Neurobiology of Prader-Willi Syndrome:

Arriving at a Phenomenological Explanatory Model with Mechanistic Insights

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Disclosures

- Grants: FPWR
- Consultation: Soleno, Acadia, ConSynance
- Royalties: Neurobehavioral manifestations of Prader-Willi Syndrome (Cambridge)- images will be used in the presentation
- **Non-FDA indicated use of FDA approved medications is common in psychiatry and will be discussed in this presentation**

Objectives

- Understanding the genetic and neurobiological causes of behavioral abnormalities in Prader-Willi Syndrome
- Appreciating the central role of the hypothalamus and its connected brain structures in the behavioral, and cognitive manifestations of Prader-Willi Syndrome
- Discussing the challenges and limitations of current treatments for Prader-Willi Syndrome, and exploring potential new approaches
- Discuss a novel phenomenological explanatory model for abnormal response monitoring in PWS, based on the interplay between genetic, neural, and environmental factors

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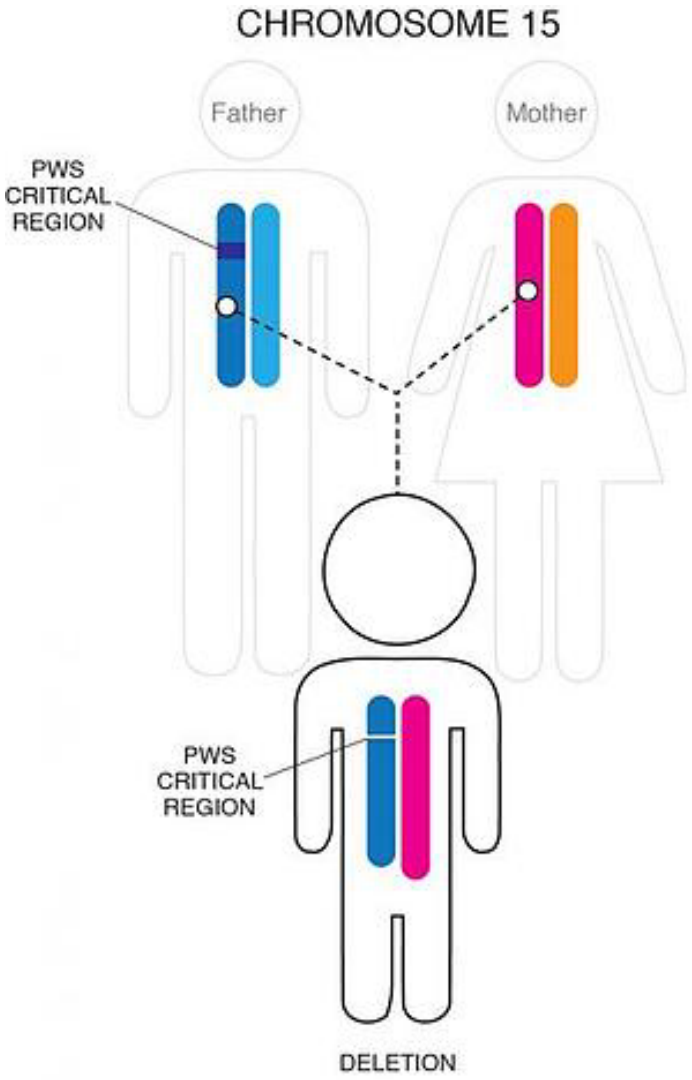
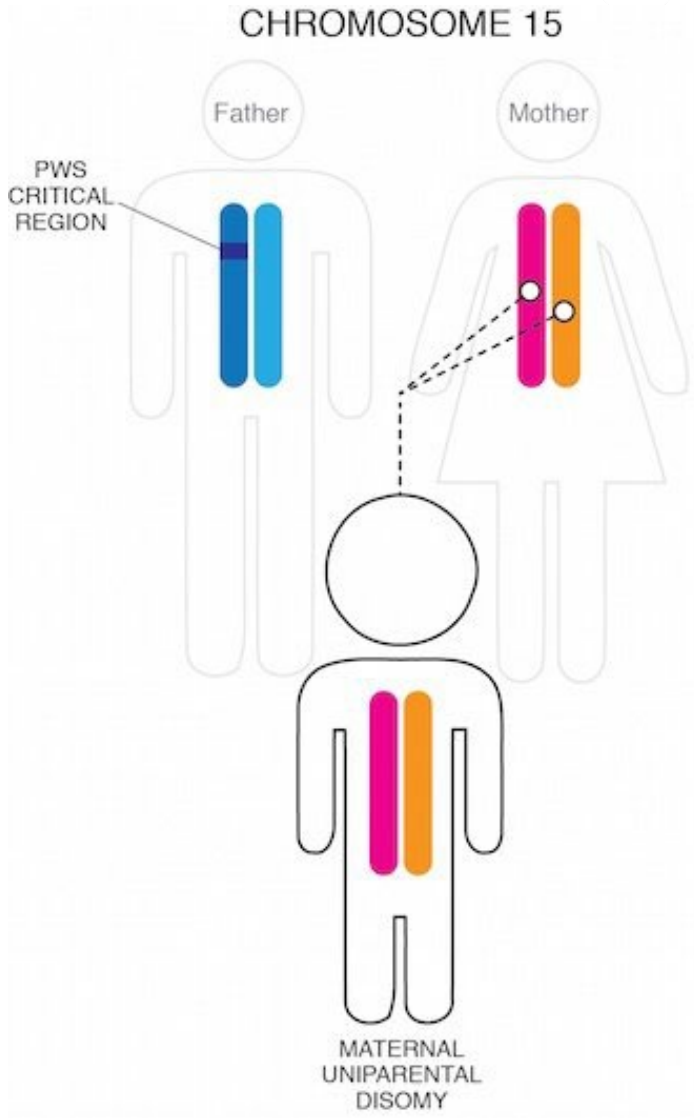
What Do Most Doctors Know About PWS

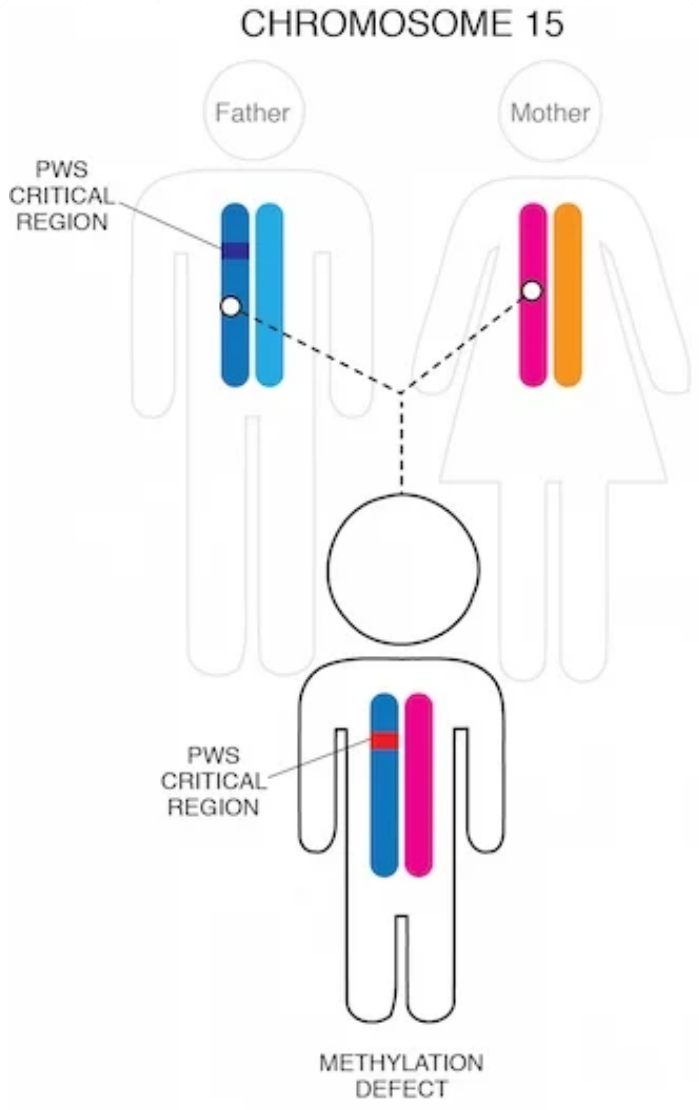
A 12-year-old male presents to the pediatric clinic, he is 4'2" inches tall with a weight of 151 lbs. On exam, he has small feet and hands. Parents report that he was "born hypotonic". Over the past three years he is described as having "insatiable hunger" to the point that he has been found to eat out of the garbage can when others aren't looking and is continually preoccupied with food. His parents describe that he has been getting more aggressive lately, especially when asked to stop eating. What is the most likely finding on genetic testing?

THE FULL PICTURE IS MORE COMPLEX

Genetics



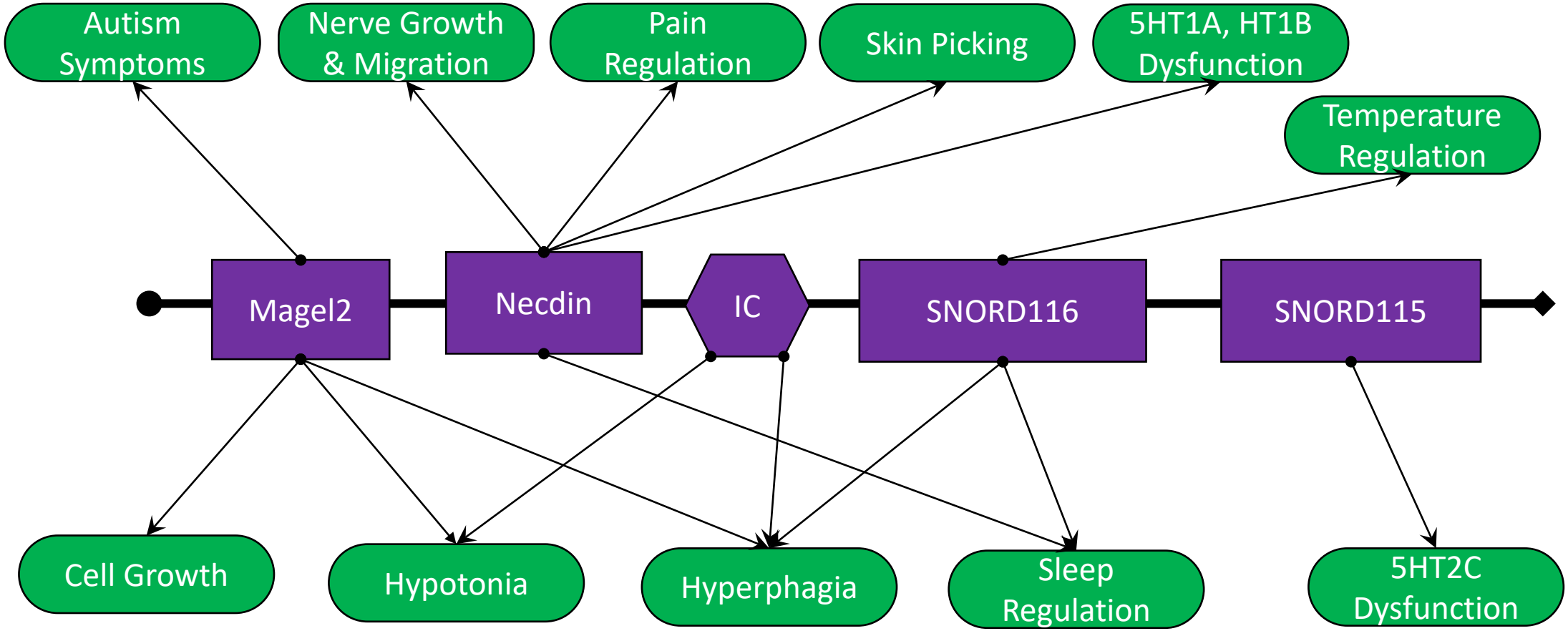




Source: FPWR

1:22000 to 25000 live births

Coding Regions of PWR Critical Region (15q11-13)



5HT1A: serotonin 1A receptor; 5HT1B: serotonin 1B receptor; IC: imprinting center. Genes and gene clusters affected in PWS: Magel2, Necdin, SNORD116, SNORD115.

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Neurobiology

- **Development of the Hypothalamus (2 gm culprit)**
- Nerve migration
- Neurotransmitter functioning
  - Release
  - Receptor

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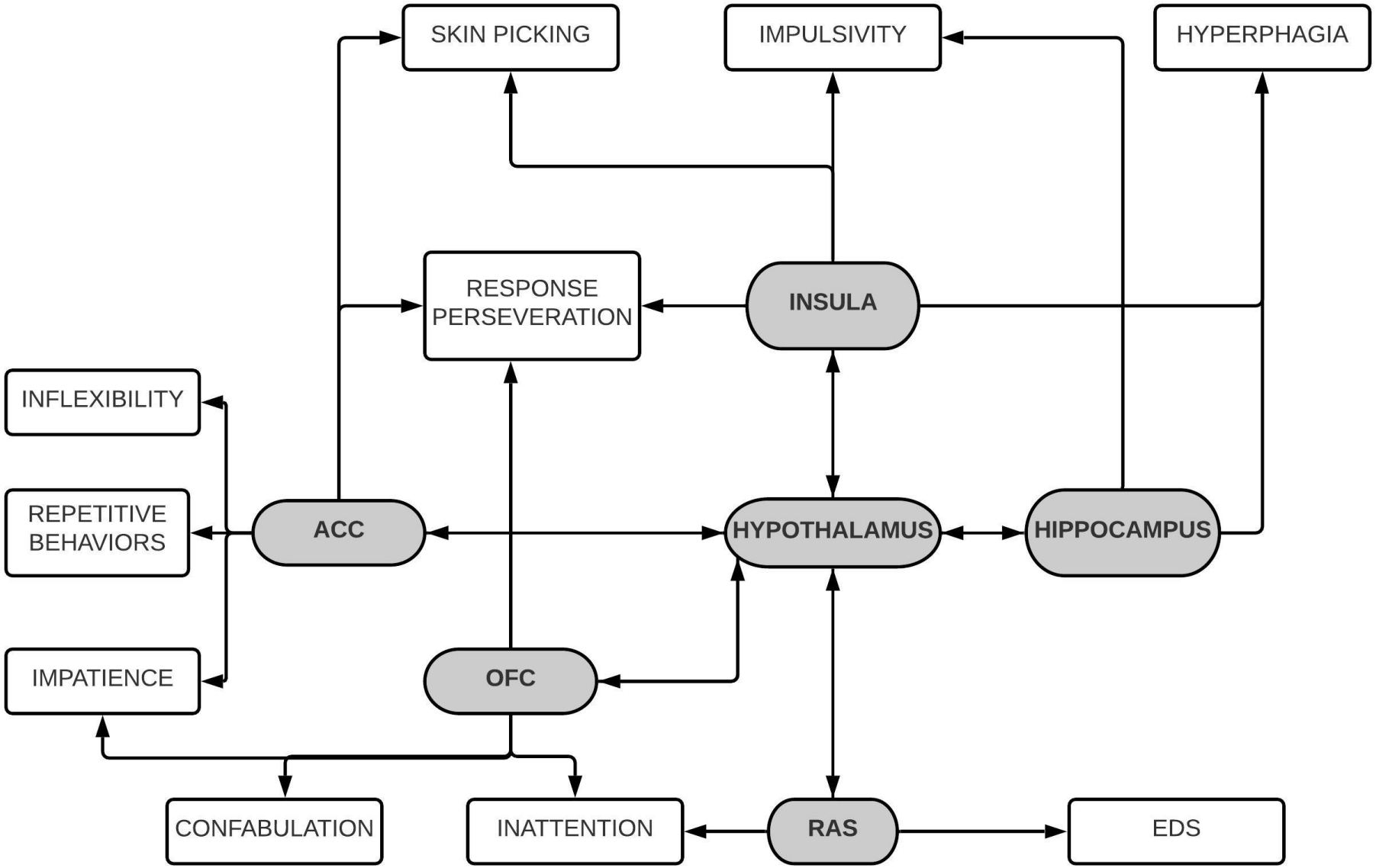
Central role of hypothalamus



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Response Perseveration

- RESPONSE PERSEVERATION: the inappropriate repetition of a particular response despite the absence or cessation of reward.

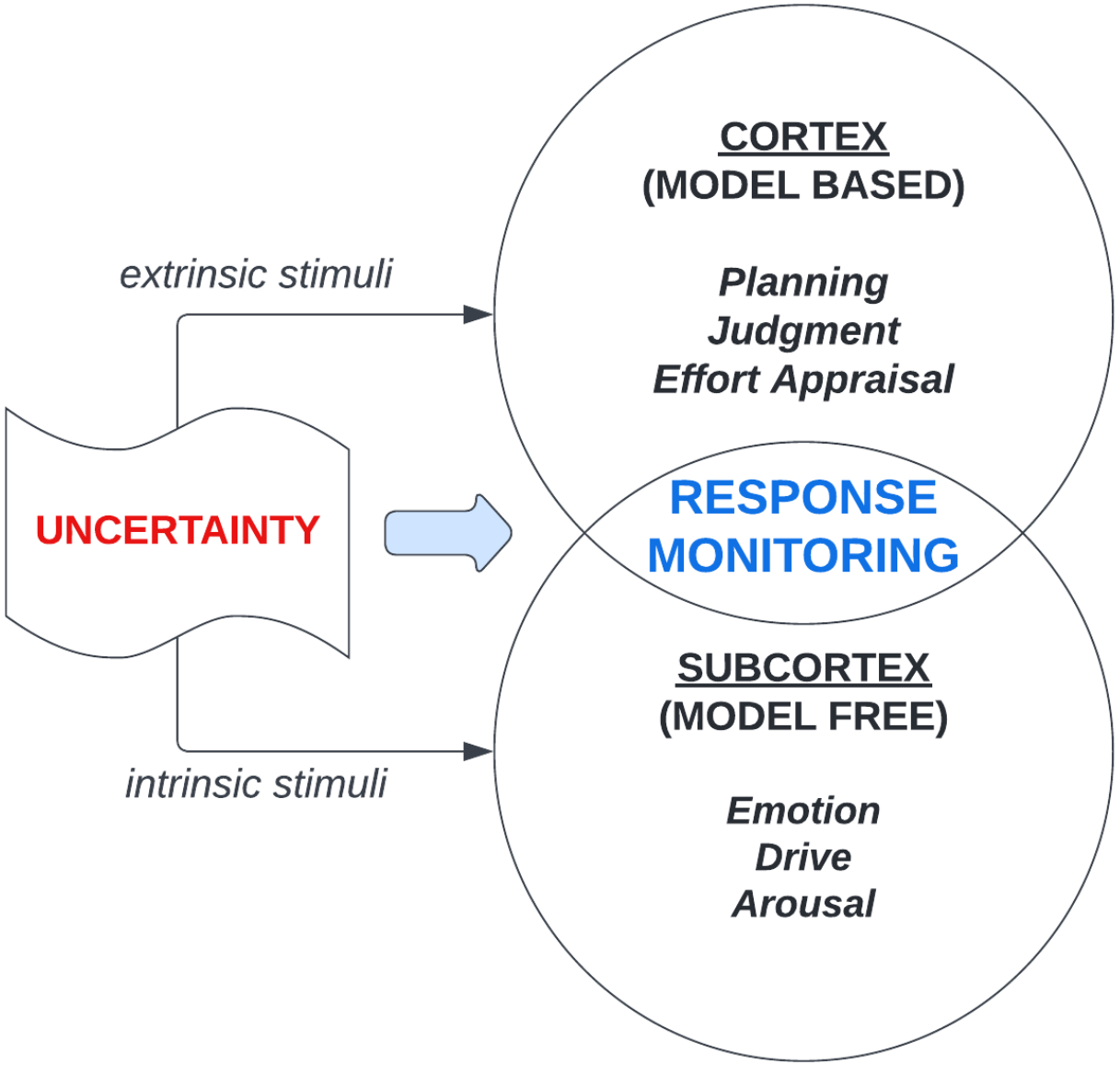
- In PWS:

Related to compulsivity
Repetitive questioning and intrusive behavior ***despite negative response by caregivers.***

Is it Anxiety?
Or is it Impulsivity???

Response Monitoring

RESPONSE MONITORING: The capacity to flexibly adapt to dynamic environments.



BEHAVIORAL RESPONSE (DECISION)

ADAPTIVE

or

MALADAPTIVE

Response Perseveration
Anxiousness
Impulsive Aggression
"Getting Stuck"
Confabulation
Skin/Rectal Excoriation

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Impulsivity

The tendency to engage in rash, ill-considered action in response to intense negative emotions

Associated with low volumes of pre-frontal cortex

Reactive Aggression

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Psychosis in PWS

- Not sch … ses might p…
- Sudde…
- Sleep …
- Confus… paranoi…
- Rapid …

ORIGINAL ARTICLE

AMERICAN JOURNAL OF medical genetics PART A WILEY

Cycloid Psychosis Comorbid with Prader–Willi Syndrome: A Case Series

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Abstract

Psychosis is a relatively common psychiatric phenomenon seen in patients with Prader–Willi Syndrome (PWS). However, the presentation is atypical and difficult to classify within currently defined affective or psychotic disorders. This distinct presentation may be better understood as a phenomenon called "cycloid psychosis," described as an episodic psychosis with rapid full recovery between episodes. This study retrospectively analyzed the cases of 12 patients with genetically confirmed PWS who presented to an ambulatory psychiatric center for a change in behavior consistent with psychosis. Each case was then assessed for symptoms of cycloid psychosis, bipolar disorder, depression with psychotic features, schizophrenia, and schizoaffective disorder. Out of the 12 patients, 11 (91.7%) met the currently described diagnostic criteria for cycloid psychosis. Of the 12 patients, 7 (58.3%) also met the diagnostic criteria for bipolar disorder, and 1 (8.3%) also met the diagnostic criteria for schizoaffective disorder. None of the patients met the criteria for schizophrenia or depression with psychotic features. The findings in this study suggest that cycloid psychosis and bipolar disorder may both be comorbid with PWS. Psychiatric comorbidities in patients with PWS are atypical and clinicians should be aware of conditions such as cycloid psychosis when managing this vulnerable population.

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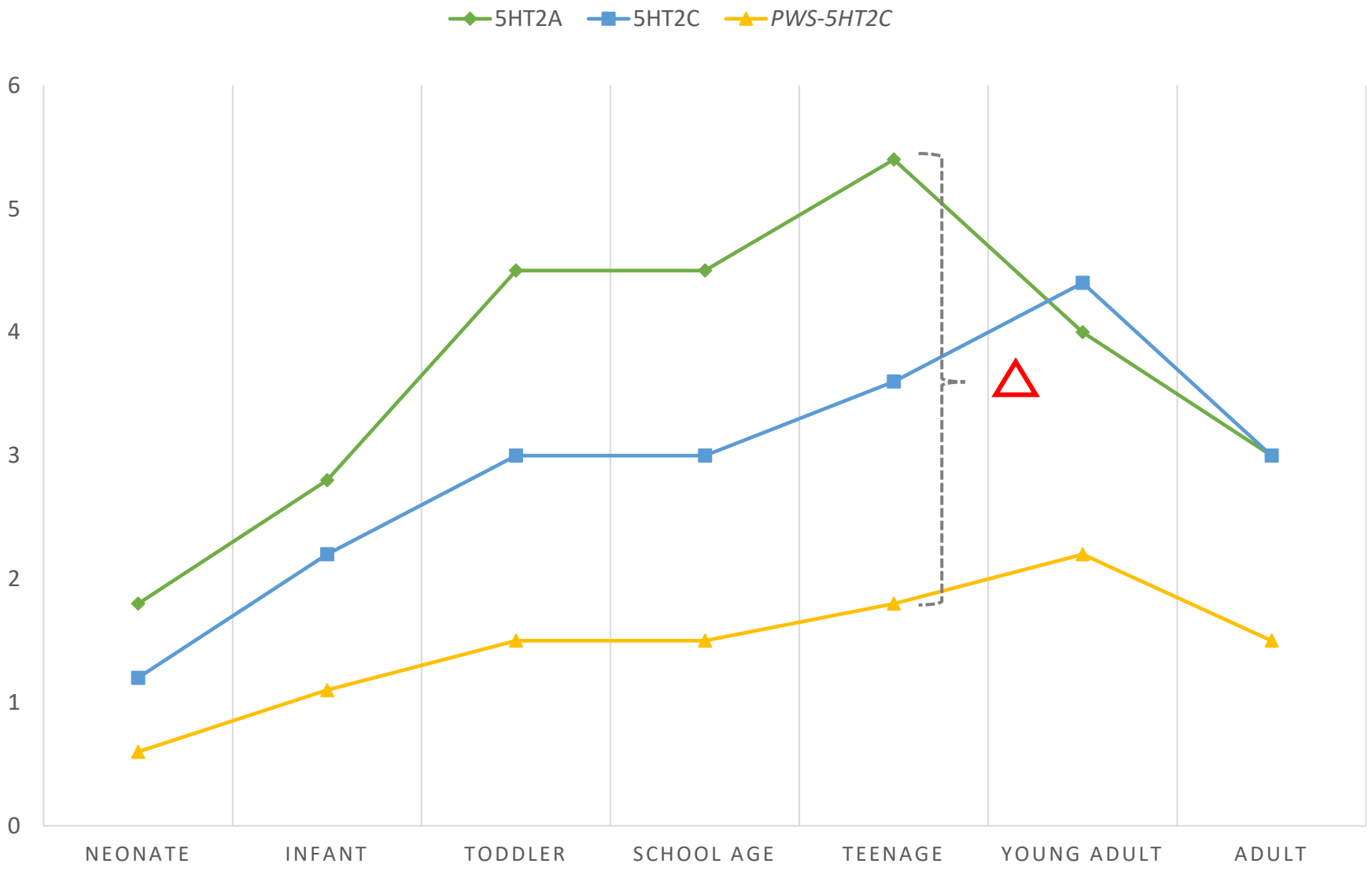

- **Normalized mRNA expression of the excitatory serotonin receptor 2A (5HT2A) and inhibitory serotonin receptor 2C (5HT2C) in the prefrontal cortex.**
- **In PWS, there is a reduced expression of 5HT2C (SIMULATED)**
- **This difference (Δ) in PWS, leads to over-activation with the clinical presentation of impulsivity and higher risk of psychosis during adolescence and young-adulthood.**

Psychiatric Medications in PWS

- Benzodiazepines
  - E.g. Alprazolam, clonazepam, lorazepam
- Serotonin Receptor Inhibitors
  - E.g. Sertraline, citalopram, fluoxetine
- Antipsychotics
  - Typical e.g. haloperidol, chlorpromazine
  - Atypical e.g. risperidone, aripiprazole
- Mood Stabilizers
  - Lithium
  - Anticonvulsants- valproate, lamotrigine, topiramate, gabapentin, carbamazepine, oxcarbazepine

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Psychiatric Medications in PWS- continued

- Buspirone
- Mirtazapine
- Bupropion
- NAC
- Early evidence: DCCR (OC sx), pitolisant, cannabinoids
- Alpha-2 Agonists: Guanfacine XR
  - Selective α2 adrenoceptor agonist
  - Moderates left DLPFC activation
  - ADHD- FDA approval
  - Reduces ADHD/impulsiveness in autism
  - Most common S/E- sedation/fatigue

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Summary: What PWS Teaches Us

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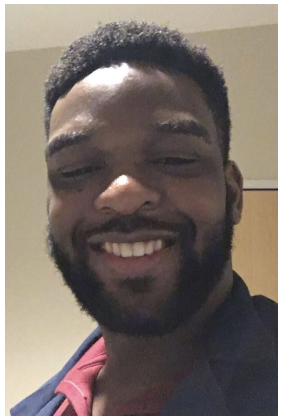
A Growing Research Division



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Thank You!!!

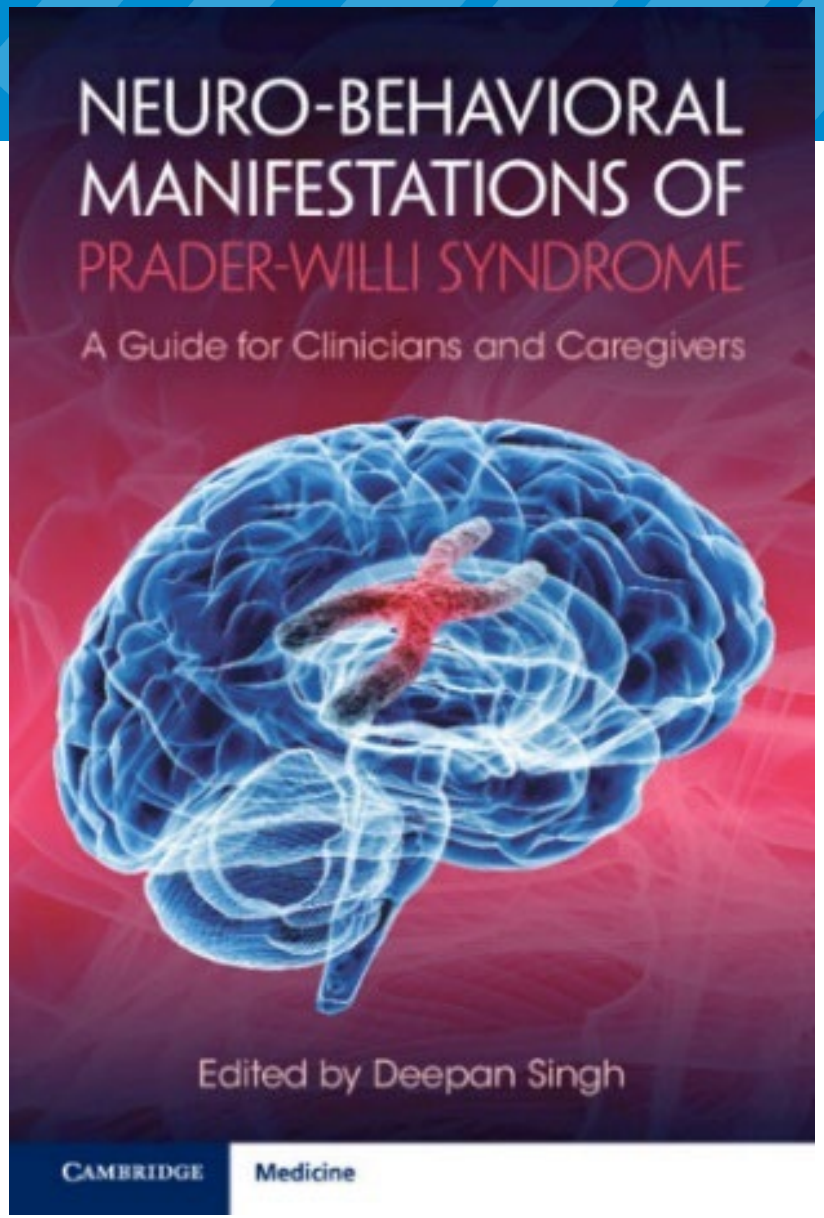
Current PWS Research at Maimonides:

Guanfacine XR

Bright Light Therapy

Hyperphagia (Gedeon-Richter)

Phone: (718) 283-8170



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