Prader-Willi Syndrome
Overview: behaviours and psychopathology

Tony Holland
University of Cambridge

Cambridge Intellectual and Developmental Disabilities Research Group
www.CIDDRG.org

Outline

- Terminology and conceptual models (ID)
  - Challenging behaviour
  - Psychopathology
- The ‘behavioural phenotype’ of PWS
  - Eating disorder
  - Repetitive and ritualistic behaviours
  - Skin picking
  - Affective disorder and psychotic illness
- Direct and indirect mechanisms linking genotype to phenotype
- Potential new treatments
- Implications

Prader-Willi Syndrome (PWS)

Professor Andrea Prader
1919 – 2001

Professor of Paediatrics
University of Zurich

with Labhart and Willi first described the syndrome in 1956

Characteristics (phenotype)

Early hypotonia and failure to thrive

Developmental delay and LD

Short stature and immature sexual development – relative hormonal deficiencies

Characteristic physical appearance

At risk of severe obesity – over-eating behaviour

High risk of specific behaviours and psychiatric disorders

Genetic origin – absence of expression of paternally expressed/maternally imprinted gene(s) Chr 15q11-13

PWS over the lifespan

Intra-uterine (placental)

- Poor growth
- Limited foetal movement
- High rates atypical births

Gender specific genomic imprinting

C/D box snoRNA SNORD 116 (HBII-85)

Infancy

- Extreme hypotonia
- Failure to thrive

Childhood

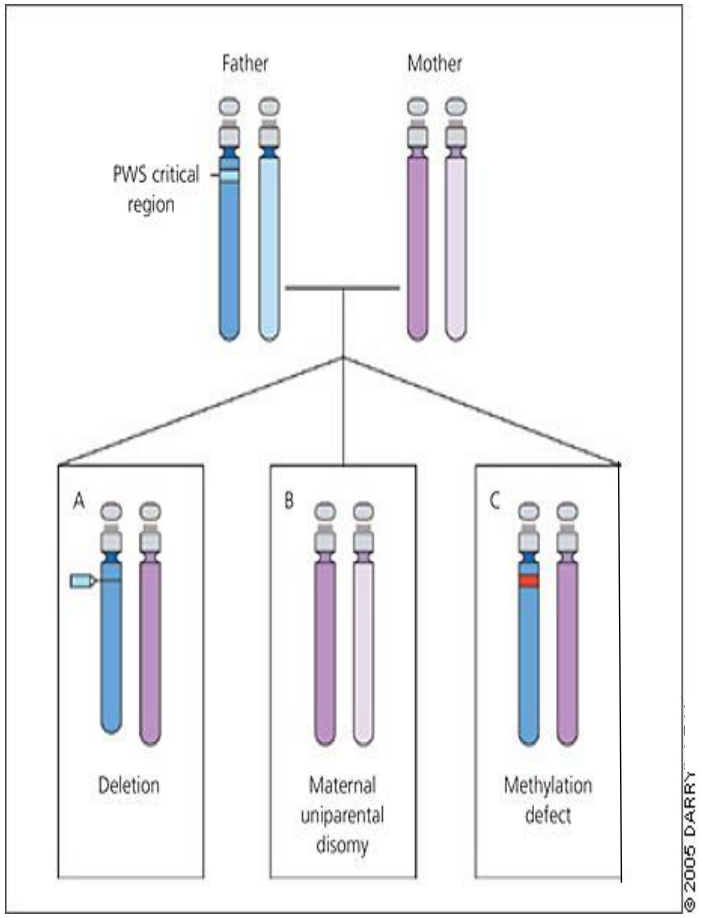
- Developmental delay – intellectual disabilities
- Short statute – relative growth hormone deficiency
- Sexual immaturity – sex hormone deficiencies
- Over-eating - risk of severe obesity and its complications
- Scoliosis, respiratory disorders, maladaptive behaviours

Adulthood

- Increased risk of obesity (with greater independence)
- Age-related physical and psychiatric morbidity

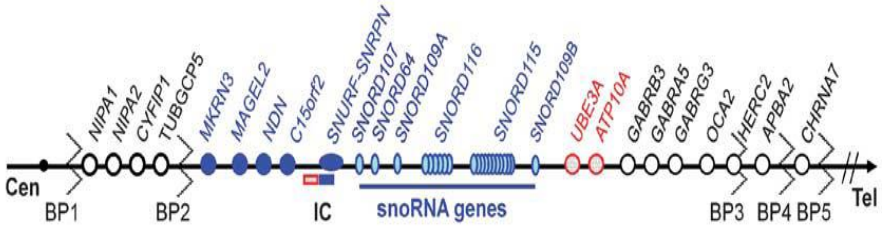
McAllister et al, International Journal of Obesity 2011

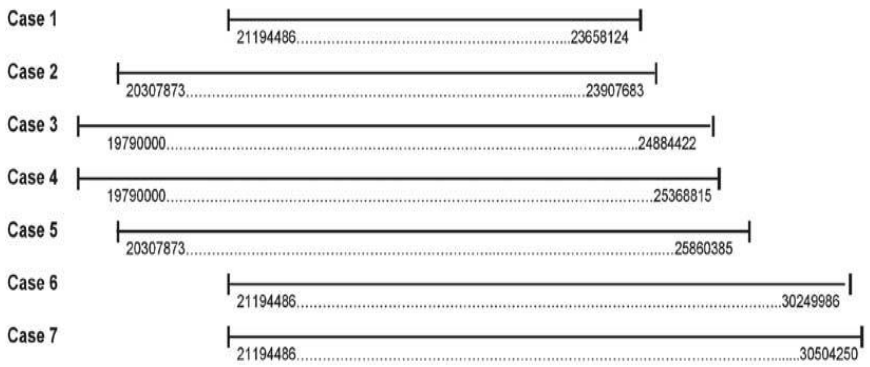
Schematic of chromosome abnormalities resulting in PWS (fully elucidated 1990+)



70% 25% <5%

Chromosome 15





Soo-Jeong et al 2012 Unique and atypical deletions in PWS reveal distinct phenotypes European Journal of Human Genetics (2012) 20, 283-290

Challenging behaviour in people with intellectual disabilities (ID)

- **Applied behavioural analysis**

  External factors over time shape and predispose to, precipitate and maintain such behaviours (e.g. demand avoidant, attention-maintained);

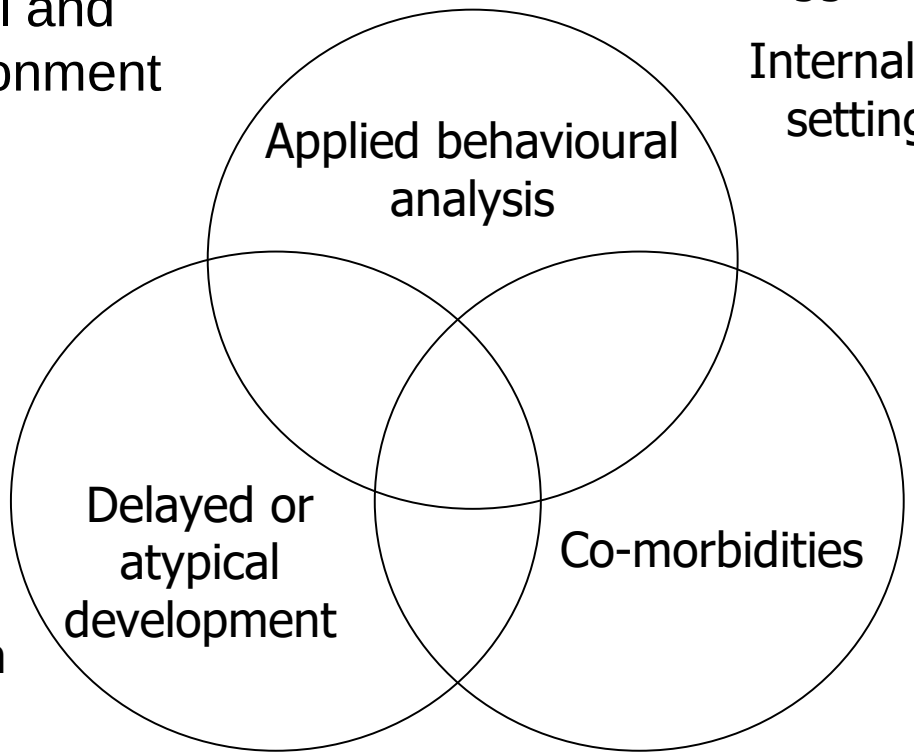
- **Co-morbid physical or psychiatric disorders**

  Changes in physical and mental state result in, or increase the propensity to, problem behaviours in response to environmental contingencies;

- **Delayed or atypical development**

  Behaviours are a manifestations of delayed or atypical development that may be syndrome specific (e.g. autism spectrum disorder, behavioural phenotypes of syndromes).

Theoretical models for understanding challenging behaviour



FORMULATION: biological, psychological and social factors predisposing to, precipitating or maintaining such behaviours or abnormal mental state

Behavioural Phenotype of PWS

Questions

- What problems occur in excess in PWS and why?
- Are these maladaptive behaviours and psychiatric disorders associated with each other?
- What is the relationship between PWS genotypes and behavioural phenotypes?
- What separate or shared mechanisms directly or indirectly link genotype to phenotype?
- How are they best managed/treated?

Behaviour in PWS

Population-based study

Informant reported
Prevalence (%) of specific behaviours (n=65)

	Definite	sometime	none
Excessive eating	78	21	1
Repetitive/ritualistic	70	23	7
Tempers	67	27	6
Skin picking	59	22	19
Mood swings	38	19	43

Holland et al, 2003 Psych. Med. 33:141-153

Prader Willi Syndrome

Factor Analysis - behaviours reported in population-based study

Factor 1	Factor 2	Factor 3
Eating	Obsessive	Mood Swings
Lying	Tempers	Skin picking
Stealing	Possessive	Stubborn
	Aggression	Argumentative

Weight chart of young adult with PWS

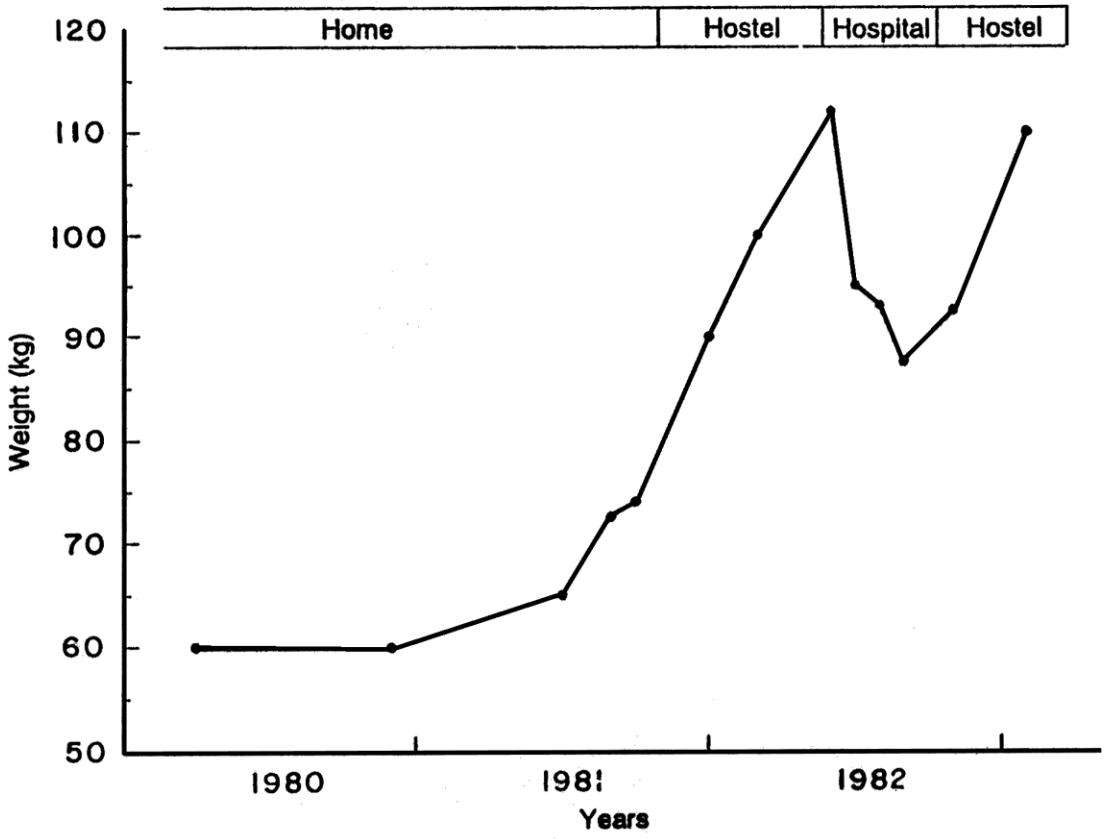
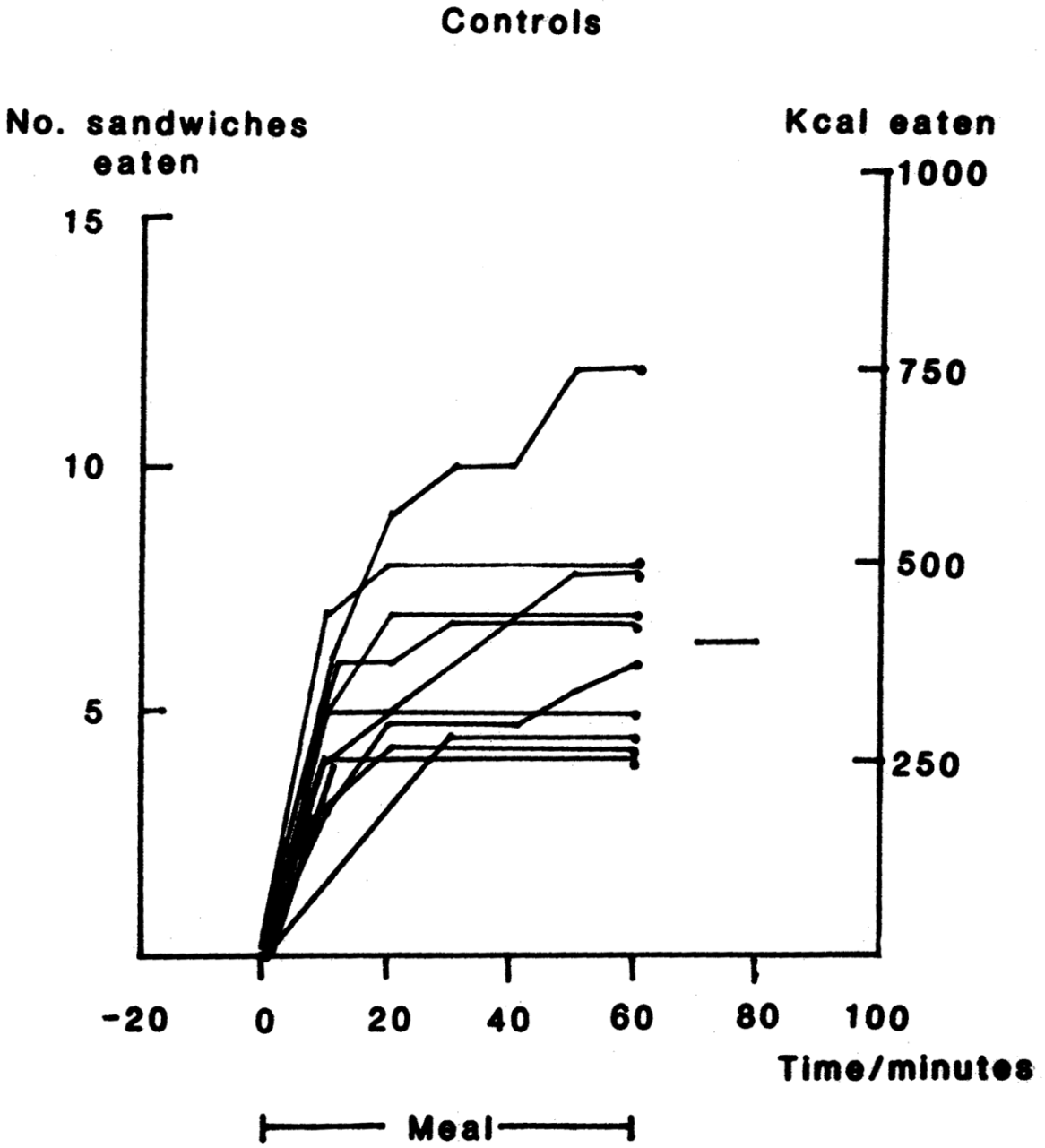
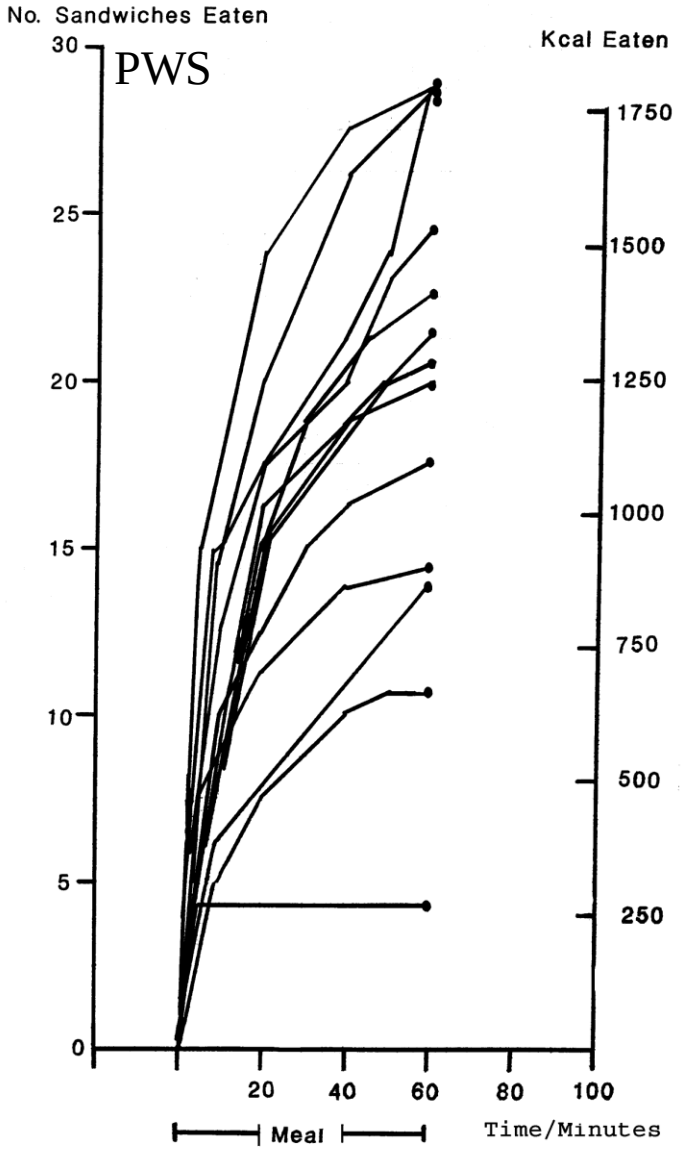


Figure 2 The weight chart of a person with Prader–Willi syndrome showing the large weight increase which occurred when access to food was unsupervised in a group home for people with learning disabilities.

Journal of Intellectual Disability Research 39, 3 3–3· 1



Holland et al. (1993). Measurement of excessive appetite and metabolic changes in Prader-Willi Syndrome. *International Journal of Obesity*: 17:527-532.

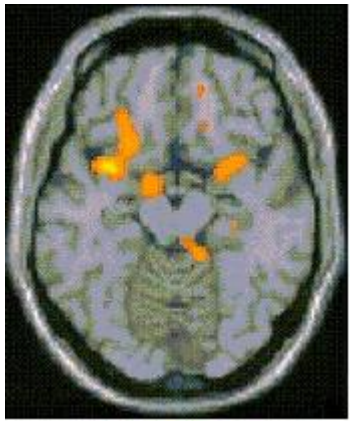

No. Sandwiches Eaten
PWS
Kcal Eaten
30
25
20
15
10
5
0
1750
1500
1250
1000
750
500
250
20
40
60
80
100
Meal
Time/Minutes

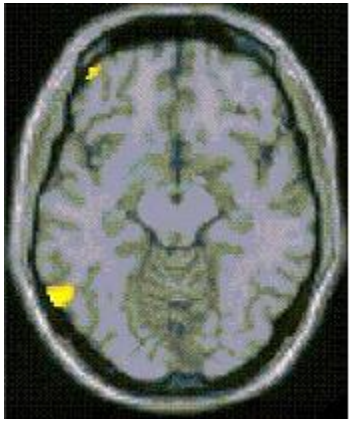
PET functional brain imaging study

Hunger condition

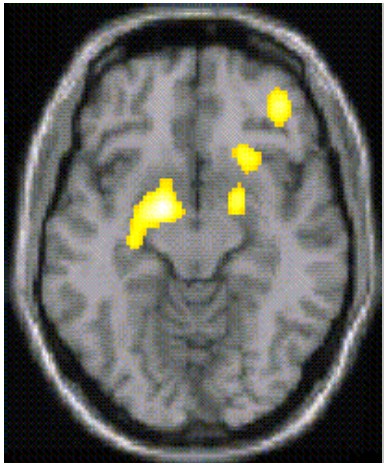
Post meal condition

Controls





PWS



The high calorie meal (in comparison to fasting) did not result in the same pattern of brain activation that was found following food intake in those without PWS

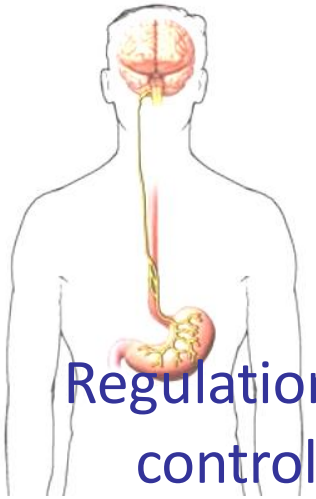
No activations survived the analysis once the correction for multiple comparisons was applied

Hinton et al (2006). Neural Representations of hunger and satiety in Prader-Willi syndrome. *International Journal of Obesity* 30:313-321

Hypothesis Paper

The Paradox of PWS: a genetic model of starvation

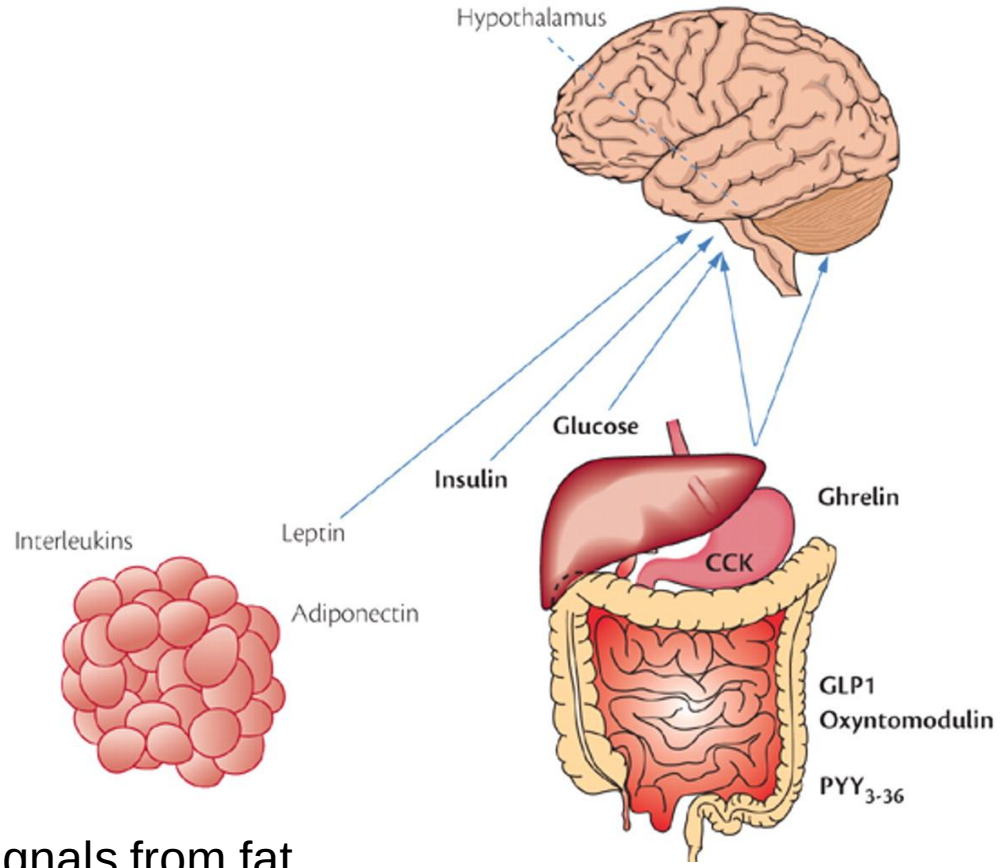
Holland et al, Lancet, 2003, 362, 989-991



Brain control of food intake

Regulation of food intake is controlled by a combination of signals to and from the brain.

People with PWS have delayed and impaired satiety and may be lacking or insensitive to peripheral signals to the brain.



Signals from fat cells

Signals from the gut

Farooqi, Oxford Textbook of Medicine

Eating disorder
Interventions

- Biological abnormality of satiety and/or reward mechanisms associated with food;
- No specific treatment as yet of the eating disorder;
- Supervised access to food prevents obesity (and associated morbidity) and may help wellbeing;
- Strategies to help manage the tension between choice and the need to control access to food.

Repetitive and ritualistic behaviours and temper outbursts

- Characteristics
- Mechanisms
- Implications

Population-based Study of PWS Obsessive Compulsive Symptoms

Symptom	PWS (n=80)	contrast (n=36)	
Ask/tell	36/80 (46%)	4/33 (14%)	**
Routines	26/80 (32%)	4/33 (12%)	*
Hoarding	19/80 (24%)	1/33 (3%)	**
Repetitive	18/80 (23%)	3/33 (9%)	NS
Ordering	11/80 (14%)	0	*
Cleaning	2/80 (2%)	0	NS
Counting	0	0	
Checking	0	0	

Clarke et al 2002 BJ Psych; 180-358

Repetitive behaviour in PWS and autism

Childhood Routines Inventory

	PWS N=80;		Autism N=89	
Total score	13.1	(5.1)	14.1	(4.2)
Just right factor score	3.4	(1.6)	3.8	(1.4)
Repetitive factor score	3.6	(1.6)	3.8	(1.2)
Total freq/intensity	52.6	(16.6)	54.3	(15.6)
Just right freq/intensity	13.1	(5.2)	14.3	(5.1)
Repetitive freq/intensity	14.6	(5.8)	15.5	(4.7)

Strongly significant negative association between DQ and frequency/intensity scores in PWS less so in autism

Greaves et al, 2006 JIDR, 50, 92-100

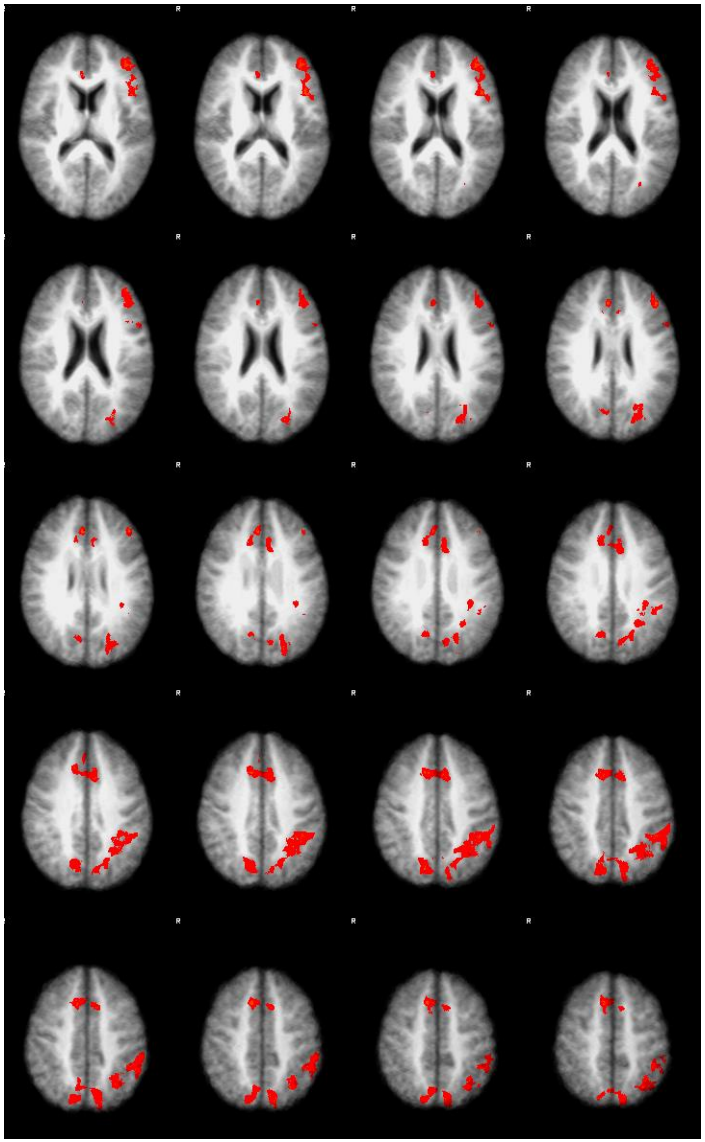
Hypothesis: genes to behaviour in PWS

Woodcock et al 2009 JIDR, 53: 493-500

- Repetitive and ritualistic behaviours and temper outbursts cluster together;
- Children with PWS reported to show a preference for predictability with negative emotional behaviour and arousal following change (Woodcock et al, 2009);
- Repetitive questions focused on the future and occurred more frequently following change in routine;
- Change produces high demand on cognitive resources – in PWS specific deficit in task switching from one cognitive set to another (cognitive endophenotype) (Woodcock et al Cognitive neuropsychology)

Brain activity when switching

CONTROL



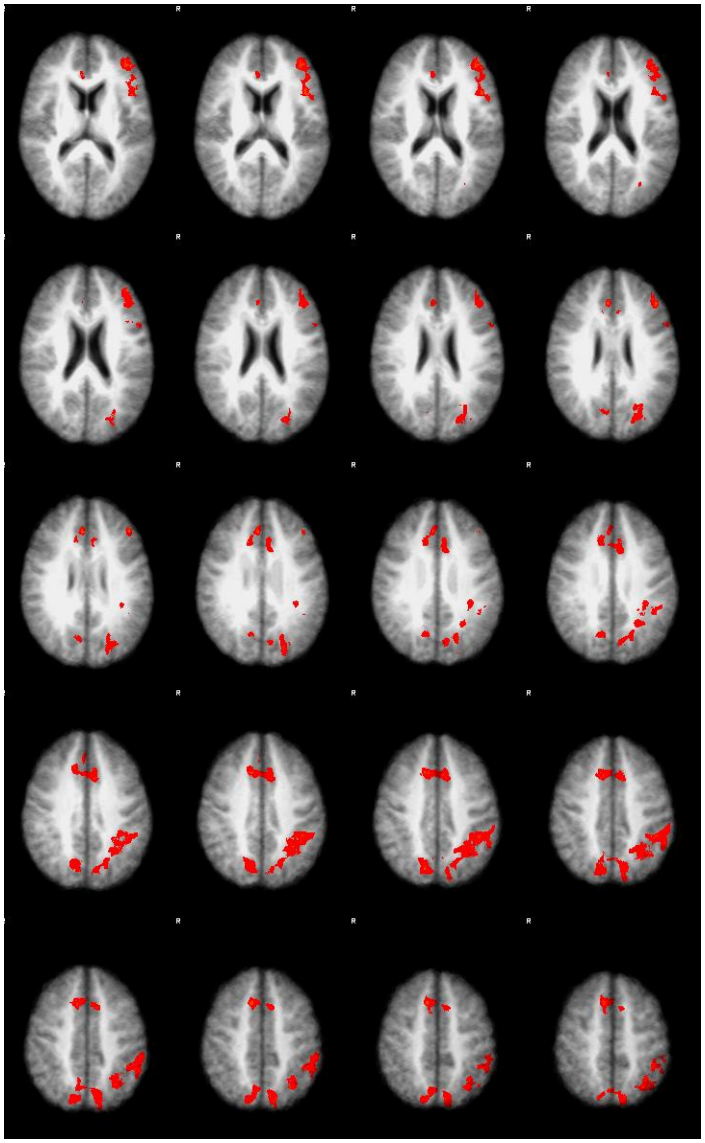
Prefrontal-anterior cingulate-parietal activation –

as previous research

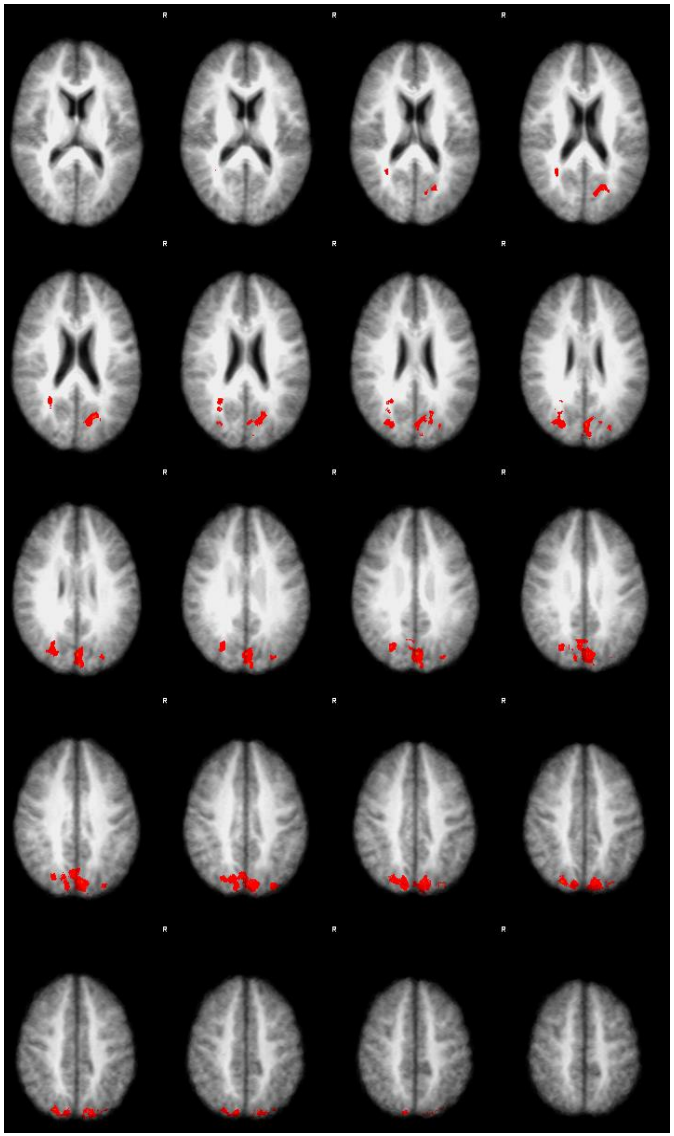
Woodcock, Oliver et al,
University of Birmingham, UK

Brain activity when switching

CONTROL



PWS

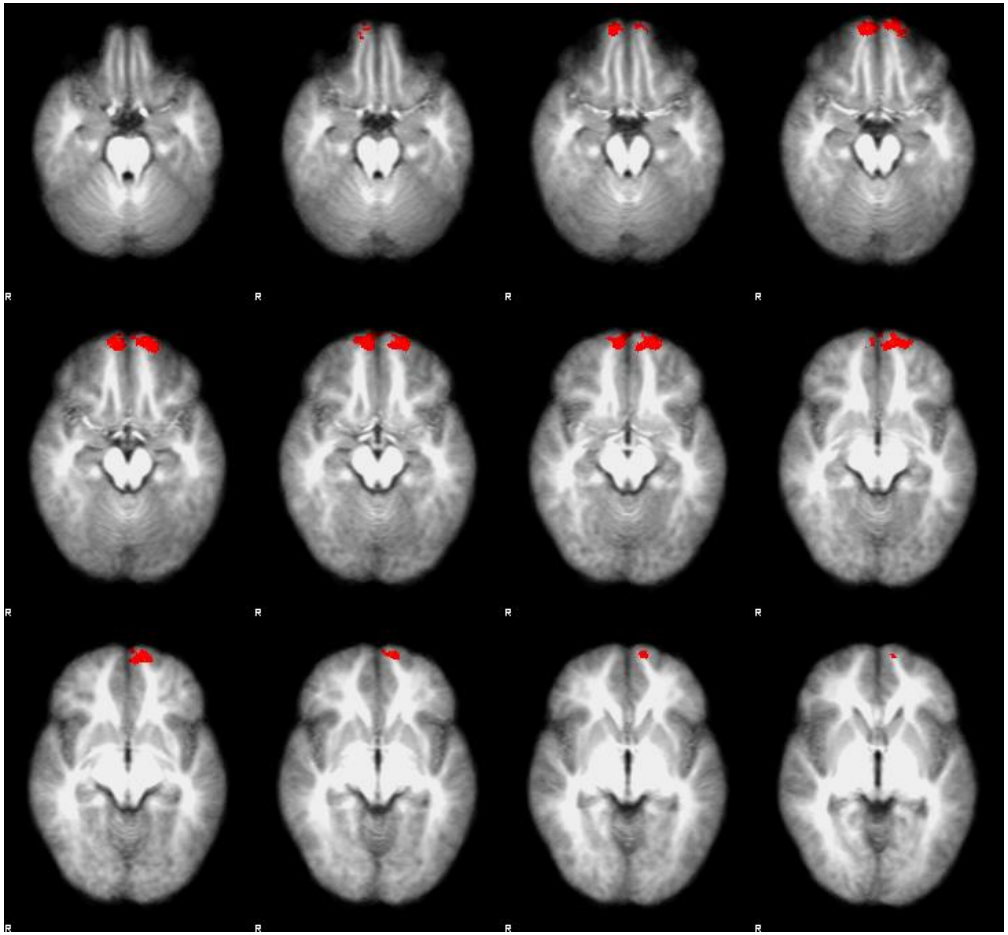


Mainly occipital + small clusters of parietal activation

ROI analysis: no significant activity in network activated in controls during switching

Brain activity when switching

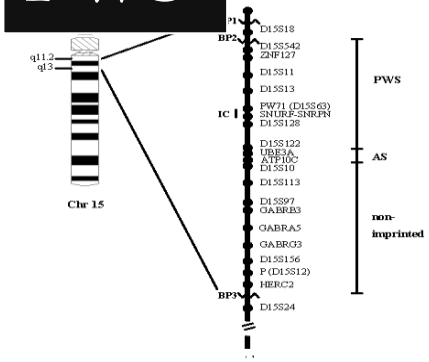
PWS > CONTROL



Significantly greater switch-related activity in PWS vs. control participants in some frontal polar regions

Woodcock, Oliver et al,
University of Birmingham, UK
Cognitive Neuropsychology
on-line

PWS

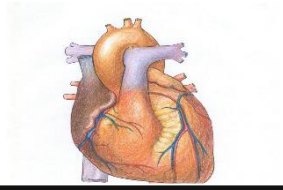


Courtesy of Woodcock, University of Birmingham, UK

Brain functional abnormalities

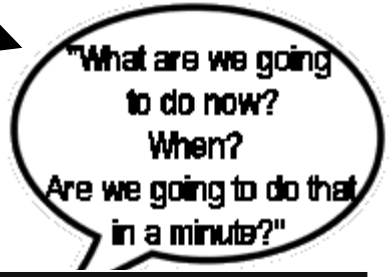
Deficit in attention switching

UNEXPECTED CHANGE



Physiological arousal

Temper outbursts



Repetitive questions

Implications

- Biological determined deficit in set-switching predisposes to pattern of repetitive and ritualistic behaviours and temper outbursts
- Pattern of behaviour becomes established through reinforcement over time
    - Early intervention to minimise establishment of behaviours
    - Psychologically informed support strategies
    - Training to improve set-switching
- Why deficit in set-switching?
- Common genetic basis for relationship between PWS and autism?

Skin picking in PWS

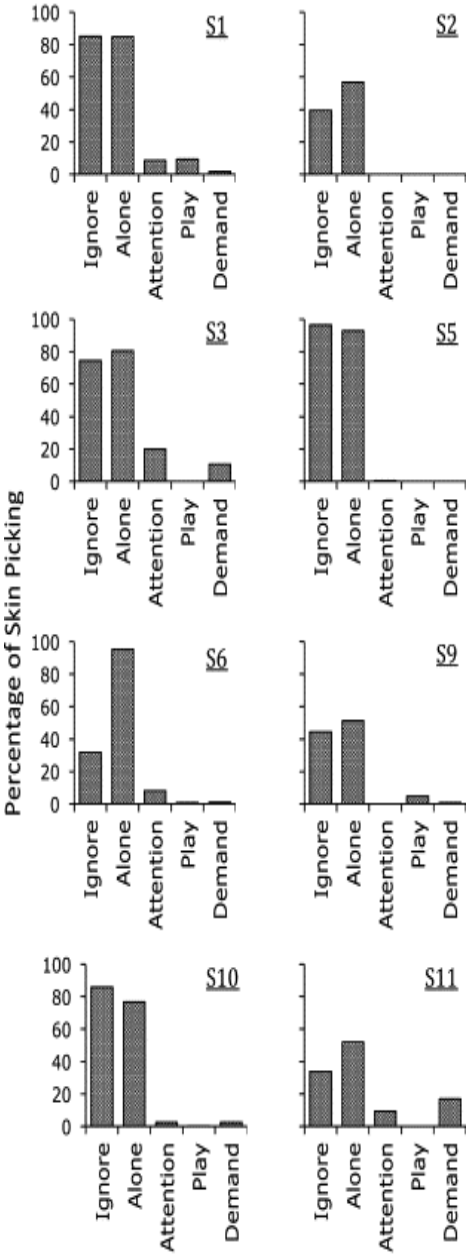
- Possibilities
  - Mood related
  - Part of ‘obsessive compulsive disorder’
  - Absence of negative feedback due to high pain threshold
  - Functional

Modulation of the glutaminergic pathway using N-Acetylcysteine in 35 children and adults with PWS. Assessed before and after 12 weeks of treatment on numbers and size of lesions. All improved 10 did not resolve completely.

Miller et al (2013) An open label pilot study of N-Acetylcysteine for skin picking in PWS. Am J Med Gen Part A 164A: 421-424

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

Differentially high levels of skin picking were observed in the *alone* and *ignore* conditions for eight of the twelve participants (i.e., S1, S2, S3, S5, S6, S9, S10, and S11). Fig. 1 shows the mean percentage of skin picking observed in each condition of the functional analysis for these eight participants.



Mental illness

- Characteristics
- Prevalence
- Mechanisms
- Implications

Psychiatric illness in PWS

- Kollrack and Wolff 1966
- Since then, over 20 studies describing the association of PWS with psychiatric illness
- Most describe an affective psychosis with characteristic features
- However, some methodological problems:
  - Small sample size
  - Not genetically confirmed

Population-based Study of PWS Psychotic Illness (Boer et al, Lancet, 2002)

Number with psychotic illness (7/25 28%)

	Age 18-27	age 28+
Del (15q11-13)	0/4	1/9 (11%)
UPD	0/3	5/5 (100%)
Other	0/3	1/1*
Total	**0/10**	**7/15 (49%)**

*Imprinting centre defect

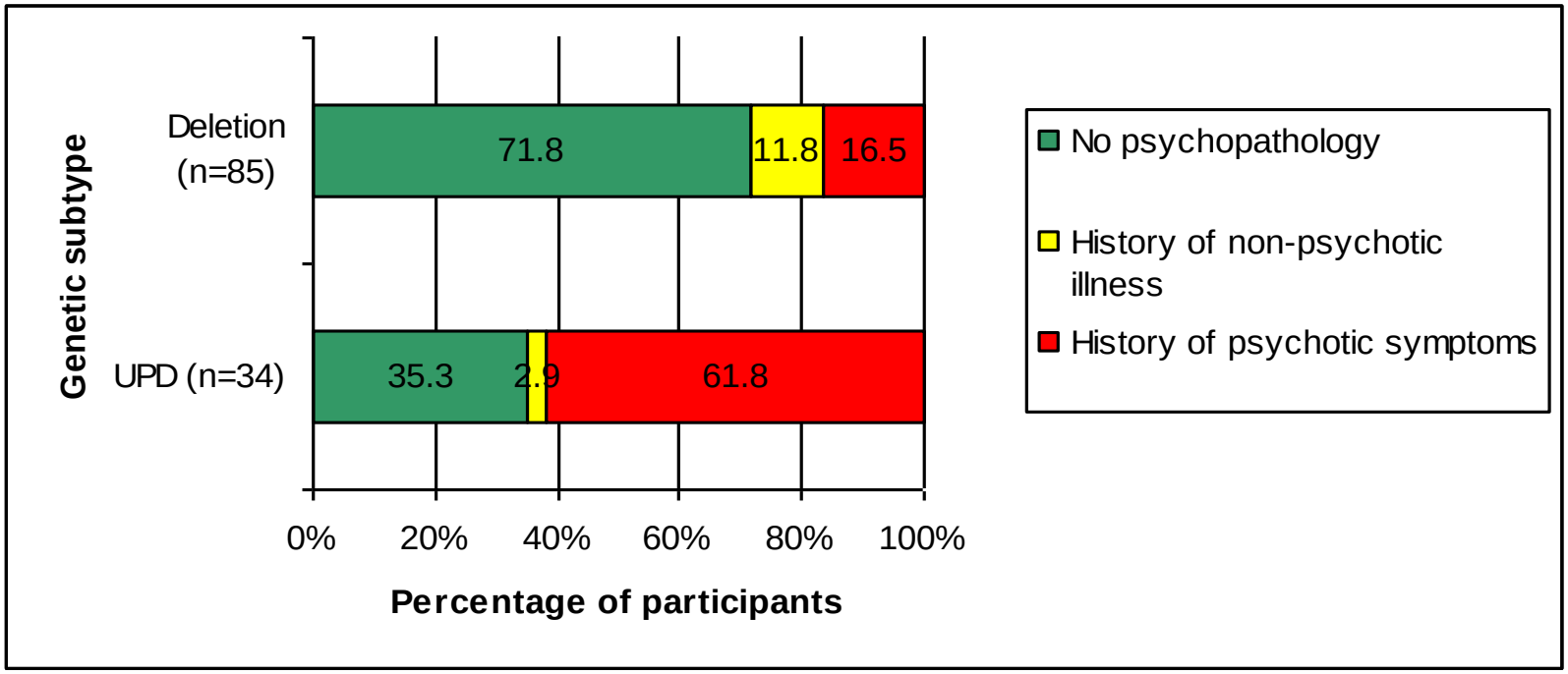
Method
Soni et al 2008

- 46 of 119 (38.7%) adults screened positive for psychopathology
  - 24 Deletion, 22 mUPD
- Further assessment included:
  - Psychiatric Assessment Schedule for Adults with Developmental Disability (PAS-ADD)
  - Operational criteria checklist for psychotic and affective illness (OPCRIT)
  - Family History Questionnaire
  - modified Life Events Questionnaire
  - Wechsler Adult Intelligence Scale (WAIS)

Soni et al 2008, Psychological Medicine, 38, 1505

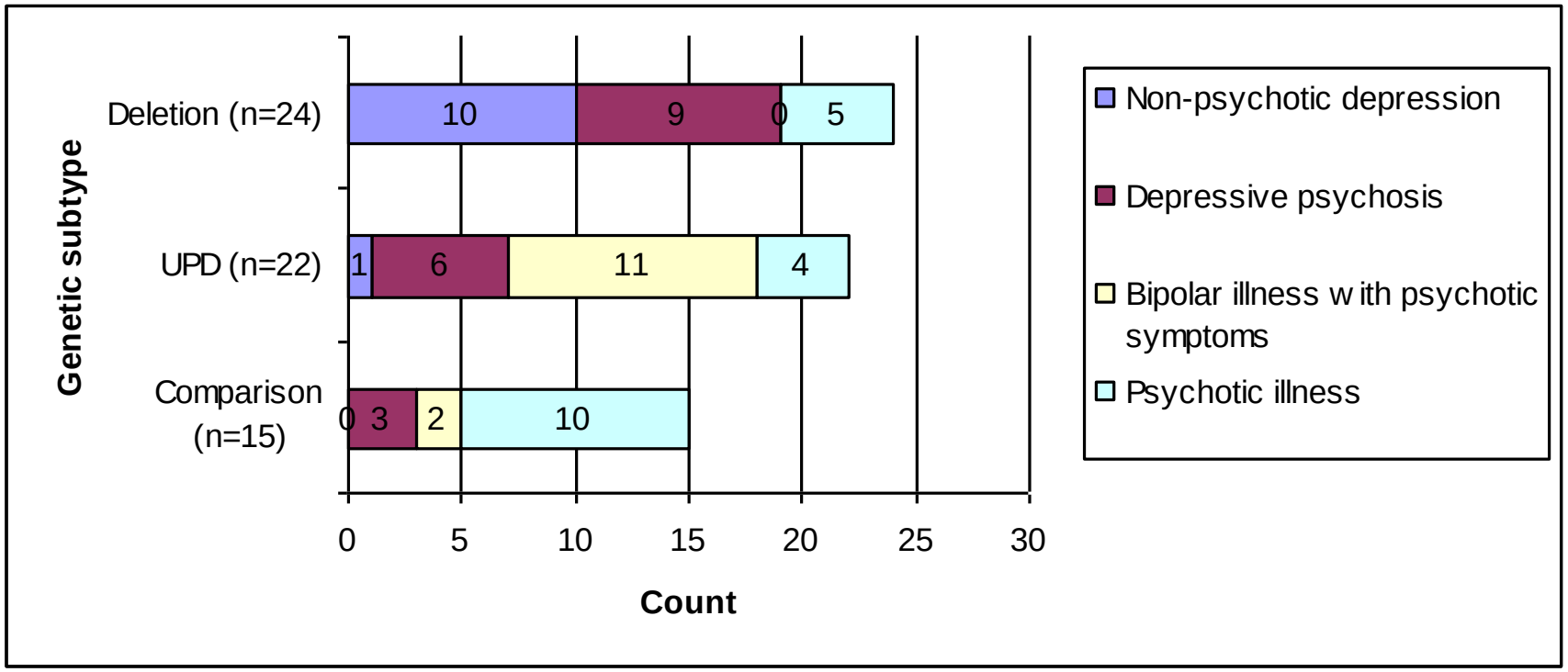
Prevalence of psychiatric illness

Psychotic illness more common in mUPD than deletion
p<0.001, effect size 0.45

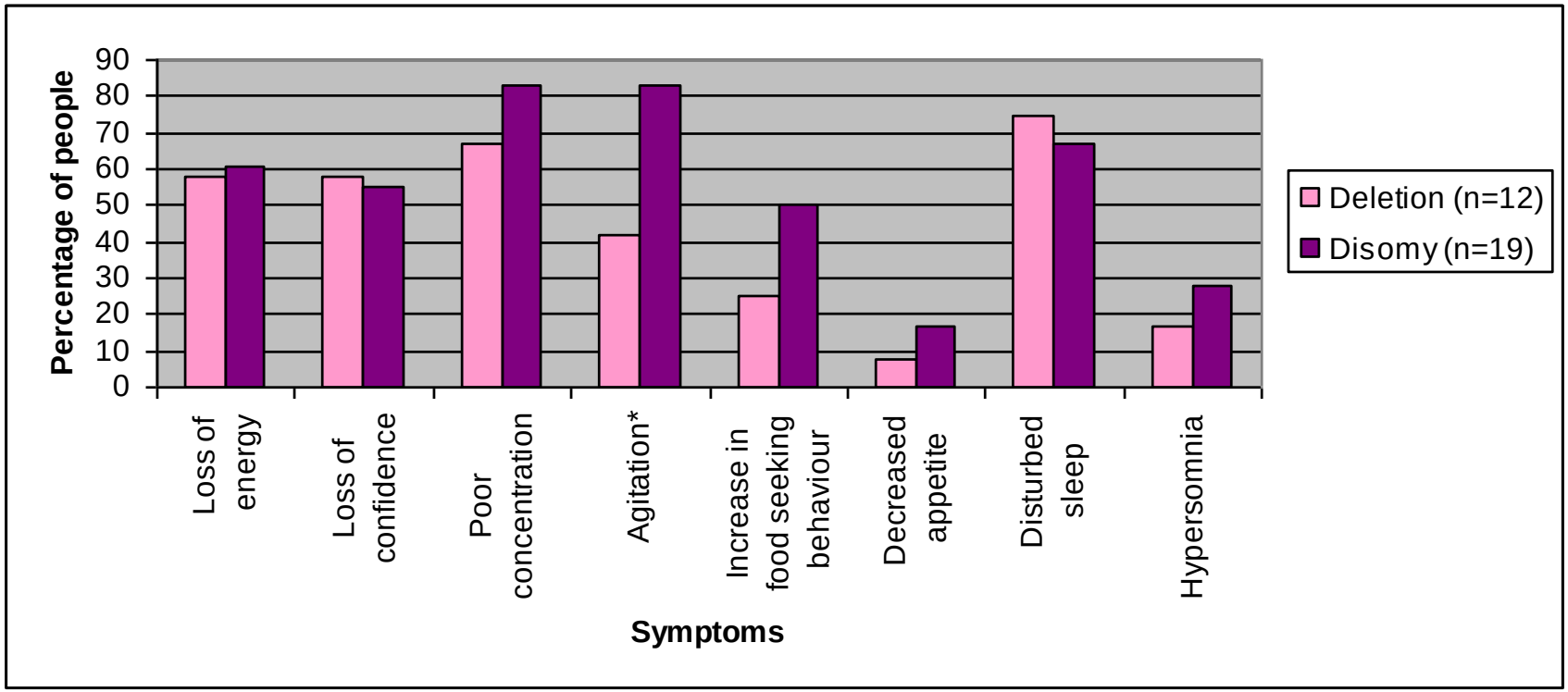


Psychiatric Diagnosis

Non-psychotic depressive illness more common in deletion than mUPD p=0.005, effect size 0.43

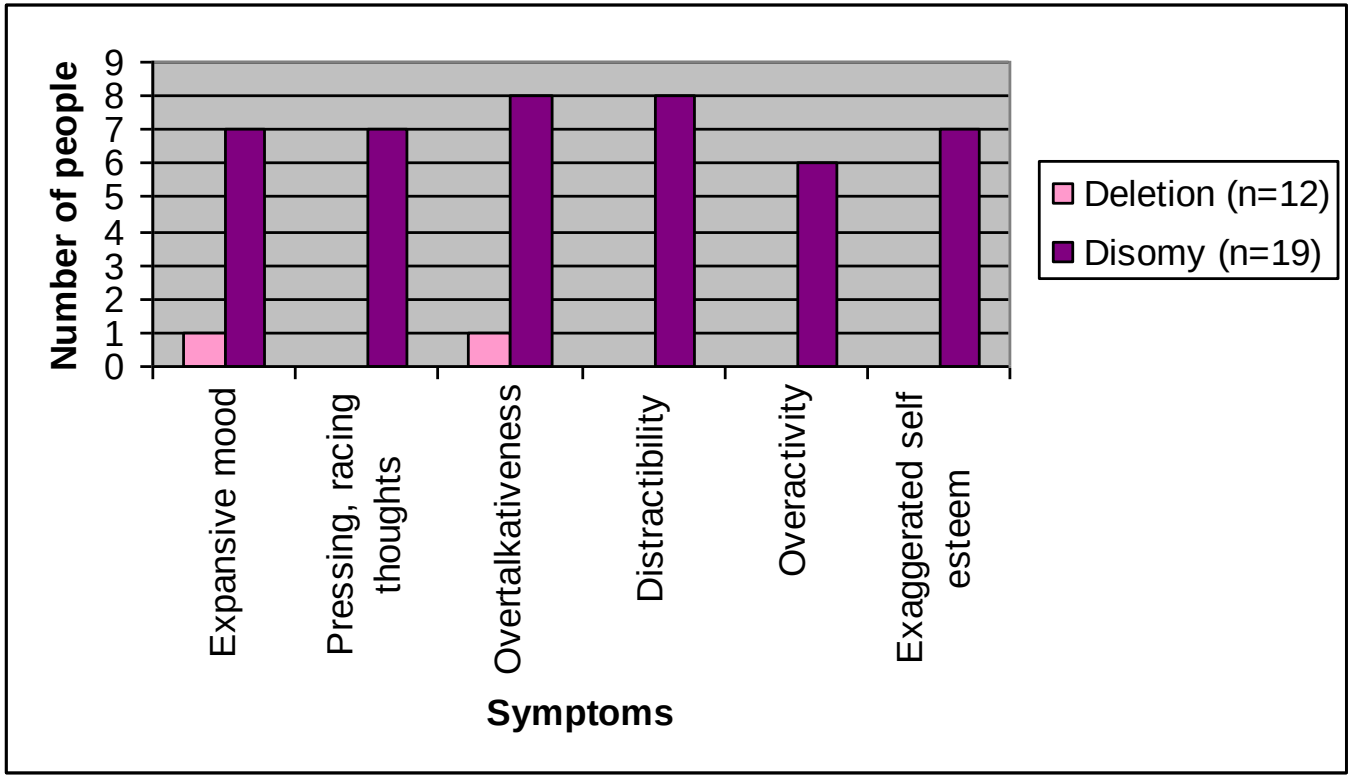


Graph to show symptoms in participants with psychotic symptoms (n=31)

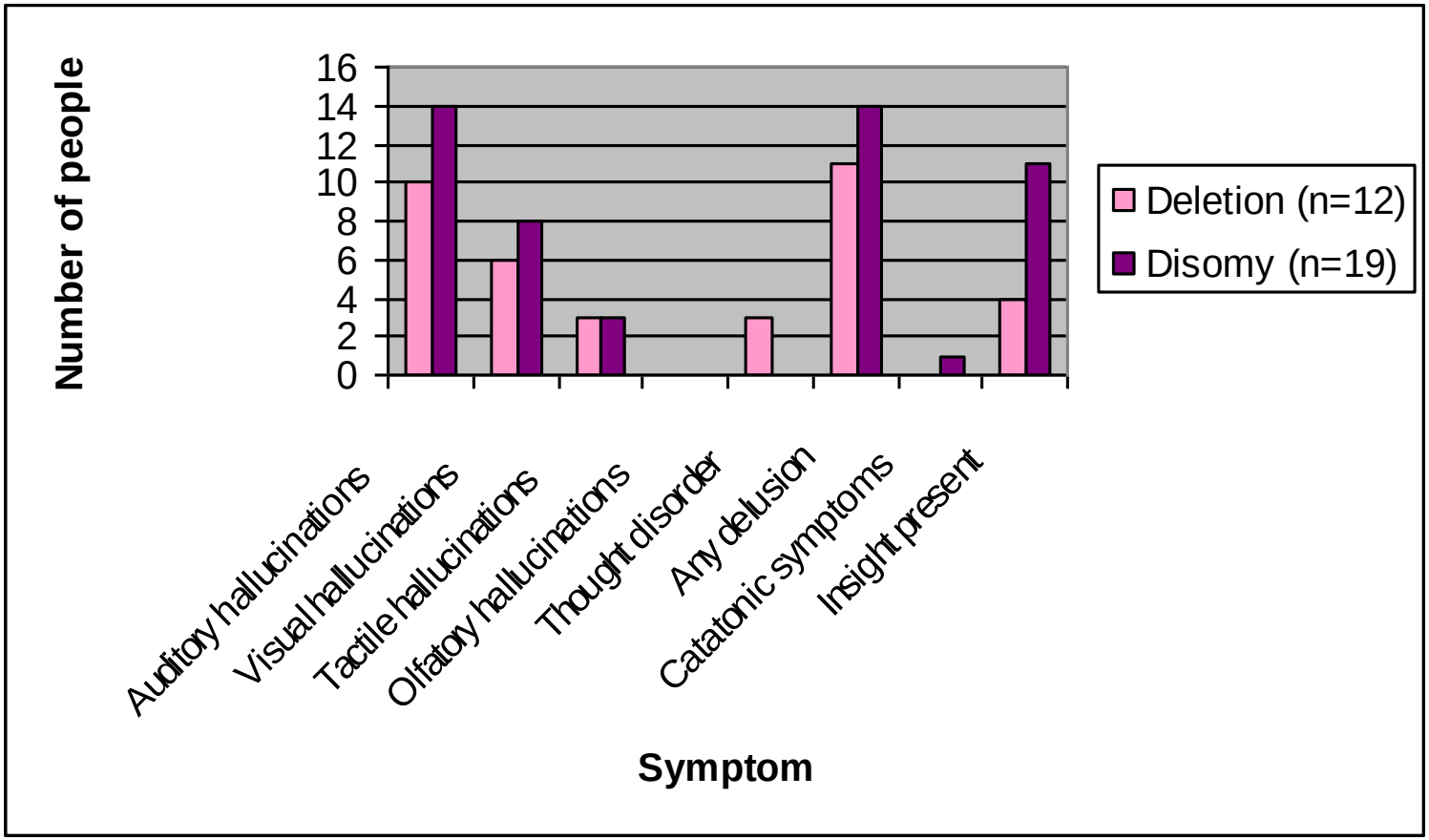


*Difference between genetic subtypes on scores of "agitation": Fishers Exact test 2 sided; $p<0.05$

Symptoms of hypomania in people with psychotic symptoms (n=31)



Frequency of psychotic symptoms



Summary of phenomenology

- Evidence of mood related psychiatric illness;
- Hypomanic symptoms and agitation more pronounced in those with mUPD;
- Delusions predominately persecutory in both deletion and mUPD;
- Auditory and visual hallucinations present in both groups;

Mr RT (aged 18 years): Reason for Referral

- Two weeks earlier some concern that his mood had become low – started on Fluoxetine
- Marked and sudden (over hours) deterioration in his mental state following a visit to his family.
- Resulted over several days in three admissions to general hospital
  - Confusion
  - Anxious++
  - Unable to talk coherently – referring to ‘blackmail’
  - Staff ‘not using their real names and lying to him’
  - Crawling on hands and news chasing a butterfly that was not there

Present history (continued)…

- Over the day ‘appeared to loose his ability to walk’
- Twisting hands and wrists into odd positions
- Unresponsive to staff
- Referred to crisis intervention team
  - didn’t come so taken to A & E
  - Thought to have an infection
  - Prescribed antibiotics and sent home

Next day…

- Did not move from the floor all night – couldn't hold himself up
- "It's not my fault"
- Using unrelated words "black, sky, fish" in response to questions
- Staring at his hands – grabbing things – hitting staff – saying strange things
- Taken back to hospital – further tests (MRI. LP etc) - IV antibiotics
- Discharged 4 days later some improvement – 'returning to his normal self'

Three days later..

- Further deterioration whilst at his parents – taken to Hospital near where his parents lived.
  - Grabbing things, hitting staff
  - Believed he was pregnant after a sex change – urine sample bottle was ‘his baby’
  - Agitated and couldn’t keep still in bed
  - Not making any sense – eventually unresponsive to staff
  - Behaviour changed from being very aggressive to being immobile

  - Diagnosis; delirium (?previous throat infection)
  - Discharged home to his parents

Five days after first seen at A & E

- Deteriorated whilst at his parents
- Confused, aggressive, change in behaviour
- Cutting his hair, eating napkins and ‘appearing unwell’
- Parents did not feel safe taking him to hospital so called an ambulance – admitted to Peterborough General Hospital.
- Seen by liaison psychiatrist started on aripiprazole 5mg daily plus Lorazepam 0.5mg twice daily and admitted to the IASS unit, Cambridge three days later

Progress

- On admission to IASS mildly incoherent, having difficulty processing what staff were saying
- General continued improvement over two weeks – some mood fluctuations – periods when he thought ‘god would kill his Mum and Dad’ and the continuation of some other abnormal beliefs
- Sometimes feels ‘he is going to be harmed’
- Occasional grandiose ideas – God had put pictures in a football magazine for him “because he had been good”
- Little memory of previous admissions but now orientated in time and place
- Over time accepted that he had been ill
- Appetite and sleep returned to normal
- No pressure of speech or flight of ideas

- Two months since being back at his group home – doing well on medication

Interventions for co-morbid psychiatric disorder

- Determined by the formulation
- If there is evidence of a co-morbid psychiatric disorder (e.g., psychotic illness)?
  - Immediate
  - Short term
  - Long term
- Pharmacological
- Psychological
- Social

Interventions for co-morbid psychiatric disorder

- Short term
  - Keep safe (?admission)
  - Lower demand
  - Keep family/care workers informed
  - Use of medication to bring mental state and therefore behaviour under control
- Medium term
  - Establish formulation to inform treatment
  - Evaluate progress and treatment (risk)
  - Structure, predictability
  - Medication

Interventions for co-morbid psychiatric disorder

- Longer-term
  - Support (weight control, visual support etc)
  - Monitor
  - Activity (structure)
  - Medication

Psychiatric medications some basic rules

- The prescribing of medication should be guided by a diagnosis and formulation;
- Medication should be prescribed for diagnosed conditions where there is evidence, at least in the general population, of benefit;
- In PWS if psychiatric medications are indicated start at lower and normal dose and increase with care;
- Before starting psychiatric medications collect baseline data (mental state/behaviour) so that benefit or not can be determined;
- Medication is but part of the intervention and should be prescribed in the context of an overall treatment plan that considers the short, medium and longer term.

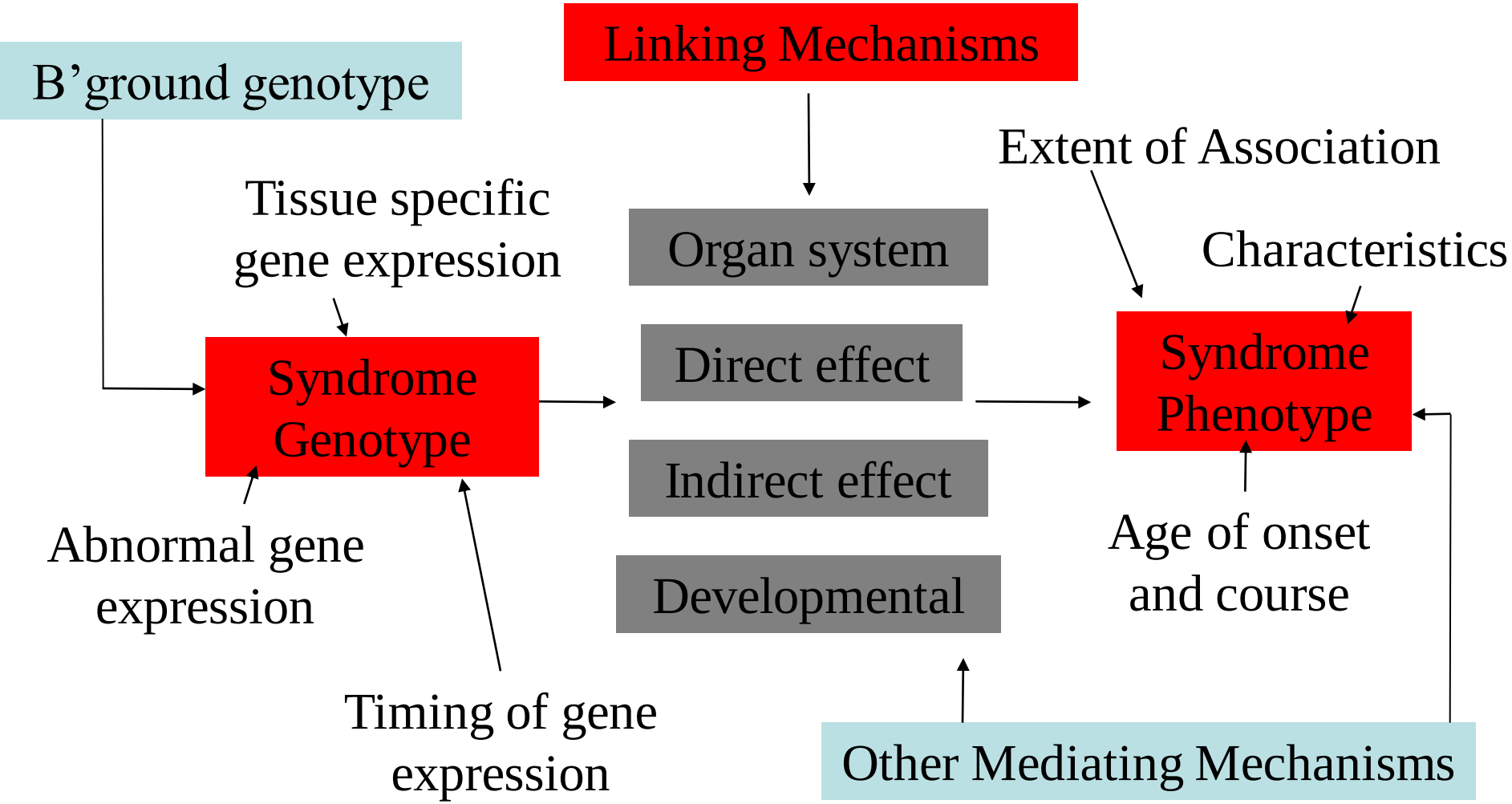
Psychiatric medications for serious co-morbid mental illness in PWS

Some uncertainties:

- Depression and associated anxiety: SSRI such as citalopram
- Psychosis: antipsychotics such as risperidone, aripiprazole – avoid olanzapine!
- Mood stabilisers: carbamazepine, sodium valproate, lithium, lamotrigine

Investigating behavioural phenotypes in PWS

a) Eating; b) emotion regulation; and c) mood disorder and psychosis



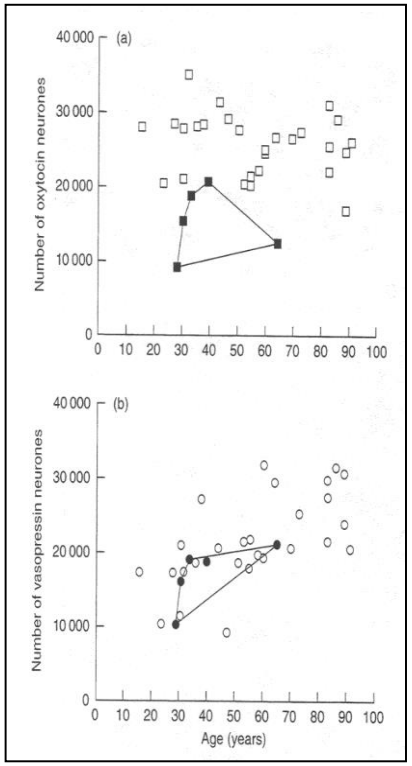
Oxytocin in PWS

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 newborns 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

Aims of VNS study

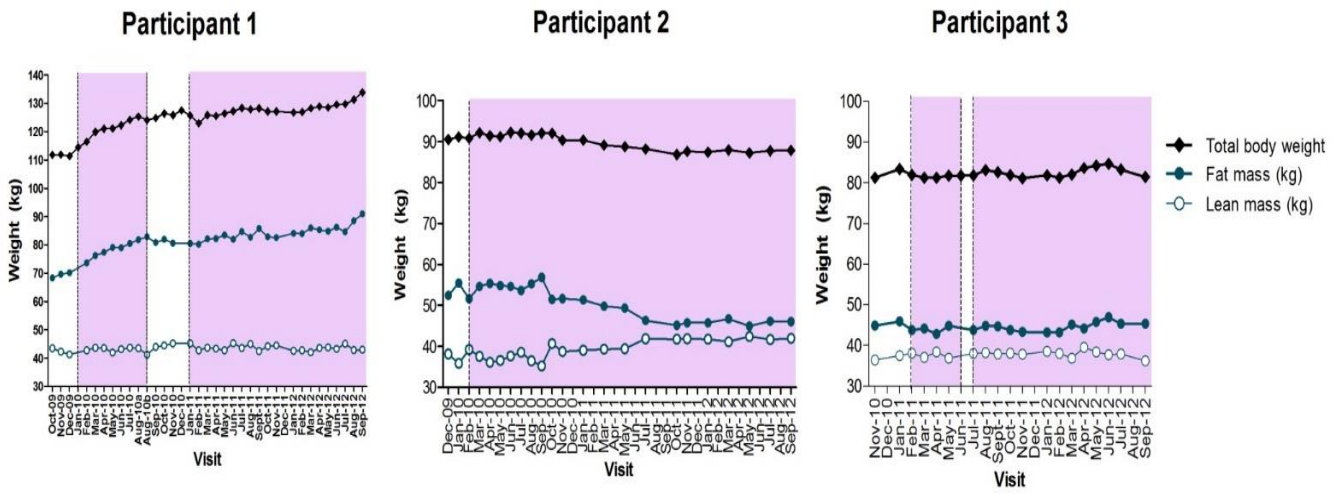
- To determine the acceptability and safety of VNS when used in people with PWS;
- To determine whether there is sufficient evidence of an effect on eating behaviour and weight to justify a more extensive trial;
- Three participants: VNS inserted, standard ramping up protocol, minimum of one year at approved level of stimulation, repeated measures of eating behaviour and weight

Funding: Dunhill Medical Trust Serendipity Fund, ACT, PWSA UK

UNIVERSITY OF CAMBRIDGE

Results

Weight and Body Composition



- Participant 1 gained weight - continued to increase when VNS off, no abnormality of BMR - VNS not physiologically responsible for increase.
- Participant 2 has shown very modest weight loss – c. 2.9% decrease in body weight.
- Participant 3 has shown relatively stable weight throughout – now showing weight loss two years 6 months later (4 kg since July 2013) – is this VNS?.

UNIVERSITY OF CAMBRIDGE

Results

Unexpected behavioural change

- Participants 2 & 3 described positive effects on temperament, behaviour and social functioning (behavioural data was not collected prior to this).
- Semi-structured interviews characterised these changes as involving increased emotional and cognitive flexibility, with reduced tendency for temper outbursts when routines or expectations are disrupted.
- Not due to alleviation of depressive symptoms.
- Participant 1 did not show the same extent of behavioural issues prior to VNS.
- **Improvements have led Participants 2 & 3 to continue VNS beyond study**

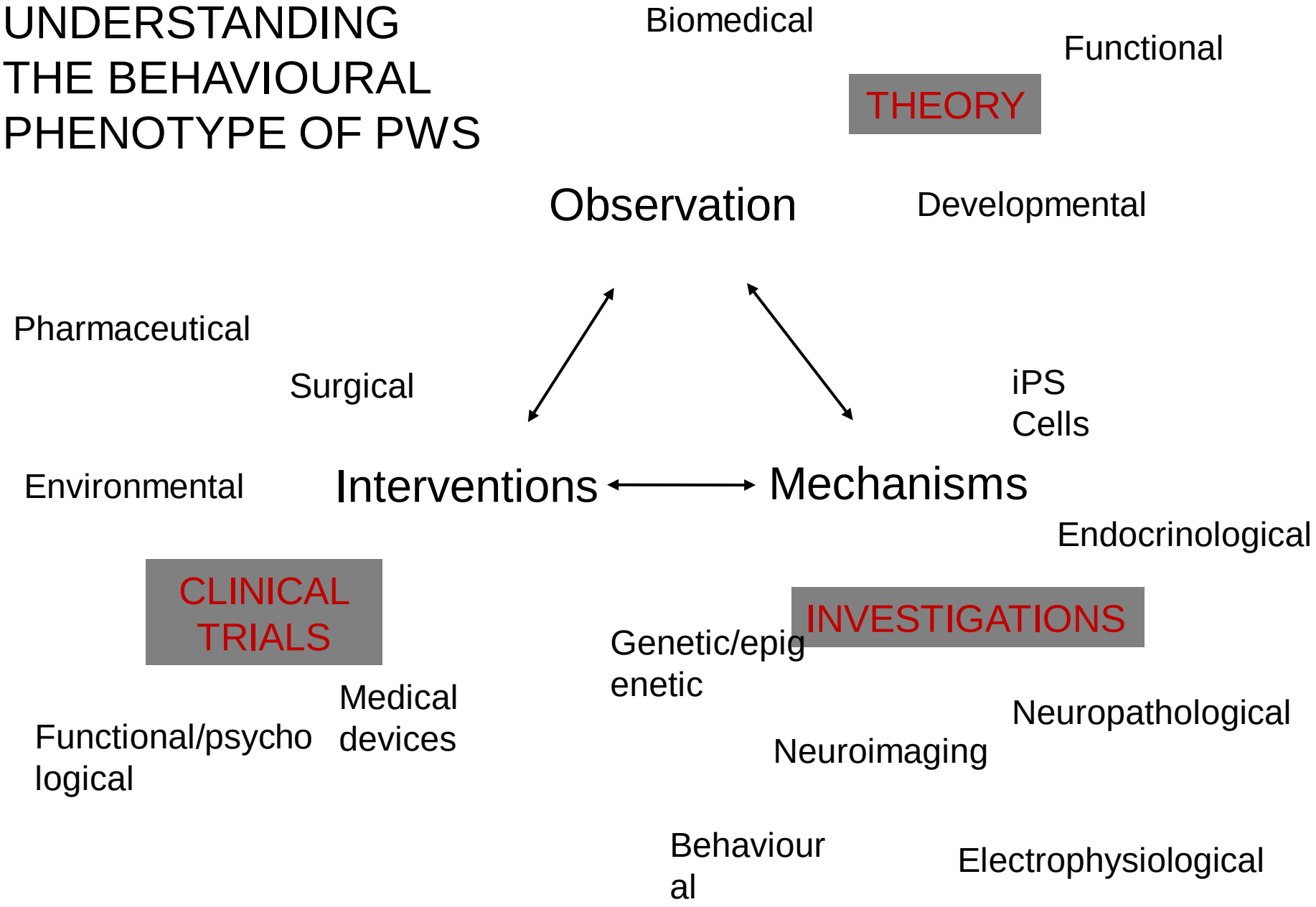
Two years on...

- K – VNS switched off. Moved to her own flat with support – severely obese – weight fluctuates
- S – VNS still activated – still described as ‘Mr Chill’ by his mother – no serious outbursts for two years - p/t job, living at home in food supervised environment – occasionally ‘steals’ food
- J – VNS still activated – lives with husband with daily support – some weight increase followed by 11 Kg loss on diet – no serious outbursts

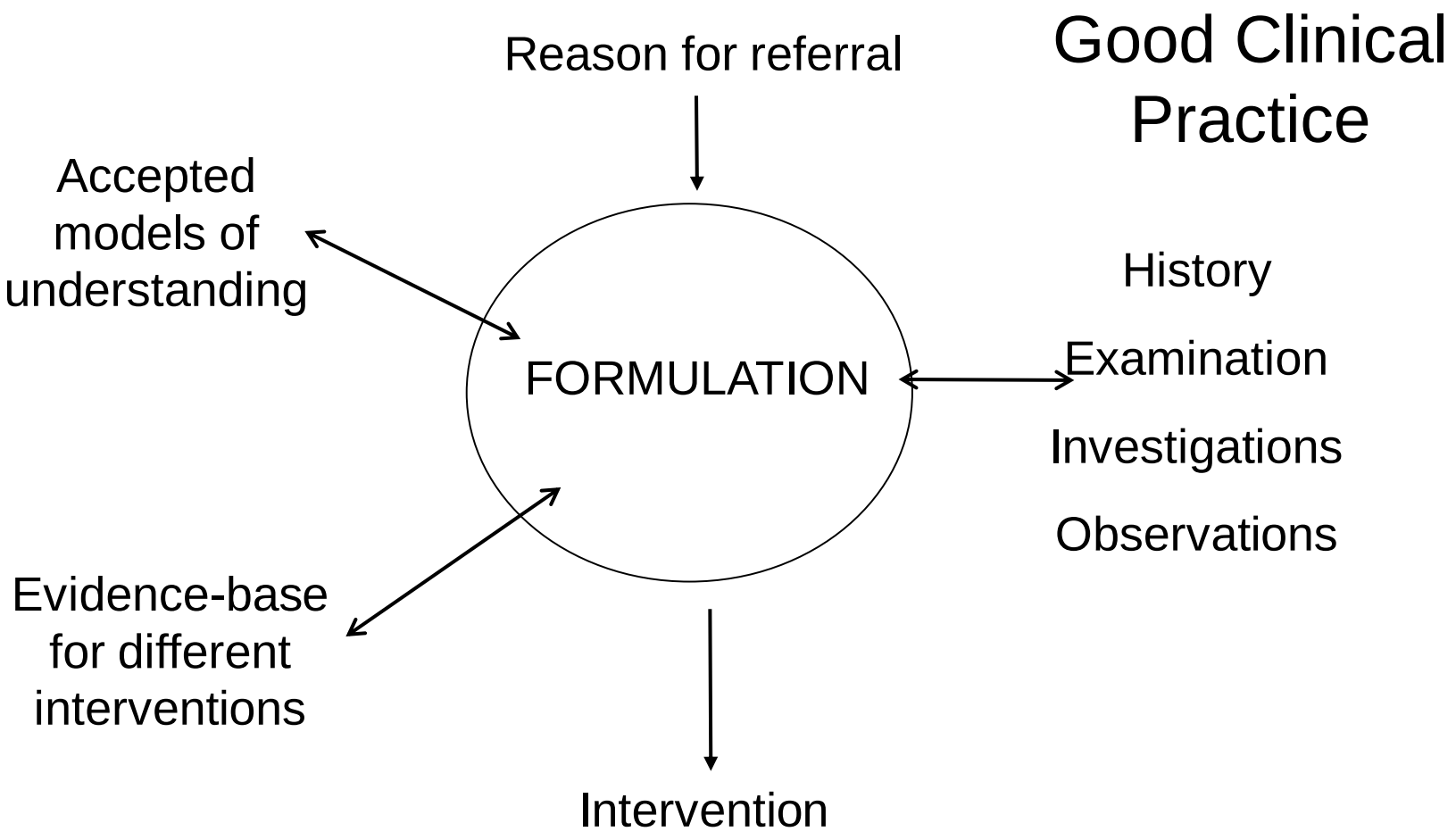
Behavioural phenotype of PWS

Behaviour	Mechanism	Environment	Intervention
Repetitive Tempers	Dev arrest Set shifting	Change Unpredictability	Functional
Skin Picking	?5-HT activity	Lack of Environment	?SSRIs
Over- eating	Abnormal satiety	Food availability	Environment ?Treatment
Affective disorder	?5-HT ‘two hits’	Demands Arousal	Medication Environment

UNDERSTANDING THE BEHAVIOURAL PHENOTYPE OF PWS



Formulation



Matrix

- Biological
- Developmental
- Psychological
- Environmental

Onset and continuation of ‘behaviour’ and/or abnormal mental state

- Predispose
- Precipitate
- Maintain

Cause for concern in people with PWS

- The onset of new maladaptive behaviours or significant change in mental state;
- An increase in the frequency and/or severity of existing maladaptive behaviours;
- Evidence of physical ill-health, complaining of pain, vomiting etc.

Final points

- Physical illness maybe difficult to detect in a person with PWS: remember obesity related problems (e.g. sleep apnoea);
- The importance of formulation to guide intervention – data collection allows the management of uncertainty;
- Combination of approaches from the pharmacological to the psychological and social;
- New problems may arise during the life course.