MENTAL HEALTH IN PRADER-WILLI SYNDROME

Behavioral phenotype, psychiatric diagnosis, and a model for intervention

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Learning Objectives

1) To describe the developmental onset and longitudinal course of phenotypic behaviors;

2) To identify psychiatric symptoms as distinct from phenotypic behavior and response to stress;

3) To discuss an algorithm for intervention highlighting:
   - eco-environmental modification,
   - strategies for improving coping skills,
   - use of behavior therapy, and
   - management with psychotropic medication.

Definitions

Mental Health = A state of psychological wellbeing and contentment

Mental Ill-health = “Dis-ease”; feeling unwell

Psychiatric diagnosis = Set of clinical symptoms occurring over a specific duration of time that interfere with level of function

Level of function = The day-to-day mood, behavior, and cognitive capacity attained by the person with PWS prior to the onset of symptoms

Eco-environmental = The environmental context in which syndrome specific behaviors are most likely to be managed

Genotype -> PWS (static)

Phenotype -> Behavior (dynamic)

Mental Health in PWS
IPWSO ECHO 2023

Nutritional Stages in PWS

0. Hypotonia, low birth weight (prenatal)

1a. Poor suck, FTT (0-9 months)

1b. No difficulty eating (9-25 months)

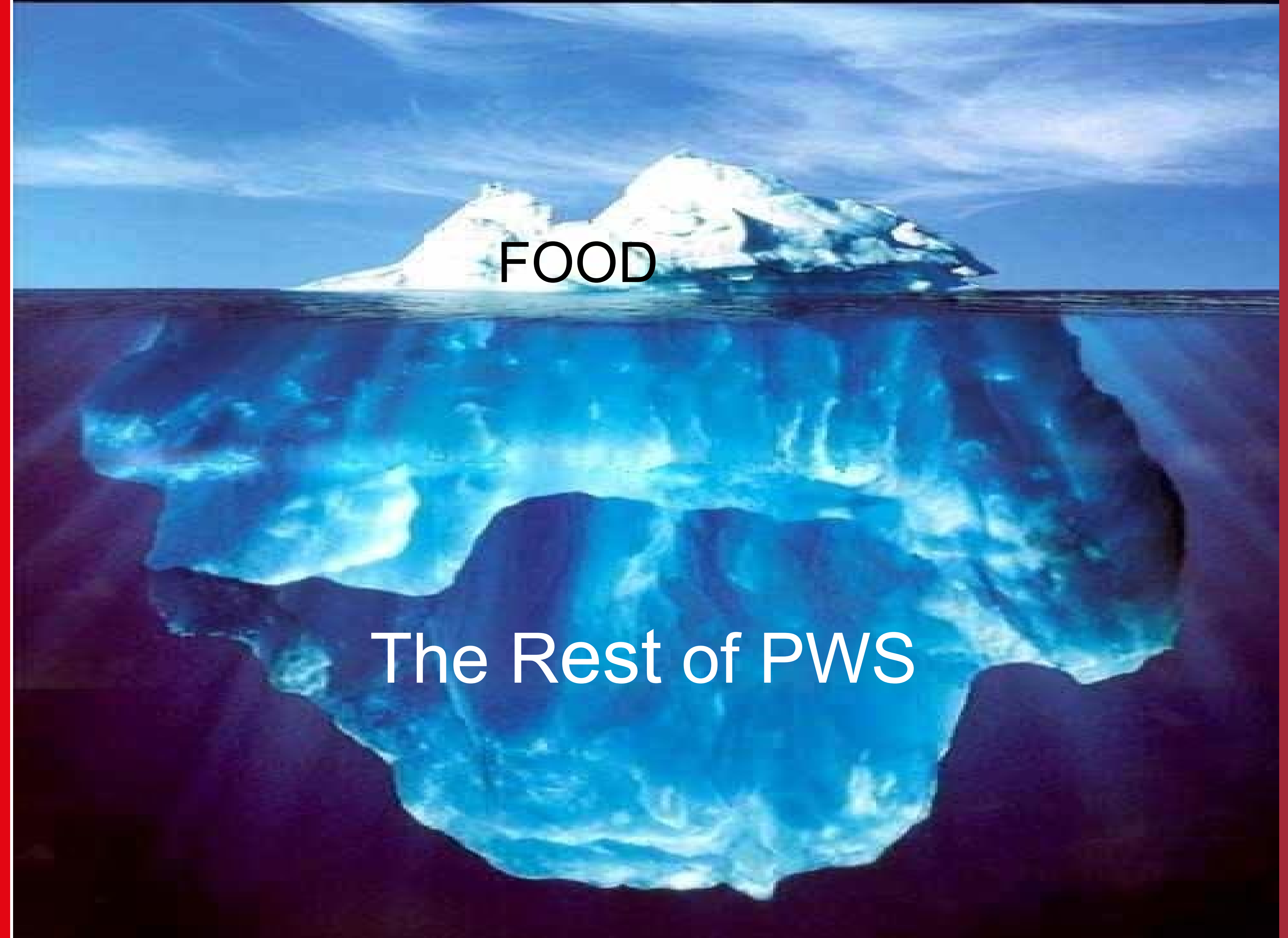
2a. Isocaloric weight increase (2.1-4.5 yrs)

2b. Increased interest, intake, weight (4.5-8 yrs)

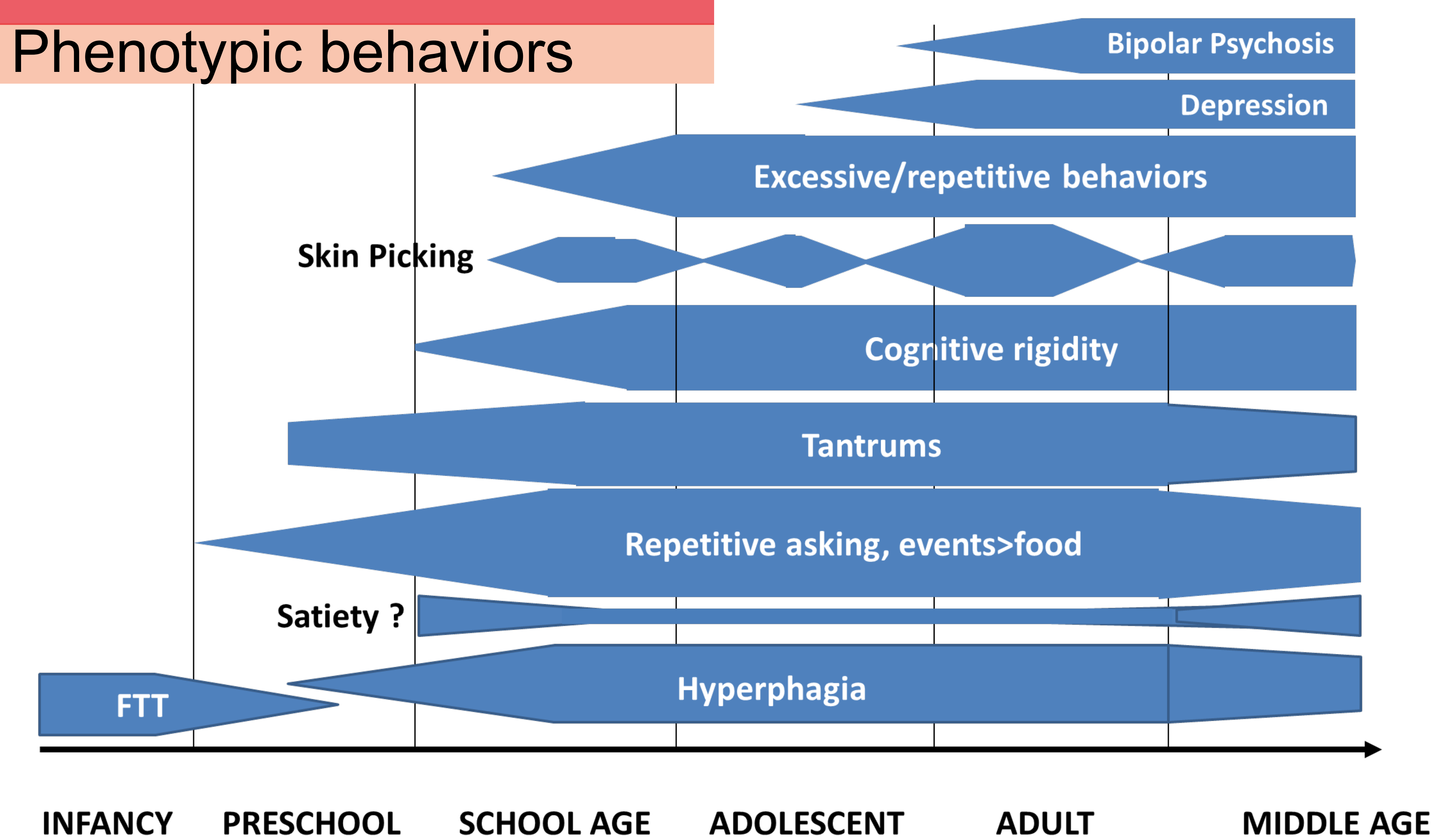
3. Hyperphagic, rarely feels full (8-adulthood)

4. Eats with satiety (>middle adulthood)

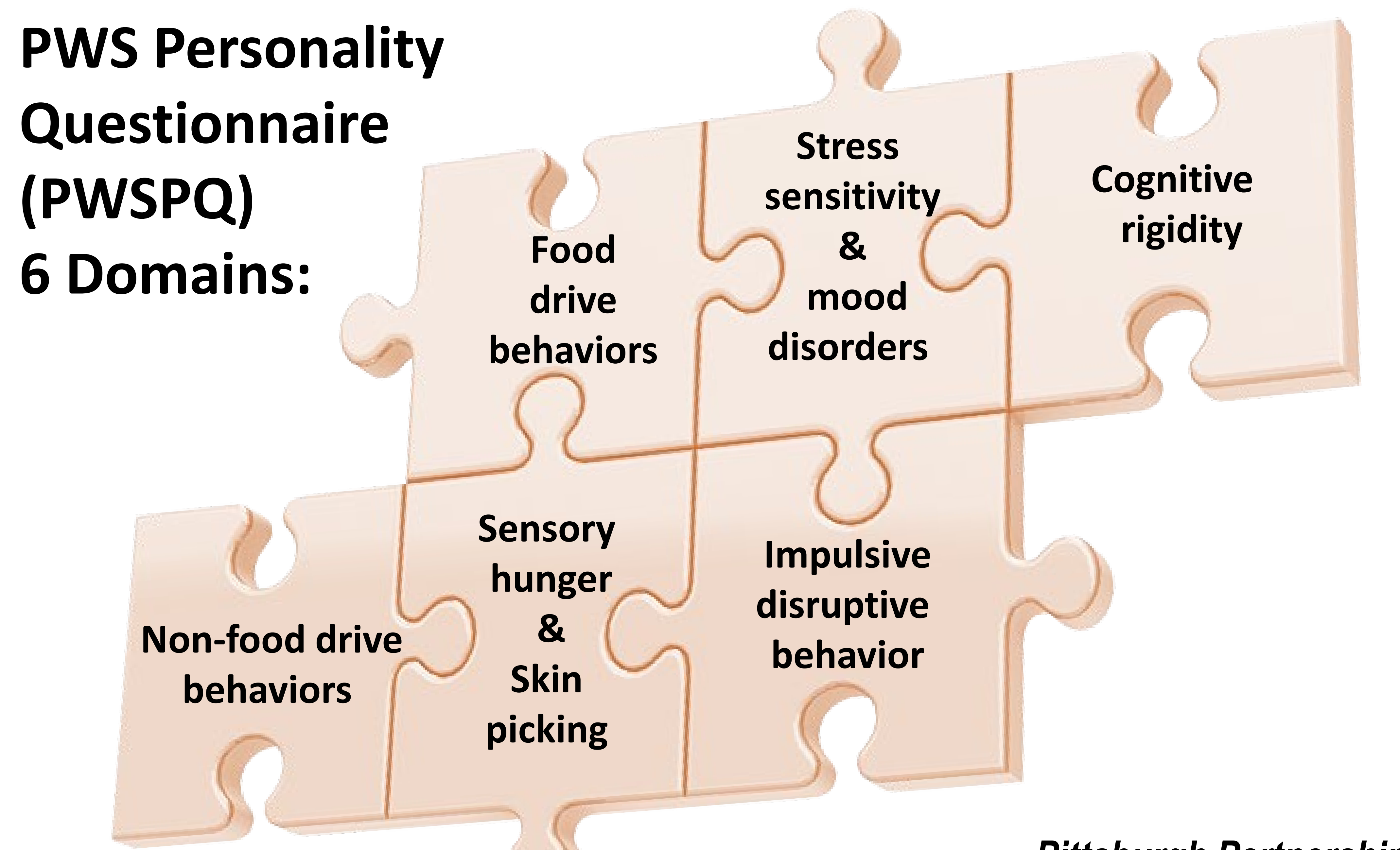
Miller J et. al., Am J Med Genet Part A 9999:1-10.


FOOD
The Rest of PWS

Phenotypic behaviors



PWS Personality Questionnaire (PWSPQ) 6 Domains:



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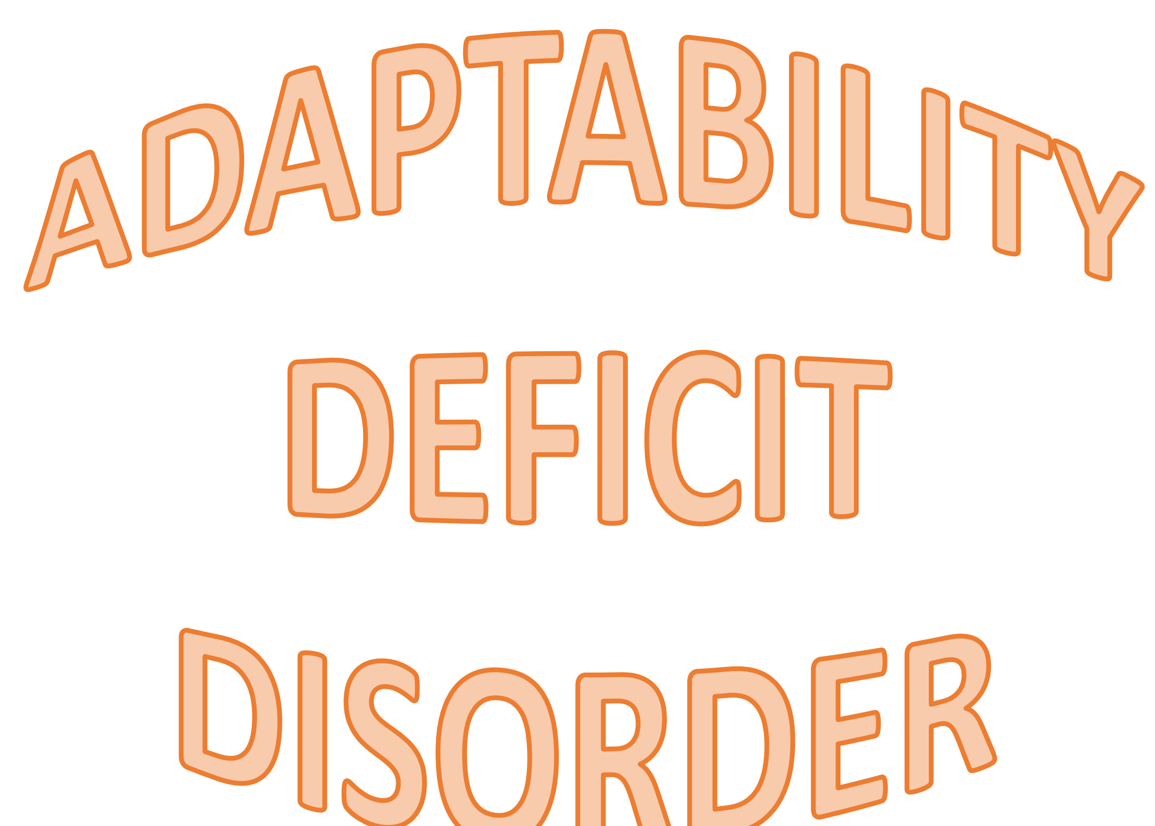
PWS BEHAVIORAL PHENOTYPE:

STRESS SENSITIVITY



NEUROPSYCHIATRIC PHENOTYPE

Paternal Deletion

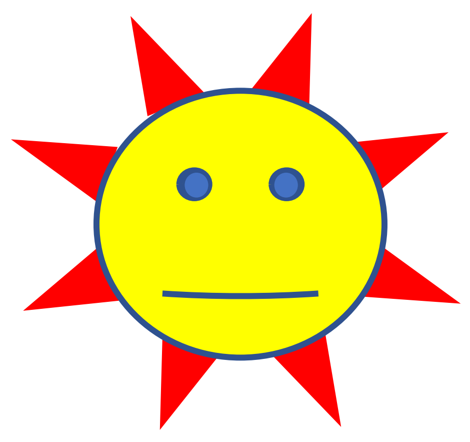
- Cognition and learning
  - VIQ=PIQ, average FSIQ=65
  - Visual>auditory processing
  - Shape discrimination (savant)
    - Jig saw puzzles
    - Social hierarchy
- Small deletion
  - Higher functioning (less impairment)
- Large deletion
  - Increased skin picking and food acquisition
  - Increased perseveration of thought and behavior
  - Increased language disorder
- Depression +/- psychosis in adulthood

Maternal Uniparental Disomy

- Cognition and learning
  - Increase Verbal IQ>Performance IQ
  - NVLD phenotype (auditoy>visual processing; dyspraxia)
  - Autism spectrum symptoms (common)
- Autism (rare)
  - Manifested early in development
  - Non-verbal
  - High rate of stereotypies
  - DO NOT display food seeking
  - DO seek social proximity
- Bipolar affective disorder +/- psychosis
  - Increases with age, 65%>age 30
- Cyclic psychosis
- Dementia?

Effect of stress on behavior in PWS

Baseline
"PWS Personality"



Increased intensity
of *typical* behaviors

Aberrant/maladaptive
behaviors

Psychiatric Evaluation

History of present illness (carer)

- Functional assessment of change

Mood and cognitive screening tests

Diagnostic interview

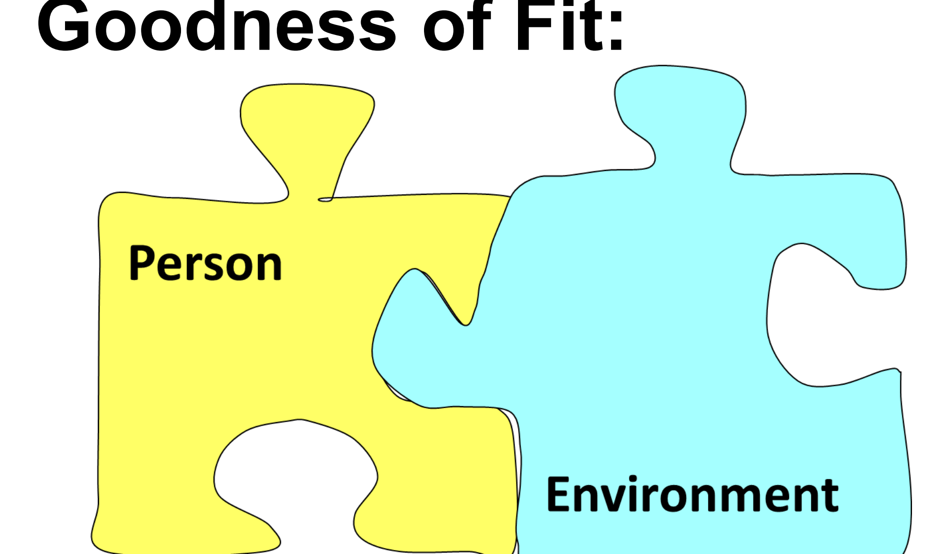
- Patient's point of view of problem

Mental status examination

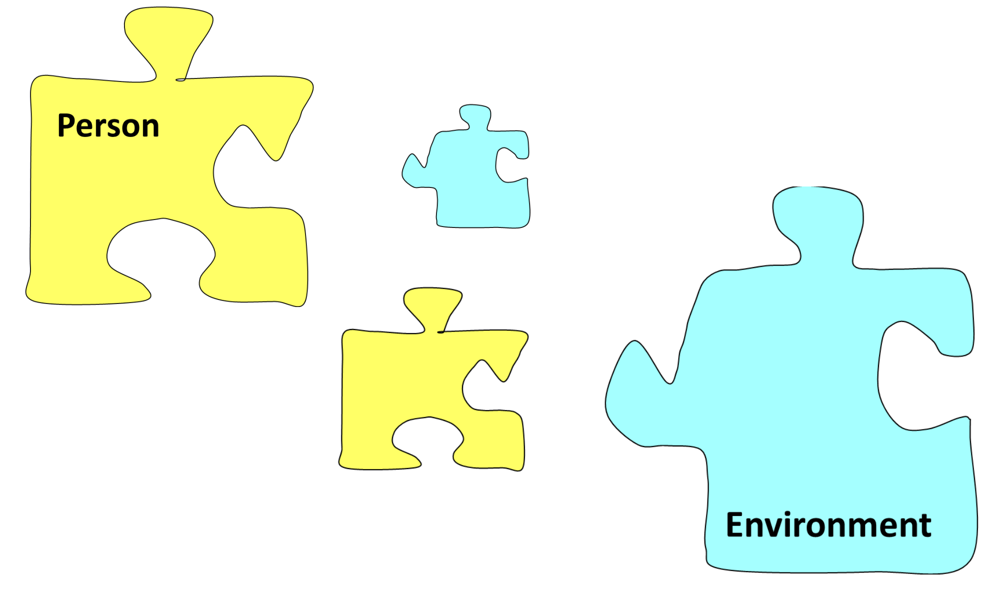
➢ **Always remember, the environment is the "shadow patient" in the psychiatric evaluation.**

Forster JL. Psychiatric phenotype. Management of PWS, 4th edition. Butler, Lee, Whitman eds. SpringerNature 2022

Goodness of Fit:



Maladaptive behavior:



Case Formulation

Predisposing factors

- PWS genotype
- Age
- IQ/developmental level
- Learning differences
- Person/environment "match"
- Person's life experience/expectations
- Family psychiatric history RISK

Precipitating factors: *STRESS*

Perpetuating factors: Environment

Protective factors: COPING

Psychiatric Diagnosis

- PWS Personality
- PWS Personality under STRESS?
- PWS Personality "PLUS"?
  - \+ Psychiatric Disorder
  - \+ Learning Disability/MR
  - \+ Medical Disorder
  - ? Iatrogenic etiology
- Environmental "insufficiency"?

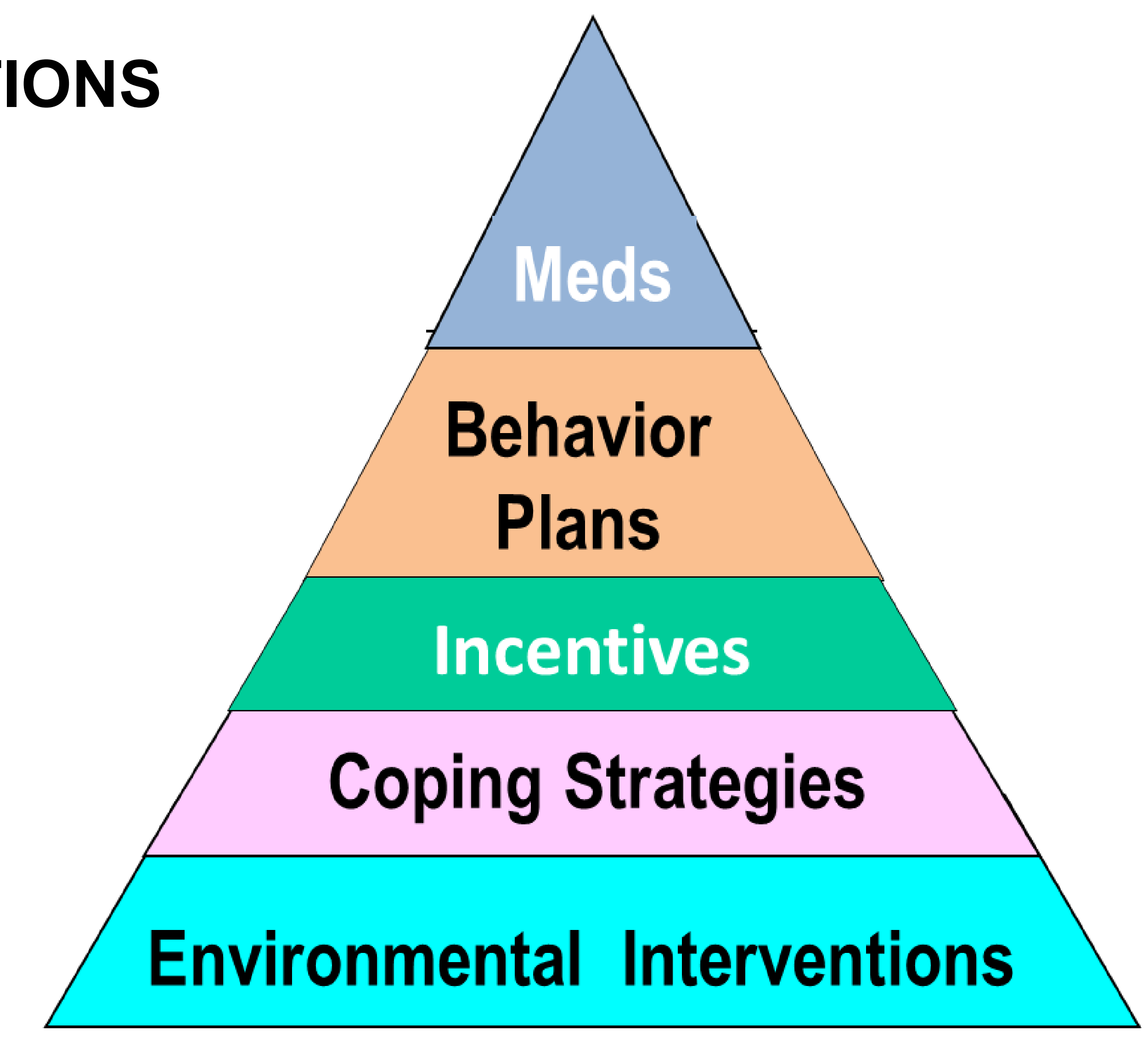
Psychiatric Diagnoses

- Personality change secondary to PWS
- Intellectual deficiency
- Neurodevelopmental disorders
  Learning disorders
- Disorder of sleep/wake
- Adjustment disorder
- Attention deficit hyperactive disorder
  Inattentive type
- Skin excoriation disorder
- Anxiety
  Worries, somatic, not OCD
- Dysthymia (persistent low mood)
  Unpredictable sadness or irritability most days, but not every day, with return to baseline on some days

Psychiatric Diagnoses

- ## Depression (low mood)
  Sadness, low energy, loss of interest; somatic, guilty preoccupation, critical, self depreciation; suicidal ideas and plan; may be psychotic
- ## Bipolar disorder
  MANIA (elevated mood) Irritable, intense, silly; increase in phenotypic behaviors; decreased sleep, increased energy, grandiose ideas; impulsive with high risk for negative outcome; psychosis. HYPOMANIA; DEPRESSION.
- ## Mood & behavioral activation
  Gradual onset of Irritability, intense tantrums, impulsive SIB (stabbing/cutting self, jumping out of a vehicle, grab steering wheel/gear shift)
- ## Psychosis
  Acute onset (delirium-like) with motor symptoms, sensory hypersensitivity, delusional thinking (paranoia, persecution, somatic), hallucinations, stop eating, loss of ability to groom
- ## Intermittent explosive disorder

INTERVENTIONS



TRAIN

Eco-environmental tool that reduces syndrome specific behaviors by managing the interaction between the person and the environment.

T - Tool
R - Reducing
A - Anxiety
I - Insecurity
N - Noncompliance

Environmental Interventions

PWS Intervention Pyramid

Eco-environmental tool that reduces syndrome specific behaviors by managing the interaction between the person and the environment.

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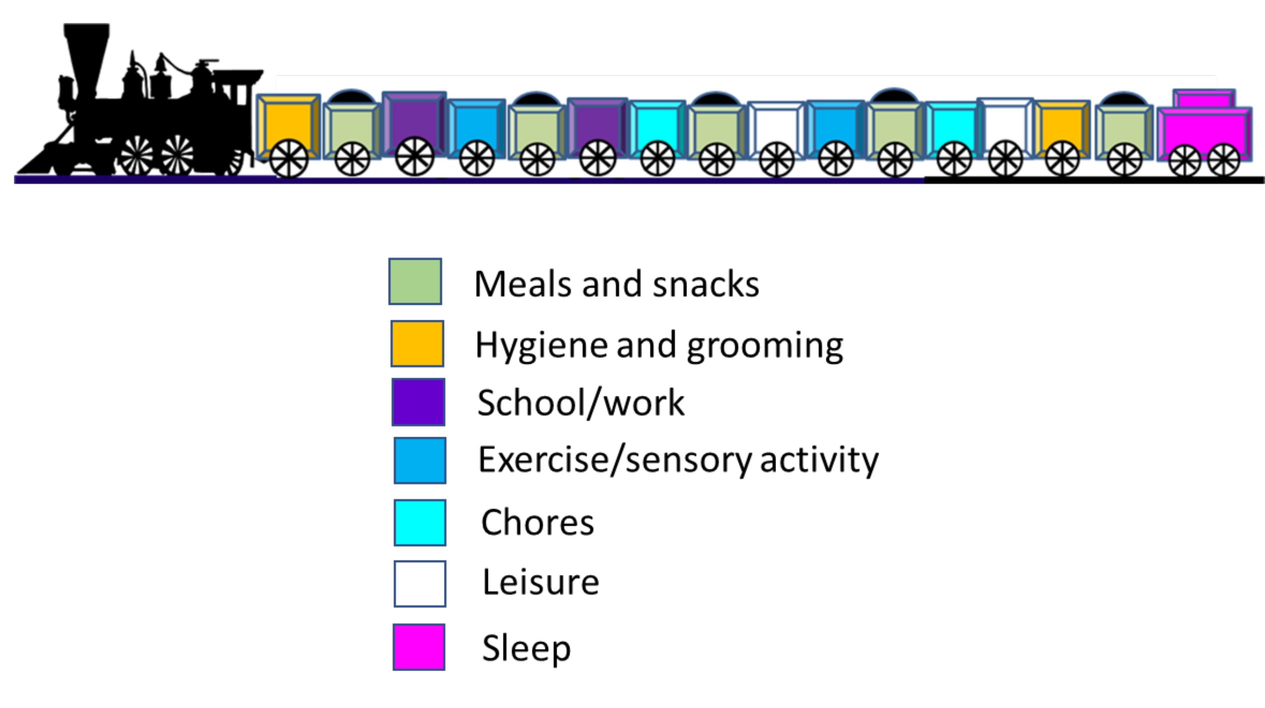

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Environmental Interventions

PWS Intervention Pyramid

TRAIN

- Linear daily schedule
- Alternates preferred/nonpreferred activities
- Minimizes stress by:
  - Managing transitions to achieve *FLOW*
  - Providing predictability
  - Minimizing uncertainty
  - Providing continuous feedback
- Achieves a *balance* of tasks and activities
- Builds self esteem through mastery
- Sets and reinforces *zeitgebers*

PWS Intervention Pyramid

FOOD SECURITY

- The person knows what they will eat, how much they will eat, when they will eat it and when they won't.
- FOOD SECURITY manages both food and behavior.
- Without FOOD SECURITY, the person constantly battles with their expectations, which inevitably leads to disappointment.
- FODD SECURITY puts a lock on the thought.
- When the person is not constantly thinking about food, they can use their mind for other things!

EVERYTHING SECURITY

Meals and snacks
Hygiene and grooming
School/work
Exercise/sensory activity
Chores
Leisure
Sleep

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Environmental Interventions

PWS Intervention Pyramid

Coping with Coaching

(will require participation of carers)

- Teach appropriate behavior in context (poor generalization)
  - Reinforce with praise
- Relaxation training for anxiety*
  - Breathing, counting, squeezing, stretching
- Anger management strategies*
- Social skills training* (e.g., BOSS Curriculum - FPWR)
  - Social stories with natural consequences
  - Apology for inappropriate behavior
- Adapted psychotherapy
- Teach *adaptive* escape and avoidance behavior

*(scripted, rehearsed and cued)

Coping Strategies

Environmental Interventions

PWS Intervention Pyramid

Incentives

Preferred interests and activities that increase or sustain:

- Motivation
- Effort
- Action/participation
- Productivity
- Attitude

Incentives

Coping Strategies

Environmental Interventions

PWS Intervention Pyramid

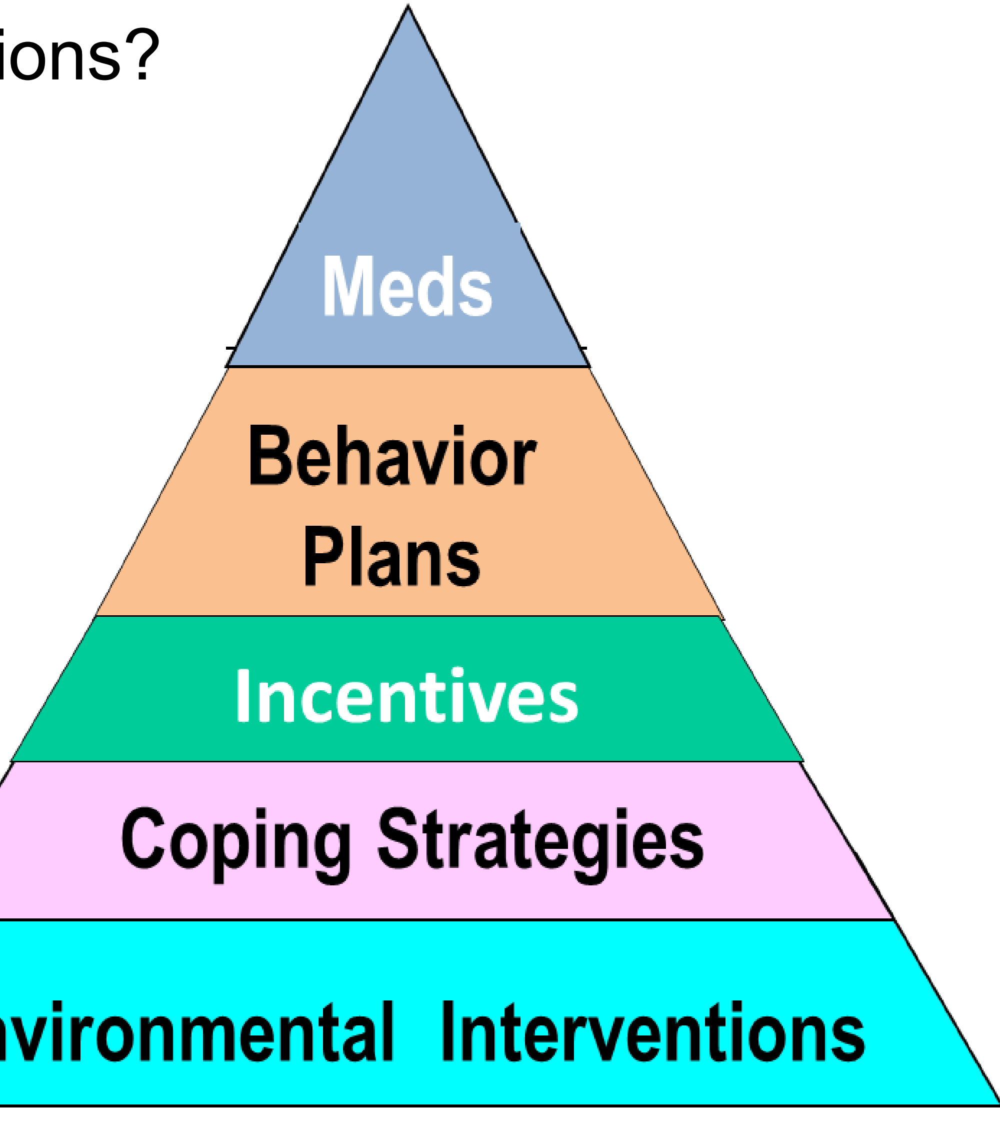
Behavior Plans

Behavior plans increase infrastructure and further individualize the daily plan.

- A predetermined way to provide feedback to the person about their behavior
- Integrated into the fabric of the day
- Expectations displayed visually
- Expectations phrased positively (*be on time*, not *don't be late*)
- Target specific behaviors
  - Reinforce the *occurrence* of desired behavior
    - What *we* want
  - Contingent rewards: praise plus tangibles (stars, tokens, points)
    - Exchanged for what *they* want

When to use psychotropic medications?

- Treat an underlying psychiatric disorder
- Augment effectiveness of other therapies
- Manage a crisis



PWS Intervention Pyramid

What do psychotropic medications do?

- Modulate stress response
  - — Decrease response/interaction with the environment (DA blocker, GABA agonists) neuroleptics, AED's, benzodiazepines, alpha adrenergic agonists, beta blockers, SSRIs, antihistamines, lithium
- Modulate the reward drive
  - — Increase response/interaction with the environment (stimulants, NE/DA agonists, opiates)

Meds

Behavior Plans

Incentives

Coping Strategies

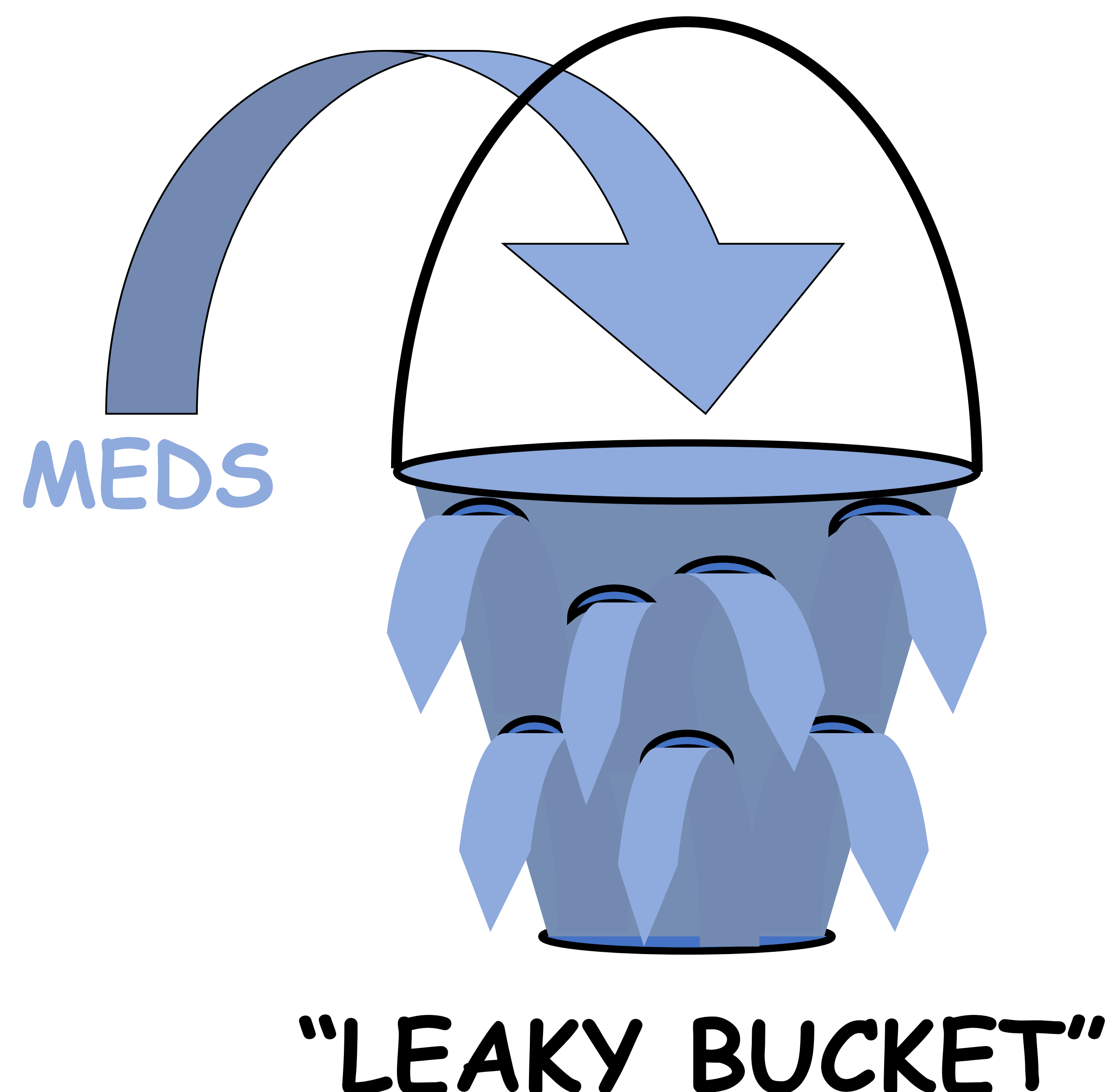
Environmental Interventions

PWS Intervention Pyramid

Pharmacotherapy in PWS

- There are no medications that are given *because* a person has PWS.
- There are no medications that cannot be used because a person has PWS.
- All medications must be used with special care: *start low, go slow.*
- Try to make one medication change at a time.
- Try to use short acting medications first.

Forster JL. Pharmacotherapy in PWS. Management of PWS, 4th edition. Butler, Lee, Whitman eds. SpringerNature 2022.



"LEAKY BUCKET"

Neurochemistry is different in PWS

- 5HT2R are deficient with a bias toward activation (5HT2A) > inhibition (5HT2C)
  [Forster J et al., 2020]
- 5HT2R are age related
  [Lambe EK et. al., 2011]
- GABA receptors are deficient
  [Lucignani G et al., 2004]
- GABA is deficient in PWS brain
  [Rice et al., 2016]
- DAT is hypomethylated
  [Weiting J et. al., 2023]

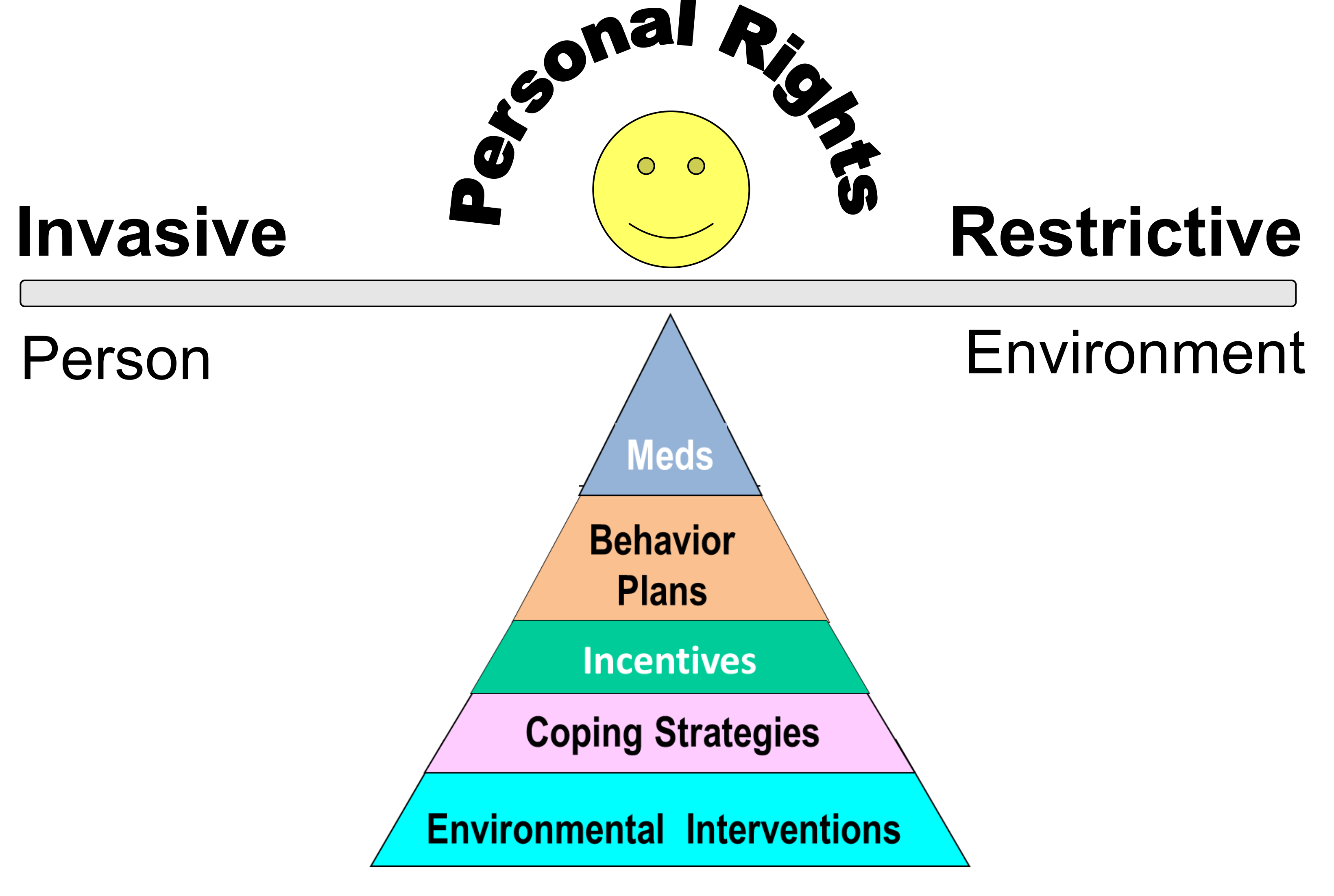
Forster J, Duis J and Butler MG. (2020) Pharmacodynamic Gene Testing in Prader-Willi Syndrome. Front. Genet. 11:579609.doi: 10.3389/fgene.2020.579609.

Cytochrome p450s in PWS

UM – ultrarapid metaboliszer
EM – extensive metabolizer (typical)
IM – intermediate metabolizer
PM – poor metabolizer

Forster J, Duis J and Butler MG. (2021) Pharmacogenetic Testing of Cytochrome P450 Drug Metabolizing Enzymes in a Case Series of Patients with Prader-Willi syndrome. Genes 12, 152. doi.org/10.3390/genes12020152.

- **CYP2D6 trends toward slower metabolism**
  - **10% more PM among DEL and UPD**
  - **DEL: 50% fewer EM; 25% more IM**
  - **UPD: typical EM, IM**
- **CYP2C19**
  - **DEL shifted toward increased metabolizer status (>UM, EM typical, <IM)**
  - **UPD all EM**
- **CYP2C9**
  - **DEL typical**
  - **UPD shifted toward decreasing metabolizer status**
- **CYP3A4 trends toward slower metabolism**
  - **GH is a substrate, so drug interactions are likely**
- **CYP1A2 (ch 15) trend toward UM status in both**
  - **DEL has more EM and inducible polymorphisms**



PWS Intervention Pyramid

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THANK YOU!

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