

**The Search for Medicine for Down's syndrome**  
*Wellcome Trust Conference Centre*

**Therapeutical Approach for common clinical aspects in  
Trisomy 21 and Alzheimer disease**

**J. LONDON**

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**Genome Campus, Hinxton, Cambridge, UK**

# Early Alzheimer disease (AD) and trisomy 21(I)

- Diminution of some brain areas
- Loss and abnormal structure of synapses
- Disturbed axonal and dendritic remodeling
- Diminution and altered morphology of dendritic spines
- Loss of functional connectivity between frontal and parietal cortices
- Abnormal hippocampic and cerebellum neurogenesis
- Cholinergic circuitry deficits
- MRI abnormalities
- **cognitive deficits**
- **Spatiotemporal abnormalities**
- **poor smelling**
- **sleep disturbancy**
- **agraphia, dysgraphia**

# Gene and risk factors for AD in T21 persons (II)

- Many chromosome 21 genes may be involved : **APP**, S100beta, BACE2, SOD1, **Dyrk1A**, DSCR1, ApoE e4
- SOD1 : deleterious or protective?
- CBS (related to homocystein) ??
- Abnormal APP metabolism :

**Measurements of Ab40, 41 and 42 and activities of secretases**

*(Nistor M. et al. Neurobiol. of aging 2007; Mehta et al 2009)*

# Alzheimer disease (AD) and trisomy 21(III)

- Conversely to the assumption that all T21 persons will develop AD, dementia **is not really more frequent** in the DS population than in the old general population **but occurs earlier and the course of the dementia is shorter**, although the biochemical and physiological hallmarks are present very early!!!

**BUT**

- Some of the deficits listed above are present:
- during **early** childhood in DS persons
- **early** in the course of the disease in AD patients

**Thus**

- Pharmacological intervention to decrease these deficits in DS may help to understand better early deficits in AD
- Finding some therapy for AD persons may help DS persons!!

# Alzheimer disease (AD) and trisomy 21(IV)

## Questions

- Is the AD type neuroanatomical-histopathology one of the cause of cognitive deficit ?
- Why there is no dementia before 40-50 years old? Is the vascular protection in DS involved??
- Why, despite the presence of these hallmarks only 40% of the DS persons will develop dementia?

## Roles of Dyrk1A overexpression in AD and DS

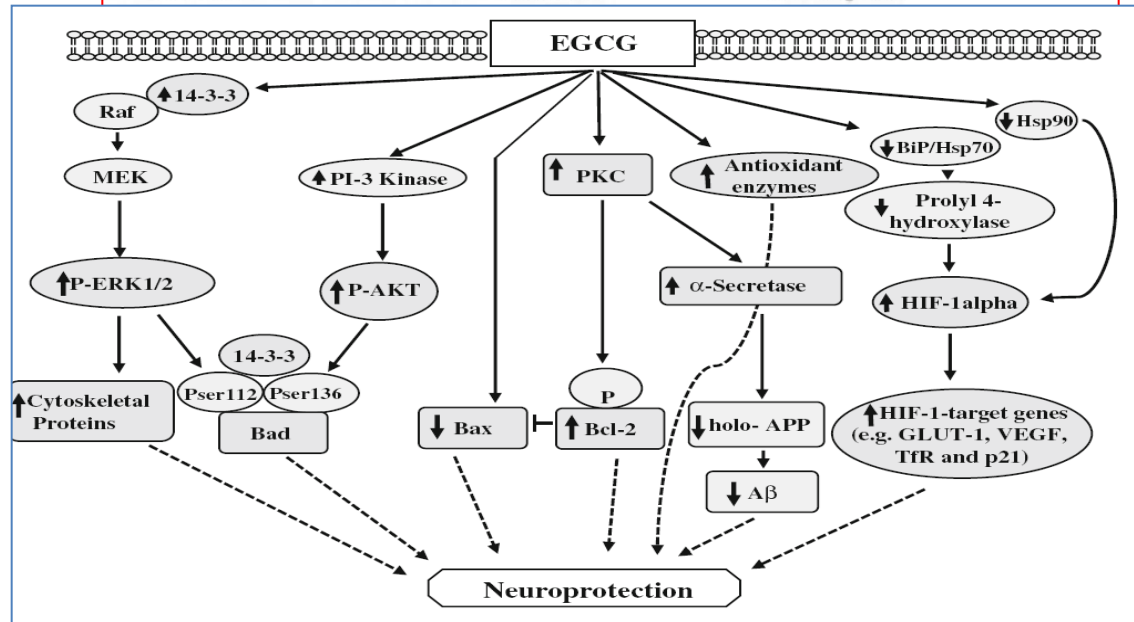
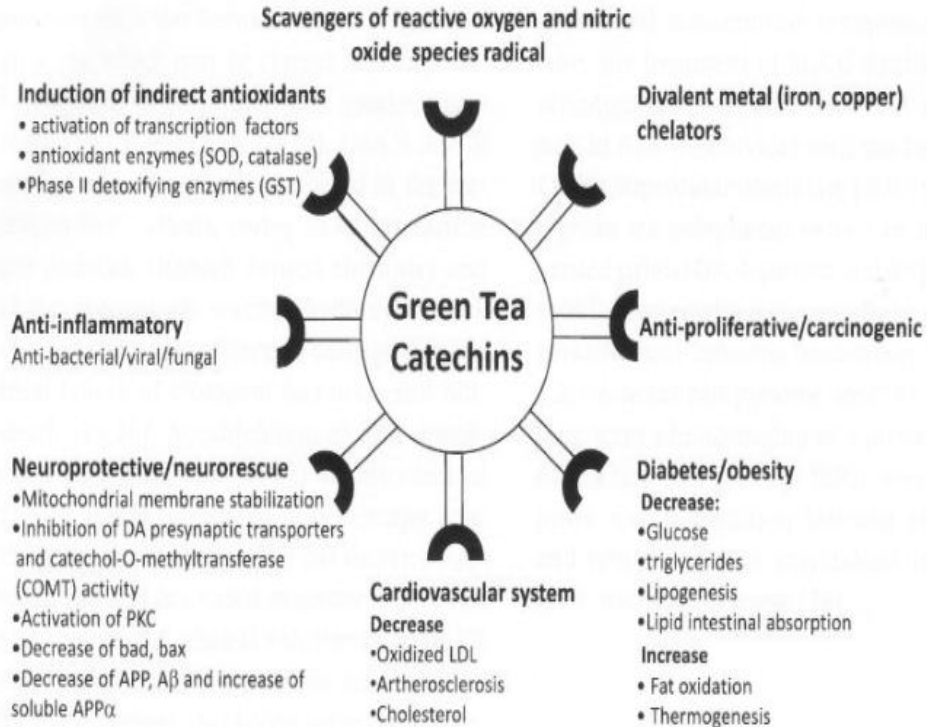
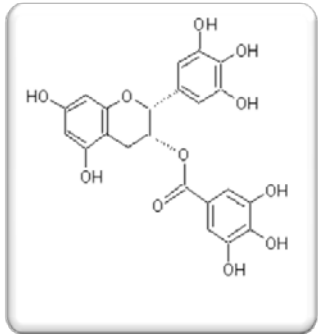
- induces cognitive deficits in mice
- Leads to abnormal morphogenesis and neurogenesis
- Alters synaptic plasticity and memory consolidation
- Is overexpressed in DS and AD brain
- Phosphorylates Tau and APP
- **These deficits in mice can be reversed by Dyrk1A inhibition**

## Aim of this talk

- Demonstrate that the clinical trials using EGCG or another compound which will be going on for cognitive improvement, might be beneficial for some of the other DS aspects such as: sleep and olfactive impairments, skin and hair problems, obesity, diabetes, anxiety and general aging.
- Some of these aspects are important for day-life and might be more easily evaluated than cognitive functions

# EGCG

Epigallocatechin-3-gallate



# Epigallocatechin gallate (EGCG)

1. Neurology
2. Sleep
3. Olfaction
4. Hair and Skin
5. Others: Obesity, anxiety, aging, diabetes



# 1. Neurology

## A) Neurogenesis

- **Neuroprotective molecular mechanisms of (-)-epigallocatechin-3-gallate: a reflective outcome of its antioxidant, iron chelating and neuritogenic properties** (*Weinreb O. Genes Nutr. 2009*)
- **Epigallocatechin-3-gallate protects motor neurons and regulates glutamate level.** (*Yu J, FEBS Lett. 2010*)
- **Dual beneficial effects of(-)-epigallocatechin-3-gallate on levodopa methylation and hippocampal neurodegeneration : *in vito* and *in vivo* studies** (*Kang KS, Plosone 2011*)
- **APP induces fundamental gliocentric shift in the progenitor pool that impairs neuronal production**(*Lu J., Plosone, 2011*)

## C) EGCG and APP metabolism

- **Reduces APP cleavage and cerebral amyloidosis in Tg mice (*Rezai-Zadeh K. 2005*)**
- **Induce  $\alpha$ secretase cleavage of APP (*Obregon DF et al 2006*)**
- **Is a potential strategy for AD (*Youdim BH 2008 and 2010*)**
- **Remodels mature amyloid  $\beta$  fibrils and reduces cell toxicity (*Bieschke 2010*)**
- **Nanolipidic particles of EGCG improve bioavailability by inducing  $\alpha$ secretase for the treatment of AD ( *Smith A. 2010*)**

# 2. Sleep

## A) AD and DS persons

### EarlyAD

- Sleep disturbances and altered circadian/ultradian patterns
- frequent daytime naps
- Sleep fragmentation
- These disturbances (or):
  - *may arise from a cholinergic deficit*
  - *correlate with the EEG power spectrum*
  - **precede degenerative events**

### DS

- Increase in sleep latency
- PS (REM) modification
- Increase in apnea episodes
- Sleep fragmentation
- **May correlate at least partially with cognitive deficits**

## B) Sleep, AD and DS mice models

1) **Several sleep studies on AD mice models (with mutated genes)** and especially: “sleep and circadian abnormalities in a transgenic model of AD: a role for cholinergic transmission” by *Wisor JP et al. 2005* and “FDG-PET imaging, EEG and sleep phenotypes as translationnal biomarkers for research on AD” by *Platt B. et al. 2011*, provide confirmation that **APP overexpression and/or deposition of A $\beta$  peptide in the brain disrupts the mechanisms that regulate sleep physiology**

### 2) In our laboratory in collaboration with Dr. J. Adrien

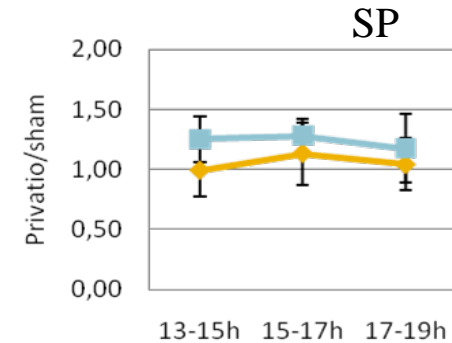
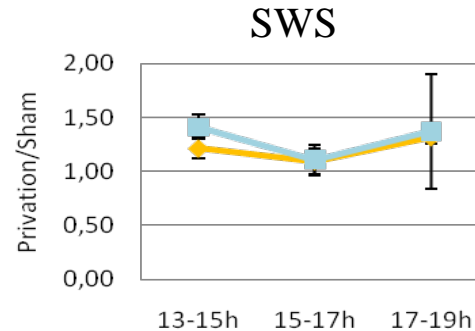
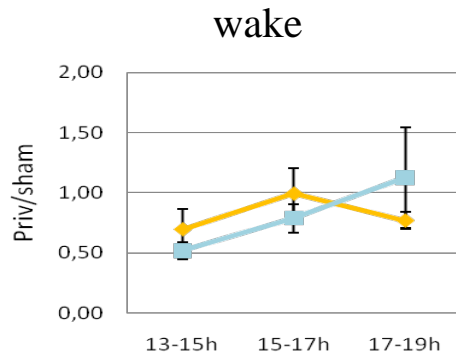
- Sleep studies on **TgwtAPP mice**: **presence of sleep fragmentation** and bad recovery after sleep deprivation; presence of SWS EEG disturbancy as in AD models.
- Sleep studies on **Tg DYRK1A**: Increase of micro-arousals; After deprivation, decrease of wake duration  
Increase of micro-arousals  
Decrease of NREM
- **EGCG treatment in control mice induces:**  
**wake increase** and decrease of total sleep;  
**less sleep fragmentation** (decrease episodes number during SP)

# Tg wt APPmice (Alloui S. , Adrien J. london J)

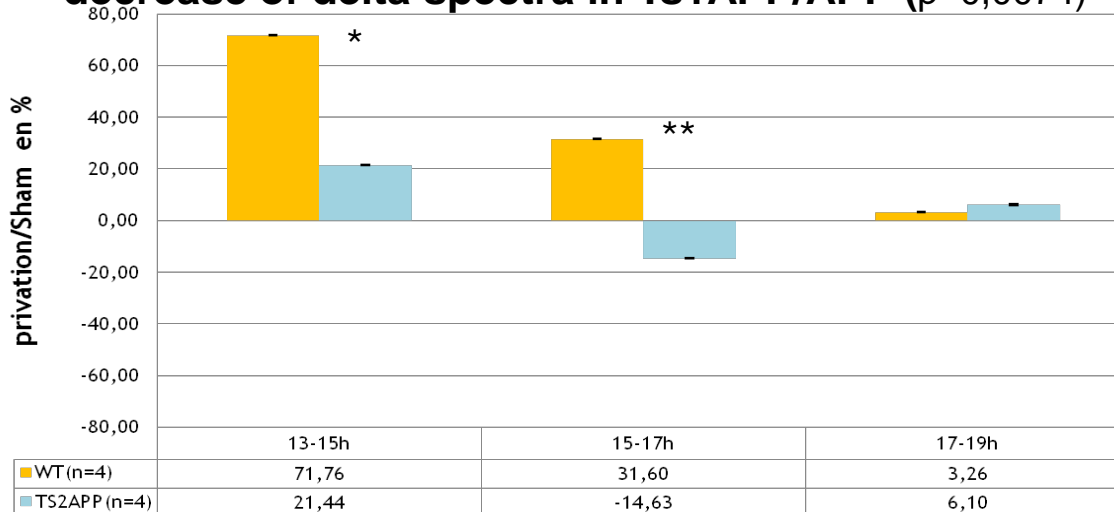
- No modification of the various base line characteristics (wake, SWS or NREM or REM)
- Modification after sleep deprivation

## sleep deprivation effect on stages duration

—●— WT(4)  
—■— Ts1APP/APP(4)

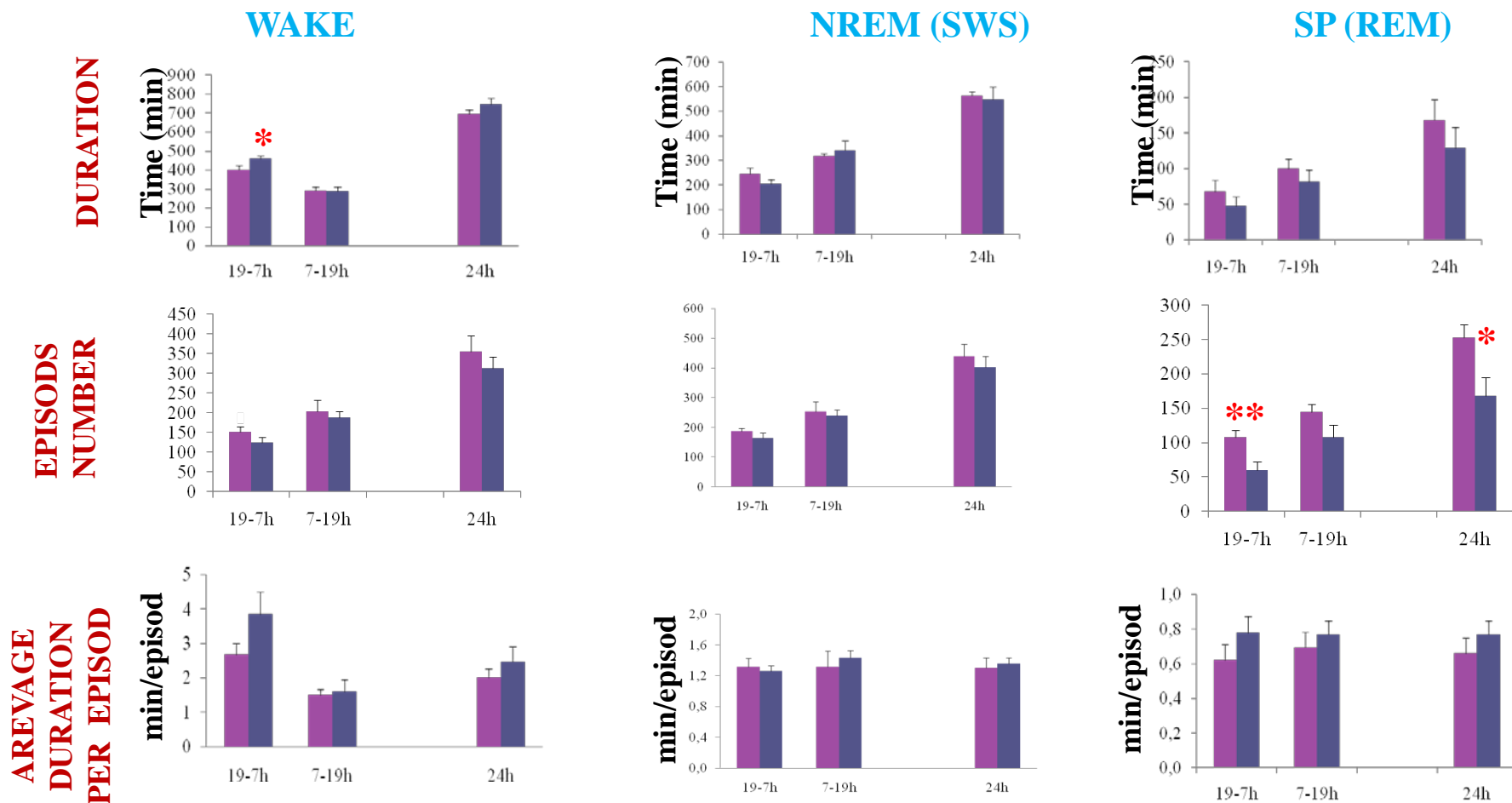


## sleep deprivation induces significant decrease of delta spectra in Ts1APP/APP (p=0,0074)



**These results show the role of APP overexpression on sleep fragmentation independant of amyloid deposit**

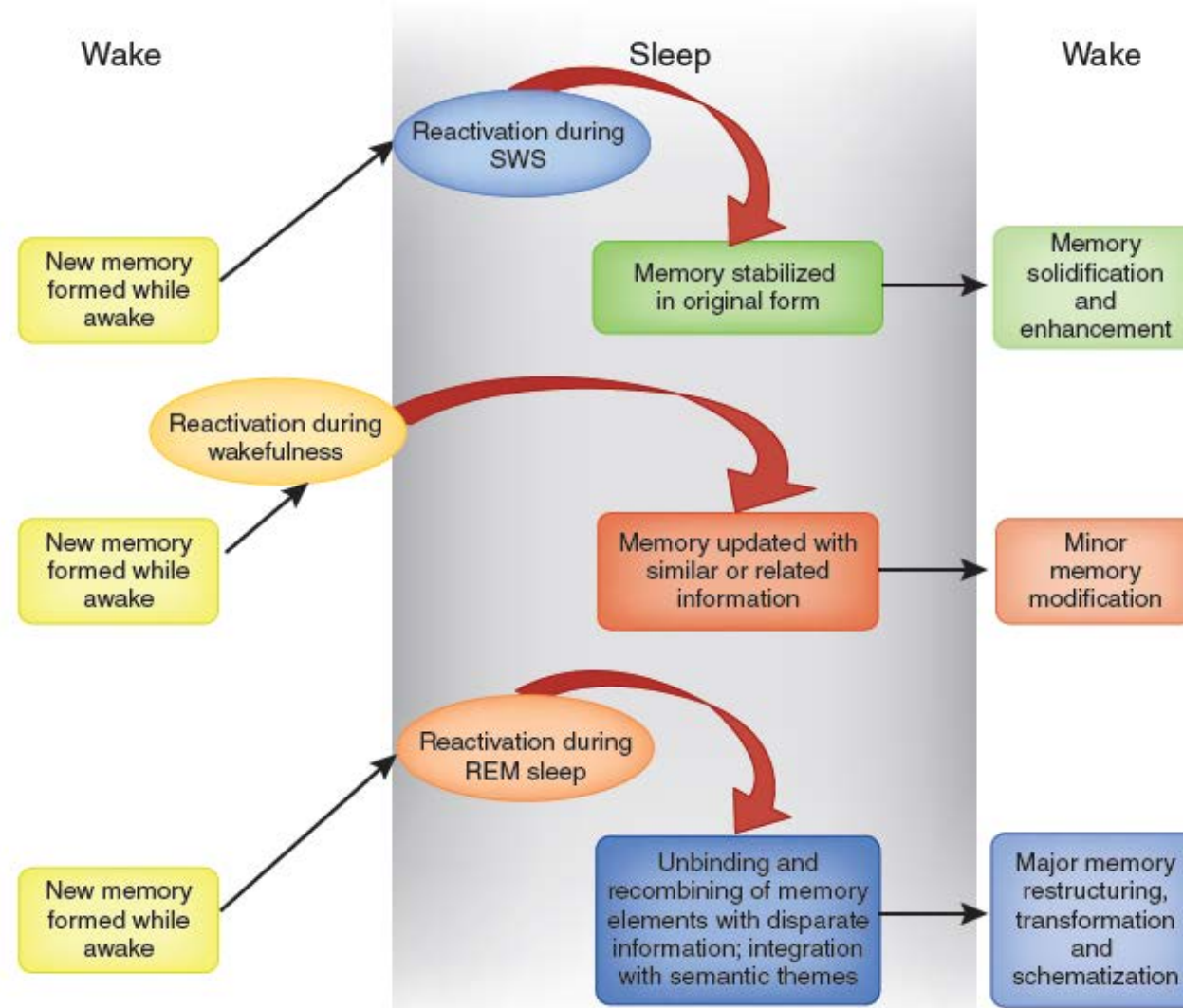
WT  
 WT EGCG TREATED



## EGCG treatment on WT mice induces

- **wake increase** and decrease of total sleep
- **Less sleep fragmentation** (decrease episodes number during SP)

What chemical basis? (catecholamine in various brain areas)



S

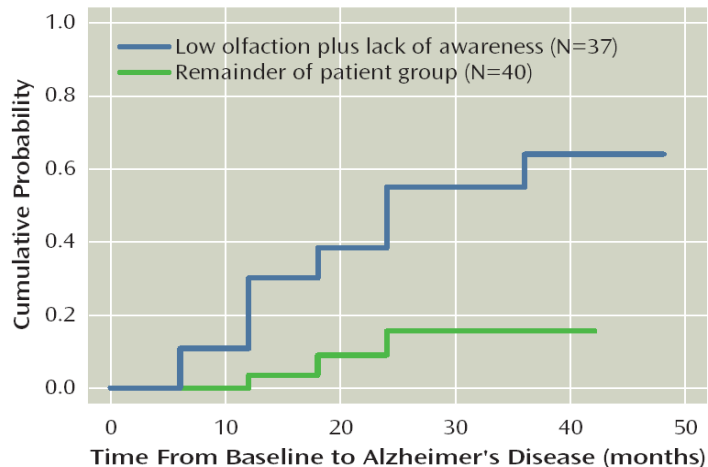
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**Figure 1** Potential influence of memory reactivation during wakefulness and different stages of sleep. Top: reactivation during SWS causes enhancement and stabilization of memory in its original form, leading to memories that are true representations of originally encoded experience. Reactivating memories during SWS by re-presenting a memory cue (such as an odor) present at initial learning leads to memory stabilization<sup>3</sup>. Middle: reactivation during wakefulness causes memory modification and updating, allowing new but related information to be incorporated into the original memory trace<sup>5,6</sup>. Bottom: reactivation during REM sleep causes substantial memory restructuring and recombination of memory fragments that become isolated in the REM-sleep brain state. Such recombination may lead to insights, creative solutions to problems and memory schematization.

# 3) Olfaction

## A) Odor deficits in AD persons

On considering the similarity between the neurodegenerative brain pathology exhibited by Alzheimer patients and Down subjects and a recent observation that the former show pathological changes also in the olfactory epithelium (neuritic plaques and neurofibrillary tangles), olfactory tasks could represent a useful noninvasive diagnostic method. (*Zucco GM and Negrin NS 1994*)!!



Olfactory deficits in patients with mild cognitive impairment predict Alzheimer's disease at follow-up. *Devanand DP, Am J Psychiatry. 2000*

FIGURE 1. Kaplan-Meier Survival Curve of Probability of Developing Alzheimer's Disease Over 4 Years in Subjects With Mild Cognitive Impairment at Baseline, by Presence or Absence of Baseline Olfactory Deficit Plus Lack of Awareness of Deficit

The first areas where NTF are present are the anterior olfactory nucleus, olfactory bulb contains senile plaques and NTF and in these areas cholinergic activities are reduced



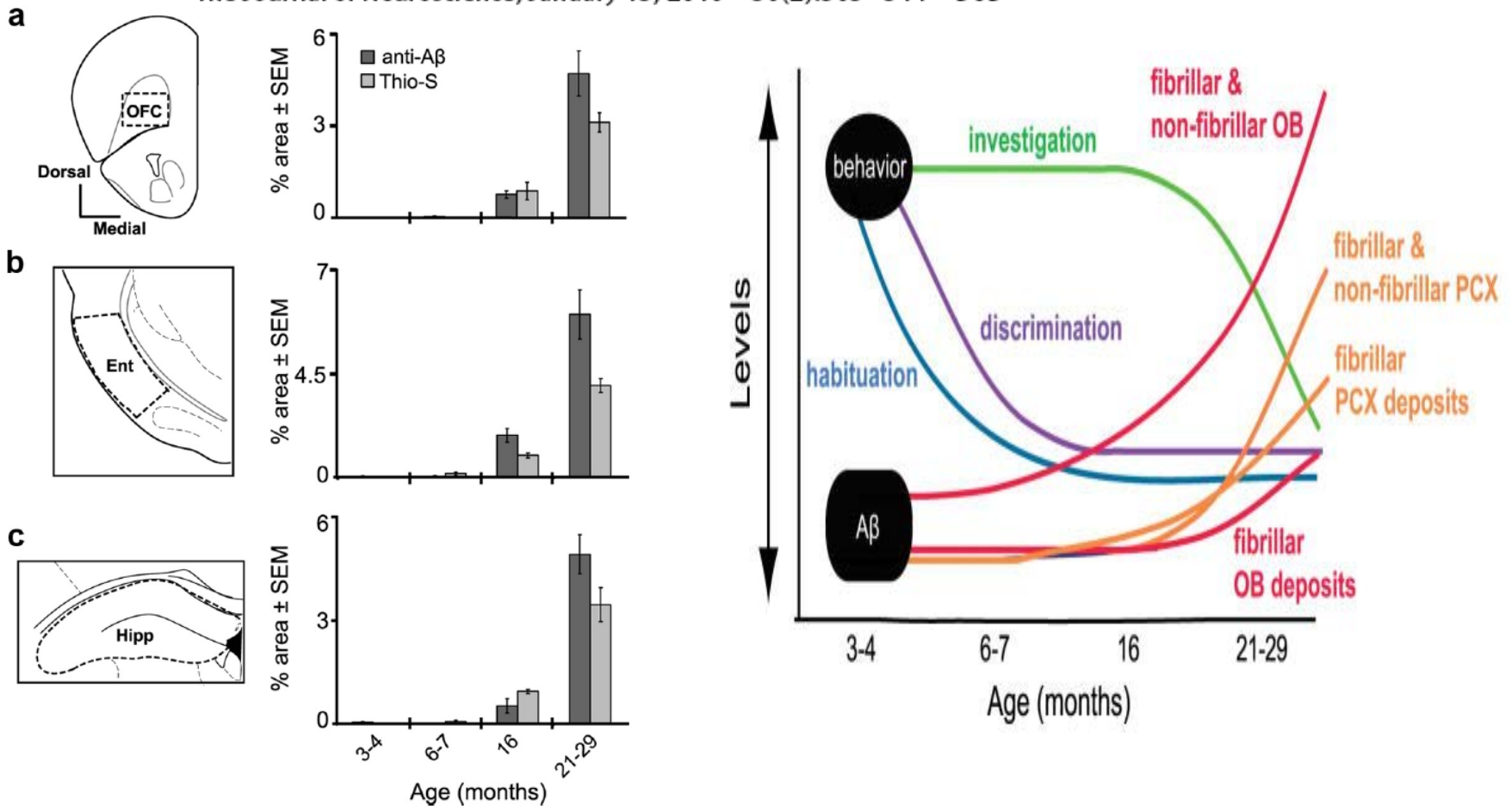
# B) Odor deficits in AD mice

Neurobiology of Disease

## Olfactory Dysfunction Correlates with Amyloid- $\beta$ Burden in an Alzheimer's Disease Mouse Model

Daniel W. Wesson,<sup>1,3</sup> Efrat Levy,<sup>2,4,5</sup> Ralph A. Nixon,<sup>2,5,6</sup> and Donald A. Wilson<sup>1,3</sup>

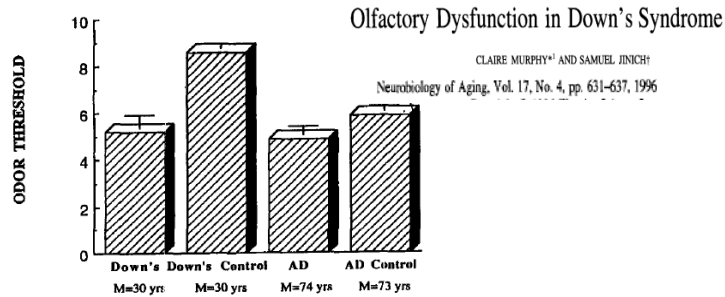
The Journal of Neuroscience, January 13, 2010 • 30(2):505–514 • 505



# C) Odor deficits in DS

CLASSIFICATION OF DOWN'S AND CONTROL SUBJECTS BASED ON MEASURES OF OLFACTORY FUNCTION

	Anosmic		Hyposmic		Normosmic	
	Down's	Controls	Down's	Controls	Down's	Controls
UPSIT scores	11	0	12	2	0	21
Olfactory threshold	1	0	13	0	9	23
Odor Memory (Pc)	1	0	13	0	9	23



-1994: link with DS  
(Zucco GM and NegrinNS)

-1998 Warner MD

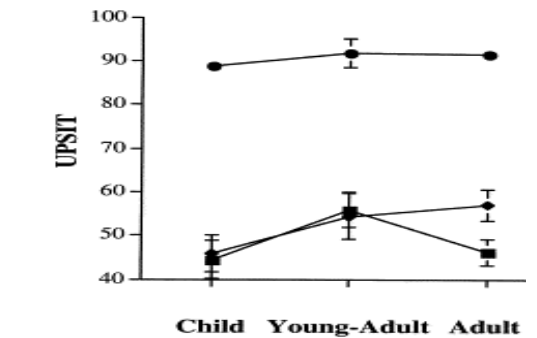
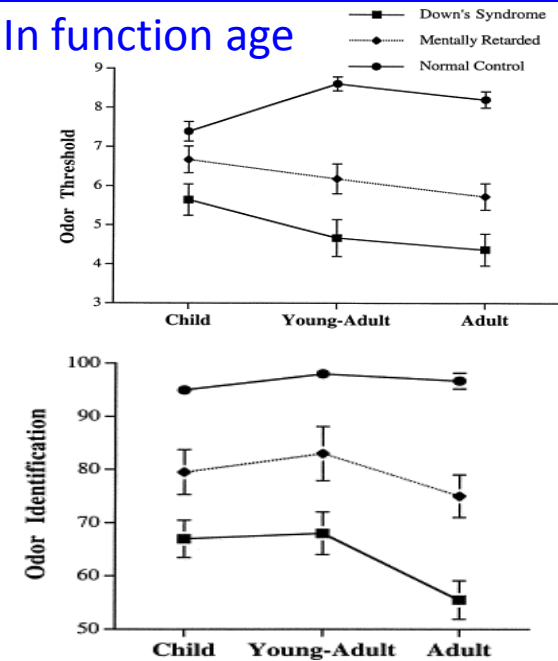
-1993 Hemdal

-1996 Murphy C.

-2002 Nijjar R. et Murphy C.

-2004 Sliger M. and Murphy C.

## In function age

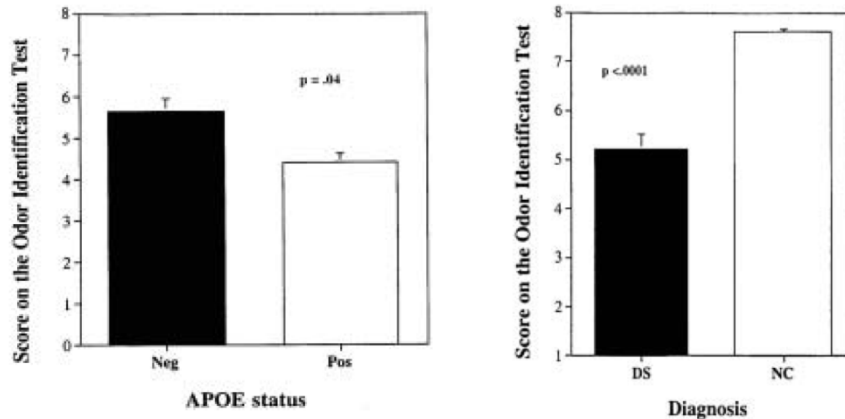


The University of Pennsylvania Smell Identification Test (UPSIT) is a 40-item odor identification test booklet composed of microencapsulated odor

Olfactory impairment increases as a function of age in persons with Down syndrome

Ram K. Nijjar<sup>1</sup>, Claire Murphy<sup>2,3\*</sup>

## In function of ApoE



Journal of Alzheimer's Disease 6 (2004) 397-402  
IOS Press

Effects of the ApoE ε4 allele on olfactory function in Down Syndrome

Melissa Sliger<sup>a</sup>, Timothy Lander<sup>b</sup> and Claire Murphy<sup>a,b,\*</sup>

#### **4. Odor deficits in DS murine models and EGCG effects????**

**Might be valuable to test?!!!**

# 4. Hair and Skin

## Potential effect of EGCG

**Hair** Phytomedicine 14 (2007) 551–555

### Human hair growth enhancement in vitro by green tea epigallocatechin-3-gallate (EGCG)

O.S. Kwon, J.H. Han, H.G. Yoo, J.H. Chung, K.H. Cho, H.C. Eun, K.H. Kim\*

*Department of Dermatology, Seoul National University College of Medicine, Laboratory of Cutaneous Aging and Hair Research, Clinical Research Institute, Seoul National University Hospital, Institute of Dermatological Science, Seoul National University, 110-744 Seoul, Republic of Korea*

### **Skin:**

Int J Clin Exp Pathol 2010;3(7):705-709

### *Original Article*

### Anti-angiogenic effects of epigallocatechin-3-gallate in human skin

Diana Santo Domingo<sup>1,2</sup>, Melissa M. Camouse<sup>1,2</sup>, Andrew H. Hsia<sup>1</sup>, Mary Matsui<sup>5</sup>, Daniel Maes<sup>5</sup>, Nicole L. Ward<sup>1,2</sup>, Kevin D. Cooper<sup>1,2,3,4</sup>, Elma D. Baron<sup>1,2,3,4</sup>

## 5) Other effects in some aspects of T21

- A) Obesity:** several studies have shown the beneficial effects of EGCG
- in human analysis ( *Lee MS et al. 20009; Hursel R. et al. 2009;Thielecke F. 2010; Basu A. 2010; Sae-tanS. 2011*)
  - in animal models (*Grove KA 2011; Friedrich M. 2011*)
- B) Diabetes**
- C) Anxiety:** reversion of caffein effect (*Park KS 2010*)
- C) Aging:** aging induced by galactose is reversed by EGCG (*He M. 2009*)

# conclusions

- Any kind of pharmacological improvement might have some benefits on other neural paradigms such as sleep and olfaction which are more easily tracable than cognitive improvements
- The EGCG trials should also give some additional indications of day-life improvement, if are performed also, olfaction tests and sleep evaluation either by questionnaires or by medical testing
- Moreover EGCG trials may give some information on other paradigms such as obesity, if subgroups of patients are evaluated for these paradigms.

## B) AD mice models

Neuroscience 131 (2005) 375–385

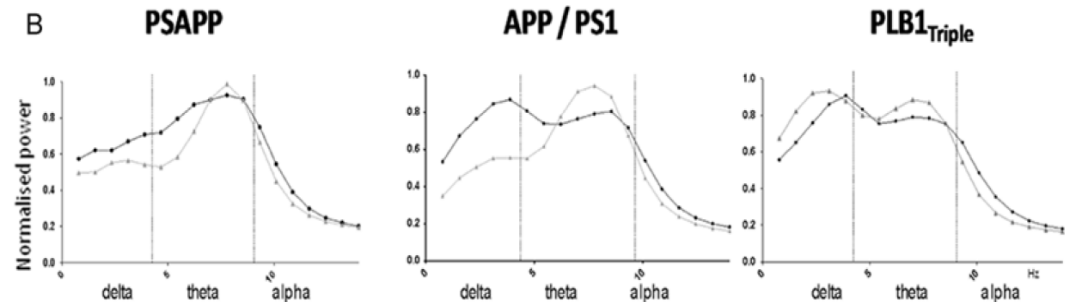
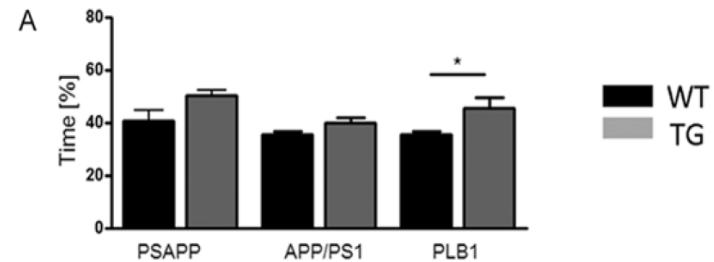
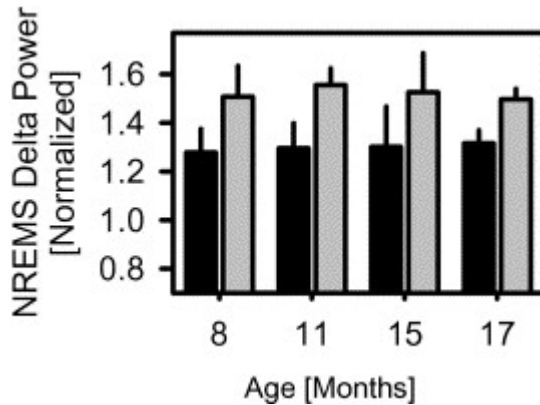
### SLEEP AND CIRCADIAN ABNORMALITIES IN A TRANSGENIC MOUSE MODEL OF ALZHEIMER'S DISEASE: A ROLE FOR CHOLINERGIC TRANSMISSION

J. P. WISOR,<sup>a1</sup> D. M. EDGAR,<sup>a</sup> J. YESAVAGE,<sup>a,c,d</sup>  
H. S. RYAN,<sup>b,d</sup> C. M. MCCORMICK,<sup>a</sup> N. LAPUSTEA<sup>b</sup>  
AND G. M. MURPHY, JR.<sup>b,c,d\*</sup>

Biochemical Society Transactions (2011) Volume 39, part 4

### FDG-PET imaging, EEG and sleep phenotypes as translational biomarkers for research in Alzheimer's disease

Bettina Platt<sup>1</sup>, Andy Welch and Gernot Riedel



Several studies and especially those of Wisor JP et al. 2005; Platt B. et al. 2011 provide confirmation that **APP overexpression** and/or deposition of A $\beta$  peptide in the brain **disrupts the mechanisms that regulate sleep physiology**.