

Neurobiology of Anxiety, Panic, and Fear: Where are we going?



Neural pathways involved in fear, panic
and anxiety

Nazan Aydın MD

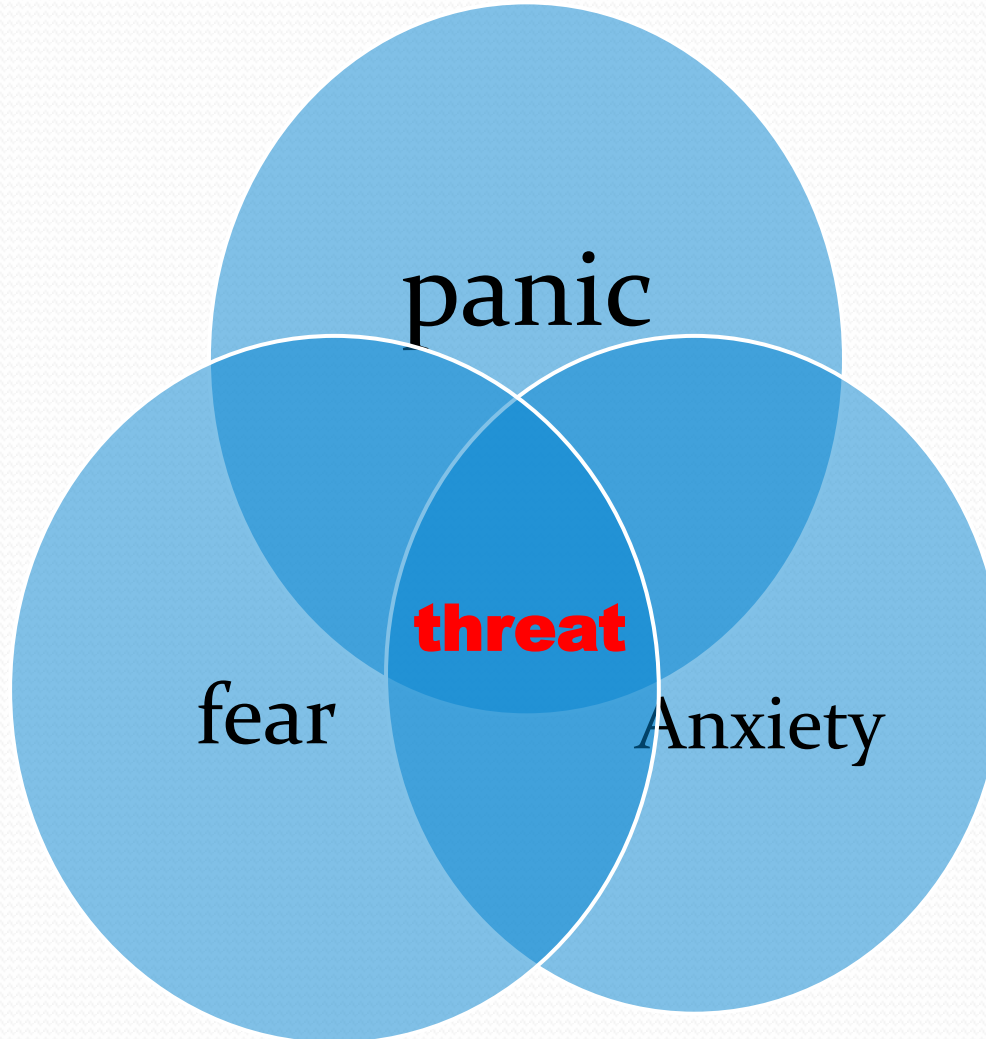
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General outlines

- Background
- Fear Network
- Experiment
- Results
- Conclusion





Correlation among defense strategies, anxiety-like emotions and their disorders.

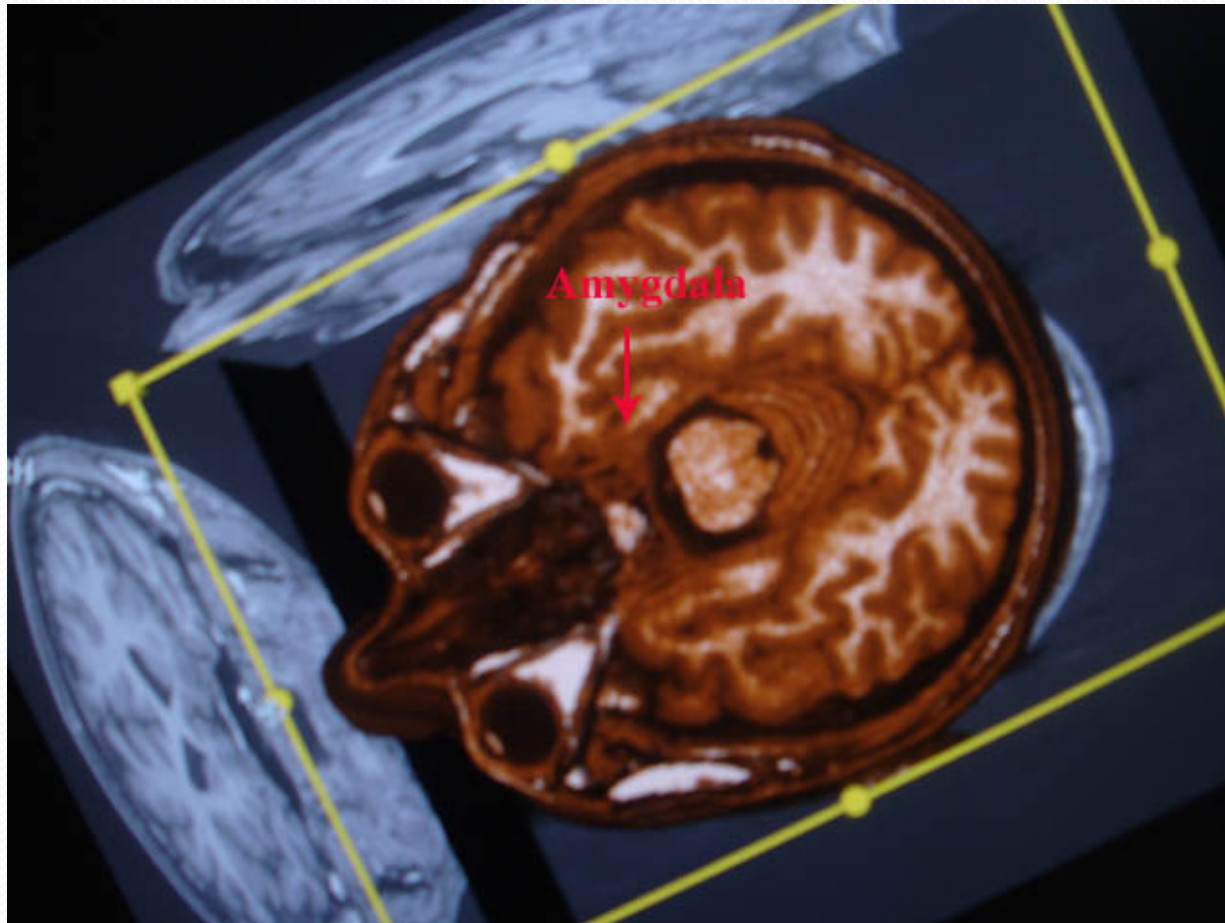
Danger source	Defense strategy	Critical brain structures	Emotion	Pathology
Potential (Conflict)	Risk Assessment (Behavioral inhibition)	Septum-Hippocampus Amygdala	Anxiety	GAD
Conditioned stimulus	Freezing behavior	Amygdala, ventral PAG	Anxiety	Anticipatory
Conditioned stimulus	Avoidance	Amygdala	Learned fear	Specific phobias
Distal	Escape	Medial hypothalamus	Innate fear	
Proximal	Flight / Freeze	Dorsal PAG	Panic	Panic disorder

GAD: generalized anxiety disorder; PAG: periaqueductal gray matter. Modified from Deakin and Graeff (1991) and Graeff (1994).



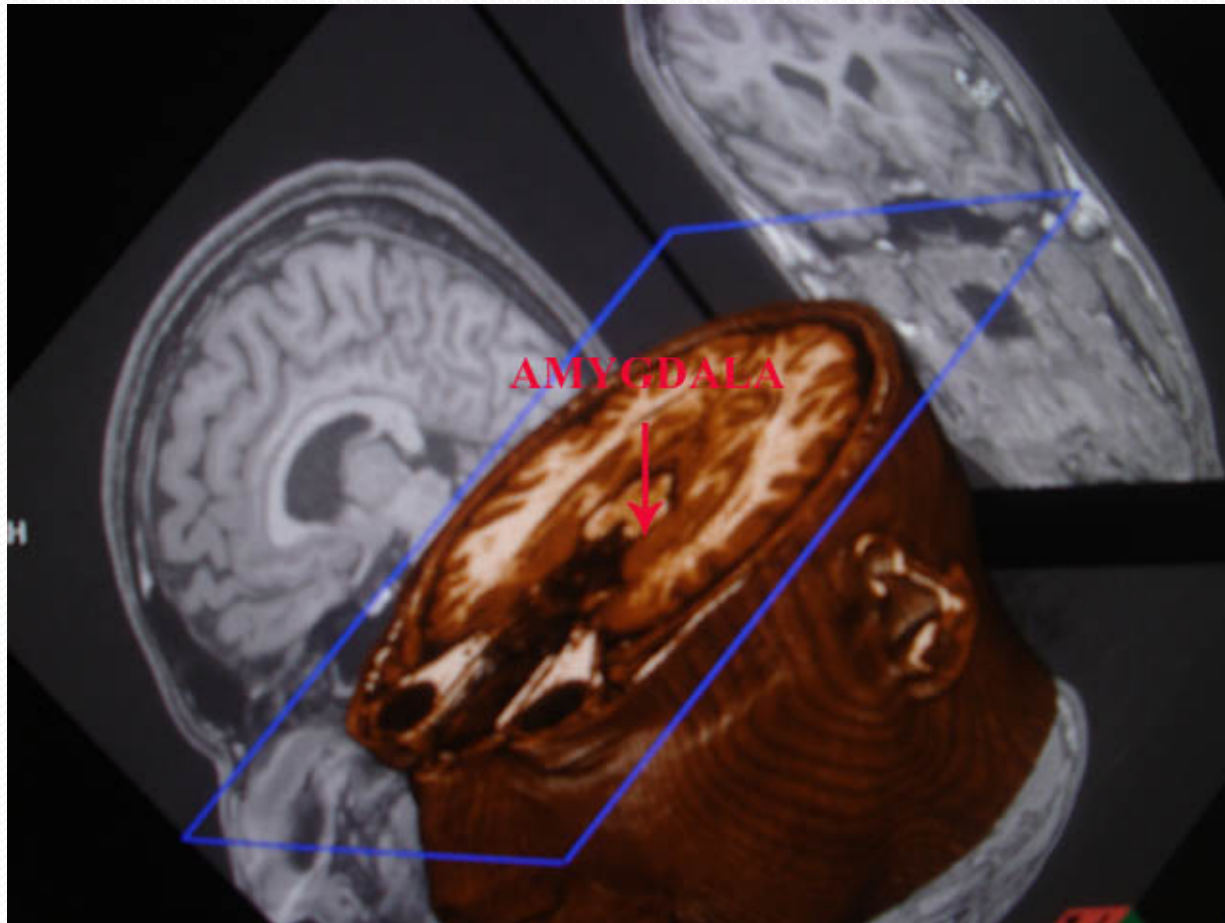


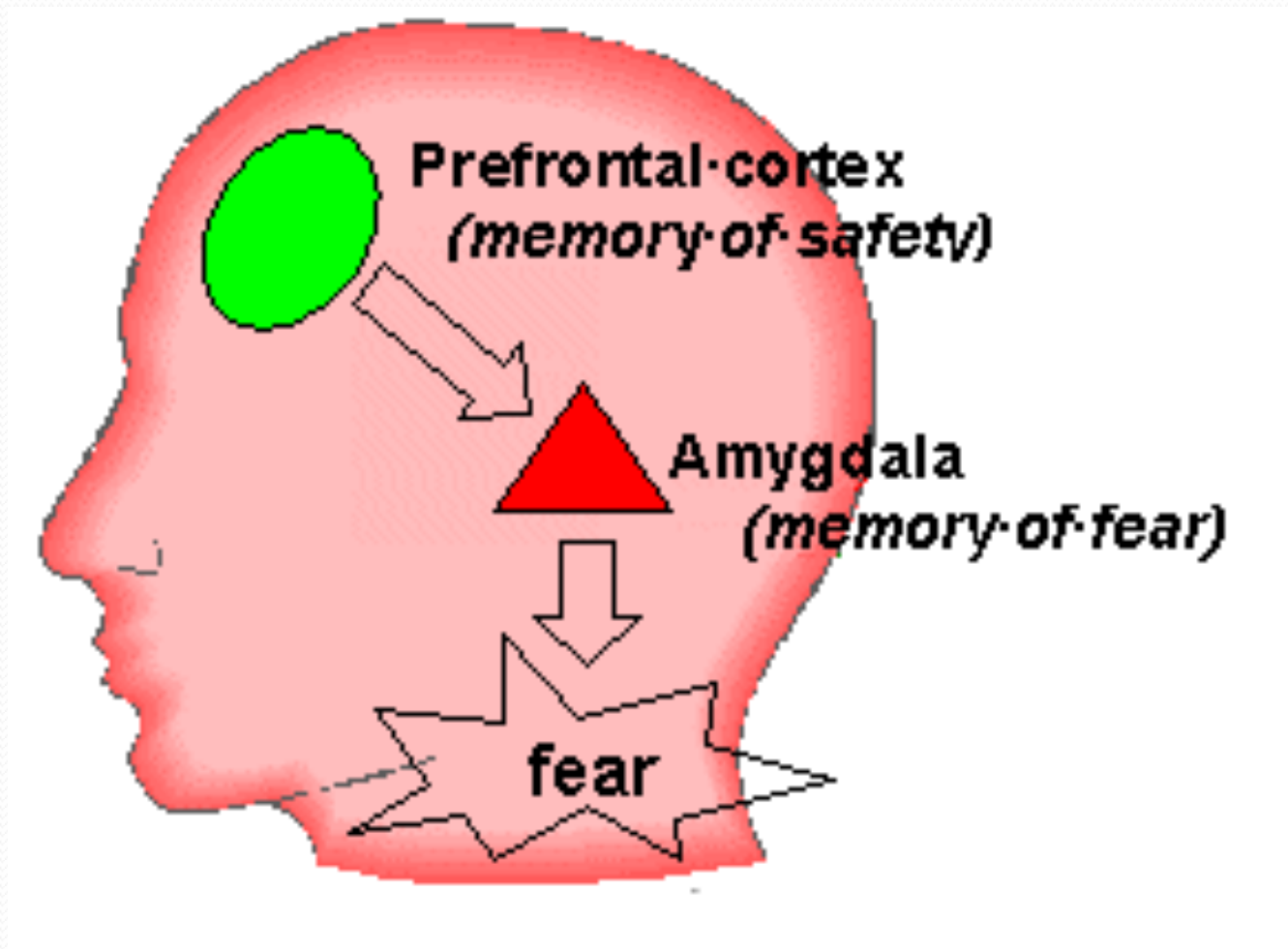
Amygdala





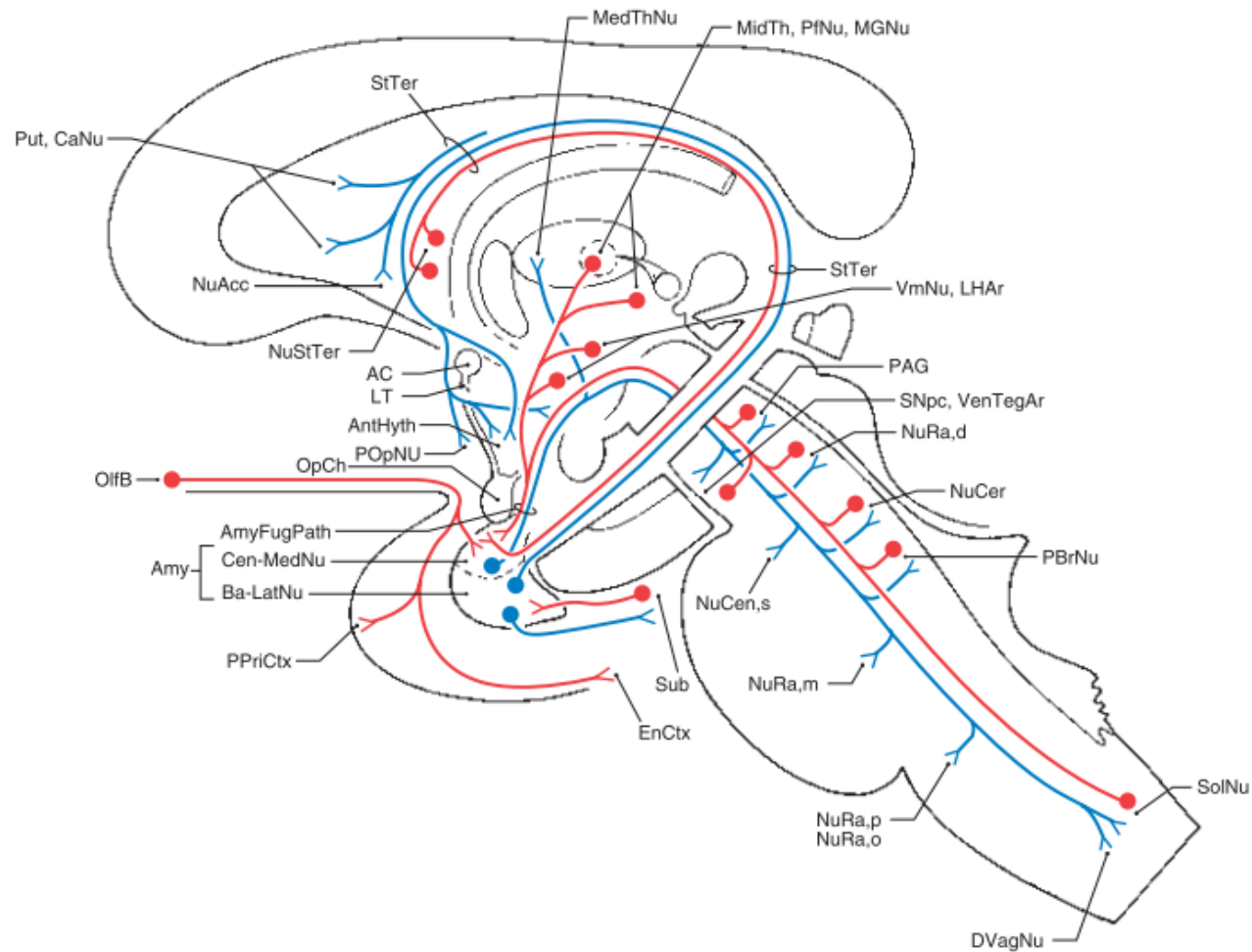
Amygdala

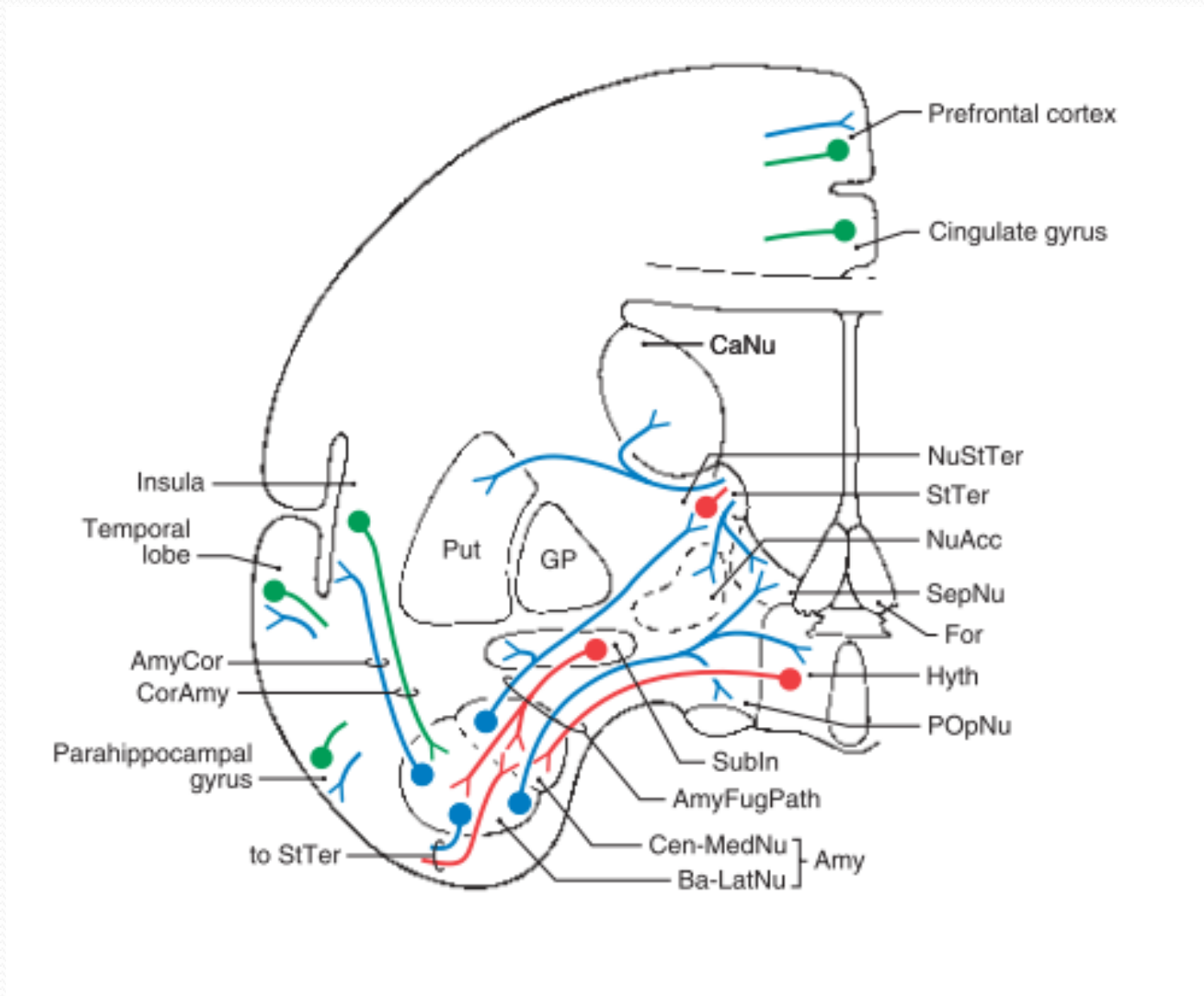




Amygdala

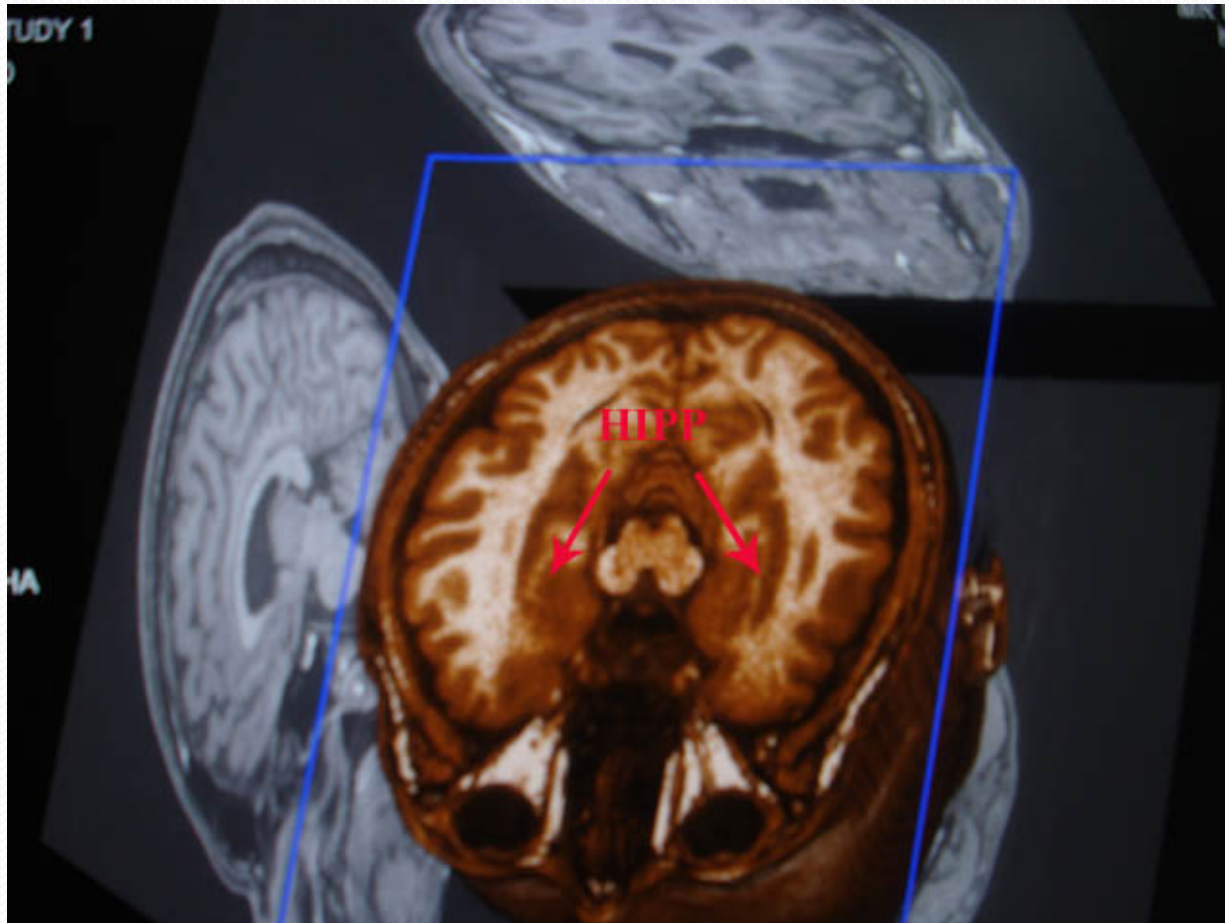
Amygdaloid Connections





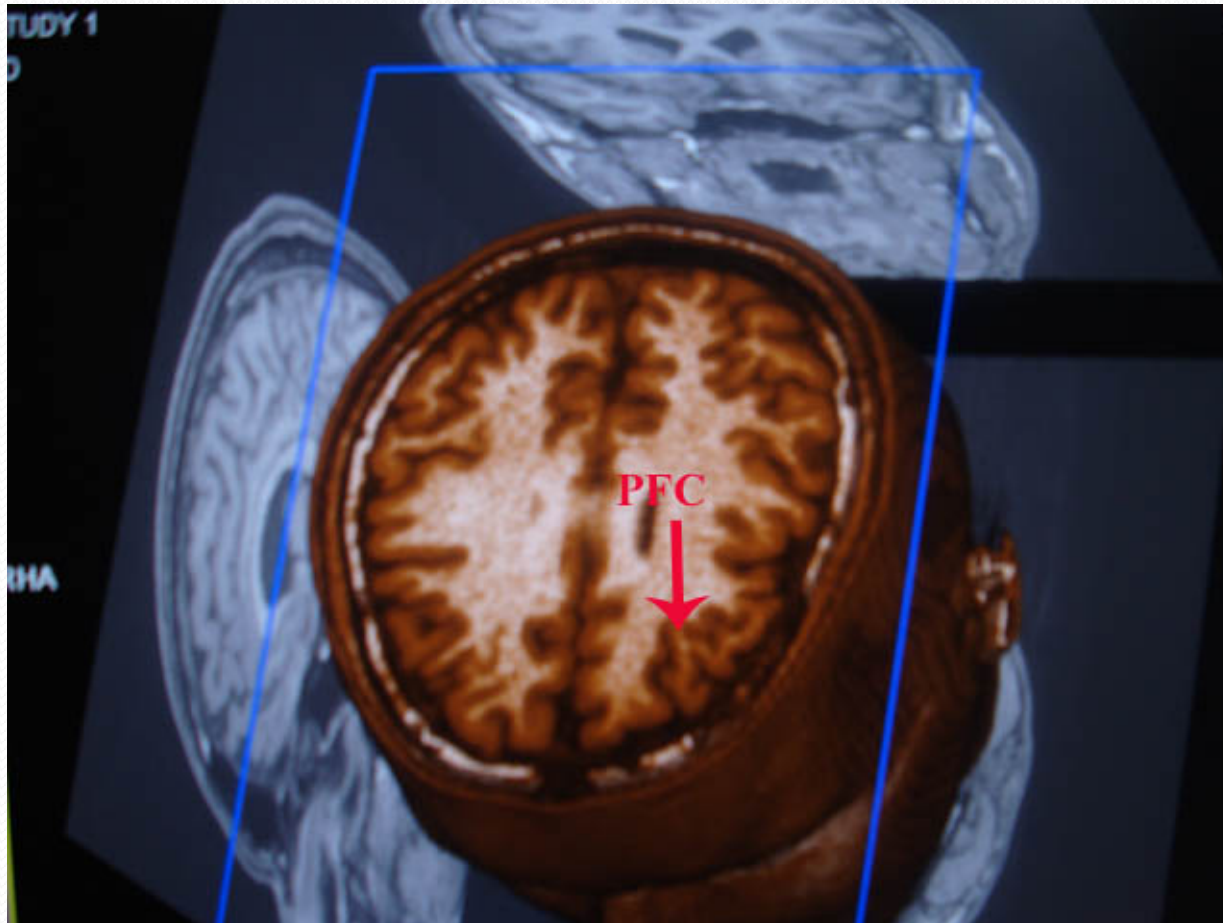


Hippocampus



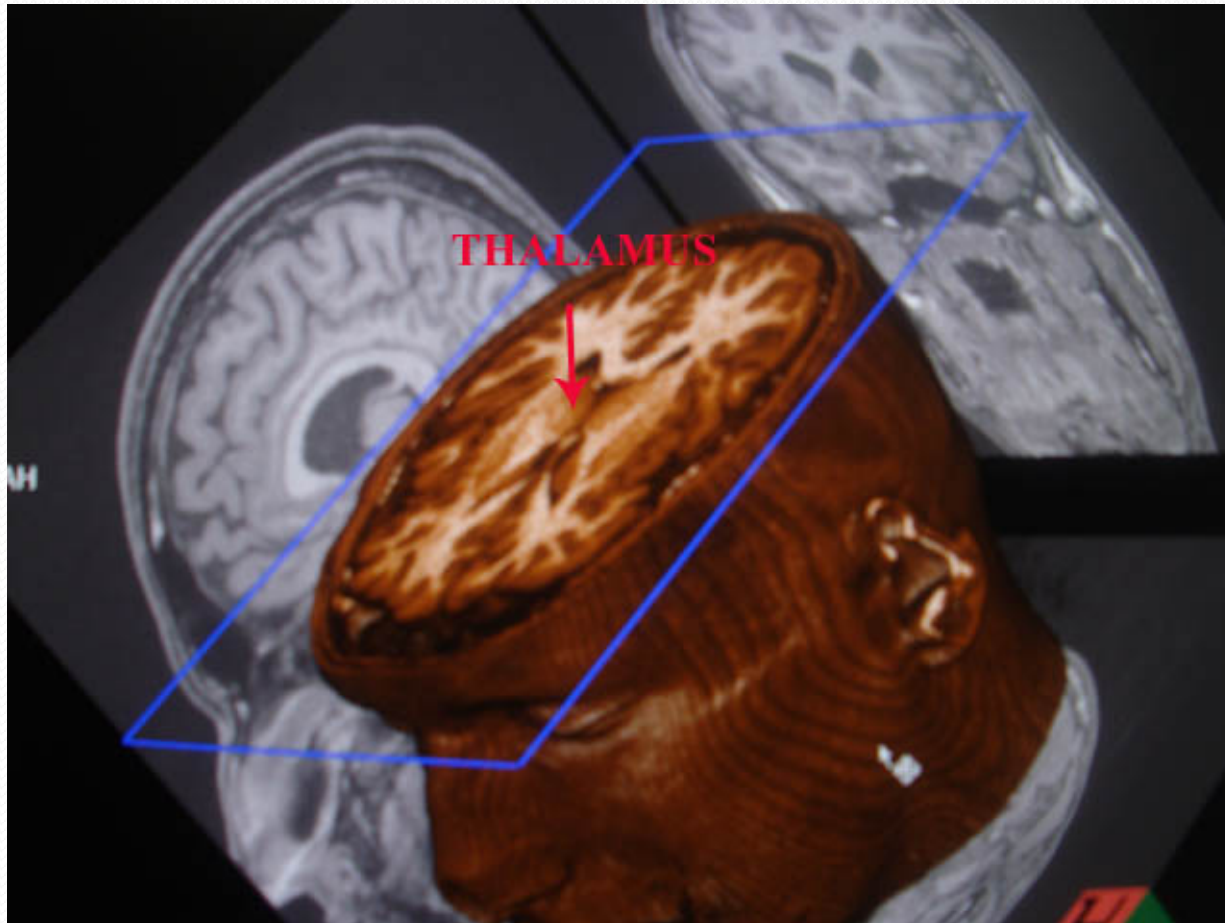


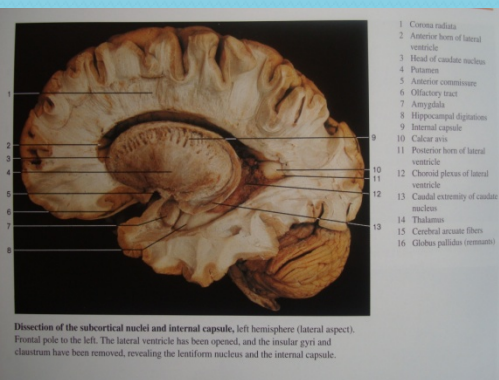
Prefrontal Cortex



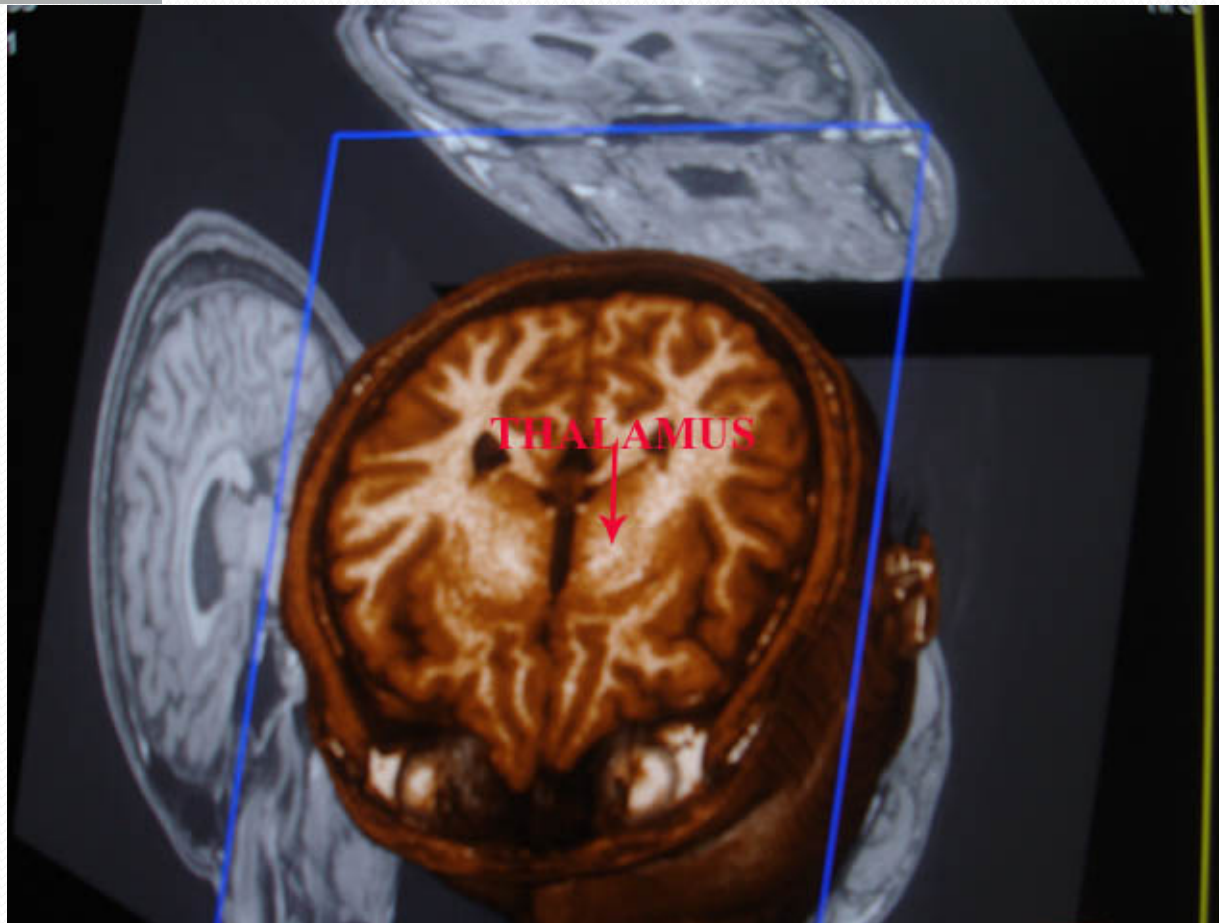


thalamus



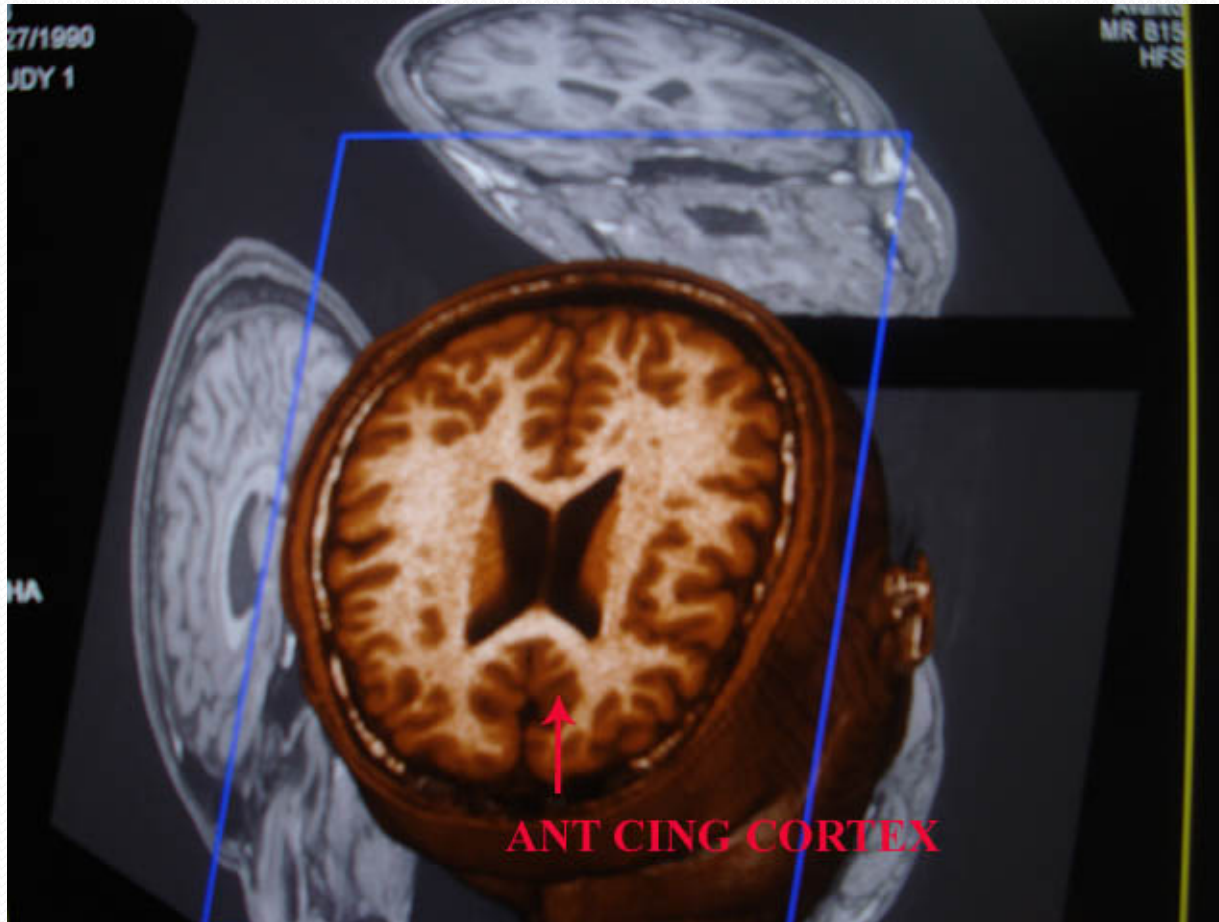


Thalamus



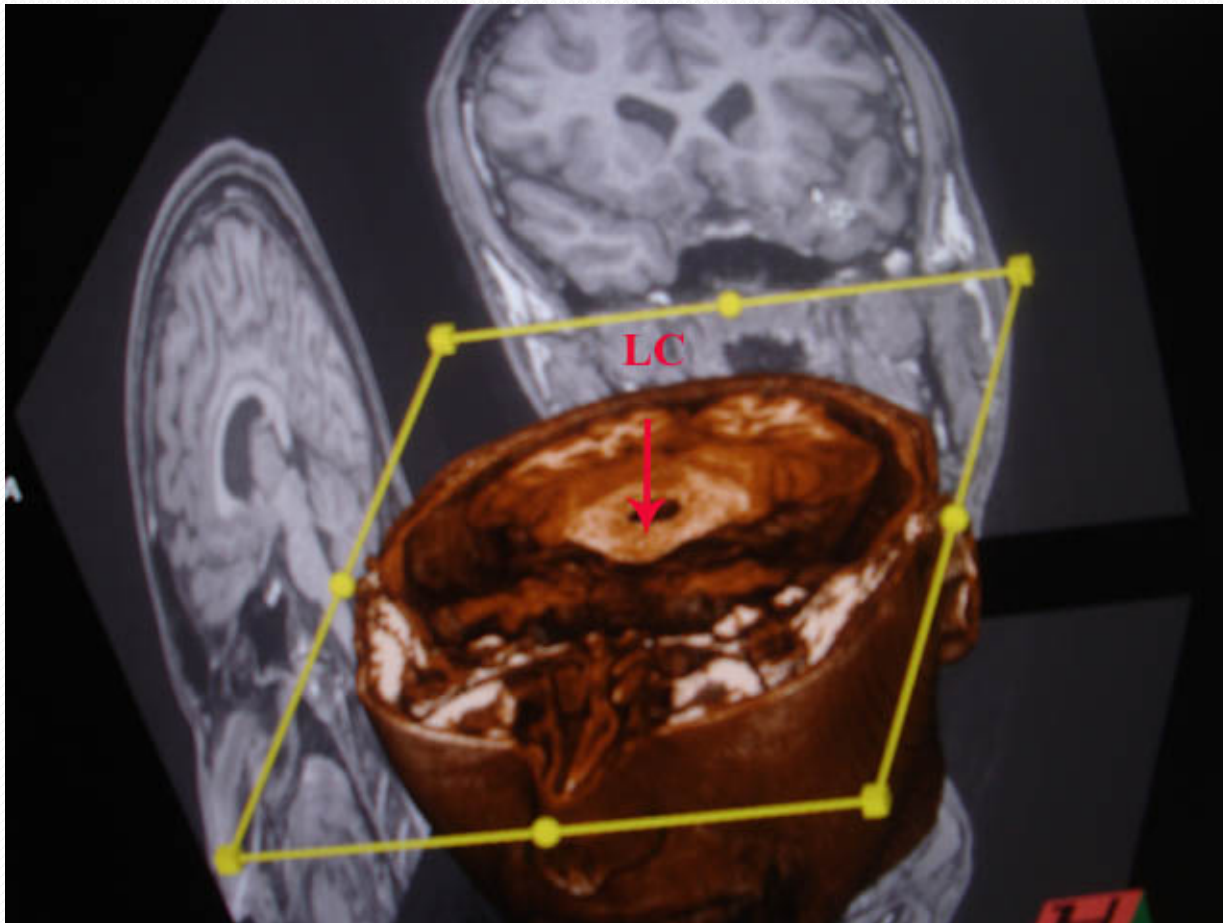


Anterior Cingulate Cortex



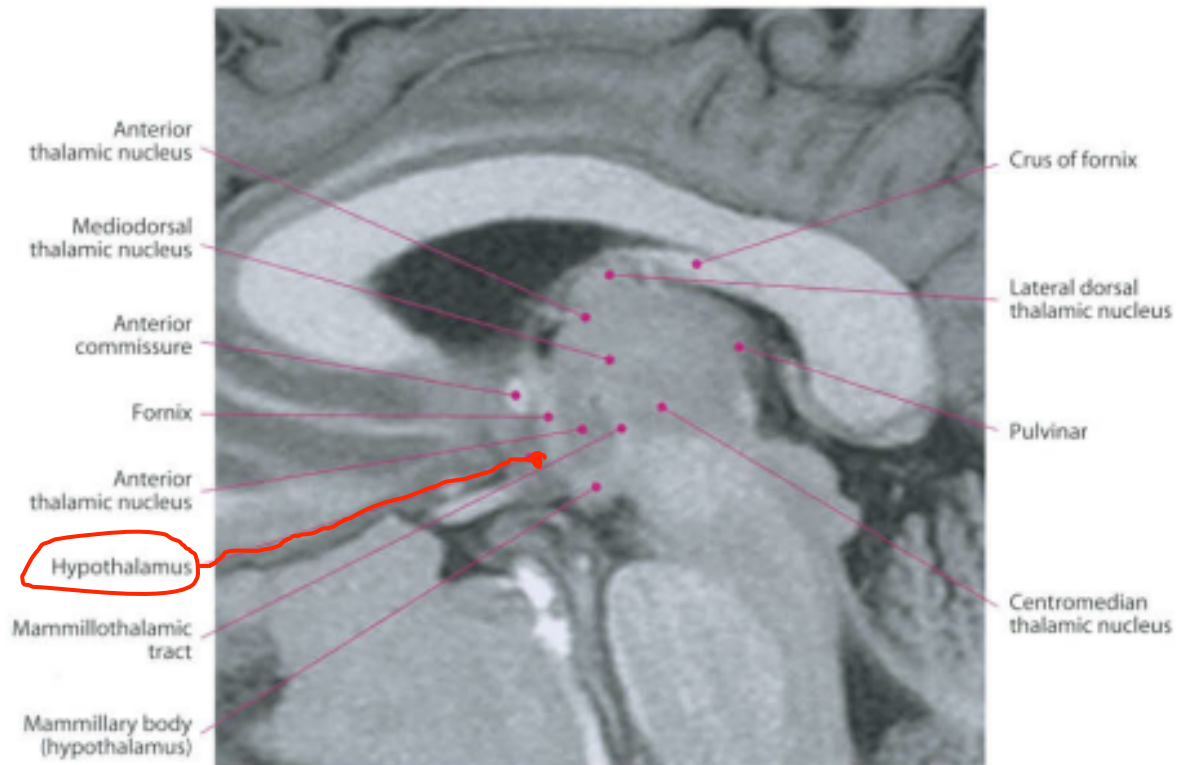


Locus Ceruleus

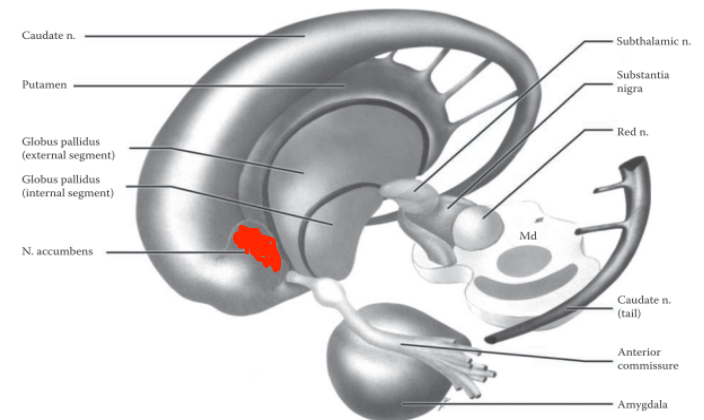
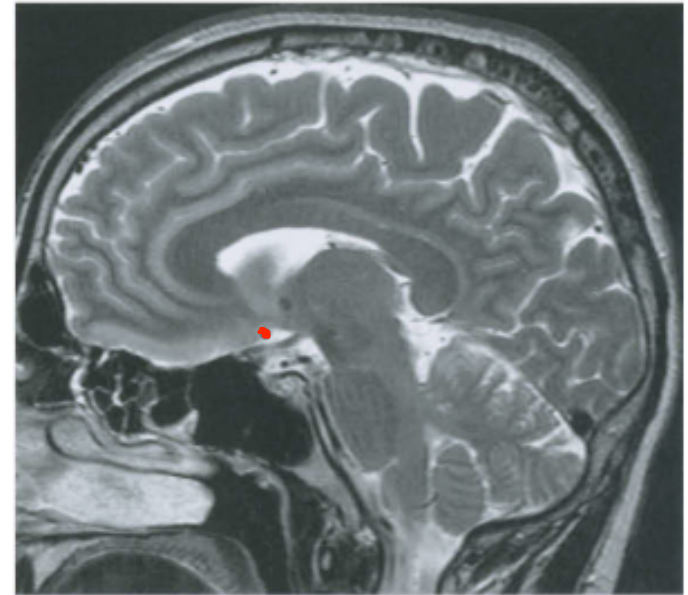
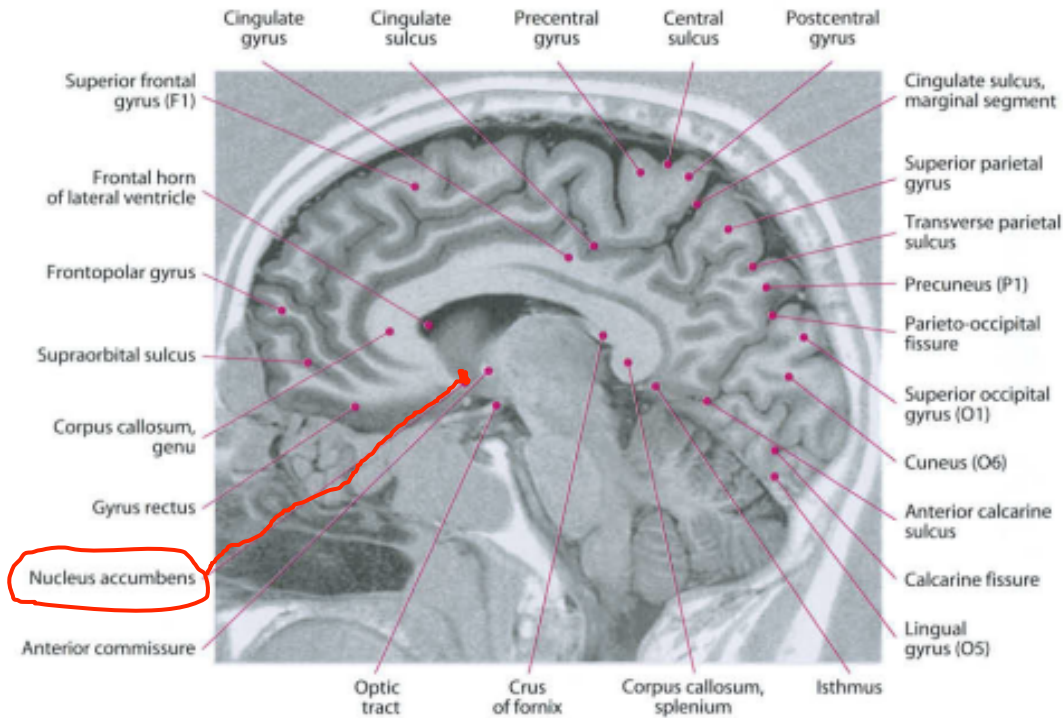




hypothalamus

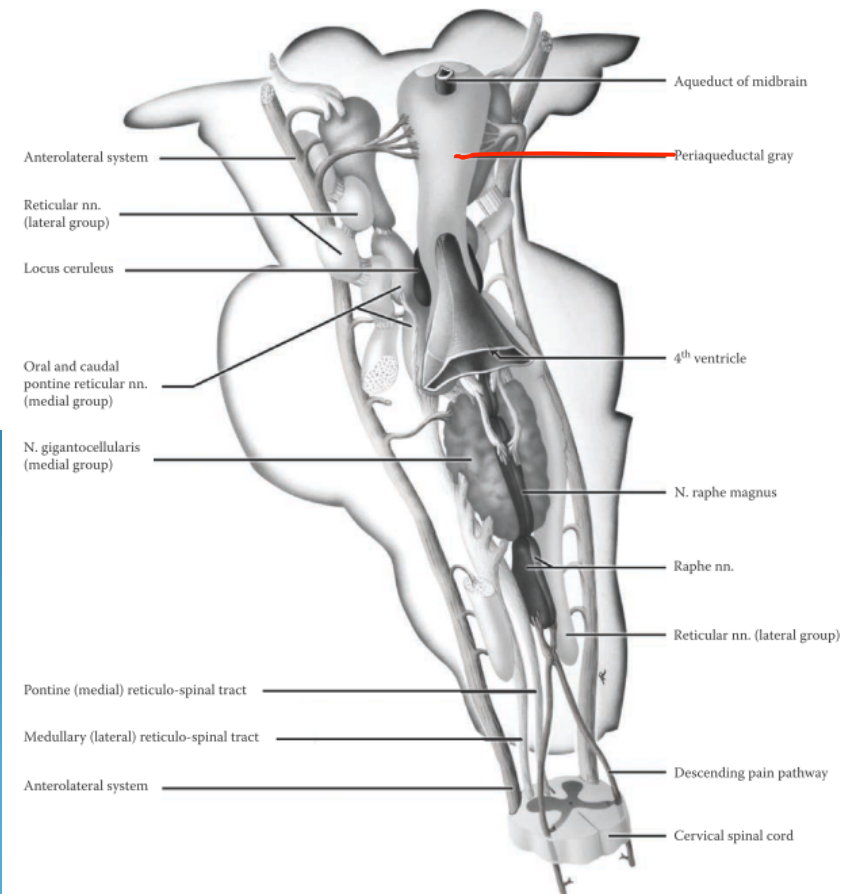
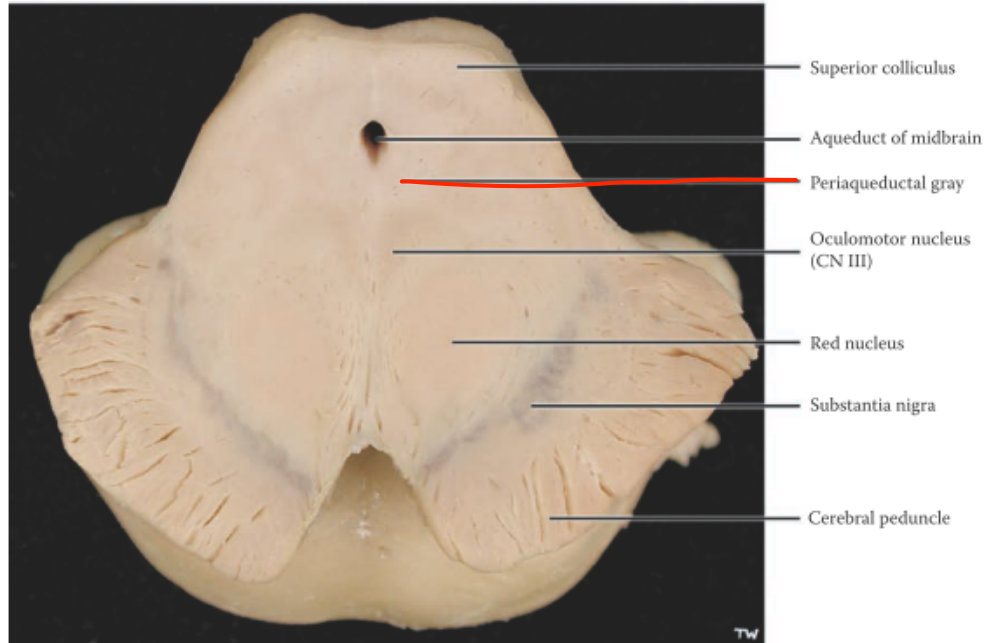


Nucleus Accumbens



Md = Midbrain

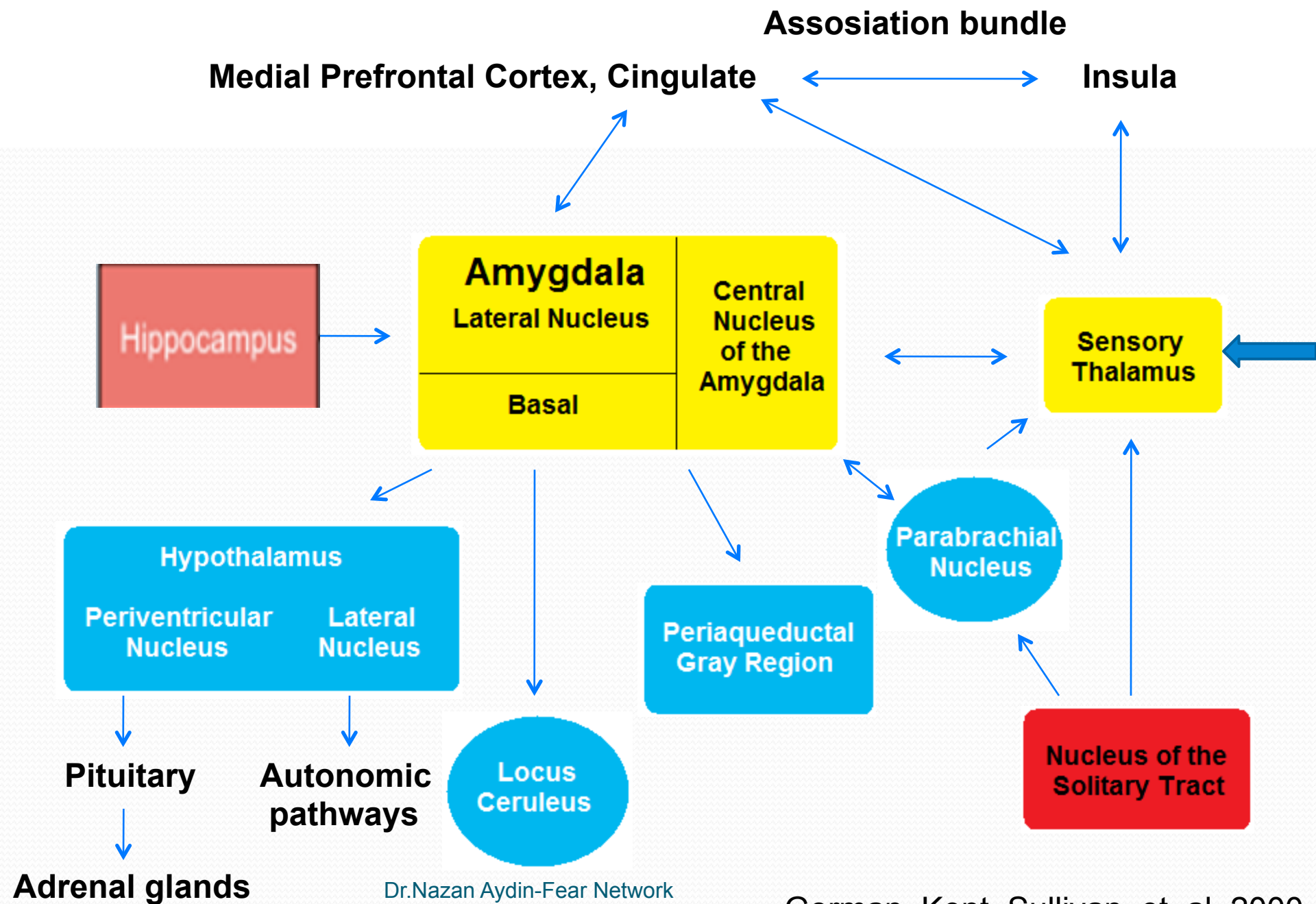
Periaqueductal Gray Region





FEAR NETWORK?

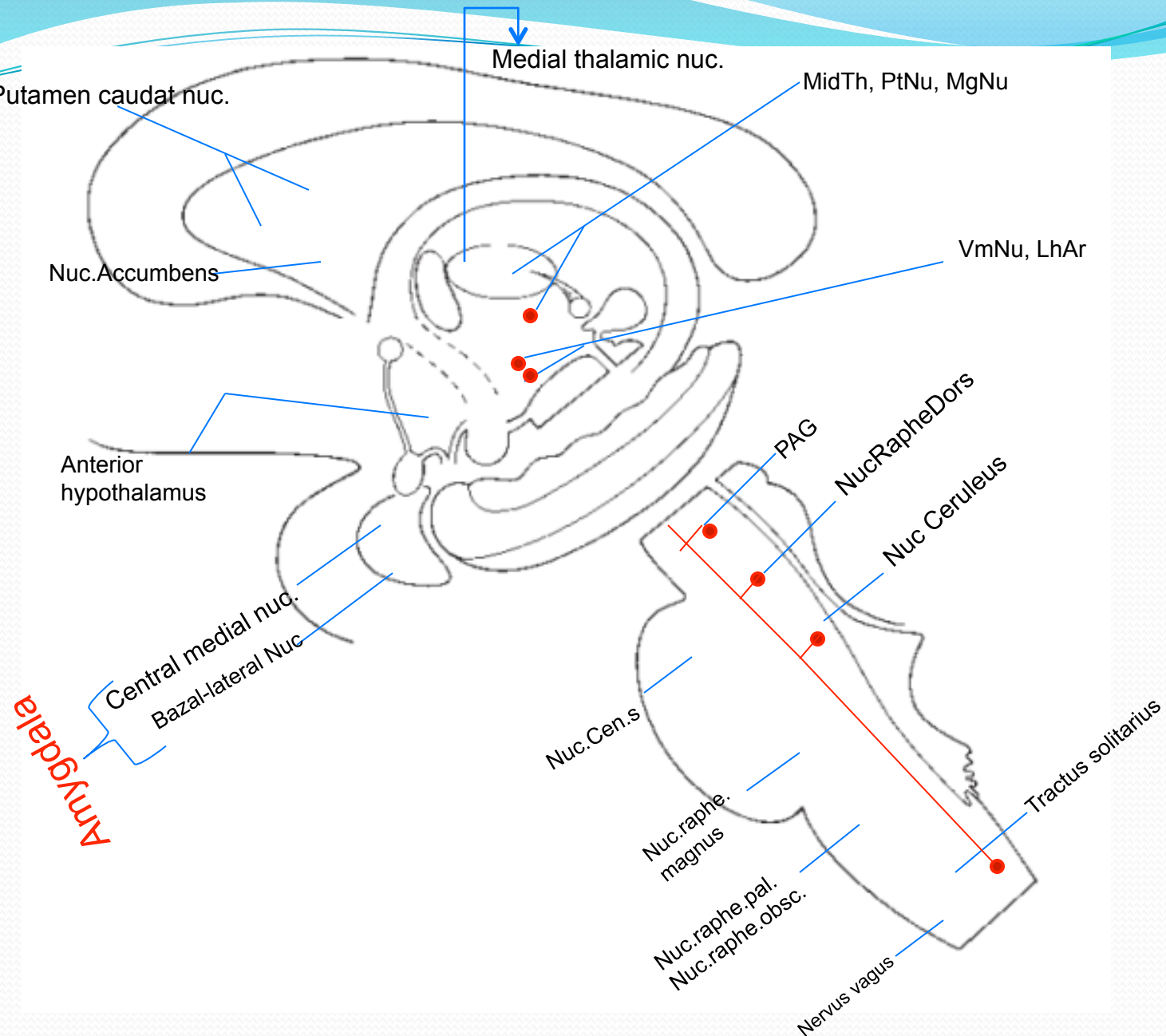




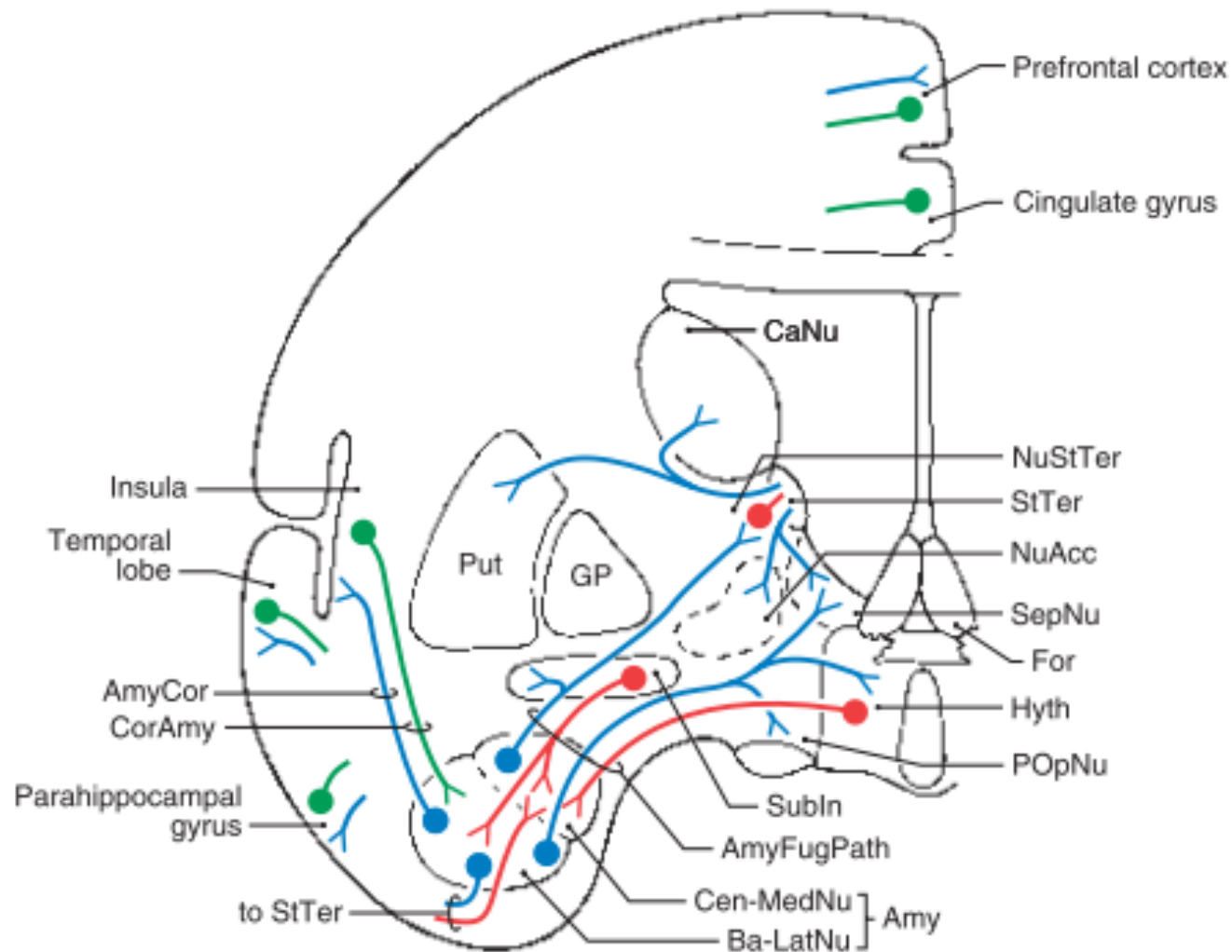
Panic disorder

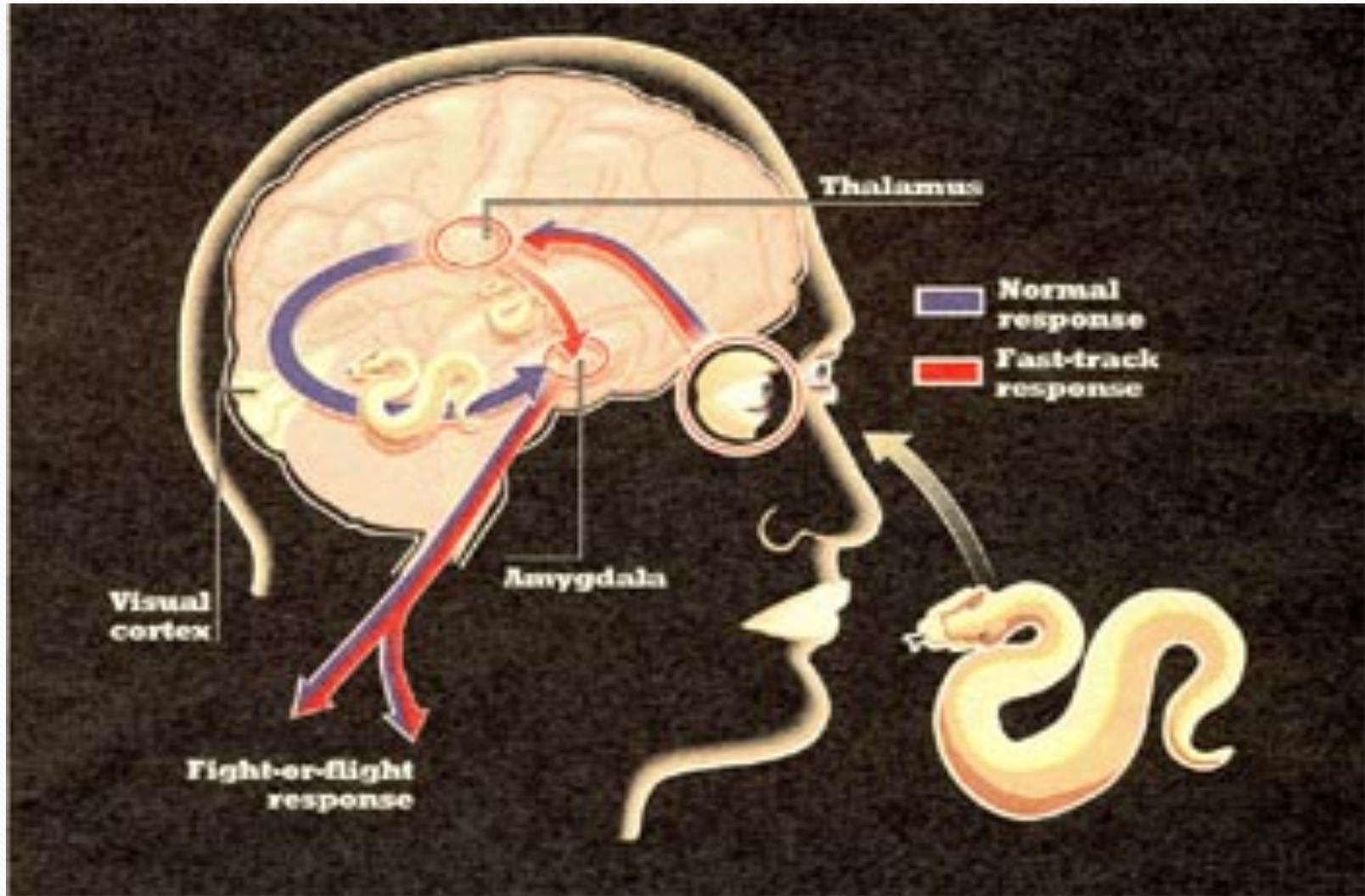


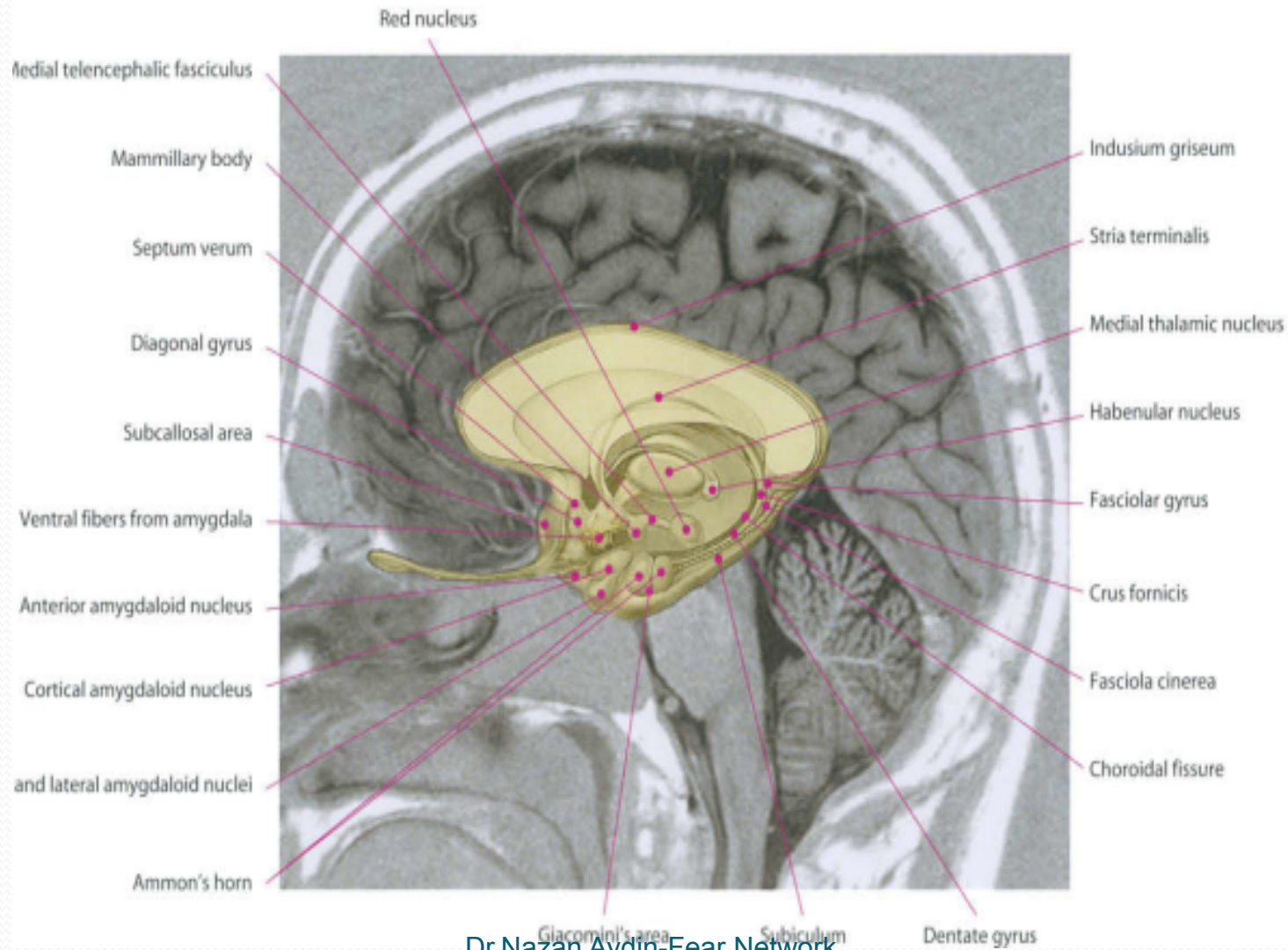
C



Panic disorder







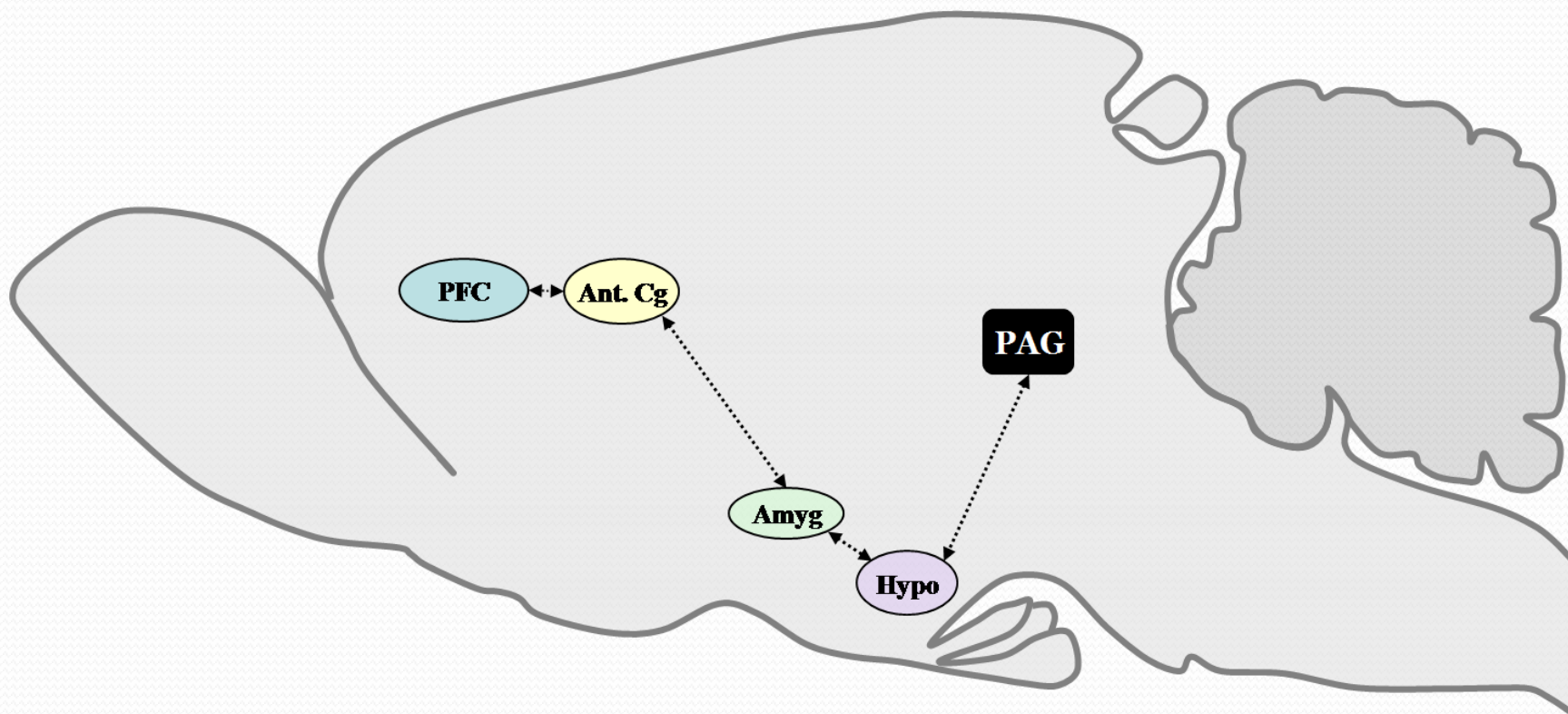
Objective and Hypothesis:

1. Our objective is to determine the regions related to fear-network by c-fos activation after evoking escaping behaviour (A model for panic disorder with agoraphobia by DBS approaches).
2. We hypothesize that '*Escitalopram*', would reduce c-fos activation, but not '*Buspirone*'.

Material and methods:

No	Category of groups	
1	dlPAG DBS	Saline
2		Buspirone
3		Escitalopram
4	dlPAG Sham (Control)	Saline
5		Buspirone
6		Escitalopram

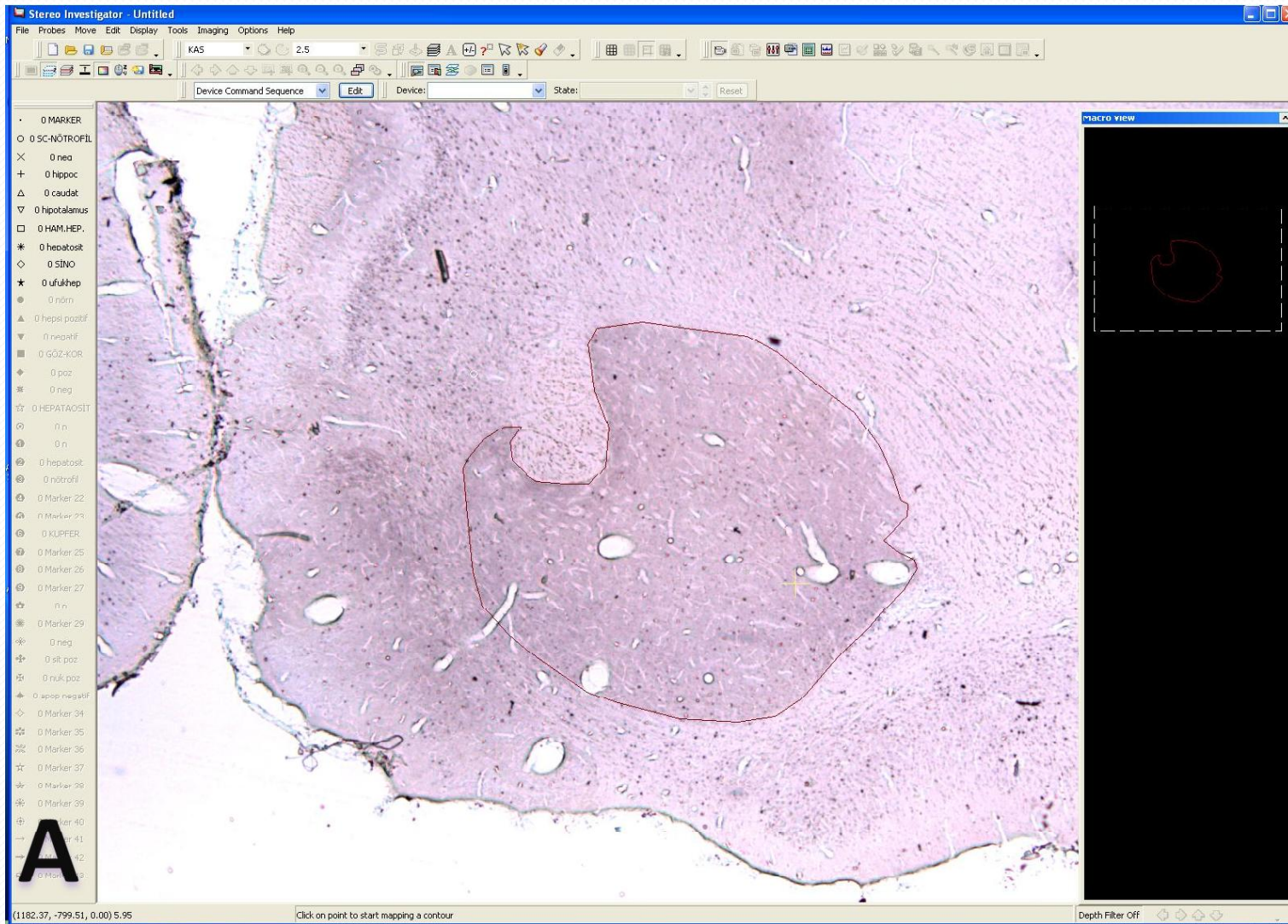
1. Rats received acute and chronic treatment with saline, Buspirone, or Escitalopram, respectively.
2. Rats were stimulated for the “escape behaviour”; and on the next day, they were tested in the open-field environment after acute and chronic treatment.



Regions for counting

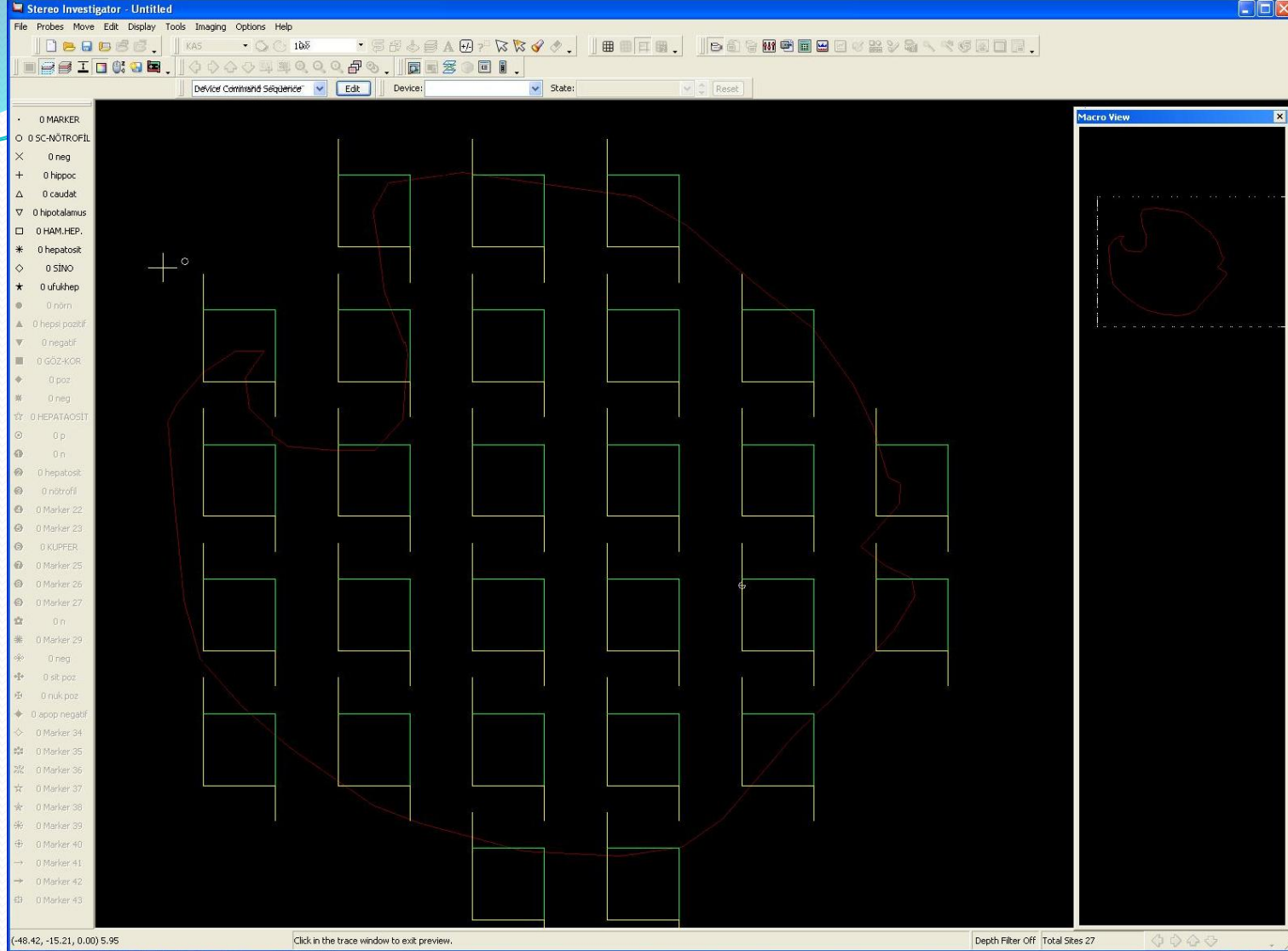
Prefrontal, Prelimbic	Limbic 1	Limbic 2
<u>Accumbens (Acb)</u>	<u>Accumbens Core (Acb C)</u>	Dorsomedial dorsal Talamus (DMD)
<u>Prelimbic (PrL),</u>	<u>Accumbens Shell (Acb Sh)</u>	Ventromedial hypothalamus dorsomedial (VMHDM)
<u>Infralimbic (IL)</u>	Dorsal Caudate Putamen (d CPU)	Ventromedial hypothalamus Central (VMHC)
Motor cortex 1 (M1),	Ventral Caudate Putamen (v CPU)	Ventromedial hypothalamus ventrolateral (VMHVL)
Motor cortex 2 (M2),	<u>Medial Amygdala (MeA)</u>	Lateral Hypothalamus (LH)
Cingulate 1 (Cg1)	Central Amygdala (CeA)	Medial Habenula (MHb)
Piriform (Pir)	Hippocampus (HC)	Lateral Habenula (LHb)
Ventral optic (VO)		
Lateral optic (LO)		

Procedure for cell counting



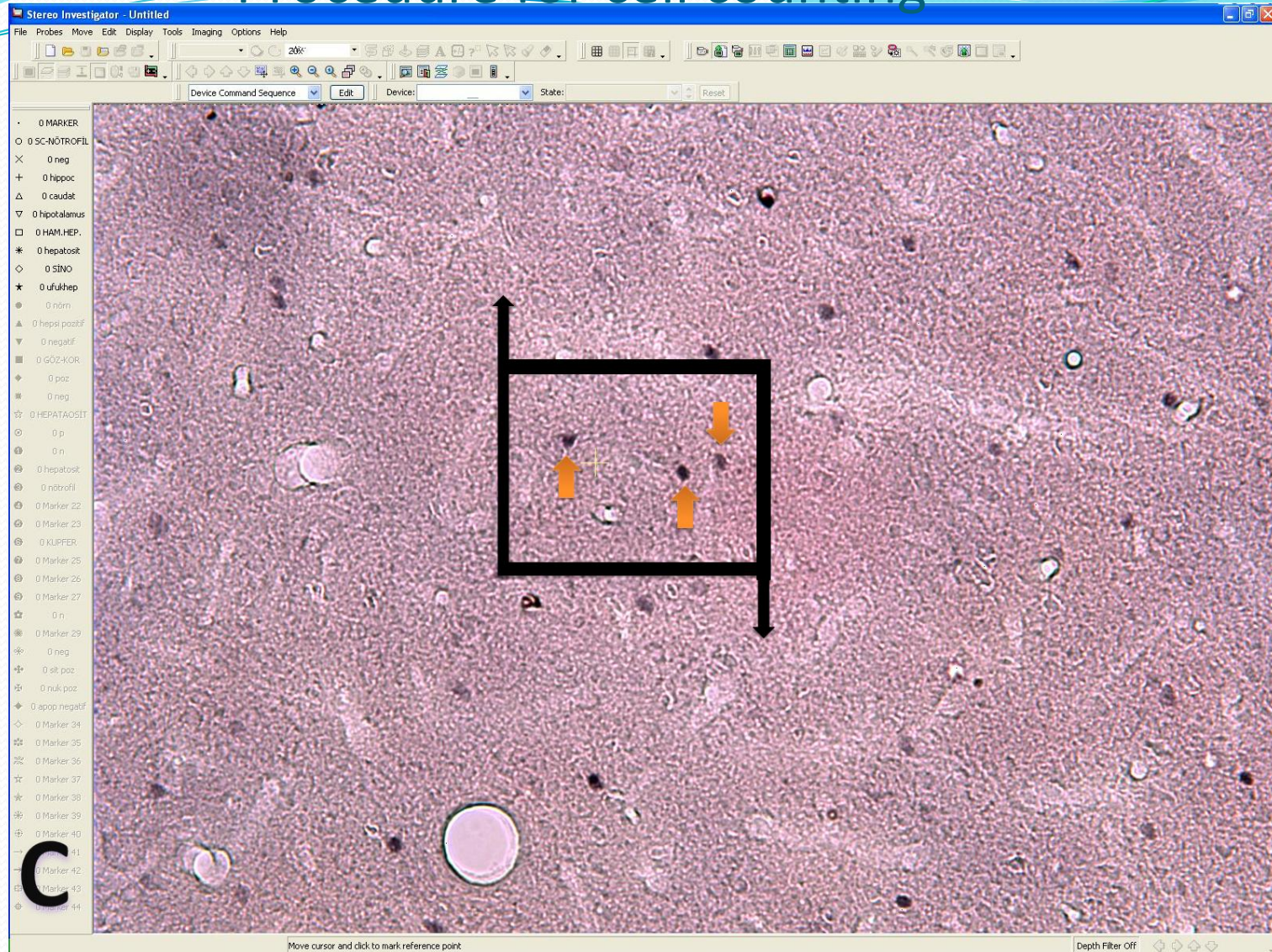
In each of the sampled sections, the areas of c fos counting were determined and traced using a stereo investigator software 7 (Micro-brightfield, Colchester, VT).

Dr. Nazan Aydin-Fear Network



The Sampling area using optical fractionator probe by the Stereo Investigator system. Optical disectors (counting frame areas) were automatically systematic-randomly distributed with equal intervals (x,y-step area) throughout the delineated area. The size of the optical disectors (counting frame areas) and the distance between optical disectors (counting frame areas) is known as the area sampling fraction (asf) were determined according to an suitable coefficient error.

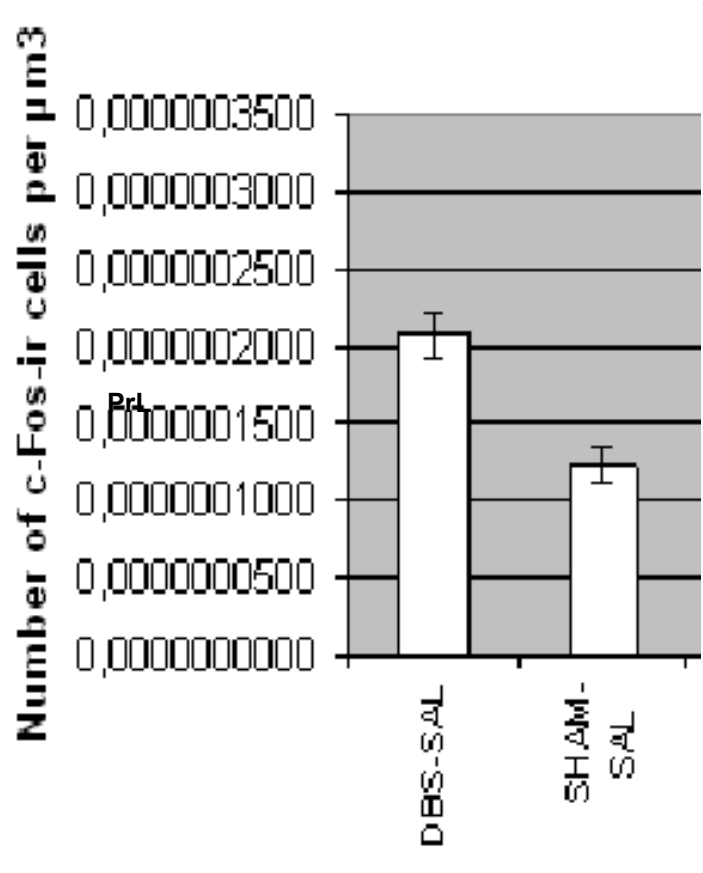
Procedure for cell counting



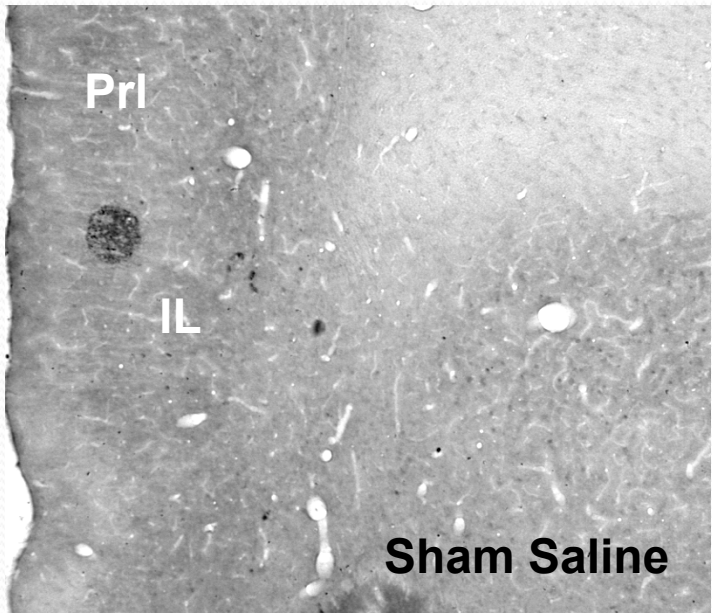
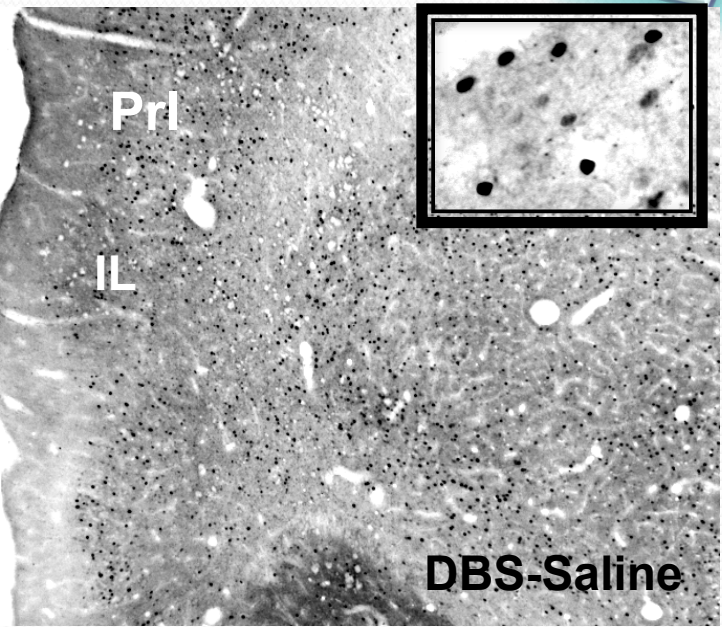
C fos were scored in the optical disectors (counting frame areas) on sections. After all this application, numerical density of c fos were estimated via stereology software :



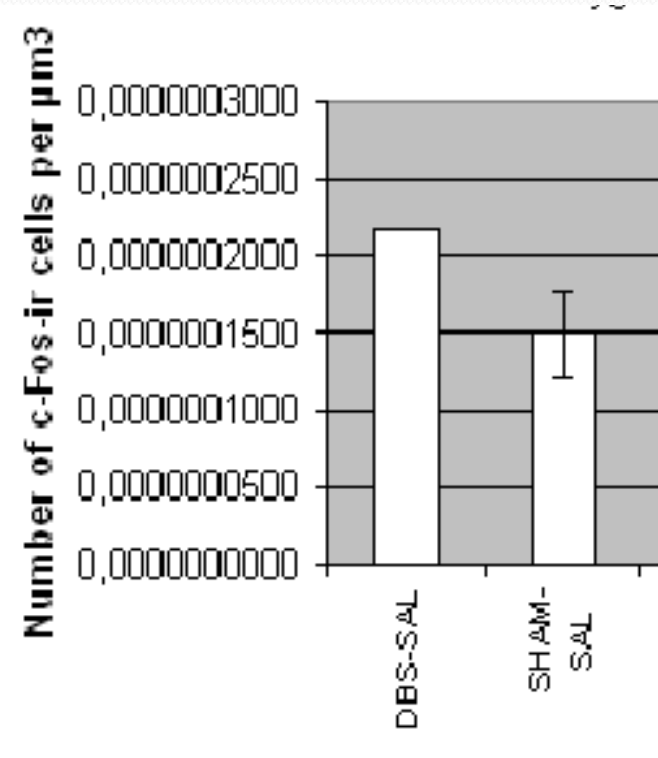
Infralimbic cortex



Infralimbic Cortex		ANOVA	P
DBS-SAL	SHAM-SAL	,001	P<0,05

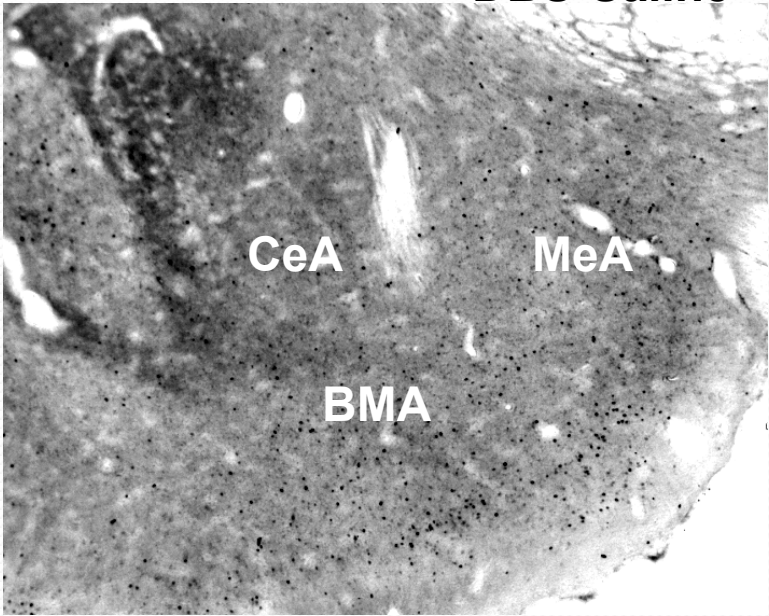


Medial Amygdaloid Nucleus

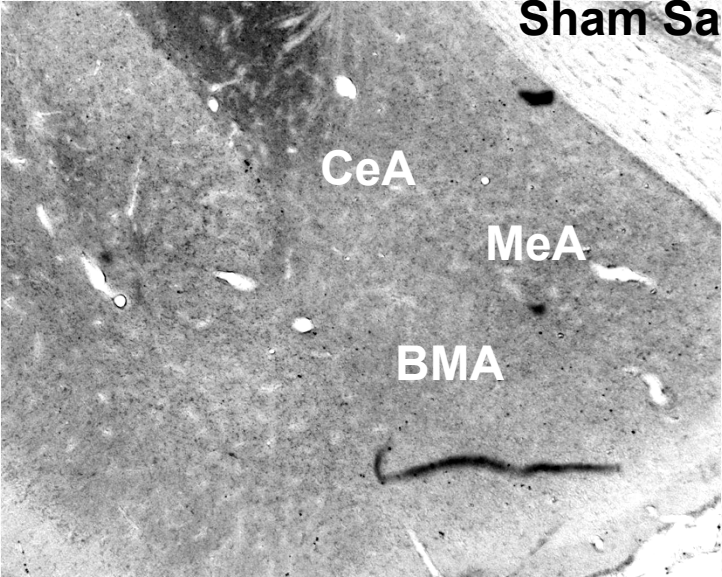


Medial Amygdaloid Nucleus		ANO VA	P
DBS-SAL	SHAM-SAL	,001	P<0,05

DBS-Saline



Sham Saline



Number of c-Fos-ir cells per μm^3

□ DBS-BUS B ■ SHAM-BUS B

0,0000004500
0,0000004000
0,0000003500
0,0000003000
0,0000002500
0,0000002000
0,0000001500
0,0000001000
0,0000000500
0,0000000000

Prelimbic
Cortex

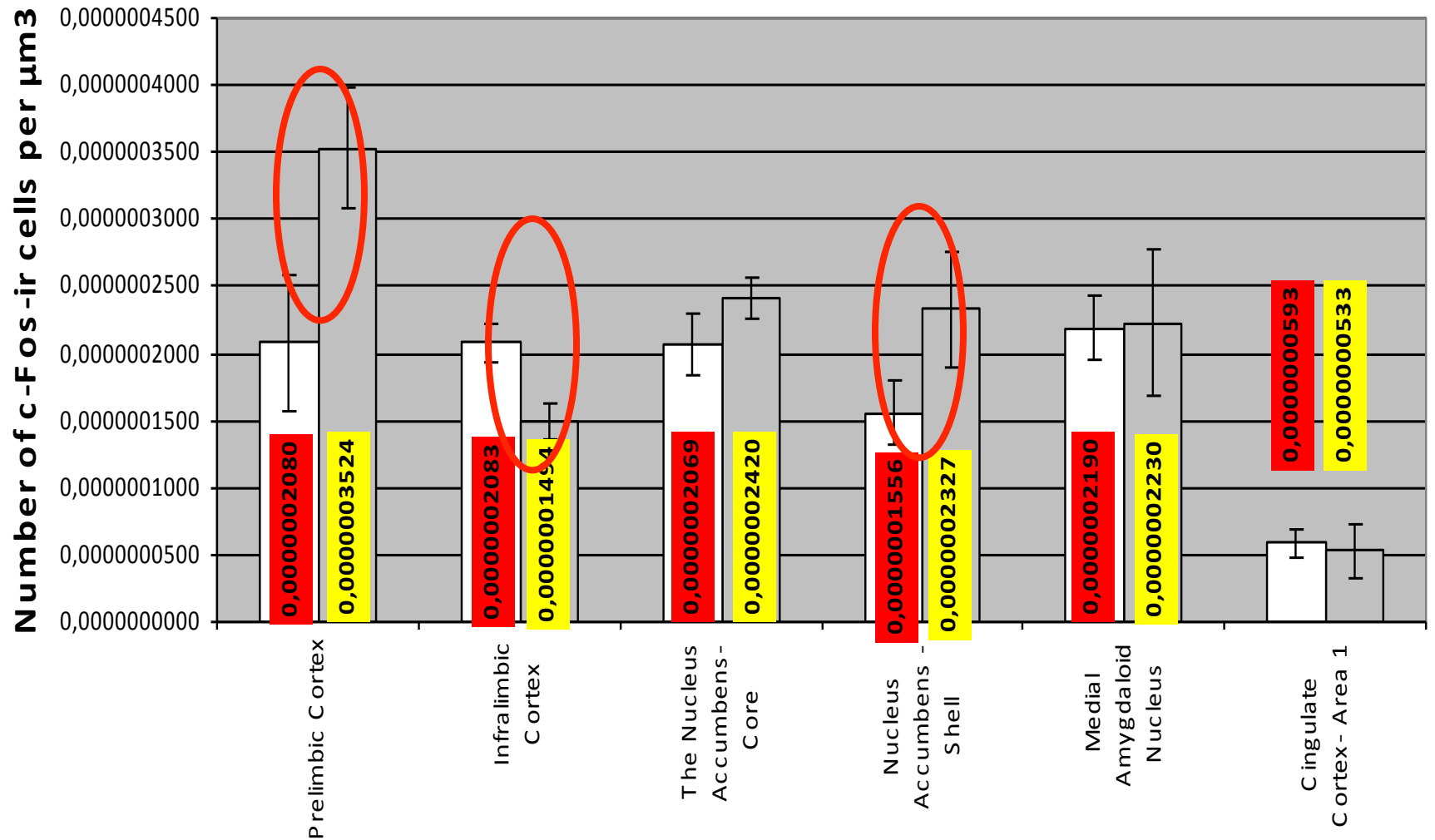
Infralimbic
Cortex

The Nucleus
Accumbens -
Core

Nucleus
Accumbens
-Shell

Medial
Amygdaloid
Nucleus

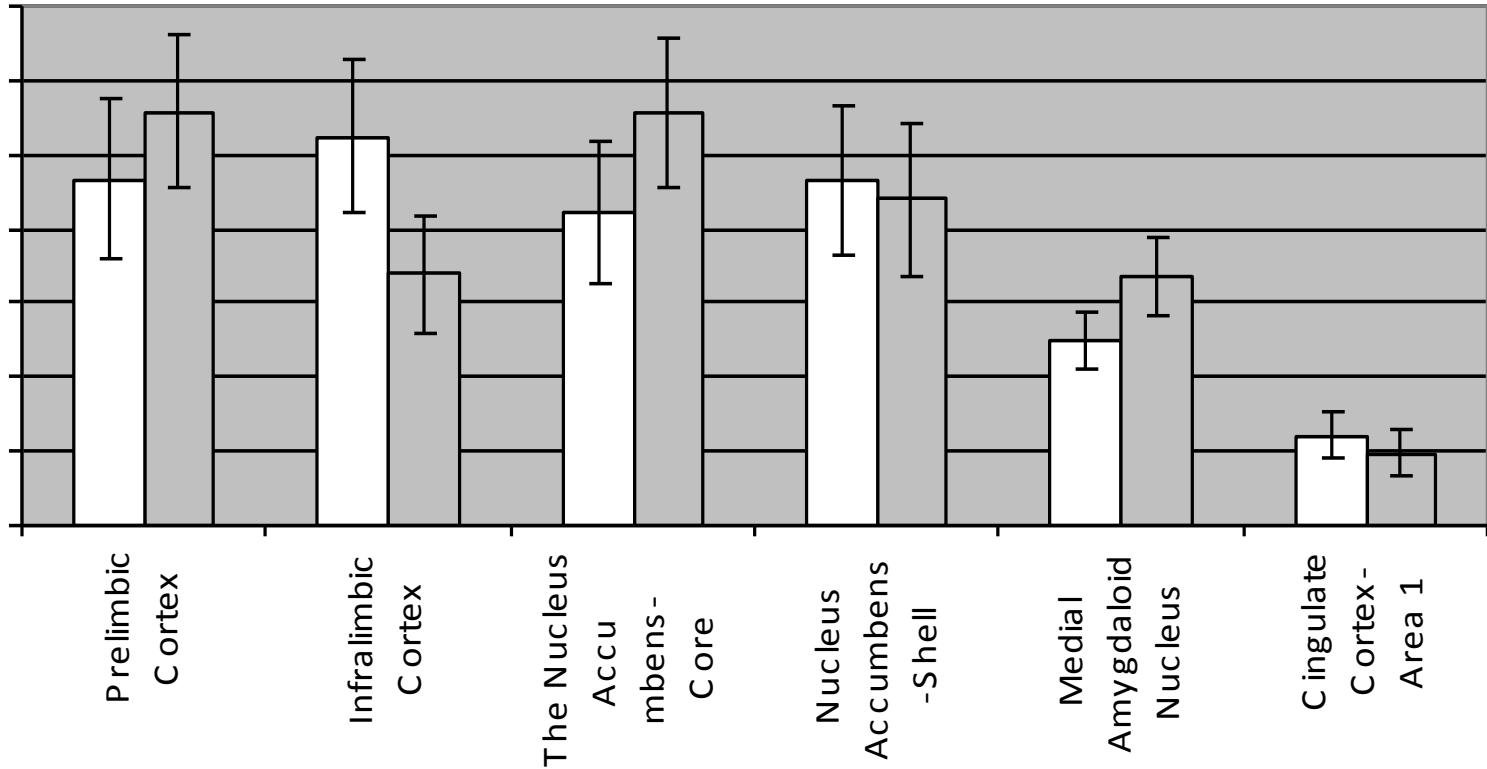
Cingulate
Cortex -
Area 1

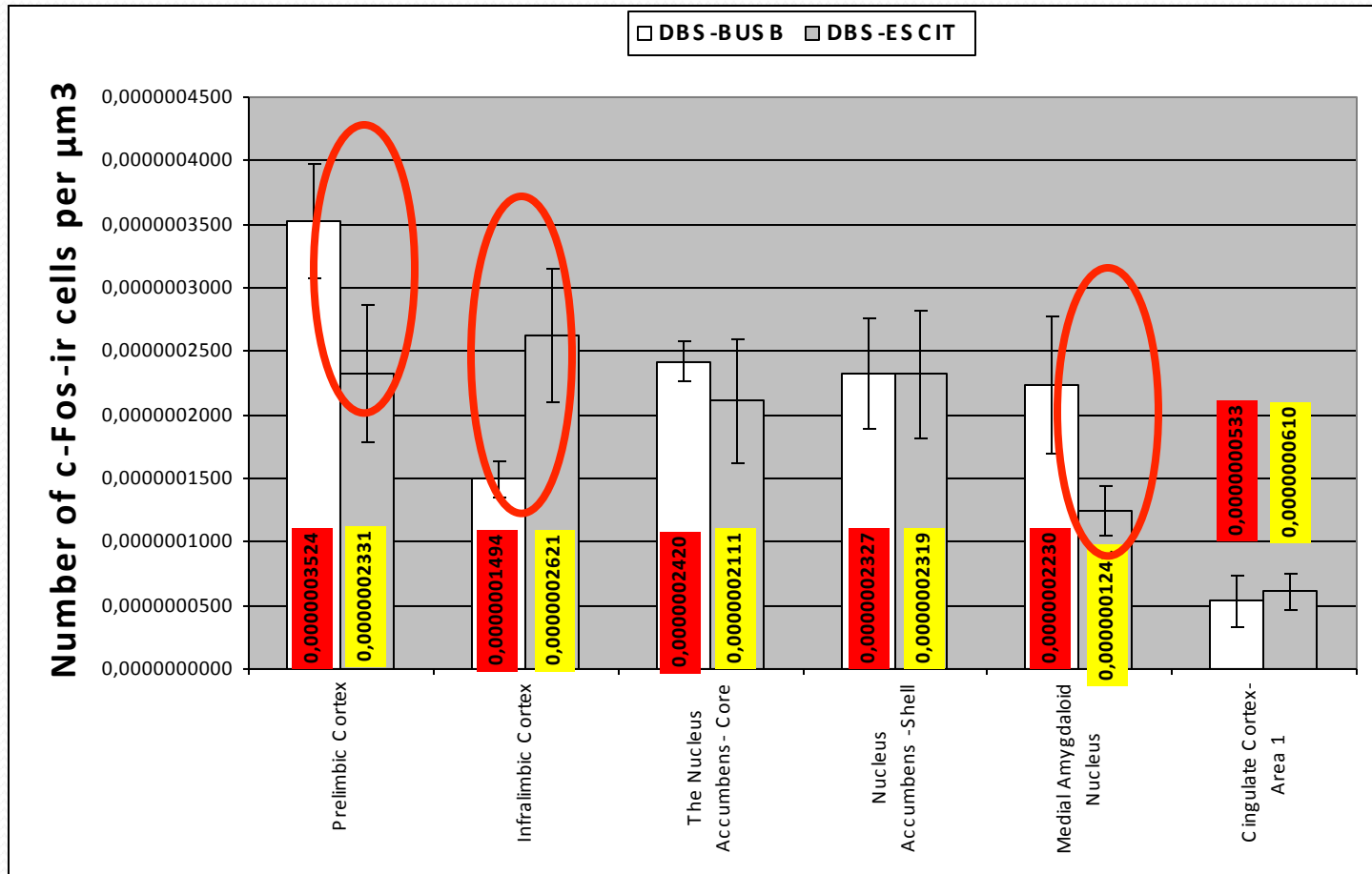


Number of c-Fos-ir cells per μm^3

□ DBS-ESCIT ■ SHAM-ESCIT

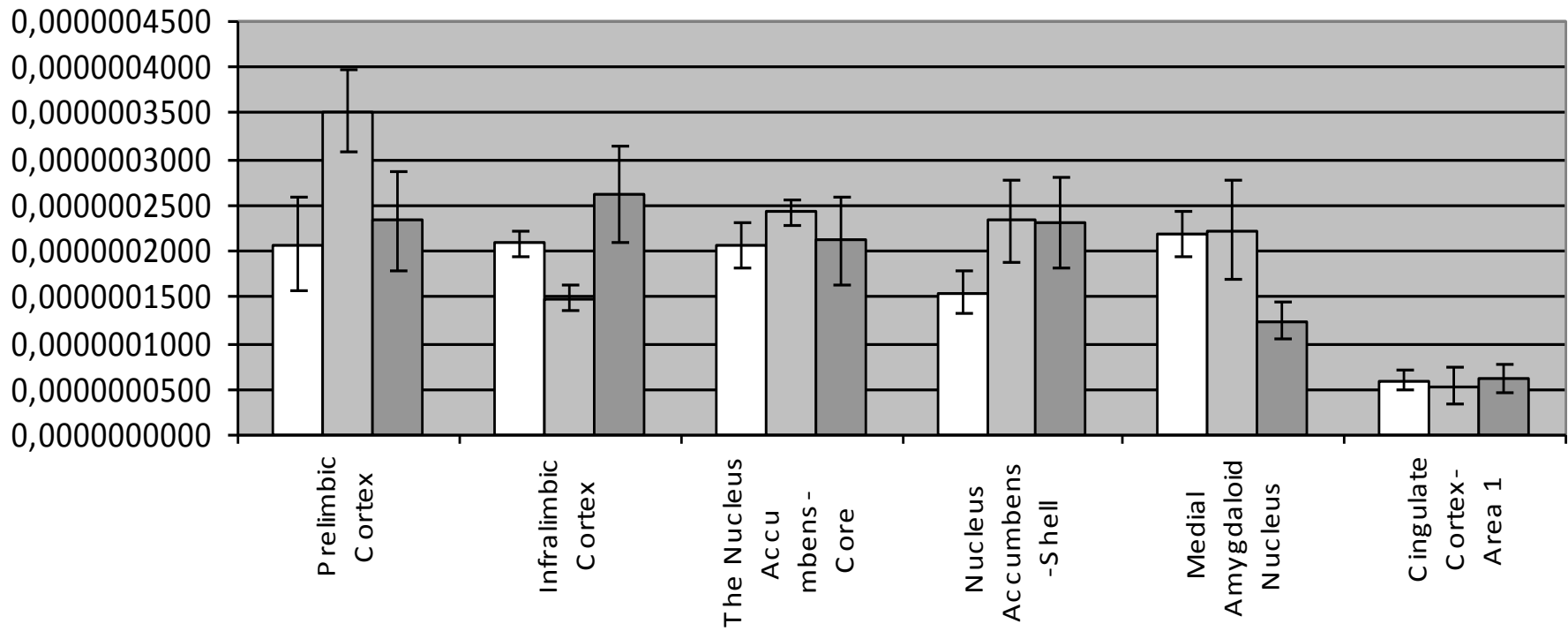
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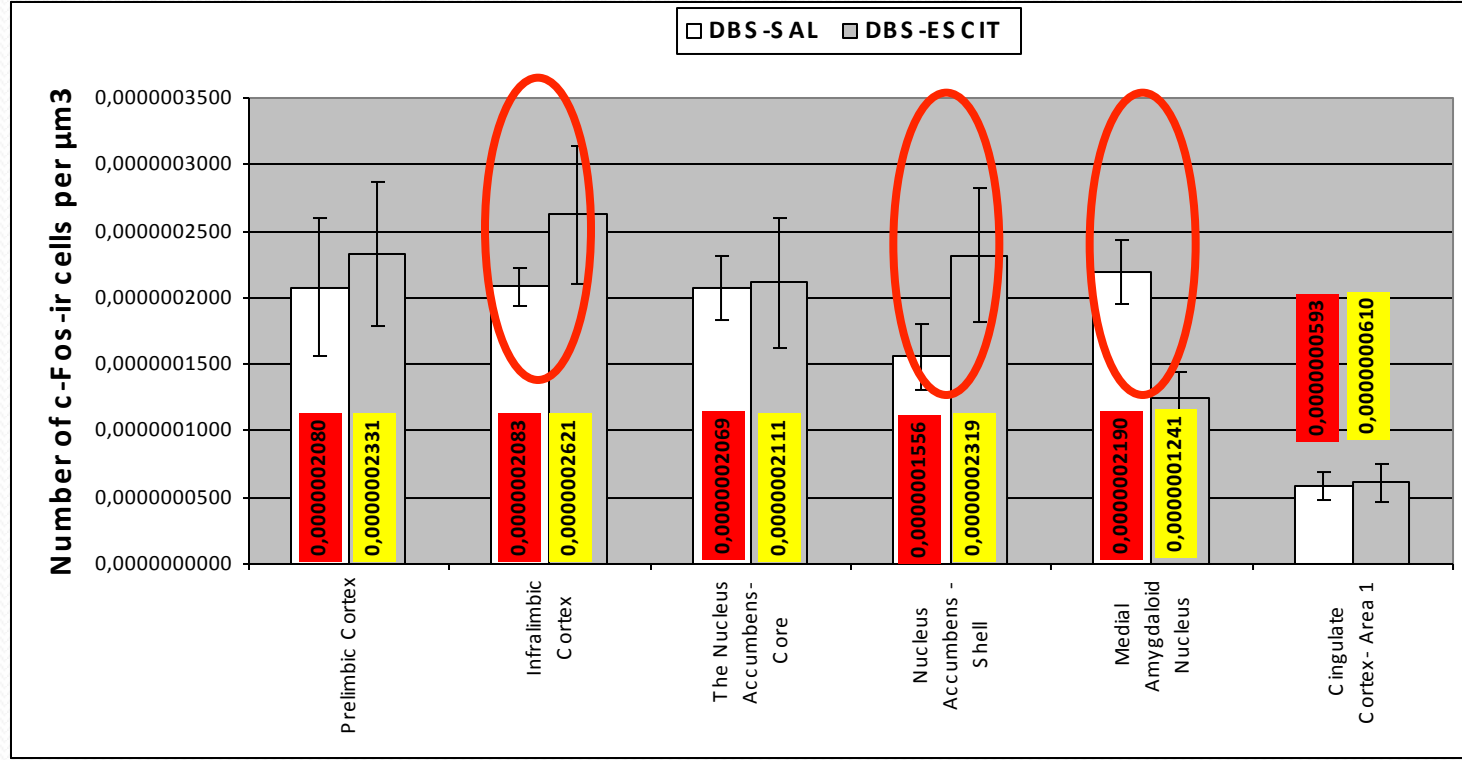


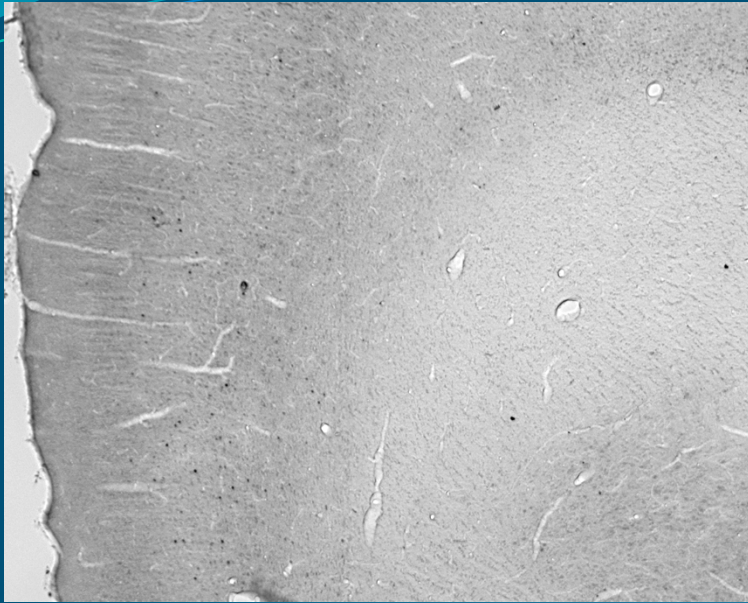


Number of c-Fos-ir cells per μm^3

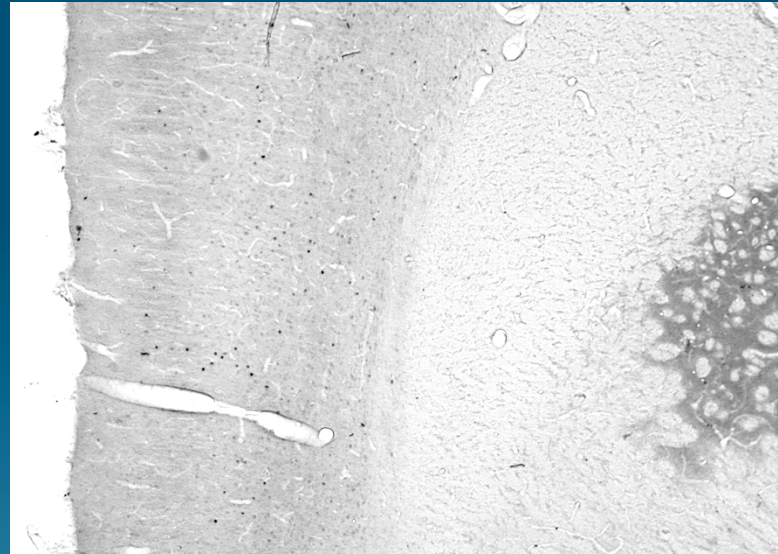
□ DBS -SAL ■ DBS -BUS B ■ DBS -E S C I T



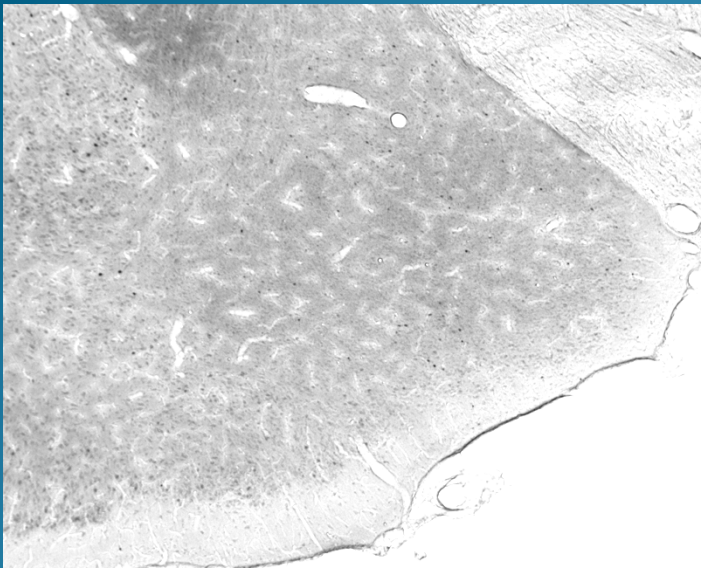




DBS -ESCIT



DBS -BUS





Conclusions

- Inherit an especially sensitive central nervous system fear mechanism
- Its center the central nucleus of the Amygdala
- Includes the hippocampus, thalamus, and hypothalamus, as well as the periaqueductal gray region, locus ceruleus, and other brainstem sites.
- Medications such as SSRIs may reduce panic attacks by decreasing the activity of the amygdala and interfering with its ability to stimulate projection sites in the hypothalamus and brainstem.
- Once the physiologic/somatic symptoms of anxiety are lessened, there is a secondary reduction in anticipatory anxiety and phobic avoidance.
- Cognitive behavioral and other effective psychotherapies most likely operate upstream from the amygdala, reducing phobic avoidance by deconditioning contextual fear learned at the level of the hippocampus and decreasing cognitive misattributions and abnormal emotional reactions by strengthening the ability of the medial prefrontal cortex to inhibit the amygdala.

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PhD. Student Ahmet Topal
Master Student Selina Aksak



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Career Development Award, 2008***