3RD INTERNATIONAL CONFERENCE ON ALZHEIMER DEMENTIA WORKSHOP
AUGUST 31ST 2015.

Exploring the kaleiodoscopic oasis of epigenetics-based Diet, Brain Games and Physical exercises in Cognitive Aging and Alzheimer's dementia: Evidence, promises and challenges

full set of slides available upon request :schiu3207@rogers.com

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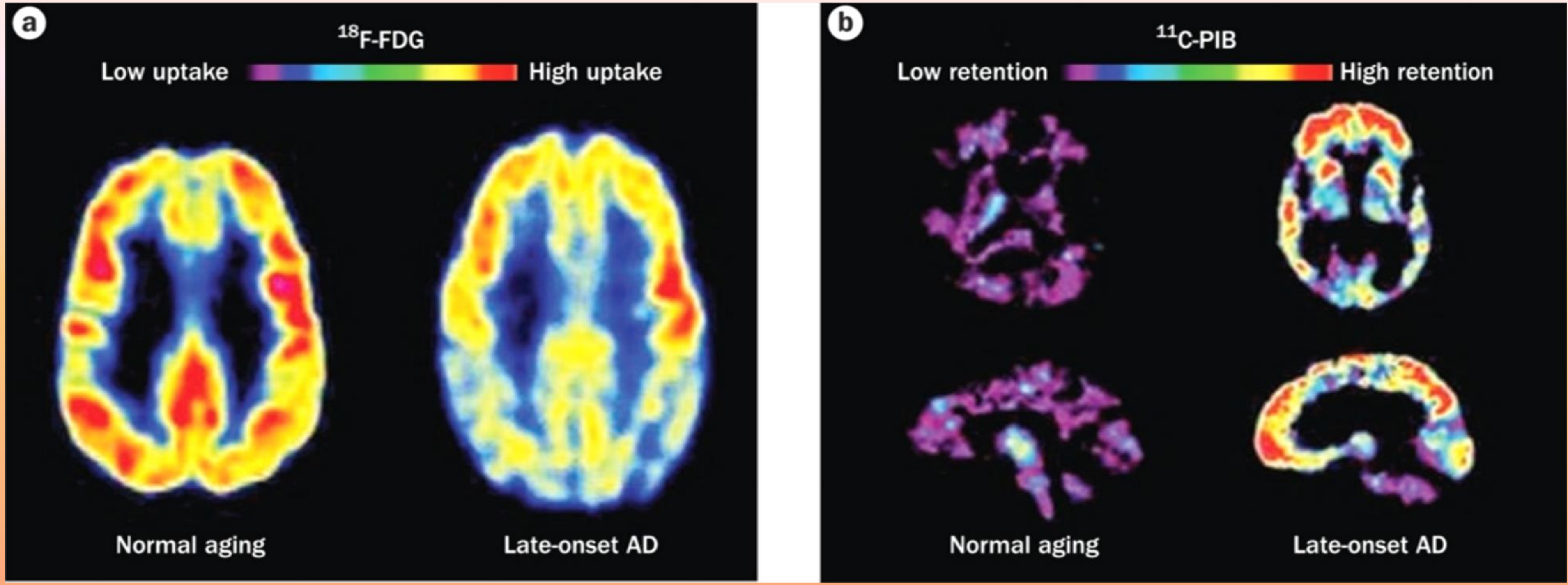
Financial Disclosure statement

- None of the presenters have received stipends or consultant fees from pharmaceutical industry , dietary supplements Co. perceived as potential significant conflict of interest for discussing research areas related directly to the specific topics discussed in the workshop .

- The group of investigators have received grant support from Stanley medical Research Institute MD USA, Michael J Fox Foundation for research on Epigenomics in schizophrenia and Parkinson Disease

Neuro-imaging in Late-stage AD



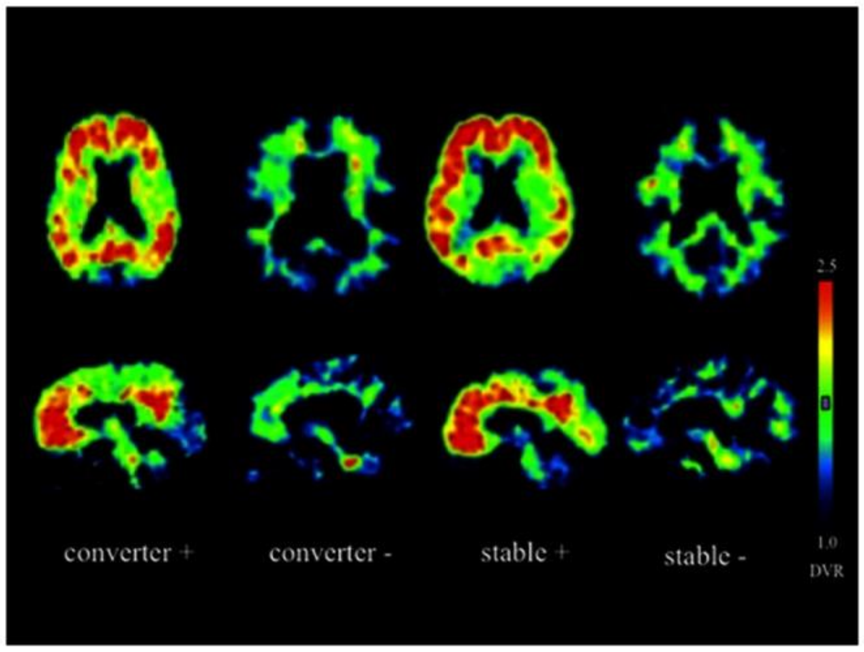
a | 18F-FDG-PET metabolic activity in late-stage AD: decreased bilateral glucose metabolism at temporal and parietal regions.

b |11C-PIB PET : High 11C-PIB level in AD brains correlated with high amyloid deposits.

Reitz et al 2012 Nat Rev Neurol.

Opportunities for Prevention and Treatment of Alzheimer's dementia role of PIB PET imaging

Hatashita S, Yamasaki H (2013) Diagnosed Mild Cognitive Impairment Due to Alzheimer's Disease with PET Biomarkers of Beta Amyloid and Neuronal Dysfunction. **PLoS ONE 8(6): e66877**



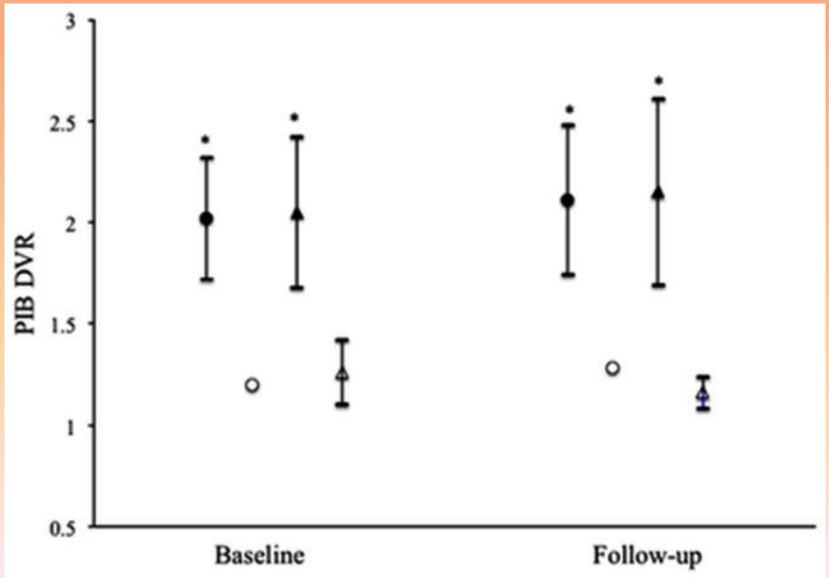
PIB-PET DVR images from 4 representative MCI converters and stable patients with (+) and without amyloid deposition (−) at baseline.

30/68 MCI Converted over 19 months

The annual rate of MCI conversion :23.4%.

A positive Ab PET biomarker significantly identified MCI due to AD in individual MCI subjects with a sensitivity (SS) of 96.6% and specificity(SP) of 42.1%. Positive predictive value:56.8%

A positive Ab biomarker in APOE e4/4 carriers distinguished with a SS of 100%.



The cortical PIB DVR (distribution volume ratio) values in PIB-positive MCI converters (closed circles, n = 29),

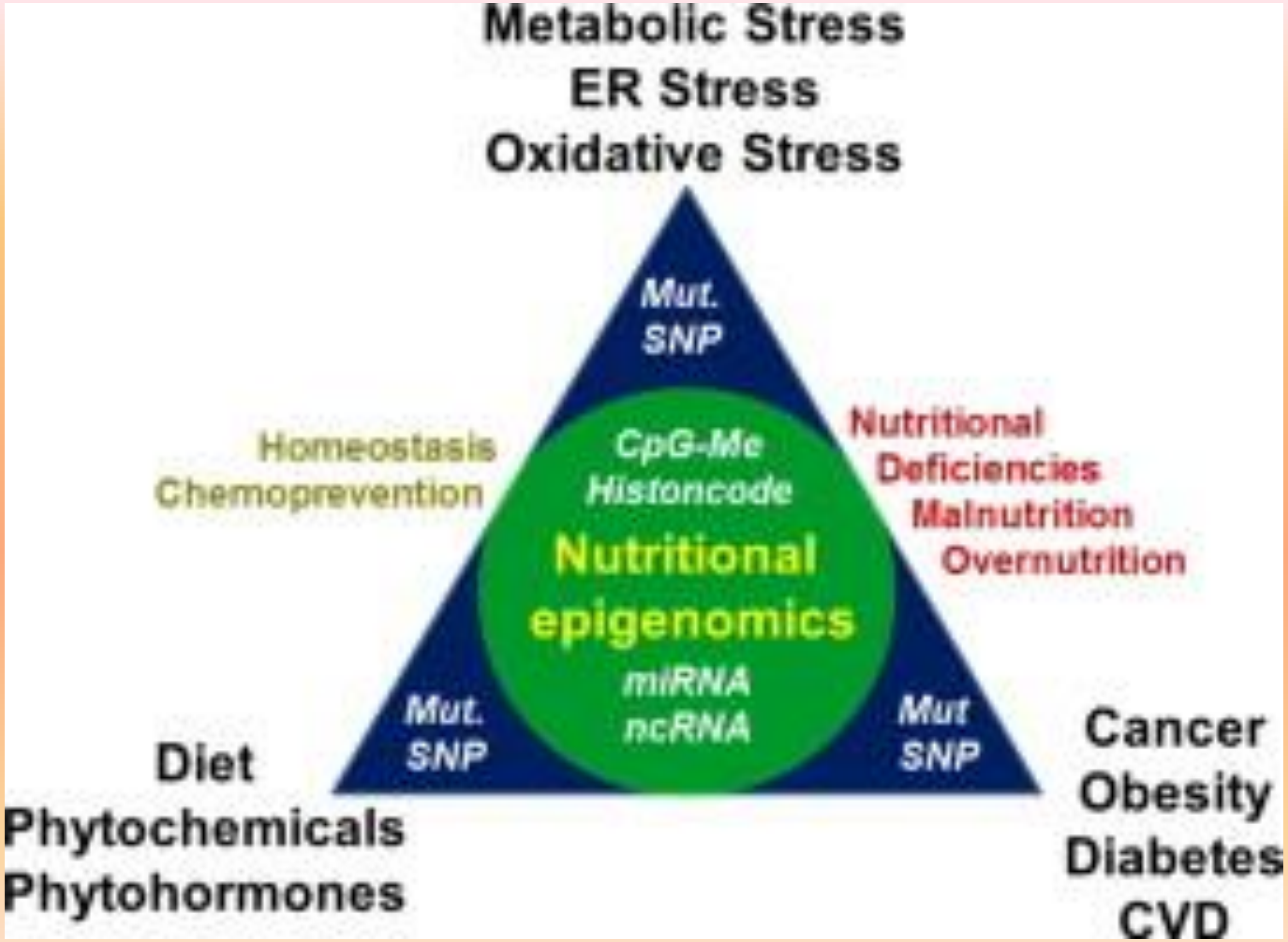
PIB-negative MCI converter (open circles, n = 1),

PIB-positive stable MCI patients (closed triangles, n = 22) ,

and PIB-negative stable MCI patients (open triangles, n = 16)

at baseline and follow-up.

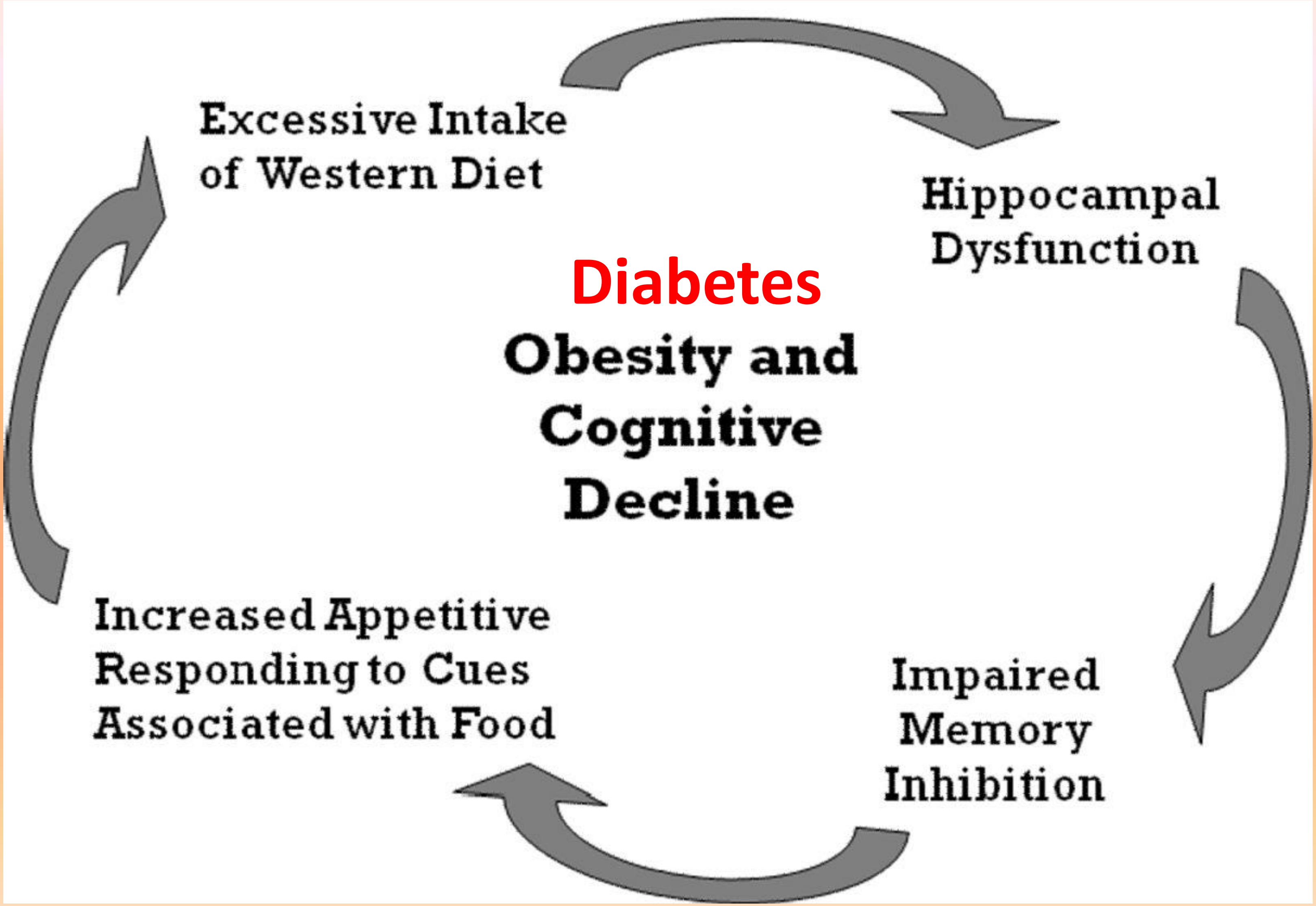
Nutritional Epigeneomics:
guide to Personalized and Precision Medicine in AGING



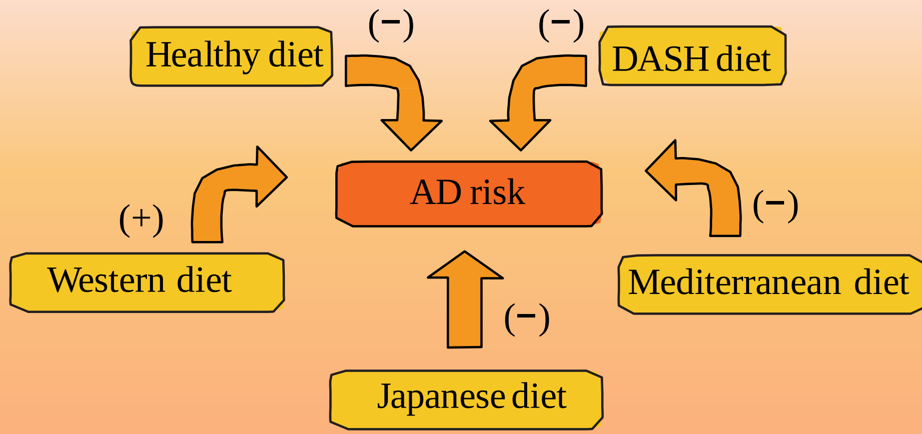
Epigenetics Video

http://www.dailymotion.com/video/xhqafg_chromatin-histones-and-epigenetics_tech

Obesity and Diabetes and Cognition



Confusion of the Roles of DIETS in Alzheimer Dementia Risk

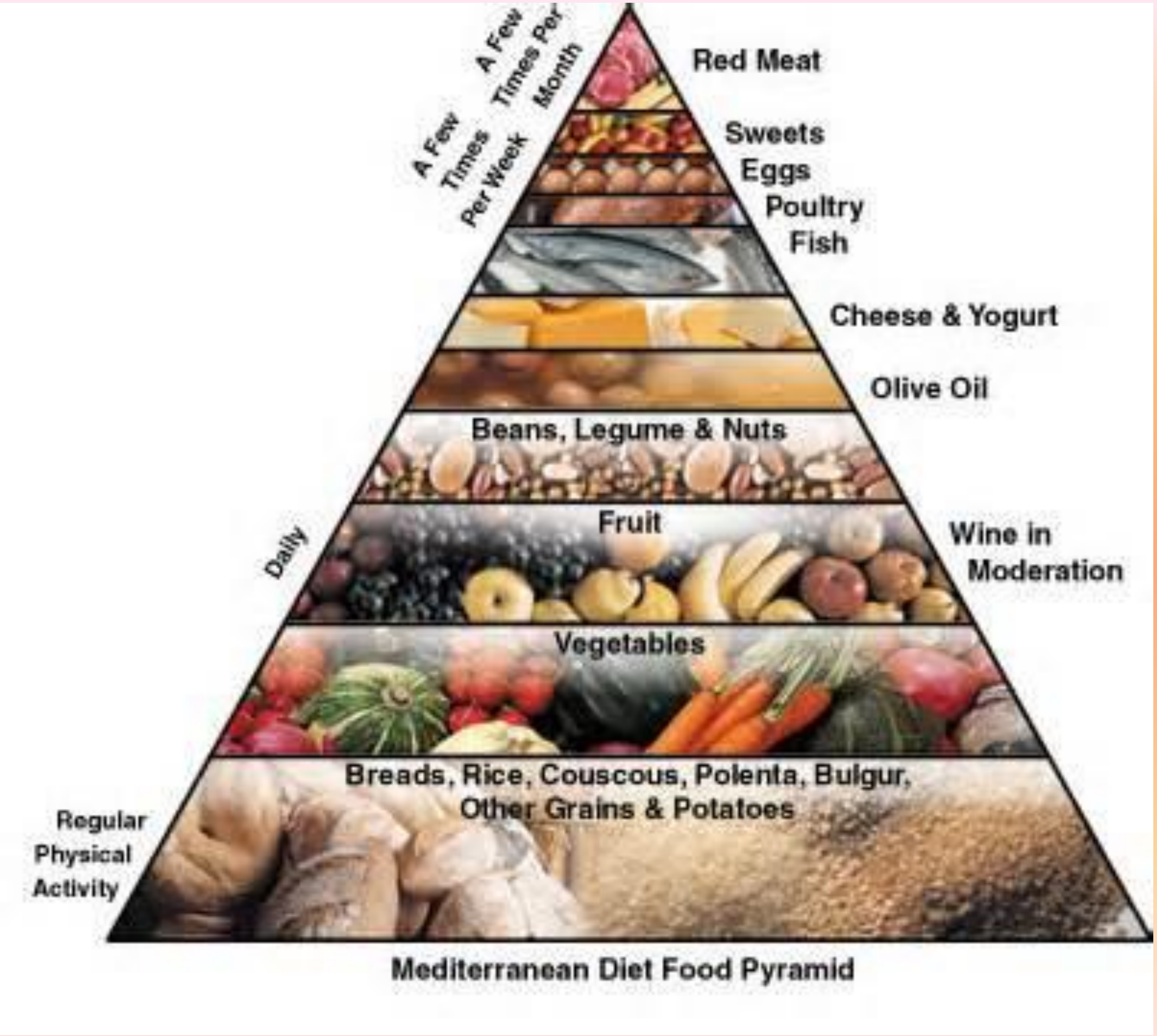


Low Carb Diet

Atkins diet

Figure 2: Dietary patterns that influence the risk of AD. Healthy diet, DASH-diet, Mediterranean diet, and Japanese diet might decrease the risk of AD. Western diet might increase the risk of AD. DASH diet: the Dietary Approaches to Stop Hypertension.

Mediterranean DIET Food Pyramid : the secret towards cognitive aging ??



Polyphenol-rich foods in MD-diet offer better Cognitive Health in High Cardiovascular risk elderly subjects

Pedret CV et al J Alzheimer Dis 2012 29:773-782

Table 1
Socio-demographic and anthropometric characteristics, physical activity, cardiovascular risk factors and APOE genotype of the study population ($n = 447$)

Variables	Mean or median	Range
Age (years)	66.9	(54.7–80.2)
Women, *n* (%)	233 (52.1)	
Education (years)	7.18	(0–14)
Body mass index (kg/m^2)	28.5	(18.8–36.8)
Leisure-time physical activity (Kcal/d)	235*	(0–1382)
Home physical activity (Kcal/d)	179*	(0–1755)
Energy expenditure in physical activity (MET-min/d)	492*	(0–2028)
Family history of early-onset CVD, *n* (%)	133 (29.8)	
Smoking, *n* (%)	72 (16.1)	
Diabetes, *n* (%)	250 (55.9)	
Antidiabetic medication, *n* (%)	180 (72.0)	
Hyperlipidemia, *n* (%)	322 (72.0)	
Lipid-lowering agents, *n* (%)	218 (67.7)	
Hypertension, *n* (%)	336 (75.2)	
Antihypertensive medication, *n* (%)	296 (88.1)	
APOE 4 genotype, *n* (%)†	79 (17.8)	
Serum C-reactive protein (mg/l)	0.48	(0.01–9.95)
Total polyphenol excretion (mg GAE/g Cr)‡	136	(31–773)

*Median. †Sum of E4/3 and E4/4 genotypes (E2/4 excluded). ‡GAE/g Cr, gallic acid equivalents (GAE)/g of creatinine. Abbreviations: MET-min, minutes at a given metabolic equivalent level (units of energy expenditure in physical activity, 1 MET-min roughly equivalent to 1 Kcal); CVD, cardiovascular disease; APOE, apolipoprotein E.

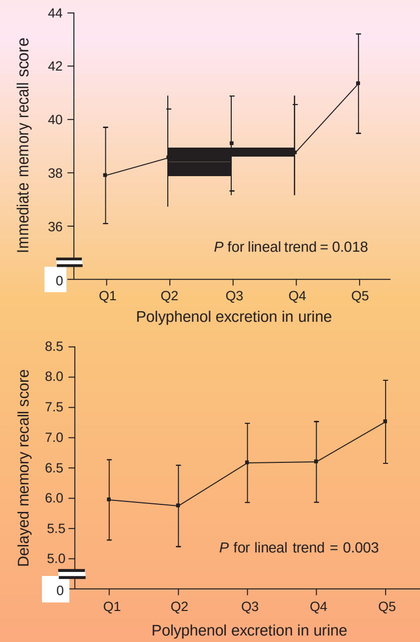


Fig. 2. RAVLT scores across quintiles of urinary polyphenol excretion.

Table 2
Daily intake of energy and food groups of the study population ($n = 447$)

Variables	Mean or median	Range
Total energy (Kcal/d)	2362	(1066–3898)
Cereals/grains (g/d)	252	(0–704)
Vegetables (g/d)	406	(0–1480)
Legumes (g/d)	19	(0–103)
Fruits (g/d)	470	(0–1190)
Total nuts (g/d)	5.13	(0–60)
Walnuts (g/d)	1.10	(0–30)
Meat and meat products (g/d)	89	(2–229)
Fish and seafood (g/d)	114	(7–427)
Dairy products (g/d)	359	(0–1367)
Total olive oil (ml/d)	38	(0–75)
Virgin olive oil (ml/d)	4*	(0–70)
Total alcohol (g/d)	4*	(0–92)
Wine (ml/d)	21*	(0–702)
Coffee (ml/d)	21*	(0–350)

*Median.

***Total olive oil related to immediate verbal memory**

***Virgin Oil and Coffee linked to delayed verbal memory**

- **Walnuts associated with better working memory**
- **Wine linked with MMSE**

Urinary Polyphenols associated with better scores in

- **Immediate verbal memory**
- **Conclusion: Polyphenol-riched food is closely related to**
- **Better cognitive performance among high CV risk elderly**

Recent Prospective studies of MD-diet in Cognition

Epidemiology • Volume 24, Number 4, July 2013 *Mediterranean Diet and Cognitive Function*

TABLE. Recent Prospective Studies of Mediterranean Diet and Cognitive Function

First Author (Year)	Study Name	Country	Cohort Size	% Women	Follow-up (Years)	Outcome	Effect Estimate (95% CI)[a]	*P* Trend
Samieri (2013)[16]	Women's Health Study	USA	6,174	100	3–10	mean global cognition	0.02 (−0.02 to 0.08)[b]	0.63
						mean verbal memory	0.03 (−0.02 to 0.07)[b]	0.44
						Global cognition change		0.26
						Verbal memory change		0.40
Samieri (2013)[17]	nurses' Health Study	USA	16,058	100	11–15	mean tICS	0.06 (0.01 to 0.11)[b]	0.004
						mean global cognitive status	0.05 (0.01 to 0.08)[b]	0.002
						mean verbal memory	0.06 (0.03 to 0.10)[b]	<0.001
			14,560			tICS change	0.004 (−0.011 to 0.019)[b]	0.31
			14,337			Global cognitive status change	−0.001 (−0.010 to 0.007)[b]	0.84
			14,341			Verbal memory change	−0.001 (−0.011 to 0.010)[b]	0.70
Kesse-Guyot (2013)[18]	SU.VI.maX Study	France	3,083	46	11–15	Composite cognitive score[c]	−0.18 (−1.09 to 1.37)[d]	0.27
						Composite cognitive score[c]	−0.41 (−1.23 to 0.40)[e]	0.12

CI indicates confidence interval; tICS, telephone interview for cognitive status.
[a]From analyses accounting for most covariates.
[b]Highest vs. lowest quintile on mediterranean diet score.
[c]Based on six cognitive function tests.
[d]Lowest vs. highest tertile on mediterranean diet score.
[e]Lowest vs. highest tertile on mediterranean style dietary pattern score.

1. Samieri's study (**Women's Health Study): Md-diet components associated with better cognitive outcome**
2. **Samieeri,s Nurses Health study: Adherence to MD-diet associated with higher cognitive scores.**
3. **SUVImax Study: Lower adherence to MD-diet linked to poor cognitive function**

Cognitive benefits of Mediterranean Diet: promises and caveats

1. Epidemiological evidence suggests
   possible association among fish consumption,
   Mono-unsaturated fatty acid and
   polyunsaturated fatty acids (n=3 PUFA)

2. **Fruit and Vegetables** may protective against mild cognitive impairment and AD

3. **Red wine** may be associated with reduced risk of Incident dementia and AD. The role of alcohol remains controversial

4. **Walnuts e**merge as prominent role of MD-diet: the cliché " **You are going nuts**" will have to be revised.

5. **Higher Adherence to MD-diet has been shown to slow cognitive decline**

Deciphering epigenetics Code

Epigenetics extends beyond transcripton : **“above the genome**”

Heritable changes in gene expression patterns

Not encoded in primary DNA sequence

Creation of novel cellular **Phenotype *without* Genotype change**
(classic definition of Riggs Porter 1996)

Deciphering the Epigenetics Code:

Epigenetic control:

enduring effects on gene expression outlasting transient signal

Imprinting, memory consolidation

Long term changes in neuronal patterns and connectivity

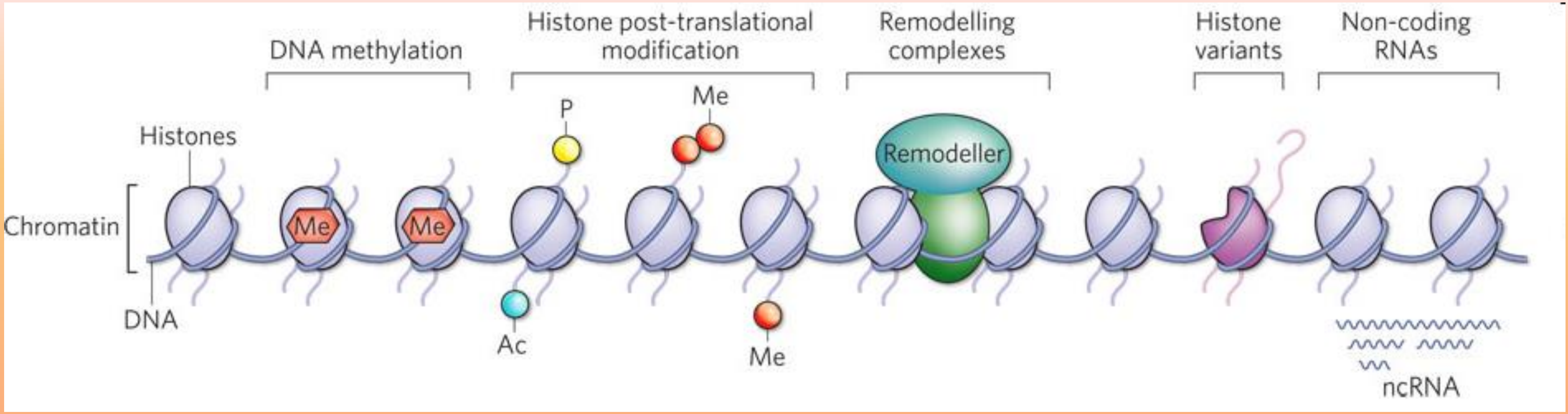
Perturbations in neuronal plasticity and microglia integrity—

Evidence accumulating for

Neurodegeneration disorders : dementia and Parkinson disease

Neuropsychiatric disorders : schizophrenia, Bipolar disorder

Epigenetics:
fine tuning of gene regulation, brain plasticity and neurogenesis



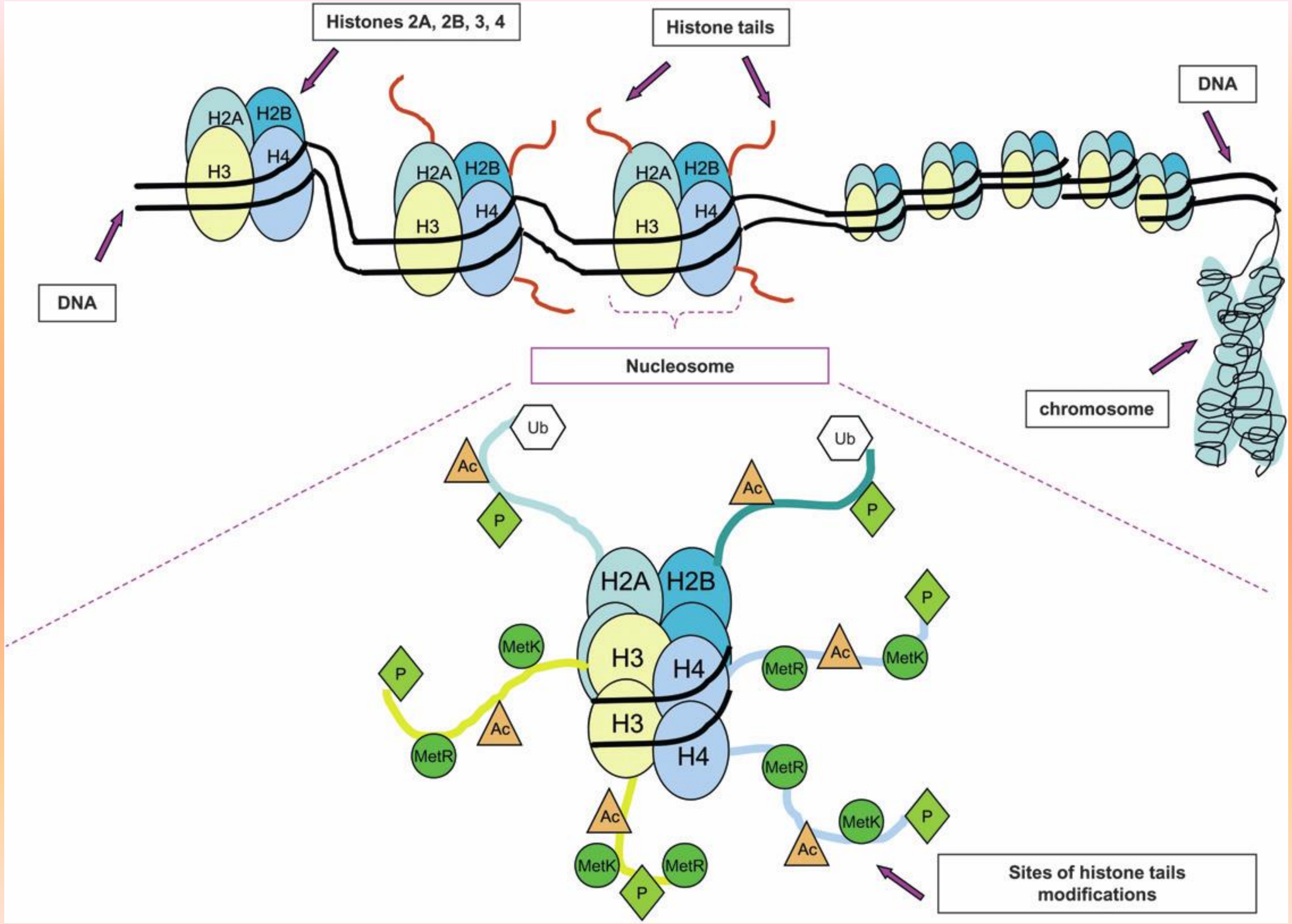
Key elements of epigenetics
•DNA methylation
*Chromatin methylation
*non-coding RNS

Contribute towards "**on" "Off" processes**
Regulation of Histone modifications
Scaffold for Protein interactions
Orchestrating multiple signal pathways for differentiation, survival and pivotal role in
Active across life span
From prenatal to postnatal to aging

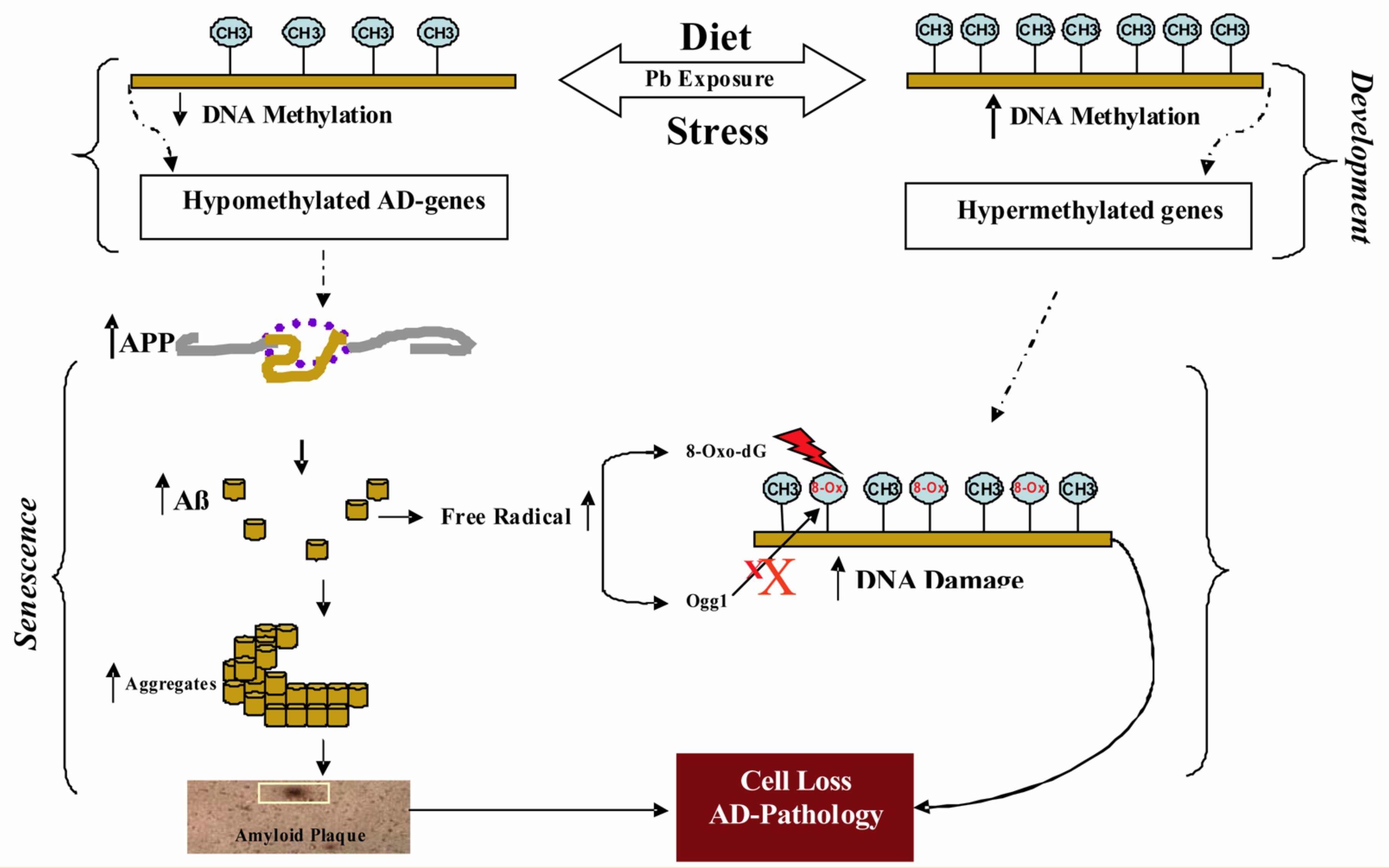
Modified from Dulac C Nature 465:78-735 , 2010, Heieh J, fisch A Neurol dis 39:73-84 2010

Role of Nucleosome in regulating Histone and DNAmethylation

Choi et al Int Biomed Research Journal

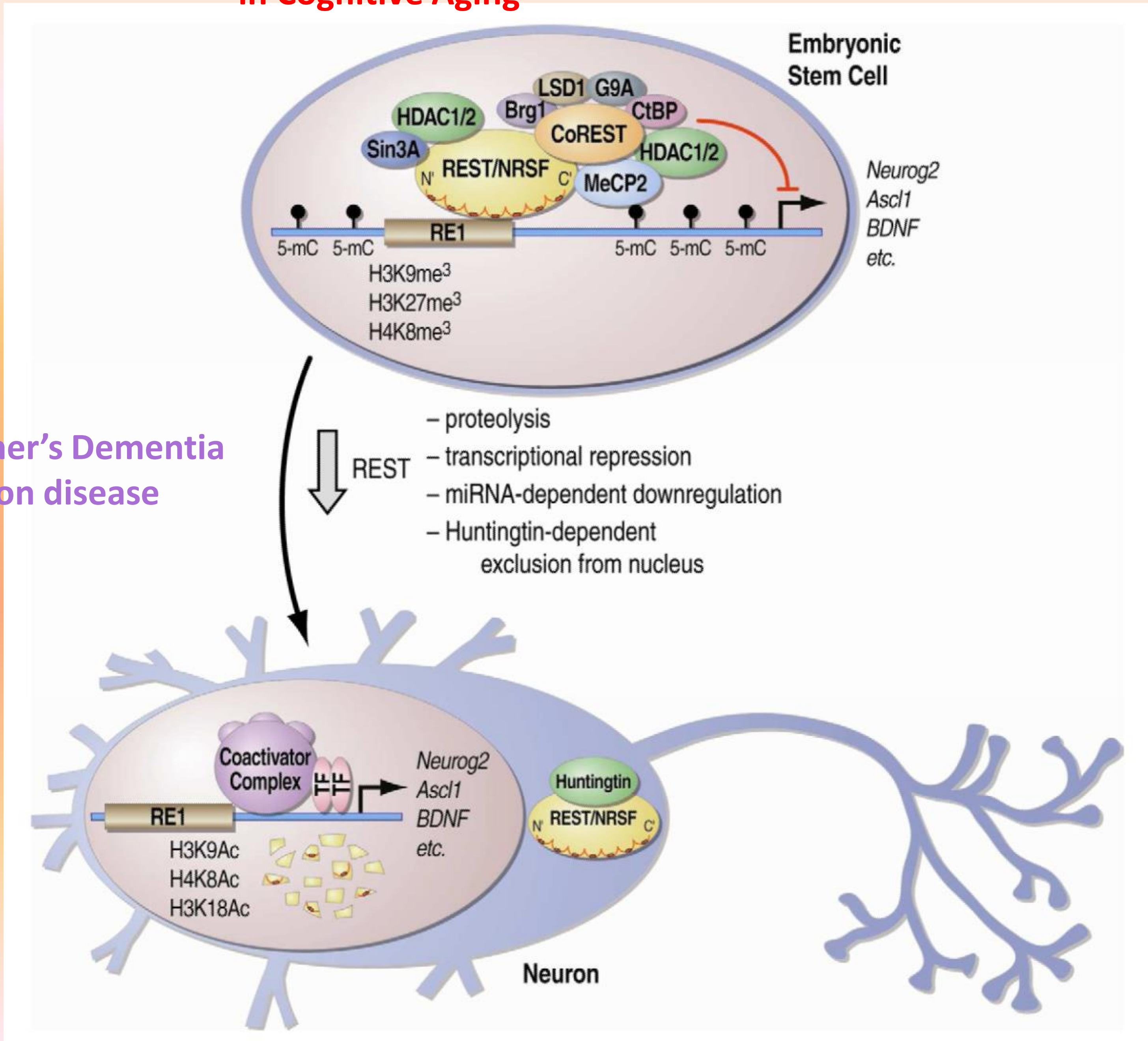


Model of Dietary stress impact on AD Genes

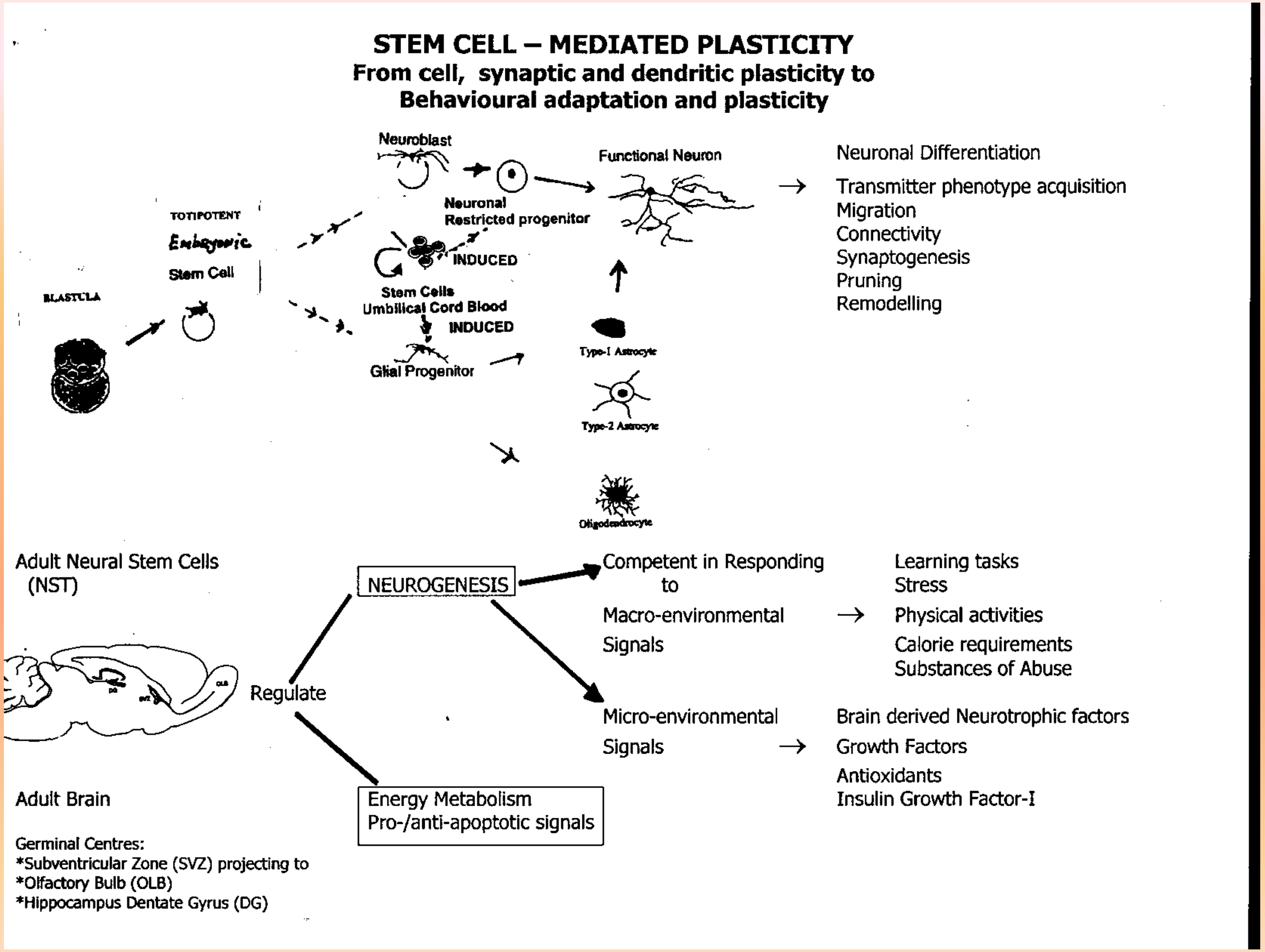


Multi-layered Control and Regulation of Transcription-Epigenetics Complex in Cognitive Aging

Alzheimer's Dementia
Parkinson disease

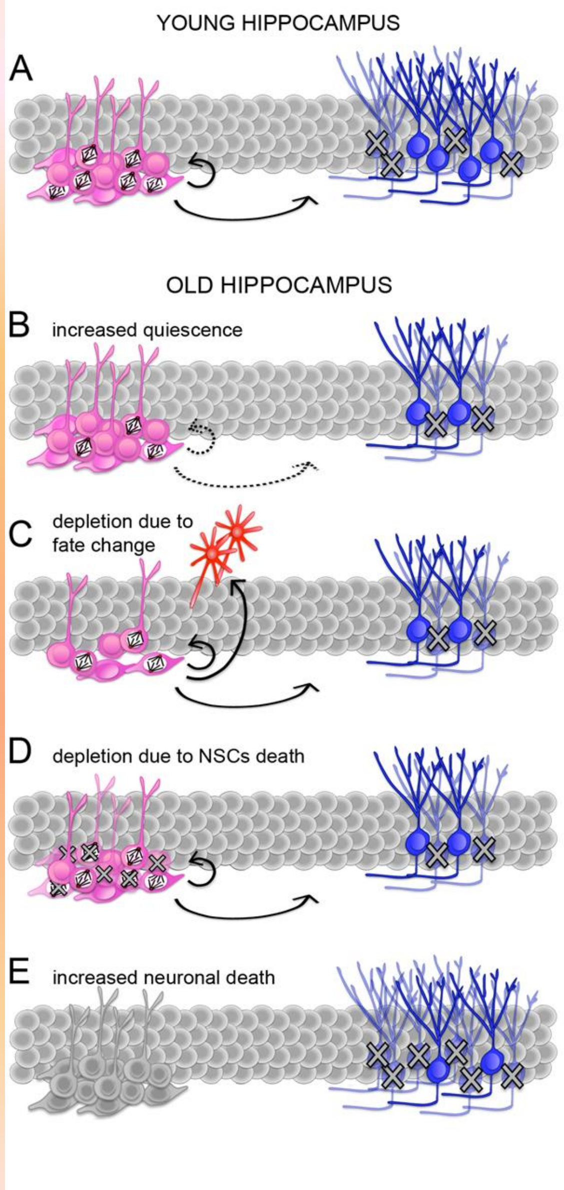


Neural stem cell (NST): master conductor of neurogenesis and synaptic plasticity

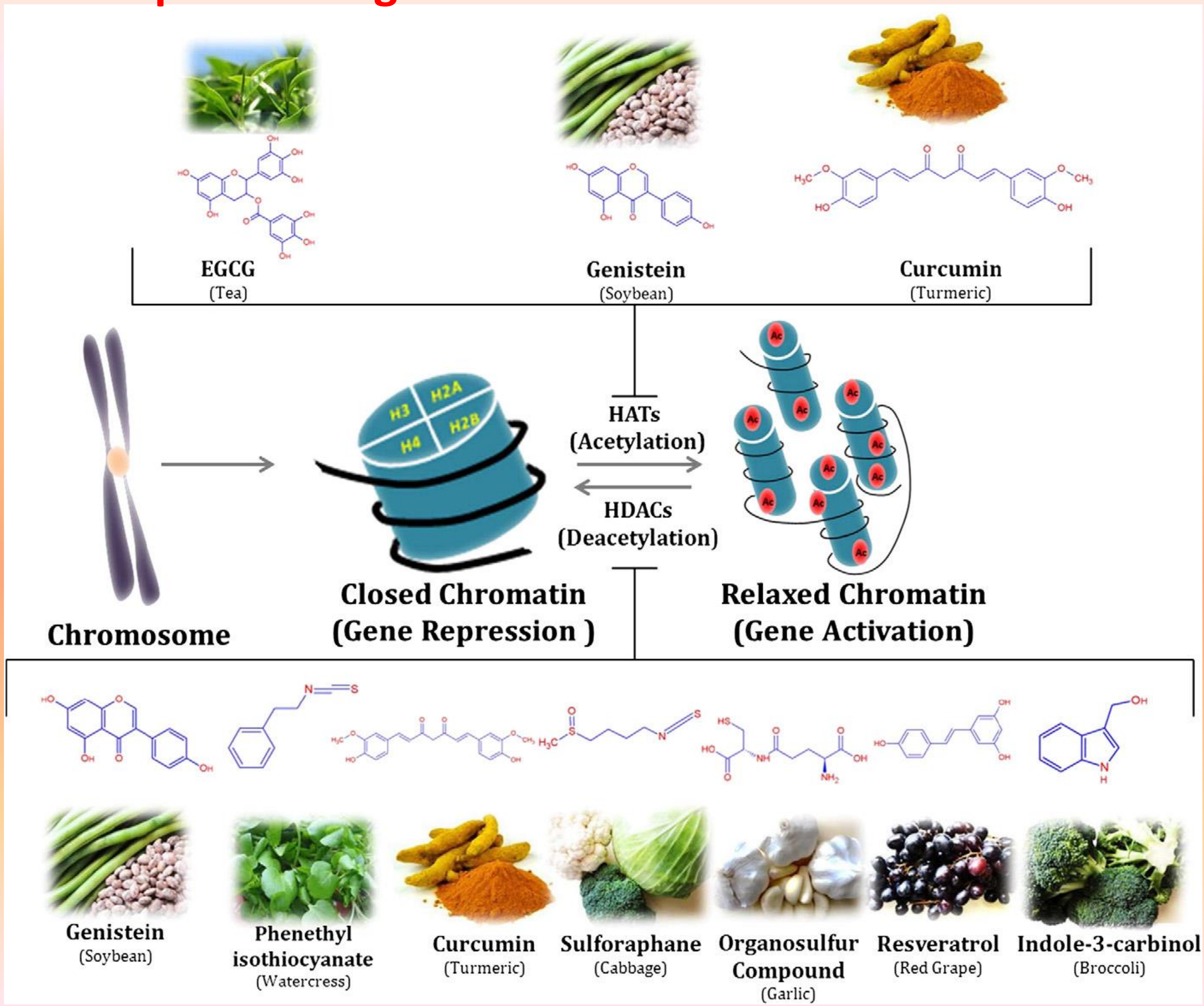


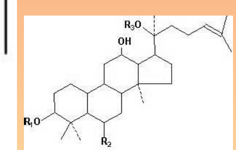
Chiu S, Goble L. et al Internet J psychiatry 2012.

Neurogenesis and Aging ; effect on Hippocampus



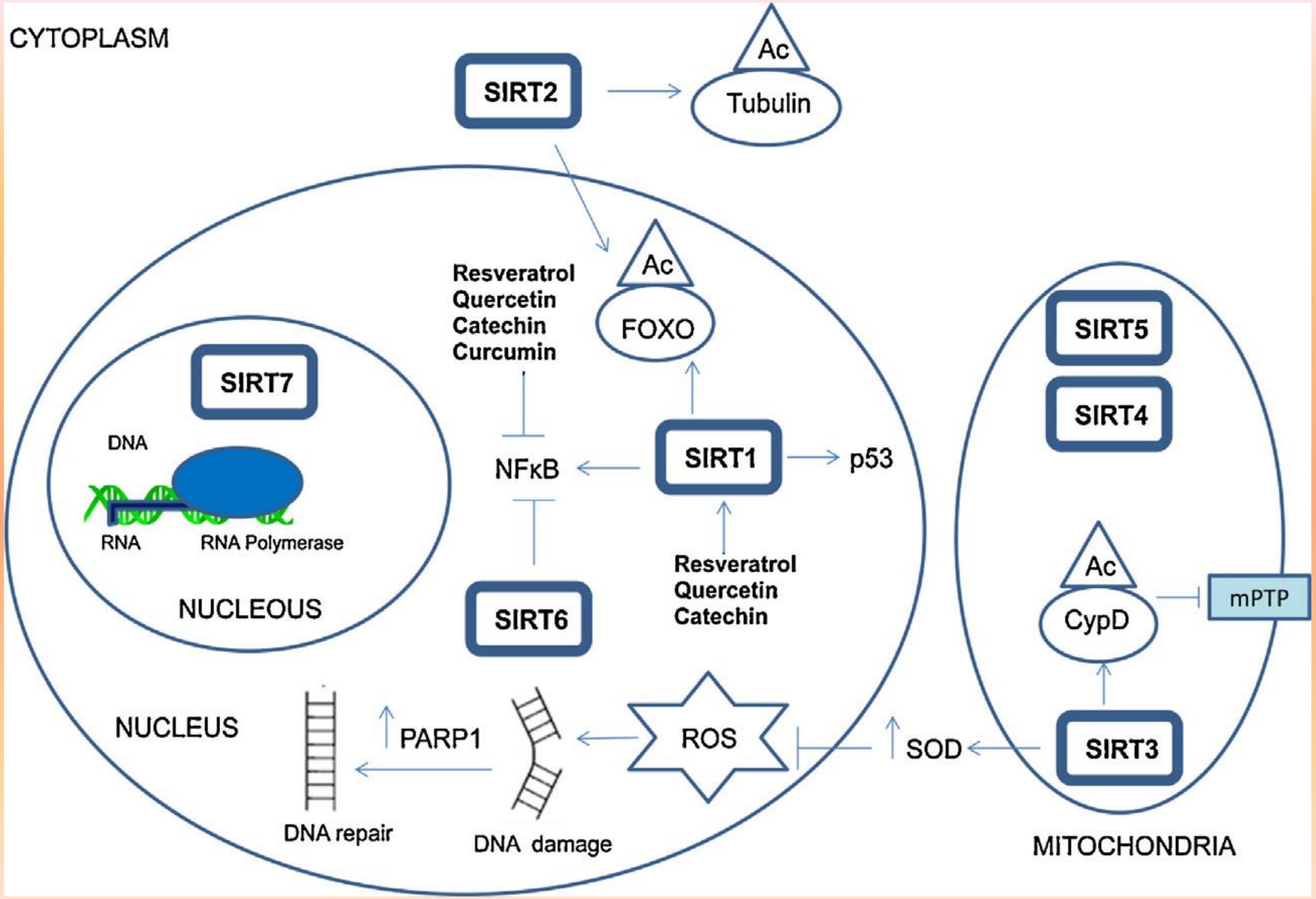
Latest NEWCOMER : EPIGENOMICS- DIET to Optimize Cognitive AGING and to Prevent AD?



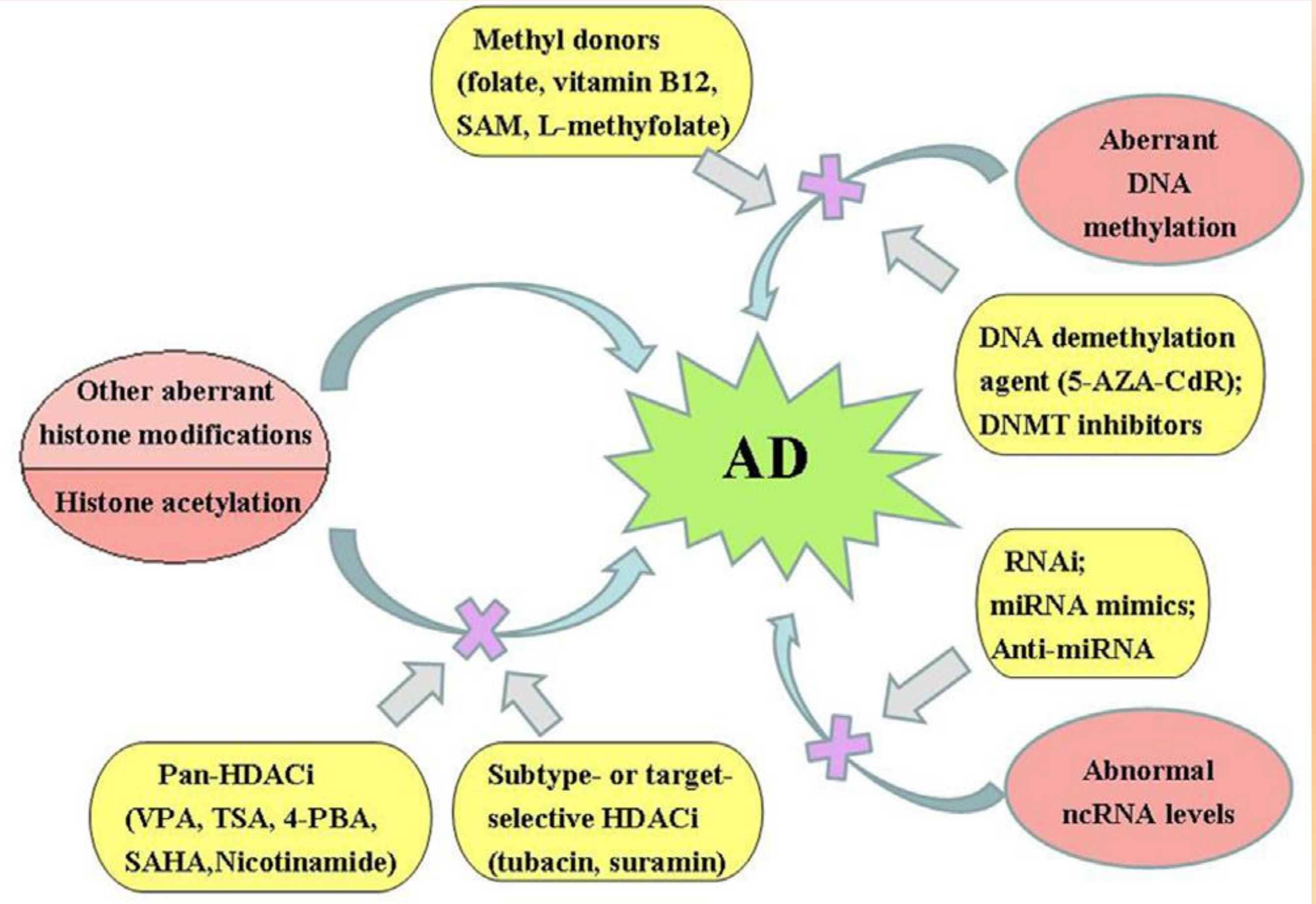


Panax Ginseng

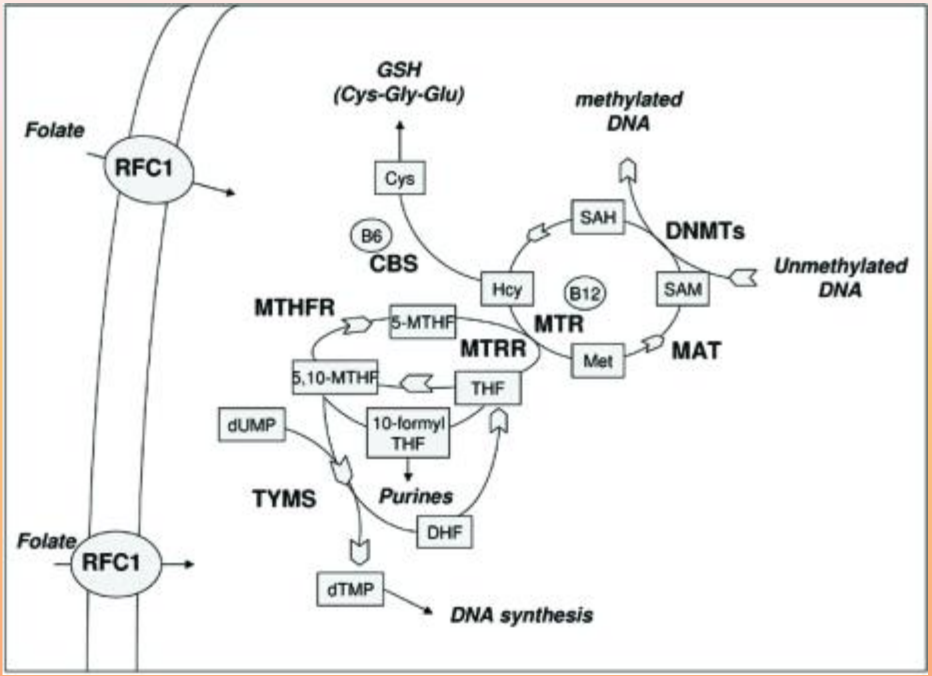
Sirtunins: NAD-family of HDAC inhibitor targeting aging brain



Epigenetics targets in Cognition



One-carbon Metabolism: folate, SAM and Tetrahydrolate



Methyl-folate

efficacy in Depression

Studies in AD at risk not found

Metabolites: Cys = cysteine; dTMP = deoxythymidine monophosphate; dUMP = deoxyuridine monophosphate; DHF = dihydrofolate; 10- formyl-THF = 10- formyl-tetrahydrofolate; GSH = glutathione; Hcy = homocysteine; Met = methionine; 5-MTHF = 5- methyltetrahydrofolate; 5,10-MTHF = 5,10-methylentetrahydrofolate; SAH = S-adenosylhomocysteine; SAM = S-adenosylmethionine; THF = tetrahydrofolate

Enzymes: CBS = cystathionine β-synthase; DNMTs = DNA methyltransferases; MAT = methionine adenosyltransferase; MTHFR = methylenetetrahydrofolate reductase; MTR = methionine synthase; MTRR = methionine synthase reductase; RFC1 = reduced folate carrier.

Cofactors: B6 = vitamin B6; B12 = vitamin B12.

Panax Ginseng
Elixor of Life from Botanicals to Rx Targets

First described by CA Meyer .Grown in China ,Korea, Japan, ,USA
Processed Ginseng root :**Red Ginseng , White Ginseng**
Composition of Ginsenosides vary: harvest times and age.
Formulated Ginseng products differ in bioequivalence
Common Ginseng Family members:

1. Panax ginseng (Asian ginseng)
2. American ginseng (Panax quinquefolium) :Wisconsin, Ontario
3. Tien Chan Ginseng (Panax noto-ginseng) China
4. Japanese Ginseng (Panax jaonices)

CNS Biosynthesis of Neuro-steroids(NS) From Cholesterol Precursor

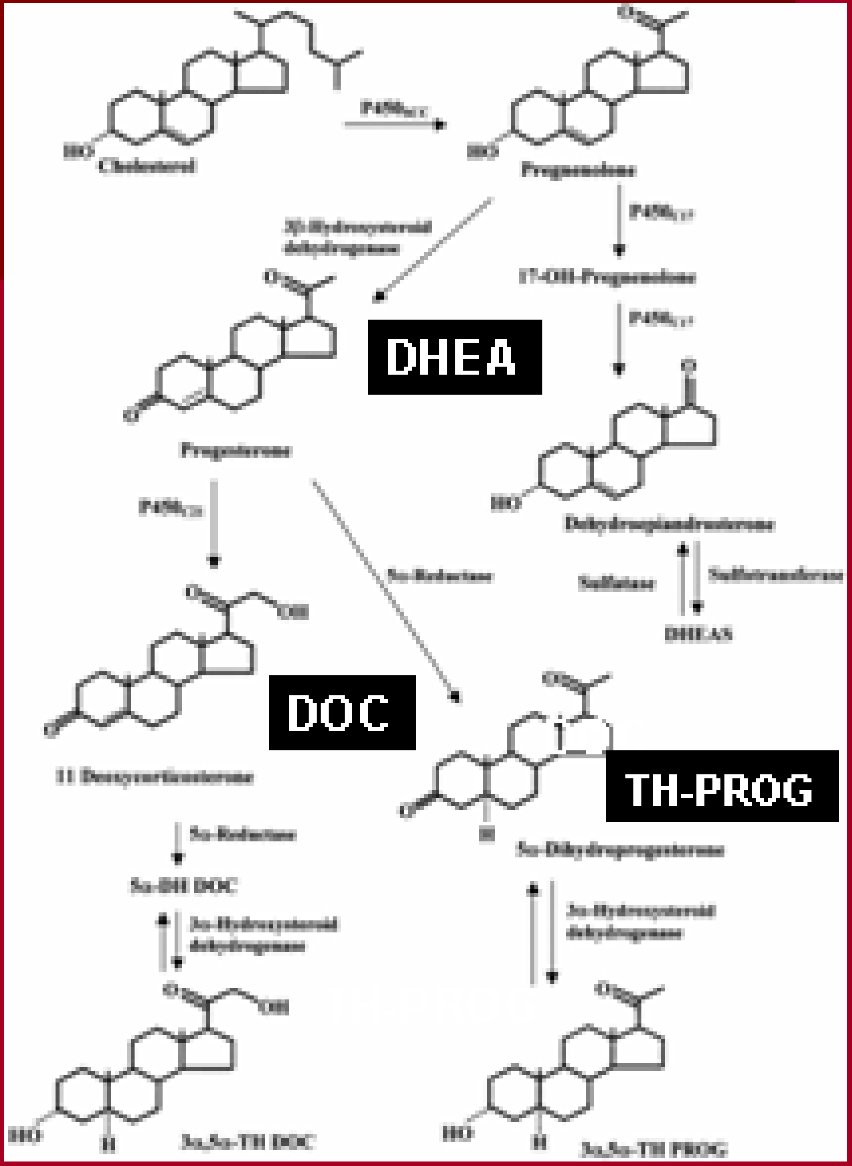
Key function in Modulating Neuronal Excitability

↓

NS implicated in Stress, depression Psychotic disorder and Dementia

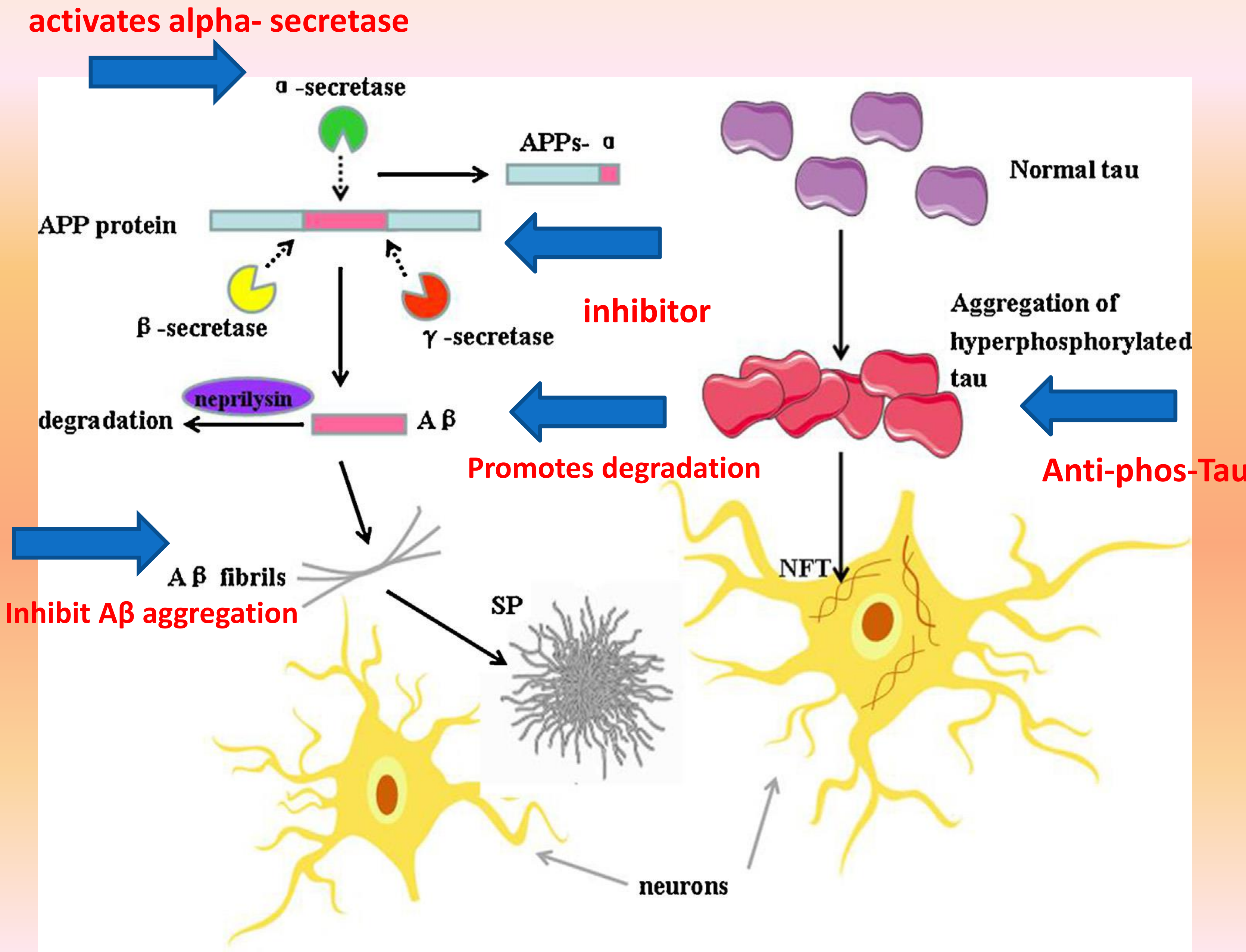
↓

DOC
3alpha5alphaDHEA
3alpha5alphaTH-Prog



Adapted from Pisu & Serra (2004) Life science 74:3181-97

Multi-targets of Ginseng towards Amyloid-Tau cascade



RCT trial of standardized Ginseng Extract in AD

Lee ST et al (Alzheimer Dis Assoc Disord 2008;22:222–226)

TABLE 1. Baseline Characteristics

Characteristics	Control Group (n = 39)	Ginseng Group (n = 58)	P
Male sex, n (%)	13 (33.3)	20 (34.5)	0.978
Mean age, y	65.6 ± 8.7	66.6 ± 9.6	0.544
Baseline ADAS-cog	20.8 ± 8.5	21.9 ± 9.3	0.449
Baseline ADAS-noncog	6.8 ± 4.6	6.4 ± 4.5	0.697
Baseline MMSE	22.0 ± 3.9	21.5 ± 3.8	0.435
CDR			
1, no. (%)	33 (84.6)	49 (84.5)	0.971
2, no. (%)	6 (15.4)	9 (15.5)	0.971

Statistical significances of differences between groups (P values) were determined by Student t test (continuous values) or by using w^2 test (CDR).

ADAS-cog indicates cognitive subscale of Alzheimer disease assessment scale; ADAS-noncog, noncognitive subscale of Alzheimer disease assessment scale; CDR, clinical dementia rating scale; MMSE, mini-mental state examination; SD, standard deviation.

- **Panax Ginseng at 12 weeks improved cognition in AD**
- **Post-ginseng treatment:**
- **MMSE and ADAS cog score significantly reduced as compared with Placebo**
- **No biomarker of responses reported**
- **At 24 wks earlier Cognitive effects reversed**
- **Panax Ginseng Highly tolerated**

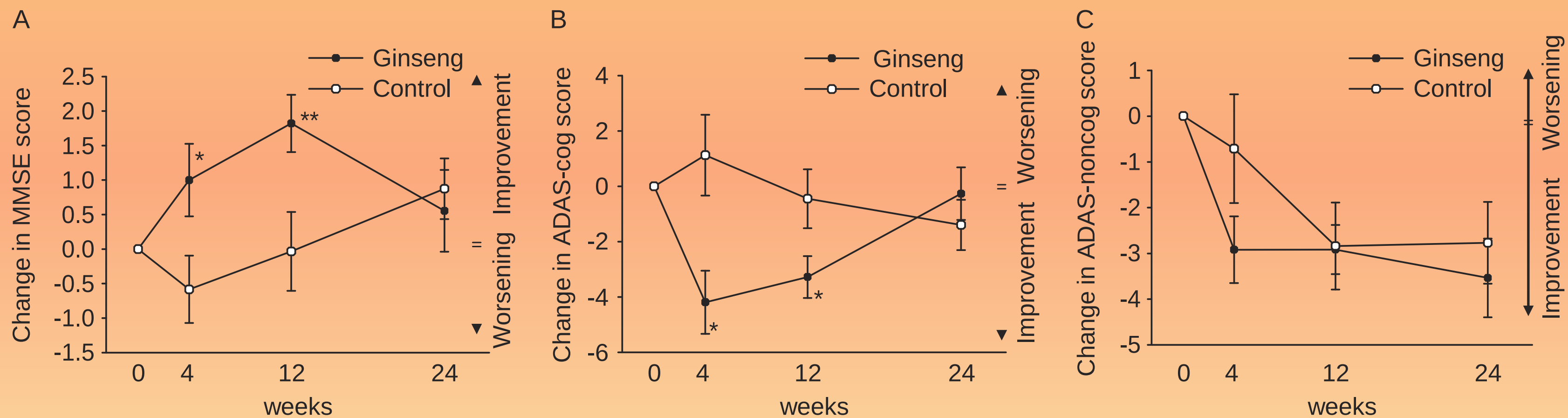
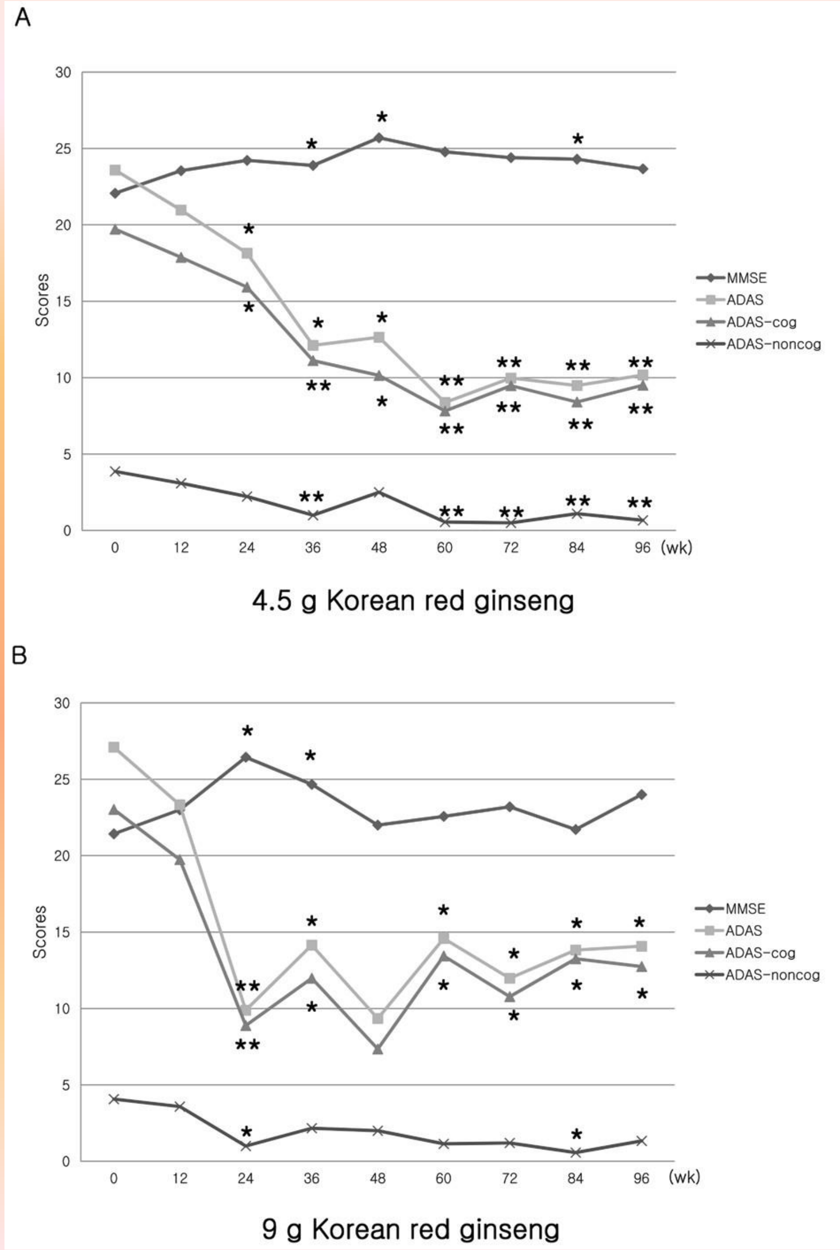


FIGURE. 1. Changes in outcome variables. During 12 weeks of the ginseng treatment, ginseng improved MMSE (A) and ADAS-cog (B) compared with the control group, but did not significantly affect ADAS-noncog scores (C). At 24 weeks (12 wk after withdrawing ginseng), these improved scores returned to the control level. *P < 0.05, **P < 0.01 versus the control group. ADAS-cog indicates cognitive subscale of Alzheimer disease assessment scale; ADAS-noncog, noncognitive subscale of Alzheimer disease assessment scale; MMSE, mini mental state examination.

Korean Red Ginseng Extract in AD : 2-yr study



RCT trial of Standardized Ginseng extract :Ginsana-115 in Schizophrenia
Response Rate on Sub-syndromal Depression

Chiu et al study (2012) funded by Stanley Medical Research Institute

Can Panax Ginseng be efficacious in Prodromal AD Phase

Depressive Symptom Response	**Response rate >= 30% reduction in HAM-D score**	**Pearson Chi-square** (Phi Coefficient)	Significance level	**NNT** (Number Needed to Treat)
Ginseng 200 mg	**70.0 %**	5.74 (0.52)	P < 0.01 df =1	**1.9**
Placebo Control	**18.2 %**			

Number to Treat calculated from reciprocal of the difference of non-response rate of treatment group and control group is derived from evidence based.The smaller the number, the more robust the effect size.

Turmeric root of Curcuma Longata from curry pot to Brain food??

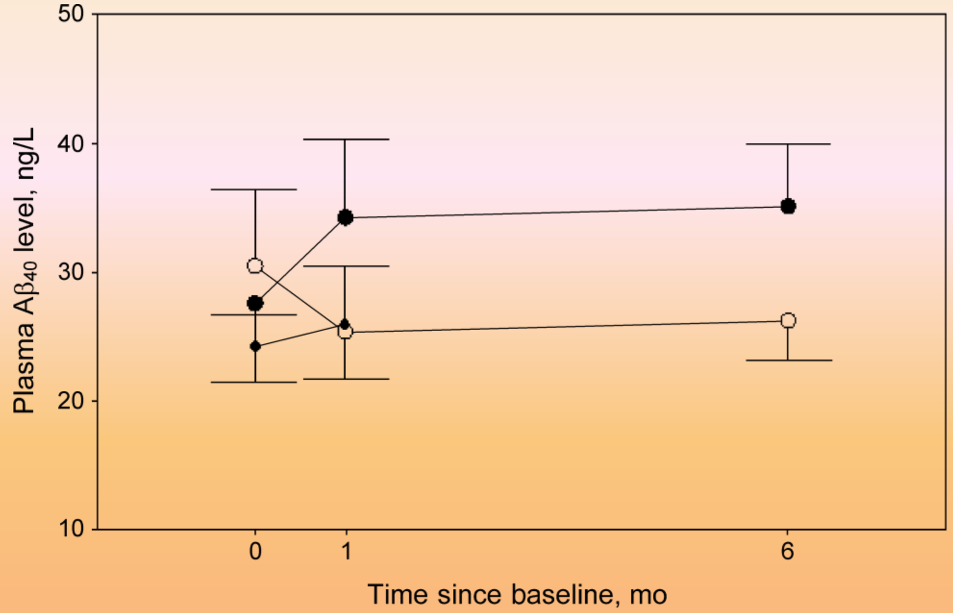


FIGURE 1. Mean T SE plasma A''$_{40}$ levels in dose groups among subjects completing the 6-month study: placebo (open circles), 1 g/d curcumin (small closed circles), and 4 g/d curcumin (large closed circles).

RCT trial of Curcumin extract in AD subjects

Summary of Curcumin in Alzheimer disease

Table 1: Clinical studies of curcumin use in Alzheimer's disease.

Study ID	Study design	Sample size	Follow-up period	Curcumin dose	Other medication	Main findings	Adverse events	Current status
Completed studies								
Baum et al. 2008 [28]	Randomized, double-blind, placebo controlled	36	6 months	1 g/day or 4 g/day	Gingko biloba standardized leaf extract 120 mg/day, other medication not reported	No differences between curcumin and placebo	No differences between placebo and both curcumin dose groups	Completed and published
Ringman et al. 2012 [29]	Randomized, double-blind, placebo controlled	36	24 weeks + 48 weeks open-label	2 g/day or 4 g/day	Acetylcholinesterase inhibitors and memantine allowed	No differences between curcumin and placebo	No differences between placebo and curcumin	Completed and published
Hishikawa et al. 2012 [30]	Case study, open-label	3	1 year	100 mg/day	Donepezil (dose not reported)	Increase in the NPI-Q score	Not reported	Completed and published
Ongoing trials								
NCT00595582	Open-label	10	24 months	5.4 g/day	Bioperidine	All patients did not terminate the study	Dyspepsia (20% of the sample)	Completed
NCT01001637	Randomized, double-blind, placebo controlled	26	2 months	4 g/day or 6 g/day	Allowed stable doses of concomitant medications	—	—	Still recruiting
NCT01383161	Randomized, double-blind, placebo controlled	132	18 months	180 mg/day	Permitted only aspirin (81 mg/die)	—	—	Still recruiting
NCT01811381	Randomized, double-blind, placebo controlled	80	12 months	800 mg/day	Not allowed treatment for cognitive impairment (i.e. cholinesterase inhibitor, memantine) < 6 months prior to study enrollment	—	—	Recruiting will start in September 2013
ACTRN12613000681752	Randomized, double-blind, placebo controlled	200	12 months	500 mg/day for 2 weeks, then 1,000 mg/day for other 2 weeks and then 1500 mg/day onwards	Not allowed warfarin	—	—	Not yet recruiting

Legend. Neuropsychiatric Inventory Questionnaire: NPI-Q.

Curcumin on beta-amyloid level in healthy subjects related to reduced oxidative stress

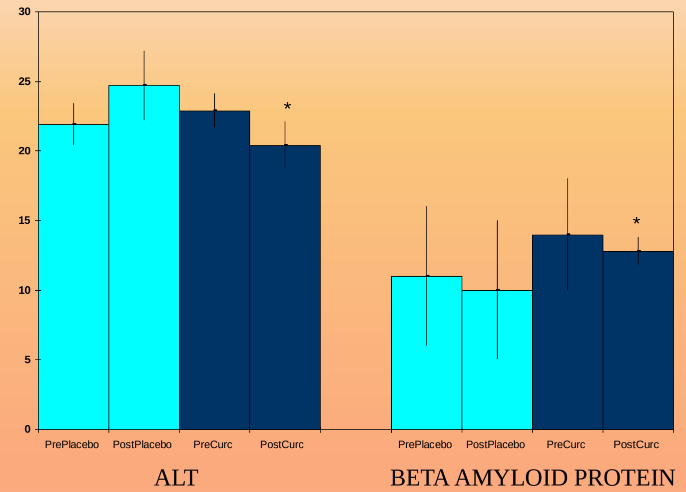
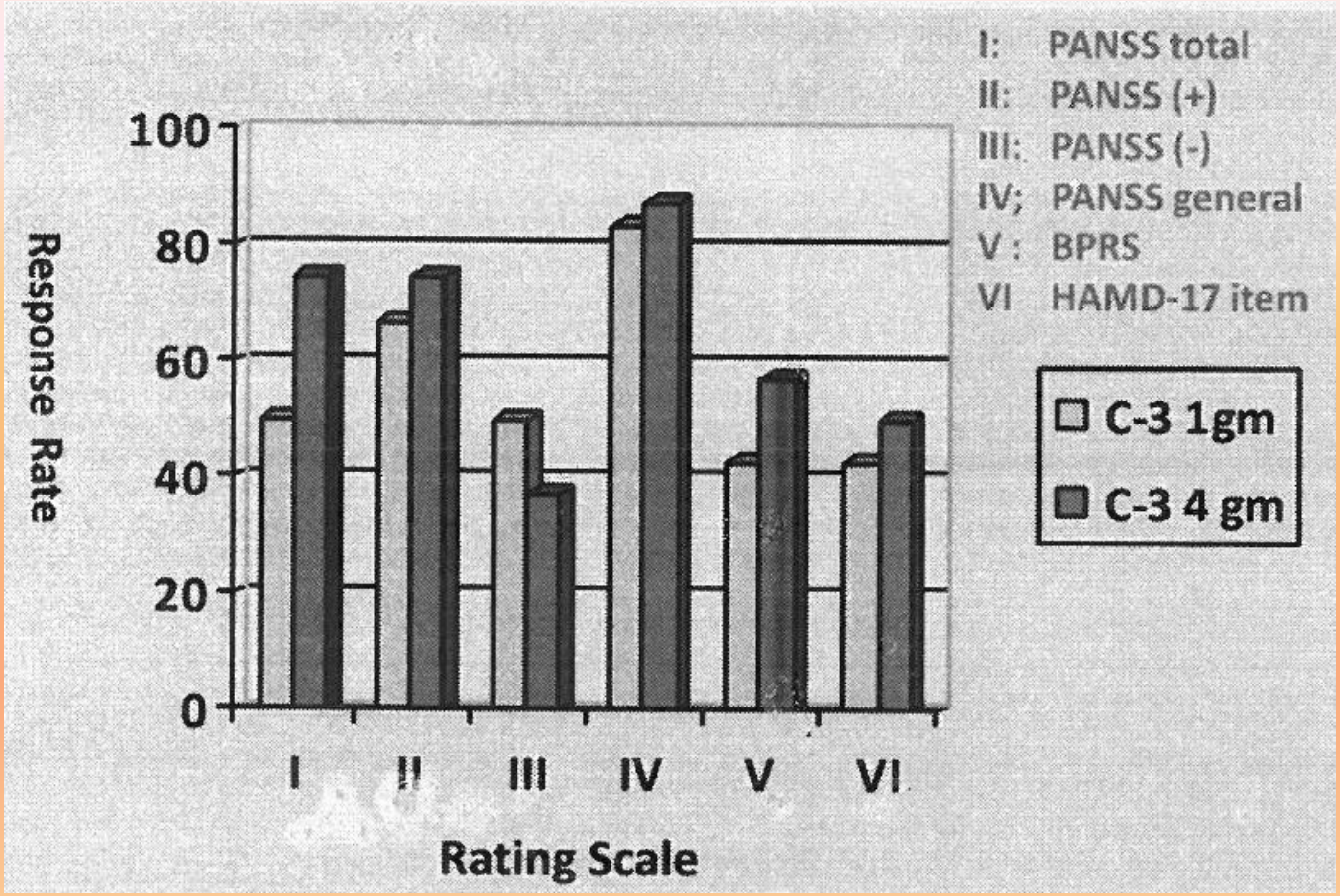


Figure 6 Curcumin effects on plasma activities of alanine aminotransferase (ALT) (U/L) and beta amyloid protein (pmole means ± SEM for N = 19 pre- and post-treatment of 4 weeks. *Significantly different from pre-value, paired t-test, $p < 0.05$.

DiSilvestro et al. Nutrition Journal 2012, 11:79

Open label study of Curcumin C-3 Complex in schizophrenia

Chiu, Woodbury, Cernovsky, Yves, Husni, Copen (2013)

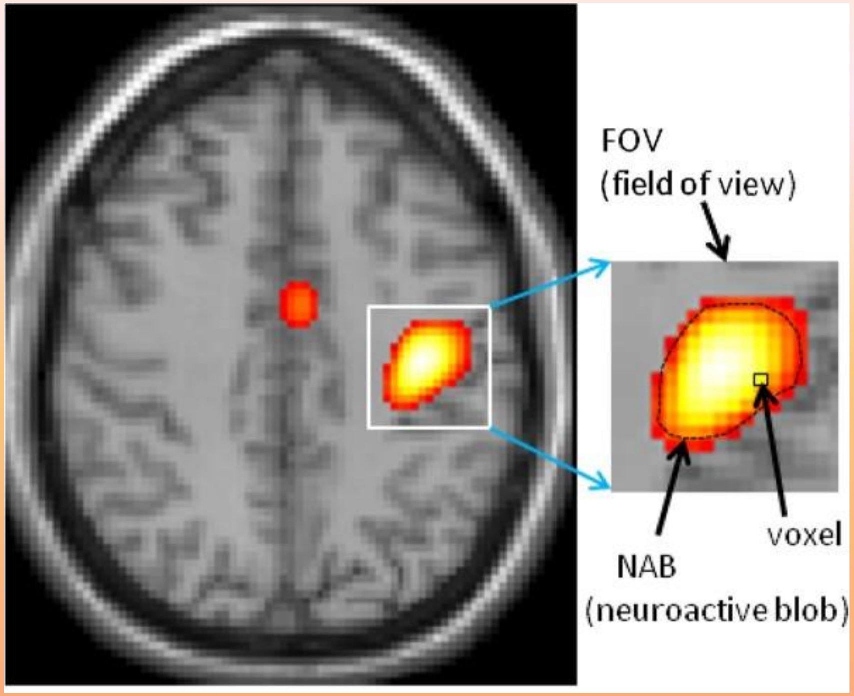


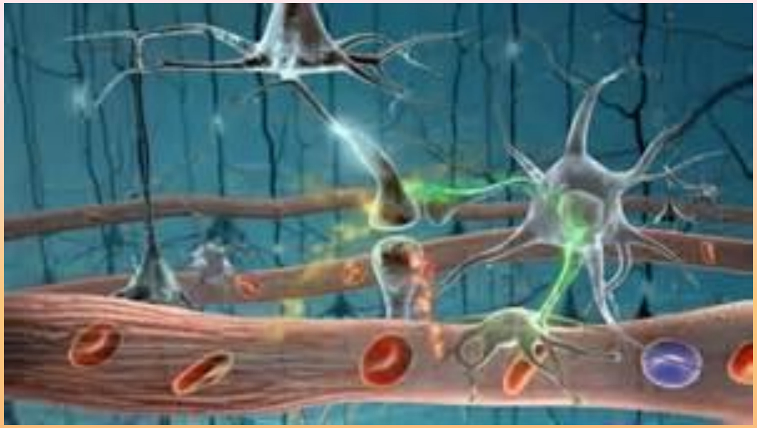
Spinoff from the study:

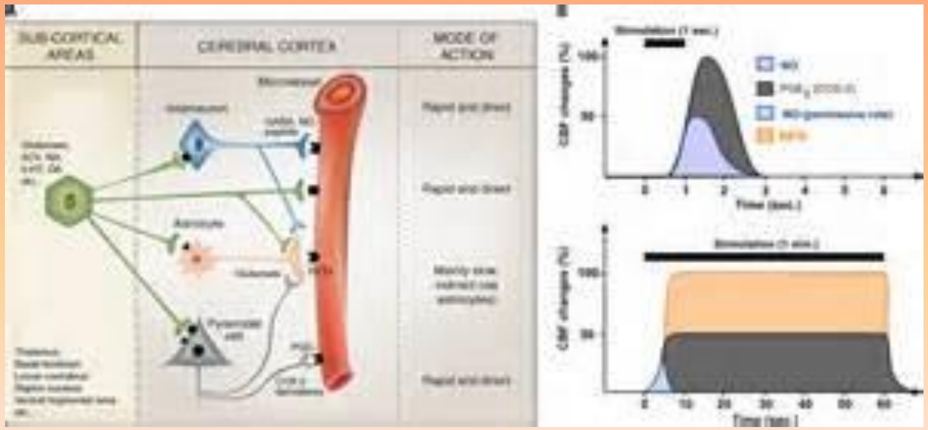
Can Liposome Curcumin C-3 Complex may reduce neuropsychiatric symptoms in AD ??

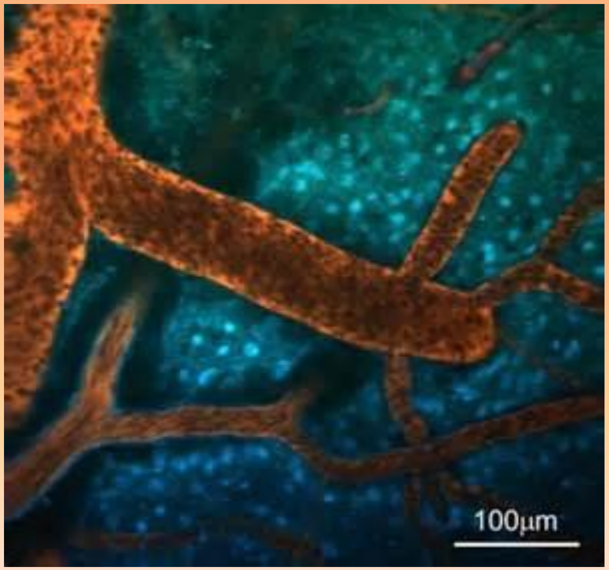
Curcumin C-3 Complex: Patented product Sabinsa Corp NJ USA

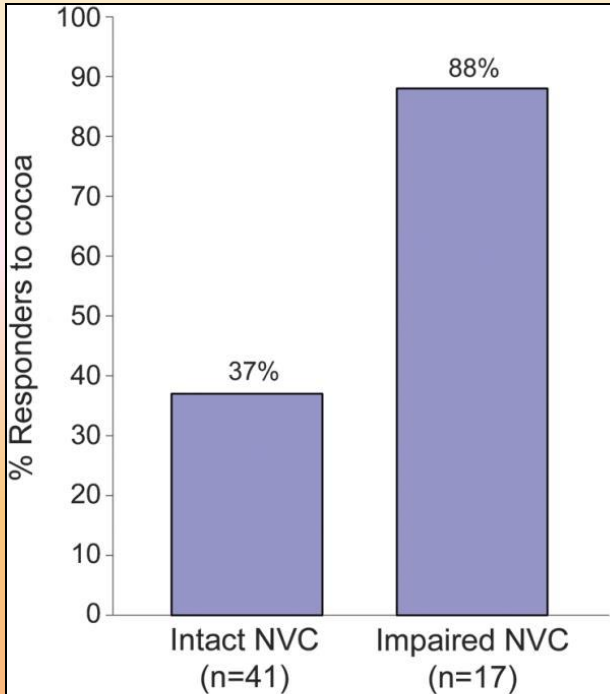
Neurovascular Coupling:
fNMR BOLD signal and 2-photon microscopy







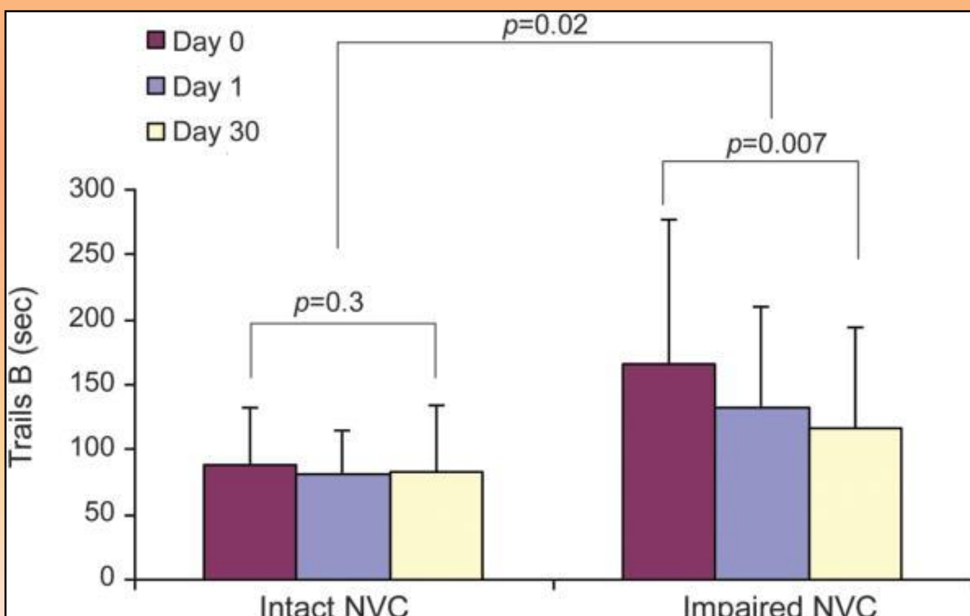




Neurovascular coupling, cerebral white matter integrity, and response to cocoa in older people.

Sorond, Farzaneh; MD, PhD; Hurwitz, Shelley; Salat, David; Greve, Douglas; Fisher, Naomi **Neurology. 81(10):904-909, September 3, 2013.**

Response to cocoa according to baseline neurovascular coupling statusFigure 1. Response to cocoa was defined as an increase in neurovascular coupling (NVC) relative to baseline, and calculated as follows: NVC at 4 weeks - NVC at baseline.



Effect of cocoa consumption on Trails B scores according to baseline neurovascular coupling statusFigure 2. Trails B scores at baseline and after 24 hours and 30 days of cocoa consumption are shown for those with intact and impaired neurovascular coupling (NVC) at baseline.

COCOA effects on Brain Health

Neurovascular coupling, cerebral white matter integrity, and response to cocoa in older people.
Sorond, Farzaneh; MD, PhD; Hurwitz, Shelley; Salat, David; Greve, Douglas; Fisher, Naomi

Neurology. 81(10):904-909, September 3, 2013.
DOI: 10.1212/WNL.0b013e3182a351aa

Table 2
Neurovascular coupling and white matter structure[a]

Table 2 Neurovascular coupling and white matter structure[a]

Structure	NVC+ (n = 17)	NVC− (n = 7)	p	Overall mean	Overall r	p
WM	384,663 (60,920)	358,407 (36,672)	0.45	377,005 (55,508)	0.23	0.28
WM/ICC	412,291 (37,737)	393,091 (25,875)	0.31	406,691 (35,281)	0.27	0.20
WMH	10,866 (4,652)	12,310 (6,420)	0.70	11,437 (5,040)	−0.00	0.99
FA WM	0.363 (0.024)	0.353 (0.017)	0.35	0.36 (0.02)	0.39	0.07
FA WMH	0.320 (0.023)	0.288 (0.029)	0.02	0.31 (0.03)	0.54	0.01
MD WM	0.833 (0.035)	0.854 (0.023)	0.10	0.84 (0.03)	−0.40	0.06
MD WMH	1.206 (0.087)	1.264 (0.042)	0.07	1.22 (0.08)	−0.36	0.09

Abbreviations: FA = fractional anisotropy; ICC = intracranial cavity; MD = mean diffusivity; NVC = neurovascular coupling; WM = white matter; WMH = white matter hyperintensities.
[a] Values are mean (SD).

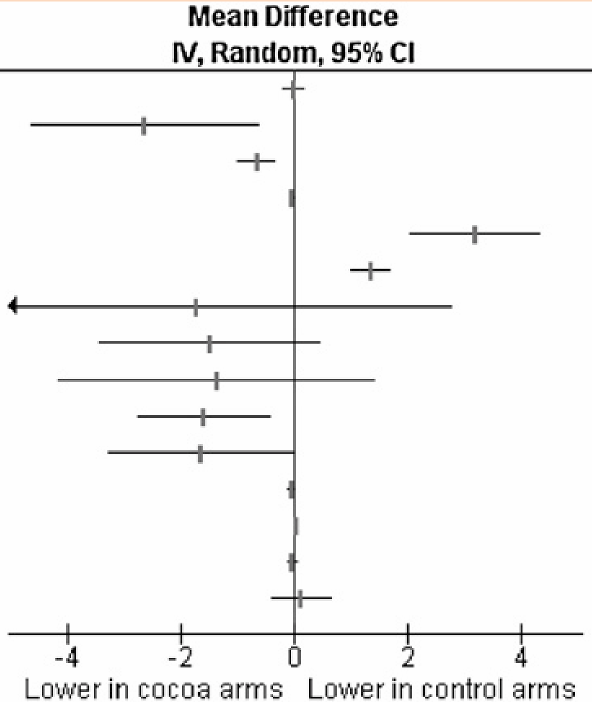
Table 3 Responses to 1 day and 1 month of cocoa consumption[a]

	Flavanol-rich cocoa			Flavanol-poor cocoa		
	Day 0 (n = 31)	Day 1 (n = 31)	Day 30 (n = 29)	Day 0 (n = 29)	Day 1 (n = 29)	Day 30 (n = 29)
Clinical measures						
SBP, mm Hg	124 (13)	122 (13)	128 (17)	127 (16)	123 (17)	125 (17)
DBP, mm Hg	69 (9)	66 (10)	69 (10)	68 (11)	65 (11)	67 (12)
Cognitive measures						
MMSE	27.8 (1.9)	28.1 (2.2)	27.5 (2.2)	28.0 (1.8)	28.1 (1.8)	28.4 (1.3)
Trails A, s	39 (17)	36 (17)	37 (24)	35 (11)	33 (9)	33 (11)
Trails B, s	108 (68)	96 (57)	90 (64)	118 (90)	96 (57)	96 (59)
Cerebrovascular hemodynamics						
BFV, cm/s	55 (11)	53 (13)	52 (10)	55 (12)	54 (10)	54 (11)
Cerebral VR, %ΔBFV/mm Hg CO_2	1.5 (0.6)	1.3 (0.6)	1.4 (0.5)	1.4 (0.5)	1.3 (0.5)	1.4 (0.5)
NVC, %Δ	7 (9)	10 (12)	8 (7)	11 (10)	12 (14)	12 (10)

Abbreviations: BFV = blood flow velocity; DBP = diastolic blood pressure; MMSE = Mini-Mental State Examination; NVC = neurovascular coupling; SBP = systolic blood pressure; VR = vasoreactivity.
[a] Values are mean (SD or percent).

Review of Cocoa effects on CV Biomarkers

Study or Subgroup	Mean Difference	SE	Cocoa Total	Control Total	Mean Difference IV, Random, 95% CI
serum glucose, mmol/L	-0.02	0.0995	231	228	-0.02 [-0.22, 0.18]
serum insulin, μU/mL	-2.65	1.0204	77	76	-2.65 [-4.65, -0.65]
HOMA-IR	-0.67	0.1582	91	90	-0.67 [-0.98, -0.36]
Triglycerides, mmol/L	-0.05	0.0204	515	431	-0.05 [-0.09, -0.01]
FMD, % at 2 hours	3.19	0.5842	187	186	3.19 [2.04, 4.34]
FMD, %, chronic	1.34	0.1735	193	189	1.34 [1.00, 1.68]
Syst BP, mmHg, 2 hr	-1.75	2.3061	106	106	-1.75 [-6.27, 2.77]
Syst BP, mmHg, chronic	-1.5	0.9847	489	461	-1.50 [-3.43, 0.43]
Diast BP, mmHg, 2hr	-1.38	1.4082	106	106	-1.38 [-4.14, 1.38]
Diast BP,mmHg, chronic	-1.6	0.5969	473	445	-1.60 [-2.77, -0.43]
MAP, mmHg, chronic	-1.64	0.8291	95	68	-1.64 [-3.27, -0.01]
LDL chol, mmol/L	-0.07	0.0332	535	451	-0.07 [-0.14, -0.00]
HDL chol, mmol/L	0.03	0.0153	535	451	0.03 [0.00, 0.06]
Total chol, mmol/L	-0.04	0.0357	535	451	-0.04 [-0.11, 0.03]
CRP, mg/L	0.12	0.2755	232	230	0.12 [-0.42, 0.66]



Chocolate effect on BMI

the latest anti-obesity medical food ?

Table. Chocolate Consumption Frequency Predicts Lower BMI: Regression Results[a]

	Chocolate Consumption Frequency, Association With BMI	
Adjustment Model	**13 (SE)**	***P* Value**
Unadjusted	−0.142 (0.053)	.008
Age and sex adjusted	−0.126 (0.053)	.02
Age, sex, and activity adjusted	−0.130 (0.052)	.01
Age, sex, activity, and calorie adjusted	−0.146 (0.059)	.01
Age, sex, activity, and satfat adjusted	−0.190 (0.059)	.001
Age, sex, activity, satfat, and CES-D adjusted	−0.191 (0.059)	.001
Age, sex, activity, satfat, fruit and vegetable, and CES-D adjusted	−0.201 (0.060)	.001
Age, sex, activity, satfat, fruit and vegetable, CES-D, and calories adjusted	−0.208 (0.060)	.001

Abbreviations: BMI, body mass index; CES-D, Center for Epidemiological Studies Depression scale; satfat, saturated fat.

[a]A model containing calories (and activity, as well as age and sex) was included, since calories and activity are usual predictors of BMI. However, calories were otherwise not in adjustment models because chocolate inherently contains calories and adjustment could justly be deemed inappropriate—overstating the benefits of chocolate to BMI. Closely similar results were obtained using an alternate activity measure. Significance was identical for all except the third and fourth models, where significance was stronger (*P* = .006 and *P* = .007, vs *P* = .01 and *P* = .01).

Golomb et al .ARCH INTERN MED/VOL 172 (NO. 6), MAR 26, 2012

Nobel prize laureates love chocolate
global view of chocolate: health food

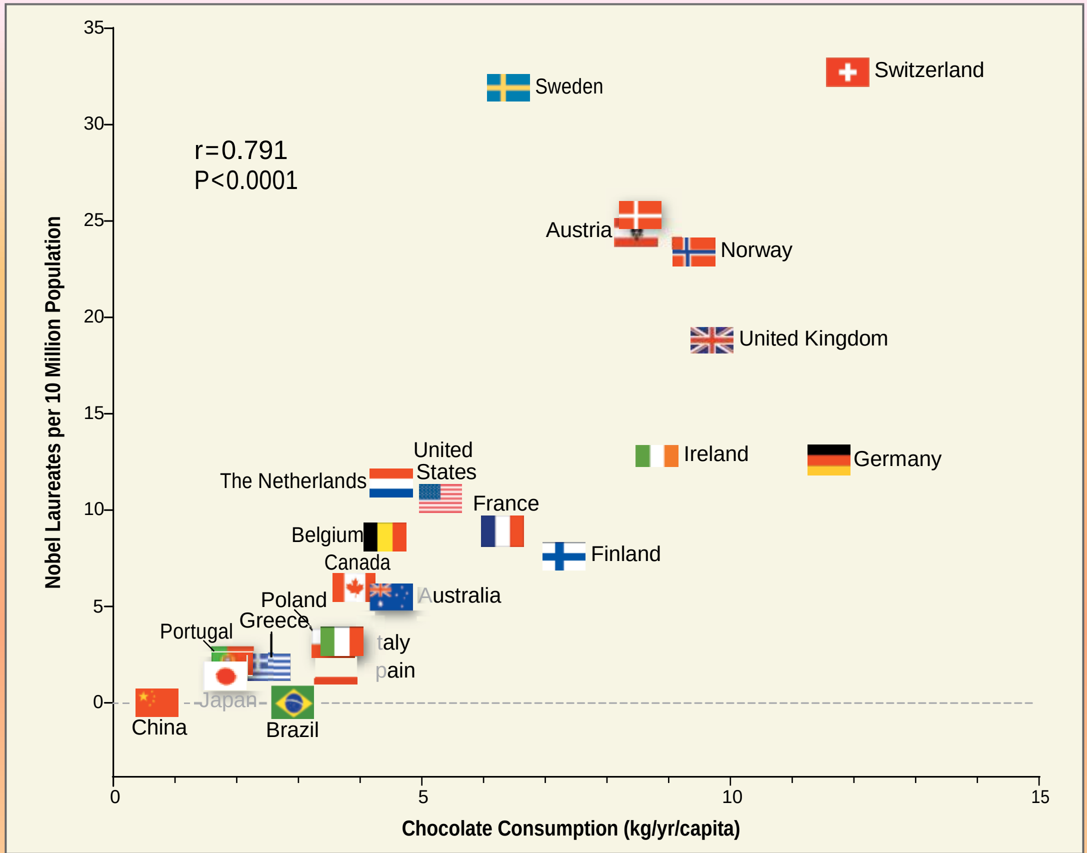
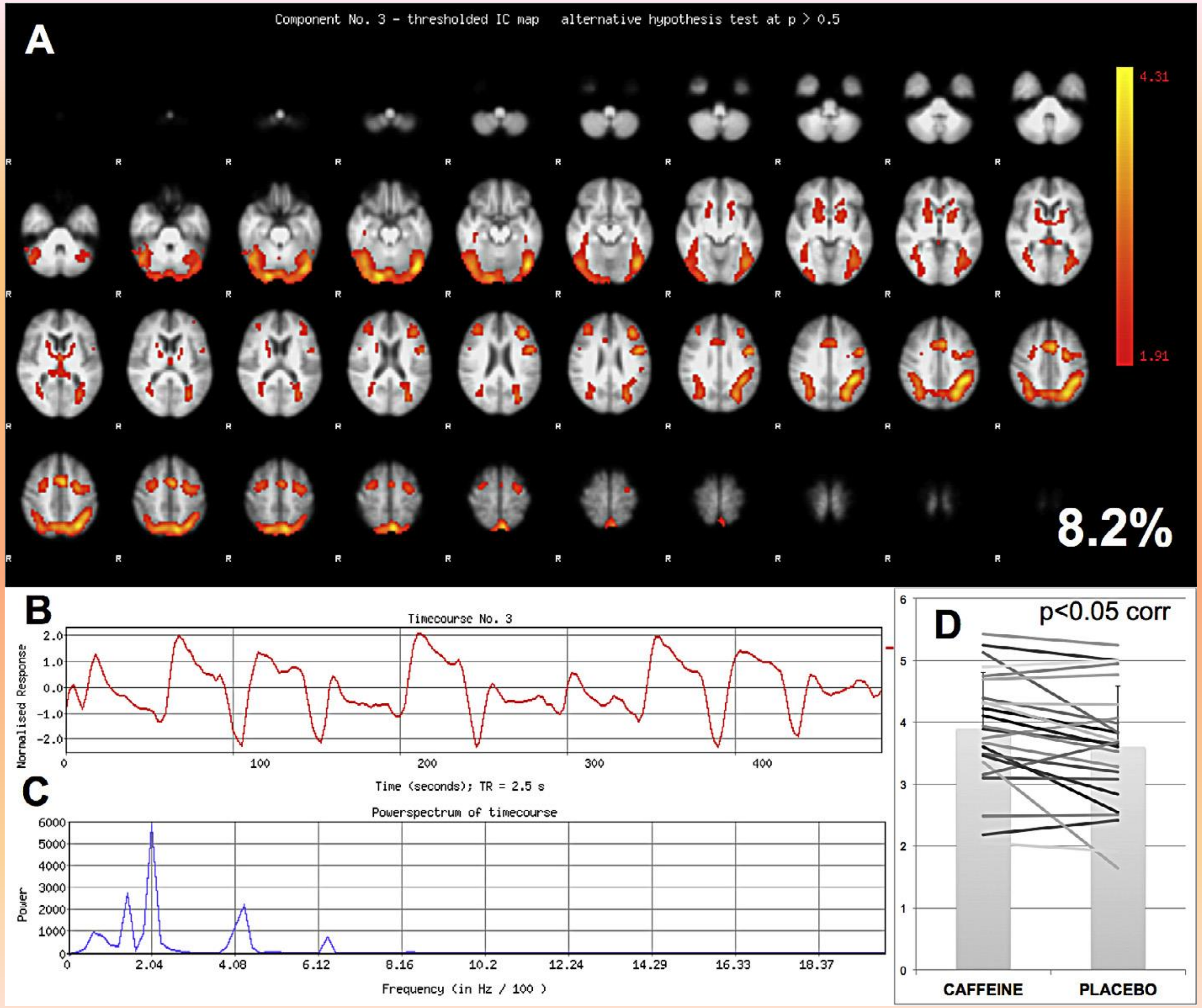


Figure 1. Correlation between Countries' Annual Per Capita Chocolate Consumption and the Number of Nobel Laureates per 10 Million Population.

Correlation between chocolate Consumption and number of Nobel Laureates

Franz H. Messerli,. **Chocolate Consumption, Cognitive Function, and Nobel Laureates** NEJM 367:16 2012.

Acute Caffeine enhances working memory neural connectivity in elderly

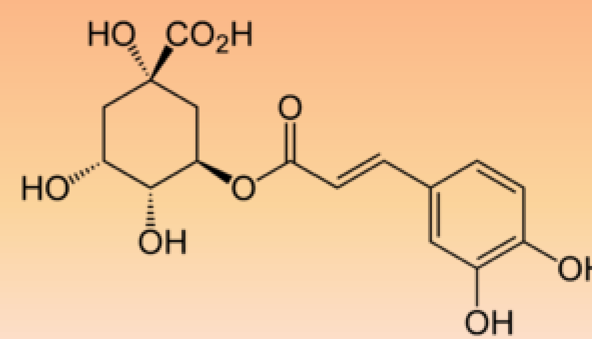


Has Dr. OZ has unlocked Epigenetics Code in Green Coffee Bean ?

Potent **HDAC inhibitor** in vitro recombinant assay

* To regulate metabolic functions
* To improve insulin resistance
* To promote lipolysis
* To orchestrate chromatin remodeling
* To coordinate neurogenesis and synaptogenesis

Chlorogenic acid



Recent study showed coffee enriched with chlorgenic acid exerted cortical EEG activating responses and mood in normal healthy elderly subjects

Cropley et al Psychopharmacology (2012) 219:737–749

The neuroprotective effects of caffeine: A prospective population study (the Three City Study).

Ritchie, K; Carriere, I; de Mendonca, A; MD, PhD; Portet, F; MD, PhD; Dartigues, J; MD, PhD; Rouaud, O; Barberger-Gateau, P; MD, PhD; Ancelin, M

Neurology. 69(6):536-545, August 7, 2007.
DOI: 10.1212/01.wnl.0000266670.35219.0c

Table 3 Age, education, baseline cognitive performance, and center-adjusted OR of cognitive decline according to baseline caffeine intake (longitudinal)

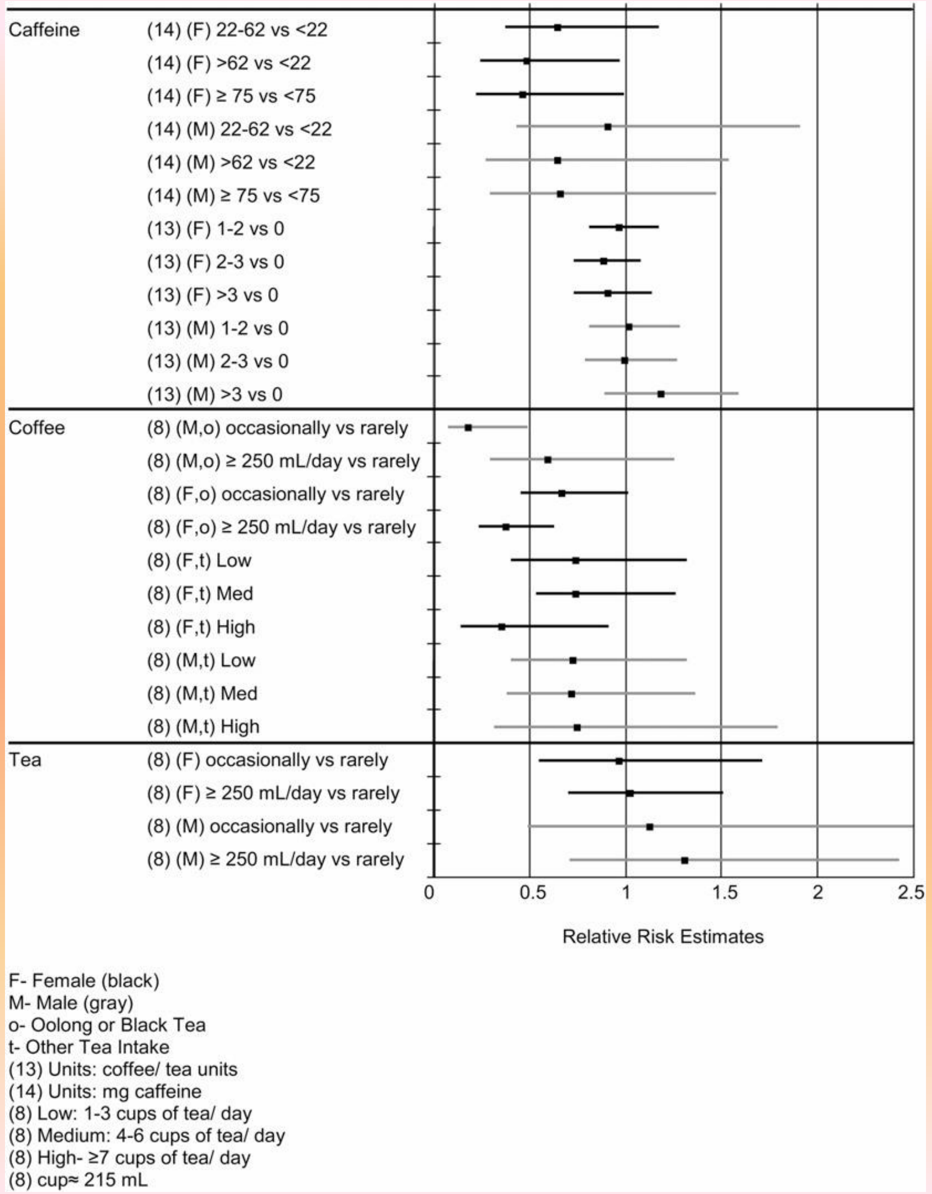
	Men, n = 2,820			Women, n = 4,197		
	OR (CI)	p	p Trend	OR (CI)	p	p Trend
ΔIsaacs ≤ −6						
1-2 units	0.92 (0.73; 1.17)	0.50		0.91 (0.75; 1.10)	0.33	
2-3 units	1.08 (0.85; 1.38)	0.51		0.82 (0.67; 1.00)	0.05	
>3 units	1.18 (0.87; 1.59)	0.29	0.19	0.66 (0.52; 0.83)	0.0005	0.0003
ΔBenton ≤ −2						
1-2 units	0.99 (0.80; 1.24)	0.96		0.95 (0.79; 1.14)	0.58	
2-3 units	1.11 (0.88; 1.40)	0.36	0.94	0.99 (0.82; 1.20)	0.92	0.21
>3 units	0.92 (0.69; 1.23)	0.57		0.83 (0.66; 1.04)	0.10	
ΔMMSE ≤ −2						
1-2 units	1.02 (0.81; 1.28)	0.87		0.97 (0.81; 1.17)	0.78	
2-3 units	1.00 (0.79; 1.27)	0.99		0.89 (0.73; 1.08)	0.23	
>3 units	1.19 (0.89; 1.59)	0.25	0.40	0.91 (0.73; 1.14)	0.42	0.24

Decrease of at least two points from the baseline for Mini-Mental State Examination and Benton test or of at least six points for the Isaacs test.
MMSE = Mini-Mental State Examination.

Wolters Kluwer Health | OvidSP

Table 3 Age, education, baseline cognitive performance, and center-adjusted OR of cognitive decline according to baseline caffeine intake (longitudinal)

Epidemiological evidence of Coffee, Caffeine and Tea in protecting against cognitive decline



Relative risk (solid line) and 95% confidence interval (dashed lines) for the association between heart failure and cups of coffee per day compared with no consumption in a meta-analysis of studies published in 2001 to 2011.

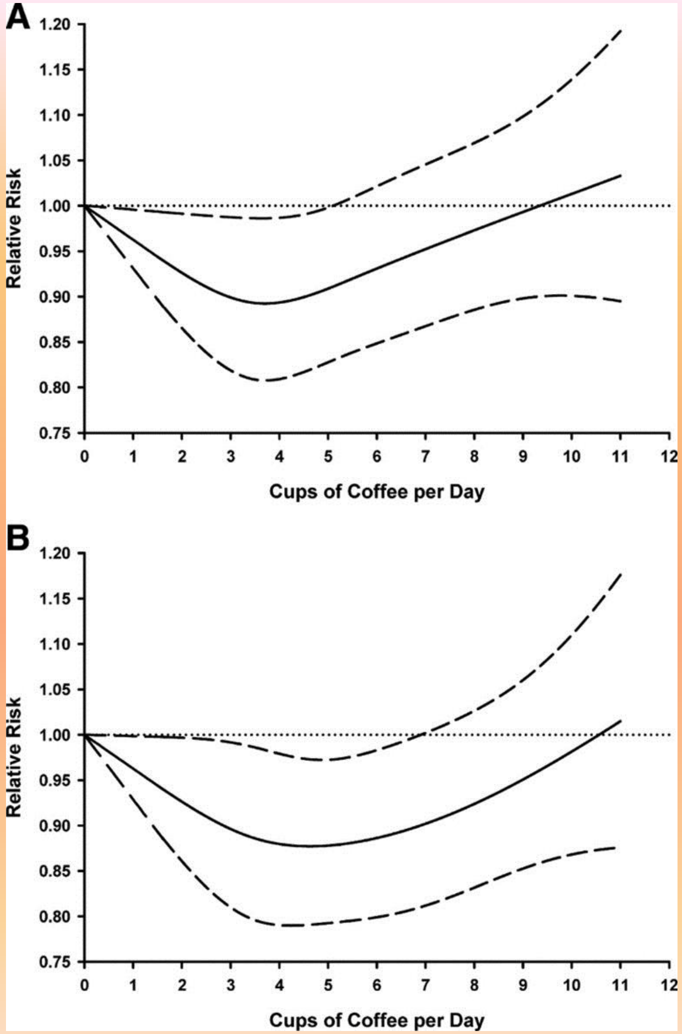
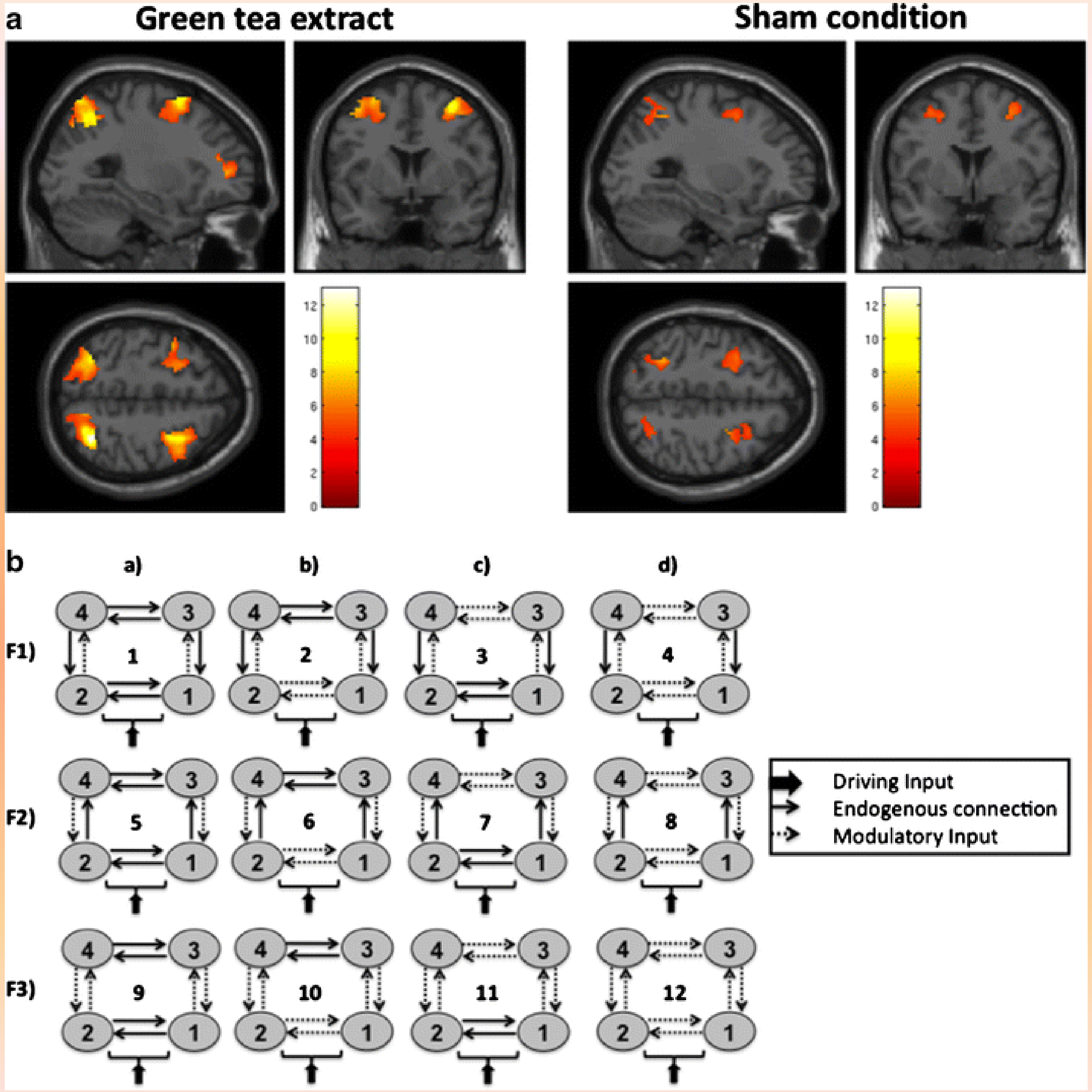


Figure 2. Relative risk (**solid line**) and 95% confidence interval (**dashed lines**) for the association between heart failure and cups of coffee per day compared with no consumption in a meta-analysis of studies published in 2001 to 2011.
A, represents the primary analysis, including all 5 studies, and
B, excludes the Wilhelmsen study. Coffee consumption was modeled with restricted cubic splines in a multivariable, random-effects, dose-response model.
The **dotted line** indicates the value for no association

Mostofsky E et al. Circ Heart Fail 2012;5:401-405

American Heart Association

It is TEA Time: imaging evidence for Cognition enhancement



Beyond Dietary Supplements and Diet Menu Go For South African Safari

In search of Elixor of Longevity in South Africa from Bushman medicine to novel CNS therapeutics ?

Zembrin®, a patented extract from carefully selected *Sceletium tortuosum* used for centuries by the **San Bushmen in South Africa**

- to combat stress and fatigue
- to enhance mood
- To relieve thirst hunger

Patented by HGH Pharmaceutical Inc South Africa

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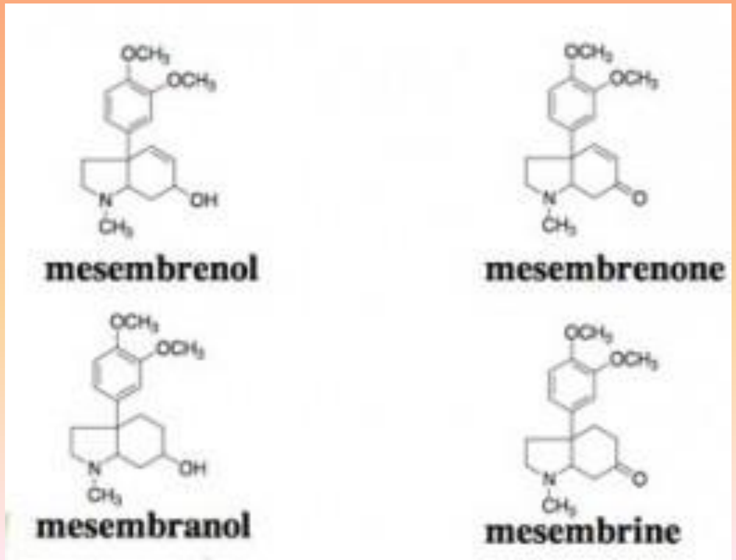


A recent fNMR study showed 25 mg Zembrin extract
* Amygdala reactivity to fearful faces under low perceptual load conditions was attenuated
*Amygdala–hypothalamus coupling was also reduced under the emotion-matching task

*Zembrin targets SSRI and cAMP signaling mediated by Phosphodiesterase subtype4

Turberg D. Neuropsychopharmacology (2013) 38, 2708–2716

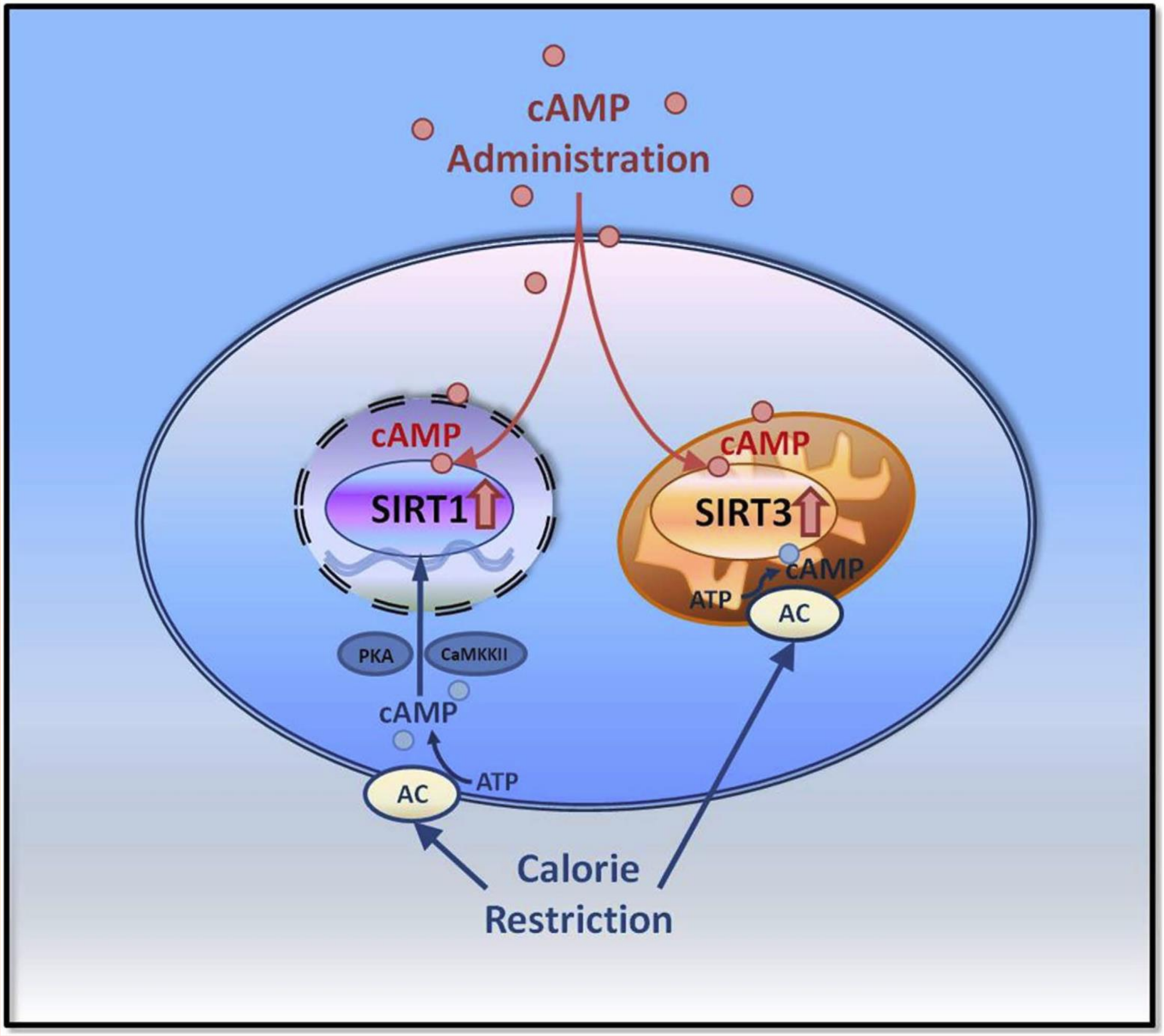
RCT study of Zembrin extract on Cognition in Healthy control Subjects
Chiu, Woodbury, Yves, Cernovsky , Nigel G. (2014)

TABLE I

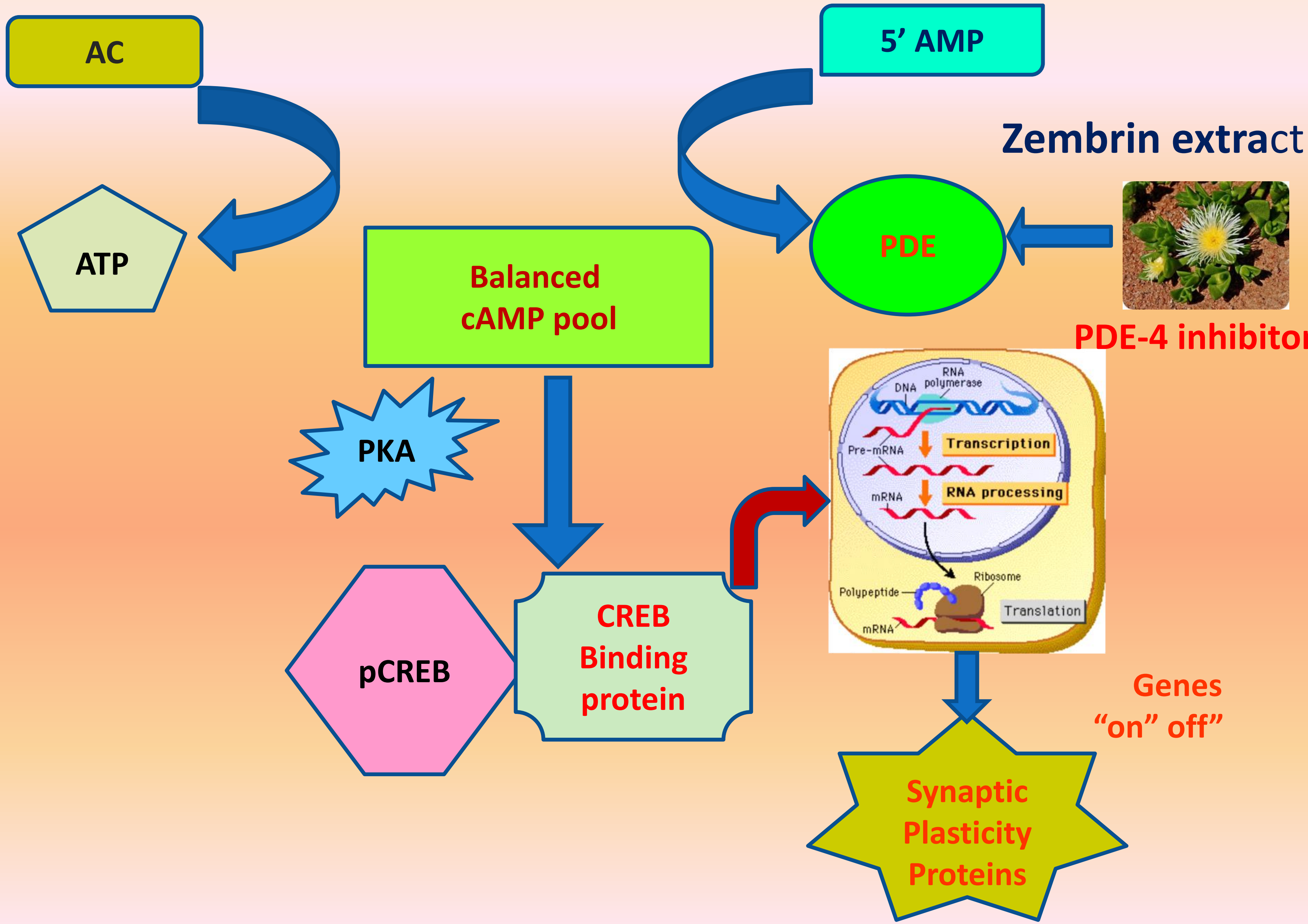
Zembrin effects on Cognitive Domains of neuro-battery of test :baseline, Post-placebo and Post-Zembrin.

CNS Vital Signs	Mean percentiles and SEM for groups			F and p values (ANOVA)
Key domains:	Baseline	Post -3 weeks Zembrin (N=17) [% change]	Post-3 weeks placebo (N=18) [% change]	
Neurocognitive Index (NCI)	36.3 (4.5)	43.9 (6.8) [7.6]	47.2 (7.7) [10.9]	F=.992 P=.376
Composite Memory	38.9 (5.3)	32.9 (8.5) [-6,0]	41.0 (9.0) [2.1]	F=.269 P=.765
Verbal Memory	36.9 (5.1)	41.6 (7.7 [4.7]	43.7 (8.9) [6.8]	F=.302 P=.740
Visual Memory	45.6 (5.5)	29.5 (8.6) [-16.1]	39.6 (7.2) [-6.0]	F=1.403 P=.253
Processing Speed	56.7 (5.7)	77.4 (6.8) [20.7]	54.7 (8.8) [-2.0]	F=2.557 P=.085
Executive Function	36.8 (5.4)	60.8 (6.6) [24.0]	50.1 (7.7) [13.3]	F=3.603 P=.032
Psychomotor Speed	54.8 (5.6)	60.4 (8.2) [5.6]	52.4 (8.5) [-2.4]	F=.252 P=.778
Reaction Time	45.8 (5.1)	58.1 (6.3) [12.3]	59.1 (6.8) [13.3]	F=1.686 P=.193
Complex Attention	38.5 (5.3)	46.2 (7.8) [7.7]	44.9 (8.5) [6.4]	F=.407 P=.667
Cognitive Flexibility	35.4 (5.3)	60.2 (6.5) [24.8]	49.7 (7.5 [14.3]	F=4.016 P=.022

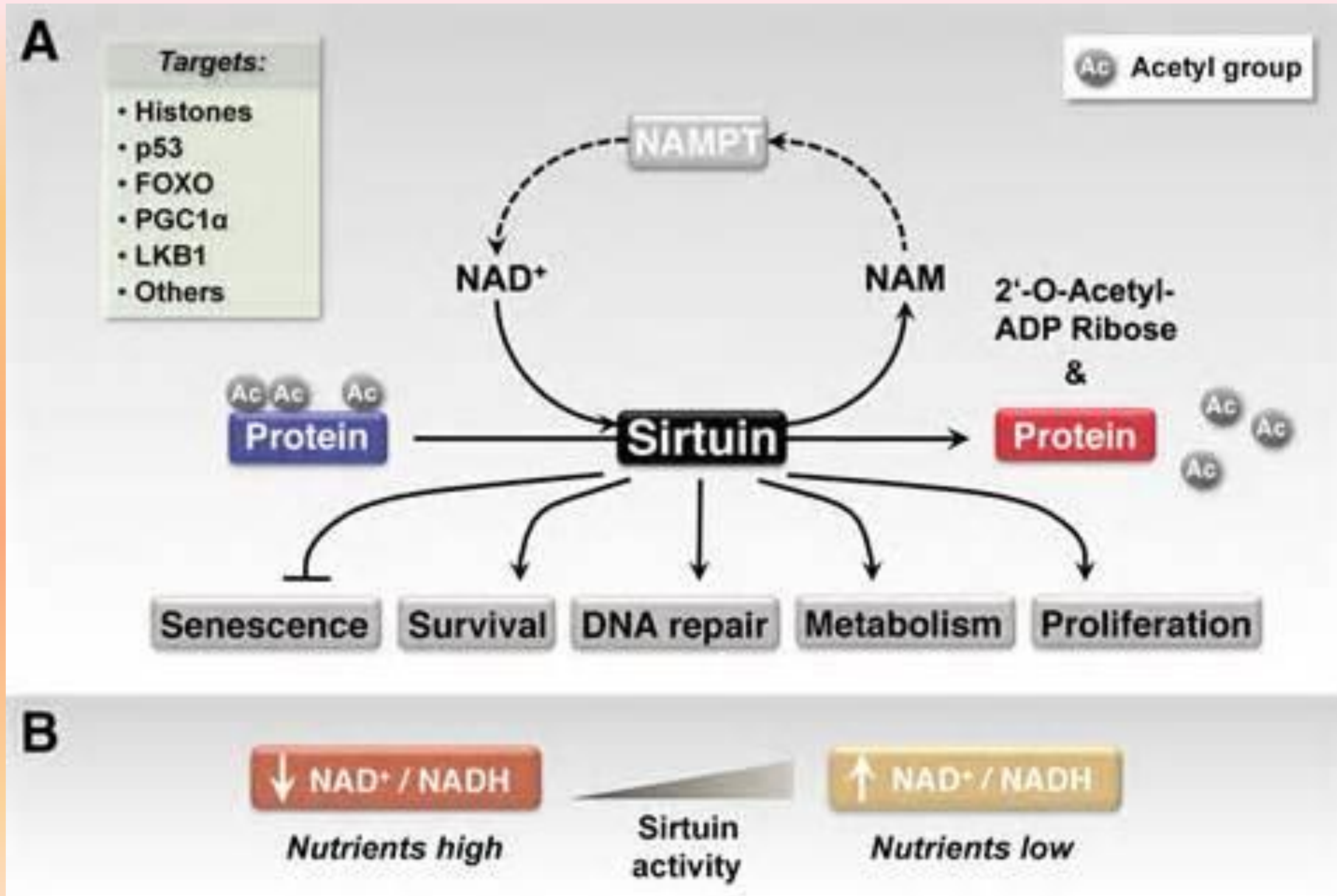
cAMP Binds to SIRT1- SIRT-3 : anti-aging phenotype



Zembrin extract targets Epigenome linked to PDE-4/cAMP/CREB cascade in Cognition



Role of Sirtuin Epigenetic Modulator in Aging



Sirtunin: NAD-dependent Histone deaceytase inhibitor

Summary of Role of Sirtunin in aging, Stress buffer and energy metabolism

Sirtuin or **Sir2 proteins**

a class of Protein that possess histone deacetylase activity (HDAC family III)

Sirtuins regulate diverse biological pathways

The name Sir2 comes from the yeast gene 'silent mating-type information regulation 2the gene responsible for cellular regulation in yeast and extended to mammalians Sirtunin

Multiple roles of Sirtuins

I)Aging

2)Regulation of Transcription cascade

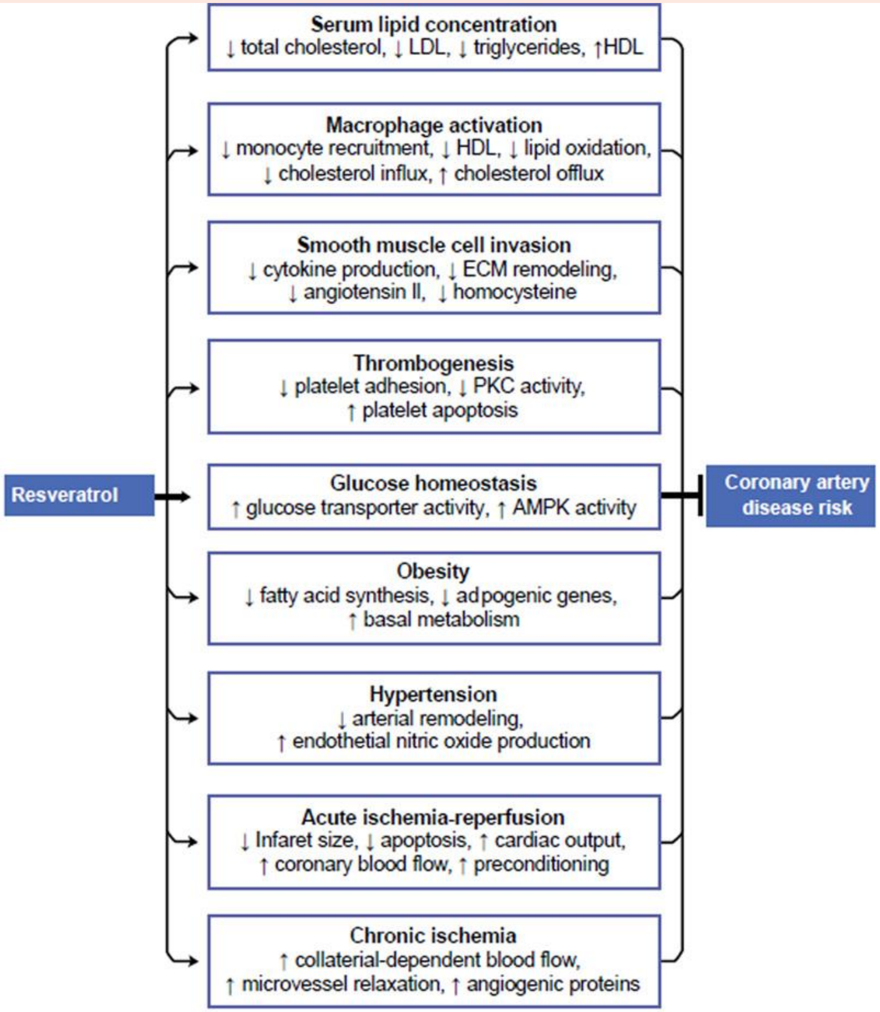
3) Modulaitng Cell growth, differentiation, survivial Death

4) Regulating stress resistance,

5 Setting the biological clock of wakefulness and energy metablism

6) May provide new therapeutic potential in Cancer, and Neurdegenerative disroder

Multiple Cardiovascular protective effects of Resveratrol



Abbreviations: AMPK: AMP-activated protein kinase; ECM: Extracellular matrix: HDL: High-density lipoprotein; LDL: Low-density lipoprotein; PKC: Protein kinase C

From Cardioprotection to Boosting Brain Health ???

Study of Grape Juice Supplementation In Cognition in healthy elderly subjects.

Krikorian et al, Br J Nutr. 103(5):730-4.

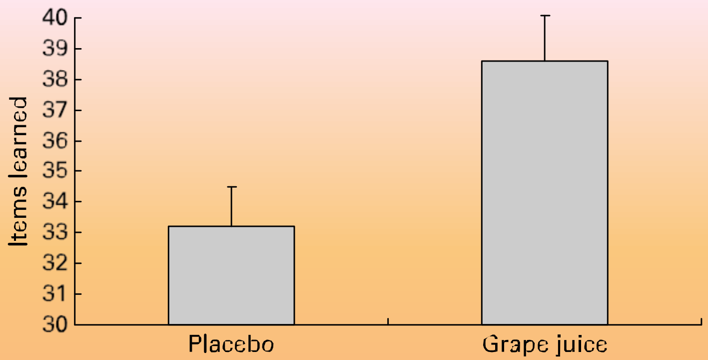


Fig. 1. List acquisition performance assessing verbal learning on the California Verbal Learning Test. Values are adjusted means, with standard errors represented by vertical bars. Subjects consuming Concord grape juice demonstrated significant improvement (F(1, 8) ¼ 5·55; P¼ 0·04; Cohen's f ¼ 0·28).

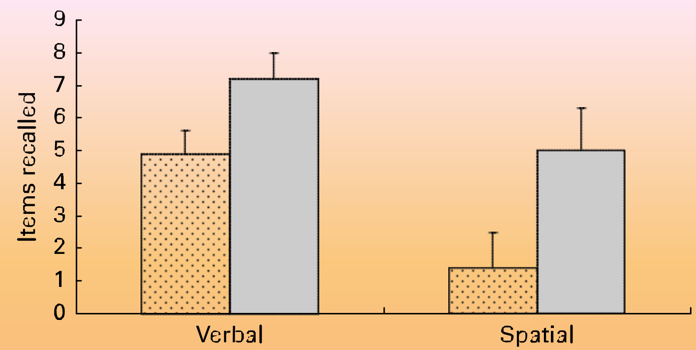


Fig. 2. Delayed recall performance for verbal material on the California Verbal Learning Test (F(1, 8) ¼ 3·37; P¼ 0·10; Cohen's f ¼ 0·35) and for visual-spatial material on the Spatial Paired Associate task (F(1, 8) ¼ 3·23; P¼ 0·12; Cohen's f ¼ 0·67). Subjects consumed either Concord grape juice (□) or a placebo drink (▩). Values are adjusted means, with standard errors represented by vertical bars.

Table 1. Unadjusted mean values for memory, mood, anthropometric and metabolic measures by group*

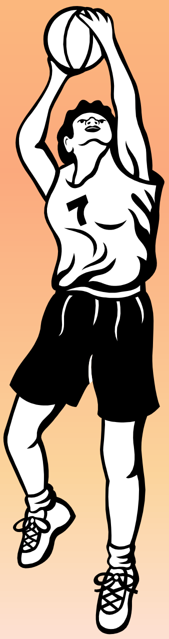
	Placebo (n 7)			Concord grape juice (n 5)		
	Baseline	Final	Difference	Baseline	Final	Difference
CVLT learning	33·2	33·2	0·0	35·2	38·6	3·4
CVLT recall	5·4	5·0	20·4	6·0	7·2	1·2
S-PAL	2·4	2·0	20·4	2·8	4·5	1·7
GDS	7·8	7·2	20·6	3·0	5·0	2·0
Weight (kg)	74·3	74·9	0·6	79·4	80·4	1·0
Waist (cm)	92·7	93·0	0·3	96·7	97·5	0·8
Glucose (mg/l)	1002	999	23	915	987	72
Insulin (mU/ml)	11·9	11·1	20·8	9·6	12·6	3·0

CVLT, California Verbal Learning Test; S-PAL, Spatial Paired Associate Learning Test; GDS, Geriatric Depression Scale.
*Baseline refers to measures obtained at the pre-intervention assessment. Final refers to measures obtained during the final week of the intervention. Difference ¼ final score less baseline score.

Healthy Cognitive Aging :
Role of Exercises and e-Games

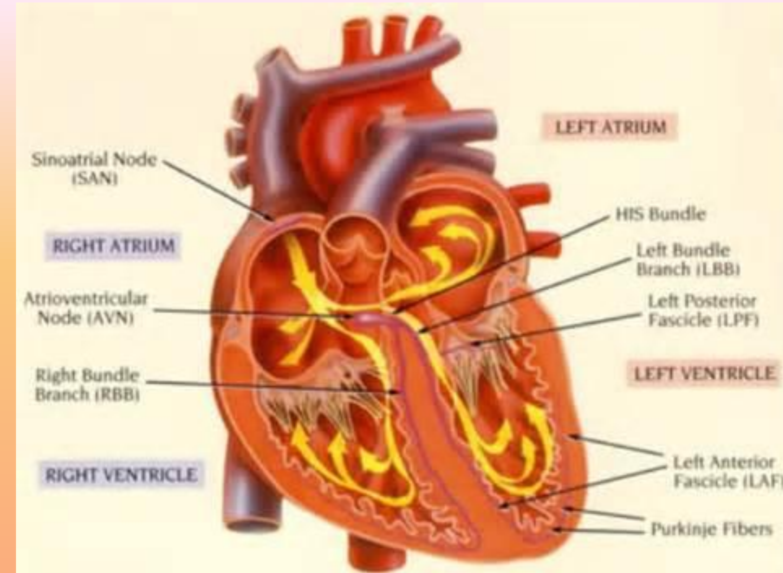
Part IV: Integrative approach Towards Cognitive Aging

HEALTH AND WELLNESS

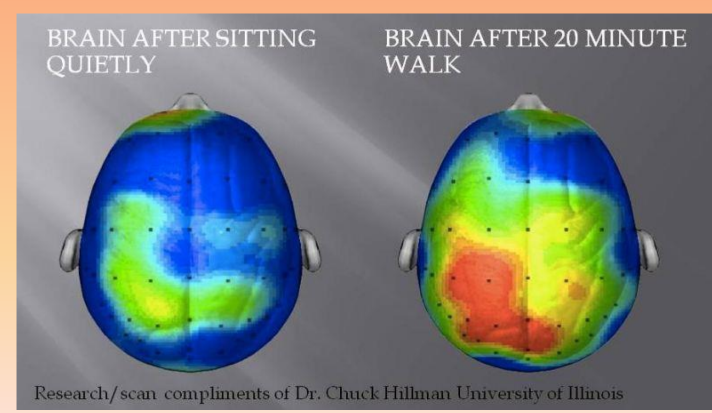


Acknowledgement:
R. Kononiuk BA Kinesology UWO

Part IV: Exercise on Cognition in Elderly

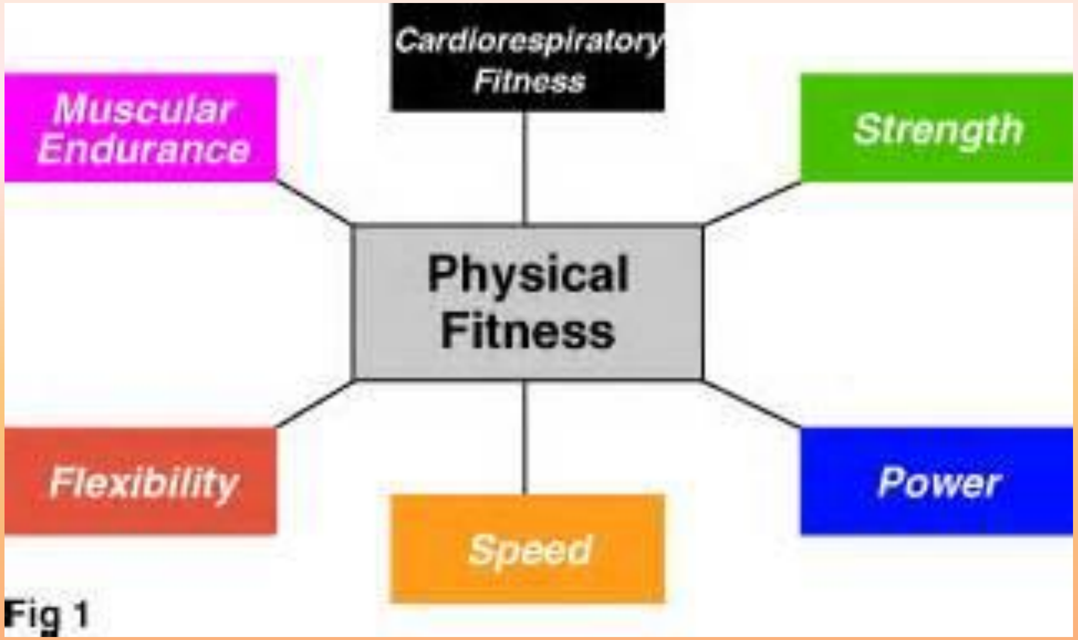


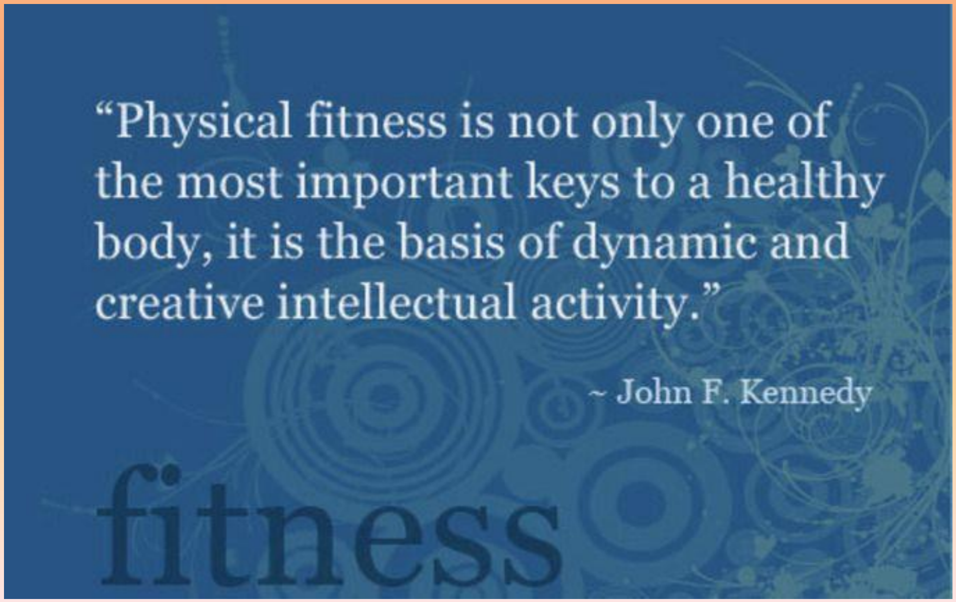
Cardiac output: Heart rate x stroke volume



Walking-induced EEG spectral changes

ELEMENTS of Physical FITNESS





Summary of Cardiorespiratory Fitness and Brain changes

Table 1 | Cross-sectional (CS) and exercise intervention (INVN) studies examining the relationship between cardiorespiratory fitness and brain structure.

Author	Year	Study type	Imaging modality	Analysis	Fitness measure	Group	Subjects (Number of females)	Mean age (years)
Bugg and Head	2011	CS	T1	ROI	Questionnaire	OA	52 (37)	69
Burns et al.	2008	CS	T1	Whole brain	VO_2 peak Questionnaire	Early AD	57 (31)	74
						OA	64 (34)	73
Colcombe et al.	2003	CS	T1	Whole brain	Rockport 1 mile walk	OA	55 (31)	66
Erickson et al.	2009	CS	T1	ROI	VO_2 peak	OA	165 (109)	67
Erickson et al.	2010	CS	T1	Whole brain	Total number of blocks walked during 1 week	OA	299 (182)	78
Floel et al.	2010	CS	T1	Whole brain	Ergometer test, Lactate step test, Questionnaire	OA	75 (47)	60
Gordon et al.	2008	CS	T1	Whole brain	VO_2 max	YA	20 (10)	22
						OA	40 (23)	72
Ho et al.	2011	CS	T1	Whole brain ROI	Questionnaire	OA	226 (130)	78
Honea et al.	2009	CS	T1	Whole brain	VO_2 peak,	Early AD	61 (37)	74
					Questionnaire	OA	56 (33)	73
McAuley et al.	2011	CS	T1	ROI	VO_2 peak, Rockport 1 mile walk	OA	86 (53)	65
Sen et al.	2012	CS	T1	Whole brain	Bicycle ergometer test	OA	715 (386)	65
Szabo et al.	2011	CS	T1	ROI	VO_2 peak, Questionnaire	OA	158 (105)	66
Verstynen et al.	2012	CS	T1	ROI	VO_2 max	OA	179 (109)	67
Vidoni et al.	2012	CS	T1	ROI	VO_2 peak	AD	37 (20)*	74
						OA	53 (29)	73
Weinstein et al.	2012	CS	T1	ROI	VO_2 max	OA	142 (91)$^{+}$	67
Marks et al.	2011	CS	DTI	ROI	VO_2 peak, self report of activity per week	OA	15 (7)	66
Johnson et al.	2012	CS	DTI	Whole brain	Composite score: VO_2 peak, total time on treadmill, 1 minute heart rate recovery	OA	26 (14)	65
Marks et al.	2007	CS	DTI	ROI	Equation derived estimate	YA	13	24
						OA	15	70
Head et al.	2012	CS	PiB	ROI	Questionnaire	OA	163	45–88
Liang et al.	2010	CS	PiB	ROI	Questionnaire	OA	54	55–88
Colcombe et al.	2006	INVN	T1	Whole brain	VO_2 peak	OA	59	66
Erickson et al.	2011	INVN	T1	ROI	VO_2 max	OA	120	55–80
Ruscheweyh et al.	2011	INVN	T1	Whole brain	Ergometer test, Questionnaire, Lactate step test	OA	62 (43)	60
Voss et al.	2012	INVN	DTI	ROI	Composite score: VO_2 max, Rockport 1 mile walk	OA	70 (45)	65

AD, Alzheimer's disease; DTI, diffusion tensor imaging; OA, older adults; PiB, Pittsburgh Compound B amyloid imaging; ROI, regions of interest analysis; T1, T1-weighted imaging; YA, young adults.

**Nine subjects from each group excluded from T1 analysis, gender distribution of excluded subjects unknown.*

+139 participants completed the spatial working memory task.

Brain volume and Fitness in Elderly

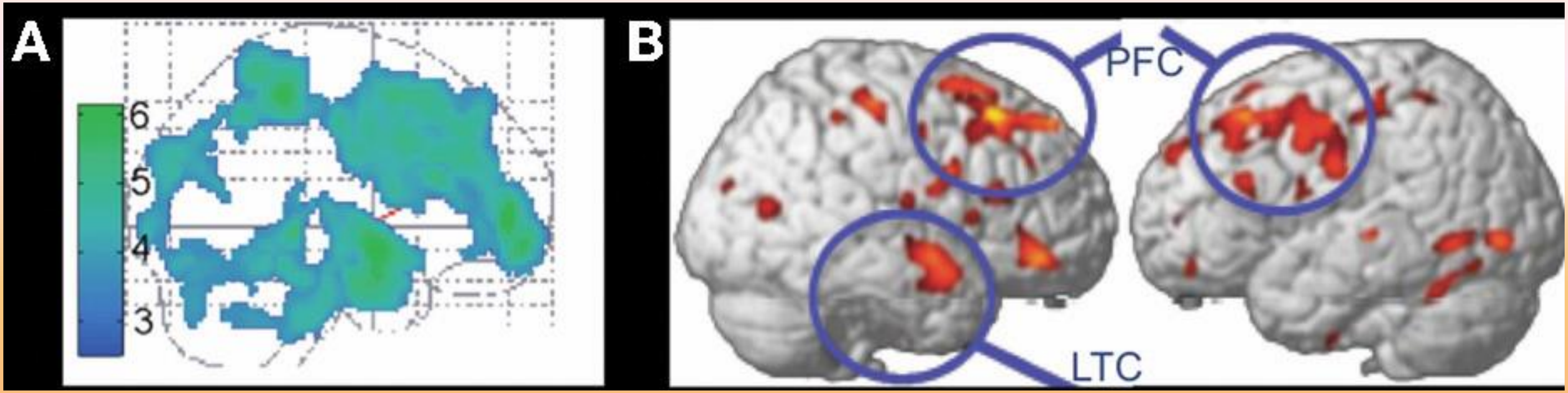
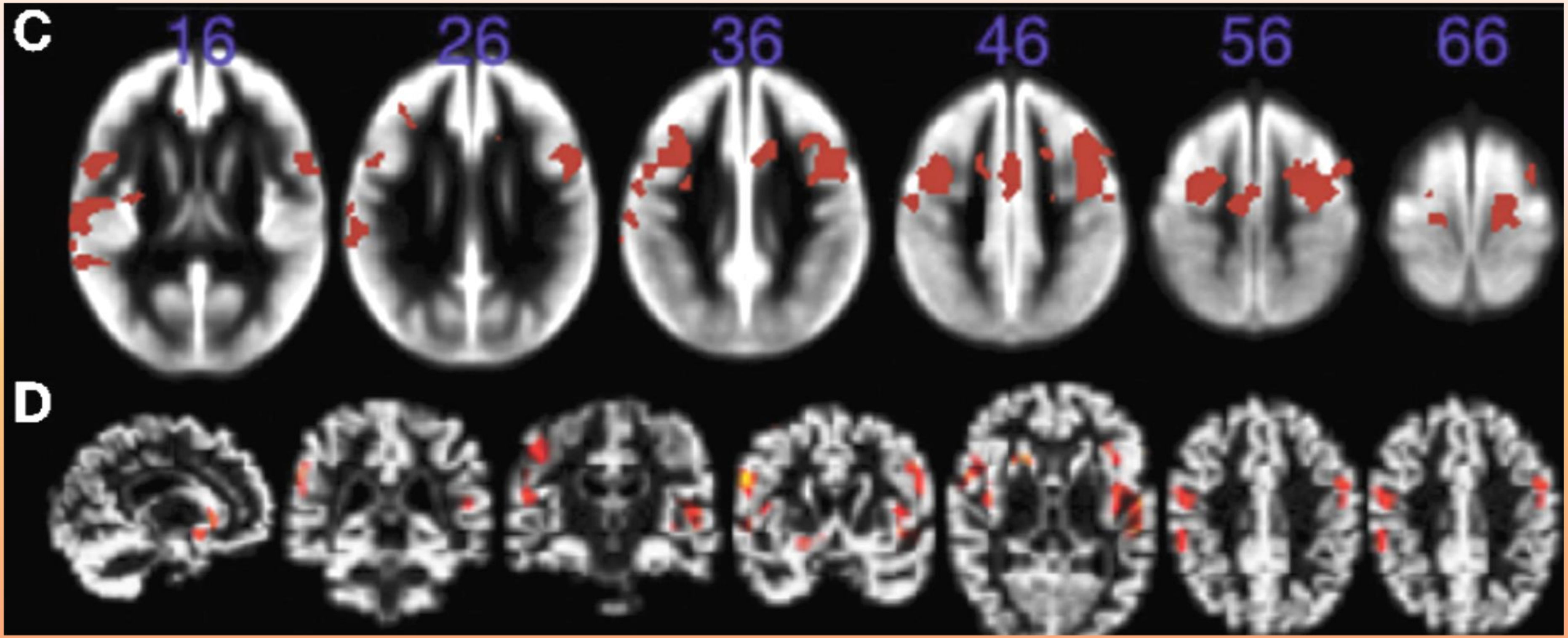


FIGURE2 Structural MRI studies showing positive relationships with brain volume and fitness.

A) Gray matter regions, including **prefrontal cortex and parietal regions** showing **fitness-related preservation in older adults.**
From Colcombeetal.(2003), Figure1,p.178.Adaptedwith permission.

(B) Regions showing increased brain volume in older adults who walked **more than 72blocks perweek.**From Ericksonetal.(2010), Figure2B,p.1419.Adaptedwithpermission.

Caradiorespiratory Fitness and Brain Volume among Elderly



(C) Gray matter regions : bilateral prefrontalcortex,showing a positive relationship with Fitness in older adults. The blue numbers represent MNI coordinates in the axial(z)plane. From Weinsteinetal.(2012), Figure1A,p.815.Adaptedwithpermission.

(D) Brainregions showing a positive relationship with fitness in olderadults.
From Gordonetal.(2008),Figure3A,p.835.
Adapted with permission.LTC,lateral temporalcortex; PFC,prefrontal cortex.

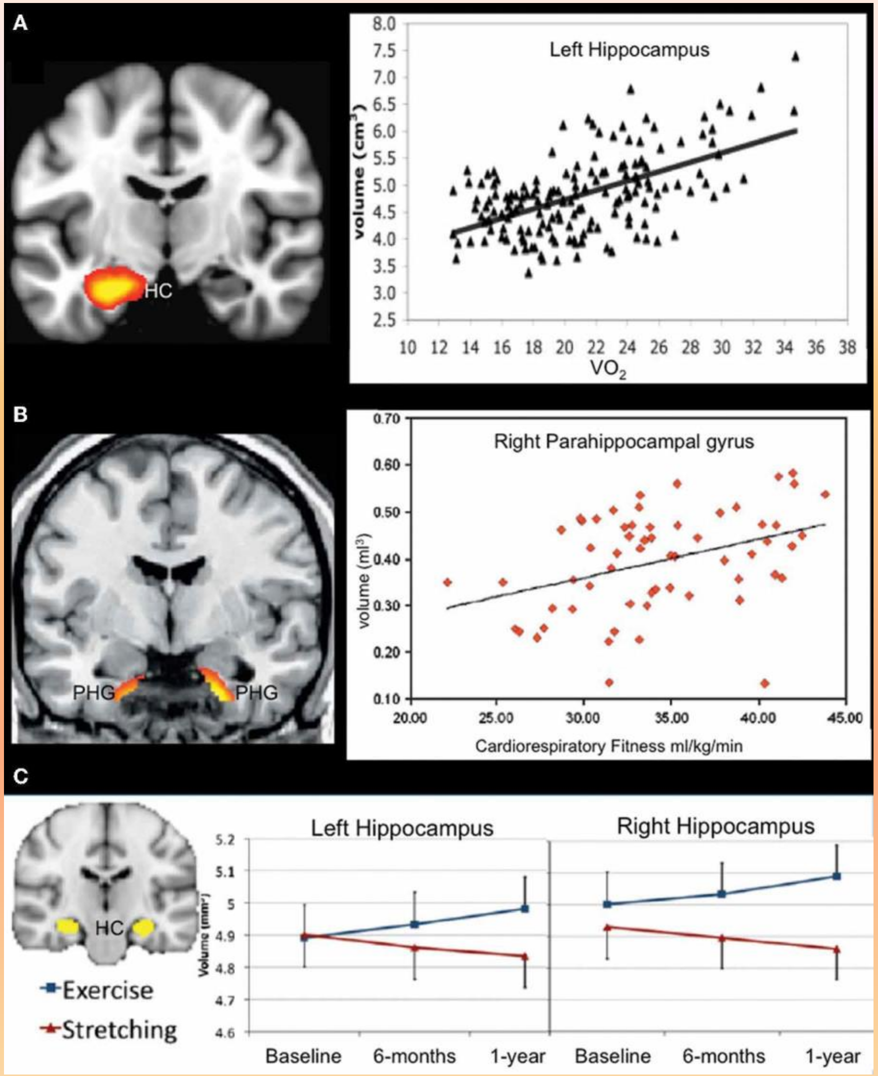
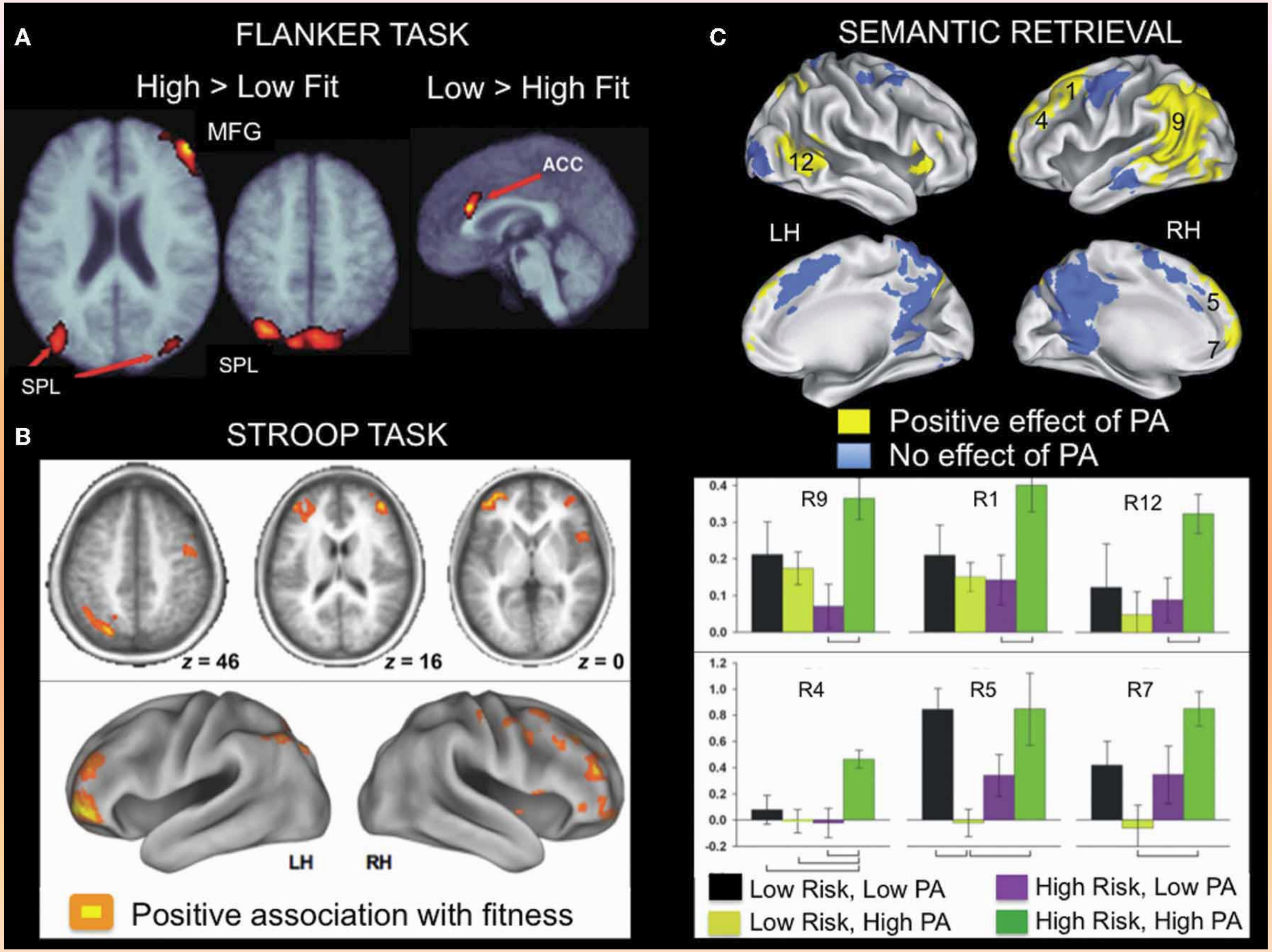


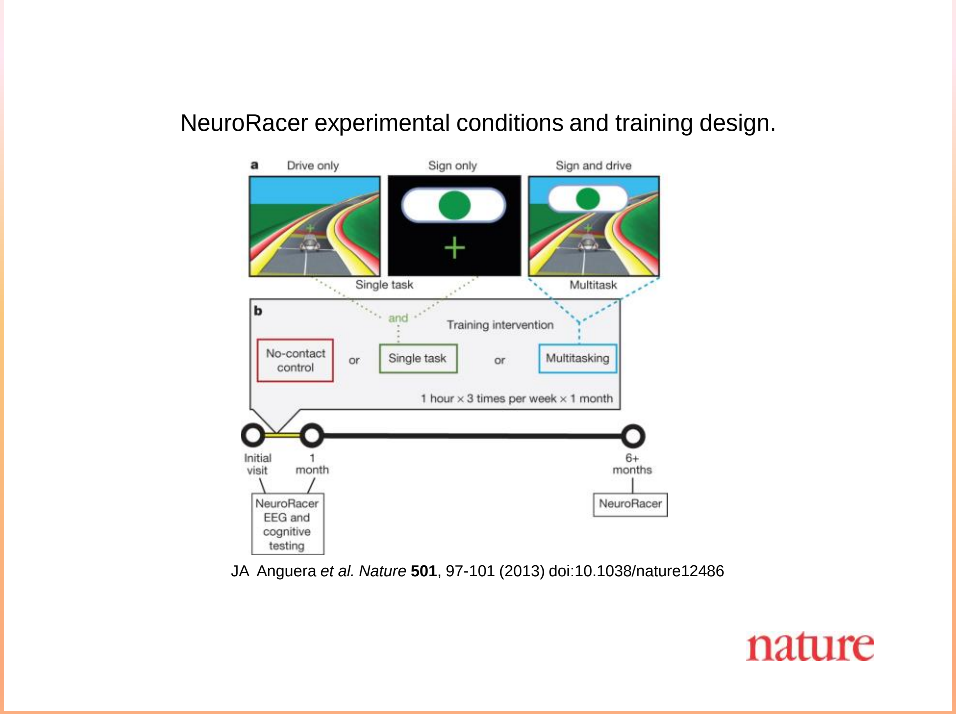
FIGURE 3 | Structural MRI studies using a regions-of-interest approach showing a positive relationship between fitness levels and medial temporal lobe volume. (A) Aerobic fitness is associated with bilateral hippocampal volume in older adults (only data from left hippocampus are displayed). From Erickson et al. (2009), Figure 2, p. 1034. Adapted with permission. **(B)** Increased parahippocampal volume is associated with aerobic fitness in early AD patients. From Honea et al. (2009), Figure 3B, p. 194. Adapted with permission. **(C)** Aerobic exercise training increases bilateral hippocampal volume in older adults. From Erickson et al. (2011), Figure 1A, p. 3019. Adapted with permission. HC, hippocampus; PHG, parahippocampal gyrus.

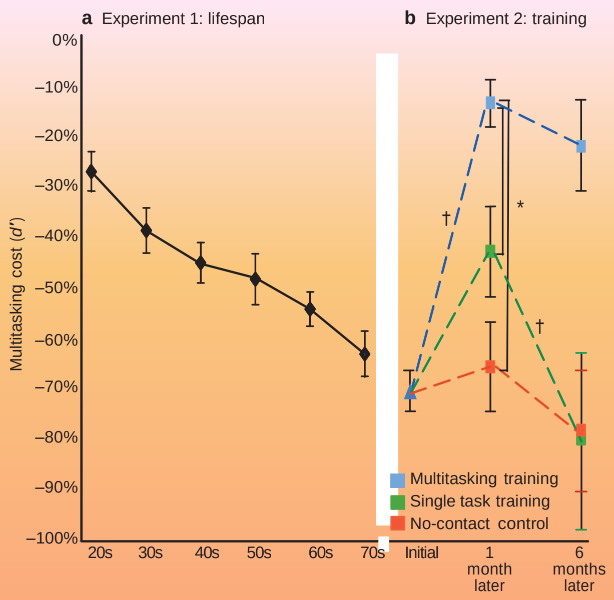
fNMR studies linking Fitness and Brain regional activation



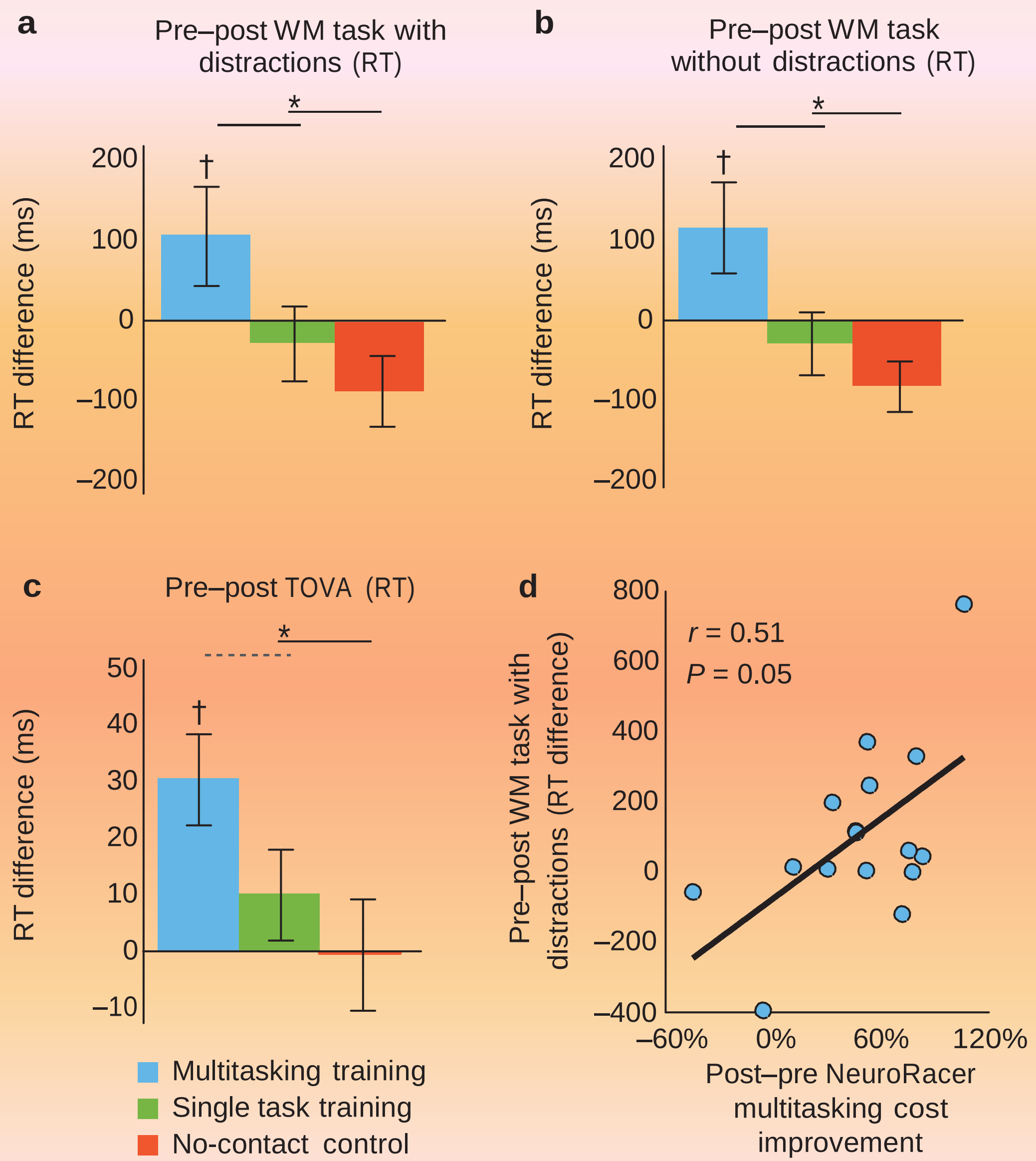
Part IV e-Games on Cognition

Video Game Training enhances cognition control results in elderly subjects





- **Effect of aging on Multi-tasking Ability**
- **Standardized Video training games: Drive, Sign- and Sign-Driving**
- **EEG Correlates and Outcome measures**

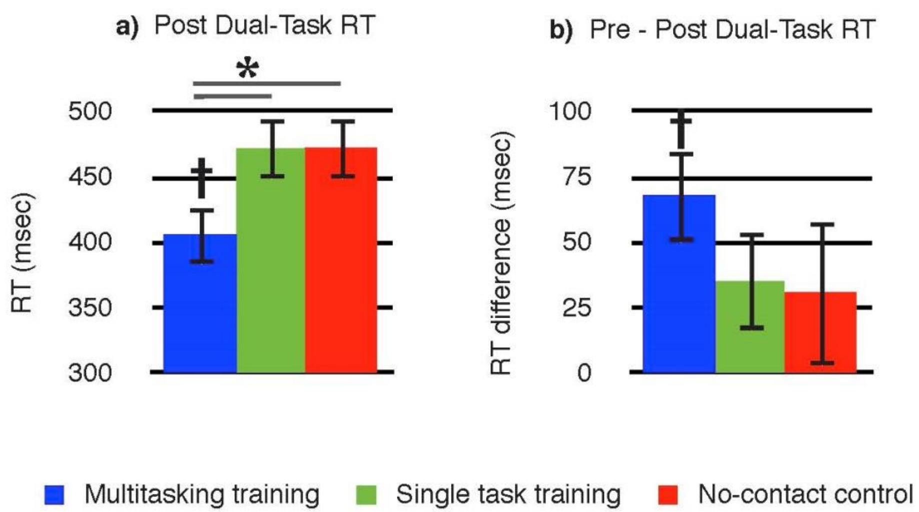


a, Response time (RT) change for a delayed-recognition working memory (WM) task with the presence of distraction (n546).

b, Response time change for a delayed-recognitionWMtask without distraction.

c, Response time change for the test of variables of attention (TOVA).

d, Correlation between data from(a) and NeuroRacermultitasking cost improvement 1month after training for the MTT group (n516). {P,0.05 within group improvement from pre to post, *P,0.05 between groups, - - -



<u>Supplementary Figure 17</u>. Dual-task performance assessed with ANCOVA and ANOVA (RT on 2nd task – RT on 1st task). a, ANCOVA showing post-training performance for each group (using pre-training performance as a covariate). b, ANOVA (pre-post RT difference score) performance for each group. †= $p < .05$ within group improvement from Pre to Post, *= $p < .05$ between groups. Error bars represent standard error.

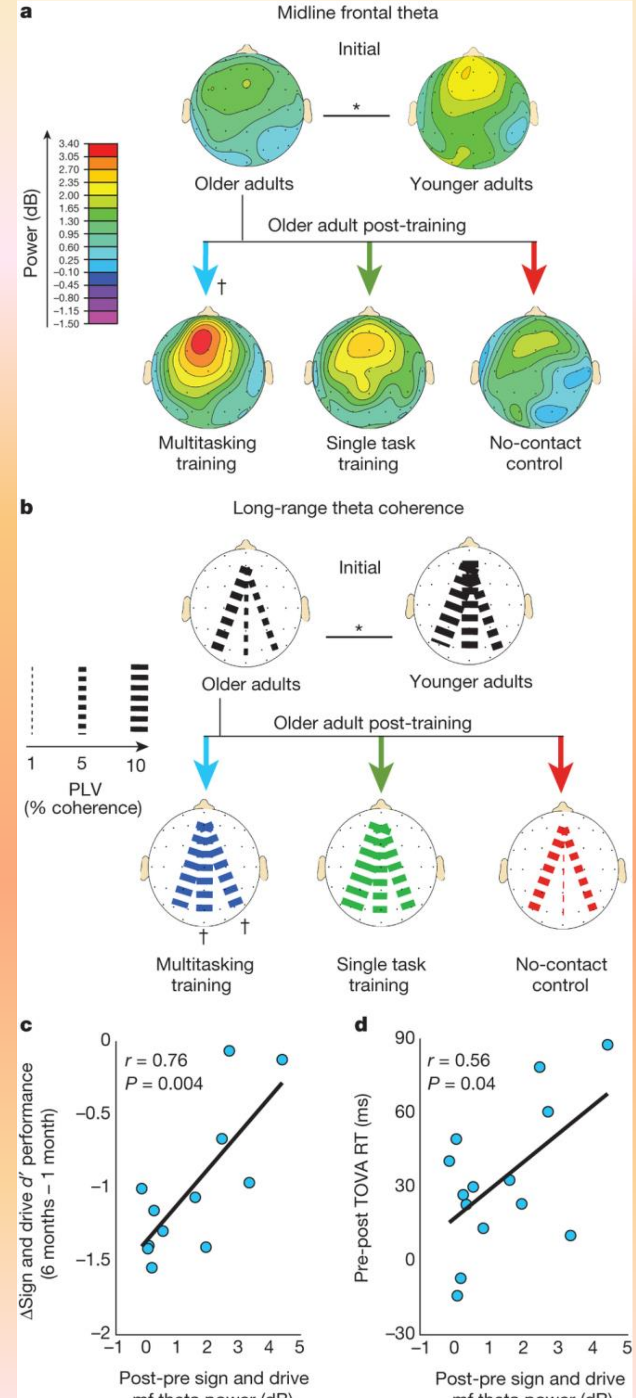
Figure 4 | ‘**Sign and drive’ midline frontal theta activity and long-range theta coherence** in younger adults and older adults pre- and post-training.

a, b, For older adult training assessments, a group X session X condition ANOVA for each neural measure revealed **significant interactions**

b), follow-up analyses : improvement only forMTT during ‘sign and drive’ (n515). For younger (n518) vs older adult (n544) assessments, **neural measures revealed significant reductions in older adults**

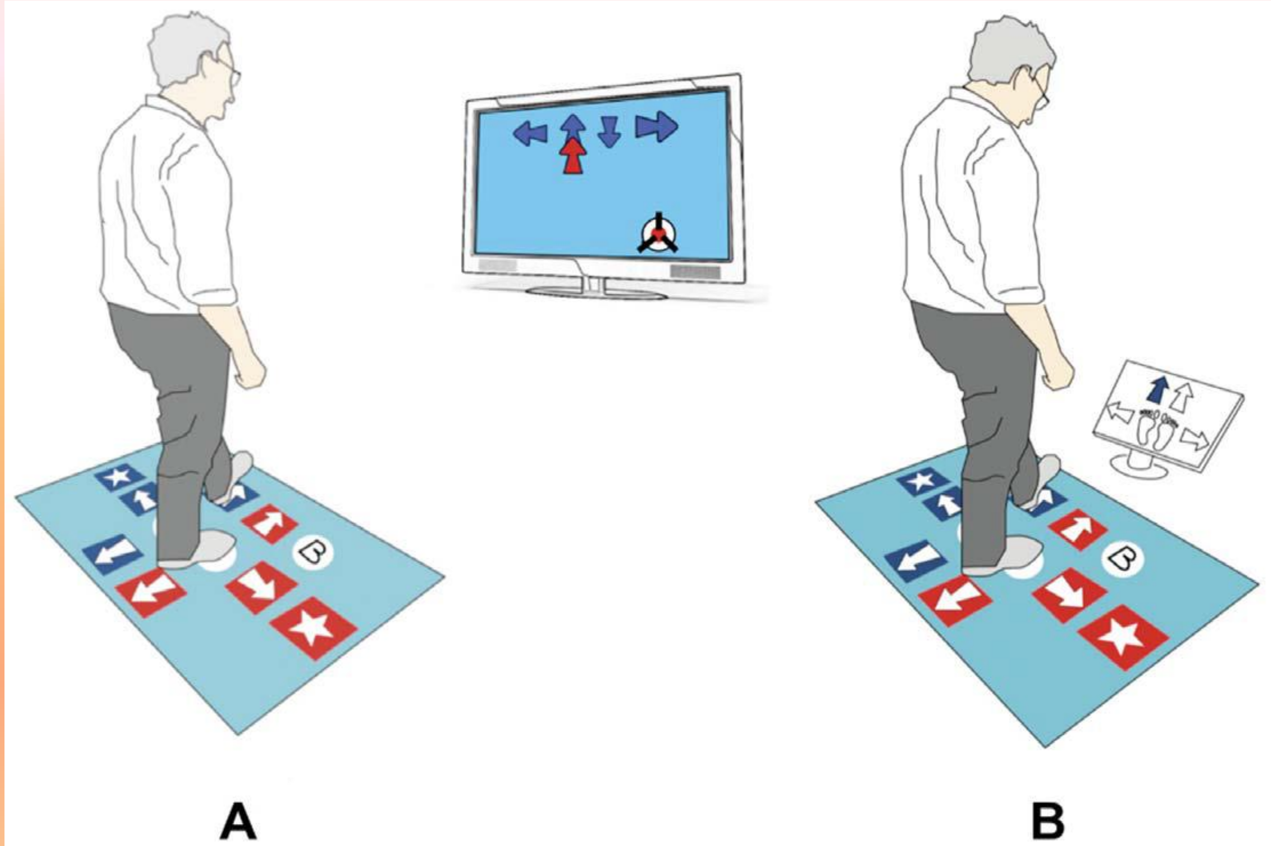
c, Correlation in the MTTgroup between the change in midline **frontal theta power and multitasking behavioural** gain preservation 6 months later

d, MTT group :change in midline **frontal (mf) theta power is correlated behavioral improvement on the TOVA** (n514). {P,0.05 within group improvement from pre- to post-training, *P,0.05 between groups.



Training results on Stepping task using Home-based VideoTechnology

Schoene D, Lord SR, Delbaere Ket al. (2013)\ A Randomized Controlled Pilot Study of Home-Based Step Training in Older People Using Videogame Technology. PLoS ONE 8(3):



Intervention: Intervention group (IG) participants provided with a computerized step pad system connected to their TVs and played a step game ad libitum

Conditions: (2–3 sessions per week for 15–20 minutes each) for eight weeks

Weekly task : choice stepping reaction time (CSRT) task

Outcome Measures; at baseline and 8 weeks

CSRT, Physiological Profile Assessment (PPA),
neuropsychological and functional mobility

Table 2. Results of DDR stepping on outcome measures.

Item	Groups	Baseline Mean (SD)	Re-assessment Mean (SD)	Group x time interaction (p-value)	% change from baseline[a]
CSRT RT	DDR	755681	679667	.001	10
	CON	730674	738692		21
CSRT MT	DDR	252644	210647	.018	17
	CON	245644	241663		2
CSRT resp	DDR	10076116	890697	.000	12
	CON	9756104	9796134		0
PPA	DDR	1.7560.6	1.1560.8	.001	34
	CON	1.5560.8	1.5660.8		21
Sway path	DDR	3866132	3016133	.049	22
	CON	3556118	330695		7
Sway AP	DDR	44616	34613	.577	23
	CON	36611	3269		11
Sway ML	DDR	53621	33616	.139	38
	CON	38615	36616		5
Hand RT	DDR	233629	224625	.122	4
	CON	227633	232634		22
Knee ext	DDR	28.968.1	29.567.8	.439	2
	CON	32.4610.5	31.8611.2		22
MET	DDR	21.761.9	22.161.4	.044	2
	CON	21.462.3	21.061.5		22
Proprioception	DDR	3.061.7	2.361.1	.489	23
	CON	2.260.9	2.461.5		29
TUG	DDR	9.661.3	9.161.4	.843	5
	CON	9.861.4	9.361.8		5
5 STS	DDR	11.562.3	10.762.8	.430	7
	CON	10.862.4	10.362.1		5
AST	DDR	9.261.8	8.861.7	.423	4
	CON	9.364.7	9.062.1		3
TMT B-A	DDR	47621	43615	.443	9
	CON	61636	74661		221
TUG animals	DDR	14.165.6	11.563.7	.049	18
	CON	11.962.9	12.063.5		21
INHIB					
time20trials	DDR	51617	4267	.126	18
	CON	53611	51617		4
time/trial	DDR	2.560.8	2.160.3	.094	16
	CON	2.560.5	2.460.7		4
errors	DDR	1.061.9	0.961.3	.546	10
	CON	1.161.5	1.261.4		29
Icon-FES	DDR	16.364.5	15.963.7	.648	2
	CON	17.665.6	17.265.0		2

Results

- **32** subjects completed study
- Intervention showed significant
- positive change in
- A) CSRT

  B) PPA composite scores
- C) Postural sway
- D) Contrast sensitivity
- C) Dual task ability

- ## Conclusion
- Step Pad training
- can be safety conducted at home
- to improve physical ability in
- the elderly without major cognitive
- or physical impairments

- ## Caveat

  Can Step Pad training be used to
- prevent gait and postural control
- in at risk elderly cohort

Schoene D, Lord SR, Delbaere K, Severino C, Davies TA, et al. (2013) A Randomized Controlled Pilot Study of Home-Based Step Training in Older People Using Videogame Technology. PLoS ONE 8(3): e57734. doi:10.1371/journal.pone.0057734

Effects of Multi-component Exercises on Cognitive measures in mild amnestic cognitive impaired cohort

Suzuki et al. BMC Neurology 2012, 12:128

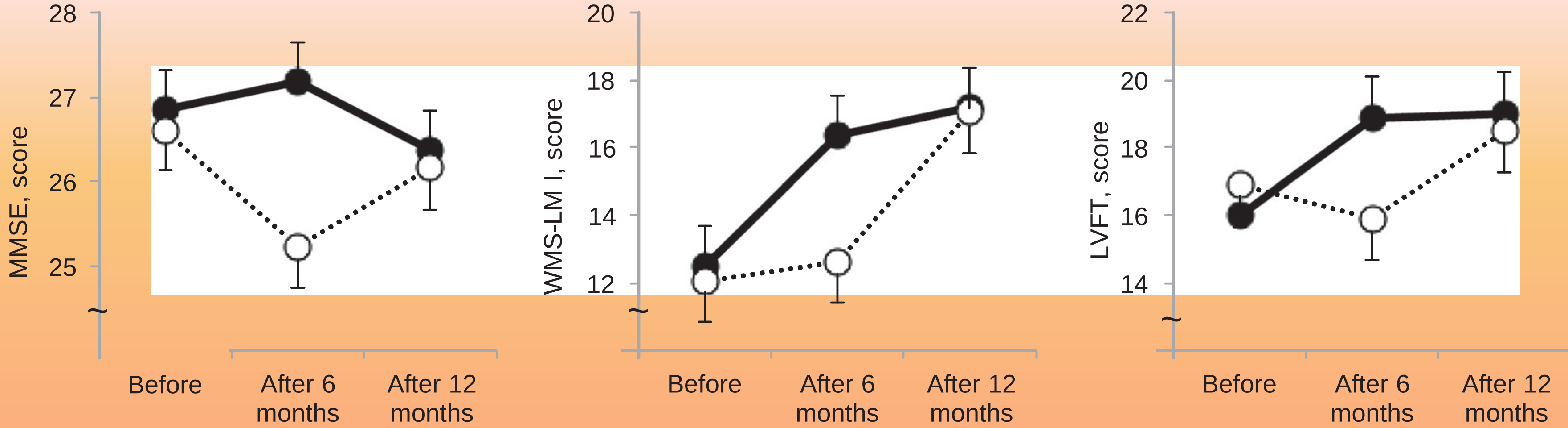


Figure 2 Changes in the MMSE, WMS, and LVFT scores. MMSE; mini-mental state examination, WMS-LM I; Logical Memory I subtest of the Wechsler memory scale-revised, LVFT; letter verbal fluency test. Panels showed change in MMSE, WMS-LM I, and LVFT scores before, after 6 months, and after 12 months intervention. Solid and dashed lines indicate the exercise and control groups, respectively. Group mean and standard errors are shown in older adults with amnestic mild cognitive impairment. The linear mixed models revealed significant group × time interactions in MMSE (P = 0.04), WMS-LM I (P = 0.03), and LVFT (P = 0.02).

RCT trial: older adults (27 men) aMCI ranging (mean age, 75 years);

Intervention: randomized into either a multicomponent exercise (n = 25) or an education control group (n = 25). multicomponent exercise group supervised physiotherapists for 90 min/d, 2 d/wk, for a total of 80 times

Duration: 12 months.se model : Mixed Exercise: Aerobic, muscle strength and gait balance

VIDEO Games Training among the eldery: Synthesis of studies

Table 3. Video Game Studies Reported by Design, Age Range, N, Intervention, Control, Duration, Significant Findings, and Effect Sizes.

Study	Age range	N	Intervention	Control	Duration	Significant Findings	Effect Sizes
Randomized Controlled Trial							
Goldstein, 1997	72–85	22	SuperTetris	No contact	5 weeks: at least 300min/week; playing time varied: 25.5–36.5 hrs	IG improved RT. IG and CG improved executive function, no difference between groups.	d = 1.11
Non-Randomized and Pre-post Designs							
Ackerman, 2010	50–71	78	Wii Big Brain Academy	None	4 weeks: 5G/week for 60 min	IG improved on task-specific fluid, crystallized and perceptual speed measures.	d = 1.70
Basak, 2008	63–75	39	Rise of Nations	No contact	4–5weeks: 3G/week for 90 min	IG improved memory, executive function, and visuo-spatial abilities.	Executive control: $g^2 = 0.42$ N-back: $g^2 = 0.10$ Memory: $g^2 = 0.09$ Reasoning: $g^2 = 0.11$
Belchoir, 2008	67–84	58	UFOV or Medal of Honor	Tetris or no contact	2 weeks: 2–3G/week for 90 min	UFOV IG improved processing speed more than no contact controls, no difference between Medal of Honor and Tetris groups.	UFOV: d = 1.62; Tetris: d = 0.36
Clark, 1987	57–83	14	Pac Man or Donkey Kong	No contact	7 weeks: 120 min/week	IG improved RT	d = 0.33; 0.56
Drew, 1986	61–78	13	Atari Crystal Castles	Contact with researcher	8 weeks: 2G/week for 60 min	IG improved psychomotor speed and global cognition.	WAIS: d = 0.77 WAIS verbal: d = 0.39 WAIS performance: d = 0.71
Dustman, 1992	62–71	60	Breakout, Galazian, Frogger, Kaboom, Ms. Pacman, Pengo, and Qix	Movie viewing or no contact	11 weeks: 3G/week for 60 min	IG improved RT. IG and CGs improved executive function.	RT: d = 0.97 Attention: d = 0.25
Torres, 2008	70–86	43	QBeez, Super Granny 3, ZooKeeper, Penguin Push, Bricks, Pingyn, memory games	Muscle relaxation or no contact	8 weeks: 1G/week	IG showed less cognitive decline compared to CG	d = 0.67

Abbreviations: CG: Control Group; IG: Intervention Group; RT: Reaction Time; UFOV: Useful Field of View.

doi:10.1371/journal.pone.0040588.t003

Part V
Summary and Conclusion

Summary of Multi-targets of Flavonoids and Polyphenol-enriched foods in Aging and AD

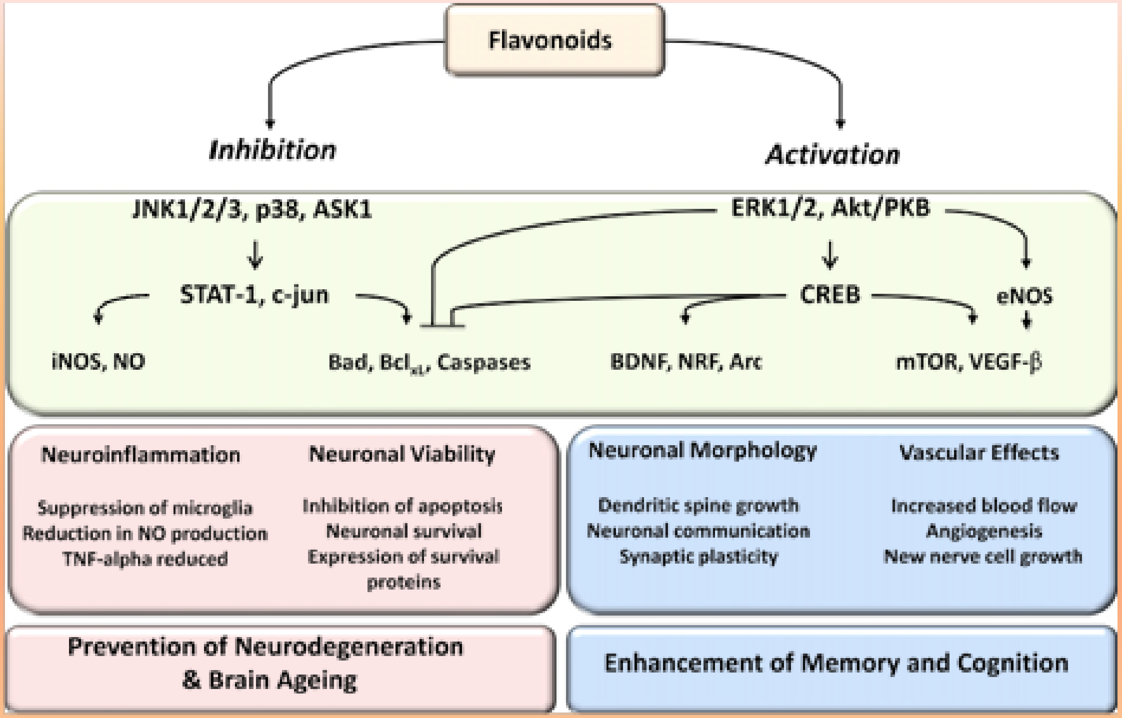


Fig. 3. Signaling pathways underlying neuronal survival and cognitive performance. Flavonoids activate the ERK–CREB pathway and the PI3-kinase–mTOR cascade lea changes in synaptic plasticity and potentially angiogenesis/neurogenesis through the activation of eNOS. On the other hand they are known to inhibiting proapoptotic s through the inhibition of JNK and ASK1. The inhibition of these kinases along with the activation of ERK1/2 leads to a suppression of apoptosis and neuroinflammation a the neurodegeneration associated with them.

Strategies to prevent Alzheimer's Dementia and Cognitive Decline
Promises, Evidence and Challenges

NIH Consensus Workshop
concludes
Insufficient evidence to recommend specific preventive Strategies for prevention of Alzheimer dementia and related Dementia syndrome

Methodological caveats may have masked the efficacy of epigenomics targeting medical foods, nutritional supplements

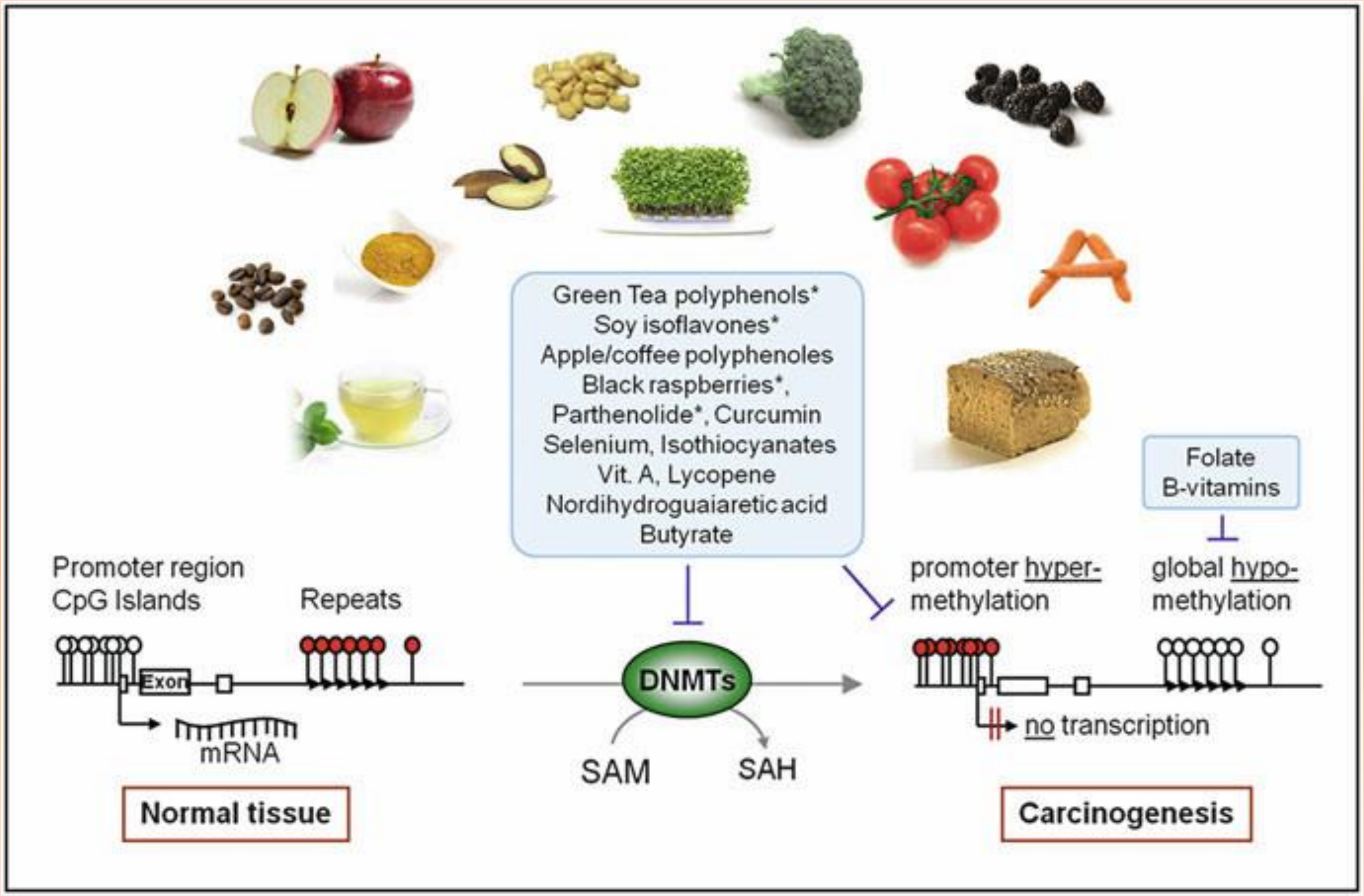
Diet : Mediterranean diet coupled with Epigenomics may offer new horizons of preventive and treatment trials

Neurodegeneration and Carcinogenesis : the Odd Couple

. EPIGENOMICS DIET FOR COGNITION

Can Epigenomics Diet work for both cancer prevention and Slowing cognitive decline and Alzheimer's dementia ?

Overlapping targets for neurodegeneration and Cancinogenesis



Multi-Domain Paradigms for Cognitive Decline Prevention

Schneider et al J Nutrition Health and AGING Volume 17, Number 3, 2013

Table 1

overview of completed multidomain intervention trials targeting cognition

Study	Country	Design	Population	Intervention	Duration of intervention	Outcome measures	Results
				Completed Trials			
SimA	Germany	randomized controlled trial	healthy elderly (n = 375)	Psychoeducational training; cognitive training; Physical training; Psychoeducational and physical training; cognitive and physical training; control group	9 months	cognition; Physical function; emotional status; independent living; health status	combined physical training and cognitive training improved psychomotor performance and reduced symptoms of dementia which neither treatment alone achieved
Fabre et al.	France	randomized controlled trial	healthy elderly (n = 32)	Aerobic training; Mental training; Both combined; control group	2 months	Physiological measures; cognition	combined aerobic and mental training provided greater effects on memory scores that either treatment alone
ShArP-P	US	randomized controlled pilot trial	elderly people at risk for cognitive decline (n =73)	Physical training; cognitive training; Physical and cognitive training	4 months	cognition; Physical function; Attendance rate	Attendance rates higher in cognitive training groups than in physical training alone; No significant change from baseline in cognition among treatments
de Jong et al.	Netherlands	randomized controlled trial	Frail elderly (n = 130)	enriched foods plus social program; regular foods plus exercise; enriched foods plus exercise; regular foods plus social program	17 weeks	cognition; Biochemical indexes	No effect of either intervention on cognitive measures
cetin et al.	Turkey	randomized controlled trial	elderly people living in retirement homes (n = 43)	vitamin e supplementation; exercise; vitamin e plus exercise; control group	6 months	cognitive function (eeG)	Shortened P3 latency values found in both exercise groups with no additive effect of vitamin e supplementation; P3 amplitude values unaltered among all groups
Smith et al.	US	randomized controlled trial	overweight/obese elderly with high blood pressure (n = 124)	dASh (dietary Approaches to Stop hypertension) diet; dASh diet plus weight management (exercise plus behavior modification); control group	4 months	cardiovascular measures; cognition	combined dASh diet plus weight management improved executive function, memory, learning measures relative to control group, while the dASh diet alone group did not improve compared to control; combined dASh diet plus weight management and dASh diet alone improved psychomotor speed measures relative to control group

Transfoming Nutraceuticals to CNS Drugs via Nanotechnology

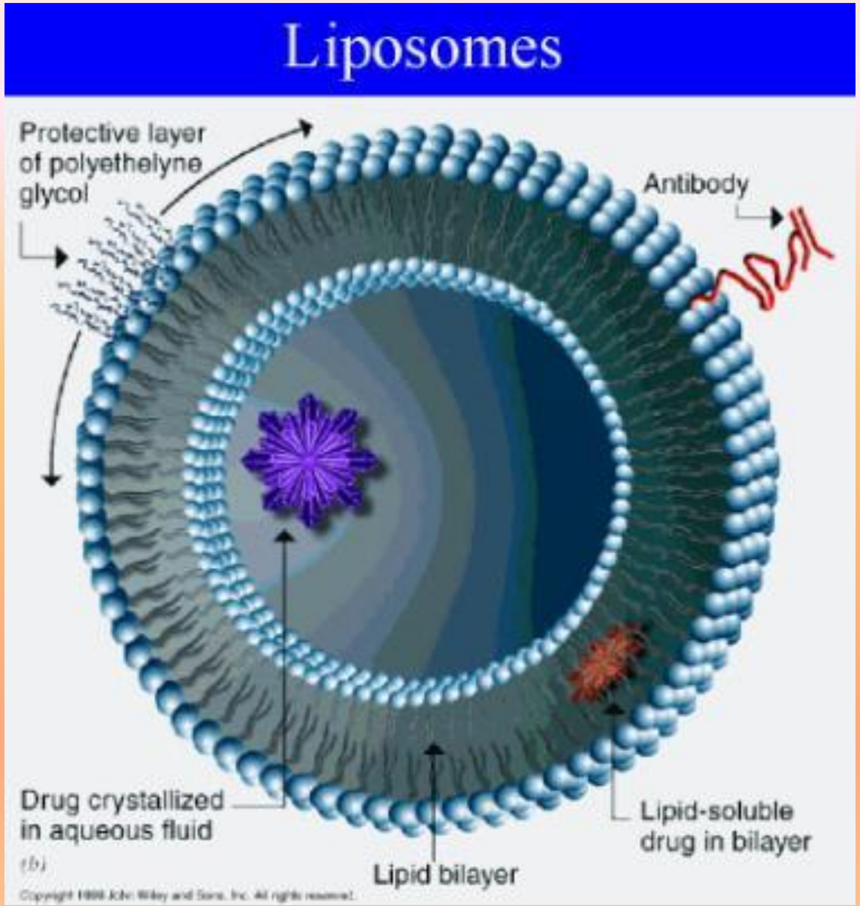
Nanotechnology :

Use of bio-compatiable materials to encapsulate active drugs for Target sites
Successfully applied in cancer chemotherapy
Emerging Role in Neurodegenerative disorders
Liposomal rivagstigmine has been formulated for neuroprotective effects

Clinical Trials of highly promising Supplements:
Ginseng, Curcumin , Ginko bilinka, Vitamin E ,Vitamin D-3 .methyl-folate
Results : findings equivocal , efficacy yet to be proven.

Methodological issues:
Product Quality, multiple chemically active moieties
Delivery system problematic
clinical trials: Underpowered

Nanotechnology: Bridging Epigenetics targets and CNS pharmaceuticals for treatment and prevention of Alzheimer's Dementia



Liposome formulated Curcumin

Patented by SignPath Pharm PA USA .
Active in transgenic models of Parkinson Disease
Clinical trial in PD under way
Ready for clinical trials in AD ????
(JCIM Chiu et al, Nov JCIM 2013)

Omega-3 fatty acid : Liposome template
Recent studies successfully formuated PUFA as the lipid shell trapping the active drug
Oncology therapeutics can benefit AD R&D

Liposome Rg3 ginsenoside Ginseng

Enhanced activity in cancer model
Approved by China FDA for Cancer treatment
Next generation of AD drug
Patented by DalianFusheng Pharm. Dalian China

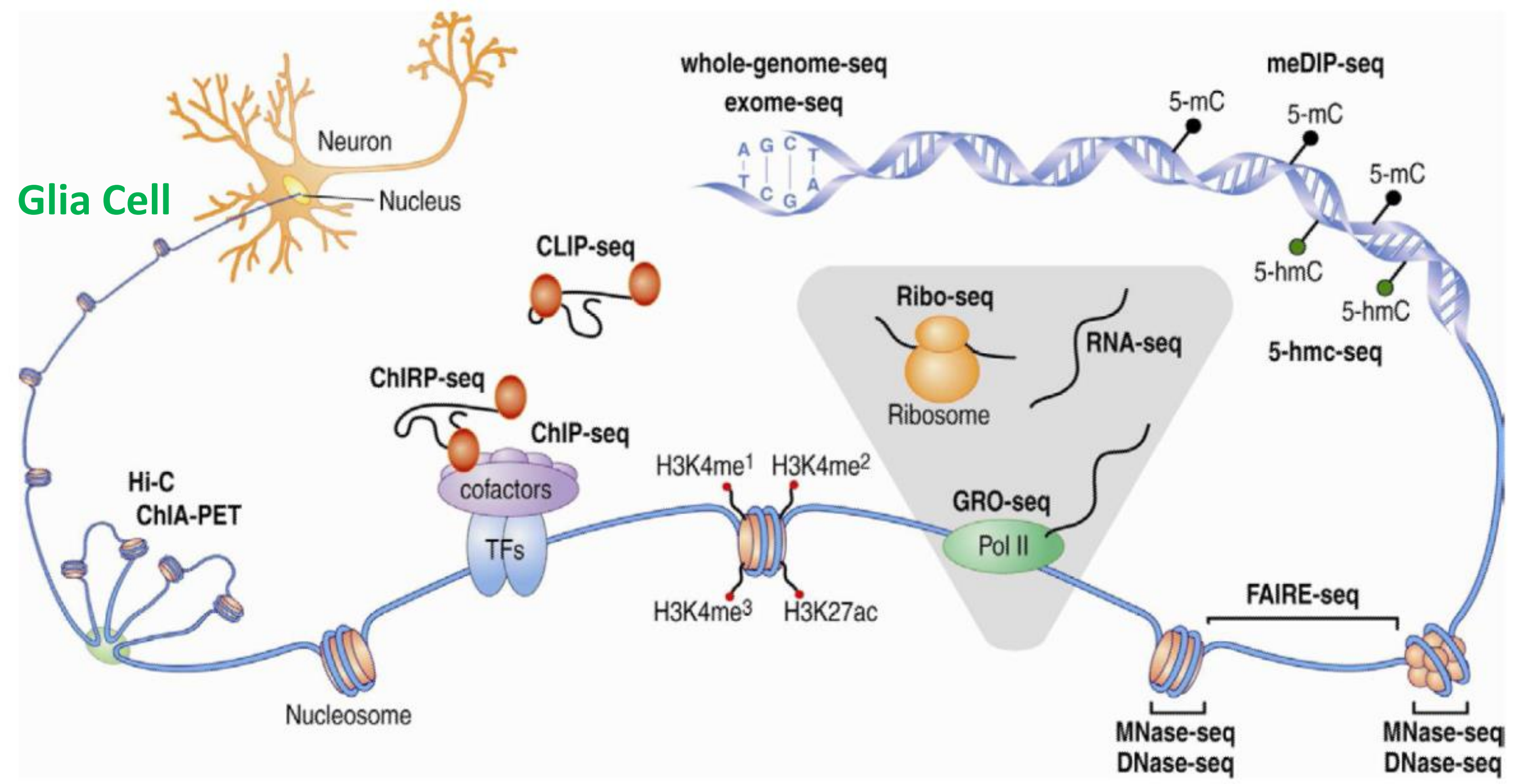
Take home message Old Supplements New Drug templates:

Chocolate, green tea. Green coffee, Grapes, Garlic , BlueBerry.
Safari Busman treasure: Sceletium Tortuosum (Zembrin@)

Translating sequencing technology to Personalized Brain Health medicine

Teleste P Et al Neruon 2013 77(4): 606-623

Glia Cell



Future direction:

Whole epigenome association technology available to define Personalised Medicine comprising Nutraceuticals, exercise and brain games based on Epigenetics of Neuron/Glia signatures, diversity and function