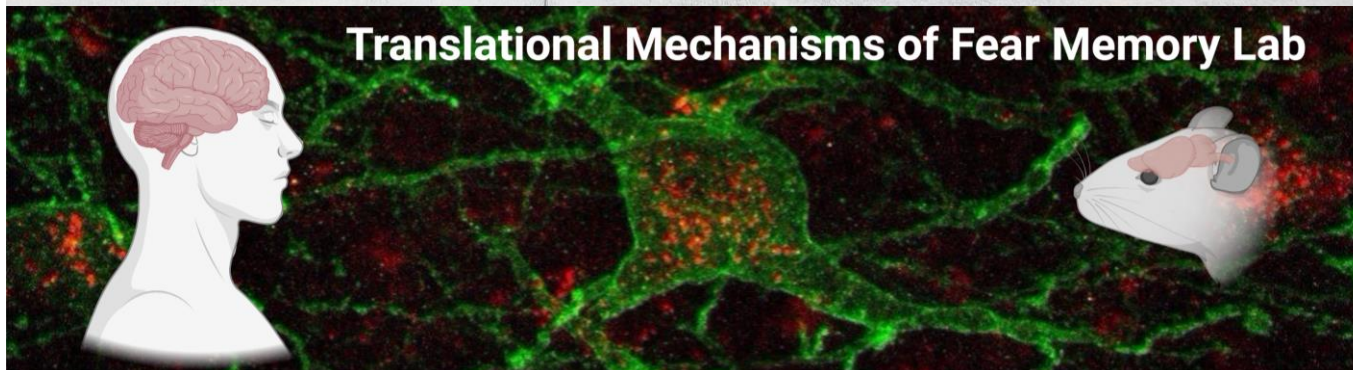




Translational Mechanisms of Fear Memory Lab

“Un fármaco da valentía a los machos y miedo a las hembras”

Raül Andero Galí, PhD
ICREA Research Professor

Jornadas Investigación con Dimensión de Género 2021

UAB

Universitat Autònoma
de Barcelona

cibersam

Centro de Investigación Biomédica En Red
de Salud Mental



INc
Institut de
Neurociències



ICREA

Disclosures

International Patent PCT/US2015/037629, *Methods of managing conditioned fear with neurokinin receptor antagonists.*

ACER THERAPEUTICS

Introduction



Fear

Anxiety

Introduction

Fear



Anxiety

Introduction

Fear



Anxiety



“...**Fear** is a generally adaptive state of apprehension that begins rapidly and dissipates quickly once the **threat** is removed. **Anxiety** is elicited by less specific and less predictable threats...”

Michael Davis

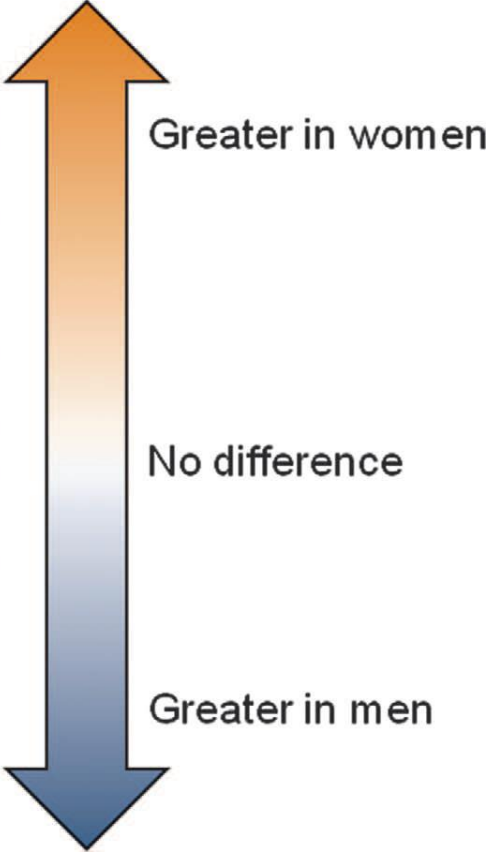
Introduction

DSM-5 (Diagnostic and Statistical Manual of Mental Disorders 5, 2013)



Introduction: Prevalence fear-related disorders

Disorder	Women/Men Lifetime Incidence Ratio
PTSD	2.08 ^a
Panic Disorder	1.96 ^b
Generalized Anxiety	1.88 ^b
Major Depressive Disorder	1.75 ^b
OCD*	1.6 ^c
Alzheimer's Disease	1.30 ^d
Bipolar Disorder	~1.0 ^e
Schizophrenia	0.71 ^f
Parkinson's Disease	0.53 ^g
Drug Use Disorder	0.51 ^h
Alcohol Dependence	0.46 ^b
ADHD	0.42 ⁱ





Cover et al. 2014 *Translational Psychiatry*

Becker et al. *Biology of Sex Differences* (2016) 7:34
DOI 10.1186/s13293-016-0087-5

Biology of Sex Differences

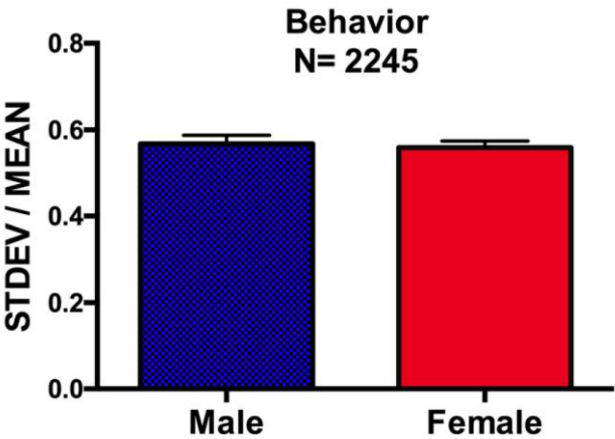
RESEARCH

Open Access

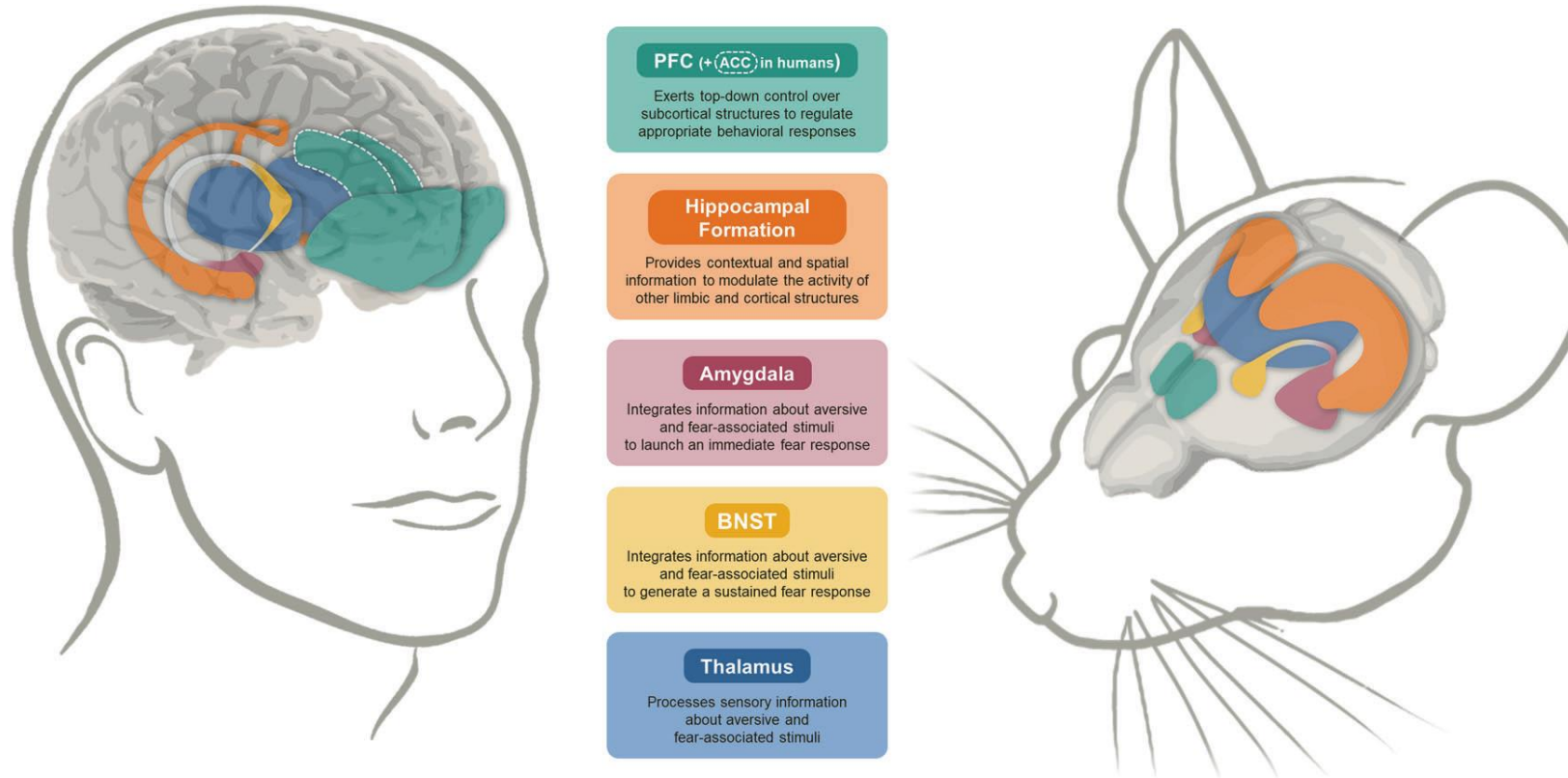


Female rats are not more variable than male rats: a meta-analysis of neuroscience studies

Jill B. Becker^{1,2*}, Brian J. Prendergast³ and Jing W. Liang⁴



Introduction: Brain structures in fear memory



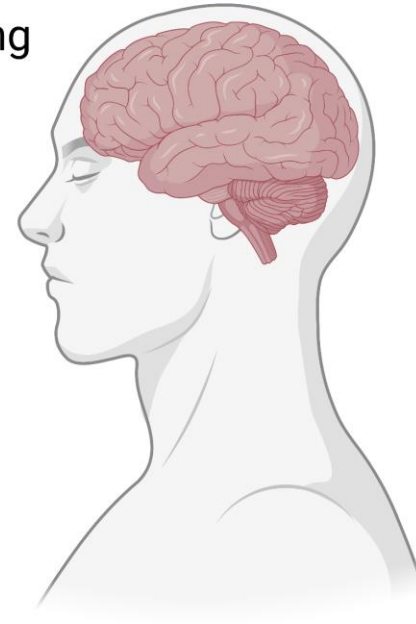
Flores et al. 2018 *Molecular Psychiatry*

5.5 males to 1 female - Zucker and Berry 2010 *Nature*

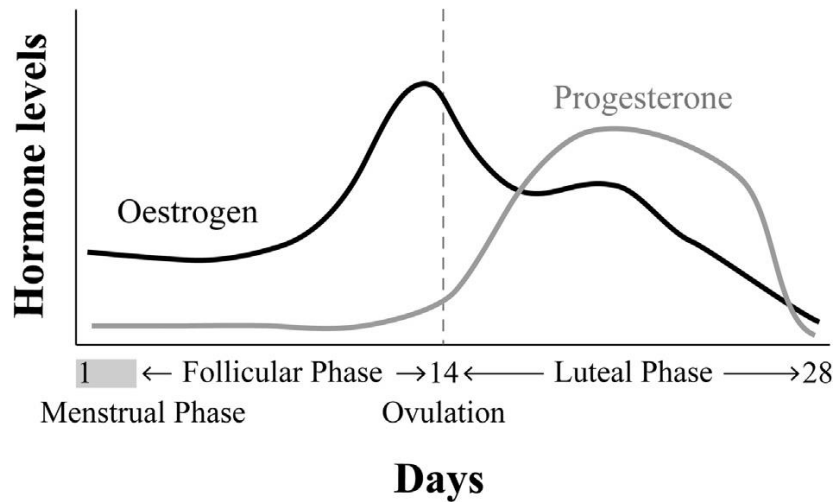
Introduction: men vs women brain



Magnetic Resonance Imaging

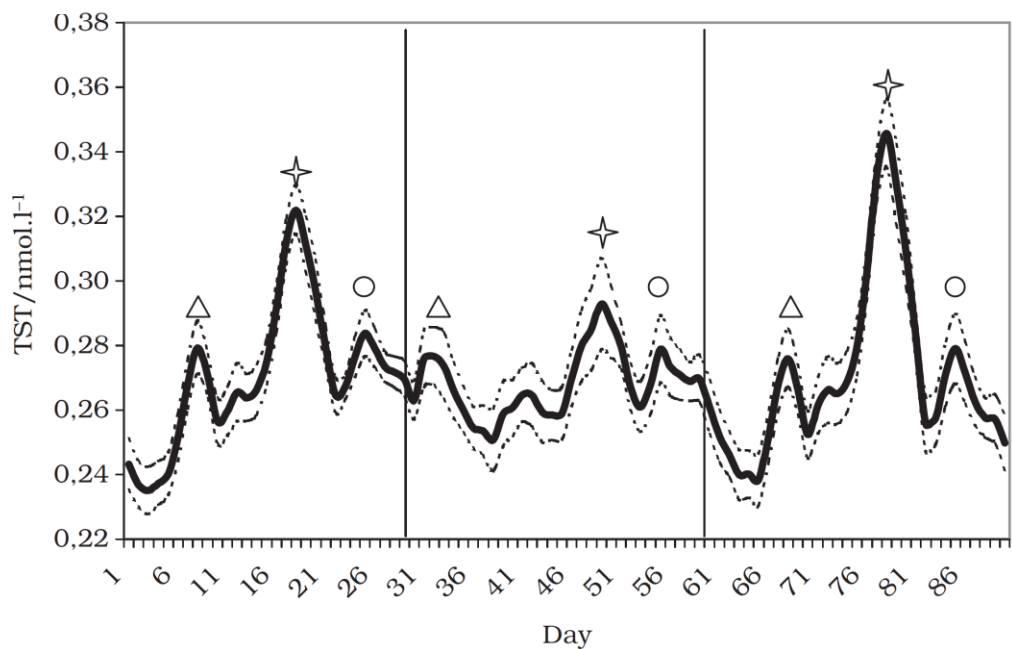


Introduction: men vs women sex hormones

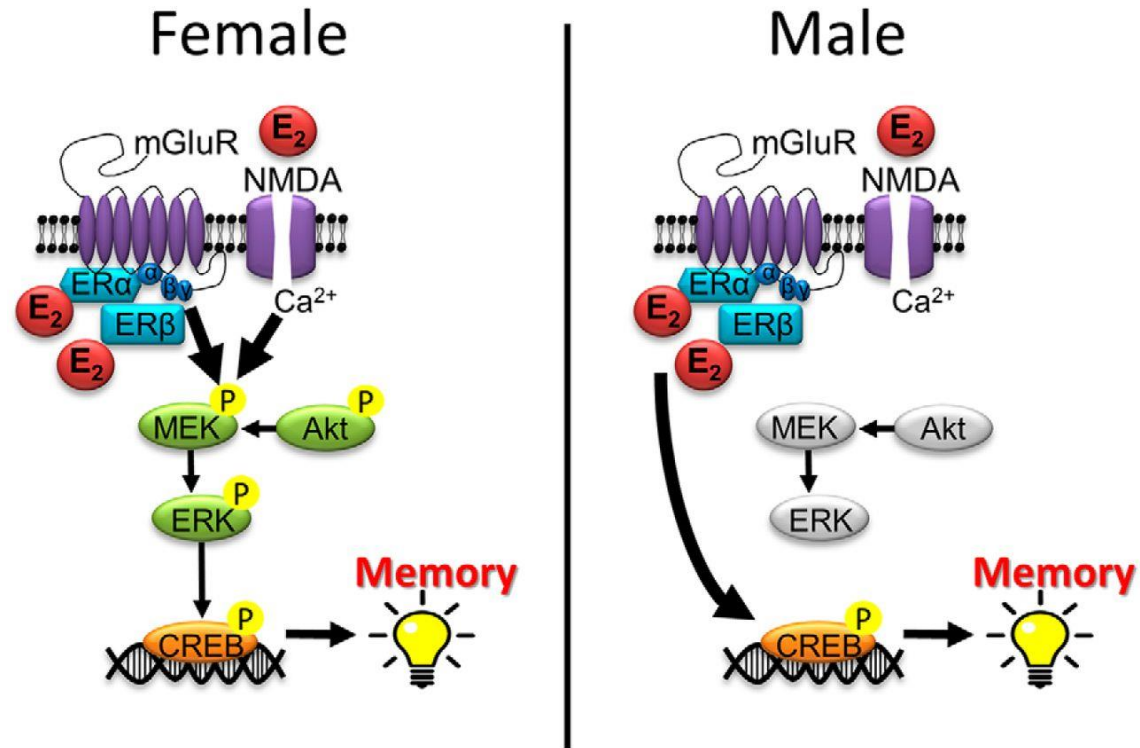


Oestrogen and Progesterone
(Vink et al 2017 *Trends in Cardiovascular Science*)

Testosterone
(Celec et al 2003 *Biological Rhythm Research*)



Introduction: men vs women molecular biology



ARTICLE



<https://doi.org/10.1038/s41467-021-22911-9>

OPEN

Sex differences in fear memory consolidation via Tac2 signaling in mice

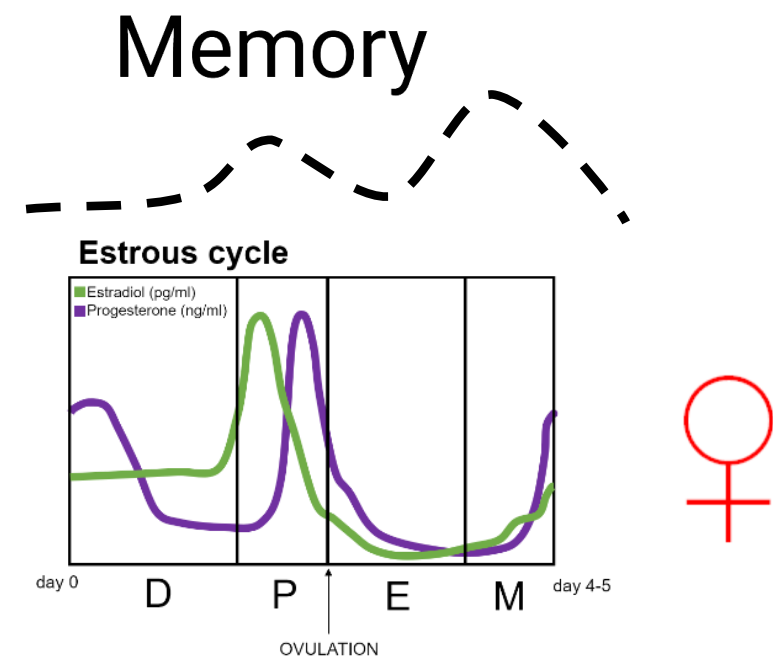
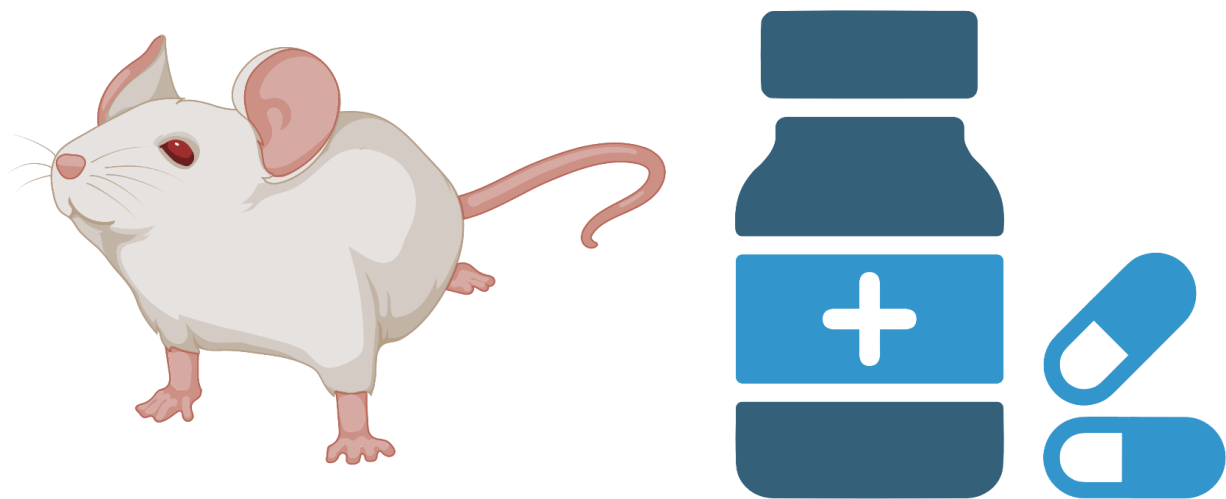
A. Florido ^{1,2}, E. R. Velasco ¹, C. M. Soto-Faguás^{1,3,4}, A. Gomez-Gomez⁵, L. Perez-Caballero ^{1,2},
P. Molina^{1,6}, R. Nadal ^{1,2,7,8}, O. J. Pozo ⁵, C. A. Saura ^{1,3,4} & R. Andero ^{1,2,7,8,9}✉

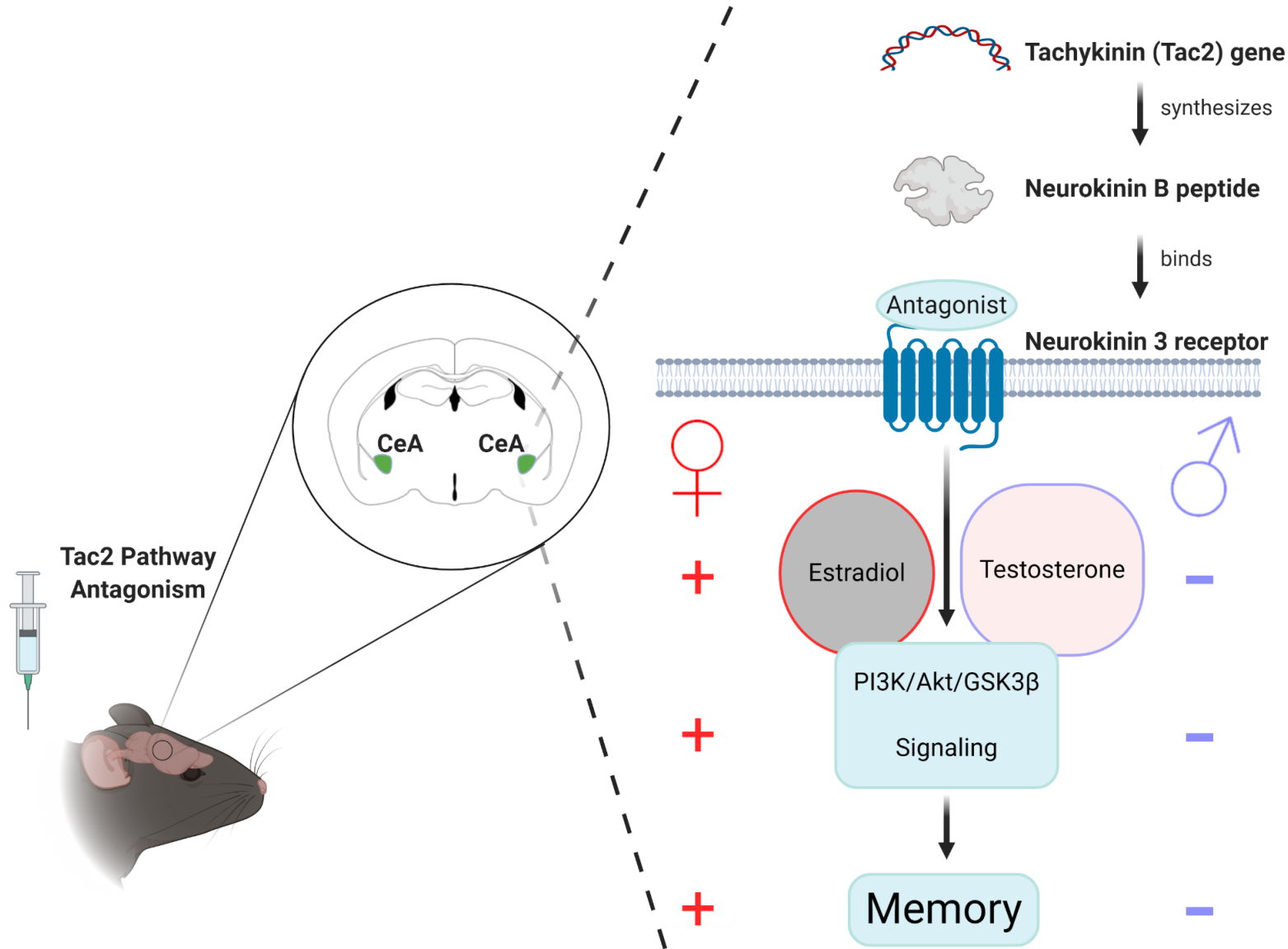


Sex Differences in Fear Memory Consolidation



Sex Differences in Fear Memory Consolidation





Article

Placebo-Controlled Evaluation of Four Novel Compounds for the Treatment of Schizophrenia and Schizoaffective Disorder

Herbert Y. Meltzer, M.D.

Lisa Arvanitis, M.D.

Deborah Bauer, M.S.

Werner Rein, M.D.

Meta-Trial Study Group

Objective: Four studies using identical protocols evaluated the safety and efficacy of four novel, evidence-based targets for antipsychotic agents: a neurokinin (NK₃) antagonist (SR142801), a serotonin 2A/2C (5-HT_{2A/2C}) antagonist (SR46349B), a central cannabinoid (CB₁) antagonist (SR141716), and a neurotensin (NTS₁) antagonist (SR48692).

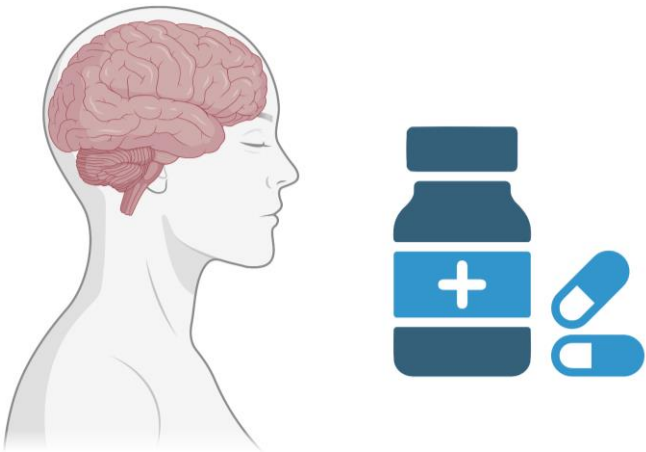
Method: Adults with schizophrenia or schizoaffective disorder (N=481) were randomly assigned in a 3:1:1 ratio to receive fixed doses of investigational drug, placebo, or haloperidol for 6 weeks. Primary efficacy variables included changes from baseline in total score on the Positive and Negative Syndrome Scale, severity of illness score on the Clinical Global Impression (CGI), and total score and psychosis cluster score on the Brief Psychiatric Rating Scale (BPRS).

Results: Significantly greater improvement in all primary efficacy variables was seen in the group receiving haloperidol than in the group receiving placebo at 6 weeks (endpoint analyses), indicating the validity of the study. The group receiving the NK₃ antagonist showed significantly greater improvement over baseline than the group receiving placebo as measured by Positive and Negative Syndrome Scale

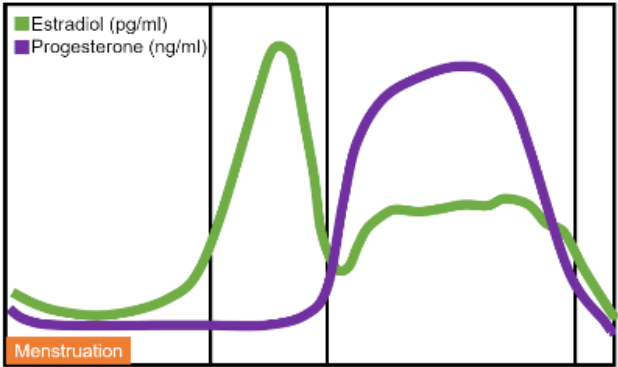
total score, CGI severity of illness score, and BPRS psychosis cluster score. Reductions in the Positive and Negative Syndrome Scale total and negative scores in the group receiving the 5-HT_{2A/2C} antagonist were significantly larger than those in the group receiving placebo. The improvements in psychopathology produced by the NK₃ and 5-HT_{2A/2C} antagonists were smaller than those produced by haloperidol, although the response to the NK₃ antagonist was positively correlated with plasma levels. The groups receiving the CB₁ and NTS₁ antagonists did not differ from the group receiving placebo on any outcome measure. All investigational drugs were well tolerated.

Conclusions: The novel design used in this study permitted the use of a smaller number of patients receiving placebo to test the efficacy of the four novel compounds. The NK₃ and 5-HT_{2A/2C} antagonists showed evidence of efficacy in the treatment of schizophrenia and schizoaffective disorder. Study limitations preclude a definitive conclusion on the efficacy of CB₁ and NTS₁ antagonists in the treatment of schizophrenia. Further study of these two promising nondopaminergic mechanisms to treat schizophrenia and schizoaffective disorder appears indicated.

Potential Implications



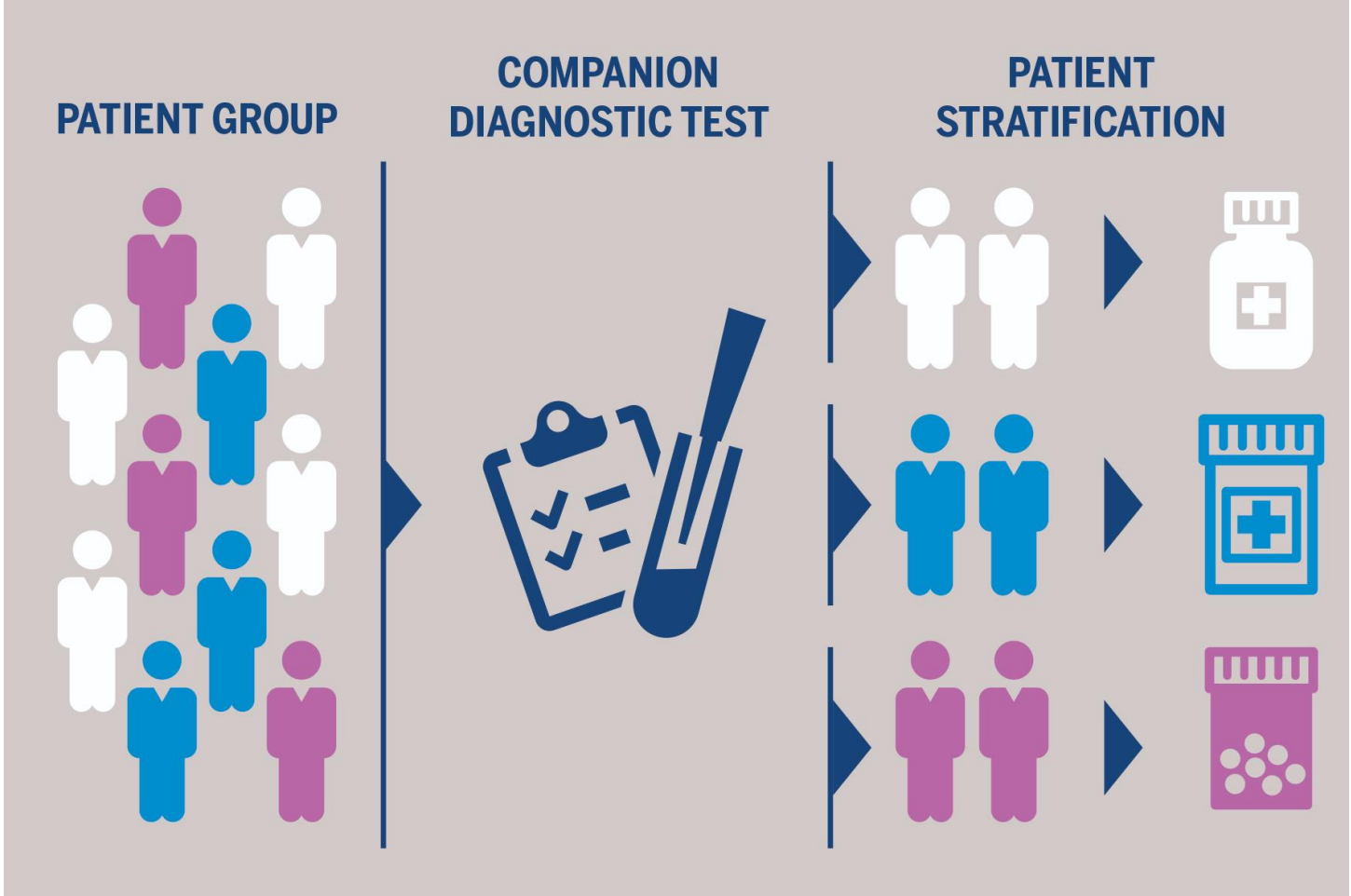
Menstrual cycle

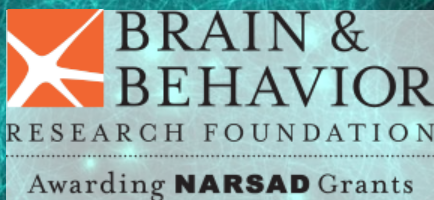


Potential Implications



Potential Implications





Laura Pérez
PhD



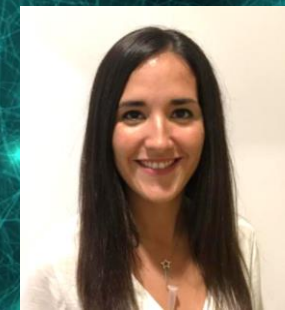
Ignacio Marin
PhD



Eric Velasco
MD



Antonio Florido



Patricia Molina



Maria López

www.anderolab.com @AnderoLab



Main Collaborators

Oscar Pozo (IMIM, Spain)

Rafael Maldonado (UPF, Spain)

Carles Saura (UAB, Spain)

Vadim Bolshakov (Harvard, US)

Roser Nadal (UAB, Spain)

Gleb Shumyatsky (Rutgers, US)

Isabel Perez-Otaño (CSIC, Spain)

Elena Martin-García (UPF, Spain)

Kerry Ressler (Harvard, US)

Tanja Jovanovic (Wayne State, US)

Jose Rodríguez-Romaguera (UNC, US)

Lluïsa Garcia-Esteve (UB-Clínic, Spain)

Adriana Lori (Emory, US)

Torsten Klengel (Harvard, US)

Emily Newman (Harvard, US)

Carmen Sandi (EPFL, Switzerland)

Narcis Cardoner (UAB, Spain)

Antonio Armario (UAB, Spain)

Isaac Galatzer-Levy (NYU & Facebook, USA)

Rachel Ross (Albert Einstein, US)

Newton Canteras (Univ São Paulo, Brazil)

Enric Canela (UB, Spain)

