1. Animal learning and memory

    Classical conditioning

    Operant conditioning

    Memory

2. Emotional and cognitive stimulus processing

    Processing of rewarding stimuli

    Aversive stimuli, fear and the amygdala

    Stress, learning and memory

3. Animal models of human affective disorders

    Translational experimental psychiatry

    Manipulations and readouts

    Animal models relevant to anxiety and depression

    Immune system and depression

4. Pre-clinical psychopharmacology

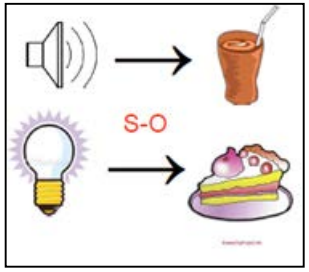
    SSRIs and affective disorders

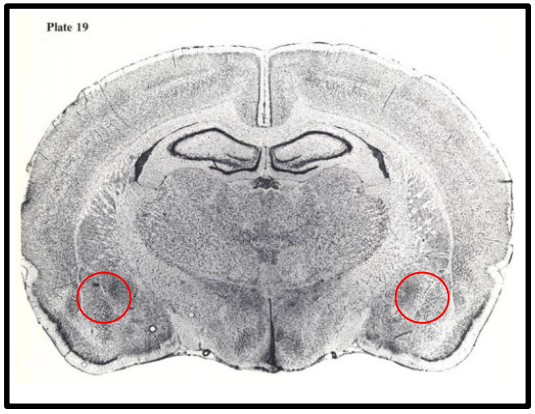
    Anti-depressants: the next generation?

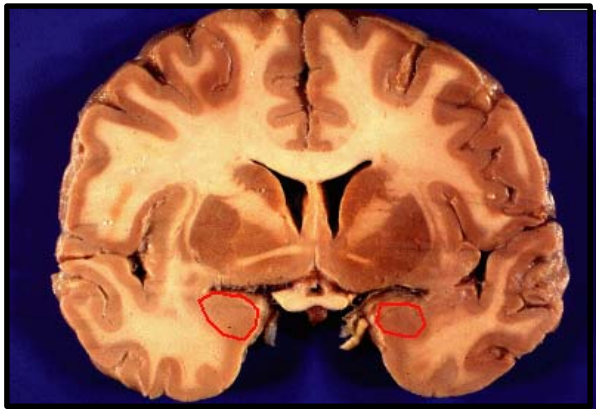
Animal models of affective disorders: Translational experimental psychiatry

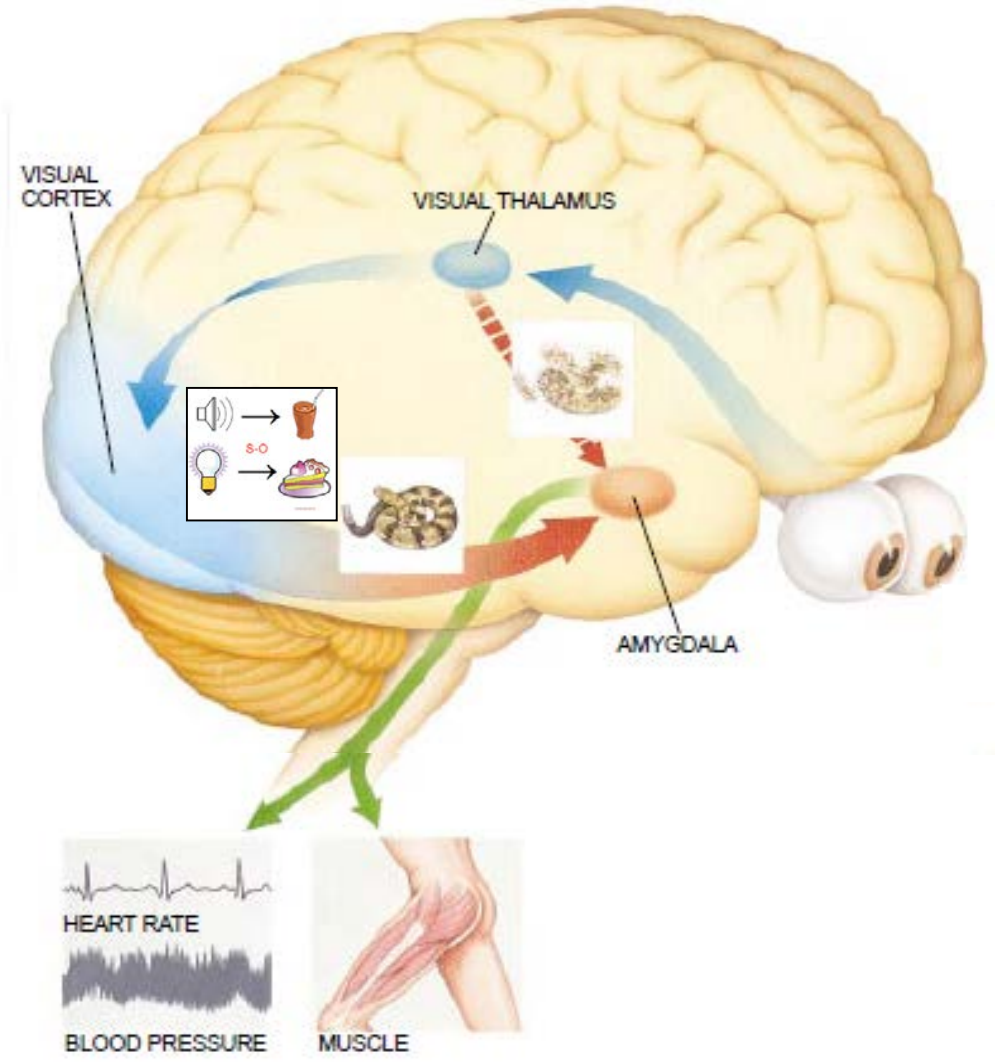
- Homology across species in the emotional processing of rewards and punishers
- Psychiatric disorders
- Psychiatric classification of the emotional (affective) disorders
- Depression
- Psychology of depression
- Neurobiology of depression
- Genes and depression endophenotypes
- Genes X Environment and depression aetiology

Universal neurobiology for processing emotional (important) stimuli across mammals





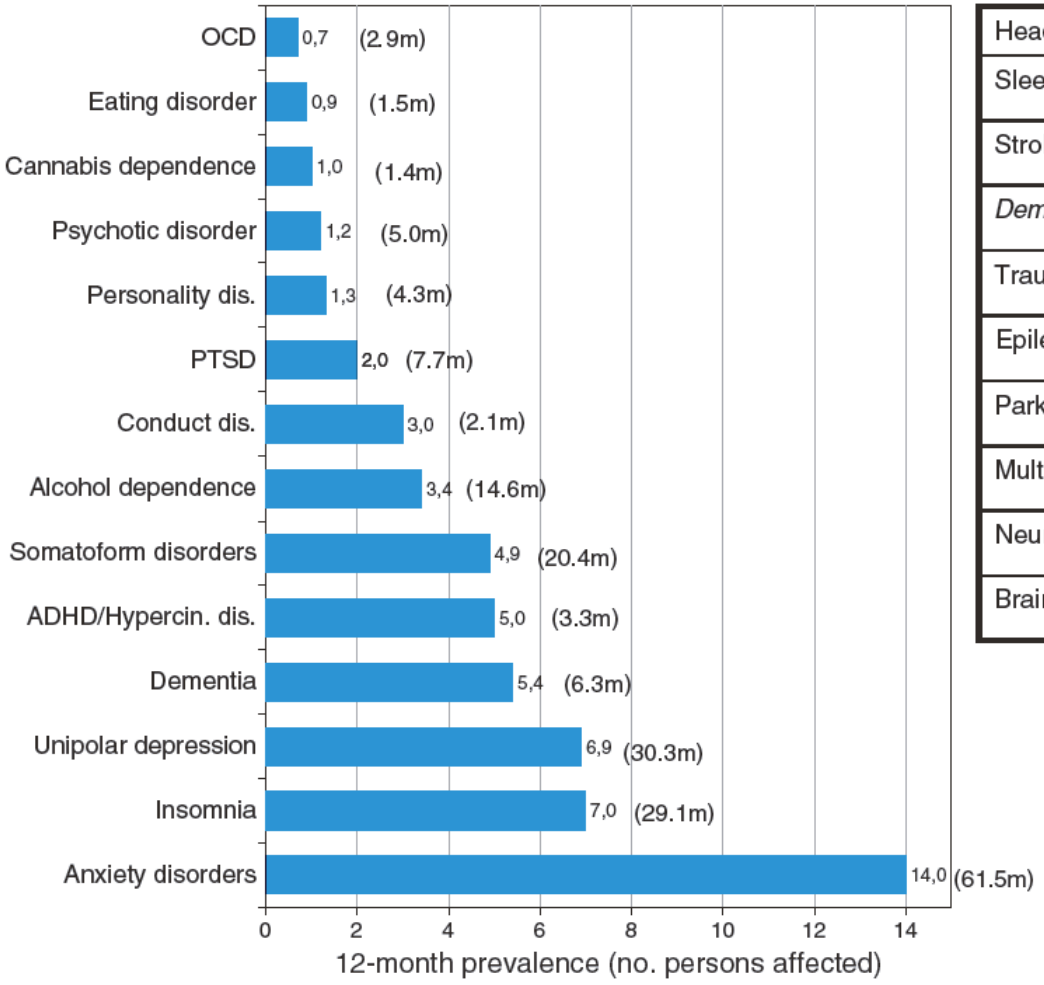




Burden of psychiatric disorders and other disorders of the brain:

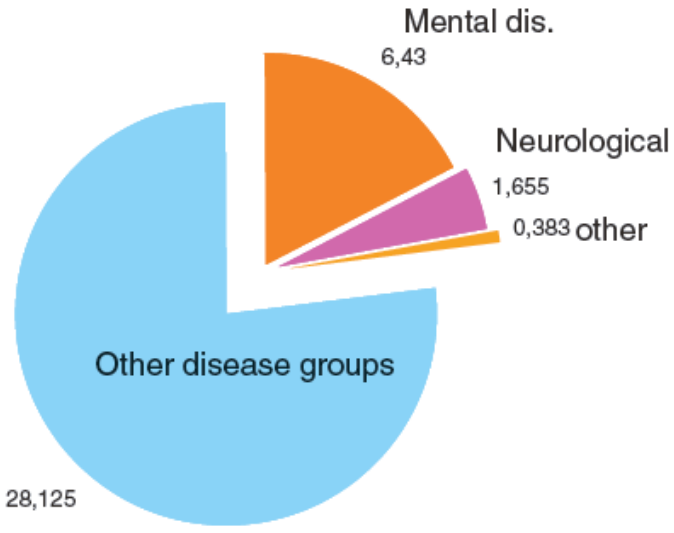
Report of the European College of Neuropsychopharmacology/European Brain Council 2011

Mental Disorders by prevalence (and estimated number of persons affected in millions)



Neurological disorders: Number of persons affected (in millions)

Headache*	152,8
Sleep Apnoea	12,50
Stroke	8,24
*Dementias***	*6,34*
Traumatic brain injury	3,75
Epilepsy	2,64
Parkinsons Disease	1,25
Multiple Sclerosis	0,54
Neuromuscular dis.	0,26
Brain Tumours	0,24



more stress, higher sensitiviy of diagnosis

Wittchen et al. (2011) Eur Neuropsychopharmacol 21: 655

Some of the Diagnostic Categories of Affective Disorders

- Depressive Disorders:
  - Major Depressive Disorder
  - Persistent Depressive Disorder (Dysthymia)
- Anxiety Disorders:
  - Separation Anxiety Disorder
  - Specific Phobia
  - Social Anxiety Disorder
  - Panic Disorder
  - Agoraphobia afraid of open space (large car par, also small spaces like elevator)
  - Generalized Anxiety disorder excessive worrying that something bad might happen without any logical reason for it to occur
- Trauma-, Stressor-Related Disorders:
  - Posttraumatic Stress Disorder
  - Acute Stress Disorder
- Obsessive-Compulsive Disorders:
  - Obsessive-Compulsive Disorder
  - Body Dysmorphic Disorder

American Psychiatric Association (2013) Diagnostic and Statistical Manual of Mental Disorders, 5th edition

Major depressive episode

Features: At least 2 weeks of depressed mood, loss of interest or pleasure in nearly all activities, fatigue, plus at least 4 additional symptoms. Leading to clinically significant distress or impairment in social, occupational, or other important area of functioning, or functioning requires more effort.
Depressed mood: “sad”, “hopeless”, “no feelings”, “frustration”, “anger”
Loss of interest/pleasure: “don’t care anymore”, “not interested”

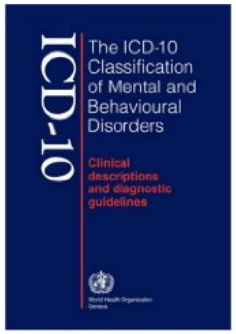
Associated descriptive features: Tearfulness, irritability, brooding, rumination, anxiety, phobias, worry over physical health, pain, panic attacks. Difficulty in intimate relationships, less satisfying social interactions, difficulties in sexual functioning. Marital problems (e.g. divorce), occupational problems (e.g. loss of job), academic problems (e.g. truancy, school failure). Alcohol or other Substance abuse. Attempted or completed suicide.

Associated laboratory findings: No laboratory findings that are diagnostic of major depressive episode have been identified. State-dependent abnormalities include: Sleep-EEG (40-60% outpatients, 90% inpatients; dysregulation in neurotansmitters e.g. serotonin, noradrenaline, dopamine, acetylcholine, GABA; dysregulation in neuropeptides e.g. corticotropin releasing hormone (CRH), neuropeptide Y; increased cortisol; fMRI findings; structural MRI findings.

Gender, Age, Culture: Female (4-10%) > Male (3-5%); Children – Elderly; Cross-cultural

Course: Symptoms develop over days-weeks; typical episode 4 months; 20-30% 12 mth; 5-10% > 2 years

Diagnostic symptoms for major depressive disorder



Symptom type	ICD-10 classification
	At least two of:
Typical/Core	**Depressed mood : pre-occupation with negative events and feelings of sadness, helplessness**
Typical/Core	**Loss of interest/motivation or enjoyment/pleasure**
Typical/Core	**Fatigue: Loss of energy, reduced activity, apathy**
	At least three of:
Common	Reduced concentration and attention
Common	Reduced self-esteem and self-confidence
Common	Ideas of guilt and unworthiness
Common	Bleak and pessimistic views of the future
Common	Ideas or acts of self-harm or suicide
Common	Disturbed sleep
Common	Diminished appetite
Common	Suicide attempt/plan

neurobiologically speaking, one can combine it in many ways to get a depression, but those depressions need not to be neurobiologically the same. So there might be the same phenotype (depression) but with a different biological substrate. Therefore, one would like need to develop different drugs for the same disorder.
Also, different neurocircuits are disturbed, so it really is very heterogenous

ICD-10: International Classification of Diseases: Mental and Behavioural Disorders, WHO (1992)

RDoC: forget about explaining depression, AD, anxiety etc. Think about sepcific domains and valence systems etc (0th column). Then understand how these domains are control with regard to genes, molecules, cells, circutis etc (0th row). this can be studied in humans but also in animals. This approach backtranslates human studies to animals and vice versa (evolutionary)
RDoC removes barrier between psychiatry and neuroscience

The research domain criteria (RDoC) matrix

Domains/constructs	Units of analysis: Genes	Molecules	Cells	Circuits	Physiology	Behavior	Self-reports	Paradigms
Negative valence systems								
Positive valence systems								
Cognitive systems								
Systems for social processes								
Arousal/regulatory systems								

Morris & Cuthbert (2012) *Dialogues Clin Neuroscience* 14: 29

Research domain criteria (RDoC): Constructs within Domains

Table 2 Research domain criteria, October 2012 (constructs are listed within each domain)

Negative valence domain	Positive valence systems	Cognitive systems	Systems for social processes	Arousal/modulatory systems
Acute threat ('fear')	Approach motivation	Attention	Affiliation and attachment	Arousal
Potential threat ('anxiety')	Initial responsiveness to reward	Perception	Social communication	Biological rhythms
Sustained threat	Sustained responsiveness to reward	Working memory	Perception and understanding of self	Sleep-wake
Loss	Reward learning	Declarative memory	Perception and understanding of others	
Frustrative nonreward	Habit	Language behavior		
		Cognitive (effortful) control		

Cuthbert & Insel (2013) *BMC Medicine*11: 126

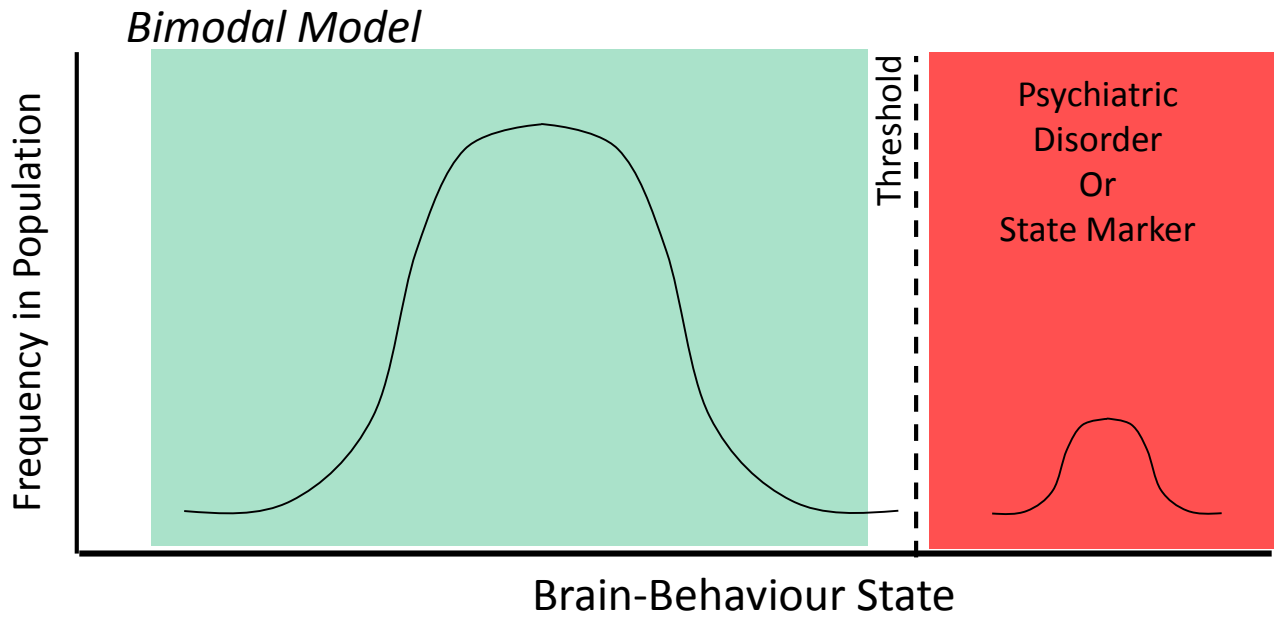
Depression is altered emotional processing of aversive and rewarding stimuli

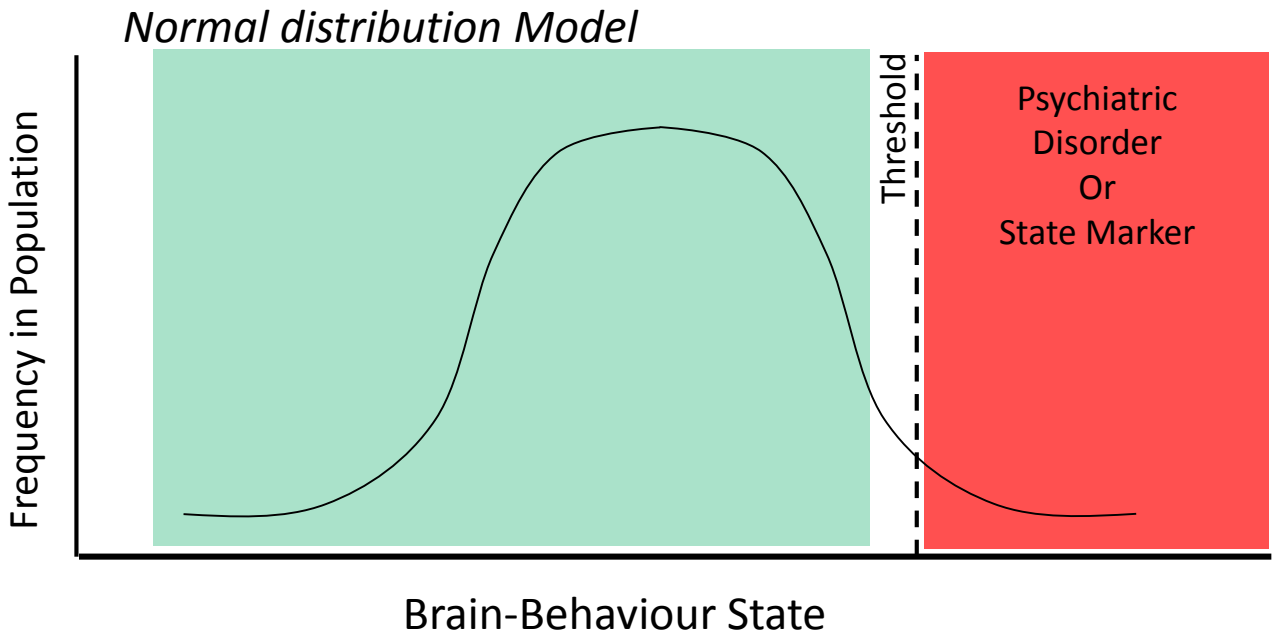
Aversive life events/stimuli	Rewarding life events/stimuli
Reactivity to UCS (↑)	Motivation/Interest (↓)
Learning about CS (↑)	Learning about CS (↓)
Uncontrollability of stimuli (↑)	Uncontrollability of stimuli (↑)
Expectancy of stimuli (↑)	Expectancy of stimuli (↓)
Fatigue due to aversive stimuli (↑)	Pleasure from (=↓)

(↑) (↓) Direction of change, Depression vs Healthy control
(=↓) Evidence is not convincing
Not all patients will exhibit all symptoms/states

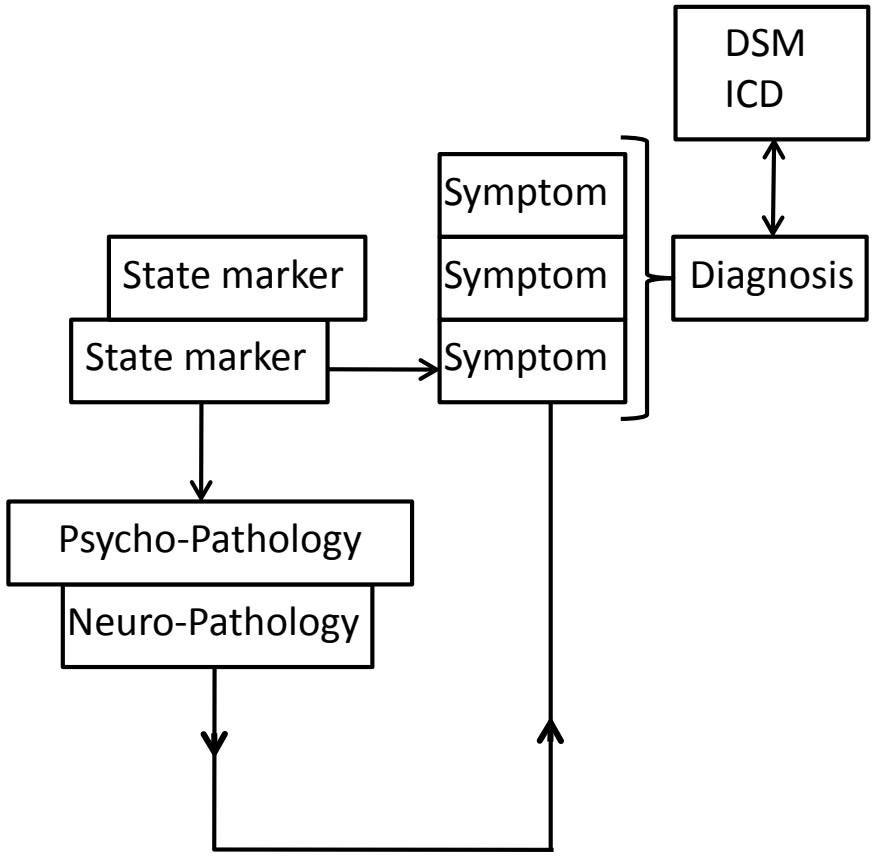
Pryce & Seifritz (2011) *Psychoneuroendocrinol* 36: 308

Models for the conceptualising of psychiatric disorders in populations

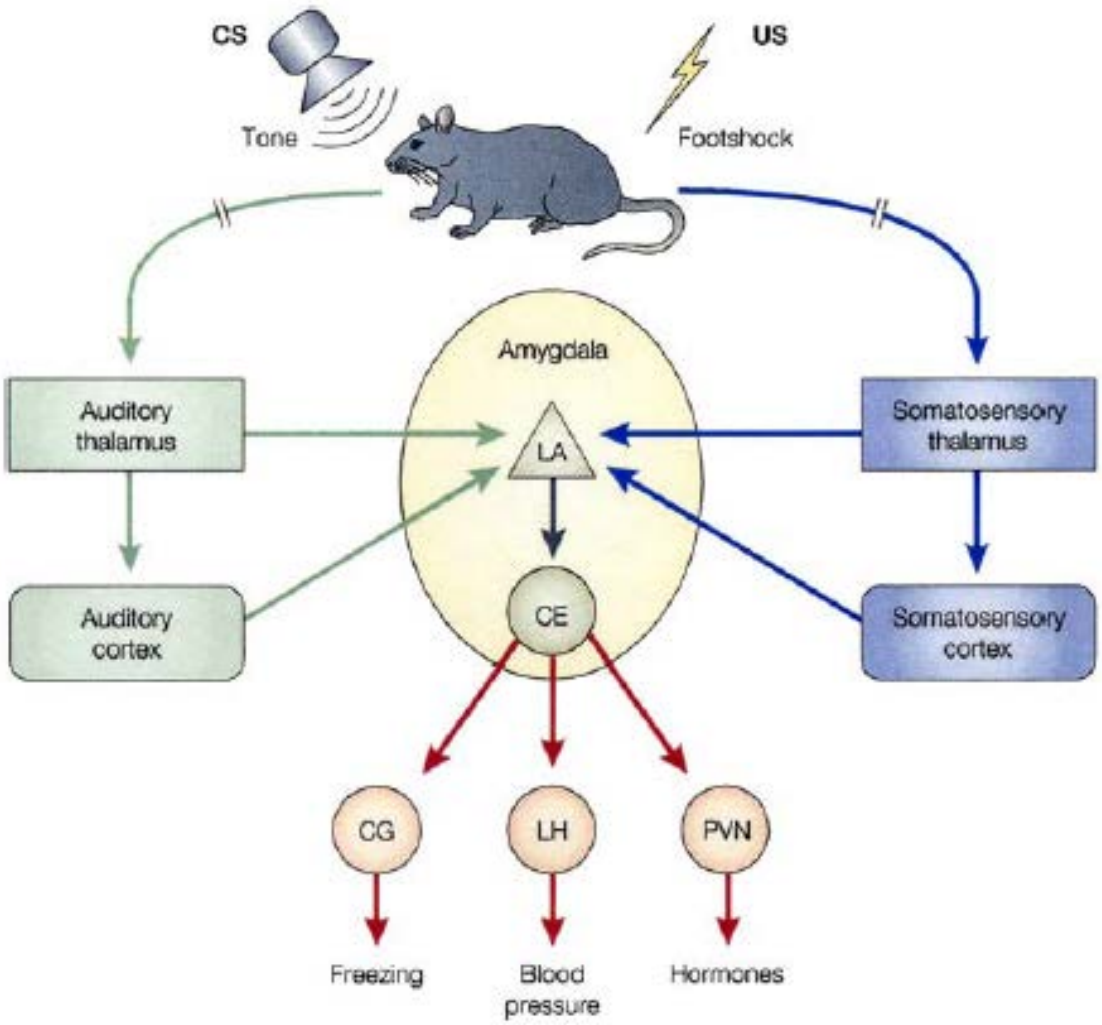


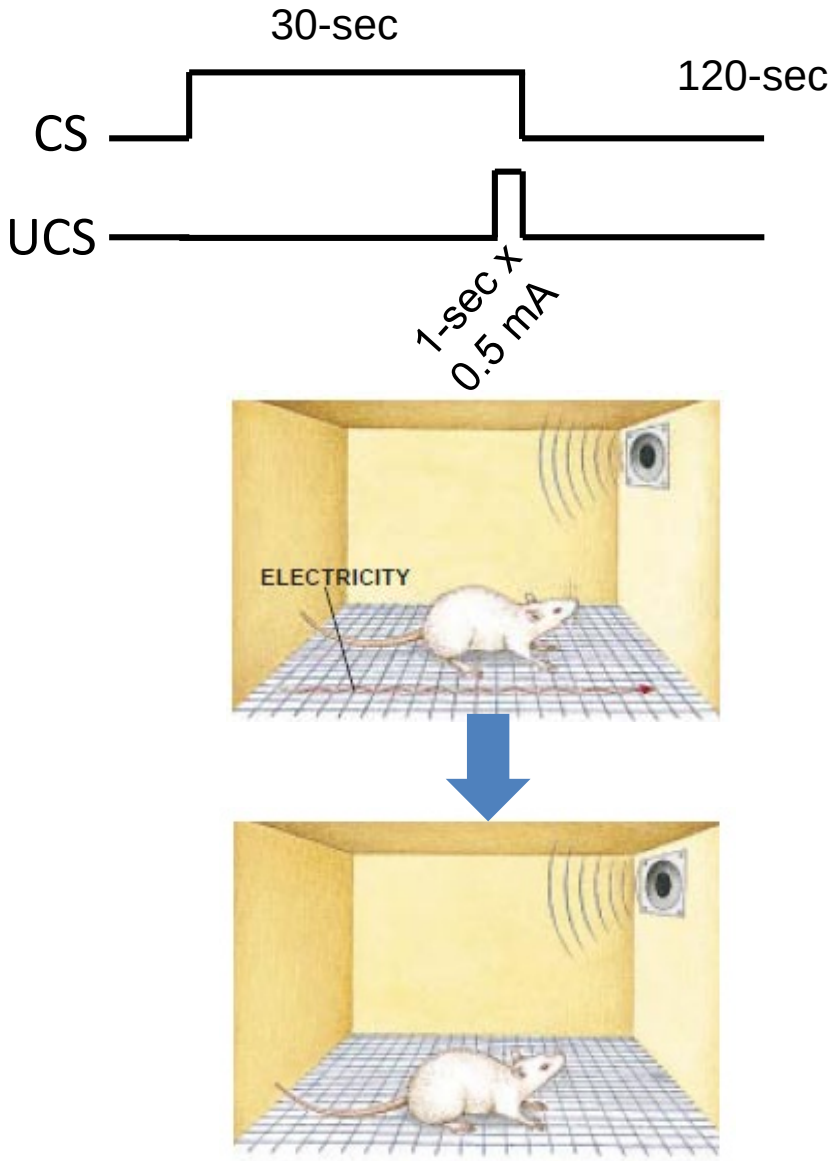


Understanding a complex psychiatric disorder in terms of neuro-behavioural components



Neural pathways underlying fear conditioning – measured as freezing





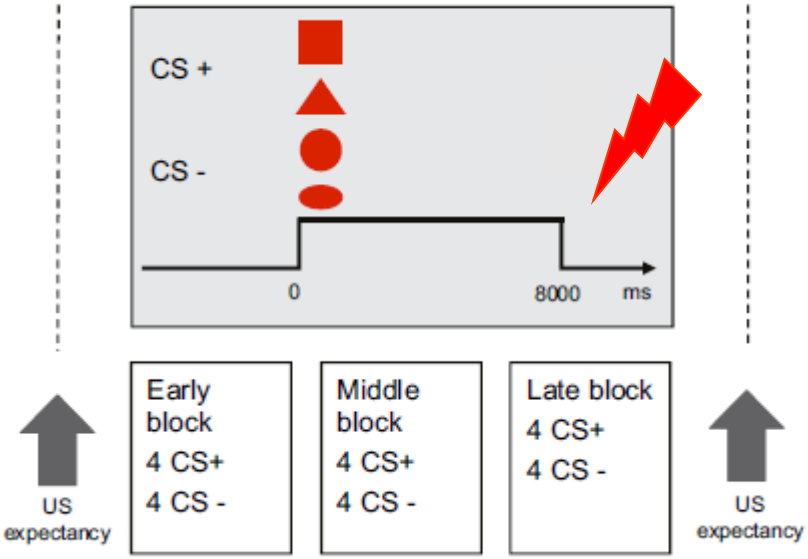
Phelps & LeDoux (2005) Neuron 48: 175

Example of a State Marker in Depression:
Increased conditioned fear responses in depressed patients relative to healthy controls

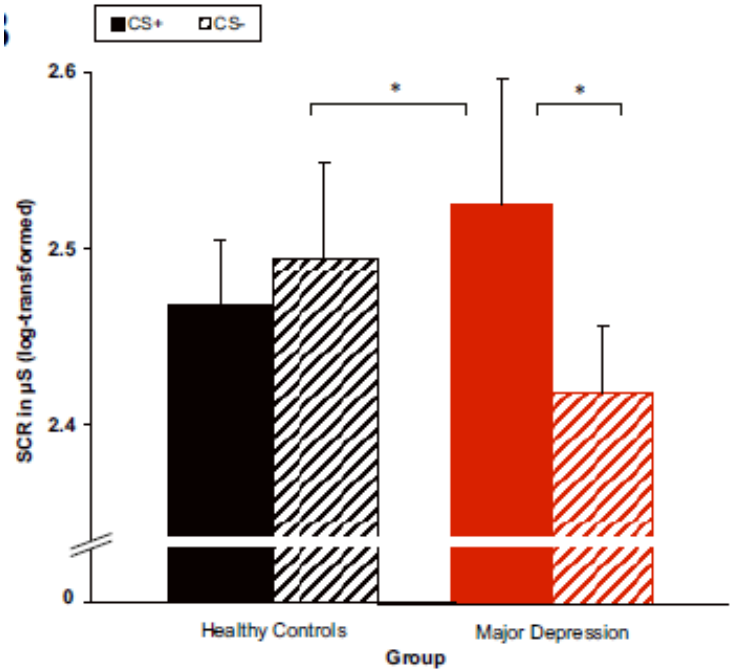
Depressed patients exhibit increased CS-UCS fear conditioning, measured using skin conductance

Depressed patients and healthy controls show similar and accurate expectancy of UCS depending on CS

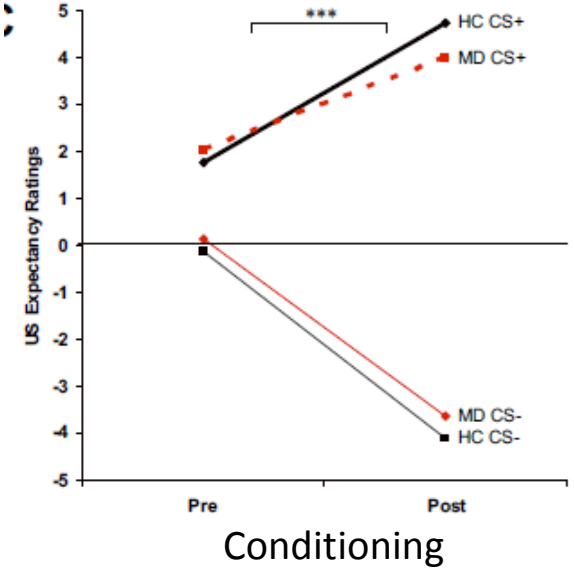
Fear Conditioning Protocol



Skin Conductance Response



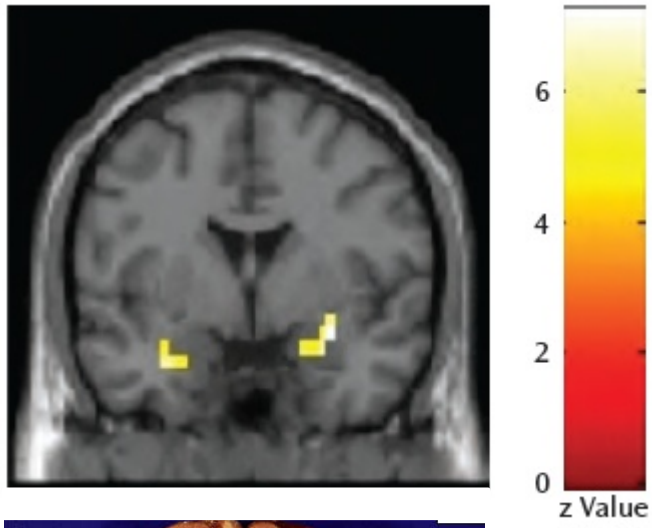
UCS Expectancy Rating



Nissan et al (2010) Biol Psychiatry 68: 544

Example of a State Marker in Depression:
Increased reactivity of the amygdala to fearful and sad stimuli using BOLD fMRI

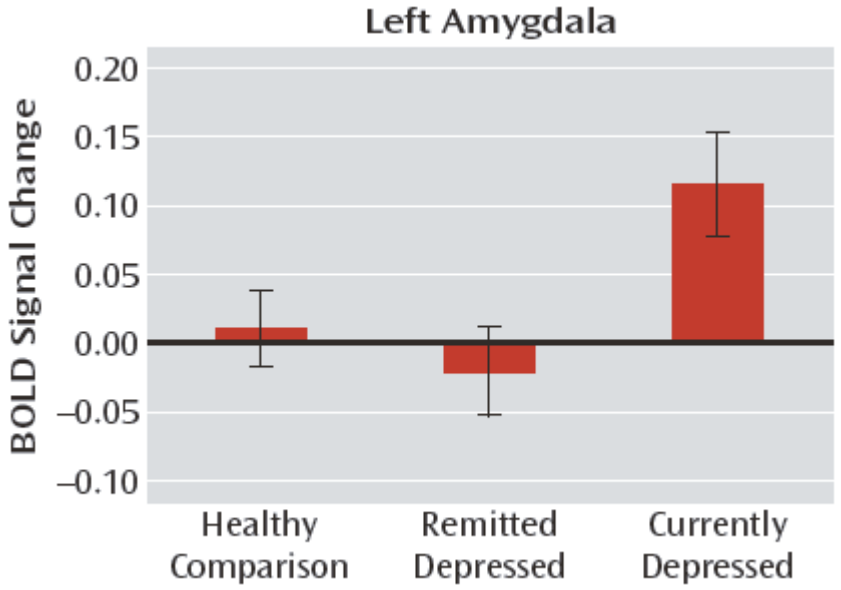
Emotional faces as stimuli

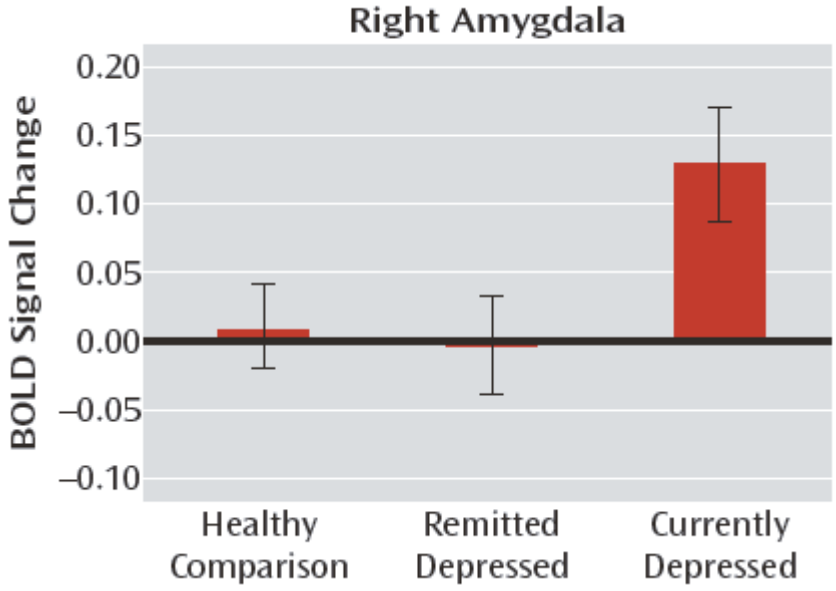


BOLD, Blood oxygen-level dependent contrast:

Fearful – Neutral

Sad - Neutral

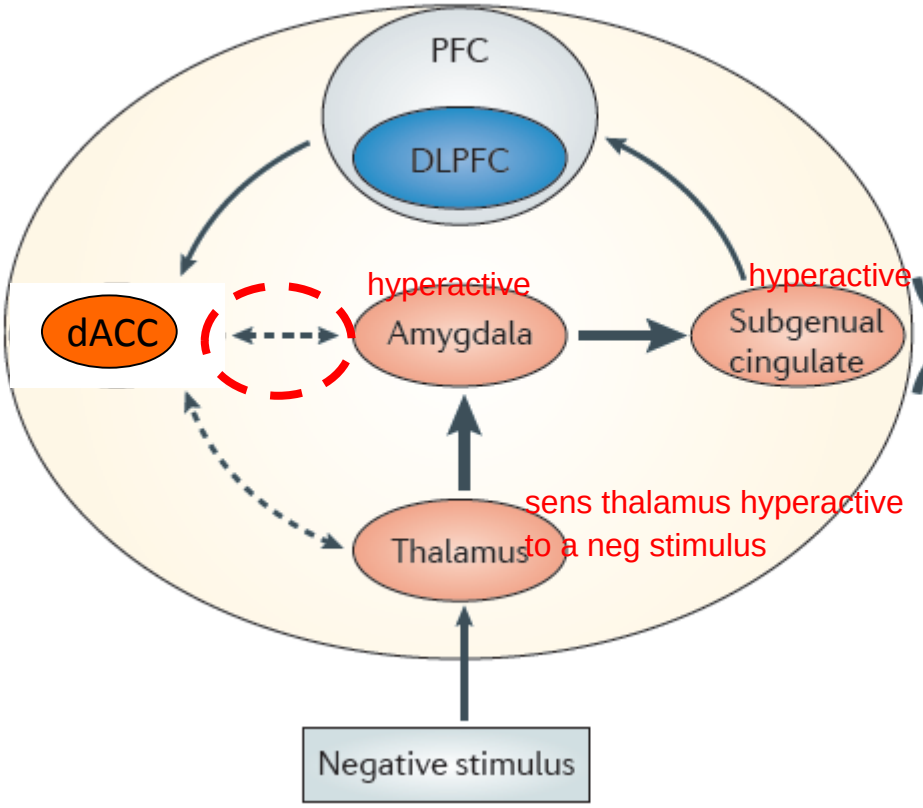




Arnone et al. (2012) *Am J Psychiatry* 169: 841

Neurocircuitry model of processing aversive stimuli in Depression based on fMRI findings

the region for it to be hyperactive is because other regions inhibit their acitvity (regulation), like the PFC, but they seem to be hypoactive

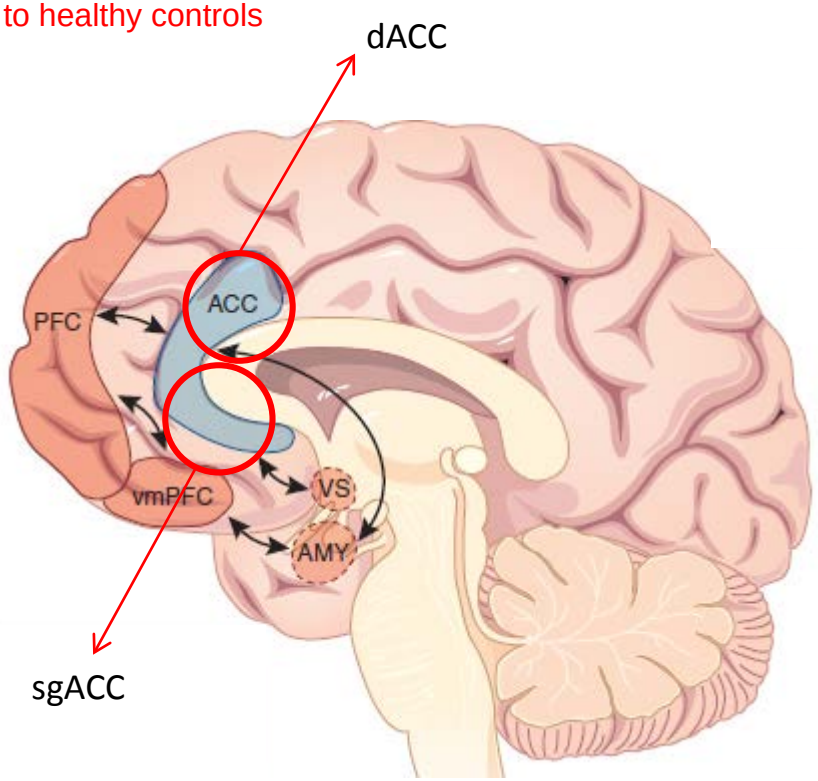


leads to

Increased processing of negative stimulus

compared to healthy controls

ACC, Anterior cingulate cortex
dACC, dorsal ACC
sgACC, Subgenual ACC (Subgenual cingulate)
PFC, Prefrontal cortex
VS, ventral Striatum



Hyper-active region in MDD

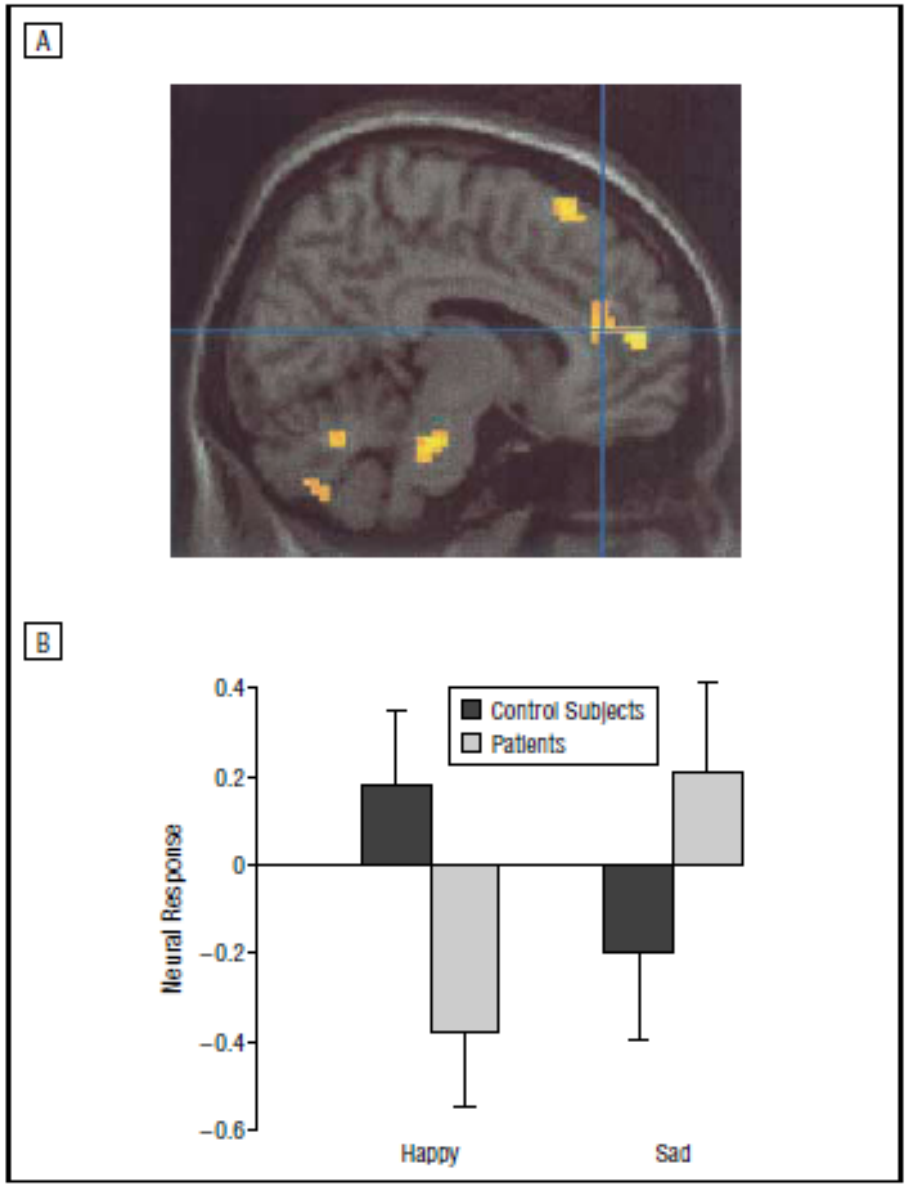
Hypo-active region in MDD

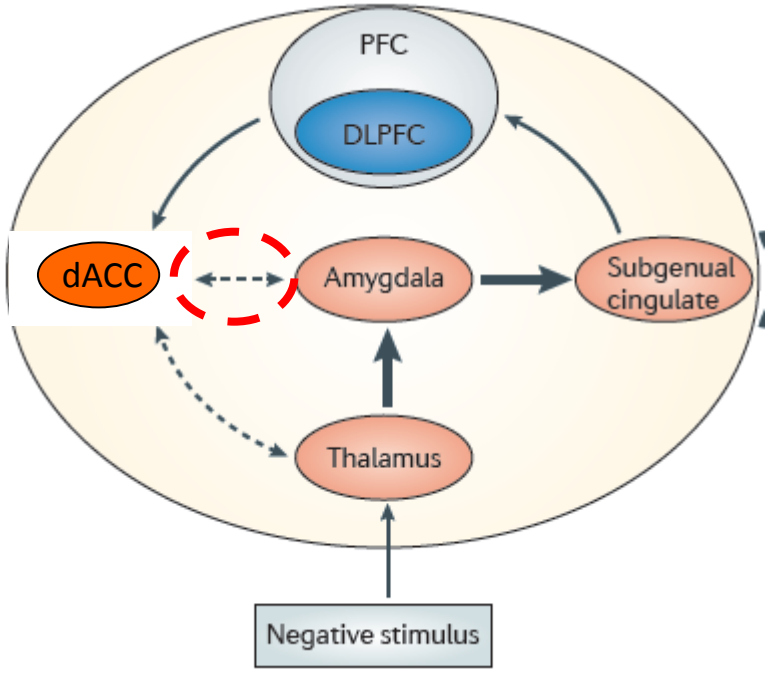
Intact connectivity

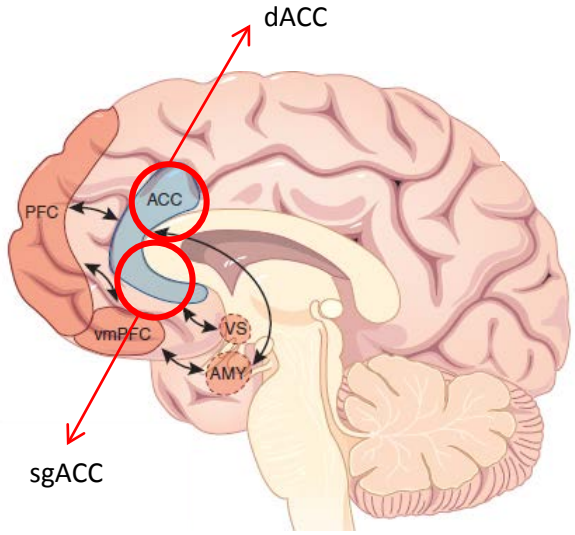
Reduced connectivity

Disner et al (2011) Nature Rev Neurosci 12: 467

Increased neural response to sad stimuli in dorsal anterior cingulate cortex in depression

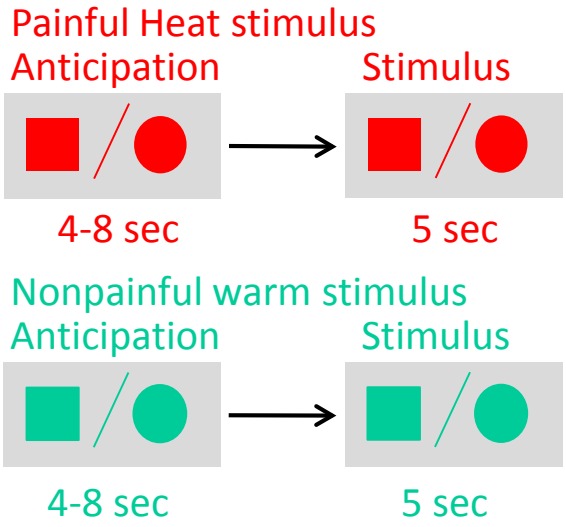


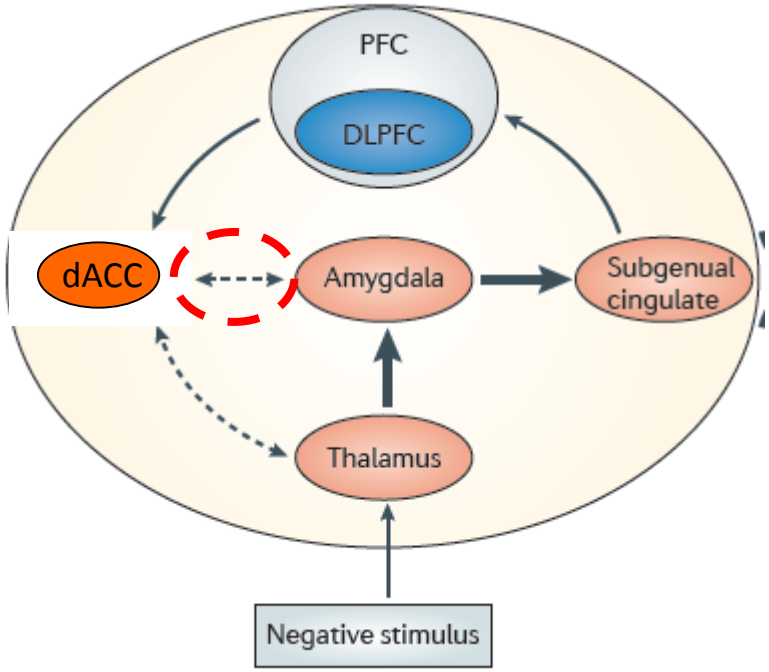




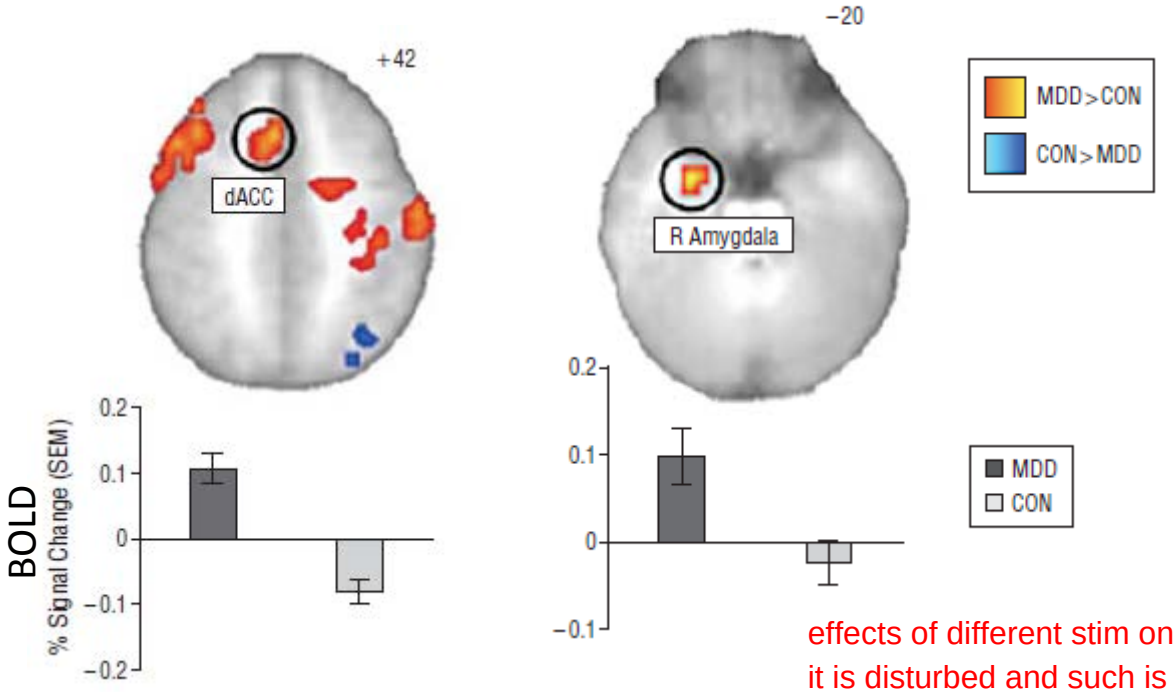
Elliott et al (2002) Arch Gen Psychiatry 59: 597

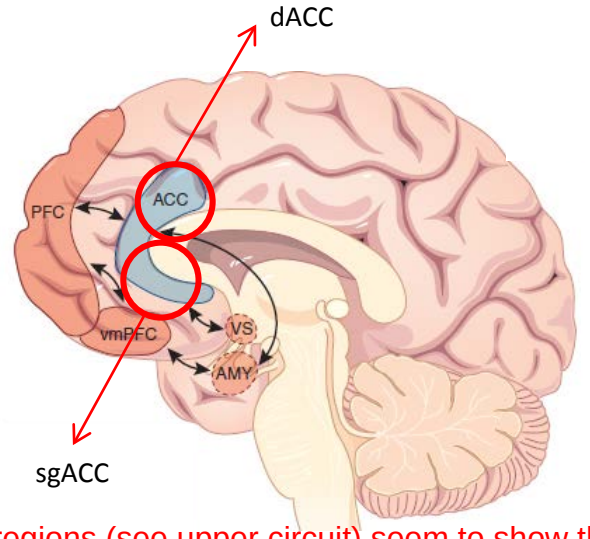
Increased neural response to painful stimuli in amygdala and dACC in depression





Anticipation period [painful heat - nonpainful warmth]

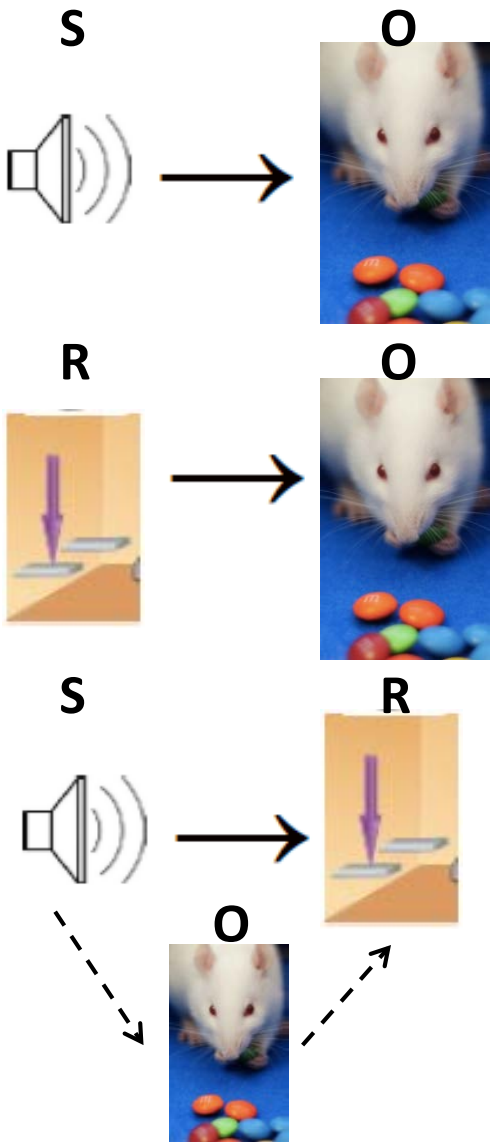




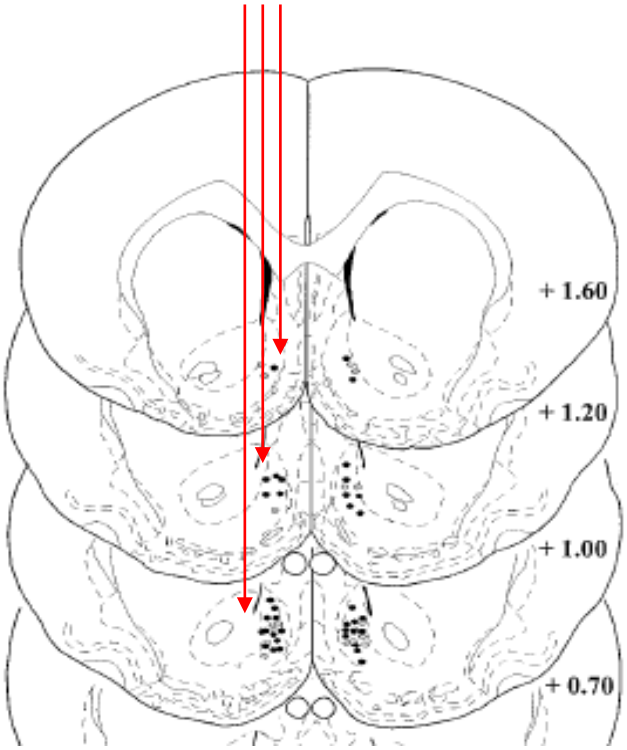
effects of different stim on speci brain regions (see upper circuit) seem to show that in depression it is disturbed and such is the response of depressed people

Strigo et al. (2008) Arch Gen Psych 65: 1275

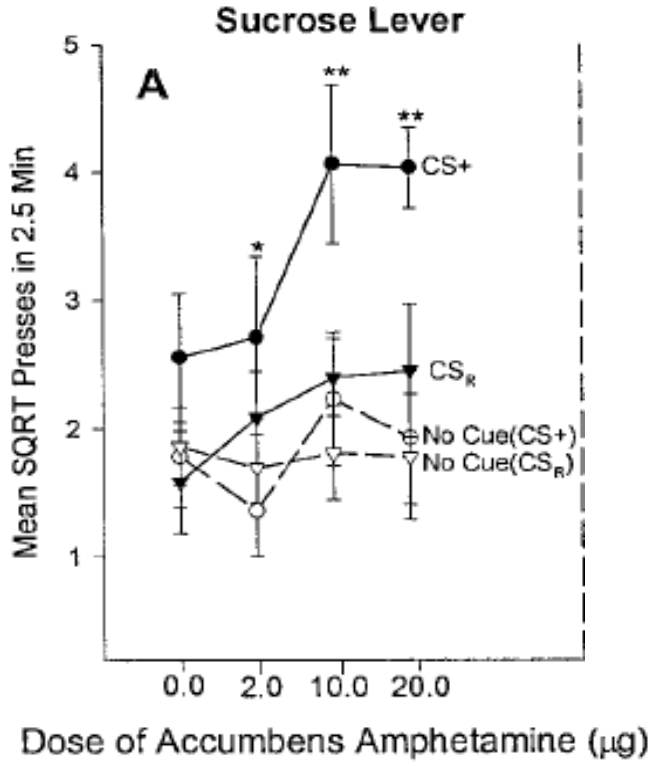
Incentive motivation for Reward (Wanting) is increased by Dopamine: Using Pavlovian-to-Instrumental transfer to measure motivation



Amphetamine into Nucleus accumbens:
Dopamine releaser at D1 and D2 receptors



Amphetamine
Vehicle



○ Period before CS switched ON

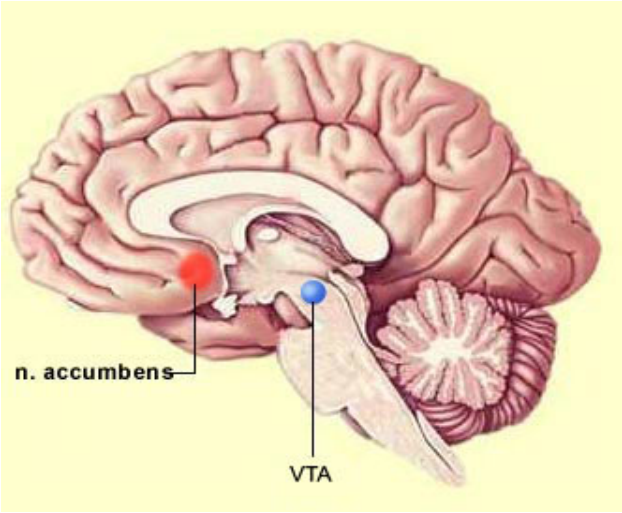
● Tone CS associated with sucrose

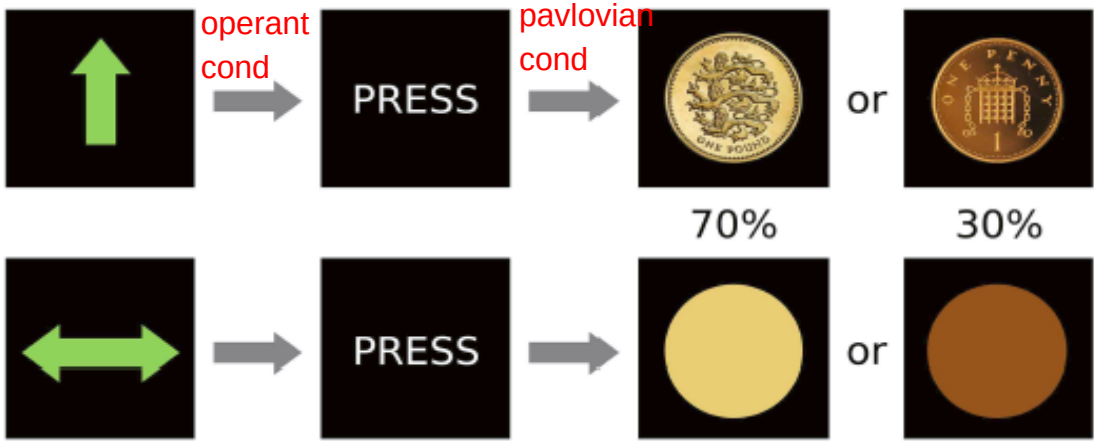
▼ Random CS NOT associated with sucrose

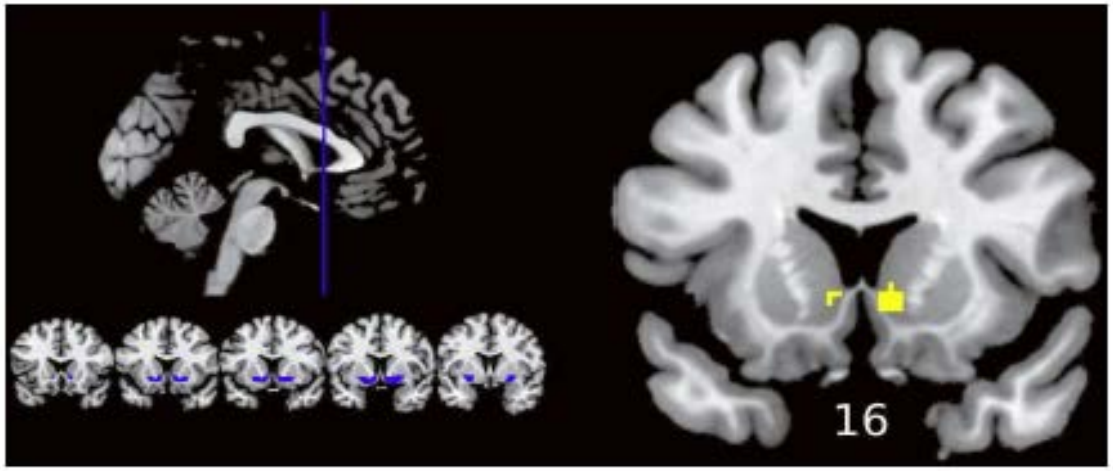
Wyvell & Berridge (2000) J Neurosci 20: 8122

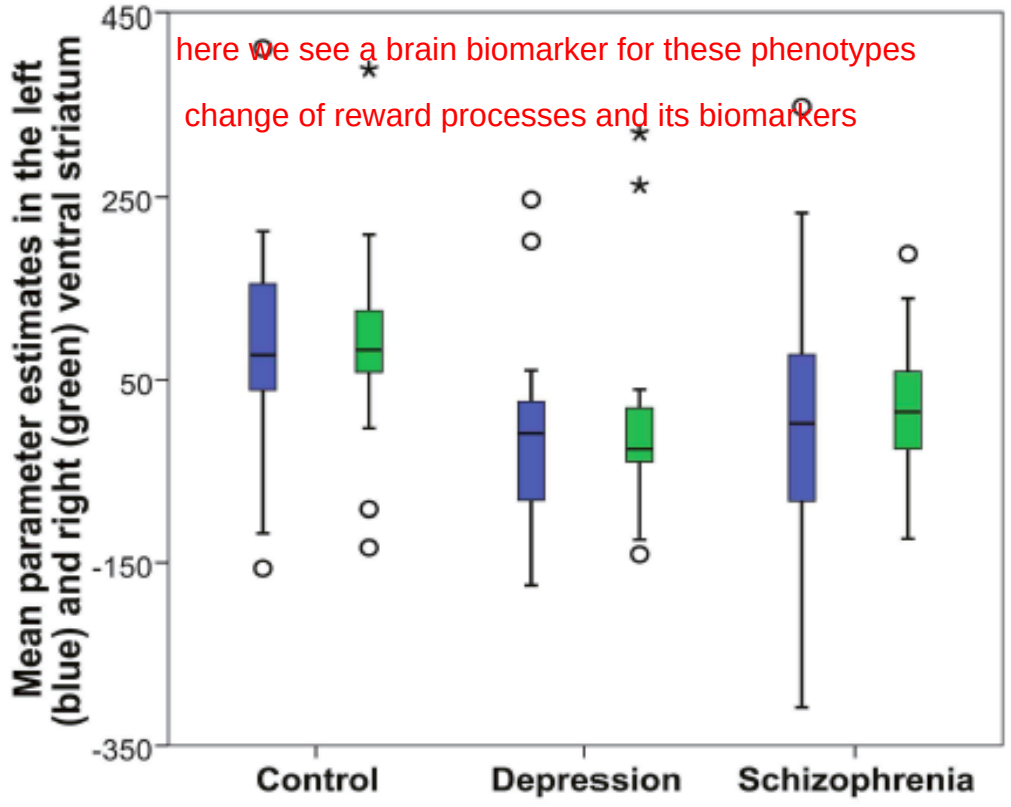
Example of a State marker in depression

Decreased nucleus accumbens response to reward in depression





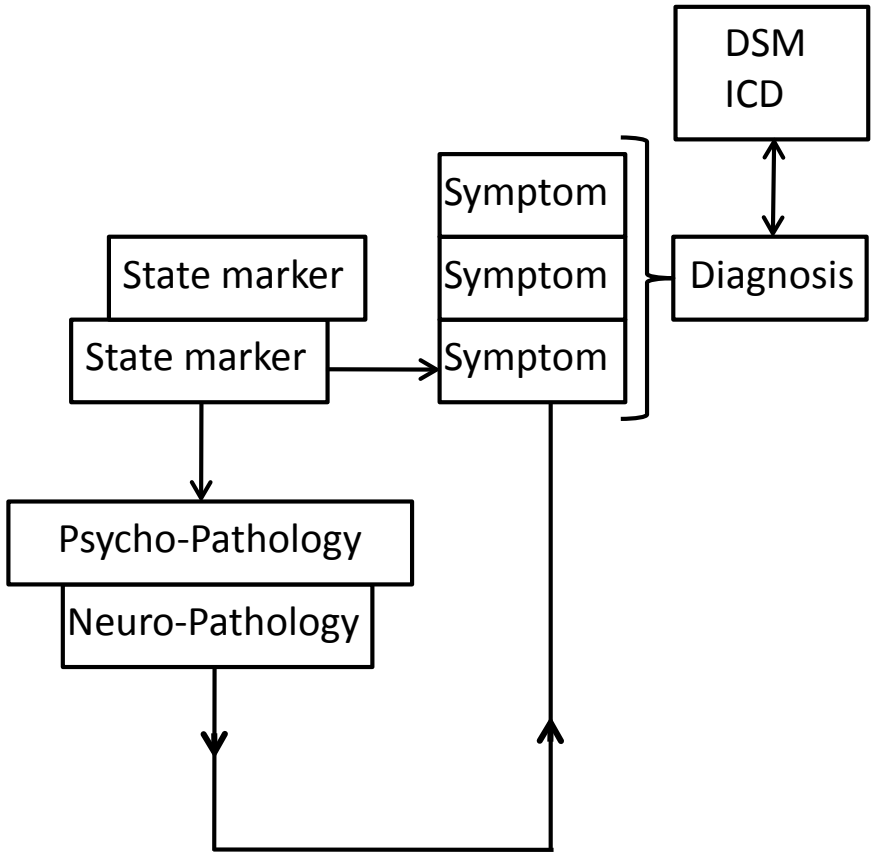




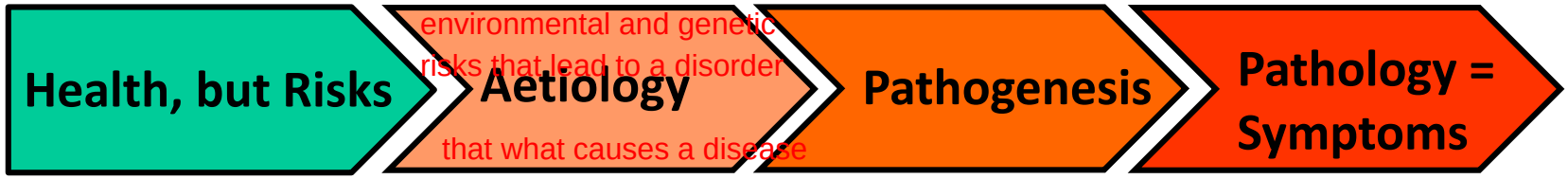
Arrondo et al. (2015) *Front Psychol* 6: 1280

skipped

Understanding a complex psychiatric disorder in terms of neuro-behavioural components

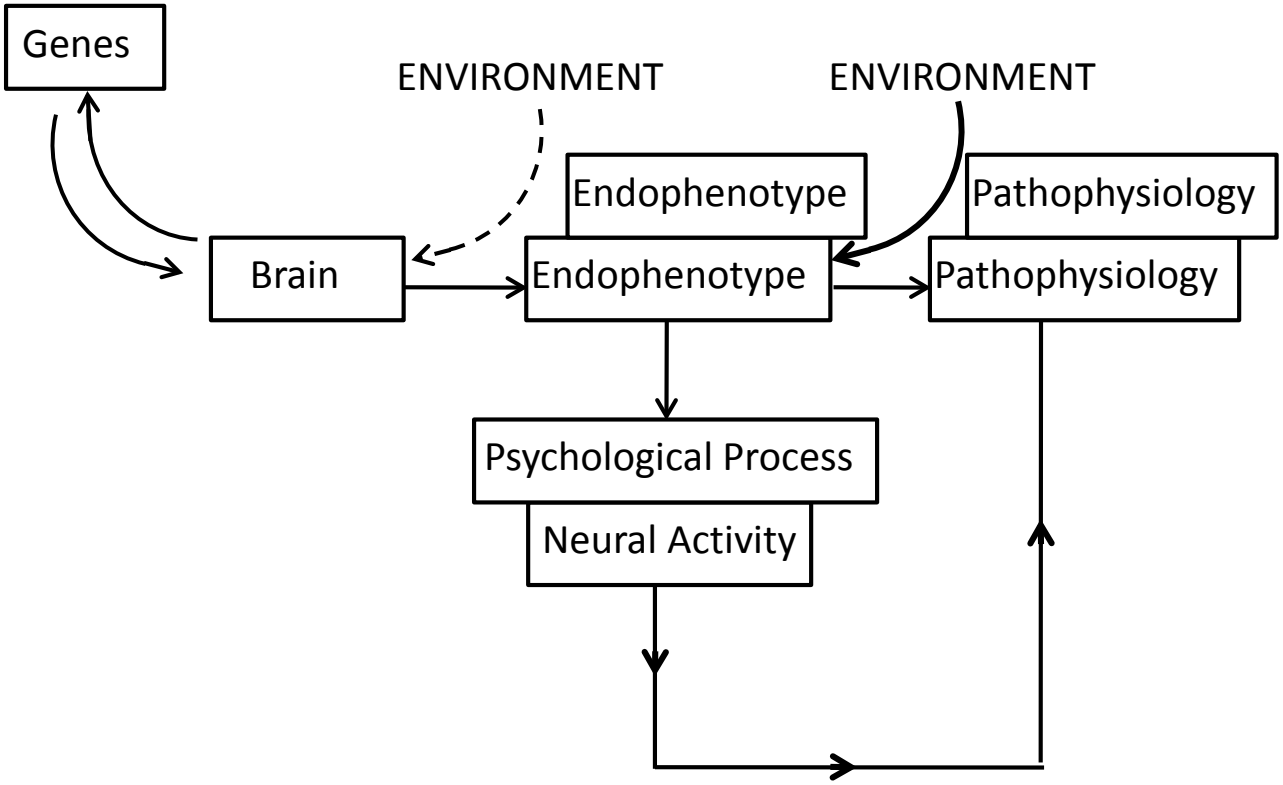


The Causation of Psychiatric disorders



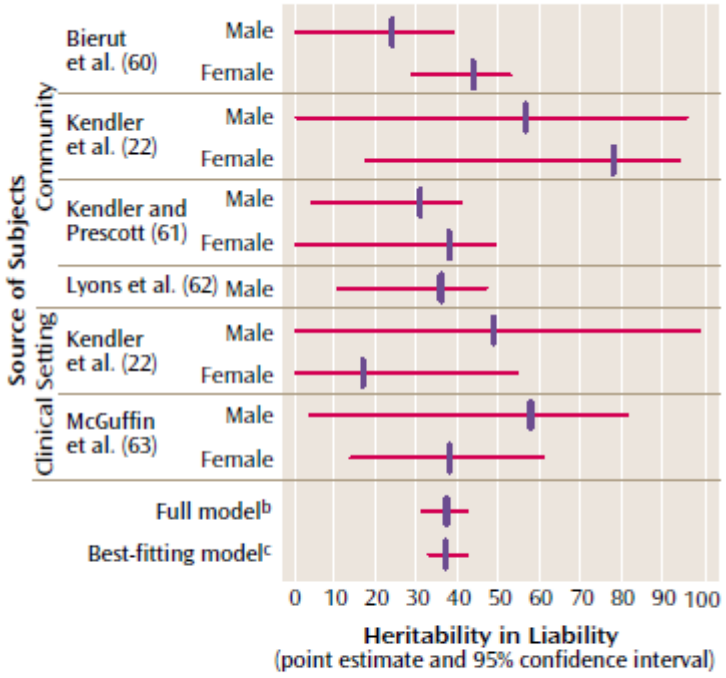
Understanding a complex psychiatric disorder in terms of neuro-behavioural components

endophenotye: a brain/psyhcological processes controlled genetically which is relevant to a disorder that it either behavioural or brain related here.



Heritability of Depression and Specific risk alleles for Depression

FIGURE 1. Estimates of the Heritability in Liability to Major Depression in Studies of Male and Female Twins[a]



[a] Vertical bars indicate point estimates; horizontal bars indicate 95% confidence intervals.
[b] Aggregate values across studies of heritability in liability to major depression.
[c] Most parsimonious submodel, consisting of aggregate value across studies of a^2.

a couple of possible endophenotypes

Gene	Protein	Polymorphism	Odds Ratio
SLC6A4	Serotonin transporter	44 bp Ins/Del	1.11
SLC6A3	Dopamine transporter	40 bp VNTR 9/10	2.06
DRD4	Dopamine receptor 4	48 bp VNTR 3	1.74
MTHFR	Methylenetetrahydrofolate reductase	C677T	1.20
GNB3	Guanine nucleotide binding-protein	C825T	1.38
APOE	Apolipoprotein E	ε2 / ε3	0.51

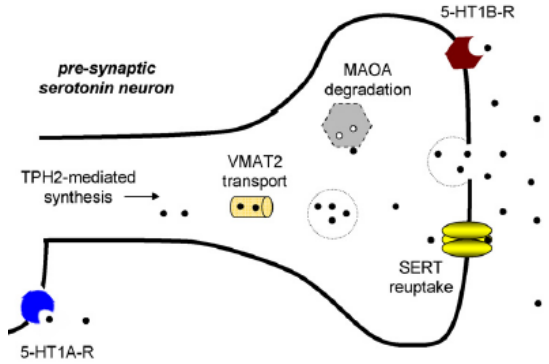
APOE: also risk factor in AD

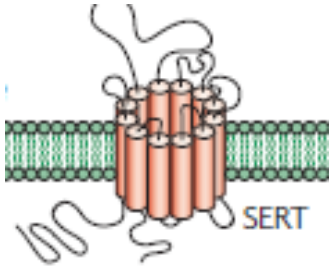
Sullivan et al. (2000) Am J Psychiatry 157: 1552

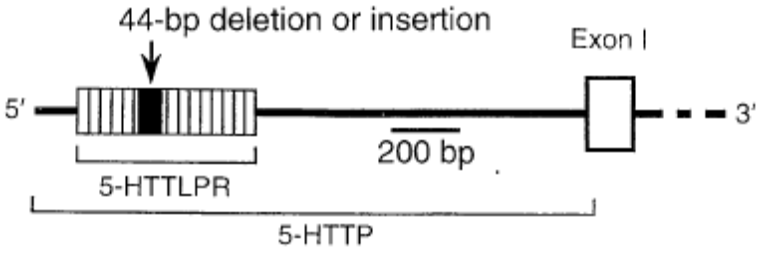
Lopez-Leon et al. (2008) Mol Psychiatry 13: 772

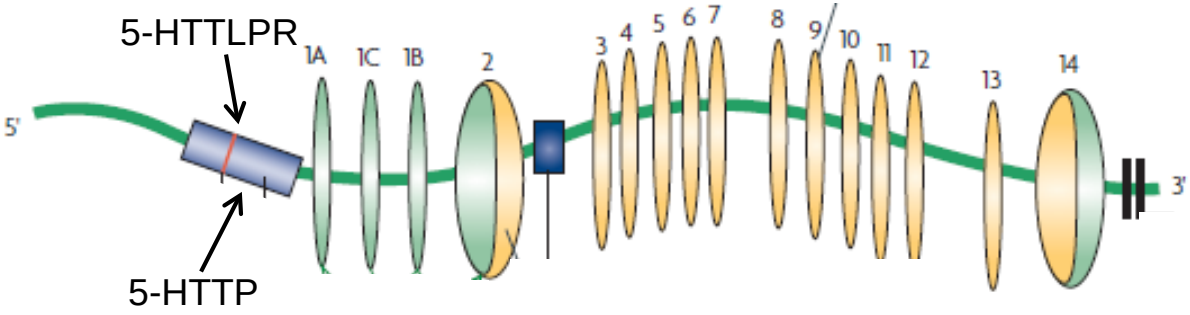
Serotonin transporter promoter (5-HTTP) gene-linked polymorphic region (5-HTTLPR):

(*s*)*hort* and (*l*)*ong* genotypes, and their impact on 5-HTT (SERT) expression and function



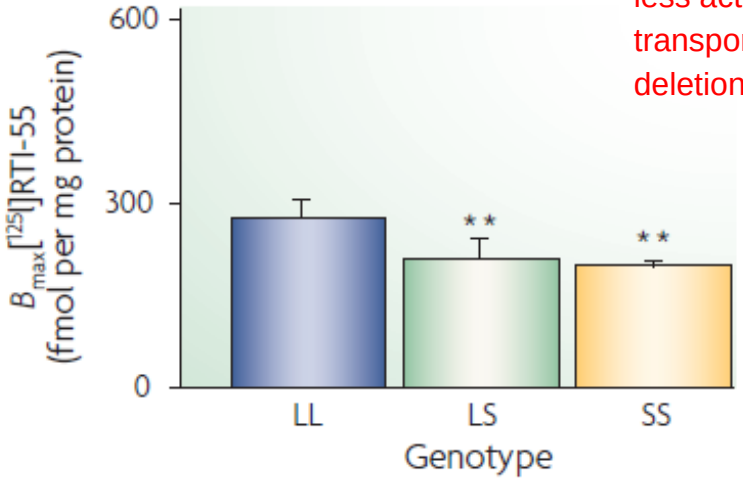






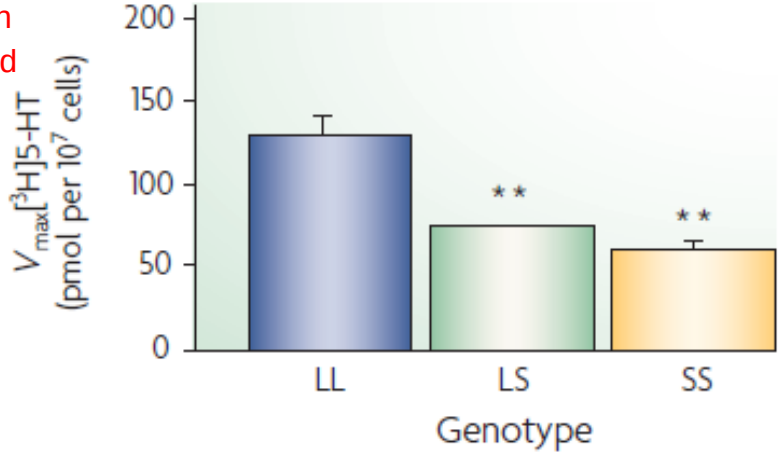
SLC6A4 5-HTTLPR genotypes

SERT binding sites



less active serotonin transporter when deletion occurred

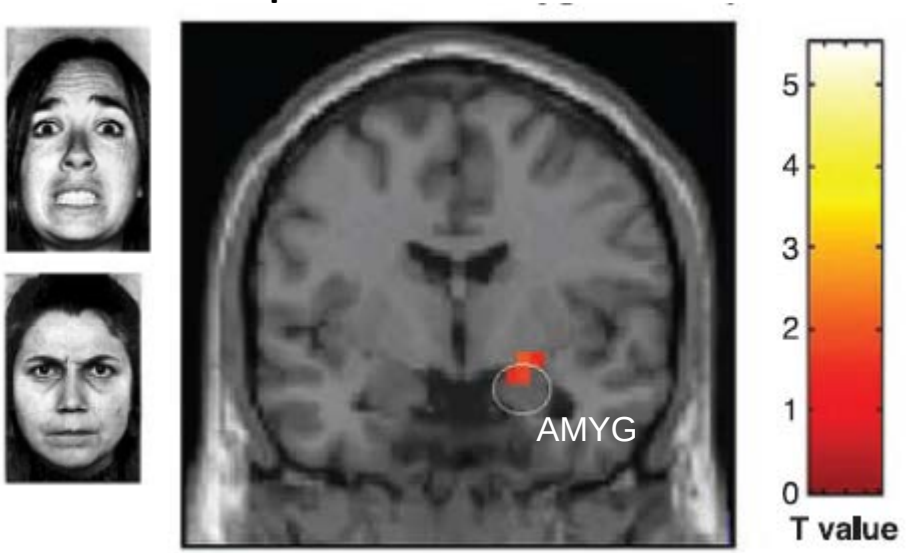
Serotonin uptake by SERT



Murphy & Lesch (2008) Nature Rev Neurosci 9: 85

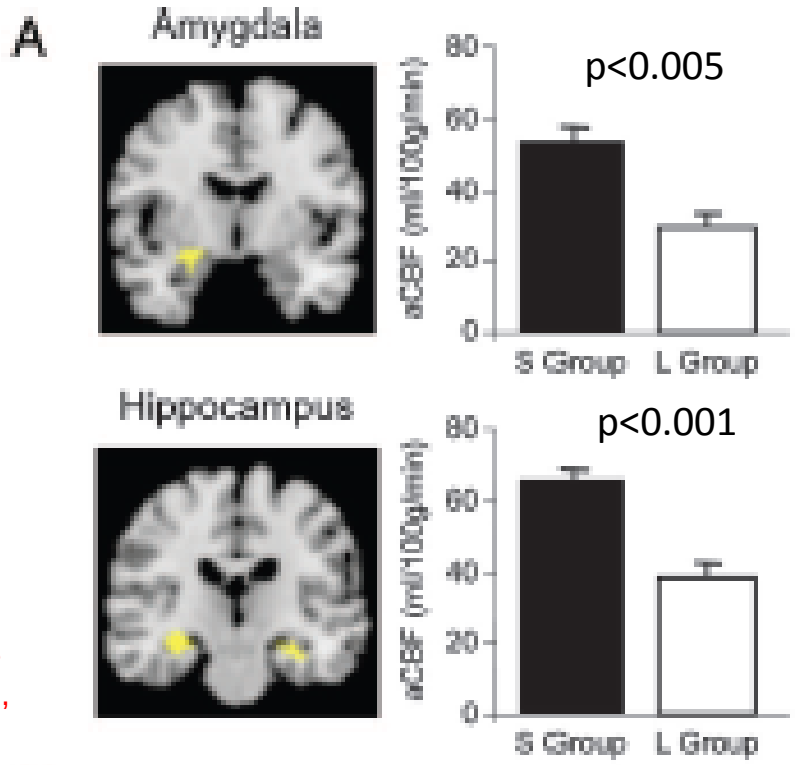
5-HTTLPR genotype and Brain Endophenotype for depression in healthy subjects

BOLD fMRI response to fearful face



when short transporters, more reactivtiy of amyg
to fearful faces what we see in depressed patients too
but this is in healthy patients. therefore, they show the same
brain endophenotype (a risk factor for depression here), which is
increased amyg activity on fearful faces. they are healthy though,
but acctivity resembles those of depressed people
=> short allele of SERT is genetic endohphenotye

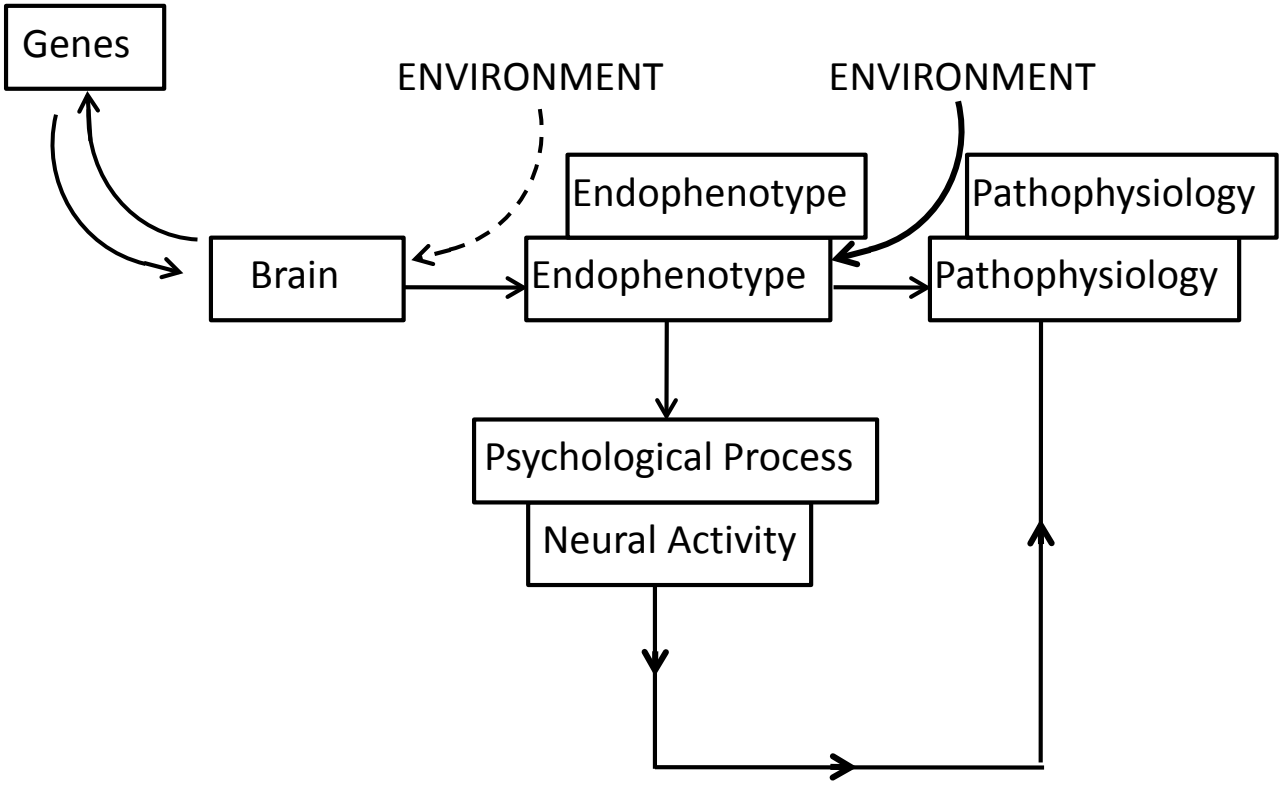
Absolute Cerebral Blood Flow at Rest



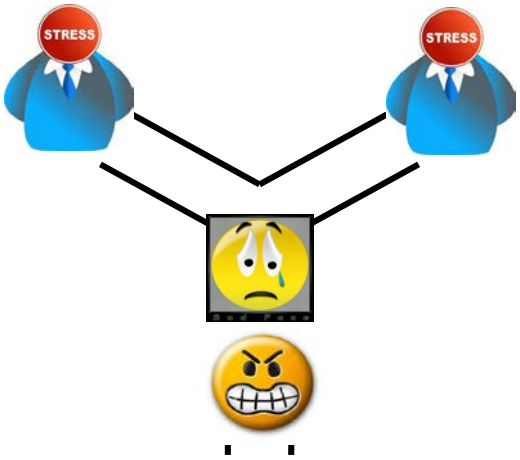
Hariri et al. (2002) Science 297: 400

Canli et al (2006) PNAS 103: 16033

Understanding a complex psychiatric disorder in terms of neuro-behavioural components



Environment: From Uncontrollability to Helplessness to Depression



Uncontrollable Stressful life events:

- Employment
- Finance
- Health
- Housing
- Family
- Social relationships

Aetiological phase
Learned helplessness

No Control/Contingency

Aversive event ⇄ Response → No Reinforcement → **Generalized Helplessness**

Maintenance phase

Aversive events

Emotionality ↑

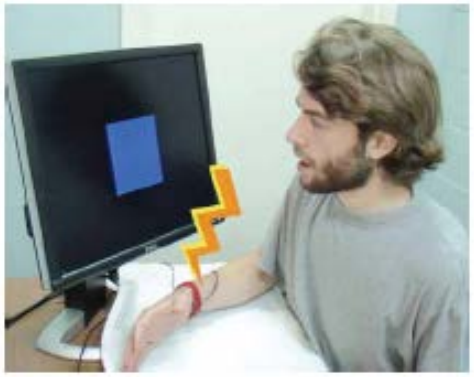
Motivation ↓

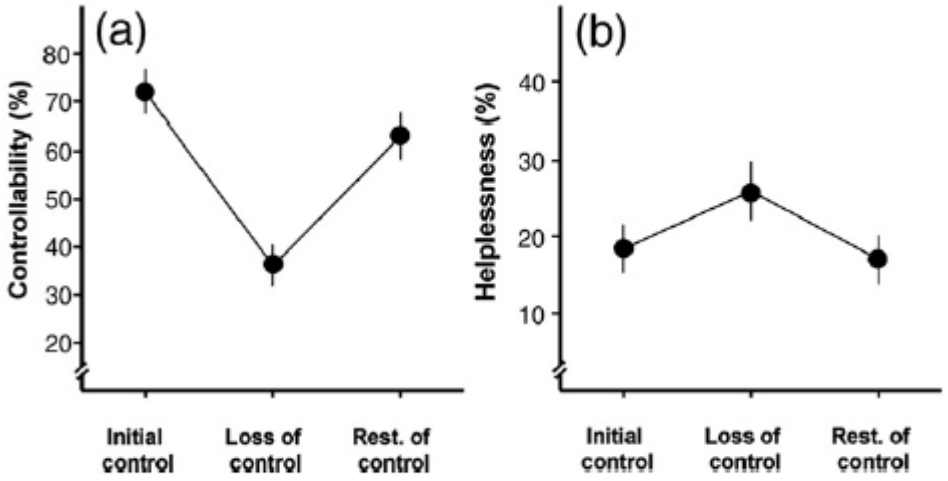
Cognition ↓

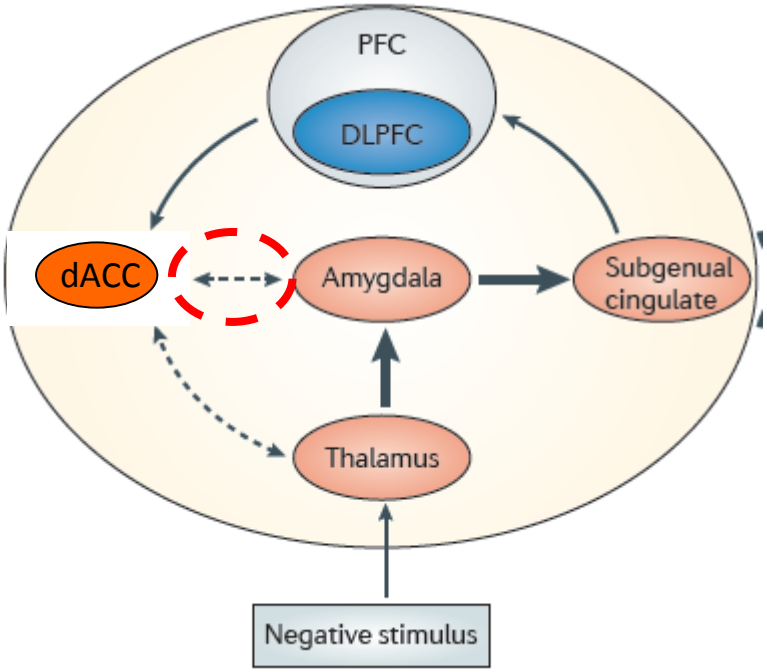
MDD symptoms

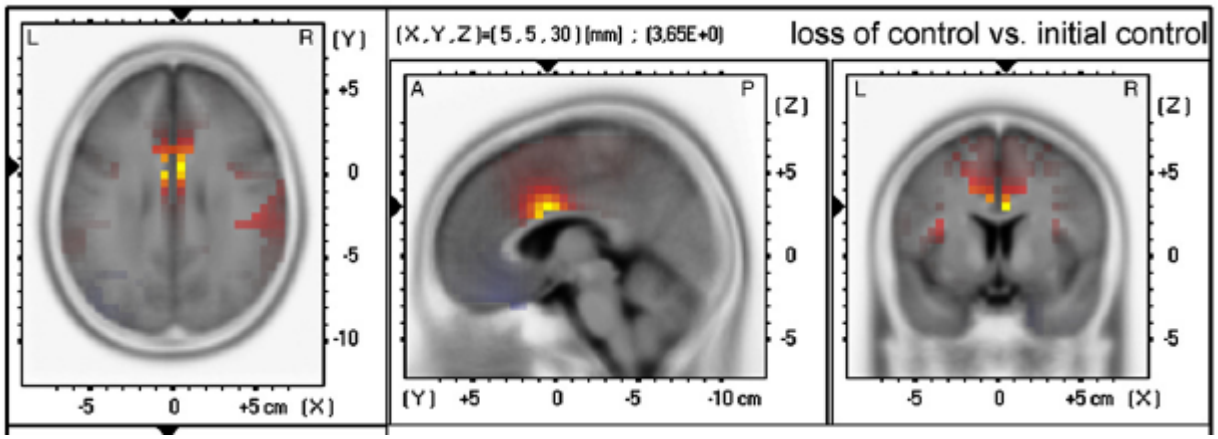
Increased neural response to uncontrollability of painful stimuli in dACC in healthy humans

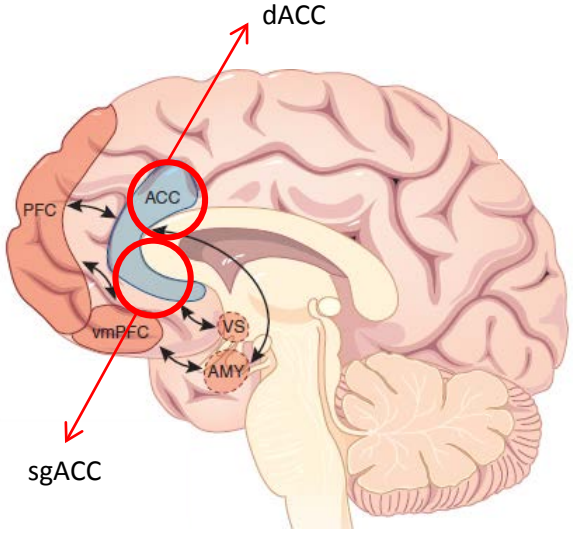
dACC activity increases when exposed to uncontrollable stim (like stress)
this exp is in healthy individuals





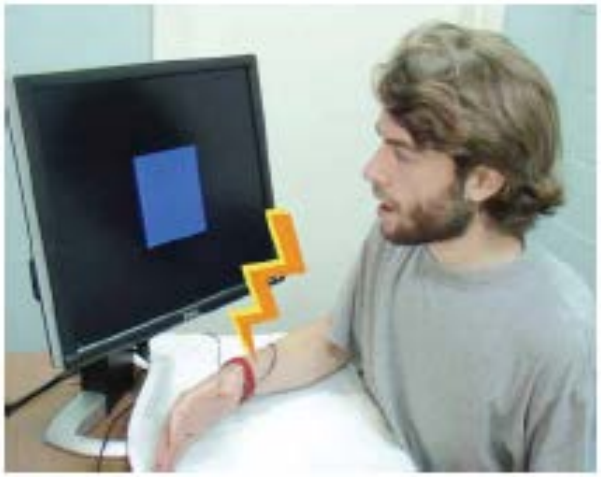




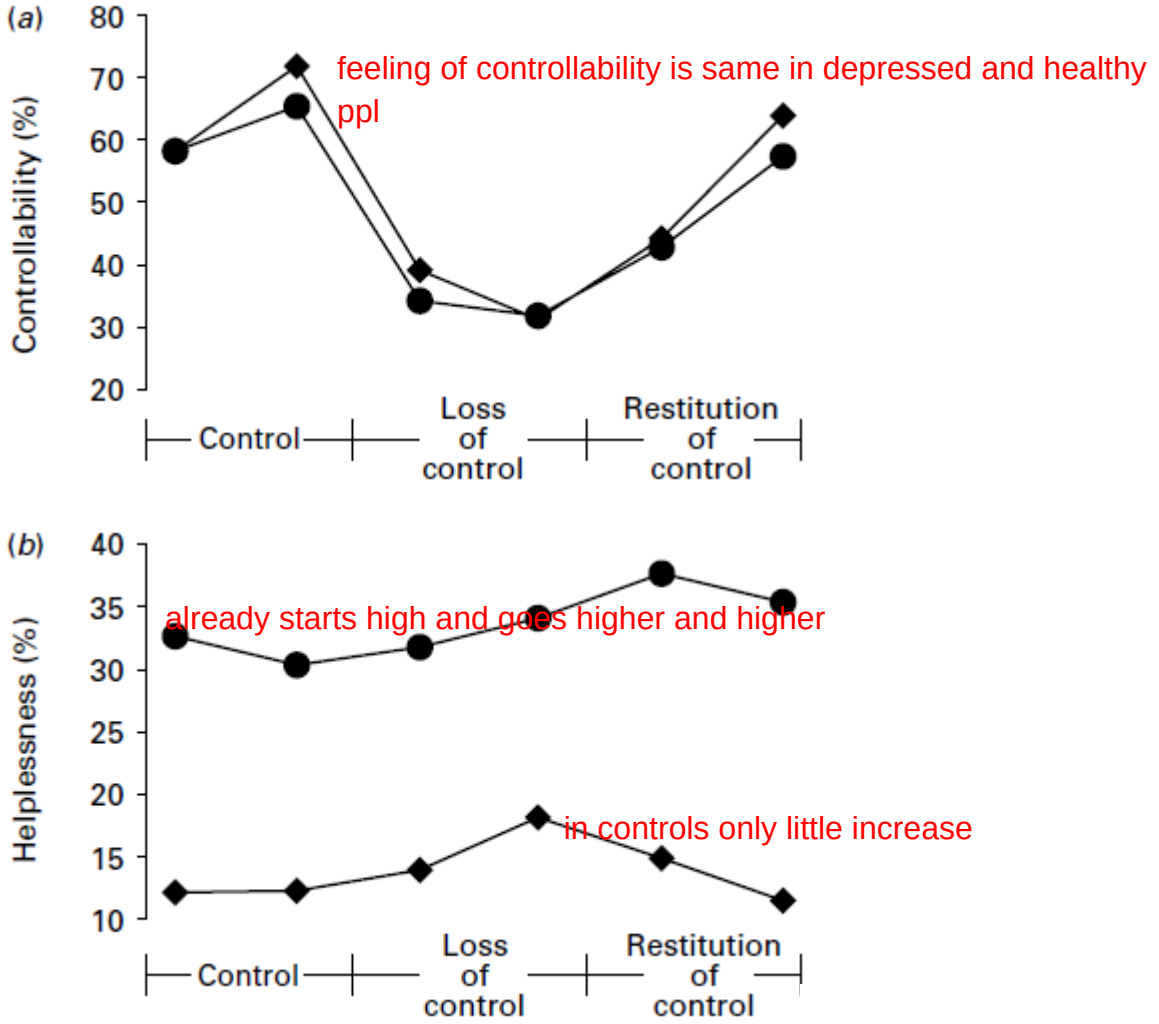


Diener et al. (2010) NeuroImage 50: 717

Example of a State Marker in Depression:
Increased feelings of Helplessness, especially after loss of control, in Depressed subjects

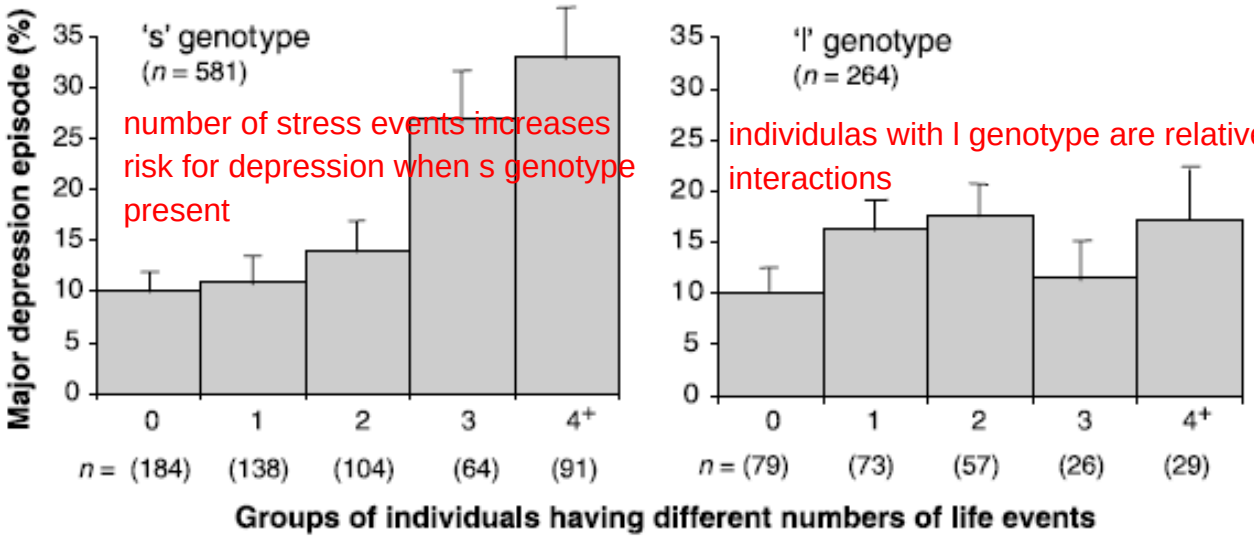


- Healthy Subjects
- Depressed Subjects



Diener et al. (2008) Psychological Medicine 39: 77

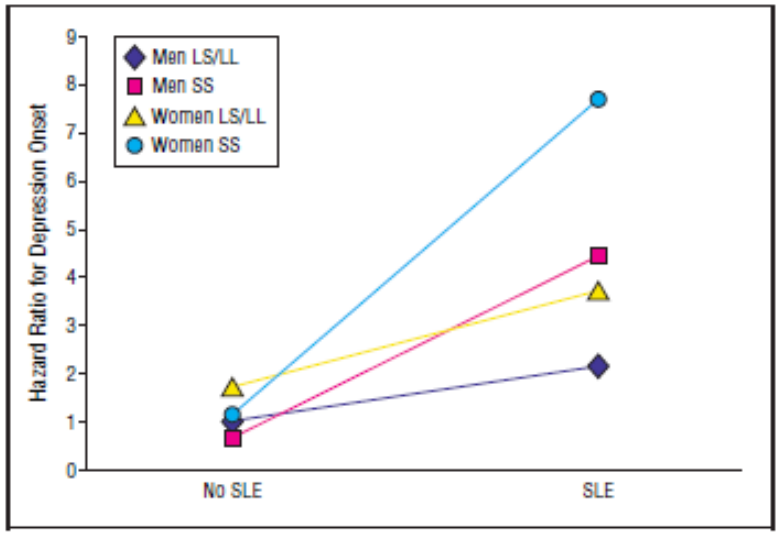
5-HTTLPR Genotype interacts with Stressful life events to increase prevalence of depression



number of stress events increases risk for depression when s genotype present

individulas with l genotype are relatively stable to gene-environemnt interactions

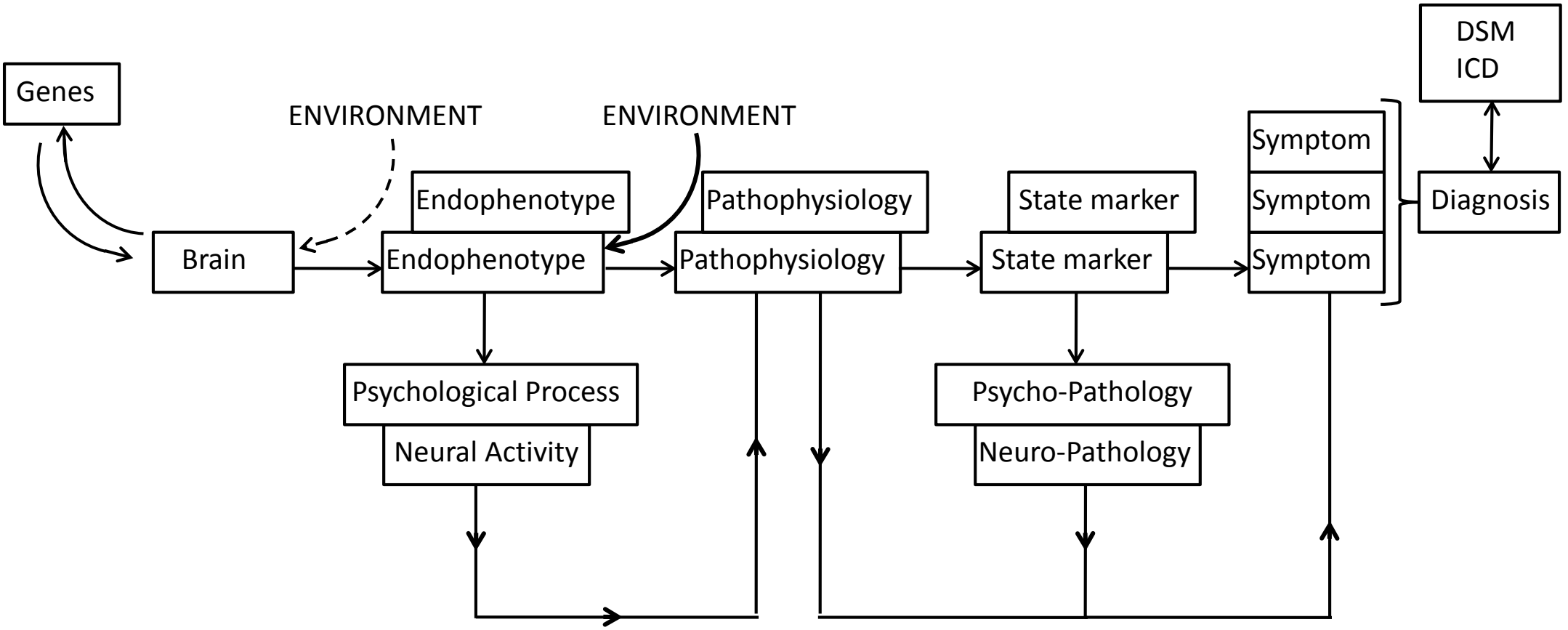
Caspi et al. (2003) Science 301: 386



Kendler et al. (2005) Arch Gen Psych 62: 529

helplessness very important in depression

Understanding a complex psychiatric disorder in terms of neuro-behavioural components



Pryce & Seifritz (2011) Psychoneuroendocrinology 36: 308

Translational experimental psychiatry

- Some homologous neurobiology for processing emotional stimuli across mammals
- Disorders of emotional processing (e.g. Depression, Post-traumatic stress disorder) are prevalent
- Psychiatry uses a diagnosis system based on groups of behavioural symptoms, not on underlying biology
- The relationship between symptom and neurobiology is not taken into consideration in the diagnostic system
- Models for the conceptualising of psychiatric disorders in populations
- Psychiatric disorders need to be understood in terms of their neuro-behavioural components
- Depression can be viewed as altered emotional processing of aversive and rewarding stimuli
- Increased conditioned fear responses in depressed patients relative to healthy controls
- Increased reactivity of the amygdala to fearful and sad stimuli using BOLD fMRI in depression
- Neurocircuitry model of processing aversive stimuli in depression based on BOLD fMRI findings
- Increased reactivity of the dorsal anterior cingulate cortex to fearful and sad stimuli in depression
- The risk allele - endophenotype concept
- Molecular genetics of depression
- Serotonin transporter gene polymorphism and emotional endophenotypes in neurobiology and behaviour
- Environmental factors and depression
- Uncontrollable environments and helplessness
- Gene X Environment interaction in the aetiology of depression