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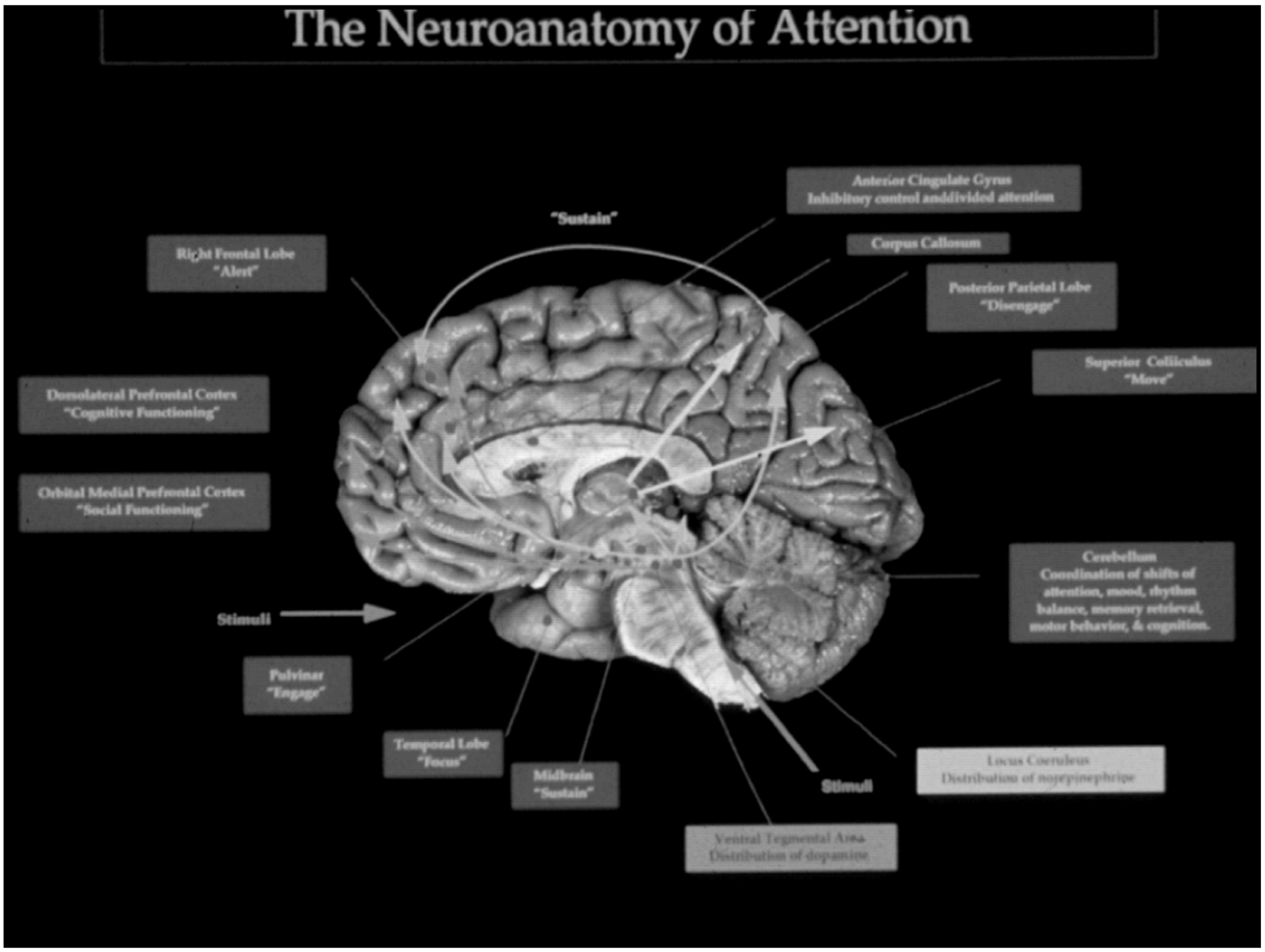
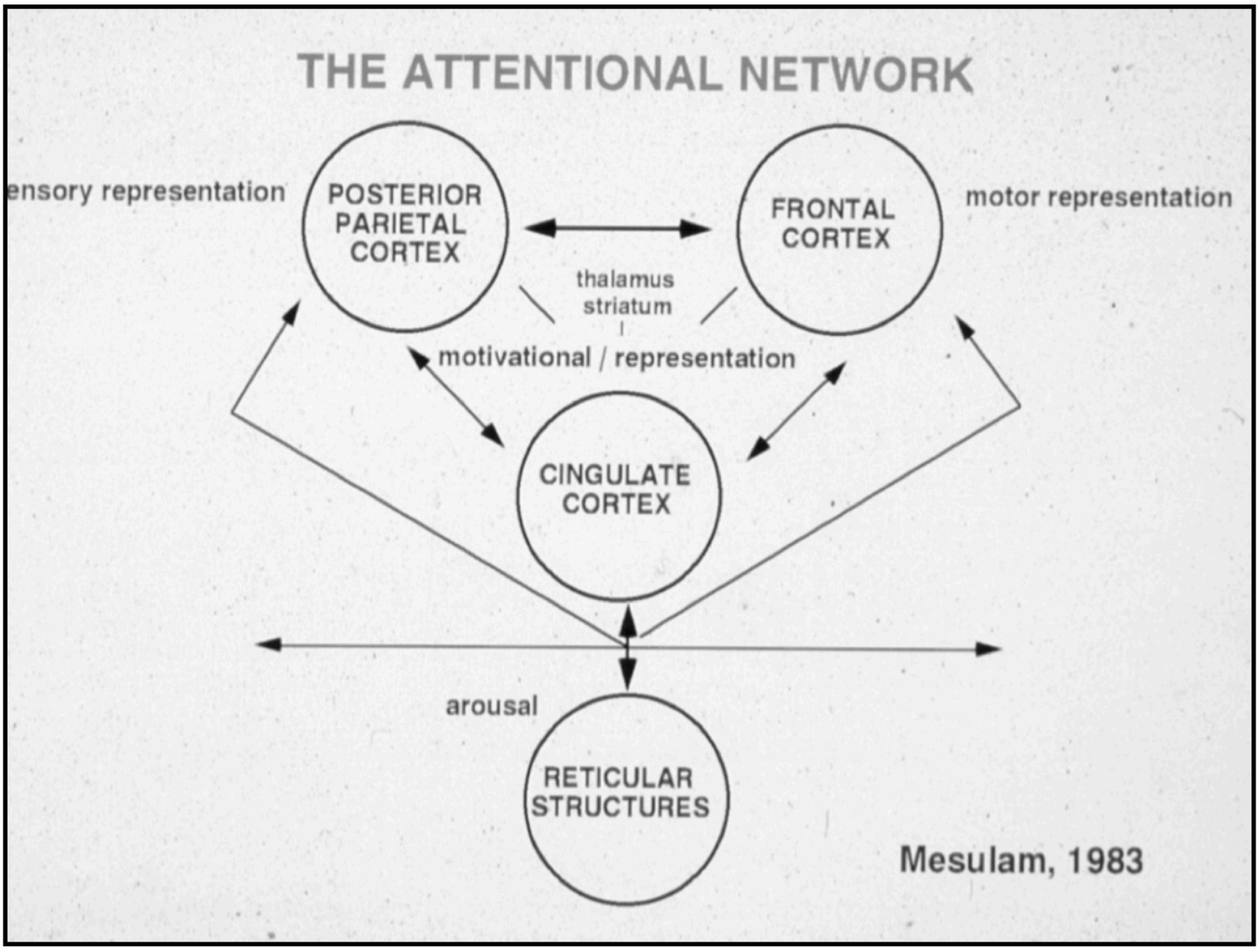
ADHD: Biology

- Cognitive and electrophysiological processes may demonstrate various biologic genetic endophenotypic underpinnings of ADHD
  - Processes of working memory
  - Processes of fine motor control
  - Set-shifting processes
  - EEG spectral power differences
- Total cerebral volume is approximately 3% smaller in youth with ADHD.
- Neurobiology and specific abnormalities




THE ATTENTIONAL NETWORK
ensory representation
POSTERIOR PARIETAL CORTEX
FRONTAL CORTEX
motor representation
thalamus
striatum
motivational / representation
CINGULATE CORTEX
arousal
RETICULAR STRUCTURES
Mesulam, 1983

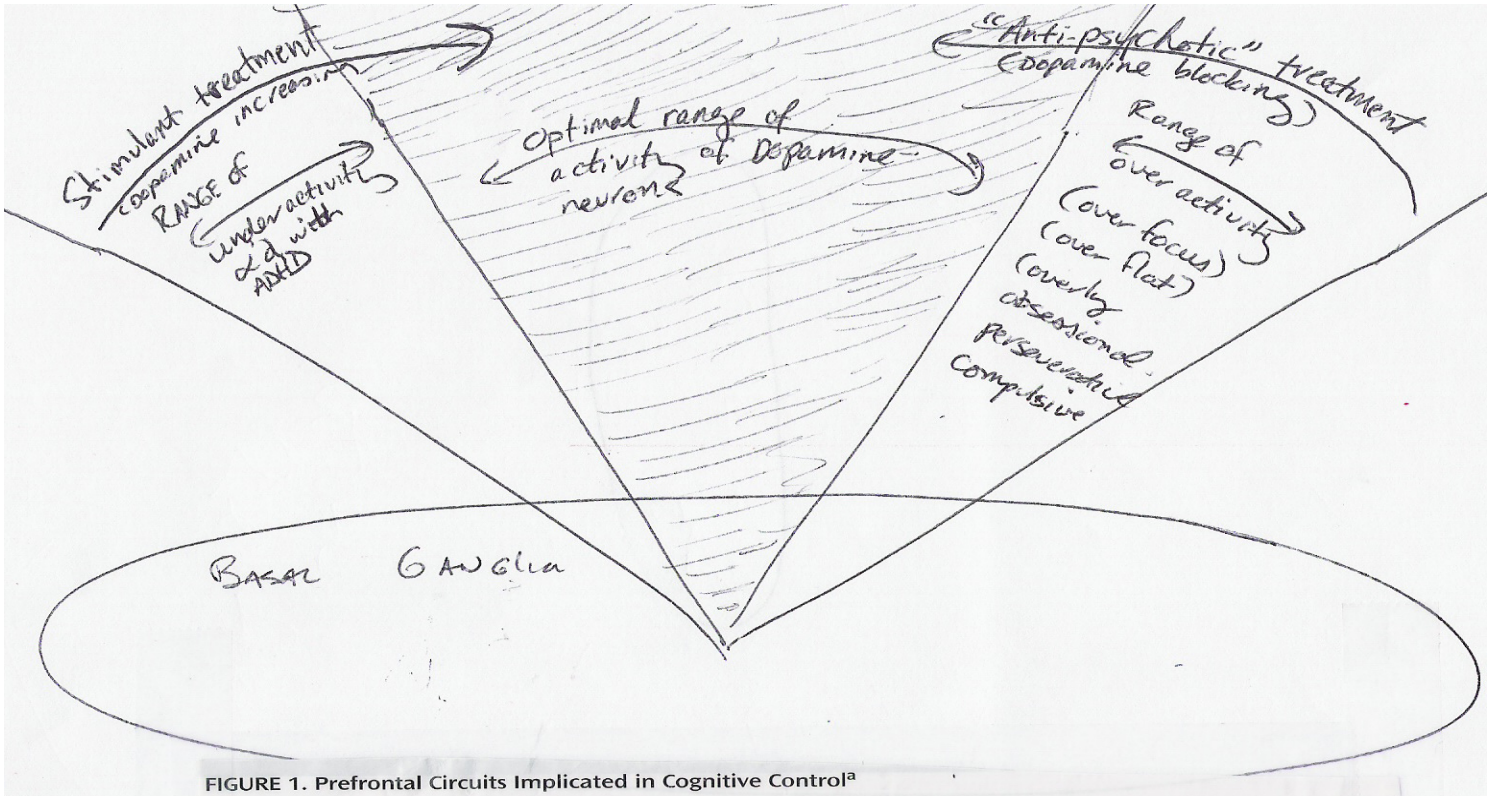
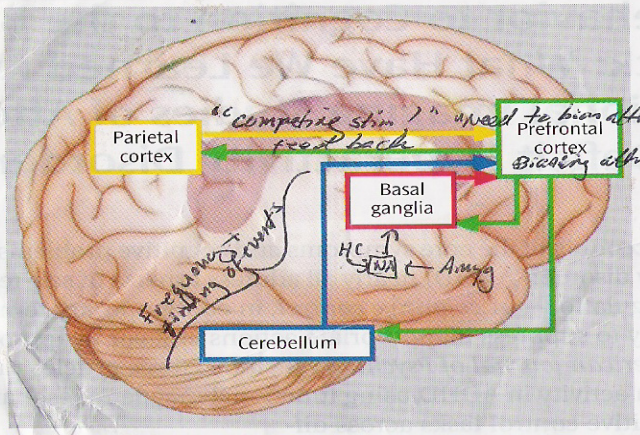


FIGURE 1. Prefrontal Circuits Implicated in Cognitive Control[a]



- Need to predict future events critical to ability to detect unexpected events

[a] Each circuit has projections both to and from the prefrontal cortex. The basal ganglia, cerebellum, and posterior systems signal the prefrontal cortex when new or competing sensory information is encountered so that the prefrontal cortex can immediately determine whether it provides new and important information or whether it can safely be ignored.

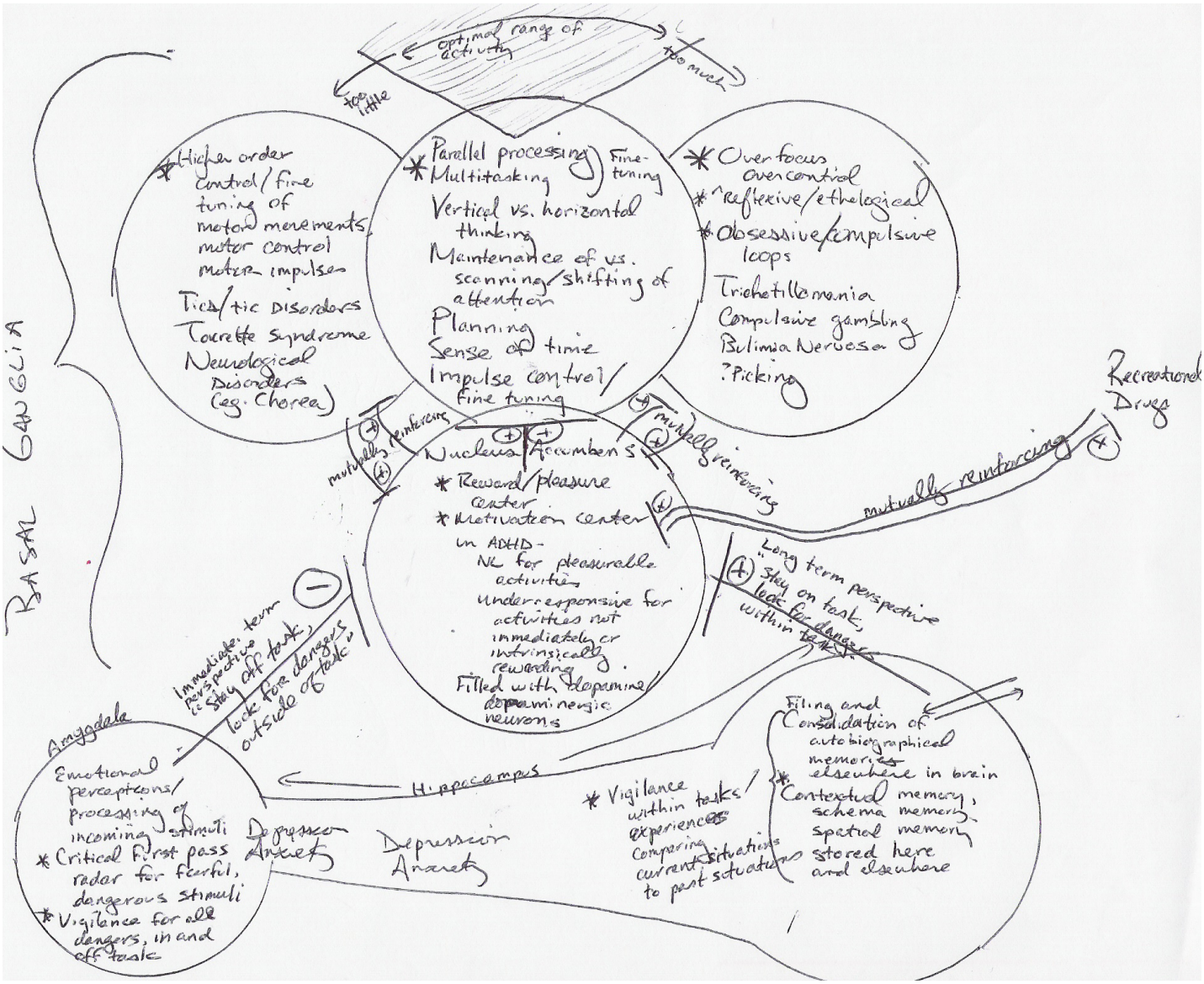
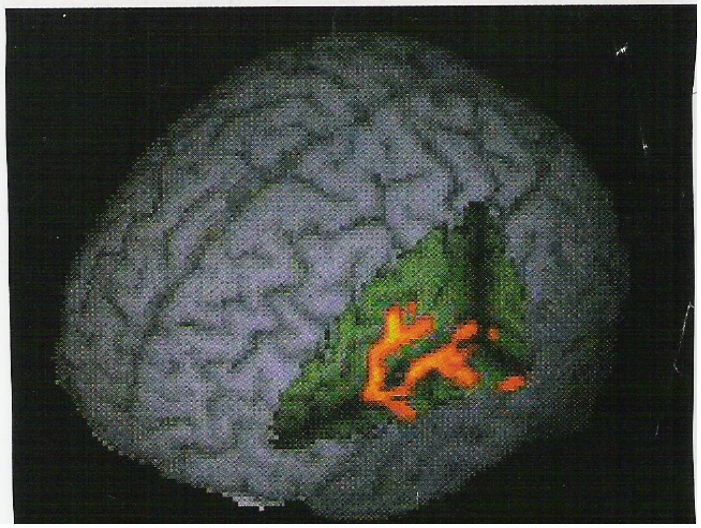
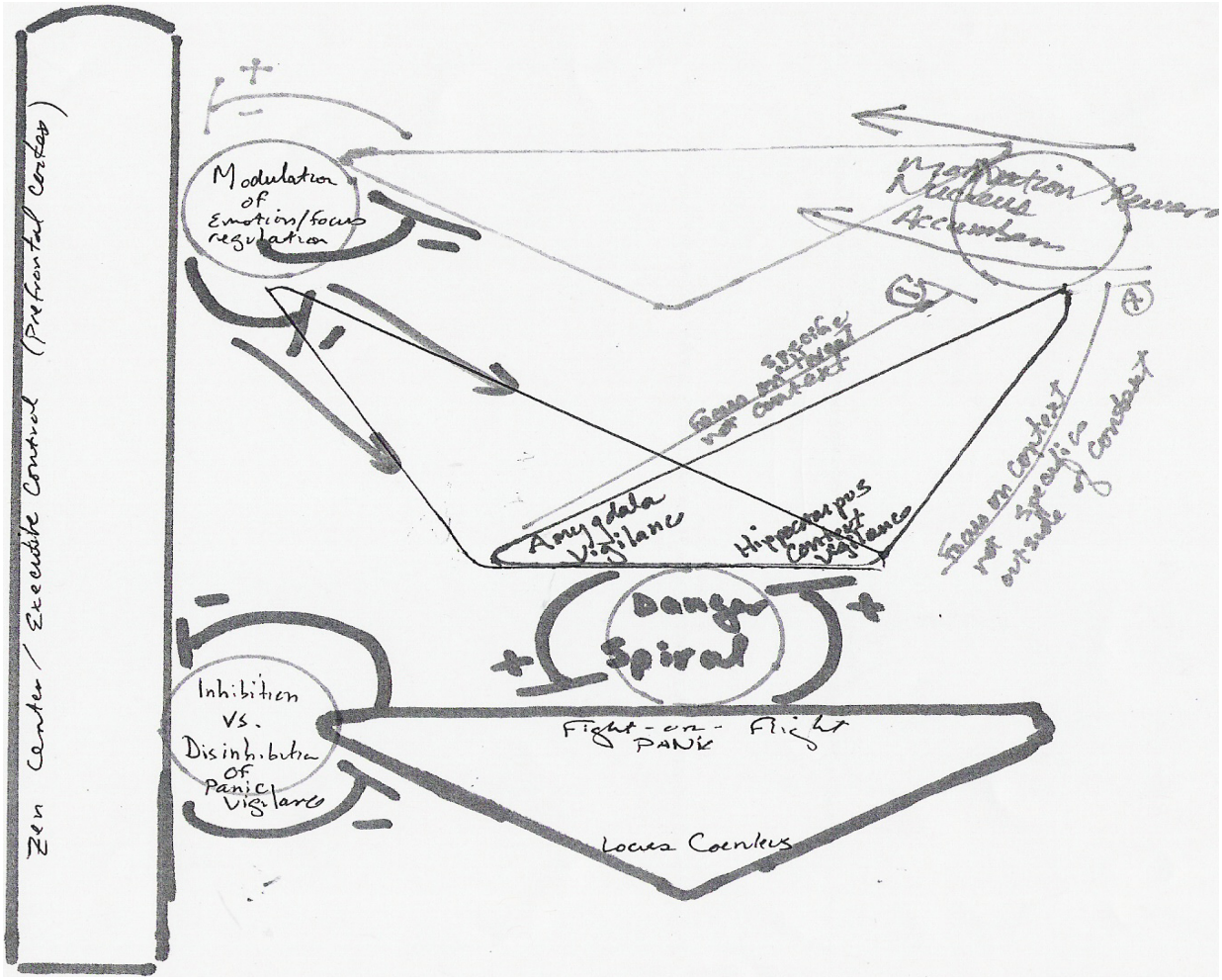


FIGURE 5. Right-Sided Regions of Significantly Greater Activation in Healthy Comparison Subjects Relative to Children and Adolescents With ADHD During a Switch Task





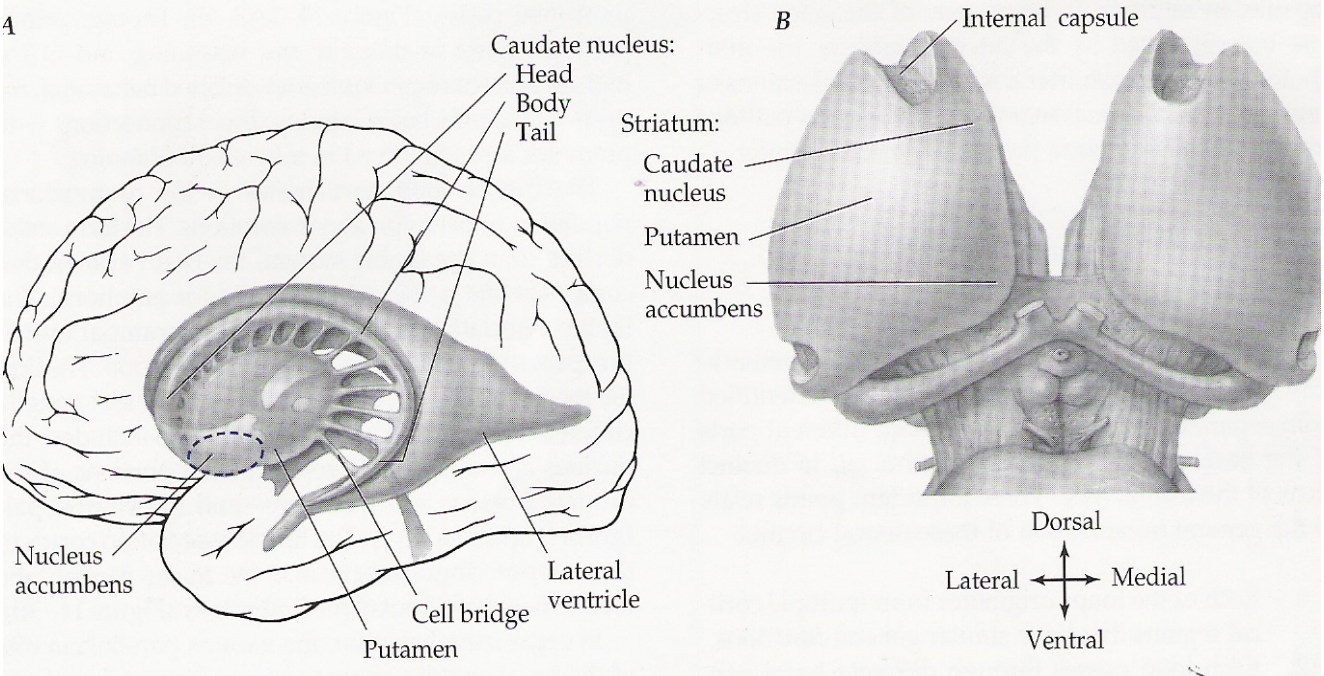
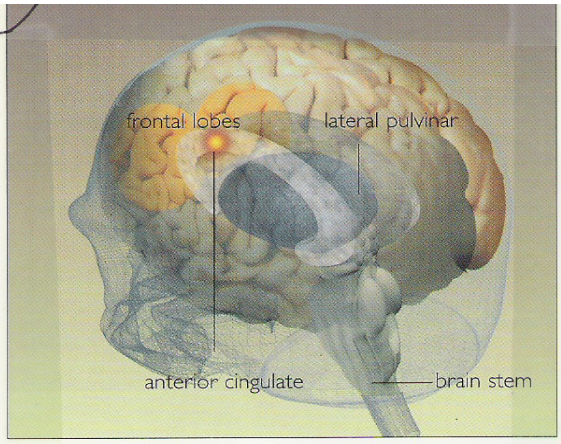
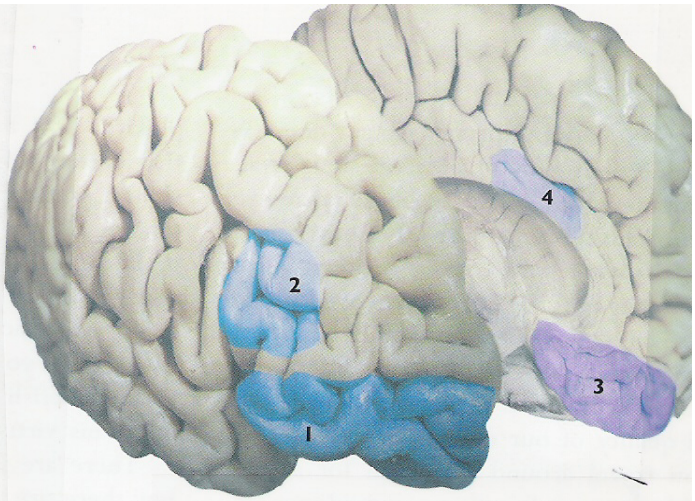


Figure 14–2. ***A.*** The striatum in relation to the ventricular system. The striatum consists of the caudate nucleus, putamen, and nucleus accumbens. Only the caudate nucleus has a C-shape, which is similar to that of the lateral ventricle. The nucleus accumbens is located ventromedially, primarily on the medial striatal surface. ***B.*** Ventral view of the striatum, diencephalon, and midbrain showing how the caudate nucleus, putamen, and nucleus accumbens are continuous ventromedially.



Focus



brain. The ones known to be particularly involved in activating the prefrontal lobe are dopamine and noradrenaline. Stimulation of this group of reticular neurons also creates alpha brainwaves – oscillations of electrical activity at 20–40 Hertz – which are associated with alertness.

Orientation is done by neurons in the superior colliculus and parietal cortex. The superior colliculus turns the eyes to the new stimulus, while the parietal cortex disengages attention from the current stimulus. Damage to the superior colliculus may cause oculomotor apraxia – in which eyes can't lock on to a new target. This makes a person functionally blind.

Damage to the parietal cortex may make a person unable to disengage from a stimulus.

Focus is brought about by the lateral pulvinar – a part of the thalamus – which operates rather like a spotlight, turning to shine on the stimulus. Once it is locked on, it shunts information about the target to the frontal lobes, which then lock on and maintain attention.

1) Orbito-frontal cortex: this area inhibits inappropriate actions, freeing us from the tyranny of our urges and allowing us to defer immediate reward in favour of long-term advantage.

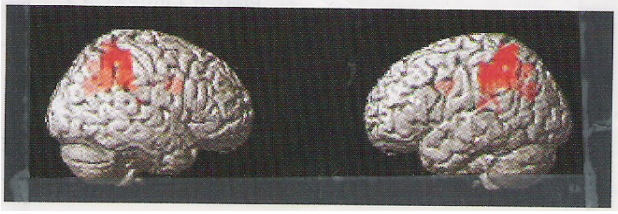
2) Dorsolateral prefrontal cortex: things are held 'in mind' here, and manipulated to form plans and concepts. This area also seems to choose to do one thing rather than another.

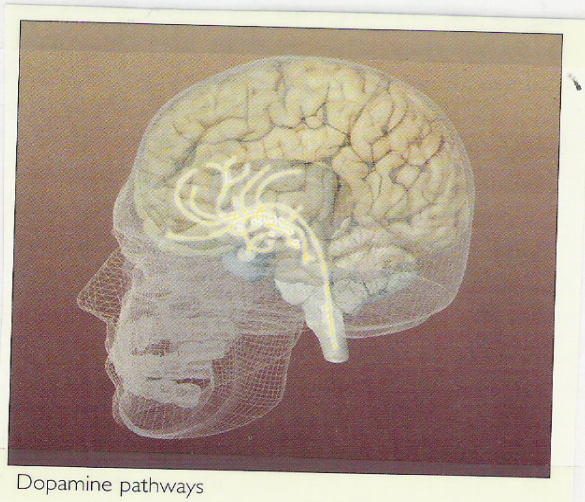
3) Ventromedial cortex: this is where emotions are experienced and meaning bestowed on our perceptions.

4) Anterior cingulate cortex – helps focus attention and 'tune in' to own thoughts.

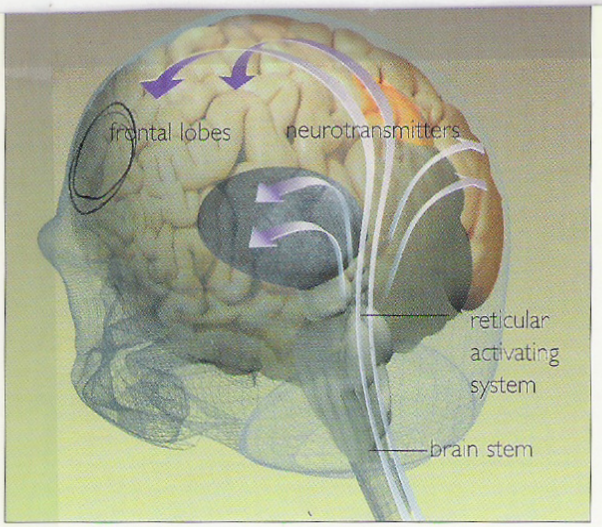
TAMM, MENON, AND REISS

FIGURE 3. Surface Rendering of Regions of Significantly Greater Activation in Healthy Subjects Relative to the ADHD Group

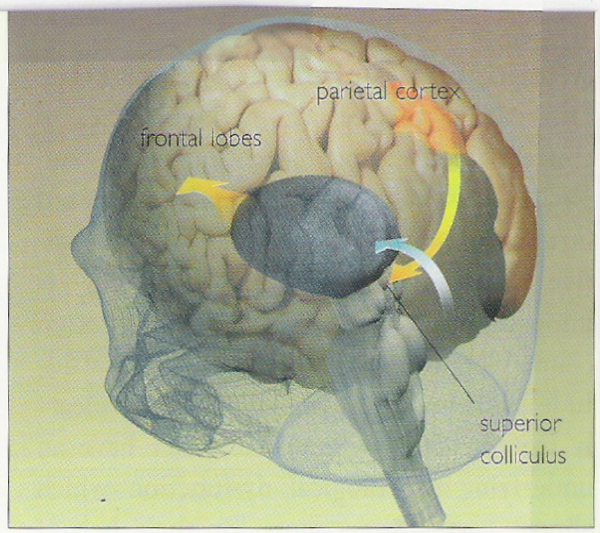




Dopamine pathways



AROUSAL



ORIENTATION

ATTENTION

The brain started as the body's alarm system, and alertness can be thought of as a special mechanism to ensure that the brain is at its most efficient when danger is about.

If the brain picks up a stimulus that may be a threat – a rustle in the bushes, say – the reticular activating system releases a rush of adrenaline throughout the brain. This closes down all unnecessary activity, so an alert brain shows up on a brain scanner as very quiet. It also inhibits body activity: the heart rate slows and breathing becomes shallow and quiet.

While the brain waits on alert for something to which to react, activity is maintained in the superior colliculus, the lateral pulvinar (a part of the thalamus) and the parietal cortex. These areas are concerned with orienting and focusing. Once a cue comes the appropriate area of the brain springs into activity and shows a greater level of activity than a brain that was not previously alert.

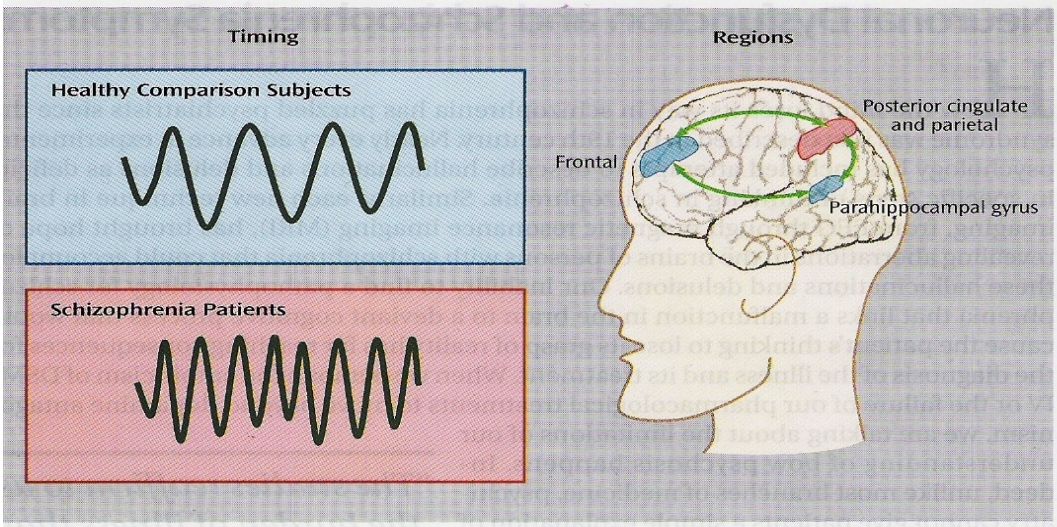
Attention is necessary for thinking, and possibly for consciousness. The brain constantly scans the environment for stimuli. This is done largely by automatic mechanisms in the brainstem. Even people in Persistent Vegetative State show scanning eye movements, which are part of this system.

Attention requires three elements: arousal, orientation, focus.

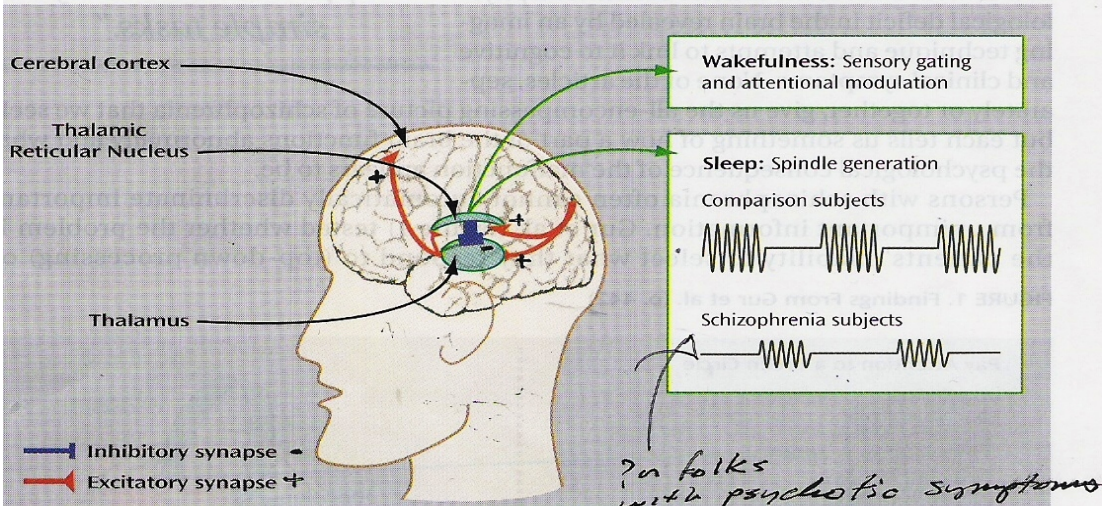
Arousal is dependent on a group of nuclei in the midbrain – the top of the brainstem – called the Reticular Activating System. The core of the brainstem is made up of neurons that have unusually long dendrites stretching up and down. Some of these travel right up to the cortex. Some of them are responsible for consciousness; concussion often results from disturbance of the system, and damage to them may result in permanent coma. Others control the sleep/wake cycle. A third group is responsible for controlling the level of activity in the brain. When they are stimulated they release a flood of neurotransmitters, which sets neurons firing throughout the

- Attention circuitry

IGURE 2. Findings From Garrity et al. (p. 450)

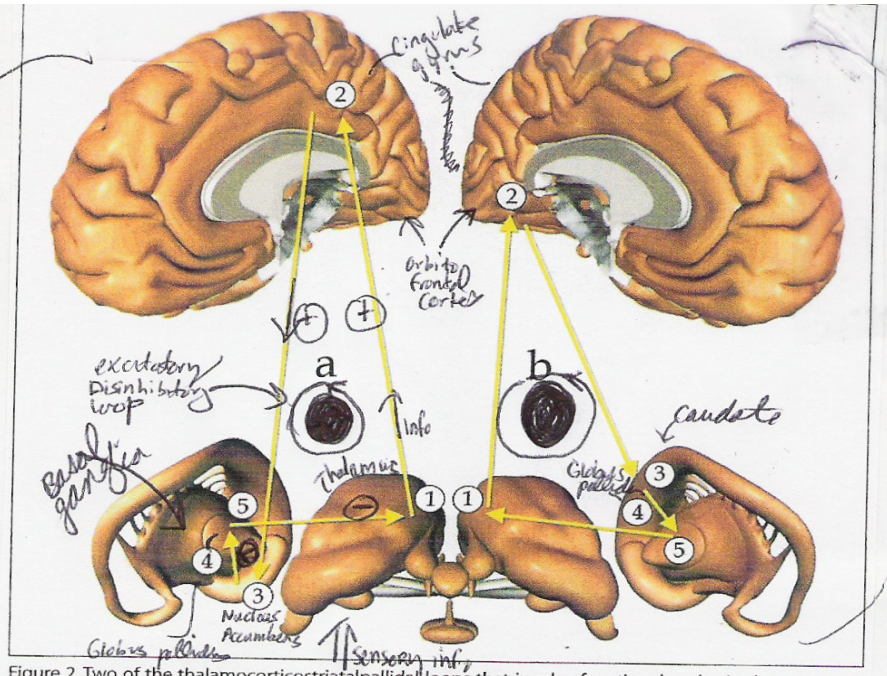


IGURE 3. Findings From Ferrarelli et al. (p. 483)



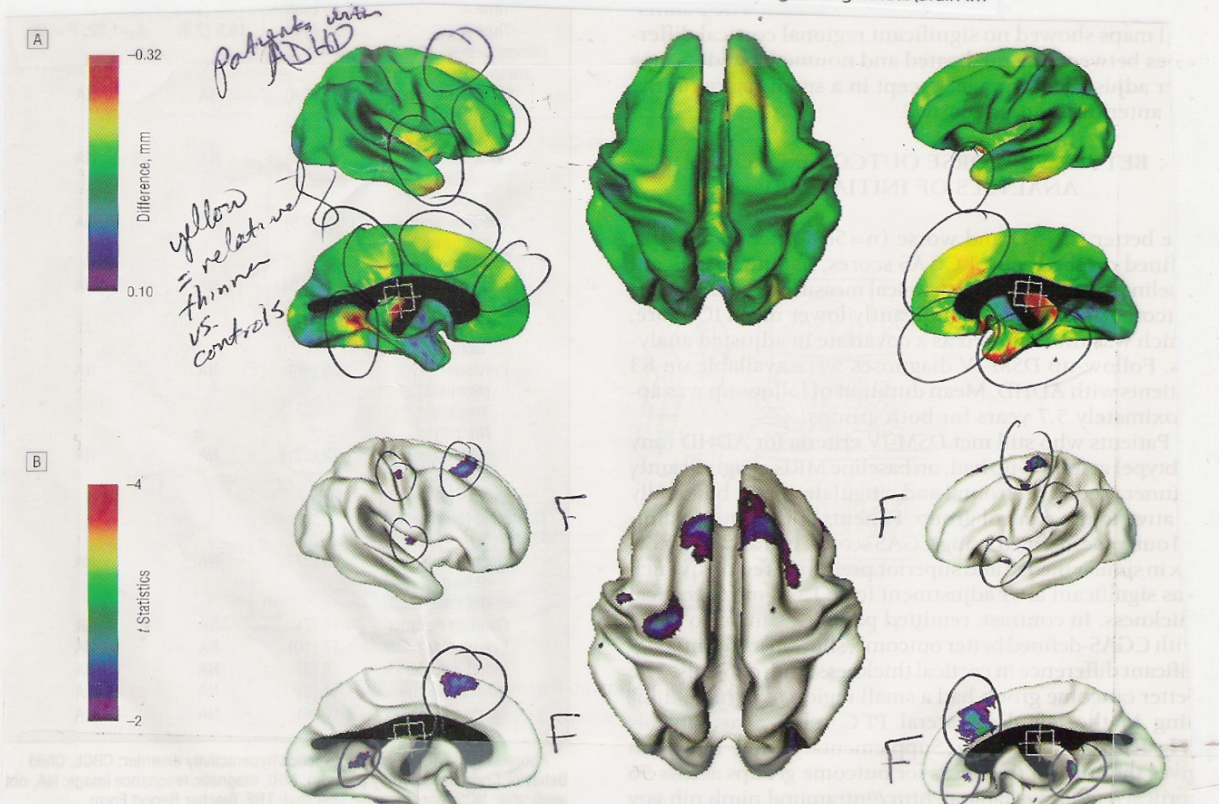
- Cortical-striatal-thalamic-cortical (CSTC) loop
  - External information reaches the prefrontal cortex (PFC, the C of the CSTC loop, portions of which subserve different but overlapping functions)
  - The information if then channeled from the PFC to the striatum (including the basal ganglia)
  - Then it's channeled from the striatum (basal ganglia) to the thalamus (a central sensory processing unit)
  - Then, completing the loop, the processed information is fed back to the cortex.
  - This loop is affected by:
    - Noradrenergic (norepinephrine) projections from the locus coeruleus
    - Dopaminergic projections from the ventral tegmental area
    - Histaminergic projections from the hypothalamus
    - Acethycholinergic (aka cholinergic) projections from the pedunculopontine tegmentum
    - With the exception of the histaminergic projections, both low and high levels of the neurotransmitters in the projections impair cognition
    - The goal of treatment, then, is to fine tune these neurotransmitters and the projections that utilize them
  - Multiple CSTC loops, each with different but overlapping functions

Sustained representation that focuses motivation and attention on particular stimulus."



Sustain... Focus/ motivation ... sensa... context/ stimuli

Figure 2. Two of the thalamocorticostriatalpallidal loops that involve functional nodes in the prefrontal cortex as key components. Figure 2a depicts the loop through the cingulate gyrus and nucleus accumbens. Information is transmitted from the dorsomedial nucleus of the thalamus (1) to the cingulate gyrus (2). Excitatory projections from the cingulate reach the nucleus accumbens (3) The nucleus accumbens sends inhibitory signals to the internal globus pallidus (4). The inhibition from the nucleus accumbens disrupts the tonic inhibition that the internal globus pallidus normally exerts on the thalamus and enhances thalamo-cortical transmission. The circuit can generate a sustained representation that focuses motivation and attention on a particular stimulus. Figure 2b depicts a similar circuit through the orbitofrrontal cortex. This circuit courses through the ventral anterior and dorsomedial nuclei of the thalamus (1), the orbitofrontal cortex (2), the dorsolateral caudate (3), the dorsomedial globus pallidus (4), and then back to the thalamus. The dorsolateral prefrontal circuit is not shown. It has nodes in the ventral anterior and dorsomedial nuclei of the thalamus, Brodmann areas 9 and 10, the dorsolateral caudate, the dorsomedial globus pallidus, and then back to the same thalamic nuclei from which the signal originated. (Brain im-



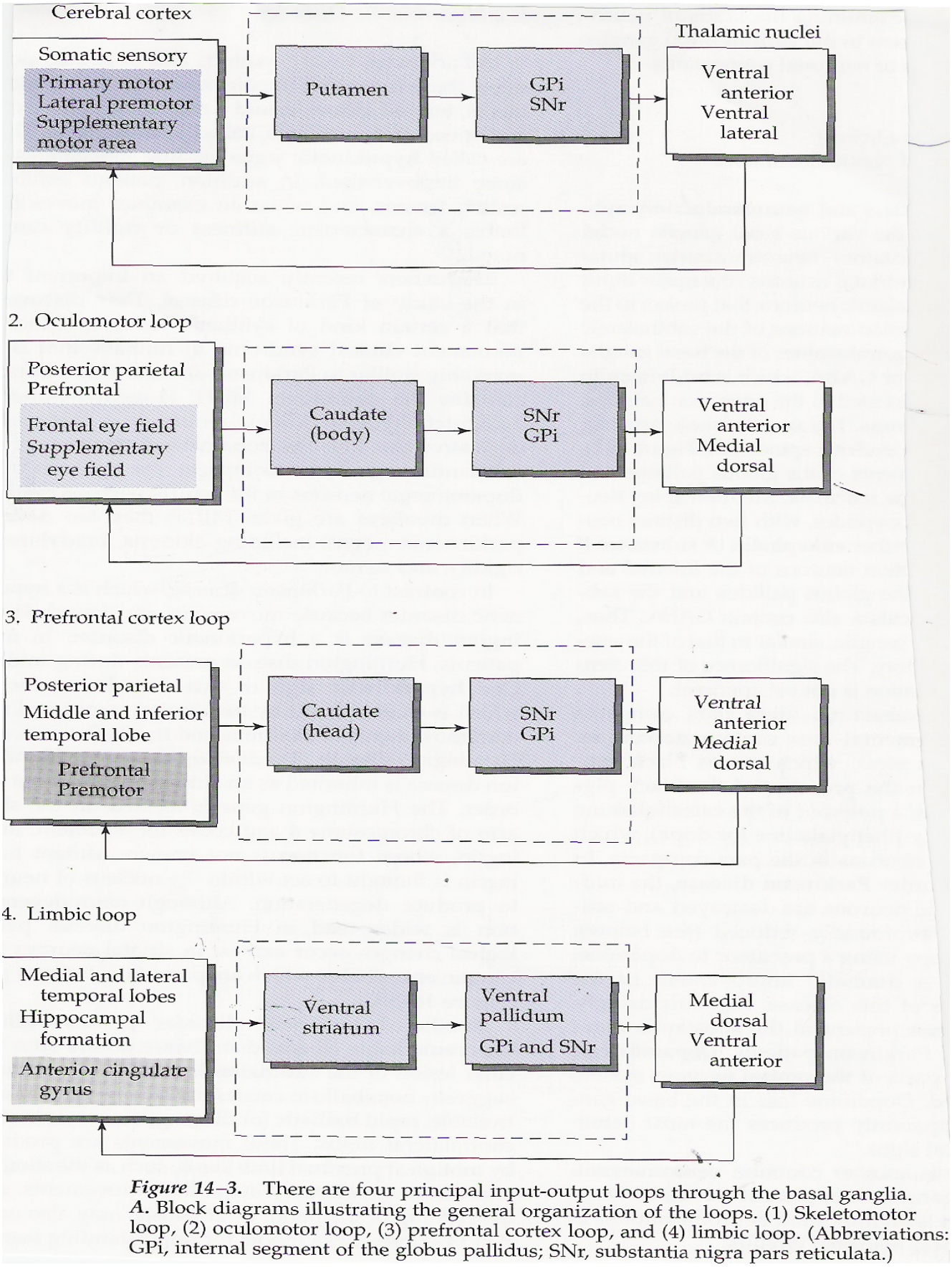


Figure 14–3. There are four principal input-output loops through the basal ganglia. *A.* Block diagrams illustrating the general organization of the loops. (1) Skeletomotor loop, (2) oculomotor loop, (3) prefrontal cortex loop, and (4) limbic loop. (Abbreviations: GPi, internal segment of the globus pallidus; SNr, substantia nigra pars reticulata.)

- The dorsal anterior cingulate cortex (dACC) as one C in CSTC (**selective attention/orienting)**
  - involved in
    - selective attention
    - goal-directed behavior
    - monitoring of conflict situations

        - control of emotional output
    - disruption affects or contributes to
        - distractibility
        - forgetfulness
        - losing things
        - ability to listen
        - attention to fine details
        - making of careless mistakes
        - less activation in children and adults with ADHD; not alleviated by medications
    - treated by
        - (affecting histamine)
            - stimulants
            - Provigil
            - reduction in antihistamines
        - (affecting acetylcholine)
            - nicotine/nicotinergic agonists/partial agonists
            - reduction in anticholinergics
- The dorsolateral prefrontal cortex (DLPFC) as the C in CSTC **(sustained attention)**
    - involved in
        - sustained attention
        - problem solving
        - cognitive flexibility
        - self monitoring
        - planning
    - disruption affects or contributes to
        - lack of organization
        - avoidance of tasks that involve sustained attention
        - not following through on projects
        - in ADHD, less activation of this circuit during tasks of attention and problem solving; instead, a much more diffuse pattern of activity throughout the brain thought to be a compensatory mechanism and part of the increased size of the occipital lobe seen in ADHD; some of these differences can be reversed with medication treatment
    - treated by
        - (affecting dopamine)
            - stimulants
            - Wellbutrin
            - Provigil (indirectly in the cortex)
            - Armodafinil (Nuvigil)
            - Strattera (indirectly in the cortex)
        - (affecting norepinephrine)
            - stimulants
            - Straterra
            - Wellbutrin
            - guanfacine
            - clonidine
- Prefrontal motor cortex as the C in CSTC (important in **motor activity**)
    - inolved in
        - modulation of motor activity
        - dopaminergic input from the brainstem stimulates dopamine-1 receptors in the prefrontal motor cortex
        - the prefrontal motor cortex then
            - directly and indirectly modulates activity in the striatum/basal ganglia (the S in CSTC)
            - inhibits (in a feedback manner and via glutamatergic transmission) the dopaminergic neurons in the brainstem which impacts dopaminergic input from the brainstem to the striatum
            - dysfunction may occur due to
    - abnormal activation in the striatum
        - abnormal functioning of the inhibitory feedback to the brainstem
    - treated by
        - dopamine-1 stimulation in the prefrontal motor cortex, and/or
        - dopamine-2 blockade in the striatum
        - primary treatment: stimulants
- Lateral orbital frontal cortex (LOFC or, here, OFC; as another C in the CSTC) (important in **impulse control**)

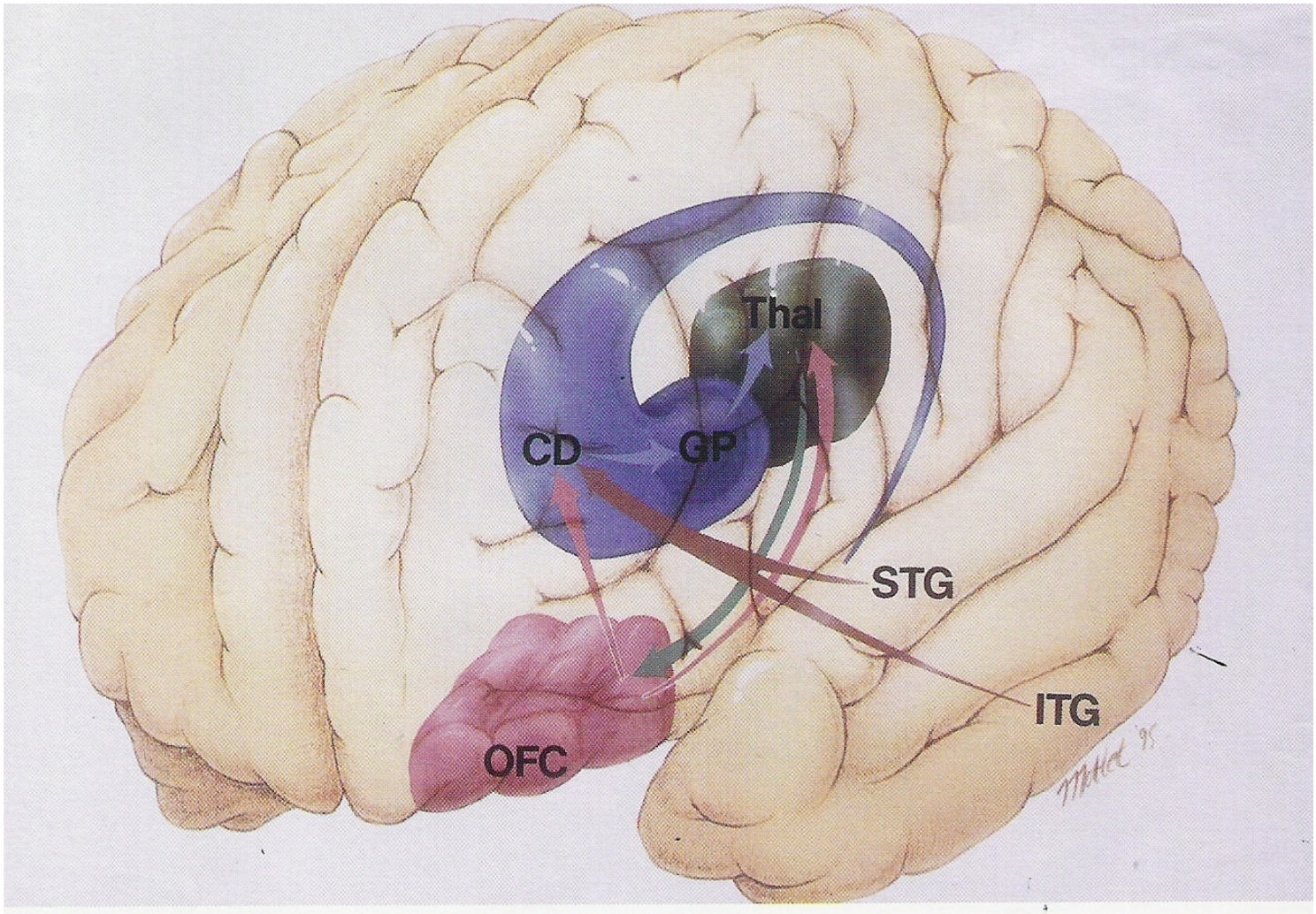


FIGURE 4–11. Lateral orbitofrontal cortex (OFC)–basal ganglia loop.
CD=caudate nucleus; GP=globus pallidum; ITG=inferior temporal gyrus; STG=superior temporal gyrus; Thal=thalamus

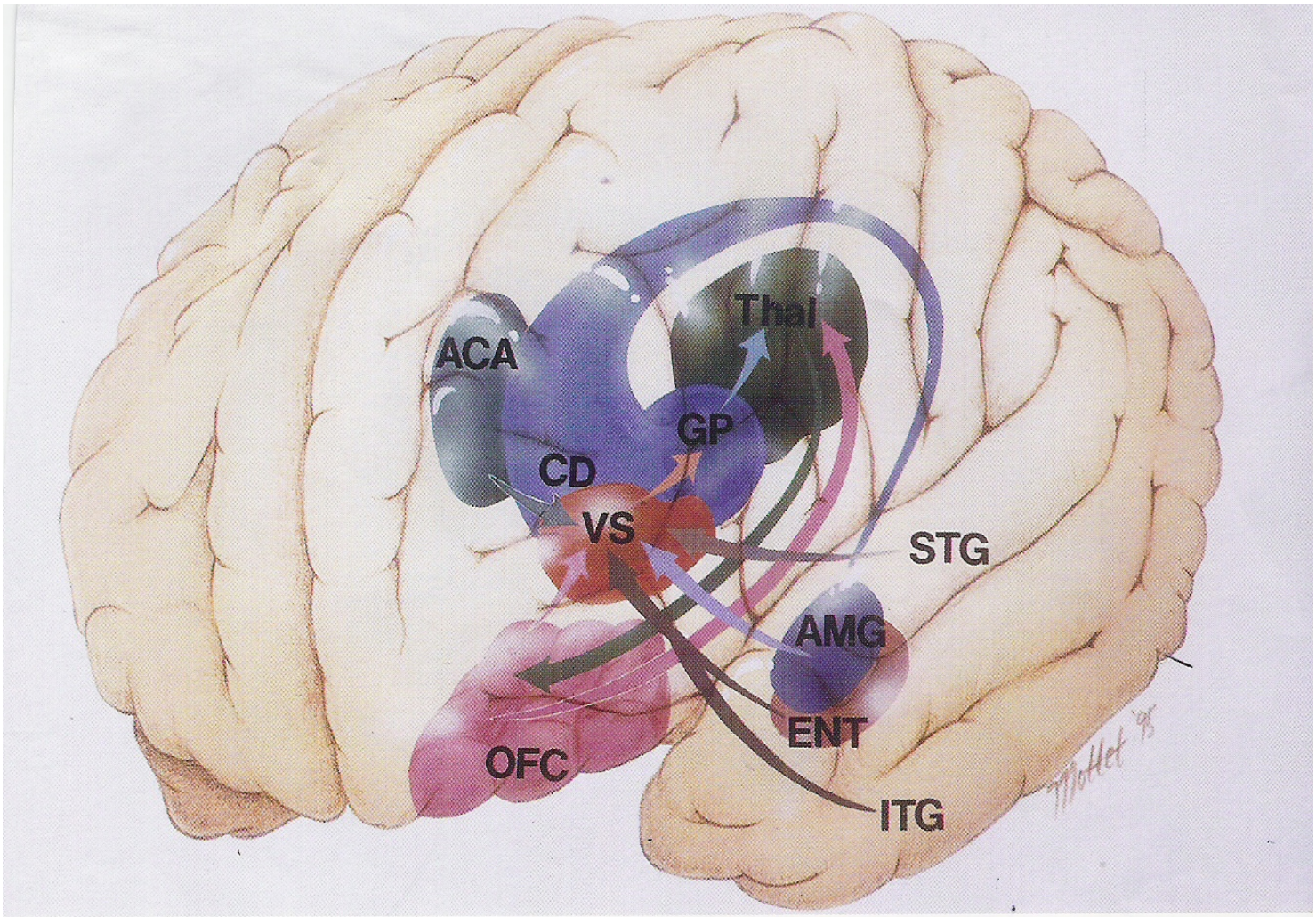
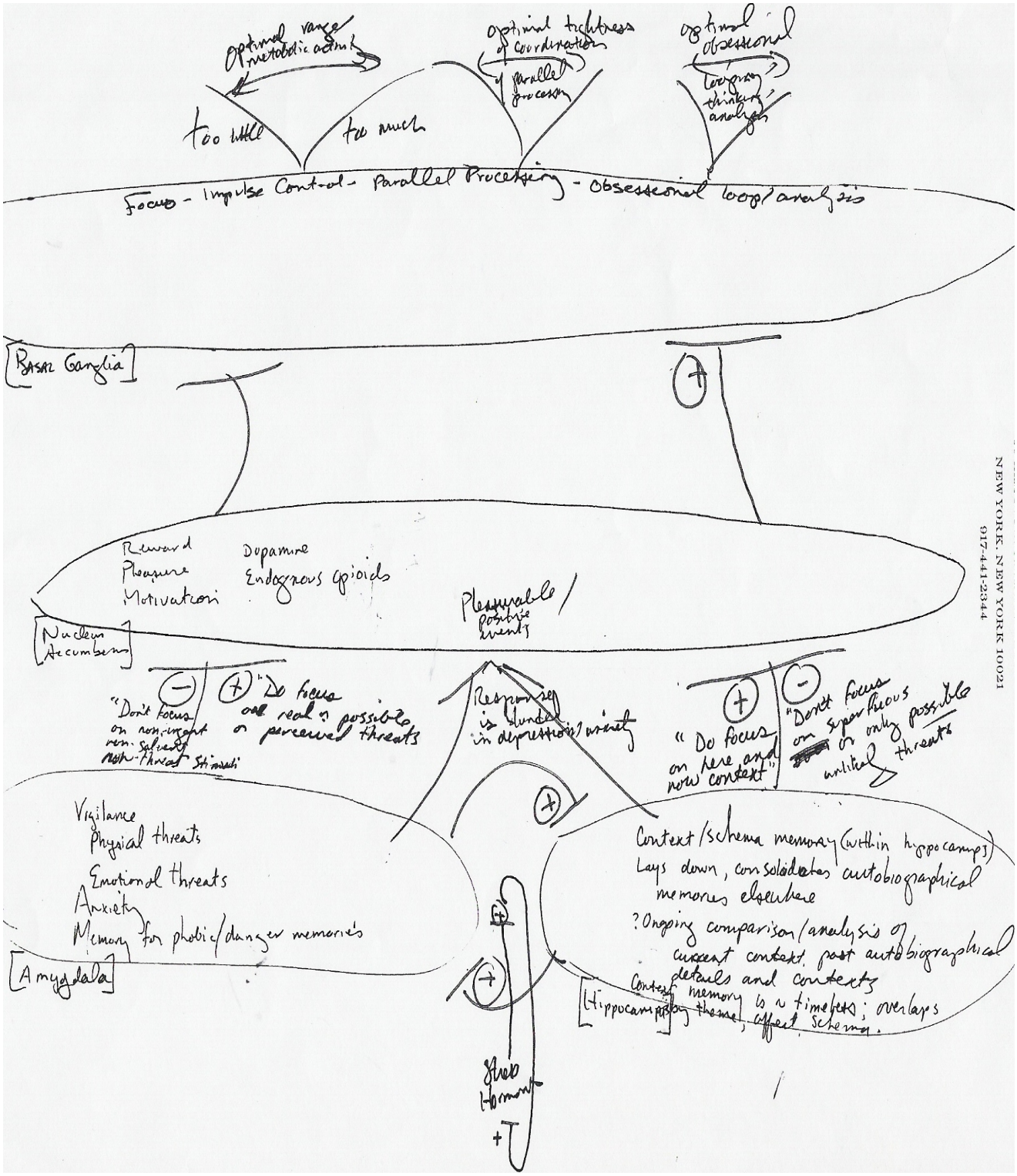


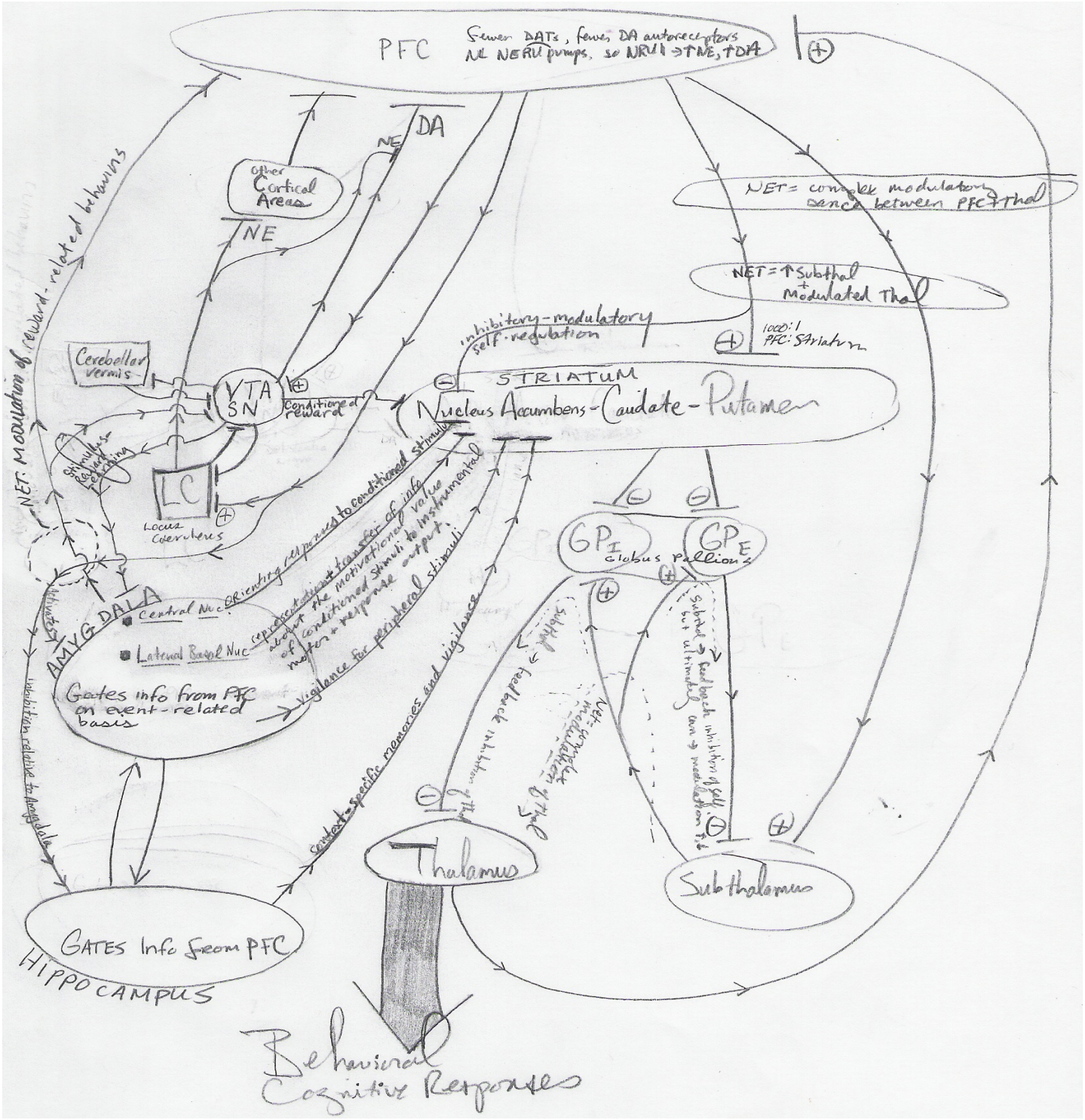
FIGURE 4–12. The medial orbitofrontal cortex (OFC)–basal ganglia loop.
ACA=anterior cingulate area; AMG=amygdala; CD=caudate nucleus; ENT=entorhinal cortex; ITG=inferior temporal gyrus; STG=superior temporal gyrus; Thal=thalamus; VS=ventral striatum.

- modulation/mediation of
  - information about the internal environment
  - impulse control, inhibition of inappropriate responses
  - regulating emotions
  - inhibiting inappropriate emotions
- involves
  - dopaminergic input from the brainstem stimulates dopamine-1 receptors in the OFC; involves norepinephrine as well
- the OFC then
  - modulates the striatum/basal ganglia/nucleus accumbens (especially the latter; the S in CSTC)
  - inhibits motor responses to emotional stimuli
  - inhibits (in a feedback manner and via glutamatergic transmission) the dopaminergic neurons in the brainstem which impacts dopaminergic input from the brainstem to the striatum
- dysfunction may be due to OFC not functioning properly with consequent reduction in inhibitory feedback, directly or indirectly, to striatum
- treated by
  - stimulating dopamine-1 receptors in the OFC, and/or
  - blockade of dopamine-2 receptors in the nucleus accumbens
  - medications
    - stimulants
    - Strattera
    - Wellbutrin
    - guanfacine
    - clonidine

- Striatum/basal ganglia (the S in the CSTC loop)
    - Anatomical changes
        - increased number of subcortical hyperintensities in youth with ADHD or OCD or Tourette syndrome.
        - caudate nucleus (CN)
            - reversed pattern of asymmetry of the head of the CN
            - volume reduction overall
            - smaller right CN
            - smaller left CN
            - decreased blood flow
        - globus pallidus (GP)
        - volume reduction/volume expansion
        - smaller left GP
    - in one study, children with ADHD demonstrated the same abnormalities relative to their unaffected identical twin siblings of children with ADHD (who did not show these abnormalities)
- other changes
    - reduced metabolism
    - abnormalities were also seen in the fibers of the basal ganglia. The fiber abnormalities are less pronounced when children are treated with stimulant medications
- dopamine; differences in dopamine neurochemistry in midbrain and basal ganglia; reduction in dopamine release from the
    - striatum
    - nucleus accumbens
    - Volkow, 2006: never-medicated adults with ADHD vs, control subjects demonstrate dysfunctional dopamine functioning in the left caudate and the left nucleus accumbens (both part of the basal ganglia).
- medication effects
    - Ludolph et al, 2006: methylphenidate treatment of ADHD results in an equalizing effect in the areas of the brain that, pre-treatment have abnormal dopamine metabolism (decreased in the left putamen, right amygdala, right dorsal midbrain and increased in the left insular cortex, left amygdala, and right anterior cortex
    - methylphenidate increases blood flow in the caudate nucleus
    - Newcorn et al, 2006 (and see below): methylphenidate, more than Strattera, increased activation of the caudate nucleus bilaterally, left frontopolar cortex, right motor cortex, and right inferior temporal cortex
- Prefrontal cortex (PFC) and it's subunits (the C in the CSTC)
    - anatomical changes
        - overall volume reduction
        - global thinning of medial and superior PFC, especially in youth with worse outcome
        - better clinical outcome is associated with right parietal cortex that, over time, converges with the cortical thickness seen in controls
        - volume reduction on right side
        - volume reduction right anterior white matter regions
        - smaller dorsolateral prefrontal cortex
        - smaller left orbitofrontal cortex
        - decreased blood flow as well
    - anterior cingulate cortex (ACC)
        - volume reduction
        - hypoactive in boys with ADHD and failure to activate properly in adults with ADHD; this is corrected with methylphenidate treatment
        - Ritalin increases activity in the dorsal ACC in patients with ADHD
    - other changes
        - decreased blood flow in prefrontal cortex with increased intellectual strength
        - reduced dopamine and norepinephrine tone in the prefrontal cortex
    - medication effects; Newcorn et al, 2006 (and see above and below):
        - methylphenidate and Strattera increase activation in overlapping regions of the right ventrolateral prefrontal cortex and the dorsal anterior cingulate gyrus
        - methylphenidate, more than Strattera, increased activation of the caudate nucleus bilaterally, left frontopolar cortex, right motor cortex, and right inferior temporal cortex
        - Strattera, more than methylphenidate, increased activation in the bilateral posterior parietal cortex, left insula, middle and superior temporal gyri and posterior cingulate gyrus
        - methylphenidate increased blood flow here BUT in folks where tasks of sustained visual vigilance led to decreased blood flow to the caudate and GP with relatively increased flow to the prefrontal cortex, methylphenidate led to relative increased blood flow to caudate and GP and less to prefrontal cortex.
        - medication treatments appear to enhance dopamine 1 and norepinephrine alpha2a receptor stimulation in the prefrontal cortex.
- Cortical areas:
    - reduced metabolic rates in
        - premotor cortex
        - somatosensory cortex
        - left anterior frontal cortex in adolescents, which correlates with symptom severity

        - increase metabolic rate
            - occipital cortex
            - prefrontal cortex
            - frontal cortex (in addition to changes in the prefrontal cortex) in adults
        - dopamine and norepinephrine
            - differences in dopamine neurochemistry in the right parietal cortex and the left parieto-occipital cortices
            - dopamine and norepinephrine beta and alpha 1 receptor stimulation in posterior cortical areas
        - medication changes; Newcorn et al, 2006 (and see above):
            - methylphenidate and Strattera increase activation in overlapping regions of the right ventrolateral prefrontal cortex and the dorsal anterior cingulate gyrus
            - methylphenidate, more than Strattera, increased activation of the caudate nucleus bilaterally, left frontopolar cortex, right motor cortex, and right inferior temporal cortex
            - Strattera, more than methylphenidate, increased activation in the bilateral posterior parietal cortex, left insula, middle and superior temporal gyri and posterior cingulate gyrus
    - Corpus callosum.
        - volume reduction
    - Hippocampus and amygdala (Pleason, 2006)
        - Increased size hippocampus bilaterally; this may be compensatory
        - Decreased size amygdala bilaterally
    - Corticopontocerebellar (CPCb) circuit
        - The fiber pathways that communicate between the frontal lobes and the cerebellum.
        - Abnormalities are seen in these fibers in ADHD
        - The fiber abnormalities are less pronounced when children are treated with stimulant medications.
    - Cerebellum (Cb)
        - smaller smaller Cb overall
        - right Cb
        - in those with worse outcomes, progressively smaller right and left inferior-posterior lobes during adolescence
        - smaller posterior vermis
        - smaller superior vermis
        - smaller left and total posterior superior and inferior lobes of vermis
        - decreased blood flow
            - corrected by methylphenidate when symptoms shown to be improved
            - worsened by methylphenidate when symptoms shown to not be improved
    - Parallel frontostriatal circuits:
        - Executive function: dorsolateral prefrontal cortex (DLPFC) dorsolateral caudate dorsomedial globus pallidus thalamus
        - Disinihibition, irritability: orbitofrontal cortex (OFC), ventromedial caudate, M-dorsomedial globus pallidus, thalamus
        - Apathy, inertia: anterior cingulate, nucleus accumbens, R-L globus pallidus, thalamus
- Anatomy of learning disorders; some anatomical differences were found in the following areas (Autti, 2006):
    - Anterior cingulate cortex—greater volume
    - Left frontoparietal lobe—greater volume
    - Left thalamus—less volume
    - Posterior internal capsule—less volume



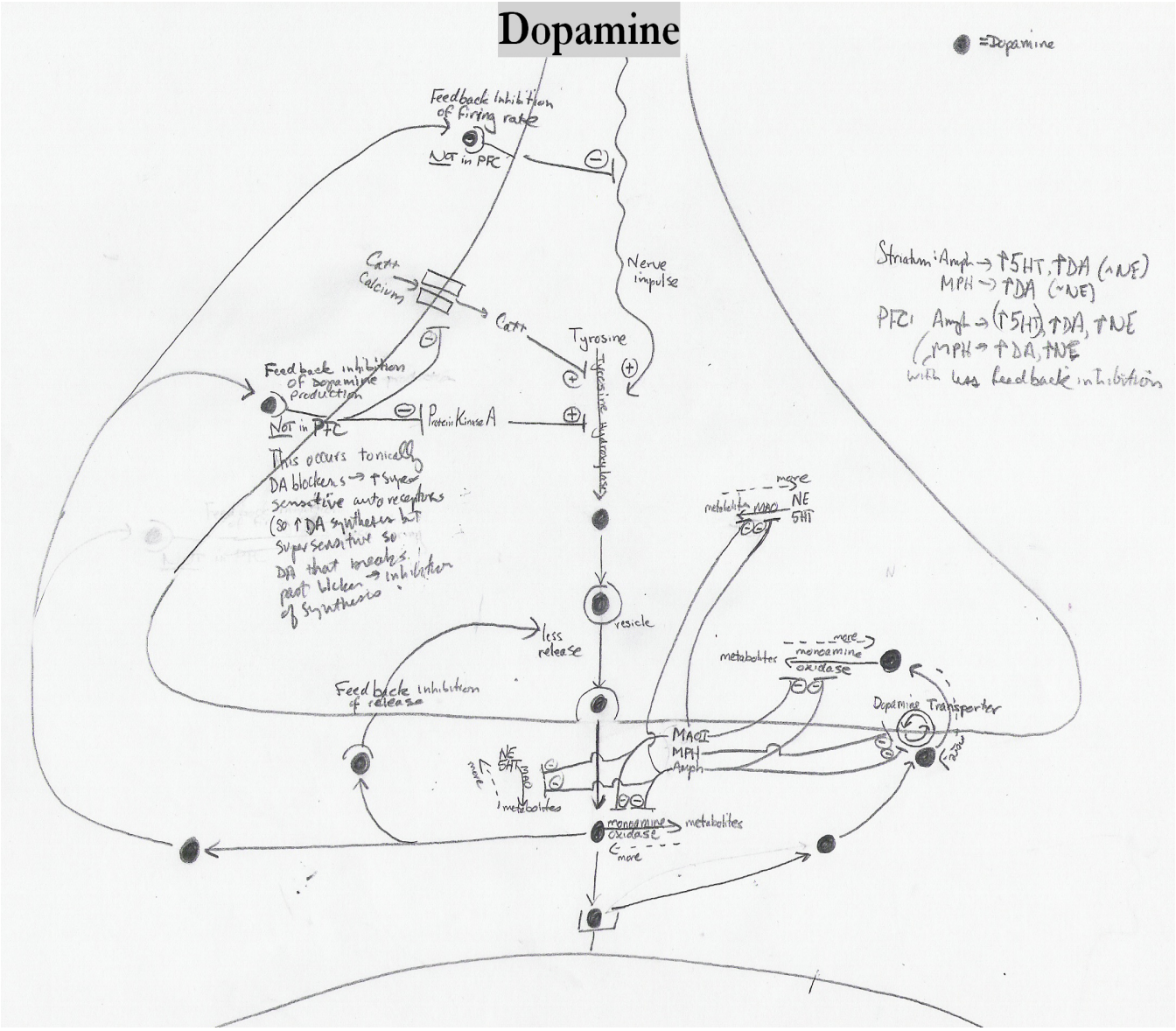


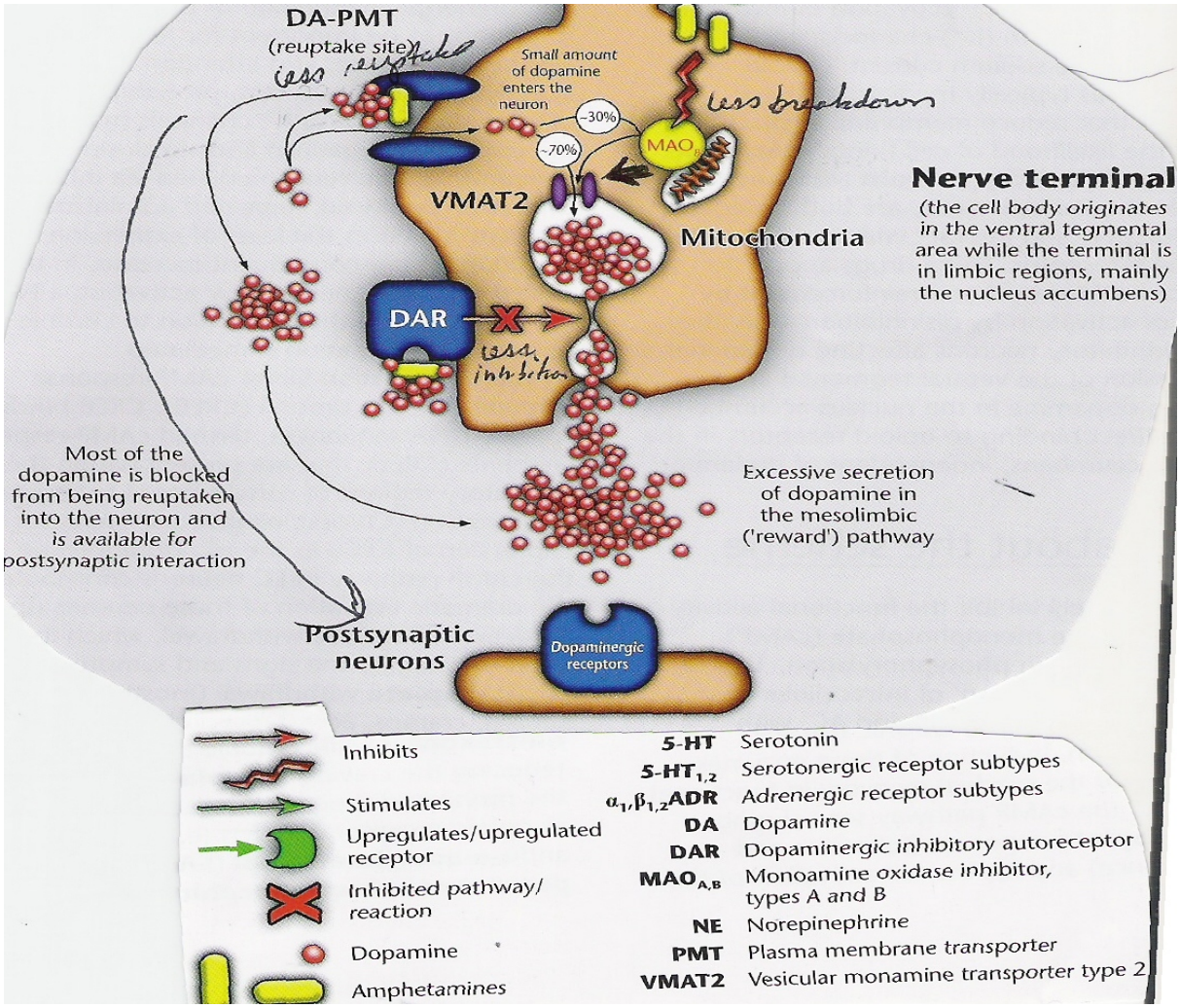
- Smoking during pregnancy doubles the risk of ADHD
- Genetics:
    - The estimated heritability (from 20 twin studies) of ADHD (which is the percentage of the etiology that can be attributed to genetic rather than environmental factors) is 0.8 (maximum is 1.00) with a range of ~0.58-1.0. This is the highest rate of heritability of all psychiatric disorders.
        - Impulsivity/hyperactivity dimension—91% per parent report, 69% per teacher report
        - Inattentive dimension—69% per parent report, 39% per teacher report
    - Compare the heritability of ADHD to other heritable conditions:
        - Height 85-92%
        - **ADHD 75-80%**
        - Schizophrenia ~72%
        - Weight 70%
        - Intelligence 52%
        - Personality 50%

- Alzheimer's disease 50%
- Panic disorder ~43%
- Vocational interests 42%
- Scholastic achievement 38%
- Memory 22%
- Hypertension 20%
- Life span 3%

- There is a genetic overlap of ADHD and autism on a few aspects
- About 50% of first degree relatives of clients with ADHD also have ADHD.
    - Parents of children with ADHD are 0-7.6 times more likely to have ADHD.
    - Siblings of children with ADHD are 2.1-3.5 times more likely to have ADHD.
- Children of parents with ADHD are 7 times more likely (up to 50% risk) to develop the disorder than children with parents without ADHD.
- If your sibling has ADHD, risk your risk for the disorder is 20-25%.
- If your identical twin has ADHD, your risk for having the disorder is 80-90%; among fraternal twins, the risk is 30-40%.
- For second-degree relatives, including aunts, uncles, or first cousins, the risk can be as high as 12%.
- Candidate genes include those that code for:
    - Dopamine system genes
        - dopamine 1, 2, 4, 5 receptor subtypes
            - dopamine 4 receptor (DRD4) gene
                - heavily expressed in the prefrontal cortex, where it modulates excitatory signaling
                - likely modulates working memory and cognition, with dopamine levels that are too low or too high causing impairment in these areas
        - blocking DRD4 (with minimal blockade of other dopamine receptors) may help treat cognitive deficits (which may explain why Clozaril, which blocks DRD4 receptors more so than other dopamine receptors, as opposed to traditional antipsychotics, which don't, treats cognitive dysfunction associated with schizophrenia)
        - stimulants may work, in part, by activating pre-synaptic inhibitory autoreceptors in neurons of the dorsolateral prefrontal cortex (in which DRD4 receptors are prevalent)
            - The 7-repeat allele variant was found
        - to be less efficient in it's affinity/binding as well as it's activity
        - to have a pooled odds ratio of 1.4-1.9 for association between ADHD and the variant; twice as prevalent in folks with ADHD; may account for 25-50% of the genetic risk for ADHD
        - to be associated with poor performance (more inaccuracy and impulsivity) on neuropsychological tests
        - to have more side effects in preschoolers treated with methylphenidate (see PATS study in "Stimulants").
        - NIMH PATS (pre-school ADHD) study, 2006: association between ADHD and DRD4; this variant (when treated with stimulants) is associated with:
            - picking
            - irritability at higher doses
            - social withdrawal at higher doses
        - to be associated with a thinner right orbitofrontal/inferior prefrontal and posterior parietal cortex; this overlapped with regions that were generally thinner in subjects with ADHD compared with controls (Shaw et al, 2007)
        - to be associated with better clinical outcome and a distinct trajectory of cortical development, demonstrating normalization of the right parietal cortical region (which has in the past been associated with better clinical outcome) (Shaw et al, 2007)
        - in individuals lacking the 7-repeat allele, externalizing behavior was negatively correlated with IQ (in those with 1 or 2 copies of the 7-repeat allele, these were not correlated); also, those youth with ADHD but without the 7-repeat allele demonstrated several neuropsychological deficits assessing attentional networks involving the dorsolateral prefrontal cortex whereas those with the 7-repeat allele did not.
            - dopamine 5 receptor (DRD5); odds ratio >1. Also associated with ODD.
        - dopamine transporter (DAT1/SLC6A3)
            - 480-bp allele may be too active in ADHD (perhaps by 15%) and lead to too little available dopamine
            - Two variable-number tandem repeat polymorphisms within the 3' untranslated region and intron 8 is associated with combined-type ADHD
            - Laucht et al, 2007: risk of ADHD mediated by concomitant presence of psychosocial adversity
        - dopamine beta-hydroxylase—9q33
        - dopamine decarboxylase—7p13
    - Noradrenergic alpha-2a, 2c receptors.
    - Serotonin
        - 2A receptor
        - 1B receptor
    - COMT
        - Prefrontal cortical function is influenced by a valine/methionine variant in the COMT; this variant is associated with early-onset antisocial behavior in children with ADHD
        - Sengupta et al, 2006: not associated with birth weight and conduct disorder in children with ADHD
    - Synaptosomal associated protein of 25 kD (SNAP-25)
        - this protein is critical in neurotransmitter release
        - two variants also associated with more side effects in preschoolers treated with methylphenidate (see NIMH PATS study in "Stimulants")
        - these variants associated with (in treatment with stimulants):
            - tics
            - buccal-lingual movements
            - irritability

- Monoamine-A oxidase
- Thyroid hormone receptor beta (THRB) gene
- Chromosome
    - 4
    - 5q33.3—MEGF protein, Sorting nexing 24, Synphilin
    - 6
    - 8
    - 11q22—APP beta-secretase, Down syndrome cell adhesion molecule like-protein 1b
    - 12p13—Neurotrophin 3, Synaptobrevin 1, ERC protein 1, Betaine/GABA transporter
    - 15q15—Nicotinic receptor alpha 7 subunit, Connexin-36, Meis2, SNAP23, MAP1a
    - 16p13—NUDE, Stannin, NMDA-2a receptor
    - 17p11—peripheral myelin protein 22, Tektin 3, adenosine A2b receptor, Nuclear receptor co-repressor
- Note that there are strong genetic contributions to temperament, thus making interpretations of the above genetic variations controversial.




DA-PMT
(reuptake site)
less reuptake
Small amount of dopamine enters the neuron
~30%
~70%
MAO
less breakdown
VMAT2
Mitochondria
DAR
less inhibition
Nerve terminal
(the cell body originates in the ventral tegmental area while the terminal is in limbic regions, mainly the nucleus accumbens)
Most of the dopamine is blocked from being reuptaken into the neuron and is available for postsynaptic interaction
Excessive secretion of dopamine in the mesolimbic ('reward') pathway
Postsynaptic neurons
Dopaminergic receptors
Inhibits
Stimulates
Upregulates/upregulated receptor
Inhibited pathway/ reaction
Dopamine
Amphetamines
5-HT Serotonin
5-HT1,2 Serotonergic receptor subtypes
α1,β1,2ADR Adrenergic receptor subtypes
DA Dopamine
DAR Dopaminergic inhibitory autoreceptor
MAOA,B Monoamine oxidase inhibitor, types A and B
NE Norepinephrine
PMT Plasma membrane transporter
VMAT2 Vesicular monamine transporter type 2