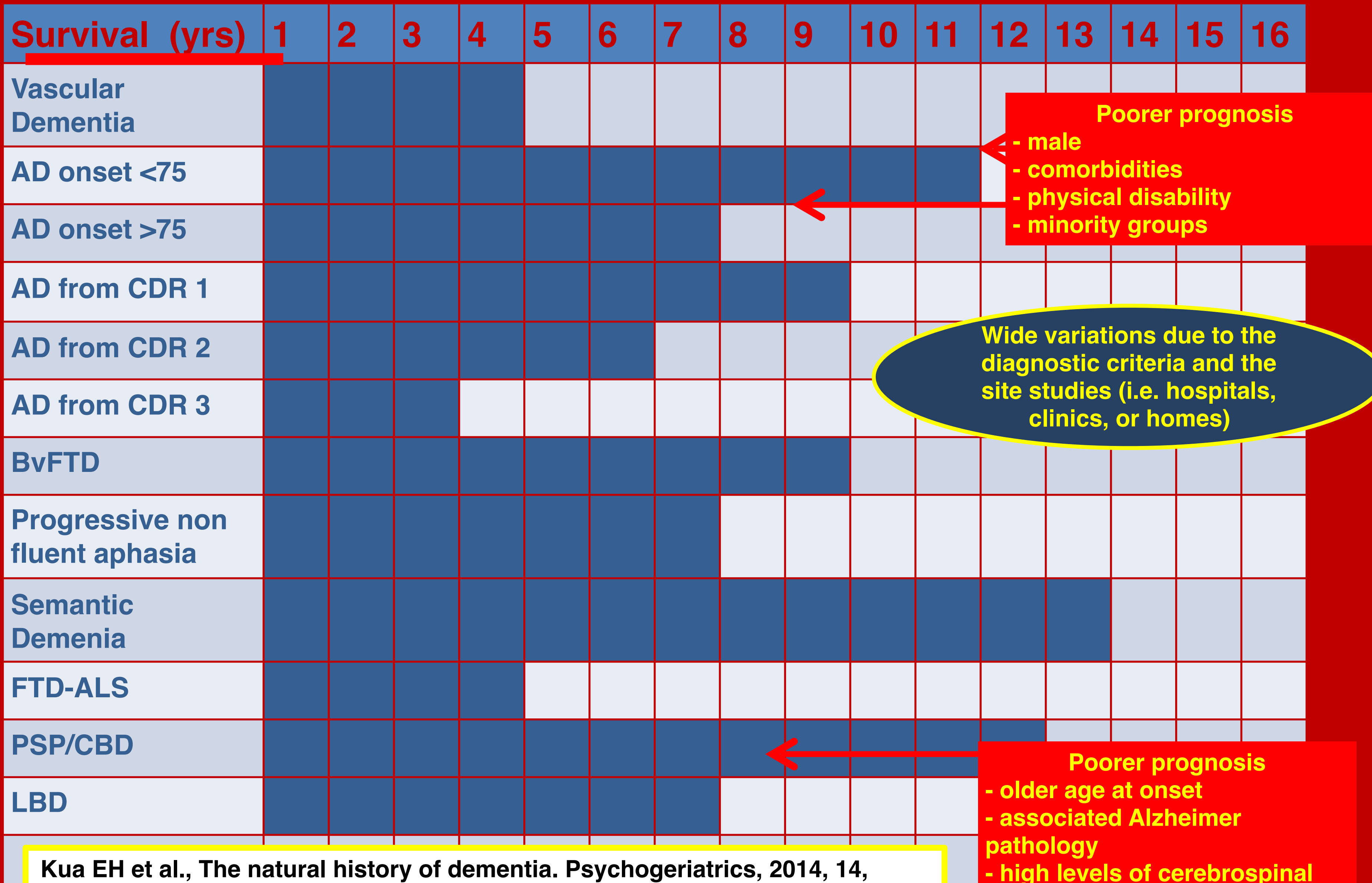
Non-Pharmacological Therapy in Dementia

Paolo Livrea

Cagliari -10 novembre 2017

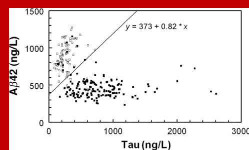


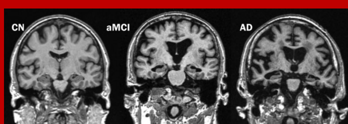
Kua EH et al., The natural history of dementia. Psychogeriatrics, 2014, 14,

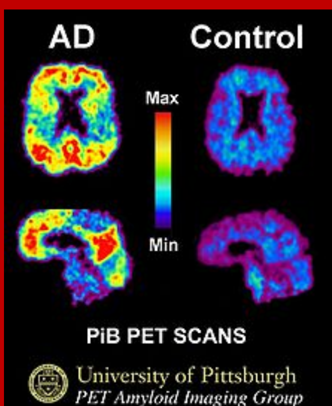
Fitzpatrick et al., Survival after dementia onset. AD vs. VD. J Neurol Sci, 2004,

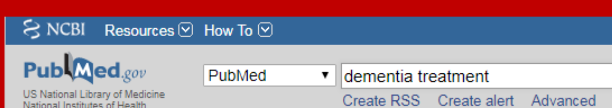
Kansal et al., Survival in Frontotemporal Dementia Phenotypes: A Meta-AnalysisDement Geriatr Cogn Disord

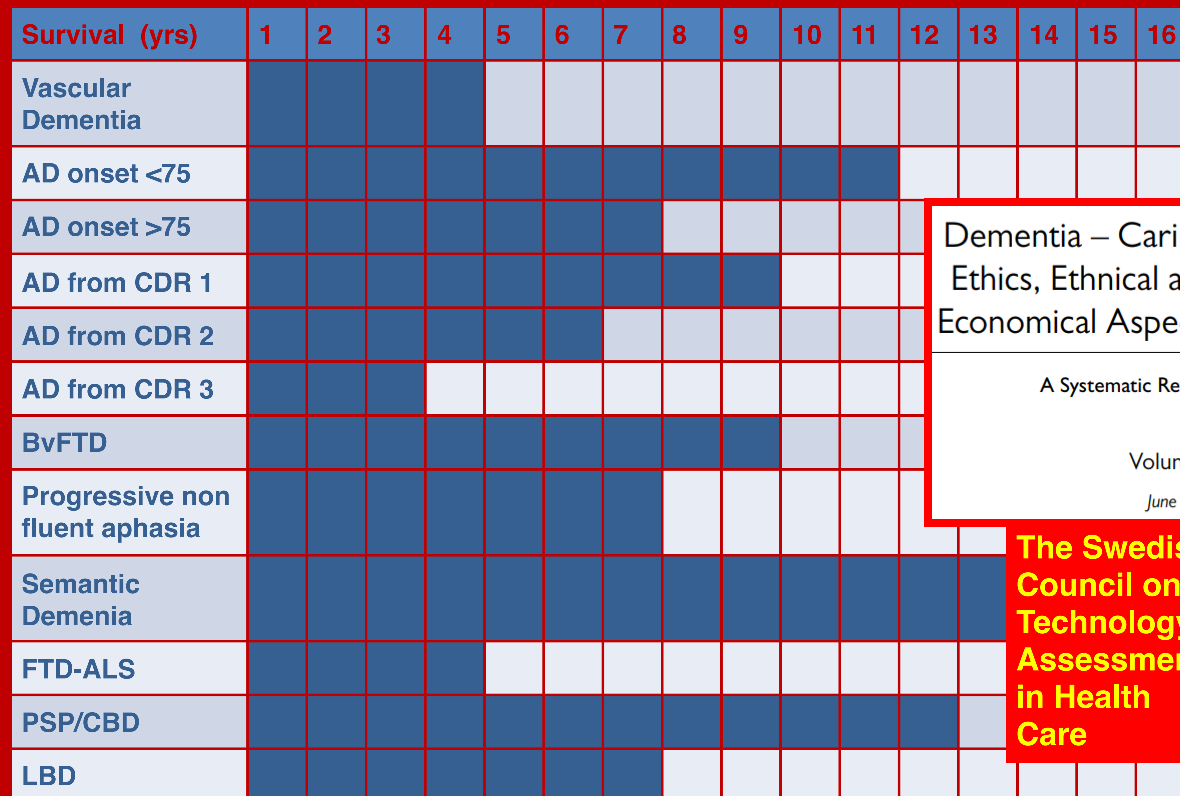
Survival and mortality differences between dementia with Lewy bodies vs Alzheimer disease. Neurology, 2006, 67.











Dementia – Caring, Ethics, Ethnical and Economical Aspects

A Systematic Review

Volume 3

June 2008

The Swedish Council on Technology Assessment in Health Care

33. Care Interventions - patient's perspective. pp 140

Dementia in Latin America: Epidemiological Evidence and Implications for Public Policy

Nilton Custodio et al

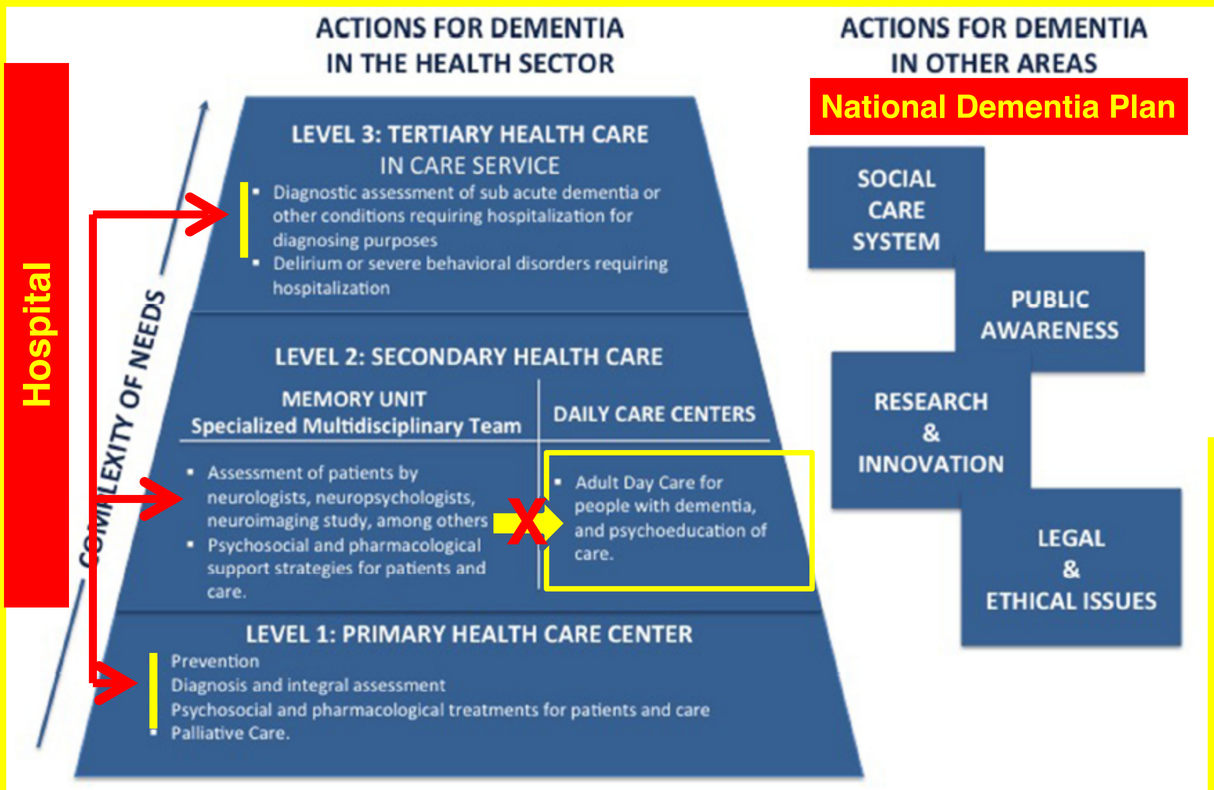
frontiers in Aging Neuroscience 9: 221-232

RESEARCH ARTICLE Open Access

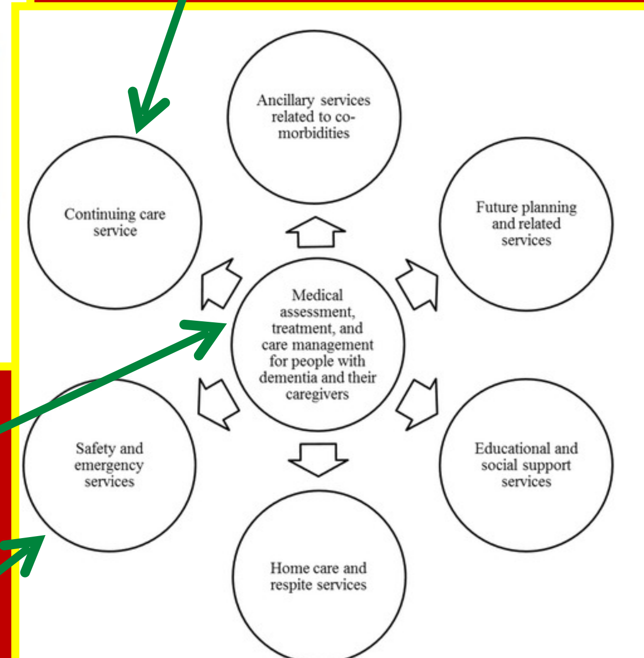
Provision of dementia-related services in Canada: a comparative study

Helen Tam-Tham[1*], Alberto Nettel-Aguirre[1,2], James Silvius[3], William Dalziel[4], Linda Garcia[5,6], Frank Molnar[4] and Neil Drummond[7]

BMC Health Services Research (2016) 16:184



Continuing care services provide increased care at a hospital or housing alternative



Medical assessment, treatment, and care management includes risk factors, diagnosis, and behavioural and psychological symptoms of dementia. it brings together all the dementia-related types of services located on the peripherv

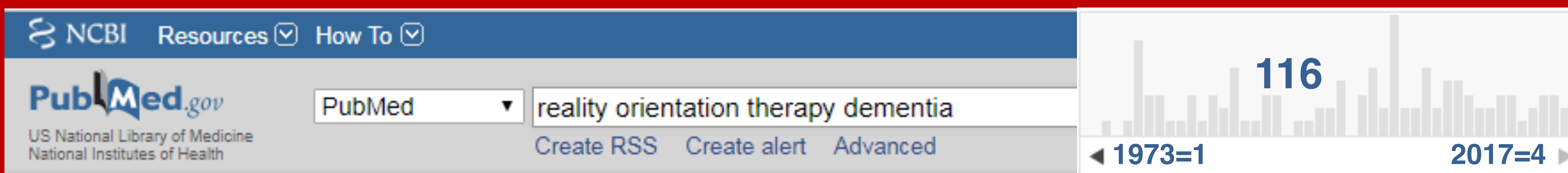
Safety and emergency services relate to transportation, falls, wandering, and contingency services

Reality Orientation Therapy (ROT) – 1966

Taulbee, L.R., Folsom, J.C., **1966**. Reality orientation for geriatric patients. Hospital & Community Psychiatry 17, 133–135

Brook, P., Degun, G., Mather, M., **1975**. Reality orientation, a therapy for psychogeriatric patient: a controlled study. British Journal of Psychiatry 127, 42–45

Orientation information (eg : time, place and person-related) which is thought to provide the person with a greater understanding of their surroundings, possibly resulting in an improved sense of control and self-esteem.



Cochrane Database Syst Rev. 2000;(4):CD001119.

Reality orientation for dementia.

Spector A[1], Orrell M, Davies S, Woods B.

Cochrane Database Syst Rev. 2007 Jul 18;(3):CD001119.

WITHDRAWN: Reality orientation for dementia.

Spector A[1], Orrell M, Davies S, Woods B.

Change of title: "Cognitive stimulation to improve cognitive functioning in people with dementia" which includes reality orientation as well as cognitive stumulation

- **Six RCTs analysis**
- **125 subjects (67 in experimental groups, 58 in control groups)**

- **Changes in cognitive and behavioural outcomes showed a significant effect in favour of treatment**

- **There is some evidence that RCT has benefits on both cognition and behaviour for dementia sufferers.**

Am J Alzheimers Dis Other Demen. 2015 Aug;30(5):527-32. doi: 10.1177/1533317514568004. Epub 2015 Jan 14.

The effectiveness of reality orientation in the treatment of Alzheimer's disease.

Camargo CH[1], Justus FF[2], Retzlaff G[2].

- **RCT**
- **weekly RO sessions for 6 months**
- **14 AD + donepezil**
- **Mean CERAD battery, MMSE, and Clock Drawing Test scores improved in the treatment group**

Cognitive Stimulation - 1994

Breuil, V., De Rotrou, J., Forette, F., Tortrat, D., Ganansia Ganem, A., Frambourt, A., et al., 1994. Cognitive stimulation of patients with dementia: preliminary results. International Journal of Geriatric Psychiatry 9 (3), 211–217.

The emphasis is on improving performance in everyday life, rather than on cognitive tests, building on the person's strengths and developing ways of compensating for impairment.

'Cognitive stimulation'

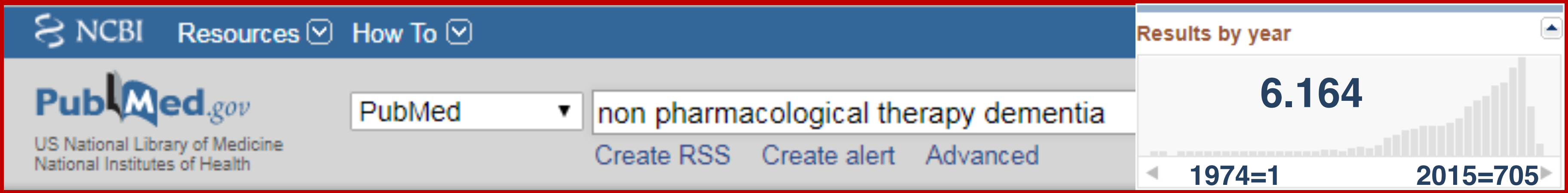
engagement in a range of activities and discussions (usually in a group) aimed at general enhancement of cognitive and social functioning

'Cognitive training'

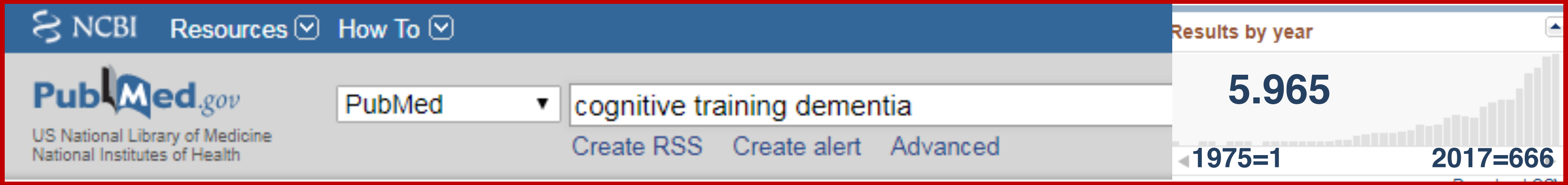
guided practice on a set of standard tasks designed to reflect particular cognitive functions with a range of difficulty levels to suit the individual's level of ability

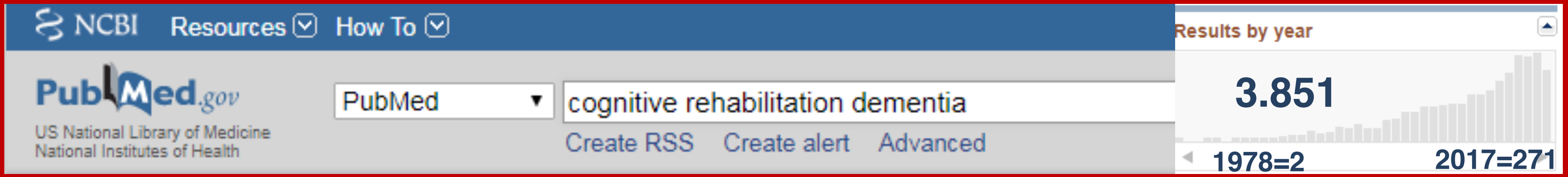
'Cognitive rehabilitation'

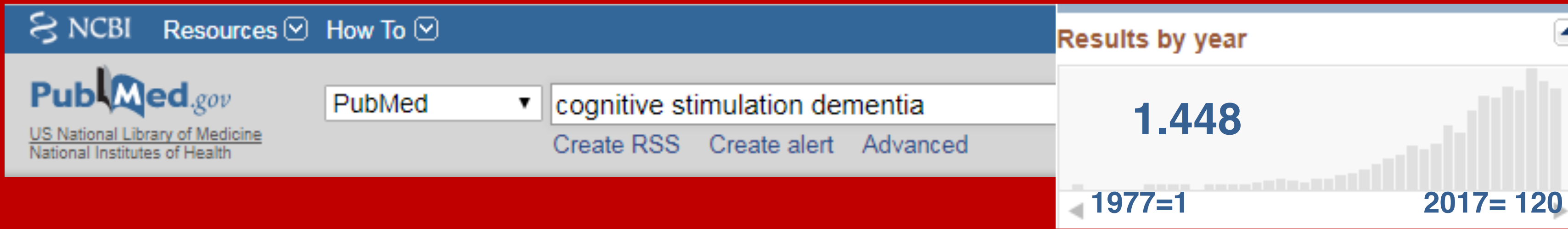
as an individualised approach where personally relevant goals are identified, and the therapist works with the person and his/her family to devise strategies to address these

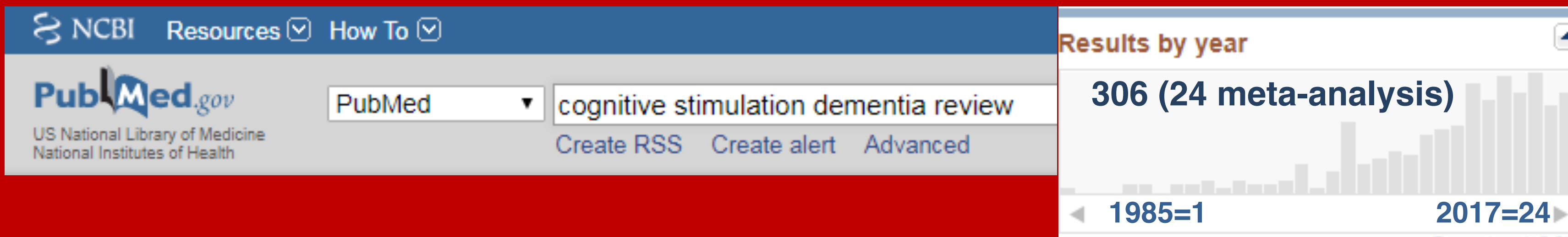


Cognitive Stimulation Therapy in Dementia









Cognitive Stimulation as a Therapeutic Modality for Dementia: A Meta-Analysis

Psychiatry Investig 2017;14(5):626-639

Kayoung Kim[1], Ji Won Han[2], Yoonseop So[3], Jiyeong Seo[...], You Joung Kim[...], Joon Hyuk Park[...], Seok Bum Lee[6], Jung Jae Lee[6], Hyun-Ghang Jeong[7], Tae Hui Kim[8], and Ki Woong Kim[1,2,9,10] ✉

- 7,354 articles
- 30 RCTs selected
- 14 RCTs finally included in the meta-analysis
- 731 participants with dementia
  - 412 received CS
  - 319 received usual care

Mean difference between the Cognitive Stimulation and control groups:

- 2.21 ADAS-Cog p=0.00007
- 1.41 MMSE p<0.00001
- Quality of life p=0.003

Conclusions. Cognitive Stimulation is effective for improving cognition and quality of life in people with dementia; however, its effects are small to moderate.

Cognitive Stimulation as a Therapeutic Modality for Dementia: A Meta-Analysis

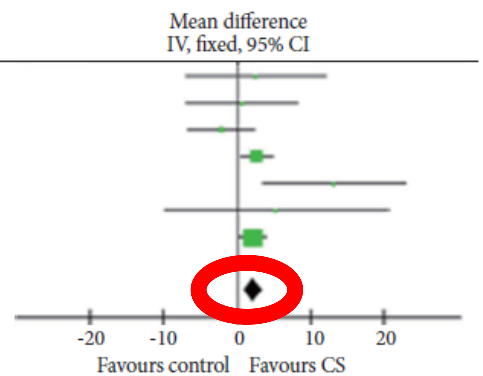
Kayoung Kim[1], Ji Won Han[2], Yoonseop So[3], Jiyeong Seo[4], You Joung Kim[2], Joon
Seok Bum Lee[6], Jung Jae Lee[6], Hyun-Ghang Jeong[7], Tae Hui Kim[8], and Ki Woong Kim[1,2,9,10]

Psychiatry Investig
2017;14(5):626-639

Cognitive stimulation versus no cognitive stimulation. 1

Study or subgroup	CS Mean	CS SD	CS Total	Control Mean	Control SD	Control Total	Weight	Mean difference IV, fixed, 95% CI
Bottino et al.[42]	2.17	8.33	6	-0.43	8.92	7	1.9%	2.60 (-6.79, 11.99)
Buschert et al.[45]	0.7	8	8	0	6.93	7	2.9%	0.70 (-6.86, 8.26)
Coen et al.[46]	0.2	7.2	13	2.3	4.1	12	7.9%	-2.10 (-6.65, 2.45)
Onder et al.[49]	0.2	6.69	70	-2.5	6.55	67	33.3%	2.70 (0.48, 4.92)
Requena et al.[41]	6.5	14.06	20	-6.6	20.48	30	1.8%	13.10 (3.51, 22.67)
Spector et al.[50]	4.3	17.33	17	-1	20.5	10	0.7%	5.30 (-9.84, 20.44)
Spector et al.[13]	1.9	6.2	97	-0.3	5.5	70	51.5%	2.20 (0.42, 3.98)
Total (95% CI)			231			203	100.0%	2.21 (0.93, 3.49)

Heterogeneity. $Chi^2=8.92$, df=6 (p=0.18): $I^2=33\%$
Test for overall effect Z=3.38 (p=0.0007)

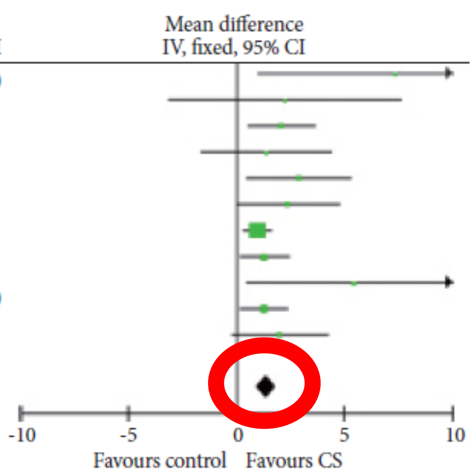


Outcome:

Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog)
P<0.0007

Study or subgroup	Cognitive stimulation Mean	Cognitive stimulation SD	Cognitive stimulation Total	Control Mean	Control SD	Control Total	Weight	Mean difference IV, fixed, 95% CI
Baldelli et al.[43]	3	5.32	13	-4.4	9.15	10	0.5%	7.40 (1.03, 13.77)
Bottino et al.[42]	0.83	4.53	6	-1.43	5.3	7	0.7%	2.26 (-3.08, 7.60)
Breuil et al.[53]	1.4	2.7	28	-0.7	3.1	27	7.9%	2.10 (0.56, 3.64)
Buschert et al.[45]	0.5	3.14	8	-0.9	2.83	7	2.0%	1.40 (-1.62, 4.42)
Coen et al.[46]	0.8	3.6	14	-2.1	2.5	11	3.2%	2.90 (0.50, 5.30)
Ishizaki et al.[47]	0.1	3.3	14	-2.3	2.7	11	3.4%	2.40 (0.05, 4.75)
Niu et al.[48]	0.81	1.11	16	-0.19	0.66	16	46.6%	1.00 (0.37, 1.63)
Onder et al.[49]	0.2	3.35	70	-1.1	3.27	67	15.2%	1.30 (0.19, 2.41)
Requena et al.[41]	1.5	7.38	20	-3.97	10.71	30	0.7%	5.47 (0.46, 10.48)
Spector et al.[13]	0.9	3.5	97	-0.4	3.5	70	16.1%	1.30 (0.22, 2.38)
Yamanaka et al.[51]	1.63	4.2322	26	-0.4	4.2175	30	3.8%	2.03 (-0.19, 4.25)
Total (95% CI)			312			286	100.0%	1.41 (0.98, 1.84)

Heterogeneity. $Chi^2=10.95$, df=10 (p=0.36): $I^2=9\%$
Test for overall effect Z=6.39 (p<0.00001)



Outcome:

MMSE
P<0.00001

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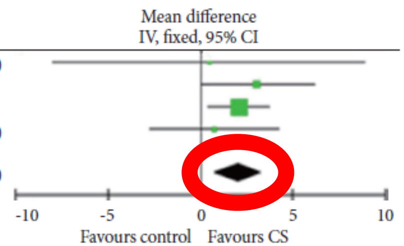
Psychiatry Investig
2017;14(5):626-639

Cognitive stimulation versus no cognitive stimulation. 2

Study or subgroup	CS Mean	CS SD	CS Total	Control Mean	Control SD	Control Total	Weight	Mean difference IV, fixed, 95% CI
Buschert et al.[45]	-0.4	10.61	8	-0.9	5.52	7	2.5%	0.50 (-7.91, 8.91)
Coen et al.[46]	3.6	3.7	14	0.5	4.4	13	18.6%	3.10 (0.02, 6.18)
Spector et al.[13]	1.3	5.1	97	-0.8	5.6	70	64.2%	2.10 (0.44, 3.76)
Yamanaka et al.[51]	0.19	6.0678	26	-0.57	7.1752	30	14.7%	0.76 (-2.71, 4.23)
Total (95% CI)			145			120	100.0%	2.05 (0.72, 3.38)

Heterogeneity. Chi²=1.11, df=3 (p=0.77): I²=0%
Test for overall effect Z=3.02 (p=0.003)

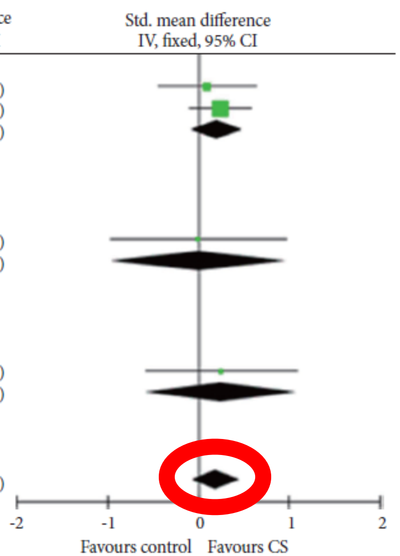


Outcome:

Quality of life
P<0.003

Study or subgroup	CS Mean	CS SD	CS Total	Control Mean	Control SD	Control Total	Weight	Std. mean difference IV, fixed, 95% CI
5.1.1 Barthel ADL								
Baldelli et al.[44]	15.37	34.94	71	11.88	40.48	16	23.0%	0.10 (-0.45, 0.64)
Onder et al.[49]	-0.9	8.37	70	-2.9	8.19	67	59.9%	0.24 (-0.10, 0.58)
Subtotal (95% CI)			141			83	82.9%	0.20 (-0.09, 0.49)
Heterogeneity. Chi²=0.20, df=1 (p=0.66): I²=0%								
Test for overall effect Z=1.37 (p=0.17)								
5.1.2 MOSES-self care								
Ferrario et al.[52]	-0.3	9.88	13	-0.3	5.89	6	7.2%	0.00 (-0.97, 0.97)
Subtotal (95% CI)			13			6	7.2%	0.00 (-0.97, 0.97)
Heterogeneity. Not applicable								
Test for overall effect Z=0.00 (p=1.00)								
5.1.3 Stewart ADL scale								
Baldelli et al.[43]	1.5	39.47	13	-8.9	39.2	10	9.9%	0.25 (-0.57, 1.08)
Subtotal (95% CI)			13			10	9.9%	0.25 (-0.57, 1.08)
Heterogeneity. Not applicable								
Test for overall effect Z=0.60 (p=0.55)								
Total (95% CI)			167			99	100.0%	0.19 (-0.07, 0.45)

Heterogeneity. Chi²=0.37, df=3 (p=0.95): I²=0%
Test for overall effect Z=1.44 (p=0.15)
Test for subgroup differences: Chi²=0.18, df=2 (p=0.92): I²=0%



Outcome:

ADL
N.S.

Cognitive Stimulation as a Therapeutic Modality for Dementia: A Meta-Analysis

Psychiatry Investig 2017;14(5):626-639

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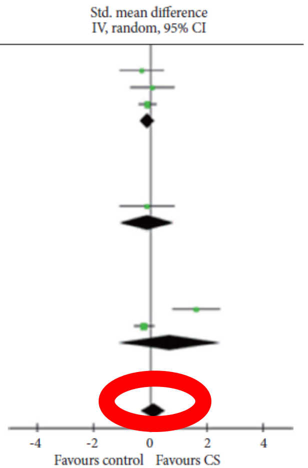
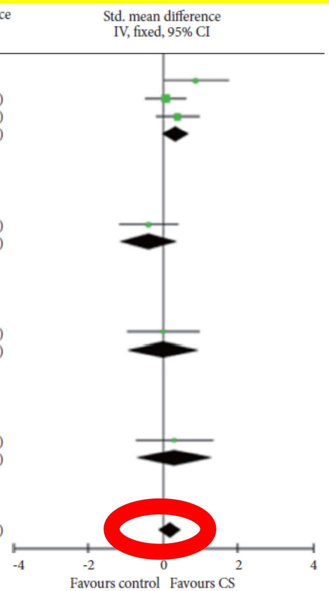
Seok Bum Lee[6], Jung Jae Lee[6], Hyun-Ghang Jeong[7], Tae Hui Kim[8], and Ki Woong Kim[1,2,9,10]

Cognitive stimulation versus no cognitive stimulation. 3

Study or subgroup	Cognitive stimulation Mean	SD	Total	Control Mean	SD	Total	Weight	Std. mean difference IV, random, 95% CI
2.1.1 Behavior Rating Scale (CAPE)								
Coen et al.[46]	0	3.6	14	1.4	5.4	13	14.6%	-0.30 (-1.06, 0.46)
Spector et al.[50]	1.1	6.08	17	0.6	7.07	10	14.3%	0.08 (-0.71, 0.86)
Spector et al.[13]	0.2	6.1	97	0.7	5.5	70	23.2%	-0.08 (-0.39, 0.22)
Subtotal (95% CI)			128			93	52.1%	-0.09 (-0.36, 0.18)
Heterogeneity. Tau²=0.00, Chi²=0.46, df=2 (p=0.79): I²=0%								
Test for overall effect Z=0.68 (p=0.50)								
2.1.11 Multidimensional Observation Scale for Elderty Subjects (MOSES)-irritable, withdrawn								
Ferrario et al.[52]	-1.3	6.31	13	-0.5	9.44	6	11.5%	-0.10 (-1.07, 0.86)
Subtotal (95% CI)			13			6	11.5%	-0.10 (-1.07, 0.86)
Heterogeneity. Not applicable								
Test for overall effect Z=0.21 (p=0.83)								
2.1.12 Neuropsychiatric inventory (NPI)								
Niu et al.[48]	2.06	1.39	16	0	1.03	16	13.7%	1.64 (0.83, 2.46)
Onder et al.[49]	-0.9	15.9	70	2.5	17.19	67	22.7%	-0.20 (-0.54, 0.13)
Subtotal (95% CI)			86			83	36.4%	0.68 (-1.13, 2.49)
Heterogeneity. Tau²=1.60, Chi²=16.84, df=1 (p<0.0001): I²=94%								
Test for overall effect Z=0.74 (p=0.46)								
Total (95% CI)			227			182	100.0%	0.11 (-0.32, 0.55)
Heterogeneity. Tau²=0.19, Chi²=17.88, df=5 (p=0.003): I²=72%								
Test for overall effect Z=0.51 (p=0.61)								
Test for subgroup differences: Chi²=0.69, df=2 (p=0.71): I²=0%								



Study or subgroup	CS Mean	SD	Total	Control Mean	SD	Total	Weight	Std. mean difference IV, fixed, 95% CI
3.1.1 GDS-30								
Baldelli et al.[44]	2.1	4.61	13	-2.3	4.99	10	11.5%	0.89 (0.02, 1.76)
Baldelli et al.[44]	3.21	7.98	71	2.57	10	16	29.7%	0.08 (-0.47, 0.62)
Requena et al.[41]	5.6	7.87	20	2.03	9.07	30	26.7%	0.41 (-0.16, 0.98)
Subtotal (95% CI)			104			56	67.9%	0.34 (-0.01, 0.70)
Heterogeneity. Chi²=2.48, df=2 (p=0.29): I²=19%								
Test for overall effect Z=1.88 (p=0.06)								
3.1.2 GDS-15								
Coen et al.[46]	-0.9	3	13	0.1	1.9	13	14.5%	-0.39 (-1.16, 0.39)
Subtotal (95% CI)			13			13	14.5%	-0.39 (-1.16, 0.39)
Heterogeneity. Not applicable								
Test for overall effect Z=0.97 (p=0.33)								
3.1.3 MOSES-depressed/anxious mood								
Ferrario et al.[52]	-1.08	9.5	13	-1.17	4.62	6	9.3%	0.01 (-0.96, 0.98)
Subtotal (95% CI)			13			6	9.3%	0.01 (-0.96, 0.98)
Heterogeneity. Not applicable								
Test for overall effect Z=0.02 (p=0.98)								
3.1.4 Montgomery Asberg Depression Rating Scale (MADRS)								
Buschert et al.[45]	1.5	5.33	8	-0.4	6.4	7	8.4%	0.31 (-0.72, 1.33)
Subtotal (95% CI)			8			7	8.4%	0.31 (-0.72, 1.33)
Heterogeneity. Not applicable								
Test for overall effect Z=0.59 (p=0.56)								
Total (95% CI)			138			82	100.0%	0.20 (-0.09, 0.50)
Heterogeneity. Chi²=5.47, df=5 (p=0.36): I²=9%								
Test for overall effect Z=1.35 (p=0.18)								
Test for subgroup differences: Chi²=2.99, df=3 (p=0.39): I²=0%								



Outcome:

behavioral and psychological symptoms N.S.

Outcome:

mood N.S.

Note

Severe Mood Symptoms or Behavioral and Psychological Symptoms were excluded from most clinical trials on the efficacy of CST

Heterogeneity in Protocols of activities

Ageing Research Reviews 12 (2013) 253–262
Contents lists available at SciVerse ScienceDirect
Ageing Research Reviews
journal homepage: www.elsevier.com/locate/arr
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Review

Cognitive stimulation for dementia: A systematic review of the evidence of effectiveness from randomised controlled trials

Elisa Aguirre[a,*], Robert T. Woods[b,1], Aimee Spector[c,2], Martin Orrell[a,3]

Formal RO

RO board, multisensory stimulation

Classroom RO

Physical therapy augmented by RO sessions

Daily personal diary, group activities (dominoes, spelling, bingo) naming objects, reading RO board

Cognitive stimulation

Current events; discussion of hobbies and activities; *education regarding Alzheimer's disease*; life story work; links with daily life encouraged

Drawing, associated words, object naming, categorizing objects

Multi-component cognitive group intervention – for AD group emphasis on cognitive stimulation (for MCI group more emphasis on cognitive training)

Temporal and spatial orientation, discussion of interesting themes, reminiscence activities, naming people, daily activities, *planning use of calendars and clocks*

Current information, topics of general interest, historical events and famous people, attention, memory and visuo-spatial

Orientation, categorizing objects, sounds, number, physical and word games, current events

Repetition of orientation information (e.g., time, place, weather), charts, pictures, touching objects and material

Orientation, categorizing objects, sounds, number, physical and word games, current events

Ageing Research Reviews 12 (2013) 253–262

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Review

Cognitive stimulation for dementia: A systematic review of the evidence of effectiveness from randomised controlled trials

Elisa Aguirre[a,*], Robert T. Woods[b,1], Aimee Spector[c,2], Martin Orrell[a,3]

Cochrane Library

Cochrane Database of Systematic Reviews

Cognitive stimulation to improve cognitive functioning in people with dementia (Review)

Woods B, Aguirre E, Spector AE, Orrell M

- 15 included RCTs
- 6 studies outpatients community;
- 9 studies residents in care homes
- diagnosis of dementia
  - Alzheimer's disease
  - vascular dementia
  - mixed Alzheimer's and vascular dementia
  - other types of dementia
- all levels of cognitive impairment
- 718 participants (mean age 78.8 years)
  - 407 in experimental groups
  - 311 in control groups

30 min	45 min	60 min	90 min	120 min
30 min 5 times a week 4 weeks	45 min 2 times a week for 7 weeks	60 min 5 times a week 21 weeks	90 min 1 time a week 5 months	120 min 1 time a week 6 months
30 min 5 times a week 3 months	45 min 5 times a week 24 months	60 min 2 times a week 5 weeks	90 min 1 time a week 8 weeks	
30 min 5 times a week 20 weeks	45 min 2/3 times a week 7 weeks	60 min 5 times a week 1 month		
30 min 3 times a week 25 weeks	45 min 2 times a week 7 weeks	60 min 3 times a week 3 months		

Heterogeneity in CS Session duration

Ageing Research Reviews 12 (2013) 253–262
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Review

Cognitive stimulation for dementia: A systematic review of the evidence of effectiveness from randomised controlled trials

Elisa Aguirre[a,*], Robert T. Woods[b,1], Aimee Spector[c,2], Martin Orrell[a,3]

Heterogeneity in Therapy maintainence

4 weeks

30 min
5 times a week
4 weeks

60 min
5 times a week
1 month

30 min
5 times a week
20 weeks

5 weeks

60 min
2 times a week
5 weeks

7 weeks

45 min
2 times a week
for 7 weeks

45 min
2/3 times a
week
7 weeks

45 min
2 times a week
7 weeks

8 weeks

90 min
1 time a week
8 weeks

12 weeks

30 min
5 times a week
3 months

60 min
3 times a week
3 months

20 weeks

90 min
1 time a week
5 months

21 weeks

60 min
5 times a week
21 weeks

24 weeks

120 min
1 time a week
6 months

25 weeks

30 min
3 times a week
25 weeks

104 weeks

45 min
5 times a week
24 months

Study or Subgroup	Cognitive stimulation Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
1.1.1 ADAS-Cog								
Bottino 2005	2.17	8.33	6	-0.43	8.92	7	2.1%	0.28 [-0.82, 1.38]
Buschert 2011	0.7	8	8	0	6.93	7	2.5%	0.09 [-0.93, 1.10]
Coen 2011	0.2	7.2	13	2.3	4.1	12	4.1%	-0.34 [-1.13, 0.45]
Onder 2005	0.4	6.69	70	-2.5	6.55	67	22.5%	0.44 [0.10, 0.77]
Requena 2006	6.4	14.06	20	-6.6	20.48	30	7.6%	0.70 [0.12, 1.29]
Spector 2001	4.3	17.33	17	-1	20.5	10	4.2%	0.28 [-0.51, 1.06]
Spector 2003	1.9	6.2	97	-0.3	5.5	70	26.9%	0.37 [0.06, 0.68]
Subtotal (95% CI)			**231**			**203**	**70.0%**	**0.37 [0.17, 0.56]**
Heterogeneity: Chi² = 4.88, df = 6 (P = 0.56); I² = 0%								
Test for overall effect: Z = 3.74 (P = 0.0002)								
1.1.2 Wechsler Memory Scale								
Woods 1979	4.7	12.02	5	-0.6	7.85	5	1.6%	0.47 [-0.80, 1.74]
Subtotal (95% CI)			**5**			**5**	**1.6%**	**0.47 [-0.80, 1.74]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.73 (P = 0.47)								
1.1.3 Global cognitive score (includes MMSE & CERAD)								
Breuil 1994	5.8	7.3	29	1	7.8	27	8.9%	0.63 [0.09, 1.17]
Subtotal (95% CI)			**29**			**27**	**8.9%**	**0.63 [0.09, 1.17]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.29 (P = 0.02)								
1.1.4 MMSE								
Baldelli 1993a	3	5.32	13	-4.4	9.15	10	3.3%	0.99 [0.11, 1.87]
Baldelli 2002	2.34	4.78	71	-0.12	5.06	16	8.6%	0.50 [-0.04, 1.05]
Subtotal (95% CI)			**84**			**26**	**11.9%**	**0.64 [0.17, 1.10]**
Heterogeneity: Chi² = 0.83, df = 1 (P = 0.36); I² = 0%								
Test for overall effect: Z = 2.69 (P = 0.007)								
1.1.5 CAPE-I/O								
Baines 1987	1.4	4.59	5	0.1	6.4	5	1.7%	0.21 [-1.03, 1.46]
Ferrario 1991	1.23	3.64	13	0	2.93	6	2.7%	0.34 [-0.63, 1.32]
Subtotal (95% CI)			**18**			**11**	**4.4%**	**0.29 [-0.48, 1.06]**
Heterogeneity: Chi² = 0.03, df = 1 (P = 0.87); I² = 0%								
Test for overall effect: Z = 0.74 (P = 0.46)								
1.1.6 RCP Cognition								
Wallis 1983	5.9	35.5	10	1.7	27.04	9	3.2%	0.13 [-0.78, 1.03]
Subtotal (95% CI)			**10**			**9**	**3.2%**	**0.13 [-0.78, 1.03]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.27 (P = 0.78)								
Total (95% CI)			**377**			**281**	**100.0%**	**0.41 [0.25, 0.57]**
Heterogeneity: Chi² = 7.98, df = 13 (P = 0.84); I² = 0%								
Test for overall effect: Z = 5.04 (P < 0.00001)								
Test for subgroup differences: Chi² = 2.24, df = 5 (P = 0.82), I² = 0%								

Meta analysis
Cognitive
outcome

Cognitive stimulation interventions benefit (p<0.0001):

- **ADAS-Cog**
- **Global Cognitive Score**
- **MMSE**


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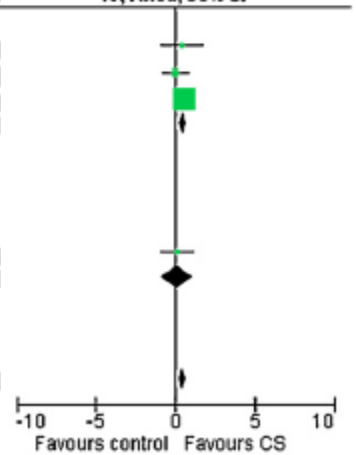
Review

Cognitive stimulation for dementia: A systematic review of the evidence of effectiveness from randomised controlled trials

Elisa Aguirre[a,*], Robert T. Woods[b,1], Aimee Spector[c,2], Martin Orrell[a,3]

Study or Subgroup	Cognitive stimulation Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
1.5.1 Holden Communication Scale								
Baines 1987	2	7.56	5	-2.6	12.5	5	4.7%	0.40 [-0.86, 1.66]
Spector 2001	-0.7	10.5	17	-0.5	9.4	10	12.1%	-0.02 [-0.80, 0.76]
Spector 2003	0.2	6.1	97	-3.2	6.3	70	75.4%	0.55 [0.23, 0.86]
Subtotal (95% CI)			**119**			**85**	**92.1%**	**0.47 [0.18, 0.75]**
Heterogeneity: Chi² = 1.75, df = 2 (P = 0.42); I² = 0%								
Test for overall effect: Z = 3.22 (P = 0.001)								
1.5.2 MOSES - Withdrawn behaviour								
Ferrario 1991	1.31	6.31	13	0.5	9.44	6	7.9%	0.10 [-0.86, 1.07]
Subtotal (95% CI)			**13**			**6**	**7.9%**	**0.10 [-0.86, 1.07]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.21 (P = 0.83)								
Total (95% CI)			**132**			**91**	**100.0%**	**0.44 [0.17, 0.71]**
Heterogeneity: Chi² = 2.24, df = 3 (P = 0.52); I² = 0%								
Test for overall effect: Z = 3.15 (P = 0.002)								
Test for subgroup differences: Chi² = 0.49, df = 1 (P = 0.48), I² = 0%								

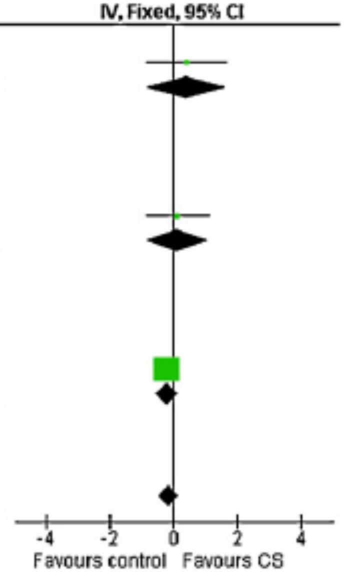


Meta analysis Communication and social interaction

Cognitive stimulation interventions benefit (p<0.002):

- **Holden Communication Scale**

Study or Subgroup	Cognitive stimulation Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
1.11.1 Problem Behaviour Rating Scale								
Baines 1987	3.6	11.4	5	-1.8	12.8	5	6.0%	0.40 [-0.86, 1.66]
Subtotal (95% CI)			**5**			**5**	**6.0%**	**0.40 [-0.86, 1.66]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.63 (P = 0.53)								
1.11.2 MOSES - Irritable								
Ferrario 1991	0.69	2.45	13	0.16	6.89	6	10.1%	0.12 [-0.85, 1.09]
Subtotal (95% CI)			**13**			**6**	**10.1%**	**0.12 [-0.85, 1.09]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.24 (P = 0.81)								
1.11.3 NPI								
Onder 2005	-0.9	15.9	70	2.5	17.19	67	83.9%	-0.20 [-0.54, 0.13]
Subtotal (95% CI)			**70**			**67**	**83.9%**	**-0.20 [-0.54, 0.13]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.19 (P = 0.23)								
Total (95% CI)			**88**			**78**	**100.0%**	**-0.14 [-0.44, 0.17]**
Heterogeneity: Chi² = 1.13, df = 2 (P = 0.57); I² = 0%								
Test for overall effect: Z = 0.86 (P = 0.39)								
Test for subgroup differences: Chi² = 1.13, df = 2 (P = 0.57), I² = 0%								



Meta analysis Behaviour seen as a problem

Cognitive stimulation has no effet


Ageing Research Reviews 12 (2013) 253–262

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Review

Cognitive stimulation for dementia: A systematic review of the evidence of effectiveness from randomised controlled trials

Elisa Aguirre[a,*], Robert T. Woods[b,1], Aimee Spector[c,2], Martin Orrell[a,3]

What do Cochrane systematic reviews say about non-pharmacological interventions for treating cognitive decline and dementia?

Sao Paulo Med J. 2017;135(3):309-2

Characteristics, main findings and quality of evidence from systematic reviews focusing on patient-directed interventions

Intervention	Population/comparison	Benefits, harms and safety	Evidence quality (GRADE approach*)
Cognitive training[20]	Alzheimer's disease; vascular dementia/ control in the short term.	No effect: overall measurement of cognition, participant's capacity for activities of daily living, participant's mood, immediate verbal memory scores, self-reported burden of care.	Low to modera
Cognitive rehabilitation[20]	Alzheimer's disease; vascular dementia/ control in the short term.	Benefit: participant's self-reported performance in relation to individual goals; participant's mood; self-reported mood.	High
Cognitive stimulation[22]	Dementia/control.	Benefit: cognition; self-reported quality of life and well-being; staff ratings of communication and social interaction. No effect: mood; activities of daily living; general behavioral function; behavioral problem.	Not assessed

Bahar-Fuchs A, Clare L, Woods B. Cognitive training and cognitive rehabilitation for mild to moderate Alzheimer's disease and vascular dementia. Cochrane Database Syst Rev. 2013;(6):CD003260.

Woods B, Aguirre E, Spector AE, Orrell M. Cognitive stimulation to improve cognitive functioning in people with dementia. Cochrane Database Syst Rev. 2012;(2):CD005562.

Results from systematic reviews for 24 types of non-pharmacological interventions in Dementia

Cognitive stimulation beneficial effects

- Cognitive function: benefit from CS even three months after the treatment (SMD 0.41, 95% CI 0.25 to 0.57);
- Self-reported quality of life and well-being: benefit from CS (SMD 0.38, 95% CI: 0.11, 0.65);
- Staff ratings of communication and social interaction: benefit from CS (SMD 0.44, 95% CI 0.17 to 0.71);
- Mood, activities of daily living, general behavioral function and behavioral problems: no effect.

- **Meta-analyses of 15 RCTs of cognitive stimulation for dementia (718 participants)**

NCBI Resources How To

PubMed.gov
US National Library of Medicine
National Institutes of Health

PubMed | music dementia

Create RSS Creat

Results by year

674

REVIEW

Translational Neurodegeneration (2017) 6:2

Music therapy is a potential intervention for cognition of Alzheimer's Disease: a mini-review

Rong Fang[1†], Shengxuan Ye[2†], Jiangtao Huangfu[3] and David P. Calimag[1*]

12 RCTs

Many RCTs have demonstrated that Music Therapy can reduce:

- **cognitive decline especially in**
- **autobiographical and episodic memories**
- **psychomotor speed**
- **executive function domains**
- **global cognition**

MT is a promising intervention for strategy of dementia especially of AD and it must be started as early as possible.

Different techniques of Mus Therapy

- **Listening to the music**
- **Singing songs**
- **Music therapist**
- **Background music**
- **Music with activities**
- **Multisensory stimulati**

Neuropsychiatr Dis Treat. 2015 Feb 4;11:291-6.

Adjunct effect of music the

Li CH[1], Liu CK[2], Yang YH[3], Chou MC[4], Chen CH, Lai CL.

Aging Clin Exp Res. 2012 Jun;24(3):227-32. doi: 10.3275/7874. Epub 2011 Jul 21.

Improvement of autobiographic memory recovery by means of sad music in Alzheimer's Disease type dementia.

Meilán García JJ[1], Iodice R, Carro J, Sánchez JA, Palmero F, Mateos AM.

J Clin Exp Neuropsychol. 2015;37(5):503-17. doi: 10.1080/13803395.2015.1026802. Epub 2015 May 8.

Music enhances verbal episodic memory in Alzheimer's disease.

Palisson J[1], Roussel-Baclet C, Maillet D, Belin C, Ankri J, Narme P.

Dement Geriatr Cogn Disord. 2006;22(1):108-20. Epub 2006 May 23.

Investigating the enhancing effect of music on autobiographical memory in mild Alzheimer's disease.

Irish M[1], Cunningham CJ, Walsh JB, Coakley D, Lawlor BA, Robertson IH, Coen RF.

Neurologia. 2017 Jun;32(5):300-308. doi: 10.1016/j.nrl.2015.12.003. Epub 2016 Feb 17.

Music therapy and Alzheimer's disease: Cognitive, psychological, and behavioural effects.

[Article in English, Spanish]

Gómez Gallego M[1], Gómez García J[2].

Geriatr Gerontol Int. 2016 Feb;16(2):191-9. doi: 10.1111/ggi.12453. Epub 2015 Feb 5.

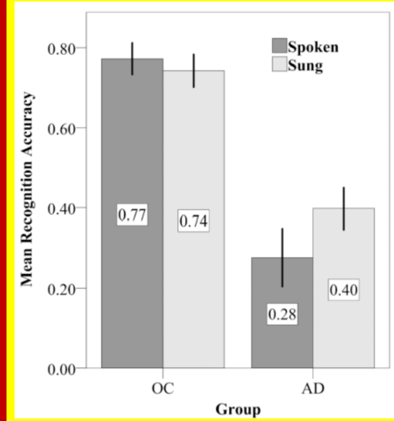
Effectiveness of a community-based multidomain cognitive intervention program in patients with Alzheimer's disease.

Kim HJ[1,2], Yang Y[3], Oh JG[2], Oh S[4], Choi H[1,2], Kim KH[1], Kim SH[1,2].

Neuropsychologia. 2010 August ; 48(10): 3164–3167. doi:10.1016/j.neuropsychologia.2010.04.033.

Music as a Memory Enhancer in Patients with Alzheimer's Disease

Nicholas R. Simmons-Stern, **Andrew E. Budson**, and **Brandon A. Ally**



Lyrics of songs when:

- accompanied at encoding by a sung
- recording accompanied by a spoken recording

Patients with AD demonstrated better recognition accuracy for the sung lyrics than the spoken lyrics, while healthy older adults showed no significant difference between the two conditions.

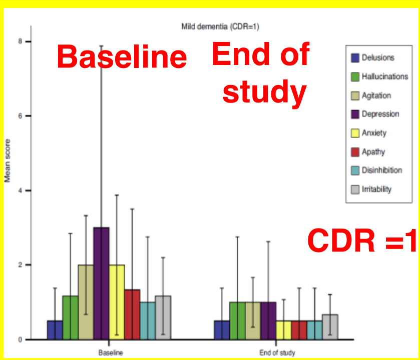
Music processing is spared by the neurodegenerative effects of Alzheimer's disease.
Musically-associated stimuli allow for a more diversified encoding compared to verbal

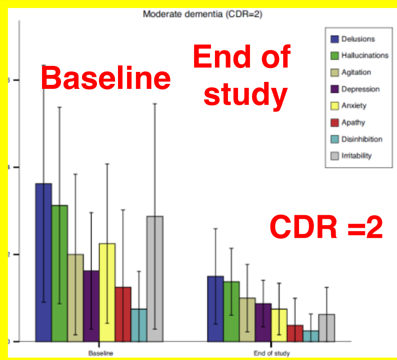
Music therapy and Alzheimer's disease: Cognitive, psychological, and behavioural effects☆

M. Gómez Gallego[a,*], J. Gómez García[b]

42 patients with mild to moderate Alzheimer disease underwent music therapy for 6 weeks

	Baseline		6 sessions		12 sessions		Within-subjects effects		
	Mean	SD	Mean	SD	Mean	SD	*F*	*P*	Partial η
MMSE									
Orientation	4.07	2.30	5.00	2.48	5.85	2.21	40.42	.000	0.76
Language	6.42	1.28	6.64	1.23	7.43	1.34	4.79	.047	0.27
Memory	3.35	1.54	3.64	1.21	4.71	1.26	29.89	.000	0.69
Attention	1.02	1.30	1.43	1.50	1.64	1.33	2.98	.108	0.19
Total	15.02	5.40	16.71	5.51	19.64	4.84	34.65	.000 *	0.72
NPI									
Delusions	2.29	2.92	2.26	2.89	1.07	1.20	7.75	.015	0.37
Hallucinations	2.29	2.43	2.21	2.42	1.21	1.25	6.34	.026	0.33
Agitation	2.00	1.79	2.07	1.77	1.00	0.78	9.10	.010	0.41
Depression	2.21	3.19	2.29	3.14	0.93	1.07	4.36	.057	0.25
Anxiety	2.14	1.95	2.10	1.94	0.64	0.63	14.89	.002	0.53
Euphoria	1.86	2.62	1.79	2.71	1.14	1.09	2.51	.136	0.16
Apathy	1.29	2.01	1.20	2.08	0.43	0.75	5.63	.034	0.30
Disinhibition	0.86	1.29	0.76	1.18	0.36	0.63	3.95	.068	0.23
Irritability	2.14	2.55	2.09	2.37	0.64	0.62	6.44	.025	0.33
AMB	0.50	1.60	0.32	1.62	0.14	0.53	1.52	.239	0.10
Total	17.71	11.59	17.60	11.46	7.57	5.01	28.29	.000 *	0.68
HADS									
Anxiety	13.07	2.17	11.57	2.65	10.71	3.49	15.98	.000	0.28
Depression	9.35	2.56	8.07	2.16	5.71	1.81	21.33	.000	0.62
Total	22.43	3.34	19.64	4.12	17.14	4.09	18.95	.001 *	0.69





Changes in NPI

Music therapy improved some cognitive, psychological, and behavioural alterations in patients with mild and moderate AD

BMJ Open Systematic review of systematic reviews of non-pharmacological interventions to treat behavioural disturbances in older patients with dementia. The SENATOR-OnTop series

Iosief Abraha,[1] Joseph M Rimland,[1] Fabiana Mirella Trotta,[1] Giuseppina Dell'Aquila,[1] Alfonso Cruz-Jentoft,[2] Mirko Petrovic,[3] Adalsteinn Gudmundsson,[4] Roy Soiza,[5] Denis O'Mahony,[6] Antonio Guaita,[7] Antonio Cherubini[1]

BMJ Open 2017;**7**:e012759.

Cognitive/emotion-oriented interventions for behavioural disturbances

	Intervention	Duration	Outcome
Cognitive Stimulation 8 reviews 238 RCT	Pleasurable activities, such as word games, puzzles, music, cooking, gardening and discussing past and present events, and is usually carried out by trained personnel with small groups of four to five people	45 min, minimally 2 times/week	Only one review found one RCT study with significnt reduction of behavioural symptms
Reminiscence therapy 3 reviews 9 RCT 400 patients	Discussion of past experiences, events and activities with family members or other groups of people. Materials: photographs, books, old newspapers and familiar items from the past to inspire reminiscences and facilitate people to share and value their experiences	30-60 min/day; 1 session per week; 4-12 weeks	In 3 studies significant improvements in depression, communication, positive mood and cognition. No effect in other studies except better well-being and social engagement
Validation therapy 2 reviews; 3 RCT 153 patients	Structured therapeutic activity in a group setting or individually; simple concrete words; speaking in a clear, low and empathic tone of voice; rephrasing and paraphrasing unclear verbal communication; responding to meanings through explicit and implicit verbal and non-verbal communication	30 min /day; 1-4 sessions per week; 24-52 weeks	Behavior and depression improved
Simulated presence therapy 2 review 9 RCT 131 patients	Use of video/audiotapes made by family members and/or psychologists about cherished memories from earlier parts of a person's life, in an effort to stir remote memory	Audiotape or videotape prepared by a family member or psychologist . Once/day, several	Verbally disruptive behaviours decreased by 46% during the videotape. Significant decline in agitation level

Reality orientation therapy combined with cholinesterase inhibitors in Alzheimer's disease: randomised controlled trial

GRAZIANO ONDER, ORAZIO ZANETTI, EZIO GIACOBINI, GIOVANNI B. FRISONI, LUISA BARTORELLI, GABRIELE CARBONE, PAOLA LAMBERTUCCI, MARIA CATERINA SILVERI and ROBERTO BERNABEI

BRITISH JOURNAL OF PSYCHIATRY (2005), 187, 450–455

25 Weeks - Individual Home + AChEIs

- RCT
- ROT combined with cholinesterase inhibitors
- 79 of 156 patients treated (MMSE 14-27) with donepezil (> 3 months) randomly assigned to receive ROT
- ROT at home 3 days a week, 30min/day, 25 consecutive weeks
- Trained careghivers

	Mean change in score (standard error)[1]		*P*
	Treatment group (*n*=70)	Control group (*n*=67)	
Patients			
MMSE	0.2 (0.4)	−1.1 (0.4)	0.02
ADAS–Cog	0.4 (0.8)	−2.5 (0.8)	0.01
Neuropsychiatric Inventory	0.9 (1.9)	−2.5 (2.1)	0.23
Barthel Index	−0.9 (1.0)	−2.9 (1.0)	0.18
Number of impaired IADL	0.0 (0.2)	−0.2 (0.2)	0.34
Caregivers			
Hamilton Rating Scale for Depression	−0.9 (0.4)	−1.0 (0.4)	0.83
Hamilton Anxiety Scale	−0.3 (0.4)	−0.5 (0.4)	0.80
Caregiver Burden Inventory	−2.0 (1.4)	−1.3 (1.5)	0.72
SF–36	−1.3 (1.4)	−1.1 (1.4)	0.90

ADAS–Cog, Alzheimer's Disease Assessment Scale – Cognition; IADL, Instrumental Activities of Daily Living; MMSE, Mini-Mental State Examination; SF–36, Medical Outcomes Study 36-item Short-Form General Health Survey.
1. Adjusted for baseline value of the outcome measure.

Reality orientation enhances the effects of donepezil on cognition in Alzheimer's disease

Maintenance Cognitive Stimulation Therapy: An Economic Evaluation Within a Randomized Controlled Trial

Francesco D'Amico PhD [a,*], Amritpal Rehill BSc [a], Martin Knapp PhD [a], Elisa Aguirre PhD [b], Helen Donovan DClinPsych [c], Zoe Hoare PhD [d], Juanita Hoe PhD [e], Ian Russell DSc [f], Aimee Spector PhD, DClinPsy [g], Amy Streater MSc [b], Christopher Whitaker MSc [d], Robert T. Woods MA, MSc [h], Martin Orrell PhD, FRCPsych [e]

JAMDA 16 (2015) 63e70

Cost-effectiveness

- RCT. CST added to usual care or usual care alone for 24 weeks
- 236 participants with mild-to-moderate dementia (0.5 - 2.0 CDR) received CST for 7 weeks
- To examine whether longer-term (maintenance) CST is cost-effective when added to usual care

Results:

- CST appears cost-effective when looking at
  - self-rated quality of life
  - cognition (MMSE)
  - proxy-rated quality-adjusted life years
- CST in **combination with ACHEIs** offered cost effectiveness gains when outcome was measured as cognition.

Conclusions:

- Continuation of CST is cost-effective for people with mild-to-moderate dementia.

Maintenance cognitive stimulation therapy for dementia: single-blind, multicentre, pragmatic randomised controlled trial

Martin Orrell, Elisa Aguirre, Aimee Spector, Zoe Hoare, Robert T. Woods, Amy Streater, Helen Donovan, Juanita Hoe, Martin Knapp, Christopher Whitaker and Ian Russell

The British Journal of Psychiatry (2014) 204, 454–461

7 + 24 weeks maintenance

- 236 people with dementia
- 7-week, 14-session Cognitive Stimulation Theray (CST) programme
- Then, additional 6 months treatment/controls usual care
- 50% of treated subjects and 50% of controls were taking AChEIs

At 3 months:
- **Proxy-rated quality of life (QoL-AD) P = 0.01**
- **Dementia Quality of Life scale (DEMQOL) P = 0.03**
- **Activities of daily living P = 0.04**

At 6 months:
- **Quality of Life in Alzheimer's Disease (QoL-AD) P = 0.03**

At 3 and 6 months:
- **The intervention subgroup taking AChEIs showed higher cognitive benefits (MMSE)**

Continuing CST improves quality of life; and improves cognition for patients taking AChEIs

The impact of individual Cognitive Stimulation Therapy (iCST) on cognition, quality of life, caregiver health, and family relationships in dementia: A randomised controlled trial

Martin Orrell et al.

Individual
Home
25 weeks

PLOS Medicine https://doi.org/10.1371/journal.pmed.1002269 March 28, 2017

- **RCT**
- **356 people with mild to moderate dementia (MMSE score >10)** (and their trained caregivers) randomly assigned
- iCST (3 sessions/week ; 30-min sessions) or treatment as usual
- **iCST** sessions, **delivered at home by a caregiver**
- Specific iCST package: General; level A; level B
- Treatment as usual for controls: group activities offered by day centres, hobbies, gardening,support groups, or visits to places of interest

- **Drop out:**
  - **iCST = 54/180;**
  - **Treatment as usual = 44/176**
- **Less than half of the iCST group completed at least two sessions per week (72/180, 40%) and 22% (39/180) did not complete any sessions**

- In this setting iCST has **no effect on cognition** or QoL for people with dementia
- Participating in iCST appeared to enhance the **quality of the caregiving relationship and caregivers' QoL** →

- **Risk of institutionalisation may be reduced or delayed**
- **iCST in individually tailored home care packages may help to maintain people with dementia in their home situation for longer time**

Maximal oxygen uptake (VO2max)

Physical activity and Dementia

NCBI Resources How To

PubMed.gov
US National Library of Medicine
National Institutes of Health

PubMed | physical activity dementia

Create RSS Create alert Advanced

Results by year

3.207

1972=2 2017=353

NCBI Resources How To

PubMed.gov
US National Library of Medicine
National Institutes of Health

PubMed | physical activity therapy dementia

Create RSS Create alert Advanced

Results by year

1.815

1974=2 2016=167

NCBI Resources How To

PubMed.gov
US National Library of Medicine
National Institutes of Health

PubMed | physical activity therapy review dementia

Create RSS Create alert Advanced

Results by year

552

1988=1 2016=64

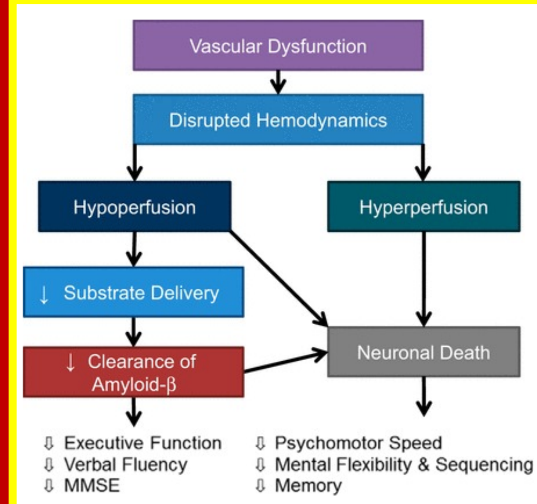
American Physiological Society
Advances in Physiology Education
PUBLISHED ARTICLE
ARCHIVES
SUBSCRIPTIONS
SUBMISSIONS
CONTACT US

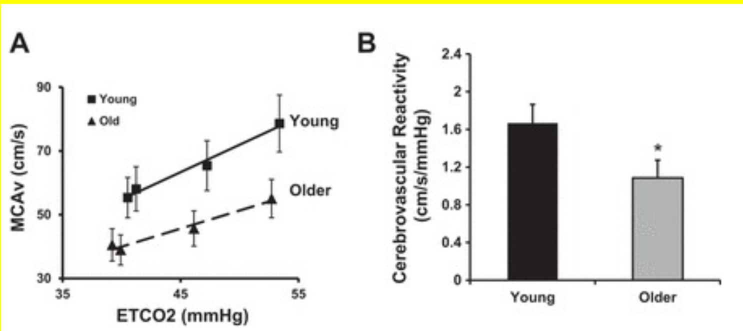
Adv Physiol Educ. 2015 Jun; 39(2): 55–62.
doi: 10.1152/advan.00101.2014
PMCID: PMC4587595

Exercise, cognitive function, and aging

Jill N. Barnes

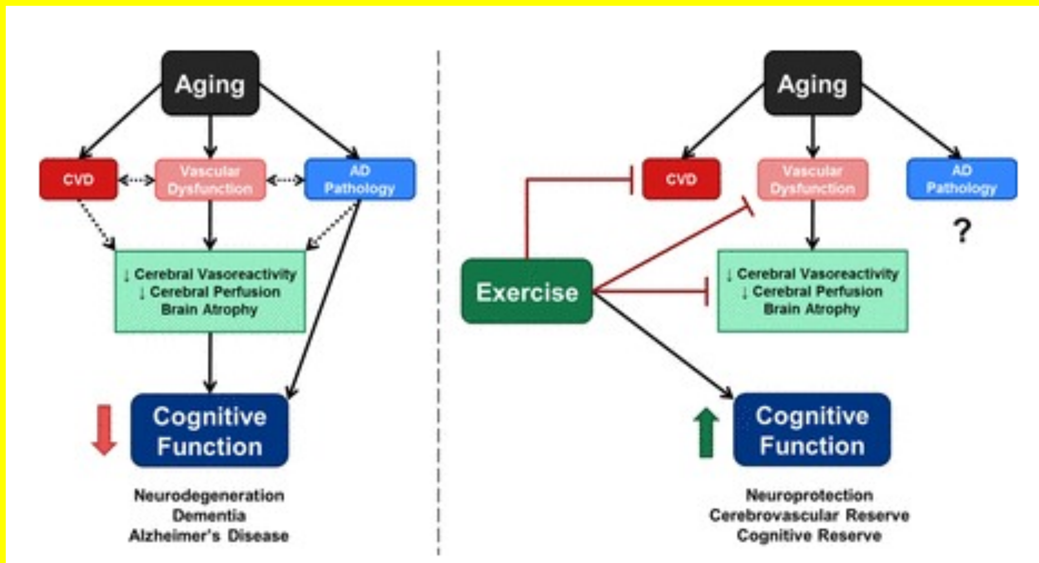
Author information ▶ Article notes ▶ Copyright and License information ▶

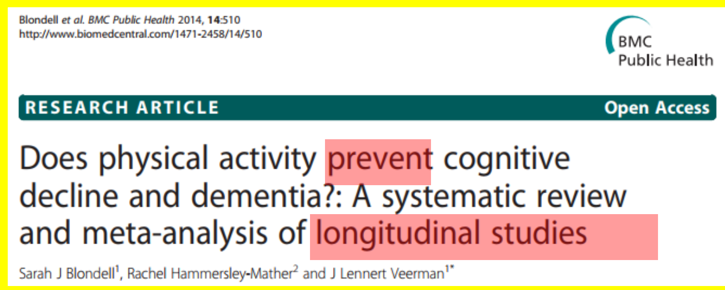




Age-associated reductions in cerebrovascular function.
The increase in middle cerebral artery velocity (MCAv) relative to the stepped increases in exhaled end-tidal CO_2 (ETCO2) is greater in young healthy adults (age: 18–35 yr) compared with older healthy adults (age: 58–76 yr). The slope of the line indicates cerebrovascular reactivity

The potential interactions of how variables associated with aging may interact to affect cognition and how exercise may inhibit this process.




Blondell et al. BMC Public Health 2014, 14:510
http://www.biomedcentral.com/1471-2458/14/510

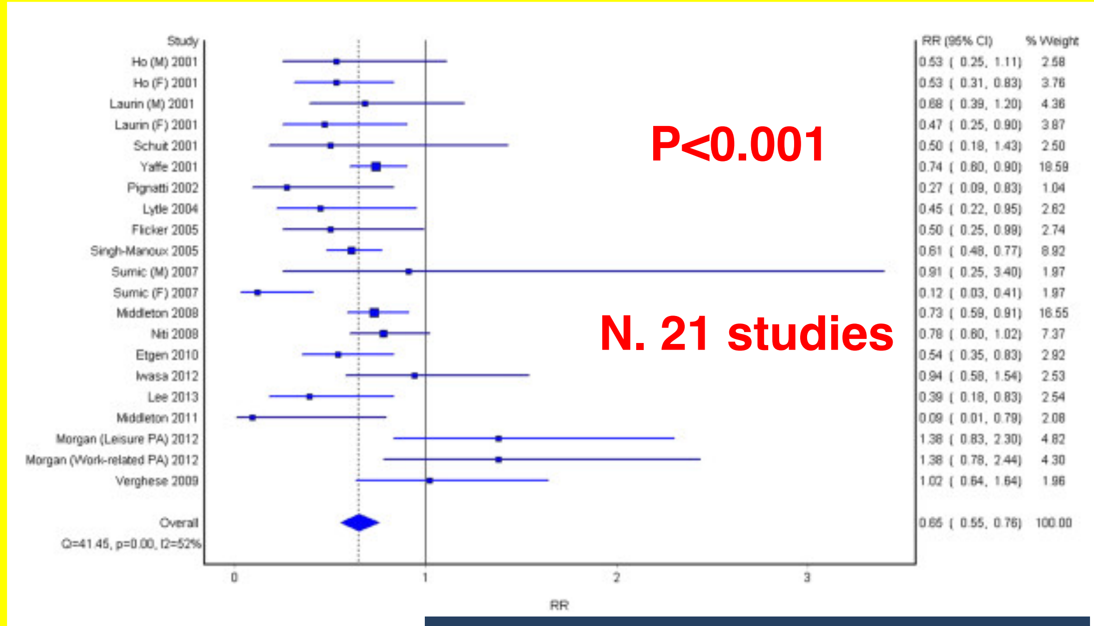
BMC Public Health

RESEARCH ARTICLE Open Access

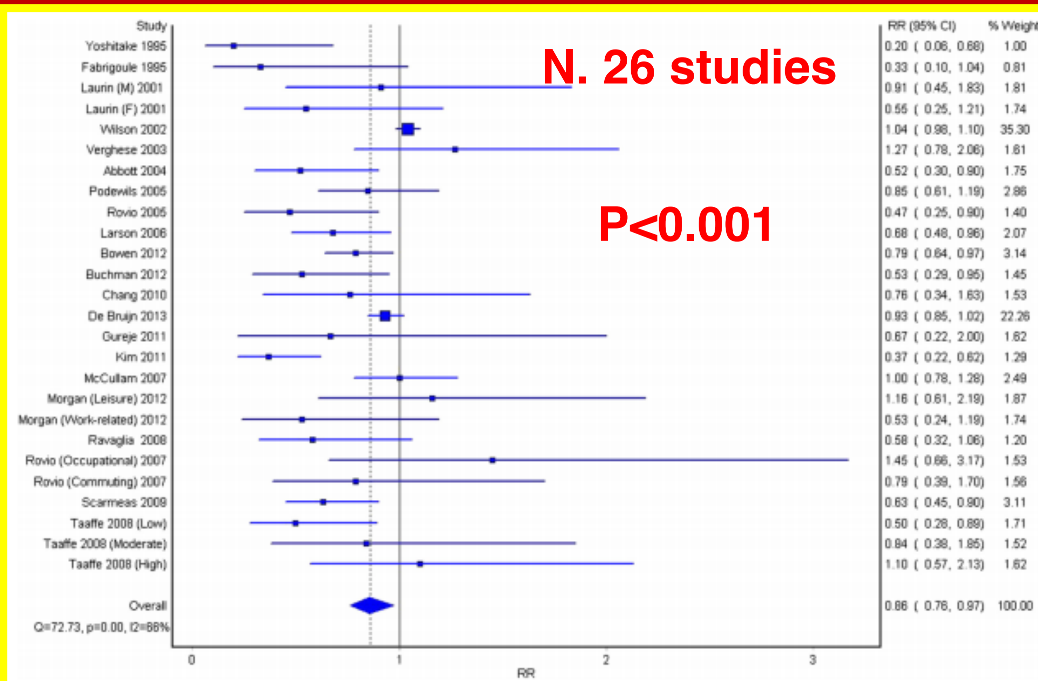
Does physical activity prevent cognitive decline and dementia?: A systematic review and meta-analysis of longitudinal studies

Sarah J Blondell[1], Rachel Hammersley-Mather[2] and J Lennert Veerman[1*]

Twenty-one cohorts on physical activity and cognitive decline and twenty-six cohorts on physical activity and dementia



Significant association between high physical activity and prevention of cognitive decline



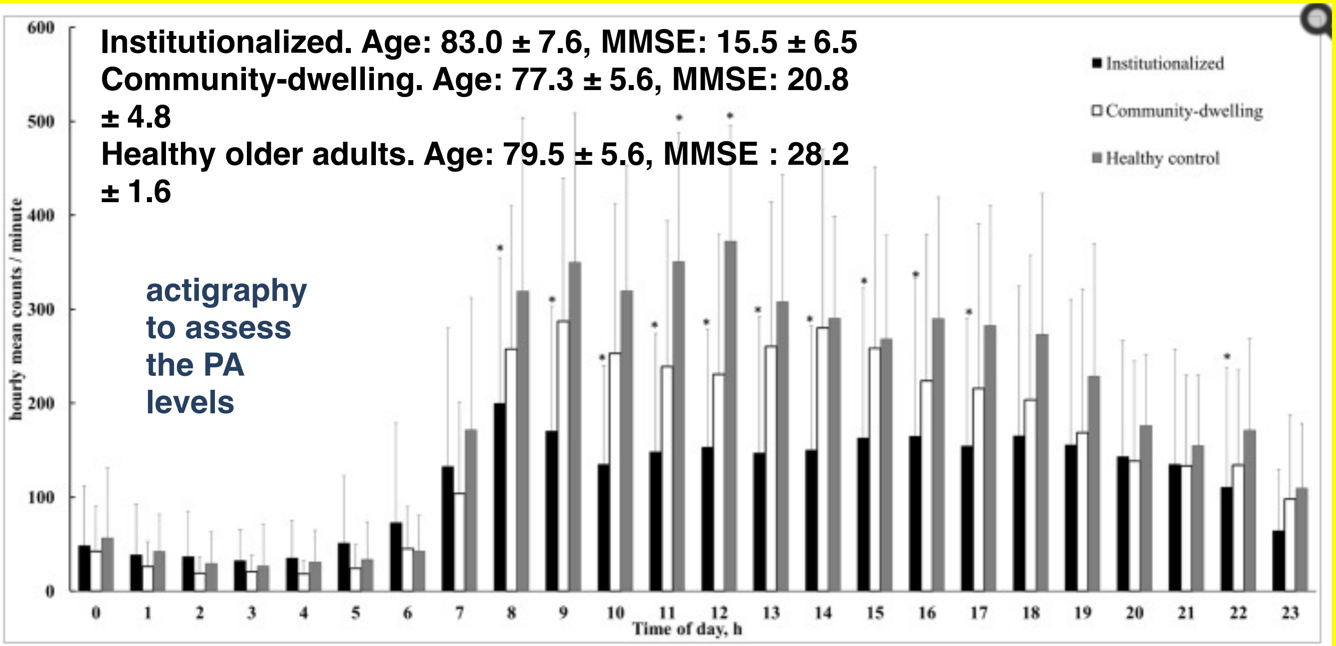
Longitudinal observational studies show an association between higher levels of physical activity and a reduced risk of both cognitive decline or dementia

Significant association between high physical activity and prevention of dementia

PLOS | ONE PLOS ONE | DOI:10.1371/journal.pone.0152457 March 31, 2016

RESEARCH ARTICLE

Older Adults with Dementia Are Sedentary for Most of the Day



Does inactivity worsen Dementia?

These are the first results that objectively characterize institutionalized as well as community-dwelling dementia patients' PA levels and confirm that dementia patients are inactive

Exercise programs for people with dementia.

Forbes D[1], Forbes SC, Blake CM, Thiessen EJ, Forbes S.

Cochrane Database Syst Rev. 2015 Apr 15;(4):CD006489.

- Meta-analyses of 17 trials with 1067 participants
- High heterogeneous:
  - subtype and severity of participants' dementia
  - type, duration, and frequency of exercise

- no clear evidence of benefit from exercise on:
  - cognitive functioning
  - quality of life, mortality, and healthcare costs (appropriate data were not reported)
- benefit of exercise programs on the ability of people with dementia to perform ADLs in 6 trials with 289 participants
- reduction of the burden experienced by informal caregivers providing care in the home when they supervise the participation of the family member with dementia in an exercise program

Promising evidence that exercise programs may improve the ability to perform ADLs in people with dementia

---

Review Article

Effects of Physical Activity Programs on the Improvement of Dementia Symptom: A Meta-Analysis

BioMed Research International. Vol. 2016, Article ID 2920146, 7 pages

Han Suk Lee,[1] Sun Wook Park,[2] and Yoo Jung Park

9 RCTs
(2005-2015)

improvement in the dementia symptoms:
- physical capacity = 1.05 (high effect size, 95% CI: 0.03 to 0.73)
- ability of ADL = 0.73 (slightly high effect size, 95% CI: 0.23 to 1.23)
- cognitive function = 0.46 (medium effect size, 95% CI: 0.26 to 0.66)
- psychological state was 0.39 (lower than the medium effect size, 95% CI: 0.01 to 0.77)

- The physical activity for patients with dementia had an effect on the improvement of physical capacity
- The combined exercise was the most effective physical

Combined Cognitive stmulation and Physical Activity

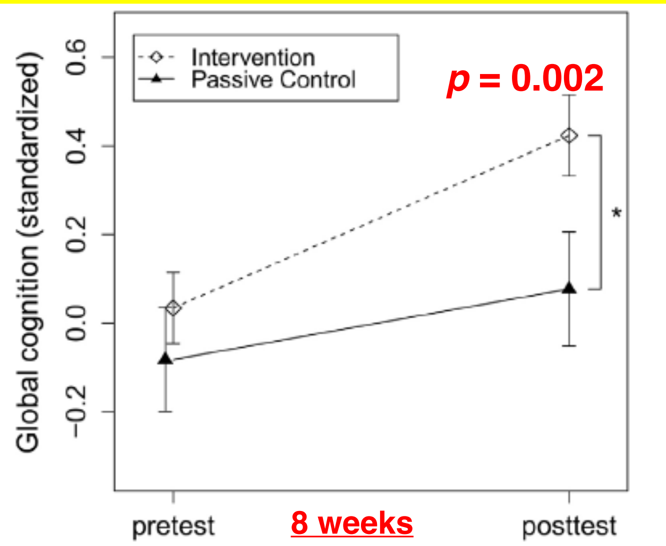
Gains in cognition through combined cognitive and physical training: the role of training dosage and severity of neurocognitive disorder

Panagiotis D. Bamidis[1*†], Patrick Fissler[2†], Sokratis G. Papageorgiou[3†], Vasiliki Zilidou[1], Evdokimos I. Konstantinidis[1], Antonis S. Billis[1], Evangelia Romanopoulou[1], Maria Karagianni[1,4], Ion Beratis[3], Angeliki Tsapanou[3], Georgia Tsilikopoulou[3], Eirini Grigoriadou[1,4], Aristea Ladas[1,5], Athina Kyrillidou[1,4], Anthoula Tsolaki[1,4], Christos Frantzidis[1], Efstathios Sidiropoulos[1], Anastasios Siountas[1], Stavroula Matsi[3], John Papatriantafyllou[3], Eleni Margioti[3], Aspasia Nika[3], Winfried Schlee[6], Thomas Elbert[7], Magda Tsolaki[4,8], Ana B. Vivas[5‡] and Iris-Tatjana Kolassa[2‡]

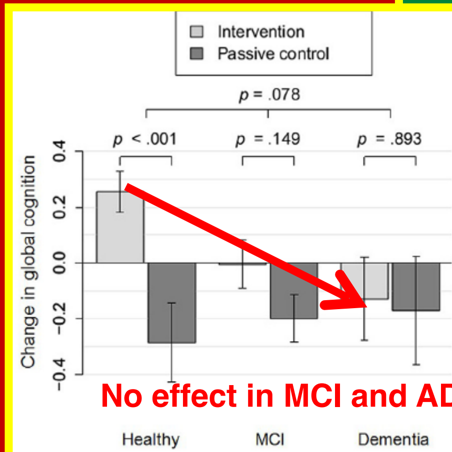
ORIGINAL RESEARCH
published: 07 August 2015
doi: 10.3389/fnagi.2015.00152

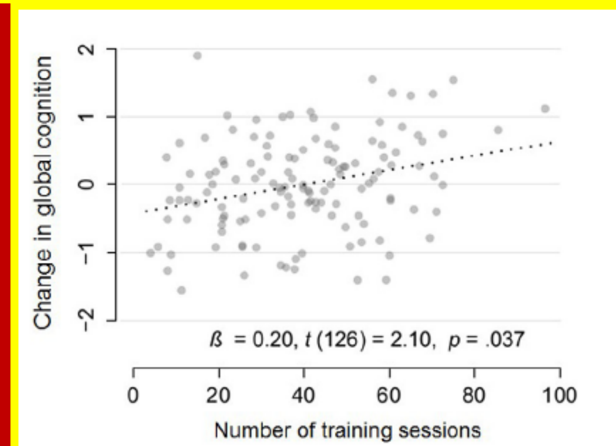
frontiers in Aging Neuroscience

- RCT
- N. 322. Physical + Cognitive training - Passive control (85)
- Age; 71.3 ± 7.1 yrs
- Education: 10.9 ± 4.9 yrs
- Cognitive Training sessions: N. 22.8 ± 10.0
- Physical Training sessions: N. 14.5 ± 11.2
- Combined Training: 8 weeks
- Lost: Physical+Cognitive training 31%; Passive control 22%
- *Brain Fitness Program* (Posit Science Corporation, San Francisco, CA)
- Computerized physical training program *FitForAll*



Intervention effects on global cognition

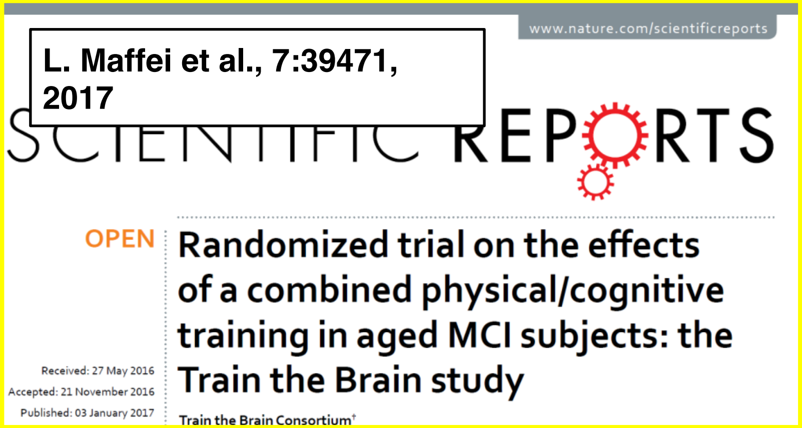




Change in cognitive performance	*p*-value
Global cognition	0.002
Executive function	0.01
Working memory	0.20
Episodic memory	0.03

The results indicate that combined physical and cognitive training improves global cognition in adose-responsive manner but these benefits may be less pronounced in older adults with more severe neurocognitive disorder

L. Maffei et al., 7:39471, 2017


www.nature.com/scientificreports

SCIENTIFIC REPORTS

OPEN

Randomized trial on the effects of a combined physical/cognitive training in aged MCI subjects: the Train the Brain study

Received: 27 May 2016
Accepted: 21 November 2016
Published: 03 January 2017

Train the Brain Consortium†

Effectiveness and action mechanisms of physical/cognitive training in elders already suffering from Mild Cognitive Impairment (MCI)

113 MCI subjects aged 65–89

Intervention group n=55
MCI-training
(intervention 7 months)

RCT

Control group n=58
MCI-no training
(normal life 7 months)

Evaluations:

- Basal
- after 7 months training
- after 1 2 months training discontinuation.

- Mixed-gender classes of 7–10 subjects each
- 2 sessions of supervised cognitive training of 60 min each per day
- 3 times a week, in the morning
- 6 hours per week. Total 168 h. Special building

Effect of combined physical-cognitive training on:

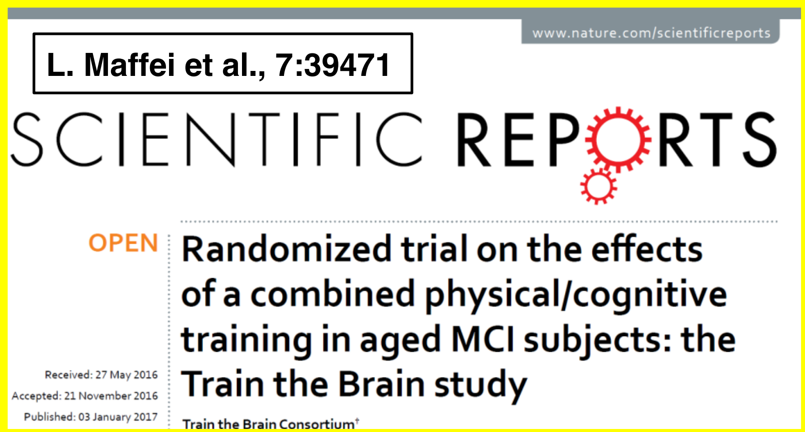
- Cognitive decline
- Gray Matter (GM) volume loss
- Cerebral Blood Flow (CBF) in hippocampus and parahippocampal areas
- Brain-blood-oxygenationlevel-dependent (BOLD) activity elicited by a cognitive task
- ADAS-Cog scale, Rey Complex Figure test, Phonemic verbal fluency
- MRI

Cognitive training

8 cycles; each cycle 18 sessions; increased cycle complexity.
Stimuli: acoustic attention, visual attention, visual memory, imagination, orientation and spatial memory, personal and temporal orientation, verbal memory, lexical abilities, memory for terms and meanings, affective memory, memory for texts, memory for faces and names, logic.
Single cognitive modality and multimodal activities. Music Therapy

Physical training

1-hour lessons 3 times per week in small groups aerobic exercise on an ergometer cycle (frpom 10 to 20 min) followed by exercises for muscle strength, physical function (static and dynamic), neuromuscular control and flexibility.


L. Maffei et al., 7:39471

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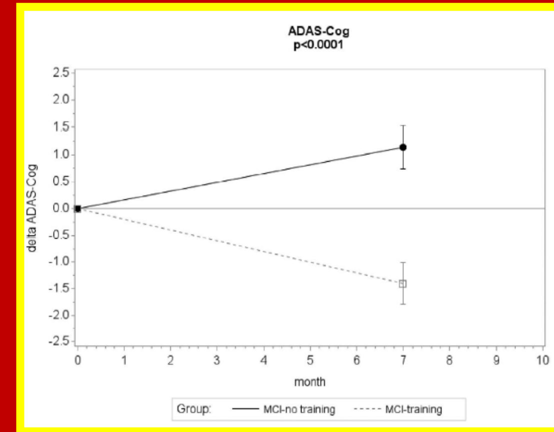
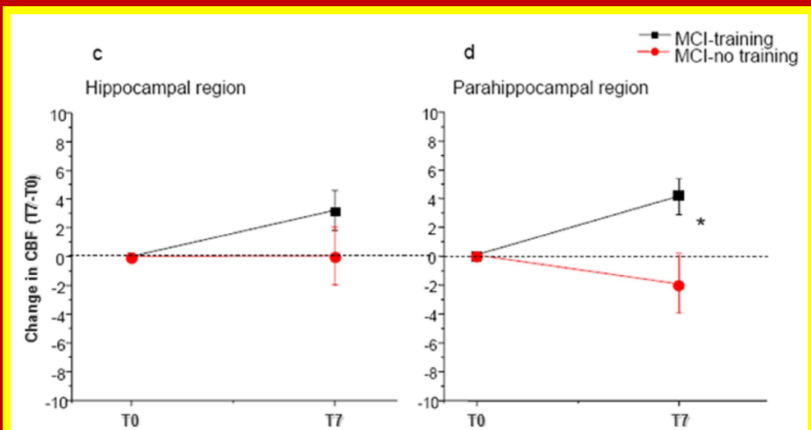
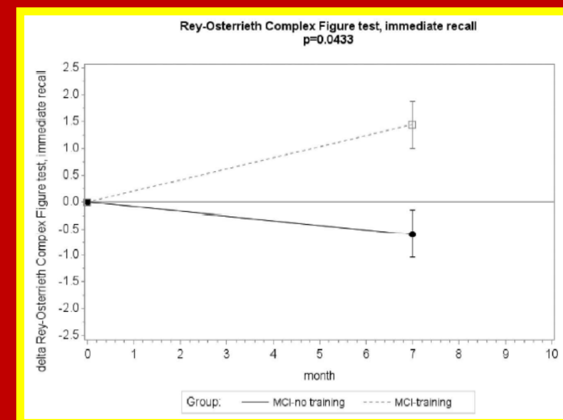
Changes in cognitive score at:

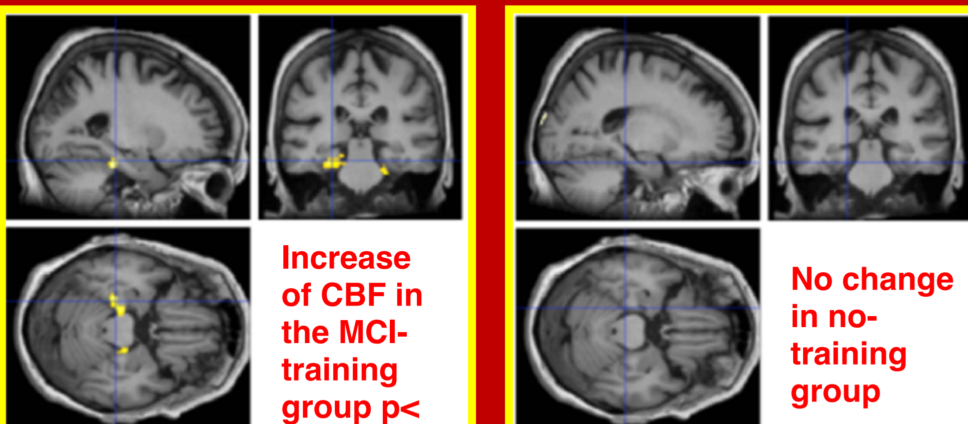
- **ADAS-score ($p < 0.0001$)**
- **Rey-Osterrieth Complex Figure test immediate recall ($p < 0.05$)**
- **Phonemic verbal fluency ($p < 0.05$)**





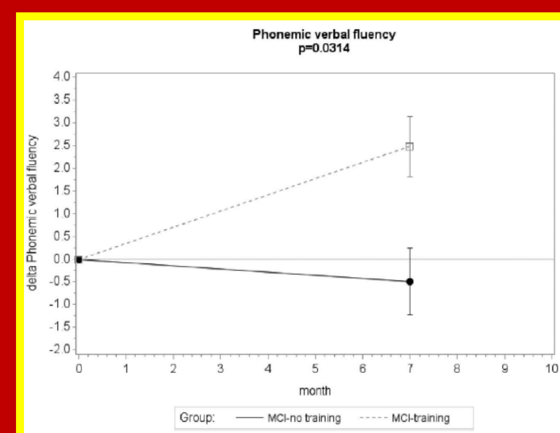
Cerebral Blood Flow (CBF) increases in Medial Temporal Lobe (MTL) regions

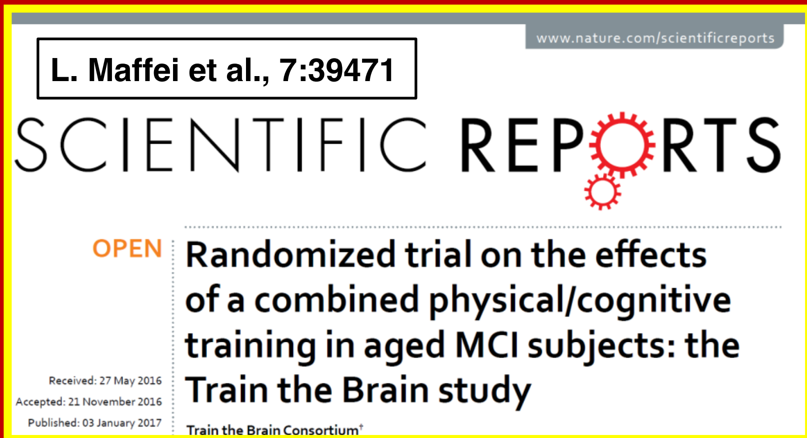




Increase of CBF in the MCI-training group $p < 0.001$

No change in no-training group




L. Maffei et al., 7:39471

www.nature.com/scientificreports

SCIENTIFIC REPORTS

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Accepted: 21 November 2016
Published: 03 January 2017

Train the Brain Consortium†

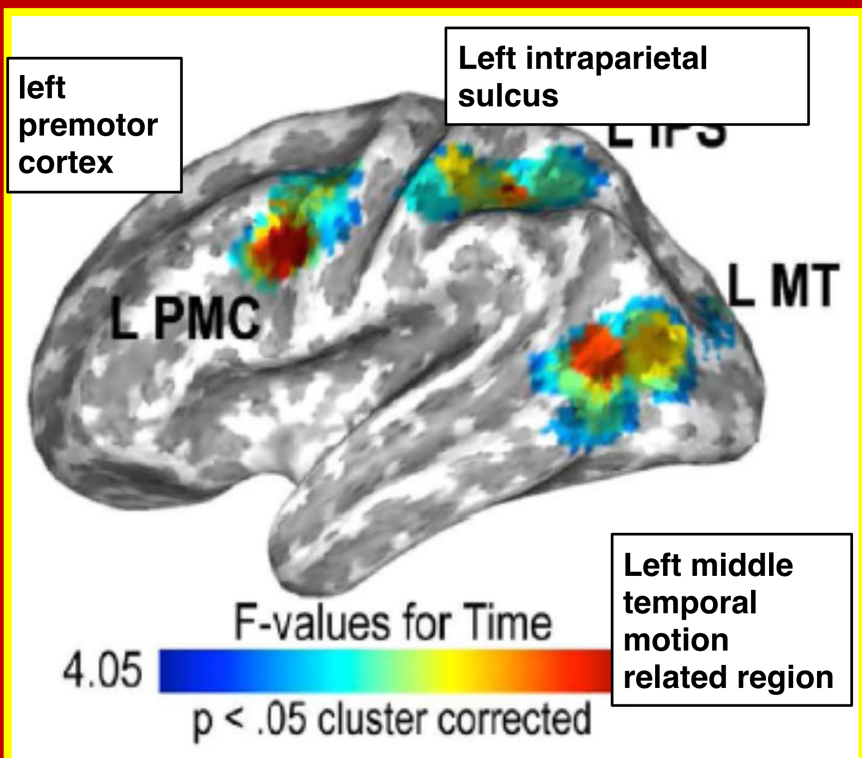
MRI Clinical score:

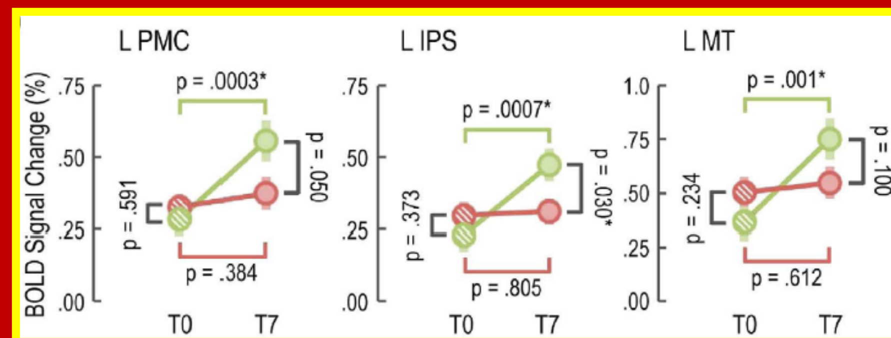
- no effect on White Matter Changes and medial temporal lobe atrophy visual rating scale

fMRI Visuo-spatial attention task-related

- Increase of BOLD signal between T0 and T7 in:
  - Left premotor cortex
  - Left intraparietal Sulcus
  - Left middle temporal motion related

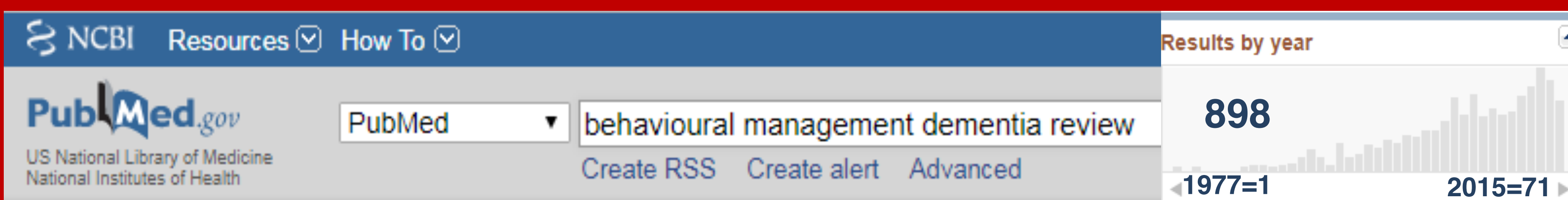
Effects of training on regional BOLD signal

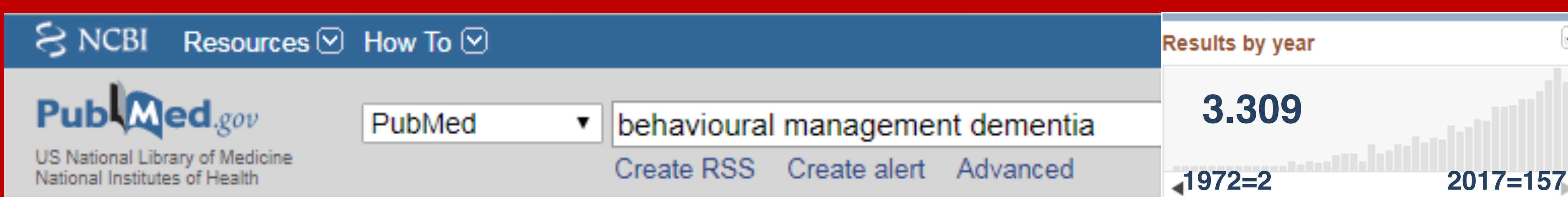




These results show that a non pharmacological, multicomponent intervention in a social setting improves cognitive status and indicators of brain health in MCI subjects

Non-pharmacological interventions to treat behavioural disturbances





ELSEVIER

CrossMark

Alzheimer's & Dementia: Translational Research & Clinical Interventions 3 (2017) 440-449

Alzheimer's & Dementia

Review Article

Neuropsychiatric signs and symptoms of Alzheimer's disease: New treatment paradigms

Krista L. Lanctôt[a,*], Joan Amatniek[b], Sonia Ancoli-Israel[c,d], Steven E. Arnold[e], Clive Ballard[f,g], Jiska Cohen-Mansfield[h], Zahinoor Ismail[i], Constantine Lyketsos[j], David S. Miller[k], Erik Musiek[l], Ricardo S. Osorio[m], Paul B. Rosenberg[n], Andrew Satlin[o], David Steffens[p], Pierre Tariot[q], Lisa J. Bain[r], Maria C. Carrillo[s], James A. Hendrix[s], Heidi Jurgens[s], Brendon Boot[t,u]

NPSs

- 97% of individuals with dementia over the disease course; all stages and etiologies
- 59% of MC
  duration p
  progressio

A five domains screening MBI checklist www.MBItest.org

Alzheimer's Association Research Roundtable in May 2016

NPSs typically emerge in three phases:

(1) irritability, depression, and nighttime behavior changes
(2) anxiety, appetite changes, agitation, and apathy
(3) excitement, motor disturbances, hallucinations, delusions, and

NPSs are associated with

- impairment in activities of daily living
- poor quality of life
- earlier institutionalization
- accelerated disease progression
- increased mortality
- caregiver stress
- increased cost of care

stem of the DSM5 provides various syndrome categories
<u>BUT</u>
NPSs in dementia <u>overlap</u> substantially among DSM5 syndromes

Poor response to Psychotropic Medication

Psychotic symptoms in AD	Prevalence	Recurrence	Phenomenology	
Delusions and hallucinatons s	• 67% AD • Associated with fast cognitive decline and death	• 2-6 times/week • Clusters of 12 weeks 2 times/ year	**Hallucinatons** • Less frequent (16%) and rarely in isolation (*) • Usually Visual • Less commonly auditory • Rarely tactile or olfactory (*) the opposite in LBD and PD	**Delusions** • More frequent (31%) and in isolation (*) • Persecutory delusions earlier than misidentification delusions (**) different from schizophrenia, psychotic depression, or mania
Agitation	• 40-80 % depending on severity of dementia • Predictive of more rapid decline, institutionaliztion and earlier death	• Persistence • Associated wih psychosis, anxiety, disinhibition		
Apathy	• With varying severity in over 50-70% of patients during AD course	• Persistence • Increasing over the disease course • Predicting conversion to MCI and to dementia	• Lack of motivation > 4 weeks • Decreased initiative in cognitive activity • Akinesia • Emotional indifference • Functional impairment • Under-recognized • Confused with depression of which may be a symptom	
Depression	• 16% in population-based studies • 44.3% in hospital-based studies	• Unipolar depressive episodes decades before dementia	• Coexistence with MCI (11-63%) doubles the risk for AD • Late onset remitting depression in 50% followed by MCI-dementia •	
Sleep	• AD > 50%;	• Persistence	• Decreased sleep efficiency, difficulty in falling asleep	

BMJ Open

Systematic review of systematic reviews of non-pharmacological interventions to treat behavioural disturbances in older patients with dementia. The SENATOR-OnTop series

Iosief Abraha,[1] Joseph M Rimland,[1] Fabiana Mirella Trotta,[1] Giuseppina Dell'Aquila,[1] Alfonso Cruz-Jentoft,[2] Mirko Petrovic,[3] Adalsteinn Gudmundsson,[4] Roy Soiza,[5] Denis O'Mahony,[6] Antonio Guaita,[7] Antonio Cherubini[1]

BMJ Open 2017;**7**:e012759.

Frequency and severity of NPSs — **Psychotropic medications** → **but** →

- In the majority of Patients only modest symptom control
- Citalopram, effective in disinhibition control, increases risk of falls, fractures, stroke and even mortality
  Brain. 2015 Jul; 138(7): 1961–1975.
- Benzodiazepines in patients with dementia may increase cognitive decline
- All antipsychotics are associated with an increased risk of cerebrovascular events, metabolic side effects, falls, cognitive decline and increased mortality

Nonpharmacological Interventions — **Alternative ?**

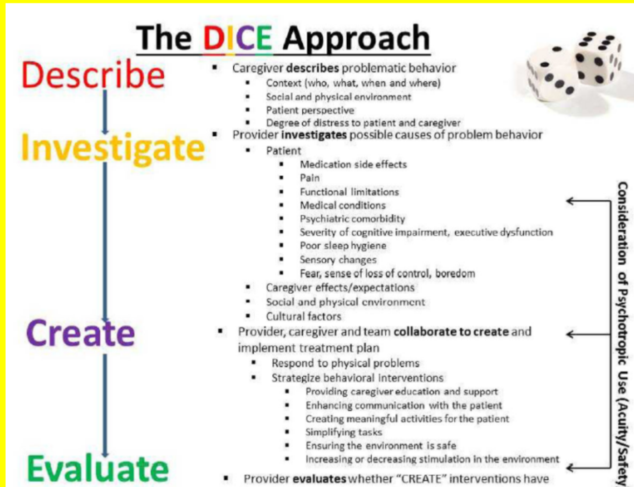
J Am Geriatr Soc. 2014 April ; 62(4): 762–769. doi:10.1111/jgs.12730.

Management of Neuropsychiatric Symptoms of Dementia in Clinical Settings: Recommendations from a Multidisciplinary Expert Panel

Helen C. Kales, MD[1,2,3], Laura N. Gitlin, PhD[4,5,6,7], and Constantine G. Lyketsos, MD[5] for the Detroit Expert Panel on the Assessment and Management of the Neuropsychiatric Symptoms of Dementia

Non-pharmacologic treatments as preferred treatments remain inadequate in real-world clinical settings

"DICE" Approach:
Describe, Investigate, Create and Evaluate



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BMJ Open 2017;**7**:e012759.

56 Systematic Reviwes and 141 primary studies

Categories of non-pharmacological interventions		Systematic Reviwes	Primary studies
Sensory stimulation interventions	• acupressure • aromatherapy • massage and touch therapy • light therapy • sensory garden and horticultural activities • music/dance therapy • snoezelen • transcutaneous electrical nerve stimulation	12	27
Cognitive/emotion-oriented interventions	• cognitive stimulation • reminiscence therapy • validation therapy • simulated presence therapy	33	70
Behaviour management techniques		6	32
Other therapies	• exercise therapy • animal-assisted therapy • special care unit and dining room environment-based interventions	5	12
Total		56	141

BMJ Open Systematic review of systematic reviews of non-pharmacological interventions to treat behavioural disturbances in older patients with dementia. The SENATOR-OnTop series

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BMJ Open 2017;**7**:e012759.

Sensory stimulation interventions. 1

	Intervention	Duration	Outcome
Shiatsu and acupressure (1 RCT with 133 participants)	Employs gentle manipulations, stretches and pressure with the fingers, elbows, knees and feet (or acupoints of the human body)	once a day, 6 days per week, for a 4-week period.	Agitation, aggression and physically non-aggressive behaviour declined significantly
Aromatherapy (2 RCT with 428 participants)	Use of plant products or aromatic plant oils to produce essential oils and blends of aromatic compounds. Aromatherapy can be delivered through massage or topical application, inhalation and water immersion	variable (once-twice/day); one to six months	More well-designed, large-scale randomised controlled trials are needed before clear conclusions
Massage and touch therapy (8 RCT)	Effleurage Swedish massage technique; upper extremities including head, shoulders, and hands	10 to 15 minutes Massage therapy during the 1-hour agitation window on 6 separate days during a 2-week intervention period	Improvement for wandering, verbally and physically agitated ehavioural symptoms and

BMJ Open

Systematic review of systematic reviews of non-pharmacological interventions to treat behavioural disturbances in older patients with dementia. The SENATOR-OnTop series

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BMJ Open 2017;7:e012759.

Sensory stimulation interventions. 2

	Intervention	Duration	Outcome
Bright Light Therapy (4 reviews)	High intensity, low glare ambient lighting installed in activity and dining areas	Four lighting conditions, each presented during multiple three week intervention periods: • AM bright light (7–11 AM); • PM bright light (4–8 PM); • All Day bright light (7 AM – 8 PM) • Lighting intensity at 2,000 – 3,000 lux and at 500–600 lux during the remainder of daylight hours •	Bright light therapy did not reduce agitation and may increases agitation risk in certain individuals with dementia
Sensory garden and horticultural activities (2 reviews, 35 studies; 4 RCT)	Stimulating sight, vision, hearing, smell, touch and performing outdoor plant-related activities	Monday-Friday over a 2 week period	Significant improvement in total sleep minutes

BMJ Open

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BMJ Open 2017;**7**:e012759.

Sensory stimulation interventions. 3

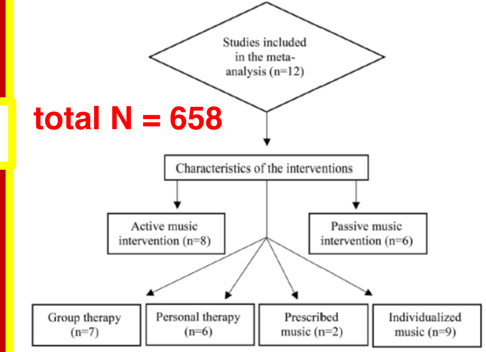
	Intervention	Duration	Outcome
Music therapy (6 reviews; 94 studies; 61RCT)	Participants can passively listen to music or actively participate by singing, playing an instrument. • Recorded music • Live music • Selected music • Individualised music • Classical/relaxation music • Popular/native music • Listening at mealtime • Individualized or group interventions	• Mean of 40 min/ day • 2–3 days/week for 1 week to 12 months Different single or combined activities: listening, moving/ dancing, singing/ playing a musical instrument.	Improved physical and verbal, aggressive and nonaggressive, behaviour. Consistent reduction of behavioural disturbances. Reduced incidence of agitated behaviour during mealtime. Decrease in NPI Improvement in: delusions, agitation, anxiety, apathy, irritability, aberrant motor activity, and night-time disturbances
Dance therapy (2 reviews; 1 RCT)	• Warm-up, theme development, and closure; a dance therapist trained the staff and supervised the process	Nine sessions, lasting 30 to 45 min each, once-a-week	Self-care ability and IADLs improved slightly

Effects of Music on Agitation in Dementia: A Meta-Analysis

frontiers in Psychology

May 2017 I Volume 8 I Article 742

*Siv K. A. Pedersen[1], Per N. Andersen[2], Ricardo G. Lugo[1], Marita Andreassen[1] and Stefan Sütterlin[1,3]**

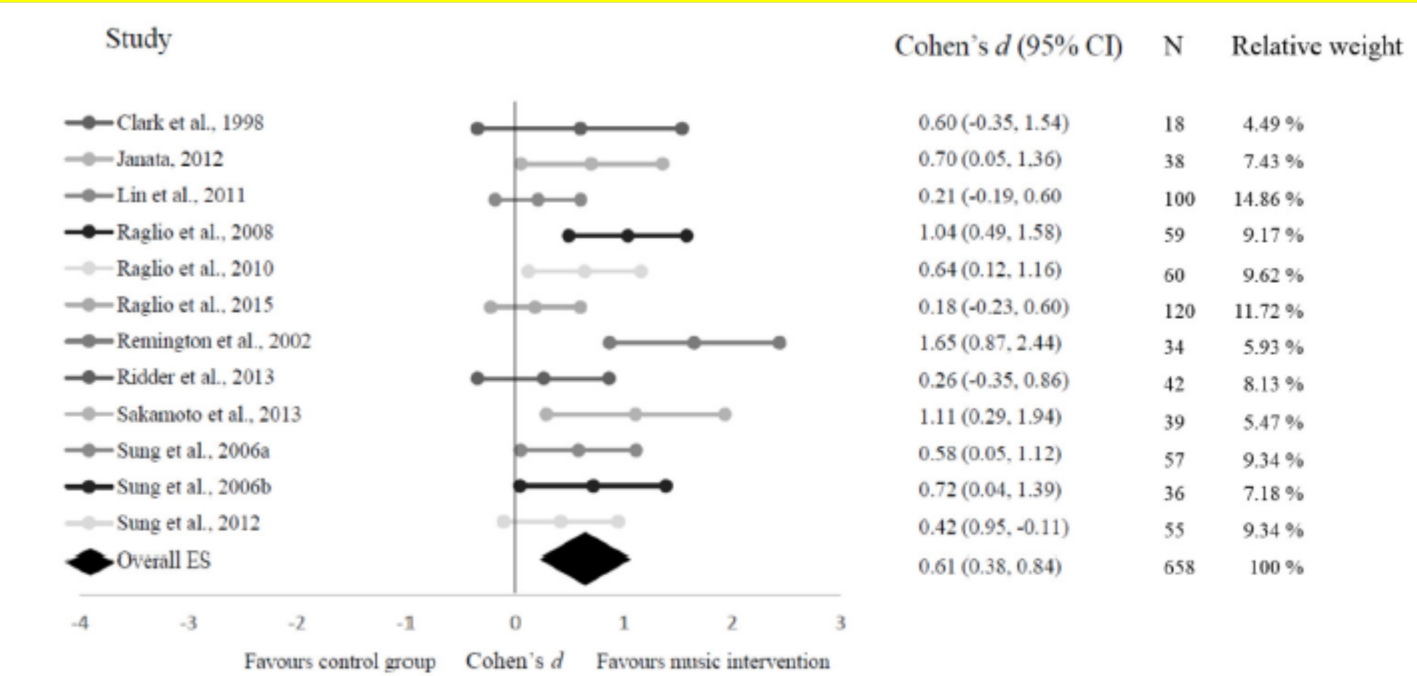


total N = 658

Severity of Dementia (MMSE;CDR;GDS):
Moderate to severe=n7; Severe=3; Mild to moderate=1; Mild to severe=1

Definitions:

- **"the clinical and evidence-based use of music interventions to accomplish individualized goals within a therapeutic relationship by a credentialed professional who has completed an approved music therapy program" (American Music Therapy Association, 2006)**
- **"developmental, adaptive, and rehabilitative goals in the areas of psychosocial, cognitive, and sensorimotor behavior of individuals with disabilities" (Hallam et al., 2009)**



Music intervention had a medium overall effect on agitation in dementia, suggesting robust clinical relevance

Cochrane Database Syst Rev. 2017 May 2;5:CD003477. doi: 10.1002/14651858.CD003477.pub3.

Music-based therapeutic interventions for people with dementia.

van der Steen JT[1], van Soest-Poortvliet MC[2], van der Wouden JC[3], Bruinsma MS[4,5], Scholten RJ[6], Vink AC[7].

- 17 RCTs
- 620 participants
- dementia of varying degrees of severity
- 5 studies individual music intervention
- 12 studies groups of participants
- at least 5 sessions

Very low quality evidence of:

- uncertain effect on anxiety and social behaviour
- long-term outcomes

Low-quality evidence of little effect on:

- emotional well-being and quality of life (standardized mean difference, SMD 0.32, 95% CI -0.08 to 0.71; 6 studies, 181 participants)
- overall behaviour problems (SMD -0.20, 95% CI -0.56 to 0.17; 6 studies, 209 participants)
- cognition (SMD 0.21, 95% CI -0.04 to 0.45; 6 studies, 257 participants)

Moderate-quality evidence of:

- reduced depressive symptoms (SMD -0.28, 95% CI -0.48 to -0.07; 9 studies, 376 participants)
- no decrease agitation or aggression (
participants)

Future studies are necessary:

- larger sample sizes
- 'positive' outcomes such as emotional well-being and social outcomes must be included
- duration of effects in relation to the overall duration of treatment and the number of sessions

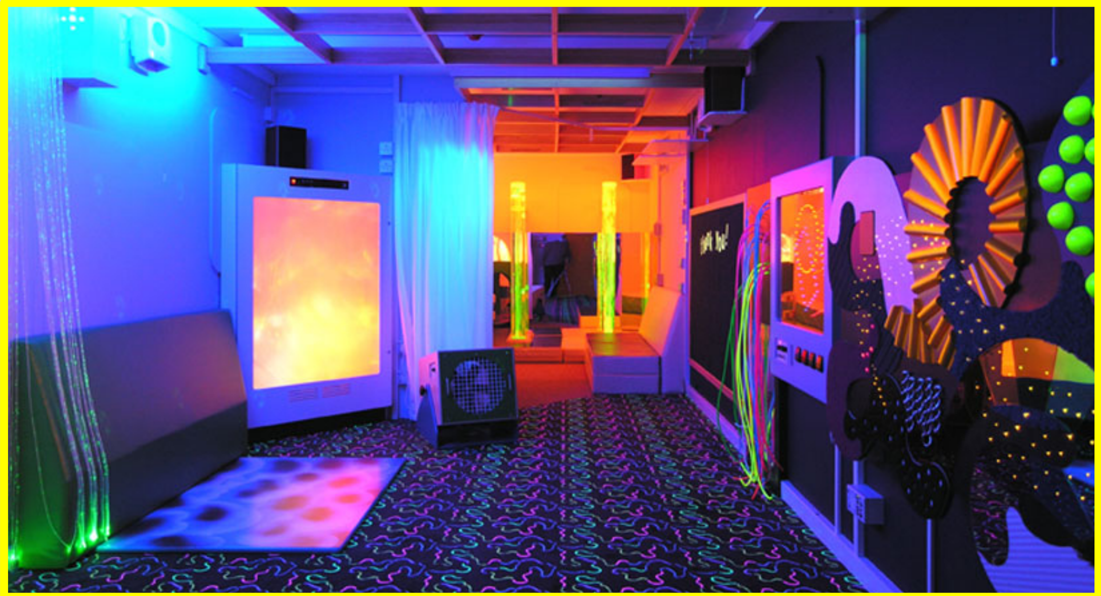
BMJ Open **Systematic review of systematic reviews of non-pharmacological interventions to treat behavioural disturbances in older patients with dementia. The SENATOR-OnTop series**

Iosief Abraha,[1] Joseph M Rimland,[1] Fabiana Mirella Trotta,[1] Giuseppina Dell'Aquila,[1] Alfonso Cruz-Jentoft,[2] Mirko Petrovic,[3] Adalsteinn Gudmundsson,[4] Roy Soiza,[5] Denis O'Mahony,[6] Antonio Guaita,[7] Antonio Cherubini[1]

BMJ Open 2017;**7**:e012759.

Sensory stimulation interventions. 4

	Intervention	Duration	Outcome
Snoezelen multisensory stimulation therapy (SMST) (2 reviews; 3 RCT; 311 patients)	It comprises multiple stimuli and is aimed at stimulating the primary senses of sight, hearing, touch, taste and smell in specially designed rooms. The diverse sensory-stimulating effects/material include music, aroma, bubble tubes, fibre optic sprays and moving shapes projected across walls	SMTS • integrated into 24 h daily care for 3 months • 8 daily SMTS 30 min sessions	Improvement in apathy, mood anxiety, disorderd behaviour, MMSE Only short term effect



BMJ Open

Systematic review of systematic reviews of non-pharmacological interventions to treat behavioural disturbances in older patients with dementia. The SENATOR-OnTop series

Iosief Abraha,[1] Joseph M Rimland,[1] Fabiana Mirella Trotta,[1] Giuseppina Dell'Aquila,[1] Alfonso Cruz-Jentoft,[2] Mirko Petrovic,[3] Adalsteinn Gudmundsson,[4] Roy Soiza,[5] Denis O'Mahony,[6] Antonio Guaita,[7] Antonio Cherubini[1]

BMJ Open 2017;**7**:e012759.

Sensory stimulation interventions. 5

	Intervention	Duration	Outcome
Transcutaneous electrical nerve stimulation (2 reviews; 9RCT)	Applying an electrical current, whose frequency can vary from low (<10 Hz) to high (>50 Hz); differences in parameters; most studies: Waveform: asymmetric biphasic square wave, Burst mode Frequency: Bursts of trains, 9 pulses/burst, pulse freq 160Hz, burst freq 2 Hz Pulse duration: 100 microsec. Amplitude: Visible muscle twitches; variable stimulation site	In most studies, 30 min/day, 5 days/week, 6 weeks	In 3 studies improvement in the rest–activity rhythm and behavior disorders In 6 studies, no improvement
Repetitive transcranial magnetic stimulation (rTMS)	Delivering strong magnetic pulses to the cortex through the scalp. Depending on stimulation parameters (e.g., duration, stimulus intensity, frequency), rTMS can enhance (high frequency) or suppress (low frequency) cortical excitability in targeted cortical regions		
Transcranial direct current stimulation (tDCS)	tDCS delivers weak electrical currents to the scalp to modulate neuronal transmembrane potential towards hyperpolarization or depolarization. Anodal or cathodal		

Effects of non-invasive brain stimulation on cognitive function in healthy aging and Alzheimer's disease: a systematic review and meta-analysis

Wan-Yu Hsu, Yixuan Kua, Theodore P. Zanto and Adam Gazzaley

HHS Public Access
Author manuscript
Neurobiol Aging. Author manuscript; available in PMC 2016 August 01.

Neurobiol Aging. 2015 August ; 36(8): 2348–2359

Effects of non-invasive brain stimulation on cognitive function in healthy aging and Alzheimer's disease: a systematic review and meta-analysis

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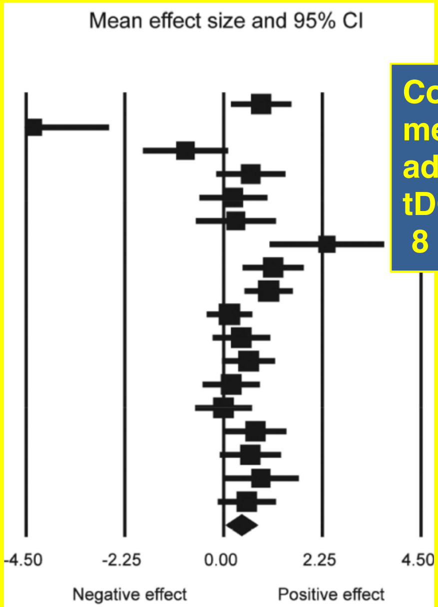
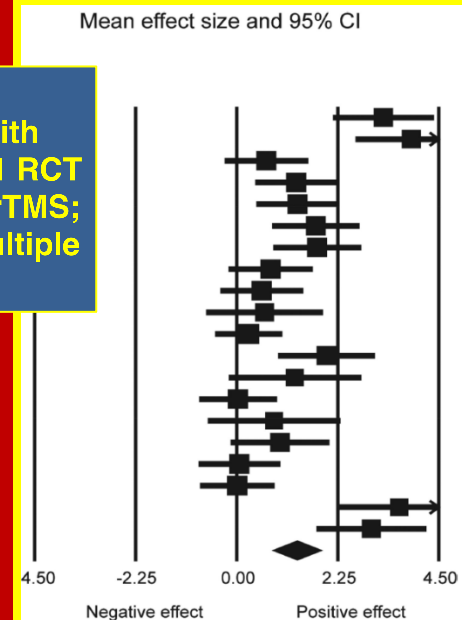


Cognitive outcome measures in healthy older adults; 14 RCT studies; 12 tDCS and 2 rTMS
8 online; 5 off line; 1 both

Cognitive outcome measures in patients with Alzheimer's disease; 11 RCT studies; 5 tDCS and 6 rTMS; 3 onlin3; 8 offline; 6 multiple session trial



Non-invasive brain stimulation has a positive effect on cognitive function in physiological and pathological aging

Few adverse effects (<5% patients): painful scalp sensation, itching, headache and dizziness

Highlights

1. We evaluated the effects of non-invasive brain stimulation on cognitive function in healthy older adults and patients with Alzheimer's disease.
2. Non-invasive brain stimulation has a positive effect on cognitive function in physiological and pathological aging.
3. In healthy older adults, "offline" design and multiple sessions of stimulation are most beneficial.
4. In patients with Alzheimer's disease, applying stimulation during the execution of the cognitive task leads to a more pronounced beneficial effect.

Subgroup analyses indicated more pronounced effects for stimulation during the execution of the task compared to the stimulation before the execution of the task

JAN
Informing Practice and Policy Worldwide through Research and Scholarship

REVIEW PAPER

Quantitative systematic review of the effects of non-pharmacological interventions on reducing apathy in persons with dementia

Emilie Dykstra Goris, Katherine N. Ansel & Debra L. Schutte

Accepted for publication 22 April 2016

Apathy prevalence = >90% AD

- failure of conitive sttimulation rehabilitation
- low performance of activities of daily living
- uncooperativeness with care
- bativeness and social isolation

Intervention 16 RCTs	RCTs N.	Outcome (short-term follow-up)
Music therapy sessions using rhythmical and melodic Instruments	4	NPI-Apathy subscale $p<0.01$
Individual CTS	1	NPI-Apathy subscale $p<0.01$
Art therapy	1	NPI-Apathy subscale $p<0.01$
To share life experience	2	NPI-Apathy subscale $p<0.01$
Conversation sessons	1	NPI-Apathy subscale $p<0.01$
Staff instruction with “do’s” and “don’ts”	1	NPI-Apathy subscale $p<0.01$
Problem-solving	1	NPI-Apathy subscale $p<0.01$

Non-pharmacological interventions for apathy varied substantially and lacked specificity, conceptual clarity and were methodologically heterogeneous

Interventions to reduce apathy may have a positive clinical impact and healthcare providers should be encouraged to incorporate positive sources of interest (Music Therapy) and intellectual stimulation into care

What do we know about the neural substrate underlying the effectiveness of Cognitive Stimulation on some cognitive and behavioural domains in Dementia ?

- Episodic memory.
  - Cognitive Stimulation and structural MRI
  - Memory tasks in aging and fMRI
  - Hippocampal connectivity and aging-dementia
  - Cognitive stimulation and large scale resting bain network connectivity. fMRI and PET
- Physical exercise
  - Structural Brain changes. MRI
  - Large scale resting brain network connectivity. fMRI
- Music effects on reward system,nucleus accumbens, basal ganglia, hypothalamus connections
- Neuropathology and neurotrasmiters in Psychiatric and Behavioural sympoms

Review · Journal of INTERNAL MEDICINE

doi: 10.1111/joim.12533

Functional brain imaging of episodic memory decline in ageing

L. Nyberg

Journal of Internal Medicine, 2017, 281; 65–74

JIM Journal of Internal Medicine Founded in 1863

Two decades of functional imaging have greatly enhanced our understanding of the cognitive neuroscience of ageing

The importance of the hippocampus can only be understood in the context of a large-scale brain network

Table 1 *Summary of the main findings related to the brain bases of episodic memory decline in ageing*

Imaging method	Key finding from age-comparative studies	Ref.
Structural MRI	Hippocampus atrophy	58
Task fMRI	Reduced hippocampus activity, mainly at encoding	16
	Reduced hippocampus–prefrontal cortex connectivity	25
	Reduced reactivation of modality-specific areas	48
Resting-state fMRI	Elevated hippocampal coupling	25
	Reduced hippocampus–precuneus connectivity	44
Amyloid PET	Increased cortical beta-amyloid deposition	73
Dopamine PET	Decline in striatal and extrastriatal dopamine	74

Nyberg L, Sandblom J, Jones S et al. Neural correlates of training-related memory improvement in adulthood and aging. Proc Natl Acad Sci USA 2003; 100: 13728–33.

Engvig A, Fjell AM, Westlye LT et al. Effects of memory training on cortical thickness in the elderly. NeuroImage 2010; 52: 1667–76.

NCBI Resources How To

PubMed.gov US National Library of Medicine National Institutes of Health

PubMed | cognitive training dementia fMRI

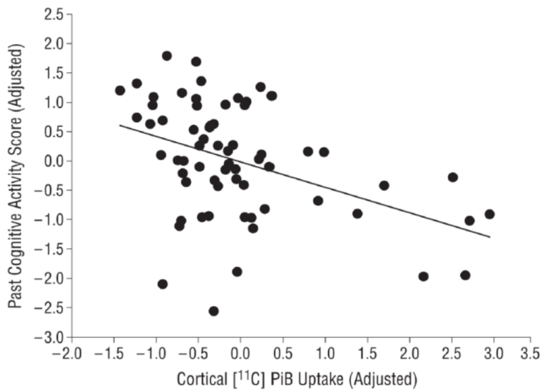
Create RSS Create alert Advanced

Arch Neurol. 2012 May ; 69(5): 623–629. doi:10.1001/archneurol.2011.2748.

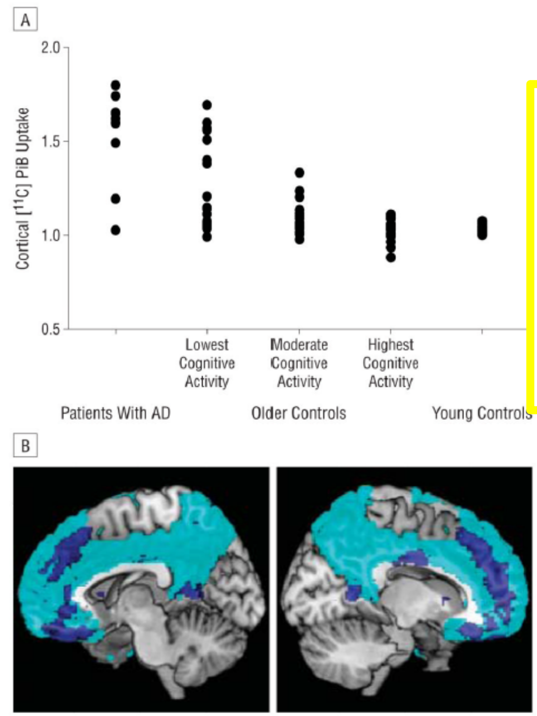
Association of Lifetime Cognitive Engagement and Low β-Amyloid Deposition

Dr. Susan M. Landau, PhD, Mr. Shawn M. Marks, BS, Dr. Elizabeth C. Mormino, PhD, Dr. Gil D. Rabinovici, MD, Dr. Hwamee Oh, PhD, Dr. James P. O'Neil, PhD, Dr. Robert S. Wilson, PhD, and Dr. William J. Jagust, MD

- 65 healthy older individuals (mean age, 76.1 yrs)
- 10 patients with Alzheimer disease (AD) (mean age, 74.8 yrs); mean MMSE = 19
- 11 young controls (mean age, 24.5 yrs)
- Years of education: 15-19
- Study from October 31, 2005, to February 22, 2011
- retrospective, self-report scales assessing participation in cognitive activities (eg, reading, writing, and playing games) and physical exercise
- [11C]PiB PET imaging



Individuals with past greater cognitive engagement show reduced amyloid burden



Cognitively normal older individuals with the lowest cognitive activity have amyloid burden
that resembles that of patients with Alzheimer disease (AD)

Regions in which past cognitive activity is inversely associated with [11C]PiB

Region
Right gyrus rectus
Right insula
Right middle temporal gyrus
Left insula
Right inferior frontal gyrus
Right inferior temporal gyrus
Right lingual gyrus
Right anterior cingulate gyrus
Left superior temporal gyrus
Left inferior parietal lobule

Regions with negative correlation

Lifestyle factors found in individuals with high cognitive engagement may prevent or slow deposition of β-amyloid, perhaps influencing the onset and progression of AD

NeuroImage

Volume 52, Issue 4, 1 October 2010, Pages 1667-1676

Effects of memory training on cortical thickness in the elderly

Andreas Engvig [a, b], Anders M. Fjell [b, c], Lars T. Westlye [b], Torgeir Moberget [d], Øyvind Sundseth [c], Vivi Agnete Larsen [b], Kristine B. Walhovd [b, c]

Systematic mental exercise induces structural changes in the aging human brain. Structural brain plasticity persists in elderly

8-week verbal memory training . Normal young and old.

After training, regional increases in cortical thickness compared with controls

MRI

2-months episodic memory training. Patients with subjective memory impairment (SMI)

- **Structural gray matter volume increases in brain regions encompassing the episodic memory network,**
- **The cortical volume expansion is comparable extent as healthy training participants.**
- **Significant hippocampal volume increases in the healthy training group but not in the SMI group**

1. **Intact brain plasticity in aging**
2. **Training-related brain changes can be evident also in the earliest form of cognitive impairment**

J Alzheimers Dis. 2014;41(3):779-91. doi: 10.3233/JAD-131889.

Effects of cognitive training on gray matter volumes in memory clinic patients with subjective memory impairment.

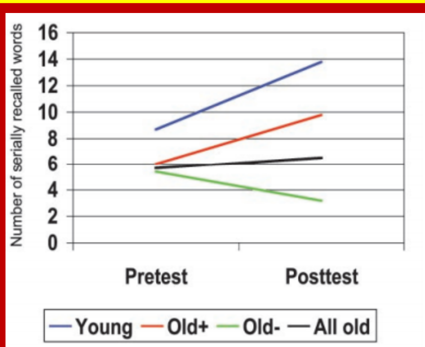
Engvig A[1], Fjell AM[2], Westlye LT[3], Skaane NV[4], Dale AM[5], Holland D[6], Due-Tønnessen P[7], Sundseth O[8], Walhovd KB[2].

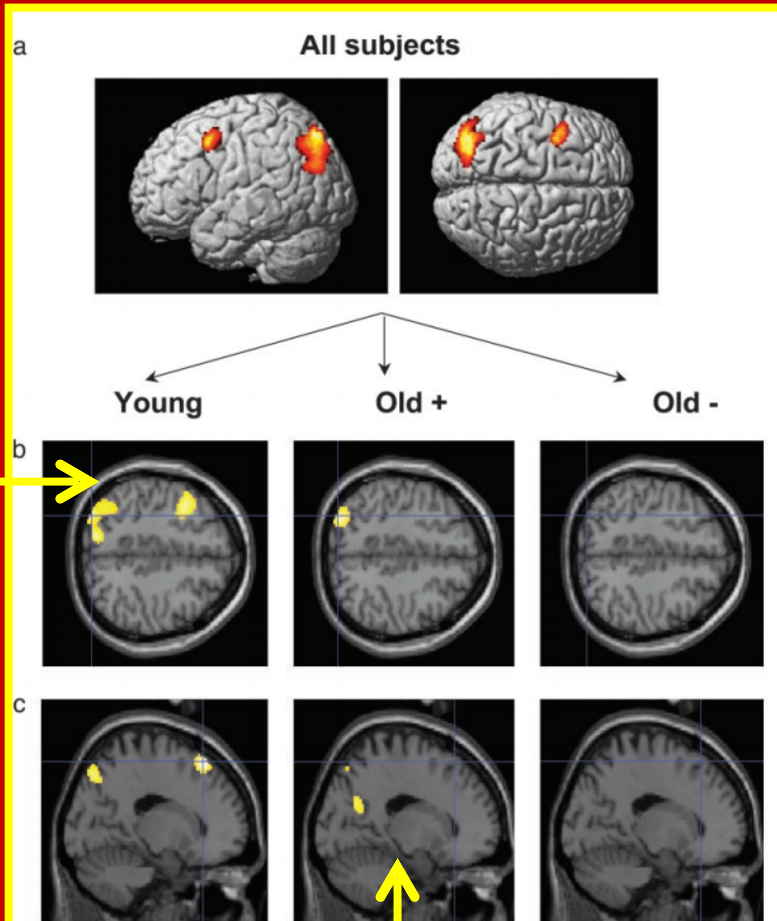
Neural correlates of training-related memory improvement in adulthood and aging

Lars Nyberg*†, Johan Sandblom‡, Sari Jones§, Anna Stigsdotter Neely*, Karl Magnu
and Lars Bäckman§

13728–13733 PNAS November 11, 2003 vol. 100 no. 23

PET scan





Visuospatial memory test
Test and retest
Yung ++
Old - +
Old - -

Younger adults show increased activity during memory encoding in occipito-parietal and frontal brain regions after learning the visuospatial mnemonic

Older adults did not show increased frontal activity, and only those elderly persons who benefited from the mnemonic showed increased occipitoparietal activity

The age-related differences in cognitive reserve capacity may reflect:

- a frontal processing deficiency
- a posterior production deficiency

Review | Journal of INTERNAL MEDICINE

doi: 10.1111/joim.12533

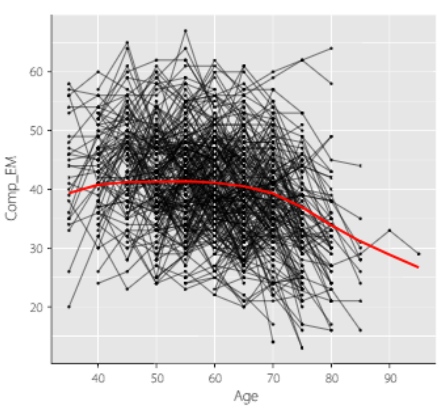
Functional brain imaging of episodic memory decline in ageing

Journal of Internal Medicine, 2017, 281; 65–74

L. Nyberg

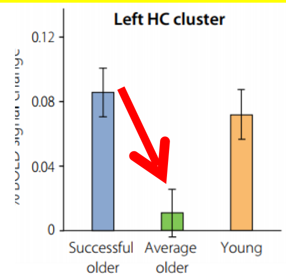
Journal of Internal Medicine
Founded in 1863

fMRI

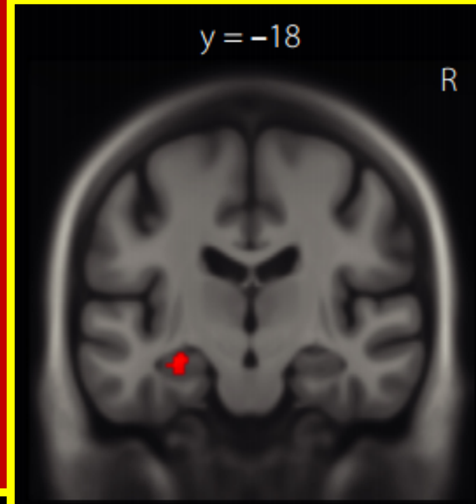


Change in episodic memory across the adult lifespan (red curve) and patterns of individual change (black lines) (Betula Study)

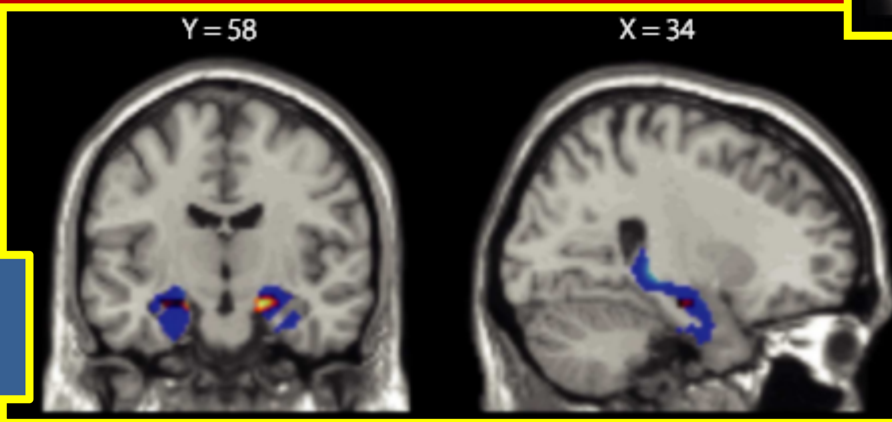
Less left hippocampal recruitment in older adults with declining episodic memory



Hippocampus and medial temporal lobe activity



Episodic encoding and retrieval



- Less recruitment during the face–name task in older adults with decline in episodic memory

Main effect of Encoding
Ageing effect on Encoding

Review
Journal of INTERNAL MEDICINE
doi: 10.1111/joim.12533

Functional brain imaging of episodic memory decline in ageing

Journal of Internal Medicine, 2017, 281; 65–74

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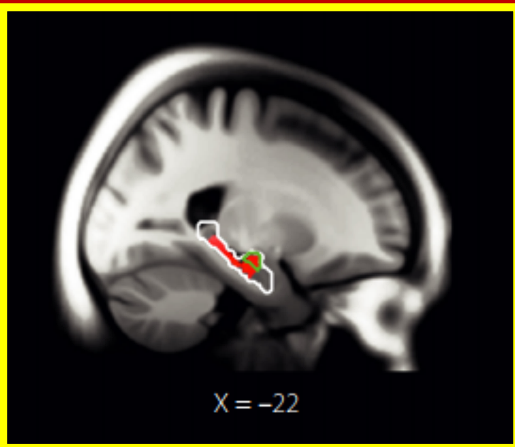
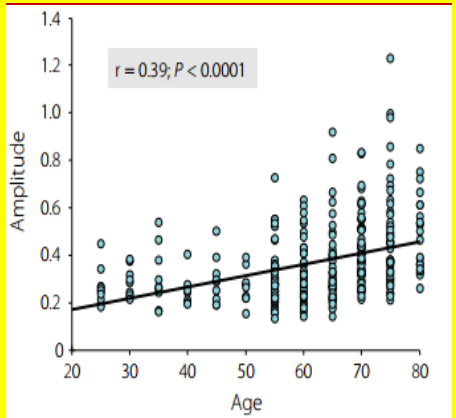
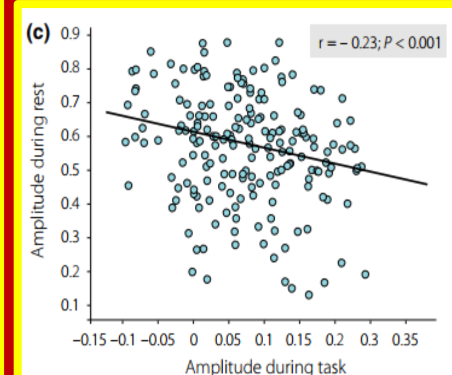
fMRI



Functional changes in the hippocampus in the Resting State



Resting State: Hippocampus amplitude connectivity increases with age



During episodic memory: Decreased Hippocampal reruitment if increased connectivity at rest

Resting state:

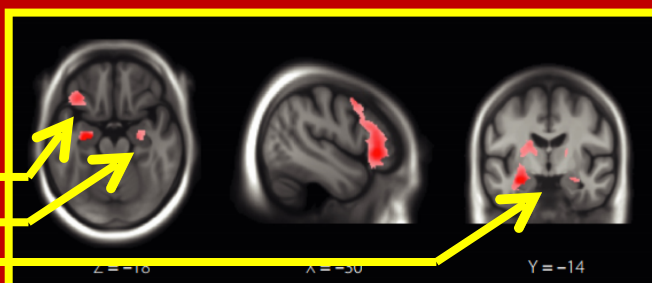
- Reduced inhibitory input from the cortex to the hippocampus results in elevated hippocampal connectivity in older age.

Episodic memory processing:

- Less efficient interactions between the hippocampus and left medial temporal and prefrontal regions

The left Hippocampus: a key hub for episodic memory. Connectivity via white matter:

- Left Prefrontal Cortex
- Right hippocampus
- Medial Temporal Lobe

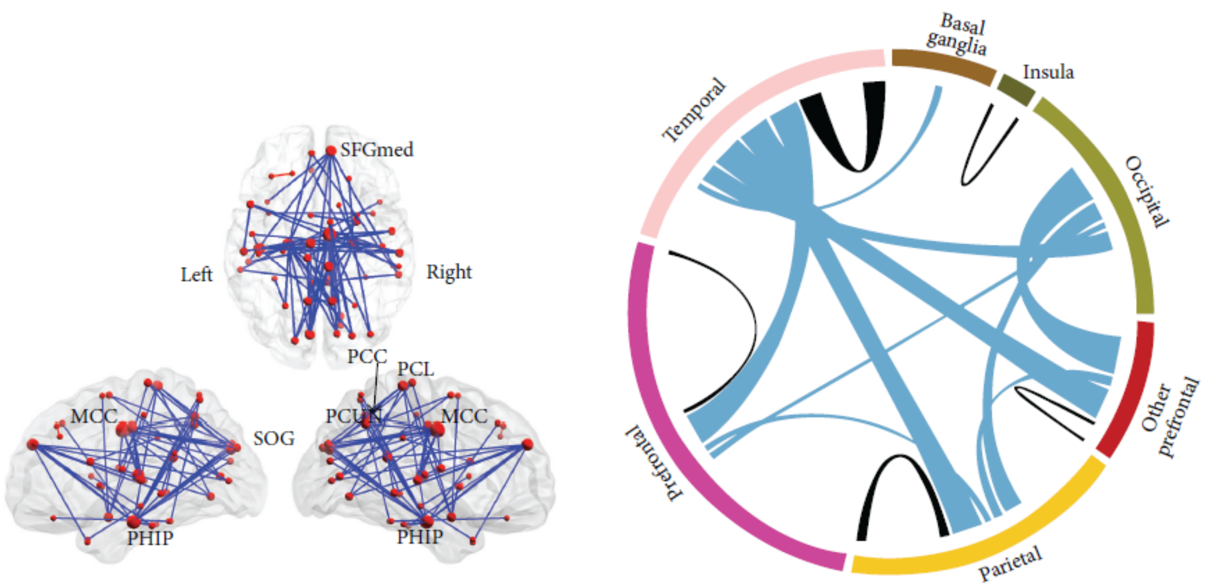


Aberrant Functional Connectivity Architecture in Alzheimer's Disease and Mild Cognitive Impairment: A Whole-Brain, Data-Driven Analysis

BioMed Research International
Volume 2015, Article ID 495375,

Bo Zhou,[1] Hongxiang Yao,[2] Pan Wang,[1] Zengqiang Zhang,[1,3] Yafeng Zhan,[4,5] Jianhua Ma,[5] Kaibin Xu,[4,6] Luning Wang,[1] Ningyu An,[2] Yong Liu,[4,6] and Xi Zhang[1]

- fMRI
- Resting state
- 27 MCI subjects
- 35 AD patients
- 27 age- and gender-matched subjects with normal cognition (NC)



(a) (b)

Decreased functional connectivities (Blue) in MCI and AD

- posterior cingulate gyrus (PCC)
- medial superior frontal gyrus (SFGmed)
- precuneus (PCUN)
- parahippocampal gyrus (PHIP)
- median- and paracingulate gyrus (MCC)
- superior occipital gyrus (SOG)
- paracentral lobule (PCL)

- **Changes in functional connectivity strength exhibited significant correlation with MMSE in AD and MCI**

The most significantly affected regions included several important nodes of the default mode network and the temporal lobe.

Effects of Cognitive Training on Resting-State Functional Connectivity of Default Mode, Salience, and Central Executive Networks

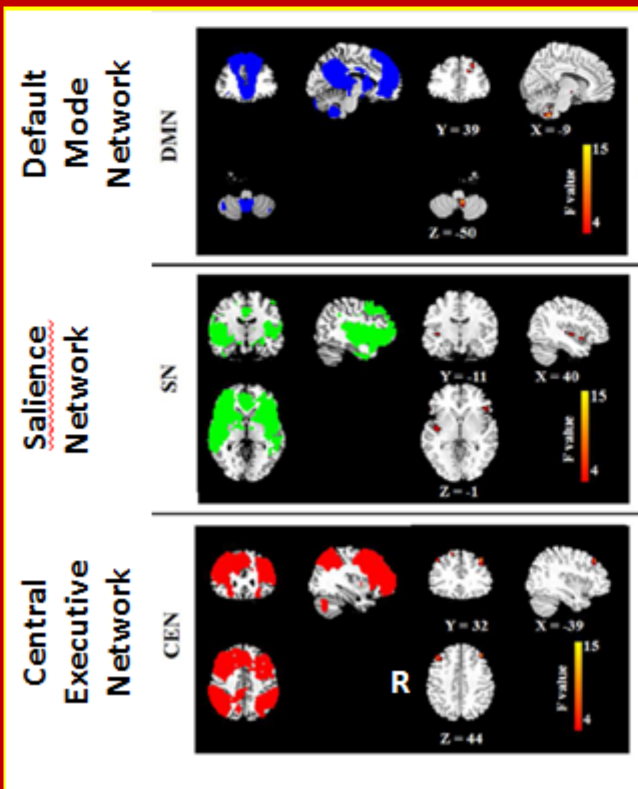
frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 12 April 2016
doi: 10.3389/fnagi.2016.00070

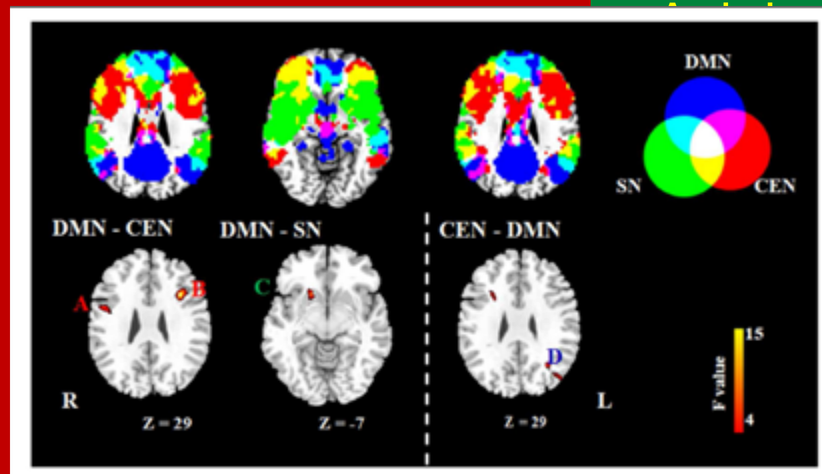
Weifang Cao[1†], Xinyi Cao[2†], Changyue Hou[1], Ting Li[3], Yan Cheng[2], Lijuan Jiang[2], Cheng Luo[1*], Chunbo Li[2,4,5*] and Dezhong Yao[1]

- 1-year cognitive training
- effect son three higher cognitive networks in healthy older adults.

- N. 23 multi-domain training group
- N.17 control group
- 24 sessions of cognitive training over a 3-months period
- Resting-State fMRI
- T1-Weighted gray matter volume (GMV)
- Functional Connectivity



The triple network model of the DMN, SN, CEN



The **functional integration** within networks and the coupling between the **Default Mode Network** and **Central Executive Network** in older adults is maintained or improved by Multiple Domain

Increased Functional Connectivity within all three networks after training

The anti-correlation between **Default Mode Network** and **Central Executive Network** is aging-sensitive

Dementia is characterized by a disruption of **Salience Network** and **Default Mode Network** connectivity

Combined omega-3 fatty acids, aerobic exercise and cognitive stimulation prevents decline in gray matter volume of the frontal, parietal and cingulate cortex in patients with mild cognitive impairment

NeuroImage 131 (2016) 226–238

Theresa Köbe [a,b,*], A.Veronica Witte [a,b,c,d], Ariane Schnelle [a,b], Anne Lesemann [a,b], Sonja Fabian [a,b], Valentina A. Tesky [e], Johannes Pantel [e], Agnes Flöel [a,b,f,*]

3T RMI

Clinical Interventions in Aging — Dovepress

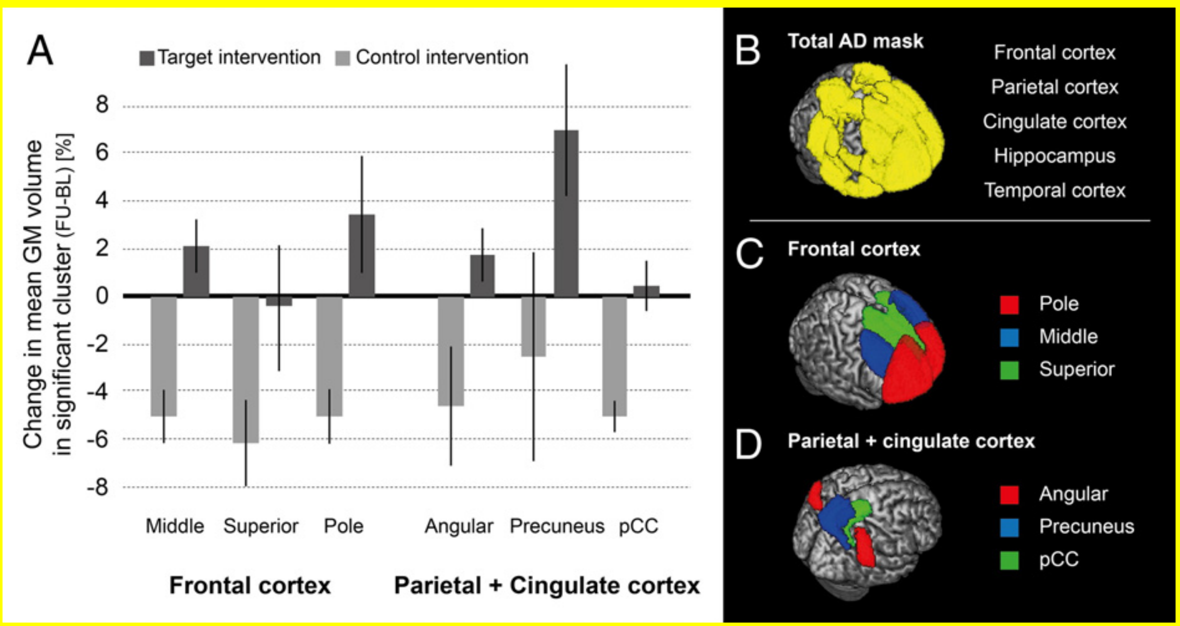
ORIGINAL RESEARCH

Feasibility and first results of a group program to increase the frequency of cognitively stimulating leisure activities in people with mild cognitive impairment (AKTIVA-MCI)

Combined 6 months intervetion

- **22 patients with MCI**
- **omega-3 FA supplementation, aerobic exercise and cognitive stimulation (target intervention) (ACTIVA)**
- **versus omega-3 FA supplementation and non-aerobic exercise (control intervention)**
- **cognitive function and gray matter volume (3T MRI)**

Regional changes in cortical gray matter volume after six months



No significant differences in cognitive performance

Gray matter volume decreased in MCI patients of the control intervention, whereas it increased or remained constant in patients of the target intervention

Reduced atrophy or even increase of gray matter volume in patients participating in six months omega-3 FA intake, aerobic exercise and cognitive stimulation

Evidence that omega-3 FA intake with combined aerobic exercise and cognitive stimulation prevents gray matter atrophy in AD-related brain regions in MCI patients, compared to omega-3 FA intake plus the control condition of stretching and

White matter microstructure mediates the relationship between cardiorespiratory fitness and spatial working memory in older adults☆

CrossMark

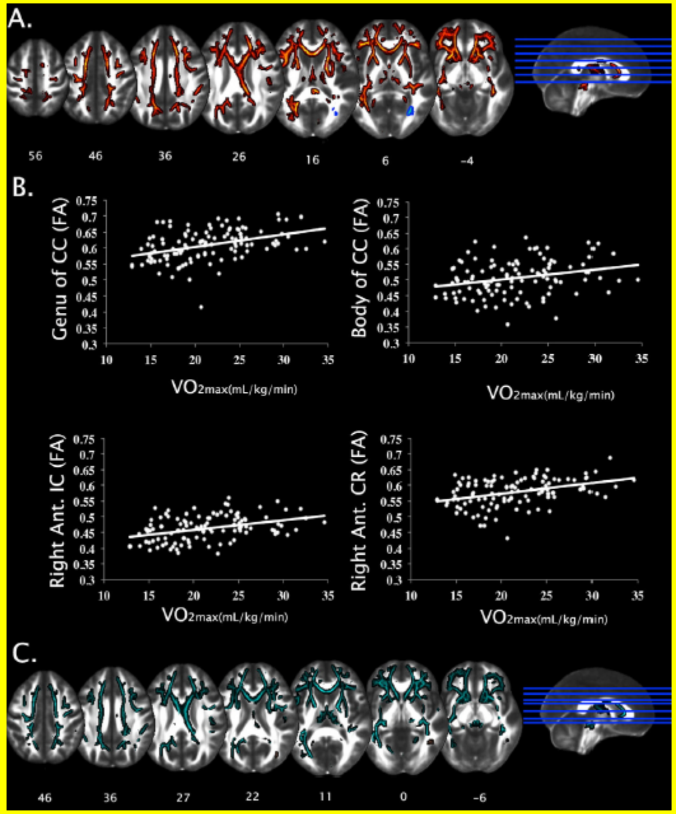
Lauren E. Oberlin [a,b,*], Timothy D. Verstynen [b,c], Agnieszka Z. Burzynska [d,g], Michelle W. Voss [e], Ruchika Shaurya Prakash [f], Laura Chaddock-Heyman [g], Chelsea Wong [g], Jason Fanning [h], Elizabeth Awick [h], Neha Gothe [i], Siobhan M. Phillips [j], Emily Mailey [k], Diane Ehlers [h], Erin Olson [l], Thomas Wojcicki [m], Edward McAuley [h], Arthur F. Kramer [g], Kirk I. Erickson [a,b]

NeuroImage 131 (2016) 91–101

Two large, separate groups 60-80 years old (Experiment 1, N = 113; mean age = 66.61. Experiment 2, N = 154; mean age = 65.66) of cognitively and neurologically healthy adult.

Diffusion tensor 3 T MRI to determine white matter microstructure (fractionsl anisotropy; FA) in the two separate groups.

<u>Cardiorespiratory fitness assessed by Maximal oxygen uptake (VO2max)</u> in units of milliliters per kilogram per minute (ml/kg/min)



Using a voxel-based regression approach, we found <u>that higher VO2max was associated with higher fractional anisotropy (FA)</u>, in a diverse network of white matter tracts

- **anterior corona radiata**
- **anterior internal capsule**
- **fornix**
- **cingulum**
- **corpus callosum**

Greater aerobic fitness levels are associated with higher levels of white matter microstructural organization, which may, in turn, preserve spatial memory performance in older adulthood

Cardiorespiratory fitness attenuates the influence of amyloid on cognition

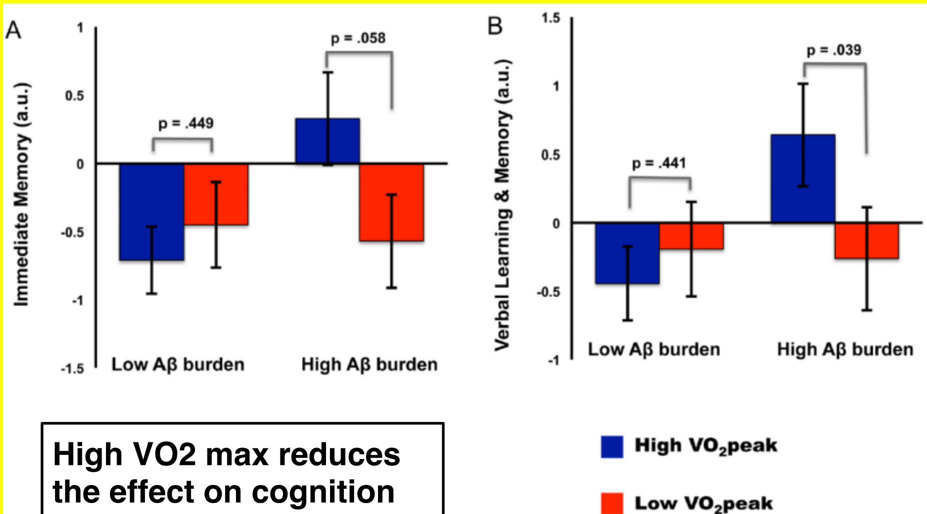
J Int Neuropsychol Soc. 2015; 21(10): 841–850

Stephanie A. Schultz[1,2,3], Elizabeth A. Boots[1,2,3], Rod... Oh[1,2,3], Jean Einerson[5], Claudia E. Korcarz[5], Dorothy F. Edwards[2,3,6], Rebecca L. Koscik[3], Maritza N. Dowling[7], Catherine L. Gallagher[1,2,8], Barbara B. Bendlin[1,2,3], Bradley T. Christian[2,9], Henrik Zetterberg[10,11], Kaj Blennow[10], Cynthia M. Carlsson[1,2], Sanjay Asthana[1,2], Bruce P. Hermann[2,3,8], Mark A. Sager[2,3], Sterling C. Johnson[1,2,3], James H. Stein[5], and Ozioma C. Okonkwo[1,2,3]

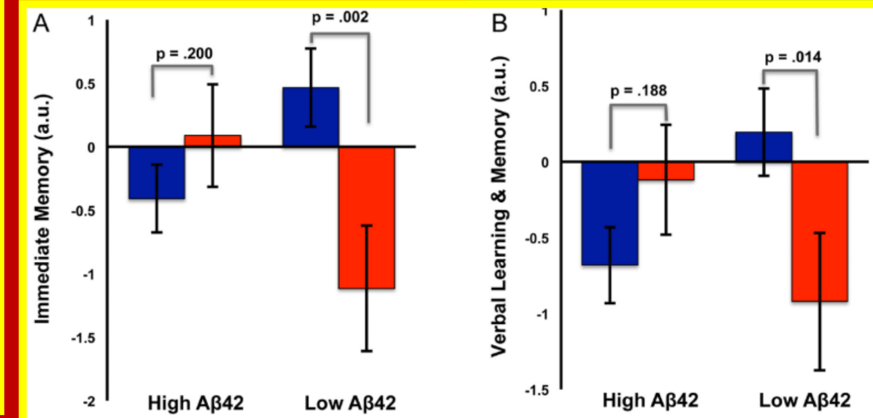
11C Pittsburgh Compound B-PET; CSF Amyloid -beta

N. 69 AD prevention, age 40-65

Graded exercise testing: Peak oxygen consumption (VO2peak) index of cardiorespiratory fitness (CRF)



High VO2 max reduces the effect on cognition induced by high Aβ burden detected by PiB-PET



High VO2 max reduces the effect on cognition induced by high Aβ burden detected by CSF Aβ42

In a late-middle-aged, at-risk cohort, higher Cardio Respiratory Fittness is associated with a diminution of high Aβ burden -related effects on cognition.

Physical exercise might play an important role in the prevention of AD

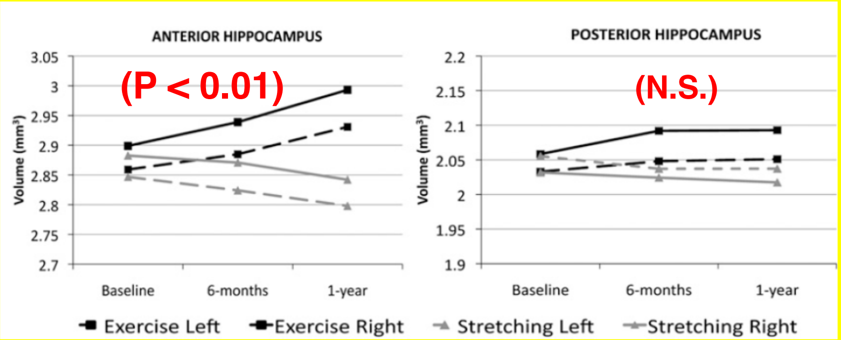
Exercise training increases size of hippocampus and improves memory

PNAS | February 15, 2011 | vol. 108 | no. 7 | 3017–3022

Kirk I. Erickson[a], Michelle W. Voss[b,c], Ruchika Shaurya Prakash[d], Chandramallika Basak[e], Amanda Szabo[f], Laura Chaddock[b,c], Jennifer S. Kim[b], Susie Heo[b,c], Heloisa Alves[b,c], Siobhan M. White[f], Thomas R. Wojcicki[f], Emily Mailey[f], Victoria J. Vieira[f], Stephen A. Martin[f], Brandt D. Pence[f], Jeffrey A. Woods[f], Edward McAuley[b,f], and Arthur F. Kramer[b,c,1]

Characteristic	Aerobic exercise	Stretching control
n	60	60
Age (y), mean (SD)	67.6 (5.81)	65.5 (5.44)
Sex (% female)	73	60
Attendance (%), mean (SD)	79.5 (13.70)	78.6 (13.61)
Fitness improvement (%), mean (SD)	7.78 (12.7)	1.11 (13.9)

RCT. Exercise training One year. Speed (≈30–100 m/min)



(P < 0.01)	aerobic exercise		stretching control	
	Baseline	1 year	Baseline	1 year
Blood BDNF	21.32 (9.32)	23.77 (8.04)	23.41 (9.67)	23.41 (9.67)

Selective increase in the anterior hippocampus and no change in the posterior hippocampus. Rogressive anterior hippocampus decease in controls.

Changes in fitness are associated with changes in hippocampal microstructure and hippocampal volume among older adults

CrossMark

Maike Margarethe Kleemeyer[a,*], Simone Kühn[a,b], John Prindle[a], Nils Christian Bodammer[a], Lars Brechtel[c], Alexander Garthe[d], Gerd Kempermann[d,e], Sabine Schaefer[a,f], Ulman Lindenberger[a,g]

NeuroImage 131 (2016) 155–161

Association:

- **Decresed diffusivity and increased tissue density**
- **Increased hippocampal volume**
- **Increased fitness**

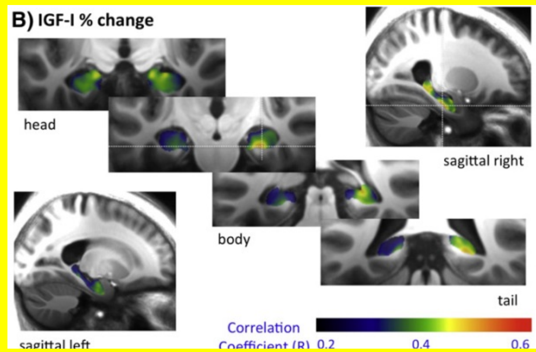
Angiogenesis, gliogenesis, and/or neurogenesis ?

Relationships of peripheral IGF-1, VEGF and BDNF levels to exercise-related changes in memory, hippocampal perfusion and volumes in older adults

CrossMark

NeuroImage 131 (2016) 142–154

Anne Maass [a,b,*], Sandra Düzel [c], Tanja Brigadski [d,e], Monique Goerke [b,f], Andreas Becke [b], Uwe Sobieray [b], Katja Neumann [a,b], Martin Lövdén [c,g], Ulman Lindenberger [c,h,i], Lars Bäckman [g], Rüdiger Braun-Dullaeus [j], Dörte Ahrens [j], Hans-Jochen Heinze [b,e,k,l], Notger G. Müller [b], Volkmar Lessmann [d,e], Michael Sendtner [m], Emrah Düzel [a,b,e,k,n,*]



Consumption of oxygen at Ventilatory Anaerobic threshold (VO_2VAT)

Early & Late Recall
Recognition Memory

- Increase in hièppocampal volume and perfusion
- Increase in episodic memory
- Increase in Insulin-like Growth Factor levels ere positively correlated with hippocampal volume changes and late verbal recall performance

---

Regional cerebral blood flow (rCBF) and volume (rCBV) measured with gadolinium-based perfusion 3 Tesla MRI. Hippocampal volumes assessed by high-resolution 7 Tesla MRI.

Fitness improvement correlated with changes in hippocampal perfusion and hippocampal head volume; hippocapal changes correlated wih changes in recognition memory and early recall for complex spatial objects.

Molecular Psychiatry **20**, 585-593 (May 2015) | doi:10.1038/mp.2014.114

Vascular hippocampal plasticity after aerobic exercise in older adults

20, 585-593, 2015

A Maass, S Düzel, M Goerke, A Becke, U Sobieray, K Neumann, M Lövden, U Lindenberger, L Bäckman, R Braun-Dullaeus, D Ahrens, H-J Heinze, N G Müller and E Düzel

Molecular Psychiatry

frontiers in
AGING NEUROSCIENCE
ORIGINAL RESEARCH ARTICLE
published: 26 August 2010
doi: 10.3389/fnagi.2010.00032

Plasticity of brain networks in a randomized intervention trial of exercise training in older adults

Michelle W. Voss[1], Ruchika S. Prakash[2], Kirk I. Erickson[3], Chandramallika Basak[1], Laura Chaddock[1], Jennifer S. Kim[1], Heloisa Alves[1], Susie Heo[1], Amanda N. Szabo[4], Siobhan M. White[4], Thomas R. Wójcicki[4], Emily L. Mailey[4], Neha Gothe[4], Erin A. Olson[4], Edward McAuley[4] and Arthur F. Kramer[1]*

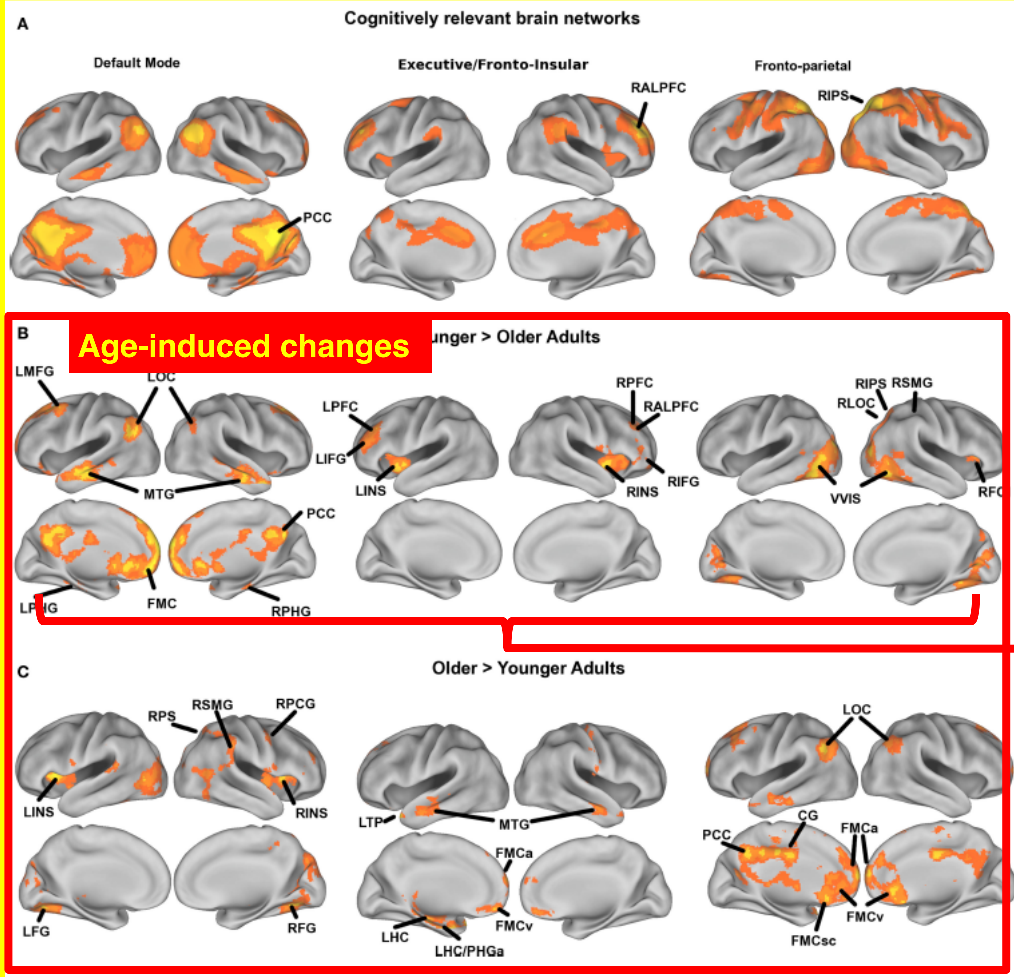


FIGURE 1 | Mean statistical maps for the average of old and young subjects, for cognitive networks, are illustrated in Figure 1A, followed by statistical maps for the contrasts of Young > Old and Old > Young in Figures 1B and 1C, respectively.

One year training

- <u>RCT. fMRI. Resting state</u>
- Strong right handedness
- Ages 18 - 35 for young adults
- Ages 55 - 80 for elderly adults
- N.30 Old training
- N.35 Old controls
- N. 32 Young controls
- Eucation >15 yrs
- Score ≥51 on mMMSE
- <3 on the(GDS)
- Normal color vision and a corrected visual acuity > 20/40
- Physically active for 30 min or more no more than two times in the last 6 months
- *Walking from 5 to 40 min 7 weeks, then 40 min/ daily session; one year; speed 30-100 m/min*
- *Flexibility, toning, and balance control condition 30)*

One year of walking <u>increased functional connectivity</u> between aspects of the <u>*frontal, posterior, and temporal*</u> cortices within the:

- <u>Default Mode Network</u>
- <u>Frontal Executive Network</u>

- Changes in functional connectivity were behaviorally relevant
- Increased functional connectivity was associated with greater improvement in executive function

Evidence for exercise-induced functional plasticity in large-scale brain systems in the aging brain

HHS Public Access

Author manuscript

Handb Clin Neurol. Author manuscript; available in PMC 2016 March 28.

Published in final edited form as:
Handb Clin Neurol. 2015 ; 129: 667–687. doi:10.1016/B978-0-444-62630-1.00037-8.

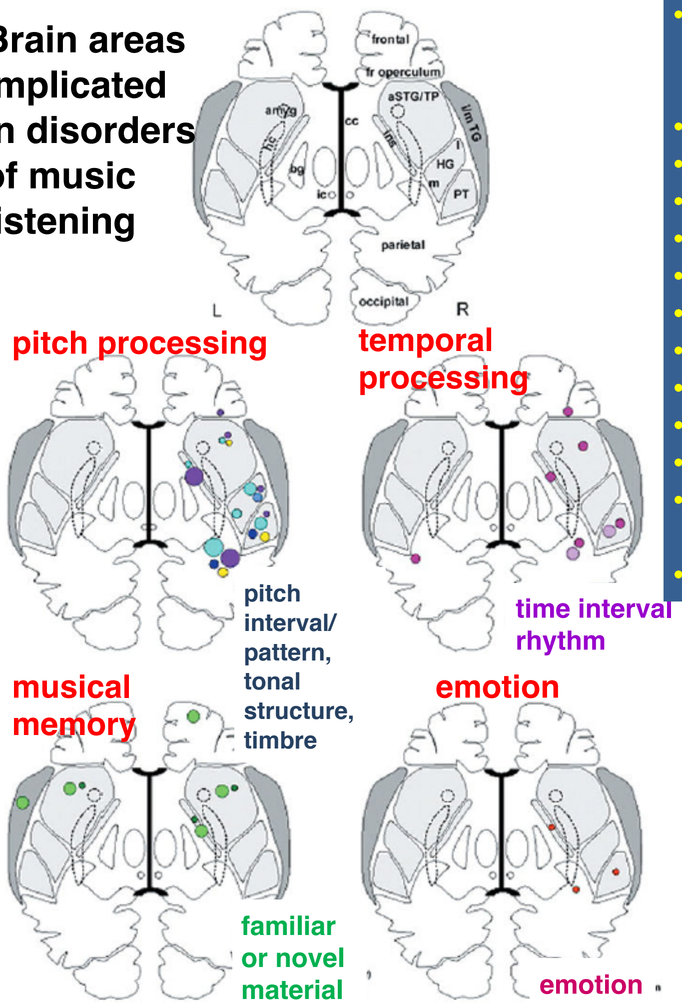
Hearing and music in dementia

Julene K Johnson[1,*] and Maggie L Chow[2]

HEARING FUNCTION IN NEURODEGENERATIVE DISEASES

- Hearing impairment
  - Peripheral auditory system function
  - Central auditory system
    - Neurofibrillary tangles in auditory system brainstem and midbrain nuclei
    - Plaques and tangles in primary auditory and auditory association cortex

Brain areas implicated in disorders of music listening



- amyg, amygdala
- aSTG, anterior superior temporal gyrus
- bg, basal ganglia
- cc, corpus callosum
- r, frontal
- hc, hippocampal
- HG, Heschl's gyrus
- ic, inferior colliculi
- ins, insula
- l, lateral
- m, medial
- thal, thalamus
- PT, planum temporale
- TG, temporal gyrus

AD

- Relative preservation of music abilities (playing)
- Familiarity recognition
- Wrong notes recognition
- Naming the tunes
- Pitch discrimination
- Short-term memory for unfamiliar melodies
- Recognition of meter (waltz vs march)
- Learn new music
- Recognition of emotions

brain regions that correlate with recognition of musical emotions

doi:10.1093/scan/nsu079 SCAN (2015) 10, 444–452

Our passions lead our reasons (Rousseau, 1781)

Brain disorders and the biological role of music

Camilla N. Clark, Laura E. Downey, and Jason D. Warren

Neural architecture of music as product of human evolution: stages I-IV

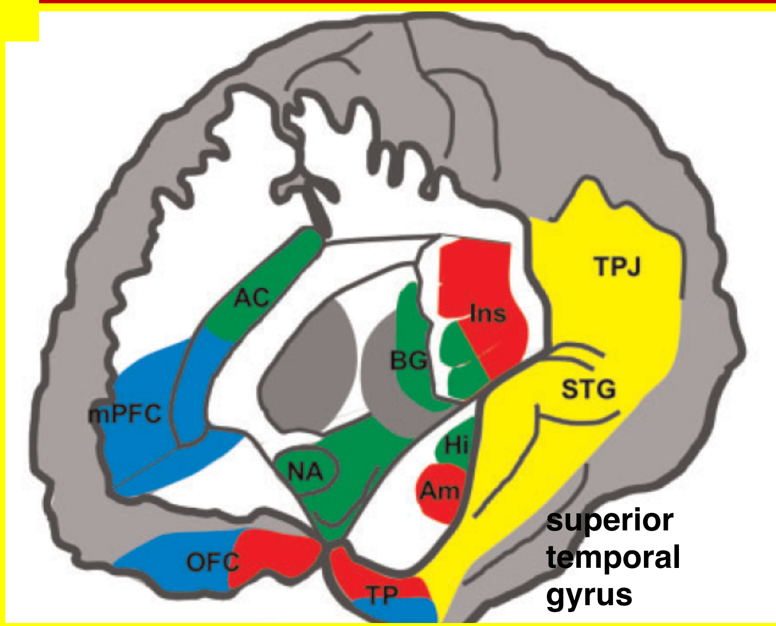
Yellow (I, II): superior temporal gyrus, temporo-parietal junction
- **perceptual analysis and imagery**

Red (III) : insula, amygdala, temporal pole, orbitofrontal cortex
- **expectancies, associations and affective evaluation**

Green (I, III): anterior cingulate , nucleus accumbens, basal ganglia, hippocampus
- **biological motivation and reward encoding, autonomic responses**

Blue (IV): medial prefrontal cortex, orbitofrontal cortex, temporal pole
- **mental state processing and behavioural evaluation**

Ancient bone flute. Danube surroundings. 40.000 yrs B.C



Neuroanatomy of music processing and related cognitive operations

Evolutionary model of music as a biologically sanctioned mechanism for transforming private, emotional mental states efficiently into public social signals

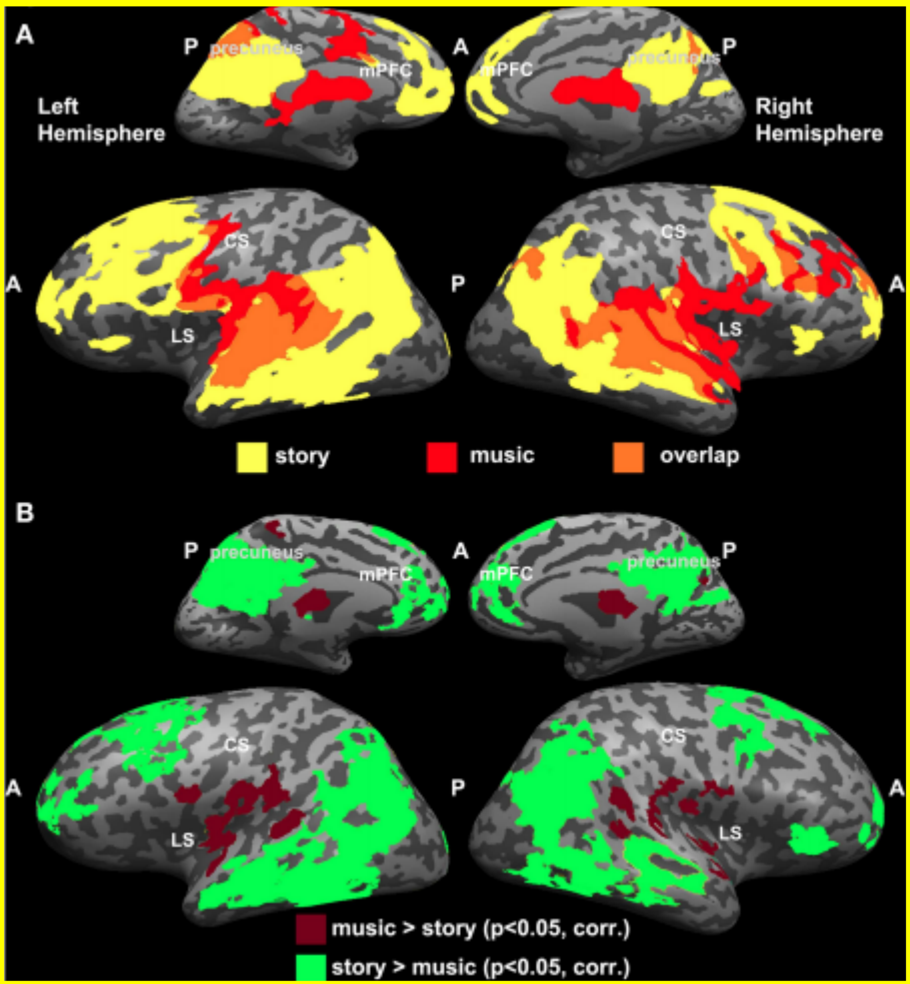
MUSIC
- **A mental tool to depict and predict potentially costly, affectively thick social routines in surrogate, coded, low-cost form**
- **Music may have led**

The neural processing of hierarchical structure in music and speech at different timescales

Morwaread M. Farbood[1], David J. Heeger[2], Gary Marcus[3], Uri Hasson[4] and Yulia Lerner[5,6]*

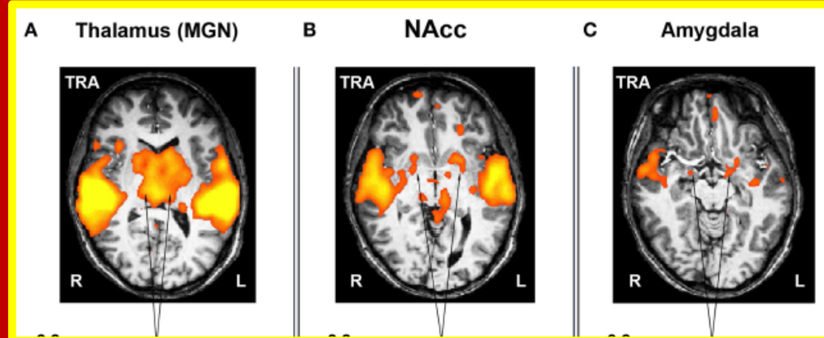
frontiers in Neuroscience

ORIGINAL RESEARCH
published: 12 May 2015
doi: 10.3389/fnins.2015.00157



Overlap Between Intact Music and Intact Story

Subcortical Structures for Music



The reliability in the subcortical regions was specific to music; comparably reliable responses in these regions were not found in the story conditions.

Surg Radiol Anat. 2015 Mar;37(2):121-5. doi: 10.1007/s00276-014-1360-0. Epub 2014 Aug 8.

Music and the nucleus accumbens.

Mavridis IN[1].

Neuroimage. 2015 Aug 1;116:68-79. doi: 10.1016/j.neuroimage.2015.05.006. Epub 2015 May 11.

Investigating the dynamics of the brain response to music: A central role of the ventral striatum/nucleus accumbens.

Mueller K[1], Fritz T[2], Mildner T[3], Richter M[3], Schulze K[4], Lepsien J[3], Schroeter ML[5], Möller HE[3].

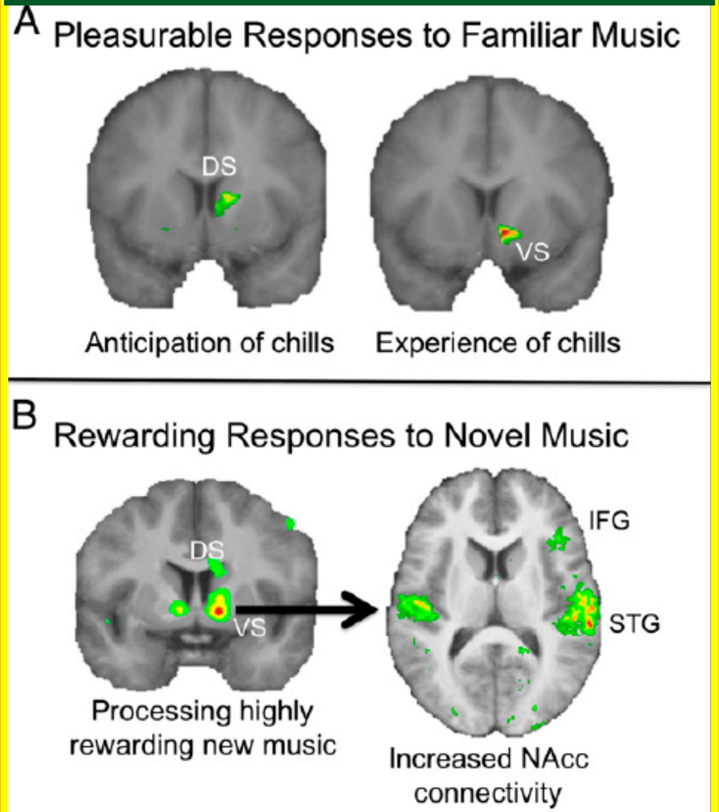
- The ventral striatum/nucleus accumbens is activated during music listening with increasing pleasantness.
- A hippocampal early response to the musical stimuli occurs when known music is listened

From perception to pleasure: Music and its neural substrates

Robert J. Zatorre[a,1] and Valorie N. Salimpoor[a,b]

10430–10437 | PNAS | June 18, 2013 | vol. 110 |

Auditory cortices are the site of processing not only of incoming auditory information, but also of more abstract computations related to perception, imagery, and temporal prediction



PET and fMRI neural correlates of processing highly rewarding music

Mesolimbic striatal system, which is involved in reward, motivation, and pleasure in other domains, mediates pleasure associated with music

Listeners while hearing their selected pleasurable music had increased activity

- in the ventral striatum (VS) during peak emotional moments ("chills")
- In the dorsal striatum (DS) preceding chills, in the same regions that showed dopamine release

cortical loops that enable predictions and expectancies to emerge from encoded and stored tonal patterns

Reward value of new music:

- activity in the ventral striatum, particularly the Nucleus Accumbens
- Nucleus accumbens showed increased functional connectivity with the superior temporal gyri (STG) and the right inferior frontal gyrus (IFG)

ELSEVIER

CrossMark

Alzheimer's & Dementia: Translational Research & Clinical Interventions 3 (2017) 440-449

Alzheimer's & Dementia

Review Article

Neuropsychiatric signs and symptoms of Alzheimer's disease: New treatment paradigms

Krista L. Lanctôt[a,*], Joan Amatniek[b], Sonia Ancoli-Israel[c,d], Steven E. Arnold[e], Clive Ballard[f,g], Jiska Cohen-Mansfield[h], Zahinoor Ismail[i], Constantine Lyketsos[j], David S. Miller[k], Erik Musiek[l], Ricardo S. Osorio[m], Paul B. Rosenberg[n], Andrew Satlin[o], David Steffens[p], Pierre Tariot[q], Lisa J. Bain[r], Maria C. Carrillo[s], James A. Hendrix[s], Heidi Jurgens[s], Brendon Boot[t,u]

The neurobiology of NPSs in AD

Distinct syndromes have different neurobiological underpinnings

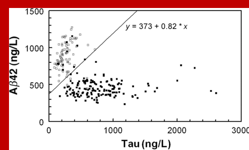
Significant involvement of AD pathology
- in key components of the limbic system
- amygdala
- basal forebrain
- hypothalamus
- brainstem

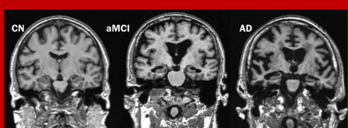
Neurofibrillary tangles are abundant in
- amygdala
- basal nucleus of Meynert
- the locus coeruleus
- substantia nigra
- dorsal raphe nucleus
- hypothalamus

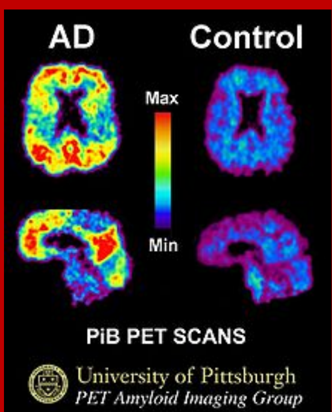
The degree to which pathologic involvement of these structures correlates with NPSs has not been well

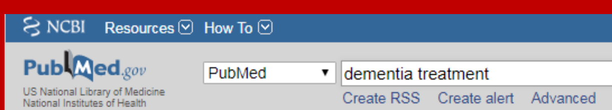
! Neuropathology !
Treatments for mood and psychotic symptoms
<u>may not work because of</u>
lack of target engagement in a degenerating brain

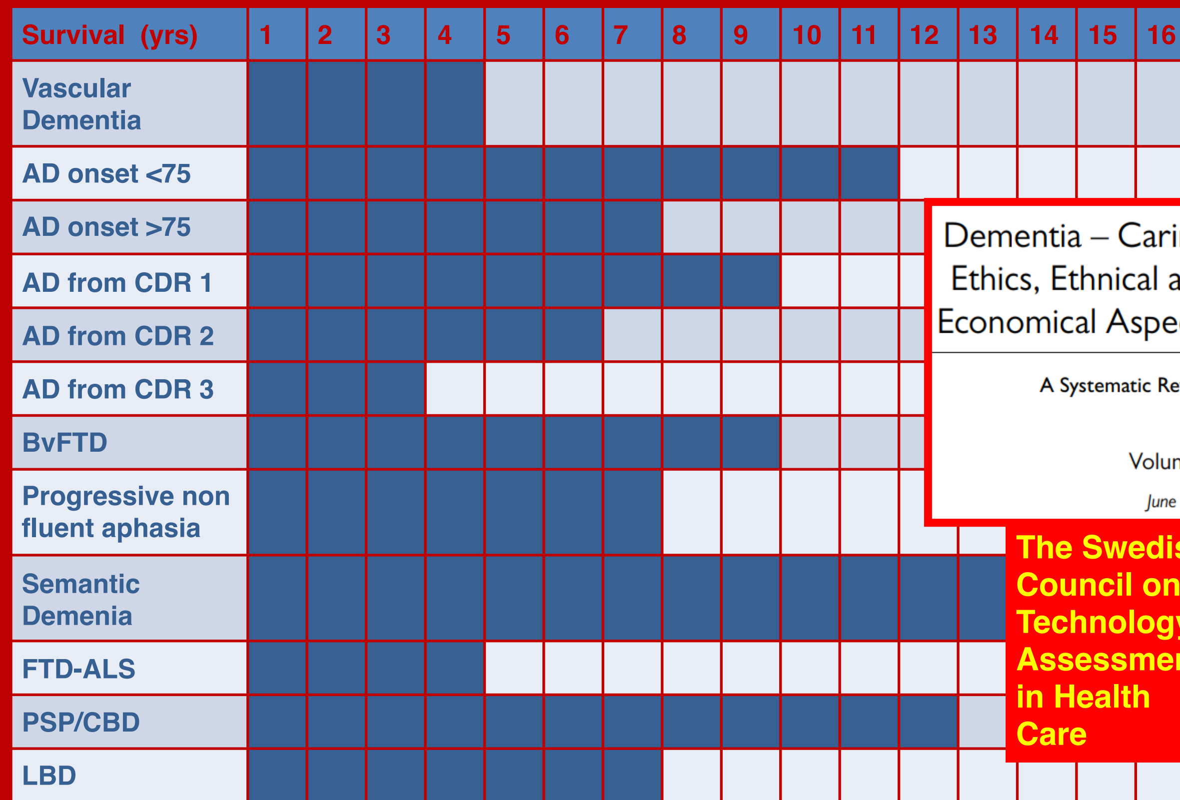
Psychotic symptoms in AD	Neurobiology of NPSs in AD		
Delusions and hallucinatons	• Misidentifications associated with lower cell counts in the Hippocampal CA1 region • Cholinergic los (effectiveness of AChIs)	• Disruption of serotoninergic signaling in raphe nuclei	• Weak association with apolipoprotein E (APOE) epsilon 4 allele • 5-HT 2A receptor single-nucleotide polymorphism 102 T allele associated with delusions, whereas the C allele protective
Agitation	Increased neurofibrillary tangles and intraneuronal phospho-Tau: • frontal cortex • anterior and posterior cingulate • amygdala • Hippocampus	• Decreased cortical cholinergic marker • Decreased brain stem serotoninergic marker. • RCT Citalopram effective	
Apathy	Atrophy, low metabolism/ perfusion in: • anterior and posterior cingulate • arbitofrontal area • prefrontal, anterior temporal, right temporo-parietal, right inferior and media frontal gyrus, right gyrus lingualis	• Deficit in cholinergic frontostriatal circuit. • Deficit in the dopaminergic reward system (connections to amygdala and nucleus accumbens)	• High CSF Tau and Phospho-tau levels
Depression	• Amyloid deposition burden • high blood pressure • left hippocampal atrophy • WMH burden	• Negative RCT of SSRI in AD depression (HTA-SADD trial)	
Sleep	Beta amyloid burden and	• Orexine stimulates	• Low amyloid beta and high CSF tau











Dementia – Caring, Ethics, Ethnical and Economical Aspects

A Systematic Review

Volume 3

June 2008

The Swedish Council on Technology Assessment in Health Care

33. Care Interventions - patient's perspective. pp 140

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