

Gene Expression of Regulators of Serotonin in Dorsal Raphe Neurons of Subjects Diagnosed with Depression

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Depression

- Depression is a chronic, recurring and potentially life-threatening illness that affects up to 20% of the population across the globe.
- Major depressive disorder affects approximately 15 million adults in US, or about 7 percent of the U.S. population age 18 and older in a given year.
- Depression - leading cause of disability in the U.S. for ages 15-44 and the 4th leading contributor to the global burden of disease in 2000.
- Depression - second largest killer after heart disease by 2020. (World Health Organization)
- 15% of depressed people will commit suicide.

Gender and Depression

Lifetime prevalence of depression in women is twice the rate of men.

Major depressive disorder (MDD) - 2nd leading cause of disease burden for women in the U.S.

Depressed women - greater frequency of symptoms: sleep disturbances, increased appetite and weight gain, psychomotor retardation, ruminations, feelings of worthlessness or guilt, suicide attempts.

Comorbidities frequently in depressed women include anxiety disorders (panic and phobic symptoms) and eating disorders.

Neuropharmacological evidence - Gender differences in treatment responses.

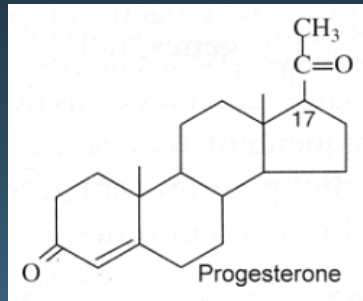
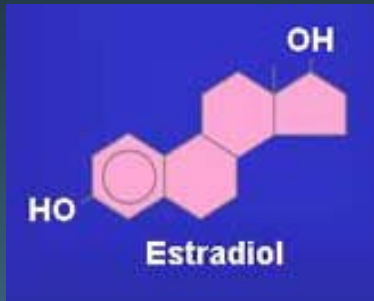
- women respond better to serotonin-selective reuptake inhibitors (SSRIs).



Biological mechanisms -?

Hormones, 5-HT,
Psychosocial /
other physiological
factors – Stress

Ovarian Hormones and Serotonin System

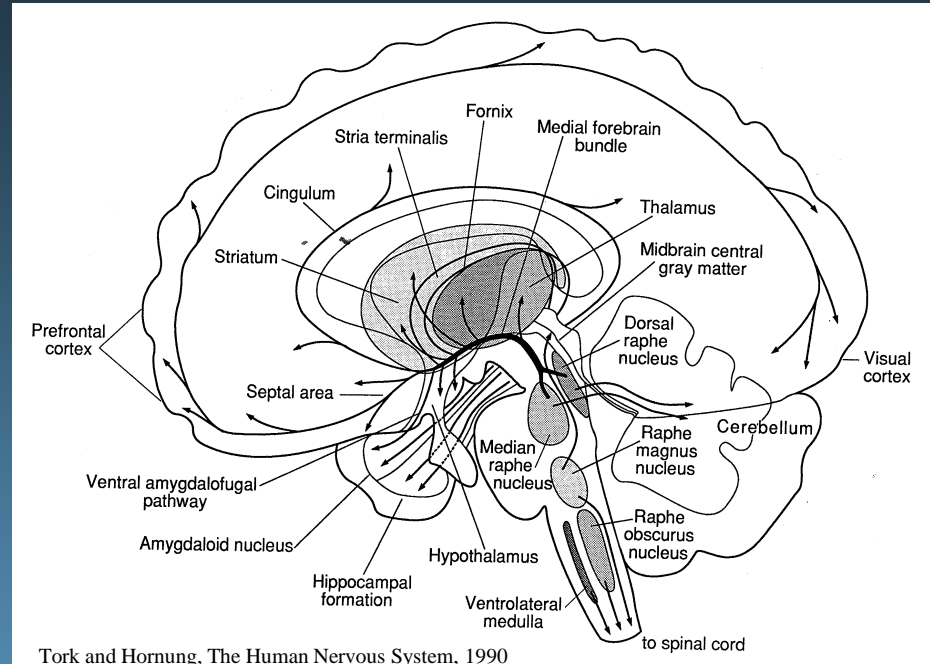


▶ profound effects on 5-HT system

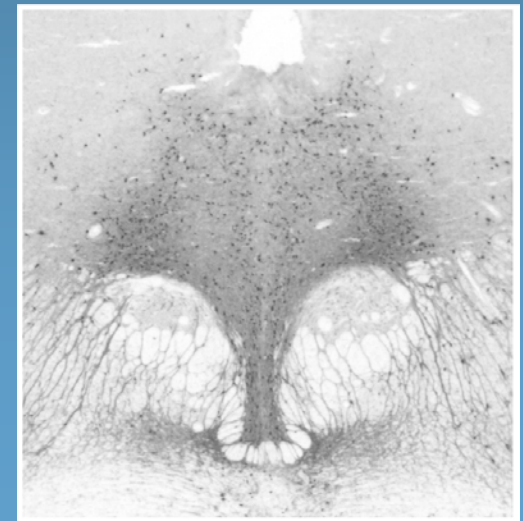
OVX monkeys receiving E + P -
increased TPH2 mRNA and protein,
decreased SERT mRNA
decreased 5-HT_{1A} receptor
sites and mRNA in the dorsal raphe

▶ HRT can augment the therapeutic responses of SSRIs in depressed women

SSRI-treated depressed women
receiving HRT have higher
remission rates.



Transverse section of human midbrain illustrating TPH-immunoreactive 5-HT neurons.



Significance/Rationale

Serotonin hypothesis of depression

Considerable evidence from clinical and postmortem studies support deficiency in 5-HT neurotransmission - underlying mechanisms yet to be defined.

Human postmortem research

Limitation: Majority of studies conducted in male subjects.

No systematic investigation into the biological mechanisms underlying the pathophysiology of depression in women.

Questions

- **Could the 5-HT system play a role in the pathophysiology of major depressive disorder (MDD) in women?**
- **Are there gender-specific changes in serotonin-related genes in the dorsal raphe of subjects with MDD?**

Postmortem Subjects

- **Matched Study Design**
 - **Gender**
 - **Age**
 - **Postmortem interval (PMI)**
 - **All subjects had negative toxicological screening for antidepressant drugs and other psychoactive substances.**
- **6 Female Subjects - Axis I diagnosis Major Depression**
- **6 Male subjects - Axis I diagnosis Major Depression**
- **6 Psychiatrically Normal Control Subjects for each gender group**

Group	Age of onset of Depression (yrs)	Duration of Illness (yrs)	Depressive Episode	Suicide
Female MDD	37	26	2-S, 4-M	2-S, 4-N
Male MDD	56	6	3-S, 3-M	4-S, 2-N

Experimental Methods

1

Tissue sectioning human midbrain samples.

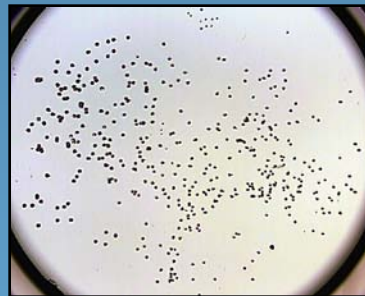
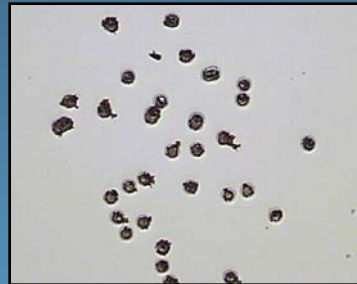
Rapid immunohistochemical staining for tryptophan hydroxylase.



TPH2-immunofluorescent 5-HT neurons in dorsal raphe

2

Laser-capture microdissection of TPH2-stained DR neurons.



Harvested 5-HT neurons from DR with LCM (~1500 neurons sampled/subject)

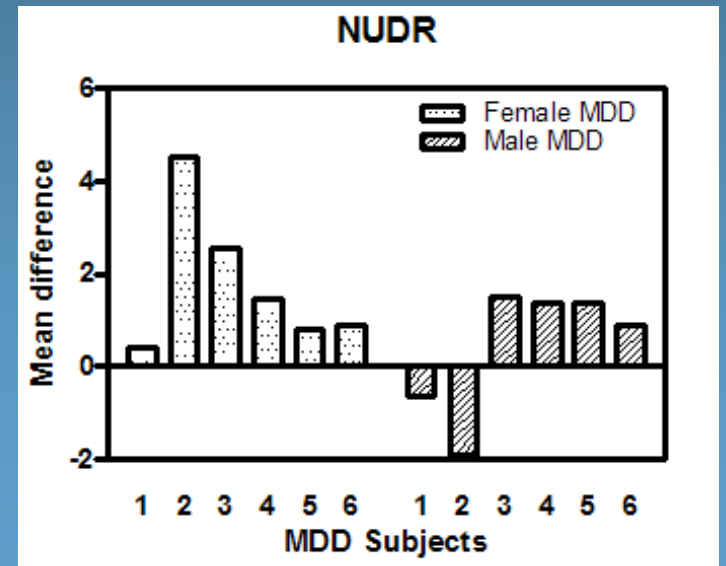
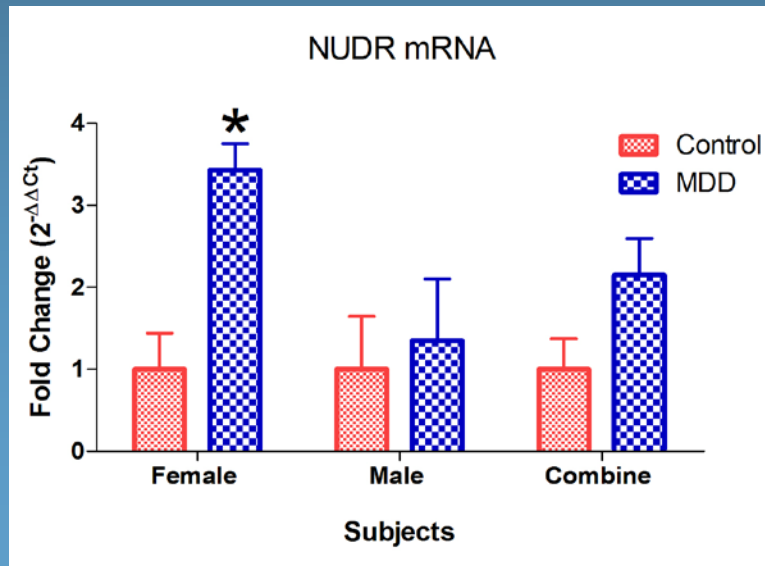
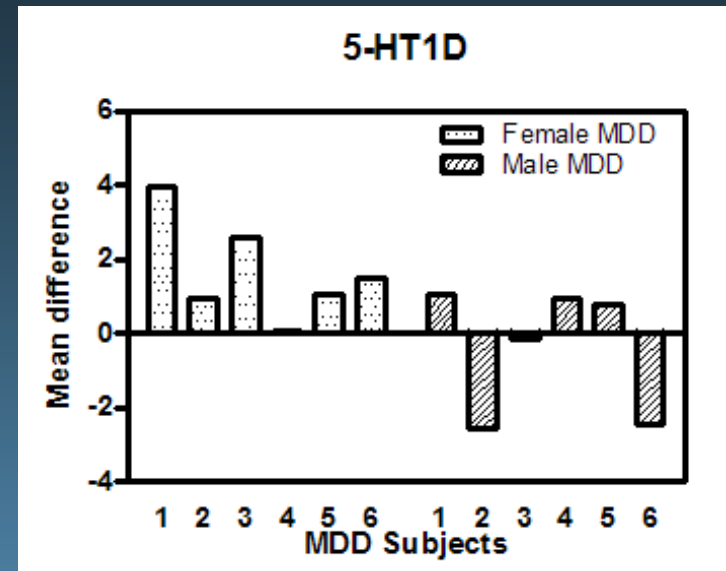
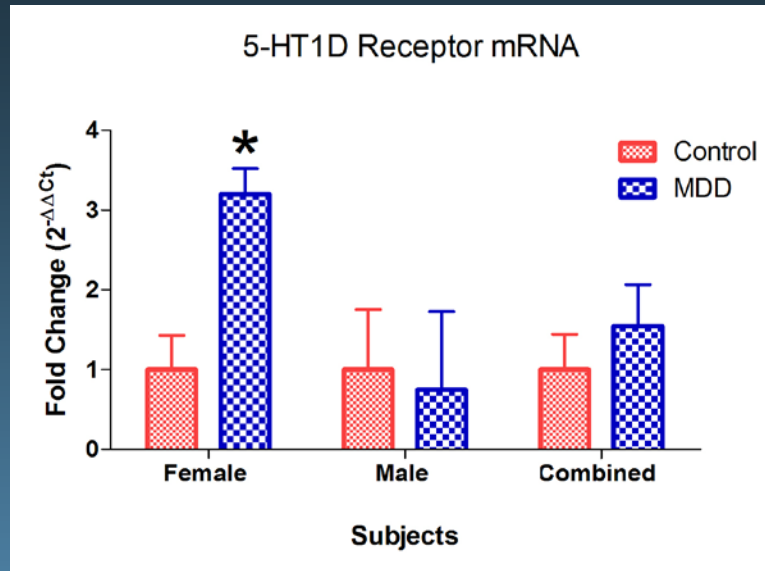
3

Real-time PCR for mRNA quantification.

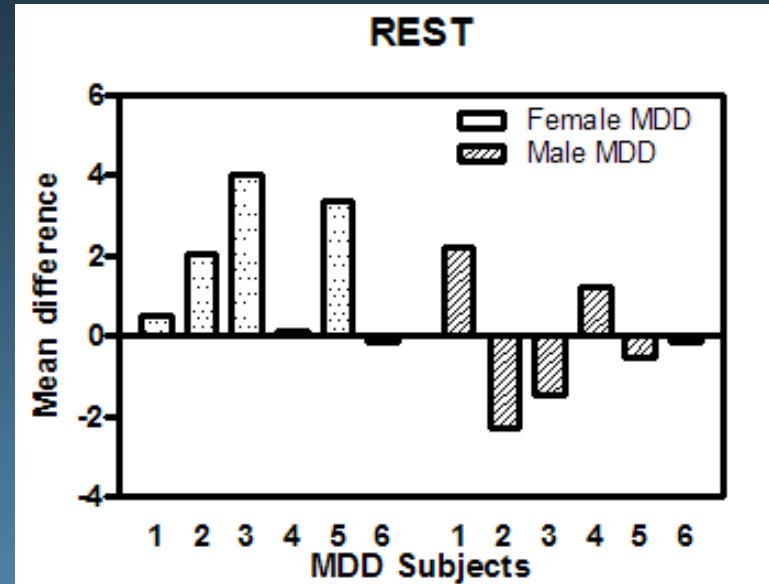
Transcripts measured:

- TPH1
- TPH2
- TPH2-Truncated isoform
- 5HT1A receptor
- 5HT1B receptor
- 5HT1D receptor
- SERT
- 5-HT1A transcription factors:
 - NUDR
 - FREUD-1
 - REST
- Estrogen receptor ER α , ER β
- Trk-B receptor
- Internal Controls
 - GAPDH
 - RNA Polymerase II

Results



Results



No significant changes:

TPH1
TPH2
TPH2-Truncated isoform
5HT1A receptor \uparrow ($P=0.06$, ♂)
5HT1B receptor \uparrow ($P=0.07$, ♀)
SERT
FREUD-1
Estrogen receptor $ER\alpha, ER\beta$
Trk-B receptor

Conclusions

- A gender-specific increase in 5-HT_{1D} receptor, NUDR and REST mRNA in dorsal raphe neurons of only women diagnosed with MDD. These results suggest that different biological mechanisms underlie the pathophysiology of major depression in women as compared to men.
- The increase in 5-HT_{1D} presynaptic receptor mRNA in depressed women suggests enhanced autoreceptor inhibition of serotonin neurons which may lead to reduced serotonin concentrations in the synapse.
- These differences are directing us to classify depression and its treatments not only on the basis of symptoms but also on the basis of gender.

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