New Information on the Neuroscience of PTSD & Depression:

how it affects torture treatment & outcomes

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Case Example

- 65-year-old Oromo male
- In the U.S. five years
- Interviewed the first time April, 2011

- Symptoms:
  - Almost no sleep, nightly nightmares, very irritable, very poor concentration and memory, sad much of the time, crying when angry, auditory hallucinations of people calling his name, and feeling that people were trying to harm him.

His Traumas

- During the Communist Regime, he was in prison for two years with frequent torture -- beaten many times to loss of consciousness, had weights tied to his testicles.
- Released, but later imprisoned again
- Son and brother were killed by security guard
- 10 friends were killed
- Saw many dead bodies on the street

Mental Status

- Sad appearing
- Gave very confusing history
- Disoriented to time and place
- Couldn't give president's name
- Couldn't subtract three from 20
- Couldn't remember 3 objects in 3 minutes
- Family (his daughter) didn't allow him to babysit the grandchildren or cook

Diagnosis

- PTSD
- Major Depression with psychosis
- Dementia
- Diabetes
- Hypertension

- Ancient Egyptians thought the source of emotions was the heart.
- The Greeks described various body fluids: blood, phlegm, bile as sources of emotion.
- It has taken historically a long time to understand that the brain not only controls motor and sensory modalities but also emotions. It is not a “black box”.

The brain is very sensitive to the environment

- It responds to both internal and external environment, including trauma.
- It is capable of rapid physiological and affective changes, depending upon the heredity and stress (genes & environment).

Prognosis of the Effects of Trauma

- What came before – experience & heredity
- **What was the Experience of Trauma – Type & Duration**
- What came after the Trauma – Support and brain changes from the trauma

All of us who treat patients need to know how the brain interacts with our work.

Information about the brain helps us in understanding

- How psychotherapy affects the outcome?

Information about the brain helps us in understanding why

- Medicines act differently on various symptoms of PTSD & Depression and need to be tailored to each individual.
- In the future, we should have a better idea of what medicines will work for a particular individual prior to treatment.

Current Information is based on

- Newer study methods,
  including neuroimaging (MRI and fMRI)
- Animal studies, including “knockout mice”
- DNA
- Micro assays
- Viral-mediated gene transfer, among others

- The more we learn about the Brain, the more complicated it seems. . .
- “The human brain is too complicated to be understood by the human brain.”

There are about 100 billion neurons in the brain

Each neuron has about 10,000 connections

Goal: I will provide information on some current thinking about torture and its effects on(PTSD and depression) on and from the brain.

- This information is incomplete and simplistic and does not do justice to the interplay and multiple connections within the brain.
- The purpose is to provide some understanding of the effects of trauma and torture on the brain and to help clinicians better understand their patients

Topics will be

- The Amygdala
- The Locus Ceruleus
- The Hippocampus
- The Serotonin Transporter Gene
- Psychiatric pharmacogenomics

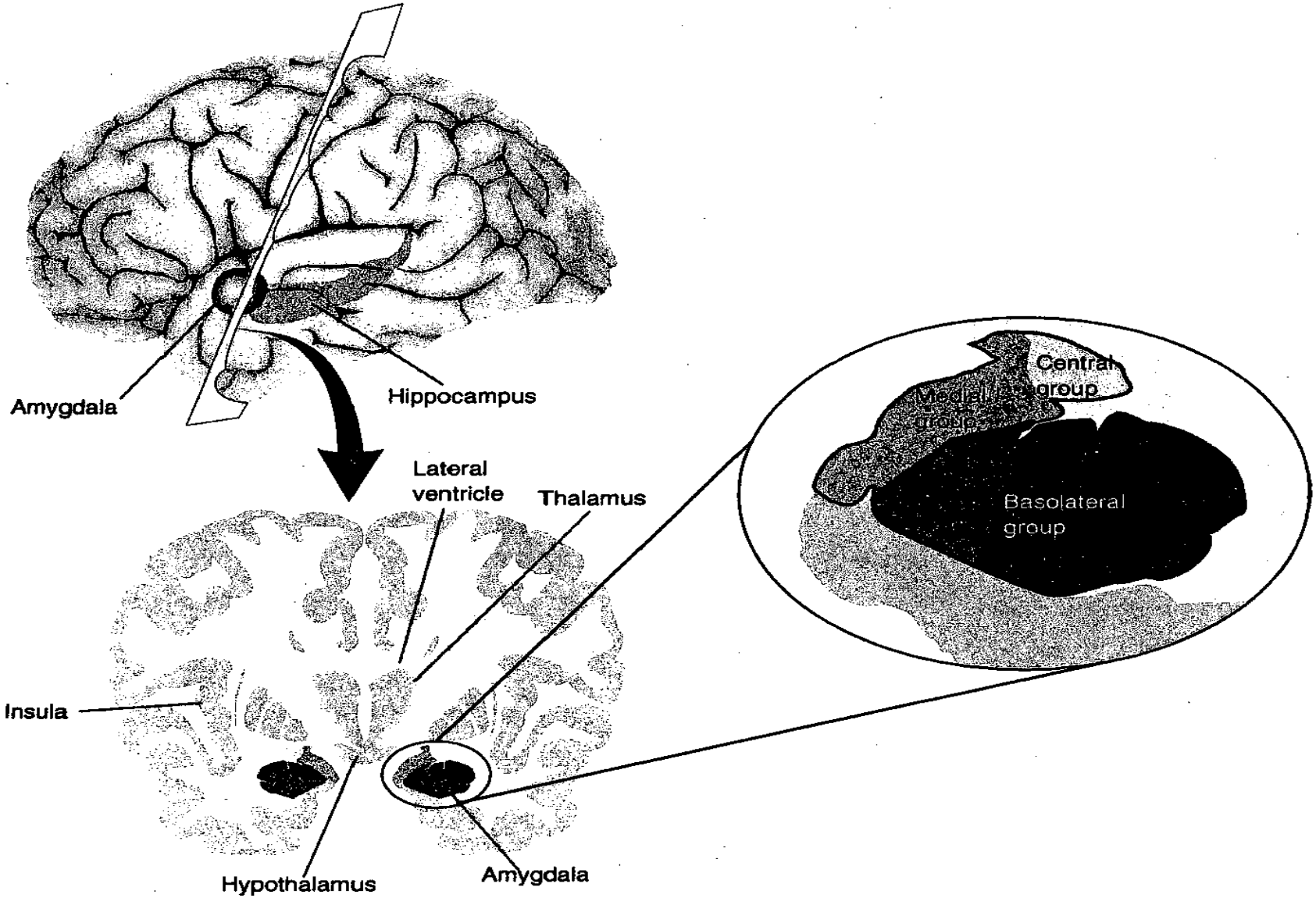


FIGURE 2.6 ● The location and groups (often called *nuclei*) of the amygdala

The Amygdala

- Assigns emotional significance to current experiences.
- One's sensation of anxiety results from projections from the amygdala.
- Electrical stimulation of the amygdala releases feelings of fear and autonomic nervous system responses associated with fear.
- Functional imaging shows activation of the amygdala during exposure to fearful stimuli.

Amygdala & Prefrontal Cortex

- One theory of PTSD is that there is impaired fear extinction from the amygdala. The inhibiting of the fear reaction is through connections from the prefrontal cortex, which may be impaired in PTSD.

- Increasing the inhibition of the amygdala through the prefrontal cortex may explain why psychotherapy is effective.

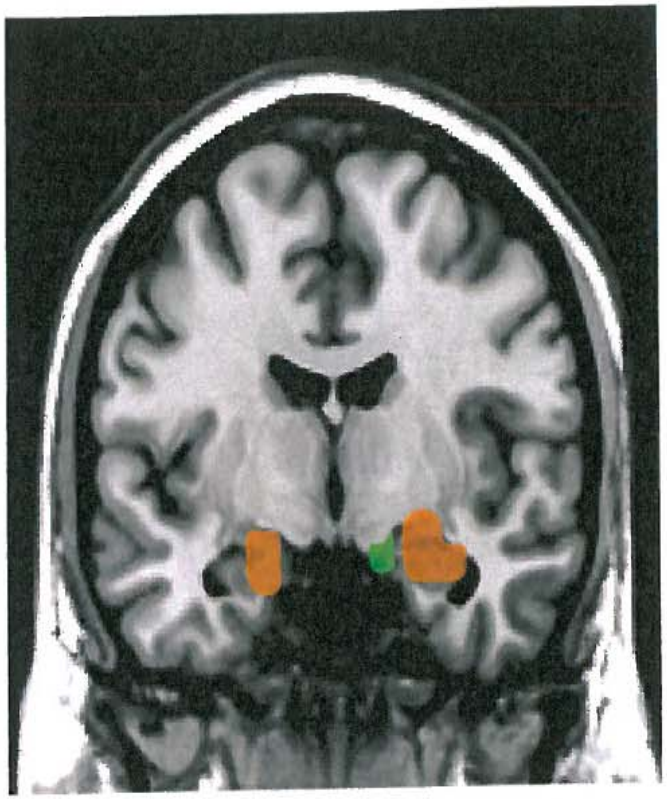


FIGURE 23–1. Combined results from two functional magnetic resonance imaging studies in normal subjects in which emotionally arousing images were presented extremely briefly prior to a longer presentation of a neutral image, resulting in masking of the briefly presented images. Although the subjects had no conscious awareness of the masked images, the amygdala was activated by both fearful faces[2] (*gold*) and angry faces[3] (*green*), but not by happy or neutral faces.

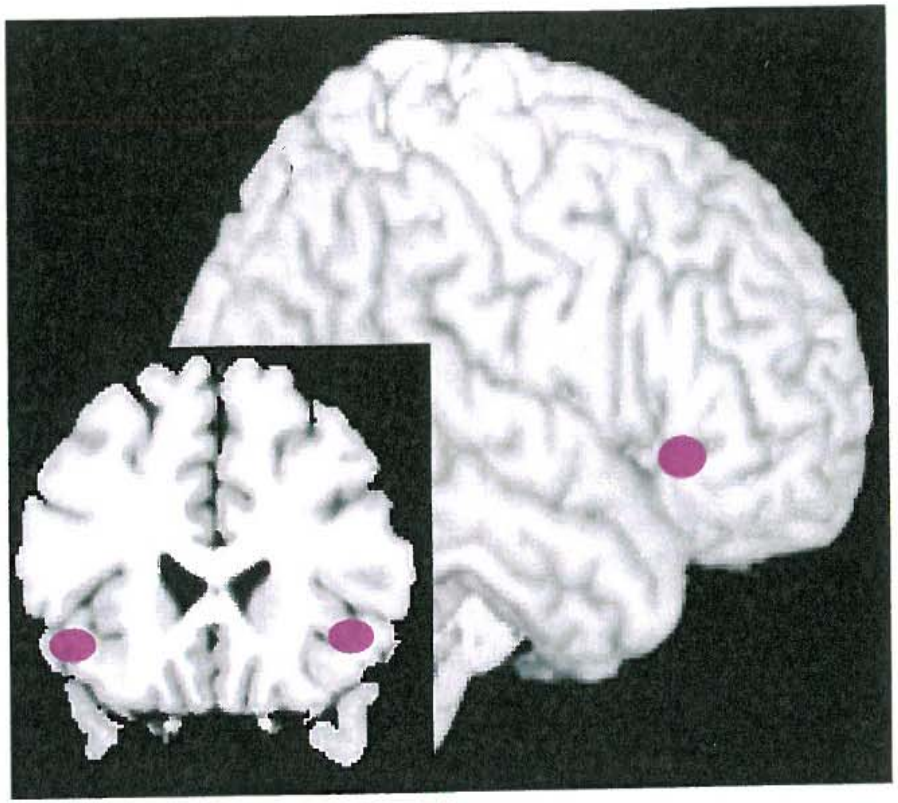
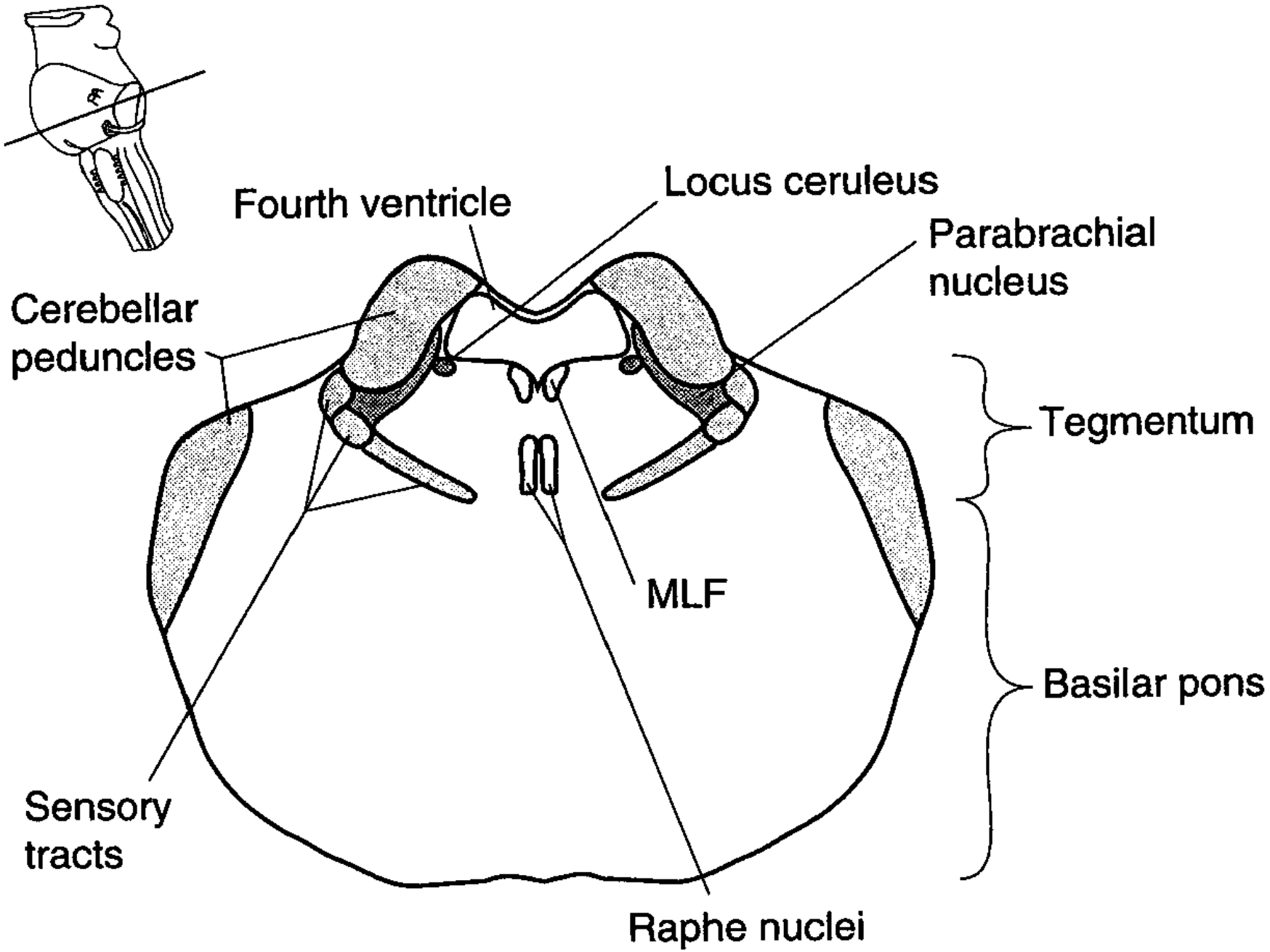


FIGURE 23–2. Combined results from two functional magnetic resonance imaging studies in normal subjects that support top-down modulation of emotions by prefrontal cortex.[4,5] Activation in the amygdala was strong with a simple matching task using emotionally arousing pictures (not shown). Tasks requiring conscious evaluation of the same pictures evoked stronger responses in ventral prefrontal cortex (*pink*) that correlated negatively with activity in the amygdala.

Amygdala continued

- There is considerable evidence that the antibiotic D-Cycloserine (a NMDA receptor agonist) facilitates fear extinction with or without exposure therapy.


Fourth ventricle
Locus ceruleus
Parabrachial nucleus
Cerebellar peduncles
Tegmentum
MLF
Basilar pons
Sensory tracts
Raphe nuclei

Locus Ceruleus

- A small group of neurons located in the pontine area of the brain are a rich source of the neurotransmitter norepinephrine.
- Fibers from the locus ceruleus affect the amygdala, hippocampus, and frontal cortex.

Locus Ceruleus CONTINUED

- The locus ceruleus in times of chronic stress increases arousal and anxiety by releasing Norepinephrine.
- Norepinephrine is thought to be disturbed in PTSD leading to hyper arousal symptoms.
- Drugs known to block norepinephrine are Clonidine, Prazosin, and Doxazosin have been used to reduce nightmares, probably related to the hyperarousal during sleep.

Locus Ceruleus Continued

- In Rodents, other drugs have been found to decrease norepinephrine, including Zyprexa and Seroquel, but not Haldol.

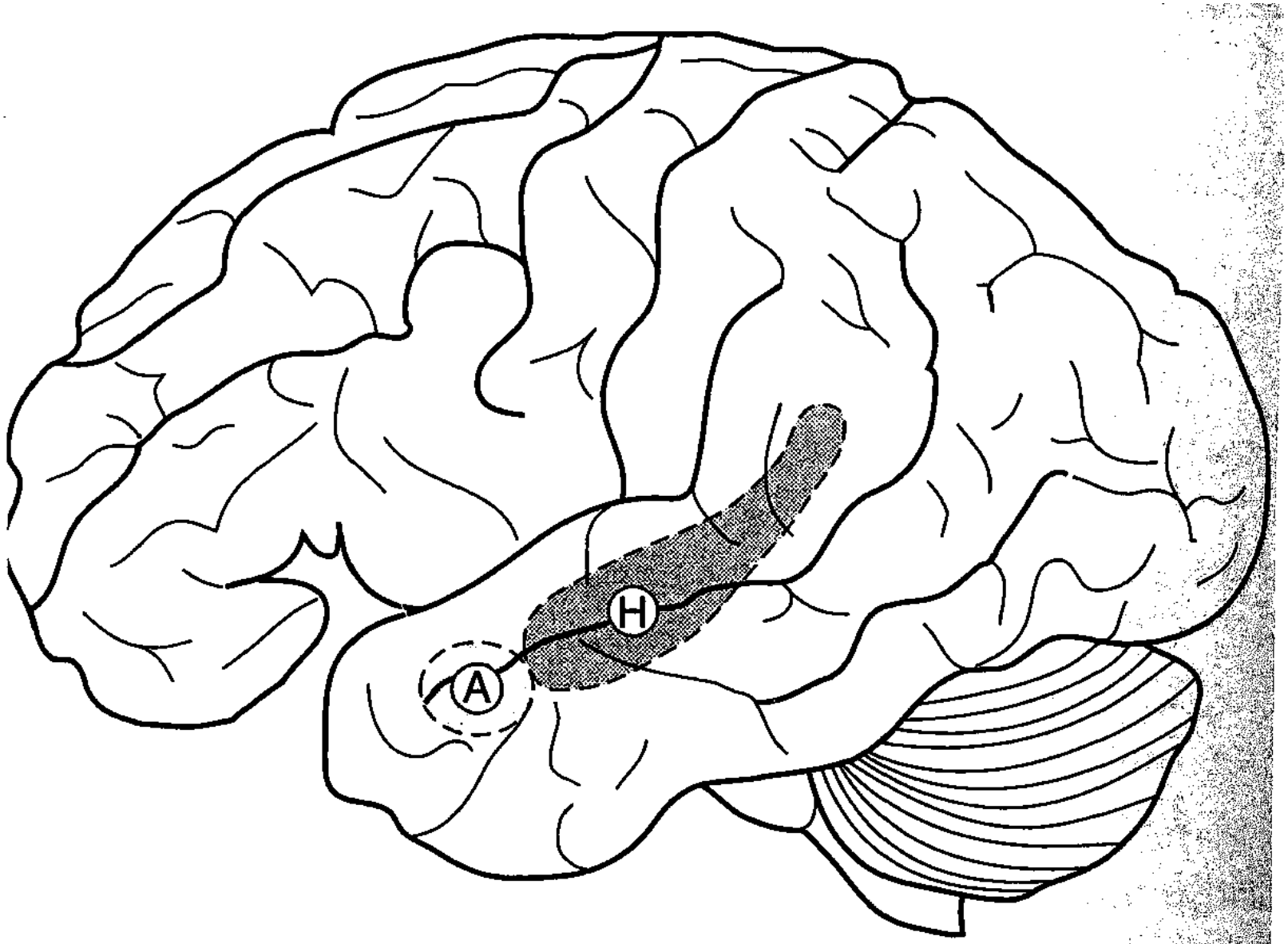


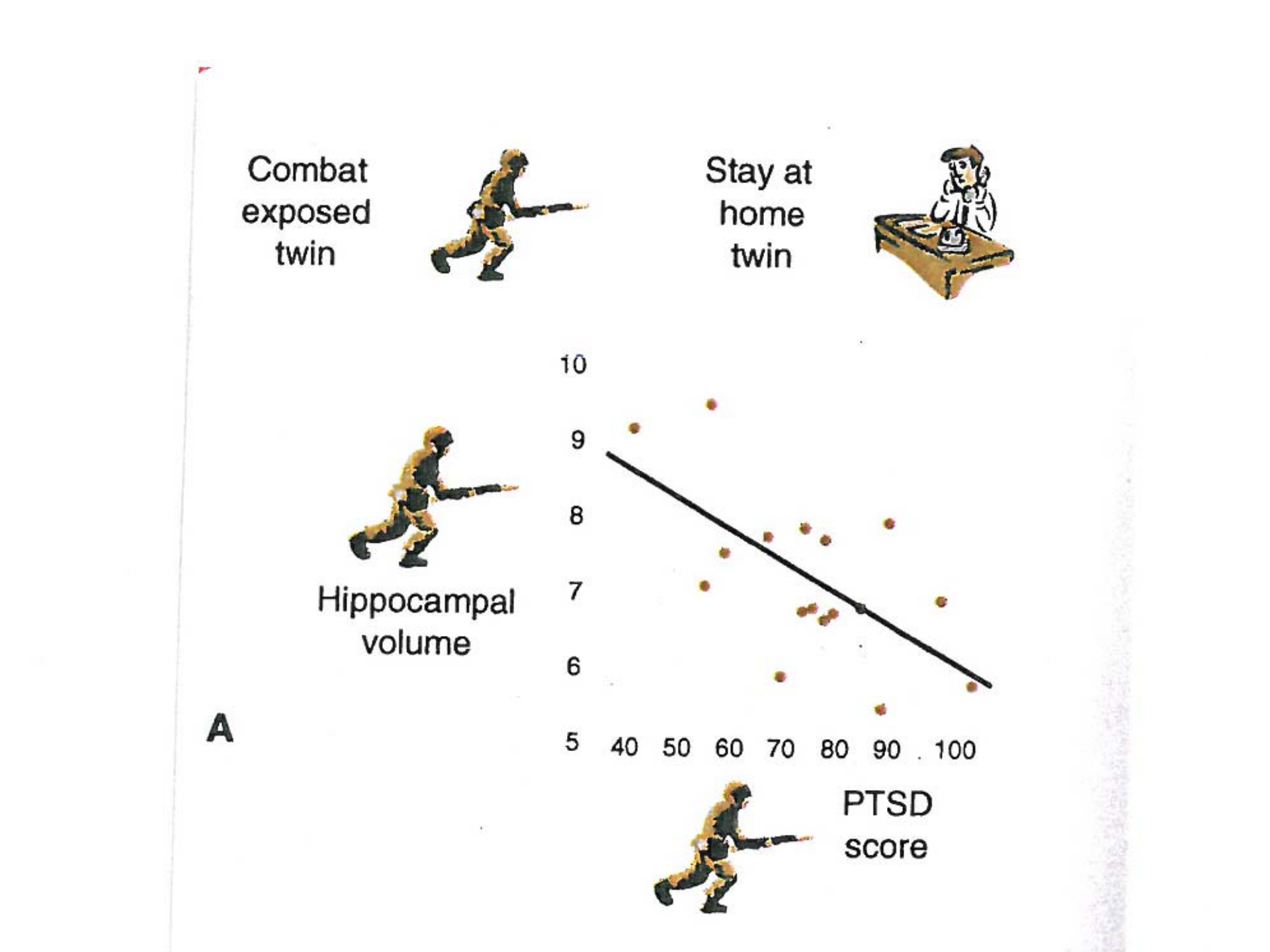
Figure 11.1. The approximate location of the amygdala (A) and hippocampus (H) in the temporal lobe is indicated. Compare with Figure 2.2.

The Hippocampus

- The Hippocampus is located within the temporal lobes and connects with the Amygdala and the Frontal Cortex.
- It is involved in the formation and the organization of memory and links the emotions to the memories.
- Damage to the Hippocampus results in profound difficulty in forming new memories and learning new material

Hippocampus CONTINUED

- Memory Impairment is the best replicated cognitive problem associated with PTSD.
- Many studies have shown a smaller volume of the Hippocampus in PTSD patients.
- Other studies have shown that a smaller Hippocampus may precede trauma and may be a predisposing factor in PTSD.


Combat exposed twin
Stay at home twin
Hippocampal volume
10
9
8
7
6
5
40
50
60
70
80
90
100
PTSD score
A

Hippocampus CONTINUED

- There is some evidence that some antidepressant drugs (SSRIs and Imipramine) may improve the total mass of the Hippocampus volume by increasing BDNF (Brain derived neurotropic factor) and may increase immediate memory recall.

Serotonin Transporter Gene

- This gene encodes Serotonin transporter (re-uptake) comes in several forms:
  - Short allele (ss)
  - Long allele (ll)
  - Mixed (sl)

The presence of ss in individuals does not cause PTSD, but it greatly increases the odds when accompanied by trauma.

Serotonin Transporter Gene:

CONTINUED

- In Rwandan Refugees, PTSD approached 100% when refugees were exposed to extreme trauma.

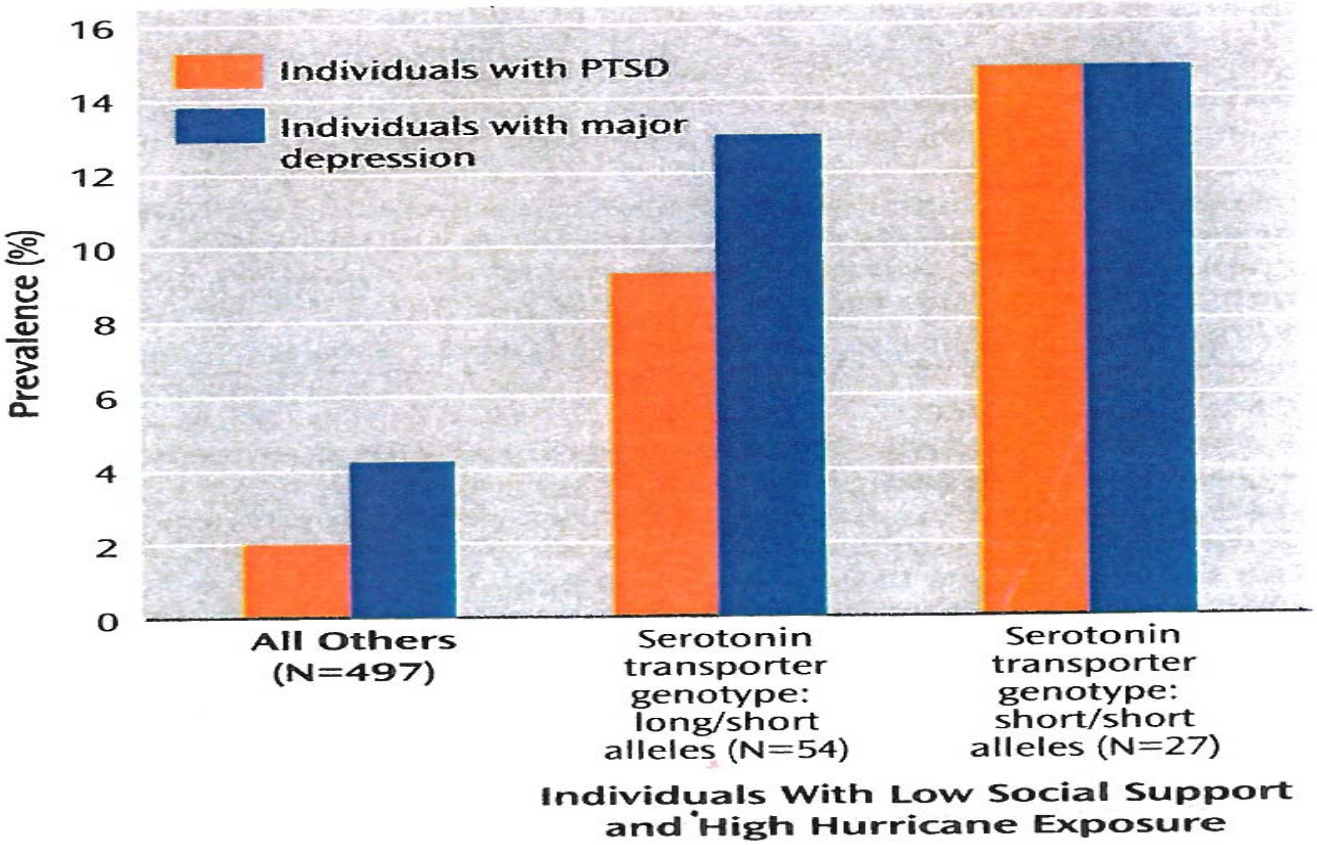
- Persons with ss were at high risk for PTSD, even after few traumatic events.

Serotonin Transporter Gene

continued

- Many studies about the Serotonin Transporter gene help explain the difference and resilience after trauma
- And demonstrate gene – environment interaction.

FIGURE 1. Prevalence of Posthurricane Posttraumatic Stress Disorder and Major Depression Diagnoses by Serotonin 5-HTTLPR Genotype, Level of Social Support, and Level of Hurricane Exposure in Adults Exposed to the 2004 Florida Hurricanes



Psychiatric Pharmacogenomics

- In any individual, there is a gene – drug interaction which accounts for the success or failure of various psychotropic drugs.

- Pharmacogenomics is the study of how an individual's DNA affects medication response.

Psychiatric Pharmacogenomics

CONTINUED

- Cytochrome P-450 (2D6) enzyme is one of many enzymes involved in metabolizing psychiatric drugs.
- There are polymorphic expressions of the 2D6 alleles indicating that there are poor metabolizers, normal metabolizers, and ultra fast metabolizers of medicine.

Psychiatric Pharmacogenomics

CONTINUED

- Poor metabolizers could get a toxic level of a drug since it is slowly metabolized, while an ultra fast metabolizer may not get a therapeutic effect.

- It is now possible to get an enzyme test for common genes involved in the metabolism of medicine, thus taking the guesswork out of prescribing new medicines (test is still very expensive).

■ DRUGS METABOLIZED BY 2D6

Antidepressants

Tricyclic antidepressants[1]

- Amitriptyline
- Clomipramine
- Desipramine
- Doxepin
- Imipramine
- Nortriptyline[2]
- Trimipramine

Other antidepressants

- Fluoxetine[3]
- Fluvoxamine[3]
- Maprotiline[3]
- Mirtazapine[3]
- Nefazodone
- Paroxetine
- Sertraline
- Trazodone[3]
- Venlafaxine[3]

Antipsychotics

- Chlorpromazine
- Clozapine[4]
- Fluphenazine[3]
- Haloperidol[3]
- Perphenazine[3]
- Quetiapine[3]
- Risperidone[3]
- Thioridazine[3]

Other psychotropics

- Aripiprazole
- Atomoxetine

Other drugs

Analgesics

- Codeine[5]
- Hydrocodone
- Lidocaine[2]
- Methadone[2]
- Oxycodone
- Tramadol[6]

Cardiovascular drugs[3]

- Alprenolol
- Bufuralol
- Carvedilol
- Diltiazem
- Encainide
- Flecainide
- Metoprolol
- Mexiletine
- Nifedipine
- Nisoldipine
- Propafenone
- Propranolol[7]
- Timolol

Miscellaneous drugs

- Amphetamine
- Benztropine[2]
- Cevimeline
- Chlorpheniramine
- Delavirdine[2]
- Dexfenfluramine
- Dextromethorphan[8]
- Donepezil[2]
- Indoramin
- Loratadine[3]

CYP2D6 Enzyme

- The Cytochrome P-450 – CYP2D6 enzyme has more than 50 distinct variant alleles which affect metabolization.
- The Majority of white Europeans are extensive metabolizers. (5-9% are poor metabolizers)
- Up to 70% of East Asians carry a distinct allele (CYP2D6 +10) which make many East Asians slow metabolizers.

CYP2D6 Enzyme

continued

- Mexican Americans and Sub-Saharan Africans are more likely to be slow metabolizers (CYP2D6 +17)

- Ultra-rapid metabolizers are highly prevalent among Ethiopean (29%), Arabs (19%), Ethiopean and Sepharder Jews (13 to 18%, respectively)

__ Lin, Psychiatric Times (2012)

Drugs Metabolized by CYP2C19 Enzyme

- Diazepam
- Omerprazole
- Citalopram
- Imipramine
- Propanolol
- Amitriptyline
- Clonipramine

2C19 Enzyme – Poor Metabolizers

Population	% of Population WHICH ARE POOR METABOLIZERS
African American	18
Chinese (China)	17.3
Filipino	23.6
White American & European	3 – 6
Indonesian	15.4
Japanese	22

1. Take Home Messages:

- Some failure of extinction of traumatic memories may be due to an overactive amygdala or an underactive prefrontal cortex.
- D-Cycloserine may help in the extinction of traumatic memories.

2. Take Home Messages:

- Norepinephrine from the locus cereleus causes hyper arousal and sleep disturbances with nightmares.
- This can be helped with Clonidine, Prazosin, and perhaps Seroquel.

3. Take Home Messages:

- Memory problems are very common after trauma and may relate to a smaller Hippocampus.
- This may explain why many PTSD patients have much difficulty learning new information.

4. Take Home Messages:

- The ss polymorphism of the Serotonin Transporter gene may explain why some people are particularly vulnerable to PTSD and depression,
- While others (ll) seem resilient.

5. Take Home Message:

- In the future, pharmacognomics may help us make more wiser and safer choices of medicine.

Case History Follow UP

- Last visit 2/6/2012
- Had been followed with supportive psychotherapy and medicine
- With additional information given from daughter
- No Insurance
- Medicine: Fluoxetine (Prozac) 40 mg. daily
- Doxazosin (similar to Prazosin) 8 mg. daily
- Haldol 1 mg. hs

Current Symptoms

- Sleeping all night
- Few nightmares
- No anger

  - Current Mental Status
  - Oriented to time and place
  - Could do serial threes
  - Knew President's name
  - Affect markedly brighter

Current Diagnosis

- Markedly improved PTSD & Depression
- No signs of Dementia

Why Improved? Psychotherapy

- The therapeutic relationship gave the person confidence in taking the medicine and
- Hope that situations in his life could improve and his symptoms could be reduced.

- Education about his trauma and his reactions to the trauma provided some cognitive understanding and control of his situation (perhaps by the prefrontal context inhibiting the amygdala).

Why Improved? Medicine

- Fluoxetine improved Depression through Serotonin mechanisms and probably improved the effectiveness of his hippocampus by increasing its volume and therefore improving memory.
- Doxazosin (similar to Prazosin) cut down Norepinephrine in the locus cereleus, decreased nightmares, and probably inhibited the amygdala hyperarousal and therefore his fear response.
- Haldol decreased hallucinations and delusions through dompamine mechanisms and probably reduced agitation.