SN EDUCATION PRESENTS

Libido Issues – DUTCH Testing
When Hormonal Bloodwork Doesn't Show the Bigger Picture

Dr Dean St Mart PhD

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Introduction

- Dr Dean St. Mart PhD.

- Formulator for Supplement Needs (www.supplementneeds.co.uk)
- Pharmacologist for Atlas Laboratories (AlphaGenix)
- Background in Drug Design and Pharmacology
- 1st Class Honours Degree in Chemistry and Pharmaceutical Chemistry
- PhD in Synthetic Organic Chemistry.

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Bloodwork

- Bloodwork takes a sample of blood – at a **specific snapshot in time**.

- It tells us nothing of cellular interactions other than **extrapolations based on molecular biology**.

Test	Result	Normal range	Units
HORMONAL HEALTH			
ESTRADIOL	139.0	41.4-159.0	pmol/l
FOLLICLE STIMULATING HORMONE	<0.3	1.5-12.4	U/l
FREE TESTOSTERONE	0.781	0.155-0.593	nmol/l
LUTEINISING HORMONE (LH)	<0.3	1.7-8.6	U/l
PROLACTIN	233	86-324	mIU/l
SHBG	15.20	18.30-54.10	nmol/l
TESTOSTERONE	27.400	8.640-29.000	nmol/l

- Normal TT:E2 ratio = 197:1

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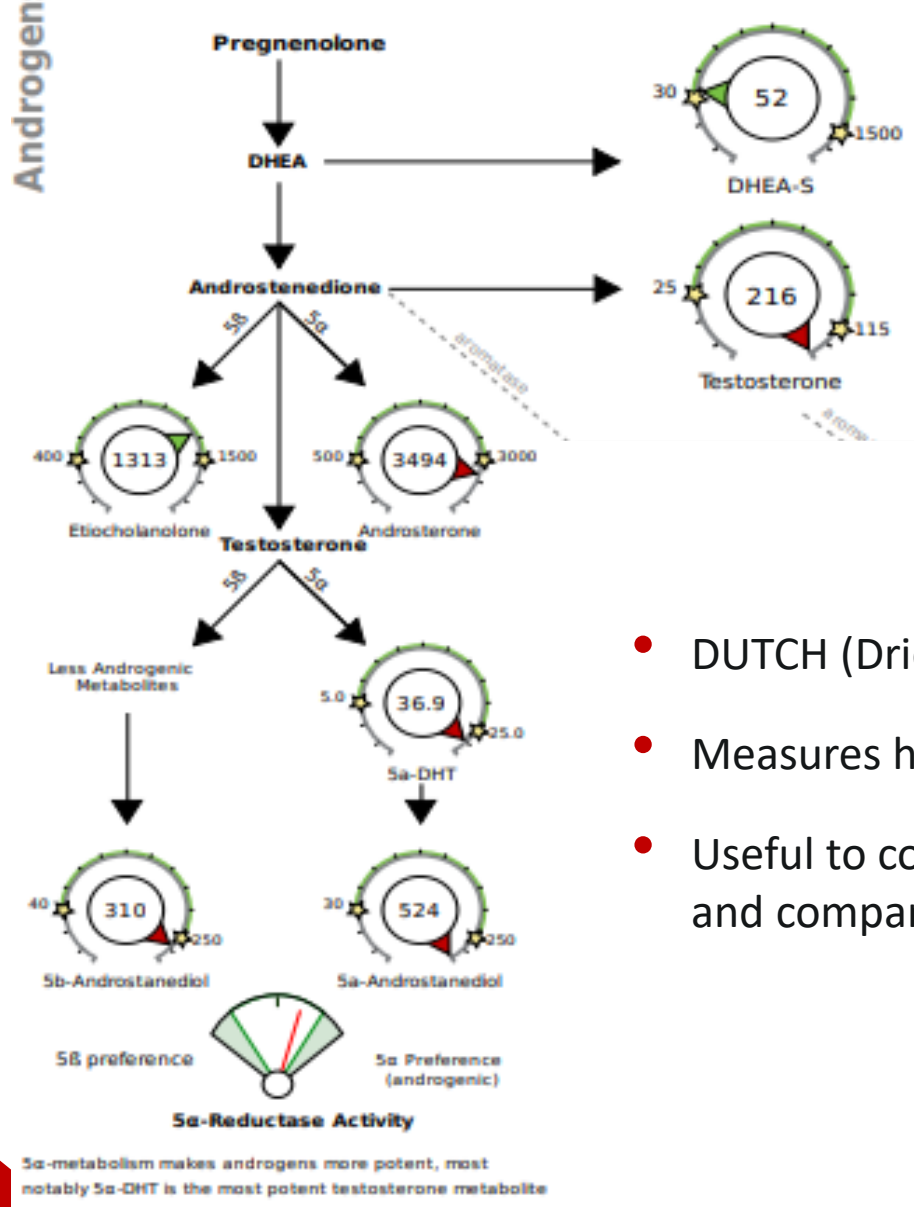
DUTCH (Dried Urine Test for Comprehensive Hormones)



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- DUTCH (Dried Urine Test for Comprehensive Hormones)
- Measures hormones and hormone metabolites (called conjugates)
- Useful to correlate levels of hormones in urine over a 24 hr period and compare to serum results.

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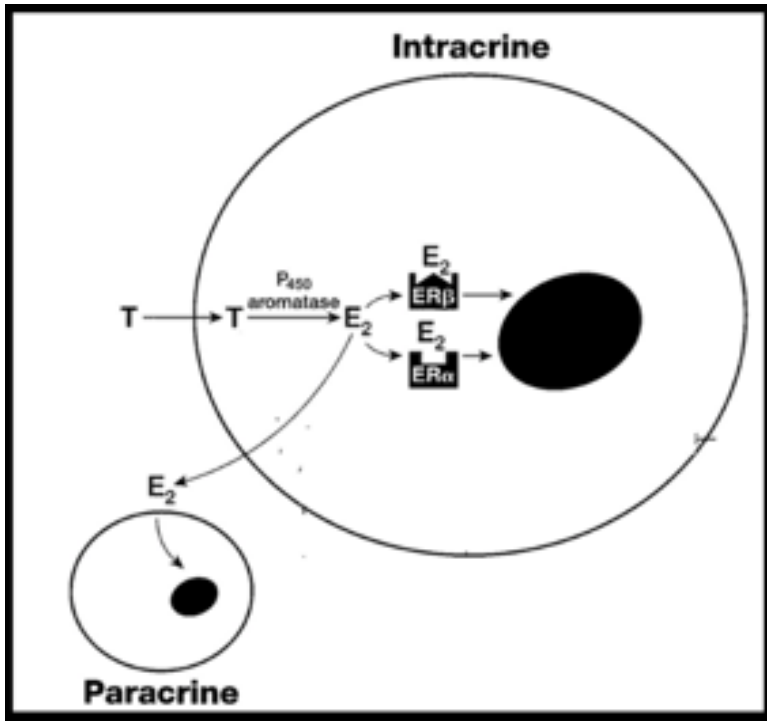
Estradiol in Serum ≠ Estradiol in Cells

Test	Result	Normal range	Units
HORMONAL HEALTH			
ESTRADIOL	139.0	41.4-159.0	pmol/l

- "Serum" Estradiol is normal….
- But…….There are physiological and psychological symptoms of elevated E2
- Based on the amount in the "serum blood", everything is "normal"…..
- Estradiol is made **Intracrine** (within cells) and can have Paracrine effects



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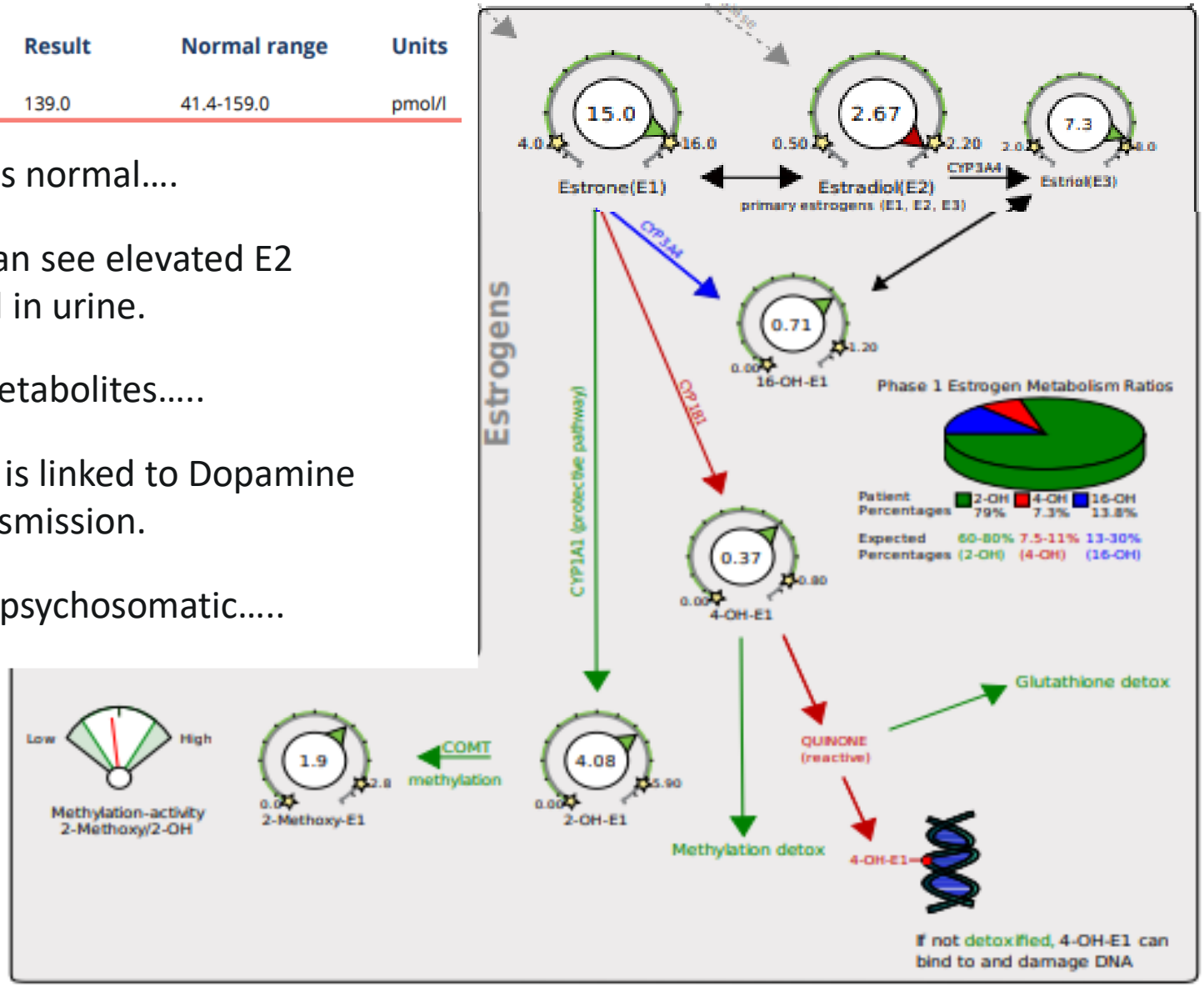
DUTCH for Estradiol Metabolism

Test	Result	Normal range	Units
HORMONAL HEALTH			
ESTRADIOL	139.0	41.4-159.0	pmol/l

- "Serum" Estradiol is normal….
- Using DUTCH we can see elevated E2 over a 24 hr period in urine.
- And elevated E1 metabolites…..
- We know Estradiol is linked to Dopamine and Serotonin transmission.
- Symptoms are not psychosomatic…..



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Estrogens and the Brain

- The effects of estrogens on cognition and mood have been well established.
- Estrogen receptors are densely populated in areas of human brain that control cognitive and emotional function.
- These include **subcortical** regions such as the **hippocampus (memory)** and **amygdala (emotion)** as well as a range of **cortical areas involved in higher order functioning**.
- Estrogens modulate the neurotransmitters responsible for cognitive and emotional processes.
- Its effects on mental state are thought to occur via an influence on the availability of these mood-relevant neurotransmitters in the synapse.

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Estrogens and Dopamine

- Evidence suggests the **regulation of D1 and D2 receptor densities** and functions by estrogens

- Estrogens **increase dopamine synthesis** in the **nucleus accumbens**.
  Cognitive processing of motivation, aversion, reward, and reinforcement learning
- **Decrease dopamine turnover** in the **nucleus accumbens**.
- Estrogens **prolong neurotransmissions by reducing dopamine transporters** in the nucleus accumbens

- **Induce presynaptic dopamine release** in the **striatum**.
  Voluntary motor control and neurons that signal social action that will result in own reward
- Estrogens **increase D2 receptor density** but **reduce dopamine receptor sensitivity** in the striatum.

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Estrogens and Dopamine

- There are **five types of dopamine receptors**, which include D1, D2, D3, D4, and D5.
- Each receptor has a different function and is found in different locations.
- The function of each dopamine receptor[4]:
  - D1: memory, attention, impulse control, regulation of renal function, locomotion
  - D2: locomotion, attention, sleep, memory, learning
  - D3: cognition, impulse control, attention, sleep
  - D4: cognition, memory, fear, impulse control, attention, sleep
  - D5: decision making, cognition, attention, renin secretion

https://www.ncbi.nlm.nih.gov/books/NBK538242/

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Estrogens and Serotonin

- **Upregulate the expression and activity of TPH** to increase 5HT biosynthesis.
- **Regulate 5HT receptors (5-hydroxytryptamine2) 5HT2A and 2C**, the receptors essential for learning / cognition. Areas of the brain concerned with the control of mood, mental state, cognition, emotion and behavior
- Regulate 5HT autoinhibition via the **5HT1A auto-receptor**, resulting in an antidepressant-like activity.
- Reduce the 5HT uptake to presynaptic cells and **prolong serotonergic neurotransmissions**.
- **Decrease 5HT metabolism** via degradation by monoamine oxidase inhibitors (MAO) after 5HT is taken up into the presynaptic neurons.

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Estrogens and Glutamate

- Estrogens also exert their effects on the **glutamatergic** neurotransmitter system, which facilitates most of our neurotransmissions in our brain and mediates our cognitive functions.

- Current reports suggest that estrogens affect **N-Methyl-D-aspartic acid (NMDA) glutamate receptors** and upregulate and increase their distributions.

- Neuroprotective effects of estrogen on cortical and hippocampal neurons against the effects of glutamate-mediated neurotoxicity.

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Estrogen Receptors

- Classic ERs are located in the nucleus and cytoplasm of the cell and belong to the nuclear receptor superfamily, members of which act as nuclear ligand-gated transcription factors,
  binding to estrogen response elements (EREs) within specific genes to alter their rate of transcription

- The two known isoforms, **ERα** and ERβ (also termed **NR3A1** and **NR3A2**)
  where NR3 has been adopted as nomenclature for steroid receptors
  are coded by separate genes and are located throughout the brain but have a **differential distribution**.

- **ERα mRNA** is widely distributed in many brain regions, including the hippocampus, hypothalamus, amygdala, and brainstem nuclei, and colocalizes with ERβ mRNA in many regions.

- **ERβ** has a more restricted distribution and is found in particular abundance in human hippocampus and selected hypothalamic nuclei, especially the supraoptic and paraventricular nuclei (PVN).

- The two forms of ER are structurally and functionally distinct,
  each **regulating unique sets of target genes** in a tissue- and cell type-specific manner.

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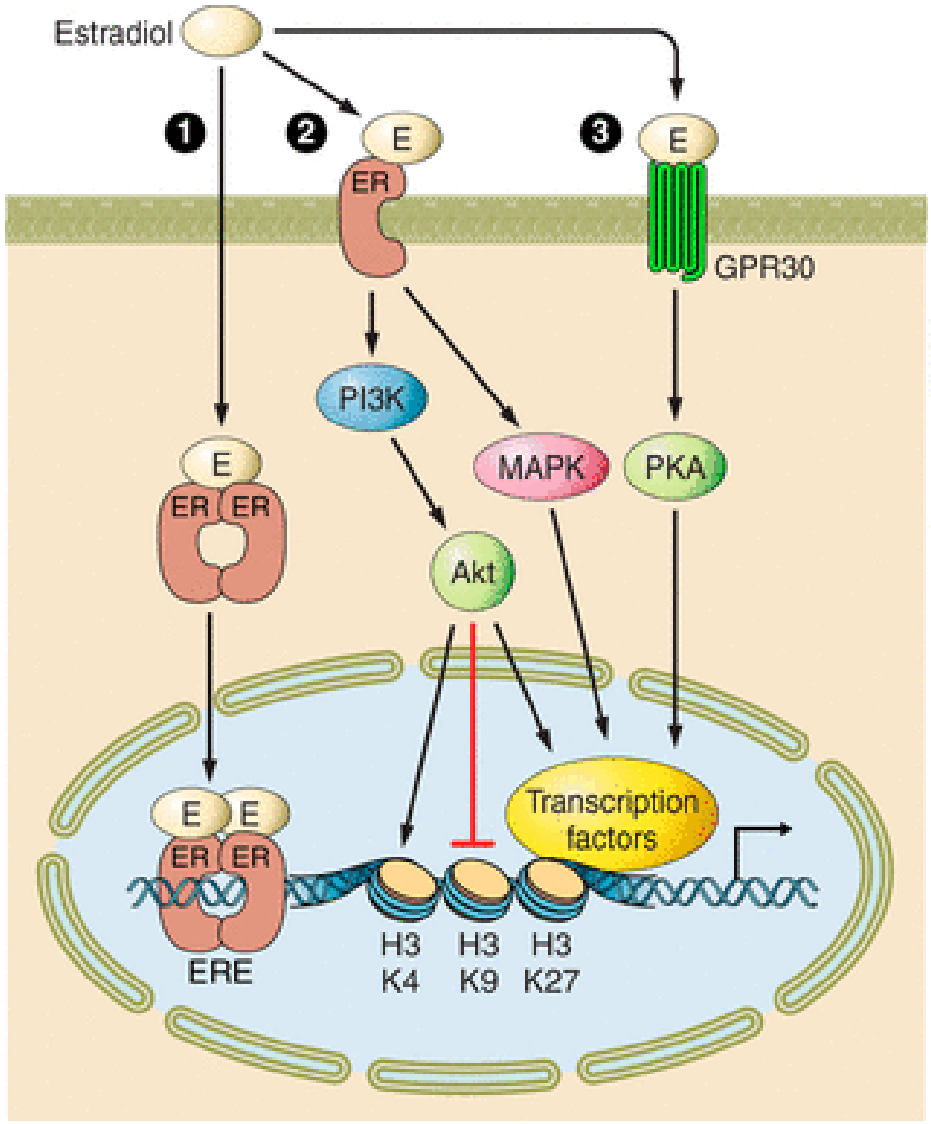
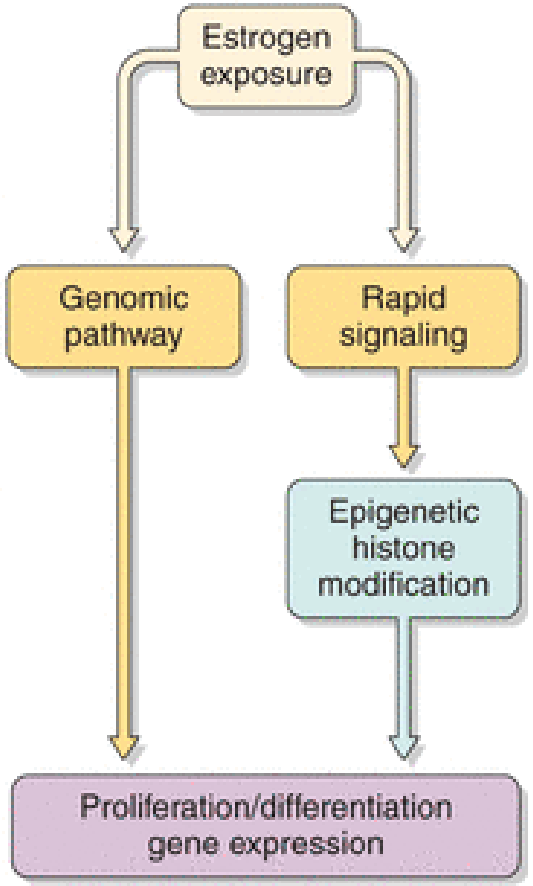
Estrogen Effects





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Estrogens and the Brain

- Aromatase enzyme, encoded by the **CYP19 gene**, are responsible for the **local synthesis of estrogens** from circulating androgens.

- Circulating testosterone therefore acts as a precursor for estrogens, which then act in a **paracrine fashion** in tissues **expressing aromatase in the periphery and the brain**.

- In the adult brain, the **highest levels of aromatase activity** are found in the **hypothalamus** of all species especially the **Preoptic Area** (POA) and **ventromedial nucleus** (VMN), where the enzyme is regulated by gonadal steroids and found at higher levels in males.

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Estrogens and the Brain

- Overall distribution patterns of ERα and ERβ in the brain provide some broad neuroanatomical clues for their involvement in specific brain functions.

- **Preoptic Area** (POA), especially the medial POA (mPOA), is the major site for **regulating male sexual behaviors**.
- This region has **2 to 3 times more dendritic spine synapses** in males compared with females, indicating **sex differences in the excitatory input.**

- The **serotonergic system of the dorsal raphe** is also an estrogen-sensitive major regulator of substantia nigra pars compacta (SNc) Dopamine neurons

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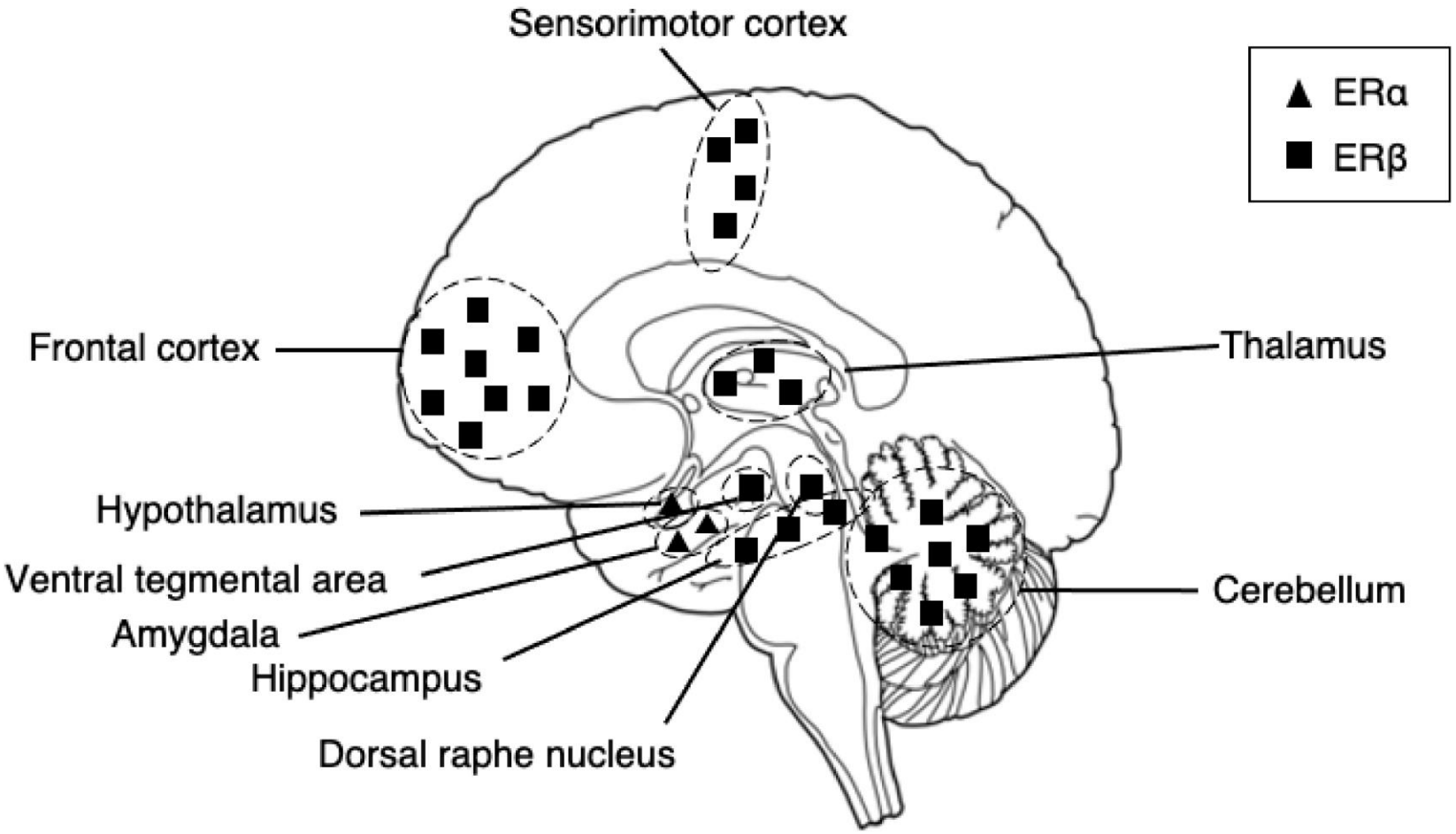
Estrogens and the Brain



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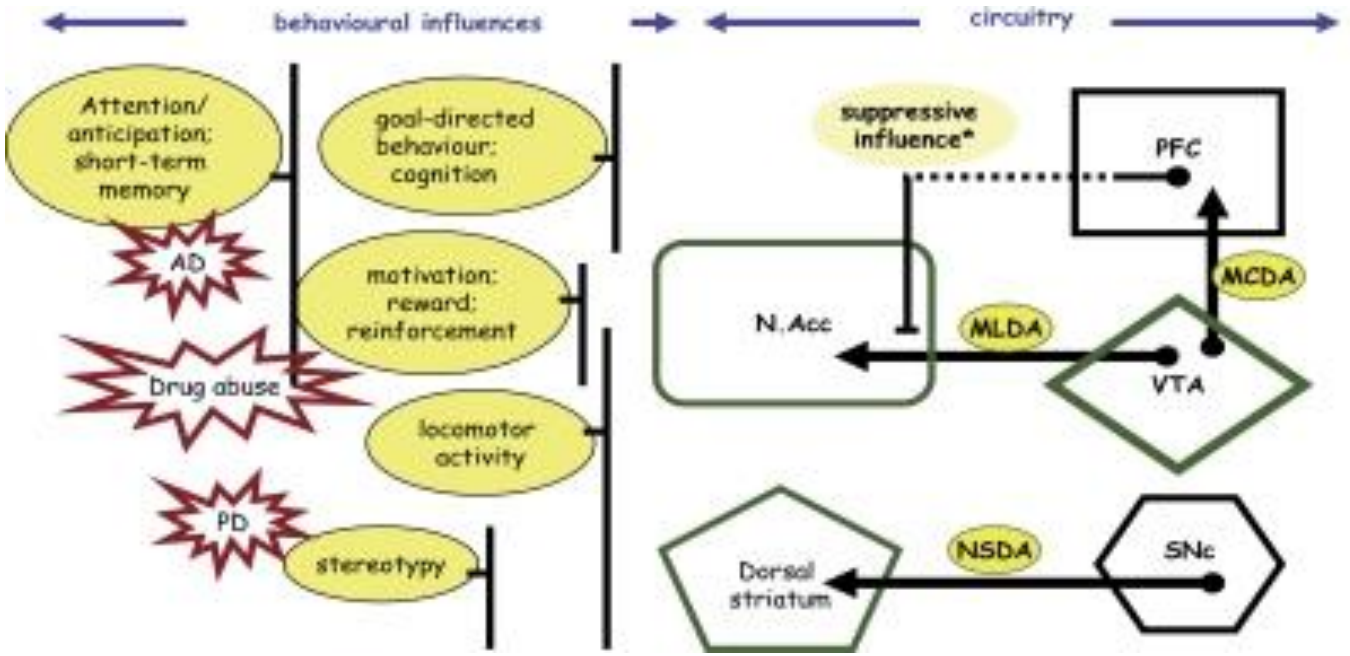
Midbrain Dopaminergic Pathways



Nigrostriatal dopaminergic (**NSDA** or mesostriatal) system regulates locomotor activity and is involved in stereotypical behaviors

Mesolimbic dopaminergic system (**MLDA**) influence on locomotor behavior and is involved primarily in regulating motivation, reward, and reinforcement.

Altered activity in the MLDA is associated with addictive behaviors and drug abuse.

Mesocortical dopaminergic system (**MCDA**) involved in higher cognitive functions

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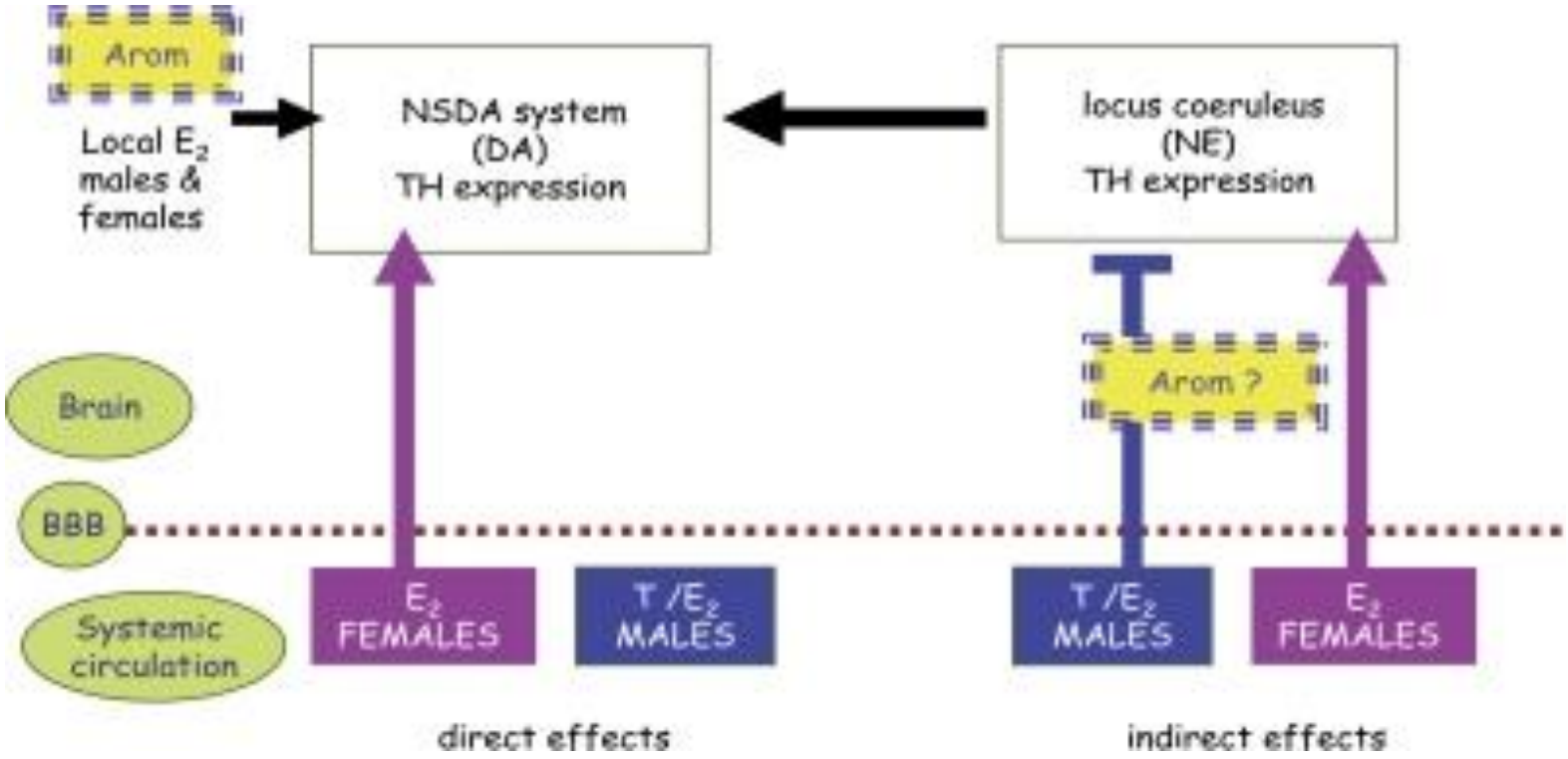
Nigrostriatal dopaminergic (NSDA) System



- Circulating estradiol (E2) up-regulates activity in the NSDA system in females but not males.
- Nigrostriatal dopaminergic (**NSDA** or mesostriatal) system regulates locomotor activity and is involved in stereotypical behaviors

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Estrogens and the Brain

- Knowing estrogens effects on the brain, we can look at the **neurotransmitter metabolite profile** to assess what effect is occurring to Dopamine levels in the brain.

- Main metabolite of Dopamine = **HVA (Homovanillic Acid)**

- Not possible to deduce from bloodwork what's happening neurotransmitter wise…..

- And hormones in bloodwork is what is present at that moment in time……
- In the serum of your blood…..
- Not what's inside your cells…..

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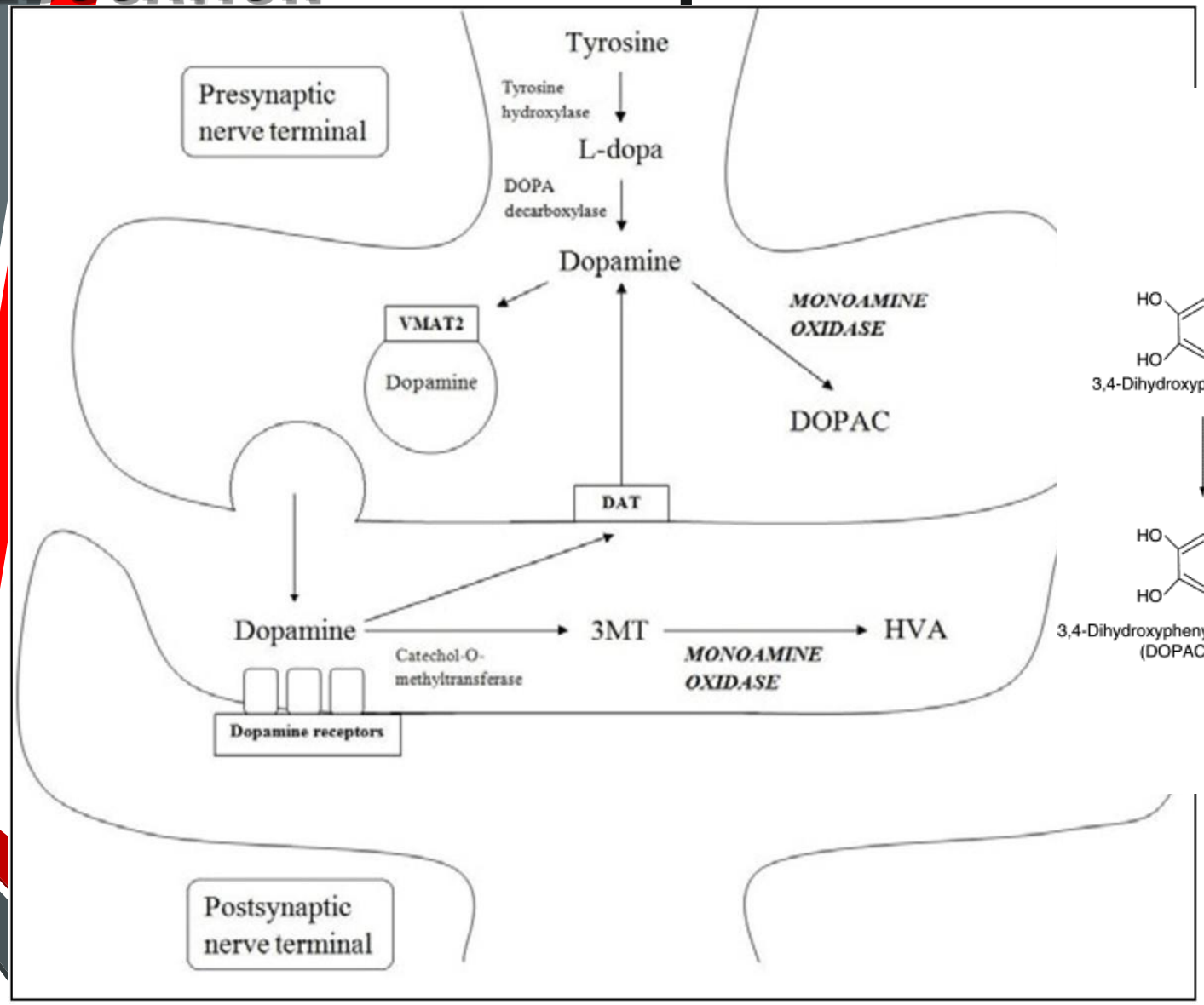
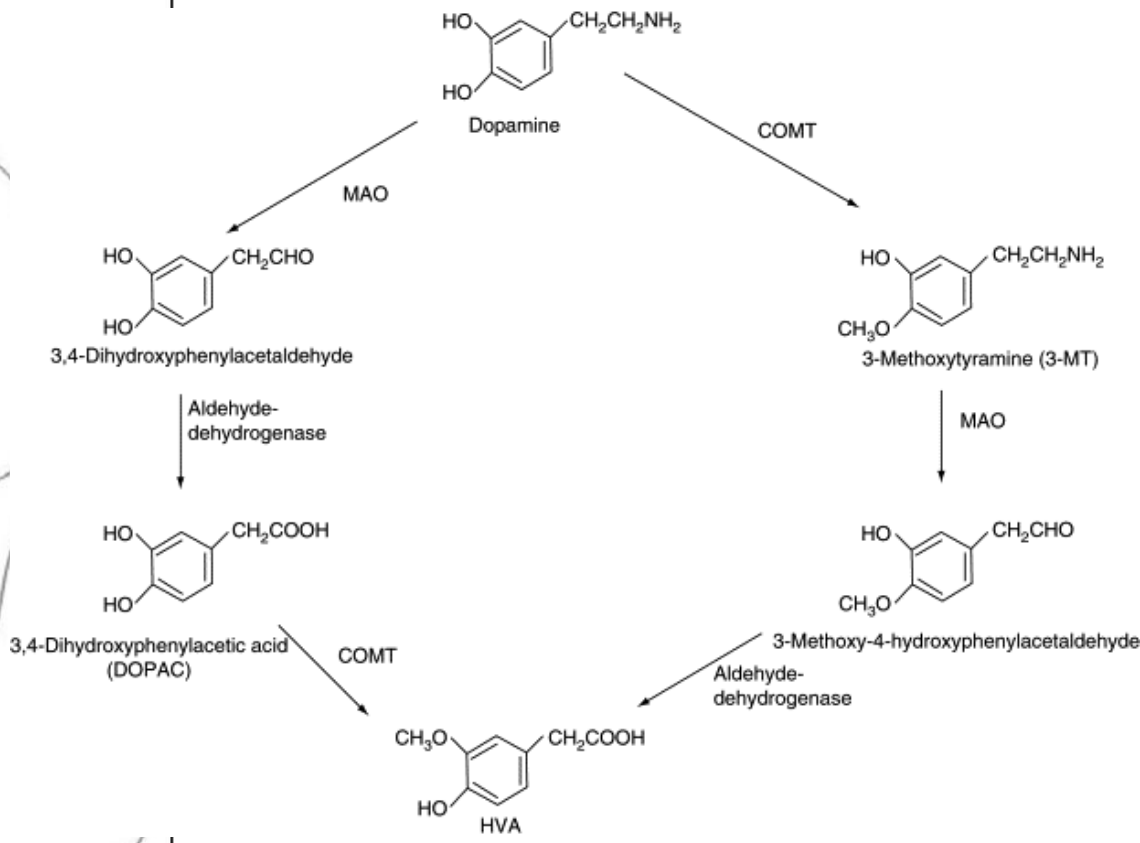
Dopamine Metabolism





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DUTCH - Organic Acid Testing

Category	Test		Result	Units	Normal Range
Nutritional Organic Acids					
Vitamin B12 Marker (may be deficient if high) - (Urine)					
	Methylmalonate (MMA)	Within range	1.9	ug/mg	0 - 3.5
Vitamin B6 Markers (may be deficient if high) - (Urine)					
	Xanthurenate	Within range	0.97	ug/mg	0.2 - 1.9
	Kynurenate	Within range	2.7	ug/mg	1 - 6.6
Glutathione Marker (may be deficient if low or high) - (Urine)					
	Pyroglutamate	Low end of range	39.2	ug/mg	38 - 83
Biotin Marker (may be deficient if high) - (Urine)					
	b-Hydroxyisovalerate	Within range	9.5	ug/mg	0 - 18

- Low Pyroglutamate = Low Glutathione -> required for E1 conjugation

Neuro-related Markers					
Dopamine Metabolite - (Urine)					
	Homovanillate (HVA)	Below range	3.4	ug/mg	4 - 16
Norepinephrine/Epinephrine Metabolite - (Urine)					
	Vanilmandelate (VMA)	Low end of range	2.6	ug/mg	2.5 - 7.5
Neuroinflammation Marker - (Urine)					
	Quinolinate	Within range	4.7	ug/mg	0 - 12.5

- Low HVA = Low Dopamine
- Low VMA = Low Norepinephrine (Made from Dopamine)

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Piecing it all together…..

- Even though TT:E2 ratio is normal – that snapshot in time is not showing the bigger picture….

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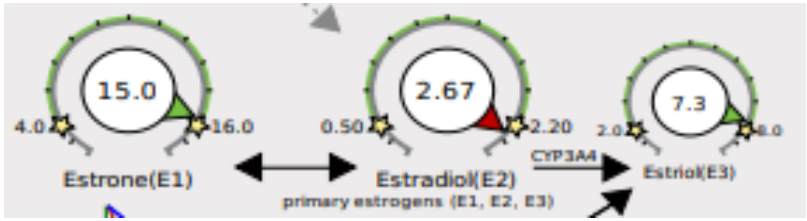

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- Libido is complex but Dopamine is vital for Sexual Excitation and Interest

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Hypothetical Strategy

- Using TRT at 125mg…..
- Already following a micro dose daily protocol.
- Not much scope to adjust the dose otherwise TT will fall…..

- **<u>Need to reduce E2:</u>**
  - Lowering Aromatisation rate -> Potential AI use or address environment factors (Bodyfat, Xenoestrogens)
  - Improve E1 metabolite clearance -> Support Methylation (COMT) and Glutathione (Phase 2 liver metabolism).

- Temptation would be to increase Dopamine…..
  - At risk of driving neuronal threshold too high…..

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