

ASSA Workshop

Changing Models of Gene-Environment Interaction

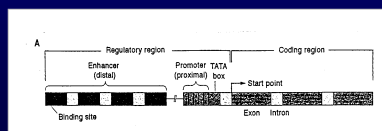


Late-life depression

Our changing views of genetics and behaviour.....

- Tabula rasa B
- Mendelian inheritance $G+E=B$
- Human Genome Project
QTL linkage – dose effect dimensional phenotypic trait $G+G+G+G+G\dots=B$
- Epigenetic regulation $G_1+E_1=B_1 f(T_1)$

The link between transcriptional regulators and enhancer regions is modified by endogeneous and exogeneous stimuli



Genetic epidemiology multiple gene/environment relationships

relation	gene without environment	environment without
1	no pathology	no pathology
2	no pathology	pathology
3	risk ↑	no pathology
4	risk ↓	pathology
5	risk ↓	no pathology
6	risk	pathology

And to make matters even more complicated...

- Diminishing of genetic effects across time
- New genes coming into play with changes in cortical development
- Small genetic differences in infancy have increasingly large phenotypic effects with age
- Factors modulating the relationship between environment and genes alter with age (ApoE 4; 'g' factor)
- Other behaviours such as anxiety inhibit stem cell production in the dentate gyrus
- Shared environment has lesser impact with age

Problems in the identification of genetic risk factors

- Measurement of the phenotype
- Focus on coding sequences not regulatory regions
- QTL requires large samples with increased risk of type I error
- Selection of controls
- « a bewildering array of seemingly positive results interlaced with numerous failed replications » (Baron 1997)

• Henderson and Blackwood *Psychol Med* 1999

The example of late-life depression

- Depression second cause of disability, premature death and socio-economic burden in 2020 (World Bank)
- 11 disability days per year for each case of depression
- Relative risk of coronary disease higher for depression than for cigarette smoking
- Rates of depression high in the elderly 12-15% over 65

Defining the phenotype.....

- **Major depression:** one of two core symptoms (depressed mood; lack of interest) and 4 or more accompanying symptoms (worthlessness, guilt, diminished concentration, fatigue, agitation, sleep disorder, weight change, suicidal thoughts) for at least two weeks (10% LT, 4/32% in institutions)
- **Minor depression:** 2-3 accompanying symptoms (4-13% in elderly)
- **Dysthymic disorder:** low intensity symptoms for at least two years (1-2% in elderly)

Risk factors for late-life depression

Meta-analysis : Illness, prior depression, bereavement, sex, sleep disturbance (Cole and Dendukuri 2003)

Risk-model : death of spouse, chronic illness (Schoevers et al. 2006)

Longitudinal studies:

Sex, education, marital status, WML (Anstey et al. 2007)

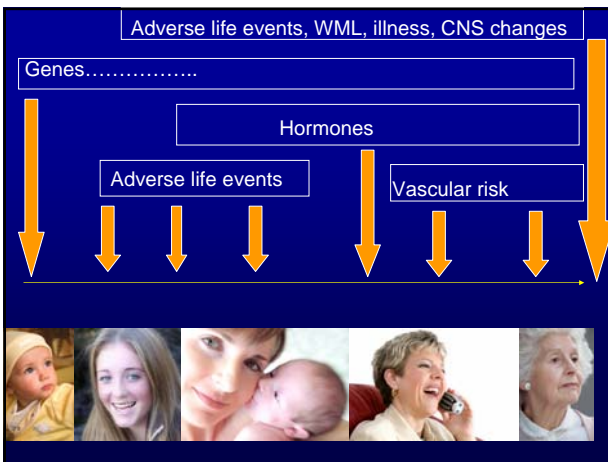
Stroke, cholesterol (Kim et al. 2006)

Review of late onset cases (Artero et al. 2006) :

Disease (dementia, diabetes, hypertension, cancer, cardiovascular disease)

Medication side-effects (β -blockers, neuroleptics, anti-hypertensive drugs)

Associated with executive rather than memory dysfunction (? Vascular depression)



ESPRIT

A population study of late-life psychiatric disorder

- 1863 community dwelling persons 65 and over
- Random selection from 15 electoral rolls in the District of Montpellier
- Inclusion 1999-2000
- + 3 follow-up waves



Medical history

- Current health
- Medication
- Disabilities
- Past and family health
- Sleep disorder
- Hormonal changes
- Trauma
- Environmental exposures
 - pesticides, nutrition...



Neurological examination-ICD 10



Cognitive functioning



- MMSE
- Benton VRT
- Word list recall
- Verbal fluency
- Trail-making A and B
- Digit span

Carotid ultra-sound



ECG

Blood pressure



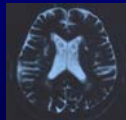
Polysomnography
(450 ss)



MRI

(800 subjects under 85)

- Detection and localization of microlesions
- Hippocampal volume



Psychiatric examination

- Mini International Neuropsychiatric Interview MINI DSM IV
- CES-D Depressive symptoms
- Spielberger Trait and state anxiety
- Spielberger-anger scale
- Barrat impulsivity scale
- Buss-Durkee aggression scale
- Childhood environment
- Life-time trauma



Biological samples



DNA and serum
Lipids, glycemia...

Biological samples



Salivary cortisol- 2 days
(3 times per day)

ESPRIT population (1863 ss)

<i>Women</i>	58.5%
<i>Mean age (SD)</i>	73.0 (5.7) yrs
65-74	66.9%
75-84	29.2%
85+	3.9%
<i>Marital status</i>	
Married	66%
Divorced	28.8%
<i>Education level</i>	
Low	23.6%
Medium	51.6%
High	24.6%
<i>Repatriated</i>	15% (1/4 trauma)

Prevalence of Psychiatric Disorder

PATHOLOGY	CURRENT (17%)	LIFE-TIME (48%)
DEPRESSION		
- MDE	3.1 %	26.5 %
- Mania	0.5%	1%
ANXIETE		
- Phobias	10.7%	21.6 %
- Generalized anxiety	4.6 %	10.8 %
- OCD	0.5 %	1 %
- Panic	0.3 %	2 %
- PTSD	0.3 %	1%
PSYCHOSIS	1.7 %	4.7 %
SUICIDE	9.8 % (ideation)	3.7 % (TS)

Ritchie et al., *Br J Psychiatry* 2004

Genes

Depression has strong heritability – 33% on the basis of twin studies (Wurtman 2005)

No « candidate gene » many QT loci with small effects interacting epistatically with a wide range of environmental pathogens

Focus on genes implicated in the serotonergic and dopaminergic systems (synthesis, catabolism and transport): SLC6A4/5-HTT, 5HTT2A, TH, COMT, TPH1, 5-HTTLPR

Meta-analysis 5-HTTLPR 21% MD SS; 17% controls – s allele probably recessive for MD (Lotrich and Pollock 2004)

Better response to SSRIs with ss variant (Serretti 2007)

5-HTT ss polymorphisms more common with age of onset before 65 (Grunblatt et al. 2006)

ESPRIT Study

	MD < 50 yrs	MD > 50 yrs	No depression
LL	35.5%	29.6%	27%
SL	43.9%	48.9%	50%
SS	20.7%	21.5%	22%

Do genes cause depression or simply make one vulnerable to adversity ?

Neuroimaging shows SS subjects have greater amygdala activation in response to fearful stimuli (Wurtman 2005)

Life-events are more likely to cause depression in SS subjects (Caspi et al. 2003)

In young adults a stressful environment gives higher rates of depressive symptoms in ss genotypes but less if had supportive environment (Taylor et al. 2006)

Higher SS genotype frequency in 75 yr olds with past/present depression (Grunblatt 2006)

Higher depressive symptomatology after hip fracture in elderly SS subjects (Lenze et al. 2005)

Life-event x gene interaction evident in elderly (Kim et al. 2007)

ESPRIT Study Environment (i) Late-life

Interactive effect between late-life LEs and depression but no interaction effect between genotype and life events in predicting current or incident depression independantly of measure (MINI, CES-D). Approaching significance at base-line in opposite direction (Wald 3.2, p<0.07) (Power, Stewart et al. 2007)

Gene environment interactive effect appears to persist in old age in an Asian but not a European population

Environment (ii) Childhood trauma

Severe early stress alters brain development

Disrupts stress-induced programming glucocorticoid, noradrenergic and vasopressin-oxytocin stress response systems and thus heightens stress response

Trauma impacts on neuronal growth and myelination leading to reduced corpus callosum and poorer development of left neocortex, hippocampus and amygdala

A perfect hot-house for depression and substance abuse



Childhood trauma

Retrospective study of 47 adults with MD and 41 controls on CTQ. MD subjects had more emotional and physical abuse and neglect. Severity of childhood trauma (notably emotional abuse) predicted age of onset (earlier) and number of lifetime episodes (Bernet and Stein 1999)

Factors related to psychiatric status (PSE) at age 36 in 3294 Ss1946 Cohort

Men	p
Father over 42 yrs	0.02
Death of father age 5-11	0.001
Separation over 4 wks	0.001
Mother's neuroticism	0.003
Women	
Divorce parents	0.001
Health 0-15 yrs	0.002
Mother's neuroticism	0.003
Father's physical health	0.001 (Rogers 1990)

Childhood trauma – predictors of depression

Community sample of 194 elderly - depressive symptoms associated with abuse and neglect in childhood (Kraaij and Wilde 2001)

ESPRIT Study Childhood event value	Men			Women		
	OR	p value		OR	p value	
Father not affectionate	1.4	NS		1.6	0.06	
Mother not affectionate	2.4	0.05		2.0	0.006	
Father alcoholic	2.6	0.03		2.2	0.02	
Home conflict	2.3	0.009		1.8	0.001	
Poverty	1.7	0.07		2.6	0.0001	
Verbal abuse	2.9	0.05		2.4	0.03	
Abused by adult	-	-		3.9	0.2	
Maltreated by teacher	2.1	NS		2.5	0.1	

Adjusted by age, sex, dementia, anxiety, hypertension

ESPRIT (CES-D>16 or anti-depressant treatment)

Childhood event	Men		Women	
	OR	p	OR	p
• Mother not affectionate	3.4	0.01	2.2	0.005
• Serious conflict	1.5	NS	1.5	0.1
• Poverty	1.4	NS	1.9	0.007
• Verbal abuse	6.1	0.0004	4.6	0.003
• Humiliation	4.7	0.02	5.1	0.004
• Excessive punishment	3.4	0.01	3.4	0.03
• Abuse by adult	-	-	5.7	0.03
• Mistreatment	-	-	8.6	0.04

Adjusted by age, sex, anxiety, dementia, hypertension

- Interaction with 5-HTTLPR polymorphism shows protective effect of L allele (Surtees et al. 2006)

Childhood trauma and 5-HTTLPR

Life-time depression

<u>LL</u>	OR	p
• Conflict	2.06	<0.039
• Poverty	3.7	<0.011
• Punishment	3.05	<0.078
• Adult friend	0.45	<0.012
<u>SS</u>		
• Mother psy	3.15	<0.021

Childhood trauma and 5-HTTLPR

Late-onset depression

<u>LL</u>	OR	p
• Poverty	2.39	<0.017
• Humiliation	3.23	<0.056
• Adult friend	0.30	<0.006
<u>SS</u>		
• Mother psy	3.36	<0.021

Environment (iii) Trauma in adulthood

PATHOLOGY	Non Repatriated	Repatriated	Repatriated (+ trauma)
MD LT	26.1 %	26.3 %	48.9%*
Phobias LT	21.2%	19.1 %	28.9%
GAD LT	10.5 %	10.2 %	20%*
Psychosis LT	4.2 %	7.2 %	6.7%*
Panic LT	2.1%	2.5%	4.4%
Suicide attempts LT	3.5 %	2.6 %	6.7%*
Ideas suicide current	9%	7.6%	13.3%*
≥ 1 anxiety s LT	29%	26.7%	42.2%*
current	13.1%	13.6%	24.4%*
≥ 1 psychiat s LT	44.7%	43.6%	62.2%*
current	15.6%	16.5%	29%**
≥ 1 psychotrope current	19.5%	18.6%	29%*

Adjusted by age, sex and education

5-HTTLPR gene x environment interaction

- Logistic model – occurrence of life-time MD or minor depression

	<i>p</i> *
1. Rapatriated	<u>0.0001</u>
2. Gene 5 HTTP	0.46
3. G X E	<u>0.002</u>

*Adjusted by sex, age, education, cognitive disorder

5-HTTLPR distribution

Subjects

	n
-Controls	632
-Repatriated	186
-Repatriated+other traumatic LE	62

Genotype

	n
- LL	189 (21.5 %)
- SL	438 (49.5 %)
- SS	253 (28.8 %)

Adult trauma G X E effects

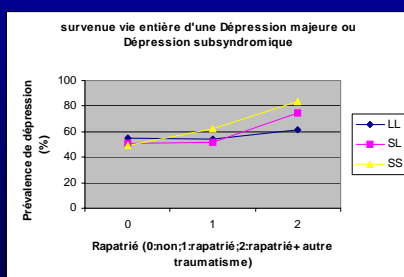
- Stratification by gene for G*E effect

	<i>p</i>	OR (IC) *
LL	NS	NS
SL	<u>0.003</u>	1.46 (1.03-2.05)
SS	<u>0.000</u>	2.50 (1.46-4.26)

- Genotype SS : 2.5 greater risk

*Adjusted

G X E interaction in traumatized repatriats



Interaction G X E and age of trauma

	<i>p</i>	OR (IC) *
- Age <35 ans	<u>0.001</u>	1.29 (1.11-1.5)
- Age =>35 ans	0.067	1.17 (0.98-1.39)

* Adjusted

Interaction G X E and age of trauma

- Stratification by gene et age

		<u>p</u>	<u>OR (IC) *</u>
LL	<35 ans	NS	NS
	=>35 ans	NS	NS
SL	<35 ans	<u>0.047</u>	<u>1.57 (1.04-2.45)</u>
	=>35 ans	0.62	1.22 (0.74-2.03)
SS	<35 ans	<u>0.002</u>	<u>2.91 (1.44-5.88)</u>
	=>35 ans	0.08	2.00 (0.9-4.44)

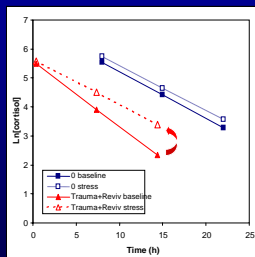
* Adjusted

Recall bias or are the effects of trauma reflected in biological markers ?

- Increased base-line cortisol secretion in depressed subjects (Harris et al. 2000; Young et al. 2001°)
- Blunted cortisol response under stress conditions (Trestman et al. 1995; Peeters et al. 2003)
- ESPRIT Overactivity of HPA axis in elderly subjects with co-morbid anxiety and depression following stress, whereas those with depression without anxiety show a blunted response (Beluche et al. 2007)

Stress reactivity

Trauma with reviviscences



Chaudieu, Beluche et al. (2007)

An « envirome » project

An « envirome » project to parallel the Human Genome Project

A repertory of expositions which modulate the appearance of mental illness in old age

A classification system of environmental risk factors such as that proposed by Gruenberg
Mental Disorders: A Guide to Prevention and Control APHA

