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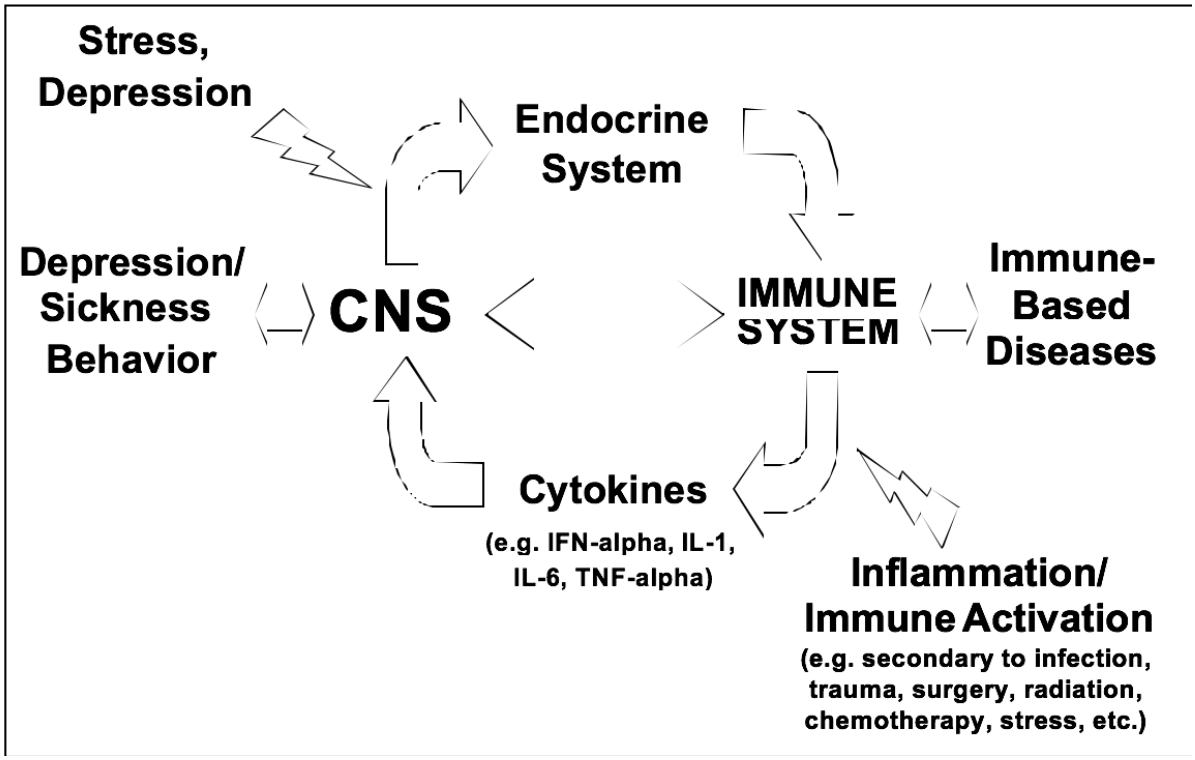
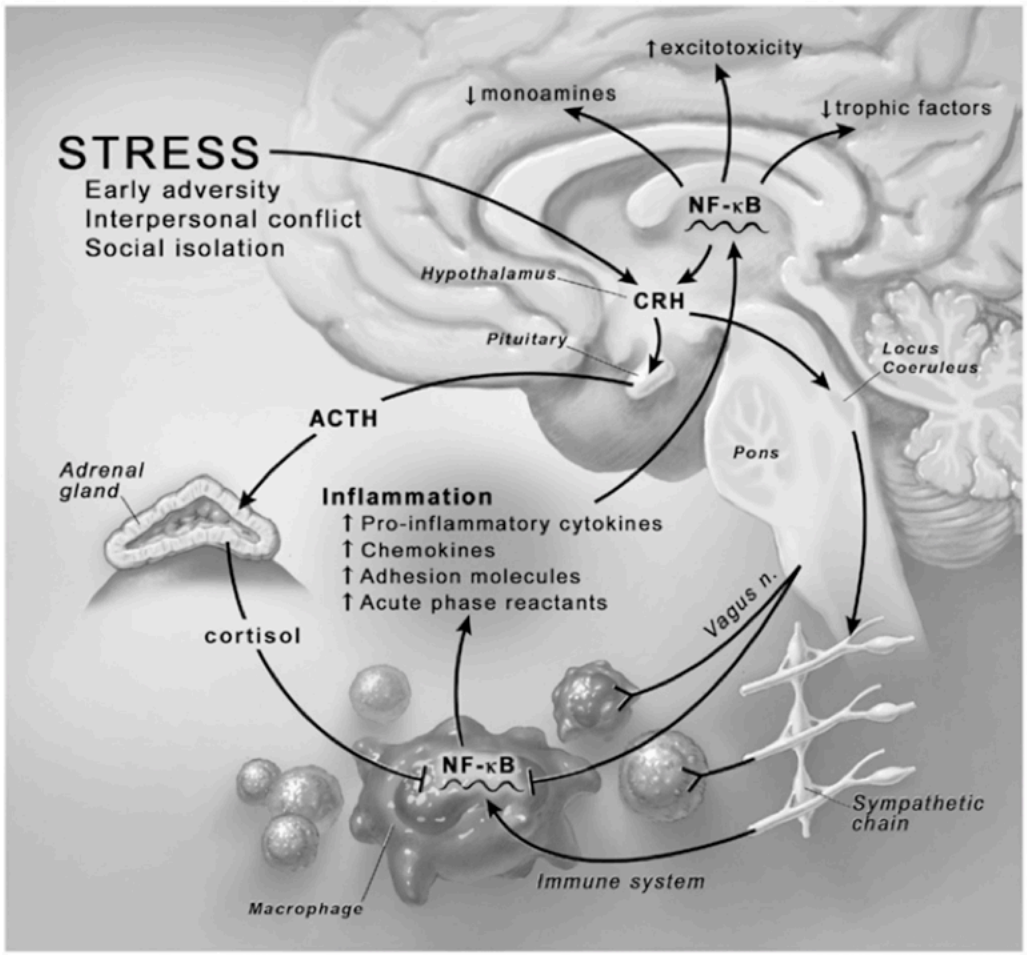
Biology and Genetics of Mood disorders and Anxiety

- Overview



  -
  - Stress jolts the amygdala (see below) to set off the panic center (locus coeruleus) to ultimately cause the release of stress hormones which feedback and make the amygdala hair trigger, ready to hijack us into anger or panic at the least provocation.
  - Stress hormones shunts blood flow from the brain's higher cognitive/memory centers to other sites more essential for emergency mobilization—leads to heightening the senses, dulling the mind, and doing what's most well-rehearsed, even if that habit is yelling or freezing in panic.
  - Memory and information processing is disturbed by stress hormones. More errors are made.
  - Sustained stress can have lasting, dulling effect on our brain



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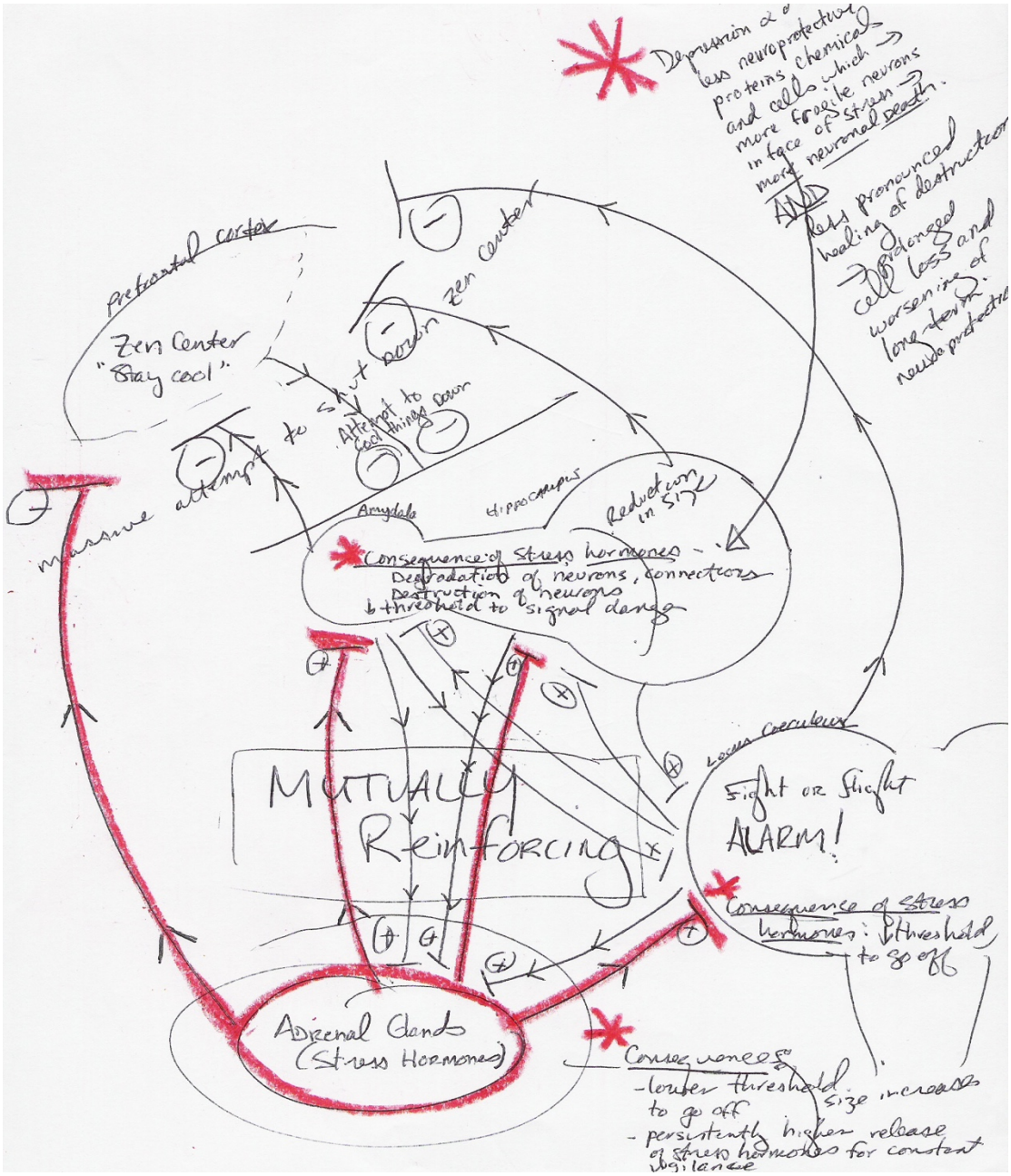
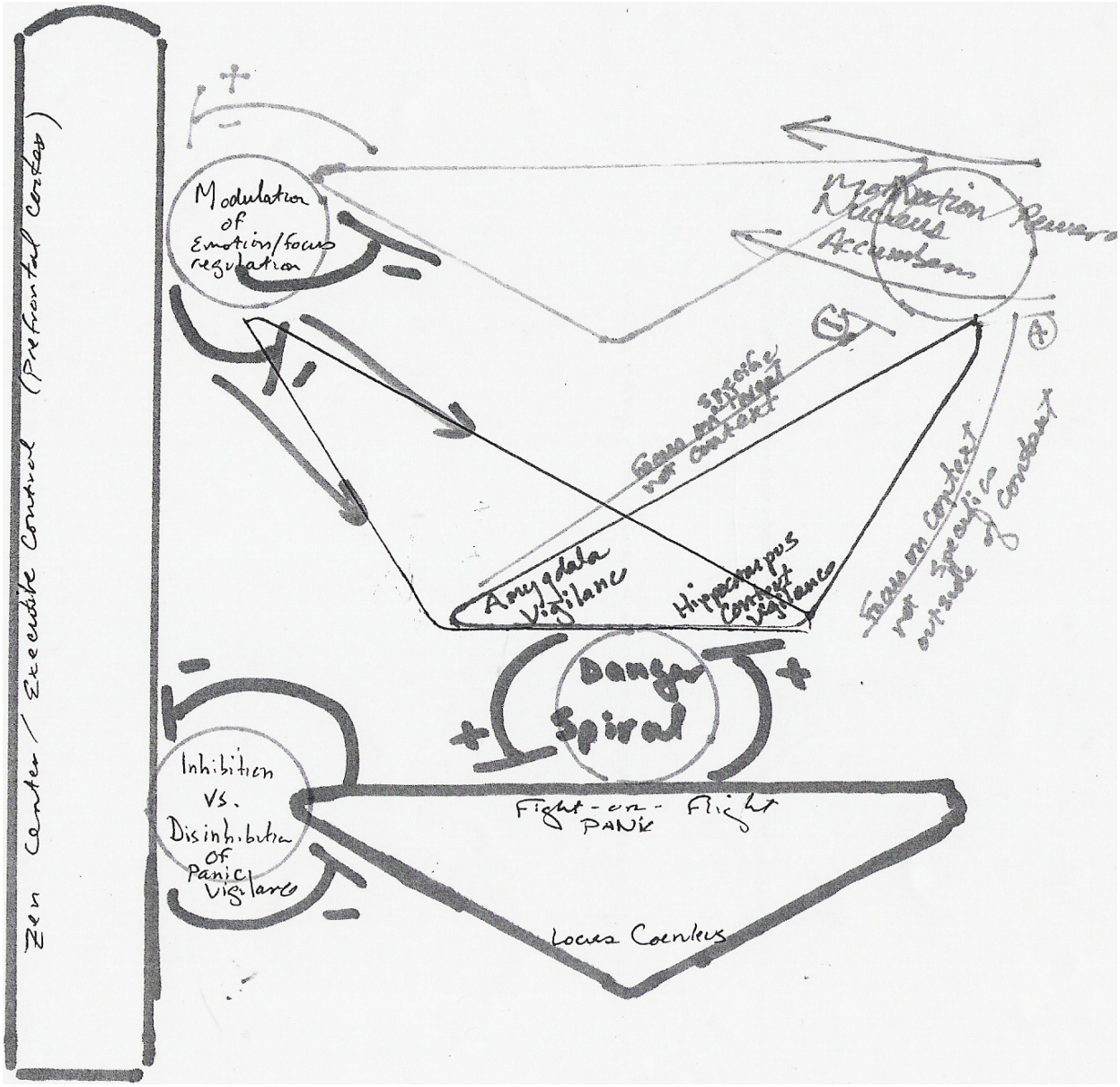
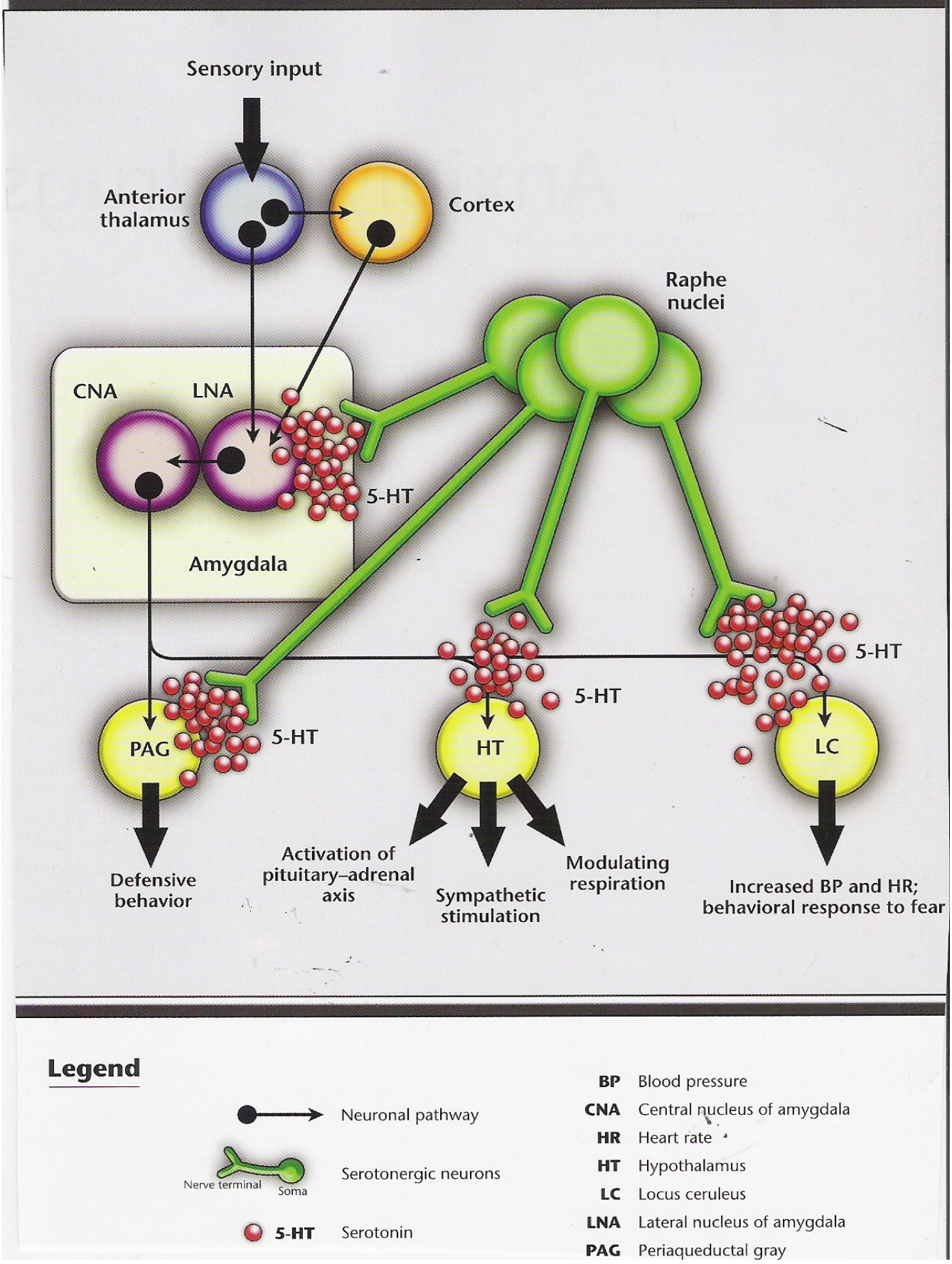
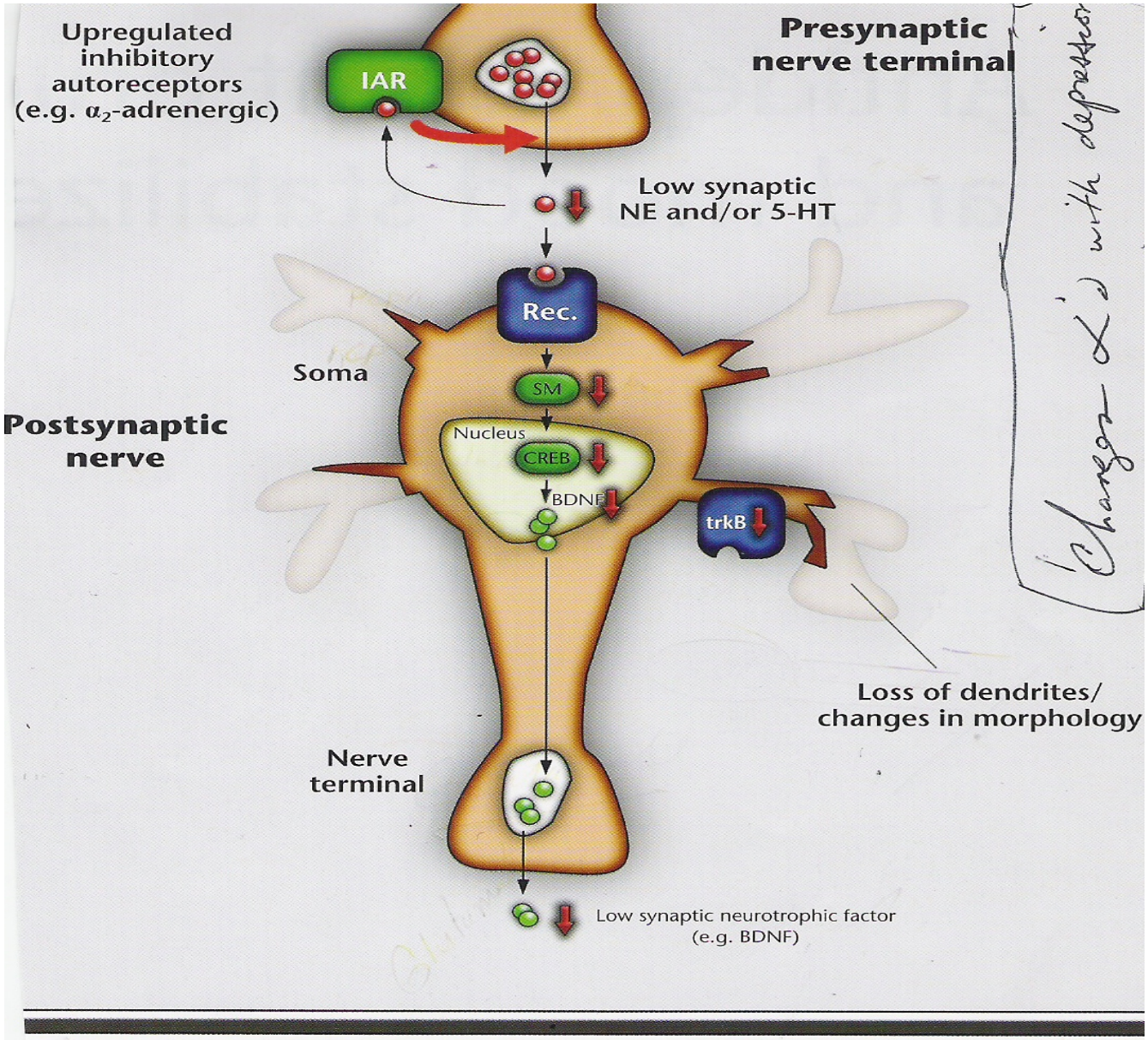
- Depression and anxiety associated with an attenuated reward system (in the nucleus accumbens) to positive stimuli or rewards; the hedonic capacity is reduced
- Major depression in youth is associated with cortical gray matter volume loss and thinning (Luby et al, 2016)
- Depression is associated with attenuated responses to positive stimuli/happy facial expressions as demonstrated in the limbic-subcortical and extrastriate visual regions; antidepressant treatment reverses these abnormalities
- Depression is associated with magnifying the significance of failure, exhibiting bias towards negative (or against positive) self-descriptors, and having excessive sensitivity to negative environmental cues and difficulty recovering once an error has been committed with detrimental sensitivity to mistakes and negative feedback; this can be seen even at the level of event-related potentials in the electroencephalograph
- If patient has unipolar depression (per 2003 study), risk in first degree relatives:
  - 18.7% risk (vs. 5.2% in controls), 4.2 fold increased risk of unipolar depression
  - 2.2% risk (vs. 0.7% in controls), 3.4 fold increased risk of bipolar disorder


Depression &
less neuroprotective
proteins chemicals
and cells which
more fragile neurons
in face of stress
more neuronal death.
AND
Less pronounced
healing of destruction
damaged
cell less and
worsening of
long-term
neuro protective
Prefrontal cortex
Zen Center
"Stay cool".
Zen center
Attempt to shut down
Attempt to cool things down
massive attempt to
Amygdala
Hippocampus
Reduction in SIZE
Consequence of stress hormones -
Degradation of neurons, connections
Destruction of neurons
↓threshold to signal danger
MUTUALLY
Reinforcing
Locus coeruleus
Fight or flight
ALARM!
Consequence of stress
hormones: ↓threshold
to go off
Adrenal Glands
(Stress Hormones)
Consequences
- lower threshold, size increases
to go off
- persistently higher release
of stress hormones for constant
vigilance


Zen Center / Executive Control (Prefrontal Cortex)
Modulation of Emotion/focus regulation
Motivation Reward Nucleus Accumbens
Focus supporting current context
Focus on context not specific to current
Amygdala Vigilance
Hippocampus Context Vigilance
Danger Spiral
Inhibition vs. Disinhibition of Panic Vigilance
Fight-or-Flight PANIC
Locus Coeruleus

The 'fear' network and the role of serotonin in surpressing anxiety



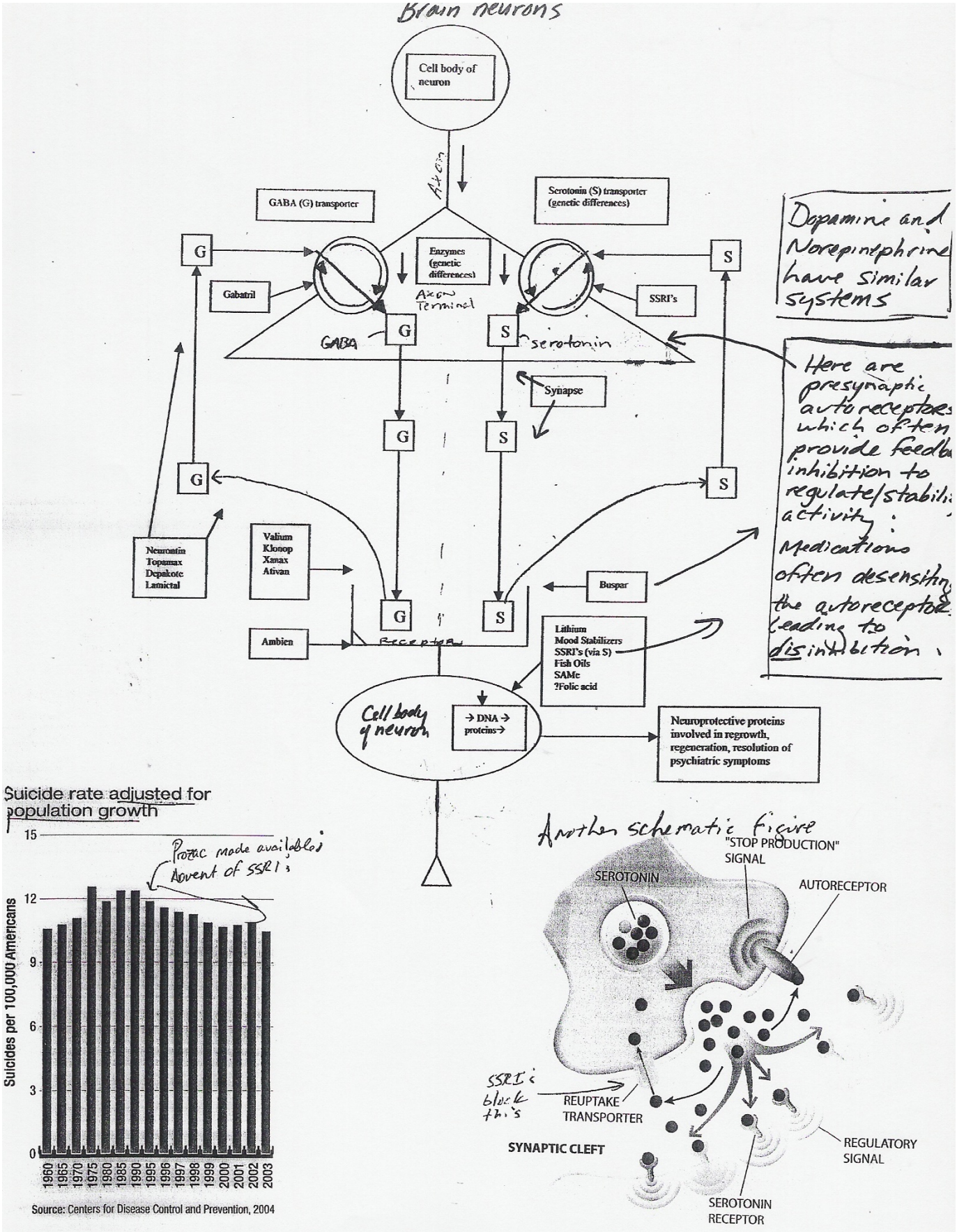


Feedback inhibition (enhanced)

Loss of dendrites and/or change in morphology

Low concentration

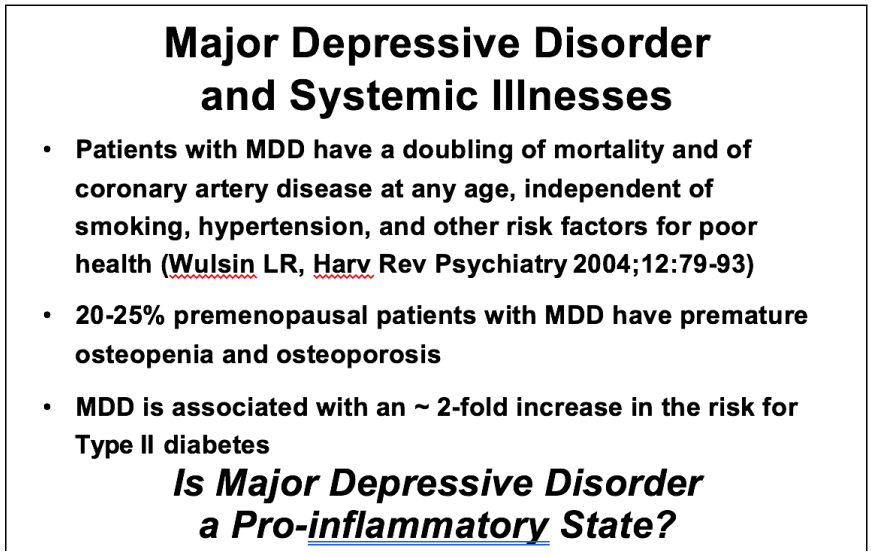
5-HT	Serotonin
BDNF	Brain-derived neurotrophic factor
CREB	Cyclic adenosine monophosphate (cAMP)-response element-binding protein
IAR	Inhibitory autoreceptor
NE	Norepinephrine
Rec.	Receptor
SM	Second messenger (e.g. cAMP)
trkB	Receptor for BDNF



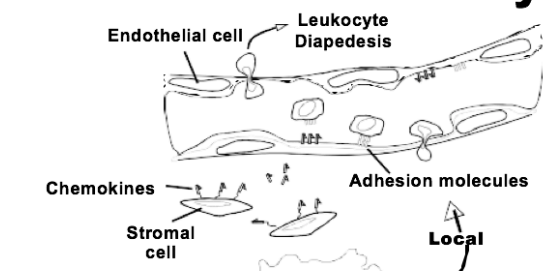
- Stress Hormones (Cortisol, ACTH, and CRF)
  - Cortisol
    - Released during times of threat and is critical to survival; enough for a single bout of fight or flight BUT, once released, stay in our body for hours and each successive upsetting incident adds more stress hormones to the levels already there,
    - Aids in survival by redistributing energy when an individual is under attack.

- Suppresses functions not needed for immediate survival, including reproduction, immune response, digestion and pain.
- Promotes vital functions, including increased heart rate and blood pressure, while shunting energy to the brain (affective regions) and muscles to speed up thought processes and fight or flee.
- Activates the amygdala which further activates the cortisol system
- It also strengthens the encoding of aversively charged emotional memory and enhances it's unconscious retrieval.
- It performs this way for short-term survival at the expense of long-term viability of the body; chronically high cortisol →
    - Gastric ulcers
    - Breaks down muscle, bone and other tissues to mobilize glucose
    - Insulin resistance
    - Visceral fat deposition
    - Pro-atherogenic sequelae
    - Inhibition of cellular immunity
    - Suppression of the brain center that mediates reward and pleasure, and
    - Excessive fear
    - Damage to hippocampal neurons (which can lead to further increases in cortisol secretion).
    - Brain toxicity
- Cortisol in depression
    - Persistant hypercortisolemia is correlated with depression (Sher et al, 2005; Lin et al, 1986; Chen et al, 1984; Asnis et al, 1981)
- Cortisol in PTSD
    - Baseline levels of cortisol are elevated in acute PTSD and normal to decreased in chronic PTSD
    - In chronic PTSD, exposure to stressor or traumatic reminder was associated with a potentiated release of cortisol
    - Supersuppression of cortisol response to low doses of DST

- Corticotropin releasing factor (CRF)/hypothalamic-pituitary-adrenal (HPA) axis
    - CRF, released from the hypothalamus, stimulates the pituitary gland to release adrenocorticotropin hormone (ACTH) which, in turn, stimulates the adrenal glands to release cortisol. This makes up the hypothalamic-pituitary-adrenal (HPA) axis, which is critical to the stress response.
    - CRF-expressing neurons in the dorsal raphe nucleus (where most of the serotonergic neurons of the brain originate) project directly to CRF-containing neurons in the amygdala.
    - Cortisol and CRH levels are elevated in some depressed patients. CRH receptors are reduced (due to excessive CRH) in the frontal lobes of patients who have suicided. CRH levels fall after successful treatment of depression (including successful treatment with Prozac). mRNA for CRH receptors is increased in the amygdala and hippocampus under stress.



Innate Immunity/Inflammation



Local Effects
- Increased vascular permeability
- Vasodilation
- Chemokine production
- Expression of adhesion molecules
- Pain

tumor
rubor
calor
dolor

Local

TNF, IL-1, IL-6 IFN-alpha

Macrophage

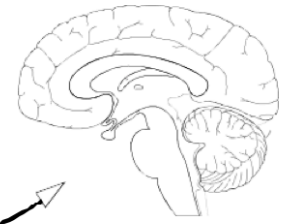
NF-κB

Pathogen
(e.g. bacteria),
Cellular Debris

Toll-like receptors (TLRs)

TNF
IL-1
IL-6
IFN-alpha

Systemic



Effects on Liver

Acute Phase Response
- C-reactive protein
- serum amyloid A
- haptoglobin
- alpha 1-antichymotrypsin

Effects on Brain
- Fever
- Fatigue
- Anorexia
- Anhedonia
- Altered sleep

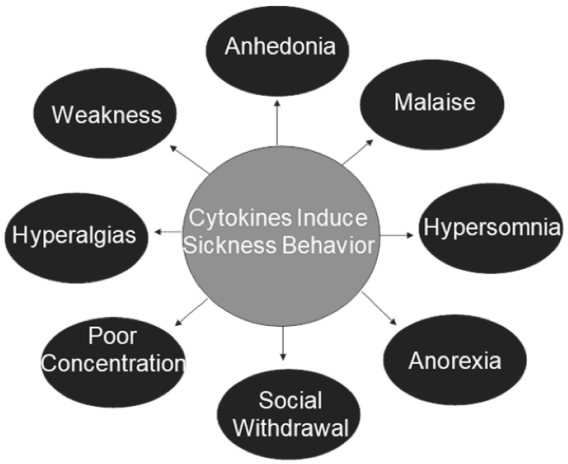
sickness behavior/ depression

Conservation of energy resources to promote increased metabolic demands of fighting infection and mounting a fever

Basis for the Hypothesis that Inflammation and an Activated Innate Immune Response may Play a Role in Depression

- Patients with depression (both medically ill and medically healthy) have been found to exhibit all the cardinal features of inflammation.
  - increased peripheral blood and csf innate immune cytokines (IL-6 and TNF-alpha most reliable)
  - increased acute phase reactants (CRP most reliable)
  - increased chemokines
  - increased cellular adhesion molecules
- In the majority of studies, inflammatory markers decrease with successful antidepressant therapy ("state marker")

Effects of Immune Activation Resemble Depressive Symptoms



- Stress → increased glutamate activity in the prefrontal cortex and anterior cingulate cortex; glutamate activates the HPA axis.
- Parents and cortisol
  - Children of parents with a history of depression, irrespective of differences in parental attachment, life events, personality, or current mental state, have higher baseline levels of salivary cortisol and higher cortisol responses to stress.
  - Children of mothers with panic disorder show early abnormalities in cortisol levels and sleep.
  - Children of mothers with low maternal investment demonstrate alterations of cortisol steroid receptor genes (not seen in children of mothers with high maternal investment
- Patients given chronic corticosteroid therapy (for medical problems) have smaller hippocampal volumes.
- Chronic administration of imipramine to healthy volunteers produced central down-regulation of the HPA axis and CRH secretion. In animals, chronic, but not acute, administration of imipramine, Prozac and an MAOI significantly reduced CRH levels.
- Individuals with high levels of depression and anxiety respond better to antidepressant medication if they carry a specific variation in the corticotrophin-releasing hormone type 1 (CRHR1) gene. Having two gene alleles for the variant was associated with a 70% greater reduction in anxiety and a 31% greater reduction in depression after treatment with either fluoxetine or desipramine in a subgroup of patients with both high anxiety and high depression.
- SSRI's --> new brain cells via a glucocorticoid receptor (that requires protein kinase A signaling, glucocorticoid receptor phosphorylation, and activation of a specific set of genes)
- Lithium and Depakote → Bcl-2 enhances other trophic factors in the brain, including ***bcl-2-associated athanogene (BAG-1),*** pERK 42, pERK 44, pRSK, pCREB, and pBAD.
  - ***CREB***
    - Cyclic adenosine monophosphate (cAMP) response element binding protein
    - CREB1 polymorphisms associated with Celexa treatment-emergent suicidality among men with depression (per STAR D)
  - ***Bcl-2***
    - Protects against
      - lethal effects of a variety of reactive oxygen species
      - MPTP and AMPA neurotoxicity
      - growth factor deprivation
      - effects of ionizing radiation
      - glucocorticoid toxicity
    - Reduces neuropathology after
      - focal ischemia
      - traumatic brain injury
    - Prevents axotomy-induced motor neuron death
    - Attenuates motor neuron degeneration in a transgenic animal model of amyotrophic lateral sclerosis
    - Regulate neurite sprouting and outgrowth, and increases axonal growth rate
    - Promotes regeneration of axons in the mammalian CNS
  - ***BAG-1***
    - regulates glucocorticoid (gc) receptor function.
      - the glucocorticoid receptor lies in the cell's cytoplasm
      - when cortisol binds to the gc receptor, it moves into the nucleus to turn on or off genes.
    - BAG-1 prevents the glucocorticoid receptor from moving to the nucleus.
      - If you pre-treat cells with lithium or valproic acid, dexamethasone (which binds to glucocorticoid receptors) does not cause as many of the glucocorticoid receptors to move into the nucleus.
      - Chronic lithium pre-treatment decreases glucocorticoid-mediated gene expression from the dexamethasone.

- Hippocampus

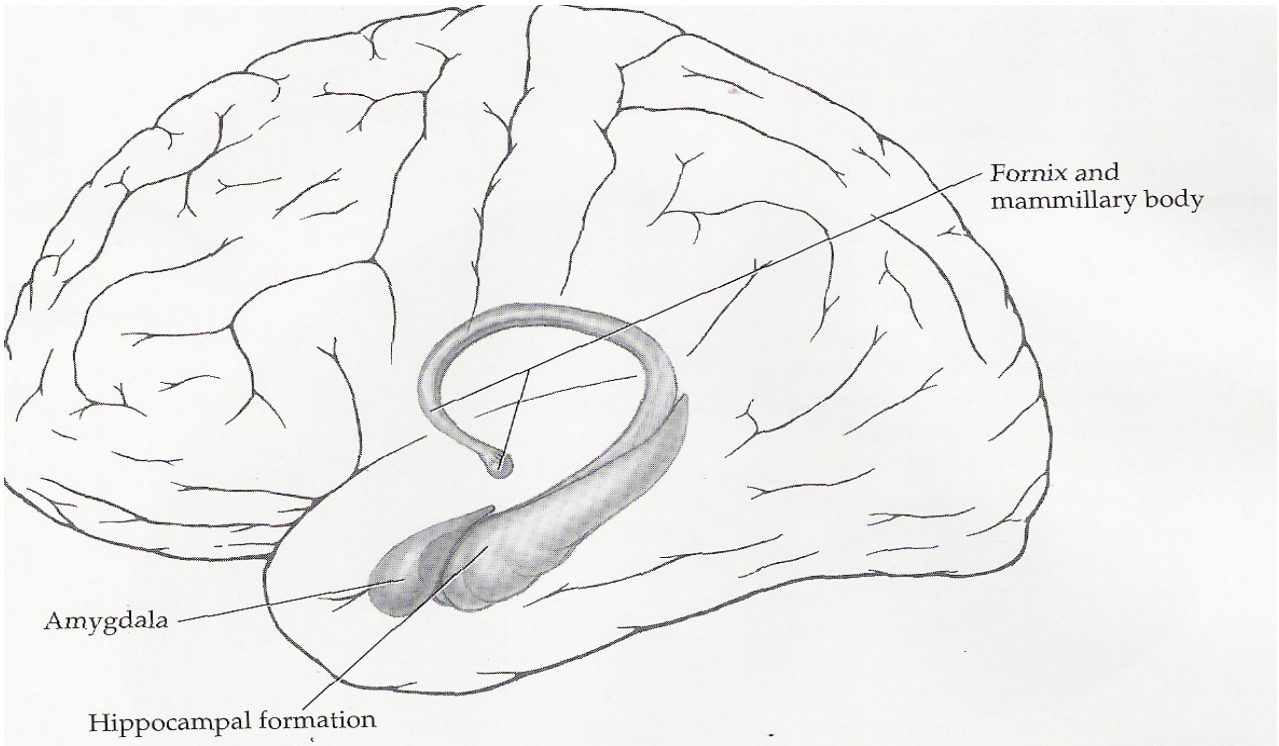


Figure 16–1. Three-dimensional view of the amygdala and the hippocampal formation. The fornix, which is the output pathway of the hippocampal formation, and the mammillary body, a target to which it projects, are also illustrated.

  - Thought to be responsible for consolidating, filing (elsewhere in the brain) and retrieving the memory of an event in time, place and context; especially dorsal aspect
  - Involved in the memory of the context of a stressful event.
  - Involved in place and contextual memory of emotional learning. (The prefrontal, insular, and mesotemporal cortex and the anterior cingulate cortex are also involved in contextual memory/processing of fear stimuli).
  - When exposed to intense sadness, folks without psychiatric illness demonstrate increased activation of the dorsolateral prefrontal cortex, tightening it's inhibitory modulatory action on the hippocampus. In bipolar depression, the dorsolateral prefrontal cortex becomes less active in the face of any emotion, disinhibiting the hippocampus and possibly underlying the emotional lability of bipolar disorder. In unipolar depression, the hippocampus and primary mood areas become underactive when exposed to any emotion (including happiness) except for exposure to mild sadness in which case the hippocampus responses vigorously and more so than under other circumstances. Indeed, the severity of unipolar depression correlates positively with the hippocampal response to mild sadness. It appears that this may be a trait phenomenon, specific to the vulnerability to depression and/or the enduring consequence of depression and not the active state of illness itself.
  - Learning and memory, altered in depression, rely on the posterior segment of the hippocampus. If asked to suppress memory, one will see greater activation of the DLPFC and reduced activation of the hippocampus; by extension, the hippocampus may be involved in repression of memory.
  - Environmental enrichment increases neurogenesis in hippocampus
  - Dissociation may be the subjective manifestation of hippocampal damage
    - Vermetten et al, 2006, 15 female patients with dissociative identity disorder (DID) compared to 23 female subjects without:: hippocampal volume 19% smaller and amygdala 32% smaller in patients with DID.

Stress and the hippocampus

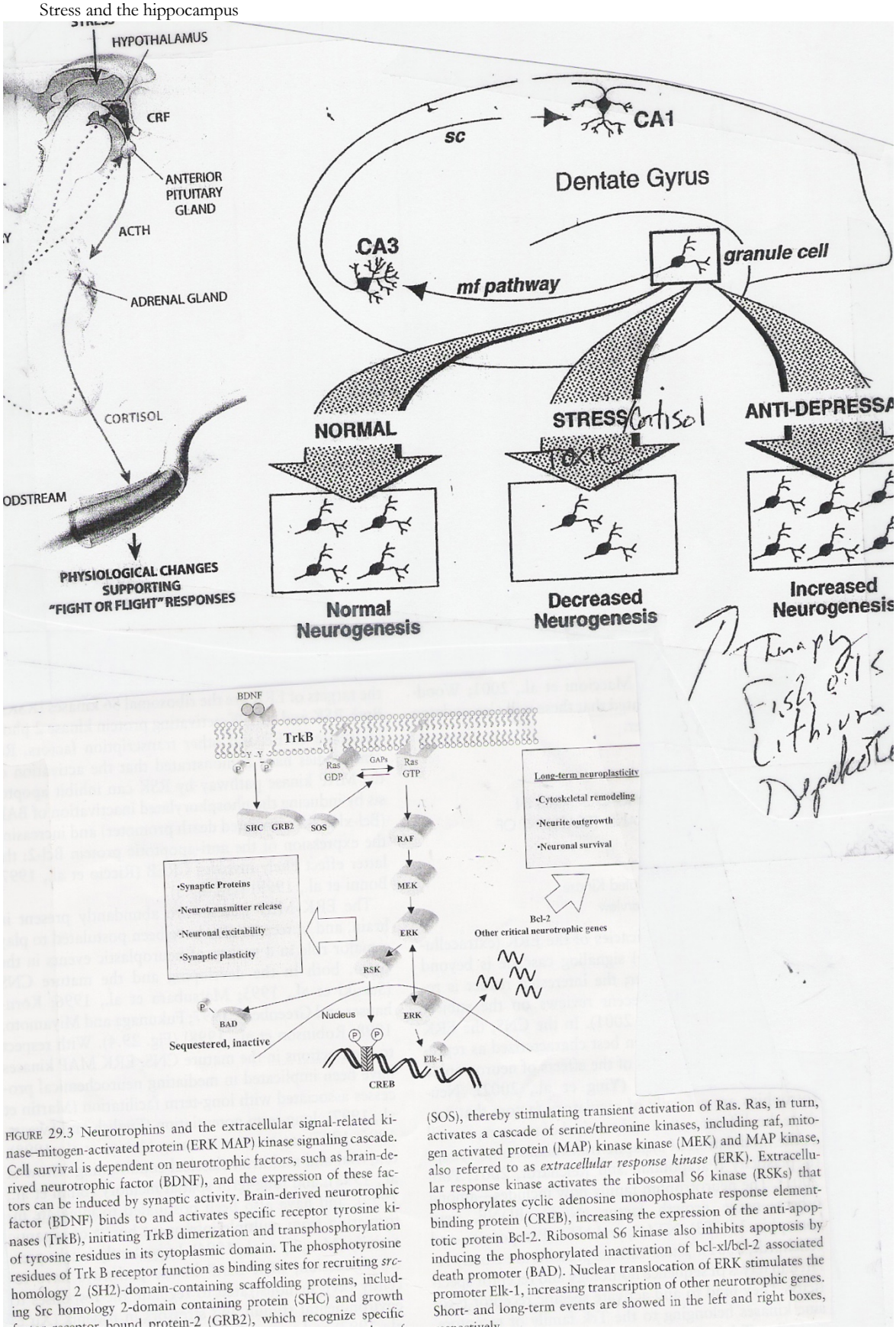


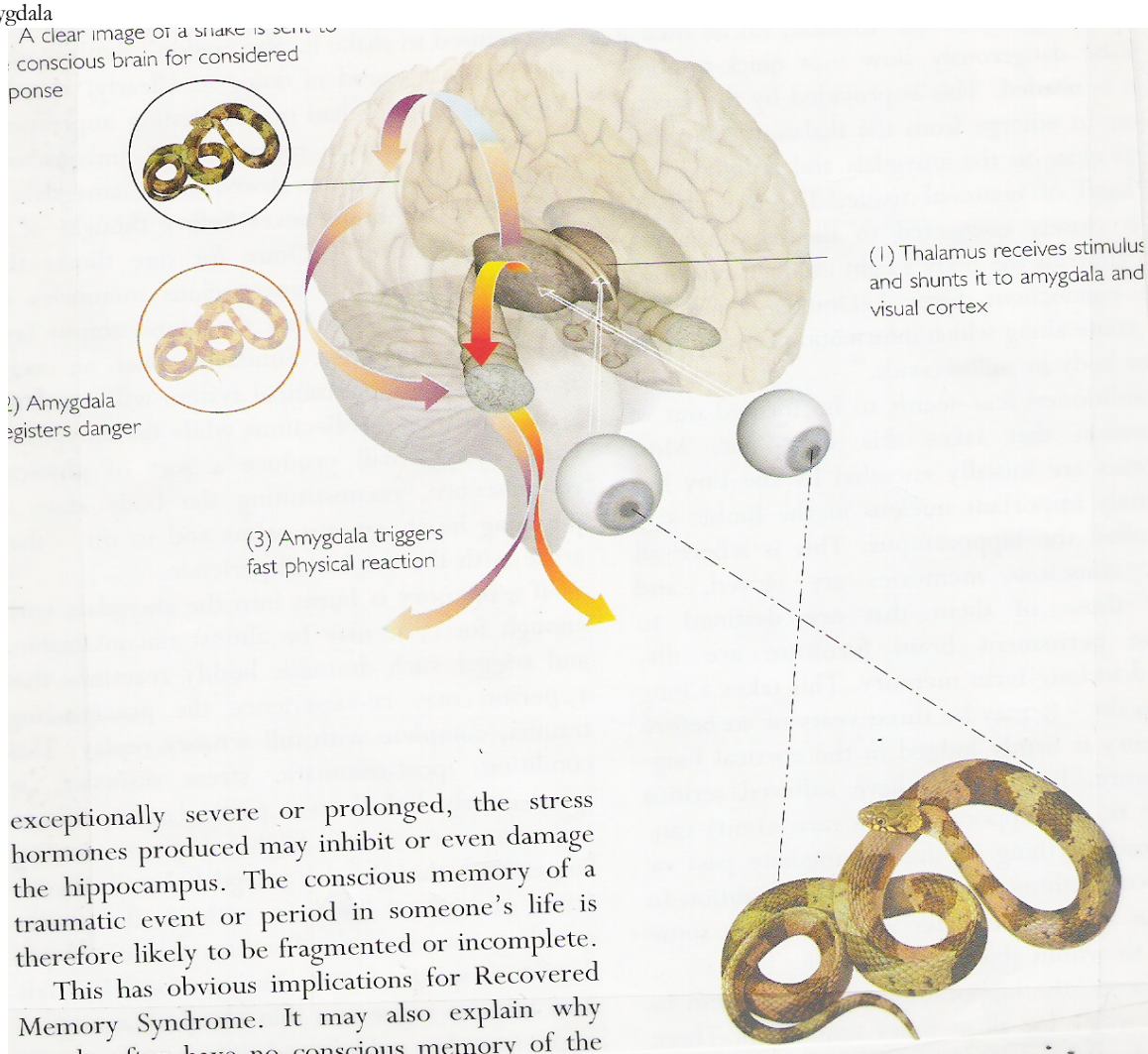
FIGURE 29.3 Neurotrophins and the extracellular signal-related kinase–mitogen-activated protein (ERK MAP) kinase signaling cascade. Cell survival is dependent on neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), and the expression of these factors can be induced by synaptic activity. Brain-derived neurotrophic factor (BDNF) binds to and activates specific receptor tyrosine kinases (TrkB), initiating TrkB dimerization and transphosphorylation of tyrosine residues in its cytoplasmic domain. The phosphotyrosine residues of Trk B receptor function as binding sites for recruiting *src*-homology 2 (SH2)-domain-containing scaffolding proteins, including Src homology 2-domain containing protein (SHC) and growth (SOS), thereby stimulating transient activation of Ras. Ras, in turn, activates a cascade of serine/threonine kinases, including raf, mitogen activated protein (MAP) kinase kinase (MEK) and MAP kinase, also referred to as *extracellular response kinase* (ERK). Extracellular response kinase activates the ribosomal S6 kinase (RSKs) that phosphorylates cyclic adenosine monophosphate response element-binding protein (CREB), increasing the expression of the anti-apoptotic protein Bcl-2. Ribosomal S6 kinase also inhibits apoptosis by inducing the phosphorylated inactivation of bcl-xl/bcl-2 associated death promoter (BAD). Nuclear translocation of ERK stimulates the promoter Elk-1, increasing transcription of other neurotrophic genes. Short- and long-term events are showed in the left and right boxes,

- In one study, rat pups were stressed during their childhood period; they were isolated from their mothers for four hours a day during their first 20 days of development. This was associated with abnormal changes in the hippocampus which is in contrast to the neuroprotective effects of removing the rat pup for only 15 minutes of each of the first 20-21 days of development—this shorter separation enhances attachment behaviors between mom and pup.
- In another study, "adolescent" rats that had a "normal" childhood were stressed by isolating them from their peers; similar abnormal changes in the hippocampus were observed.

- Stress /trauma and brain-derived neurotrophic factor (BDNF)
    - decreases the amount of brain-derived neurotrophic factor (BDNF)
        - associated with
            - Activates TrkB receptors
            - BDNF and TrkB play important role in fear memory acquisition and extinction
            - Plays a critical role in long-term potentiation in neurons; it's a molecular mediator of learning and memory
            - Involved in declarative and spatial memory processes
        - low levels of BDNF
            - associated with untreated depression
            - in the hippocampus are associated with untreated depression
            - associated with eating disorders
            - impairment of spatial learning and memory in rats
            - impairment of spatial learning (in forebrain-restricted deletion of BDNF)
            - disruption of TrkB activation in the amygdala (analogous to low levels of BDNF) blocks acquisition of fear and the consolidation of extinction
        - high levels of BDNF
            - in the reward center (nucleus accumbens) may be associated with depression
            - in the ventral tegmental area (VTA) are associated with stress susceptibility
                - stress-susceptible mice respond to stress with excessive firing in the VTA
                - excessive firing in the VTA leads to a flooding of BDNF into the nucleus accumbens
    - BDNF single polymorphism gene variant associated with
        - Familial depression
        - Poorer cognitive performance in mood disorders
        - Increased risk of rapid cycling in bipolar disorder
        - Increased susceptibility to environmental stress
        - Differential response to lithium
        - Reduction in the size of the hippocampus
        - Greater reduction in frontal gray matter volume in recent-onset schizophrenia (when one carries the met variant (as opposed to the val variant); this may be why antidepressants can prevent or delay the onset of early onset schizophrenia in youth
    - Science, 2006: using mice with no BDNF genes, it was found that BDNF mediated long-term neural and behavioral plasticity in response to aversive social experiences; absence of BDNF genes is associated with less responsivity to efficacy of Prozac (after stress-induced anxiety)
    - BDNF directly produces behavioral changes in animals similar to that from SSRI's; similar when BDNF signaling is enhanced.
    - Stress increases the amount of neurotoxic stress hormones
    - Stress → smaller hippocampal volume, ? cell loss, compromised synaptic transmission
- Deficits in verbal declarative memory (but not IQ or visual memory) are associated with combat-related PTSD
- Deficits in short-term memory in those with PTSD due to childhood abuse correlated with level of abuse severity
- Smaller hippocampal volumes are correlated with
    - Stress
    - Moderately prolonged maternal separation in animals
    - Depression
        - Specifically,
            - Recurrent depression
            - Earlier age of onset of depression
            - Longer periods of untreated depression
            - Lower likelihood of remission with treatment
        - The posterior segment of the hippocampus is most consistently involved in the volume reduction associated with depression.
        - Post-mortem studies in clients with depression have shown abnormal cell loss in the CA1 and CA4 areas of the dentate gyrus of the hippocampus, along with the entorhinal cortex, subiculum.
    - PTSD
        - Children with PTSD demonstrate smaller hippocampal volumes
        - One study of combat veterans: right hippocampus 8% smaller; size of decrease correlates with degree of difficulty with memory
        - Another study of combat vetereans: 26% smaller decrease in hippocampal volume bilaterally
        - One year of treatment with Paxil → 5% increase in hippocampal volume and a 20% increase in hippocampal-based declarative memory function
        - The monozygotic (identical) twins of folks with PTSD also have decreased hippocampal volumes (may be vulnerability factor)
    - History of child abuse associated with 5-8% smaller left hippocampal volume
    - Mixed trauma: 12% decrease in hippocampal volume bilaterally
    - Increased risk of dementia
    - Cushing's disease; this is reversible

- Pediatric depression, like adult depression, is associated with structural and functional changes in the frontal cortex and subcortical regions (e.g., the amygdala) of the brain; hippocampal atrophy can occur later in depression and may be associated with persistence or recurrence of the disorder.

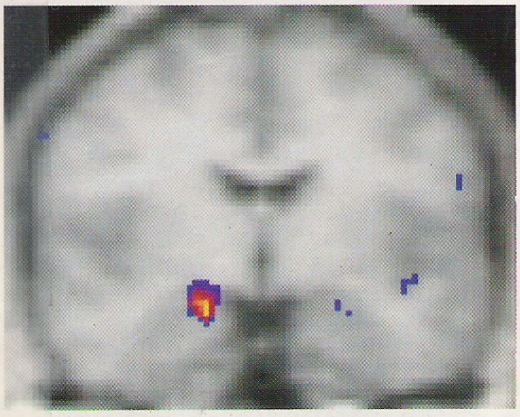
- Antidepressants and the hippocampus
  - Antidepressants
    - increase BDNF
      - BDNF directly produces behavioral changes in animals similar to that from SSRI's; similar when BDNF signaling is enhanced.
      - BDNF is necessary and sufficient for antidepressant-induced behavioral changes in animals
    - increase a protein named CREB (which, when low, is associated with early death even in the absence of depression).
    - lead to neuronal regeneration in the hippocampus and other regions of the brain; but as they increase neurogenesis in certain areas of the hippocampus, they lead to a simultaneous elimination of neurons in the dentate gyrus (in rats) which suggests an increase in competition between neurons for the ability to best innervate their targets in the hippocampus
    - Celexa treatment response has been associated with reduced activity in several areas of the brain important to mood and anxiety, including but not limited to the amygdala and the hippocampus; this is thought to represent a therapeutic change in the brain important to Celexa's efficacy.
    - Regional transcranial magnetic stimulation→ increased BDNF in hippocampus (all fields), dentate gyrus, parietal cortex, piriform cortex
    - Normalize default mode brain network (Posner et al, 2013)
  - The co-administration of an SSRI and olanzapine (but not either agent alone) is associated with hippocampal fibroblast growth factor-2 expression.
  - "Compounds" known to stimulate neurogenesis in the hippocampus (as of 5/05)
    - SSRI's
    - TCA's
    - Norepinephrine reuptake inhibitors
    - PDE4 inhibitors
    - Second generation (atypical) antipsychotics
    - NK1 inhibitor
    - Vassopressin1b inhibitor
    - ECT
    - Exercise
    - Enriched environments
  - Prozac and nortriptyline, even in the absence of depression or anxiety, started within a month of having a stroke →
    - Better recovery
    - Better cognitive functioning
    - Live longer
    - Less likely to die from cardiovascular causes
    - Foster nerve/neuron growth
    - May protect against future strokes



exceptionally severe or prolonged, the stress hormones produced may inhibit or even damage the hippocampus. The conscious memory of a traumatic event or period in someone's life is therefore likely to be fragmented or incomplete.

This has obvious implications for Recovered Memory Syndrome. It may also explain why people often have no conscious memory of the

fMRI activation of the right amygdala in response to masked fearful faces when compared with masked happy faces[3]

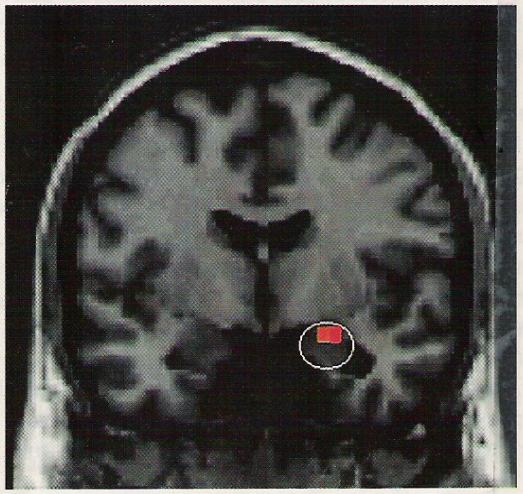


Whalen PJ, Rauch SL, Etcoff NL, McInerney SC, Lee MB, Jenike MA. Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. *J Neurosci.* 1998;18:411-418. Copyright (1998), with permission from the Society for Neuroscience.

fMRI=functional magnetic resonance imaging.

Stein DJ, Matsunaga H. *CNS Spectr.* Vol 11, No 4. 2006.

Increased responsivity of the right amygdala of subjects with the short allele of the serotonin transporter promoter polymorphism versus subjects homozygous for the long allele in response to fearful emotional expressions during fMRI[18]



Hariri AR, Mattay VS, Tessitore A, et al. Serotonin transporter genetic variation and the response of the human amygdala. *Science.* 2002;297:400-403. Copyright (2002), with permission by *Science.*

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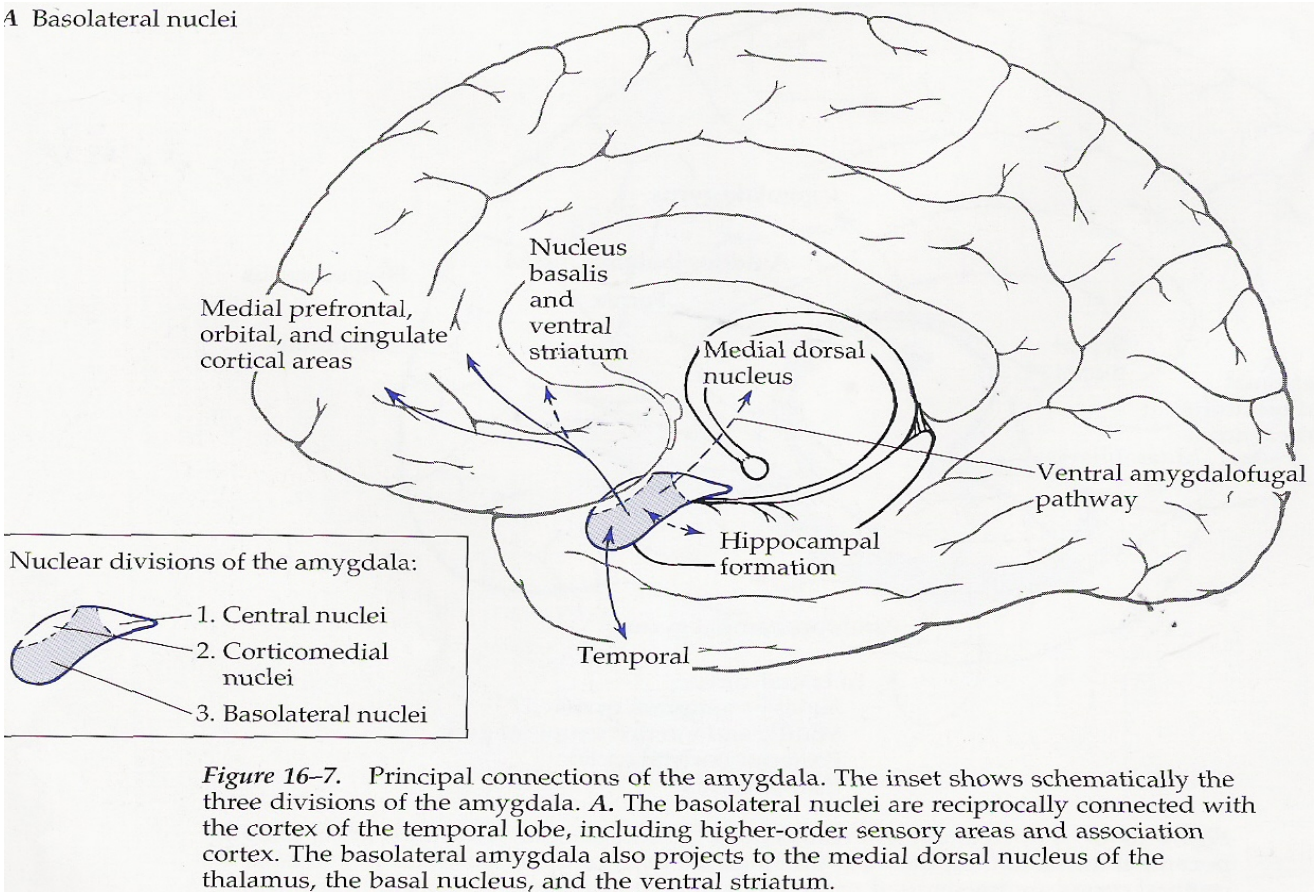


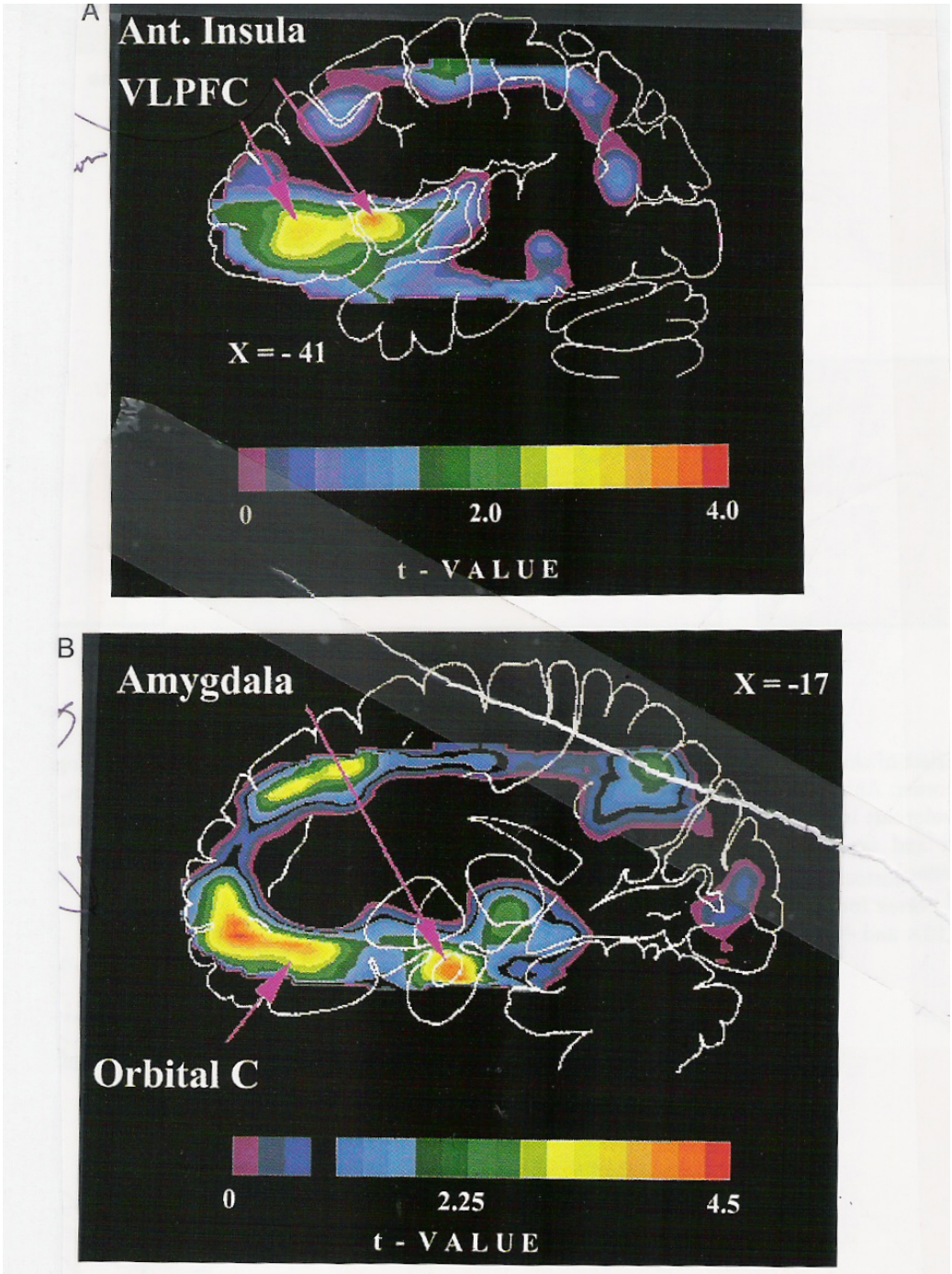
Figure 16–7. Principal connections of the amygdala. The inset shows schematically the three divisions of the amygdala. ***A.*** The basolateral nuclei are reciprocally connected with the cortex of the temporal lobe, including higher-order sensory areas and association cortex. The basolateral amygdala also projects to the medial dorsal nucleus of the thalamus, the basal nucleus, and the ventral striatum.

- Functions
  - Coordination of the regulation of emotional expression vua direct interconnections with, among other areas of the brain, the orbitofrontal cortex
  - Increased amygdala activation in folks without psychiatric disorders is associated with correct identifications of threat-related (anger and fear) expressions
  - Serves as a communications hub between the parts of the brain that process incoming sensory signals and the parts that interpret them.
  - Viewing any emotional expression (e.g., disgust, fear, happiness, even neutrality) in other people strongly activates the amygdala
  - It can signal when a threat arises and trigger a fear response, a pre-programmed repertoire of quick physiological and behavioral changes geared towards survival.
  - The process and content of thoughts (cognitions) become colored (biased) by the emotional response of fear.
  - Memories of what triggered the fear response at an emotional level are stored through circuits involving the amygdala. Such emotional memories can be reawakened, without conscious choice, by triggers that match these memories.
  - Sensory systems funnel information through the prefrontal cortex, the cingulate cortex, the hippocampus and the thalamus to the lateral nucleus of the amygdala, the orbitofrontal cortex, and the anterior cingulate cortex.
  - If information into the amygdala matches a preformed template that is potentially threatening, the amygdala will activate the threat response via the visceral motor system.
  - The viscera then send information back through the insular cortex to the anterior cingulate cortex.
  - If the threat map of the anterior cingulate cortex matches that of the amygdala (suggesting true danger), one set of responses follows
  - If there is a mismatch (e.g., visual threat from a movie activates map in the amygdala which mismatches real-life threat map from anterior cingulate cortex), a different set of responses follows.
  - Amygdala→ directly to subgenual cingulate → dorsal cingulate→ amygdala
    - serotonin transporter S-allele carriers have a selective loss of functional connectivity to from the amygdala to the subgenual cingulate
    - amygdala-cingulate connectivity predicts harm avoidance trait
- If the learned fear response is allowed to extinguish (repeated presentation of stimuli associated with threat without the presence of the threat), the amygdalar response is dampened but the hippocampal contextual memory remains so that the same stimulus in a different context could induce the same fear response.
- Depression, anxiety and the amygdala
  - Depression
    - Associated with significant increases in the metabolic activity of the amygdala.
      - Reduced amygdala activation from positive stimuli
      - Increased amygdala (especially in the left amygdala) activation from negative stimuli
      - Enhanced activity in the amygdala when shown negative images is associated with borderline personality disorder (where depressive mood, affective instability, and interpersonal reactivity is central); the fusiform gyrus (which is part of the associative visual cortex and is in a feedback loop with the amygdala) was also overactive in

response to the images. These findings suggest that the perceptual cortex of a client with borderline personality disorder may be modulated through the amygdala, leading to increased attention to emotionally relevant environmental stimuli.

- Post-mortem studies in clients with depression have shown glial cell loss in the amygdala, frontal lobes, and entorhinal cortex and abnormal cell loss in the CA1 and CA4 areas of the dentate gyrus of the hippocampus, along with the entorhinal cortex, subiculum

- Involved in social anxiety, posttraumatic stress, obsessions, compulsions, separation anxiety, and general anxiety.
  - Increased amygdala and insula reactivity to emotional faces is seen in young adults with increased anxiety-related temperamental traits (Stein et al, 2007)
  - Exaggerated activity when clients with PTSD exposed to reminders of trauma
  - Increased amygdala activation is associated with correct identifications of threat-related (anger and fear) expressions in folks without psychiatric disorders, but it is associated with misidentifications in patients with schizophrenia; in addition, greater reactivity to fearful faces in schizophrenia is associated with flat affect.
  - Recent study linked enlarged volume of the left amygdala (a major fear center in the brain) with pediatric OCD; this enlargement is reversed with SSRI treatment.
  - A small left amygdala has recently been associated with children with anxiety disorders. In a subset of these children studied, 8 weeks of successful antidepressant or psychotherapy treatment was associated with a significant increase in the size of the left amygdala.
  - Individuals with autism who had small amygdalae were slowest to distinguish emotional from neutral expressions, showed least fixation of eye fields, are the most socially impaired, have the most gaze avoidance (Nacewicz et al)
  - Amygdala-hippocampal abnormalities seen in autism (Page et al, 2006)
- A lower ratio of 5HT1a to 5HT2a activity is associated with greater reactivity of the amygdala to stress.



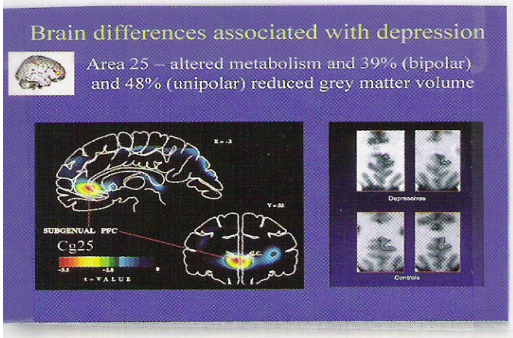
OR FIGURE 32.2 Areas of abnormally increased blood flow in subjects with major depressive disor- The image sections shown are from an image of *t*-values produced by a voxel-by-voxel computation he unpaired *t*-statistic to compare regional cerebral blood flow (CBF) between a depressed sample cted according to criteria for familial pure depressive disease (n = 13) and a healthy control sample = 33) (Drevets et al., 1992). The positive *t*-values shown correspond to areas where flow is increased ne depressives relative to the controls. The abnormal activity in these regions was replicated using ose metabolism imaging in independent subject samples (Drevets et al., 1995c, 2002a, 2002b). **A.** ttal section at 17 mm left of midline illustrating areas of increased CBF in depression in the amyg- and orbital cortex. **B.** This area of increased flow extended through the lateral orbital cortex (C) to ventrolateral prefrontal cortex (VLPFC) and anterior (Ant) insula (Drevets et al., 1992, 2002a). The ordinate locates sagittal sections in millimeters to the left of midline. **A,B.** The positron emission ography (PET) images from which the *t*-image was generated have been stereotaxically transformed ne coordinate system of Talairach and Tournoux (*Co-Planar Stereotaxic Atlas of the Human Brain*, tgart: Thieme, 1988), from which the corresponding atlas outline is shown. Anterior is left. **A** is lified from Price et al. (1996); **B** is reproduced from Drevets (1994).

- Locus Coeruleus (LC)
  - Residing in the brain stem, the LC is the home of the norepinephrine (NE) system.

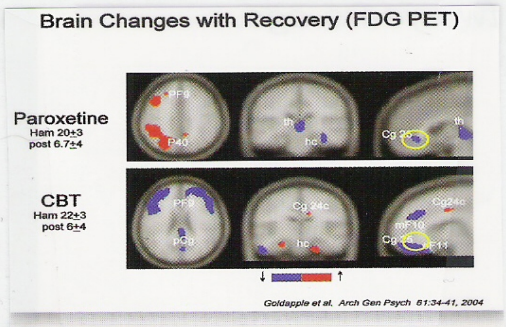
- If activated, the LC stimulates the sympathetic nervous system and the HPA axis/cortisol, enhances the role of the amygdala and other structures involved in the encoding of aversively charged memories, inhibits the parasympathetic nervous system, inhibits the medial prefrontal cortex.
- NE levels remain high in depressed patients, rising throughout the night to a peak in the AM when patients with melancholic depression experience the most intense depression. This is also the time of maximal vulnerability to heart attacks.
- SSRI's, tricyclic antidepressants (TCAs), and MAOI's all decrease the firing rate of the LC. Imipramine, Prozac, and an MAOI down-regulate the expression of the rate-limiting enzyme in the synthesis of NE and dopamine. SSRI's and TCAs modulate alpha-2 receptors (which may be the mechanism by which they downregulate the LC). Alpha-agonists like clonidine (and guanfacine) reduce presynaptic release of NE and reduce anxiety. Co-administration of an SSRI and olanzapine (but neither agent alone) potentiates LC tyrosine hydroxylase activity (which produces serotonin).
- NE is associated with insulin resistance, left ventricular hypertrophy, activation of platelets/clotting, and release of inflammatory cytokines and is arrythmogenic.

- Posterior Cingulate Cortex (PCC)
  - Happy stimuli → reduced activation right and left PCC
- Lateral Orbitalfrontal Cortex (OFC)
  - Interconnected with the amygdala
  - Mediates empathic, civil, and socially appropriate behavior
  - Hyperfunctional in OCD
  - Dysfunction may contribute to features of borderline personality disorder
- Prefrontal Cortex (PFC)
  - The logic center behind the activation and modulation of fear and anxiety.
  - Modulates and inhibits the amygdala, locus ceruleus, and HPA axis.
  - Increased PFC activity during negative emotion regulation is a predictor of depression symptom severity trajectory over 6 months in those with depression (Hellerer et al, 2013)
  - COMT enzyme
    - COMT metabolizes dopamine and other neurotransmitters)
    - COMT primarily affects dopamine metabolism in the PFC and midbrain and functioning in the frontal lobes
    - Midbrain dopamine synthesis is linked to PFC and it's regulation depends on COMT
    - The 'val' allele is associated with high enzymatic activity and consequent low dopamine
    - The 'met' allele
      - associated with low enzymatic activity and consequent high dopamine
      - associated with a dose-dependent increase in hippocampal formation and ventrolateral prefrontal cortex activation during viewing of faces displaying negative emotion.
      - associated with greater task-dependent prefrontal efficiency
      - in met/met homozygotes, limbic and prefrontal regions showed increased functional coupling, AND
      - in these met/met homozygotes, the magnitude of amygdala-orbitofrontal coupling was inversely correlated with novelty seeking, an index of temperamental inflexibility
      - HOWEVER, this allele is also associated with anxiety in women, OCD in men, panic disorder, alcoholism, aggressiveness and anger-related traits, increased reward dependence, increased sensitivity to pain, bipolar disorder, and major depression
  - The anterior cingulate cortex appears to be the bridge between the logic center of the PFC and emotional center of the amygdala.
  - PFC activity is dysregulated in all anxiety disorders.
  - Lateral frontal cortex
    - Activated with successful treatment of depression with Paxil (but not interpersonal therapy)
  - Dorsolateral Prefrontal Cortex (DLPFC)
    - Supramodal processing center
    - Executive cognitive functions
    - Involved in
      - generalized anxiety disorder
      - suppression (and ?repression) of memory via it's inhibition of the hippocampus. If asked to suppress memory, one will see greater activation of the DLPFC and reduced activation of the hippocampus.
      - bipolar disorder—loss of neuronal viability or altered function seen here (on the left side) in pediatric bipolar disorder (and both sides of the greater prefrontal cortex
  - Ventral PFC (VPFC)
    - Executive control in the regulation of emotion
    - Function abnormally in mood disorders
      - Left VPFC hyperactivity in sadness and in depression
        - Associated with reduced activity in the posterior cingulate cortex
      - Right VPFC reduced activity in mania
    - Cellular abnormalities in depression
      - Reduction in number of glial cells
      - Reduction in number of GABAergic cells
    - Anxiety disorders
      - Abnormalities in PTSD, panic disorder
        - decreased GABAa binding
        - enhanced norepinephrine release
        - enhanced activation of norepinephrine release
  - Successful antidepressant treatment reduces pregenual cingulate cortex, ventral striatum, and neocortical capacity for activation and increases the dynamic range of activity in the left prefrontal cortex.

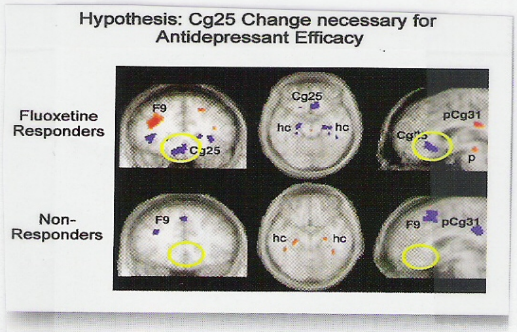
- Depression is associated with reduction in the size and metabolic activity of the left subgenual PFC, an area which helps in the assessment of whether to expect punishment or reward and assessment of whether a task has gone well or not. It is closely connected to the amygdala and participates in the extinction of conditioned fear responses. It is also the principal means for cortical restraint of the HPA axis and the SNS. Reduction of the size and metabolic activity of this area would likely increase anticipation of harm, decrease regard for oneself and what one has accomplished, disinhibit the amygdala with subsequent increase in fear and anxiety, and disinhibit the HPA and SNS, setting into motion inhibition of growth and reproduction, a catabolic state (of muscle breakdown), and increased heart rate and blood pressure.
- The enzyme catechol-0-methyl transferace (COMT) breaks down dopamine. Of two common alleles, one codes for a more active enzyme which breaks down dopamine more efficiently. If one has two copies of that particular allele, one is more likely to have diminished cognitive performance with worse signal-to-noise information processing, working memory, and executive functioning (due to diminished dopamine in the PFC).



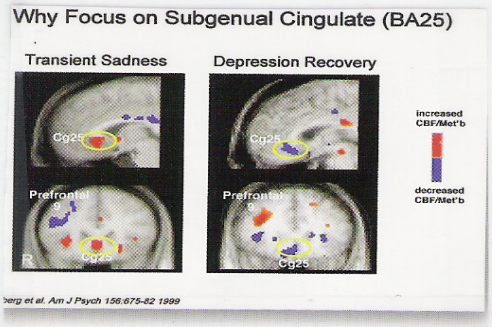
Brain differences associated with depression



Brain Changes with Recovery



Hypothesis: Cg25 Change



Why Focus on Subgenual Cingulate

Depression
Prefrontal Cortex (Subgenual)
Altered metabolism
48% reduction in size

Recovery
) Normalizes Cingulate cortex (Prefrontal cortex) (subgenual)
) Normalizes cingulate cortex (subgenual prefrontal cortex)
but via frontal lobe path

Response
Only cingulate cortex normalizes
Placebo does not change cingulate

Recovery + Cingulate Cortex
Sadness or Depression
↑ activity cingulate
↓ activity prefrontal cortex (dorsolateral)
Depression Recovery
Both normalize

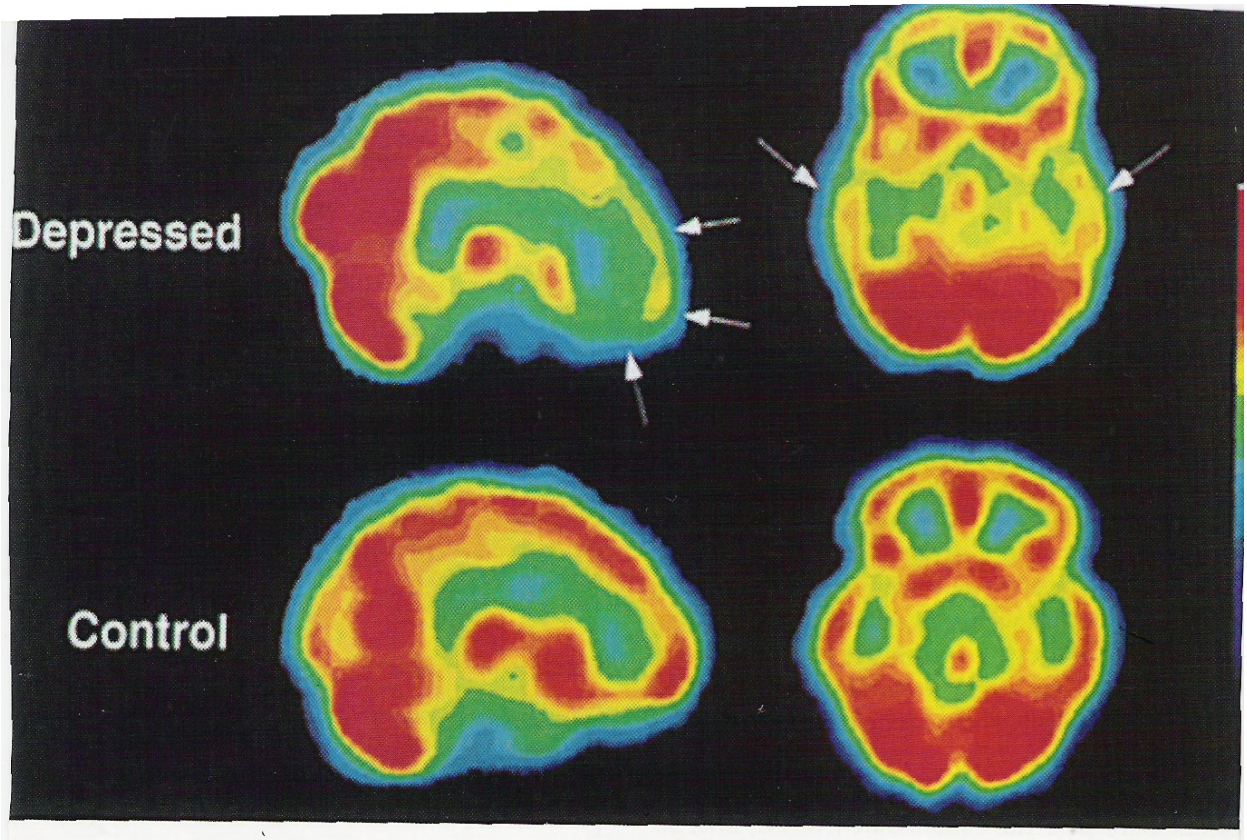


FIGURE 12–1. Single photon emission computed tomography (SPECT) ^{99m}Tc-hexamethylpropyleneamine oxime (HMPAO) images.

Sagittal (*left* images) and axial (*right* images) views are shown normalized to each subject's cerebellar perfusion for visual comparisons. Symmetric frontal and temporal hypoperfusion is present in the depressed subject (arrows, axial view). Note that frontal perfusion is most abnormal inferiorly (arrows, sagittal view). Patient: 30-year-old woman. Control subject: 28-year-old woman.

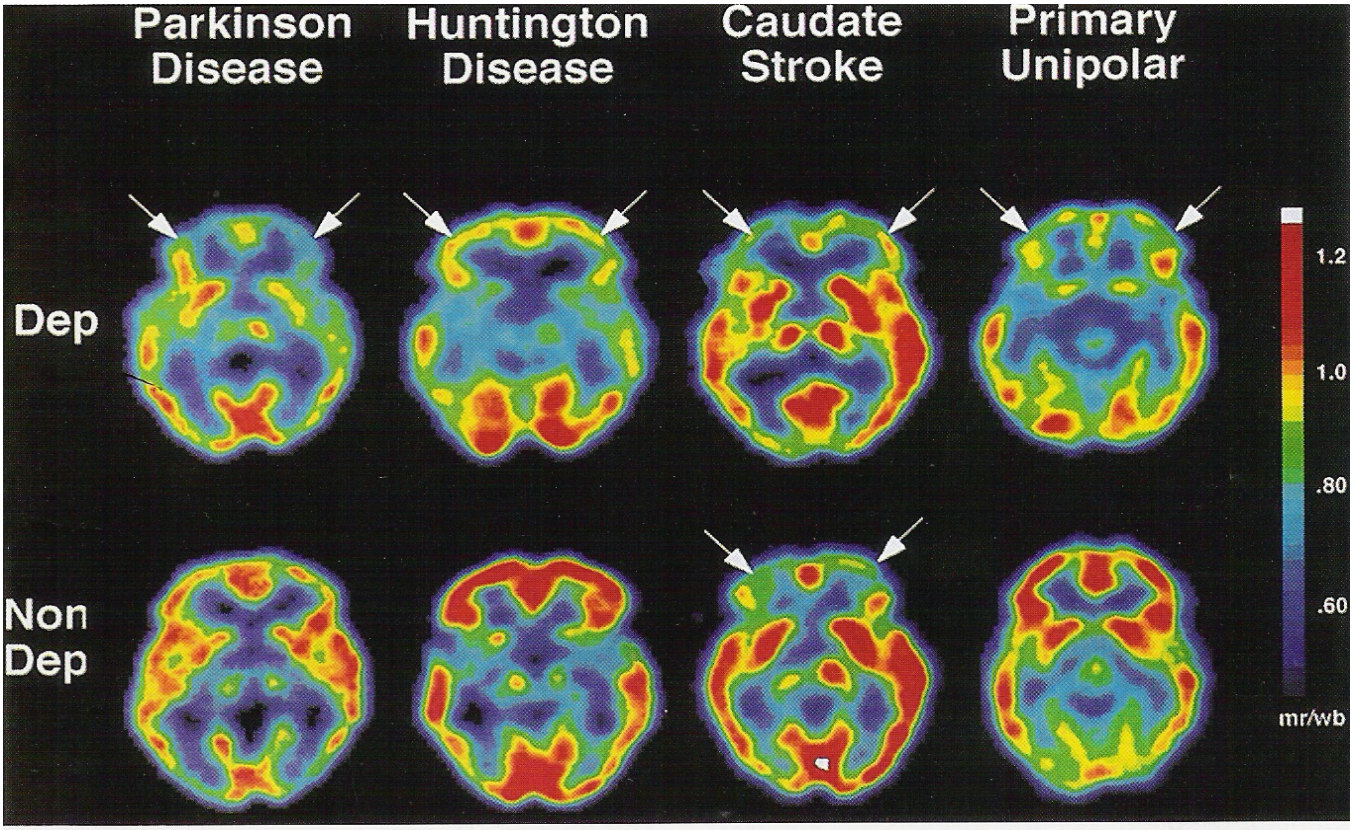
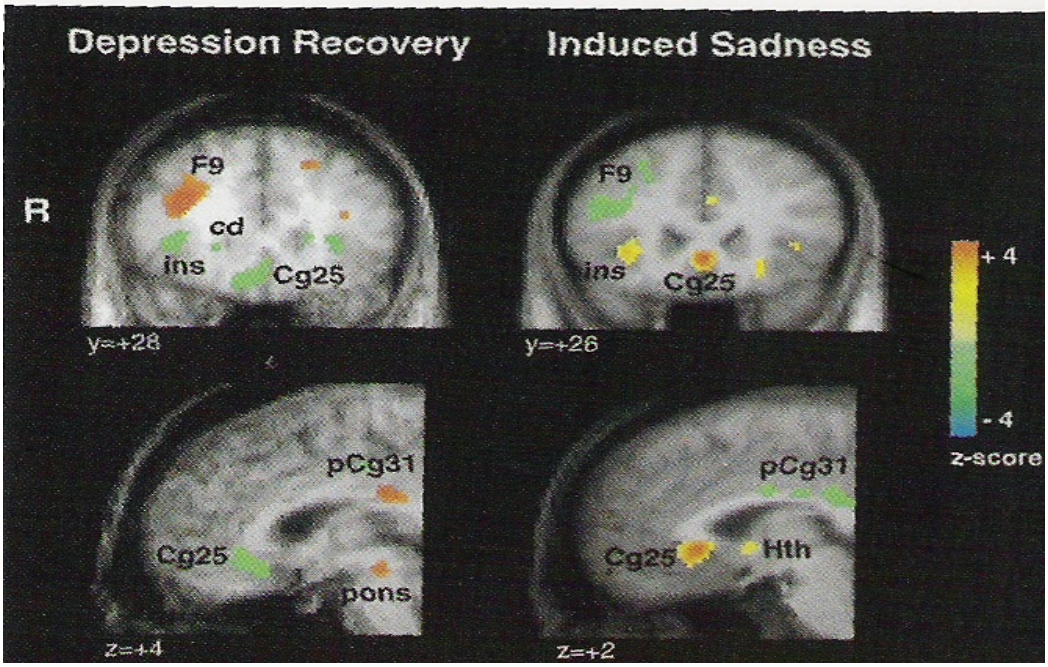


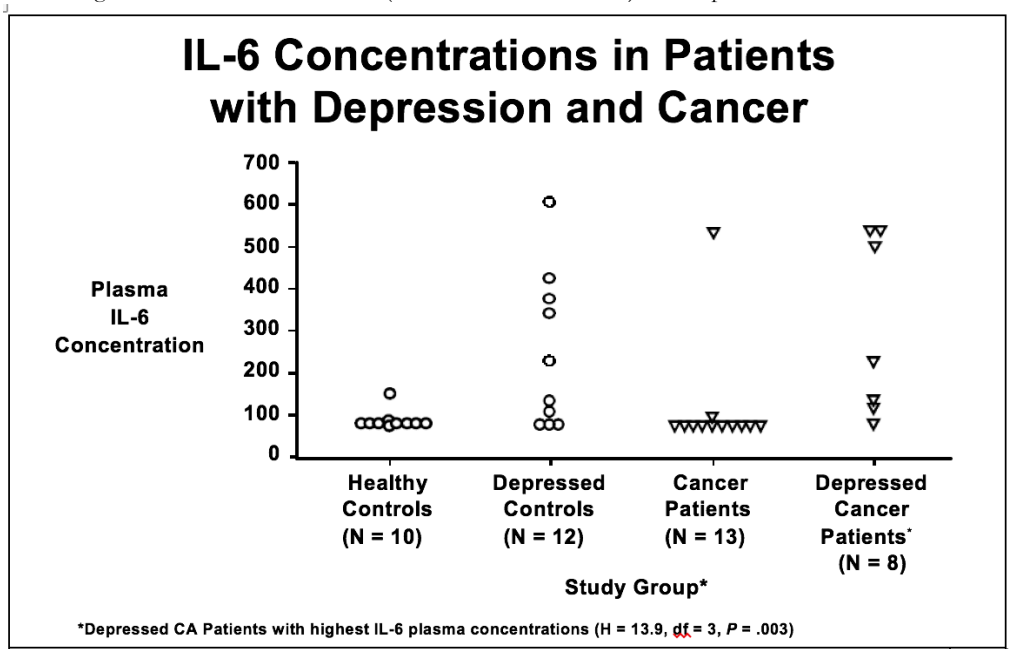
FIGURE 12–3. Fluorodeoxyglucose positron-emission tomography images in primary and secondary depression, basal ganglia level.

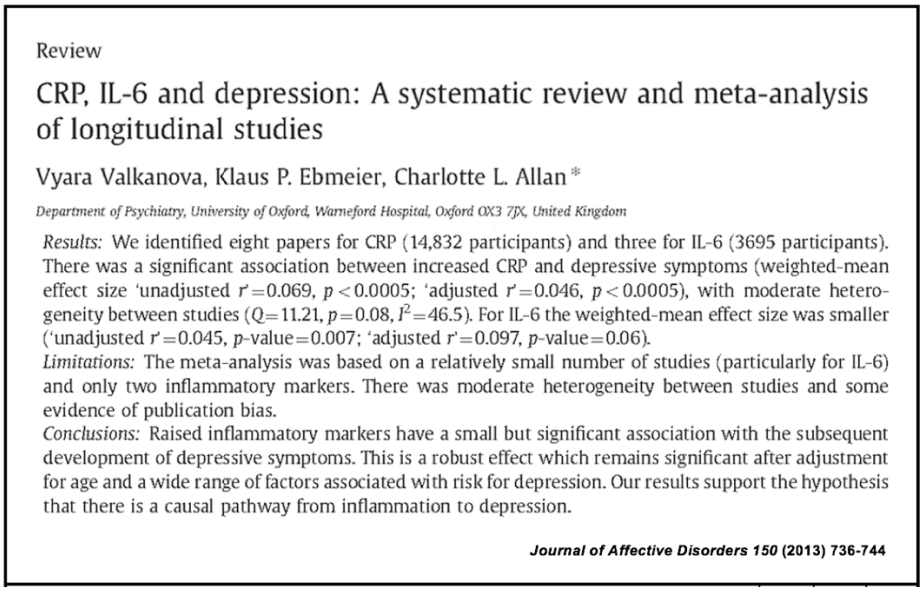
All depressed patients have bilateral frontal lobe hypometabolism, independent of disease etiology (arrows, *top row*). Frontal cortex metabolism is normal in nondepressed patients, except those with strokes (arrows, *bottom row*). Scale: relative metabolic rate (regional absolute metabolic rate/whole brain metabolic rate).

FIGURE 12–2. Reciprocal changes in cortical and paralimbic function with manipulation of mood state. Left images: *Z*-score maps demonstrating changes in regional glucose metabolism (fluorodeoxyglucose PET) in depressed patients following 6 weeks of fluoxetine treatment. Right images: changes in regional blood flow (oxygen-15 water PET) in healthy volunteers 10 minutes after induction of acute sadness. Depression recovery and induced sadness involve changes in identical dorsal frontal and ventral paralimbic brain regions. Depression recovery is associated with increases in dorsal regions and decreases in ventral regions. The reverse is seen with induced sadness, where dorsal areas decrease and ventral areas increase with change in mood state. F = frontal; cd = caudate; ins = anterior insula; Cg 25 = subgenual cingulate; Hth = hypothalamus; pCg 31 = posterior cingulate. Color scale: *red* = increases, *green* = decreases in flow or metabolism.



- Random
  - Seroquel increases indices of new neuronal growth in the anterior cingulated cortex, cerebellar vermis, and right ventral prefrontal cortex
  - Zyprexa increases indices of new neuronal growth in the ventral medial prefrontal cortex; responders show greater increases than non-responders
- Inflammatory mediators (see above also)
  - Beratis et al, 2005; Myint et al, 2005; Wichers et al, 2005a and 2005b; Capuron et al, 2003a and 2003b; Kim et al, 2002): depression is associated with elevated amounts of cytokines (part of the body's immune/inflammatory response; especially interleukin 6); these elevated cytokines appear to directly stimulate the bodies stress response (via the CRH/cortisol system) which can damage neurons in the hippocampus. Cytokines may also reduce availability of serotonin (important in maintaining normal mood) by breaking down tryptophan, a precursor to serotonin. Breaking down tryptophan in turn produces a chemical that can damage neurons in the hippocampus and that can make anxiety and depression worse. They also interact with NE and dopamine.
  - Pro-inflammatory compounds enhance the breakdown of tryptophan (which → serotonin) into various metabolites
    - One pathway
      - 3-hydroxyantheanilate directly → neuronal death
      - 3-hydroxyantranilate → quinolinic acid → excitotoxic death through NMDA receptor activation
    - Other pathway
      - kynurenic acid → block of NMDA receptors and block of quinolinic acid-induced excitotoxic death
    - In depression:
      - tryptophan breakdown higher
      - reduced kynurenic acid
        - in first episode depression, antidepressant treatment increased the kynurenic acid
        - in those with recurrent episodes, the level did not increase with antidepressant treatment
  - Cytokines induce depressed mood, irritability, anger/hostility, fatigue, lack of pleasure, anorexia, psychomotor slowing, altered sleep patterns, impaired memory, impaired concentration, increased sensitivity to pain, social isolation.

- Protein kinase C (PKC) is a "second messenger" modulated by, among other things, inflammatory mediators. Reduced PKC activity in the prefrontal cortex and hippocampus may be associated with suicide in adolescents.
- Pregnant women seeking treatment for major depression have markedly higher levels of macrophage migration inhibitory factor (MIF) than do nondepressed pregnant women of similar age (Pearce, 2005). MIF inhibits cortisol and increases production of inflammatory cytokines.
- Serotonergic medications such as SSRI's (at least Zoloft and Celexa) and imipramine have been shown to decrease cytokines.
- 

- 
Review

CRP, IL-6 and depression: A systematic review and meta-analysis of longitudinal studies

Vyara Valkanova, Klaus P. Ebmeier, Charlotte L. Allan *

Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford OX3 7JX, United Kingdom

Results: We identified eight papers for CRP (14,832 participants) and three for IL-6 (3695 participants). There was a significant association between increased CRP and depressive symptoms (weighted-mean effect size 'unadjusted $r'=0.069$, $p<0.0005$; 'adjusted $r'=0.046$, $p<0.0005$), with moderate heterogeneity between studies ($Q=11.21$, $p=0.08$, $I^2=46.5$). For IL-6 the weighted-mean effect size was smaller ('unadjusted $r'=0.045$, p-value$=0.007$; 'adjusted $r'=0.097$, p-value$=0.06$).

Limitations: The meta-analysis was based on a relatively small number of studies (particularly for IL-6) and only two inflammatory markers. There was moderate heterogeneity between studies and some evidence of publication bias.

Conclusions: Raised inflammatory markers have a small but significant association with the subsequent development of depressive symptoms. This is a robust effect which remains significant after adjustment for age and a wide range of factors associated with risk for depression. Our results support the hypothesis that there is a causal pathway from inflammation to depression.

Journal of Affective Disorders 150 (2013) 736-744

Interleukin-6 Is Elevated in the Cerebrospinal Fluid of Suicide Attempters and Related to Symptom Severity

Daniel Lindqvist, Shorena Janelidze, Peter Hagell, Sophie Erhardt, Martin Samuelsson, Lennart Minthon, Oskar Hansson, Maria Björkqvist, Lil Träskman-Bendz, and Lena Brundin

Results: IL-6 in CSF was significantly higher in suicide attempters than in healthy control subjects. Patients who performed violent suicide attempts displayed the highest IL-6. Furthermore, there was a significant positive correlation between MADRS scores and CSF IL-6 levels in all patients. IL-6 and TNF-α correlated significantly with 5-HIAA and HVA in CSF, but not with MHPG. Cytokine levels in plasma and CSF were not associated, and patients with increased blood-brain barrier permeability did not exhibit elevated cytokine levels.

Biol Psychiatry (2009) 66, 287-292

Cytokine levels in the blood may distinguish suicide attempters from depressed patients

Shorena Janelidze, Daniele Mattei, Åsa Westrin, Lil Träskman-Bendz, Lena Brundin *

Psychoimmunology Unit, Division of Psychiatry, Department of Clinical Sciences, Lund University, Lund, Sweden

We found increased levels of IL-6 and TNF-α as well as decreased IL-2 concentrations in suicide attempters compared to non-suicidal depressed patients and healthy controls. The results were adjusted for potential confounders of cytokine expression, such as age, sex, body mass index (BMI), degree of depression, anxiety, personality disturbance, abuse and type of medication.

These results demonstrate for the first time that suicidal patients display a distinct peripheral blood cytokine profile compared to non-suicidal depressed patients. Thus, our study provides further support for a role of inflammation in the pathophysiology of suicidality.

Brain, Behavior, and Immunity 25 (2011) 335-339

Basis for the Hypothesis that Inflammation may Play a Role in Depression

Positive correlation between depressive symptom severity and innate immune cytokines

Elevated innate immune cytokines predict poor response to antidepressant therapies and are elevated in patients with treatment resistance. Cytokine gene polymorphisms (IL-1, TNF) predict antidepressant treatment response.

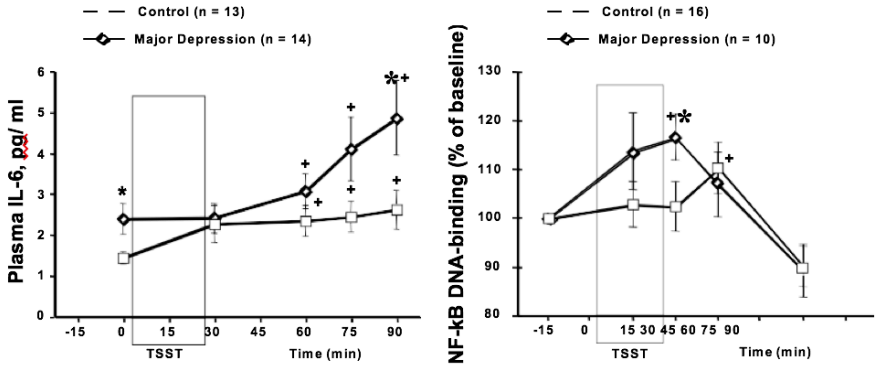
Administration of innate immune cytokines (esp. IL-1, TNF-alpha, and IL-6, as well as IFN-alpha) produce behavioral changes in laboratory animals and humans that resemble major depression.

Inhibition of cytokine signaling has been found to alleviate depressive and anxiety behaviors in patients with inflammatory disorders and in laboratory animals.

Basis for the Hypothesis that Proinflammatory Cytokines Play a Role in Depression and Depressive Symptoms

- Cytokines released peripherally have access to the brain
  - passage through leaky regions in the BBB
  - active transport
  - transmission through afferent nerve fibers (vagus)
- There is a cytokine network in the CNS
  - glia (microglia) and neurons express/produce cytokines and express cytokine receptors
- Cytokines have effects on neurotransmitter turnover, neuroendocrine function and behavior (sickness behavior)

Patients with Major Depression Exhibit an Exaggerated Inflammatory Response to Stress: A Possible Link Between Stress, Depression and Illness



*Between group comparison, $p < 0.05$

+Within group comparison vs. 0 min time pt, $p < 0.05$

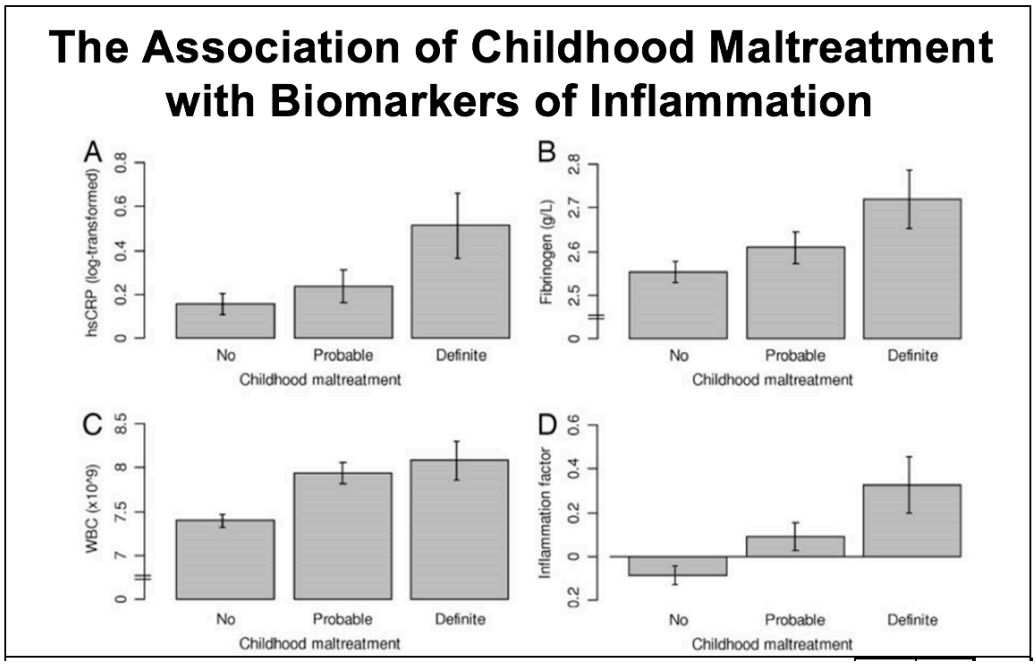
*-the majority of the depressed patients in this sample also endorsed significant early life stress as measured by the CTQ

Pace et al., *Am J Psychiatry*, 163(9):1630-1633, 2006.

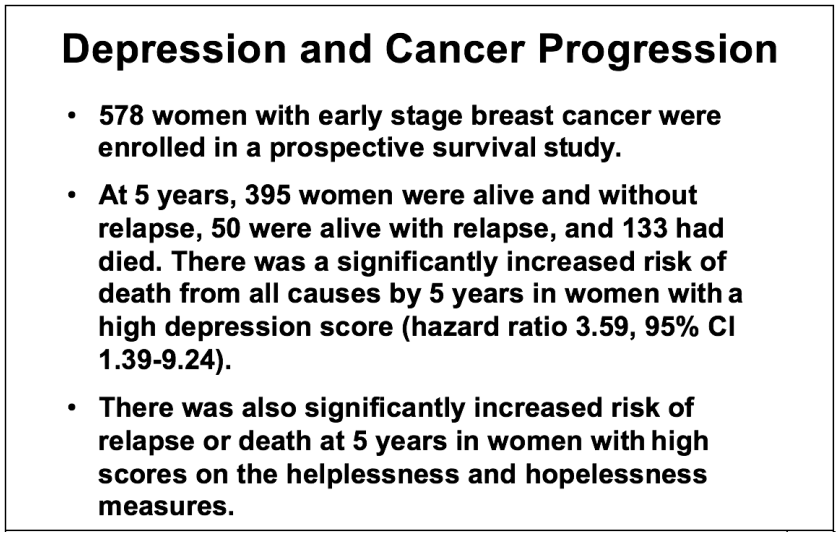
Childhood Maltreatment Predicts Adult Inflammation in a Life-Course Study

Andrea Danese, Carmine M. Pariante, Avshalom Caspi, Alan Taylor, and Richie Poulton

- The life-course association between childhood maltreatment and adult inflammation was examined in a birth cohort followed to age 32 years as part of the Dunedin Multidisciplinary Health and Development Study.
- Maltreated children showed a significant and graded increase in the risk for clinically relevant C-reactive protein levels 20 years later
- The association between maltreatment and adult inflammation also generalizes to fibrinogen and white blood cell count. Childhood maltreatment is a previously undescribed, independent, and preventable risk factor for inflammation in adulthood.



- Medical issues
  - Prophylactic use of antidepressants following stroke appeared in a meta-analysis to be effective in fending off depression and a short course of antidepressants in a placebo-controlled study was associated with long-term restoration of executive function, independent of depressive symptoms
  - Neurovegetative symptoms of depression correlate with thickening of the carotid arteries and cardiovascular disease
  - Depression associated with 36% increased risk of heart attack
  - Risk of death from heart disease and stroke increased in those with serious mental illness



Depression and cancer mortality: a meta-analysis

M. Pinquart[1]* and P. R. Duberstein[2]

[1] *Department of Psychology, Philipps University, Marburg, Germany*
[2] *Laboratory of Personality and Development, Department of Psychiatry, University of Rochester Medical Center, Rochester, NY, USA*

Results. Depression diagnosis and higher levels of depressive symptoms predicted elevated mortality. This was true in studies that assessed depression before cancer diagnosis as well as in studies that assessed depression following cancer diagnosis. Associations between depression and mortality persisted after controlling for confounding medical variables.

Conclusions. Screening for depression should be routinely conducted in the cancer treatment setting. Referrals to mental health specialists should be considered. Research is needed on whether the treatment of depression could, beyond enhancing quality of life, extend survival of depressed cancer patients.

Psychological Medicine (2010), 40, 1797–1810

Rates of depression are uniformly elevated in inflammatory conditions

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Depressive syndromes are a risk factor for the development of CAD, metabolic syndrome, cancer

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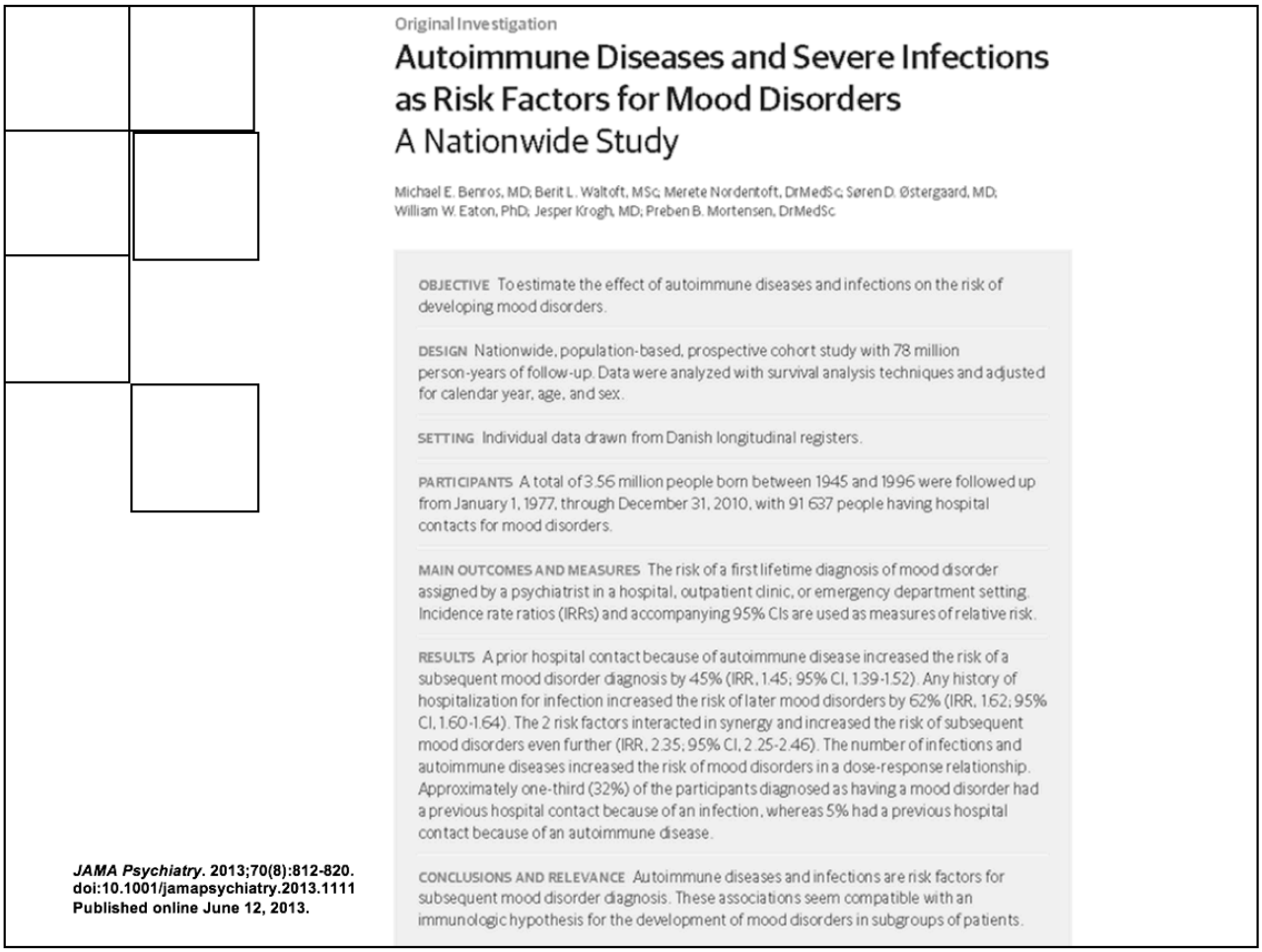
Depression increases morbidity in all inflammatory conditions and has been repeatedly shown to increase risk of mortality in context of CAD and cancer (and it's treatment)



Original Investigation

Autoimmune Diseases and Severe Infections as Risk Factors for Mood Disorders
A Nationwide Study

Michael E. Benros, MD; Berit L. Waltoft, MSc; Merete Nordentoft, DrMedSc; Søren D. Østergaard, MD; William W. Eaton, PhD; Jesper Krogh, MD; Preben B. Mortensen, DrMedSc

OBJECTIVE To estimate the effect of autoimmune diseases and infections on the risk of developing mood disorders.

DESIGN Nationwide, population-based, prospective cohort study with 78 million person-years of follow-up. Data were analyzed with survival analysis techniques and adjusted for calendar year, age, and sex.

SETTING Individual data drawn from Danish longitudinal registers.

PARTICIPANTS A total of 3.56 million people born between 1945 and 1996 were followed up from January 1, 1977, through December 31, 2010, with 91 637 people having hospital contacts for mood disorders.

MAIN OUTCOMES AND MEASURES The risk of a first lifetime diagnosis of mood disorder assigned by a psychiatrist in a hospital, outpatient clinic, or emergency department setting. Incidence rate ratios (IRRs) and accompanying 95% CIs are used as measures of relative risk.

RESULTS A prior hospital contact because of autoimmune disease increased the risk of a subsequent mood disorder diagnosis by 45% (IRR, 1.45; 95% CI, 1.39-1.52). Any history of hospitalization for infection increased the risk of later mood disorders by 62% (IRR, 1.62; 95% CI, 1.60-1.64). The 2 risk factors interacted in synergy and increased the risk of subsequent mood disorders even further (IRR, 2.35; 95% CI, 2.25-2.46). The number of infections and autoimmune diseases increased the risk of mood disorders in a dose-response relationship. Approximately one-third (32%) of the participants diagnosed as having a mood disorder had a previous hospital contact because of an infection, whereas 5% had a previous hospital contact because of an autoimmune disease.

CONCLUSIONS AND RELEVANCE Autoimmune diseases and infections are risk factors for subsequent mood disorder diagnosis. These associations seem compatible with an immunologic hypothesis for the development of mood disorders in subgroups of patients.

***JAMA Psychiatry*. 2013;70(8):812-820.**
doi:10.1001/jamapsychiatry.2013.1111
Published online June 12, 2013.

Inflammation and Treatment Resistance

Clinical Predictor of Antidepressant Non-Response	Relation to Inflammation
Obesity	**Dose response relationship between BMI and inflammatory markers**
Early Life Stress	**Increased inflammation and inflammatory response to stress in individuals exposed to early life stress**
Medical Illness	**Increased inflammatory markers in cancer and cardiovascular disease**
Personality Disorders/Anxiety	**Increased inflammatory markers in patients with Anxiety Disorders, Borderline Personality Disorder and Neuroticism**

Notes from Nemeroff lecture, April 2018

Role of inflammation/nemeroff

Med do's ass'd w/ inflammation/autoimm have higher rates of psych dos and vice versa

Symptom-less Hashimoto's→hypothyroidism eventually (and trouble w/ li)

Pts w/ mdd have doubling of mortality and of CAD at any age, indepent of smoking and htn and other risk factors; also ass c premasture osteopdenia/porosis, DM, other

Peripheral inflammation → NVS and low mood (sickness behavior)
Deprn→perip and central inflamm (you see it in blood and csf); esp CRP, IL6, TNF, chemokines, cellular adhesion molecules

In maj of studies, inflamm markers dec w/ improvement in depn

Depn ass c elevated temp in medically healthy pts; when treated, temp dec to nl

Cytokines →
Anhedonia, malaise, wkness, hyperalgia, poor conc, social w/drawal, anorexia, hypersomnia

Il-6 concentration in pts with depn and ca; healthy vs. dep vs. ca vs. depn+ca; only increased in dep pts and dep + ca

Meta-analysis of crp and il-6 in deprn; raised levels have small but sig assn with depn, even w/ adjustment of other risk factors; suggests causal pathway

Inflamm cytokines in suicidal behavior; marked increase

Il-6 markedly inc'd in csf of suic attempters, esp those with violent attempts vs. non-violent

Cytokine levels in blood may distinguish suicide attempters from depressed non-suicidal pts using crp/tng/il-6

IL-1 also

IL-1, tnf-alpha, and IL-6 and IFN-alpha → nvs/depn

Inflammation associated with treatment resistance

Cytokine mutations may be involved

Does reduction of inflammation itself → rx

Cytokines peripheral-

Circumventricular organs with non-tight junctions in caps/weakened bbb, so cytokines can enter

Transporters in caps can transport cytokines across bbb

Receptors in vagus → signals to brain

Brain has microglia which also make cytokines and have cytokine receptors. And can lead to changes in neurochemicals

Child abuse/neglect → anx and deprn; link might be stress/inflammation/brain changes during development in the midst of stress

Men with deprn and ho abuse; increased response of IL-6 to stress

Maltreated kids show inc in inflamm marker crp 20 years later; the more definite the abuse the higher the crp. Inc's risk for heart disease, stroke, dm, obesity, etc.

Decrease depressive s/s in women with met breast ca → longer survival

Depression and early stage breast ca; sig inc risk death from all causes in women with highest scores for depression

Deprn c high s/s predicts mortality in women with breast ca

Post-surg dep sx predicts survival in early breast ca more than a decade after f/u

Critical to screen and treat depression

Dep s/s risk factor for dev of CAD, met symdrome and ca

Dep inc mortality in a variety of do's w/ inflamma (ca, CAD, dm)

Bi-directional relationship

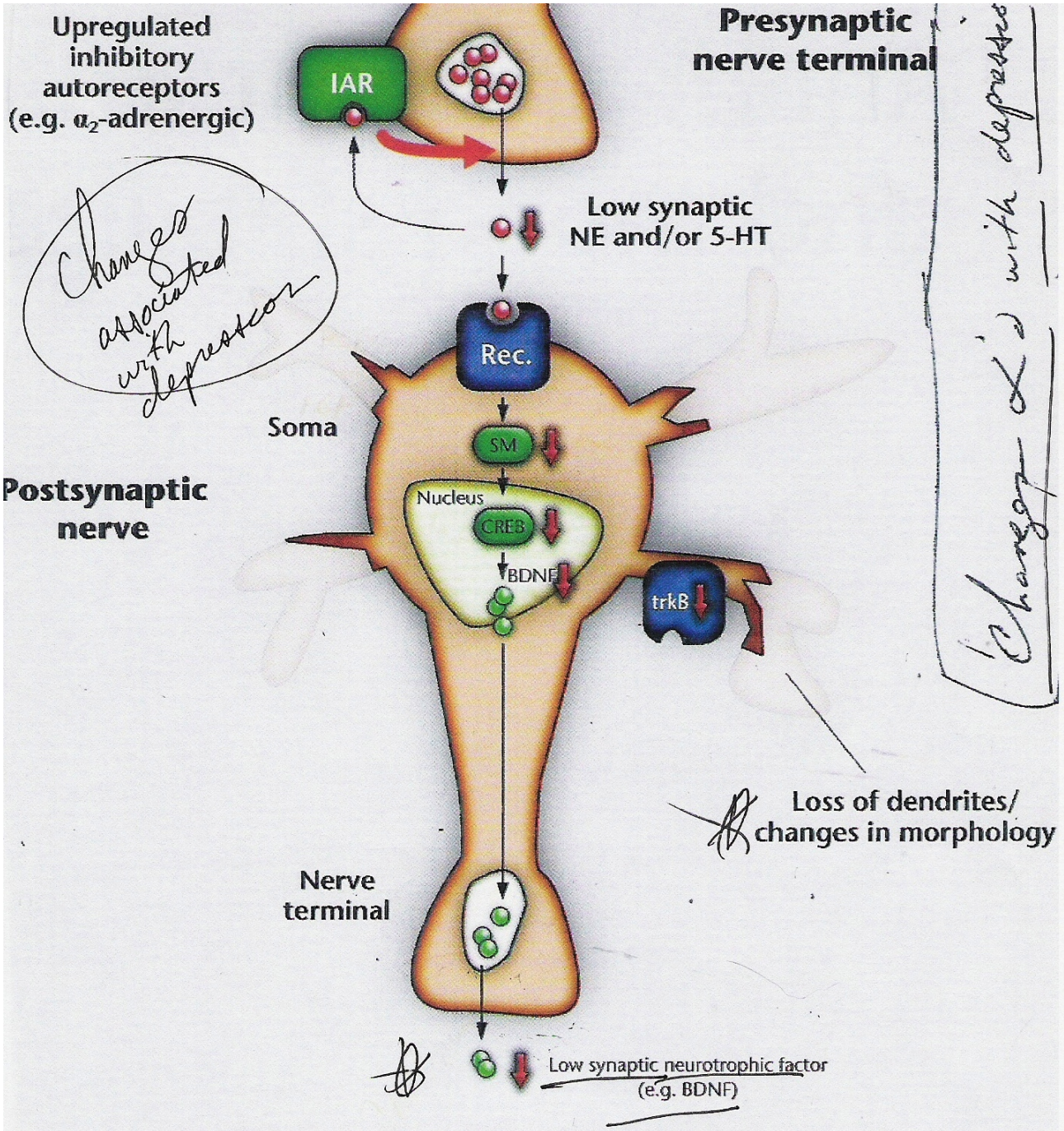
Mesenchymal stem cells; could they play a role in rx'g depression
--have been used experimentally for a variety of conditions
--they have a role in nl healing and tissue regeneration
--used in osteoarthritis, CHF, COPD

--inc anti-inflamm chems and dec inflamm mediators
--could subset of pts respond to infusion of these? Pilot data, looking at TNF in frail elderly people; got a single inj from healthy, young volunteer; 6 mo's after injection there is still a redn in CRP, TNF
--TNF inhibitor was effective AD in pts with elevated CRP but not in those without; only address a single inflamm cyto-kine
--stem cells are pan-inhibitor of inflamm (crp, TNF, IL-6, IL-1)
--co-morbid etoh and depress; etohism is ass w/ high rates of inflamm, so is depn; studying this now

?'s

1) opioids and inflammation
   opioid addicts via ivda have high levels of inflammation
2) statins are only ok with dec'g inflammn. There is a relation b/w chol and depn. Extremely low levels of ldl ass with suicide.
3) Hashimoto's
    a. Endocrin's won't do anything
    b. Educate pt
        i. Aka grade 4 hypothyroidism (symptomless hypothyroidism)
        ii. Need regular tsh tests
        iii. It will creep up over time
    c. As creeps up, T4+T3 is better than just T4 for mood and cognitive sx

AD responders tend to have normalized inflamm markers whereas those that don't respond well, usually don't



Feedback inhibition (enhanced)

Loss of dendrites and/or change in morphology

Low concentration

5-HT	Serotonin
BDNF	Brain-derived neurotrophic factor
CREB	Cyclic adenosine monophosphate (cAMP)-response element-binding protein
IAR	Inhibitory autoreceptor
NE	Norepinephrine
Rec.	Receptor
SM	Second messenger (e.g. cAMP)
trkB	Receptor for BDNF

Reuptake inhibitors

of NE:

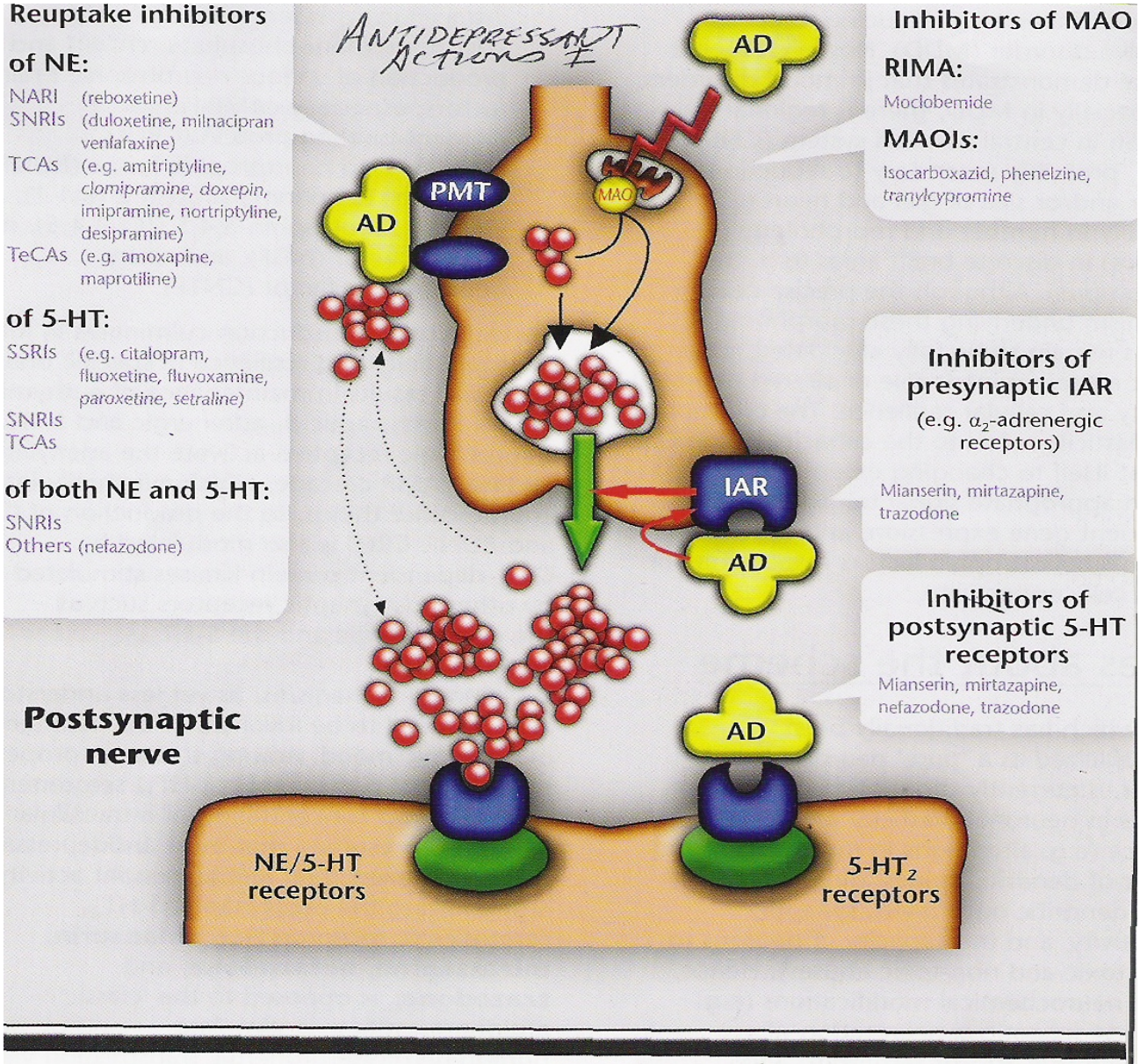
NARI (reboxetine)
SNRIs (duloxetine, milnacipran venlafaxine)
TCAs (e.g. amitriptyline, *clomipramine, doxepin,* imipramine, nortriptyline, desipramine)
TeCAs (e.g. amoxapine, maprotiline)

of 5-HT:

SSRIs (e.g. citalopram, fluoxetine, fluvoxamine, *paroxetine, setraline)*
SNRIs
TCAs

of both NE and 5-HT:

SNRIs
Others (nefazodone)



Inhibitors of MAO

RIMA:

Moclobemide

MAOIs:

Isocarboxazid, phenelzine, *tranylcypromine*

Inhibitors of presynaptic IAR

(e.g. α_2-adrenergic receptors)

Mianserin, mirtazapine, trazodone

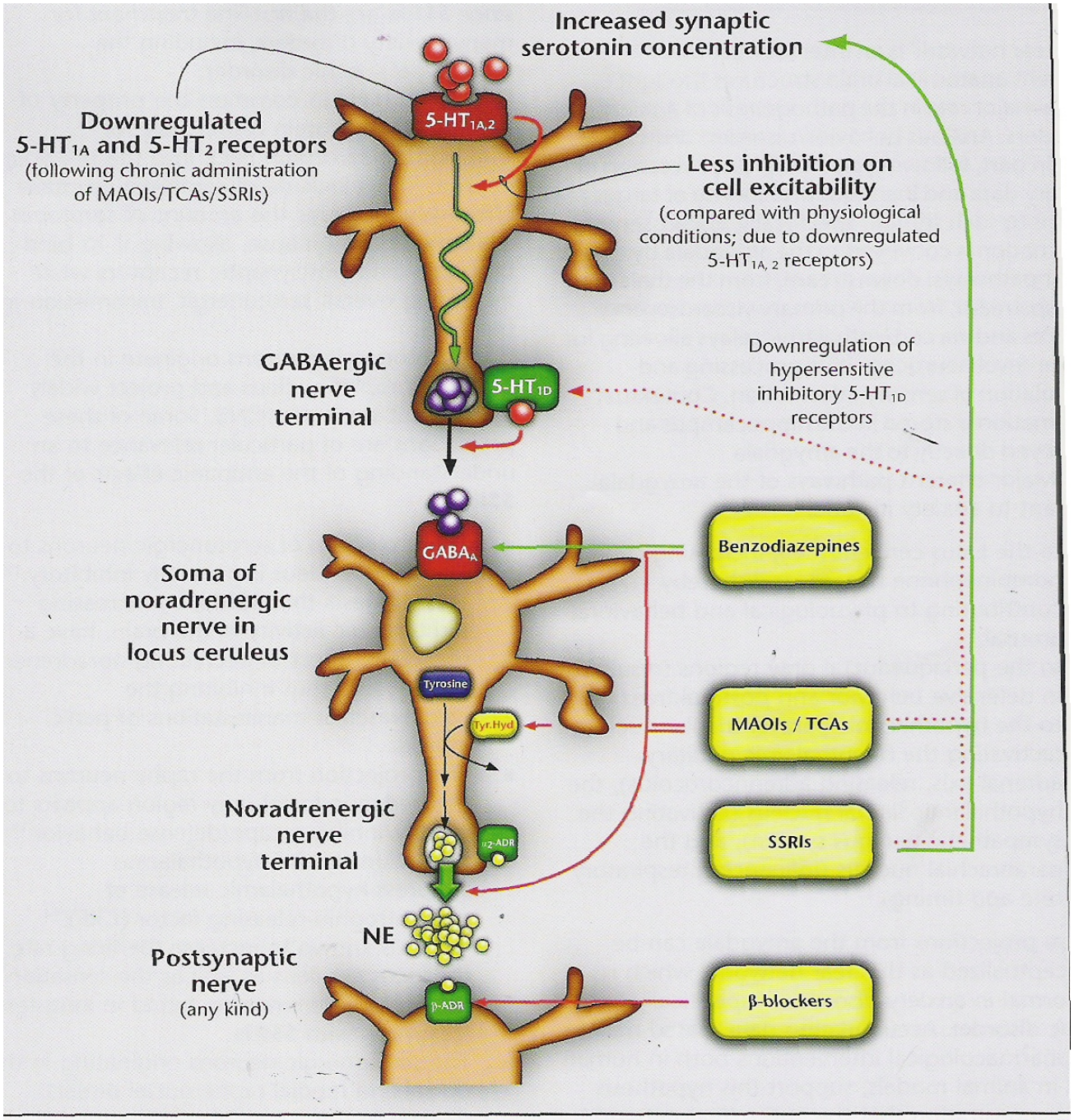
Inhibitors of postsynaptic 5-HT receptors

Mianserin, mirtazapine, nefazodone, trazodone

Inhibition
Inhibits
Enhanced secretion

5-HT Serotonin
AD Antidepressant drug
IAR Inhibitory autoreceptor

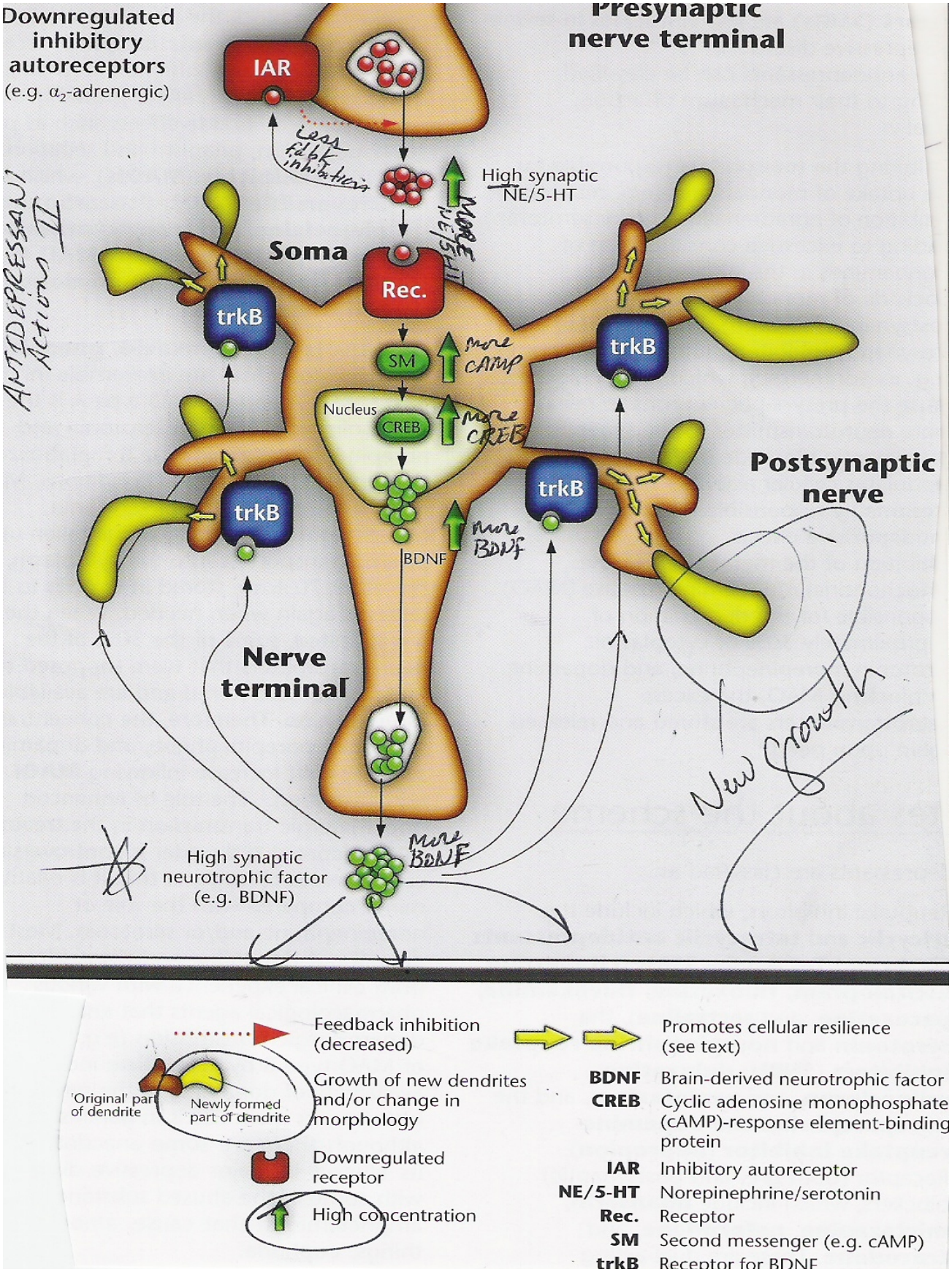
MAO Monamine oxidase
MAOI *MAO inhibitor*
NARI Seletive noradrenaline (norepinephrine) *inhibitor*
NE Norepinephrine
PMT *Plasma membrane transporter*
RIMA Reversible inhibitor of MAO type A
SNRI Serotonin–norepinephrine reuptake inhibi
SSRI Selective serotonin reuptake inhibitor
T/TeCA Tri/tetracyclic antidepressant



Legend

- Downregulate/inhibit, respectively
- Stimulate
- Serotonin
- GABA (γ-aminobutyric acid)
- Norepinephrine
- Downregulated receptor
- Upregulated receptor
- Increased firing rate

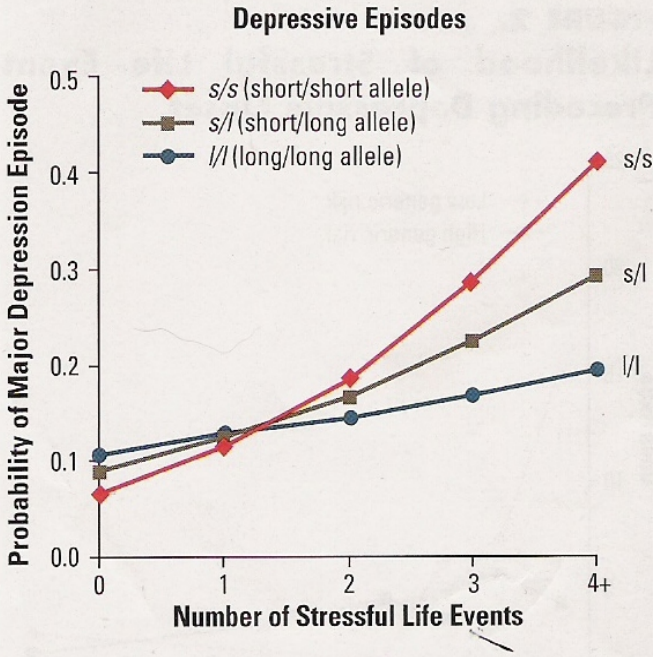
α_2-ADR	Adrenergic receptor subtype (inhibitory)
β-ADR	Adrenergic receptor subtype
5-HT$_{1A}$	Serotonergic receptor subtype
5-HT$_{1D}$	Serotonergic receptor subtype (inhibitory)
5-HT$_2$	Serotonergic receptor subtype
GABA$_A$	GABAergic receptor subtype
MAOI	Monoamine oxidase inhibitor
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant
Tyr.Hyd	Tyrosine hydroxylase



- Norepinephrine
  - Functions
    - Sharpens the senses
    - Focuses attention by activating the neurons that collect information obtained by the senses in order to rapidly and efficiently obtain information about dangers in the environment
    - It stimulates the brain to cells of the brain to more efficiently collect information about what dangers are out there
    - Raises the level of fear

        - Increases heart rate and blood pressure
        - Prepares us for fight or flight
        - Fire alarm to all areas of the brain simultaneously—sacrifices the ability to convey specific information to specific parts of the brain in order to obtain more speed.
        - Low levels stimulate the prefrontal (zen) cortex but high levels (as seen in PTSD) tend to shut the PFC down.
    - Beta adrenergic receptors
        - Chronic antidepressant/ECT → decreased activity, density of beta receptors
    - Alpha1 adrenergic receptors
        - Chronic antidepressant use→ increased numbers of alpha1 receptors
- Serotonin
    - Serotonin transporter and it's gene
        - The gene for the serotonin transporter protein (5HTTLPR) is located on chromosome 17.
        - Among other things, appears to be mediator of metabolic activity in the hippocampus and amygdala
        - The gene exists as either the short (s) allele (SLC6A4) or the long (l) allele (each individual inherits an allele from each parent).
            - The s form is less efficient at making the transporter protein and produces a transporter protein that has reduced reuptake functioning
            - Individuals with 1 or 2 of the s alleles are thought to have reduced serotonin transporter function compared to those with 2 copies of the l allele.
            - The population alleles are distributed as follows: 32% l/l, 49% s/l; 19% s/s.
                - Most people of European ancestry carry at least one s allele
            - The s allele (s/l or s/s combination) is also associated with the following:
                - Depression
                    - In addition to other studies in adults, Grunblatt et al, 2006: 544 75 y.o. folks (without dementia); s/s combination more likely with current or past depression
                    - Likelihood that life stressors will lead to depression is moderated by the type of alleles one has:
                        - s/s: highest risk
                        - s/l: medium risk
                        - l/l: lowest risk
                        - However, some evidence suggests that this effect is mediated by the increased rate of neuroticism with s/s; note also that the co-morbid presence of non-verbal learning issues also correlates with increased risk of depression after life stress

The Association Between the Probability of a Major Depression Episode and the Number of Stressful Life Events



Life events predicted a diagnosis of major depression among s carriers (*b* 0.52, SE 0.16, z 3.28, *P*=.001 among *s/s* homozygotes, and *b* 0.39, SE 0.09, *z* 4.24, *P*<.001 among *s/l* heterozygotes) but not among *l/l* homozygotes (*b* 0.16, SE 0.13, *z* 1.18, *P*=.24).

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- Kocsis JH. *CNS Spectr*. Vol 11, No 12 (Suppl 15). 2006.

- Depression in general
  - s allele (s/l or s/s) associated with 25% risk of depression and perceived stress in coronary heart disease vs. 17% risk of same if l/l.
  - risk of depression associated with the s allele can be reduced by the presence of positive social supports
- Less response to antidepressants (though evidence is mixed)
  - For nortriptyline (which primarily raises norepinephrine)
    - GG NET G1287A genetic variation: 83% response rate
    - s/l (promoter region): 76% response rate
    - l/l (promoter region): 48% response rate
    - l/l (intron region): 30% response rate
  - For SSRI's (which raise serotonin primarily)
    - s/l (intron region): 69% response rate
    - 9% response rate with other variations
  - poorer response to Prozac, Luvox, and Paxil
  - increased adverse effects to serotonin reuptake inhibitors
    - Most recent evidence seen in 7/07 with Celexa (Hu et al, 2007)
  - increased risk of antidepressant-induced mania

- OCD
  - In general
  - Denys et al, 2007: prediction of response to Paxil and Effexor, RCT, DB, 12 weeks, 91 patients, Paxil up to 60 mg and Effexor up to 300 mg
    - Whole group
      - S/L genotype of serotonin transporter polymorphism: 64% response rate
    - Paxil group
      - G/G genotype of the 5HT2a receptor polymorphism: majority of responders

- Effexor group
    - S/L genotype of serotonin polymorphism: majority of responders
- Anxiety
    - PTSD
        - Emory study, 2011: risk of PTSD after trauma associated with s-allele
    - Youth and shyness
        - s/l or s/s: more likely to be extremely shy at 7 years if their mothers had less social support but not if mothers had good social support
        - Youth with l/l tended to be outgoing no matter how much social support their mother had
    - Youth and response to stress (same study as above)
        - s/s: more likely to react poorly to life stresses by developing depression or maladaptive behaviors
        - l/l: shielded from risk
        - s/l: risk falls in the middle
- Bipolar disorder
- Pervasive childhood aggression
- "Failure to use nonverbal communication to regulate social interaction" in youth with autism
- increased temperamental neuroticism (e.g., anxiety, angry-hostility, impulsivity, harm-avoidance)
- suicide attempts
- externalizing behaviors, if family history alcoholism
- greater amygdala neuronal activity in response to fearful stimuli
- selective loss of functional connectivity to from the amygdala to the subgenual cingulate
    - amygdala→ directly to subgenual cingulate → dorsal cingulate→ amygdala
    - amygdala-cingulate connectivity predicts harm avoidance trait
- human infants showed more distress when presented with sudden or novel stimuli, especially if they also lacked the long form of the dopamine transporter.
- lower serotonin levels in monkeys (which was in turn associated with more aggressive and impulsive traits); low serotonin levels in the monkeys with (s) alleles can be normalized if the monkeys are raised by parents instead of peers.
- infant monkeys demonstrate more distress in examination, regardless of rearing condition; they also showed a deficit in orienting to a novel stimulus (only in the peer-raised group).
- in mice: s/l higher ACTH responses to stressful rearing than l/l

- The l allele (or l/l combination) is associated with the following:
    - Increased adverse side effects with SSRI's (e.g., Hu et al, 2007)
    - Temperamental agreeableness
    - Alcohol use
    - Externalizing behaviors if l/l when parental history of antisocial behaviors
    - OCD: Cavalinni, et al, has demonstrated an association between the (l)/(l) allele combination of 17q11 with tics and high scores on the "repeating/counting" factor (in OCD)
    - Autism: higher severity of "stereotyped and repetitive motor mannerisms"
- Difference in the alleles account for only a small portion of the vulnerabilities and strengths discussed above.

- Mice who have a loss of serotonin reuptake function due to removal of both alleles have increased anxiety-like behaviors and exaggerated stress responses (both in terms of behavior as well as hypothalamic-pituitary-adrenal).
- One genetic mutation (I425V) results in increased production of the serotonin transporter, which leads to increased recycling of serotonin in the synapse with subsequent decrease in serotonin availability for neurons.

- 5-HT1a receptor
    - Located on cell body of some serotonergic neuron
        - Inhbits serotonin release via GABA
        - Must downregulate in order for SRI's to work
        - 1a partial agonists hasten downregulation
    - Also located on axon terminal of other (pre-synaptic) serotonergic neurons
        - Control via glutamate the release of
            - Dopamaine, in striatum, VTA
            - Norepinephrine, in locus c
            - Acetylcholine in BF
            - Histamine
        - Meds that bind 1a as direct or partial agonists
            - Buspar (weak)
            - **Trintellix**
            - **Viibryd**
            - **Abilify**
            - **Rexulti**
            - **Vraylar**
            - **Latuda**
            - **Seroquel**
            - Clozaril
            - Gepirone
            - Adoprazine
            - F15063

        - F15599
    - Activation
        - → inhibition of neuron firing rate by serotonin acting on 5HT1a receptors on the neuronal cell body
        - → inhibition of serotonin release
        - →inhibition of serotonin release by 5HT1B/D receptors on nerve terminals
    - Cortisol reduces numbers of 5HT1a receptors
    - Chronic antidepressant use → desensitization of presynaptic 5HT1a, 1b, and 1d receptors.
    - Genetics
        - Genetic absence of 5HT1a receptors DURING DEVELOPMENT (not later)→ increased anxiety behavior in animal adulthood
        - There are two alleles (G or C)
            - In folks with schizophrenia:
                - CC genotype is associated with substantial improvement with antipsychotic medications in negative symptoms
                - Presence of G allele associated with no improvement
                - Presence of GG genotype associated with worsened depressive symptoms
    - BLOCKING or desensitizing/downregulating 5HT1a receptors (and/or 5HT1B/D pre-synaptic autoreceptors)
        - → increased firing rate
        - → increase serotonin release
        - Buspar is a PARTIAL agonist
        - Remeron and Abilify also partial agonists here.
    - A reduction in the mRNA for the serotonin 5-HT1a receptor has been demonstrated in patients with depression.
    - A lower ratio of 5HT1a to 5HT2a activity is associated with greater reactivity of the amygdala to stress.
    - Animals bred to not have the 5-HT1a receptor showed an inability to regenerate hippocampal neurons damaged after irradiation, even after treatment with SSRIs and TCAs.
    - Patients with panic disorder have nearly a third less 5-HT1a receptors in the anterior cingulate, posterior cingulate, and dorsal raphe as compared to normal controls.
- 5HT1b receptor; p11 protein may help facilitate binding of serotonin to 5HT1b post-synaptically
    - on axon terminals
    - also on pre-synaptic dendrites
    - antagonism or partial agonism via PFC increases
        - Dopamine, in VTA
        - Norepinephrine, in LC
        - Acetylcholine, in BF
        - Histamine, in TMN
    - meds that bind there
        - Abilify
        - Saphris
        - Clozaril
        - Seroquel
        - Geodon
        - Trintellix (most potent so far)
        - In development
            - Agonists
                - Anpirtoline
                - CP94253
            - Antagonists
                - GR127935
                - SB-216641
- 5HT1d receptor, 5HT2a receptor polymorphisms might be associated with OCD.
- 5HT2 receptors
    - Activates PLC via G-protein
    - Lithium AND 5HT2 agonism leads to synergistically high c-fos expression, but chronic lithium inhibits PI hydrolysis activation.
    - 5HT2c
    - 5HT2d
    - 5HT2a receptor
        - polymorphism in 5HT2a receptor might be associated with OCD.
        - polymorphism in the SNP rs7997012 gene allele variant is associated with 18% lower risk of SSRI non-response.
        - T/T or T/C (versus C/C) genotypes of T102C polymorphism associated with responsivity to the protective aspects of nurturing mothering
        - Regulates glutamate and GABA
            - Either stimulats glutamate to stimulate other pathways, or
            - Stimulates GABA to inhibit other pathways
            - As such, regulates downstream
                - Dopamine
                - Norepinephrine
                - Acetylcholine
                - Histamine
                - Serotonin
        - BLOCKING 5HT2a→
            - ?antipsychotic effect
            - ?antidepressant effect
            - ?counteracting of sexual dysfunction from SSRI's

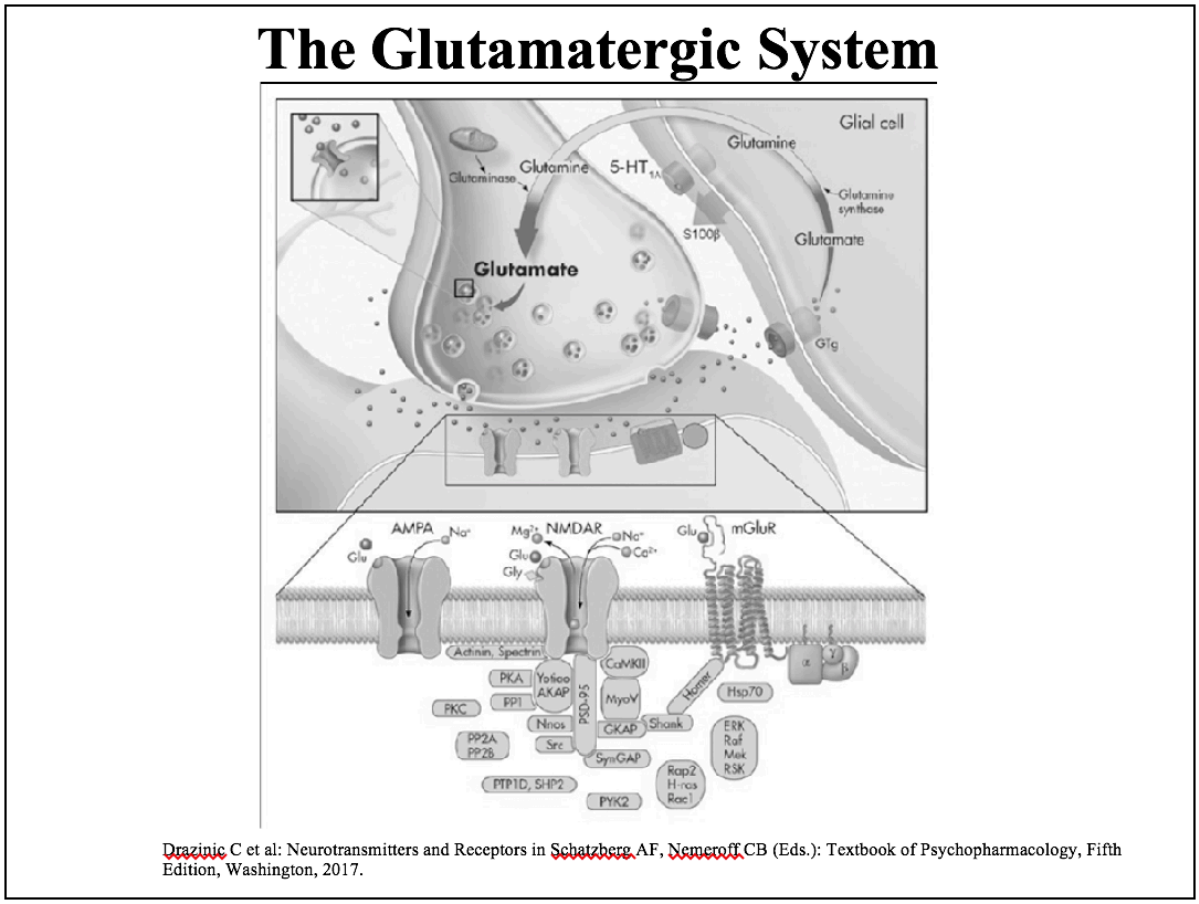
        - Reduction of anxiety
        - Treatment of insomnia
    - 2A blockers
        - Abilify
        - Saphris
        - Clozaril
        - Iloperidone
        - Latuda
        - Zyprexa
        - Invega
        - Risperdal
        - Seroquel
        - Geodon
        - Remeron
        - Trazodone
        - Pimavanserin
- 5HT3
    - regulates via GABA inhibition of glutamate the following (which are increased with meds that block 5HT3 receptors)
        - Dopamine
        - Norepinephrine
        - Acetylcholine
        - Histamine
        - Serotonin
    - so med with 5HT3 blocking greatly increases glutamate firing
    - SSRI without 5HT3 blocking → 5HT3 agonism→ inhibited glutamate firing
        - If add 5HT3 blocker, increase glutamate activity results
    - affects chemoreceptive trigger zone in brainstem mediating nausea and vomiting
    - affects gastrointestinal tract/mobility
    - meds that bind
        - Clozaril
        - Prozac
        - Remeron (blks)
        - Trintellix
        - Tropisteron (blks)
        - Ondansetron (blks)
        - Granisetron (blks)
- Researchers have found a mutant gene that codes for the enzyme tryptophan hydroxylase-2 (on chromosome 12) and results in an 80% reduction in serotonin. It was associated with unipolar depression and treatment resistance to SSRI's.
- Polish researchers have found evidence that anxiety disorders may be linked to a malfunction of serotonin neurotransmission or impaired activity of enzymes metabolizing the catecholamines. A gene allele of the monoamine-A oxidase uVTNR promoter was significantly higher in females with panic attacks and generalized anxiety disorder.
- Neuroticism has been linked to regions on chromosomes 1, 4, 7, 12, and 13; one loci on chromosome 1 corresponds to a region previously shown to influence rodent emotionality (an animal model of neuroticism).
- Glutamate release is increased rapidly by stress; over time glutamate release suppresses serotonergic output from the dorsal raphe nucleus of the brain.
- Lithium enhances tryptophan uptake and has various effects on serotonin metabolism
- Tegretol enhances serotonin levels in the hippocampus
- Depakote and Lamictal have serotonergic properties

- GABA
    - Function
        - chloride ion influx → less excitable, reduced firing rate
        - reduced norepinephrine (NE) function
        - reduced nigrostriatal dopamine release
        - blocks stress-induced activation in dopamine turnover
        - may augment chronic decrease in dopamine turnover seen with antipsychotics
    - Patients with anxiety disorders have been shown to have lower brain levels of GABA and diminished natural benzodiazepine binding.
        - In panic disorder, decreased binding in the insular cortex bilaterally; this was worse in the presence of co-morbid depression
    - GABA and depression
        - Reduced GABA levels in cortex, nucleus, brain stem and hippocampus in animal models of stress and depression
        - Reduced GABA levels in depression; may be related to decreased synthesis of GABA.
        - GABAa receptor antagonists induces learned helplessness behaviors in animal models; GABA injected into brain prevents learned helplessness.
        - Prozac and Celexa increases GABA concentrations, which are decreased in depression, in patients with depression.
        - SSRI's increase the neurosteroid allopregnanolone which facilitates GABAergic transmission.
    - GABA-B receptor
        - Lithium, Depakote, Tegretol, desipramine, Celexa, trazodone, ECT all upregulat GABAb receptors in the hippocampus with chronic (but not acute) administration
    - GABA-A receptor subtypes
        - Binding site for
            - GABA binds to beta unit
            - Benzodiazepines
                - bind between alpha and gamma only on receptors with alpha 1-3
                - augments receptors' responsivity to GABA
            - Lunesta binds to microdomains on gamma unit of receptors with alpha 1-3.
            - Ambien, Sonata
            - Barbiturates
                - directly increases choride influx
                - augments receptors' responsivity to GABA

- Prozac
- Neurosteroids
- Alcohol
  - augments receptors' responsivity to GABA
  - inhibits NMDA
- Depakote and several other anticonvulsants may act, among other mechanisms, via this receptor

- GABA-A alpha 1:
  - 50% of total
  - unbiquitous distribution
  - associated with sleep/sedation, amnestic properties
  - Ambien, Sonata bind to benzo site of receptors with alpha 1 subunits.
- GABA-A alpha 2 and GABA-A alpha 3:
  - 15-20%
  - located in cortex, limbic system (where benzodiazepines, and some anticonvulsants might work to treat anxiety), spinal cord
- GABA-A alpha 3:
  - in RAS, brain stem
  - associated with norepinephrine, serotonin
  - anxiolysis, muscle relaxation
- GABA-A alpha 5: <5%; located in hippocampus; associated with cognition (where benzodiazepines and some anticonvulsants may act to impair cognition)

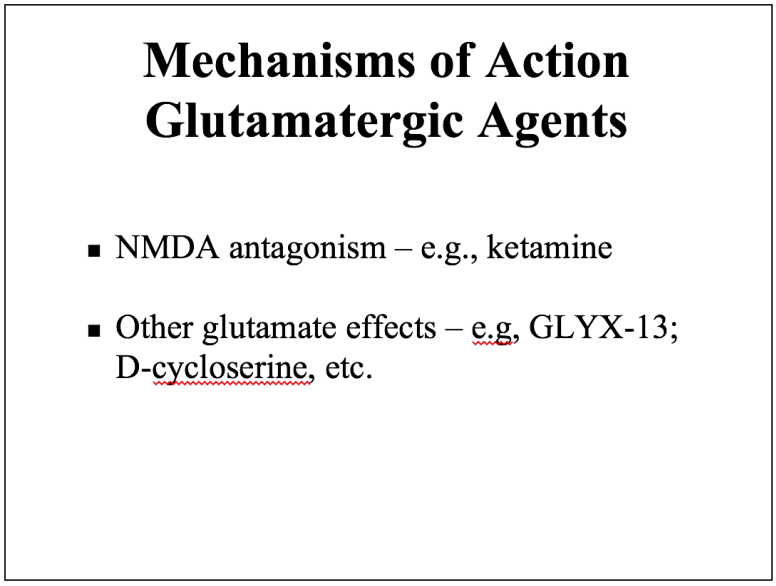
- Glutamate



Drazinic C et al: Neurotransmitters and Receptors in Schatzberg AF, Nemeroff CB (Eds.): Textbook of Psychopharmacology, Fifth Edition, Washington, 2017.

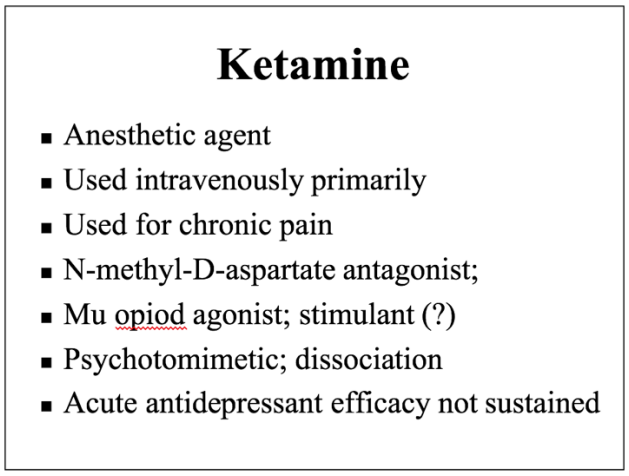
  - General
    - Glutamatergic system or NMDA receptor activity is a primary pathway of neuronal death involved
  - Mood disorders
    - Serum or plasma glutamate
      - Elevated in medicated depressed subjects
      - No baseline abnormality but reduced levels after 5 weeks of antidepressant
      - Elevated in occipital cortex major depression
    - Glycine binding site on NMDA receptors
      - Reduced in suicide victims
      - Reduced in unipolar and bipolar mood disorders
    - NR2C subunit of NMDA
      - Elevated in locus coeruleus in depressed subjects
    - Neuronal nitric oxide synthetase
      - Activated by NMDA stimulation
      - Elevated in locus coeruleus in depressed subjects
    - Glutamate+glutamine+GABA
      - Reduced levels in ACC in unmedicated and medicated unipolar depressed and bipolar disorder
      - Reduced levels in ACC of children with unipolar depression
      - Elevated in unmedicated bipolar

- Glial cells
  - Glial cell loss and reduced glial density in unipolar and bipolar mood disorders
    - DLPFC
    - OFC
    - Amygdala
  - Astrocyte pathology in DLPFC in unipolar depression
  - Decreased glial markers in unipolar and bipolar depression
  - Stress→ decreased uptake of glutamate by glial cells in hippocampus
  - Gliasgenesis and glial cell proliferation impacted by stress
  - Antidepressants enhance the proliferation of both neurons and glia.



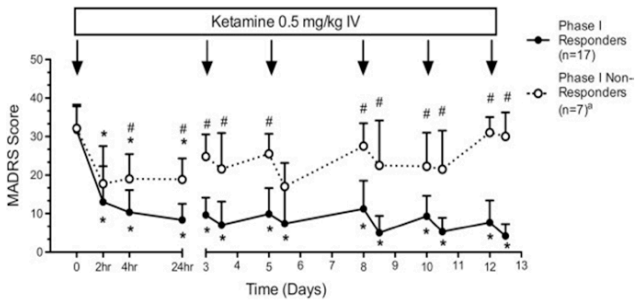
If you block NMDA →disinhibition, leading to surge in release of glut.
D-cycloserine; at 1000 mg/day may augment AD's.
Rapastinol (GLYX-13) works maybe thru glycine site; augments AD"s

- D-cycloserine
  - Partial agonist at glycine site
  - NMDA receptor antagonist at higher doses (at which point it's antidepressant properties kick in)
  - May work via blocking excessive stimulation of ***extra***-synaptic NMDA receptors (and thus increasing synaptic NMDA stimulation and consequent induction of BDNF
- Ketamine/PCP



  - NMDA antagonist via block of NMDA's calcium channel
  - May work via blocking excessive stimulation of ***extra***-synaptic NMDA receptors (and thus increasing synaptic NMDA stimulation and consequent induction of BDNF

Response to Repeated Ketamine Infusions



*p<.05

Murrough JW et al. Biol Psych, 2013.

- 3X/wk iv sustains benefit a bit, but not practical

Intranasal Esketamine vs. Placebo in TRD

- 67 subjects
- 3 doses (28 mg, 56 mg or 84 mg) – 2x/week
- All 3 doses separate significantly from placebo
- Clear dose response

Daley EJ et al JAMA Psychiatry 2018; 75:139-148.

- esketamine is more potent. 2X/wk dosing. On day 1, separation, but 2x/wk for a month, no difference, so not clear. BUT will OPIOID aspects tank this approach? One study, ketamine plus plac or naltrexone, ketamine + naltrexone or placebo at point of relapse: naltrexone not only → no antidepressant benefit but you only get the dissociative anti-NMDA response.

Ketamine and Morphine in OCD

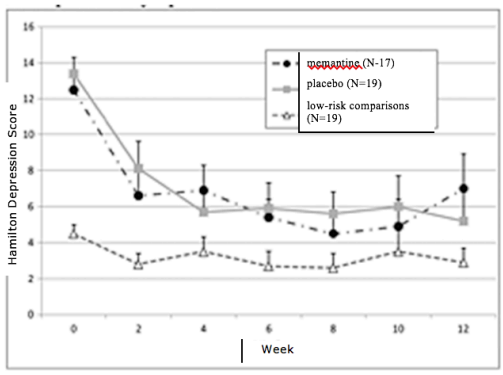
- IV ketamine significantly more effective than placebo in refracratory OCD; effects last one week in some patients (Rodriguez C et al Neuropsychopharm 38: 2475-2483, 2013).
- Oral morphine significantly more effective than placebo in refractory OCD; effects seen the next day and last for 5 days (Koran L et al, J Clin Psychopharm 66: 353-359, 2005).

- Morphine is an NMDA antag also. But ketamine acts as an opioid. Maybe the opioid effect is the primary reason ketamine works.

- Amantadine
  - Antiviral
  - Low-affinitity, non-competitive antagonist of NMDA receptors
  - Sigma agonist
  - Dopamine agonist
  - May work via blocking excessive stimulation of ***extra***-synaptic NMDA receptors (and thus increasing synaptic NMDA stimulation and consequent induction of BDNF

- Memantine

Memantine for Late-Life Depression and Apathy After Disabling Medical Event: HDRS Effect



Lenze et al. Int J. Geriatr Psychiatry, 2012.

  - Other NMDA antags like memantine don't work.
  - Non-competitive antagonist of NMDA receptors at lower (and antidepressant) doses
  - Positive effects in mood (but recent negative RCT in depression)
  - Sigma agonist
  - Affects dopamine receptors
  - Interacts with AMPA and kainate receptors at higher doses
- Lamictal
  - Inhibit excessive release of glutamate through inhibition of sodium and calcium channels and through it's effects on potassium channels.
- Zinc
  - Non-competitive NMDA antagonist via block of NMDA's calcium channel
- Riluzole
  - Suppresses presynaptic conduction of glutamatergic neurons
  - Increases glutamate uptake through astrocytes
  - May have antidepressant and antipsychotic effects

GLYX-13 in Major Depression

- U shaped dose response in rat models and in Phase 2A study
- No ketamine-like side effects
- Phase 2A study – 1,5,10 or 30 mg or placebo; i.v.
- 5 mg. and 10 mg. separated from placebo at day 7 but not at day 14; other doses did not
- Effect size for single dose 0.58

Burch RM: ACNP Annual Meeting, Dec. 2012.

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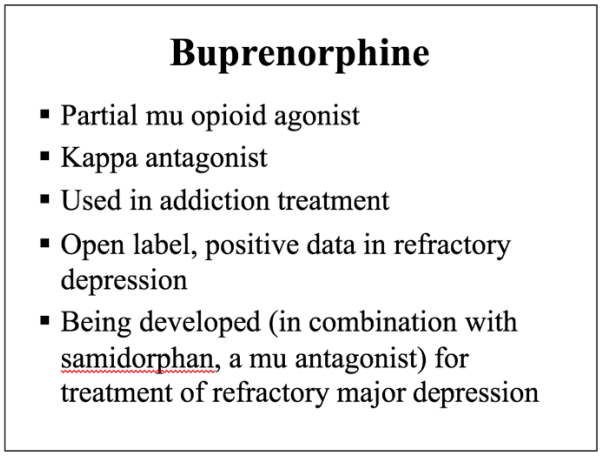
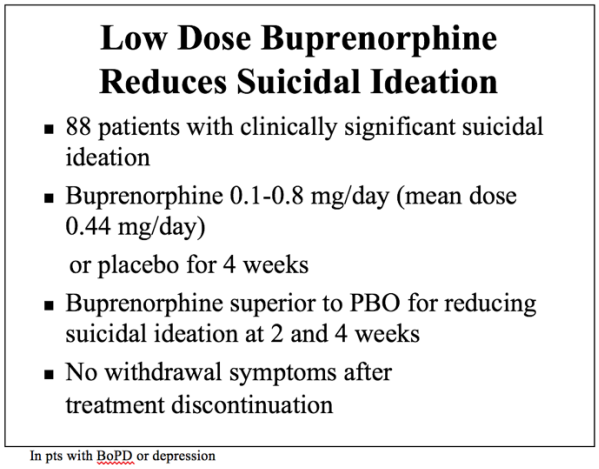
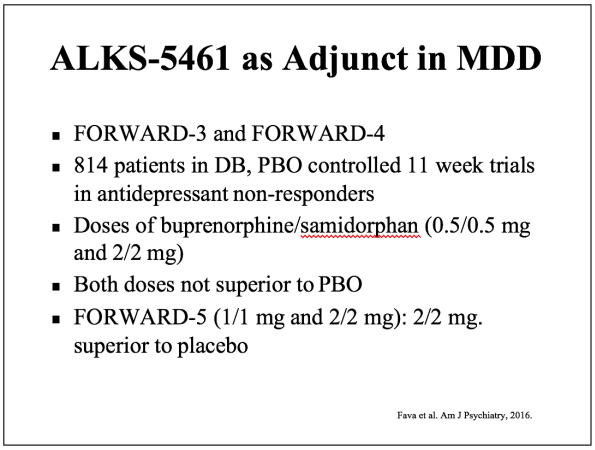
- Opioids
  - 

  - 

  - In pts with BoPD or depression
  - 

  - 2 of 3 Phase 3 studies failed. (buprenorphine plus the mu antagonist). 1 succeeded. FDA is going to be reviewed. Not addictive. No withdrawal
- Other genetic links
  - PLXNA2—anxiety and depression
  - 3p25-26

x

Drawing of patient showing omega sign and Veraguth's fold.

Greden et al, Am J Psychiatry 142(3):348-351, 1985.

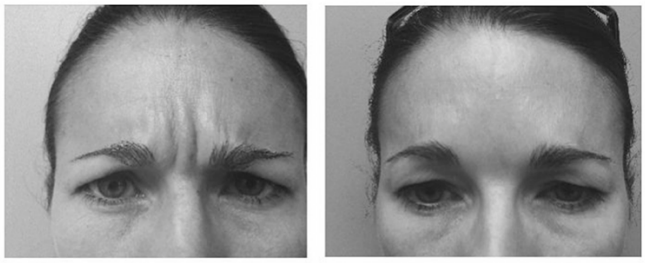
Onabotuliniumtoxin A

- ACh release inhibitor and neuromuscular blocking agent
- Pain indications – chronic migraine and cervical dystonia
- 2 positive RCT's and one positive crossover study in major depression
- Phase II Trial significant at some time points
- Effects of one injection last up to 16 weeks

OnabotulinumtoxinA (OBA) and Frown Expression

(N=30)

Frown Expression before and after OBA treatment



before after

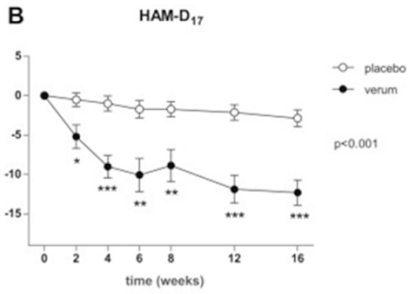
(patient went into remission)

Dose – women 29U
men 40U

Finzi, Rosenthal: ACNP Annual Meeting, 2012.

OnabotulinumtoxinA (OBA) vs. Placebo in Major Depression: HDRS-17

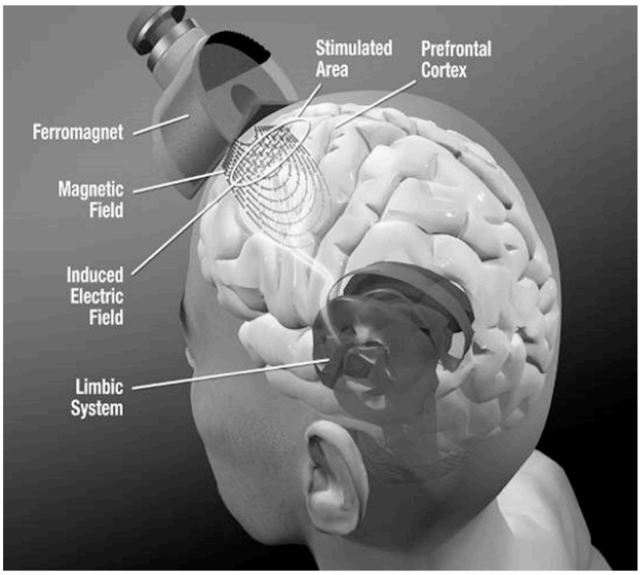
(N=30)



Dose – women 29U
men 39U

Wollmer et al. J Psychiatr Res 46: 574-581, 2012.

What is TMS?
(Transcranial Magnetic Stimulation)



- Faraday demonstrated electric currents can be converted into magnetic fields=electromagnetism
- Electric energy in insulated coil induces MRI-strength magnetic fields
- Magnetic fields pass unimpeded through the cranium for 2-3 cm
- In turn inducing an electric current in the brain
- This stimulates the firing of nerve cells and the release of neurotransmitters such as 5HT, NE, and DA