Medical Illness Affective Disorders & Obesity

Anne Farmer

MRC Social Genetic and Developmental Psychiatry Centre
Institute of Psychiatry

What this talk is about

1. Obesity & physical health in those with mental disorders
2. Physical illness in UD & BD subjects participating in genetic association studies (DeCC & BaCCs).
3. Possible links between physical illness, obesity and affective disorders

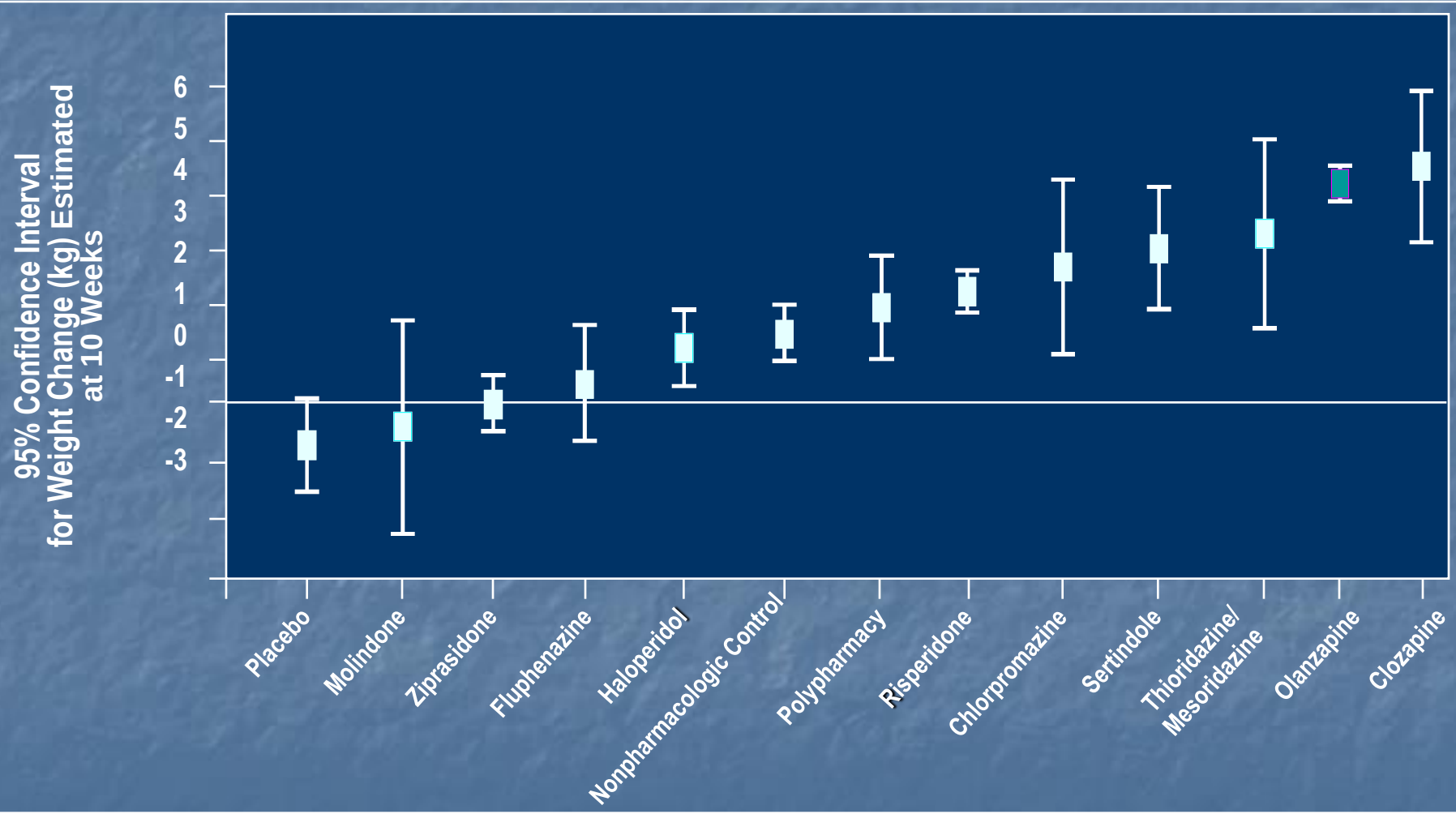
Medical illness and mental disorders

- attention mainly re schizophrenia
- Especially those associated with drug induced wt gain
- less regard paid to physical health of those with affective disorders

Disorders at increased risk in patients with schizophrenia:

- obesity,
- hyperlipidaemia
- hypertension
- diabetes,
- cardiac arrhythmias

Weight Change During Treatment of Schizophrenia



Weight gain and metabolic syndrome

- Metabolic syndrome (MS) consists of
  - abdominal obesity,
  - hypertension,
  - hypercholesterolaemia
  - insulin resistance
- precedes later development of cardiovascular disease (CVD) & Type II diabetes
- Prevalence: 25% in developed countries.

South London & Maudsley NHS Trust (November 2006)

Guidance on the management of metabolic syndrome in patients prescribed antipsychotic drugs

Introduction:

Patients with schizophrenia are at an increased risk of metabolic abnormalities because of a variety of factors including a genetic predisposition, poor diet, lack of exercise, cigarette smoking and the use of antipsychotic medications. These metabolic abnormalities including dyslipidemia, impaired glucose homeostasis, abdominal obesity and hypertension are associated with an increased the risk of coronary heart disease……(8 pages)

Depression in those with medical illness

- Many studies have shown high rates of co-morbidity between physical disorder & depression
- Depression noted in; hypothyroidism, epilepsy, migraine, IBS, fibromyalgia, CFS, obesity, cardiovascular disease…..

Medical illness in those with affective disorder

- Few studies have examined physical health in subjects with affective disorders
- 2 UK based GWAS studies: Depression and Bipolar case control studies (DeCC 01-04 & BaCCs 02-05)
- examined self reported:

BMI

Physical disorders

Aim of studies

- Examine whether subjects with recurrent depression or bipolar disorder have higher rates of medical illness compared to age matched controls

Aim of studies

- To consider whether there are possible shared aetiological factors influencing the development of affective disorder and medical illness

Affective disorder medical illness & obesity

- Since many medical disorders are related to obesity, BMI also examined
- BMI, gender and age controlled for when reporting effect size differences between cases and controls

Numbers of Participants

- Bipolar disorder 562
- Recurrent unipolar disorder 1546
- Controls (screened for mental well-being) 884

Method

- Subjects interviewed about lifetime ever physical disorders as part of a genetic case control studies
- Subjects recruited from psychiatric clinics, general practise, through self help groups and media advertisement

Method

- …from 3 UK sites; Birmingham Cardiff and London
- Control subjects recruited via a UK General Practise based genetic study who were screened by telephone interview

Diagnostic instruments

- Probands interviewed using SCAN (DSMIV & ICD10 diagnoses)
- Time frame: peak severity 4-6 weeks of worst and 2nd worst episodes of depression
- BMI derived from SCAN items

Diagnostic instruments

- Controls screened by telephone using the Past History Schedule to ensure no present or past history of clinically significant psychiatric disorder
- Controls asked present height and weight from which BMI calculated

Diagnostic assessment

- A short interview established whether any case or control had ever been treated by their GP for various medical disorders
- Replies were simply scored as “yes” “no” or “uncertain” (recoded as “no”)

Medical disorders

- Asthma
- Diabetes
- Epilepsy
- Hypercholesterol-aemia
- Hypertension
- Kidney disease
- Liver disease
- Myocardial infarction
- Osteoarthritis
- Osteoporosis
- Rheumatoid arthritis
- Hay fever
- Stroke
- Thyroid disease

GP diagnoses & reliability of self report

- GPs of 30 representative participants asked to complete a checklist regarding medical disorders and asked whether their patient had ever been treated for that disorder.

GP diagnoses & reliability of self report

- 25 GPs completed forms (83%)- 3 subjects had left the practice (forms returned incomplete) and 2 GPs failed to respond
- Mean kappa for 6 most common disorders =0.73 (sem 0.16 $p<0.001$)
- Sens=0.76 Spec=0.98

Demographics

- 35% BD 69% UD & 56% controls were female

- Mean age at interview:

  BD = 48.1 (11.5)

  UD = 47.4 (12.2)

  controls = 47.7(9.2) (p = ns)

Body Mass index (BMI)

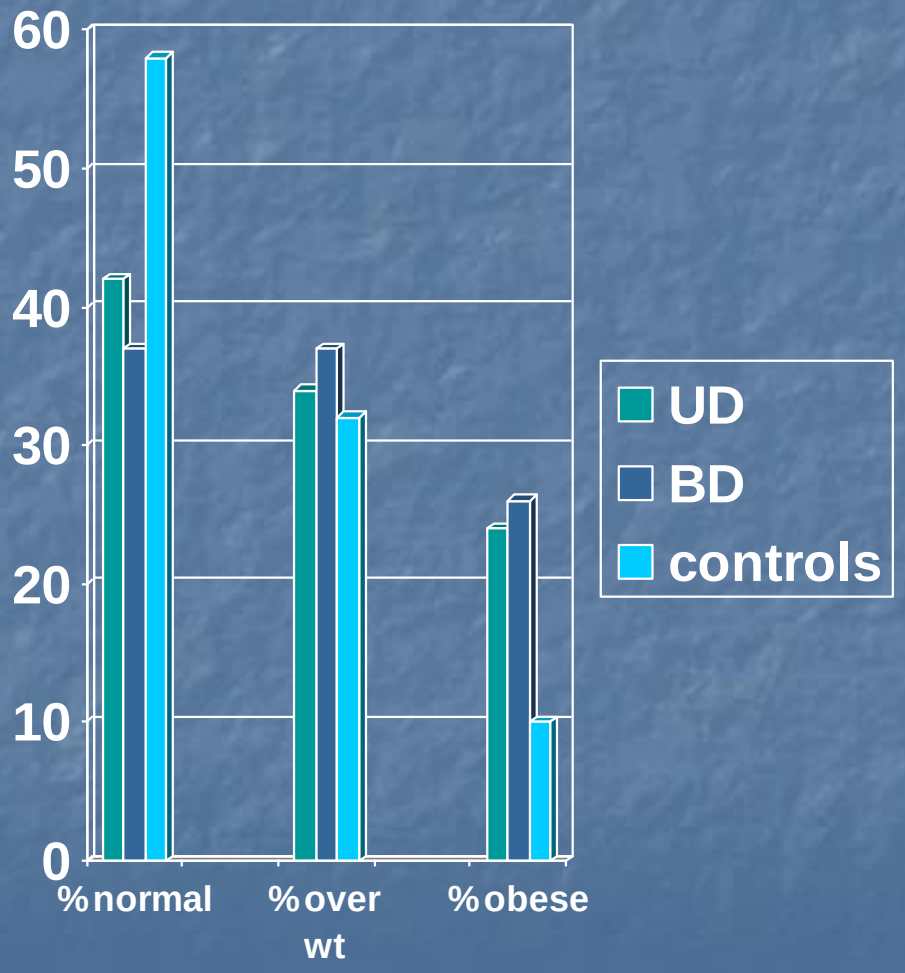
- BMI = Wt in Kgs / ht in metres squared

- Normal weight: BMI < 25
- Overweight: BMI = or >25 and < 30
- Obese: BMI= 30 and above

Body Mass Index (BMI)

Mean BMI

- **Males:**
  cases=27.07 (4.78)
  controls=26.02 (4.55)
  (p<0.001)
- **Females:**
  cases=26.85 (6.04)
  controls=24.51 (4.66)
  (p<0.001)



Lifetime prevalence of self reported medical disorders

Cases and controls

Medical disorder	Lifetime pre-valence (%) in 1547 UDcases	Lifetime pre-valence (%) in 884 controls	Lifetime pre-valence (%) in 500 BD cases
asthma	16.48	9.39	16.74
cancer	4.28	2.67	n/a
diabetes (insulin dependent)	1.10	1.25	n/a
diabetes (non insulin dependent)	2.78	1.36	3.14
epilepsy	1.81	0.34	2.73
gastric ulcer	4.98	1.24	n/a
hypercholesterolaemia	9.24	6.10	13.13
hypertension	16.49	7.13	17.08
kidney disease	1.36	1.13	n/a

Medical disorder	Life time prevalence (%) in 1546 UD cases	Life time prevalence (%) in 884 controls	Lifetime Prevalence (%) in 562 BD cases
thyroid disease	2.07	0.90	n/a
myocardial infarction	3.71	1.59	3.43
osteoarthritis	10.67	3.95	10.94
osteoporosis	3.04	1.24	3.30
rheumatoid arthritis	4.40	2.25	n/a
rhinitis (hay fever)	7.05	3.16	12.78

Case control differences….

…controlling for age, sex and BMI

Binary logistic regression:

outcome variable

- medical disorder (present/absent)

co-factors

- affective status (case or control subject),
- body mass index (BMI)
- sex
- age (above or below the median age)

Odds Ratios

	UD	BD
Gastric ulcer	4.31	n/a
Hay fever	3.29	ns
Osteoarthritis	3.05	2.63
Thyroid disease	2.78	ns
Hypertension	2.20	1.99
Asthma	2.19	1.80

Odds Ratios

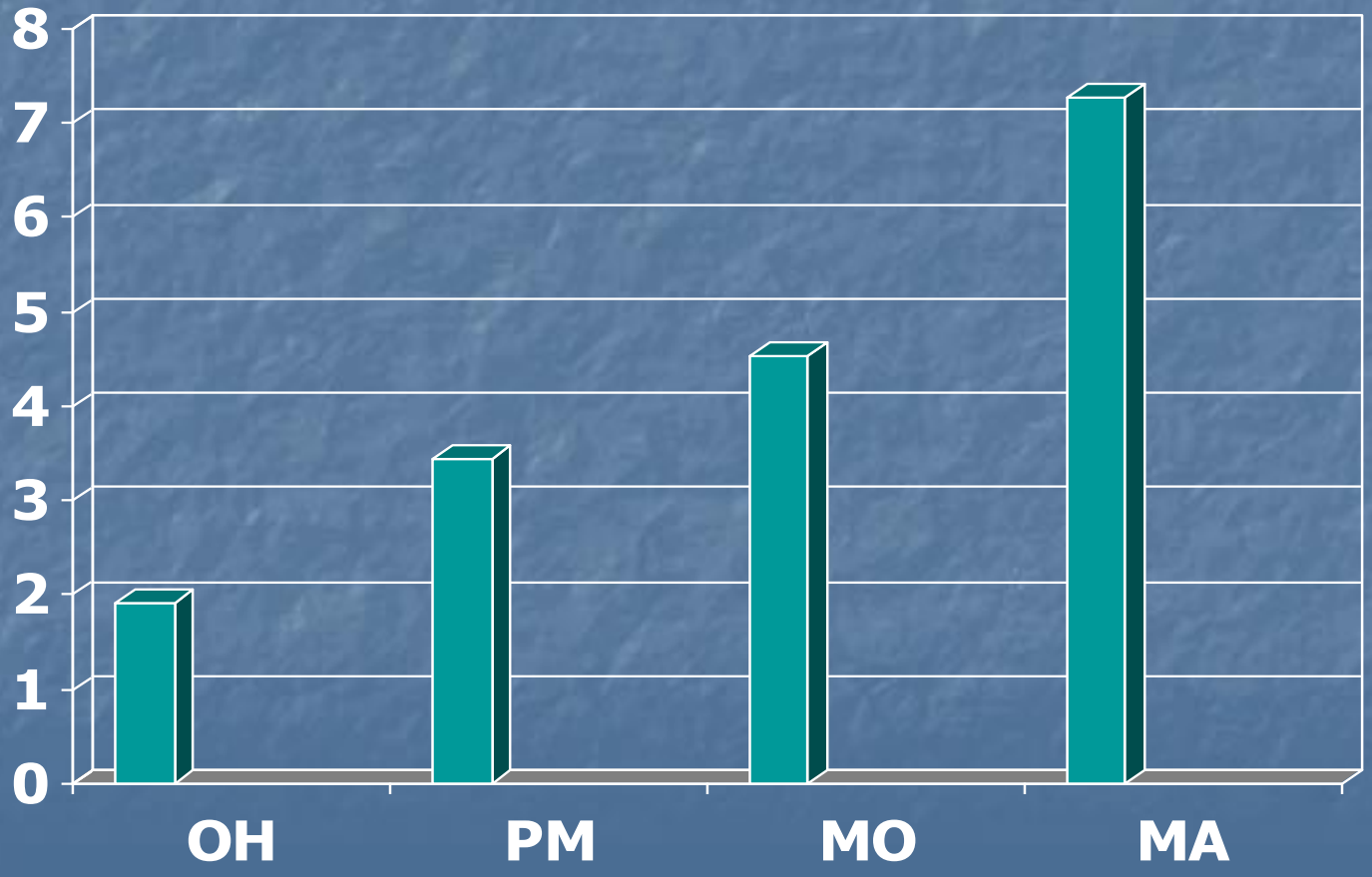
	UD	BD
Epilepsy	n/a	4.11
Migraine	*	1.67

* much higher rates of migraine with aura in UD subjects compared to controls

Lifetime prevalence (%) of headache in UD cases & controls

	Prevalence cases %	Prevalence controls %	OR (95% CI)
OH	45.3	38.7	**1.91** (1.60,2.27)
PM	14.6	6.7	**3.45** (2.58,4.69)
MO	2.7	1.0	**4.53** (2.25, 9.14)
MA	6.2	1.3	**7.27** (4.09,12.9)

Odds ratios for migraine in depressed subjects compared to controls



Limitations of study

- Large sample but non representative
- Based on self report
- Waist circumference or waist/hip ratio are better indicators of abdominal obesity than BMI

Limitations of study

- Present mood could have influenced reporting of physical ill health
- Small but significant correlation with BDI
- However present mood only contributed 1.5% variance in number of physical disorders reported

Conclusions

- Lifetime prevalence of migraine, hypertension, MI, stroke, asthma, osteoporosis, osteoarthritis and rheumatoid arthritis strikingly similarity in UD and BD
- prevalences elevated compared to controls
- despite samples being ascertained at different times and sites by different field workers.

Conclusions

- Increased cardiovascular risk associated with UD has been well documented
- less evidence for BD, though this study suggests is clearly of concern.
- BD patients show higher levels of hypertension.

Conclusions

- The underlying mechanisms linking mood disorders with conditions such as asthma and arthritis may reflect abnormalities of immune and inflammatory processes, possibly mediated by HPA axis dysfunction, that are a feature of both UD and BD.

Conclusions

- BD patients showed a high comorbidity with epilepsy compared to controls.
- General population prevalence of epilepsy is low (0.56%), so association with BD is apparent in this study only because of the high number of individuals included.

Conclusions

- possibly some people may have mistakenly reported a history of epilepsy (on an anticonvulsant)
- However unlikely, because there was good agreement between self and GP report of medical illnesses.

Conclusions

- Bipolar symptoms previously associated with epilepsy
- community based study of individuals with epilepsy, 12% had bipolar symptoms

Conclusions

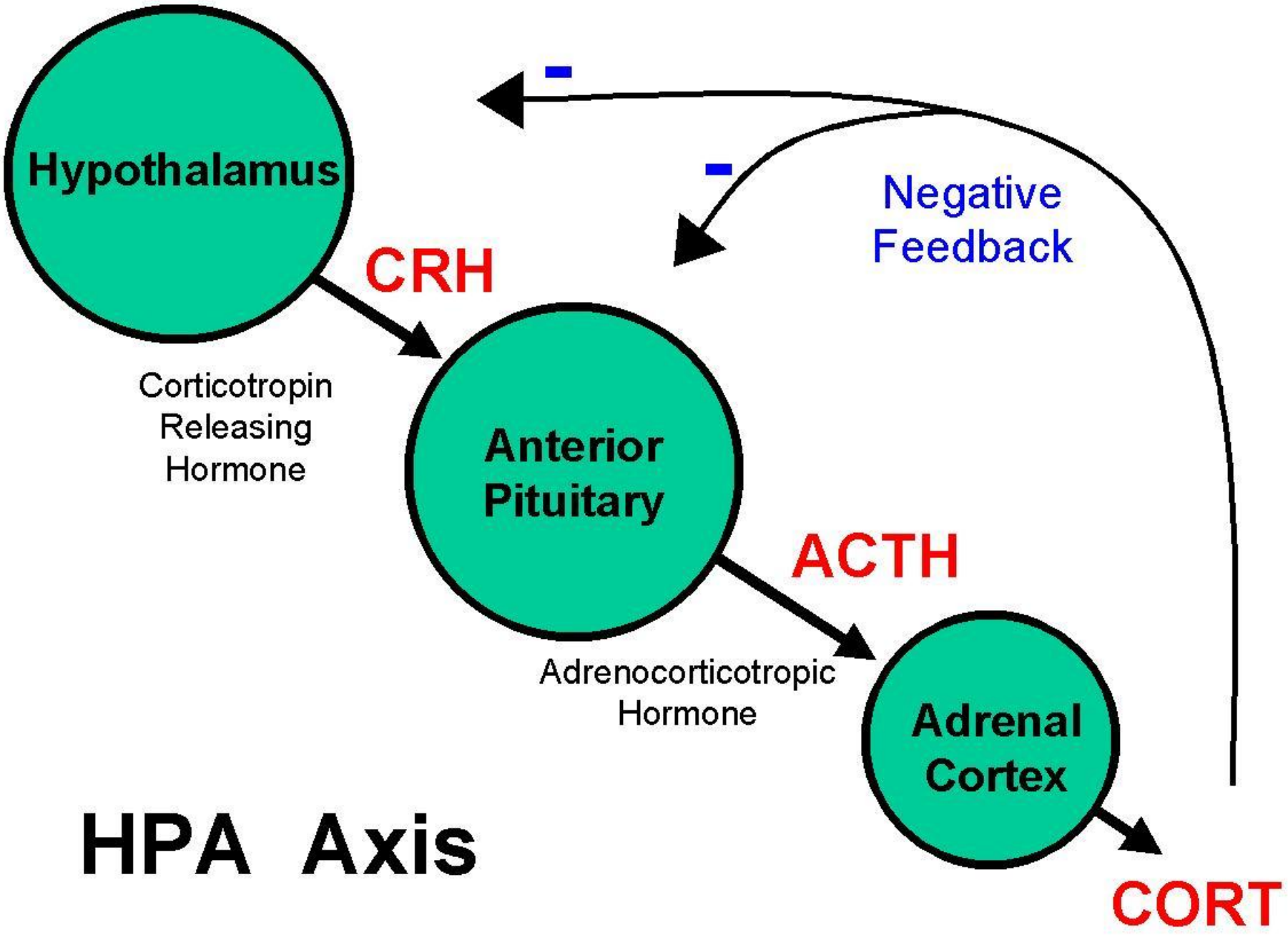
- patients with BD often show EEG abnormalities even if there is no prior diagnosis of epilepsy.
- Pathophysiology of BD shows many parallels with epilepsy
- both conditions are episodic, show kindling and sensitization and anticonvulsants are effective in BD

Case control differences

- increased rates of physical illnesses subjects with affective disorders could be due to shared aetiological risk factors

Shared aetiology

- Inference about causality require:
  - longitudinal studies
  - twin studies
  - molecular genetics


Hypothalamus
CRH
Corticotropin Releasing Hormone
Anterior Pituitary
ACTH
Adrenocorticotropic Hormone
Adrenal Cortex
CORT
Negative Feedback
-
-

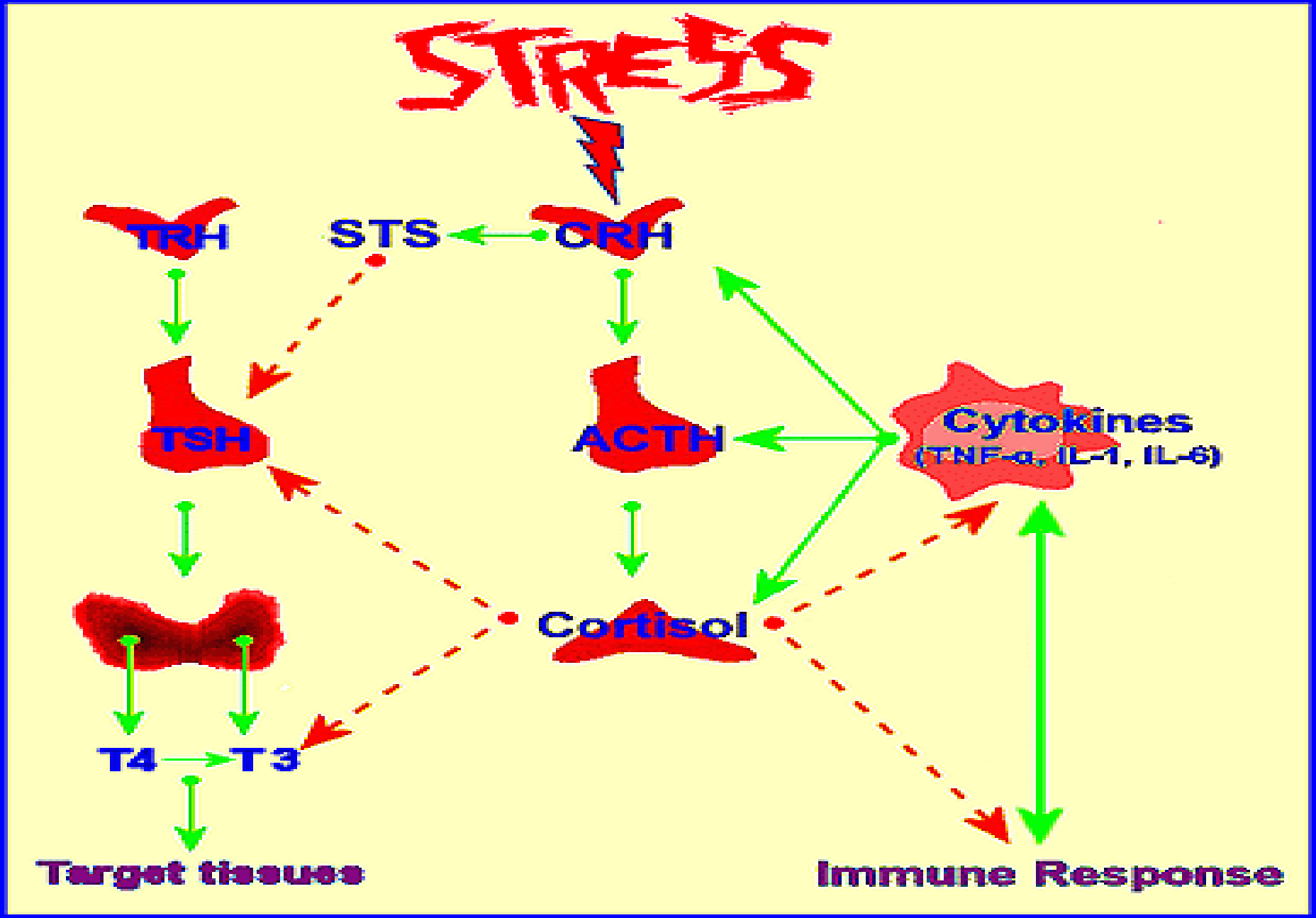
HPA Axis

Cortisol & depression

- Elevated cortisol: frequent in depression
- acute &/or protracted exposure to stress
- Acute exposure: severe & threatening life events = risk factor for depression

Stress and brain development

- Chronic stress at critical periods can reset HPA axis to higher levels of cortisol *(Charandari 03)*
- Impact related to genetic vulnerability & timing of exposure *(Seckl & Meaney 04)*


STRESS
TRH
STS
CRH
TSH
ACTH
Cytokines
(TNF-α, IL-1, IL-6)
Cortisol
T4
T3
Target tissues
Immune Response

Adipocytes as endocrine cells

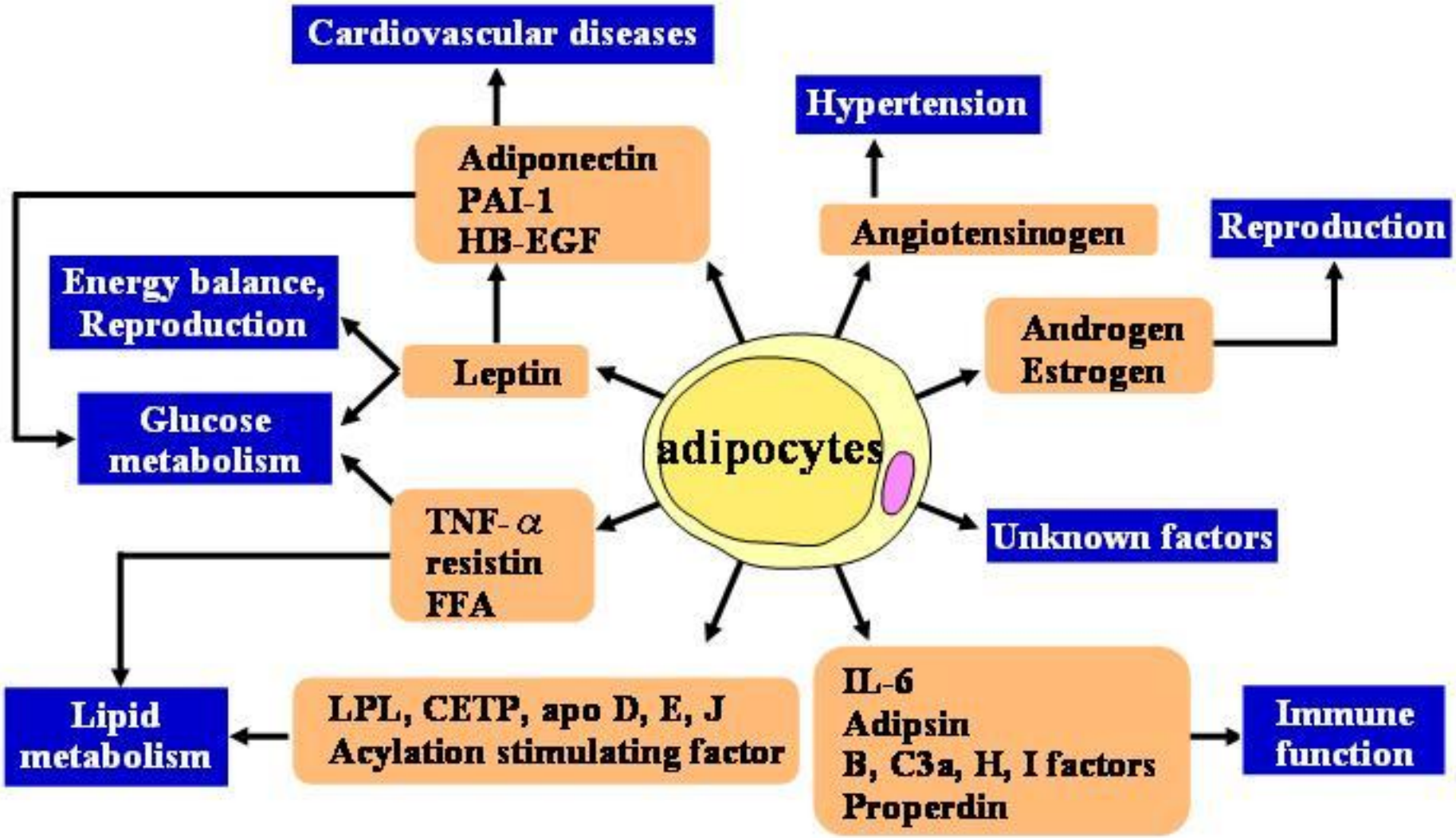


Fig. 1. Adipocytes as an endocrine cell

UD & obesity

- Depression and obesity may share similar pathophysiologically mechanisms.
- eg the HPA system in the brain governs the stress response and has been implicated in the aetiology of depression

FTO & UD

- *FTO*- fat mass and obesity gene
- contributes to common forms of human obesity
- previous research has a common single nucleotide polymorphism (SNP) in *FTO* (rs9939609) associated with BMI and increased risk for adult obesity

FTO & UD

- *FTO* - highly expressed in the hypothalamus, pituitary and adrenal glands suggesting a possible role in the HPA axis which is involved in body weight regulation
- 88 SNPs covering the FTO gene genotyped in UD cases and controls

FTO & UD

- Human studies have found that *FTO* variant (rs9939609) risk allele is associated with

  increased energy intake

  diminished satiety

- implicating the *FTO* in the regulation of appetite.

FTO & UD -results

- Cases & controls combined: associations found between several SNPs in *FTO* and BMI
- 6 SNPs remain significant following multiple testing corrections ($p<0.0014$).
- association observed in the combined sample attributable entirely to cases
- none of the SNPs significantly associated with BMI in the control sample.

FTO & UD - results

- association isolated within a group of SNPs located in the first intron of the gene. cf previous studies
- 4 of the most significant SNPs associated with BMI in our sample (rs3751812, rs8050136, rs9930333, rs9941349) are in high LD (r2>0.8) with the *FTO* variant rs9939609 previously associated with BMI.

FTO and unipolar depression

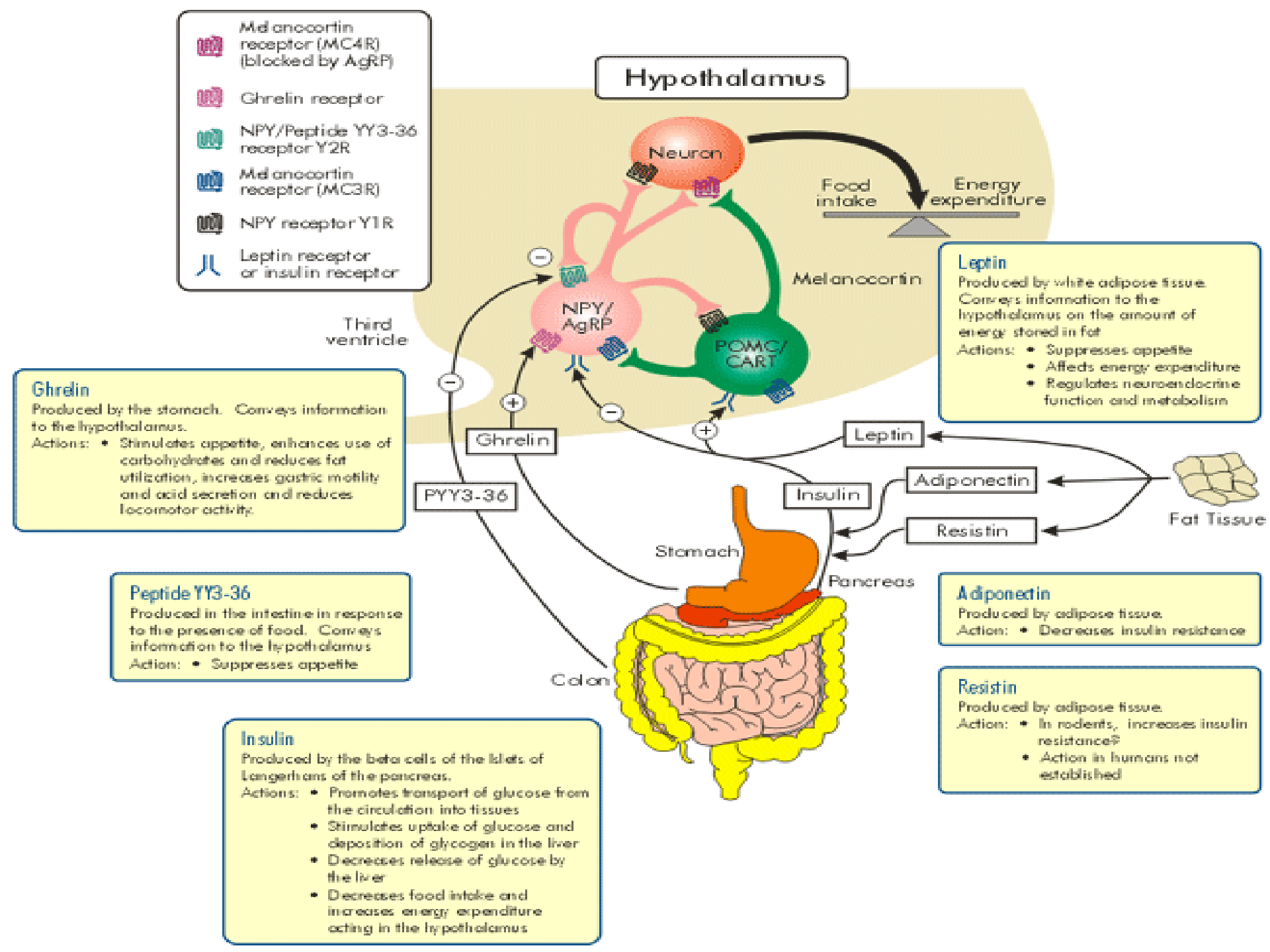
- Results suggest that although an association is observed in the whole sample, having a history of depression moderates the effect of *FTO* on BMI.
- These findings could have important implications in the prediction of which patients with depression could be at risk of obesity and overweight related disorders.

Conclusion

- Several physical disorders and obesity more frequent in depressed subjects than controls
- Dysregulation of HPA axis may be shared risk factor
- Adipocyte hormones and glucocorticoid receptors have potential for genetic research

Take home message

- A common aetiological pathway may link depression with some physical illnesses & obesity
- Genes common to depression, obesity and physical disorders may be implicated
- Some evidence links depression to genetic variation in FTO gene


Melanocortin receptor (MC4R) (blocked by AgRP)
Ghrelin receptor
NPY/Peptide YY3-36 receptor Y2R
Melanocortin receptor (MC3R)
NPY receptor Y1R
Leptin receptor or insulin receptor
Hypothalamus
Neuron
Food intake
Energy expenditure
Melanocortin
NPY/ AgRP
POMC/ CART
Third ventricle
Ghrelin
PYY3-36
Leptin
Insulin
Adiponectin
Resistin
Fat Tissue
Stomach
Pancreas
Colon
Ghrelin
Produced by the stomach. Conveys information to the hypothalamus.
Actions: • Stimulates appetite, enhances use of carbohydrates and reduces fat utilization, increases gastric motility and acid secretion and reduces locomotor activity.
Leptin
Produced by white adipose tissue. Conveys information to the hypothalamus on the amount of energy stored in fat
Actions: • Suppresses appetite
• Affects energy expenditure
• Regulates neuroendocrine function and metabolism
Peptide YY3-36
Produced in the intestine in response to the presence of food. Conveys information to the hypothalamus
Action: • Suppresses appetite
Adiponectin
Produced by adipose tissue.
Action: • Decreases insulin resistance
Resistin
Produced by adipose tissue.
Action: • In rodents, increases insulin resistance
• Action in humans not established
Insulin
Produced by the beta cells of the islets of Langerhans of the pancreas.
Actions: • Promotes transport of glucose from the circulation into tissues
• Stimulates uptake of glucose and deposition of glycogen in the liver
• Decreases release of glucose by the liver
• Decreases food intake and increases energy expenditure acting in the hypothalamus