“Cerebro, Emociones y Climaterio”

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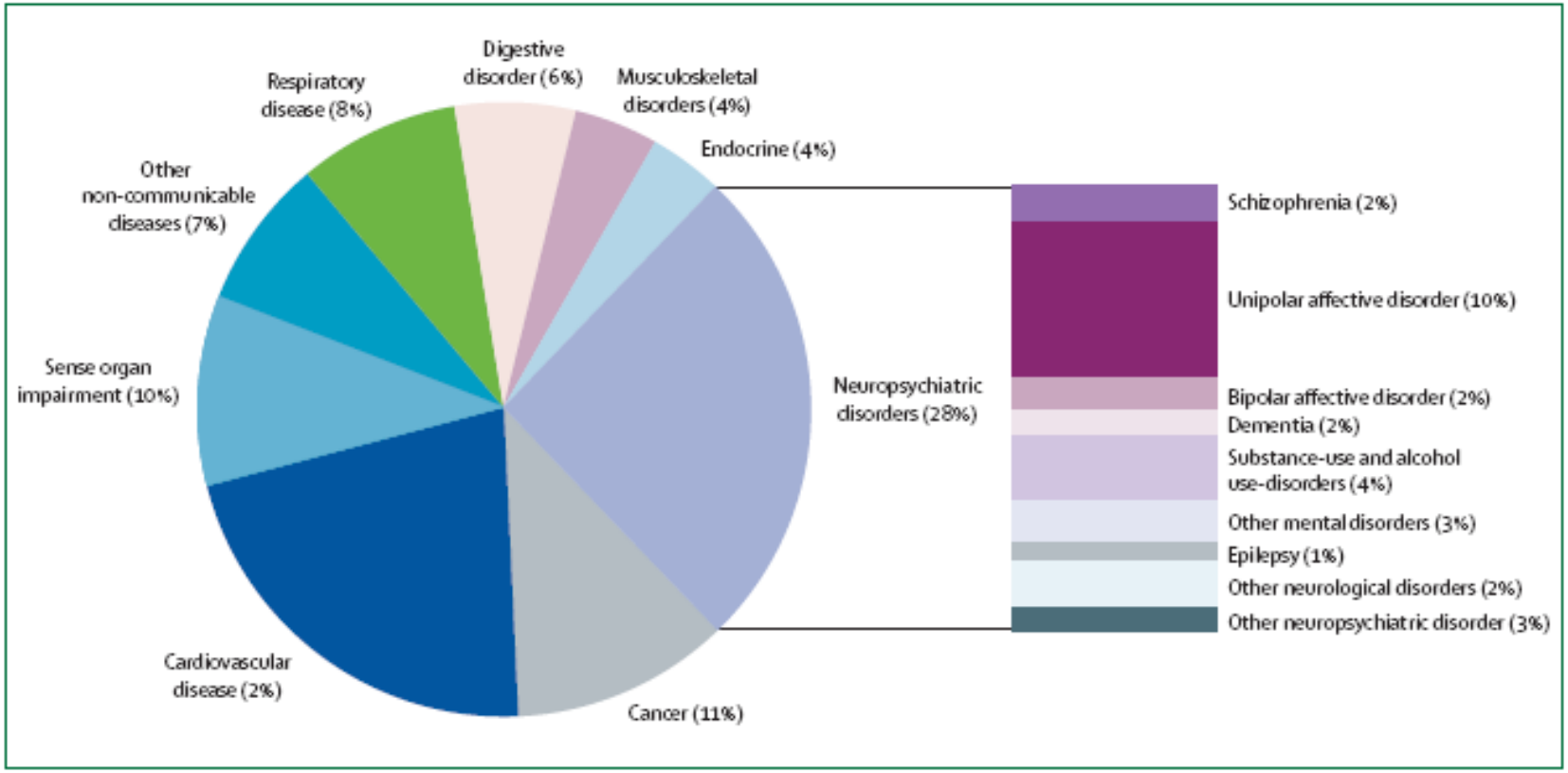
25 de Octubre de 2019


THE GLOBAL BURDEN OF DISEASE
2004 UPDATE
World Health Organization

“No hay Salud sin Salud Mental”



Contribución de diferentes enfermedades a los Años de Vida Ajustados por Discapacidad a nivel Mundial en 2005 (OMS) (AVAD: años perdidos por muerte prematura + años vividos con discapacidad). Modificado de Lancet 2007;370:859-877.

Figure 27: Ten leading causes of burden of disease, world, 2004 and 2030

2004 Disease or injury	As % of total DALYs	Rank	Rank	As % of total DALYs	2030 Disease or injury
Lower respiratory infections	6.2	1	1	6.2	Unipolar depressive disorders
Diarrhoeal diseases	4.8	2	2	5.5	Ischaemic heart disease
Unipolar depressive disorders	4.3	3	3	4.9	Road traffic accidents
Ischaemic heart disease	4.1	4	4	4.3	Cerebrovascular disease
HIV/AIDS	3.8	5	5	3.8	COPD
Cerebrovascular disease	3.1	6	6	3.2	Lower respiratory infections
Prematurity and low birth weight	2.9	7	7	2.9	Hearing loss, adult onset
Birth asphyxia and birth trauma	2.7	8	8	2.7	Refractive errors
Road traffic accidents	2.7	9	9	2.5	HIV/AIDS
Neonatal infections and other[a]	2.7	10	10	2.3	Diabetes mellitus
COPD	2.0	13	11	1.9	Neonatal infections and other[a]
Refractive errors	1.8	14	12	1.9	Prematurity and low birth weight
Hearing loss, adult onset	1.8	15	15	1.9	Birth asphyxia and birth trauma
Diabetes mellitus	1.3	19	18	1.6	Diarrhoeal diseases

Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010

Harvey A Whiteford, Louisa Degenhardt, Jürgen Rehm, Amanda J Baxter, Alize J Ferrari, Holly E Erskine, Fiona J Charlson, Rosana E Norman, Abraham D Flaxman, Nicole Johns, Roy Burstein, Christopher J L Murray, Theo Vos

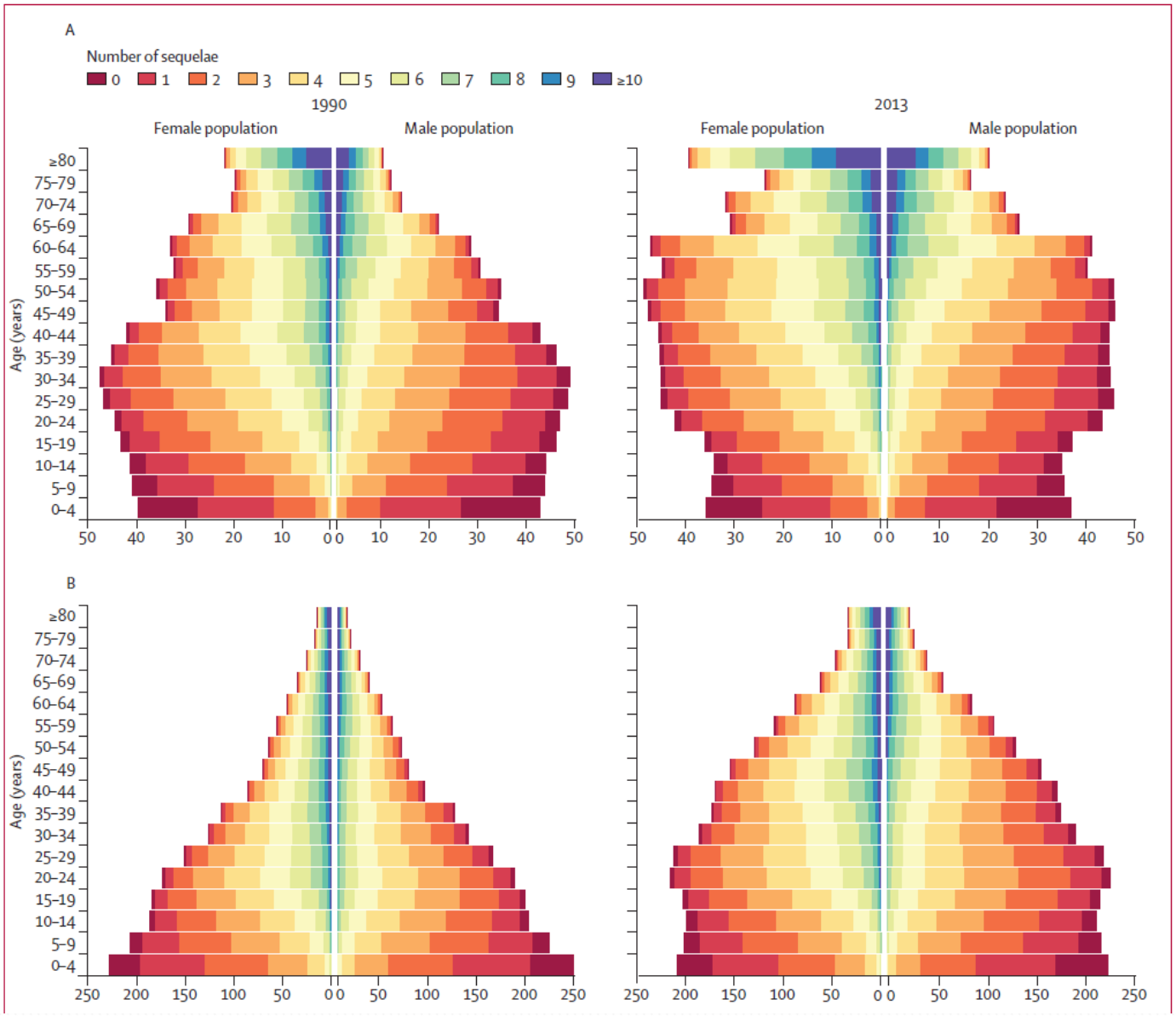
The first Global Burden of Disease study in 1990 (GBD 1990), showed that neuropsychiatric disorders—a grouping that included neurological disorders and dementia as well as mental and substance use disorders—accounted for more than a quarter of all non-fatal burden, measured in years lived with disability (YLD).[5] Five of the top ten causes of disability were included in the neuropsychiatric disorder category. Depression was the most disabling disorder worldwide measured in YLDs, and the fourth

In 2007, a new GBD study was launched[10] and high level results for the Global Burden of Diseases, Injuries, and Risk Factors Study 2010 (GBD 2010) were reported in December, 2012.[11–17] GBD 2010 was a comprehensive reanalysis of burden for 291 causes, 20 age groups, both sexes, and 187 countries in 21 world regions for 1990 and 2010. The definition of world regions was based on

Global disease burden has continued to shift from communicable to non-communicable diseases and from premature death to YLDs.[11] Mental and substance use disorders make up a substantial component of this changing global picture. Our estimates need to be regularly

Lancet 2013; 382: 1575–86

Lancet 2015; 386: 743–800



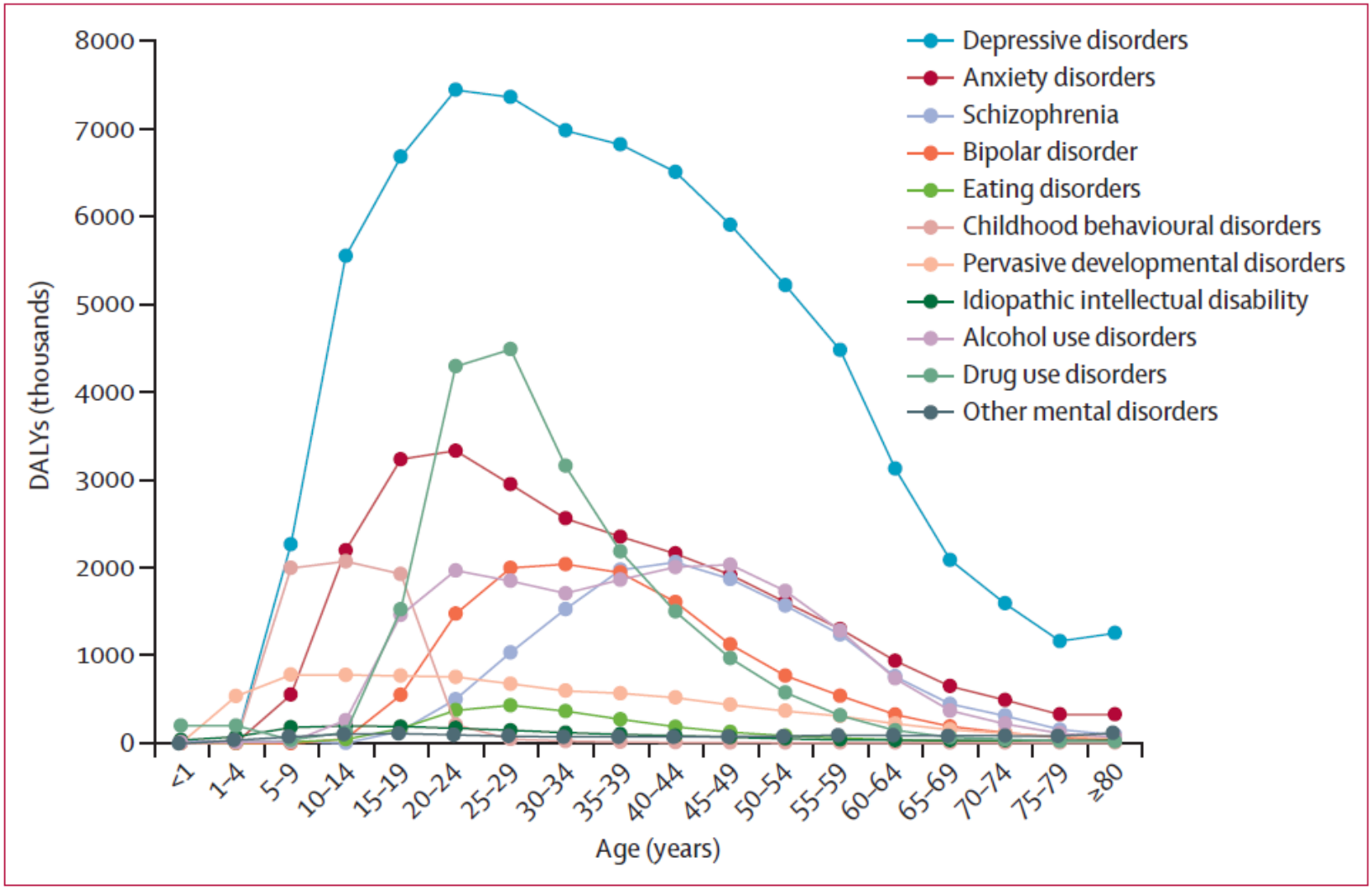


Figure 3: Disability-adjusted life years (DALYs) for each mental and substance use disorder in 2010, by age

Lancet 2013; 382: 1575–86

Curr Psychiatry Rep. 2012 August ; 14(4): 328–335.

The Depression Treatment Cascade in Primary Care: A Public Health Perspective

Brian W. Pence, PhD MPH[1], **Julie K. O'Donnell, MPH**[2], and **Bradley N. Gaynes, MD MPH**[3]

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[2]Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina, Chapel Hill, NC, USA

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Abstract

Major depressive disorder (MDD) is common and costly. Primary care remains a major access point for depression treatment, yet the successful clinical resolution of depression in primary care is uncommon. The clinical response to depression suffers from a "treatment cascade": the affected individual must access health care, be recognized clinically, initiate treatment, receive adequate treatment, and respond to treatment. Major gaps currently exist in primary care at each step along this treatment continuum. We estimate that 12.5% of primary care patients have had MDD in the past year; of those with MDD, 47% are recognized clinically, 24% receive any treatment, 9% receive adequate treatment, and 6% achieve remission. Simulations suggest that only by targeting multiple steps along the depression treatment continuum (e.g. routine screening combined with collaborative care models to support initiation and maintenance of evidence-based depression treatment) can overall remission rates for primary care patients be substantially improved.

La Paradoja Terapéutica

- Drogas más vendidas en el mercado de EEUU - 2011
  (ventas medidas en billones de U$S):

1. Atorvastatina	7.7
2. Clopidogrel	6.8
3. Esomeprazol	6.2
4. **Aripiprazol**	**5.2**
5. Salmeterol/Fluticasona	4.6
6. **Quetiapina**	**4.6**
7. Montelukast	4.6
8. Rosuvastatina	4.4
9. **Duloxetina**	**3.7**

La Paradoja Terapéutica

El incremento en la disponibilidad, uso y gasto en tratamientos medidos epidemiológicamente no ha disminuido e incluso en algunas áreas convive con un aumento en la morbi-mortalidad.

La Paradoja Terapéutica

- Explicaciones?:

Tratamiento Efectivo – Prevalencia en aumento

Tratamiento Efectivo – Problemas de acceso

Tratamientos actuales insuficientemente efectivos para influenciar el problema de Salud Pública

La Paradoja Terapéutica

-Como obtenemos mejores resultados?:

Nuevos Diagnósticos

Nuevos Objetivos Terapéuticos

Nueva Cultura de las Neurociencias Clínicas

Rethinking schizophrenia

Thomas R. Insel[1]

How will we view schizophrenia in 2030? Schizophrenia today is a chronic, frequently disabling mental disorder that affects about one per cent of the world's population. After a century of studying schizophrenia, the cause of the disorder remains unknown. Treatments, especially pharmacological treatments, have been in wide use for nearly half a century, yet there is little evidence that these treatments have substantially improved outcomes for most people with schizophrenia. These current unsatisfactory outcomes may change as we approach schizophrenia as a neurodevelopmental disorder with psychosis as a late, potentially preventable stage of the illness. This 'rethinking' of schizophrenia as a neurodevelopmental disorder, which is profoundly different from the way we have seen this illness for the past century, yields new hope for prevention and cure over the next two decades.

Table 1 | Stages of schizophrenia

	Stage I	Stage II	Stage III	Stage IV
Features	Genetic vulnerability Environmental exposure	Cognitive, behavioural and social deficits Help-seeking	Abnormal thought and behaviour Relapsing–remitting course	Loss of function Medical complications Incarceration
Diagnosis	Genetic sequence Family history	SIPS Cognitive assessment Imaging	Clinical interview Loss of insight	Clinical interview Loss of function
Disability	None/mild cognitive deficit	Change in school and social function	Acute loss of function Acute family distress	Chronic disability Unemployment Homelessness
Intervention	Unknown	Cognitive training? Polyunsaturated fatty acids? Family support?	Medication Psychosocial interventions	Medication Psychosocial interventions Rehabilitation services

Stage I, pre-symptomatic risk; stage II, pre-psychotic prodrome; stage III, acute psychosis; stage IV, chronic illness.

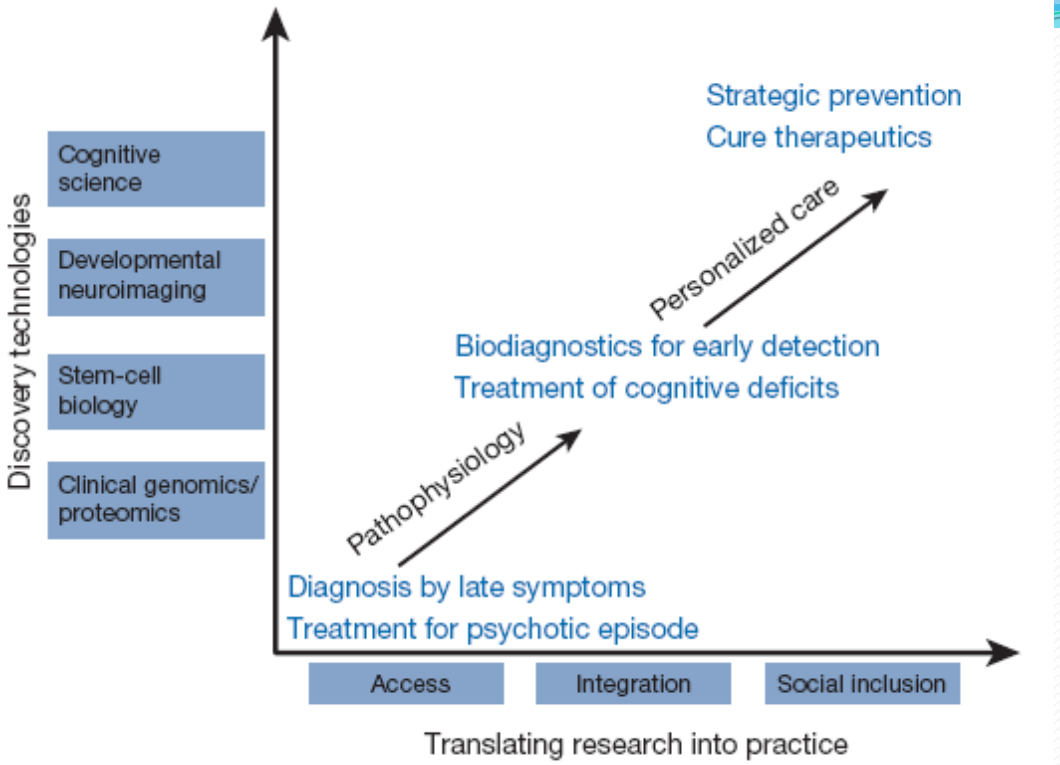


Figure 2 | A vision for schizophrenia over the next two decades. Currently diagnosis follows psychosis (stage III) and treatment focuses on reducing psychotic symptoms. The use of discovery technologies, which have already transformed the understanding and treatment of many other medical disorders, can transform our understanding of schizophrenia, yielding earlier diagnosis (stages I or II) with treatments focused on the cognitive deficits of this disorder. The ultimate goal, however, is cure and prevention based on an understanding of individual risk and the development of personalized care. In practice this means not only identifying risk and preemptive interventions but ensuring access to these interventions, integrating care and ensuring full social inclusion for people at any stage of the schizophrenia trajectory.

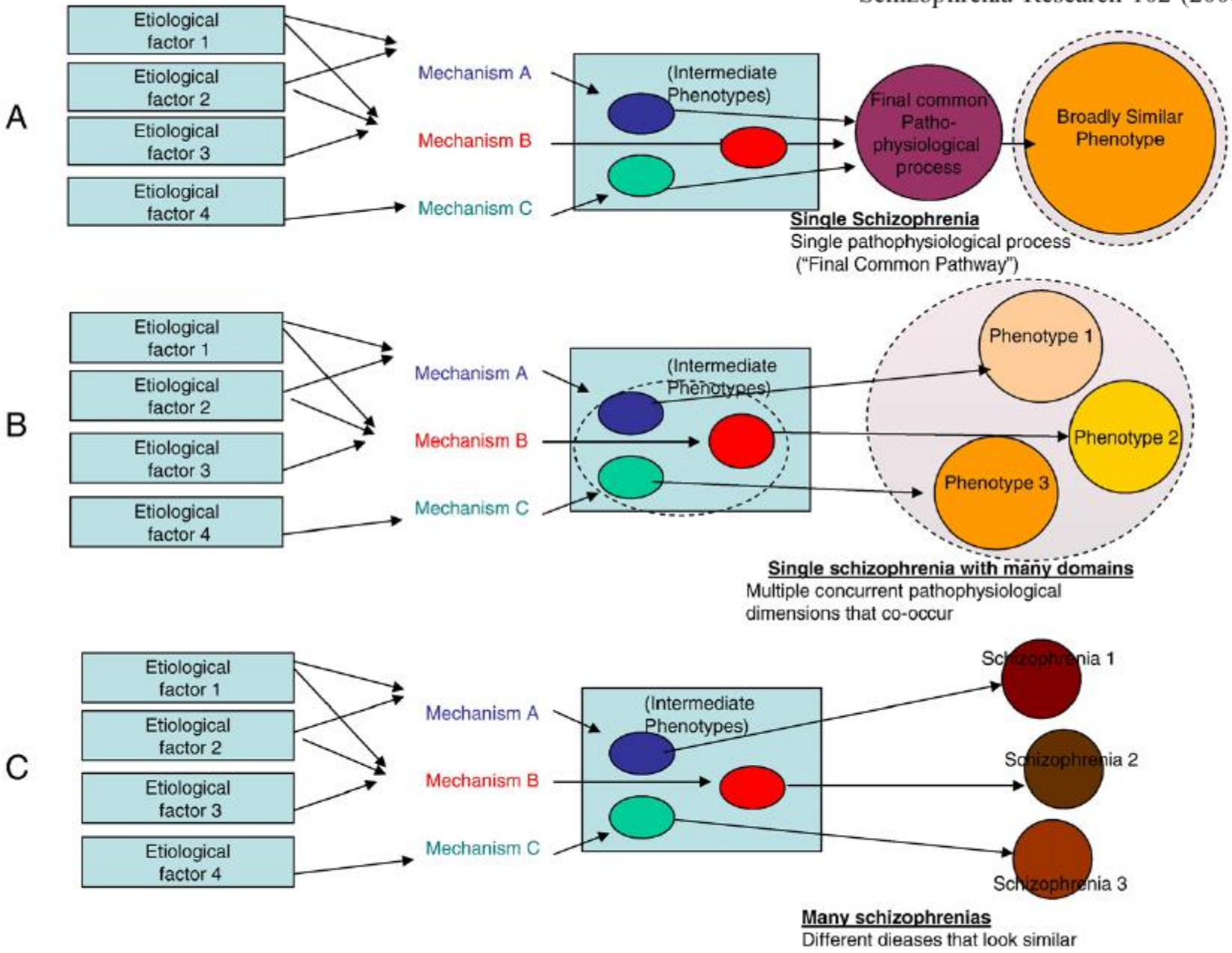


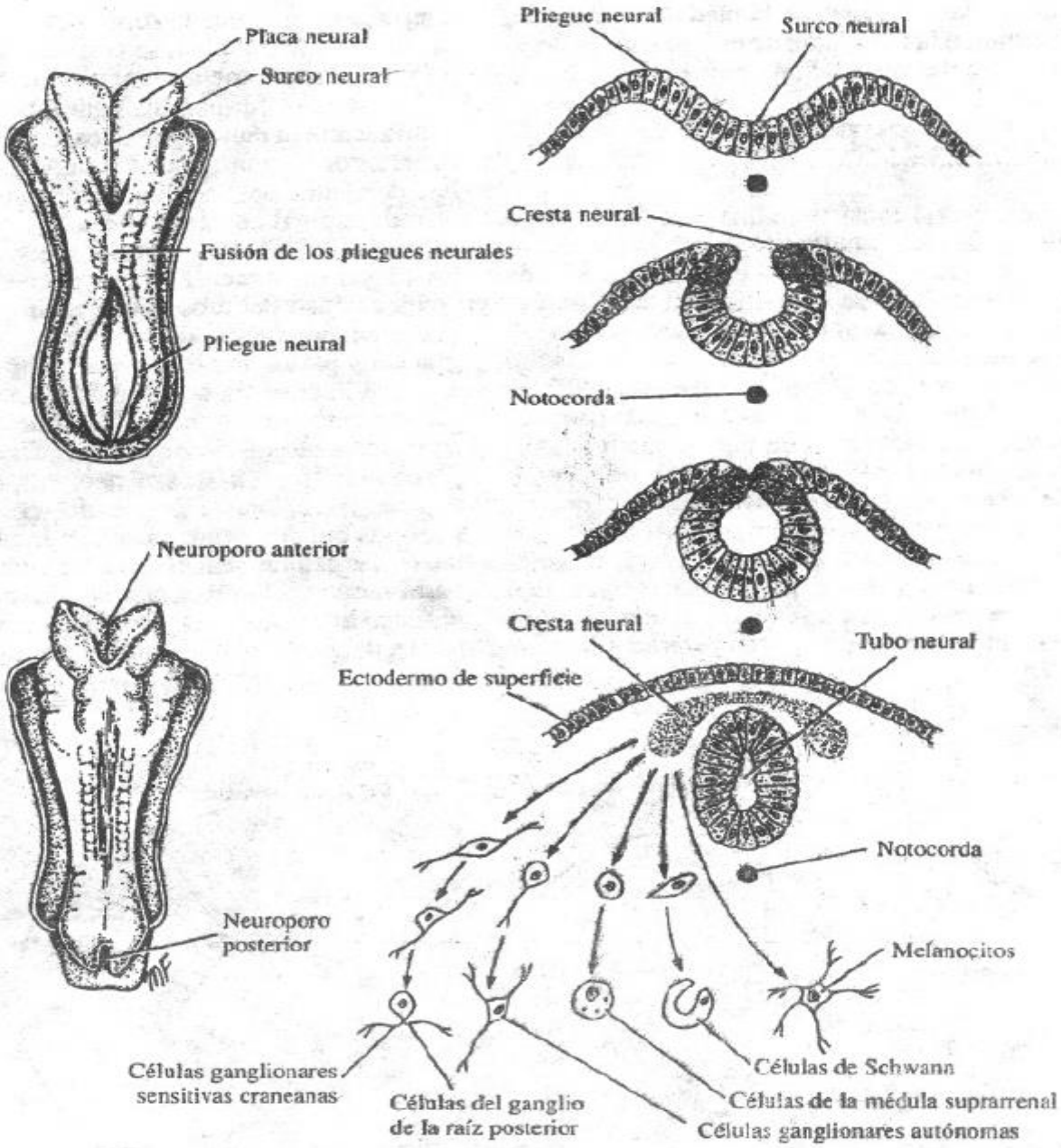
Fig. 2. Etiology to pathophysiology to illness: models of schizophrenia.

Modelo Teórico Actual de los Trastornos Mentales

Síntomas Mentales.

Alteraciones Neurobiológicas.

Síntomas Físicos y/o
Enfermedad Médica.



ig. 18-1. Formación de la placa neural, el surco neural y el tubo neural. Las células de la cresta neural se diferencian en las células del anglio de la raíz posterior, los ganglios sensitivos de los nervios craneanos, los ganglios autónomos, las células del neurilema (células de chwann), las células de la médula suprarrenal y los melanocitos.

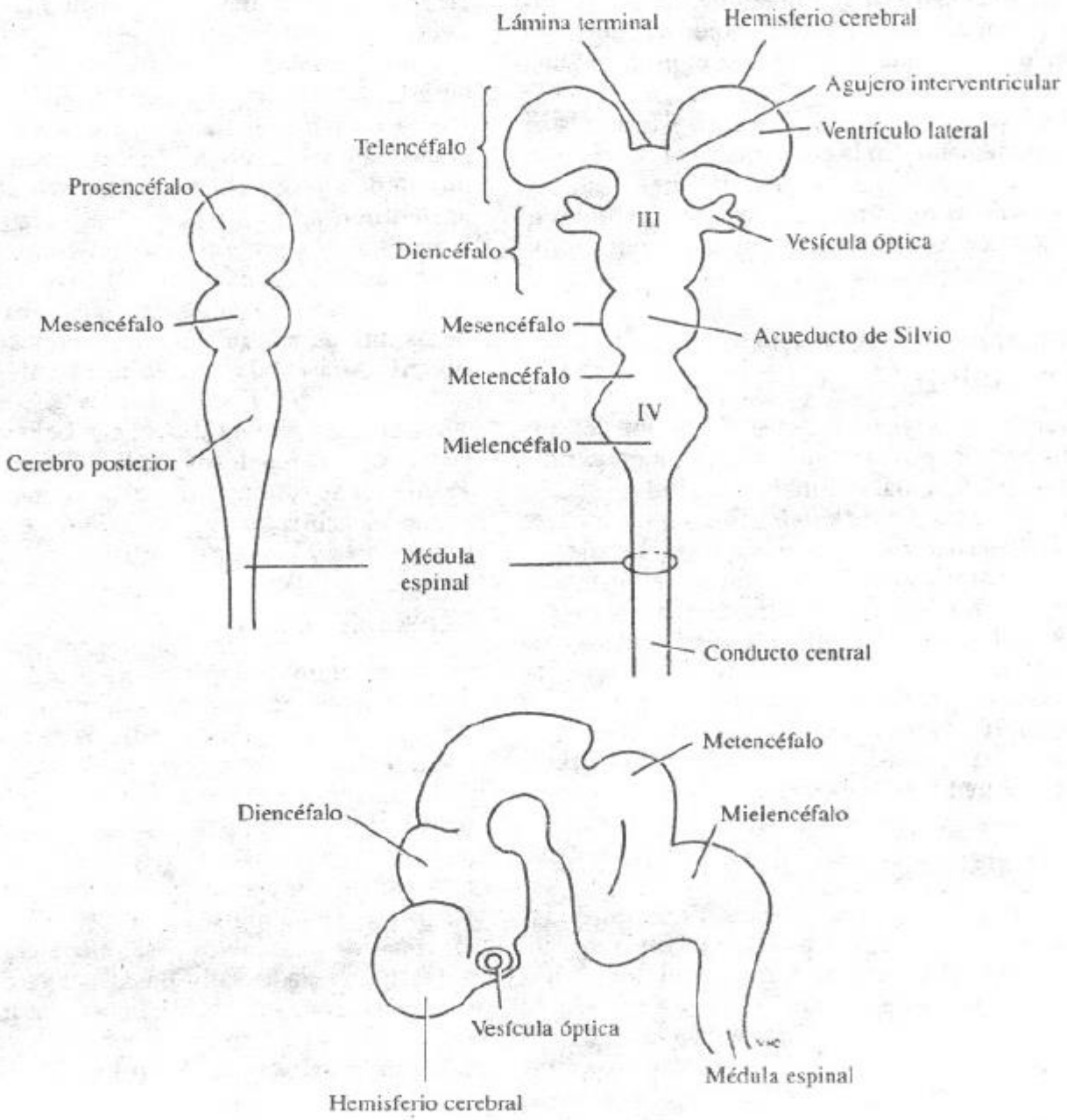


Fig. 18-4. División de la vesícula del encéfalo anterior en el telencéfalo y el diencéfalo y de la vesícula del encéfalo posterior en el metencéfalo y el mielencéfalo. También se muestra la forma en la cual el hemisferio cerebral de cada lado se desarrolla como un divertículo a partir del telencéfalo.

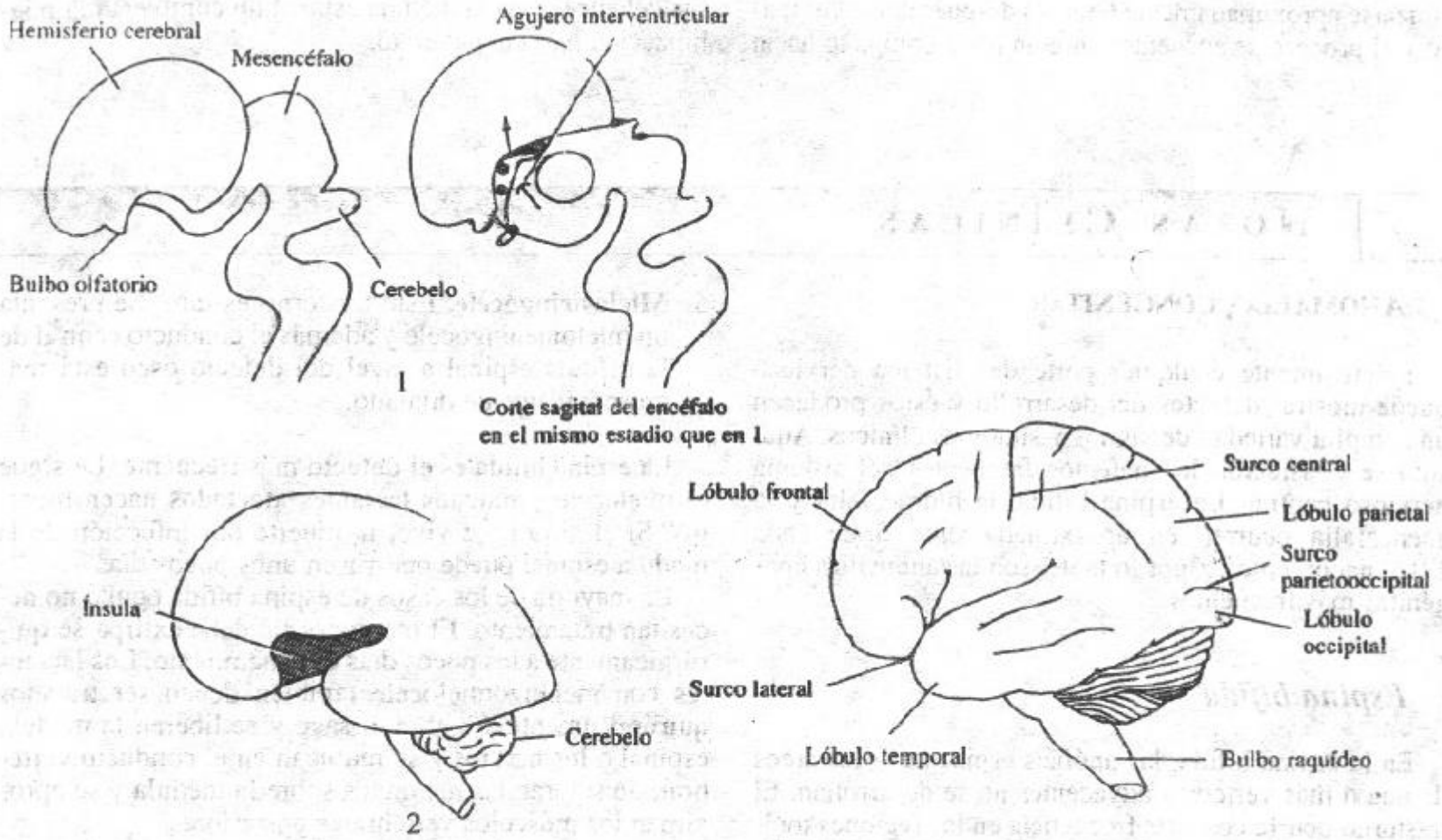


Fig. 18-13. Etapas sucesivas en el desarrollo de la corteza cerebral.

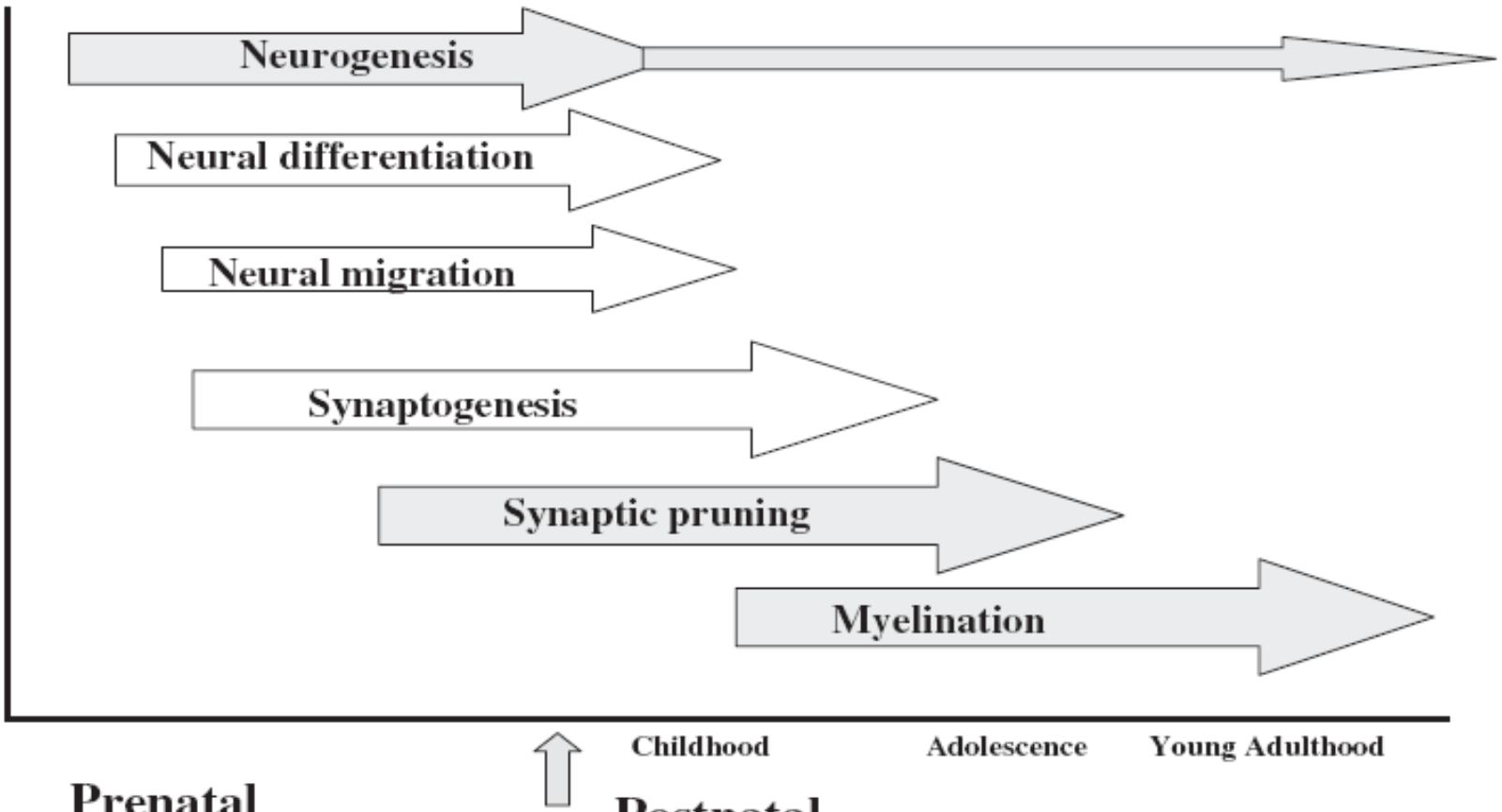
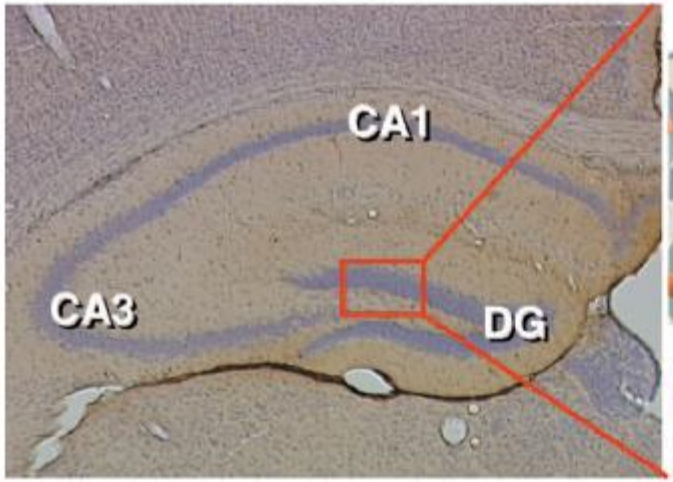


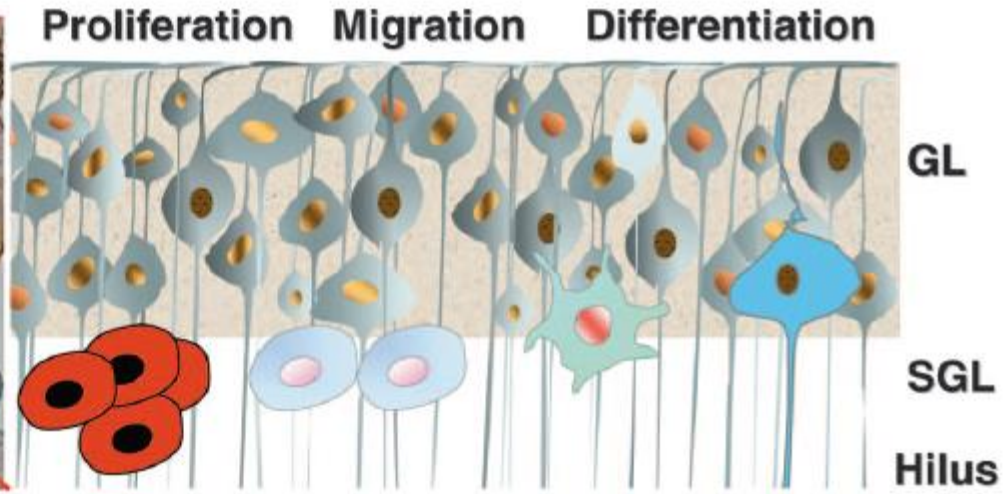
FIGURE 3: An Outline of Childhood Brain Development

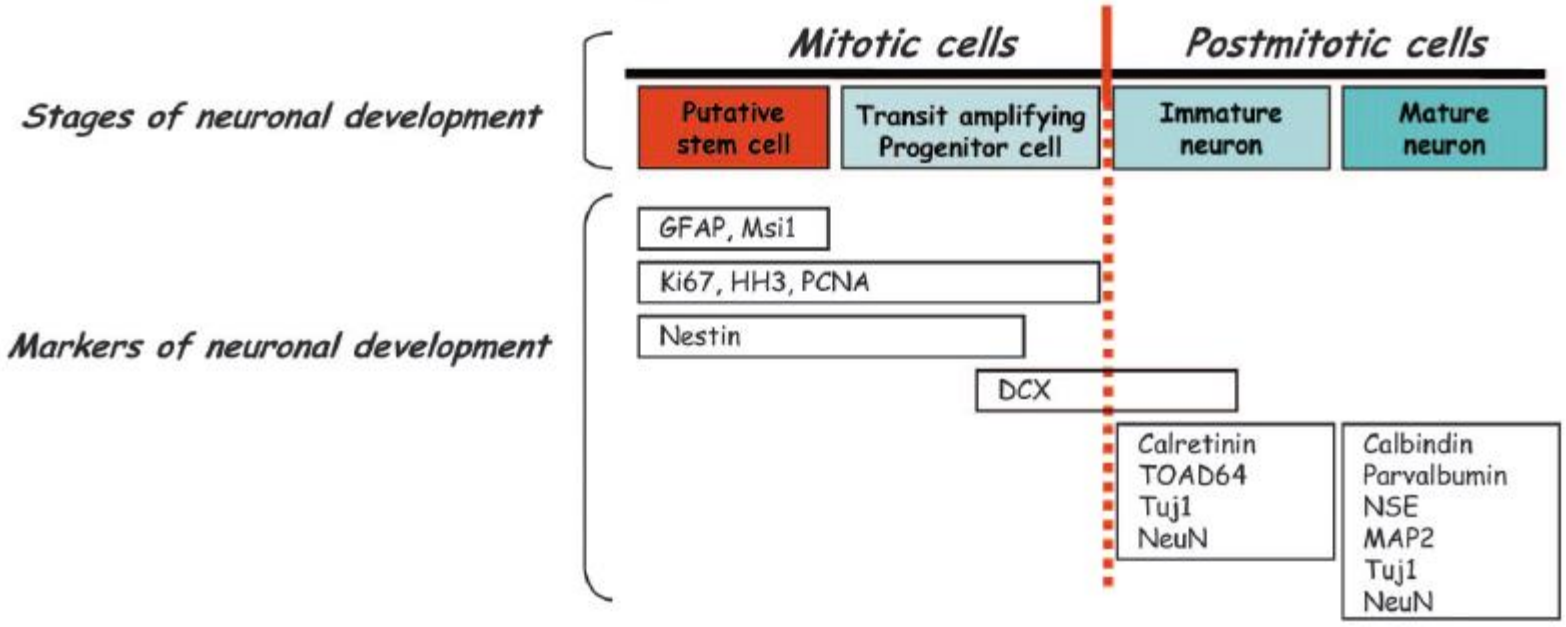
Adult Neurogenesis: From Precursors to Network and Physiology

Physiol Rev 85: 523–569, 2005;

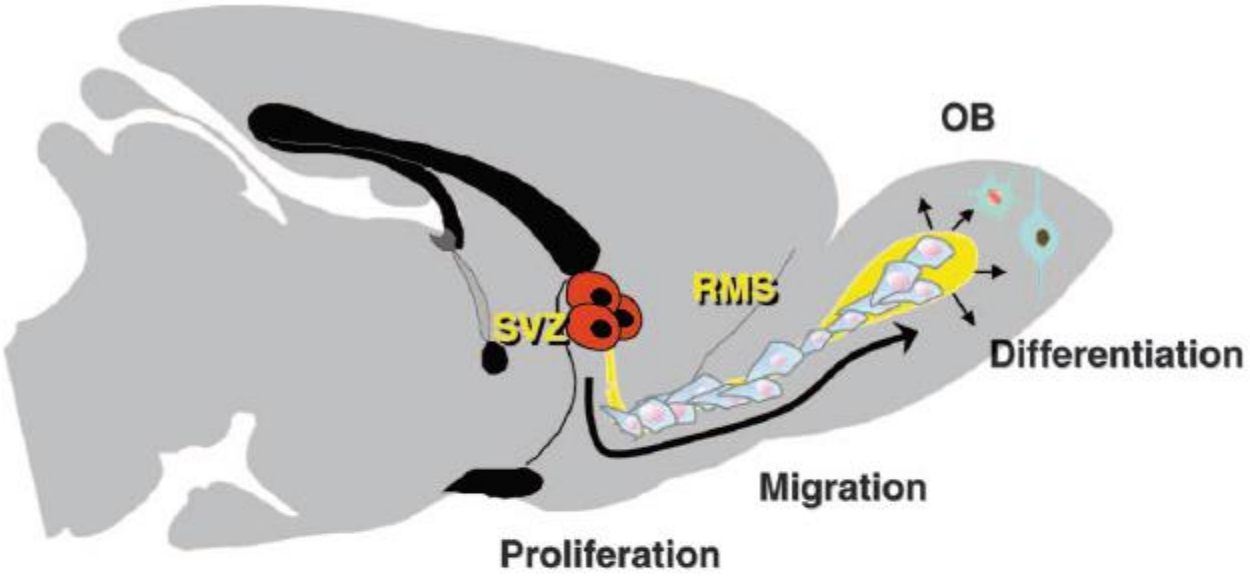
DJOHER NORA ABROUS, MURIEL KOEHL, AND MICHEL LE MOAL







Physiol Rev 85: 523–569, 2005;



Neuronal lineage	B	C	A	
Cell identity	SVZ astrocyte Putative stem cell	Transit amplifying progenitor	Migrating neuroblast	Immature and mature neurons
Identified markers	GFAP Vimentin Nestin	Dlx2 Nestin	PSA-NCAM Dlx2 Tuj1 Hu	DCX, calretinin NeuN TH Calbindin GAD65

TABLE 1. *Extrinsic factors regulating in vivo cell proliferation and neurogenesis in the subventricular zone/olfactory bulb system and the dentate gyrus of the hippocampal formation under physiological conditions*

Physiol Rev 85: 523–569, 2005;

Factors	Subventricular Zone/Olfactory Bulb				Dentate Gyrus				Reference Nos.
	Cell proliferation	Neurogenesis	Neuronal differentiation	Long-term survival	Cell proliferation	Neurogenesis	Neuronal differentiation	Long-term survival	
Hormones and peptides									
Corticosterone									
Suppression (adx)	0				↗	↗	0	0	71, 74, 176, 465
Cort. treatment					↘	↘	0		17, 71, 76, 212
Estradiol									
Estrus cycle	0				↗proE	0		↘	536
OVX	0				↘				29, 536
OVX + acute 17β-E	↗				↗ then ↘		0		29, 422, 536
OVX + chronic 17β-E					0	0	0		435
17β-E					↗ (4h)				421
Prolactin	↗	↗			0				506
PACAP	↗				↗				362
Neurosteroids									
DHEA					↗	↗	0	0	254
PregS	↗				↗	↗			349
Allopreg					↘				349
Neurotransmitters									
Glutamate									
Ent. Cx. lesion					↗				73
NMDA activation					↘				73, 76
NMDA blockade					↗	↗			46, 73, 76, 177, 390
AMPA potentiation					↗				27
mGluR II blockade					↗				581
Serotonin									
5-HT depletion	↘				↘				29, 61
Lesion + graft					↗				63
Reuptake inhibition	0				↗	↗	0	0	10, 335, 483
5-HT_{1A} blockade					↘				451
5-HT_{1A} activation	↗	↗	0		↗	↗	0		30, 483
5-HT_{1B} blockade	↗				0				30
5-HT_{1B} activation	↗				0				
$5\text{-HT}_{2A/2C}$ blockade	0				↘				
$5\text{-HT}_{2A/2C}$ activation	↗				0				
5-HT_{2C} blockade	0				0				
5-HT_{2C} activation	↗	↗	0		0	0			
Norepinephrine									
Depletion	0				↘	↘	0	0	292
Reuptake inhibition					↗				335
No donor	↗				↗	↗			587
Growth or trophic factors									
bFGF	↗	↗	↗		0	0	0		238, 240, 291
EGF	↗	↘	↘		0	↘	↘		291
HB-EGF	↗	↗	0		↗	↗			236, 238, 240
TGF-α	↗								98
IGF-I					↗	↗ (ovx)	0 or ↗ (hpx)	0	1, 310, 435, 542
BDNF	↗	↗	0						593
CNTF	↗				↗	↗	↗		141
VEGF	↗				↗				241
Morphogenic factors									
Shh					↗	↗	0	0	295
BMP	↘	↘	↘						311
Noggin	↗	↗	↗						311
Vitamins and retinoids									
Vitamin E									
Deficiency					↗			↘	86, 87
Supplementation (tocopherol)					↘	↗		↗	83, 102
Retinoic acid (chronic treatment)	↘				↘	↘	↘	↘	99

- Las celulas que conforman el SNC se dividen, migran, adquieren nuevas características y funciones de acuerdo a las señales externas que van recibiendo desde su microambiente neuroinmunoendócrino.
- Ese microambiente NIE a su vez está concéntricamente inmerso en otros ambientes que lo influyen y modulan en diferentes sentidos

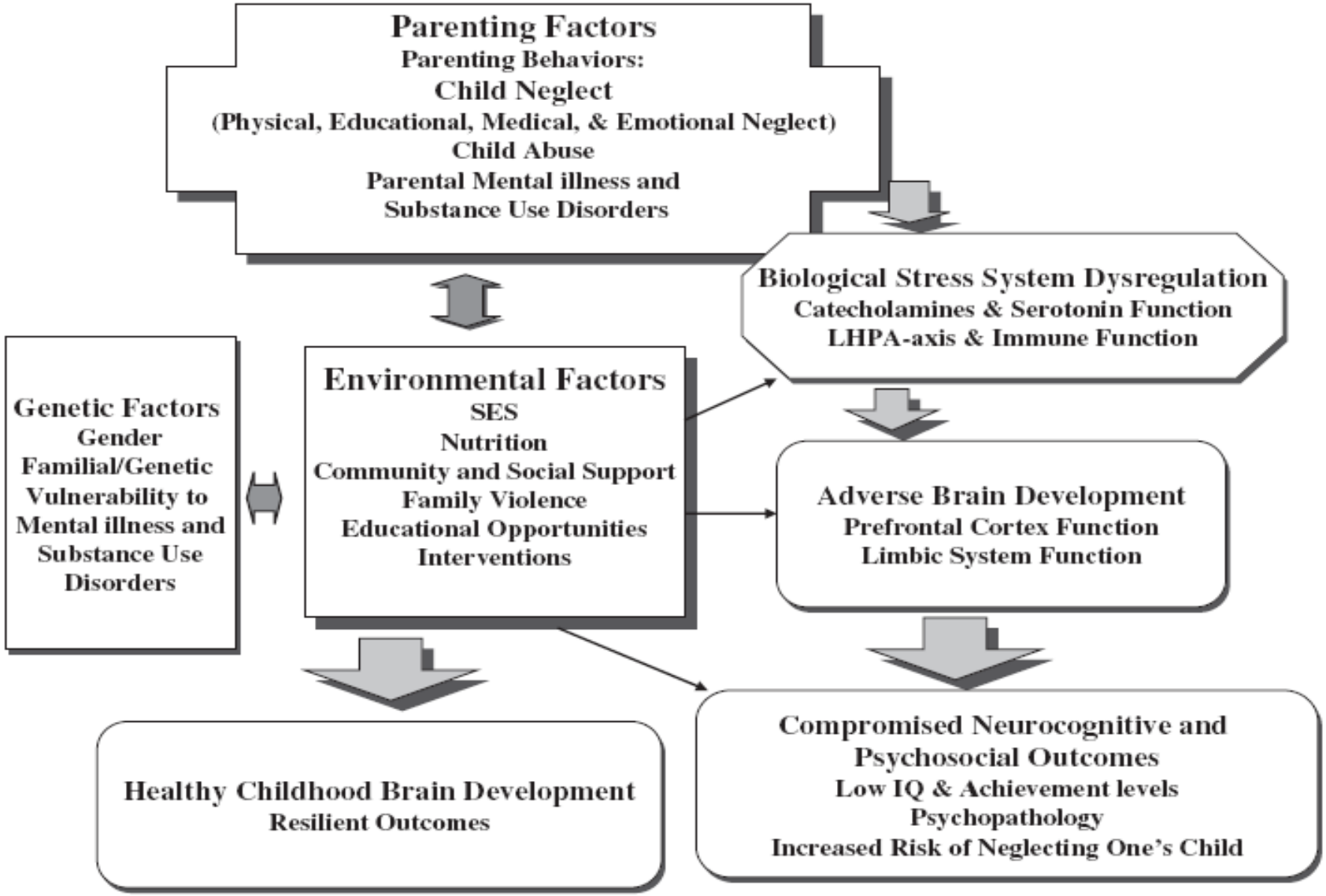


FIGURE 1: A Developmental Traumatology for the Psychobiology of Neglect
NOTE: SES – socioeconomic status; LHPA axis – limbic-hypothalamic-pituitary-adrenal axis.

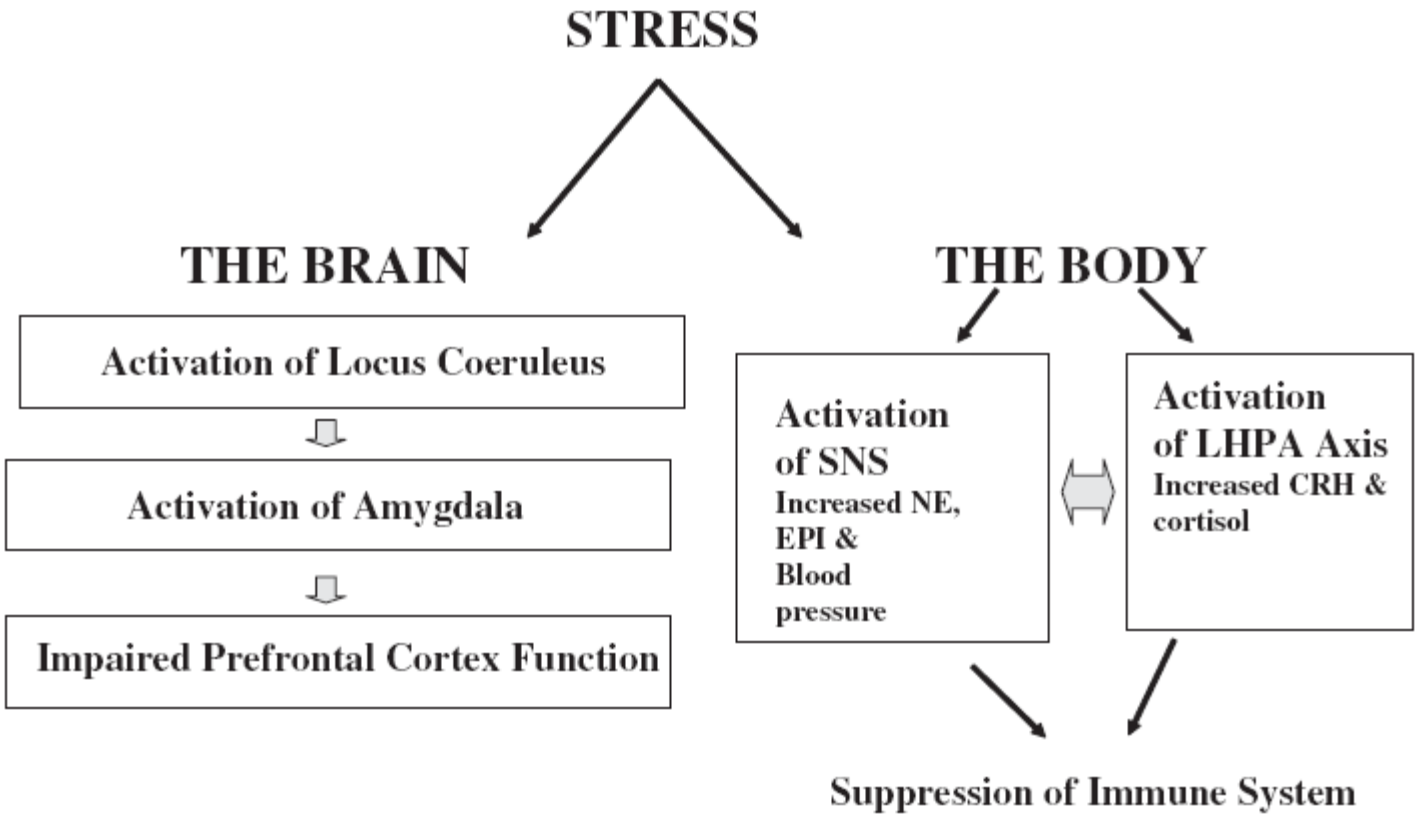


FIGURE 2: An Outline of Biological Stress Response Systems
NOTE: SNS – sympathetic nervous system; NE – norepinephrine; EPI – epinephrine; LHPA – limbic-hypothalamic-pituitary-adrenal; CRH – corticotrophin-releasing hormone.

Sex Differences in Brain Maturation during Childhood and Adolescence

Michael D. De Bellis[1,2], Matcheri S. Keshavan[1], Sue R. Beers[1], Julie Hall[2], Karin Frustaci[2], Azadeh Masalehdan[2], Jessica Noll[2] and Amy M. Boring[2]

[1]University of Pittsburgh Medical Center and [2]Developmental Traumatology Neuroimaging Laboratory, Western Psychiatric Institute and Clinic, 3811 O'Hara Street, Pittsburgh, PA 15213, USA

Brain development during childhood and adolescence is characterized by both progressive myelination and regressive pruning processes. However, sex differences in brain maturation remain poorly understood. Magnetic resonance imaging was used to examine the relationships between age and sex with cerebral gray and white matter volumes and corpus callosal areas in 118 healthy children and adolescents (61 males and 57 females), aged 6–17 years. Gender groups were similar on measures of age, handedness, socioeconomic status and Full Scale IQ. Significant age-related reductions in cerebral gray and increases in white matter volumes and corpus callosal areas were evident, while intracranial and cerebral volumes did not change significantly. Significant sex by age interactions were seen for cerebral gray and white matter volumes and corpus callosal areas. Specifically, males had more prominent age-related gray matter decreases and white matter volume and corpus callosal area increases compared with females. While these data are from a cross-sectional sample and need to be replicated in a longitudinal study, the findings suggest that there are age-related sex differences in brain maturational processes. The study of age-related sex differences in cerebral pruning and myelination may aid in understanding the mechanism of several developmental neuropsychiatric disorders.

It is well known that cognitive and emotional development differs between boys and girls [for review see (Nagy Jacklin and Martin, 1999)], though the timing, patterning and neurobiological parallels of such differential development remain poorly understood. Normal pubertal development is associated with marked increases in plasma levels of sex steroids (Ducharme and Forest, 1993). Preclinical studies suggest that sex steroid receptors are widely distributed throughout the brain and influence neurodevelopment [for review see (McEwen, 1981)]. Cognitive abilities, particularly visuo-spatial skills, differ between males and females (Hampson and Kimura, 1992; Kimura, 1996; Janowsky *et al.*, 1998). Sex differences in brain development may be related to the prevalence, course and treatment of several neuropsychiatric disorders, such as autism, attention deficit hyperactivity disorder and schizophrenia (Seeman, 1997; Cohen *et al.*, 1999).

We investigated the relationship between age, sex and cerebral GM and WM volumes and CC area using high-resolution MRI volumetric analyses in a large community sample of healthy, age-matched and sociodemographically similar male and female children and adolescents. We specifically investigated age-

Neuropsychopharmacology www.nature.com/npp

NEUROPSYCHOPHARMACOLOGY REVIEWS

Sex differences in the developing brain: insights from multimodal neuroimaging

Antonia N. Kaczkurkin[1], Armin Raznahan[2] and Theodore D. Satterthwaite[1]

Youth (including both childhood and adolescence) is a period when the brain undergoes dramatic remodeling and is also a time when neuropsychiatric conditions often emerge. Many of these illnesses have substantial sex differences in prevalence, suggesting that sex differences in brain development may underlie differential risk for psychiatric symptoms between males and females. Substantial evidence documents sex differences in brain structure and function in adults, and accumulating data suggests that these sex differences may be present or emerge during development. Here we review the evidence for sex differences in brain structure, white matter organization, and perfusion during development. We then use these normative differences as a framework to understand sex differences in brain development associated with psychopathology. In particular, we focus on sex differences in the brain as they relate to anxiety, depression, psychosis, and attention-deficit/hyperactivity symptoms. Finally, we highlight existing limitations, gaps in knowledge, and fertile avenues for future research.

Neuropsychopharmacology (2018) 0:1–15; https://doi.org/10.1038/s41386-018-0111-z

RELEVANCE FOR PSYCHOPATHOLOGY

There are marked sex differences between males and females in terms of the prevalence and clinical presentation of psychiatric disorders. Males demonstrate a greater prevalence of neuropsychiatric disorders such as autism, attention-deficit/hyperactivity disorder, Tourette's disorder, and conduct disorder [5, 98–100]. Conversely, females demonstrate a greater prevalence of depressive disorders, anxiety disorders, and eating disorders [6, 7, 11]. Although social factors are undoubtedly important, sex differences in brain development during the critical period of youth suggest that some of this differential risk for specific symptoms may be due to differential vulnerabilities of maturing brain circuitry. Below, we review relevant literature for a subset of disorders which have marked sex differences in their prevalence, including anxiety, depression, psychosis, and attention-deficit/hyperactivity disorder (ADHD).

ORIGINAL ARTICLE

Age-Related Changes in Frontal and Temporal Lobe Volumes in Men

A Magnetic Resonance Imaging Study

George Bartzokis, MD; Mace Beckson, MD; Po H. Lu, MA; Keith H. Nuechterlein, PhD; Nancy Edwards, MA; Jim Mintz, PhD

Background: Imaging and postmortem studies provide converging evidence that, beginning in adolescence, gray matter volume declines linearly until old age, while cerebrospinal fluid volumes are stable in adulthood (age 20-50 years). Given the fixed volume of the cranium in adulthood, it is surprising that most studies observe no white matter volume expansion after approximately age 20 years. We examined the effects of the aging process on the frontal and temporal lobes.

Methods: Seventy healthy adult men aged 19 to 76 years underwent magnetic resonance imaging. Coronal images focused on the frontal and temporal lobes were acquired using pulse sequences that maximized gray vs white matter contrast. The volumes of total frontal and temporal lobes as well as the gray and white matter subcomponents were evaluated.

Results: Age-related linear loss in gray matter volume in both frontal ($r=-0.62$, $P<.001$) and temporal ($r=-0.48$, $P<.001$) lobes was confirmed. However, the quadratic function best represented the relationship between age and white matter volume in the frontal ($P<.001$) and temporal ($P<.001$) lobes. Secondary analyses indicated that white matter volume increased until age 44 years for the frontal lobes and age 47 years for the temporal lobes and then declined.

Conclusions: The changes in white matter suggest that the adult brain is in a constant state of change roughly defined as periods of maturation continuing into the fifth decade of life followed by degeneration. Pathological states that interfere with such maturational processes could result in neurodevelopmental arrests in adulthood.

Arch Gen Psychiatry. 2001;58:461-465

Behav Brain Res. 2008 Sep 1;192(1):137-42. Epub 2008 Feb 17.

Training-induced structural changes in the adult human brain.

Draganski B, May A.
Wellcome Trust Centre for Neuroimaging, NHNN Institute of Neurology, University College London, London, UK.

Structural and functional brain reorganisation can occur beyond the developmental maturation period and this was recently recognised as an intrinsic property of the human central nervous system. Brain injury or altered afferent input due to environmental changes, novel experience and learning new skills are known as modulators of brain function and underlying neuroanatomic circuitry. During the past decade invasive animal studies and in vivo imaging techniques have delineated the correlates of experience dependent reorganisation. The major future challenge is to understand the behavioural consequences and cellular mechanisms underlying training-induced neuroanatomic plasticity in order to adapt treatment strategies for patients with brain injury or neurodegenerative disorders.

PMID: 18378330 [PubMed - indexed for MEDLINE]

Gray and white matter changes associated with tool-use learning in macaque monkeys

M. M. Quallo[a,b], C. J. Price[c], K. Ueno[d], T. Asamizuya[d], K. Cheng[d,e], R. N. Lemon[a,b], and A. Iriki[a,b,1]

[a]Laboratory for Symbolic Cognitive Development, [d]fMRI Support Unit, and [e]Laboratory for Cognitive Brain Mapping, RIKEN Brain Science Institute, 2-1 Hirosawa, Wako-shi, Saitama 351-0198, Japan; and [b]Sobell Department of Motor Neuroscience and Movement Disorders and [c]Wellcome Trust Centre for Neuroimaging, University College London Institute of Neurology, London WC1N 3BG, United Kingdom

Communicated by William T. Newsome, Stanford University School of Medicine, Stanford, CA, September 1, 2009 (received for review March 8, 2009)

Navigation-related structural change in the hippocampi of taxi drivers

Eleanor A. Maguire*†, David G. Gadian‡, Ingrid S. Johnsrude†, Catriona D. Good†, John Ashburner†, Richard S. J. Frackowiak†, and Christopher D. Frith†

†Wellcome Department of Cognitive Neurology, Institute of Neurology, University College London, Queen Square, London WC1N 3BG, United Kingdom; and ‡Radiology and Physics Unit, Institute of Child Health, University College London, London WC1N 1EH, United Kingdom

Communicated by Brenda Milner, McGill University, Montreal, Canada, January 28, 2000 (received for review November 10, 1999)

. Science. 1995 Oct 13;270(5234):305-7.

Increased cortical representation of the fingers of the left hand in string players.

Elbert T, Pantev C, Wienbruch C, Rockstroh B, Taub E.
Department of Psychology, University of Konstanz, Germany.

Magnetic source imaging revealed that the cortical representation of the digits of the left hand of string players was larger than that in controls. The effect was smallest for the left thumb, and no such differences were observed for the representations of the right hand digits. The amount of cortical reorganization in the representation of the fingering digits was correlated with the age at which the person had begun to play. These results suggest that the representation of different parts of the body in the primary somatosensory cortex of humans depends on use and changes to conform to the current needs and experiences of the individual.

PMID: 7569982 [PubMed - indexed for MEDLINE]

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BRAIN RESEARCH REVIEWS 62 (2010) 197–211

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BRAIN RESEARCH REVIEWS

Review

Characteristics of the athletes' brain: Evidence from neurophysiology and neuroimaging

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Athlete
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ABSTRACT

We review research on athletes' brains based on data obtained using non-invasive neurophysiological and neuroimaging methods; these data pertain to cognitive processing of visual, auditory, and somatosensory (tactile) stimulation as well as to motor processing, including preparation, execution, and imagery. It has been generally accepted that athletes are faster, stronger, able to jump higher, more accurate, more efficient, more consistent, and more automatic in their sports performances than non-athletes. These claims have been substantiated by neuroscientific evidence of the mechanisms underlying the plastic adaptive changes in the neuronal circuits of the brains of athletes. Reinforced neural networks and plastic changes are induced by the acquisition and execution of compound motor skills during extensive daily physical training that requires quick stimulus discrimination, decision making, and specific attention. In addition, it is likely that the manner of neuronal modulation differs among sports. We also discuss several problems that should be addressed in future studies.

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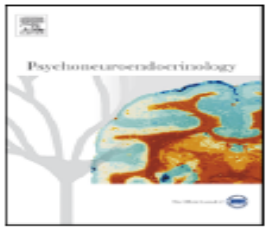

Testosterone reduces amygdala—orbitofrontal cortex coupling

Guido van Wingen [a,b,*], Claudia Mattern [c], Robbert Jan Verkes [a,d], Jan Buitelaar [a,d], Guillén Fernández [a,b]

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KEYWORDS
fMRI;
Connectivity;
Amygdala;
Testosterone;
Emotion;
Regulation

Summary Testosterone influences various aspects of affective behavior, which is mediated by different brain regions within the emotion circuitry. Previous neuroimaging studies have demonstrated that testosterone increases neural activity in the amygdala. To investigate whether this could be due to altered regulation of amygdala functioning which is thought to be mediated by the prefrontal cortex, we studied the effects of exogenous testosterone on the interaction between the amygdala and other brain regions. Healthy middle-aged women received a single nasal testosterone dose in a randomized, placebo-controlled, crossover manner, and performed an emotional face matching task while their brain activity was measured with functional MRI. The results show that testosterone rapidly reduced functional coupling of the amygdala with the orbitofrontal cortex, and enhanced amygdala coupling with the thalamus. This suggests that testosterone may reduce the regulatory control over the amygdala, or that testosterone shifts amygdala output away from the orbitofrontal cortex towards the thalamus. Testosterone also reduced functional coupling with the contralateral amygdala. Because interhemispheric amygdala coupling is lower in men than in women, this result suggests that circulating testosterone may contribute to this sexual dimorphism.

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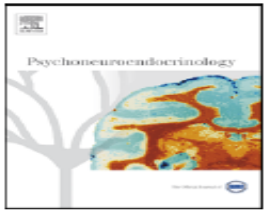

Testosterone administration modulates neural responses to crying infants in young females

Peter A. Bos [a,*], Erno J. Hermans [b,c], Estrella R. Montoya [a], Nick F. Ramsey [d], Jack van Honk [a,e]

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KEYWORDS
fMRI;
Testosterone;
Social;
Crying;
Separation call;
Emotion;
Maternal care

Summary Parental responsiveness to infant vocalizations is an essential mechanism to ensure parental care, and its importance is reflected in a specific neural substrate, the thalamocingulate circuit, which evolved through mammalian evolution subserving this responsiveness. Recent studies using functional Magnetic Resonance Imaging (fMRI) provide compelling evidence for a comparable mechanism in humans by showing thalamocingulate responses to infant crying. Furthermore, possibly acting on this common neural substrate, steroid hormones such as estradiol and testosterone, seem to mediate parental behavior both in humans and other animals. Estradiol unmistakably increases parental care, while data for testosterone are less unequivocal. In humans and several other animals, testosterone levels decrease both in mothers and fathers during parenthood. However, exogenous testosterone in mice seems to increase parenting, and infant crying leads to heightened testosterone levels in human males. Not only is the way in which testosterone is implicated in parental responsiveness unresolved, but the underlying mechanisms are fully unknown. Accordingly, using fMRI, we measured neural responses of 16 young women who were listening to crying infants in a double blind, placebo-controlled, counterbalanced, testosterone administration experiment. Crucially, heightened activation in the testosterone condition compared to placebo was shown in the thalamocingulate region, insula, and the cerebellum in response to crying. Our results by controlled hormonal manipulation confirm a role of the thalamocingulate circuit in infant cry perception. Furthermore, the data also suggest that exogenous testosterone, by itself or by way of its metabolite estradiol, in our group of young women acted on this thalamocinculate circuit to, provisionally, upregulate parental care.

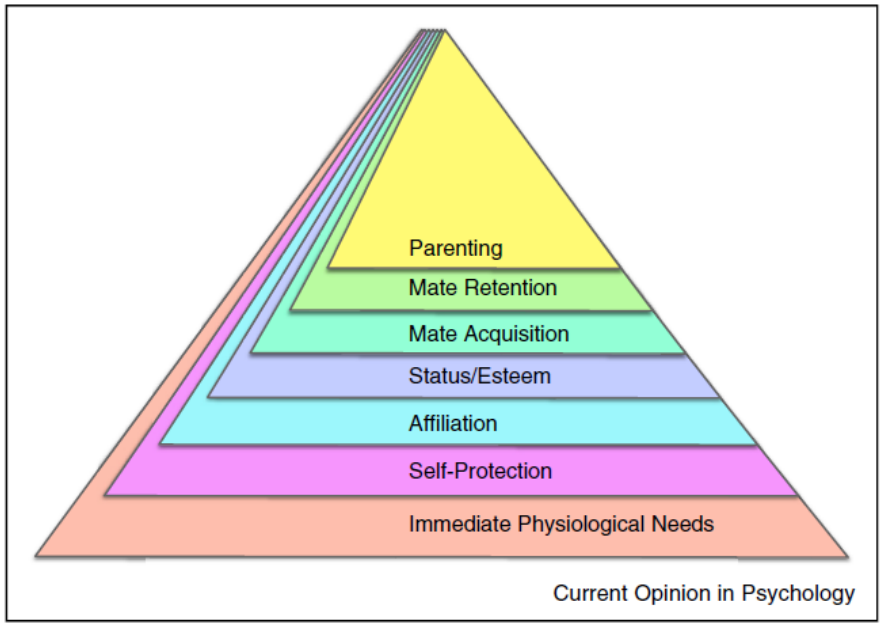
Current Opinion in Psychology 2016, **10**:27–32

Evolution and consumer behavior

Kristina M Durante[1] and Vladas Griskevicius[2]

An evolutionary theoretical approach considers the adaptive function of behavior. This article discusses what it means to use an evolutionary approach to generate predictions, and discusses two specific evolutionarily informed theories that have uncovered novel insights into consumer behavior. First, the fundamental motives framework highlights the social challenges faced by our ancestors (e.g., finding mates, avoiding disease) that continue to influence modern consumers in specific and often contradictory ways. Second, the ovulatory shift hypothesis highlights that women experience an increase in mating motivation near ovulation (e.g., increased desire to attract men and outcompete rival women) that has important implications for consumers. An evolution-informed approach can generate new insights about consumer behavior.

Figure 1



Hierarchy of fundamental human motives [13]. Note — once a motivational system has developed, its activation can be triggered in response to environmental cues indicating a threat or opportunity related to a specific evolutionary challenge.

40. Durante KM, Li NP, Haselton MG: **Changes in women's choice of dress across the ovulatory cycle: naturalistic and laboratory task-based evidence**. *Pers Soc Psychol Bull* 2008, **34**:1451-1460.

41. • Durante KM, Griskevicius V, Hill SE, Perilloux C, Li NP: **Ovulation, female competition, and product choice: hormonal influences on consumer behavior**. *J Consum Res* 2011, **37**:921-934.
Three studies found that at peak fertility women nonconsciously choose products that enhance appearance (e.g., choosing sexy rather than more conservative clothing). This effect was driven by a desire to outdo attractive rival women.

42. Haselton MG, Mortezaie M, Pillsworth EG, Bleske-Rechek A, Frederick DA: **Ovulatory shifts in human female ornamentation: near ovulation, women dress to impress**. *Horm Behav* 2007, **51**:40-45.

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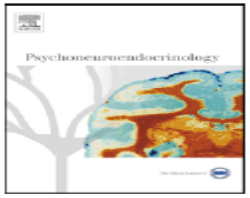

Multidimensional assessment of empathic abilities: Neural correlates and gender differences

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KEYWORDS
Empathy;
Gender;
Social cognition;
Perspective taking;
Affective responsiveness;
Emotion recognition

Summary Empathy is a multidimensional construct and comprises the ability to perceive, understand and feel the emotional states of others. Gender differences have been reported for various aspects of emotional and cognitive behaviors including theory of mind. However, although empathy is not a single ability but a complex behavioral competency including different components, most studies relied on single aspects of empathy, such as perspective taking or emotion perception. To extend those findings we developed three paradigms to assess all three core components of empathy (emotion recognition, perspective taking and affective responsiveness) and clarify to which extent gender affects the neural correlates of empathic abilities. A functional MRI study was performed with 12 females (6 during their follicular phase, 6 during their luteal phase) and 12 males, measuring these tasks as well as self-report empathy questionnaires.

Data analyses revealed no significant gender differences in behavioral performance, but females rated themselves as more empathic than males in the self-report questionnaires. Analyses of functional data revealed distinct neural networks in females and males, and females showed stronger neural activation across all three empathy tasks in emotion-related areas, including the amygdala. Exploratory analysis of possible hormonal effects indicated stronger amygdala activation in females during their follicular phase supporting previous data suggesting higher social sensitivity and thus facilitated socio-emotional behavior. Hence, our data support the assumption that females and males rely on divergent processing strategies when solving emotional tasks: while females seem to recruit more emotion and self-related regions, males activate more cortical, rather cognitive-related areas.

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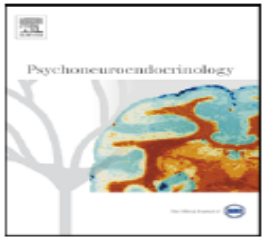

Organizational effects of fetal testosterone on human corpus callosum size and asymmetry

Lindsay R. Chura [a,1,*], Michael V. Lombardo [a,1], Emma Ashwin [a], Bonnie Auyeung [a], Bhismadev Chakrabarti [a,b], Edward T. Bullmore [c], Simon Baron-Cohen [a,*]

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KEYWORDS
Fetal testosterone;
Corpus callosum;
Asymmetry;
Brain development;
Organizational effects

Summary Previous theory and research in animals has identified the critical role that fetal testosterone (FT) plays in organizing sexually dimorphic brain development. However, to date there are no studies in humans directly testing the organizational effects of FT on structural brain development. In the current study we investigated the effects of FT on corpus callosum size and asymmetry. High-resolution structural magnetic resonance images (MRI) of the brain were obtained on 28 8—11-year-old boys whose exposure to FT had been previously measured *in utero* via amniocentesis conducted during the second trimester. Although there was no relationship between FT and midsaggital corpus callosum size, increasing FT was significantly related to increasing rightward asymmetry (e.g., Right > Left) of a posterior subsection of the callosum, the isthmus, that projects mainly to parietal and superior temporal areas. This potential organizational effect of FT on rightward callosal asymmetry may be working through enhancing the neuroprotective effects of FT and result in an asymmetric distribution of callosal axons. We suggest that this possible organizational effect of FT on callosal asymmetry may also play a role in shaping sexual dimorphism in functional and structural brain development, cognition, and behavior.

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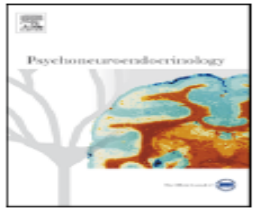

High pregnancy anxiety during mid-gestation is associated with decreased gray matter density in 6—9-year-old children

Claudia Buss [a], Elysia Poggi Davis [a,b], L. Tugan Muftuler [c], Kevin Head [c], Curt A. Sandman [a,*]

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KEYWORDS
Pregnancy anxiety;
Pregnancy;
Prenatal stress;
Longitudinal;
MRI;
Gray matter volume

Summary Because the brain undergoes dramatic changes during fetal development it is vulnerable to environmental insults. There is evidence that maternal stress and anxiety during pregnancy influences birth outcome but there are no studies that have evaluated the influence of stress during human pregnancy on brain morphology. In the current prospective longitudinal study we included 35 women for whom serial data on pregnancy anxiety was available at 19 (±0.83), 25 (±0.9) and 31 (±0.9) weeks gestation. When the offspring from the target pregnancy were between 6 and 9 years of age, their neurodevelopmental stage was assessed by a structural MRI scan. With the application of voxel-based morphometry, we found regional reductions in gray matter density in association with pregnancy anxiety after controlling for total gray matter volume, age, gestational age at birth, handedness and postpartum perceived stress. Specifically, independent of postnatal stress, pregnancy anxiety at 19 weeks gestation was associated with gray matter volume reductions in the prefrontal cortex, the premotor cortex, the medial temporal lobe, the lateral temporal cortex, the postcentral gyrus as well as the cerebellum extending to the middle occipital gyrus and the fusiform gyrus. High pregnancy anxiety at 25 and 31 weeks gestation was not significantly associated with local reductions in gray matter volume. This is the first prospective study to show that a specific temporal pattern of pregnancy anxiety is related to specific changes in brain morphology. Altered gray matter volume in brain regions affected by prenatal maternal anxiety may render the developing individual more vulnerable to neurodevelopmental and psychiatric disorders as well as cognitive and intellectual impairment.
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Prenatal stress programs neuroendocrine stress responses and affective behaviors in second generation rats in a sex-dependent manner

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The Roslin Institute and R (D) SVS, University of Edinburgh, Easter Bush Campus, Midlothian, EH25 9RG, UK

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ABSTRACT

An adverse environment in early life is often associated with dysregulation of the hypothalamo-pituitary-adrenal (HPA) axis and higher rates of mood disorders in adulthood. In rats, exposure to social stress during pregnancy results in hyperactive HPA axis responses to stress in the adult offspring and heightened anxiety behavior in the males, but not the females. Here we tested whether, without further intervention, the effects of prenatal stress (PNS) in the first filial generation (F1) are transmitted to the F2 generation via the maternal line. F1 control and PNS female rats were mated with control males and housed under non-stress conditions throughout pregnancy. HPA axis responses to acute stress, anxiety- and depressive-like behavior were assessed in the adult F2 offspring.

ACTH and corticosterone responses to an acute stressor were markedly enhanced in F2 PNS females compared with controls. This was associated with greater corticotropin releasing hormone (*Crh*) mRNA expression in the paraventricular nucleus and reduced hippocampal glucocorticoid (*Gr*) and mineralocorticoid receptor (*Mr*) mRNA expression. Conversely, in the F2 PNS males, HPA axis responses to acute stress were attenuated and hippocampal *Gr* mRNA expression was greater compared with controls.

F2 PNS males exhibited heightened anxiety-like behavior (light-dark box and elevated plus maze) compared with F2 control males. Anxiety-like behavior did not differ between F2 control and PNS females during metestrus/diestrus, however at proestrus/estrus, F2 control females displayed a reduction in anxiety-like behavior, but this effect was not observed in the F2 PNS females. Heightened anxiety in the F2 PNS males was associated with greater *Crh* mRNA expression in the central nucleus of the amygdala compared with controls. Moreover, Crh receptor-1 (*Crhr1*) mRNA expression was significantly increased, whereas *Crhr2* mRNA was significantly decreased in discrete regions of the amygdala in F2 PNS males compared with controls, with no differences in the F2 females. No differences in depressive-like behavior (sucrose preference or forced swim test) were observed in either sex. In conclusion, the effects of maternal stress during pregnancy on HPA axis regulation and anxiety-like behavior can be transmitted to future generations in a sex-dependent manner. These data have implications for human neuropsychiatric disorders with developmental origins.

Review Article

Depression as a Neuroendocrine Disorder: Emerging Neuropsychopharmacological Approaches beyond Monoamines

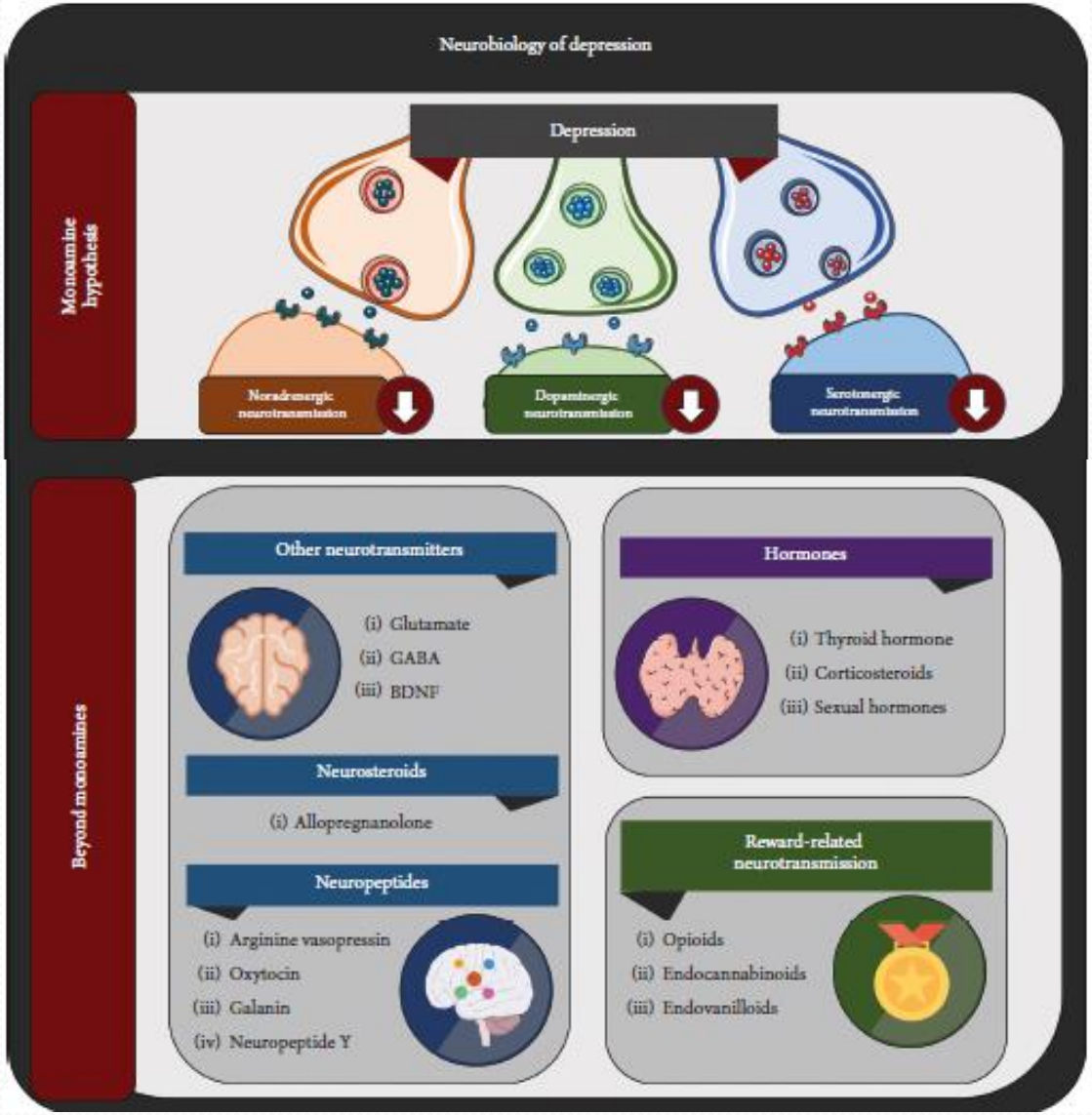
La depresión se reconoce actualmente como un problema crucial en la práctica clínica diaria, a la luz de las tasas de prevalencia cada vez mayores, así como de discapacidad, morbilidad y mortalidad relacionadas con este trastorno. Los medicamentos antidepresivos disponibles actualmente son notoriamente problemáticos, con tasas de remisión subóptimas y perfiles de efectos secundarios problemáticos. Sus mecanismos de acción se centran en la hipótesis de las monoaminas para la depresión, que se centra en la alteración de la neurotransmisión serotoninérgica, noradrenérgica y dopaminérgica en el cerebro. Sin embargo, las teorías sobre la fisiopatología de la depresión han evolucionado notablemente, y la comprensión de la depresión como un trastorno neuroendocrino complejo con importantes implicaciones sistémicas ha despertado interés en una miríada de nuevos enfoques neuropsicofarmacológicos. Los objetivos farmacológicos innovadores más allá de las monoaminas incluyen a la neurotransmisión glutamatérgica y GABAérgica, al factor neurotrófico derivado del cerebro, varios ejes endocrinos, así como varios neurosteroides, neuropéptidos, opioides, endocannabinoides y endovanilloides. Esta revisión resume el conocimiento actual sobre estos objetivos farmacológicos y su potencial utilidad en el manejo clínico de la depresión.

Advances in Pharmacological Sciences
Volume 2019, Article ID 7943481, 20 pages

Review Article

Advances in Pharmacological Sciences
Volume 2019, Article ID 7943481, 20 pages

Depression as a Neuroendocrine Disorder: Emerging Neuropsychopharmacological Approaches beyond Monoamines



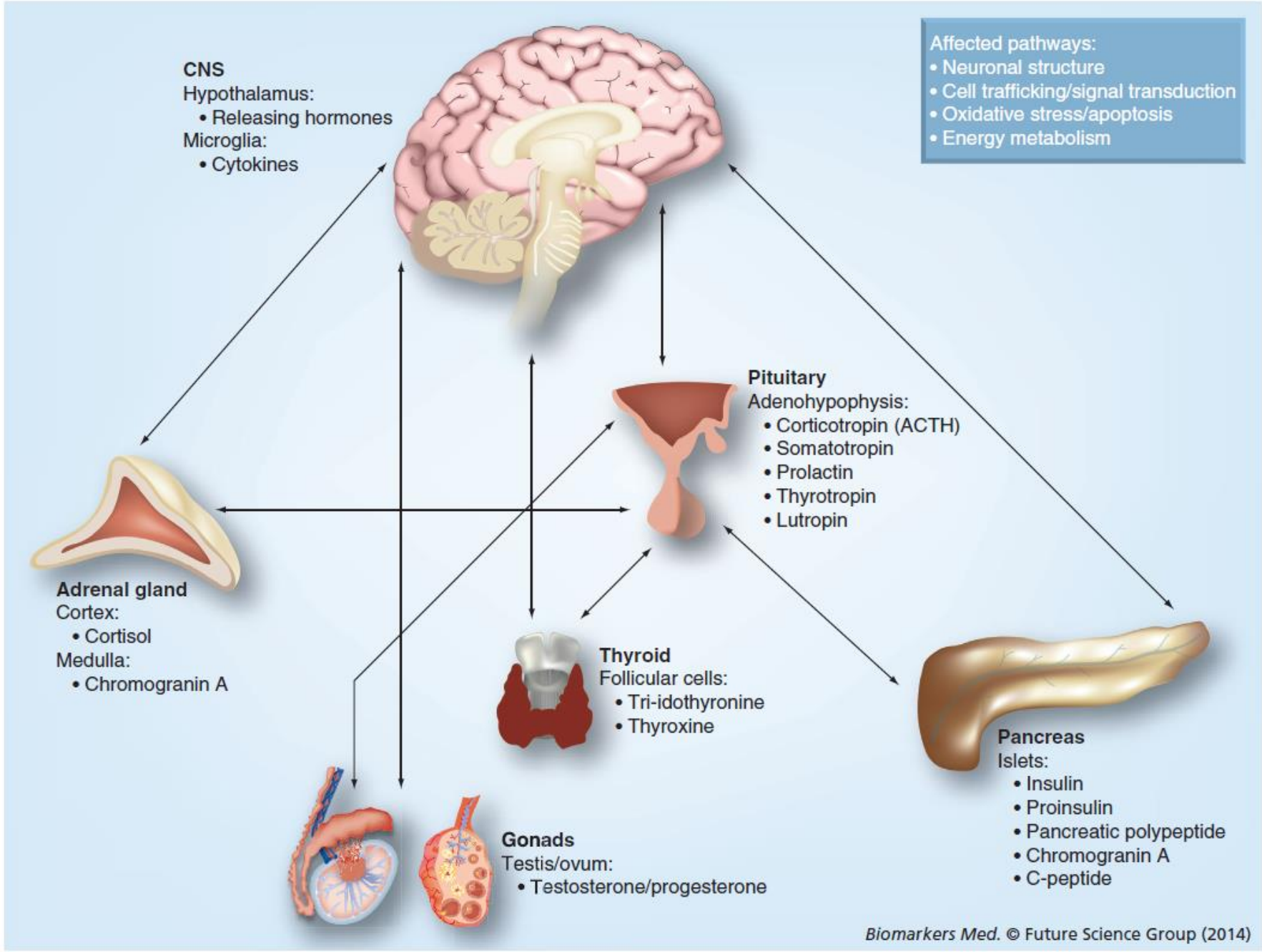


Figure 1. Peripheral and central signaling molecules affected in schizophrenia associated with the immune, metabolic or hormonal systems. Arrows indicate interaction via the vascular system.

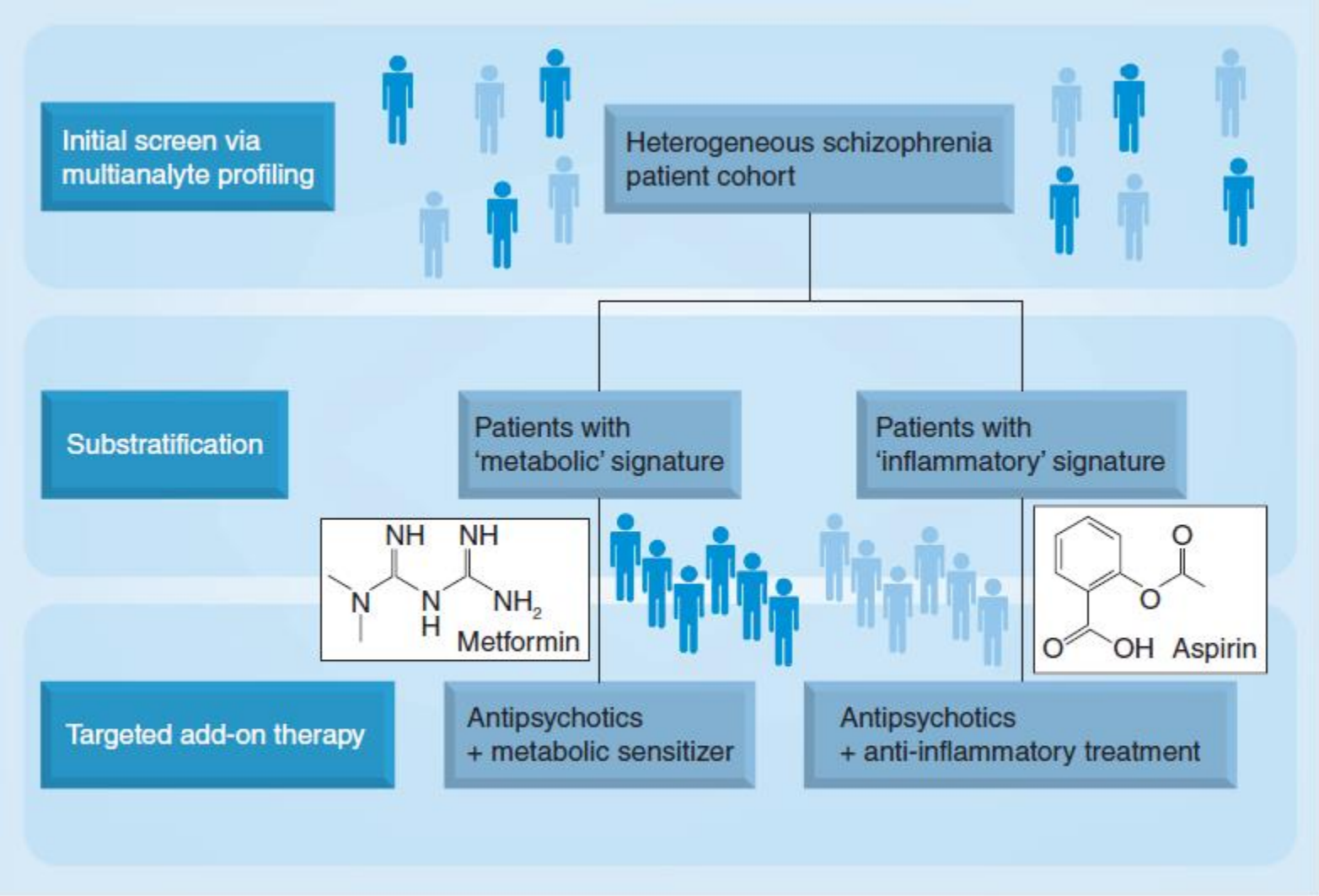


Figure 2. Stratification of schizophrenia patients prior to treatment based on proteomic profiles displaying immune or hormonal abnormalities.

Dialogues Clin Neurosci. 2010;12:345-357.

Pharmacologic treatment of schizophrenia

John M. Kane, MD; Christoph U. Correll, MD

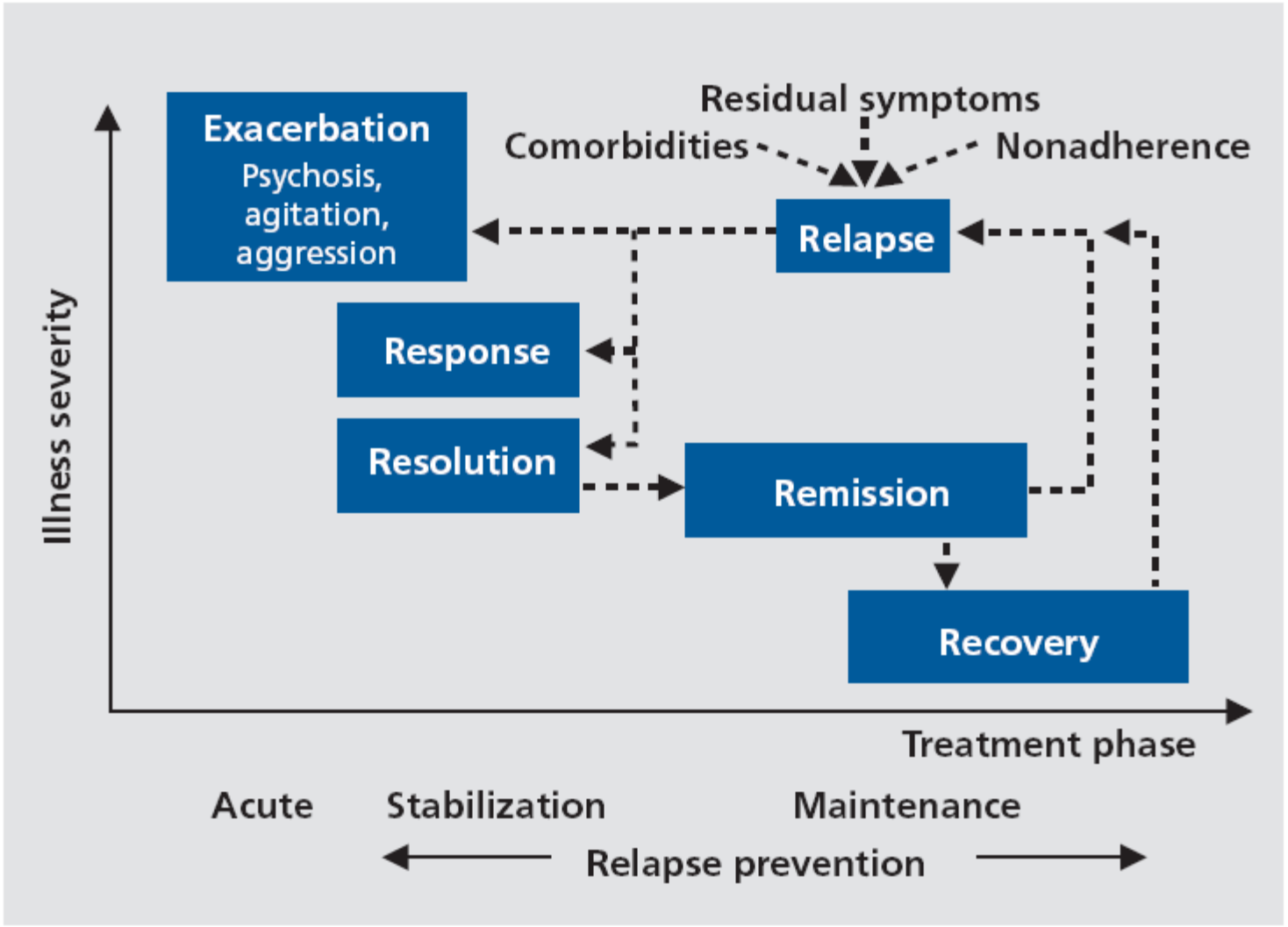
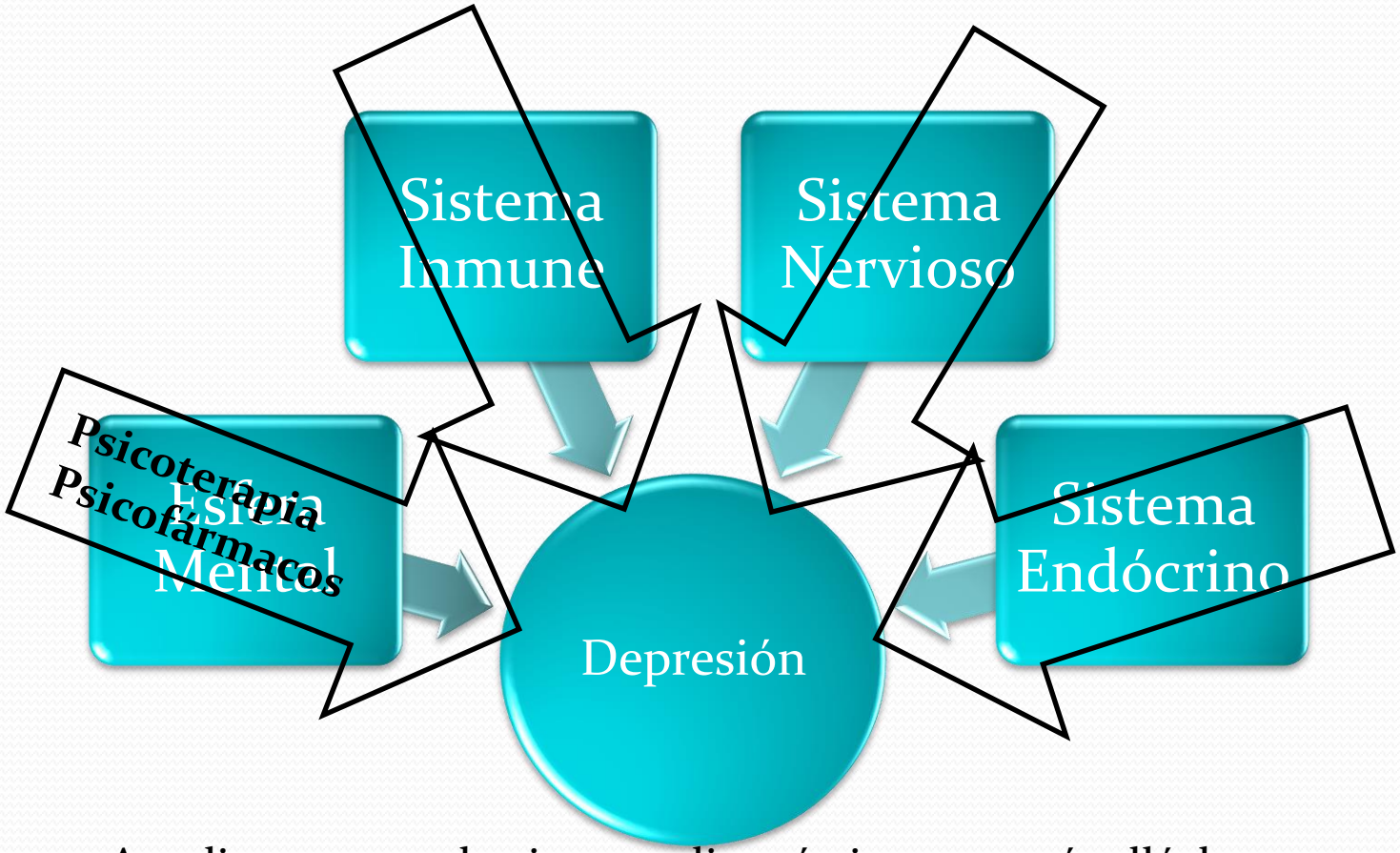


Figure 1. Treatment stages.

Modelo Sistémico-PINE de los Trastornos Mentales



Ampliar nuestros horizontes diagnósticos, ver más allá de nuestro campo en particular

Intervenir con mas herramientas sobre un número mayor de variables

Diagnóstico y Tratamiento de los Trastornos Mentales de camino al futuro

- Diferentes causas dentro de los mismos Trastornos Mentales
- Diferentes Vías Fisiopatológicas
- Diagnósticos Fisiopatológicos específicos basados en Biomarcadores
- Intervenciones Terapéuticas más dirigidas y específicas
- Mayor cantidad de opciones terapéuticas
- Mejores índices de Respuesta y Remisión

brain sciences

Brain Sci. 2018, 8, 154; doi:10.3390/brainsci8080154 www.mdpi.com/

MDPI

Review

Sex: A Significant Risk Factor for Neurodevelopmental and Neurodegenerative Disorders

Paulo Pinares-Garcia [1,2], Marielle Stratikopoulos [1,2], Alice Zagato [1,3], Hannah Loke [1] and Joohyung Lee [1,2,*]

Abstract: Males and females sometimes significantly differ in their propensity to develop neurological disorders. Females suffer more from mood disorders such as depression and anxiety, whereas males are more susceptible to deficits in the dopamine system including Parkinson's disease (PD), attention-deficit hyperactivity disorder (ADHD) and autism. Despite this, biological sex is rarely considered when making treatment decisions in neurological disorders. A better understanding of the molecular mechanism(s) underlying sex differences in the healthy and diseased brain will help to devise diagnostic and therapeutic strategies optimal for each sex. Thus, the aim of this review is to discuss the available evidence on sex differences in neuropsychiatric and neurodegenerative disorders regarding prevalence, progression, symptoms and response to therapy. We also discuss the sex-related factors such as gonadal sex hormones and sex chromosome genes and how these might help to explain some of the clinically observed sex differences in these disorders. In particular, we highlight the emerging role of the Y-chromosome gene, *SRY*, in the male brain and its potential role as a

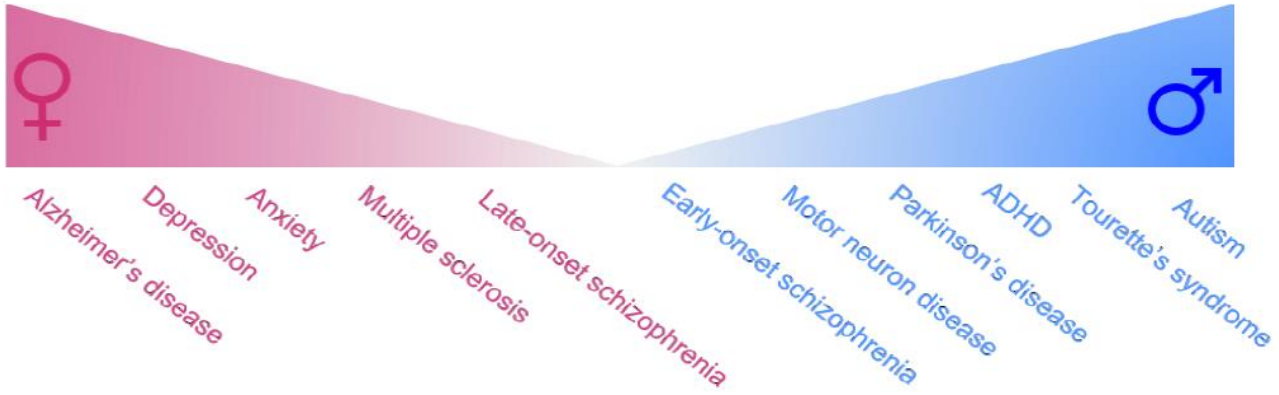


Figure 1. Sex differences in the prevalence of neurodegenerative and neuropsychiatric disorders. Abbreviations: ADHD, Attention-deficit hyperactivity disorder.

NEUROPSYCHOPHARMACOLOGY REVIEWS

Sex differences and the neurobiology of affective disorders

David R. Rubinow[1] and Peter J. Schmidt[2]

Observations of the disproportionate incidence of depression in women compared with men have long preceded the recent explosion of interest in sex differences. Nonetheless, the source and implications of this epidemiologic sex difference remain unclear, as does the practical significance of the multitude of sex differences that have been reported in brain structure and function. In this article, we attempt to provide a framework for thinking about how sex and reproductive hormones (particularly estradiol as an example) might contribute to affective illness. After briefly reviewing some observed sex differences in depression, we discuss how sex might alter brain function through hormonal effects (both organizational (programmed) and activational (acute)), sex chromosome effects, and the interaction of sex with the environment. We next review sex differences in the brain at the structural, cellular, and network levels. We then focus on how sex and reproductive hormones regulate systems implicated in the pathophysiology of depression, including neuroplasticity, genetic and neural networks, the stress axis, and immune function. Finally, we suggest several models that might explain a sex-dependent differential regulation of affect and susceptibility to affective illness. As a disclaimer, the studies cited in this review are not intended to be comprehensive but rather serve as examples of the multitude of levels at which sex and reproductive hormones regulate brain structure and function. As such and despite our current ignorance regarding both the ontogeny of affective illness and the impact of sex on that ontogeny, sex differences may provide a lens through which we may better view the mechanisms underlying affective regulation and dysfunction.

Neuropsychopharmacology (2018) 0:1–18; https://doi.org/10.1038/s41386-018-0148-z

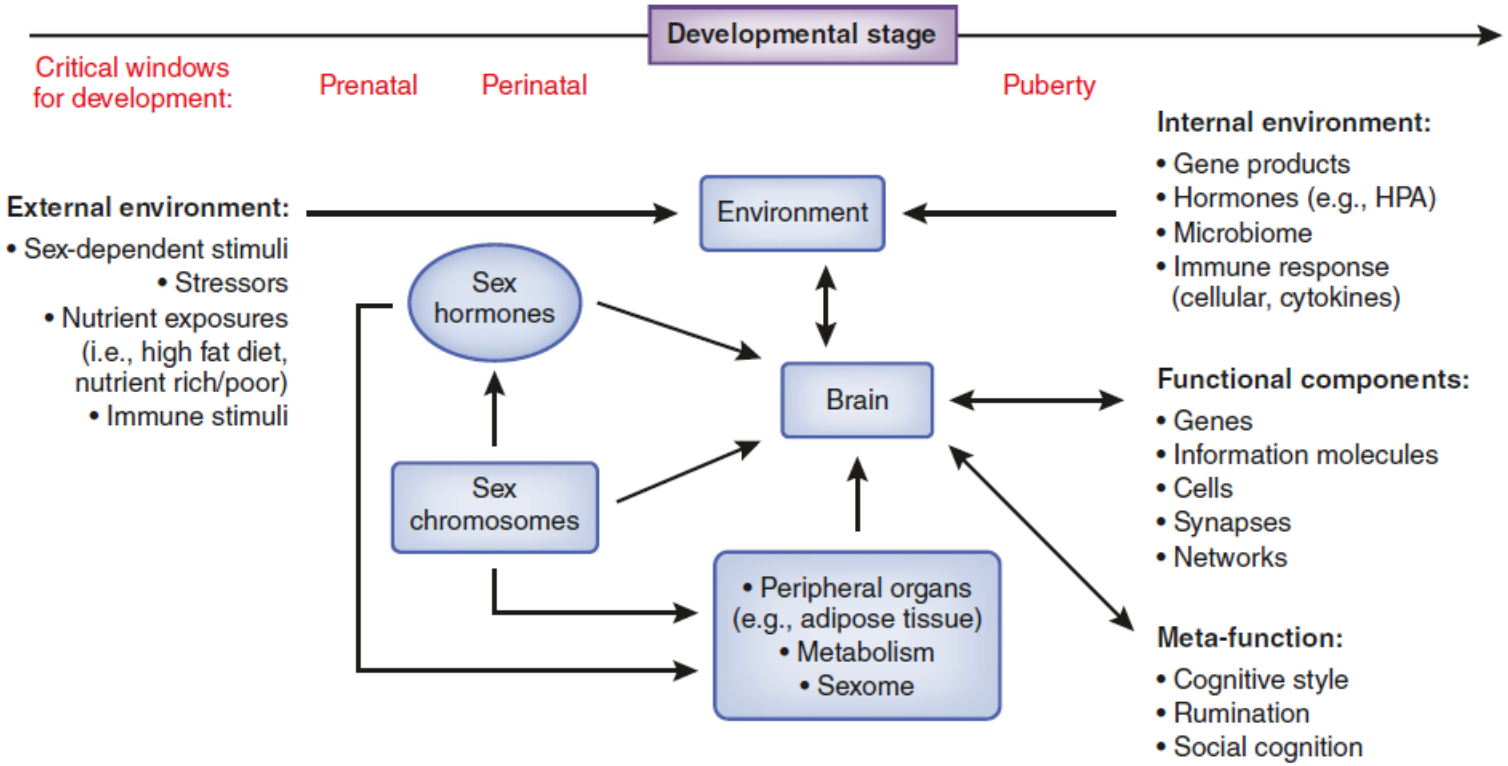
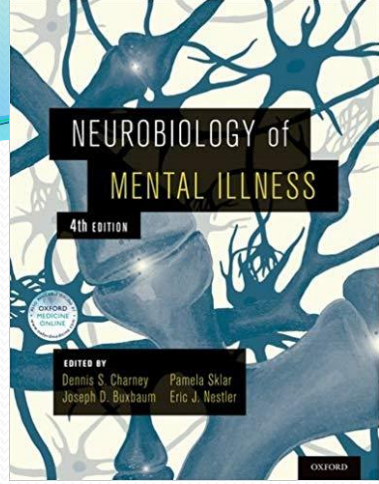


Fig. 1 Schematic depiction of the multiple levels at which sex influences brain function. Sex is a ubiquitous, context-creating modulator of brain and behavior, accomplished through both organizational effects that program subsequent brain sensitivities and development, and activational effects that acutely impact neural function. Sex influences the internal environment in which brain function occurs (e.g., differential exposure to stress or immune soluble molecules) as well as modulating the impact of the external environment (e.g., diet or stressors, particularly in the prenatal environment, or even social responses from others based on sex). Sex chromosomes impact brain development directly, may impact physiology through differences in exposure to gene products (e.g., sex-linked genes or differences in gene dosage), and alter brain function developmentally and activationally through sex-determined gonadal function and differential exposure to sex hormones. Sex differences in peripheral organs (e.g., adipose, liver) lead to differential exposure of the brain to hormones as well as medications (through effects on metabolism). The sexome refers to the cumulative array of sex-related modulatory effects on intracellular molecular interactions. Sex differences appear at all levels of neural organization, from cell to circuit. Finally, reported sex differences in meta-cognitions may influence perception and processing of environmental stimuli, thus influencing affective generation and regulation (references appear in the text)

Un poco de historia:



- Aristóteles: cambios conductuales provocados por la castración
- Berthold-1849: reversión de la castración
- Brown Sequard-1860 aprox.:organoterapia, administración de extracto de órganos para tratar trastornos anímicos y rejuvenecimiento (elixir de Brown Sequard)
- Doisy-1929: aislamiento de Theelin luego denominada estrona
- Werner-1934: descripción de la eficacia antidepresiva de un preparado de estradiol llamado Theelin en un estudio en perimenopáusicas y posmenopáusicas tempranas
- 1935: aislamiento del Estradiol y luego del Etinilestradiol
- Siglo XX: doble tasa de depresión en mujeres y trastornos afectivos en relación a alteraciones endócrinas reproductivas (menarca, embarazo y posparto, perimenopausia y durante el ciclo menstrual así como la manipulación de los esteroides gonadales o de los estados reproductivos)

Hormonas Esteroideas - Esteroides Sexuales

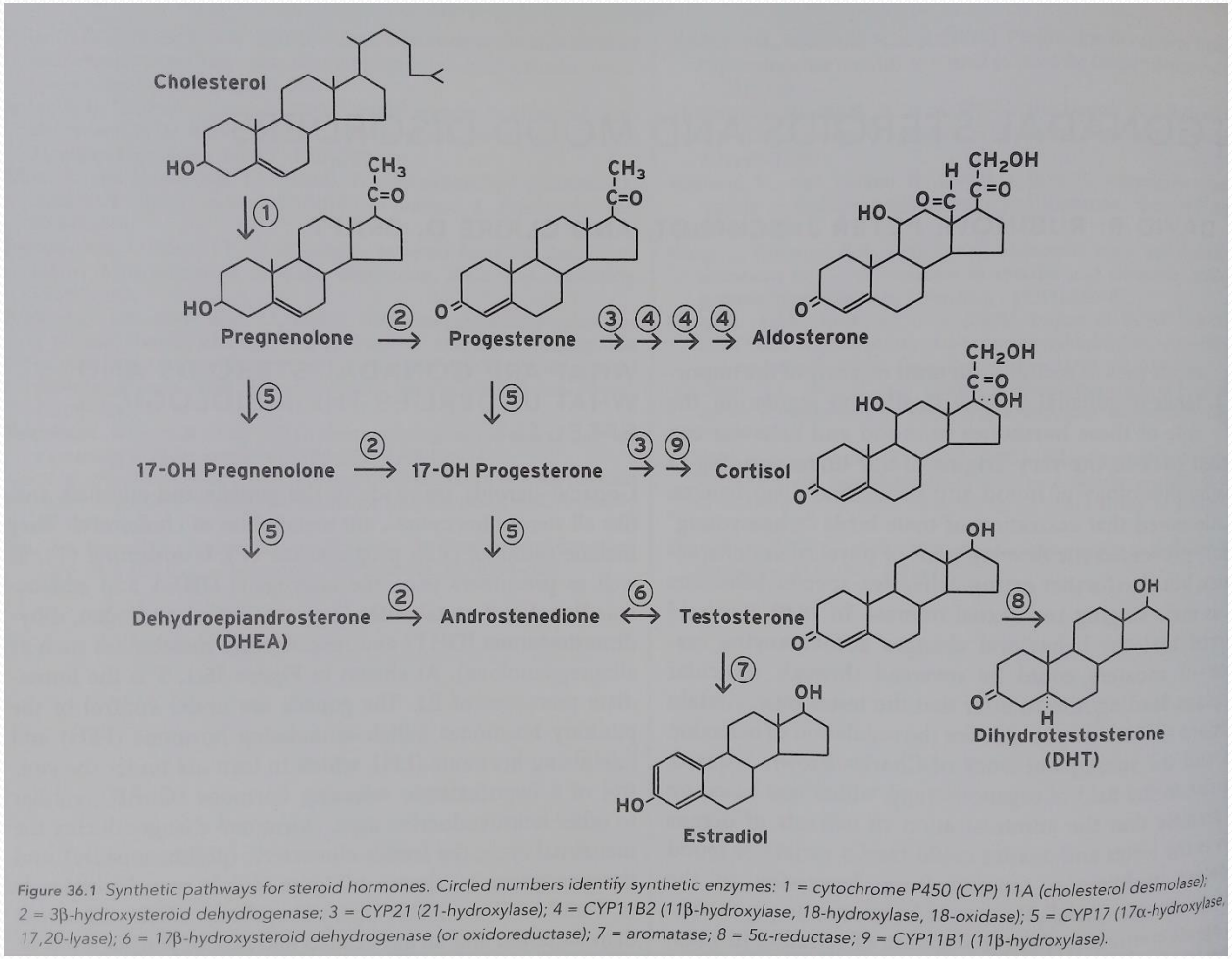
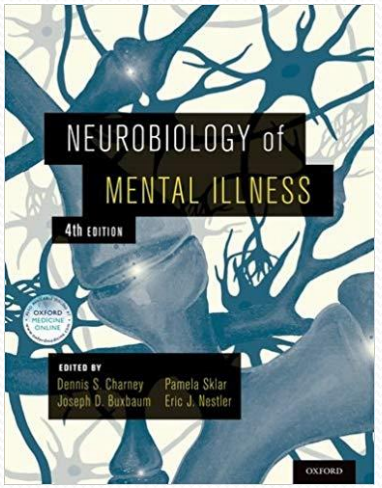
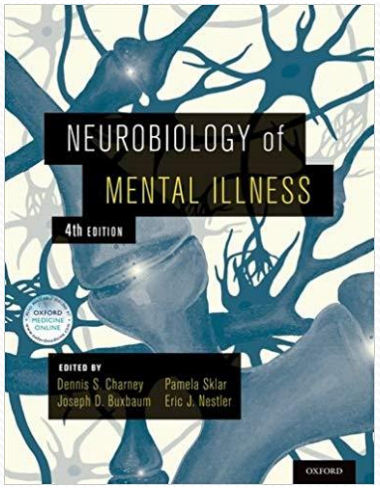


Figure 36.1 *Synthetic pathways for steroid hormones. Circled numbers identify synthetic enzymes: 1 = cytochrome P450 (CYP) 11A (cholesterol desmolase); 2 = 3β-hydroxysteroid dehydrogenase; 3 = CYP21 (21-hydroxylase); 4 = CYP11B2 (11β-hydroxylase, 18-hydroxylase, 18-oxidase); 5 = CYP17 (17α-hydroxylase, 17,20-lyase); 6 = 17β-hydroxysteroid dehydrogenase (or oxidoreductase); 7 = aromatase; 8 = 5α-reductase; 9 = CYP11B1 (11β-hydroxylase).*



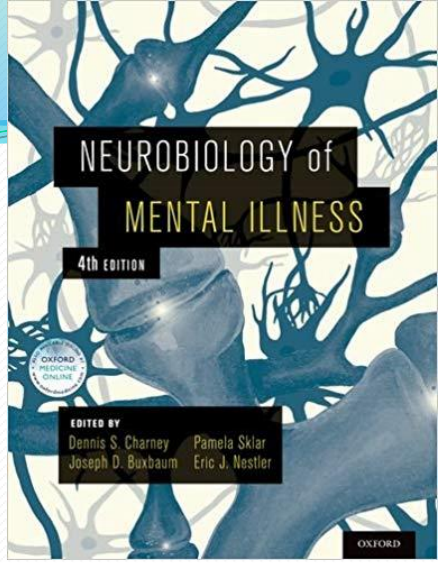
- Funciones principales y secundarias
- Funciones periféricas y centrales

Hormonas Esteroideas



- Por su acción: Sexuales
  Equilibrio y adaptación
  Neuroprotectoras
- Lugar de serceción: Gónadas
  Glándulas Adrenales
  Cerebro
- Mecanismo de acción: Receptores Específicos Intracelulares
  Receptores Específicos de Membrana
  Receptores de otras Moléculas
- Efectos: Primario en Sistema Endócrino u otros órganos

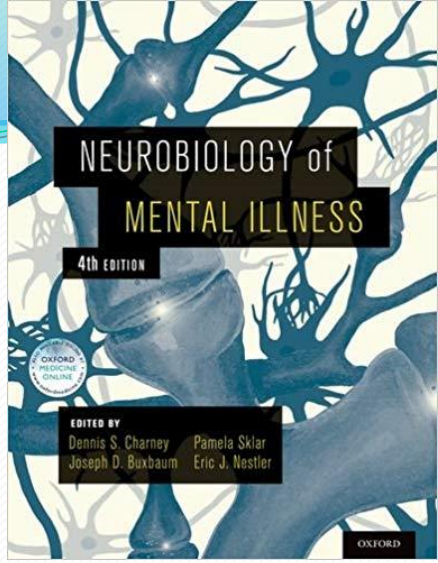
  Secundario en Cerebro y Mente (Endocrinología Conductual)



- El rango y variación en el potencial neurorregulatorio de los esteroides gonadales se multiplica y depende de múltiples variables.
- 1. Rc-E-Co Activador, Co Represor, Co Integrador
- 2.Rc hormonales en diferentes formas con diferente distribución, acción y afinidad por diferentes ligandos
- 3. Otras moléculas que tiene el poder de activar Rc Esteroideos (Cross-talk)
- 4. Efecto gonadal lento por acción genómica más efecto rápido por acción en canales iónicos y otros Rc de membrana
- 5. Esteroides gonadales que regulan la supervivencia celular por diferentes mecanismo demostrados en estudios de diferentes modelos de daño neuronal. Mediados por Rc estrogénico, no mediados por Rc estrogénicos por ejemplo efecto antioxidante, mediados por efectos en proteínas de supervivencia celular

Girdler, 2011), E2 "beneficially" modulates the following putative system disturbances in depression:

1. *Neurotransmitter deficiencies*—E2 regulates the synthesis, metabolism, and receptor concentration/trafficking of the classical neurotransmitters implicated in depression (i.e., serotonin, dopamine, and norepinephrine).
2. *Stress*—E2 regulates both basal and stress-induced ACTH and cortisol in animals through effects on GR and corticotropin-releasing hormone (CRH; although P may have more regulatory effects in humans).
3. *Neuroplasticity*—E2 has a significant impact on neuronal plasticity-related processes, acting like antidepressants (and opposite to stress) in stimulating BDNF, a critical growth factor observed to be deficient in depression; increasing activity of the transcription factor cAMP response element-binding protein (CREB) and trkA (neurotrophic tyrosine kinase receptor type 1); and decreasing glycogen synthase kinase (GSK)-3β in rat brain, the same direction of effects as seen with mood stabilizers. Consistent with these effects, as mentioned previously, E2 is neuroprotective in a variety of models, including oxidative damage, glutamate excess, and β-amyloid toxicity.
4. *Cellular energetics*—E2 improves mitochondrial respiratory efficiency and prevents the oxygen free radicals that are believed to adversely affect mitochondrial energetics in depression.
5. *Inflammation*—At multiple levels, E2 prevents or counteracts the proinflammatory processes described as contributing to depression.
6. *Brain systems*—The ability of gonadal steroid hormones to regulate activation in brain regions implicated in depression can be inferred from imaging studies conducted over the menstrual cycle or after gonadal steroid administration.



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Review Article

Translational Significance of Selective Estrogen Receptor Modulators in Psychiatric Disorders

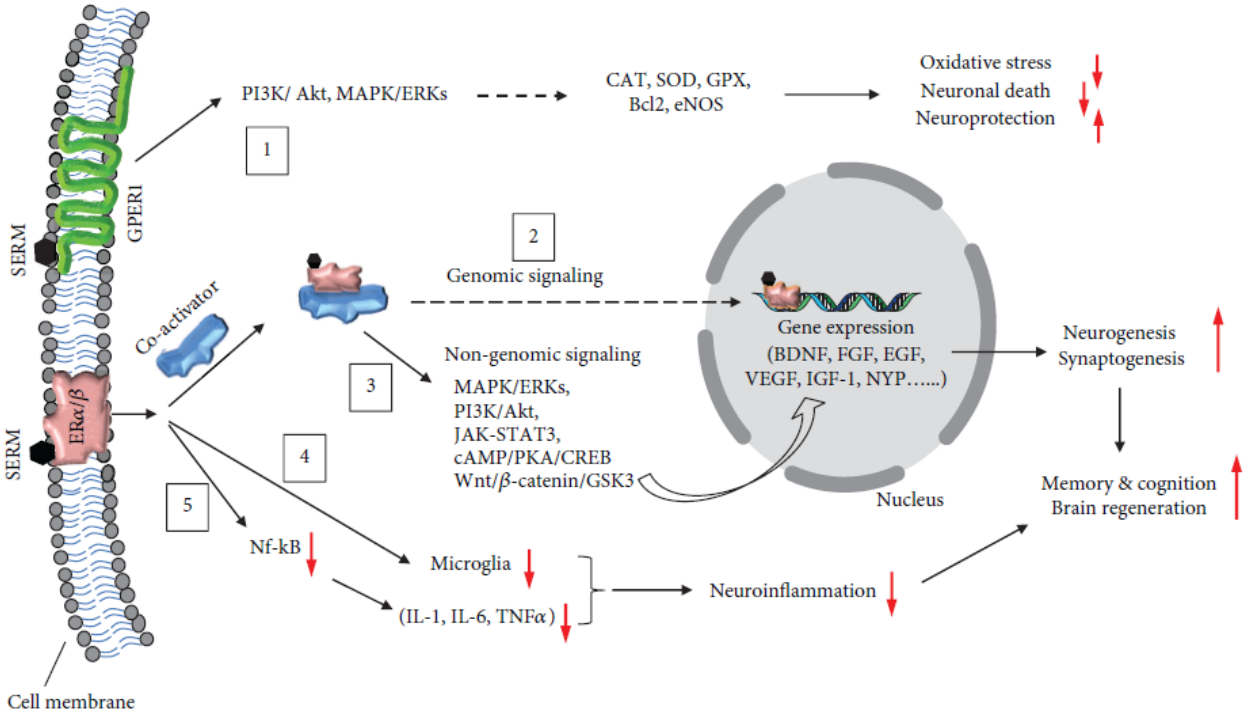
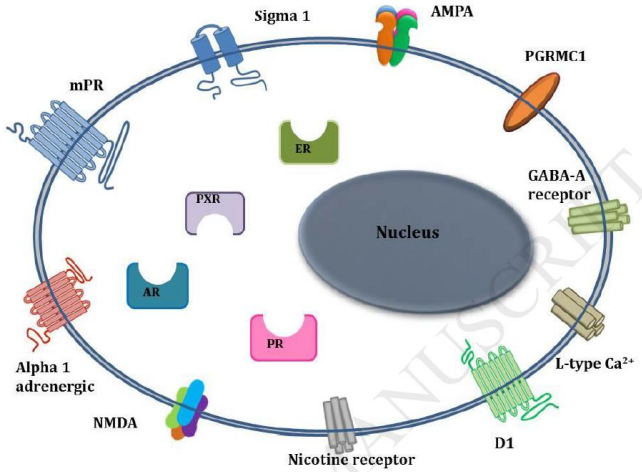


FIGURE 1: Possible signaling mechanisms of SERM actions in neurocognition and neuroprotection. Over the last few years, others and we have shown that SERMs can mediate their actions by initiating genomic (gene expression) and/or nongenomic signaling that involve kinases and phosphatases. In CNS tissues, SERMs can bind and activate both classical estrogen receptors-α and β (ERα or ERβ) as well as nonclassical transmembrane G protein-coupled ER (GPER1). Via agonist action at GPER1, SERMs can activate the PI3K/Akt and MAPK/ERK pathways (Figure 1, box 1), which have been shown to be involved in neuroprotection and reduction of oxidative stress and neuronal cell death by increasing the expression of antioxidant enzymes (CAT, SOD, GPx, and eNOS), Bcl2, and other trophic factors. Via agonist action at the classical ERα or ERβ, SERMs can activate gene expression/genomic signaling (Figure 1, box 2) of various growth factors and proteins involved in synaptic plasticity, neurogenesis, memory, and cognition. SERMs can also enhance interaction of ERα or ERβ with MNAR/PELP1, a scaffold/coactivator protein highly expressed in neurons and astrocytes [165,166]. The resultant ER-MNAR/PELP1 complex can then initiate nongenomic signaling by activating the PI3K/Akt, MAPK/ERK, and Wnt/β-catenin/GSK3β signaling pathways (Figure 1, box 3). These pathways have been shown to regulate neurogenesis, synaptogenesis, and cognitive behaviors in the normal and model animals of diseases. SERMs can reduce brain inflammation by acting on astroglia via ERα or ERβ. They can reduce microglia proliferation (Figure 1, box 4) as well as production of inflammatory cytokines and chemokines including IL-1, IL-6, and TNFα via inhibition of nuclear factor-kappa-B (Nf-KB) transactivation (Figure 1, box 5). Inhibition of this pathway has been shown to induce neuroprotection and reduce neuronal cell death in various cellular and animal models of brain injury. Red arrows indicate increase (upward) or decrease (downward) in the magnitude of response by SERMs.

Figr-2



2.2. Receptors for neuroactive steroids

The enzymatic conversions mentioned in the previous section determine the steroid receptors that will be activated in the brain. Some steroid metabolites act through classical steroid receptors, such as PROG (PR), androgen (AR) and estrogen (ER) receptors. These classical steroid receptors are transcription factors and are present in different isoforms, like for instance PR-A and -B, ER-alpha and -beta. Estradiol also binds to G-protein coupled estrogen receptor (GPER), a membrane receptor (Hadjimarkou and Vasudevan, 2018). Other steroid metabolites may activate non-classical steroid receptors, which include gamma-amino butyric acid (GABA) A and B receptors, N-methyl-D-aspartate (NMDA) receptor, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, dopamine 1 (D1) receptor, the nicotine receptors, the α-1 adrenergic receptor, the sigma-1 receptor and L-type Ca^{2+} channels (Giatti *et al.*, 2015a; Vega-Vela *et al.*, 2017) (Fig. 2).

Behav Neurosci. 2012 February ; 126(1): 4–16. doi:10.1037/a0026708.

Estrogen effects on the brain: actions beyond the hypothalamus via novel mechanisms

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The investigation of cellular and molecular actions of estrogens on the brain has contributed to at least two important areas of knowledge. First, the mechanism of estrogen action has expanded to include indirect genomic and non-genomic actions of these hormones along with their traditional genomic effects. This has led to the finding of estrogen receptors in many parts of the brain in neuron cell bodies, dendrites, pre-synaptic terminals, mitochondria and glial cell processes using high-resolution immunocytochemical techniques involving electron microscopy. Second, these findings have revitalized studies of estrogen actions on diverse functions in many parts of the brain, such as the action of estradiol on hippocampus and prefrontal cortex in both rodent and monkey models and the effects of aging on estrogen actions and on autonomic centers in the brain stem. These potentially affect cognition, mood, and blood pressure regulation, and potentially alter inflammatory processes and innate and acquired immune function not only in the brain but throughout the body.

Physiol Rev 95: 785–807, 2015
Published June 24, 2015; doi:10.1152/physrev.00036.2014

ESTROGEN EFFECTS ON COGNITIVE AND SYNAPTIC HEALTH OVER THE LIFECOURSE

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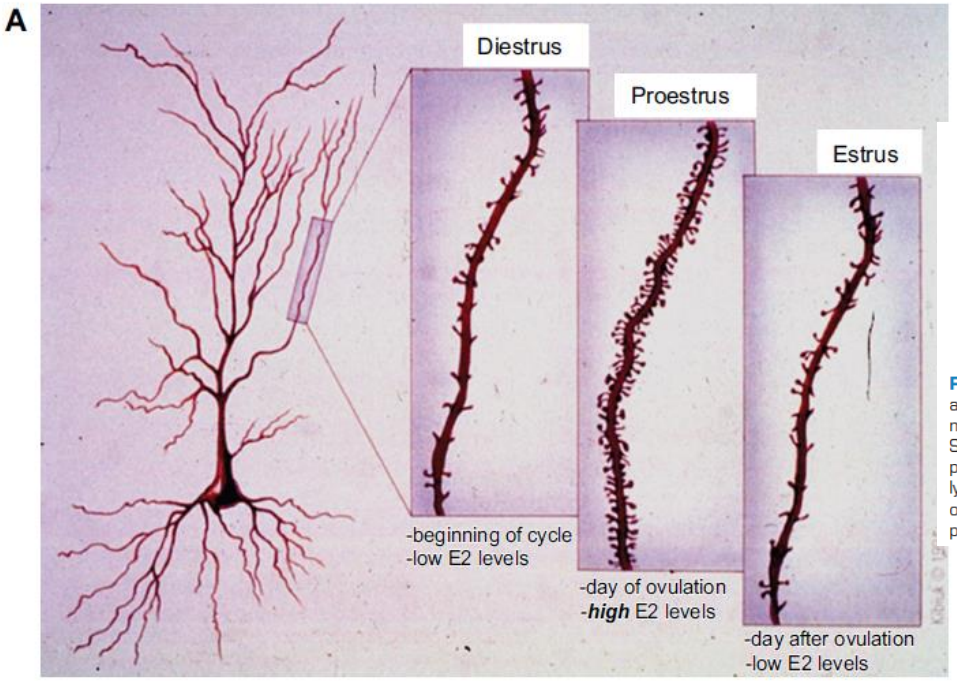
Fishberg Department of Neuroscience and Kastor Neurobiology of Aging Laboratories, Friedman Brain Institute, Department of Geriatrics and Palliative Medicine, Graduate School of Biomedical Sciences, Icahn School of Medicine at Mount Sinai, New York, New York; and Harold and Margaret Milliken Hatch Laboratory of Neuroendocrinology, The Rockefeller University, New York, New York

Los estrógenos facilitan las funciones cognitivas al ejercer efectos sobre regiones cerebrales como la corteza prefrontal e hipocampo. Los estrógenos inducen espinogénesis y sinaptogénesis en estas dos regiones del cerebro iniciando un conjunto complejo de vías de transducción de señales a través de receptores de estrógenos (ER). Junto con los efectos genómicos clásicos mediados por la activación de ER alfa y ER beta, hay unidades de membrana ER alfa , ER beta y receptor 1 de estrógeno acoplado a proteínas G (GPER1) que pueden mediar rápidamente efectos no genómicos. Todas los ER clave presentes en todo el cuerpo también están presentes en las sinapsis de hipocampo y corteza prefrontal. Esta revisión resume las acciones de los estrógenos en el cerebro a partir del punto de vista de sus efectos sobre la estructura y función de la sinapsis, señalando también el papel sinérgico de progesterona. Primero comenzamos con una revisión de los subtipos de ER en el cerebro y cómo su abundancia y

las distribuciones se alteran con el envejecimiento y la pérdida de estrógenos (por ejemplo, ovariectomía o menopausia) en el roedor, en monos y en el cerebro humano. Como hay mucha evidencia de que la pérdida de estrógenos inducida por la menopausia puede exacerbar los efectos del envejecimiento en las funciones cognitivas, luego revisamos los ensayos clínicos de las terapias de reemplazo hormonal y su efectividad en los síntomas cognitivos experimentados por las mujeres. Finalmente, resumimos los estudios realizados en modelos de primates no humanos relacionados con la edad y la menopausia que son altamente relevantes para desarrollar intervenciones efectivas para mujeres menopáusicas.

Juntos, destacamos una nueva comprensión de cómo los estrógenos afectan las funciones cognitivas superiores y la salud sináptica, algo que va mucho más allá de sus efectos en la reproducción.



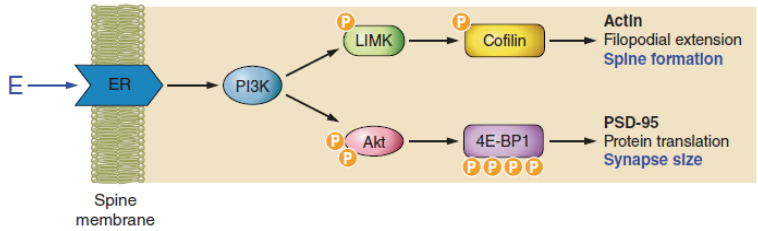


FIGURE 4. Nongenomic estrogen-initiated signal transduction leading to spinogenesis and changes in synapse size. Estrogen initiates a complex set of signal transduction pathways in the hippocampal neuron via membrane-bound estrogen receptors. Rapid activation of Akt (protein kinase B) via PI3K is mediated by ER α. Subsequently, activated Akt initiates translation of PSD-95 by disinhibiting the initiation factor 4E-binding protein 1 (4E-BP1). Estradiol-mediated phosphorylation of cofilin occurs via activation of LIMK. Cofilin depolymerizes actin and is inactivated by phosphorylation. Therefore, in the presence of estrogen, cofilin repression of actin polymerization is removed, resulting in an increase in filopodial density. The signal transduction pathways illustrated here are an oversimplification of a large body of work performed in an in vitro cell line.

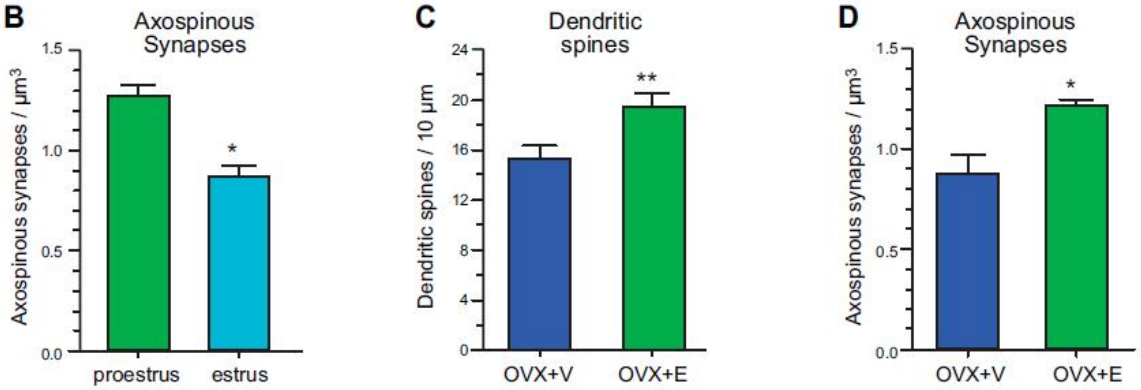


FIGURE 1. Estradiol regulates spine synapses on hippocampal pyramidal neurons, which are sites of excitatory neurotransmission important for learning and memory. *A*: in the diestrus phase, which is the beginning of the estrus cycle when estradiol levels are low, spine densities are also low. During proestrus when ovulation occurs, estrogen levels peak and spine densities increase in parallel. In the estrus phase, the day after proestrus, the system begins to reset itself for the next cycle and spine densities return to baseline. [Image adapted from McEwen and Schmeck (134a) with permission.] *B*: axospinous synapse density is higher in the proestrus phase compared with the estrus phase. *C* and *D*: in ovariectomized (OVX) rats, estradiol (E) treatment increases dendritic spine density (*C*) as well as axospinous synapse density (*D*). V, vehicle-treated. Histograms (*B–D*) are plotted from data originally presented in Gould et al. (58) and Woolley and McEwen (236).

Review article

Is the membrane estrogen receptor, GPER1, a promiscuous receptor that modulates nuclear estrogen receptor-mediated functions in the brain?

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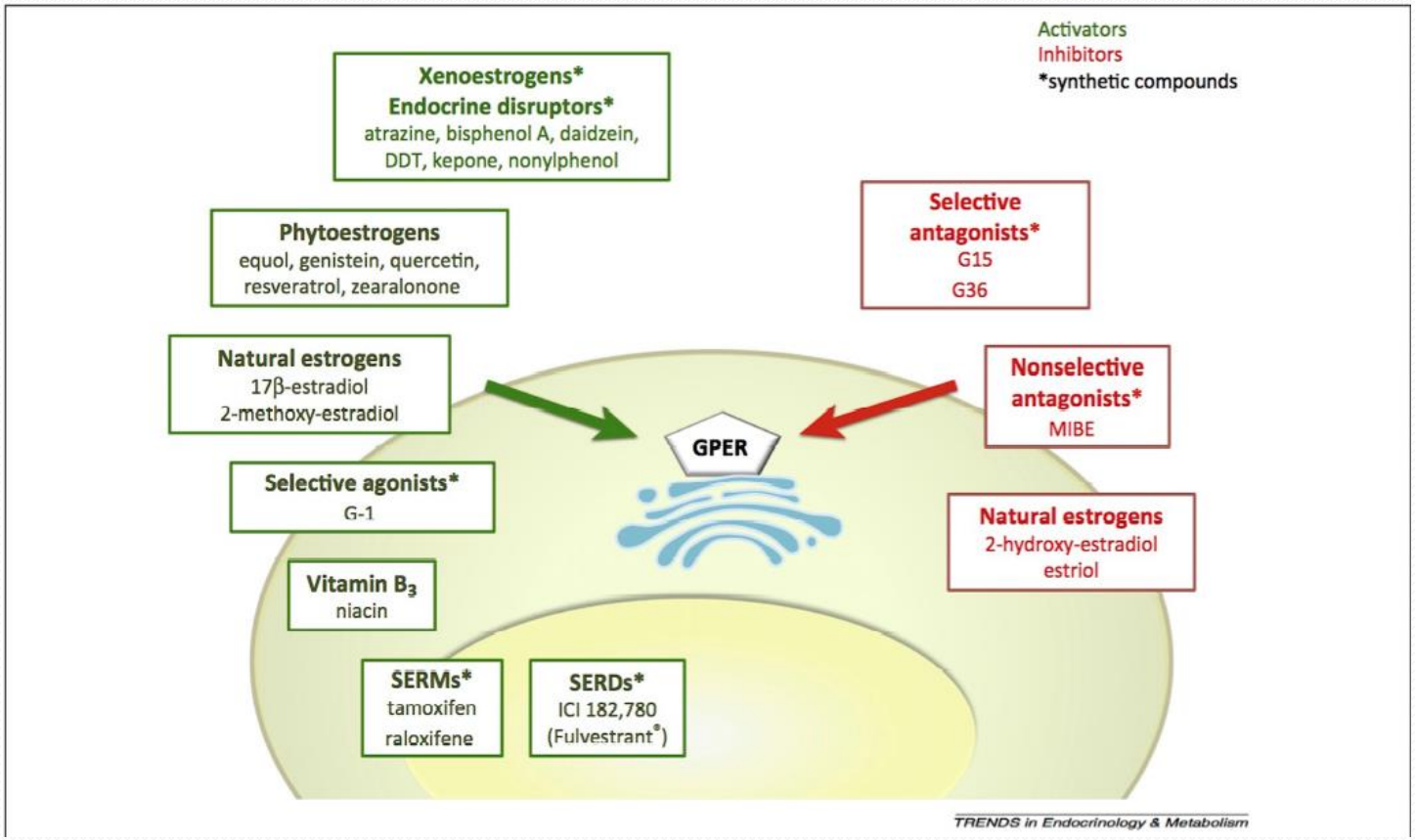
Las señales estrogénicas regulan lentamente la transcripción génica así como rápidamente la activación de quinasas y los niveles de calcio. Tanto la señalización rápida no genómica como la señalización transcripcional genómica a través de receptores de estrógenos intracelulares (ER) pueden cambiar el comportamiento. La señalización rápida no genómica se inicia desde la membrana plasmática por un receptor acoplado a proteín G llamado GPER1 que se une al 17β-estradiol. GPER1 o GPR30 es uno de los candidatos para un ser ER de membrana (mER) que no solo está altamente expresado en patologías, como cánceres, sino también en varias regiones del cerebro relacionadas a los comportamientos. En el cerebro, la señalización GPER1, en respuesta a los estrógenos, facilita la neuroprotección, los comportamientos sociales y la cognición. En esta revisión, describimos varias características notables de GPER1, como la capacidad de unirse a varios esteroides endógenos, así como moléculas sintetizadas artificialmente para unirse al GPER1. Adicionalmente, GPER1 se localiza en la membrana plasmática en las líneas celulares de cáncer de mama, pero puede estar presente en el endoplasma retículo o aparato de Golgi en el hipocampo. Inusualmente, GPER1 también puede translocarse al espacio perinuclear desde la membrana plasmática. Exploramos la idea de que la localización subcelular y la promiscuidad del ligando pueden determinar las variadas cascadas de señalización aguas abajo del GPER1 activado.

Vajaria, R., Hormones and Behavior (2018), https://doi.org/10.1016/j.yhbeh.2018.06.012



Please cite this article as: Barton, M., Not Lost in Translation: Emerging Clinical Importance of the G Protein-Coupled Estrogen Receptor GPER, *Steroids* (2016), doi: http://dx.doi.org/10.1016/j.steroids.2016.02.016

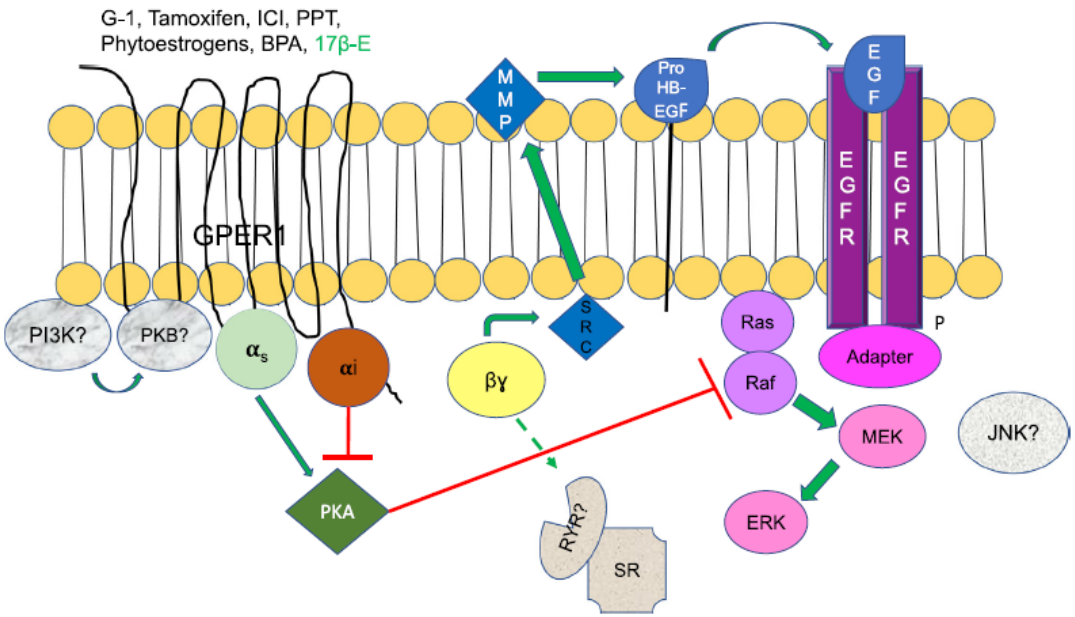


Fig. 1. GPER1 signals via a number of different downstream cascades in a cell dependent manner. Several different ligands can bind the GPER1, with the primary endogenous ligand, 17β-E, shown in green. One of the first described was the activation of the PKA pathway via the Gαs subunit and subsequent activation of adenylyl cyclase. The βγ subunit can activate SRC which then activates the matrix metalloprotease (MMP) to cleave pro-heparin bound epidermal growth factor (pro-HBEGF) to active EGF. EGF as the ligand to the EGFR activates the ERK pathway. This pathway is attenuated by the inhibition of Raf by PKA while the PKA pathway is dampened by the recruitment of $G\alpha_i$ by GPER1. GPER1 can activate the phosphatidylinositol-3-kinase (PI3K)-Akt and c-Jun N-terminal kinase (JNK) pathways, though the mechanisms remain unknown (shown by textured symbols). The increase calcium in a ryanodine receptor (RyR)-dependent manner can be blocked by pertussis toxin and hence, could be $G\beta\gamma$ dependent (shown by dashed line). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Vajaria, R., Hormones and Behavior (2018), https://doi.org/10.1016/j.yhbeh.2018.06.012

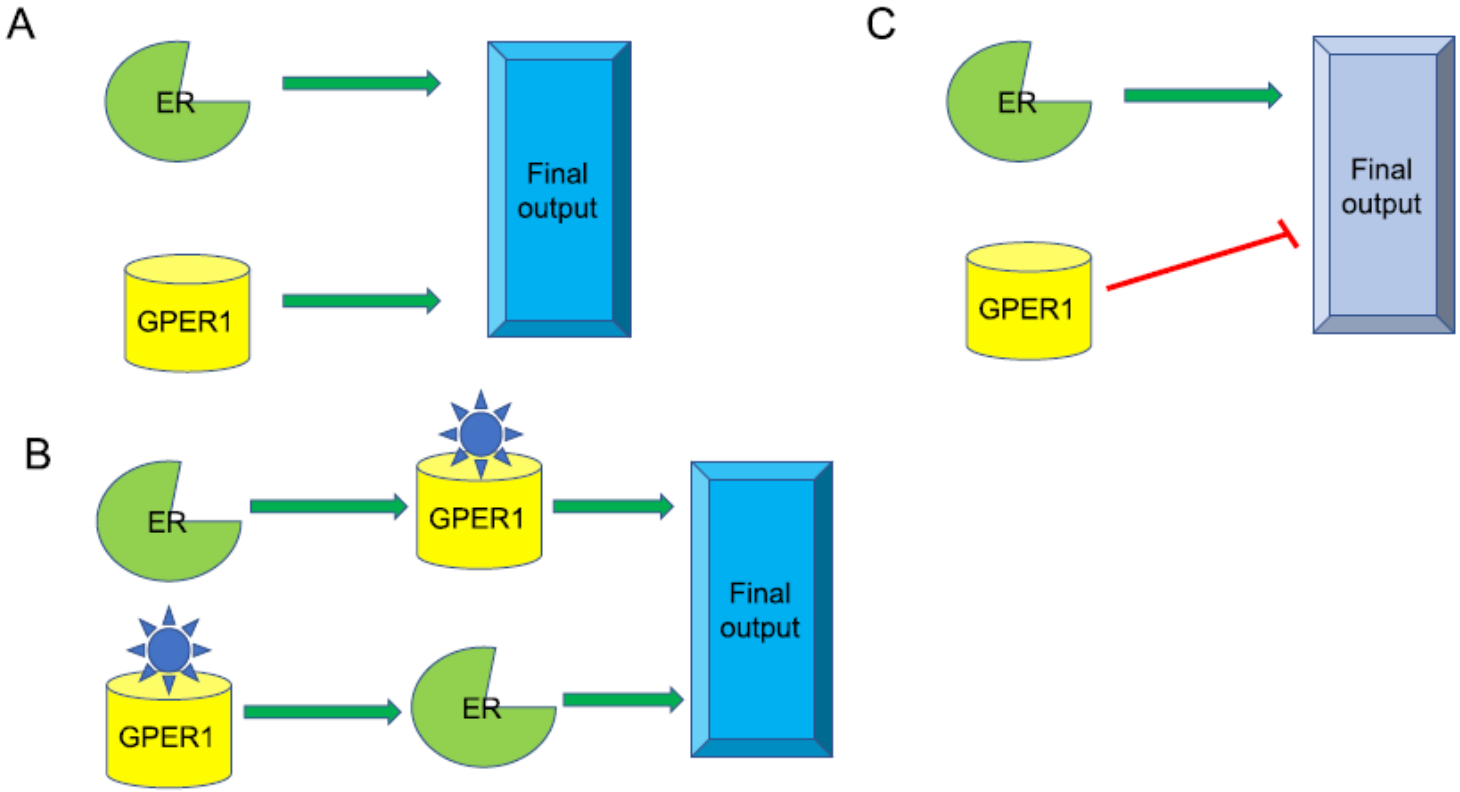


Fig. 2. Estrogen receptor and GPER1 can crosstalk to determine the final output in the organism. Estrogen receptor and GPER1-mediated signaling may be arranged synergistically in parallel (A) or series (B) to increase final output. In these scenarios, GPER1 signaling may be permissive or necessary for the final output. Conversely, GPER1 may also antagonize ERα-mediated signaling to decrease or abolish the final output (C). It is not necessary that ERα and GPER1 be present in the same cell. Apart from these depicted scenarios, ERα or GPER1 may uniquely signal in some tissues in response to 17β-estradiol. The ability of GPER1 to bind several ligands (shown by the star) may be important in conveying information about the environment (external or internal) to outputs that are important for species survival such as reproduction.

Vajaria, R., Hormones and Behavior (2018), https://doi.org/10.1016/j.yhbeh.2018.06.012

REVIEW

Estrogens, Neuroinflammation, and Neurodegeneration

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Inflammatory activation of microglia is a hallmark of several disorders of the central nervous system. In addition to protecting the brain against inflammatory insults, microglia are neuroprotective and play a significant role in maintaining neuronal connectivity, but the prolongation of an inflammatory status may limit the beneficial functions of these immune cells. The finding that estrogen receptors are present in monocyte-derived cells and that estrogens prevent and control the inflammatory response raise the question of the role that this sex steroid plays in the manifestation and progression of pathologies that have a clear sex difference in prevalence, such as multiple sclerosis, Parkinson's disease, and Alzheimer's disease. The present review aims to provide a critical review of the current literature on the actions of estrogen in microglia and on the involvement of estrogen receptors in the manifestation of selected neurological disorders. This current understanding highlights a research area that should be expanded to identify appropriate replacement therapies to slow the progression of such diseases. (*Endocrine Reviews* 37: 372–402, 2016)

Stress. 2017 September ; 20(5): 476–494. doi:10.1080/10253890.2017.1369523.

Hypothalamic–pituitary–adrenal and hypothalamic–pituitary–gonadal axes: sex differences in regulation of stress responsivity

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Abstract

Gonadal hormones play a key role in the establishment, activation, and regulation of the hypothalamic–pituitary–adrenal (HPA) axis. By influencing the response and sensitivity to releasing factors, neurotransmitters, and hormones, gonadal steroids help orchestrate the gain of the HPA axis to fine-tune the levels of stress hormones in the general circulation. From early life to adulthood, gonadal steroids can differentially affect the HPA axis, resulting in sex differences in the responsivity of this axis. The HPA axis influences many physiological functions making an organism's response to changes in the environment appropriate for its reproductive status. Although the acute HPA response to stressors is a beneficial response, constant activation of this circuitry by chronic or traumatic stressful episodes may lead to a dysregulation of the HPA axis and cause pathology. Compared to males, female mice and rats show a more robust HPA axis response, as a result of circulating estradiol levels which elevate stress hormone levels during non-threatening situations, and during and after stressors. Fluctuating levels of gonadal steroids in females across the estrous cycle are a major factor contributing to sex differences in the robustness of HPA activity in females compared to males. Moreover, gonadal steroids may also contribute to epigenetic and organizational influences on the HPA axis even before puberty. Correspondingly, crosstalk between the hypothalamic–pituitary–gonadal (HPG) and HPA axes could lead to abnormalities of stress responses. In humans, a dysregulated stress response is one of the most common symptoms seen across many neuropsychiatric disorders, and as a result, such interactions may exacerbate peripheral pathologies. In this review, we discuss the HPA and HPG axes and review how gonadal steroids interact with the HPA axis to regulate the stress circuitry during all stages in life.

Adaptación y subsistencia. Reproducción

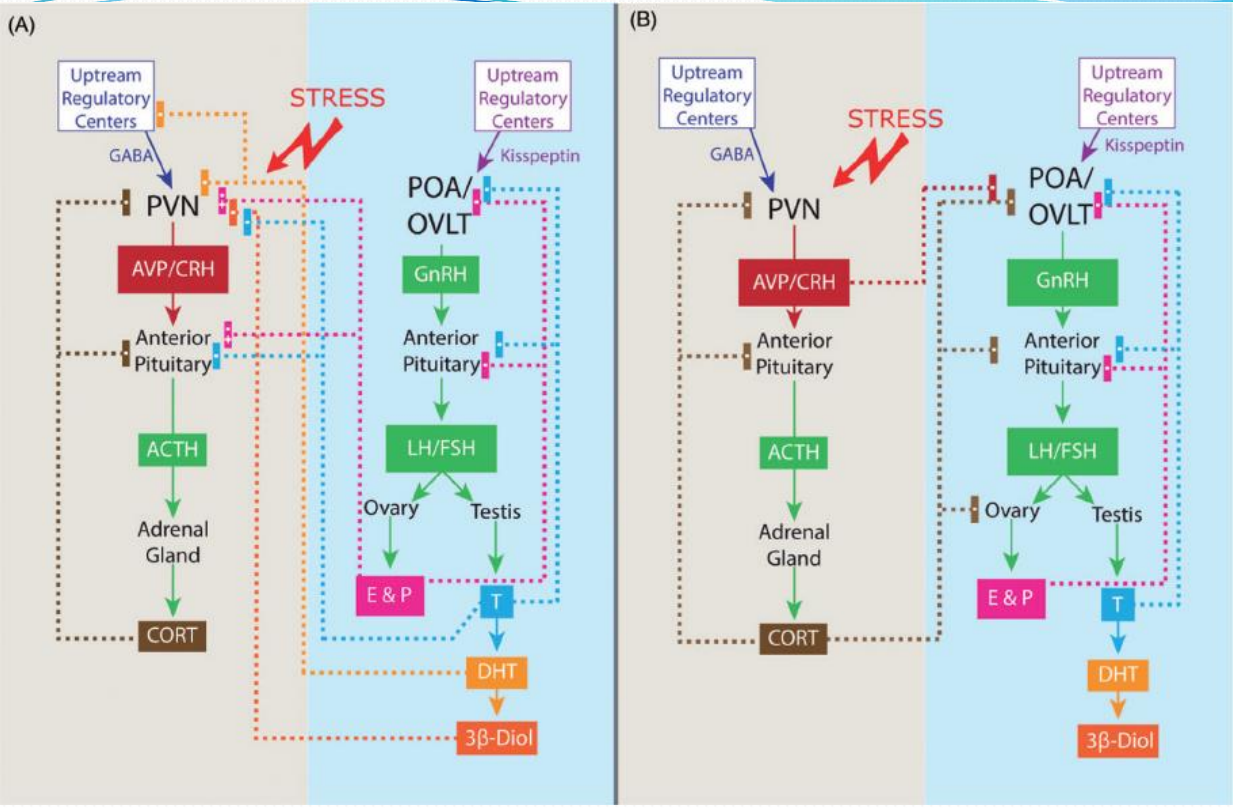

Figure 3.
Schematic diagram demonstrating the reciprocal interaction between the HPA and HPG axes. Panel A: Hormones of the HPG axis are involved in the regulation of the HPA axis at different levels, as delineated by dotted lines. Both axes are influenced by upstream regulatory centers. In the case of the HPA axis, most of these centers release GABA either directly into the PVN or in its immediate periphery. In the case of the HPG axis, upstream centers release kisspeptin to regulate GnRH activity. Panel B: Hormones from the HPA axis are involved in the regulation of the HPG axis at different levels, as delineated by dotted lines. Abbreviations: PVN: paraventricular nucleus of the hypothalamus; AVP: arginine vasopressin; CRH: corticotropin releasing hormone; ACTH: adrenocorticotropic hormone; CORT: corticosterone; POA: pre-optic area; OVLT: organum vasculosum lamina terminalis; GnRH: gonadotropin releasing hormone; LH: luteinizing hormone; FSH: follicle stimulating hormone; E: estrogen; P: progesterone; T: testosterone; DHT: dihydrotestosterone.

Stress. 2017 September ; 20(5): 476–494.

Physiol Behav. 2018 April 01; 187: 42–50. doi:10.1016/j.physbeh.2017.09.025.

Sex Differences in Stress Regulation of Arousal and Cognition

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Abstract

There are sex differences in the prevalence and presentation of many psychiatric disorders. For example, posttraumatic stress disorder (PTSD) and major depression are more common in women than men, and women with these disorders present with more hyperarousal symptoms than men. In contrast, attention deficit hyperactivity (ADHD) and schizophrenia are more common in men than women, and men with these disorders have increased cognitive deficits compared to women. A shared feature of the aforementioned psychiatric disorders is the contribution of stressful events to their onset and/or severity. Here we propose that sex differences in stress responses bias females towards hyperarousal and males towards cognitive deficits. Evidence from clinical and preclinical studies is detailed. We also describe underlying neurobiological mechanisms. For example, sex differences in stress receptor signaling and trafficking in the locus coeruleus-arousal center are detailed. In learning circuits, evidence for sex differences in dendritic morphology is provided. Finally, we describe how evaluating sex-specific mechanisms for responding to stress in female and male rodents can lead to better treatments for stress-related psychiatric disorders.

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ORIGINAL RESEARCH
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Stress Induced Hormone and Neuromodulator Changes in Menopausal Depressive Rats

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Objective: Previously, we showed that neuromodulators are important factors involved in depression, here we aim to further investigate the interactions between neuromodulators and sex hormone involved in menopause related depression in rats.

Methods: Menopausal depression was made with bilateral ovariectomies in female SD rats followed by chronic mild unpredictable stress treatment for 21 days. Thirty six rats were randomly divided into four groups: sham surgery group, sham/stress group, surgery group, surgery/stress group. Then open-field locomotor scores and sucrose intake were employed to observe behavior changes. The levels of norepinephrine (NE), dopamine (DA), serotonin (5-HT) in the cerebral spinal fluid and serum adrenocorticotropic hormone (ACTH), cortisone were determined with High-performance liquid chromatography (HPLC). Serum estradiol (E2), follicle-stimulating hormone (FSH), and luteinizing hormone (LH) were measured with radioimmunoassay.

Results: The open-field locomotor scores and sucrose intake were significantly decreased after the surgery and stress treatment ($p < 0.01$). The Serum E_2 level decreased significantly after the surgery ($p < 0.01$), but serum LH, FSH levels increased significantly in the surgery group than the sham surgery group ($p < 0.01$). The cortisone levels increased significantly in sham/stress group than that in the sham surgery group during the first 2 weeks at stressful treatment, but decrease afterwards. The monoamine levels in the surgery/stress group were much lower than those in the sham surgery group ($p < 0.01$). The correlation analysis found that LH and FSH are related more to the neurotransmitter release than E_2.

Conclusion: Ovary removal rats showed depression-like behaviors, with LH and FSH increase and monoamine decrease, and the levels of these monoamines in the stress treated groups changed only after the stressful treatment. The LH, FSH hormone increasing might be the reason for the lower monoamine release, which in turn might be the reason for depressed syndromes in the menopause. The cortisone and ACTH in the serum in the surgery/stress group were much higher than that in the sham surgery group.

Keywords: ACTH, cortisone, menopausal, LH, FSH, monoamine, depression

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Estrogens as neuroprotectants: Estrogenic actions in the context of cognitive aging and brain injury

E.B. Engler-Chiurazzi[a,b,*], **C.M. Brown**[a,c], **J.M. Povroznik**[a,d], and **J.W. Simpkins**[a,b]

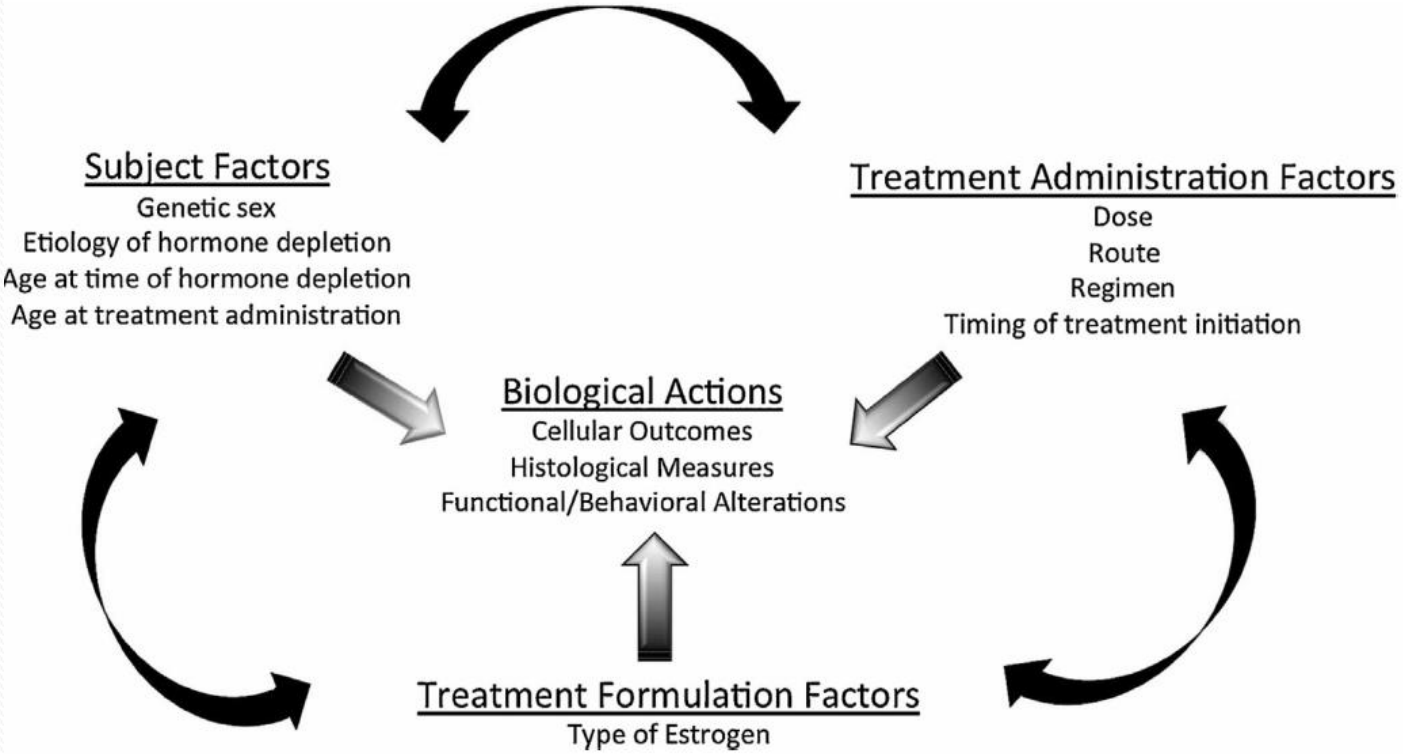
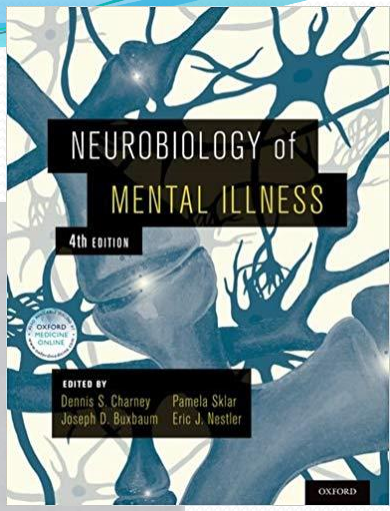


Fig. 1.

Estrogen as a conditional neuroprotectant. Estrogen acts as a neuroprotectant whose biological actions are modulated by subject factors, treatment administration factors, and treatment formulation factors.



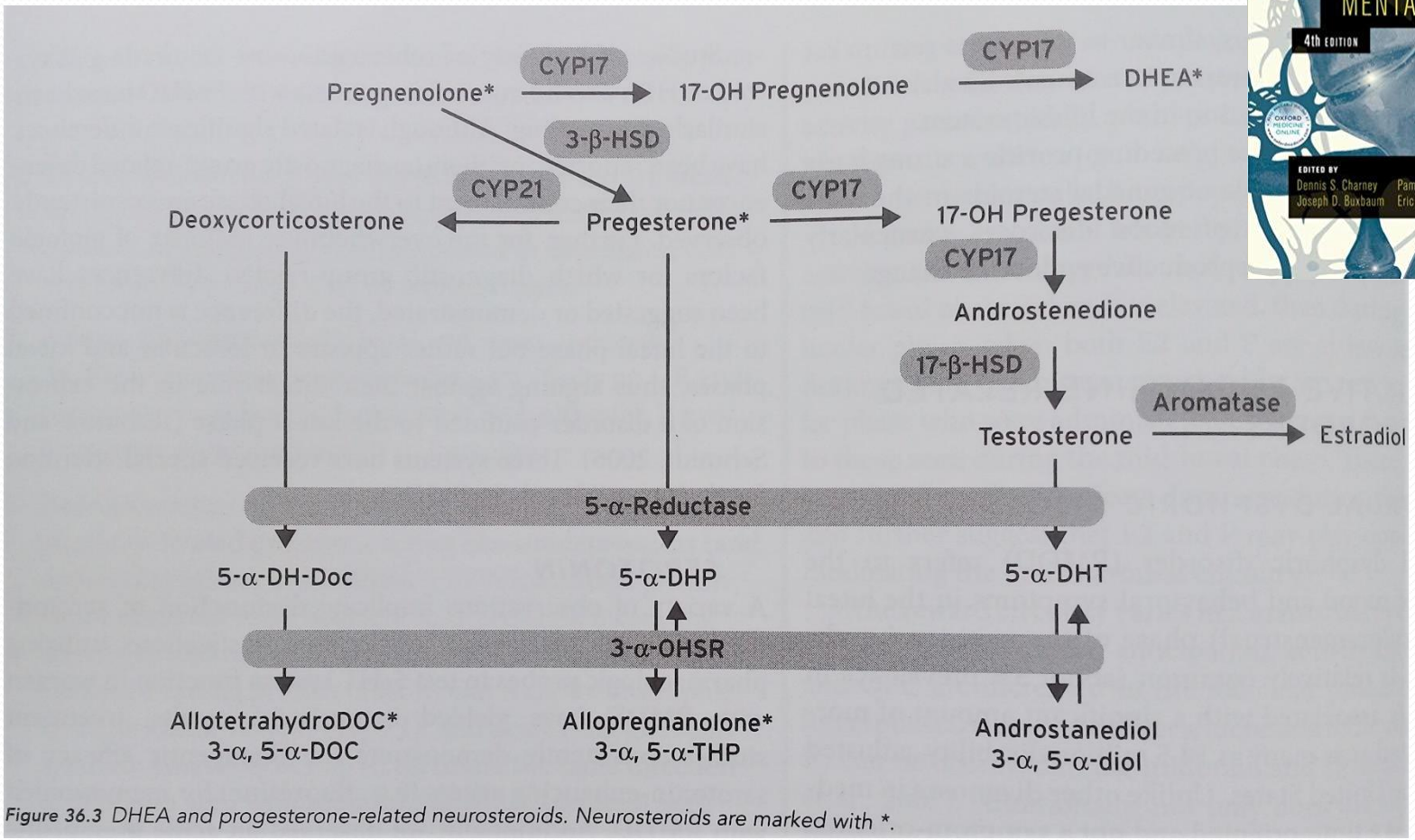


Figure 36.3 DHEA and progesterone-related neurosteroids. Neurosteroids are marked with *.

Implicación de los neuroesteroides en la conducta normal y patológica

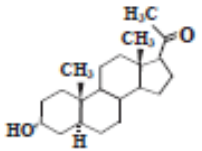
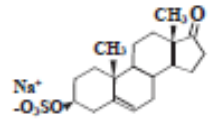
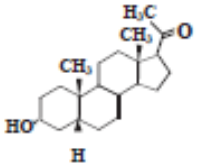
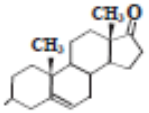
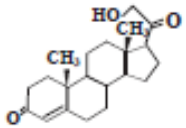
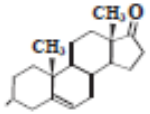
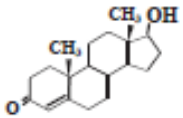
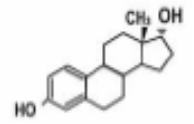
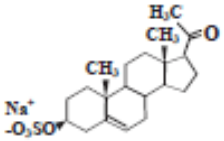
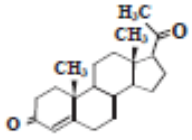
E. Martín-García, S. Darbra, M. Pallarès

IMPLICACIÓN DE LOS NEUROESTEROIDES EN LA CONDUCTA NORMAL Y PATOLÓGICA

Resumen. Introducción. *El sistema nervioso sintetiza esteroides (denominados entonces neuroesteroides) de novo a partir del colesterol. Estas sustancias participan en numerosas funciones relacionadas con la modulación alostérica de los principales receptores ionotrópicos del sistema nervioso central (SNC).* Objetivo. *Describir los procesos conductuales y cognitivos más importantes en los que participan los neuroesteroides, y que pueden abrir nuevas perspectivas de investigación enfocadas sobre todo a su posible uso terapéutico en patologías del SNC como el deterioro cognitivo asociado a enfermedades neurodegenerativas, a adicciones como el alcoholismo, a los trastornos de ansiedad y a la epilepsia y la conducta convulsiva.* Desarrollo. *Se describe sucintamente el concepto de neuroesteroide, su síntesis, sus acciones sobre los receptores para neurotransmisores y su distribución por el tejido nervioso. Posteriormente se revisan de una manera extensa, actualizada, y crítica los principales procesos psicológicos en los que están implicados.* Conclusiones. *Los neuroesteroides presentan un importante potencial terapéutico. En la conducta epileptiforme, los efectos anticonvulsionantes de estas sustancias no se hacen tolerantes con su administración repetida, como ocurre en el caso de las benzodiacepinas, aunque el estudio de análogos sintéticos y de agentes que aumentan la síntesis de neuroesteroides en el SNC parece determinante debido a la limitación que plantea la utilización sistémica de hormonas a largo plazo. En los trastornos de ansiedad presentan ventajas comparables a los ansiolíticos prototípicos, las benzodiacepinas, pero también sus principales efectos adversos, como la sedación. En el deterioro cognitivo, el enorme potencial facilitador cognitivo observado en modelos animales no se reproduce en humanos con demencia, aunque se precisen ensayos clínicos controlados para evaluar beneficios y riesgos de los tratamientos sustitutivos con esteroides. [REV NEUROL 2007; 44: 661-76]*

Palabras clave. *Alcoholismo. Alopregnanolona. Aprendizaje y memoria. Deterioro cognitivo. Epilepsia y convulsiones. Neuroesteroides. Síndrome de abstinencia alcohólica. Sulfato de pregnenolona. Trastornos de ansiedad.*

Tabla I. Resumen de los efectos modulatorios de los neuroesteroides en los diferentes tipos de receptores (adaptado de [3]).

Neuroesteroide	Receptor	Tipo de modulación	Neuroesteroide	Receptor	Tipo de modulación
 Alopregnanolona 3α-hidroxi-5α-pregnan-20-ona 3α,5α tetrahidroprogesterona 3α,5α-TH PROG	$GABA_A$ 5-HT_3 nAChR	Positiva Negativa Negativa	 Sulfato de dihidroepiandrosterona 3β-hidroxiandrost-5-en-17-ona sulfato DHEAS	$GABA_A$ NMDA σ tipo I	Negativa Positiva Positiva
 Pregnanolona 3α-hidroxi-5β-pregnan-20-ona 3α,5β tetrahidroprogesterona 3α,5β-TH PROG	$GABA_A$	Positiva	 Dihidroepiandrosterona 3β-hidroxiandrost-5-en-17-ona DHEA	$GABA_A$ NMDA	Negativa Positiva
 Dioxicorticosterona 21-hidroxipregn-4-ena-3,20-diona DOC	$GABA_A$	Positiva	 Estradiol 1,3,5(10)-estratrieno-3, 17β-diol 17β-E	NMDA Kainato 5-HT_3	Negativa Positiva Negativa
 Testosterona 17β-hidroxiandrost-4-en-3-ona T	$GABA_A$ 5-HT_3	Positiva Negativa	 17α-estradiol 1,3,5(10)-estratrieno-3, 17α-diol 17α-E	5-HT_3	Negativa
 Sulfato de pregnanolona 3β-hidroxipregn-5-en-20-ona sulfato PregS	$GABA_A$ NMDA AMPA Kainato Glicina 5-HT_3 σ tipo I nAChR	Negativa Positiva Negativa Negativa Negativa Sin efecto Negativa Negativa	 Progesterona Pregn-4-en-3, 20-ona PROG	$GABA_A$ Kainato Glicina 5-HT_3 nAChR	Positiva Positiva Negativa Negativa Negativa

Review

Levels and actions of neuroactive steroids in the nervous system under physiological and pathological conditions: Sex-specific features

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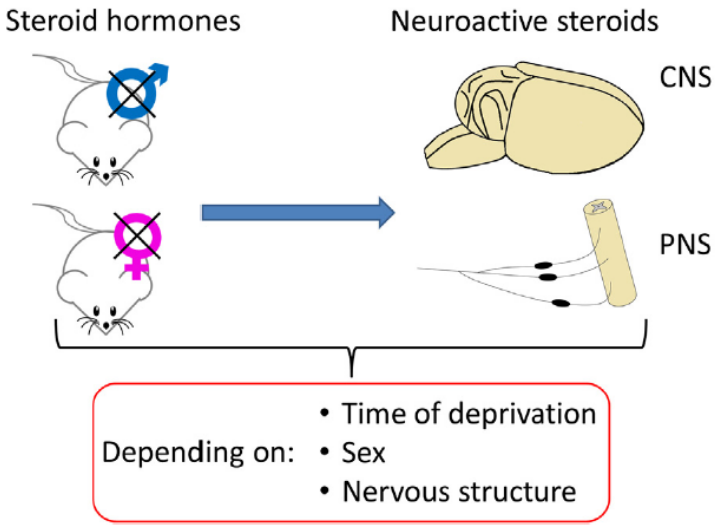


Fig. 1. Gonadectomy revealed an influence of peripheral steroid hormones on the levels of neuroactive steroids in central (CNS) and peripheral (PNS) nervous system. Deprivation of gonadal hormones affects the levels of neuroactive steroids in the CNS and the PNS depending on the time after gonadectomy, the sex of the animals and the region of the nervous system analyzed.

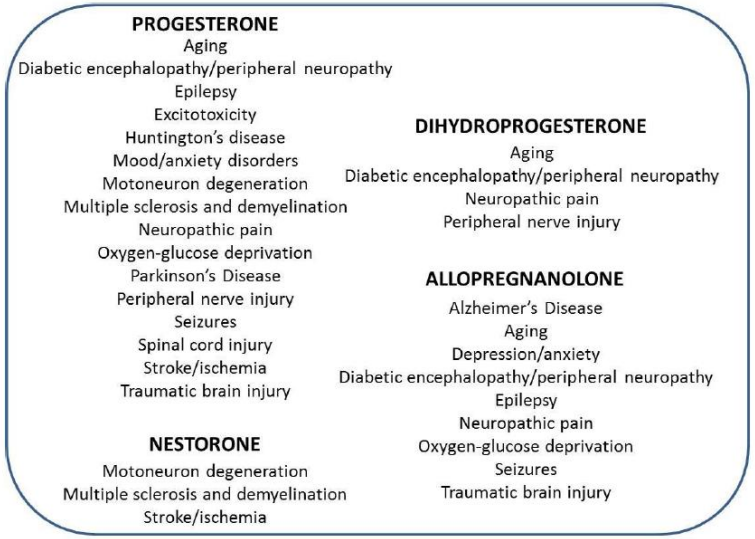
aspects of the steroidogenic activity in the CNS are not affected by the decrease in peripheral steroids after gonadectomy and adrenalectomy. For instance, the expression of StAR in the brain of male and female rats was not affected three weeks after gonadec-

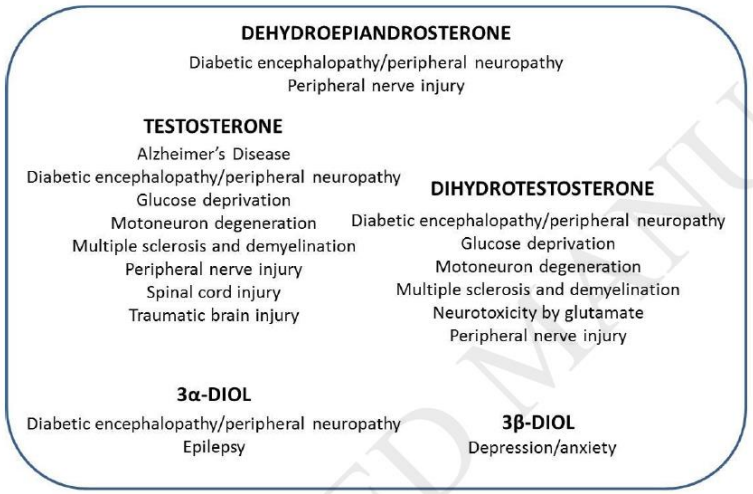
	CSF	PL	HIP	CC	CB	SC	SN
PREG	♂	♀	♂	♂	♂	♀	♀
PROG	♀	–	–	♂	♂	–	–
DHP	–	♀	♀	♀	♀	♀	♀
THP	♂	♀	♀	♀	–	–	♀
Isopregnanolone	♀	♀	–	♀	♀	♀	♂
DHEA	♀	–	♀	♀	–	–	♀
T	♂	♂	♂	♂	♂	♂	♂
DHT	♂	♂	♂	♂	♂	♂	♂
3α-diol	–	♂	♂	♂	♂	♂	♂
17β-E	♀	♀	♀	♀	♀	♀	♀

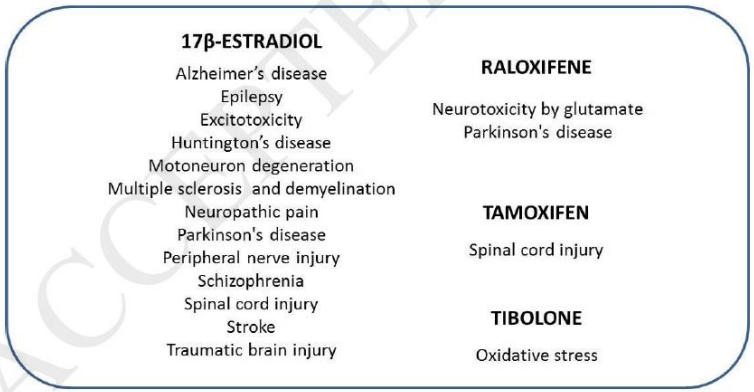
Fig. 2. Sex differences in neuroactive steroid levels in plasma, cerebrospinal fluid and different regions of the nervous system of rats. For each compartment and each neuroactive steroid the sex that have higher levels is indicated. The symbol - indicates that the levels of the neuroactive steroid is similar in males and females. CSF: cerebrospinal fluid; PL: plasma; HIP: hippocampus; CC: cerebral cortex; CB: cerebellum; SC: spinal cord; SN: sciatic nerve. PREG: pregnenolone;

6. Conclusions

The studies reviewed in this paper indicate that neuroactive steroids are involved in the physiological regulation of neurogenesis, neuronal survival, neuritogenesis, neuronal differentiation, synaptogenesis, glial differentiation, myelin formation, synaptic function and synaptic plasticity. Through these regulatory actions, neuroactive steroids participate in the control of mood, behavior and cognition. In addition, under pathological conditions neuroactive steroids exert neuroprotective actions, promoting neuronal survival and remyelination and decreasing neuroinflammation. Interestingly, the levels of neuroactive steroids are different in males and females. These sex differences are not only true for their peripheral levels, as in the case of sex hormones, but also for their levels in the CNS and PNS. In addition, sex differences in the levels of neuroactive steroids are observed under physiological and pathological conditions. Therefore, sex differences in the levels of neuroactive steroids may contribute to generation of sex differences in the physiological function of the nervous system, in the response of nervous tissue to neurodegenerative and neurotoxic stimuli and in the manifestation of neurodegenerative and psychiatric disorders. Furthermore, sex differences in the levels and actions of neuroactive steroids suggest that these molecules may represent therapeutic approaches for sex-specific treatments of pathological alterations of the nervous system.







4.2. Neuroactive steroids exert neuroprotective actions

4.2.1. Steroid hormones and neurosteroids

In agreement with changes in neuroactive steroid levels and neurosteroidogenesis induced by neuropathological events, these molecules also exert a variety of important neuroprotective effects in the CNS and PNS (Fig. 3). For instance, 17β-E and PROG are known to exert neuroprotective actions in

Brexanolone injection in post-partum depression: two multicentre, double-blind, randomised, placebo-controlled, phase 3 trials

Samantha Meltzer-Brody, Helen Colquhoun, Robert Riesenberg, C Neill Epperson, Kristina M Deligiannidis, David R Rubinow, Haihong Li, Abdul J Sankoh, Christine Clemson, Amy Schacterle, Jeffrey Jonas, Stephen Kanes

Summary

Background Post-partum depression is associated with substantial morbidity, and improved pharmacological treatment options are urgently needed. We assessed brexanolone injection (formerly SAGE-547 injection), a positive allosteric modulator of γ-aminobutyric-acid type A ($GABA_A$) receptors, for the treatment of moderate to severe post-partum depression.

Methods We did two double-blind, randomised, placebo-controlled, phase 3 trials, at 30 clinical research centres and specialised psychiatric units in the USA. Eligible women were aged 18–45 years, 6 months post partum or less at screening, with post-partum depression and a qualifying 17-item Hamilton Rating Scale for Depression (HAM-D) score (≥26 for study 1; 20–25 for study 2). Women with renal failure requiring dialysis, anaemia, known allergy to allopregnanolone or to progesterone, or medical history of schizophrenia, bipolar disorder, or schizoaffective disorder were excluded. Patients were randomly assigned (1:1:1) to receive a single intravenous injection of either brexanolone 90 μg/kg per h (BRX90), brexanolone 60 μg/kg per h (BRX60), or matching placebo for 60 h in study 1, or (1:1) BRX90 or matching placebo for 60 h in study 2. Patients, the study team, site staff, and the principal investigator were masked to treatment allocation. The primary efficacy endpoint was the change from baseline in the 17-item HAM-D total score at 60 h, assessed in all patients who started infusion of study drug or placebo, had a valid HAM-D baseline assessment, and had at least one post-baseline HAM-D assessment. The safety population included all randomised patients who started infusion of study drug or placebo. Patients were followed up until day 30. The trials have been completed and are registered with ClinicalTrials.gov, numbers NCT02942004 (study 1) and NCT02942017 (study 2).

Findings Participants were enrolled between Aug 1, 2016, and Oct 19, 2017, in study 1, and between July 25, 2016, and Oct 11, 2017, in study 2. We screened 375 women simultaneously across both studies, of whom 138 were randomly assigned to receive either BRX90 (n=45), BRX60 (n=47), or placebo (n=46) in study 1, and 108 were randomly assigned to receive BRX90 (n=54) or placebo (n=54) in study 2. In study 1, at 60 h, the least-squares (LS) mean reduction in HAM-D total score from baseline was 19·5 points (SE 1·2) in the BRX60 group and 17·7 points (1·2) in the BRX90 group compared with 14·0 points (1·1) in the placebo group (difference −5·5 [95% CI −8·8 to −2·2], p=0·0013 for the BRX60 group; −3·7 [95% CI −6·9 to −0·5], p=0·0252 for the BRX90 group). In study 2, at 60 h, the LS mean reduction in HAM-D total score from baseline was 14·6 points (SE 0·8) in the BRX90 group compared with 12·1 points (SE 0·8) for the placebo group (difference −2·5 [95% CI −4·5 to −0·5], p=0·0160). In study 1, 19 patients in the BRX60 group and 22 patients in the BRX90 group had adverse events compared with 22 patients in the placebo group. In study 2, 25 patients in the BRX90 group had adverse events compared with 24 patients in the placebo group. The most common treatment-emergent adverse events in the brexanolone groups were headache (n=7 BRX60 group and n=6 BRX90 group *vs* n=7 placebo group for study 1; n=9 BRX90 group *vs* n=6 placebo group for study 2), dizziness (n=6 BRX60 group and n=6 BRX90 group *vs* n=1 placebo group for study 1; n=5 BRX90 group *vs* n=4 placebo group for study 2), and somnolence (n=7 BRX60 group and n=2 BRX90 group *vs* n=3 placebo group for study 1; n=4 BRX90 group *vs* n=2 placebo group for study 2). In study 1, one patient in the BRX60 group had two serious adverse events (suicidal ideation and intentional overdose attempt during follow-up). In study 2, one patient in the BRX90 group had two serious adverse events (altered state of consciousness and syncope), which were considered to be treatment related.

Interpretation Administration of brexanolone injection for post-partum depression resulted in significant and clinically meaningful reductions in HAM-D total score at 60 h compared with placebo, with rapid onset of action and durable treatment response during the study period. Our results suggest that brexanolone injection is a novel therapeutic drug for post-partum depression that has the potential to improve treatment options for women with this disorder.

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VIEWPOINT

The First Food and Drug Administration–Indicated Drug for Postpartum Depression—Brexanolone

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The burgeoning research on the short- and long-term adverse sequelae of perinatal depression on maternal, infant, and family health has prompted major medical and public health agencies to urge identification and treatment. Deaths due to psychiatric illness and drug overdose lead the causes of maternal mortality in the first year after birth.[1] Finding novel treatments with improved effectiveness for depression in postpartum women is a pressing public health goal.

We applaud Meltzer-Brody and colleagues[2] for their exploration of compounds that modulate γ-aminobutyric acid (GABA) receptors as potential treatments for postpartum depression (PPD). Brexanolone, a proprietary formulation of the neurosteroid allopregnanolone, a positive allosteric modulator of GABA type A receptors, was recently approved by the US Food and Drug Administration for the treatment of moderate to severe PPD. Sage Pharmaceuticals developed the drug and participated in the design, data analysis, interpretation, and publication of a series of studies supporting the new drug application. The results of 2 phase 3, double-blind, randomized, placebo-controlled clinical trials with similar designs (along with the integrated results of an earlier phase 2 study) were published.[2]

JAMA Psychiatry Published online June 26, 2019

Lancet 2008; 371: 760–70

Menopause

Heidi D Nelson

Menopause is the time of life when menstrual cycles cease, and is caused by reduced secretion of the ovarian hormones oestrogen and progesterone. Although menopause is a normal event for women, individual experiences vary, and some women seek medical advice for the management of symptoms. Many symptoms have been attributed to menopause, but only vasomotor dysfunction and vaginal dryness are consistently associated with this time of life in epidemiological studies. Other common symptoms such as mood changes, sleep disturbances, urinary incontinence, cognitive changes, somatic complaints, sexual dysfunction, and reduced quality of life may be secondary to other symptoms, or related to other causes. Trials of therapies for vasomotor dysfunction have shown improvements with oestrogen, gabapentin, paroxetine, and clonidine, but little or no benefit with other agents; adverse effects of these treatments must also be considered. Many questions about menopausal transition and its effects on health have not been adequately addressed.

Throughout a woman's reproductive life, estradiol, progesterone and ovarian regulatory proteins control gonadotropin secretion from the anterior pituitary through a complex mechanism of feedback and feedforward. Pulses of FSH are stimulated by the protein activin and inhibited by estradiol and inhibin B.[74] As the number of oocytes remaining in the ovaries drop, inhibin B levels decline and FSH levels rise. Low inhibin B and high FSH is the hormonal signature of menopause. More recently, progressively decreasing levels of AMH has become a further marker of approaching menopause.

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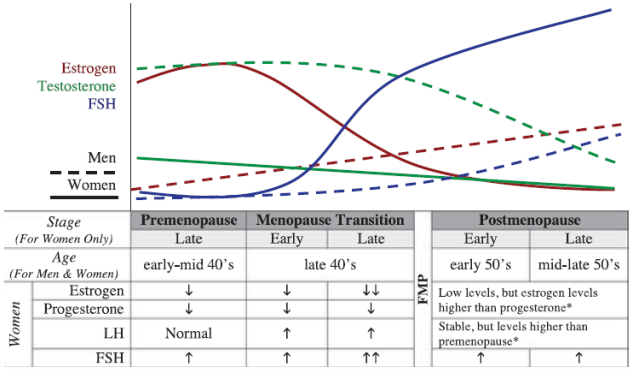
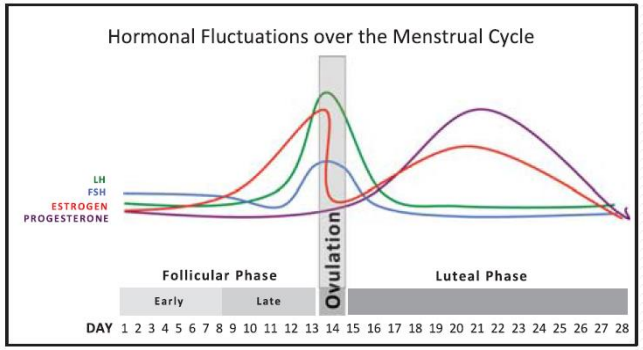


Stage (For Women Only)	Premenopause	Menopause Transition		Postmenopause	
	Late	Early	Late	Early	Late
Age (For Men & Women)	early-mid 40's	late 40's		early 50's	mid-late 50's
Women: Estrogen	↓	↓	↓↓	FMP: Low levels, but estrogen levels higher than progesterone*	
Women: Progesterone	↓	↓	↓		
Women: LH	Normal	↑	↑	Stable, but levels higher than premenopause*	
Women: FSH	↑	↑	↑↑	↑	↑



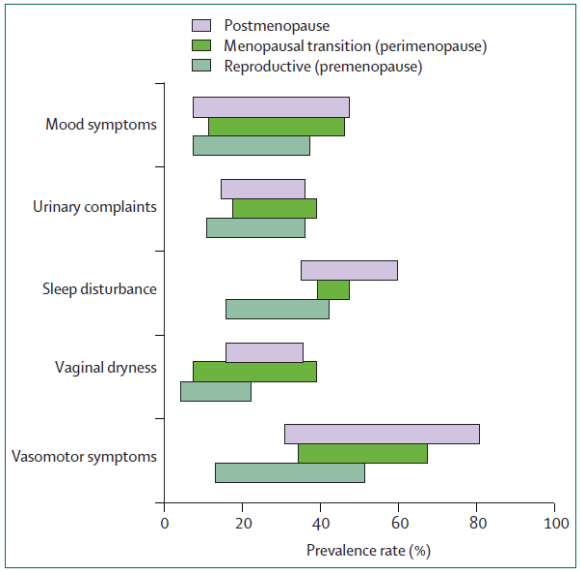


Figure 2: Prevalence rates of symptoms
51 population studies showed wide ranges of prevalence rates. Rates of vasomotor symptoms, vaginal dryness, and sleep disturbances are higher for women in menopausal transition and postmenopause than for women in reproductive stages.

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CONSENSUS RECOMMENDATIONS

Guidelines for the evaluation and treatment of perimenopausal depression: summary and recommendations

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Epidemiology

- The perimenopause is a window of vulnerability for the development of both depressive symptoms and major depressive episodes.
- The risk of depressive symptoms is elevated during the perimenopause even in women with no history of major depressive disorder.
- Most midlife women who experience a MDE during the perimenopause have experienced a prior episode of depression; therefore, the episode represents recurrence of their illness. First lifetime onset of MDD during this time is less common.
- Data are mixed about whether women who undergo surgical menopause are at increased or decreased risk for developing depression compared with women who transition through menopause naturally. However, recent large-scale studies show an elevated risk of depression in women following hysterectomy with and without oophorectomy. Women with primary ovarian insufficiency also have shown elevated rates of depression.
- Risk factors for depressive symptoms during the perimenopause include prior MDD, sociodemographic factors (*e.g.*, younger age, black race, financial difficulties), psychosocial factors (adverse life events, low social support), menopause symptoms (VMS, sleep disturbance), anxiety symptoms, and reproductive-related mood disturbance (*e.g.*, postpartum and/or premenstrual depressive symptoms).
- Risk factors for MDD during the perimenopause include mental health factors (prior MDD, current use of antidepressants, anxiety, trait anxiety, premenstrual depressive symptoms), sociodemographic factors (black race, high BMI, younger age), psychosocial factors (upsetting life events, social isolation), and menopausal symptoms (especially sleep disturbance).

Clinical presentation

- Depression during midlife presents with classic depressive symptoms, commonly in combination with menopause-specific symptoms (*i.e.*, VMS, sleep disturbance) and psychosocial challenges.
- Several common symptoms of the perimenopause (hot flashes, night sweats, sleep and sexual disturbances, weight/energy changes, cognitive shifts) complicate, co-occur, and overlap with the presentation of depression during this stage.
- Vasomotor symptoms are associated with depressive symptoms but not MDEs, except in women with first lifetime onset of a depressive episode during the perimenopause.
- Life stressors that are common for women at midlife (*e.g.*, caring for children and parents, career and relationship shifts, aging, body changes) and personal/family illness can adversely affect mood but "empty nest" and "revolving door" have little enduring effect.

Assessment and diagnosis

- Evaluation includes identification of menopause stage, assessment of co-occurring and overlapping menopause and psychiatric symptoms, consideration of psychosocial risk factors, appreciation of the differential diagnosis, and use of scales to aid in disentangling symptoms and distinguishing diagnoses.
- Women with past MDEs (not necessarily hormone related) and women with severe depressive symptoms and/or suicidal ideation should always be evaluated for a mood disorder.
- The differential diagnosis of depression during the perimenopause includes MDD, subsyndromal depression, adjustment disorder, psychological distress, bereavement, depressive episodes associated with bipolar disorder, and general medical causes of depression.
- A menopause-specific mood-disorder scale does not exist; however, several general validated screening measures (*e.g.*, PHQ-9) may be used for categorical determination of mood disorder diagnoses. Validated menopause symptom and health-related quality of life scales (*e.g.*, MRS, MENQOL, Greene Climacteric Scale, Utian Quality-of-Life Scale) include mood items and may be useful in clarifying the contribution of menopause-related symptoms.

Treatment of MDD with antidepressants and psychotherapy

- Proven therapeutic options for depression (*i.e.*, antidepressants, CBT, and other psychotherapies) should remain as front-line antidepressant treatments for MDEs during the perimenopause.
- Existing data on various SSRI and SNRI antidepressants (including citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, sertraline, and venlafaxine) suggest good efficacy and tolerability at usual doses. In women with a history of MDD, a prior adequate response to a particular antidepressant should guide treatment selection when MDD recurs during midlife years. Only desvenlafaxine has been studied and proven efficacious in large randomized placebo-controlled trials of well-defined peri-and postmenopausal depressed women.
- Selection of antidepressants during the perimenopause should consider the woman's prior antidepressant trials and responses, available data on efficacy and tolerability in this specific population, management of challenging adverse effects (*e.g.*, sexual dysfunction, weight changes) and safety (*e.g.*, drug-drug interactions), given the likelihood of concomitant use of other medications during this stage of life.
- In addition to their efficacy in treating MDD, many antidepressants (SSRIs and SNRIs) also improve menopause-related complaints (*e.g.*, VMS, pain).
- Clinicians should also consider treating co-occurring sleep disturbance and night sweats as part of treatment for menopause-related depression.

Estrogen therapy

- There is some evidence that ET has antidepressant effects of similar magnitude to that observed with classic antidepressant agents when administered to depressed perimenopausal women with or without concomitant VMS.
- Estrogen therapy is ineffective as a treatment for depressive disorders in postmenopausal women. Such evidence suggests a possible window of opportunity for the effective use of ET for the management of depressive disorders during the perimenopause.
- There is some evidence that ET enhances mood and improves well-being in non-depressed perimenopausal women.
- Hormonal contraceptives—particularly when used continuously—have shown some benefits for mood regulation and may improve depressive symptoms in women approaching menopause.
- Transdermal estradiol with intermittent micronized progesterone may prevent the onset of depressive symptoms in euthymic perimenopausal women, but the evidence is not sufficient to recommend estrogen-based therapies for preventing depression in asymptomatic peri- or postmenopausal women and the risks and benefits must be weighed.
- Estrogen-based therapies may augment clinical response to antidepressants in midlife and older women but their use should be considered with caution (*i.e.*, preferably when also indicated for other concurrent conditions such as VMS).
- Most studies on HT for the treatment of depression examined the effects of unopposed estrogen. Data on combined HT (estrogen plus progestogen) or for different progestogens are sparse and inconclusive.
- Estrogen is not FDA approved to treat mood disturbance.

Alternative therapies

- The available evidence is insufficient for recommending any botanical or complementary/alternative approaches for treating depression related to the perimenopause.
- It is reasonable to recommend exercise in peri- and postmenopausal women with depression, particularly when used in combination with recommended psychotherapies and pharmacotherapies.

Women's mental health 2

Why are women so vulnerable to anxiety, trauma-related and stress-related disorders? The potential role of sex hormones

Sophie H Li, Bronwyn M Graham

Una mayor prevalencia, gravedad y carga de ansiedad, en trastornos relacionados con el trauma y el estrés en las mujeres en comparación con hombres han sido bien documentados. Ha surgido evidencia de una variedad de campos que sugiere que las hormonas sexuales, particularmente el estradiol y la progesterona, juegan un papel importante en la generación de estas diferencias sexuales. En esta serie de artículos, nuestro objetivo es integrar la literatura que informa sobre los efectos de las hormonas sexuales en careacterísticas biológicas, conductuales y vías cognitivas, para proponer dos mecanismos generales por los cuales el estradiol y la progesterona influyen en las diferencias sexuales en trastornos de ansiedad: aumento de los factores de vulnerabilidad asociados con el desarrollo del trastorno de ansiedad; y facilitación del mantenimiento de síntomas ansiosos post-desarrollo. Las implicaciones para la investigación futura, con enfoques novedosos para el tratamiento psicológico y farmacológico de los trastornos de ansiedad, también se consideran.

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This is the second in a Series of

- Papel de las hormonas sexuales en las fluctuaciones de la gravedad de los síntomas de ansiedad.

Se han observado aumentos en la gravedad de los síntomas durante los períodos de disminución o de niveles bajos de las hormonas sexuales en mujeres con trastorno de pánico, trastorno de ansiedad social, trastorno de estrés postraumático y trastorno obsesivo compulsivo, que comparten características clínicas de ansiedad.

Aunque no está claro qué media este efecto, se sabe que las mujeres informan estrategias de afrontamiento desadaptativas más que los hombres. Una posibilidad es que las mujeres puedan alterar los tipos de estrategias de afrontamiento que usan según sus niveles de hormonas sexuales. Por ejemplo, las mujeres informan un mayor uso de estilos de afrontamiento evitativos durante la fase premenstrual (disminución de las hormonas sexuales).

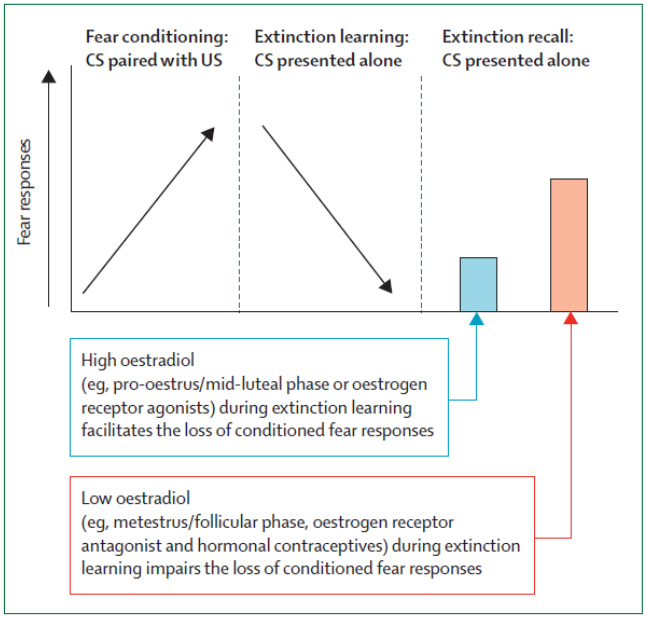
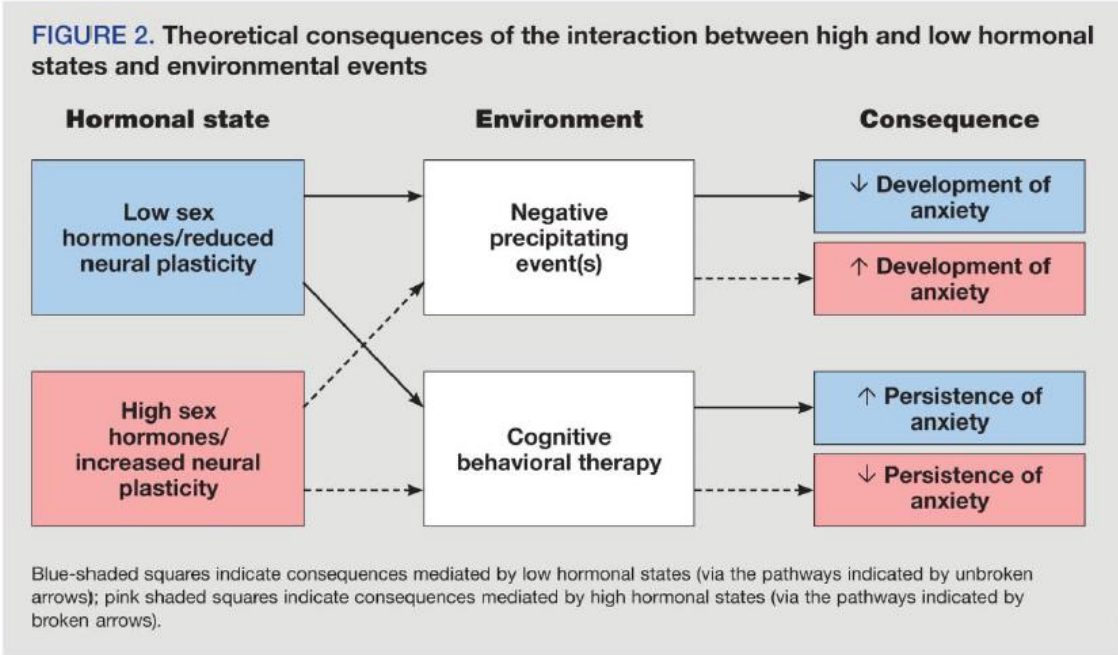


***Figure 2*: Standard cross-species fear conditioning and extinction laboratory procedure**

Fear responses increase in the presence of an initially neutral CS that is paired with an aversive US during fear conditioning. Extinction learning involves the repeated, non-reinforced presentation of the CS, which results in a decrement in fear responses because of the formation of a new safety memory. The strength of the extinction memory can be assessed at a later time by again presenting the non-reinforced CS. Good extinction recall is indexed by low fear responses and poor extinction recall is indexed by high (ie, relapsed) fear responses. Oestradiol levels at the time of extinction learning influence the strength of the extinction memory. CS=conditioned stimulus. US=unconditioned stimulus.



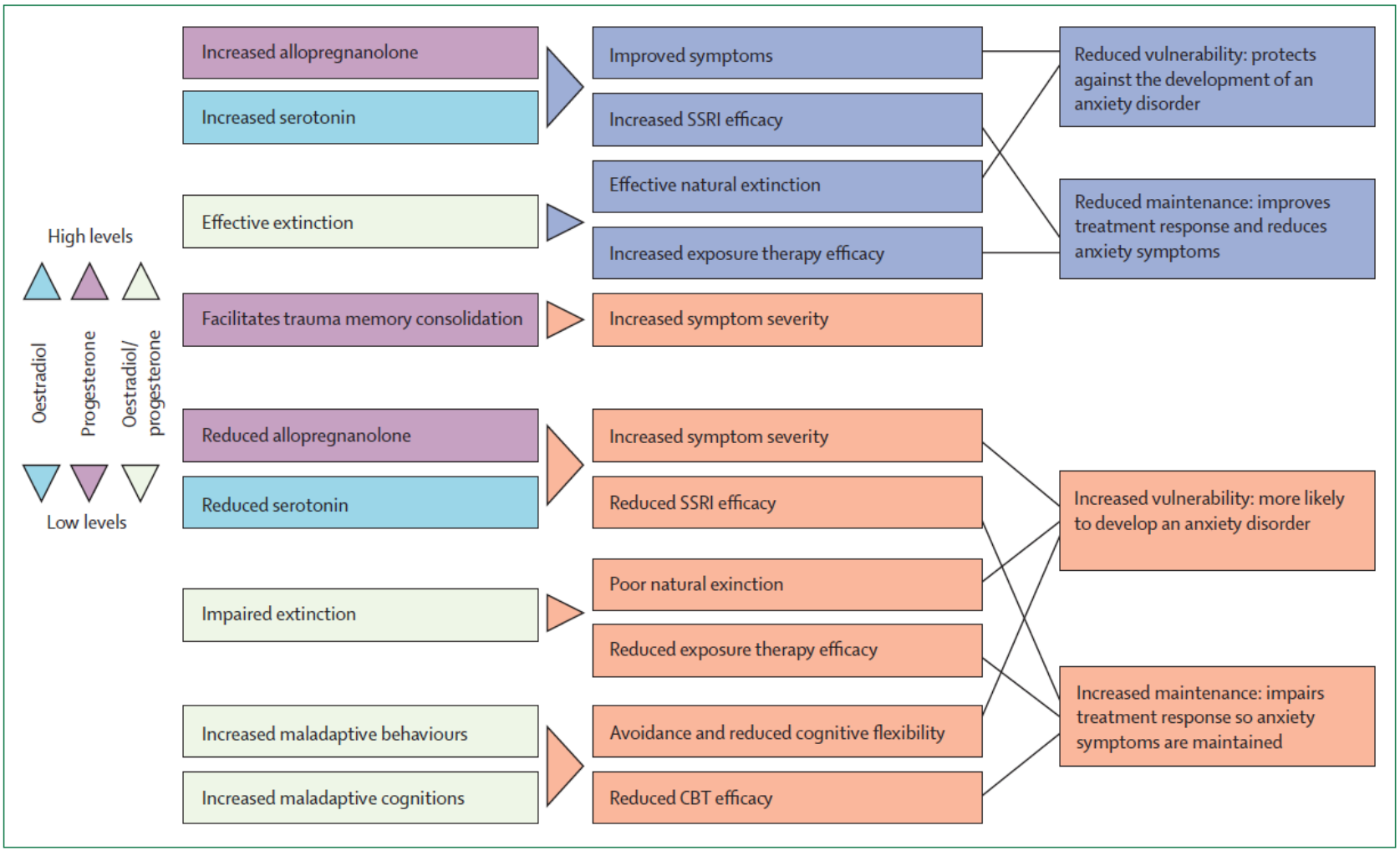


Figure 3: **Hypothesised model of the influence of sex hormones on biological, behavioural, and cognitive pathways that promote or reduce anxiety disorder vulnerability and maintenance in women**

High or low levels of oestradiol (light blue shading), progesterone (purple shading), or both (light green shading), mediate the effect specified in the second column of boxes, which reduces vulnerability in healthy women and reduces maintenance of symptoms in anxious women (dark blue shading), or increases vulnerability in healthy women and promotes maintenance of symptoms in anxious women (orange shading). CBT=cognitive behavioural therapy.

In the meantime, clinicians can help to raise the profile of this important issue, and make use of the existing research base, by integrating the following considerations into their practice:

1 Conduct an assessment of the onset and exacerbation of anxiety symptoms in relation to hormonal events (eg, use of hormonal contraction, menstrual cycle, pregnancy, parturition, perimenopause); consider changing/removing hormonal contraception if a link is established.

2 Routinely provide psychoeducation to increase women's awareness of a potential link between hormones and anxiety, both following symptom onset and pre-emptively (eg, in patients about to experience significant hormonal change, such as preadolescents, before starting hormonal contraception, and in pregnant women and perimenopausal women).

3 For patients with anxiety disorders, encourage incorporation of menstrual cycle phase (or other hormonal events) in routine monitoring of symptom fluctuation. This may increase the sense of control over symptoms by facilitating predictability and fostering targeted use of adaptive coping strategies during identified times of heightened vulnerability.

4 Consider timing exposure therapy during periods of optimal hormonal levels. Women on hormonal contraception may require more-extended treatment sessions to achieve benefit. Note that this consideration is based on one clinical study on specific phobia, however, and the utility of this approach for other anxiety disorders awaits more extensive empirical investigation.[9]

5 Women's tendency to engage in maladaptive coping styles is well established. This should be a focus of attention during clinical assessment of women. Women may especially benefit from targeted cognitive interventions for anxiety (eg, rumination-focused CBT) that directly correct these maladaptive coping styles.

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Sex steroids and schizophrenia

Julie A. Markham

Table 1 Summary of major sex differences and the impact of sex steroids in schizophrenia. Similar findings generated in preclinical paradigms are also shown. The ? symbol denotes an area remaining to be explored in animal preparations intended to model schizophrenia.

Measure in Schizophrenia	Direction of Effect
Incidence	males > females by ~40%
Age of Peak Onset	post-pubertal + earlier in males
Late Onset	females; post-menopausal
Response to Antipsychotic Drugs	Male < Female
Negative Symptoms	Male > Female
Cognitive Deficits	Male > Female
Vulnerability to Substance Abuse	Male > Female
Brain Morphological Changes	Male > Female
Gonadal Hormone Levels	↓ E in Females, ↓ T in Males
	Impact of Gonadal Steroids
Positive Symptoms	↓ by estrogen
Response to Neuroleptics	↑ by estrogen
Cognitive Functioning	↑ by estrogen
Negative Symptoms	↓ by testosterone

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Review Article

A Role for Estrogen in Schizophrenia: Clinical and Preclinical Findings

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2. Clinical Findings

2.1. Gender Differences in Schizophrenia.
2.2. Estrogen Hypothesis of Schizophrenia.
2.3. Evidence for Estrogen Dysfunction in Patients with Schizophrenia. An early study reported that, of the sam-
2.4. Clinical Trials of Adjunctive Estrogen in Schizophrenia.

3. Mechanisms of Estrogen Action in Schizophrenia

3.1. Estrogen Receptors.
3.2. Estrogen Receptors and Cognition.
3.3. Estrogen Effects on Brain Structure.
3.4. Neuroprotection by Estrogen.
3.5. Changes in Estrogen Signaling in Schizophrenia.
3.6. Estrogen Effects on Major Neurotransmitter Systems Targeted by Antipsychotics. Several converging lines of evidence
3.6.1. Estrogen Interaction with Dopamine.
3.6.2. Estrogen Interaction with Serotonin.
3.6.3. Estrogen Interaction with Glutamate.

4. Summary and Conclusions

In summary, schizophrenia is a neuropsychiatric disorder that has shown robust gender differences in numerous aspects of the illness, including an earlier age of onset, a more severe course of illness, poorer antipsychotic treatment response, and adaptability to illness in male patients with schizophrenia compared to that of women. This review has highlighted the research that has been invested to understand the potentially protective effects of estradiol with respect to these gender differences in schizophrenia. The extent of this research ranges from molecular investigations that have clearly evidenced estradiol's intricate interactions with the major neurotransmitter systems in the brain, and especially those implicated in schizophrenia, to preclinical models of the illness that have shown estradiol's potential in either enhancing cognition and memory or reversing deficits that are reflective of the positive, negative, and cognitive symptoms of schizophrenia. Recent clinical trials have provided a promising outlook on the use of estradiol and the more recent use of selective estradiol receptor modulators, as an adjunctive treatment to antipsychotics for schizophrenia patients of both genders. Future studies investigating the mechanism underlying estradiol's protective action in schizophrenia are warranted; such research is also necessary in other psychiatric disorders where gender differences are observed, including depression and anxiety.

JAMA Psychiatry | Original Investigation

Effect of Adjunctive Estradiol on Schizophrenia Among Women of Childbearing Age
A Randomized Clinical Trial

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IMPORTANCE Several lines of evidence suggest that estradiol influences the course of schizophrenia, and a previous randomized controlled trial demonstrated that transdermal estradiol improved symptoms in female patients of childbearing age. However, many initial positive findings in schizophrenia research are not later replicated.

OBJECTIVE To independently replicate the results of the effect of estradiol on schizophrenia in women of childbearing age.

DESIGN, SETTING, AND PARTICIPANTS An 8-week randomized, placebo-controlled trial performed in the Republic of Moldova between December 4, 2015, and July 29, 2016, among 200 premenopausal women aged 19 to 46 years with schizophrenia or schizoaffective disorder as defined by the *DSM-5*.

INTERVENTION Patients were randomized to receive a 200-µg estradiol patch or placebo patch changed twice a week added to their antipsychotic treatment.

MAIN OUTCOMES AND MEASURES The primary outcome was the positive subscale of the Positive and Negative Syndrome Scale (PANSS; lower scores indicated fewer symptoms and higher scores indicated more symptoms), analyzed with mixed models for repeated measures on an intention-to-treat basis.

RESULTS A total of 100 women (median age, 38 years; interquartile range, 34-42 years) were randomized to receive an estradiol patch and 100 women (median age, 38 years; interquartile range, 31-41 years) were randomized to receive a placebo patch; the median age at baseline for the entire group of 200 women was 38.0 years (range, 19.5-46.0 years). At baseline, the mean positive PANSS score was 19.6 for both groups combined; at week 8, the mean positive PANSS score was 14.4 in the placebo group and 13.4 in the estradiol group. Compared with placebo, participants receiving add-on estradiol patches had statistically significant improvements in the primary outcome measure, PANSS positive subscale points (−0.94; 95% CI, −1.64 to −0.24; $P = .008$; effect size = 0.38). Post hoc heterogeneity analyses found that this effect occurred almost entirely in 100 participants older than 38.0 years (46 in placebo group vs 54 in estradiol group; difference, −1.98 points on the PANSS positive subscale; 95% CI, −2.94 to −1.02; $P < .001$). Younger participants did not benefit from estradiol (difference, 0.08 points on the PANSS positive subscale; 95% CI, −0.91 to 1.07; $P = .87$). Breast tenderness was more common in the estradiol group (n = 15) than in the placebo group (n = 1) as was weight gain (14 in estradiol group vs 1 in placebo group).

CONCLUSIONS AND RELEVANCE The results independently replicate the finding that transdermal estradiol is an effective add-on treatment for women of childbearing age with schizophrenia and extend it, finding improvements in negative symptoms and finding that the effect could be specific to those older than 38 years. The results should be viewed in the context of the differences in the natural course of schizophrenia between females and males.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT03848234

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Editor's Note
Supplemental content

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Review Article

Translational Significance of Selective Estrogen Receptor Modulators in Psychiatric Disorders

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Accumulating data from various clinical trial studies suggests that adjuvant therapy with ovarian hormones (estrogens) could be effective in reducing cognitive deficit and psychopathological symptoms in women with psychiatric disorders. However, estrogen therapy poses serious limitations and health issues including feminization in men and increased risks of thromboembolism, hot flashes, breast hyperplasia, and endometrium hyperplasia when used for longer duration in older women (aged ≥ 60 years) or in women who have genetic predispositions. On the other hand, selective estrogen receptor modulators (SERMs), which may (or may not) carry some risks of hot flashes, thromboembolism, breast hyperplasia, and endometrial hyperplasia, are generally devoid of feminization effect. In clinical trial studies, adjuvant therapy with tamoxifen, a *triphenylethylene* class of SERM, has been found to reduce the frequency of manic episodes in patients with bipolar disorder, whereas addition of raloxifene, a *benzothiophene* class of SERM, to regular doses of antipsychotic drugs has been found to reduce cognitive deficit and psychological symptoms in men and women with schizophrenia, including women with treatment refractory psychosis. These outcomes together with potent neurocognitive, neuroprotective, and cardiometabolic properties suggest that SERMs could be the potential targets for designing effective and safer therapies for psychiatric disorders.

6. Safety of SERMs

Data from various long-term clinical trial studies in which postmenopausal women were treated for breast cancer and osteoporosis suggests that SERM therapy carries some risks such as hot flashes, leg cramps, and venous thromboembolic events. Tamoxifen treatment may also carry the additional risks of hyper-proliferation of the uterine and endometrial tissues, and may be cognitive decline in older women, especially, when it is used for longer duration [25, 160–162]. However, these risks are observed in older women and after years of treatment [25, 160, 161]. These adverse effects have not been reported in young women or in postmenopausal women who did not have previous history of complications [160, 161]. In conclusion, most of these analyses suggest that raloxifene has a favorable safety profile and its adverse effects, if any, can be reduced/minimized by changing dosing time and duration without affecting its therapeutic efficacy [162].

7. Future of SERMs in Psychiatric Disorders

Evidence for therapeutic effectiveness of SERMs in psychiatric disorders is emerging. SERMs can improve the clinical response of psychotropic drugs in patients with bipolar disorder and schizophrenia. While tamoxifen adjuvant therapy in bipolar patients requires additional studies on its safety for long-term use, raloxifene because of its favorable safety profile can be used safely in the long-term management of schizophrenia. Both of these SERMs have also been shown to prevent the development or delay the onset of cardiometabolic complications including diabetes, obesity, and atherosclerosis (reviewed in [163, 164]), which are serious adverse effects often present from the early phase of illness in both schizophrenia and bipolar patients and become more severe after treatment with psychotropic drugs [80–82]. Therefore, use of SERMs may improve therapeutic efficacy of psychotropic drugs and the quality of life of psychiatric patients after treatment. Unlike tamoxifen, raloxifene has been found to improve cognition or delay the onset of cognitive decline in postmenopausal women on osteoporosis therapy. Therefore, further studies on the potential of raloxifene to improve cognitive behaviors would be very crucial because, currently, there are no effective drugs available to improve cognition in schizophrenia.

Additional advantages of using raloxifene in schizophrenia would be a negligible or no risk of feminization in men and hypersensitization in adolescent girls or younger women that may be observed with estrogens. Because of this advantage and noteworthy brain- and behavior-repairing properties, raloxifene (or other more effective *alike* SERMs) provides an option for early intervention in schizophrenia, which might be more effective in correcting brain pathologies that lead to the development of cognitive deficit and psychosis in high-risk adolescents/individuals. Since evidence suggests that raloxifene adjuvant therapy may also reduce negative symptoms, which are more prominent in male compared to female schizophrenia patients, therefore, addition of raloxifene may enhance the potency of

The association between hormones and antipsychotic use: a focus on postpartum and menopausal women

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Alexandre González-Rodríguez and Mary V. Seeman

Abstract: During the postpartum and menopausal periods of women's lives, there is a well-established and significant drop of circulating estrogens. This may be the reason why both these periods are associated with an increased risk for onset or exacerbation of psychiatric disorders. Whether symptoms are mainly affective or mainly psychotic, these disorders are frequently treated with antipsychotic medications, which calls for an examination of the relationship between hormone replacement and antipsychotic agents at these time periods. The aim of this narrative review is to summarize what is known about the association of hormones and antipsychotics in the postnatal period and at menopause. In the review, we focus on estrogen and oxytocin hormones and include, for the most part, only papers published within the last 10 years. Both estradiol and oxytocin have at various times been implicated in the etiology of postpartum disorders, and estrogens, sometimes combined with progesterone, have been tested as potential treatments for these conditions. The role of estradiol as an adjunct to antipsychotics in the prevention of postpartum relapses is currently controversial. With respect to oxytocin, studies are lacking. Psychosis in menopausal and postmenopausal women has been successfully treated with estrogens and selective estrogen-receptor modulators, mainly raloxifene, in addition to antipsychotics. Some symptoms appear to respond better than others. No oxytocin study has specifically targeted postmenopausal women. Because of feedback mechanisms, there is a theoretical danger of therapy with exogenous hormones interfering with endogenous secretion and disturbing the balance among inter-related hormones. When used with antipsychotics, hormones may also affect the metabolism and, hence, the brain level of specific antipsychotics. This makes treatment with antipsychotics plus hormones complicated. Dose, timing and route of intervention may all prove critical to efficacy. While much remains unknown, this literature review indicates that, within standard dose ranges, the combination of hormones and antipsychotics for postnatal and menopausal women suffering severe mental distress can be beneficial, and is safe.