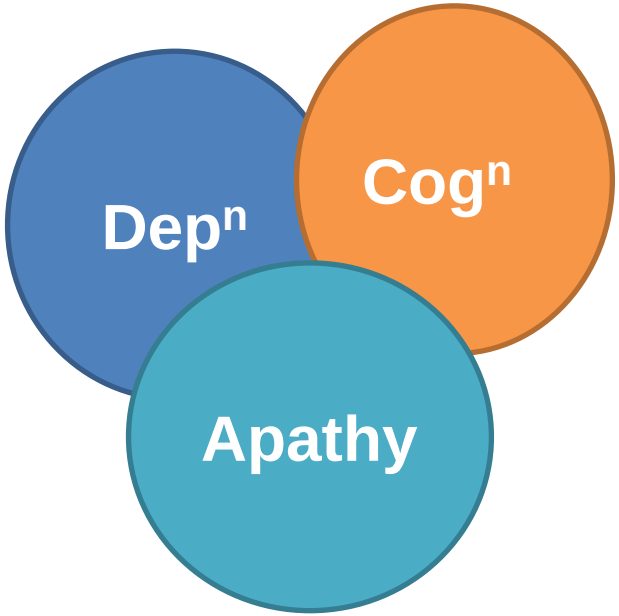
- **Apathy often misdiagnosed as depression**
- **Apathy is common in depression**
- **Apathy is unresponsive to antidepressants[1]**
- **Apathy Rx = ChE inhibitors[1], (Modafinil)[2], methylphenidate[2]**
- **Apathy and depression may be comorbid**

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

Apathy and depression may be comorbid



Conclusions



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

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