5TH 29th to 31st oct 2021
ASIAPACIFIC
Prader-Willi Syndrome Conference
One Voice Together

Cognition and behaviour

Making sense of mental ill-health in people with PWS

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Making sense of mental ill-health

A research journey

People with PWS have many strengths - see the stories on IPWSO's website and social media

- Objectives of talk
  - To provide an understanding of why people with PWS are at risk for particular difficult behaviours and mental ill-health
  - To consider the cognitive profiles associated with PWS and the impact on behaviour and mental ill-health
  - To discuss the implications of the above for prevention and treatment.

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WHO definition of Mental Health

Galdeseri et al 2015 Towards a Definition of Mental Health. World Psychiatry DOI:10.1002/wps.20231

Good mental health is **more than** 'the absence of mental disorder'. It includes the presence of:

- A dynamic internal state or equilibrium
- The ability to maintain harmony in line with universal values
- The ability to recognise, express and modulate emotions
- The ability to cope with adverse events and function socially

This definition is analogous to that for physical health

Atypical brain development in people with PWS

- Impaired development of cognitive abilities
  - Developing an accurate model of the world
  - Interpreting the behaviour of others
  - Responding efficiently to change
- Impaired ability to regulate behaviour and emotional states in response to the needs of the body and the demands of the physical and social environments
  - Food intake
  - Actual/perceived emotions and behaviour of others
  - Temperature.

Neuroscience and Biobehavioral Reviews 72 (2017) 153–167

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journal homepage: www.elsevier.com/locate/neubiorev

Review article

Cognition in people with Prader-Willi syndrome: Insights into genetic influences on cognitive and social development

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Intellectual functioning distribution of scores around a mean of 60. Del – UPD differences

Social cognition, executive functioning etc

- Theory of Mind
- Understanding facial expressions
- Knowledge of social norms
- Working memory
- Planning
- Attention (task) switching
- Concrete thinking
- Concept of time

Attainments

- Numerical skills
- Reading comprehension
- Expressive<receptive language

- Poor retention of skills
- Slow processing speed

BUT cohort effects

- Studies from earlier generations and small numbers
- Improvements in education
- Early use of growth hormone

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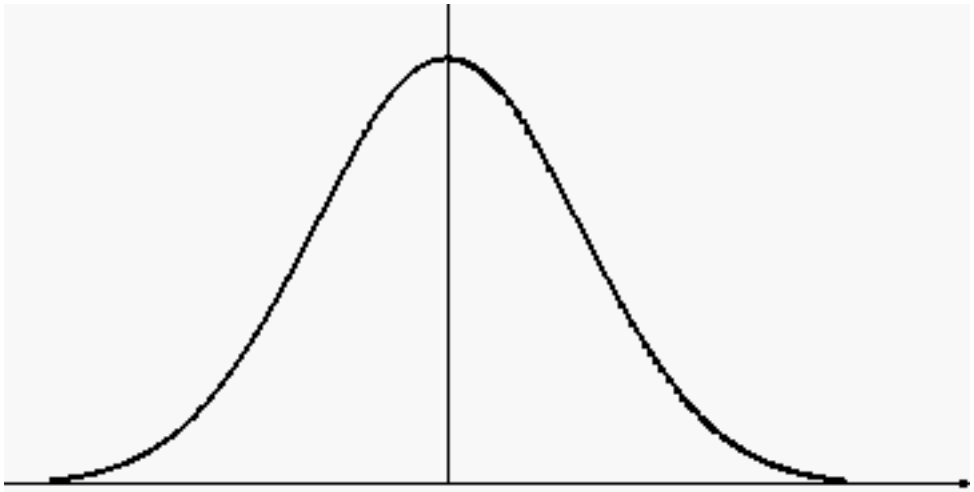
IQ and cognition in people with PWS

Normal distribution of scores

Mean FS IQ = 60
PWS Population

Mean FS IQ = 100
General Population



Variation in cognitive abilities in the PWS population – some may meet conventional IQ criteria for LD/ID (i.e. FS IQ<70), all will score below what would have been expected given their background.

Impact of specific cognitive impairments may be hidden and only apparent under specific conditions

FS = Full Scale; LD/ID = learning (intellectual) disability

Impact of cognitive impairments

- Impacts on learning and level of educational attainments and their maintenance over time
- Ability to reliably interpret and make sense of the physical and social environments
- (Predictive coding model - Friston et al)
- Ability to respond to circumstances and make decisions in an efficient and effective way

Key points 1

Good mental health requires:

- the necessary cognitive, social and functional skills
- the ability to regulated emotional and affective states in the context of the social and physical environments

Mental health is a dynamic process in the context of a changing environment

Neuropsychiatric phenotype of PWS

Atypical brain development and impact on mental health

- Numerous studies from different countries:
  - Emergence of hyperphagia in early childhood (100%)
  - Repetitive and ritualistic behaviours (50 to 60%)
  - Emotional (temper) outbursts (60 to 80%)
  - Skin picking (40 to 60%)
  - Non-psychotic mood disorders (15 to 20%)
  - Psychotic illness (predominately in those with mUPD – 60%)

(see Whittington 2003 for summary in Prader-Willi Syndrome Edited by C. Hoybye Nova Science Publishers)

What does research tell us?

- Hyperphagia
- Emotional (temper) outbursts and repetitive and ritualistic behaviours
- Skin picking
- Mental illness

Hyperphagia in PWS: from case studies to systematic observation to hypothesis testing

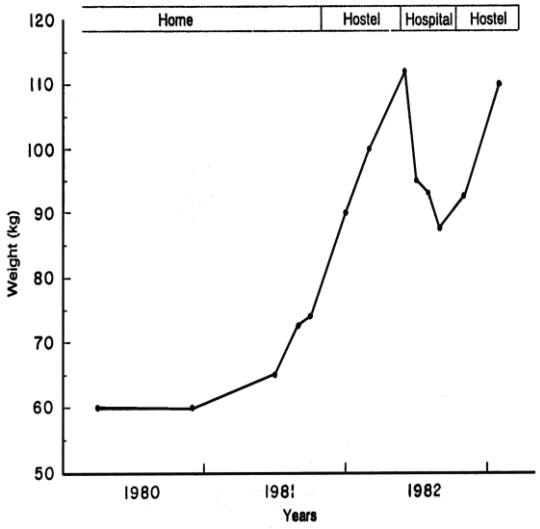
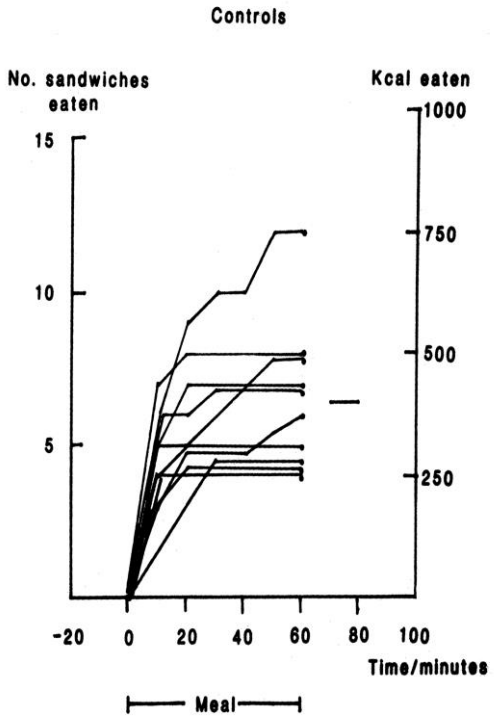
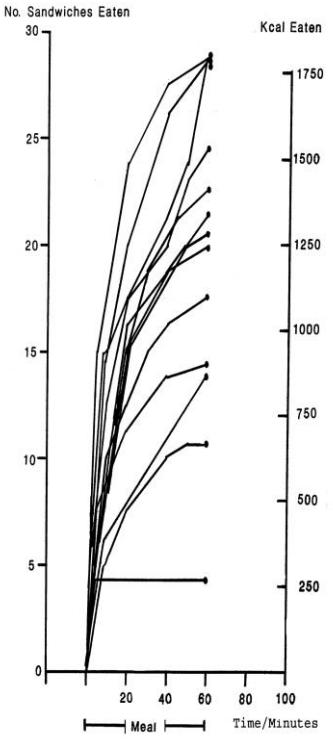


Figure 2 The weight chart of a p
Prader–Willi syndrome showing the large
weight increase which occurred when acces
to food was unsupervised in a group home
people with learning disabilities.

Journal of Intellectual Disability Research 39, 3 3–

Eating behaviour during 60 minutes access to food





Satiety cascade

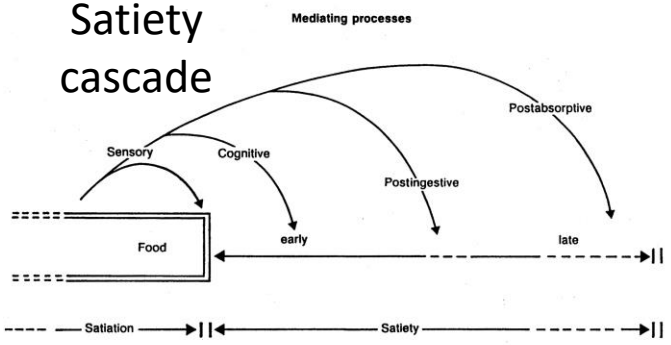


Fig. 2. The 'satiety cascade' consists of different processes, i.e. sensory, cognitive, postingestive and postabsorptive, which mediate the inhibition of eating. Aberrations or faults in these processes lead to disturbances in the expression of appetite.

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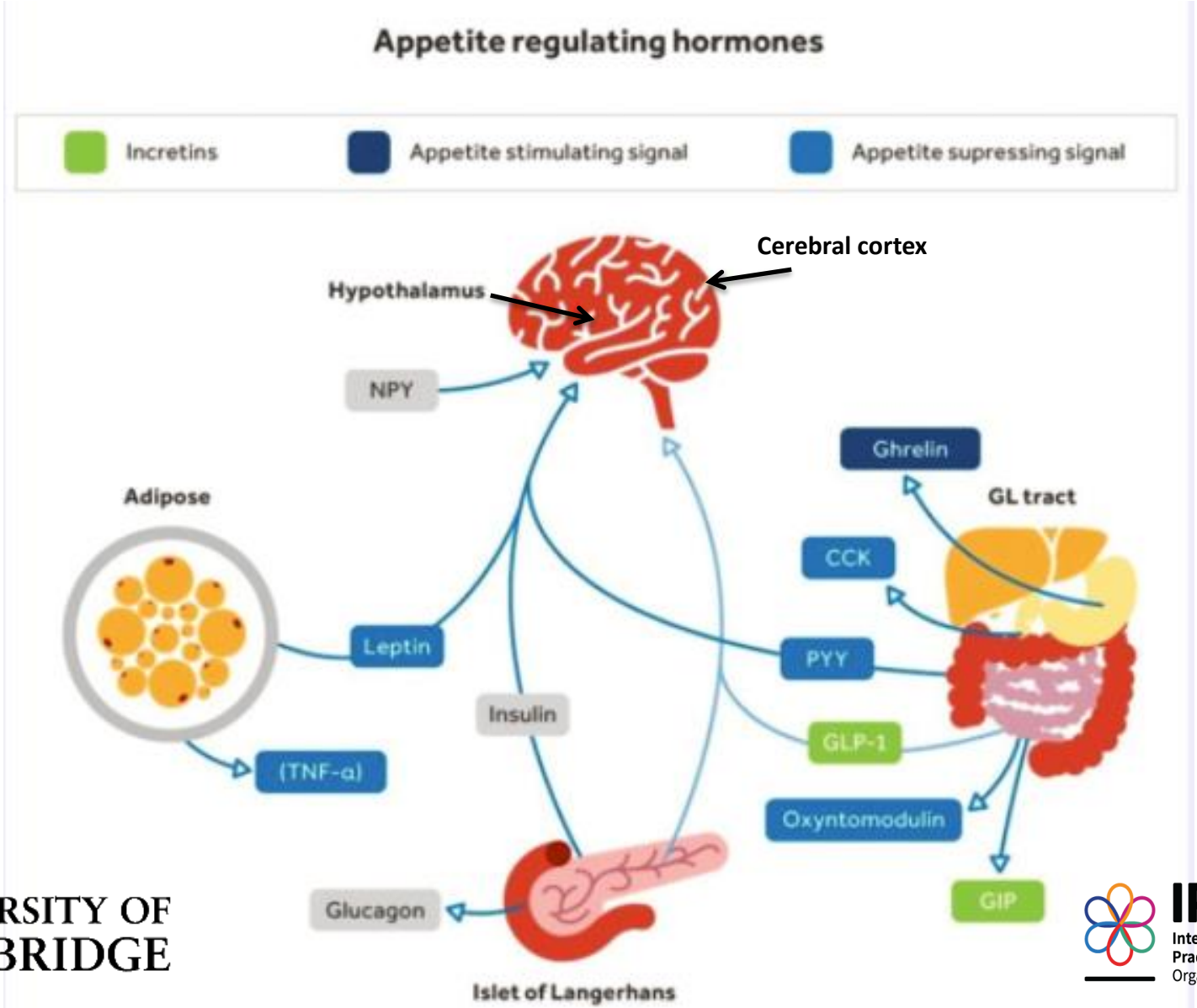
Hormone and vagus nerve links between gut and the brain:
the importance of the hypothalamus and brain cortex for conscious feelings hunger/fullness



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Key Points 2

- Hyperphagia is a consequence of a biological impairment in the ability of the brain to limit energy (food) intake in line with energy needs
- Treatment trials for hyperphagia are targeting different biological pathways but at present treatment is primarily preventing obesity through food security
- Food security may bring other benefits, such as reduced emotional outbursts

Temper outbursts in PWS

Rice et al 2018 AJMG

- Survey of 101 families
- Behaviour worse in adolescence
- Characteristic onset and course
- Triggered by:
  - Goal blockage
  - Social injustice (perceived and real)
  - Difficulty dealing with change
- Interventions
  - Give space and distract only effective intervention
  - Risperidone, sertraline, fluoxetine regularly used but of limited value

Temper outbursts in children with PWS

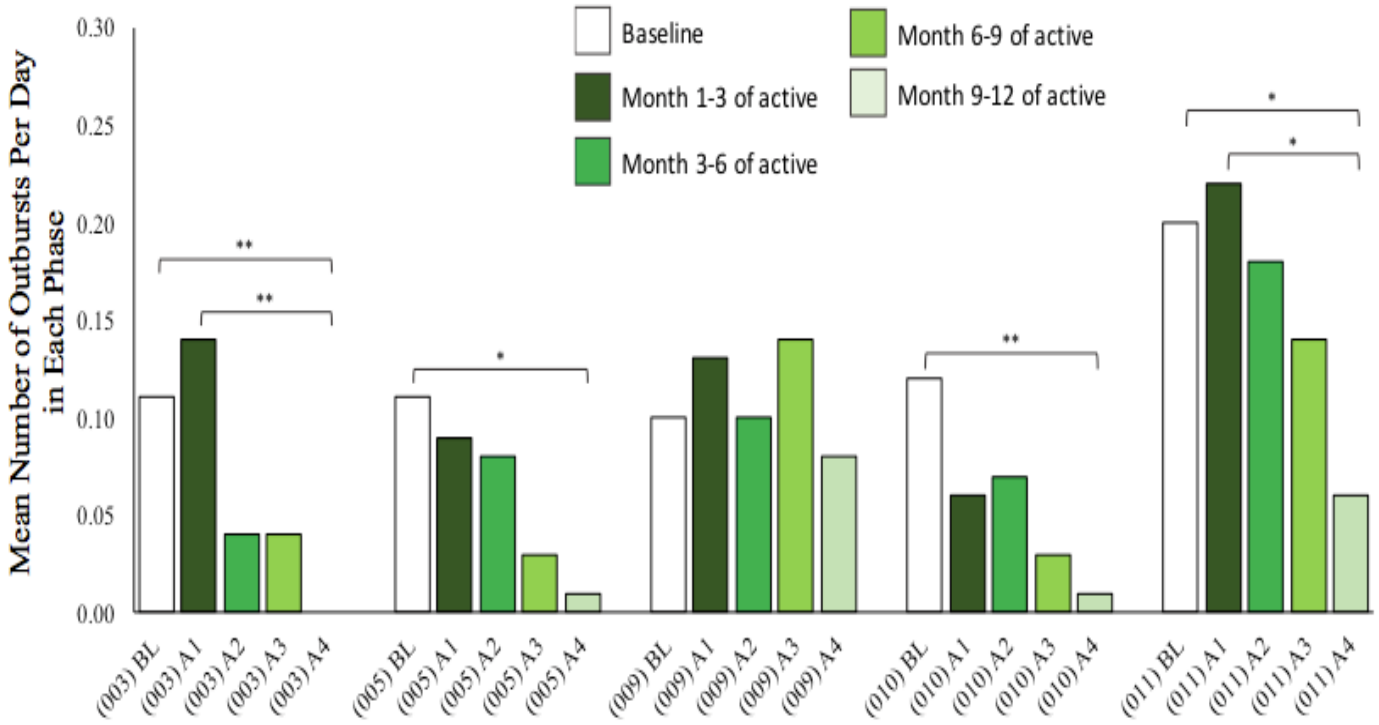
Woodcock et al 2011

- Single case design investigating the relationship between cognitive demand and outbursts
  - Increased temper outbursts when cognitive challenge required switching of attention
  - In experimental and naturalistic settings increased temper outbursts related to unexpected change

Transcutaneous Vagus Nerve Stimulation (t-VNS)

Nemos device

Mean Number of Temper Outbursts per Day



Manning et al, 2019 https://doi.org/10.1371/journal.pone.0223750

Carer Observations of Change

Trial Phase	Sub-theme
Baseline	Uncontrolled mood
	Rigidity
	Necessity for planning
	No opportunity for intervention
Active	Reduced outbrusts
	Controlled mood
	Flexibility
	Opportunity for intervention

VNS003
"Before you couldn't challenge him on certain things…but now you can and **he's prepared to sit and listen**"

VNS005
"in a way he … doesn't know what he's doing and he can't control it but [**since the VNS**] something clicks and **he just calms**"

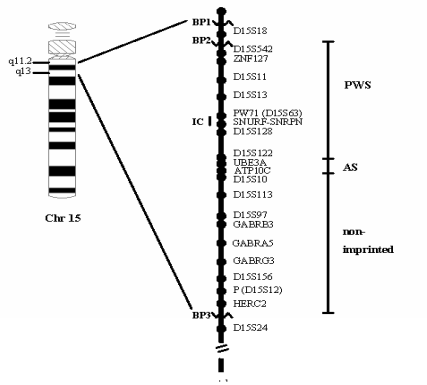
VNS011
"**she just seemed to accept the change** … a few weeks ago I don't think she would have"

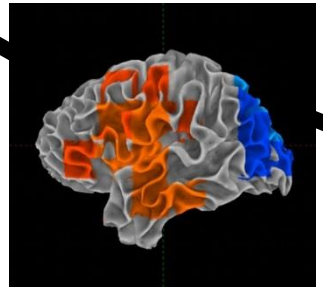
VNS010
"…**routine will change** and a lot of times the **response is not as great as you thought it would be** or she doesn't respond at all" "

Linking temper outbursts and repetitive and ritualistic behaviours

Woodcock, UK

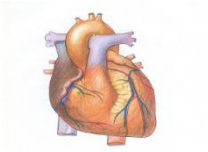
PWS





Deficit in attention switching

Brain functional abnormalities



Training to prepare for change

UNEXPECTED CHANGE

Emotional dysregulation (interventions modify autonomic nervous system response to 'threat' eg. psychological, VNS)

Physiological arousal

Temper outbursts

Repetitive questions

Severity and impact of emotional outbursts

Characteristics:

- Can be frequent, & severe
- May result in harm to self and others
- Impact on welfare of family/paid carers
- Decrease quality of life & wellbeing
- Increase financial costs
- Can involve criminal justice

Present interventions

- Prevention – environmental change
- Applied Behavioural Analysis
- Food security
- Strategies for managing outbursts
- ?Anti-anxiety, anti-psychotic medications

Present challenges

- Limited understanding of causation
- Maintenance of behavioral interventions
- No evidence for medication – may do harm
- No effective approved treatments

Body focused self-harming behaviours

(e.g. skin picking)

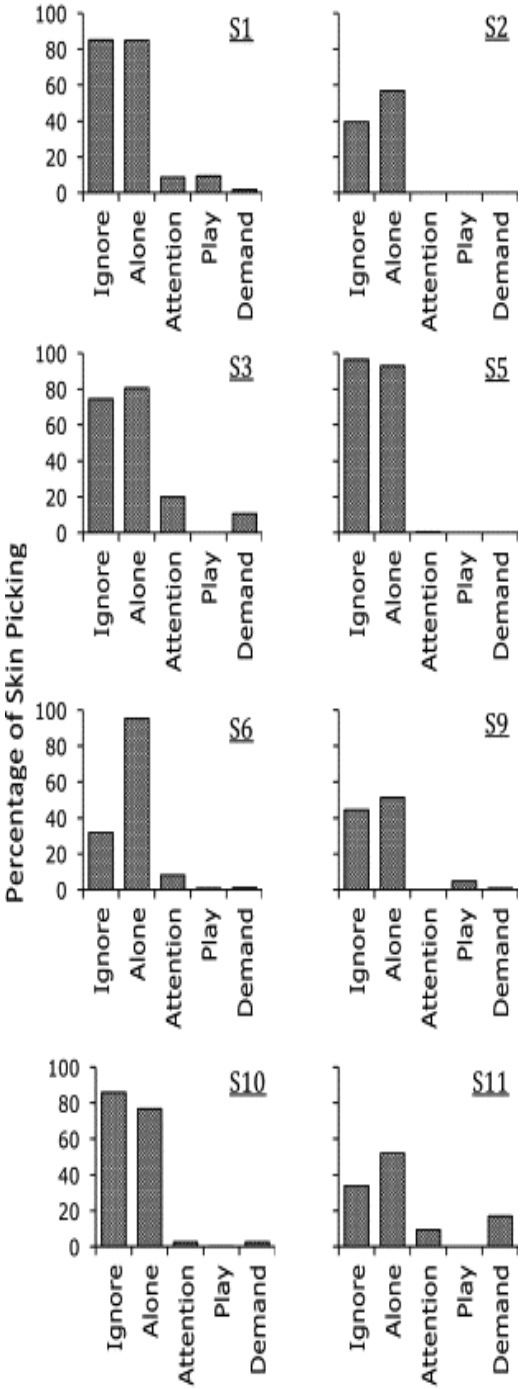
- Specific characteristics (picking at existing lesions, particular body areas)
- Influenced by environmental circumstances and by mood state

Factors characteristic to PWS that may predispose to this behaviour

- Sensory ‘hunger’ (need for stimulation)
- High pain threshold (lack of negative feedback)
- Tendency to routine and obsessive behaviours

SKIN PICKING IN PEOPLE WITH PWS

Functional analysis of eight people with PWS. High levels of skin picking were observed in the *alone* and *ignore* conditions for eight of the twelve participants



Hall et al (2014) Experimental functional analysis of severe skin-picking behavior in Prader–Willi syndrome. Res Dev Dis 35: 2284-2292

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Skin picking

Best understood as an interaction between a biological vulnerability, physical and psychological factors and environmental circumstances

- Functional analysis - behavioural interventions
- Treatment of co-morbidity (e.g. mood disorder)
- Environmental changes
- Topical treatments to skin
- Medication to modify glutaminergic pathways in the brain (N-Acetylcysteine)

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journal homepage: www.elsevier.com/locate/neubiorev

Developing an understanding of skin picking in people with Prader-Willi syndrome: A structured literature review and re-analysis of existing data

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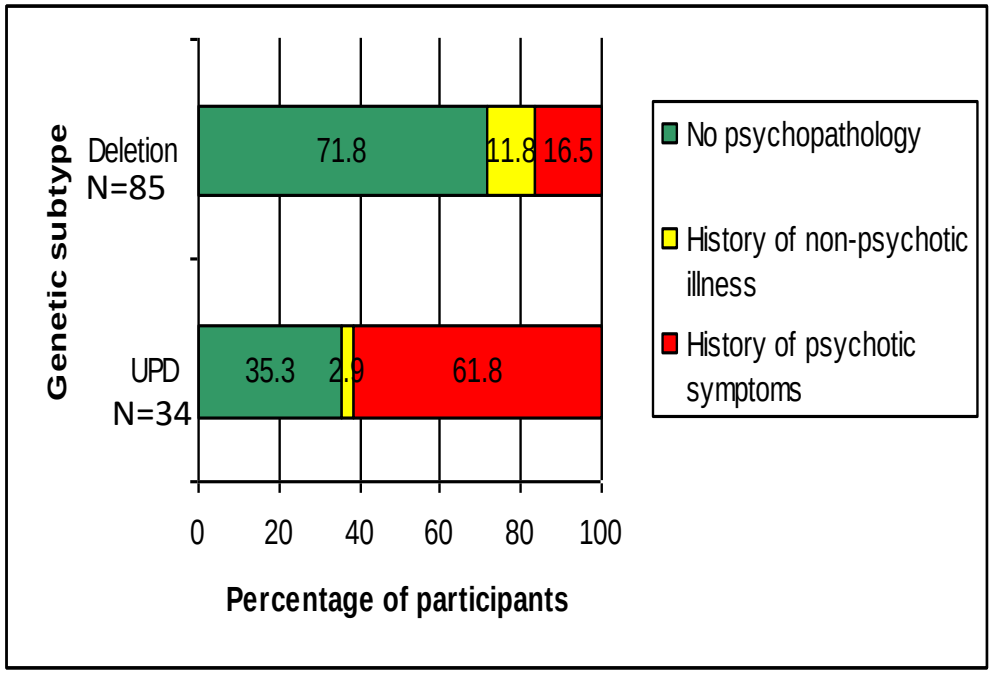
Abnormal mental state in 18 year old with PWS due to mUPD

- Sudden (over hours) deterioration in his mental state at his group home
  - Confusion (bewildered)
  - Anxious++
  - Unable to talk coherently – referring to 'blackmail'
- Seen in A/E – Diagnosis confusional state
  - Using unrelated words "black, sky, fish"
  - Staring at his hands – grabbing things – hitting staff – saying strange things
  - Staff 'not using their real names and lying to him'
  - Crawling on hands and chasing a butterfly that was not there
- Discharged after some improvement, relapsed within hours – liaison psychiatrist diagnosed atypical psychotic illness started on aripiprazole
- Mental state improved over 4 days – two months later remains well on medication.

Prevalence of psychotic and non-psychotic mental illness

- Psychotic symptoms more common in mUPD than deletion
- Psychopathology without psychotic symptoms more common in deletion than mUPD



Soni et al, 2007, 2008

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Mental illness in people with PWS

- Presents with a deterioration in behaviour and/or the onset of new bizarre behaviour
- Onset usually acute but can also be gradual
- Associated with abnormal mood state and the development of abnormal mental experiences (confusion, hallucinations, delusions)
- Interventions
  - Medication based on diagnosis
  - Reduce demands
  - Consistent informed support
  - Prevent harm

Key Points 3: ask questions?

- Difficult behaviours may occur for different reasons
- When behaviours are a problem, ask yourself is this what we have seen before or is it different?
- If this behaviour is new or has become much worse than it has been, ask why?
- Is there any evidence that the person with PWS might have developed a physical or mental illness?
  - Abnormal mental experiences
  - Altered mood
  - Physical symptoms (e.g. vomiting, complaining of pain, etc)

Environmental and psychological interventions

Early intervention
Environmental change
Psychological interventions

Mental health and wellbeing

'Biological' interventions

Medications
VNS

Environments

Behaviours reinforced and maintained
Functional analysis

Present environment
Predictability
Food security

Past experiences
Opportunities to learn

Psychotic illness

Impact of maternally expressed genes

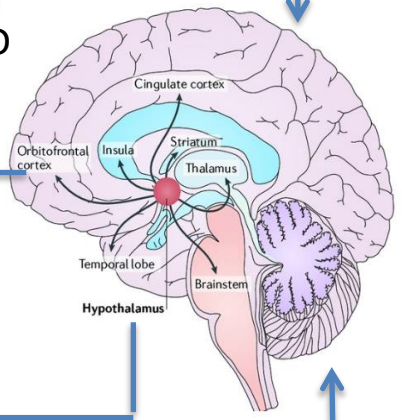
mUPD

Impaired cognition

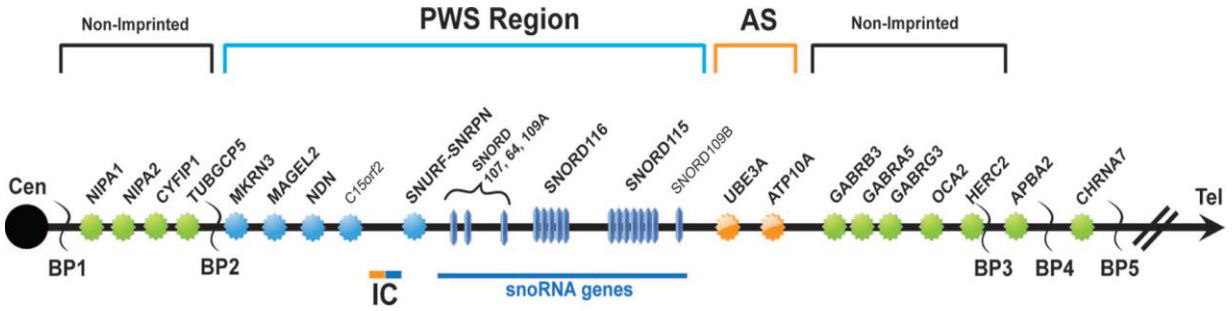
Understanding
Response to change

Impaired regulation

Mood, food intake
'Homeostasis'



Atypical brain development and function



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Interventions

informed by the formulation & understanding of the person with PWS

- Environmental – optimise understanding, reduce uncertainty
  - Structured time table
  - Visual support
  - Use of language
  - Food security
- Psychological – to manage change, to limit outbursts, to reduce skin picking
  - Applied Behavioural Analysis (predispose, precipitate, maintain)
  - Early intervention
  - Specific training (e.g. preparing for change, managing outbursts)
- Medical – to treat physical and psychiatric co-morbidities known to respond to specific treatments
  - Treatment of physical illness (e.g. sleep apnoea)
  - Treatment of psychiatric illness (e.g. mood disorder, psychosis)

Interventions

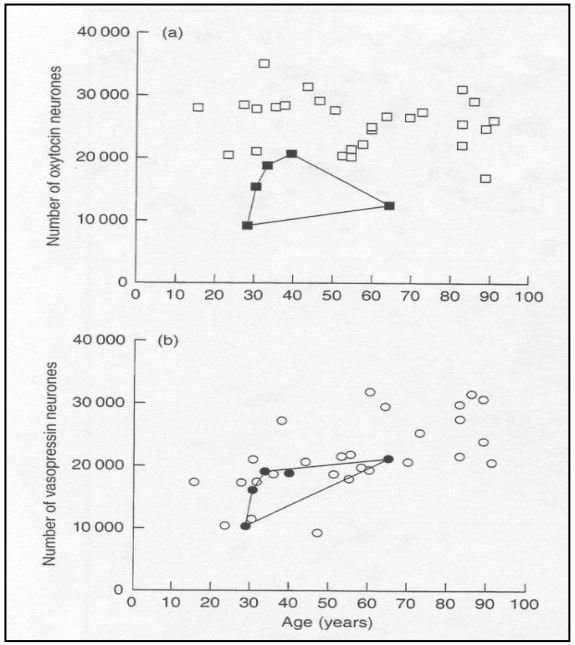
The future – behaviour and mental health

- Social support
  - Delivery of support (family, social support services)
  - Informed and well resourced social care
  - Education and opportunities in adult life (UN CRPD)
- Potential new treatments for:
  - Hyperphagia (many trials in progress or planned)
  - Behaviour (e.g. VNS, medications, psychological)
  - Social functioning (e.g. oxytocin)
- Personalised medicine
  - Pharmacogenomics (guide dose of medication)
  - Biomarkers for responders vs non-responders
- Application of neuroscience to PWS
  - Atypical brain development
  - Mechanisms underpinning behaviours, cognition etc

Oxytocin in PWS

Human PWS hypothalamus 38% reduction in total PVN neurons 42% reduction in PVN oxytocin neurons

Swaab et al. JCEM 80:573-579, 1995



Schaller et al (2010) A single postnatal injection of oxytocin rescues the lethal feeding behaviour in mouse newborn deficient for the imprinted Magel2 gene. Hum Mol Gen 19: 4895-4905

Tauber et al (2011) Oxytocin may be useful to increase trust in others and decrease disruptive behaviours in patients with PWS: a randomised placebo controlled trial in 24 patients Orphanet J Rare Dis, 6: 47-52.

Einfeld et al (2014) A double-blind randomised controlled trial of oxytocin nasal spray in PWS. Am J Med Gen part A 164A: 2232-2239

Kuppens et al 2016 Effects of oxytocin intranasal spray on social and eating behaviours in PWS – beneficial effects only <11years of age. Clinical Endocrinology, 85, 979

Miller et al (2017) A double blind placebo controlled cross-over trial of oxytocin nasal spray – eating behaviour, socialisation, anxiety and repetitive behaviour. No significant effects. Am J Med Genet 173: 1243

Dykens et al (2018) Intranasal carbotocin reduces hyperphagia in individuals with Prader-Willi Syndrome JCI Insights 2018

Final Key Points

- The prevention and effective management of problem behaviours requires understanding.
- Specific treatments at present are limited
- Cognitive impairments makes the world more uncertain for people with PWS. How can you change the environment to compensate?
- Psychiatric medications to be used with caution and guided by diagnosis
- Developing psychological interventions, new treatments for specific symptoms, more informed approaches to support – a more positive future.

THANK YOU

COMMENTS & QUESTIONS?

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