IL CERVELLO CHE CAMBIA 7
Sabato 11 novembre 2017
Genova, Aula Magna Clinica Neurologica

Quest'anno ho letto un articolo
che mi ha aperto gli occhi su…

Depressione e deficit cognitivo

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Late-Life Depressive Symptoms and Lifetime History of Major Depression: Cognitive Deficits are Largely Due to Incipient Dementia rather than Depression

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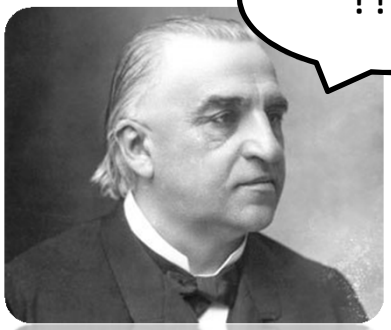
- Recente
- Clinico
- Utile

Journal of Alzheimer's Disease, 2016

Deficit cognitivo / demenza

Depressione

?!??



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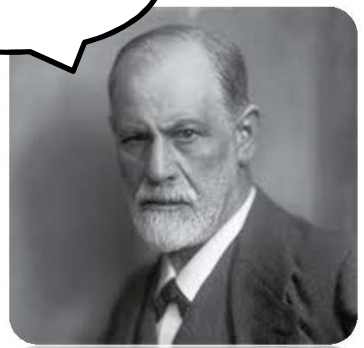


Depressione maggiore in pazienti con disturbi neurocognitivi

MCI: un paziente su tre soffre di depressione 32%(95%CI: 27-37). In ospedale: 44%, in community: 16% Depressione associata ad **aumentata probabilità di progressione a demenza** (OR: 1.28; 95%CI: 1.09–1.52).

Demenza: depressione maggiore nel 30.3% (95%CI = 22–39) di anziani ambulatoriali. Comporta aumentato carico per caregiver, mortalità, numero di ricoveri. MDD trattato in un paziente su 5.

Diagnosi di MDD:
CSDD: sensitivity 0.84, specificity 0.80
HDRS: sensitivity 0.86, specificity 0.84
GDS-30: sensitivity 0.62, specificity 0.81

Ismail et al., JAMA Psychiatry, 2017; Mourao et al., Int J Geriatr Psychiatry 2014; Goodarzi et al., JAGS, 2017

Provisional Diagnostic Criteria for Depression of Alzheimer Disease

A. Three (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning: at least one of the symptoms is either 1) depressed mood or 2) decreased positive affect or pleasure.[a]

Note: Do not include symptoms that, in your judgment, are clearly due to a medical condition other than Alzheimer disease, or are a direct result of non–mood-related dementia symptoms (e.g., loss of weight due to difficulties with food intake).

(1) Clinically significant depressed mood (e.g., depressed, sad, hopeless, discouraged, tearful)[b]
(2) Decreased positive affect or pleasure in response to social contacts and usual activities[c]
(3) Social isolation or withdrawal[d]
(4) Disruption in appetite
(5) Disruption in sleep
(6) Psychomotor changes (e.g., agitation or retardation)[e]
(7) Irritability
(8) Fatigue or loss of energy
(9) Feelings of worthlessness, hopelessness, or excessive or inappropriate guilt
(10) Recurrent thoughts of death, suicidal ideation, plan or attempt[f]

B. All criteria are met for Dementia of the Alzheimer Type (DSM-IV-TR).[g]

C. The symptoms cause clinically significant distress or disruption in functioning.

D. The symptoms do not occur exclusively during the course of a delirium.

E. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse or a medication).

F. The symptoms are not better accounted for by other conditions such as major depressive disorder, bipolar disorder, bereavement, schizophrenia, schizoaffective disorder, psychosis of Alzheimer disease, anxiety disorders, or substance-related disorder.[h]

Specify if:

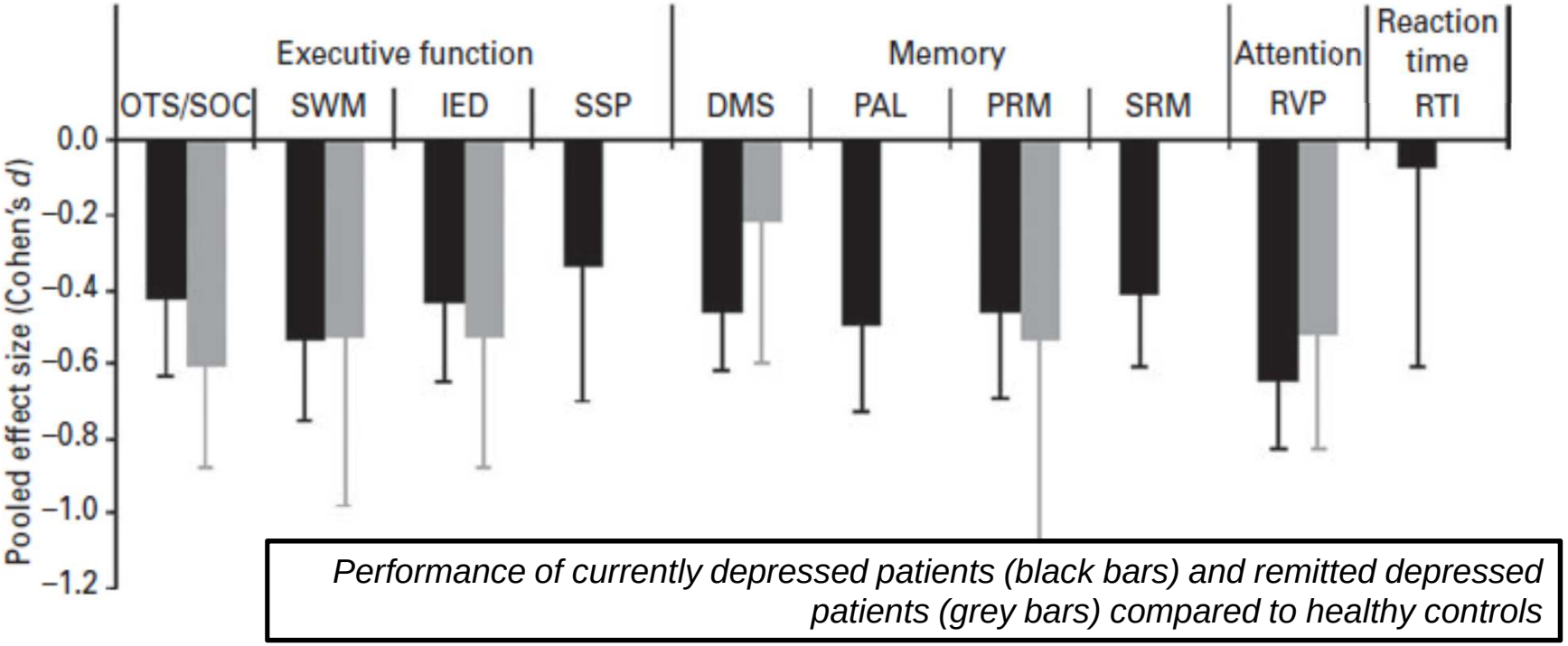
Co-occurring Onset: if onset antedates or co-occurs with the AD symptoms
Post-AD Onset: if onset occurs after AD symptoms[i]

Specify:

With Psychosis of Alzheimer Disease
With Other Significant Behavioral Signs or Symptoms
With Past History of Mood Disorder[j]

Olin et al., Am J Geriatr Psychiatry 2002; 10:125–128

Deficit cognitivi in pazienti con depressione maggiore



Performance of currently depressed patients (black bars) and remitted depressed patients (grey bars) compared to healthy controls

Active depression: moderate ES in executive function, memory and attention
Remitted depression: moderate ES in executive function and attention (ns memory)

Bora et al., Psychol Med. 2013; Rock et al., Psychological Medicine, 2014

Deficit cognitivi in pazienti con depressione maggiore

Cognitive deficits overall appear to be more common and severe among patients with **late-onset depression**

Depression as a risk factor for MCI/dementia in prospective studies:

MCI (RR: 1.97, 95% CI: 1.53–2.54)
AD (RR: 1.66, 95%CI: 1.29–2.14)
VD (RR: 2.52, 95%CI: 1.77–3.59)
any dementia (RR: 1.55, 95% CI: 1.31–2.83)

Gao et al., Int J Geriatr Psychiatry 2013; Diniz et al., Br J Psychiatry. May 2013

Panza et al., Am J Ger Psych, 2010

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Journal of Alzheimer's Disease, 2016

Study background and objective

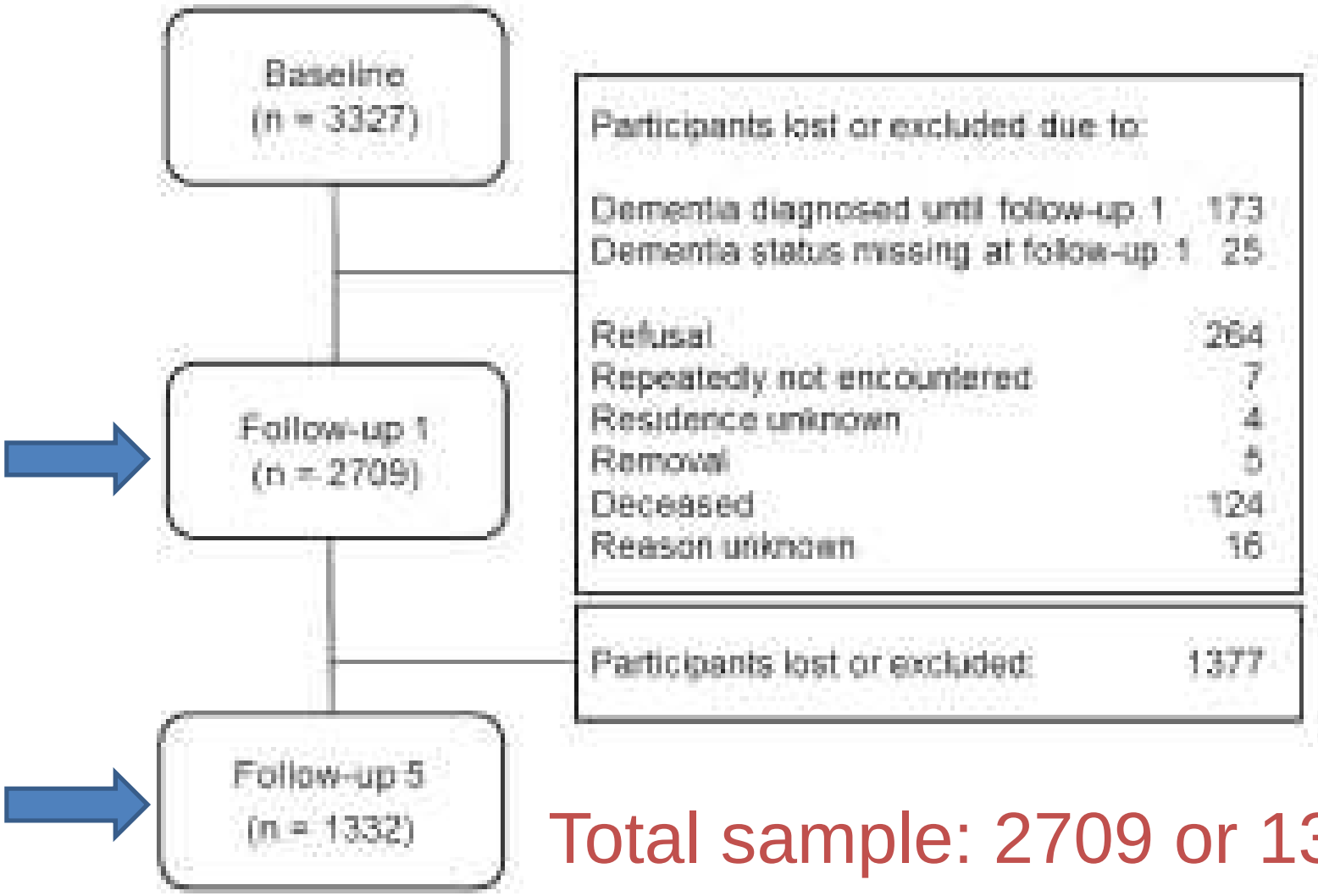
Background. Among subjects with depression and cognitive deficit to identify who develop dementia. Conflicting evidence on the topic and methodological shortcomings.

Objective. to study whether cognitive deficits in depressed participants are a sign of incipient dementia or are a “benign” symptomatic expression of depression per se. To examine the predictive value of the Degree and profile of cognitive impairment (quantitative and qualitative approach); take in account depression history.

Hypothesis. Executive dysfunction independent of incipient dementia, learning/memory deficit predictive of dementia

Disegno dello studio

- Studio longitudinale multicentrico: German study on Aging, Cognition, and Dementia in Primary Care Patients (AgeCoDe)
- Partecipanti >75 anni da Primary Care di 6 città tedesche
- Valutazione 2003-2004 e FU ogni 18 mesi
- Per lo studio: dati da Follow up 1 (baseline) e Follow up 5 (6 anni da baseline)



Total sample: 2709 or 1332?

Fig. 1. Sample selection flowchart.

Valutazioni baseline

Baseline

Sintomi depressivi: GDS 15-items (cut-off di 6 «clinically relevant»)

Storia di MDD: Sezione E della CIDI

Cognitive performance

- Fluenza verbale (animali in 60 secondi) come indice di funzioni esecutive
- CERAD recall immediato, delayed recall (10 min), riconoscimento
- SISCO memoria, Orientamento, higher cortical function
- MMSE

Follow up

Diagnosi di demenza all-cause: SIDAM (first choice) or Global Deterioration Scale >=4 or Blessed Dementia Rating Scale . Subtype «validated by geriatric expert»; NINDS-AIREN criteria

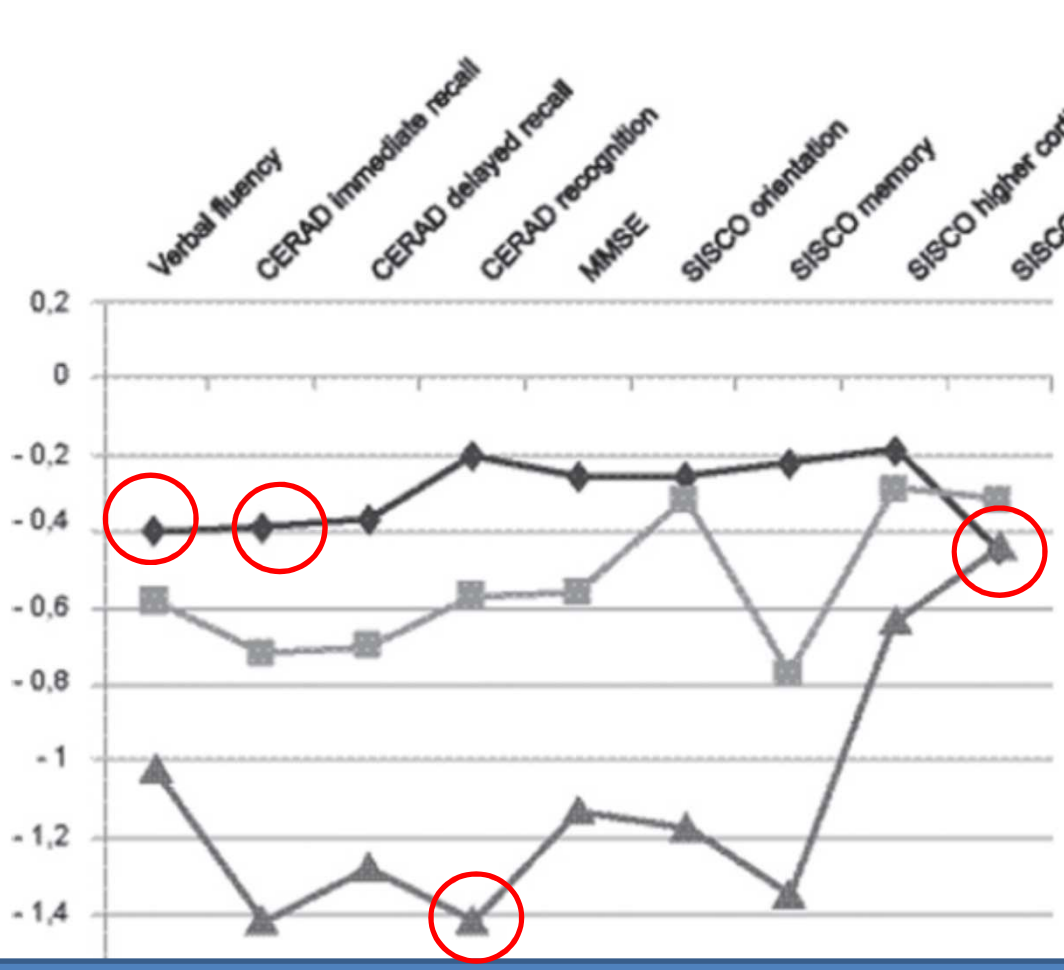
Analisi

- Soggetti divisi in **4 sottogruppi** per presenza di Depressione al baseline e Demenza entro il 5° f.u.
- DEP- DEM- utilizzati come gruppo di controllo
- 1. Analisi ANCOVA (controllando per età, sesso e scolarità) per confrontare gli score cognitivi baseline tra i 4 gruppi
- 2. Calcolo Effect Size
- 3. Regressione logistica stepwise per individuare quali test cognitivi predicessero l'incidenza di demenza (agg. per età sesso scolarità)

Table 2
Comparison of cognitive test performances adjusted for age, sex, and education (ANCOVA) between four groups of participants with and without elevated depressive symptoms at follow-up 1 and with and without subsequent dementia until follow-up 5

	Groups				Tests of between-subjects-effects	Effect sizes
	1[a] Dep- Dem-	2[b] Dep+Dem-	3[c] Dep- Dem+	4[d] Dep+Dem+	*p*	*d*
MMSE, M (S.E.)	28.03 (0.04)	27.57 (0.10)	27.02 (0.09)	25.98 (0.20)	<0.001	2 versus 1 : 0.26* ($p<0.001$) 3 versus 1 : 0.56* ($p<0.001$) 4 versus 1 : 1.13* ($p<0.001$)
Verbal fluency, M (S.E.)	20.57 (0.12)	18.41 (0.34)	17.40 (0.30)	15.05 (0.65)	<0.001	2 versus 1 : 0.40* ($p<0.001$) 3 versus 1 : 0.58* ($p<0.001$) 4 versus 1 : 1.02* ($p<0.001$)
CERAD immediate recall, M (S.E.)	19.83 (0.09)	18.24 (0.25)	16.92 (0.21)	14.12 (0.47)	<0.001	2 versus 1 : 0.39* ($p<0.001$) 3 versus 1 : 0.72* ($p<0.001$) 4 versus 1 : 1.41* ($p<0.001$)
CERAD delayed recall, M (S.E.)	6.02 (0.05)	5.18 (0.14)	4.44 (0.12)	3.15 (0.26)	<0.001	2 versus 1 : 0.37* ($p<0.001$) 3 versus 1 : 0.70* ($p<0.001$) 4 versus 1 : 1.27* ($p<0.001$)
CERAD recognition, M (S.E.)	9.08 (0.03)	8.81 (0.10)	8.30 (0.08)	7.17 (0.18)	<0.001	2 versus 1 : 0.20* ($p=0.008$) 3 versus 1 : 0.57* ($p<0.001$) 4 versus 1 : 1.41*

Risultati: baseline depression

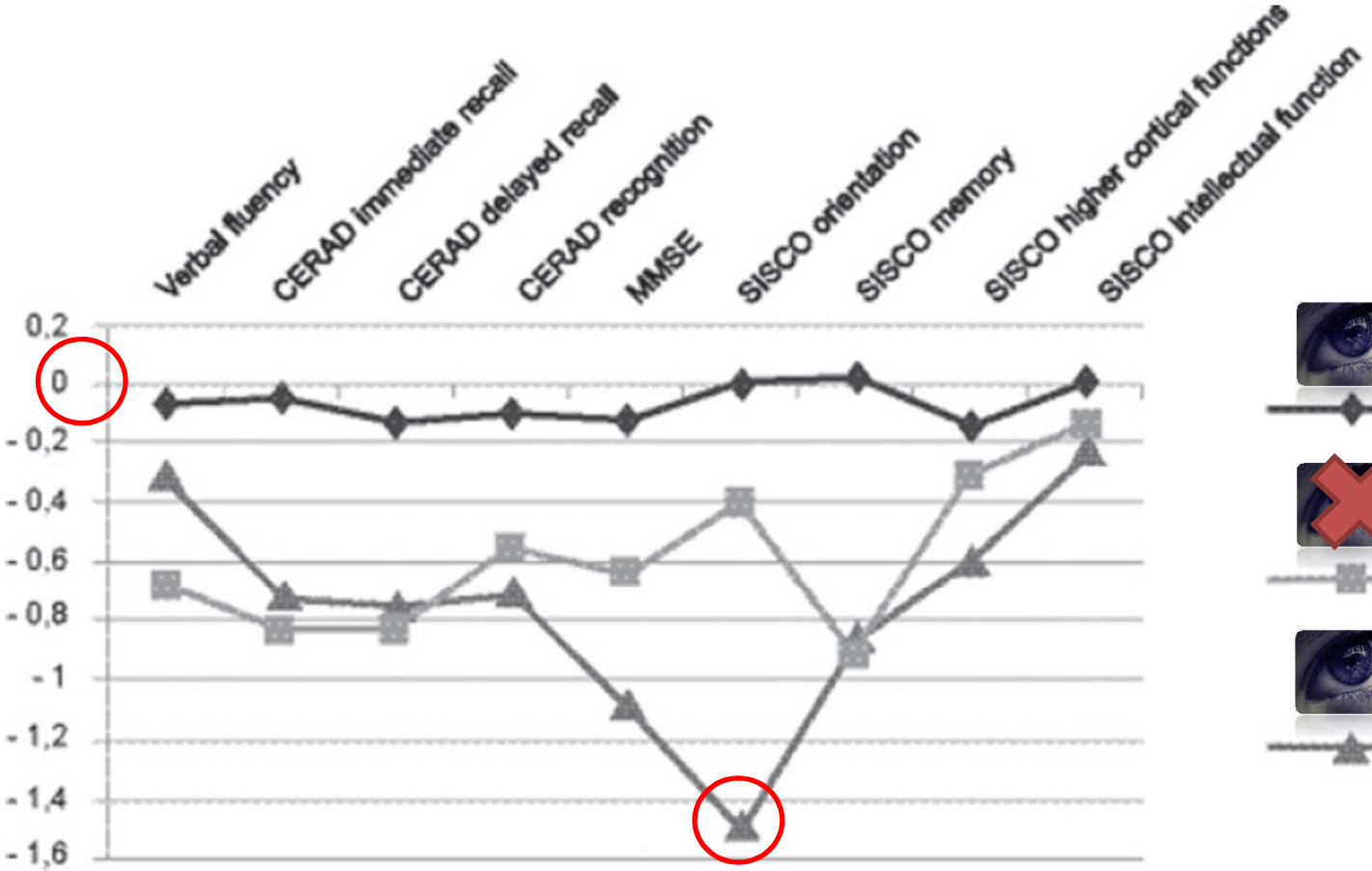


Analisi di regressione: demenza predetta da performance…

- Verbal fluency (OR 0.94), 3 tests memory and learning (0.83 – 0.90)
- Immediate recall (0.83) memory (0.75), higher intellectual (1.55)

Risultati: depression history

High concordance



Analisi di regressione: demenza predetta da performance …

- Verbal fluency (OR 0.93), 3 tests memory and learning (0.82 – 0.93)
- Immediate recall (0.88) orientation (0.43)

Discussione

Rispetto al gruppo di controllo i 3 gruppi performano peggio

- **Gruppo dep+/dem-** (*deficit cognitivo «depressivo»*): lieve deficit su tutti i test, lievemente più ingenti per fluenza verbale, immediate/delayed recall e «funzioni intellettive»
- **Gruppo dep+/dem+** (*depressione pre-demenziale*): deficit cognitivi importanti, particolarmente nel dominio dell'apprendimento e della memoria, in particolare per il riconoscimento. Congruità con precedenti evidenze: deficit di **riconoscimento** come **segno di deterioramento cognitivo** e non dovuto a depressione. (Dierckx et al.2007)

Considerazioni su pseudodemenza:

"*As pronounced impairments in depressed participants were confined to the group with incipient dementia, the term "pseudodementia" will in most cases be inappropriate for the co-occurrence of depression and cognitive impairment in old age. Due to the reviewed findings on its reversibility and potential biological mechanisms, Kennedy concluded that depressive pseudodementia is more closely related to true dementia than previously assumed*."

HOWEVER "It should be noted that our sample consisted of initially non-hospitalized, community dwelling elderly aged 75 and older. Whether our findings and conclusions hold true for severe, clinically treated cases of old age depression will need to be shown.

Executive dysfunction among depressed is mainly a consequence of depression; among non-depressed is harbinger of dementia

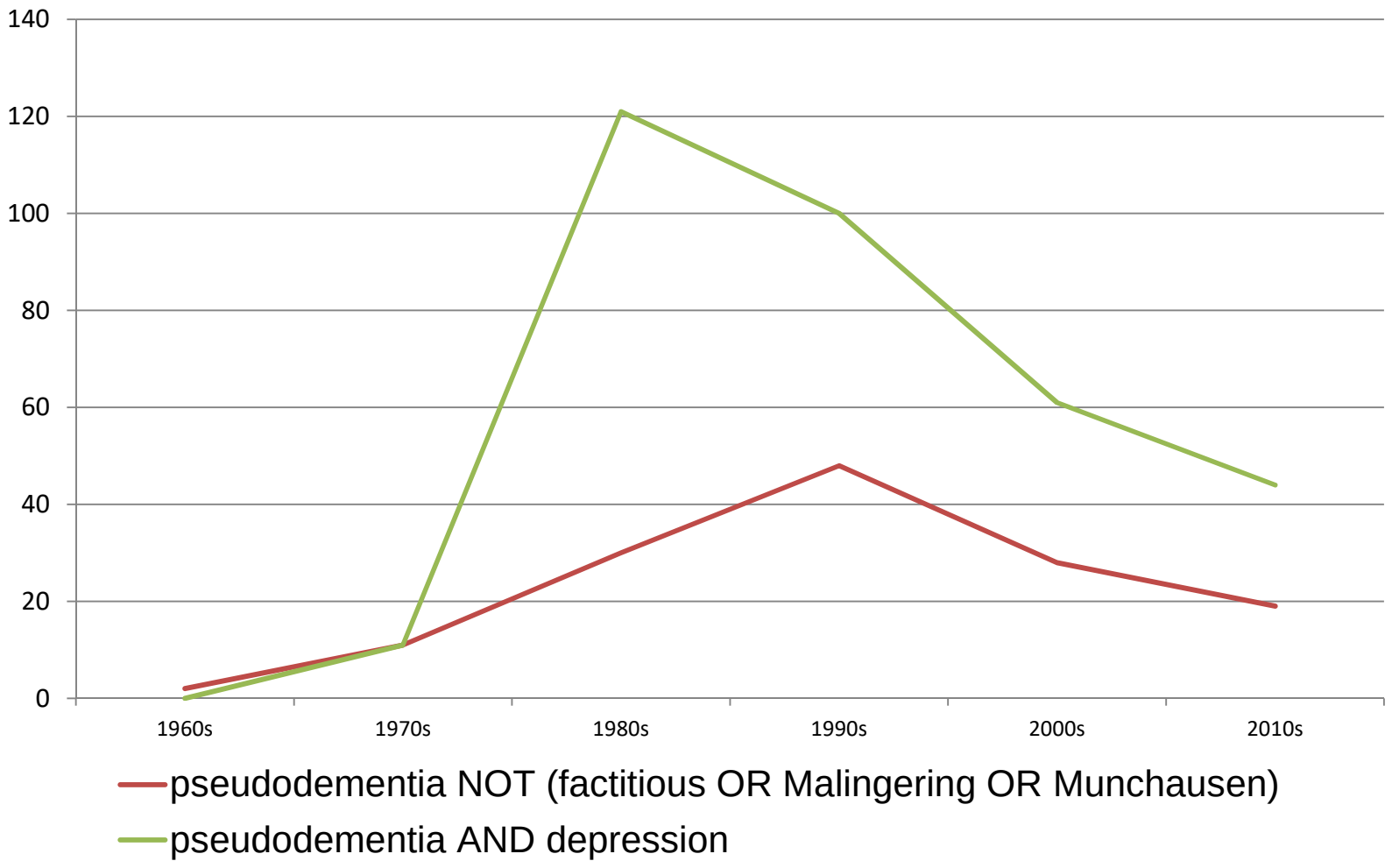
Pseudodemenza (depressiva): termine da mandare in pensione?

Coniato da Mairet nel 1883 «démence melancholique»: alterazioni cognitive simili a quelle in corso di demenza, ma reversibili e osservate in pazienti depressi.

Caduto in disuso fino alla descrizione di Kiloh (1961). Molto utilizzato fino agli anni 80-90, poi criticato per intrinseca ambiguità, non accettato da tutti gli autori.

Kiloh 1961; Berrios, 1985; Kobayashi & Kato 2011

Pseudodementia on Pubmed



	Leyhe et al., 2016	Boccia et al., 2015	Yousef et al, 1998	Dykierek et al., 1998	Grunhaus et al., 1983	Ron et al., 1979	Wells 1979	Reynolds et al., 1988
History of depressive disorders			Common in DPD			in DPD	in DPD	
Progression of symptoms and asking medical help							Rapid is suggestive of DPD	
History of onset			ambiguous in D; accurate in DPD				ambiguous in D; accurate in DPD	
Loss of social Skills							early and prominent in DPD	
Clinical Aspects : Depressed Mood Suicidal thoughts Anhedonia Fatigue Facial espression			present in DPD; usually absent in D				Affect Shallow and labile in D.	
Diurnal variation			diurnal variation of mood in DPD.				diurnal variation of mood in DPD. Nocturnal accentuation in D	Early Morning awekin g In DPD
Insight for cognitive problems			Absent in D				Absent in D	
Attitude Spontaneous complaint and Emphasize cognitive problems			in DPD unconcern in D				in DPD with strong distress Unconcern in D	
Minimize/conceal cognitive problems			in D					
Answer			Avoid answer and give trivial excuse in D				Near-miss in D; don't know in DPD	
Effort to answer			spend much effort in D				even in simple tasks In DPD Struggle in D	
Keep up							Try to keep up in D;	
Performance of similar difficulty							Variability in DPD;	
Congruence of behaviour and severity of cognitive deficit							Congruent in D	
CT scan					Alterated in D	Air encephalography : Cerebral and Cortical atrophy in D		
MRI (atrophy of left ippocampal volume or cingulate cortex)	> D	> in D also in CC						
FDG PET	Future criteria							
Amyloid PET	Future criteria for very early stage AD with depression							

Punti di forza

Reclutamento in primary care

Gruppo di controlli sani

Inclusione di aspetti qualitativi (domini cognitivi) e quantitativi (Calcolo effect size)

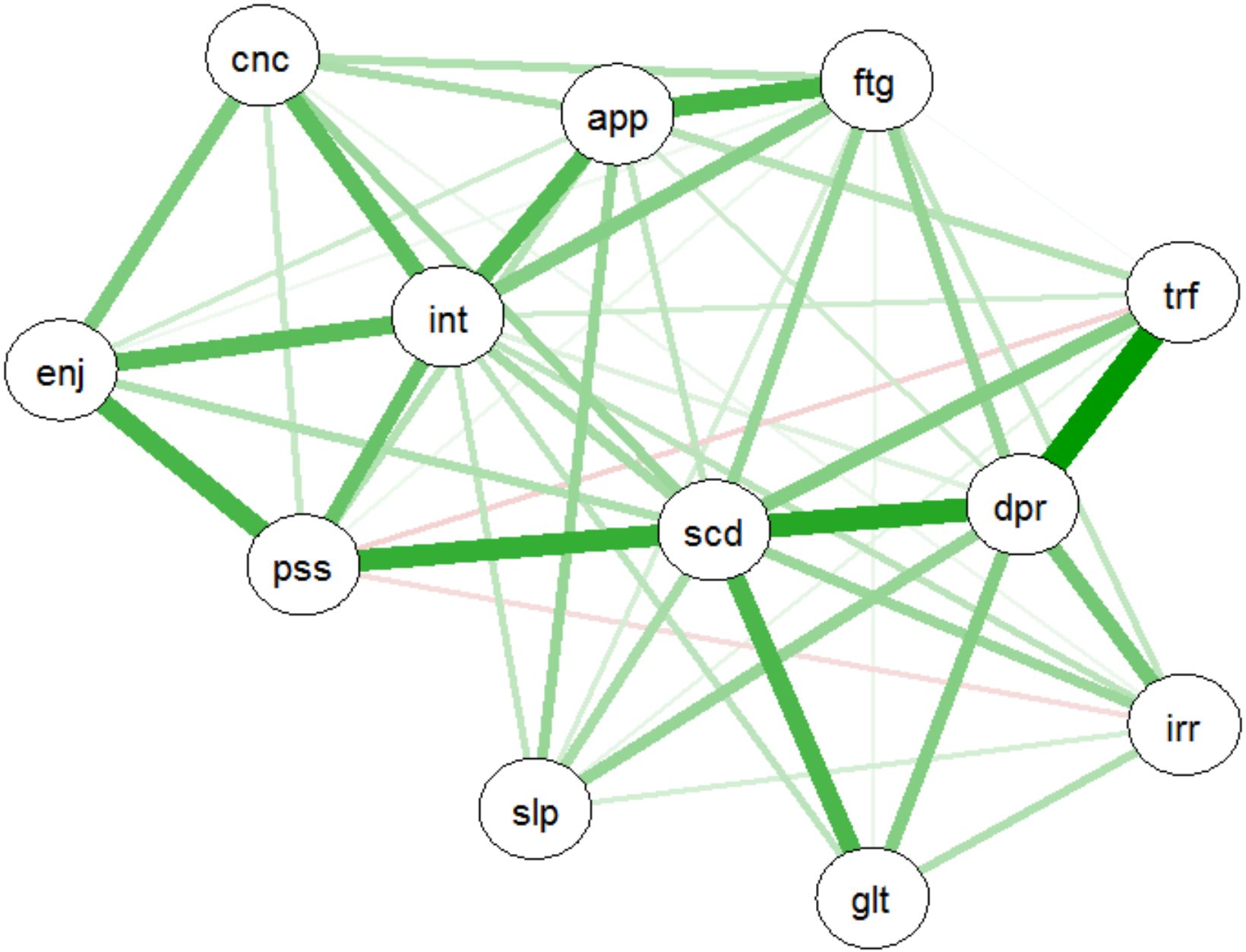
Follow up di durata discreta

Campione dimensioni appropriate

Criticità

- Reclutati soltanto pazienti >75 aa
- 50% attrition?
- Utilizzo test cognitivi relativamente poco conosciuti
- Fluenza verbale come unico indice di funzioni esecutive a fronte di diversi subtest per la memoria
- GDS-15 per valutare presenza depressione
- Analisi non aggiustate per anno di insorgenza della depressione
- Strategia analitica:
  1. mancato utilizzo analisi multivariate o test tempo-dipendenti (Cox regression)
  2. assenti analisi di accuratezza diagnostica / discriminanti
  3. regressioni condotte in modo separato nei sottogruppi (no interaction term)

Perché non valutare il potere predittivo dei differenti sintomi depressivi?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grazie

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Maggiori Performance al Sisco intellectual function sono associate con un **rischio maggiore** di **sviluppare demenza** nei pazienti **depressi**

Depressive symptoms were associated with **subsequent AD** only in **the higher-educated group** in a Dutch sample (Geerlings et al., 2000)

2 possibili Spiegazioni:

"greater cognitive reserve of the participants with **higher education** has **buffered** the early **cognitive decline processes** of AD, whereas the **noncognitive symptoms** such **as depression** were **not positively influenced** by cognitive reserve.» (Geerlings et al., 2000)

meta-cognitive processes or awareness of subjective cognitive impairment might be involved in this context. In accordance with this post hoc interpretation, Spitznagel et al. [31] found that depressive symptoms were associated with the awareness of cognitive impairment in participants with higher cognitive reserve, whereas no association was found in participants with lower cognitive reserve in a sample of participants with questionable or mild dementia