Neuropsychiatric disorders in older women: the influence of hormone exposure

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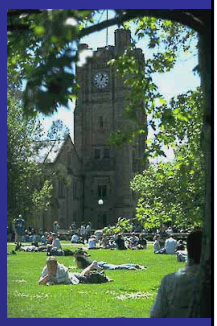

Epidemiology & Clinical Research in Nervous System Pathologies
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Overview

1. Literature
   - Hormone Therapy: risk/benefits
   - Estrogen: Cognitive function & depression
   - Biological Basis
   - Reported associations

2. Research Aims
3. Methodology
   - Population-based studies
   - Variables of Interest

4. Results
5. Further work

Hormone Therapy (HT)

HT developed to alleviate menopausal symptoms

Menopause is a physiological event occuring in all women who reach midlife

Symptoms affect women to varying extents

HT consists of estrogen +/- progesterone

Effective in reducing the most common symptoms:

- Vasomotor Symptoms (hot flushes, night sweats)
- Sleep disturbance
- Irritability, Mood swings
- Sexual problems

➢ Other positive effects too

Results of American WHI Study (2002) indicated risks associated with HT

Risks / Benefits of HT

?? Increased risk of:

- *Breast Cancer
- *Endometrial cancer (only estrogen alone in non-hysterectomised women)
- *Stroke
- *Venous thromboembolism (with oral HT)

?? Decreased risk of:

- *Osteoporotic fractures (&↑ bone mineral density)
- *Coronary Heart Disease (only long-term use)
- *New onset Type 2 Diabetes Mellitus
- *Total mortality (only early treatment)
- *Depression
- *Dementia & poor cognitive function

➢ Improvement in vasomotor symptoms and mood

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The association of estrogen exposure with depression & cognitive function

Biological Basis

- Estrogen receptors have been identified in the brain

- **ERα** (ESR1) predominately in hypothalamus
  - ➢ regulation of neuroendocrine & autonomic events
- **ERβ** (ESR2) appears to dominate in hippocampal formation
  - ➢ memory processing

- Estrogen can modulate neurotransmitter turn-over
  influence neuronal structure
  regulate serotonin receptors
  enhance serotonergic activity

Reported associations with HT

COGNITION

- Animal studies: beneficial effect on cognitive performance & reduced decline
- Observational data: risk of dementia & AD ↓ with HT use
- RCT: mixed results, some trials reported no benefit
- WHI: 2-fold ↑ vascular dementia (but not AD) with oral treatment

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DEPRESSION

- Majority of studies focused on reduction of menopausal symptoms / quality of life
- Few examined the effect of HT on psychiatric disorders
- HT + antidepressants may be more beneficial

Inconsistencies across studies

Effect of HT is dependent on:

Timing & duration of use	perimenopausal women
Type & mode of treatment	natural estrogens (17β estradiol), transdermal
Cognitive measure	short-term verbal memory
Depression scale	negative mood vs. clinical depression

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Possibly due to differences between women:

1. Endogenous hormone levels
2. Estrogen exposure across the lifetime
3. Genetic differences in estrogen receptors

1. Serum hormone levels

Menopause transition - intense & irregular fluctuations in estrogen levels
Postmenopause - estrogen levels decline

Also a period of ↑: *risk of new depressive episodes
*depressive symptoms
*complaints of memory problems

Differences between women in terms of:

- Serum estrogen levels before & after menopause
- Fluctuations in estrogen levels during this period

Are estrogen levels different between depressed and non-depressed women ?

Studies on cognitive function have produced mixed results

2. Lifetime Estrogen Exposure

Cumulative exposure to estrogen across the lifetime may be important

Factors which influence estrogen exposure:

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Cumulative exposure to estrogen across the lifetime may be important

Factors which influence estrogen exposure:

+ Influences

- Earlier age at 1st menses
- Later age at menopause

} ↑ Reproductive period

- Hormone Therapy
- Higher postmenopausal BMI

- Influences

- Amenorrhea
- Postmenopause
- Surgical menopause

Modifying Effect

- Oral contraceptives
- Pregnancy / childbirth / breastfeeding

2. Lifetime Estrogen Exposure

Reference	Analysis	Cognitive measure	Results
Smith *et al.*, Brain & Cogn. 1999; 39: 203-18.	X-sectional	Various	+ IEE (global function)
Rasgon *et al.*, Psych.Neu. 2005; 30: 558-67.	X-sectional	Global	+ duration HT use + reproductive period
Low *et al.*, Climacteric. 2005; 8: 380-89.	X-sectional	Various	**NS** reproductive period
McLay *et al.*, J. Neur.Clin. Neur. 2003;15(2):161-67.	Longitudinal	Global decline	↓ later menopause ↓ nulliparity **NS** reproductive period
Geerlings *et al.*, JAMA. 2001; 285(11): 1475-81.	Longitudinal	Incidence dementia	↑ reproductive period ↑ natural menopause

3. Genetic Differences

Polymorphisms of genes which influence the action of estrogen

Can these explain differences between women ?

- some women appear more vulnerable to low hormone levels
- certain women are more susceptible to cognitive problems and depression
- women's response to HT varies

Polymorphisms of Estrogen Receptor α and β

Associated with risk of:

Menopausal symptoms
Major Depression
Alzheimer's disease
Interaction with ApoE-ε4

3. Genetic Differences

Polymorphisms of genes Involved in estrogen metabolism or synthesis

- COMT : (Catechol-O-methyltransferase) — Reported effects on **cognition** and **mood**
- HSD17B1 gene: — May influence circulating **estrogen levels**; Associated with **depressive symptoms**
- CYP17: — Associated with ↑ **estrogen levels** & Associated with earlier age at 1st menses

Research Questions

Is there an associations between depressed mood or poor cognitive function/dementia and:

- Serum estradiol levels ?
- Hormonal exposure across the lifetime ?
- Postmenopausal hormonal therapy (type, duration, age at initiation) ?

Assess whether genetic differences help explain the associations found

Methodology - Population

Melbourne The Melbourne Women's Midlife Health Project (MWMHP)
Study of womens' experience of the menopause transition

Montpellier Three-City Study (3C) of Cerebral Aging
ESPRIT Study of Psychiatric Disorders

Cohorts	Life Stage	Age	Number of women		Follow-up
			X-sectional	Longitudinal	
Melbourne (MWMHP)	Transmenopausal	45-55	2001	438	13 years →
Montpellier (E3C & Esprit)	Postmenopausal	65-93	5400 & 1300	over 80%	6 years →

MWMHP

Selection via random digital telephone dialling

CROSS-SECTIONAL

Eligible participates: 1. Australian-born
2. 45-55 years

↓

2001 women recruited (acceptance 71%)

↓

Telephone interview:
demographic, lifestyle
health & well-being
menopausal status

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LONGITUDINAL

Eligible: 1. Menstruate in last 3mths
2. Not taking HT or OC
3. Uterus & at least 1 ovary

↓

438 women recruited (acceptance 56%)

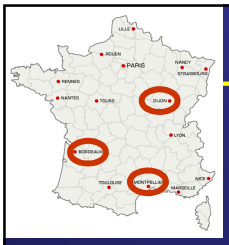
↓

Follow-up: Years 1-8 = yearly
Year 9 → = bi-yearly

↓

Questionnaires: health & well-being
menstrual diaries

Blood samples and Cognitive Tests



3C Study

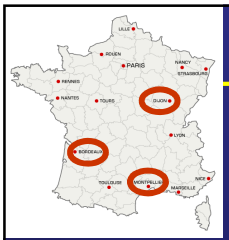
3 French Cities:
Bordeaux, Dijon, Montpellier

Eligible participates: 1. living in city
2. ≥ 65 years
3. Not institutionalised

9294 recruited: 60.7% women, mean age 74

Standardised questionnaires:
socio-demo, lifestyle, medical
Clinical examinations & blood samples

Follow-up every 2yrs: questionnaires & exams
date & cause of death



3C Study & ESPRIT

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1863 from Montpellier

+ psychiatric disorders
life events & trauma
hormonal questionnaire

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socio-demo, lifestyle, medical
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Predictor Variables

ESTROGEN EXPOSURE

Endogenous	Age at 1st menses Age at menopause	}	Number of "reproductive years" Number of years postmenopausal
	Parity & Age at birth of 1st child		
Exogenous	Oral Contraceptives Hormonal Therapy	}	Age at 1st treatment Duration Type

Predictor Variables

SERUM HORMONE LEVELS

Estradiol (E2) & Estrone (E1)
Sex-Hormone Binding Globulin (SHBG)
Free Estradiol (ratio E2/SHBG)
Testosterone & Free Testosterone
Follicle-Stimulating Hormone (FSH)

GENETIC POLYMORPHISMS

Estrogen Receptor α	3C/ESPRIT, MWMHP underway
Estrogen Receptor β	3C/ESPRIT only
COMT	MWMHP & 3C/ESPRIT
CYP17	MWMHP only
HSD17B1	MWMHP underway

Outcome Variables

Depressive Symtpoms: Centre for Epidemiological Studies Depression Scale (CES-D)

Cognition:

General Function -	MMSE
Verbal Memory -	Dubois, Word-recall, CVLT, East Boston
Working Memory -	Digit Span, Benton's Test, Faces subset
Executive Function -	Trail Making Test B, Tower of London
Verbal Fluency -	Isaac's Set Test, Animals, Boston Naming Test
Psychomotor Speed -	Trail Making A
Visuo-Spatial Ability -	Clock Drawing, Block Design, JL Orientation

Diagnosis of Dementia (incl. Alzheimer's Disease)

Comparing depressed and non-depressed women

Serum Hormone Levels

- 138 postmenopausal women from MWMHP, not using HT
- Mean age 60 years (56-66)
- Prevalence of depressive symptoms 20%

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➢ No association between absolute estrogen levels and depression

➢ 2-year decline in estradiol levels associated with ↑ risk of depression

OR: 3.5 [95%CI: 1.2-9.9]*, p=0.02

*adjustment for age, BMI, alcohol consumption, years since menopause and vasomotor symptoms

Ryan *et al*., *Menopause*. **2008**, *in press.*

Lifetime Estrogen Exposure

- 1013 postmenopausal women from ESPRIT
- Mean age 73 years (65-94)
- Prevalence of depressive symptoms 17%

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Hormonal characteristic	Multivariate-adjusted association with depression*
Age at 1st Menses	No association
Age at Menopause	**OR =0.95 [0.91-0.99], p=0.01** **Only women with no tertiary education**
Nº. of Children	No association
Age at birth 1st child	No association
Type of Menopause	No association
Oral Contraceptive use	**OR = 0.33 [0.11-0.93], p=0.04** **≥ 10 years of use**
Past Hormonal Therapy	**OR= 1.63 [1.07–2.50], p=0.03**
Current Hormonal Therapy	No association
Duration of HT use	No association

*adjustment for age, education, marital status, insomnia, physical & mental disabilities, medications & past depression.

Ryan *et al*., *International Psychogeriatrics*. **2008**. 20(6):1203-18.

HT and Depression

- 4069 postmenopausal women from 3C Study
- Mean age 74 years (65-93), Prevalence of depressive symptoms 21%
- **Incidence of Depression over 4-year follow-up**

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- **Incidence of Depression over 4-year follow-up**

  - Continuous HT users - no significant association
  - Discontinued HT - ↑risk of depression OR: 2.63 [1.52-4.55]*, p=0.0005

*adjustment for age, education, marital status, yrs menopausal, insomnia, physical & mental disabilities, comorbidity and past depression.

Stopping treatment ↑ depression risk

Decline in estradiol levels ↑ depression risk

Scali, Ryan *et al.*, *British Journal of Psychiatry*, 2008. *Submitted.*

Cognitive function & estrogen exposure

Lifetime Estrogen Exposure

- 1013 postmenopausal women from ESPRIT
- Mean age 73 years (65-94)
- Risk of poor cognitive performance (lowest quintile)

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Hormonal Variable	Verbal Fluency	Verbal Memory	Visual Memory	Executive Function	Psychomotor Speed	Global Function
Age at 1st Menses			-		-	
Age at Menopause	+					
Nº. of Children						
Age at birth 1st child	+		+		+	+
Current HT use		+ (p=0.08)	+	+ (p=0.09)	+ (p=0.09)	
Past HT use						

Adjustment for age, education, marital status, depression, caffeine intake, physical disabilities & comorbidity.

Ryan *et al*., *Psychoneuroendocrinology*, 2008. *In press.*

Lifetime Estrogen Exposure

Longitudinal analysis :

- Model the risk of cognitive decline over 4-year period
- Multivariate adjustment
- Include adjustment for baseline cognitive score

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Longitudinal analysis :

- Model the risk of cognitive decline over 4-year period
- Multivariate adjustment
- Include adjustment for baseline cognitive score

No significant associations were found

Limitations: relatively short follow-up time
learning effect, most women's cognitive scores improved

Ryan *et al*., *Psychoneuroendocrinology*, 2008. *In press.*

Further Analysis

COGNITION

Poor cognitive function
Decline in cognitive function
} Serum hormone levels

Decline in cognitive function
Incidence of dementia (6-yr)
} HT use: type, mode, timing, duration

ESTROGEN POLYMORPHISMS

Associations with: Cognitive Function
Depression
Age at menopause

- Does it modify HT response (interaction) ?

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