MAJOR DEPRESSIVE DISORDER

New Clinical, Neurobiological and Treatment Perspectives

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- Lancet. 2012 Mar 17;379(9820):1045-55. Epub 2011 Dec 19.
- Kupfer DJ, Frank E, Phillips ML.
- University of Pittsburgh Medical Center, Western Psychiatric Institute and Clinic, PA, USA. Kupferdj@upmc.edu
- PMID: 22189047

Search Strategy and Selection Criteria

- PubMed from June, 2005, to June, 2010, for the terms “depression”, “antidepressants”, and “depression treatment”.
- Other bibliographies of selected articles were reviewed to obtain additional relevant references
- Excluded non-English publications.

Epidemiology, Comorbidity,Diagnosis

- 12-month prevalence of 6·6% and a lifetime prevalence of 16.2%,
- 2M=F
- Prevalent for the entire lifespan
- Not only produces decrements in health that are equivalent to those of other chronic diseases but also worsens mean health scores substantially more when co-morbid with these diseases, than when the diseases occur alone.
- A meta-analysis concluded that GPs correctly exclude depression in most individuals who are not depressed, however over-detections (false positives) can outnumber missed cases.

Comorbidity

- Comorbidity with anxiety makes it difficult to diagnose
- DSM5 may include Anxious Depression
- MDD was assumed to precede Generalized Anxiety Disorder (GAD) until a 32-year prospective follow-up study challenged this notion.
- Social phobia → severe depression.
- Comorbid personality disorder → worse prognosis, poorer treatment response
- Metabolic syndrome and MDD have a two-way relation (?increased risk for CAD)
- Depression within several weeks of admission to hospital for an acute coronary syndrome or an inadequate treatment response in depression, can double cardiac mortality in 6·7 years
- MDD is associated with a 65% increased risk of diabetes in elderly people.

Neurobiology

- Understand the pathophysiology of the illness
- Identify the neurobiological measures for guiding treatment choice

Genetics

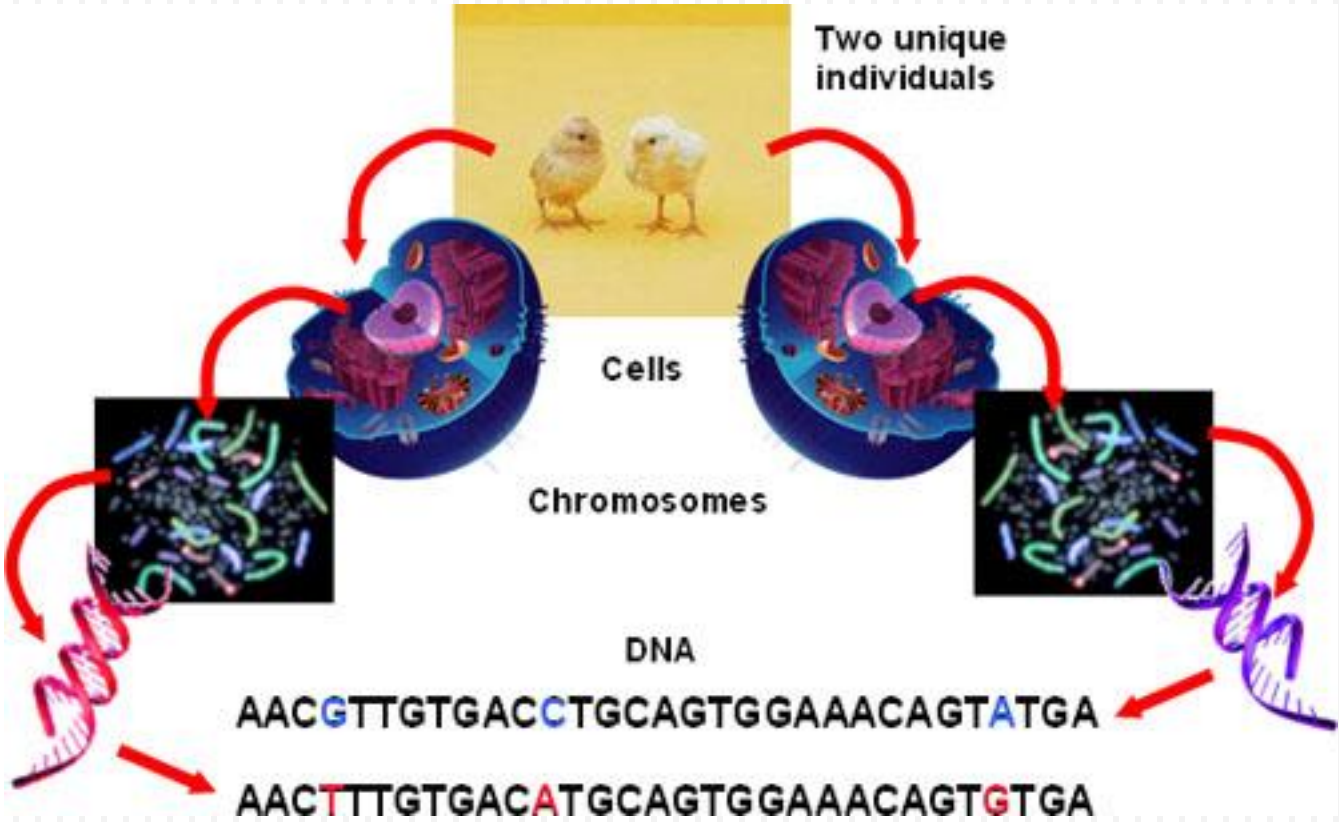
Polymorphisms

- Glucocorticoid receptor gene NR3C1 and the
- Monoamine oxidase A gene
- Glycogen synthase kinase-3β
- Group-2 metabotropic glutamate receptor gene (GRM3).

Genetics

- Functional insertion-deletion promoter variant (serotonin transporter-linked polymorphic region [5HTTLPR]) in the serotonin transporter gene (SLC6A4)
- 5HTTLPR long allele→ increased SSRI response and reduced side effects
- 5HTTLPR short allele→ increased paroxetine-induced, but decreased mirtazapine-induced side effects
- Several single-nucleotide polymorphisms (SNPs) in the gene for the serotonin type-2a receptor are associated with outcomes of SSRI treatment.

SNPs


Two unique individuals
Cells
Chromosomes
DNA
AACGTTGTGACCTGCAGTGGAAACAGTATGA
AACTTTGTGACATGCAGTGGAAACAGTGTGA

Genetics

- Glutamatergic genes (eg, GRIK4) → citalopram response and adverse effects
- Met allele of the functional Val/Met polymorphism (rs6265) in brain-derived neurotrophic factor (BDNF) → SSRI response
- Several other BDNF SNPs →Desipramine response.
- Genetic variation in a protein that helps to regulate cortisol binding to the glucocorticoid receptor (FKBP5) → antidepressant response;
- genetic variants in a potassium channel (TREK1) mediating SSRI mechanism of action → non-response to several antidepressants.
- Genetic variation in the COMT gene →alters COMT activity→ response to treatment with several antidepressants.

Genetics

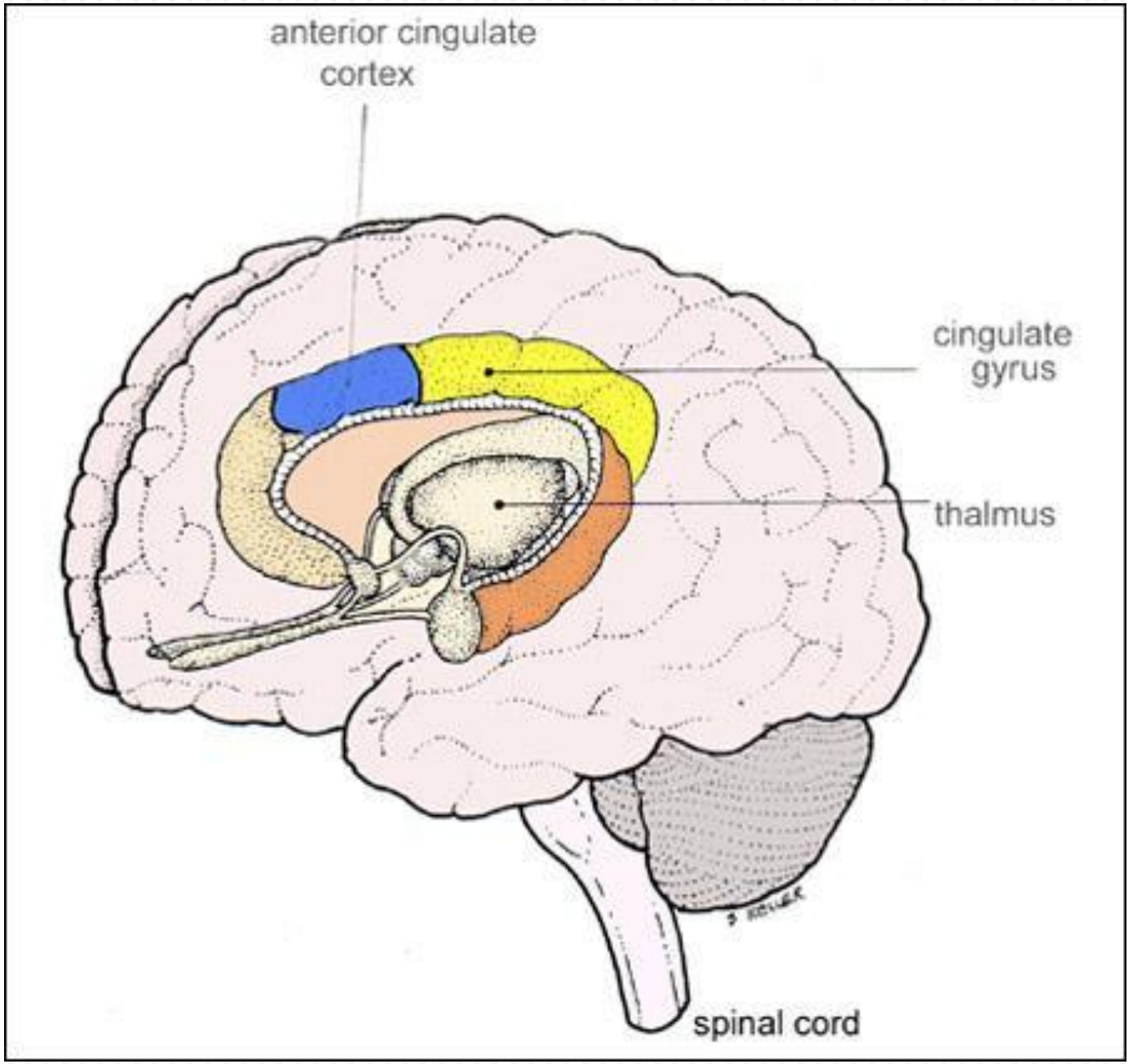
- Genome-wide association studies further suggest that effectiveness of antidepressants can be predicted by genetic markers other than traditional candidate genes:
- Genes for CRH Receptor-1 (CRHR1) and CRH binding protein (CRHBP)→ predict SSRI response in anxious depression
- Genes for uronyl-2 sulphotransferase → predict response to nortriptyline
- Interleukin-11 → predict response to escitalopram oxalate

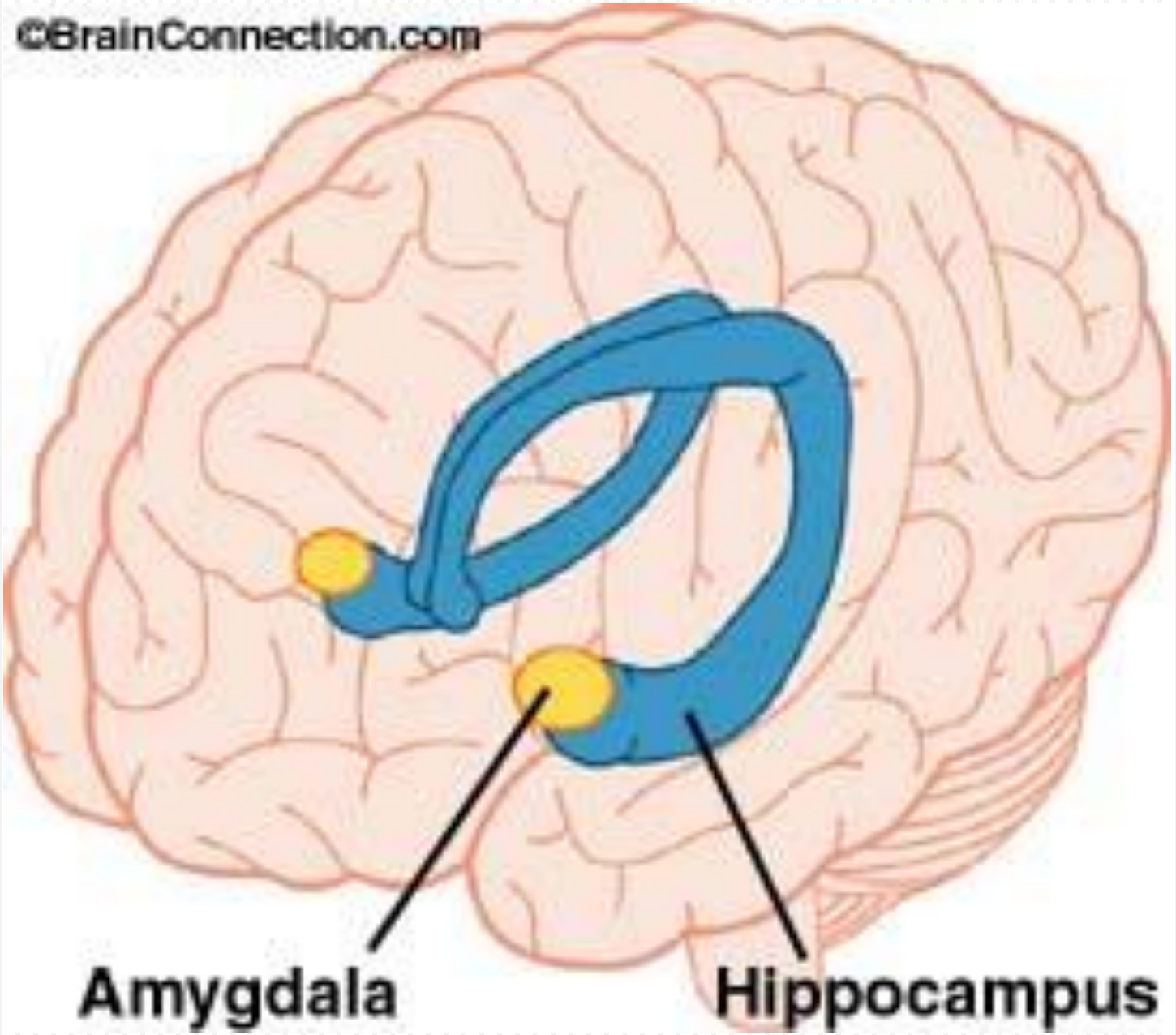
Molecular Studies

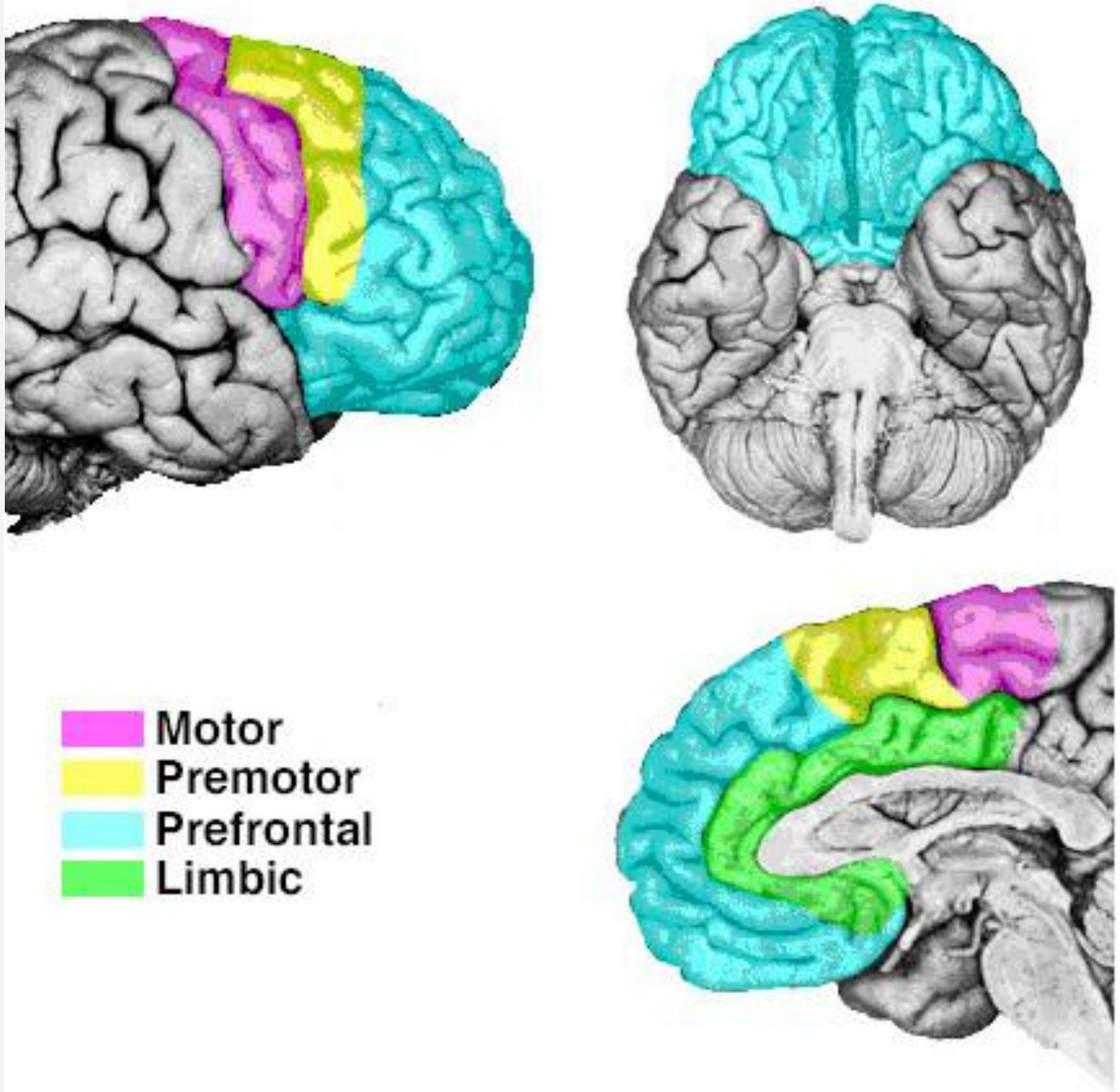
- neurotrophic factors and other growth factors
- proinflammatory cytokines
- impaired regulation of the HPA axis

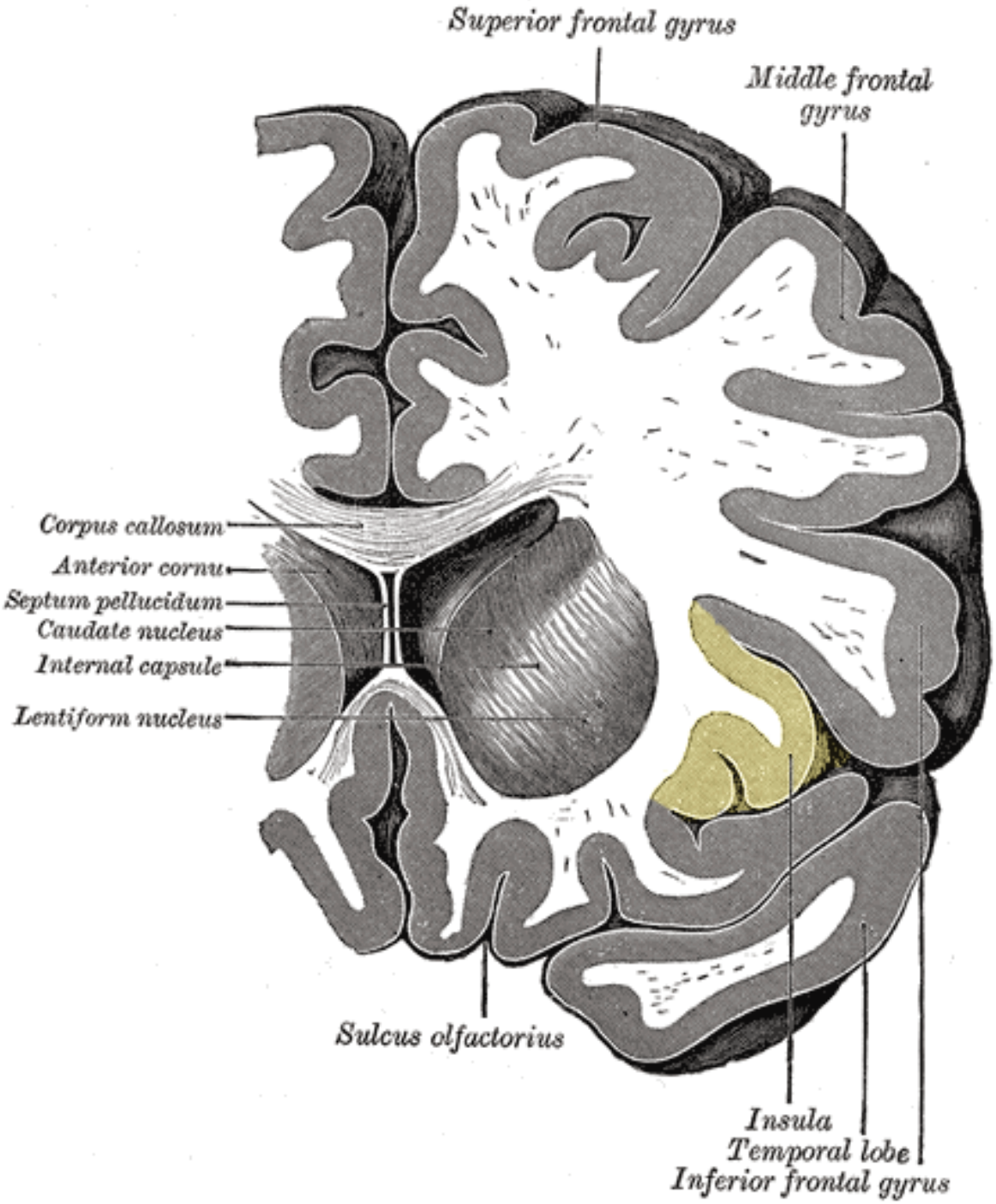
Neuroimaging Studies

- Medial prefrontal- limbic network → modulated by Serotonin
- Reward network → modulated by dopamine

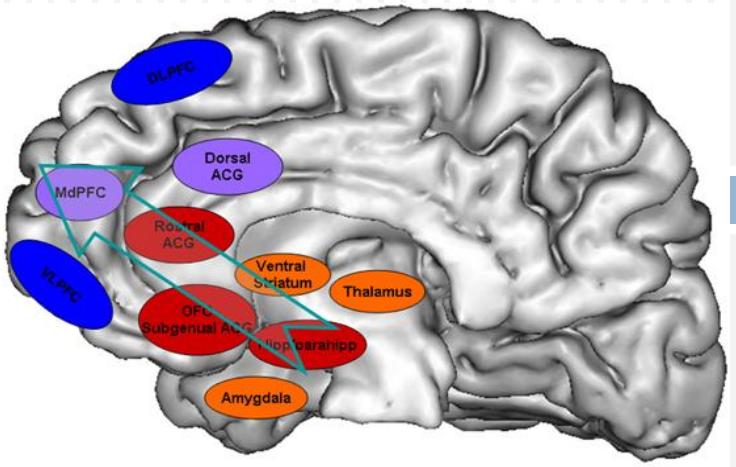

anterior cingulate
cortex
cingulate
gyrus
thalmus
spinal cord


©BrainConnection.com
Amygdala
Hippocampus


Motor
Premotor
Prefrontal
Limbic

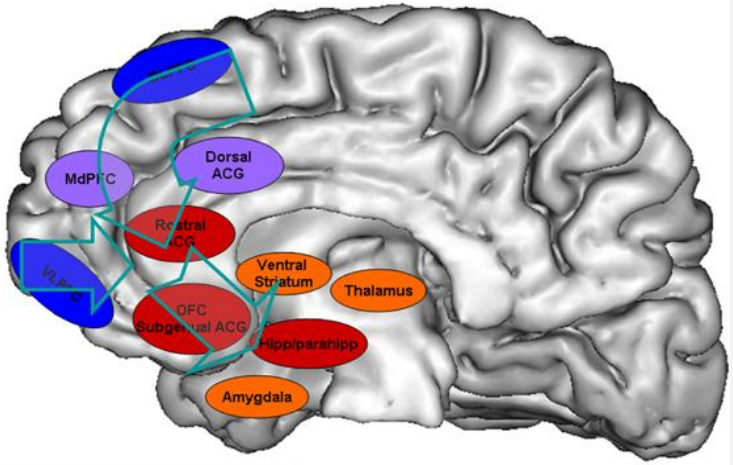

Superior frontal gyrus
Middle frontal gyrus
Corpus callosum
Anterior cornu
Septum pellucidum
Caudate nucleus
Internal capsule
Lentiform nucleus
Sulcus olfactorius
Insula
Temporal lobe
Inferior frontal gyrus

a



Orienting/Emotion Identification
Automatic Emotion Regulation
Voluntary Emotion Regulation
Regions Implicated in Both Automatic and Voluntary Emotion Regulation

b



Orienting/Emotion Identification
Automatic Emotion Regulation
Voluntary Emotion Regulation
Regions Implicated in Both Automatic and Voluntary Emotion Regulation

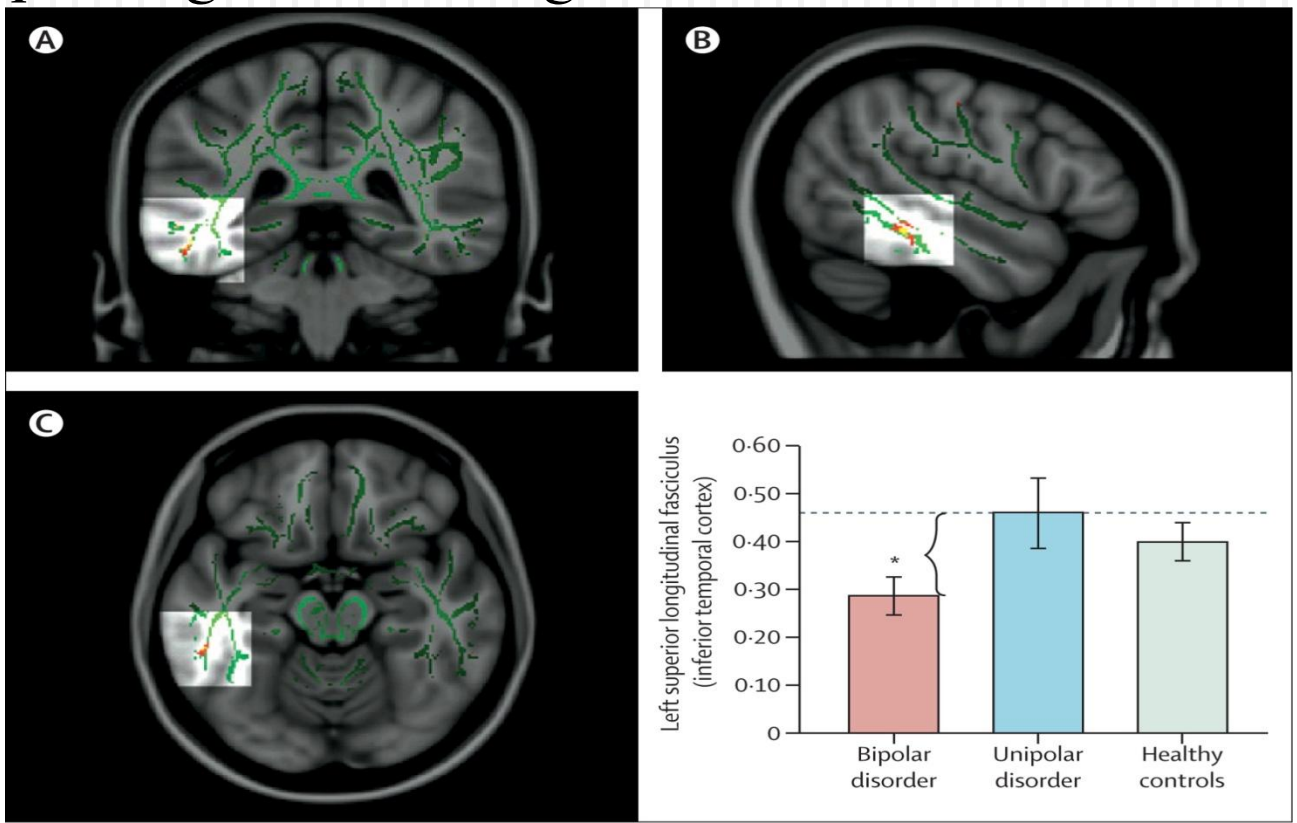
Neuroimaging Studies

Bias away from attendance to positive emotional stimuli:

- Abnormally increased amygdala, ventral striatal, and medial prefrontal cortex activity, mostly to negative emotional stimuli
- Abnormally reduced ventral striatal activity to positive emotional stimuli and during receipt and anticipation of reward
- Abnormal inverse effective connectivity in medial prefrontal cortical-amygdala during positive emotion labelling

Neuroimaging Studies

- Diffusion tensor imaging→ abnormal prefrontal cortico-subcortical whitematter connectivity between regions supporting emotion regulation



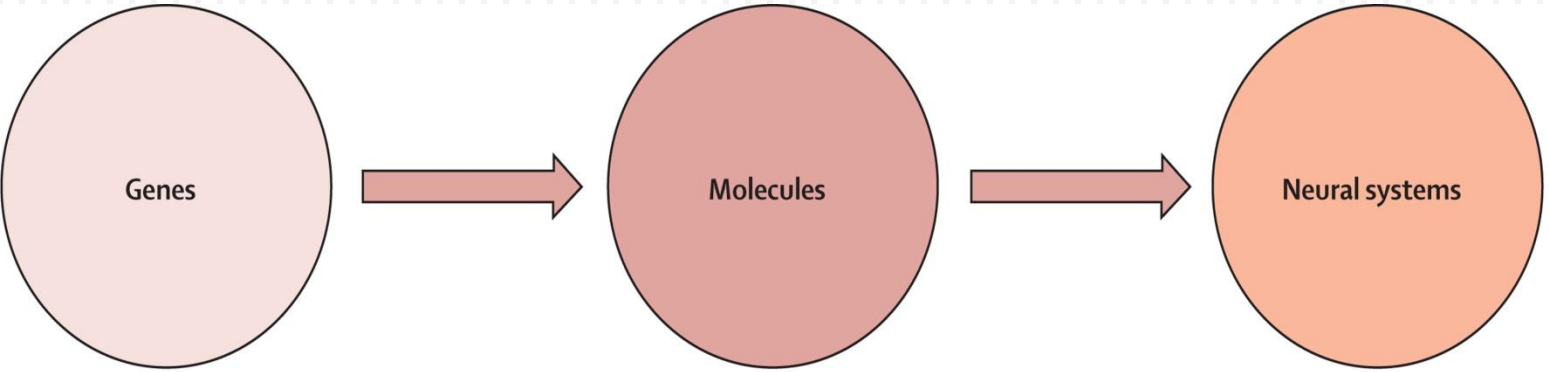
Neuroimaging Studies

- Examination of brain activity during rest→default mode network→ task- independent deactivations in vmPFC (low frequency blood oxygen level dependent temporal fluctuations (LFBF) in steady-state functional MRI)
- Increased activity in neural systems supporting emotion processing & reduced activity in neural systems supporting regulation of

Neuroimaging-Response to Treatment

- SSRIs→ response is predicted by activity in medial prefrontal-limbic network
- Ketamine→ response is predicted by desynchronisation of the anterior cingulate cortex its functional connectivity with the amygdala
- CBT→ response is predicted by reduced medial prefrontal activity& increased amygdala activation
- DBS→ response correlates with reduced activity in ventral (subgenual) regions of the anterior cingulate cortex & increased metabolism in ventral striatum

Integration of Measures



Genetic measures
- Candidate genes associated with MDD (ie, beyond the conventional monoamine focus)
- Candidate genes associated with biological mechanisms and metabolic pathways for antidepressant medications
- Serotonergic mechanisms
- Other mechanisms
- Genome-wide association studies

Molecular measures
- Neurotrophic factors and other growth factors
- Proinflammatory cytokines
- Impaired regulation of the hypothalamic-pituitary-adrenocortical axis

Neuroimaging measures

Abnormalities in anatomically-defined neural systems
- Subcortical neural systems for emotion and reward processing
- Medial prefrontal regions involved in processing and implicit regulation of emotion
- Lateral prefrontal cortical systems involved in cognitive control and voluntary or effortful regulation of emotion

Abnormalities in neurotransmitter-defined neural systems
- Medial prefrontal-limbic network, modulated by serotonin
- Reward network, centred on ventral striatum and medial prefrontal cortices, modulated by dopamine

Newer neuroimaging methodologies to study MDD
- Measurement of brain activity during rest

Neuroimaging and antidepressant treatment response

Advances in Treatment/Psychotherapy

- IPT alone, or in combination with pharmacotherapy
- Effects of acute interpersonal psychotherapy can be sustained even after remission
- CBT can be effectively implemented in non-traditional ways, e.g: via telephone and the internet
- IPT vs CBT→ Equally effective→ Except severe depression (MADRS score >30) CBT> IPT
- Mindfulness-based cognitive therapy
- Problem-solving therapy

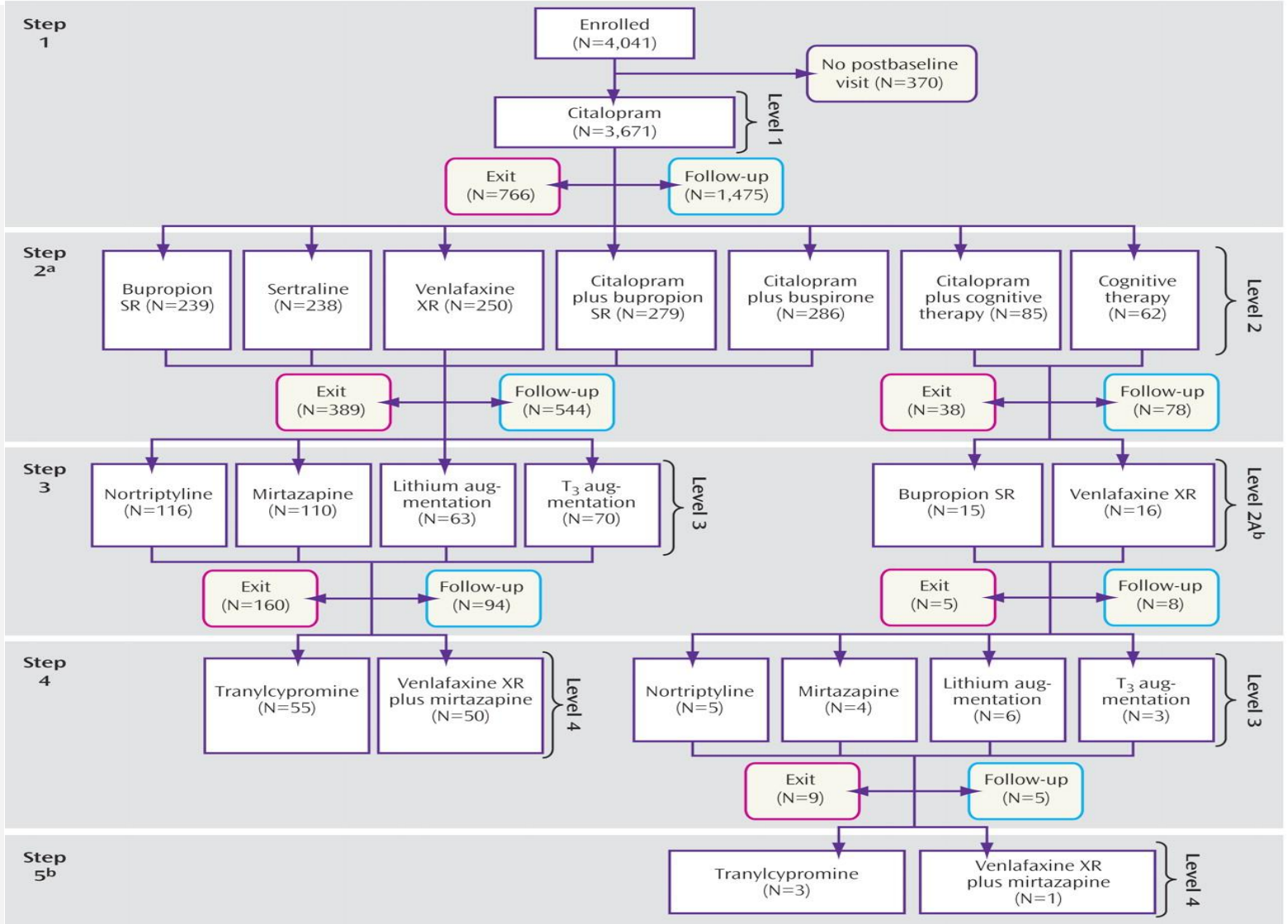
Pharmacotherapy

	Drugs	Proposed mechanism of action
Selective serotonin reuptake inhibitors	Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline	Selectively inhibits the reuptake of serotonin
Tricyclic antidepressants	Amitriptyline, desipramine, doxepin, imipramine, maprotiline, nortriptyline, protriptyline, trimipramine	Nonselectively inhibits the reuptake of monoamines, including serotonin, dopamine, and norepinephrine
Norepinephrine-dopamine reuptake inhibitor	Bupropion	Inhibits the reuptake of norepinephrine and dopamine
Serotonin modulator	Nefazodone, trazodone	Primarily antagonises 5-HT2 receptors
Serotonin-norepinephrine reuptake inhibitors	Desvenlafaxine, duloxetine, venlafaxine	Inhibits the reuptake of serotonin and norepinephrine
Noradrenergic and specific serotonergic modulator	Mirtazapine	Primarily antagonises α-2 and 5-HT2C receptors
Serotonin reuptake inhibitor and 5-HT1A-receptor partial agonist	Vilazodone	Potently and selectively inhibits serotonin reuptake and acts as a partial agonist at the 5-HT1A receptor
MAO inhibitors	Isocarboxazid, phenylzine, tranylcypromine; Selegiline	Nonselectively inhibits enzymes (MAO-A and MAO-B) involved in the breakdown of monoamines, including serotonin, dopamine, and norepinephrine MAO-B selective inhibitor

FDA=US Food and Drug Administration. MAO=monoamine oxidase. 5-HT=serotonin.

Table: Antidepressants approved by the FDA

Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study



STAR*D

- The largest depression study ever done outside the pharmaceutical industry
- Four successive treatment steps, including a switch to and augmentation with additional drug or cognitive therapy
- Goal was for full remission, rather than just response.
- Remission rates in steps one to four were disappointing: 36·8%, 30·6%, 13·7%, and 13·0%
- Cumulative remission rate of 67% after all four steps, which suggests that most patients need several sequential treatment steps to achieve remission.

STAR*D

- Showed no clear advantage of one strategy of drug over another for patients who did not achieve remission after one or more acute treatments
- No placebo control, no way to know whether any of the strategies were better than maintenance of the original treatment for an additional period
- Too few patients received psychotherapy, to make firm conclusions about its role
- Neither sociodemographic nor specifiers moderated the effect of various switching options after the first non-successful attempt at acute treatment
- No differences in outcomes were found between primary care and psychiatric settings in the first two stages of acute treatment

Augmentation/Combination

- Whether effectiveness can be improved remains controversial
- Many combination treatment trials of antidepressant drugs or antidepressant and antipsychotic combinations have been done, but caution is warranted for the recommendation of such combinations as first step treatments.
- Lithium carbonate continues to be used as an augmentation strategy, and second generation anti-psychotics have been intensively studied
- Drugs recommended for treatment-resistant depression are

Aripiprazole, Quetiapine and the combination of Olanzapine + Fluoxetine.

Treatment of Psychotic Depression

- Difficult to treat and may need several interventions
- New pharmacological strategies are being tested
- ECT is frequently used and effective
- Antidepressant+Antipsychotic > Antidepressant alone.

Drug Development

- S-adenosyl methionine (SAMe) augmentation
- NMDA glutamate-receptor antagonists providing the promise of rapid antidepressant action including → 1 dose up to 1 week
- Repeated dose IV ketamine for the acute treatment of treatment-resistant depression.
- Failures CRF1 antagonist compounds and substance-P antagonists have continually been noted.
- Agomelatine—a melatonin (MT1 and MT2) agonist and a 5-HT2C-receptor antagonist with a generally favorable tolerability and efficacy.

Suicide Risk With SSRIs

- Some work suggests that adults treated with antidepressant drugs, including SSRIs, are no more likely to attempt or complete suicide than those not treated with an antidepressant.
- Other research suggests a reduced risk of suicide attempt in adults after start of SSRI treatment, particularly with sertraline, and in men.
- In 226866 male veterans with depression, rates of suicide attempt were lower after the start of SSRI treatment than before, and compared with treatment with other antidepressants or no antidepressant.
- A study of county-level data in the USA showed that a decrease in suicide rate was associated with SSRIs when prescribed in combination with non-SSRIs or non-TCAs

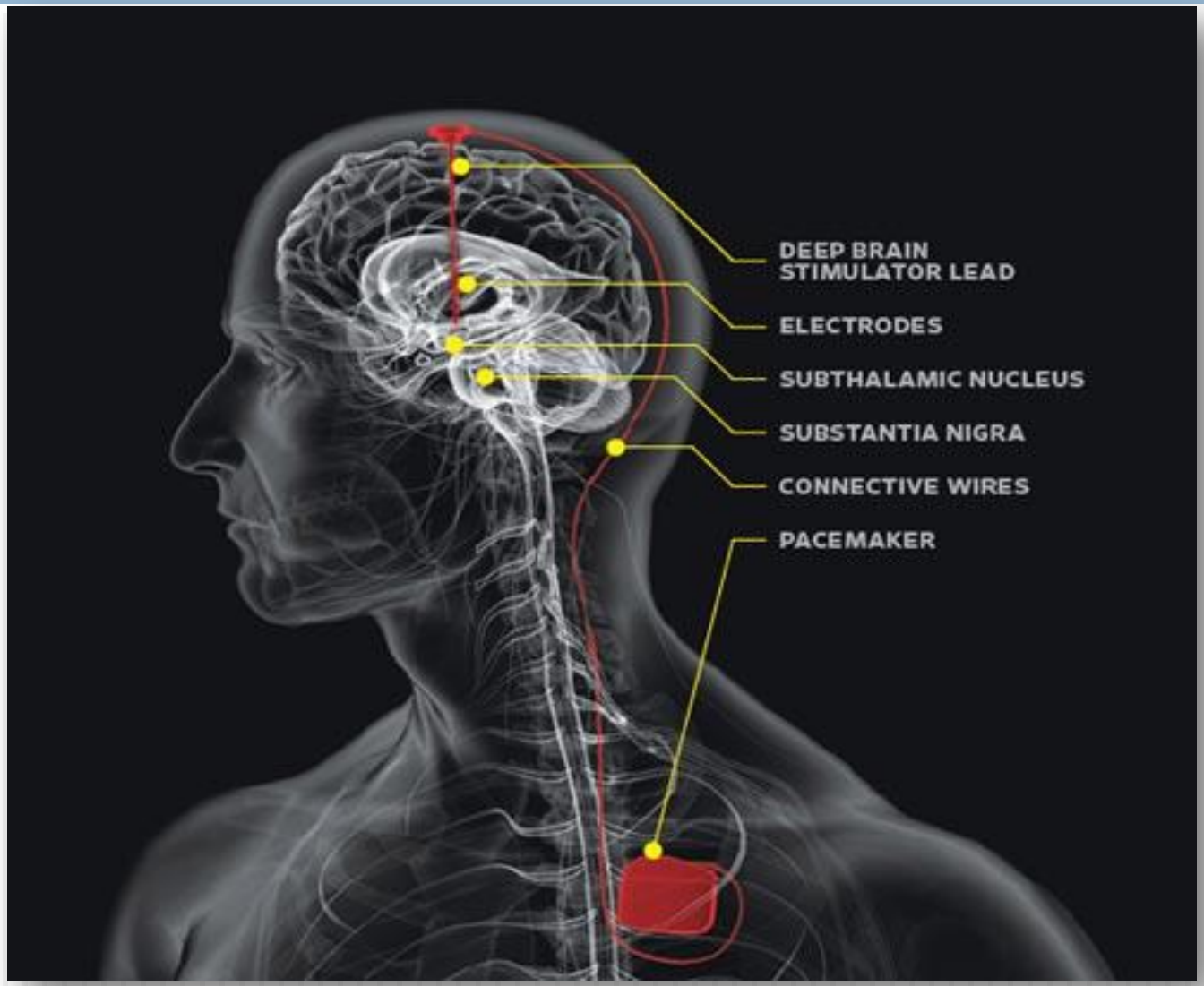
Safety in Pregnancy

- Guidelines → SSRIs should be used with caution during pregnancy, and that paroxetine be avoided
- Paroxetine might be associated with major malformations, especially cardiac defects.
- Presence of Persistent Pulmonary Hypertension in the neonate can also be associated with SSRIs taken late in pregnancy.
- Some evidence is available of an association between a Neonatal Behavioral Syndrome and exposure to SSRIs in utero during the last trimester.
- Infants with continuous exposure to mother's depression and continuous exposure to SSRIs throughout gestation were more likely to be born preterm

New Somatic Treatments- DBS

- Not FDA approved yet, but is promising for treatment-resistant depression
- ? Mechanism→ modulating neurotransmission in the cortico-striatal-thalamic-cortical circuit.
- Monitor→ possibility of suicide & affective instability

DBS

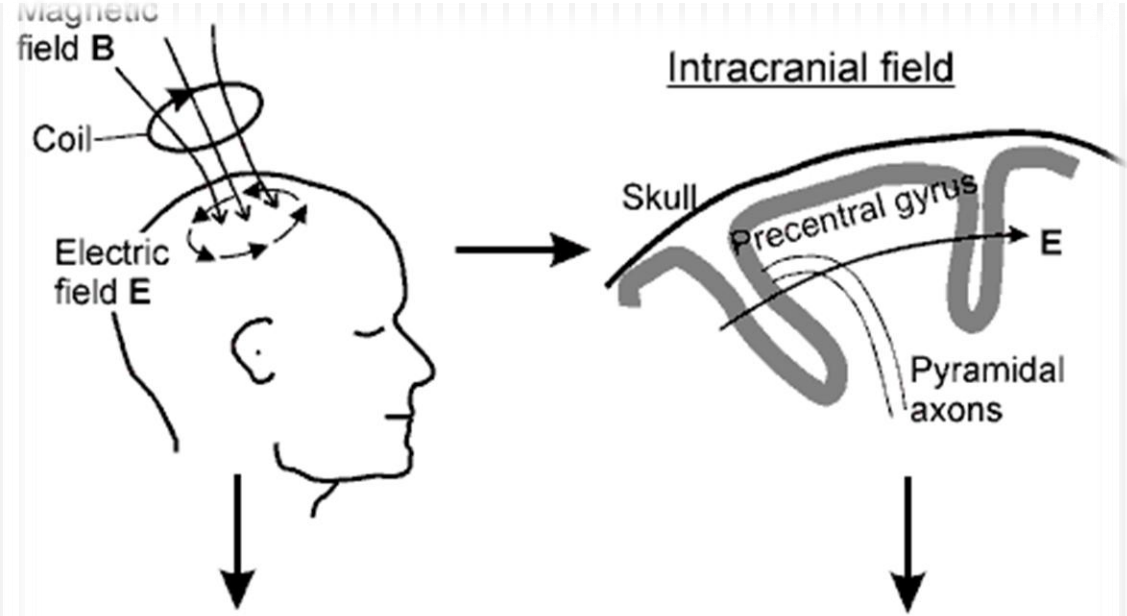

DEEP BRAIN
STIMULATOR LEAD
ELECTRODES
SUBTHALAMIC NUCLEUS
SUBSTANTIA NIGRA
CONNECTIVE WIRES
PACEMAKER

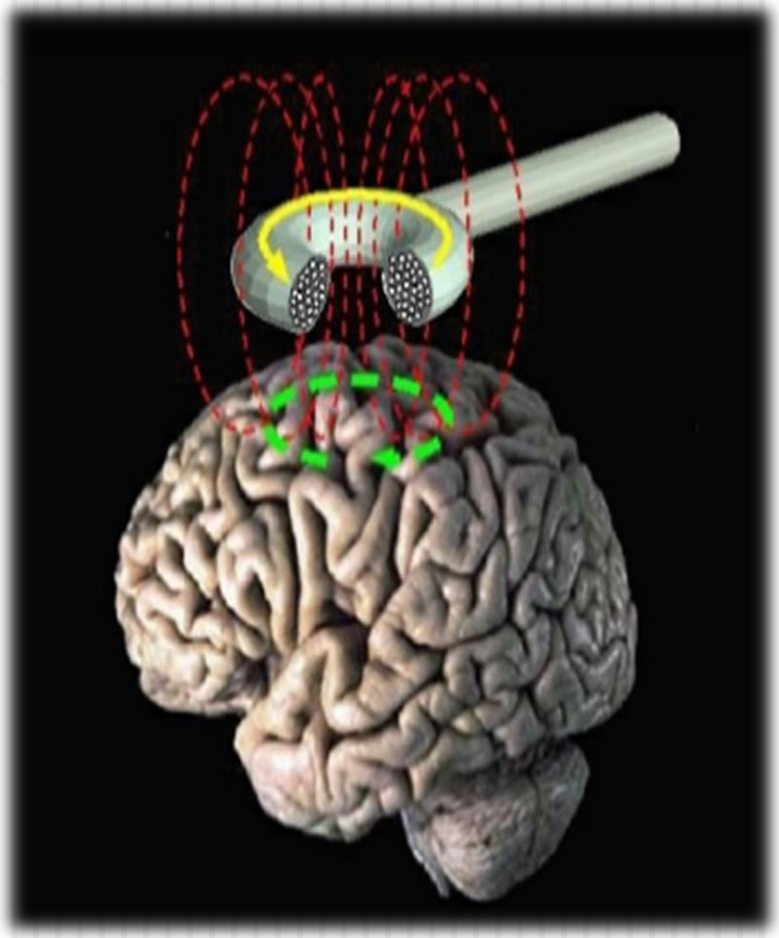
DBS

New Somatic Treatments- TMS

- FDA approved
- Mechanism→ Producing a magnetic field around the brain; the left and right DLPFC
- ? Less effective than ECT
- Monitor→ Seizure

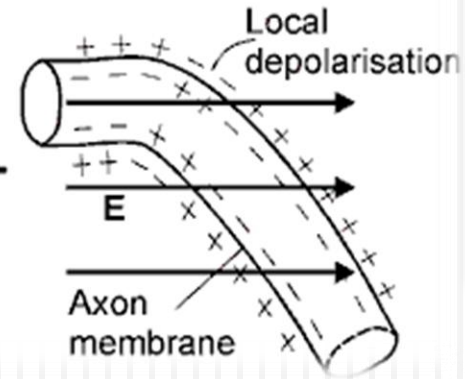
TMS





Macroscopic response

- evoked neuronal activity (EEG)
- changes in blood flow and metabolism (PET, fMRI, NIRS, SPECT)
- muscle twitches (EMG)
- changes in behaviour



TMS