Præcisionsmedicin for hjernesygdomme: Perspektiver for depression

Domus Medica 26 Oktober 2018

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Mental Health Services, Copenhagen
• Brain disorder example: Major Depressive Disorder
• Predictors of SSRI antidepressant treatment responses?
• Sex-steroid hormone transitions insights from pharmacological modelling
• Gene expression and epigenetic profiles as a biomarker for estrogen sensitivity?
• Seasonal affective disorder (winter depression)
• Perspectives for personalized prevention and treatment
Major depressive disorder

Major depressive disorder is an enormous public health problem

By 2030 expected to cause the highest ranking disability and burden of disease (*WHO global burden of disease*)

30-50% of patients with depression do not respond successfully to SSRIs

After 3 months response rates are 30% (*Voegelli et al. 2017*)

→ Optimize treatment

→ Relevant stratification needed to identify subgroups with distinct etiology or pathophysiology and treatment needs
Major depressive disorder DSM-V

A (at least 5 symptoms for 14 days, including 1 or 2)

1. Depressed mood most of the day, almost every day
2. Markedly diminished interest or pleasure in activities.
3. Significant weight loss or gain.
4. Inability to sleep or oversleeping.
5. Psychomotor agitation or retardation.
6. Fatigue or loss of energy.
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional).
8. Diminished ability to think or concentrate, or indecisiveness.
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation.

B. Symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
Problem:
It is not known which depressed patients would benefit from which treatment strategy

Objective: Predict the outcome of a pharmacological intervention

Intervention: SSRI (escitalopram 5-20 mg per day)

Planned study population:
100 depressed patients (Hamilton 17 item score >17)
Imaging 5-HT4 - a marker for brain serotonin tonus change over 3 weeks fluoxetine

[11C-SB207145 PET – effects of 3 weeks SSRI]

Baseline vs follow-up beta difference – less binding at follow-up with 3 weeks SSRI

Haahr et al 2014
Serotonin tone increases with increased risk-load for depression – compensatory mechanism?

[11C]SB207145 binding potentials

# of MDD-relatives

0 → 1 → 2

Enriched PET population, n=57
(21 women) 26 at high familial risk

Madsen et al 2014
Predictor tools – deep phenotyping

Serotonin signalling: 5-HT4 receptor PET imaging

Brain network signatures: Network recruitment in emotion and reward processing: probed fMRI paradigms. Functional connectivity: resting state fMRI EEG-based measures

Brain structure: T1 and T2 MRI based

HPA-axis dynamics: Cortisol awakening response

Blood biomarkers: Candidate genes, gene transcripts, epigenetic modifications, inflammatory markers

Non-affective and affective cognition: Neuropsychological test battery. EMOTICOM

Coping strategies and early life stress: Personality, early life stress, parental bonding quality

Clinical effect sensors: Clinical follow-up 1, 2, 3, 4, 8 and 12 weeks. Psychometrics (HamD17, BDI-II).
Twice as many women as men develop depressive episodes; hormonal contributions?

**Female life cycle of estrogen**

![Life Cycle of the Ovarian Hormone--Estrogen](image)

- Menopausal transition triggers depressive episodes
  - *Freeman 2006, 2013*

Adapted from Speroff and Fritz, 2005

Dea S. Stenbæk, cand.psych., phd-student. NRU, Copenhagen University Hospital, Rigshospitalet
Postpartum depression prevalence 13% (first 3 months),

In primiparous mothers risk for hospital admission is increased for 3 months, but not for fathers. Risk peaks day 10-19 post partum.

Table 1. Risk of First-Time Hospital Admission for Any Mental Disorder 0 to 12 Months

<table>
<thead>
<tr>
<th>Time Since Birth of First Live-Born Child</th>
<th>No. of Cases</th>
<th>Rate per 1000 Person-Years</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy†</td>
<td>337</td>
<td>0.70</td>
<td>0.53 (0.40-0.70)</td>
</tr>
<tr>
<td>0-9 d</td>
<td>79</td>
<td>4.66</td>
<td>3.60 (2.57-5.02)</td>
</tr>
<tr>
<td>10-19 d</td>
<td>160</td>
<td>9.45</td>
<td>7.31 (5.44-9.81)</td>
</tr>
<tr>
<td>20-29 d</td>
<td>48</td>
<td>2.84</td>
<td>2.20 (1.51-3.21)</td>
</tr>
<tr>
<td>1 mo</td>
<td>145</td>
<td>2.87</td>
<td>2.22 (1.65-3.00)</td>
</tr>
<tr>
<td>2 mo</td>
<td>112</td>
<td>2.22</td>
<td>1.73 (1.27-2.36)</td>
</tr>
<tr>
<td>3 mo</td>
<td>108</td>
<td>2.15</td>
<td>1.68 (1.23-2.30)</td>
</tr>
<tr>
<td>4 mo</td>
<td>71</td>
<td>1.42</td>
<td>1.11 (0.79-1.57)</td>
</tr>
<tr>
<td>5 mo</td>
<td>58</td>
<td>1.16</td>
<td>0.91 (0.64-1.31)</td>
</tr>
<tr>
<td>6 mo</td>
<td>74</td>
<td>1.49</td>
<td>1.17 (0.84-1.65)</td>
</tr>
<tr>
<td>7 mo</td>
<td>75</td>
<td>1.51</td>
<td>1.20 (0.85-1.68)</td>
</tr>
<tr>
<td>8 mo</td>
<td>65</td>
<td>1.32</td>
<td>1.04 (0.74-1.48)</td>
</tr>
<tr>
<td>9 mo</td>
<td>65</td>
<td>1.32</td>
<td>1.05 (0.74-1.49)</td>
</tr>
</tbody>
</table>

Munk-Olsen 2006, JAMA
Insights from sex-hormone manipulation risk model for depression; the brain architecture of risk

Risk model for depressive symptoms
Link to: Estradiol change

Disengagement in positive experiences
Disengagement of Hippocampus

Directly imply estradiol linked mechanisms as triggers of depressive symptoms
Highlight the immediate postpartum

Frokjaer, Biological Psychiatry 2015
Henningsson, Translational Psychiatry 2015
Macoveanu, Neuropsychopharmacology 2016
Stenbæk, Psychoneuroendocrinology 2016
Fisher, Neuropsychopharmacology 2017
Biomarker potential for risk-stratification by estrogen sensitivity?

Gene expression levels of 116 transcripts from 3rd trimester predicting postpartum depression

- Over-representation of estrogen receptor 1 transcription factor binding sites
- Enrichment of genes involved in estrogen signaling pathway
- Over-representation of estrogen-responsive transcripts

Mehta et al 2014, Psychological Medicine 2014
Estradiol and estriol plasma levels equal between postpartum depression cases and controls

Mehta D et al, Psychological Medicine, 2014
PPD biomarkers overlap with sex-hormone manipulation induced profiles

- gene-expression (19%, p-value = 0.02)
- DNA methylation (49%, p-value = $1.6 \times 10^{-5}$).

PPD biomarkers gene expression coupled to

- Delta estradiol:
  Baseline to follow-up, transcription/methylation (49%, 66%)
- Delta depression symptoms:
  Baseline to follow-up, transcription/methylation (28%, 66%)
- Delta serotonin transporter binding
  Baseline to follow-up, transcription/methylation (14%, 45%)

Our biomarker set identify (a subgroup of) estrogen sensitive women who show depressive responses to sex steroid manipulation

Mehta, Binder, Frokjaer 2018, British Journal Psychiatry (in press)
Window of opportunity for protecting mental health during perinatal hormonal transition?

Directly imply estradiol linked mechanisms as triggers of depressive symptoms
Highlight the immediate postpartum
Translation to clinical population – women at high risk for perinatal depression

**Study population:** 80 pregnant women with prior history of perinatal depression

- **Early pregnancy**
  - Screening
- **Late pregnancy**
  - Inclusion
  - Randomization
- **Day 2 pp**
  - Estradiol
  - Placebo
- **3 weeks pp**
- **8 weeks pp**
  - Last face to face visit

**Study aims**
- Illuminate targetable risk and disease mechanisms
- Test novel preventive strategy
- Evaluate candidate set of biomarkers for sensitivity to estradiol fluctuations
  - Pave the way for targeted protection of mother and infant mental health
Perimenopausal transition

Figure 2. Rate of Clinically Significant Depressive Symptoms by Treatment, Adjusting For Baseline Center for Epidemiological Studies–Depression Scale (CES-D) Score and Mean Change in Vasomotor Symptom Bother

N=172
12 months intervention
0.1mg/d estradiol
Oral progesterone every 3 m
Monthly follow-up

Effect most pronounced in early perimenopausal women

a P < .05.
TE+IMP indicates transdermal estradiol plus intermittent micronized progesterone.
Season, and mood – role of serotonin?
Adaptation to season
Season and serotonin – human brains

Genotype X season interaction

Kalbitzer et al. 2010
Lack of compensation -> winter blues?

McMahon, Frokjaer et al. Brain 2016
Provide a rationale for stratification of Major Depressive Episodes

Sertotonin brain architecture?

Sensitivity to season

High Neuroticism

HPA-axis dysfunction

Early life stress

Hormonal sensitivity

Gene-expression
Why am I excited?

- Define a set of (bio)markers predictive of response to SSRI, including serotonin dysfunction
- Employ serotonin tuning as a tool to monitor effect of prevention or treatment including non-pharmacological?
- Point to opportunity genes for response to bright light therapy?
- Biomarker tool to stratify and identify estrogen sensitive women, may translate to other hormonal transitions?
- Inform testing of a stratified approach to treatment choice or preventive strategies in high-risk groups
- Fight stigma, strengthen compliance
- Advance the etiological understanding of MDD disease mechanisms – pave the way for a stratified classification of MDD?
- Support novel personalized and targeted treatments beyond optimizing use of existing
Key collaborators and funding

Sapere Aude

Anja Pinborg, Professor, DMSc
Reproductive medicine, Copenhagen, DK

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Zachary Kaminsky, Baltimore, USA

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Study participants

Funding sources

Disclosures: None

Registration
CVK-protocol-ID: H-2-2010-108
Menopausal transition and schizophrenia on-set

Häfner et al 1993
Sex hormone fluctuations as a risk model

Work from epidemiology to neurobiology and ask: How does risk work?

Pharmacological intervention study in healthy women to characterize brain signatures of sex hormone fluctuations.
Serotonergic projections in the brain

- Appetite
- Sleep
- Mood
- Anxiety
- Aggression
- Impulsivity
- Stress regulation
- Libido

Diagram showing serotonergic projections to various brain regions:

- Striatum
- Thalamus
- Hypothalamus
- Amygdala
- Olfactory and entorhinal cortices
- Hippocampus
- Neocortex

Nuclei labeled:

- Nucleus linearis
- Dorsal raphe nucleus
- Medial raphe nucleus
- Nucleus raphe pontis
- Nucleus raphe magnus
- Nucleus raphe pallidus
- Cerebellar cortex
- Nucleus raphe obscuris

To spinal cord
Raphe nuclei – core of the serotonin system

Serotonin transporter PET-image

[11C]DASB PET visualizes raphé nuclei and projection areas

No anatomical correlate on MRI
Sex hormones and serotonin

- Serotonergic neurons are targets for estradiol and progesterone

- Hormonal replacement leads to changes in serotonin synthesis, degradation, and receptor levels
  
  \begin{itemize}
  \end{itemize}

- Estrogen has neuroprotective and antiinflammatory properties?
  
  \begin{itemize}
  \item \textit{Bethea}2009, \textit{Bethea}2011
  \end{itemize}
Brain connectivity: Default mode network

A. Autobiographical Memory
B. Envisioning the Future
C. Theory of Mind
D. Moral Decision Making

The Brain in Neutral
When you switch off, a distinctive network of brain areas not involved in focused attention bursts into action:
- Default network
- Areas involved in focused visual attention
Serotonergic modulation of spontaneous brain activity? – serotonin sensitivity in key hubs of DMN

Serotonin receptor 2A

Serotonin receptor 1A

Raphe seed FC map

[\textsuperscript{18F}]Altanserin-PET
Adams et al. 2004

[\textsuperscript{11C}]WAY-PET
Hahn et al. 2011

[\textsuperscript{11C}]DASB-PET informed
Beliveau, Frokjaer et al 2015
Model: GnRHa intervention to induce an ovarian hormone fluctuation

Intervention with Gonadotrophin-releasing-hormone agonist (GnRHa) or placebo

Goserelin 3.6 mg implant

Ovarian hormone response

<table>
<thead>
<tr>
<th>0</th>
<th>3-4</th>
<th>8-12</th>
<th>30 days</th>
</tr>
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<tbody>
<tr>
<td></td>
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</tbody>
</table>

HPG-axis

Hypothalamus

GnRH

Pituitary

LH / FSH

Inhibin

Activin

Sex Steroids

Gonad
Study design - timing

Ovarian hormone response to GnRHa

Baseline
CD 6.6±2.1

Intervention
CD 22.7±2.7

Follow-up
16.2±2.6 days

N=63

GnRHa
N=31

Placebo
N=30

N=61
Hypotheses

Relative to placebo:

• Sex hormone fluctuation (GnRHa) provokes depressive symptoms (1)

The emergence of depressive symptoms is coupled to:

• Estradiol changes (2)
• and/or changes in serotonergic signaling (3)
• changes in resting state network activity from baseline (4)
• reward processing (5)
Pituitary desensitization: LH decreased from baseline to follow-up in the GnRHa group only (p=0.0001)
Results – hormone effects of intervention

Estradiol GnRHa group

P < 0.0001
P < 0.01

Estradiol Concentration

Baseline | Intervention | Stimulation | Follow-up
Role of Serotonin Transporter Changes in Depressive Responses to Sex-Steroid Hormone Manipulation: A Positron Emission Tomography Study

Vibe Gedsoe Frokjaer, Anja Pinborg, Klaus Kähler Holst, Agnete Overgaard, Susanne Henningsson, Maria Heede, Elisabeth Clare Larsen, Peter Steen Jensen, Mikael Agn, Anna Pors Nielsen, Dea Siggaard Stenbæk, Sophie da Cunha-Bang, Szabolcs Lehel, Hartwig Roman Siebner, Jens Damsgaard Mikkelsen, Claus Svarer, and Gitte Moos Knudsen

Frokjaer et al, 2015 Biol Psy
GnRHa appears to induce depressive symptoms via estradiol and affects serotonin signaling

- Sex hormone fluctuation (GnRHa) provokes depressive symptoms

The emergence of depressive symptoms is coupled to:
- the magnitude of decrease in estradiol from baseline
- and/or changes in serotonergic signaling

Frokjaer et al, 2015 Biol Psy
Functional brain connectivity at rest

Seed based connectivity maps, N=60 baseline

Anterior cingulate  Amygdala  Hippocampus  Posterior cingulate (DMN)

Fisher, Frokjaer et al. 2017
FC-map responses to sex steroid manipulation and depressive symptoms

Points to overengagement of amygdala and disengagement of hippocampus related rs activity?

Fisher, Frokjaer et al. (NPP 2017)
Brain engagement in reward and GnRHa
GnRHa blunts brain responses to reward

Changes from baseline, GnRHa (n=26)

Macoveanu, Frokjaer et al. Neuropsychopharmacology 2015
Interpretations

- Sex-hormone manipulation (GnRHa), provoked development of subclinical depressive symptoms in (some) healthy women.

- Depressive reactions were linked to both increased cortical serotonin transporter binding from baseline, and estradiol decrease.

- Depressive reactions were linked to an over-involvement of amygdala and a disengagement of hippocampus when mind-wandering. Default mode network was unaffected.

- In contrast, when exposed to reward stimuli amygdala disengages in response to GnRHa.
Gene expression levels of 116 transcripts from 3rd trimester predicting postpartum depression

Over-representation of estrogen receptor 1 transcription factor binding sites

Enrichment of genes involved in estrogen signaling pathway*

Over-representation of estrogen-responsive transcripts

Mehta et al 2014, Psychological Medicine 2014
Aims

Bridge?

• Does the PPD biomarkers identify women who show a depressive response to GnRHa

Dyvia Mehta and Elisabeth Binder
Gene expression and DNA methylation in GnRHa cohort

Genome-wide gene expression and DNA methylation

N = 60
N = 60
N = 38
N = 38
N = 57
N = 55

Genome-wide gene expression

CD 6.6±2.1

Intervention
CD 22.7±2.7
Follow-up 1
~ 3-4 days

Follow-up 2
16.2±2.6 days

GnRHa
N=31

Placebo
N=30

N=63

N=61

Genome-wide gene expression and DNA methylation

Genome-wide gene expression
PPD biomarkers overlap with GnRHa induced profiles
- gene-expression (19%, p-value = 0.02)
- DNA methylation (49%, p-value = $1.6 \times 10^{-5}$).

PPD biomarkers gene expression coupled to
- **Delta estradiol**: Baseline to follow-up, transcription/methylation (49%, 66%)
- **Delta depression symptoms**: Baseline to follow-up, transcription/methylation (28%, 66%)
- **Delta serotonin transporter binding**: Baseline to follow-up, transcription/methylation (14%, 45%)

Our PND biomarker set identify (a subgroup of) estrogen sensitive women who show depressive responses to sex steroid manipulation

Mehta, Binder, Frokjaer 2018, British Journal Psychiatry (in press)
Perspectives

- Sex-hormone manipulation provides insights to risk mechanisms for depression
- Ideally, may guide future preventive strategies in high-risk groups
- Biomarker tool to stratify and identify estrogen sensitive women?
- Fight stigma
- May extend to other hormonal transitions and high risk groups?
- Future studies inform how exogenous exposure relate to brain architecture and mental health? Timing, critical windows.
Interpretations

- Sex-hormone manipulation (GnRHa), provoked development of subclinical depressive symptoms in (some) healthy women.

- Depressive reactions were linked to both increased cortical serotonin transporter binding from baseline, and estradiol decrease.

- Rat data support a sustained up-regulation of serotonin transporters, not in synchrony with postsynaptic receptor patterns of change – transiently compromises serotonin signaling?

- Depressive reactions were linked to an over-involvement of amygdala and a disengagement of hippocampus when mind-wandering. Default mode network was unaffected.

- In contrast, when exposed to reward stimuli amygdala disengages in response to GnRHa.
<table>
<thead>
<tr>
<th>Subcategories of Hamilton score</th>
<th>Change (Mean ± SEM)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Depressive mood (Items 1,2,3,7,14)</td>
<td>0.516 ± 0.245</td>
<td>0.0435*</td>
</tr>
<tr>
<td>2) Sleep (Items 4,5,6)</td>
<td>0.677 ± 0.357</td>
<td>0.0677</td>
</tr>
<tr>
<td>3) Anxiety (Items 10,11,15)</td>
<td>0.387 ± 0.195</td>
<td>0.0563</td>
</tr>
<tr>
<td>4) Somatic symptoms (Items 12,13)</td>
<td>0.419 ± 0.137</td>
<td>0.0047**</td>
</tr>
<tr>
<td>5) Others (items 8,9,16,17)</td>
<td>0.065 ± 0.092</td>
<td>0.4885</td>
</tr>
</tbody>
</table>

Two women approached the level of mild depression – remitted at 30 days follow-up
GnRHa and PPD 116 biomarkers gene expression

Genes significant for group status x time point

- Baseline to stimulation phase (follow-up 1): 22/116 transcripts (19% significant overlap, p-value = 0.02)
- 10 of these (45%) carried over to the suppression phase (baseline to follow-up 2)

= PPD biomarkers overlapped with GnRHa induced gene expression
GnRHa and PPD 116 biomarkers DNA methylation

Genes significant for group status x time point
Baseline to suppression phase (follow-up 2): 48/98 testable biomarker genes transcripts (49% shows sign change, $P$-value = $1.6 \times 10^{-5}$ more likely exp by chance)

= PPD biomarkers overlapped with GnRHa induced methylation
PPD 116 biomarkers – association with depressive symptoms, estradiol fluctuation, 5HTT

- Baseline to follow-up transcription/methylation ~ Delta estradiol (49%; 66%)
- Baseline to follow-up transcription/methylation ~ Delta depression (28%, 66%)
- Baseline to follow-up transcription/methylation ~ Delta serotonin transporter binding (14%, 45%)

= PPD biomarkers gene expression coupled to changes from baseline in estradiol, depressive symptoms, and serotonin transporter binding
Does estradiol affect the male brain?

Positive correlation between endogenous plasma estradiol levels and cortical 5-HT$_{2A}$ receptor binding in healthy men, no independent effect of testosterone, N=72.

Frokjaer et al. 2010
Towards a novel preventive strategy for perinatal depression – the brain architecture of risk

Risk model for depressive symptoms

Link to: Estradiol change

Decrease log2(Estradiol) from baseline

Hamilton change from baseline

Serotonin transporter

Disengagement in positive experiences

Disengagement of Hippocampus

Directly imply estradiol linked mechanisms as triggers of depressive symptoms

Highlight the immediate postpartum

Frokjaer, Biological Psychiatry 2015
Henningsson, Translational Psychiatry 2015
Macoveanu, Neuropsychopharmacology 2016
Stenbæk, Psychoneuroendocrinology 2016
Fisher, Neuropsychopharmacology 2017
Estradiol decrease and depressive symptoms (hypothesis 2)

Association between estradiol and Hamilton score changes from baseline within the GnRHa group (N=30).

Frokjaer 2015 Biol Psy
Serotonergic signalling coupled to depressive reactions provoked by GnRHa (hypothesis 3)

Model: Group X “delta-SERTBPnd” effect on “delta-Hamilton-score”

Results:
Slope difference: p=0.003
Within GnRHa: p=0.01
Within placebo: p=0.08

<table>
<thead>
<tr>
<th>Region</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neocortex</td>
<td>0.003</td>
</tr>
<tr>
<td>Prefrontal</td>
<td>0.03</td>
</tr>
<tr>
<td>Pallidostriatum</td>
<td>0.21</td>
</tr>
<tr>
<td>Midbrain</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Frokjaer 2015 Biol Psy
Combined effects of estradiol decline and serotonin transporter change from baseline on depressive symptoms

Within the GnRHa-group
Neocortical SERT change dichotomized.
SERT up: 11 (blue)
SERT down: 20 (black)
Slope difference: $p=0.02$

Combination of an increase in neocortical SERT-binding and large decrease in estradiol and is particularly adverse?
Baseline clinical profile
No differences between groups

<table>
<thead>
<tr>
<th></th>
<th>GnRHa (n)</th>
<th>Placebo (n)</th>
<th>GnRHa group</th>
<th>Placebo group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>n = 31</td>
<td>n = 30</td>
<td>23.3 ± 0.6</td>
<td>25.2 ± 1.08</td>
<td>0.13</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>n = 31</td>
<td>n = 30</td>
<td>23.20 ± 0.4</td>
<td>23.4 ± 0.7</td>
<td>0.86</td>
</tr>
<tr>
<td>Proportion of smokers in %</td>
<td>n = 31</td>
<td>n = 30</td>
<td>3.2</td>
<td>13.3</td>
<td>0.16</td>
</tr>
<tr>
<td>Alcohol (units/week)</td>
<td>n = 31</td>
<td>n = 29</td>
<td>10.0 ± 3.5</td>
<td>5.3 ± 0.7</td>
<td>0.21</td>
</tr>
<tr>
<td>Education scorea</td>
<td>n = 31</td>
<td>n = 29</td>
<td>11.9 ± 0.1</td>
<td>11.9 ± 0.76</td>
<td>0.84</td>
</tr>
<tr>
<td>Menarche (age in years)</td>
<td>n = 31</td>
<td>n = 30</td>
<td>13.3 ± 0.3</td>
<td>12.8 ± 0.2</td>
<td>0.15</td>
</tr>
<tr>
<td>Cycle length (days)b</td>
<td>n = 31</td>
<td>n = 30</td>
<td>29.5 ± 0.5</td>
<td>29.2 ± 0.7</td>
<td>0.79</td>
</tr>
<tr>
<td>Ovarian follicle count (right + left)</td>
<td>n = 31</td>
<td>n = 29</td>
<td>26.3 ± 1.9</td>
<td>27.4 ± 2.6</td>
<td>0.72</td>
</tr>
<tr>
<td>Cycle day at baselinec</td>
<td>n = 31</td>
<td>n = 30</td>
<td>6.7 ± 0.4</td>
<td>6.5 ± 0.4</td>
<td>0.66</td>
</tr>
<tr>
<td>PMSQ total scored</td>
<td>n = 31</td>
<td>n = 30</td>
<td>6.5 ± 0.8</td>
<td>7.4 ± 1.1</td>
<td>0.5</td>
</tr>
<tr>
<td>Hamilton score baselinee</td>
<td>n = 31</td>
<td>n = 30</td>
<td>1.2 ± 0.3</td>
<td>1.6 ± 0.4</td>
<td>0.34</td>
</tr>
<tr>
<td>Major depression inventory (MDI)</td>
<td>n = 31</td>
<td>n = 30</td>
<td>5.5 ± 0.6</td>
<td>5.8 ± 0.5</td>
<td>0.85</td>
</tr>
</tbody>
</table>

No difference between groups in baseline sex-hormones (estradiol, progesterone, FSH, LH and androgen status) and TSH.

**Stratification** on 5-HTTLPR genotype was perfect (10 LA/LA in each group)
GnRH-a provoked depressive symptoms relative to placebo (hypothesis 1)

Within GnRHa group: p=0.003
GnRHa blunts amygdala responses to reward

GnRHa, n= 26

Placebo, n= 29

Macoveanu, Frokjaer et al. Neuropsychopharmacology 2015
Does estradiol affect the male brain?

Positive correlation between endogenous plasma estradiol levels and cortical 5-HT$_{2A}$ receptor binding in healthy men, no independent effect of testosterone, $N=72$.

Frokjaer et al. 2010
Rapid estradiol driven structural brain changes?

Significant dynamics in hippocampal structure across the menstrual cycle with a potentially myelin-related process underlying the white matter change.

Within single subject longitudinal study 30 scans across cycle 32 years old female

Barth et al 2016, Scientific Reports
GnRHa induced depressive symptoms were coupled to increased amygdala and insula involvement in processing emotionally salient stimuli

Post GnRHa (n=30)

Henningsson, Frokjaer et al. Translation Psychiatry 2015
Insula and amygdala engagement in processing emotionally salient stimuli and associations with GnRHa induced depressive symptoms

Fear-neutral

Happy-neutral
Sex hormones and perinatal depression

- Women – increased risk during life phases of hormonal transitions such as perimenopause and peripartum

- Perinatal depression (PND) - a depressive episode with an onset in pregnancy or within four weeks following delivery

- PND coincides with dramatic changes in estradiol and progesterone - changes in hormone milieu may be a key factor

Motivated an intervention study to model risk mechanisms associated with sex steroid fluctuations
Fluctuation model (8 days perspective)

Ovarian hormone fluctuation

Prefrontal SERT

Prefrontal 5-HT$_{2A}$

Coupled to estradiol?

How far?

Counterbalancing?

? Other postsynaptic markers
? MAO-A responses
? Timing – synchrony
? Raphe nuclei
Conclusions

- A PND biomarker set identify (a subgroup of) women who show depressive responses to sex steroid manipulation
- Confirm a role of estrogen sensitivity in perinatal depression
- Highlights late pregnancy and the immediate postpartum period as critical windows of opportunity for treatment
- Tool to identify estrogen sensitive women and guide preventive strategies and treatment to high-risk individuals
- Validate biomarker, which potentially generalize to depressive episodes triggered by hormonal transitions?
Provide a rationale for stratification

5-HT brain architecture?

Sensitivity to season

High Neuroticism

HPA-axis dysfunction

Early life stress

Hormonal sensitivity

Genes

- Sensitivity to season
- High Neuroticism
- HPA-axis dysfunction
- Early life stress
- Hormonal sensitivity
- Genes
Retrospect – Jean Martin Charcot - Hysteria

Une leçon clinique à la Salpêtrière(Salon, 1887) by A. Brouillet.
Shorvon S Brain 2007;130:3342-3348
L’arc de cercle
Catalepsie

Suggestion : Terreur

Attitude provoquée
Les attitudes passionnelles
Hysterogenic zones

Shorvon S Brain 2007;130:3342-3348
Ovary compressor

From Goetz (1987).
Retrospect– Charcot - Hysteria

Shorvon S Brain 2007;130:3342-3348
Expected outcomes

• Determine if serotonergic dysfunction predicts SSRI treatment response in MDD

• Determine if treatment induced 5-HT4r changes from baseline predicts long-term efficacy/relapse rate

• Identify relationships between serotonergic (dys)function and other affected domains (e.g. EEG, cognition)

• Define a set of (bio)markers predictive of response to SSRI

• Facilitate cross-validation in independent populations and datasets

• Inform future testing of a stratified approach to treatment choice

• Advance the etiological understanding of MDD disease mechanisms – pave the way for a stratified classification of MDD?