SOBER GROUP

SEX ON BRAIN EUROPEAN RESEARCH GROUP

Effects of Gonadotropin Releasing Hormone Receptor blockage on brain development and behaviour in humans and animals

Ira Ronit Hebold Haraldsen, MD, PhD

CENTRE FOR MOLECULAR BIOLOGY AND NEUROSCIENCE
Norges veterinærhøgskole
UNIVERSITETET I OSLO
University of Glasgow
RIKSHOSPITALET

Sex on Brain European Research SOBER

Centre for Research-based Innovation

SOBER is partner of ADHA

The Innovation Centre on Ageing and Cognitive Impairment

From Alzheimer disease to healthy ageing – ADHA

CMBN – the first and largest Centre of Excellence in the field of biomedicine in Norway

CENTRE FOR MOLECULAR BIOLOGY AND NEUROSCIENCE
Senter for molekylærbiologi og nevrovitenskap

WWW.CMBN.no

Norwegian Centre of Excellence

Centre for Research-based Innovation

10 YEARS TRACK RECORD
In the proposed consortium

Publications: **> 400**
H-index: **13 - 66**

Patents: **> 100**

Prizes: **3 Anders Jahre Prizes**
is the most prestigious prize in medicine in the Nordic countries (next to the Nobel Prize)

2 King Olav V's Prizes
Mead Johnson Award
Eli Lilly Prize
Innovation Prize

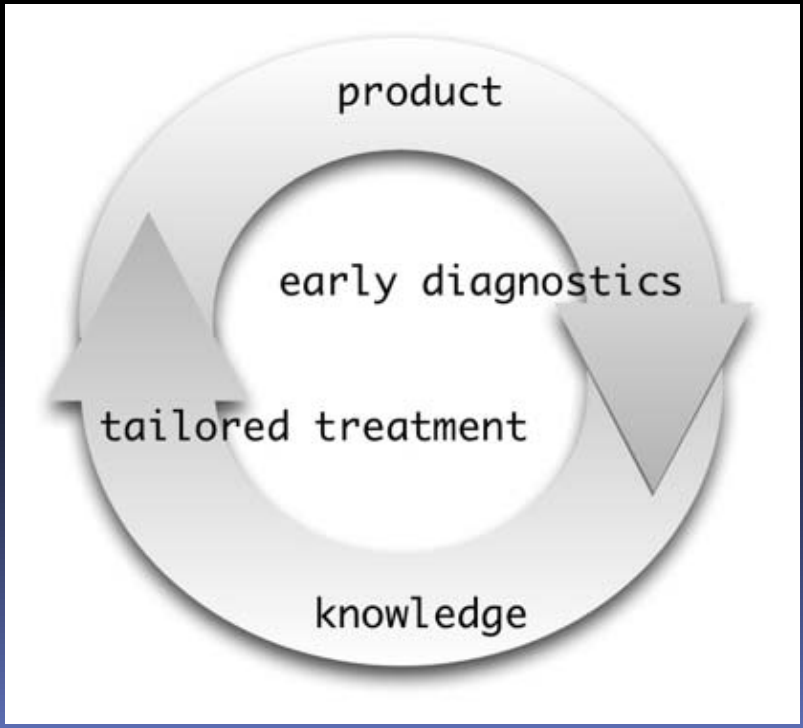
The neuroscience team in CMBN counts some of the most frequently cited scientists in the field (source: ISI Highly Cited Scientists)

Centre of excellence on research based Innovation

ADHA

From Alzheimer disease to healthy ageing – ADHA

The Innovation Centre on Ageing and Cognitive Impairment



New potential technologies

- 2010-2016
- Diagnostic drug development for dementia and cognitive impairement disorders
- Cognitive enhancer drug development

SOBER GROUP

Sex differences of the brain
GNRH

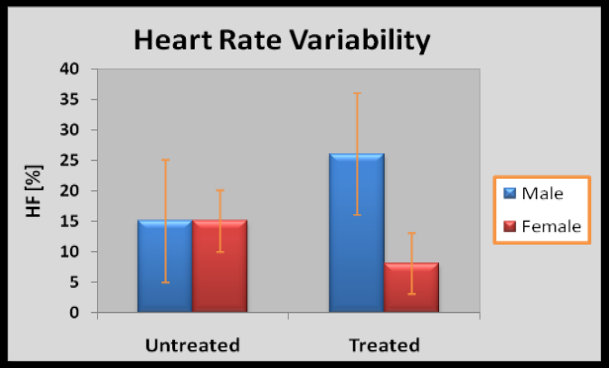
Ira Ronit Hebold Haraldsen, MD, PhD
GI-section, Department of Neuropsychiatry, Centre of Clinical Neuroscience, Oslo University Hospital – Rikshospitalet - Norway

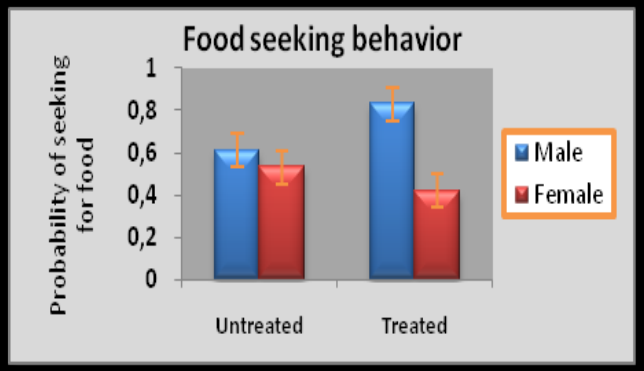
Hypothesis

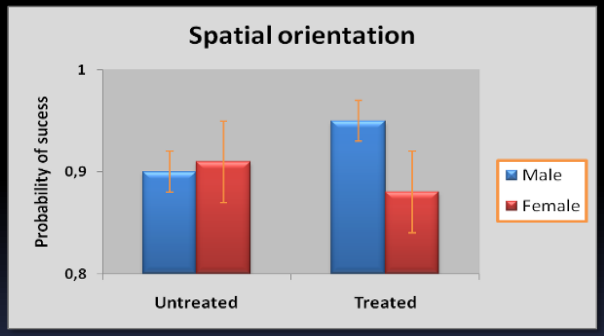
Sex differences in brain development are pre-programmed and not steroid modulated

Do sex differences in cognition and in brain morphology and physiology develop even if puberty is blocked on a steroid precursor level?

SOBER - some of our sheep results







Concept

GnRHR effects on cell respons is independent of Estrogen and Testosteron effects !

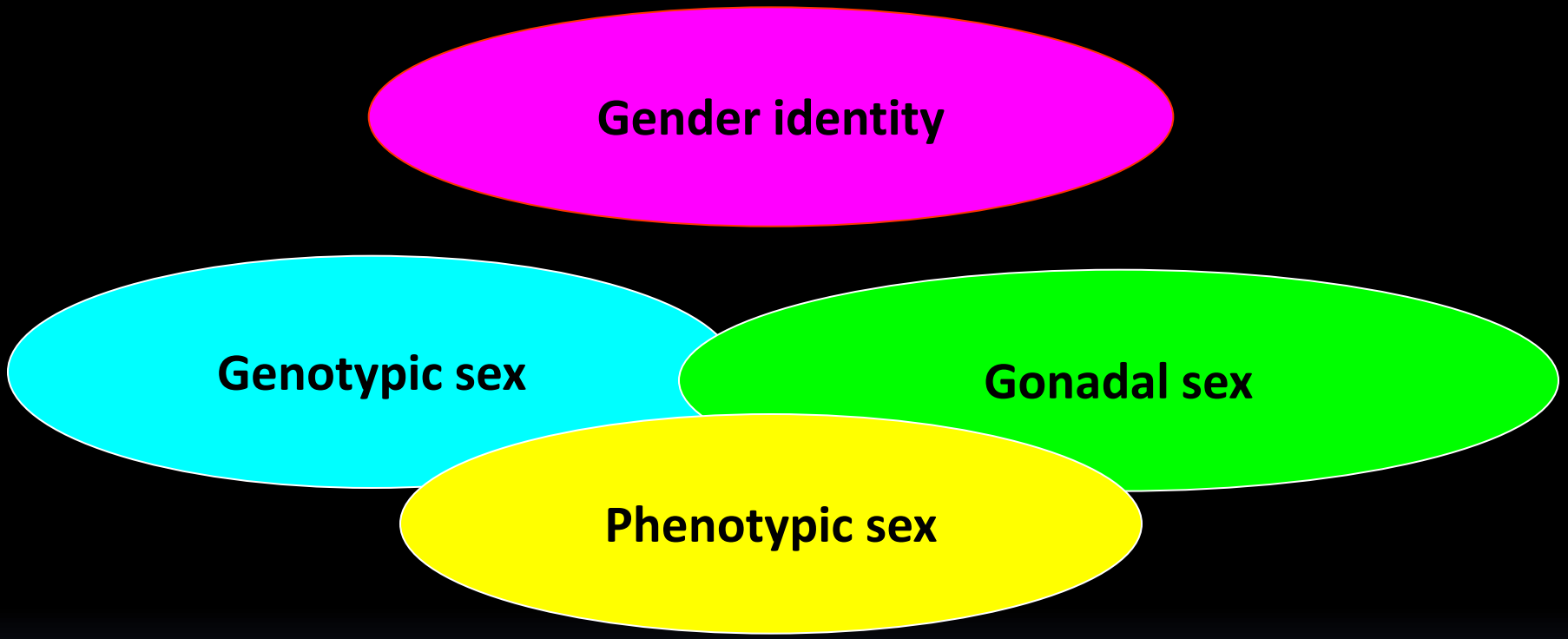
The frontal –temporal lobe function will be manipulated into more flexible neural network in boys/ male adolescents :

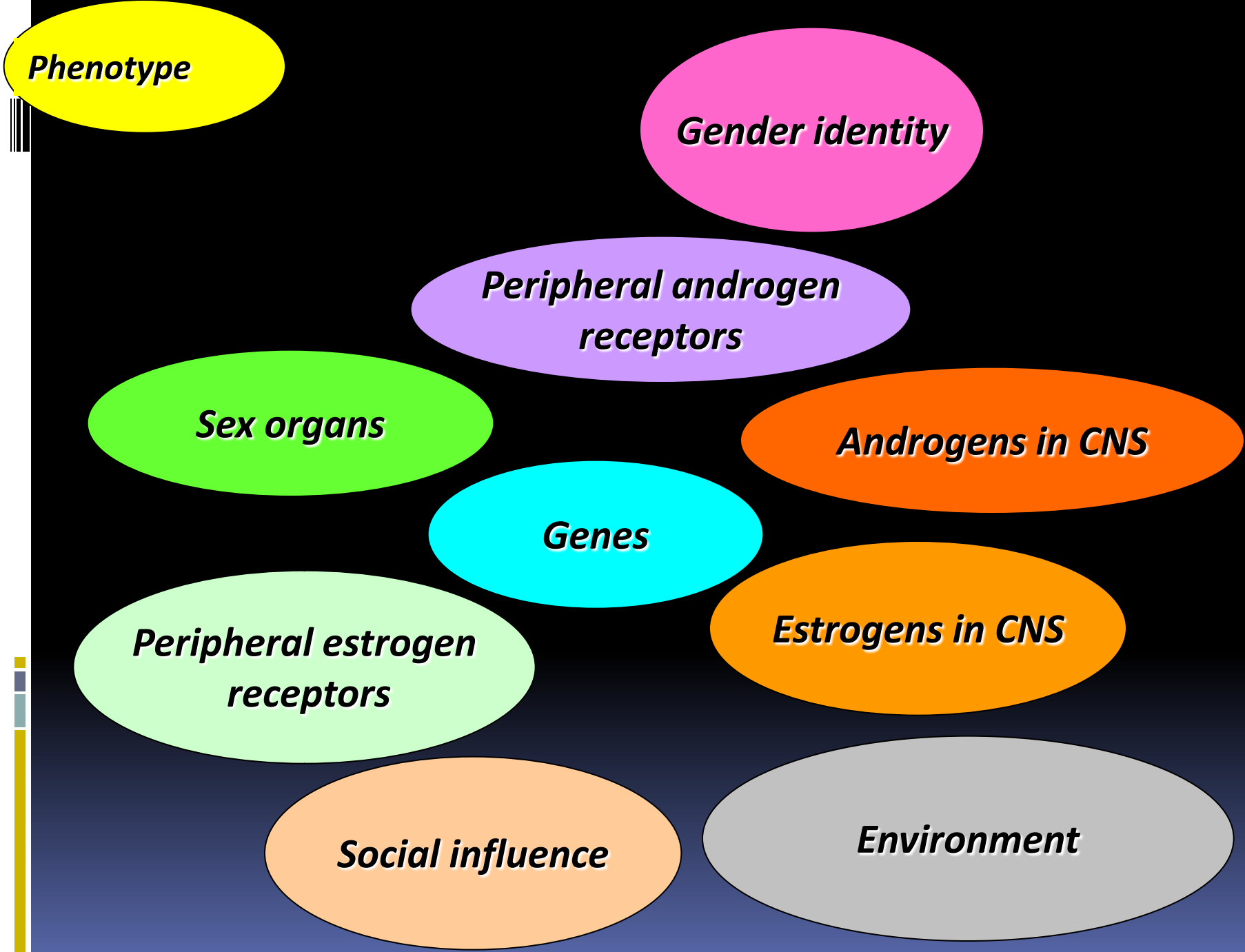
- Our pre-pubertal blocked sheep showed increased gambling attitudes, novelty seeking and spatial orientation attitudes etc

The frontal –temporal lobe function will be manipulated into more flexible neural network *In girls/female adolescents* in:

- Our pre-pubertal blocked female sheep showed reduced exploratorial behaviour (less gambling, less novelty seeking, less aggressive)

SEX




Phenotype
Gender identity
Peripheral androgen receptors
Sex organs
Androgens in CNS
Genes
Estrogens in CNS
Peripheral estrogen receptors
Social influence
Environment

MYTH - YOUNG 1961

*The term **activational** for reversible effects by hormones on stimulating sexual behaviour in adults*

*The term **organizational** for permanent effects of testosterone in perinatal life on decreasing effects of estrogens in adult life*

Although of thousands of morphological functional studies, we do not understand

- how and
- whether

these sex differences contribute to sex differences in behaviour

DIFFERENCES IN STRUCTURE OFTEN DO NOT RESULT IN CHANGED BEHAVIOUR – AND DIFFERENT BEHAVIOUR DOES NOT NECESSARILY MEAN DIFFERENT STRUCTURE

1. The function of neural circuit is advanced
2. It is difficult to link morhology to function
3. We are drawn to the idea that sex differences in brain structure generate sex differences in behaviour

- 1970 Mc Ewen – fewer dendrtic spines in the POA
- 1976 Nottebohm – sex differences in bird songs
- 1978 Gorki – preoptic area (POA/AH = SDN)

However

Lesions in POA or SDN does not result in changes of male sexual behaviour

perinatal manipulation of T system increased volume in SDN but not in behaviour

Turkengurg, Ito, Houtsmuller, Brand, Auger, McCarthy. Todd, Powers, Paredes, Roselli

ANOTHER MYTH: INTERTESTITIAL NUCLEUS OF THE AH (INAH3)

Sexual orientation

How can mice show different partner preference while lacking sex differences in these areas?

Connection and function of cells
versus
Numbers and size of cells

LeVay , Byne

WE ARE IN NEED OF :

NEUROTRANSMITTER, RECEPTOR AGONIST/ANTAGONIST, KNOCK IN AND KNOCK OUT STUDIES

Why:

Density of dendritic spine synapses on MPOA neurons correlates well with male sexual behaviour

But what functional significance has that?

What is the nature of such neurons?

SEXUAL SEX DIFFERENCES WILL NOT BE EXPLAINED BY AN OVERESTIMATING OF SEX DIFFERENCES OF THE BRAIN

SEX DIFFERENCES ARE THE NORM

SEX DIFFERENCES OF THE BRAIN PROTECT BEHAVIOURAL DIFFERENCES

Kisspetin

Kisspetin neurons stimulate GNRH neurons

A little revolution:
One single gene deletion in an ion channel

- *Trpc2 deletion wipe out sex different behaviour in males*

but

- *In females change the behaviour to male sexual behaviour*

therefore

- The mediated processes are repressed in males and activated in females

Context dependency

Søderstren, Gerall, Olster, De Vries, Rosen, Lonstein etc

- *Prenatal given hormones do not irreversible change adult sensitivity to hormones and behaviour*
  - *what is happening in puberty*
- And in some strains up to 50% of intact males behave like the opposite sex

Testing conditions

- Tactile contact (warm gloves vs plastic cups)
- Mental rotation test – figures vs human shapes
- Math tests

- Males and females can both generate male and female typical behaviour, but they use different strategies
- Sex differences are the norm
- Sex differences in brain structure may as well prevent sex differences in behaviour

- But the XX - XY difference is only expressed in only few tissues during short periods of life

- in mice only SRY is only expressed in half a day to trigger the male phenotype through the Sertoli cells

- Context may alter gen expression
- Selective genetic elimination and re-introduction and receptor blockage studies of sex dimorphic elements may enlighten
- Sex differences do not specify behaviour directly but encodes molecular products that build functioning of the brain through which behaviour is expressed.
- We do not know the consequences of SDN

SOBER Board








RIKSHOSPITALET

University of Glasgow

AstraZeneca
INTERNATIONAL

Norges veterinærhøgskole

UNIVERSITETET I OSLO

Center for the Study of Human Cognition

CENTRE FOR MOLECULAR BIOLOGY AND NEUROSCIENCE

Roehampton University London

UNIVERSITEIT GENT

VU university amsterdam

FRONT lundosloberkleyexecutivestudies

KAROLINSKA INSTITUTET ANNO 1810 Karolinska Institutet

Universitätsklinikum Hamburg-Eppendorf

Institute of Environmental Medicine

Enheten för
Kognitiv Utvecklingspsykologi

SOBER I – BIG 4 – The Human Project

Effects of Gonadotropin Releasing Hormone Receptor blockage on brain development and behaviour in humans

- Andersson, Stein - Neuropsychologist
- Bjark Halvorsen, Therese - Plastic surgeon, urologist
- Cohen-Kettenis, Peggy – director
- De Cuypere, Griet – director
- Diseth, Trond - Child psychiatrist
- Due Tønnesen, Paulina - Neuroradiologist
- Fjell Anders – Controll group – director
- Gross, Anniken - Gynecologist
- Gulbrandsen, Kjersti - Psychiatric nurse
- Haraldsen, Ira – director
- Hellem, Frøydis – Psychologist
- Heylens, Gunter - PhD
- Kaspara, Solveig - Center coordinator
- Kreukels, Baudewintje - Postdoc
- Paap, Muirne – PhD
- Richter-Appelt, Hertha – director
- Nieder, Timo – PhD

- Schreiner, Thomas- Endocrinologist
- Tønseth, Kim Plastic - Surgeon
- Walhovd, Kristine - Controll group – directors







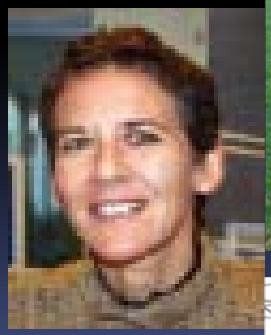

SOBER 2
An animal model

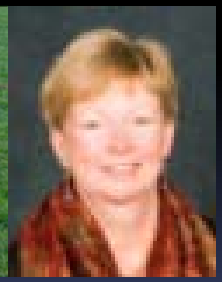
Effects of Gonadotropin Releasing Hormone Receptor blockage on brain development and behaviour in sheep

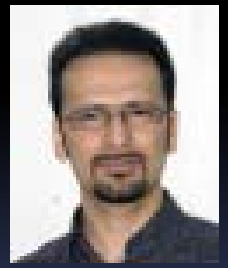
The introduction of a new animal model to evaluate sex specific consequences and mechanisms of a common hormone treatment strategy in man

The Brain biobank opened on the 1st of April 2009

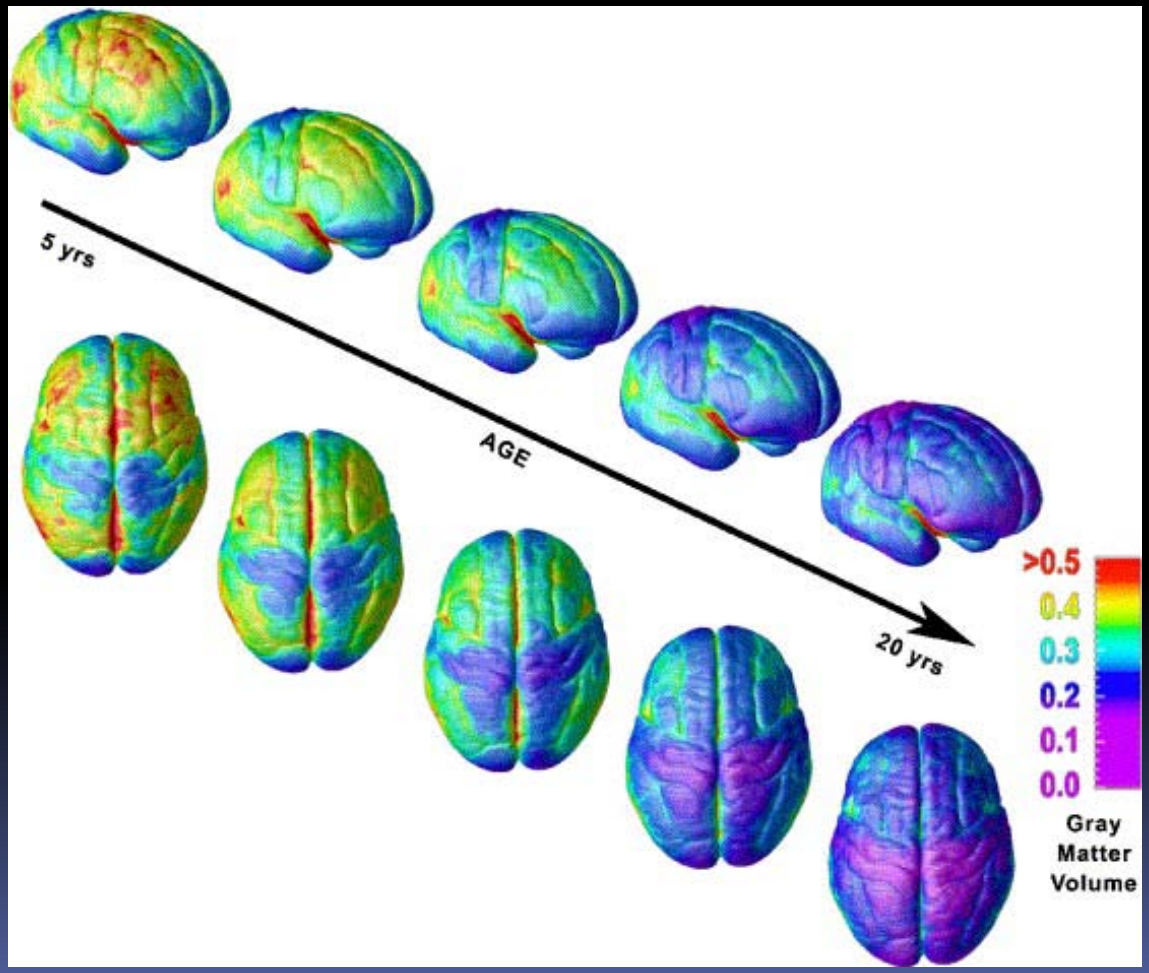
SOBER 2 - Cochno Farm - Oslo

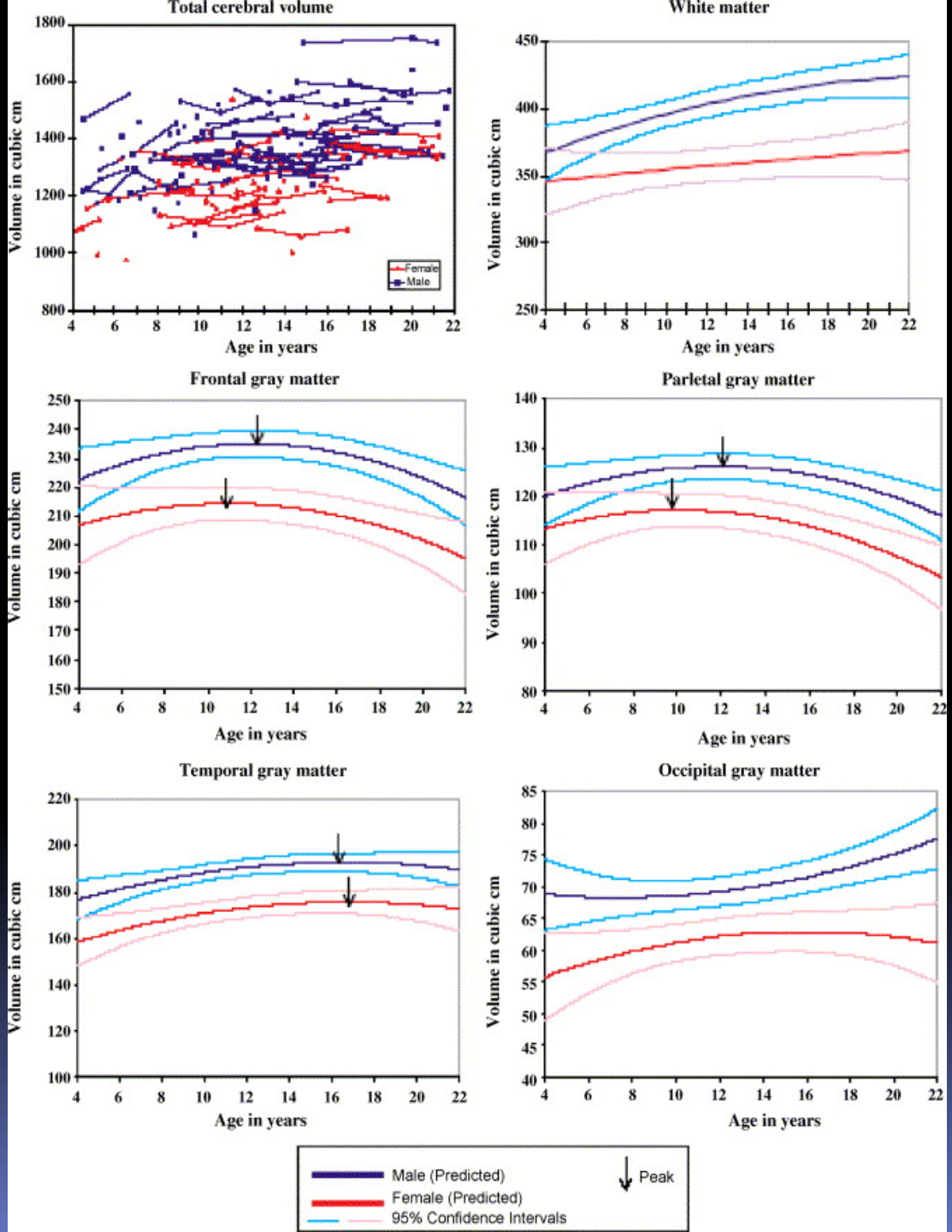




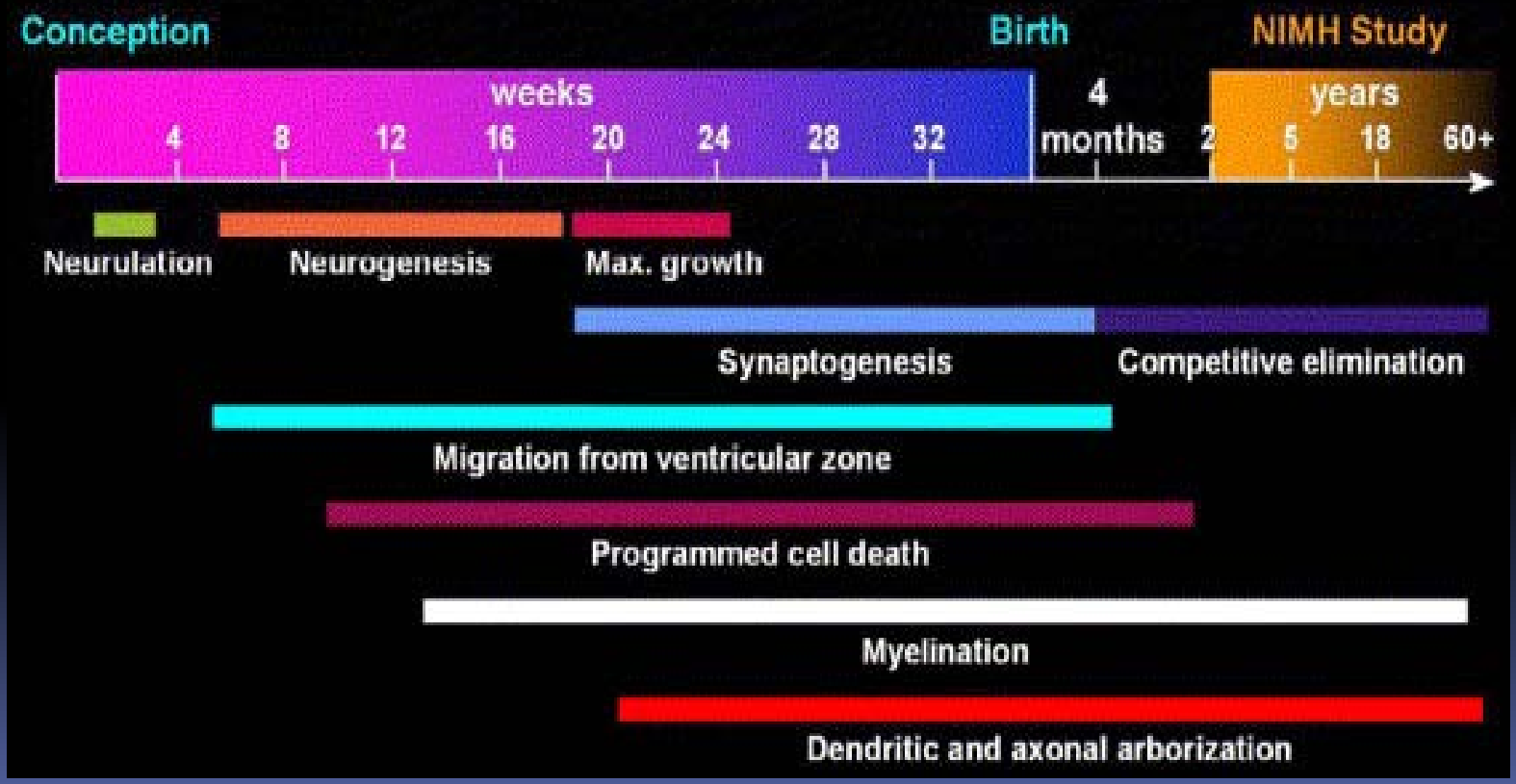


2009 – 2017
Understanding the time correlated phenomenon of puberty and sex differences of the brain


5 yrs
AGE
20 yrs
>0.5
0.4
0.3
0.2
0.1
0.0
Gray
Matter
Volume


Total cerebral volume
Volume in cubic cm
Age in years
Female
Male
White matter
Frontal gray matter
Parletal gray matter
Temporal gray matter
Occipital gray matter
Male (Predicted)
Female (Predicted)
95% Confidence Intervals
Peak

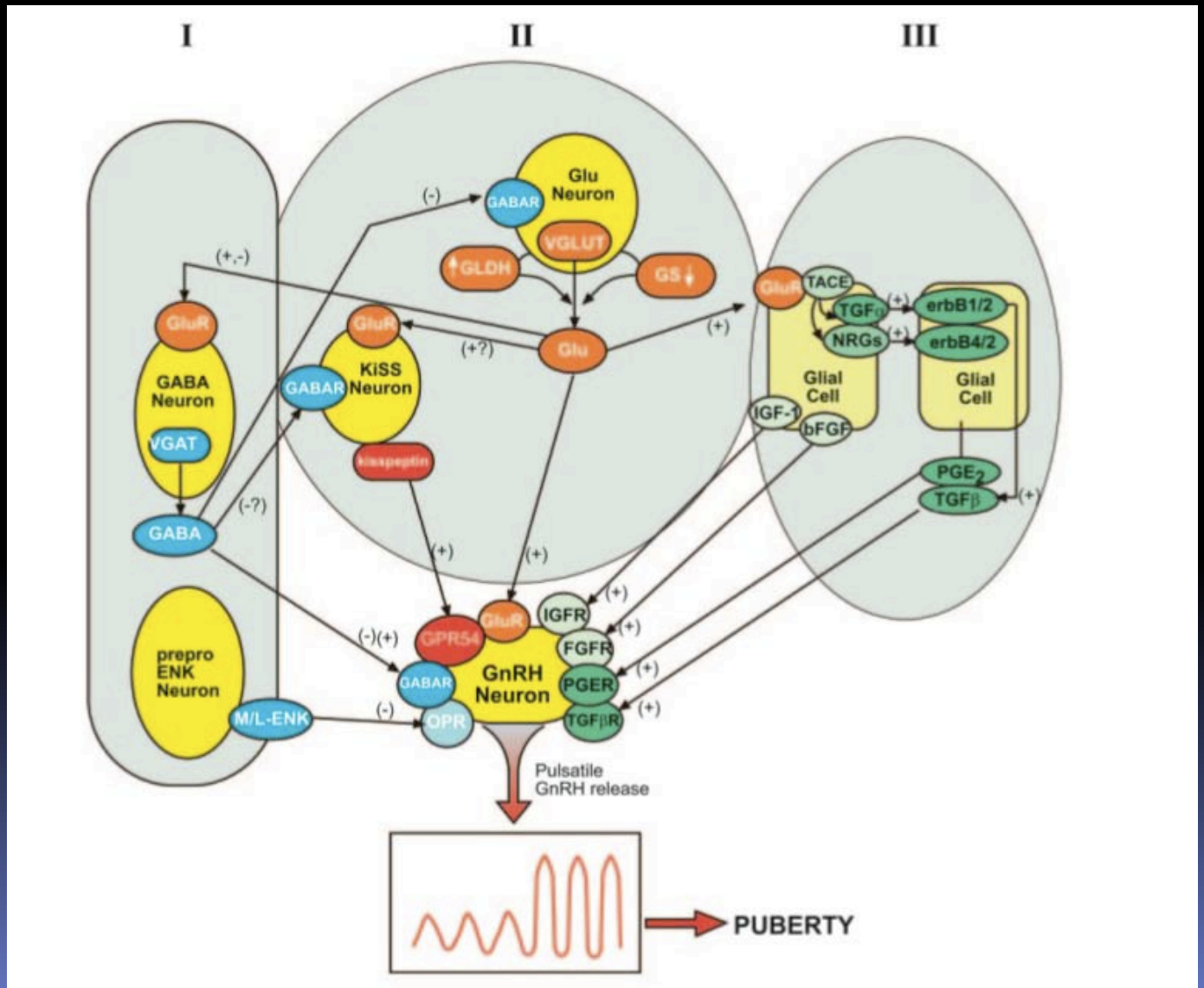
Time Course of Critical Events in the Determination of Human Brain Morphometry

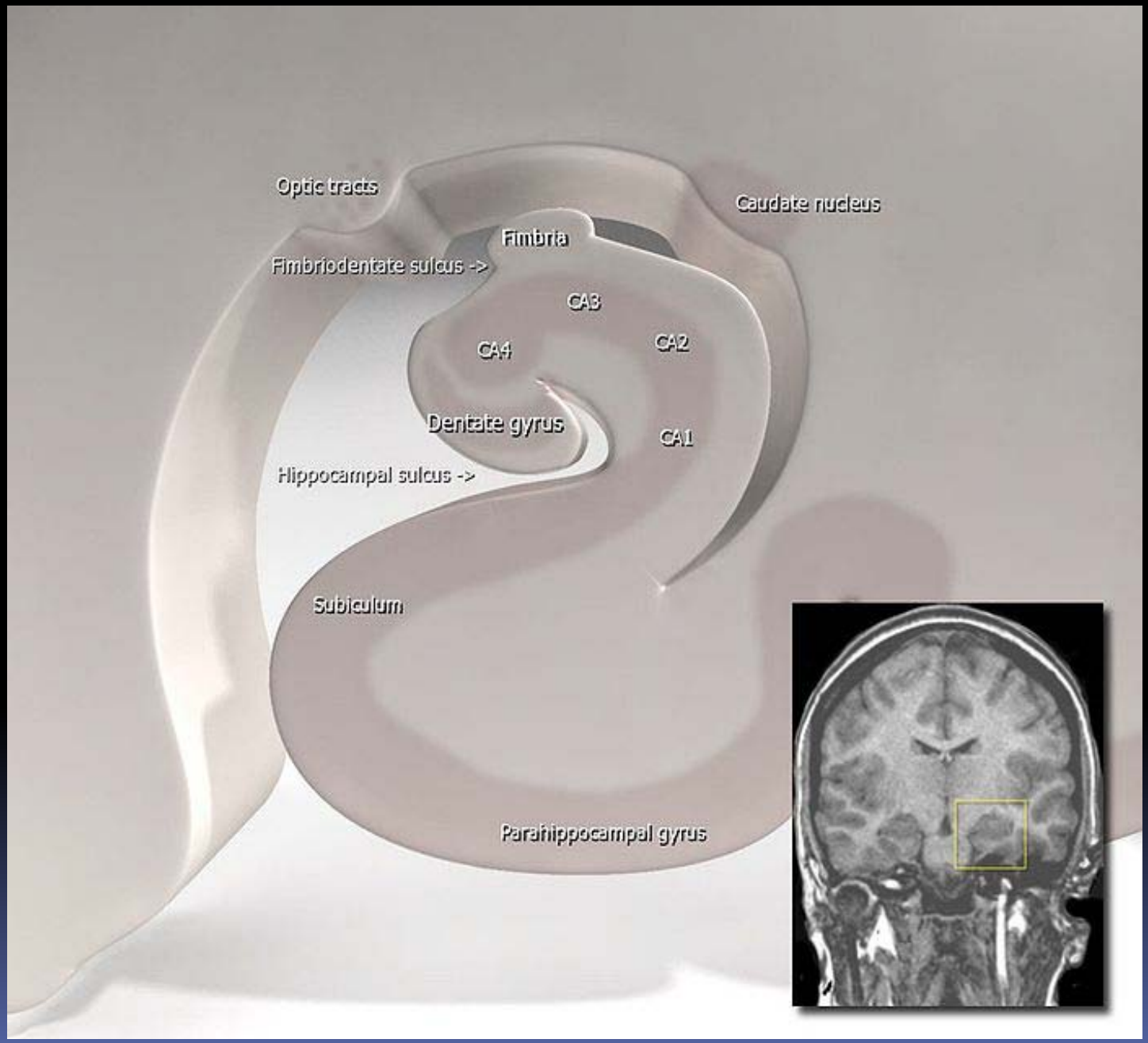


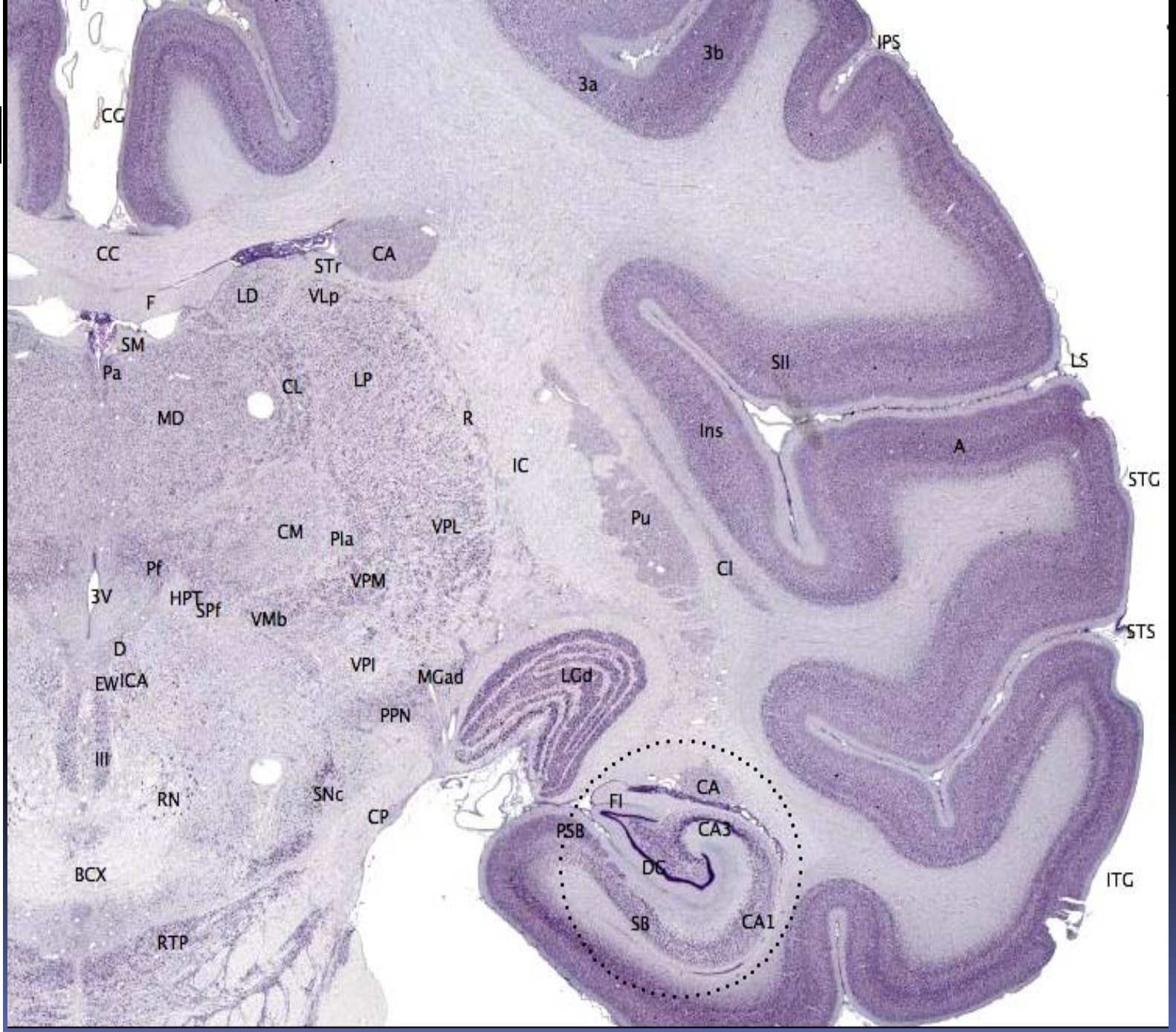
- Puberty is accompanied by a sex-specific induction of GnRH receptor gene expression
- GnRH receptors have been demonstrated in non-reproductive regions, in the hippocampus (CA1 to CA3), the frontal cortex and the dentate gyrus
- GnRH I is widely recognised as the central regulator of the reproductive system
- GnRH II is thought to have a variety of extra-pituitary functions
- We suggest a direct neuromodulatory effect of GnRH on behaviour and cognition

Endocrinology, Ojeda, 2005

Domain I Transsynaptic inhibitoric components – GABAnerigic and opiatergic neurons
Domain II Excitatory subset - glutamatergic and kisspeptin producing neurons
Domain III Astroglia and ependymogial cells




Optic tracts
Caudate nucleus
Fimbria
Fimbriodentate sulcus ->
CA3
CA4
CA2
Dentate gyrus
CA1
Hippocampal sulcus ->
Subiculum
Parahippocampal gyrus


3b
IPS
3a
CG
CC
CA
STr
F
LD
VLp
SM
Pa
CL
LP
MD
R
SII
LS
Ins
A
IC
STG
Pu
CM
Pla
VPL
Pf
VPM
Cl
3V
HPT
SPf
VMb
STS
D
VPl
MGad
LGd
EW
ICA
PPN
III
RN
SNc
CP
CA
Fl
CA3
PSB
DG
BCX
ITG
SB
CA1
RTP

Recognition memory task – our animals will help to understand sex-differences and in the long run gender identity better

- *Non-spatial factors including odor identity and whether the stimulus was a match or a non-match with a previously presented stimulus*

Similar to humans

in which single hippocampal neurons were recorded while human participants navigated through a computer-generated virtual town

- Project 1: Normal ageing and predispositions for pathological cognitive development

- Investigating sex-specific effects of GnRH blockage on hippocampus and other regions

  transgenic rodents
  genetic and genomic methods
  multilevel imaging
  electron microscopy
  in vivo multiphoton imaging

- Identifying possible correlations between sex-specific cognitive changes and the cellular results

- **Project 2:**
  Sex-specific GnRHR blocking effects on cognition in long-time treated young humans

- **Project 3:**
  F-18 protein labeling

- **Project 4:**
- Pathological ageing - Alzheimer Dementia

- **Project 5:**
- EEG-signatures of sex-specific cognitive impairment and training