International Society for CNS Clinical Trials and Methodology

"The Neurobiology of Negative Symptoms; A neuroanatomical circuit analysis "

James H. Fallon, Ph.D.
Department of Anatomy and Neurobiology
& Brain Imaging Center
School of Medicine
University of California, Irvine

Satellite Meeting on the NIMH Initiative Regarding Treatment Development for Negative Symptoms

Washington DC, USA

February 23-24, 2006

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

This analysis will be based on chemical neuroanatomical circuit modeling of CNS structures implicated in the etiology of schizophrenia, especially with regards to negative symptoms.

The circuits will be discussed at the micro- and macro-levels, with emphasis on the ‘prefrontal system’ of cortico-cortical and cortico-subcortical loops

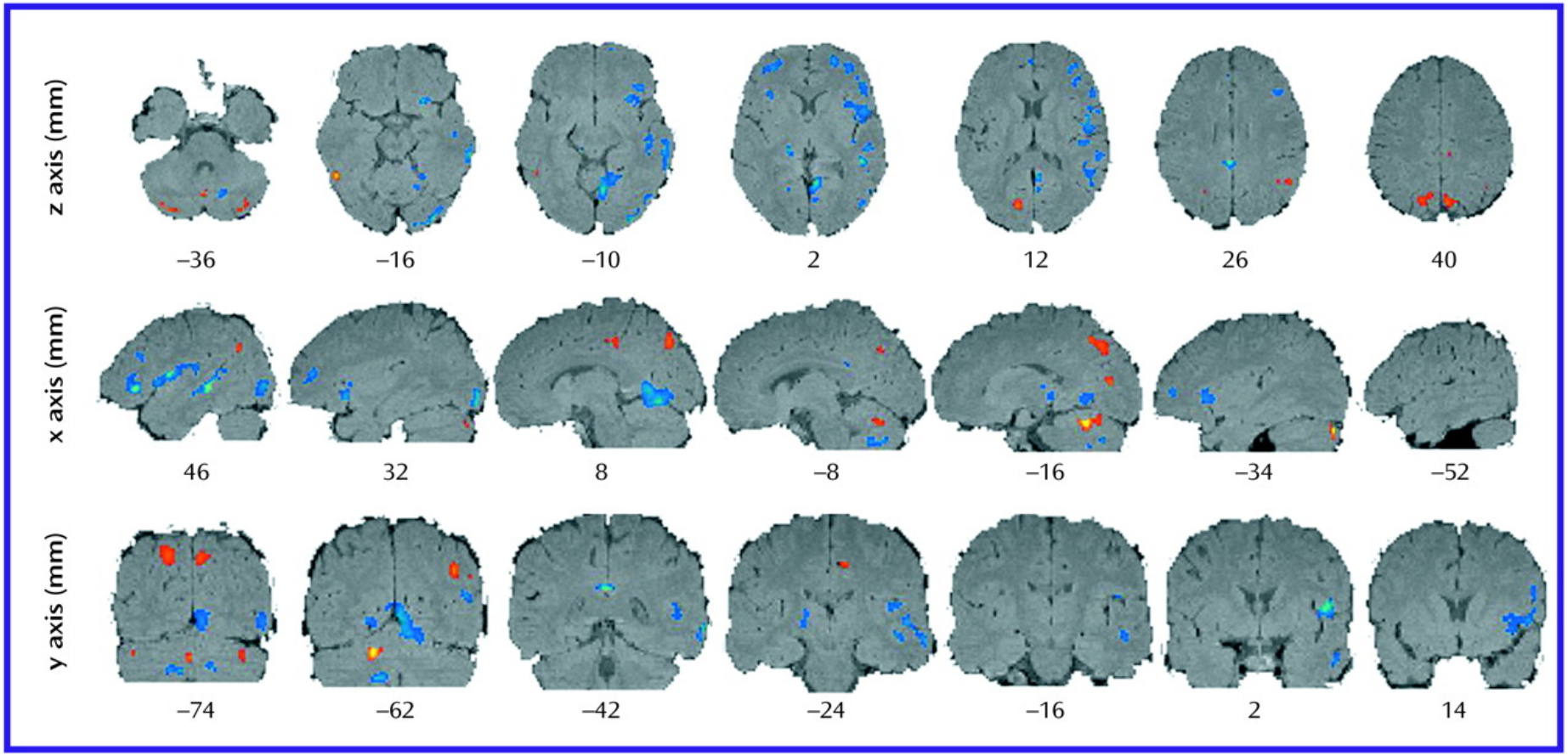
Borod et al 1993 Perception of facial emotion in schizophrenic and right brain-damaged patients.**Support is provided for the notion that negative-symptom schizophrenia is associated with right hemisphere dysfunction**

Hazlett et al 2004 Abnormal Glucose Metabolism in the Mediodorsal Nucleus of the Thalamus in Schizophrenia
Lower relative glucose metabolism in the pulvinar was associated with more hallucinations and more positive symptoms, while lower relative glucose metabolism in the mediodorsal nucleus was associated with more negative symptoms.

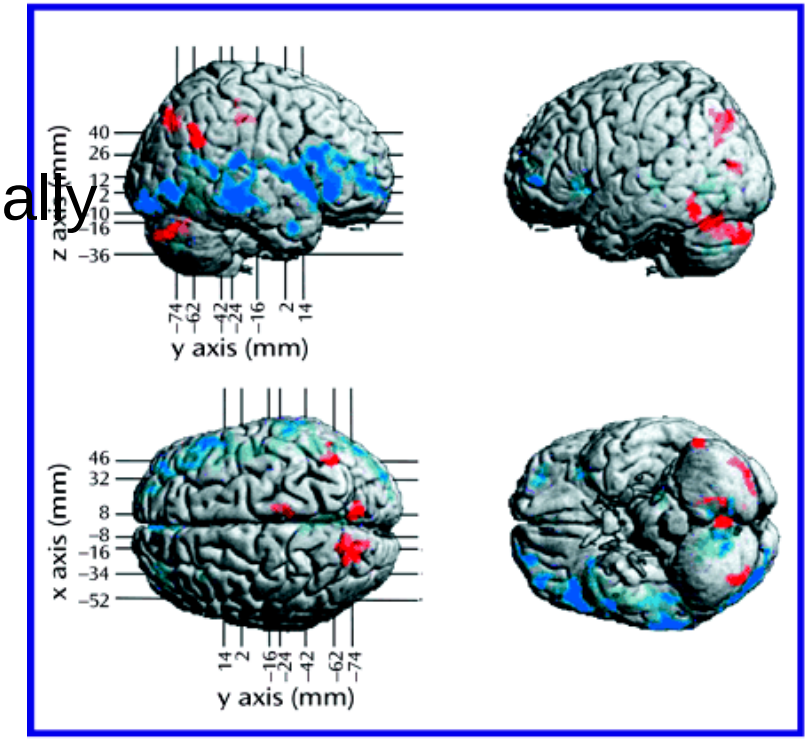
Szulc et al, 2005 The Effect of Risperidone on Metabolite Measures in the Frontal Lobe, Temporal Lobe, and Thalamus in Schizophrenic Patients. A Proton Magnetic Resonance Spectroscopy (1H MRS) Study
Negative symptoms before the treatment correlated positively with Glx (a common signal for GABA, glutamine and glutamate) levels

Goff and Coyle 2001 The Emerging Role of Glutamate in the Pathophysiology and Treatment of Schizophrenia
Antipsychotic drugs alter glutamatergic activity in multiple ways by enhancing release of glutamate in the striatum, directly interacting with NMDA receptors, altering glutamate receptor density, and changing the subunit composition of glutamate receptors. Many of these effects are regionally selective. Clozapine, aside from its interactions with aminergic receptors, may also be acting through the NMDA receptor in affecting negative symptoms

Potkin, Fallon et al 2002 A PET Study of the Pathophysiology of Negative Symptoms in Schizophrenia; Fallon et al 2003 The neuroanatomy of schizophrenia
Limbic and ventral areas, especially anteriorally, and in the right side, exhibit lower metabolism in predominantly negative symptom schizophrenics, relative to positive symptom schizophrenics

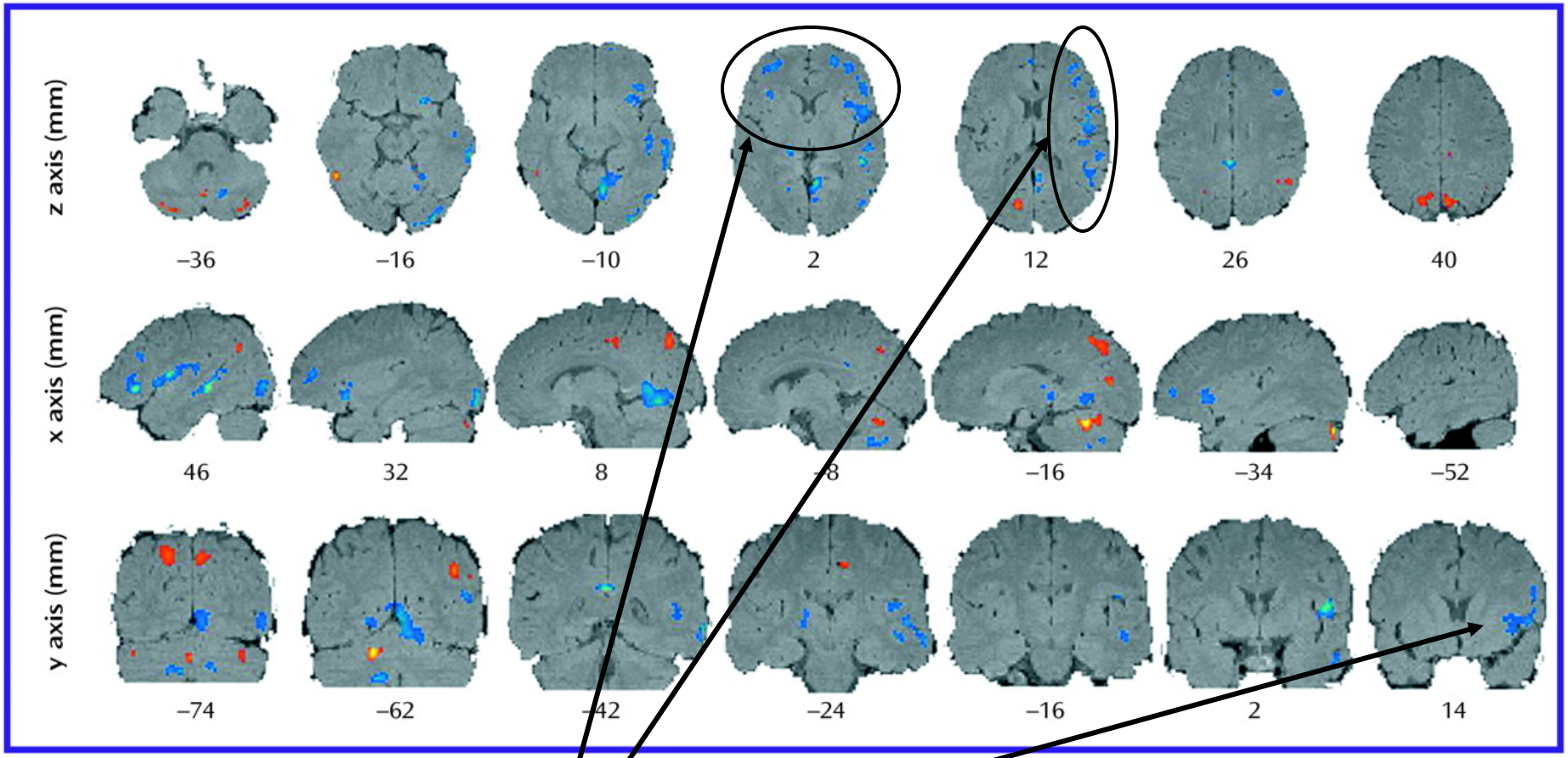


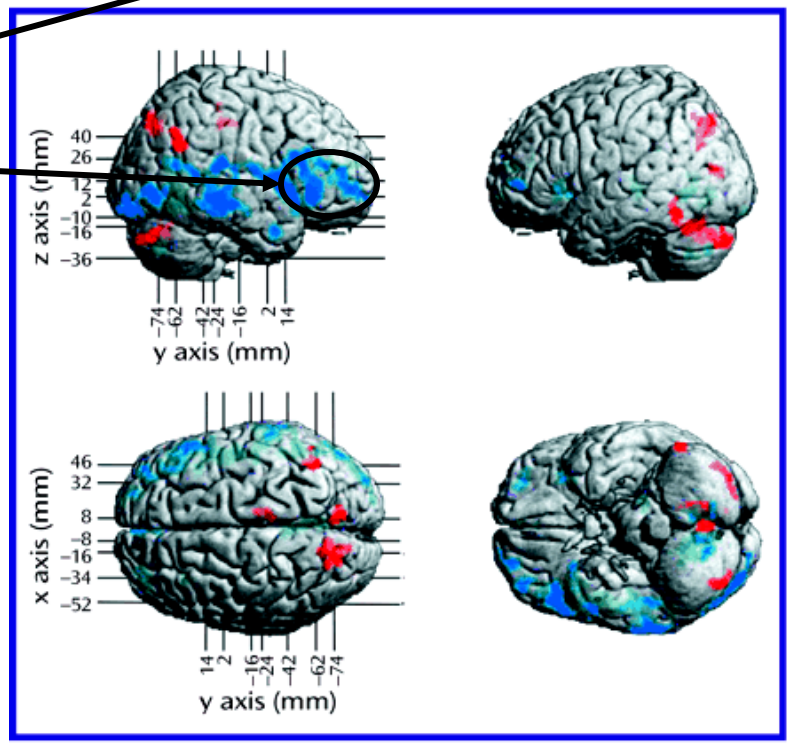
Limbic and mid-ventral areas, especially anteriorally, and in the right side, exhibit lower metabolism in predominantly negative symptom schizophrenics, relative to positive symptom schizophrenics



Potkin, Fallon et al 2002

FDG-PET; CPT Task





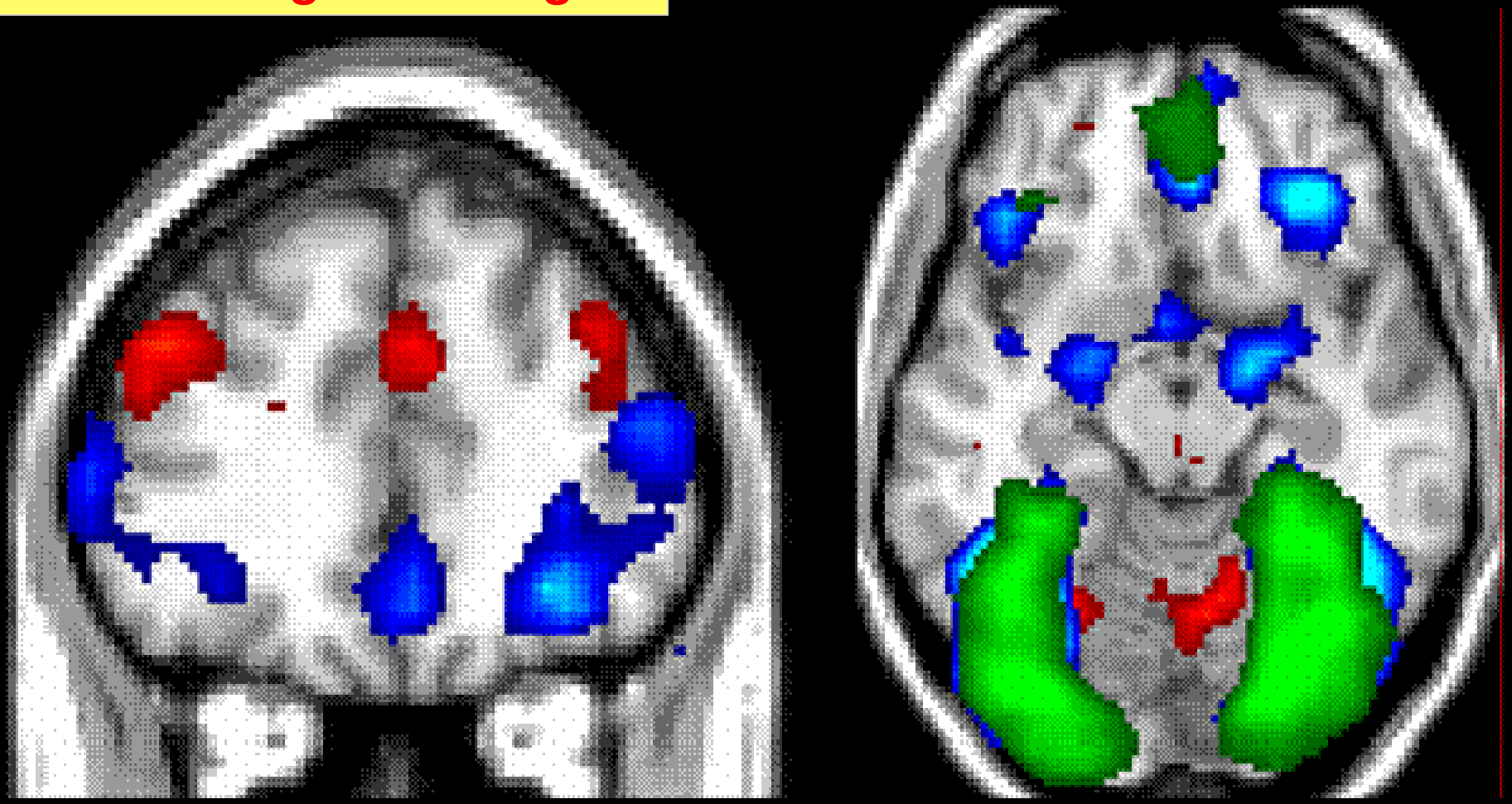
Limbic and lateral areas, especially anteriorally, and in the right side, exhibit lower metabolism in predominantly negative symptom schizophrenics, relative to positive symptom schizophrenics

Potkin, Fallon et al 2002

FDG-PET; CPT Task

Cognitive vs limbic stream activation- fMRI

Attended cognitive targets



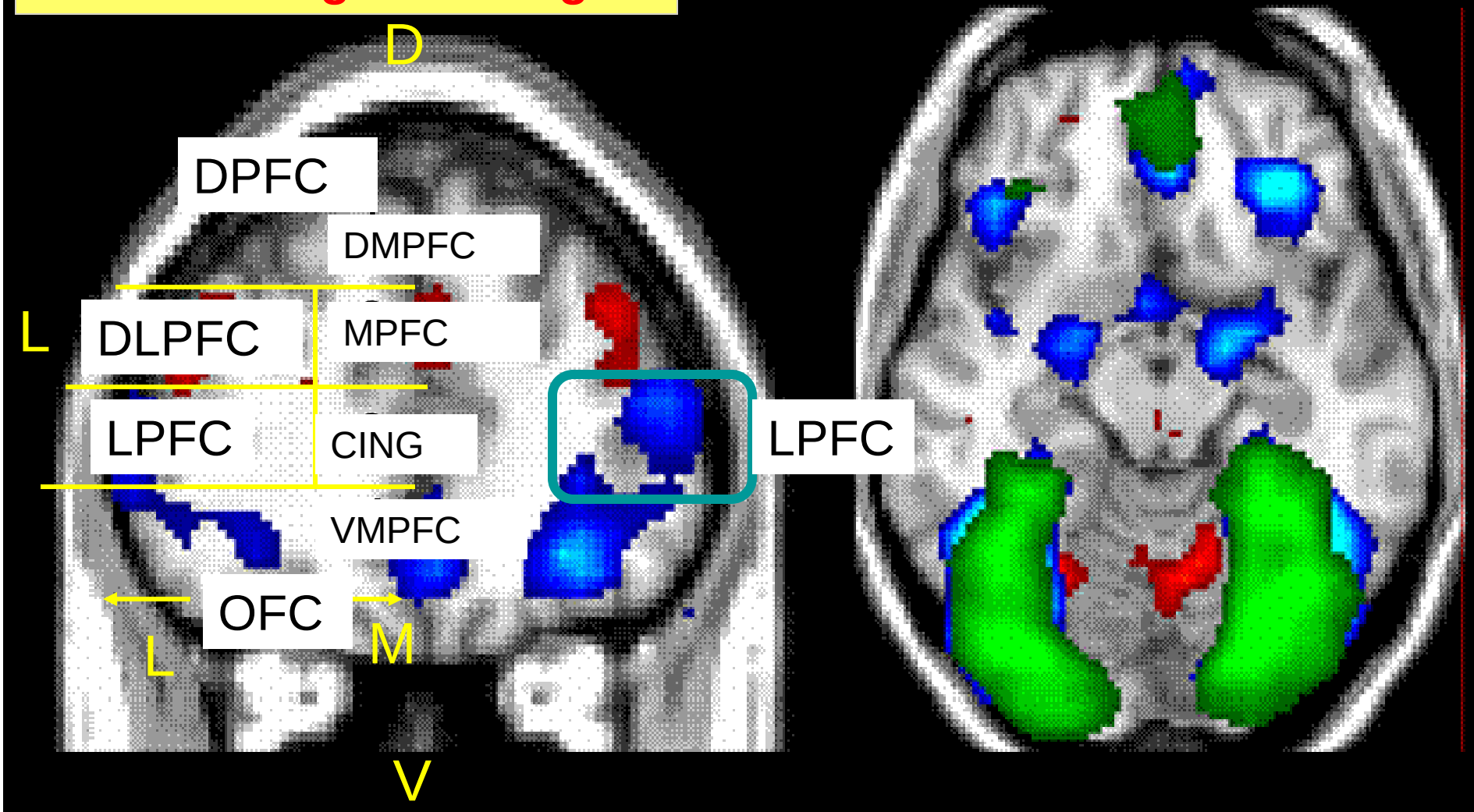
Emotional distractors response

Neutral distractors response

adapted from McCarthy, 2004

Cognitive vs limbic stream activation- fMRI

Attended cognitive targets

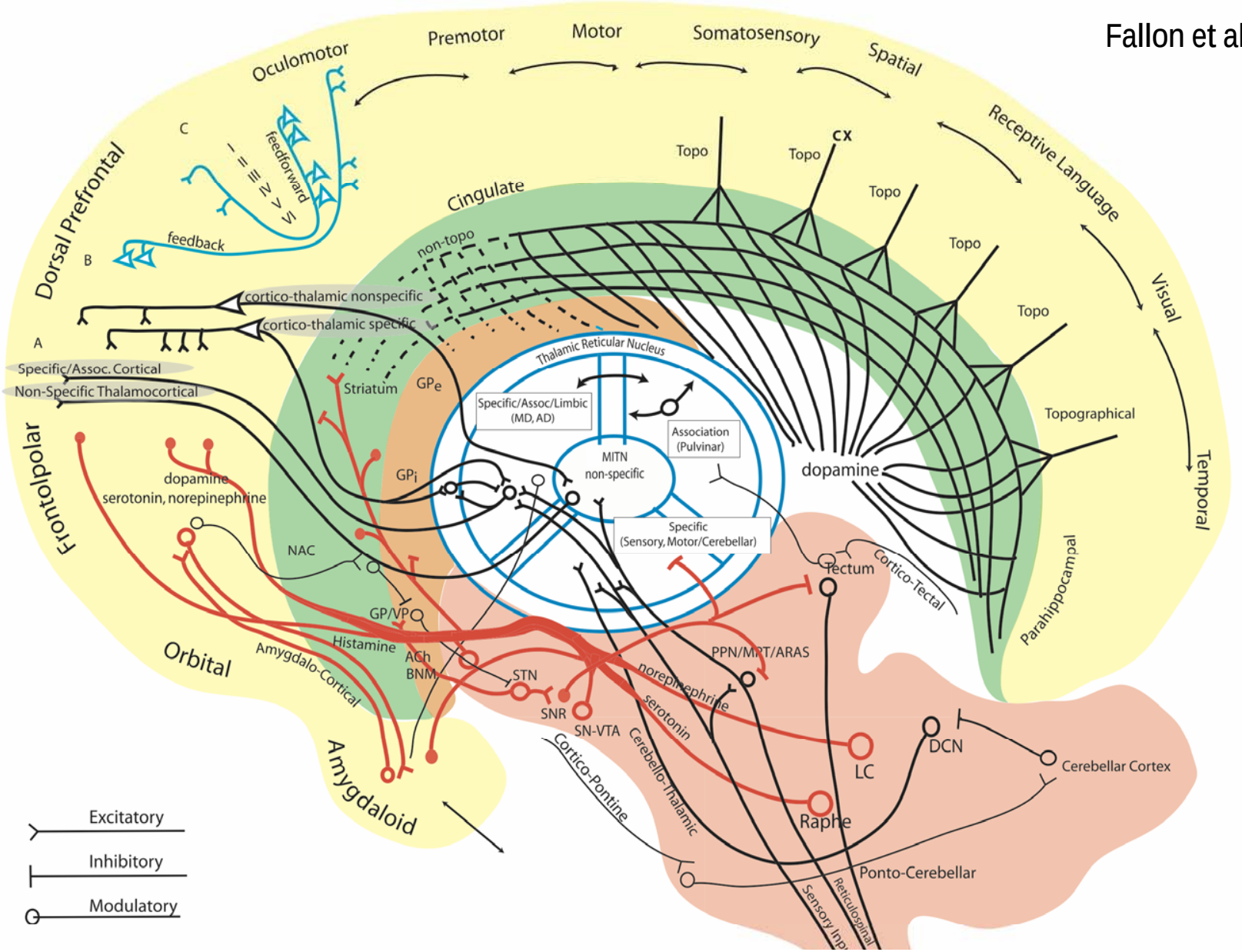


Emotional distractors response

Neutral distractors response

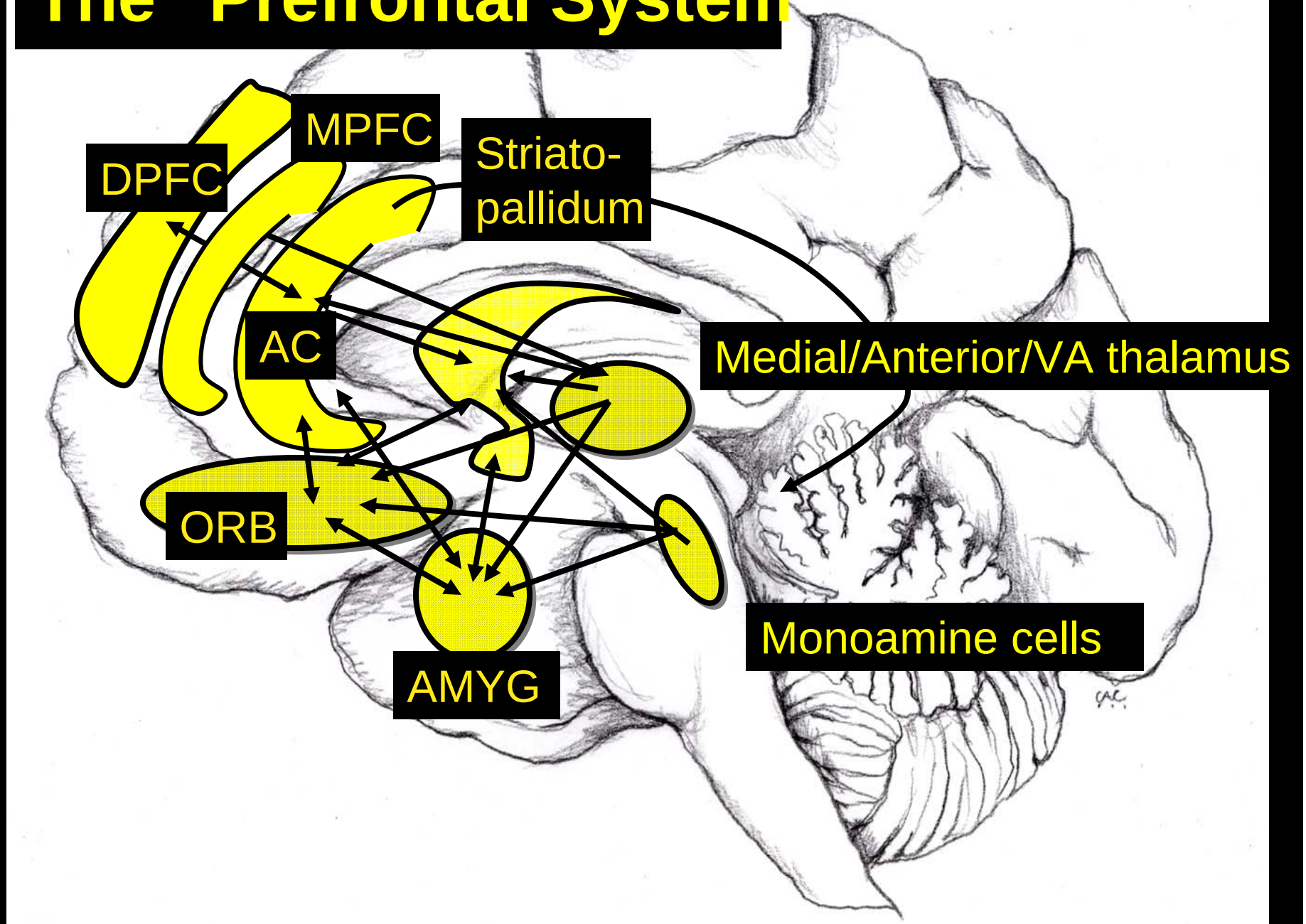
adapted from McCarthy, 2004

Fallon et al 2003



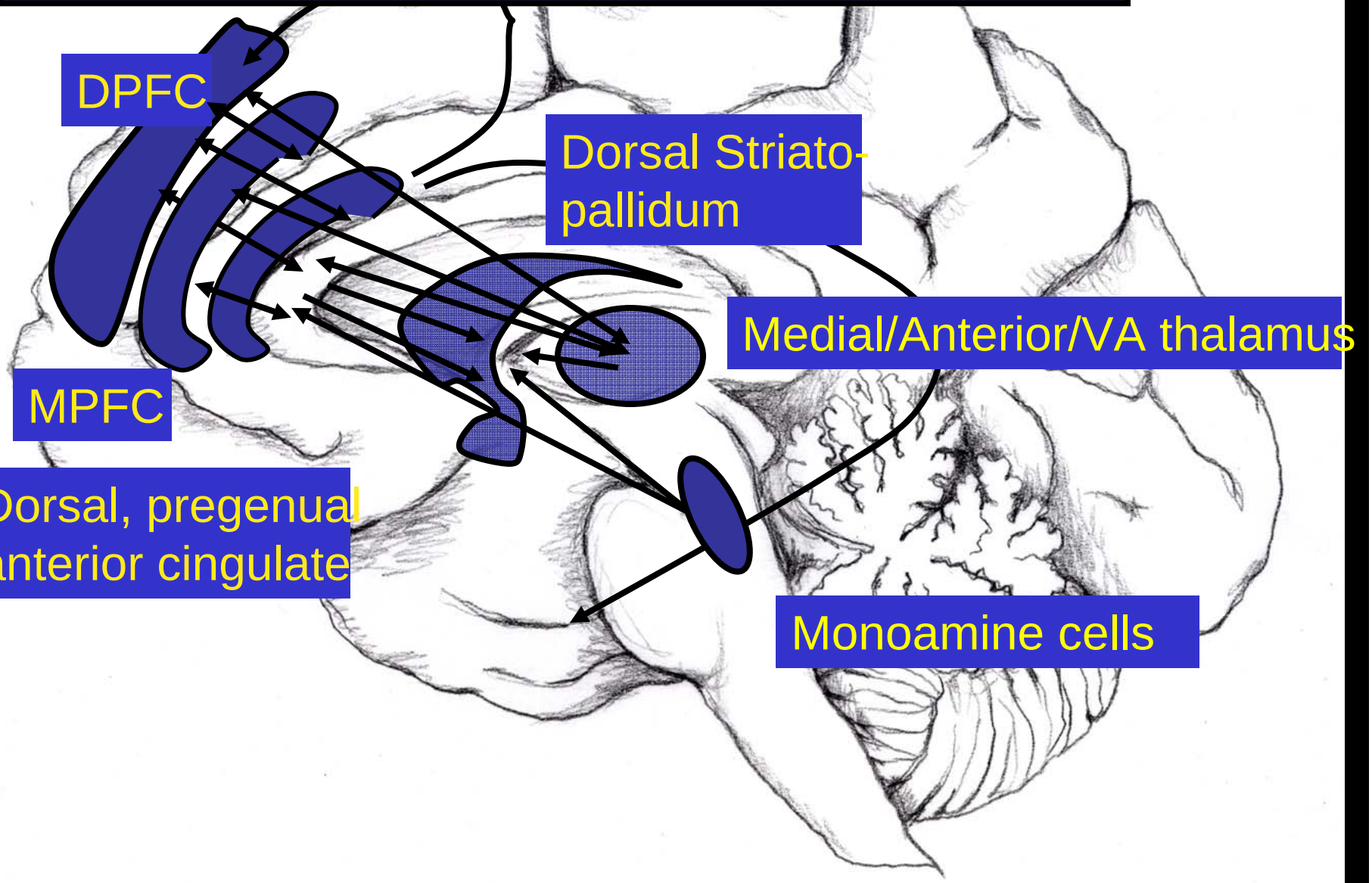
Although nearly all regions of the brain have been implicated in the etiology of schizophrenia, the “prefrontal system” is most consistently reported, especially for negative symptoms

The "Prefrontal System"



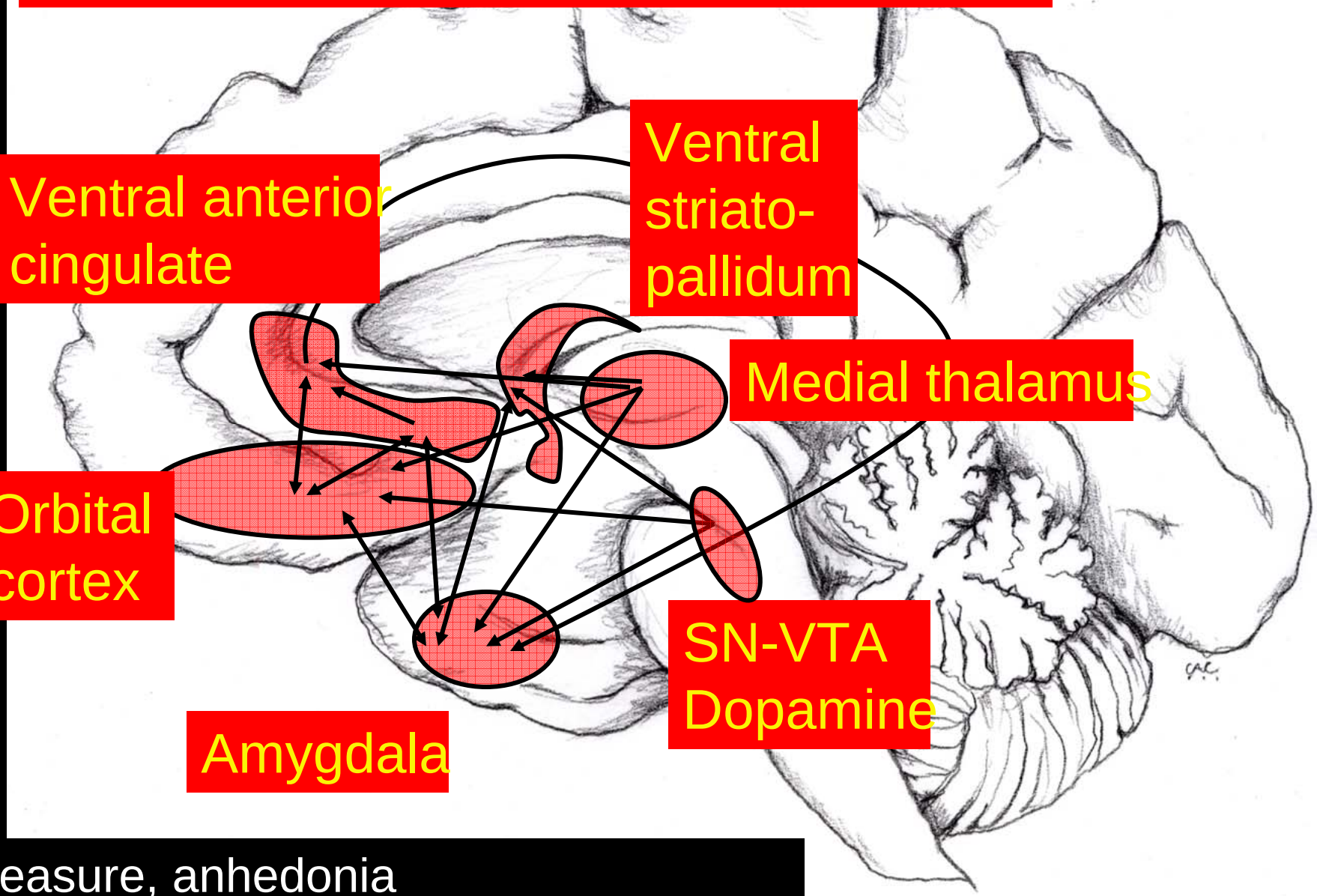
Fallon

The "Cognitive Prefrontal System"



Fallon

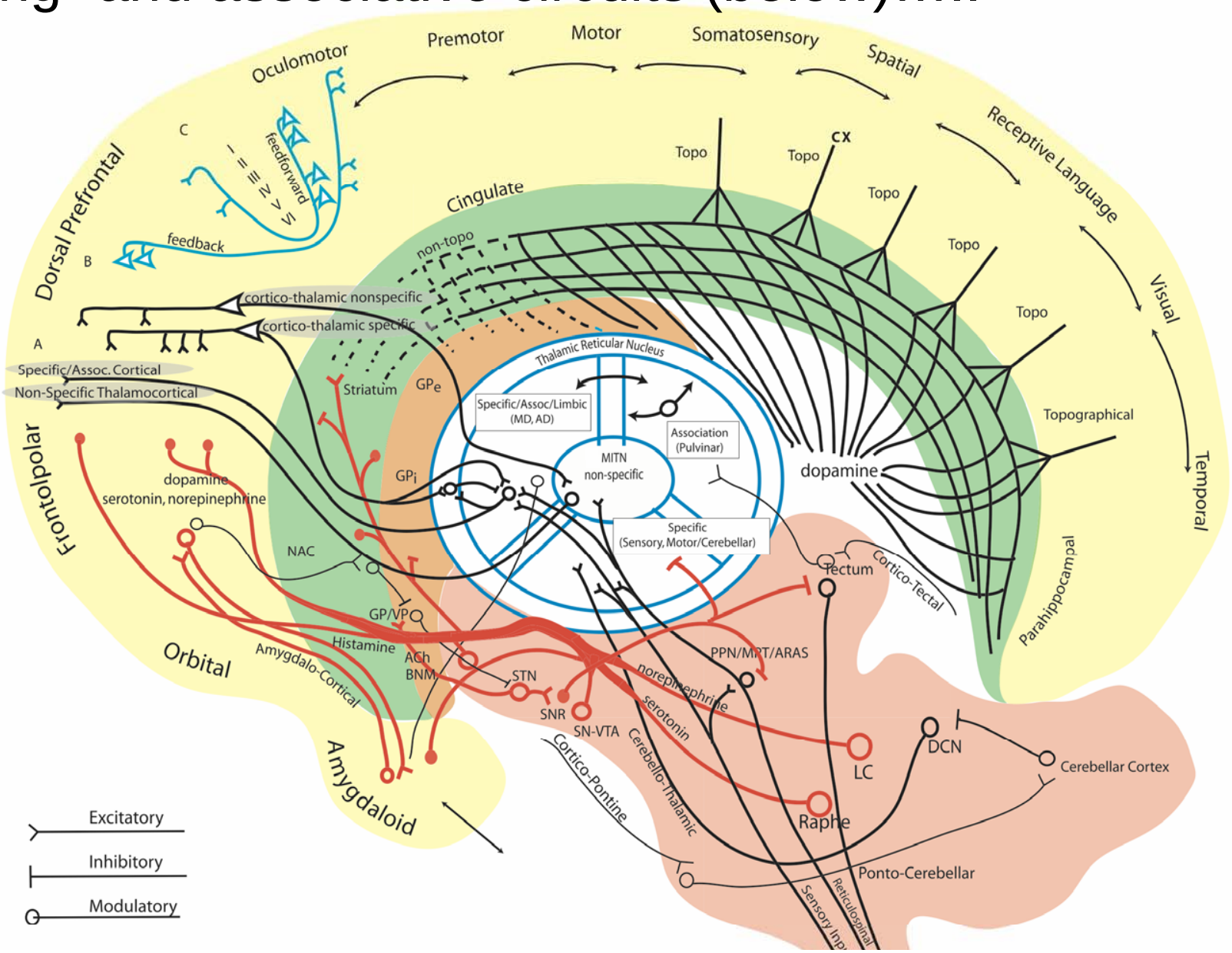
The “Limbic Prefrontal System”



pleasure, anhedonia
approach,withdrawal,
context, value, salience,
fluidity, obsession, behavioral inhibition

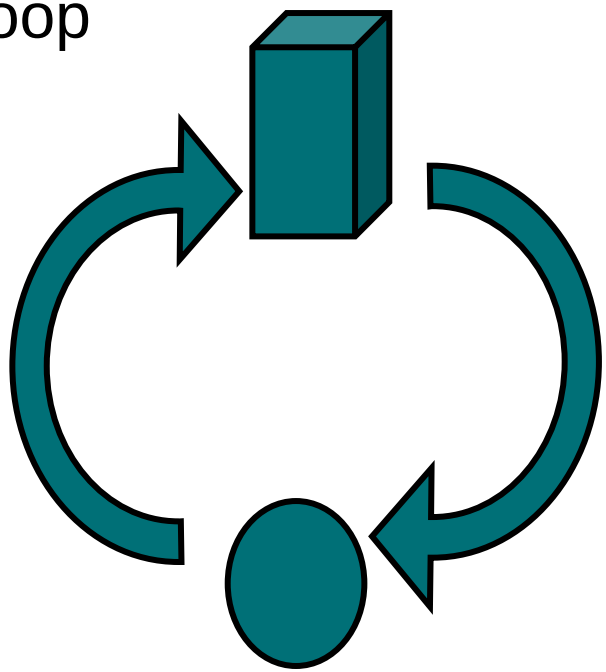
Fallon

…..In addition to those regional loops and brain-wide "long" and associative circuits (below)…..

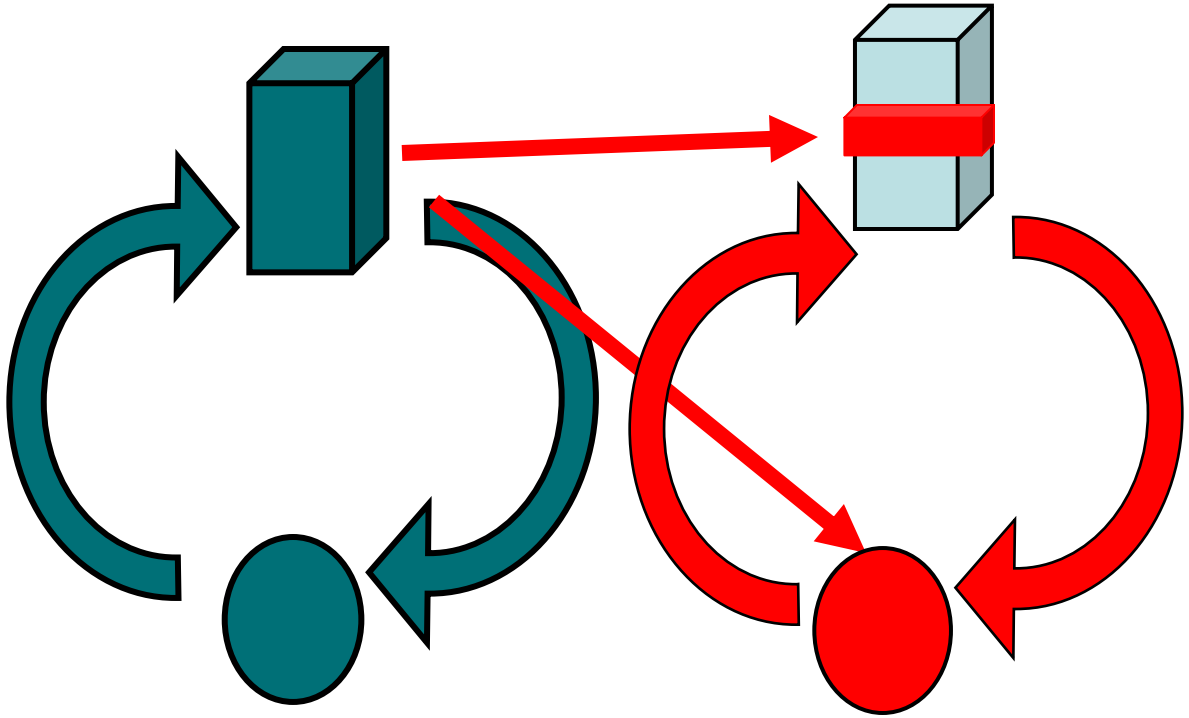


…are subregional loops that include both closed and open loop channels…(next)….

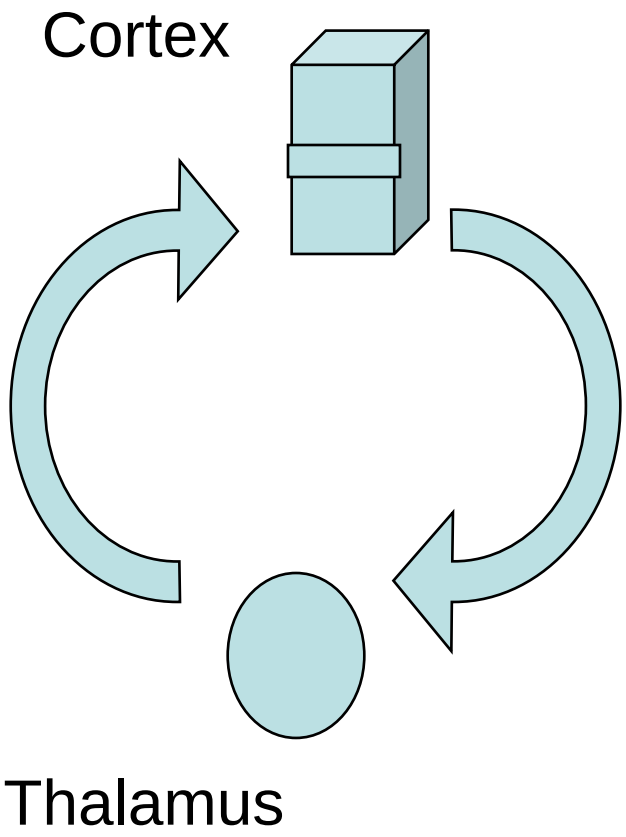
Closed loop



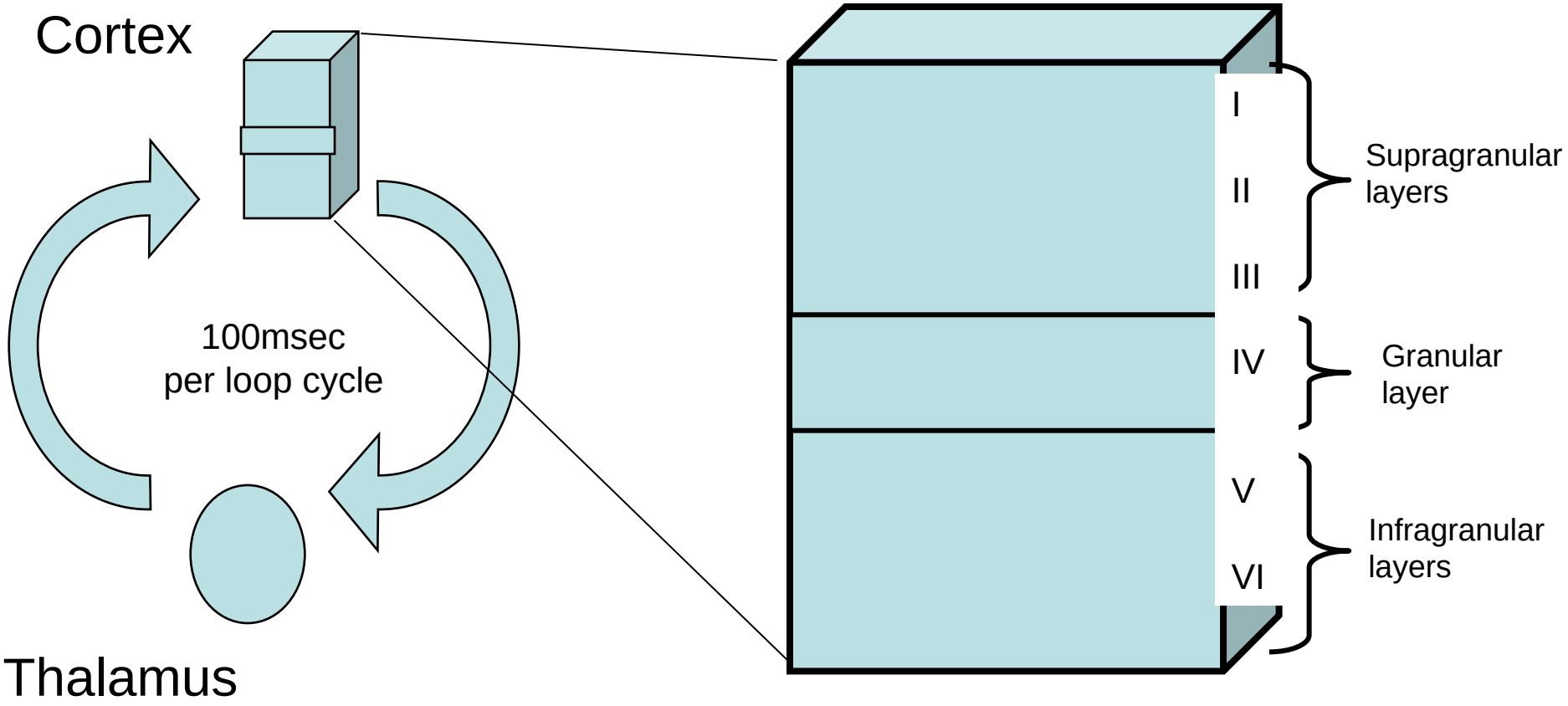
Open loop



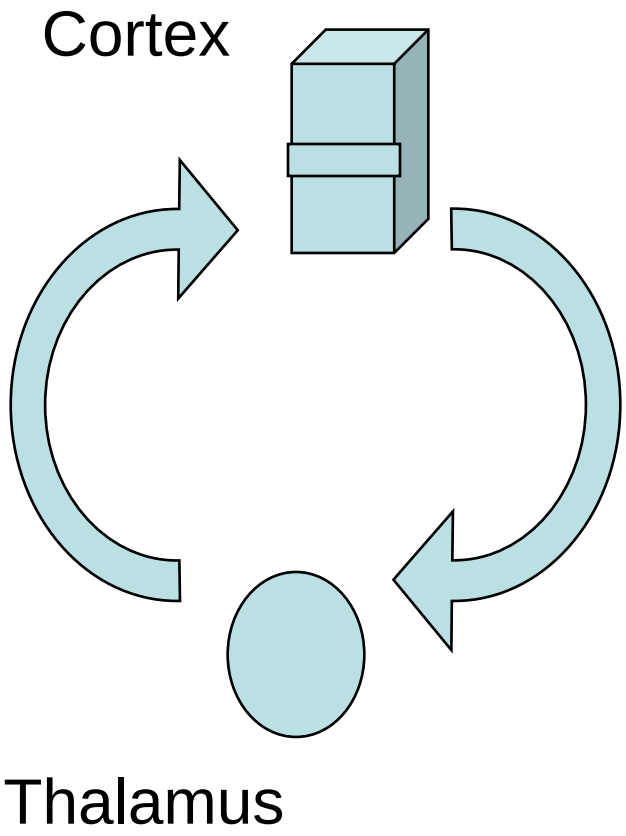
Cortico-subcortico-cortical loop
(glutamate, GABA)



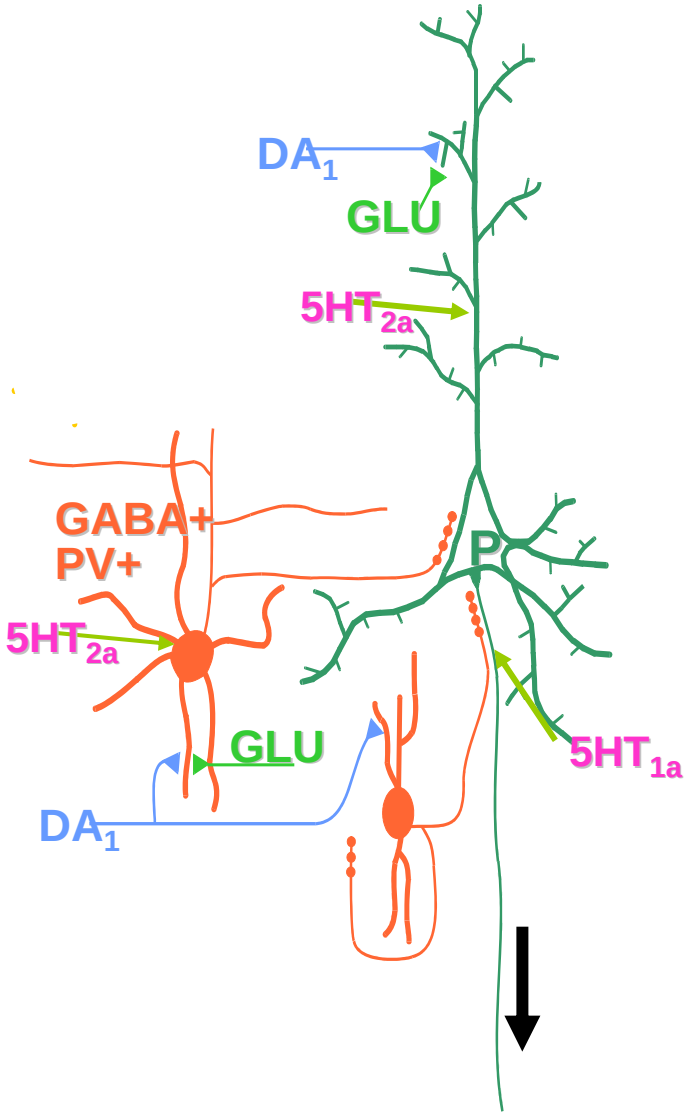
Cortico-subcortico-cortical loop
(glutamate, GABA)



Cortico-subcortico-cortical loop
(glutamate, GABA)



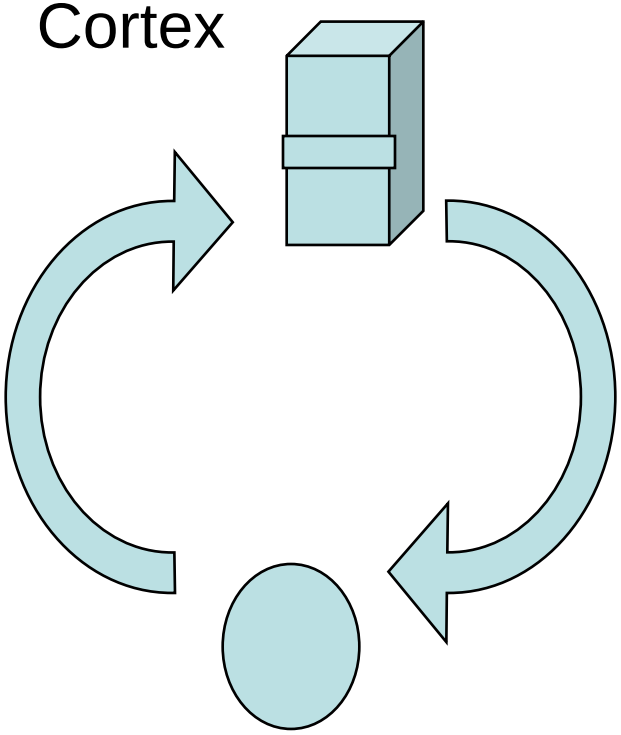
Prefrontal Cortical Neuronal Architecture



DA $_{1,2}$, GABA-A and 5-HT $_{2a,1a}$ terminals form synaptic contacts that converge on excitatory pyramidal glutamate neurons.

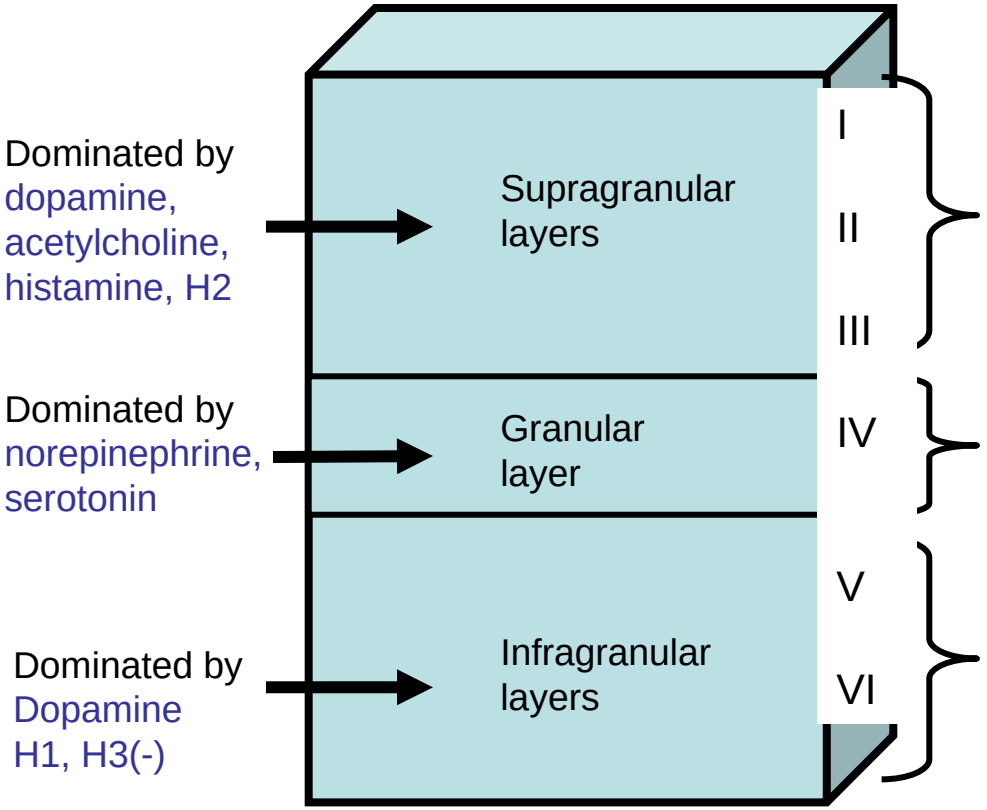
Modified after Sesack&Lewis

Cortex

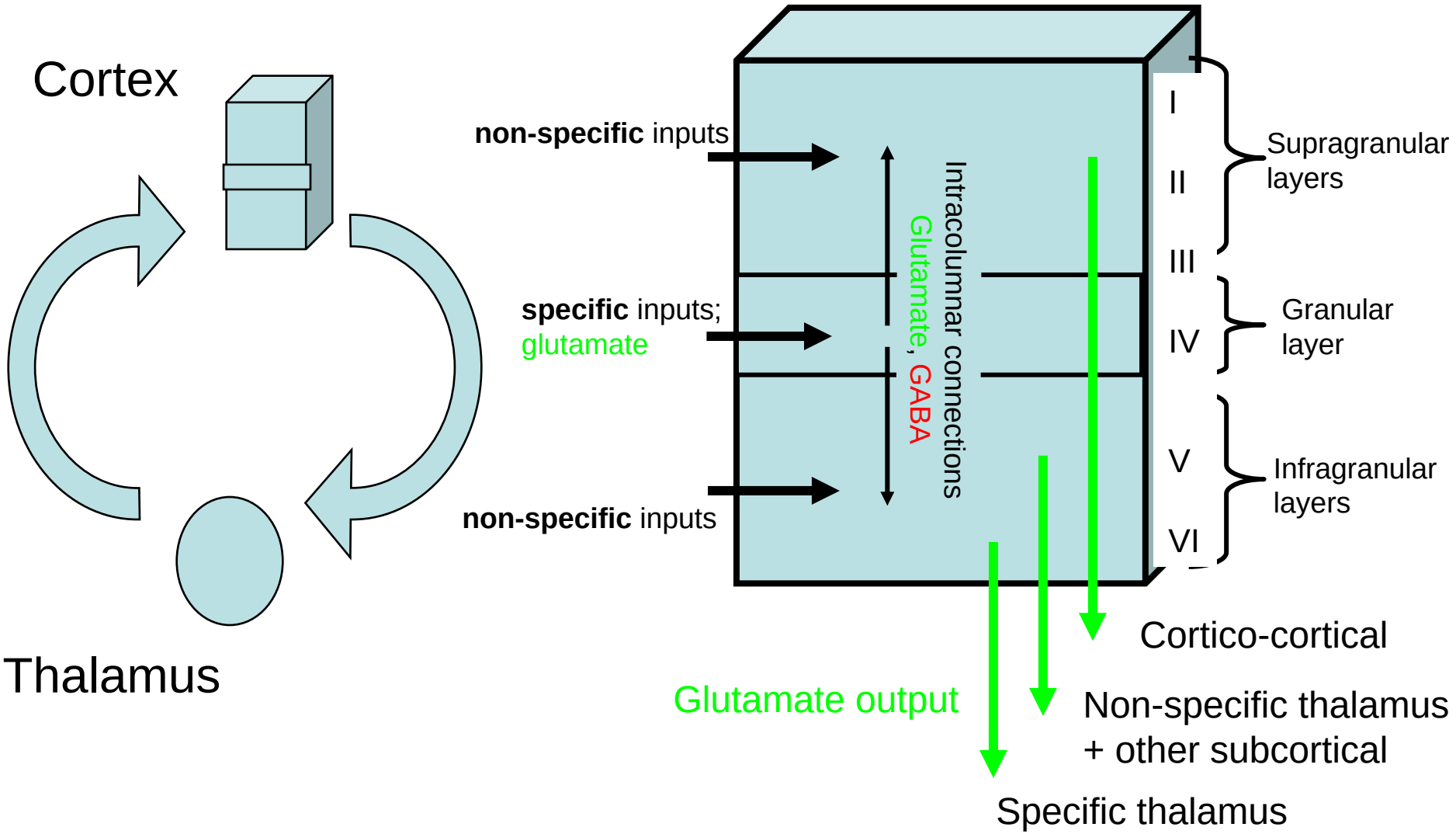


Thalamus

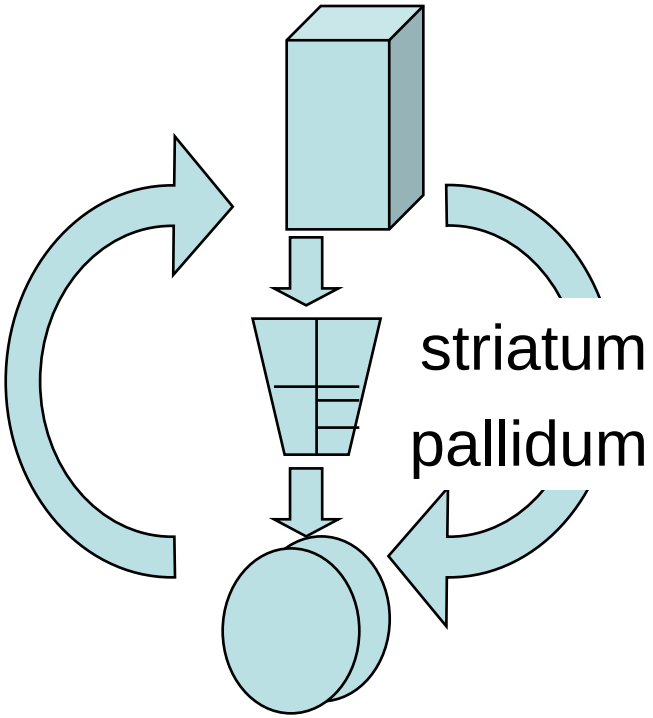
Cortical layers-Modulatory inputs



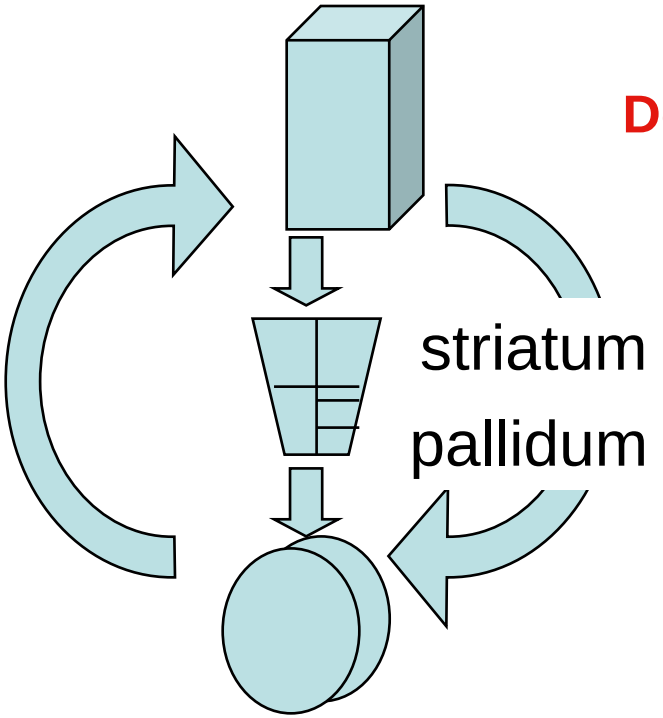
Cortico-subcortico-cortical loop
(glutamate, GABA)



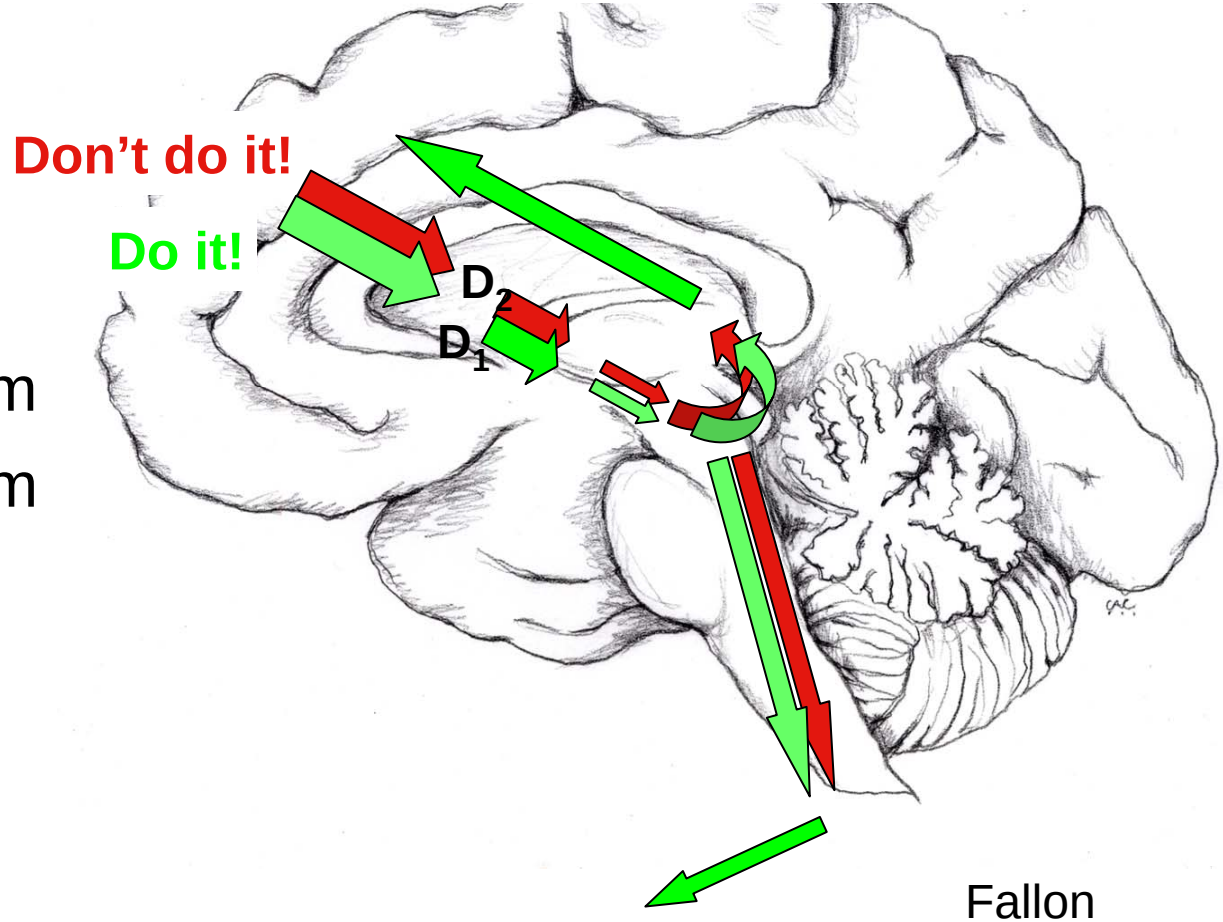
Cortico-striato-pallido-thalamic loop and motor output (Glutamate-GABA)



Cortico-striato-pallido-thalamic loop and motor output (Glutamate-GABA)

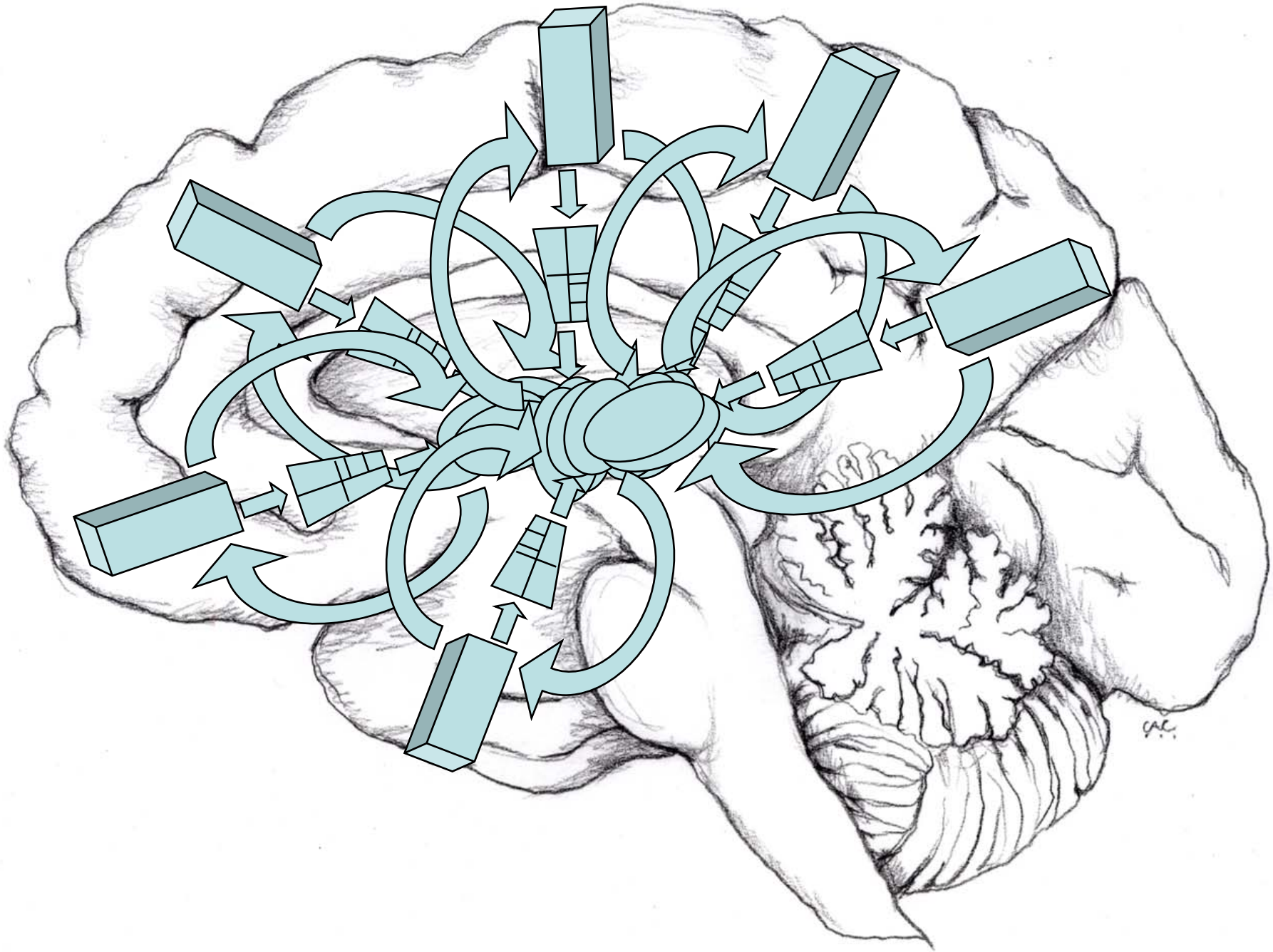


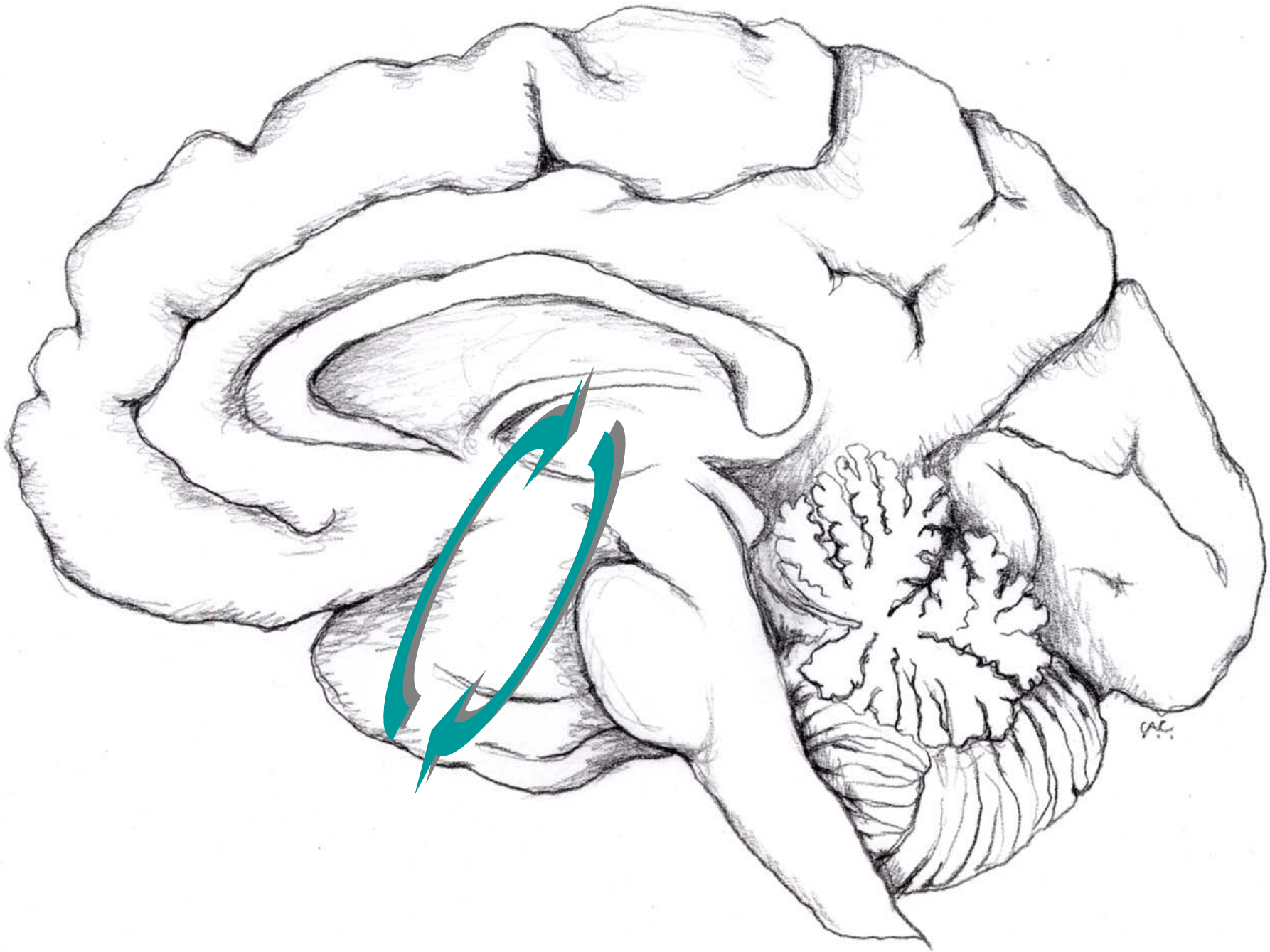
Pairs of opposing channels within each CSPT loop

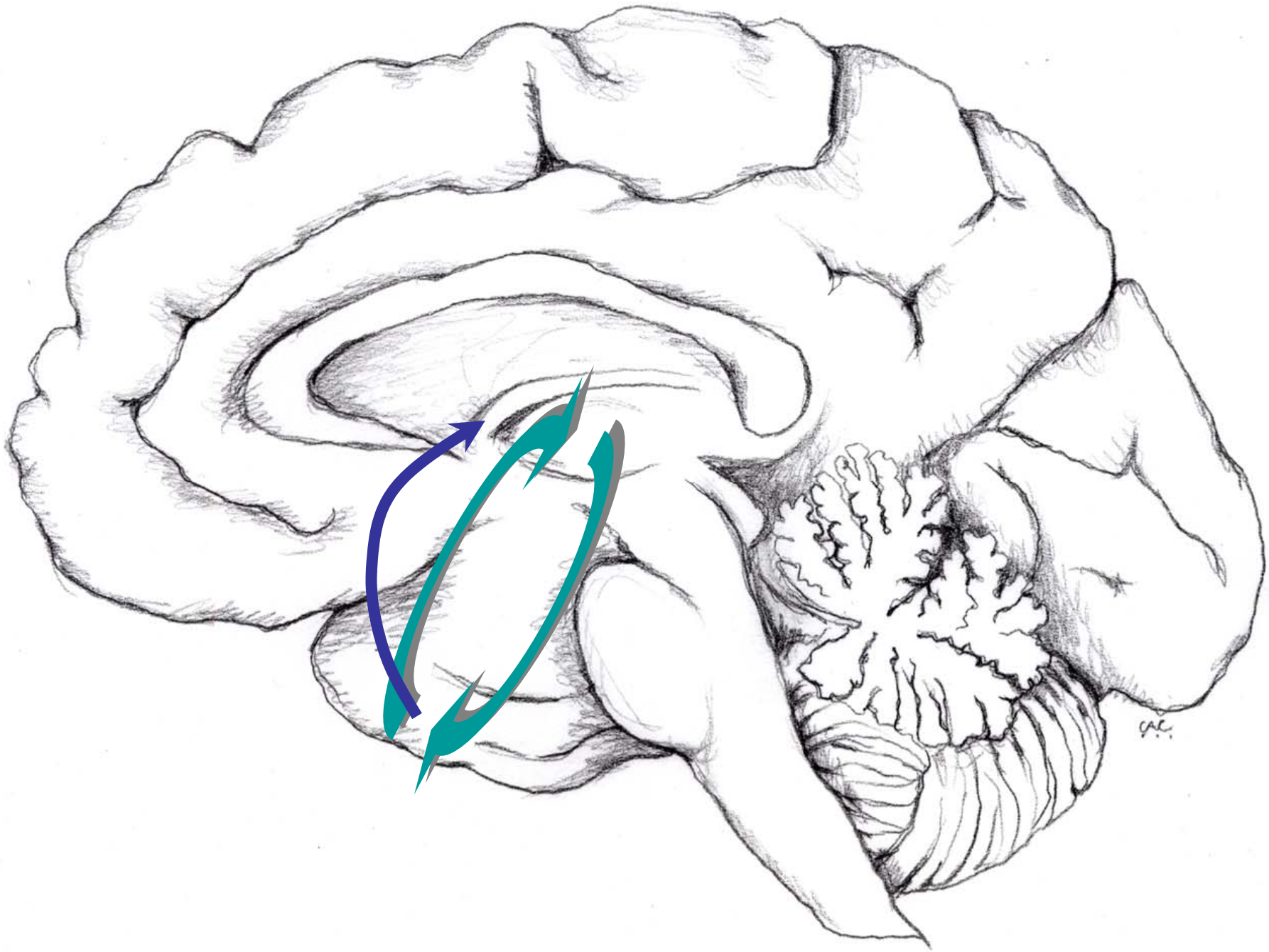


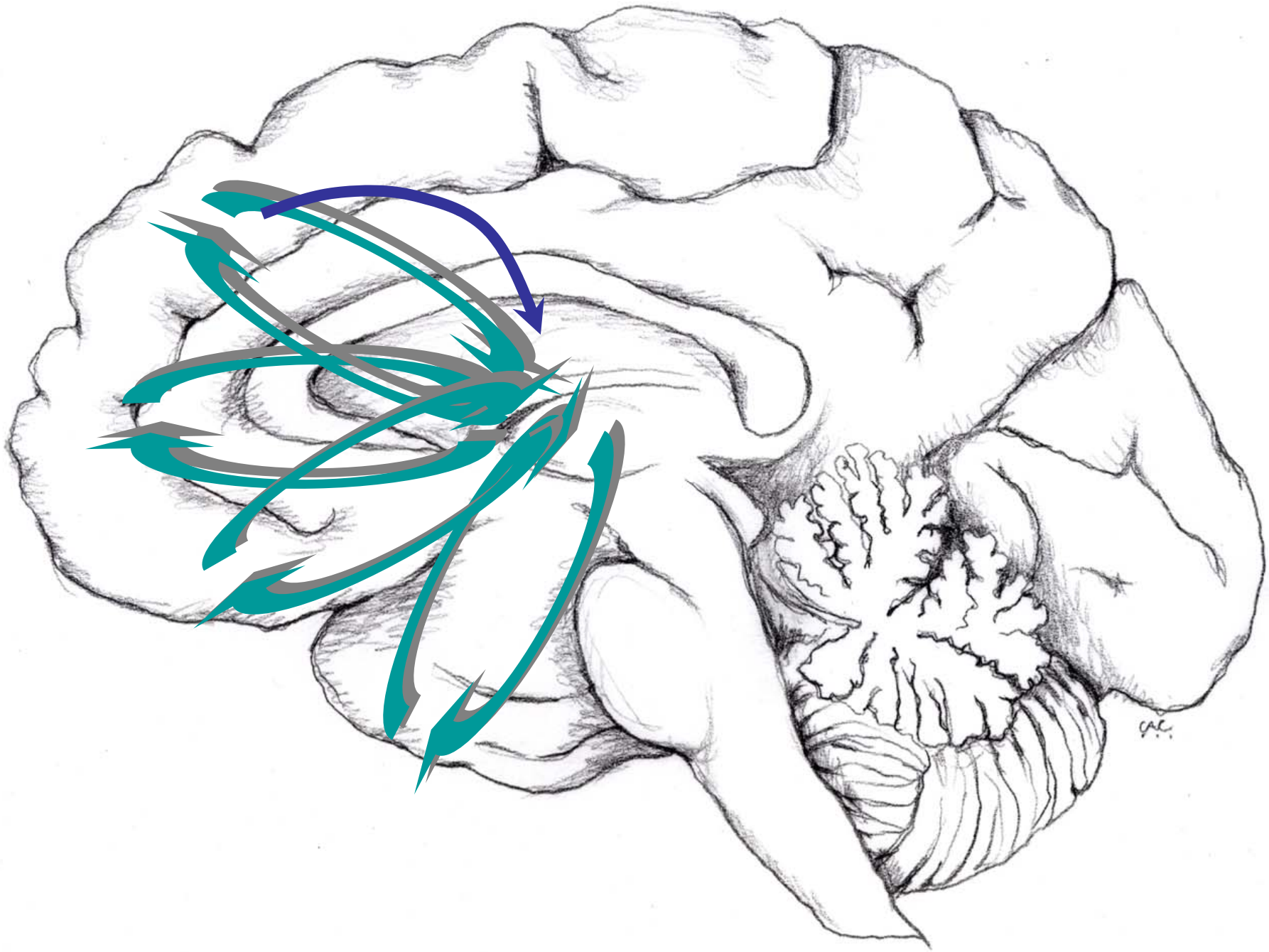
Fallon

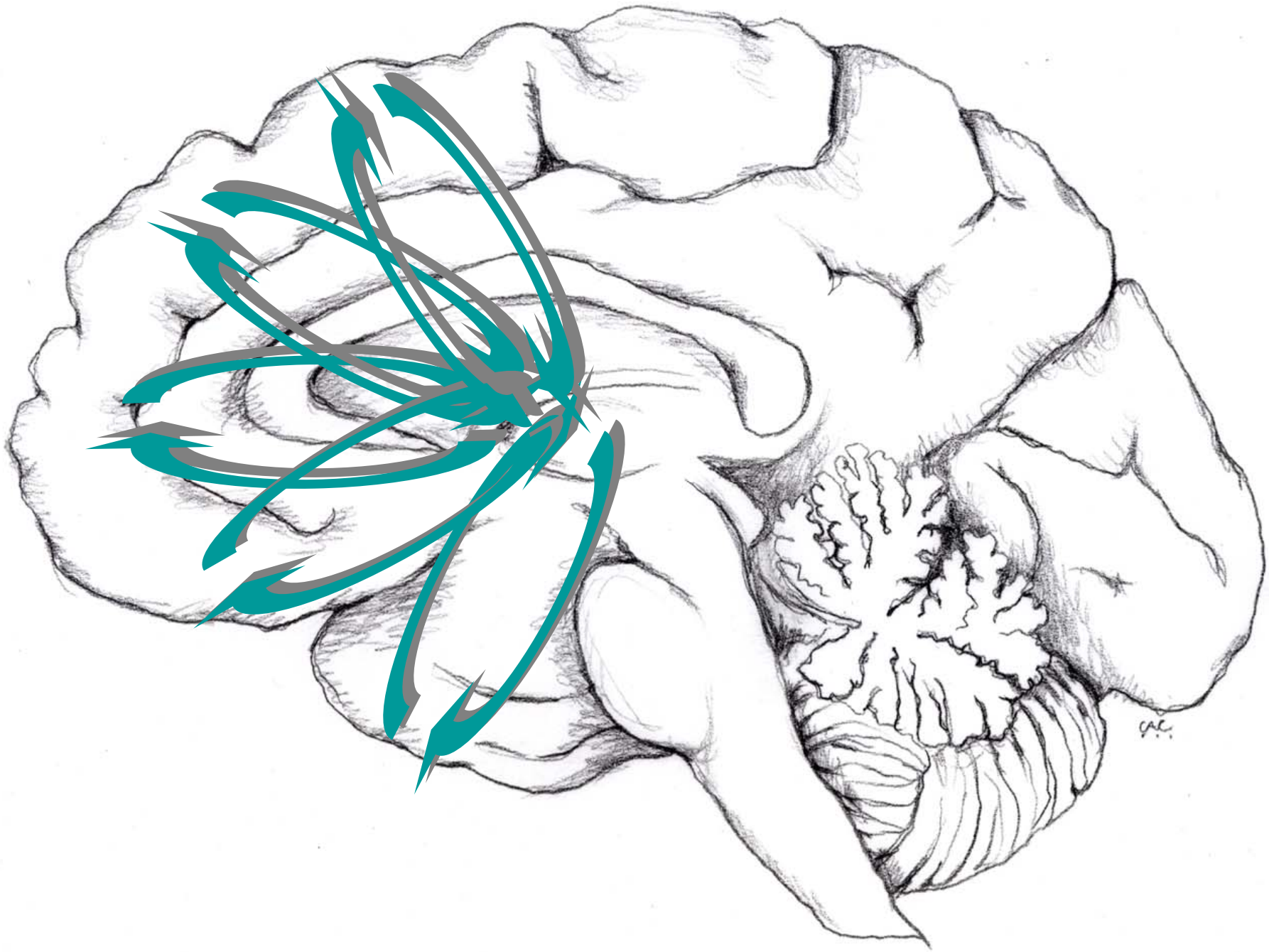
Final common path,
ie, motor/endocrine/autonomic

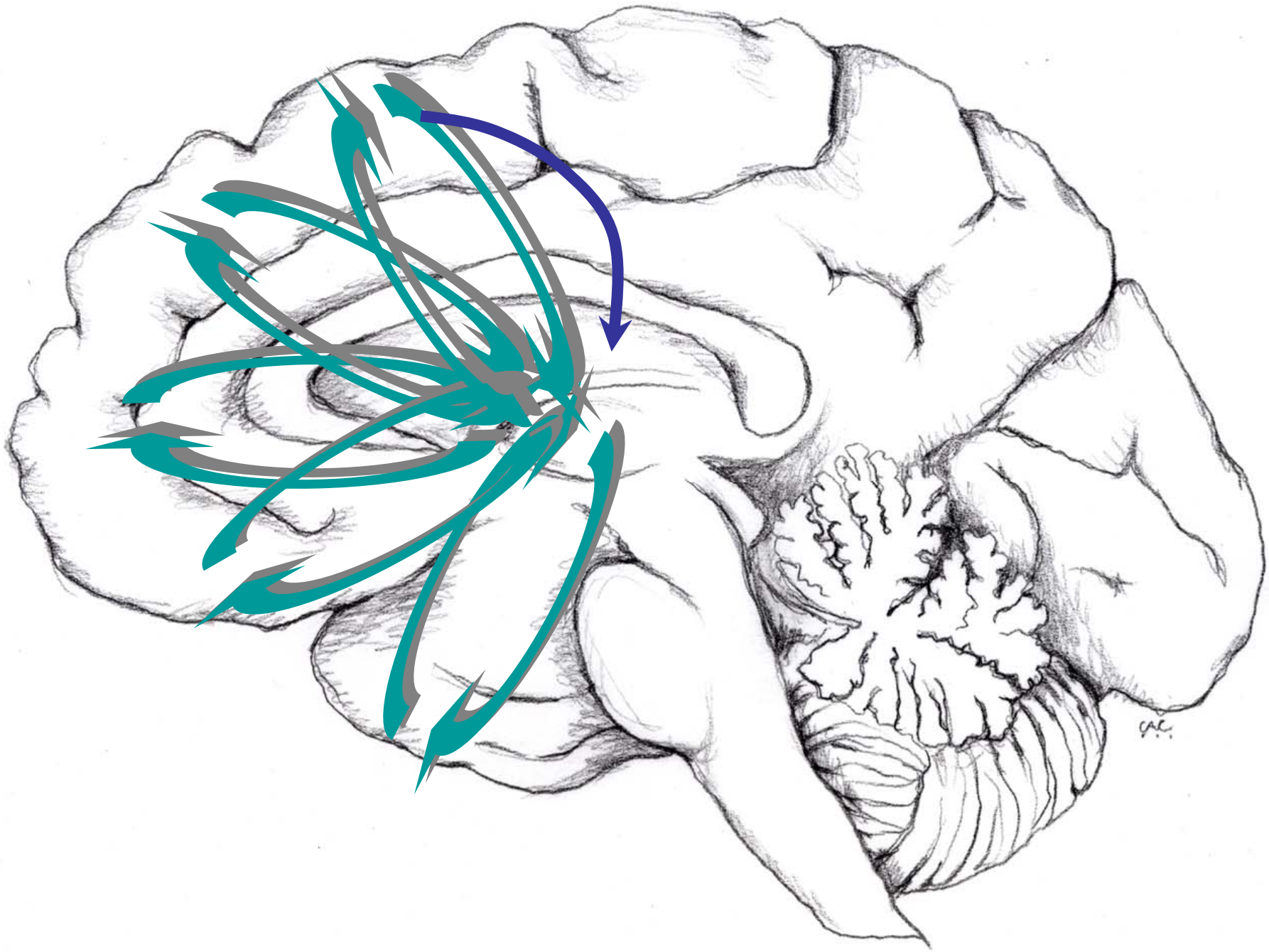


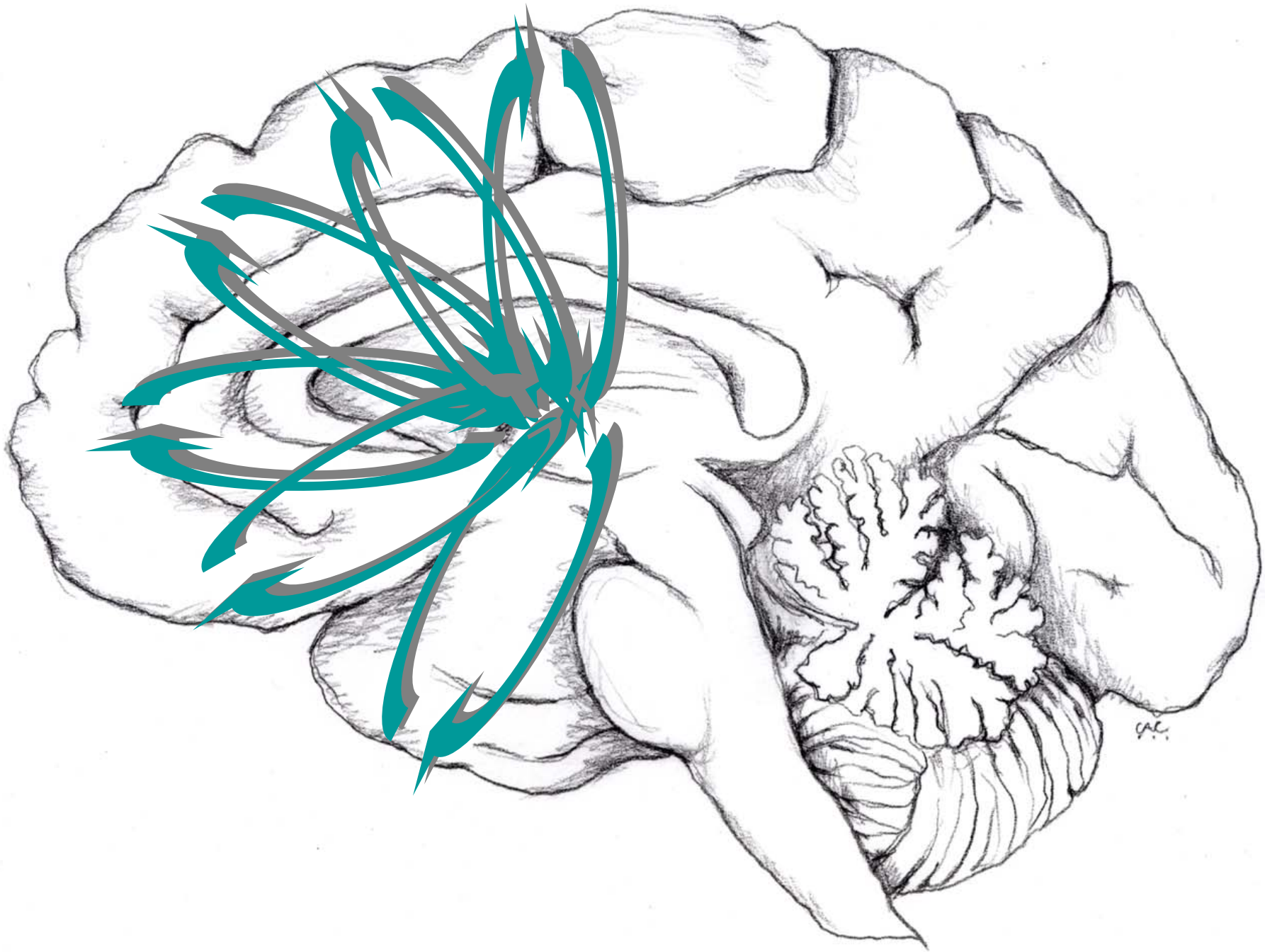


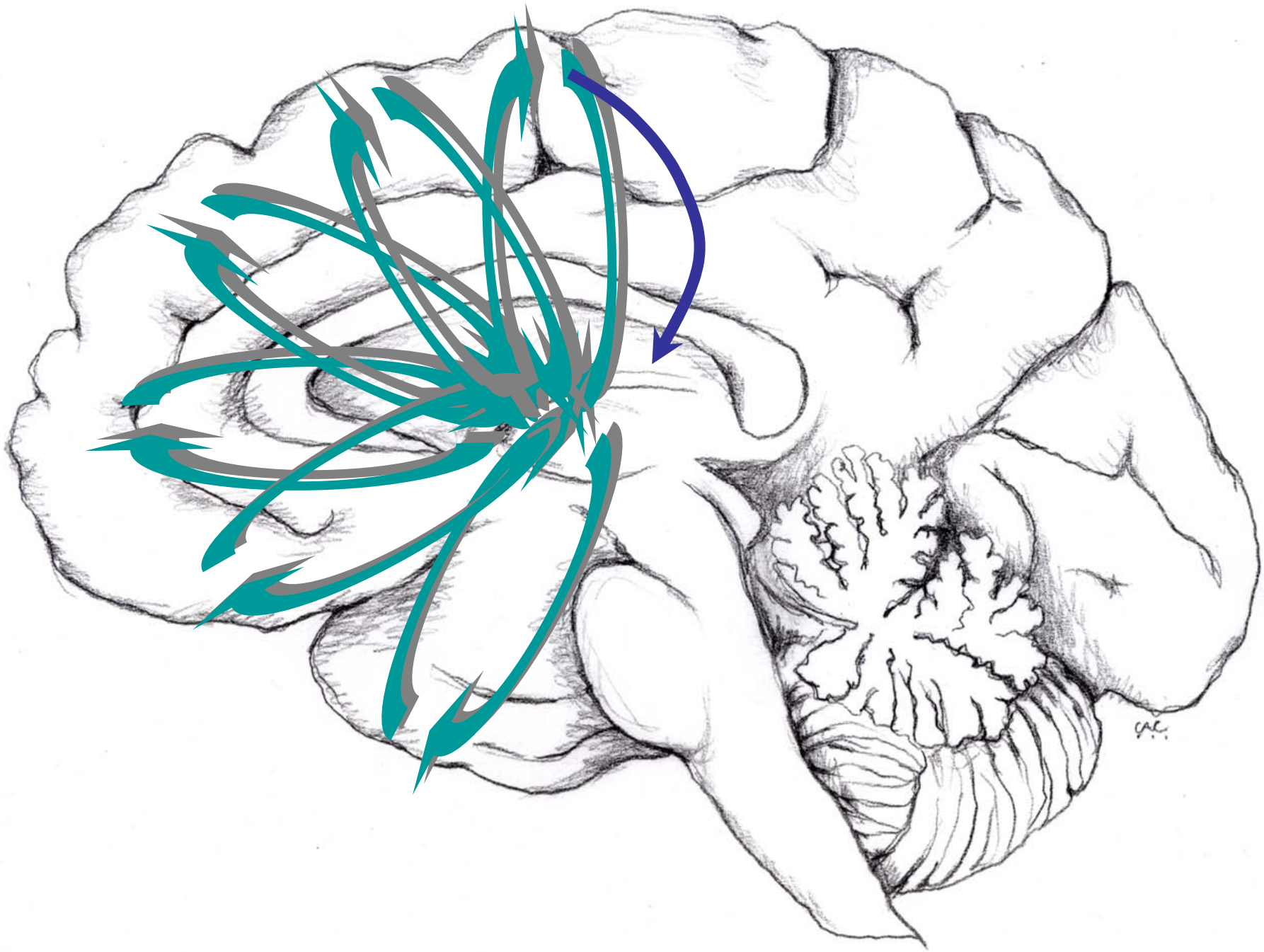


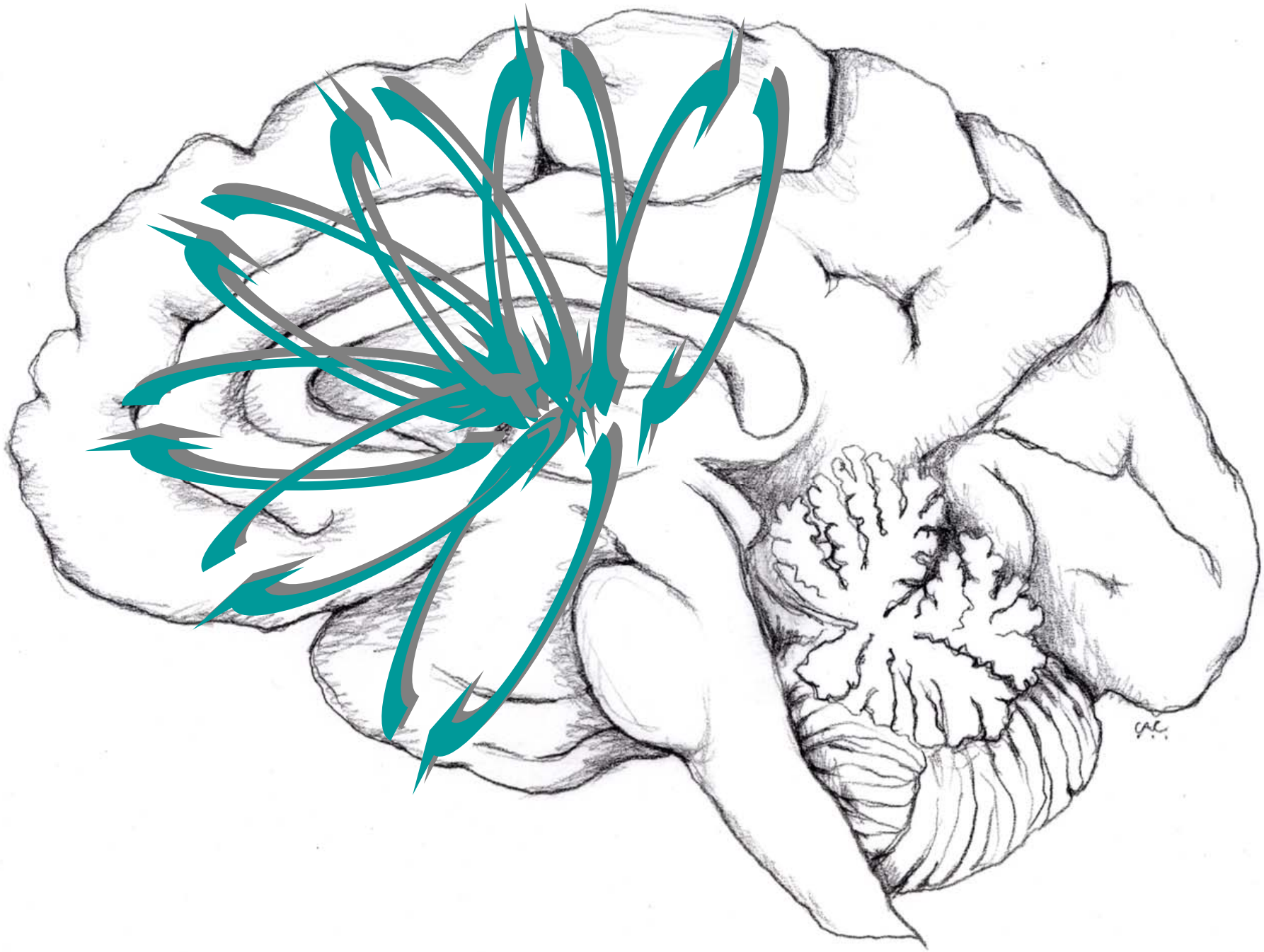


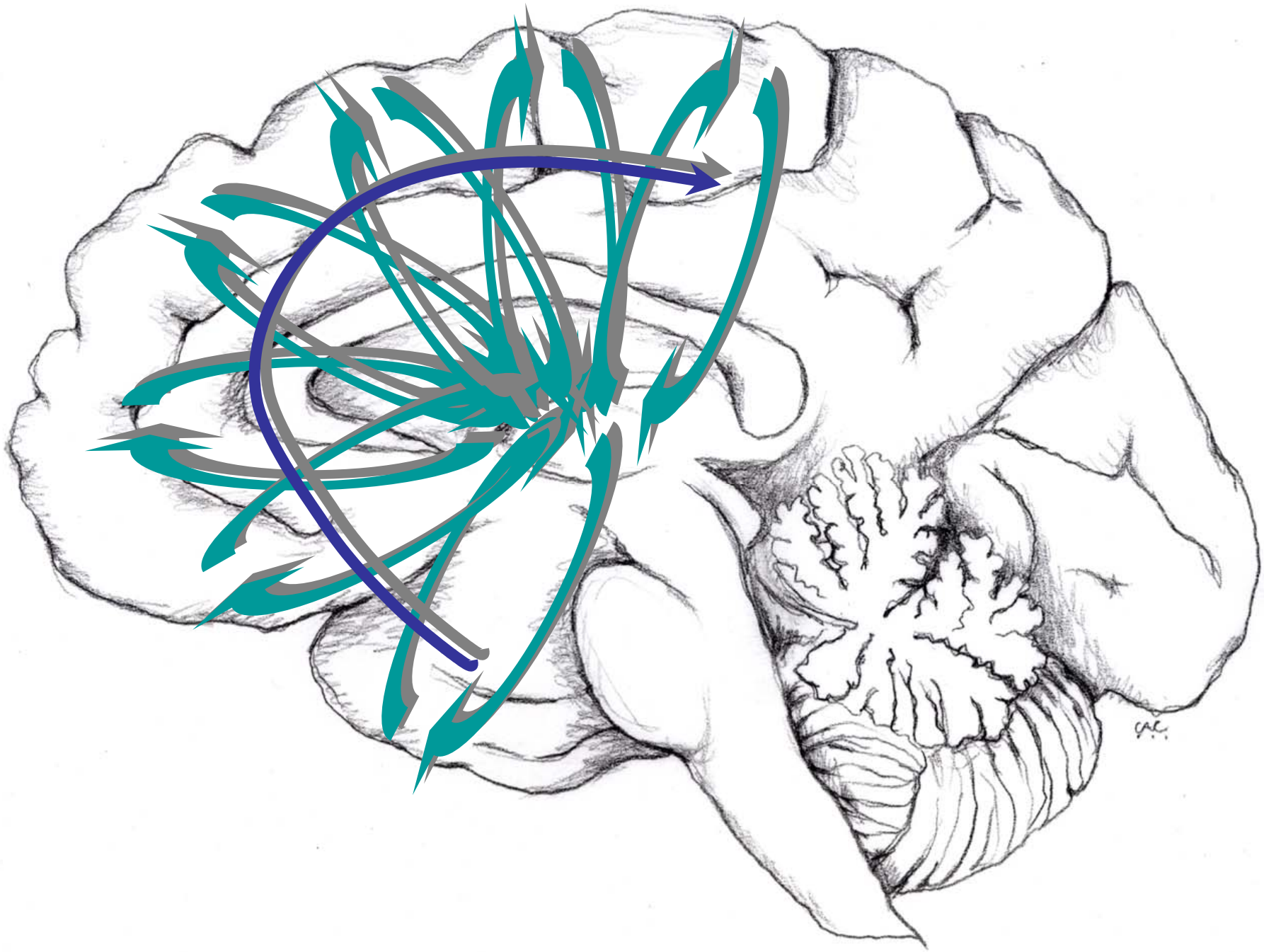


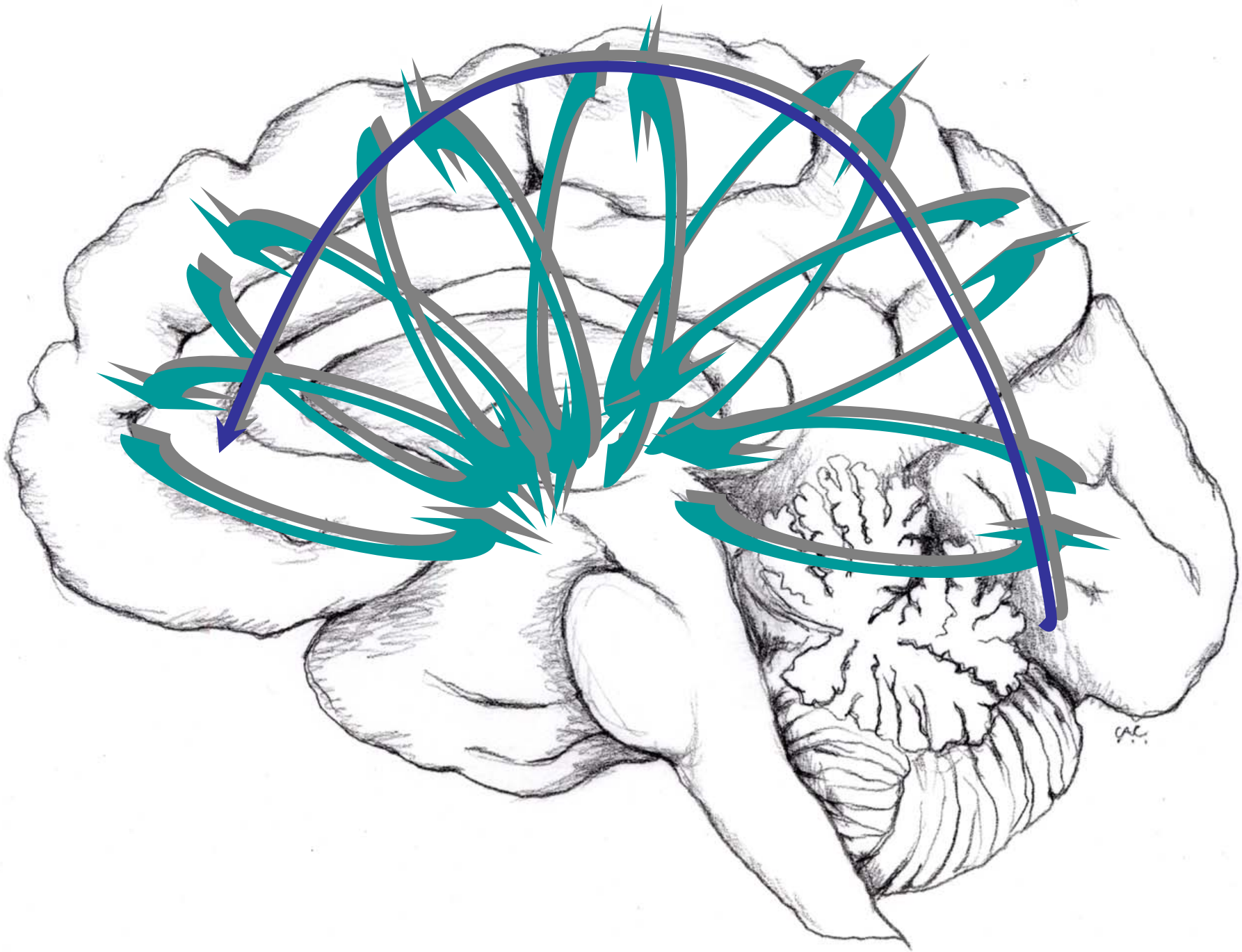


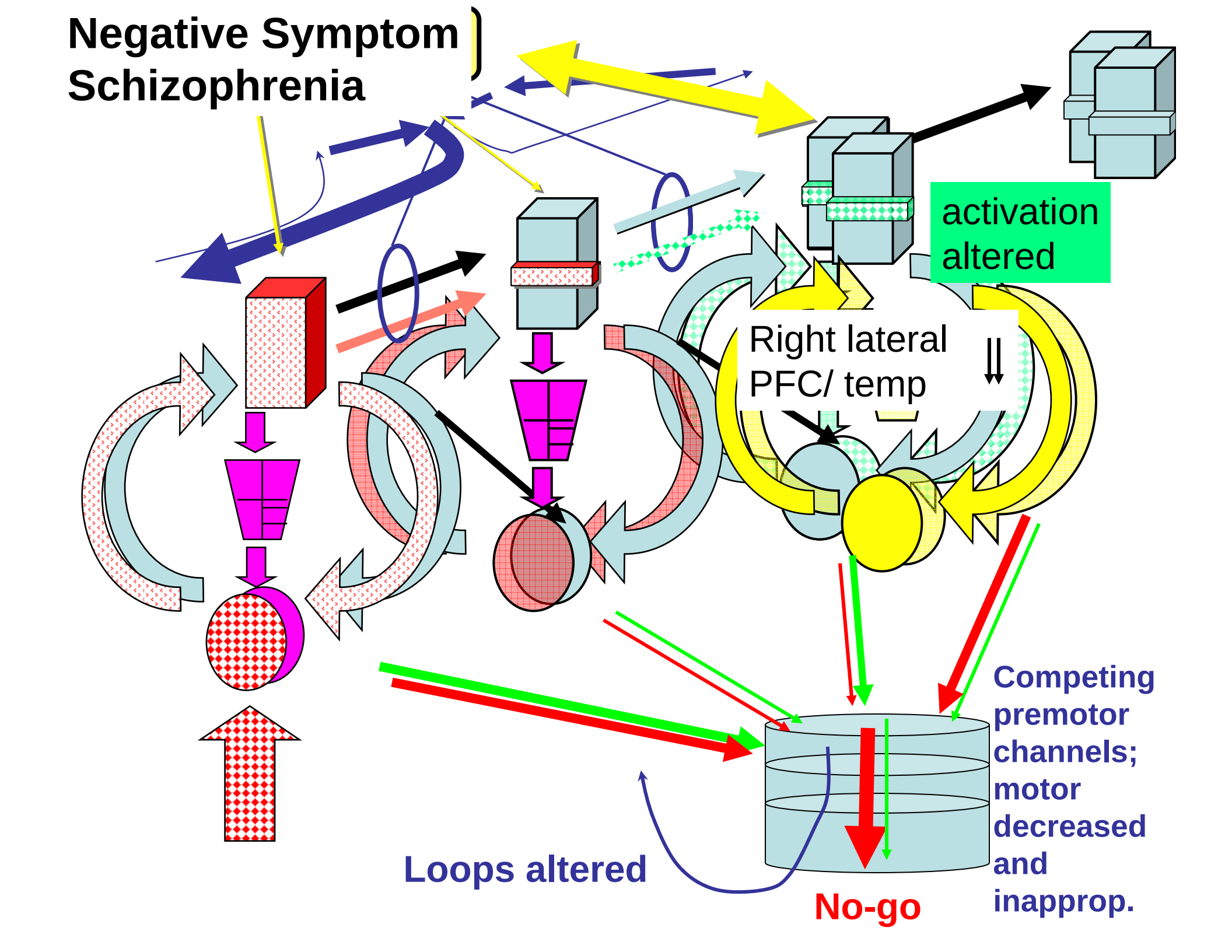






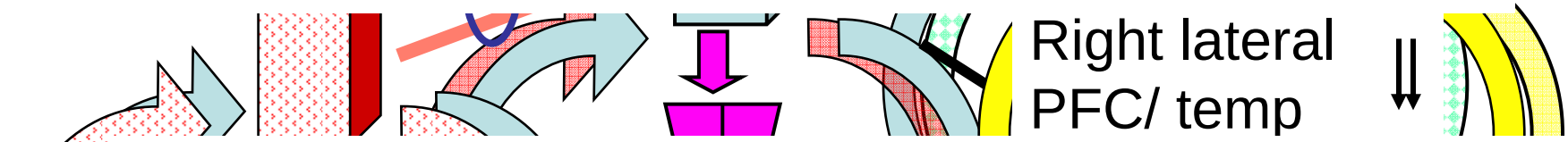





Negative Symptom Schizophrenia
activation altered
Right lateral PFC/ temp
Competing premotor channels; motor decreased and inapprop.
Loops altered
No-go

Negative Symptom Schizophrenia

Where I'm trying to take you in the last slides…



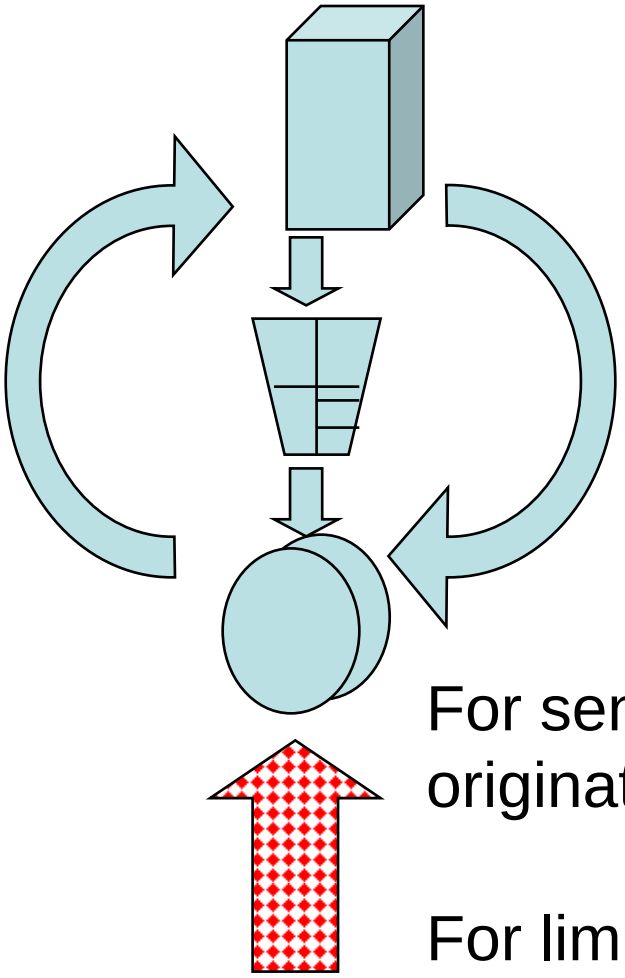
Enhancing glutaminergic drive and GABA balance in layers IV/lower III, combined with stabilization of noradrenergic & serotonergic tone and stabilization of dopaminergic effects in supragranular layers (to improve signal to noise) and infragranular layers (to stabilize & reverberation & perseveration), and blockade of inhib H3 in deep layers, may be a way to treat patients with predominantly negative symptoms.

Loops altered

No-go

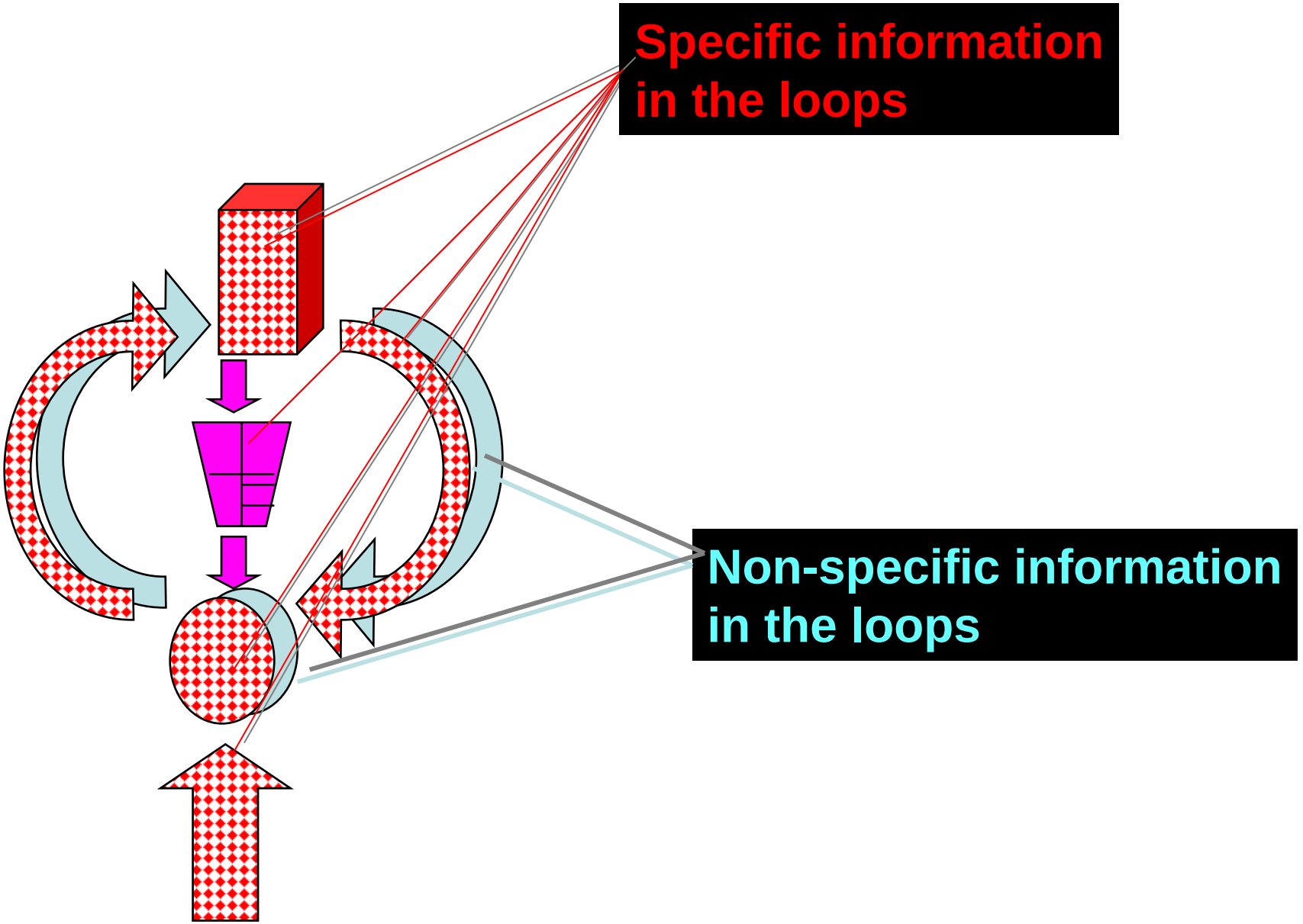
inapprop.

Specific sensory input



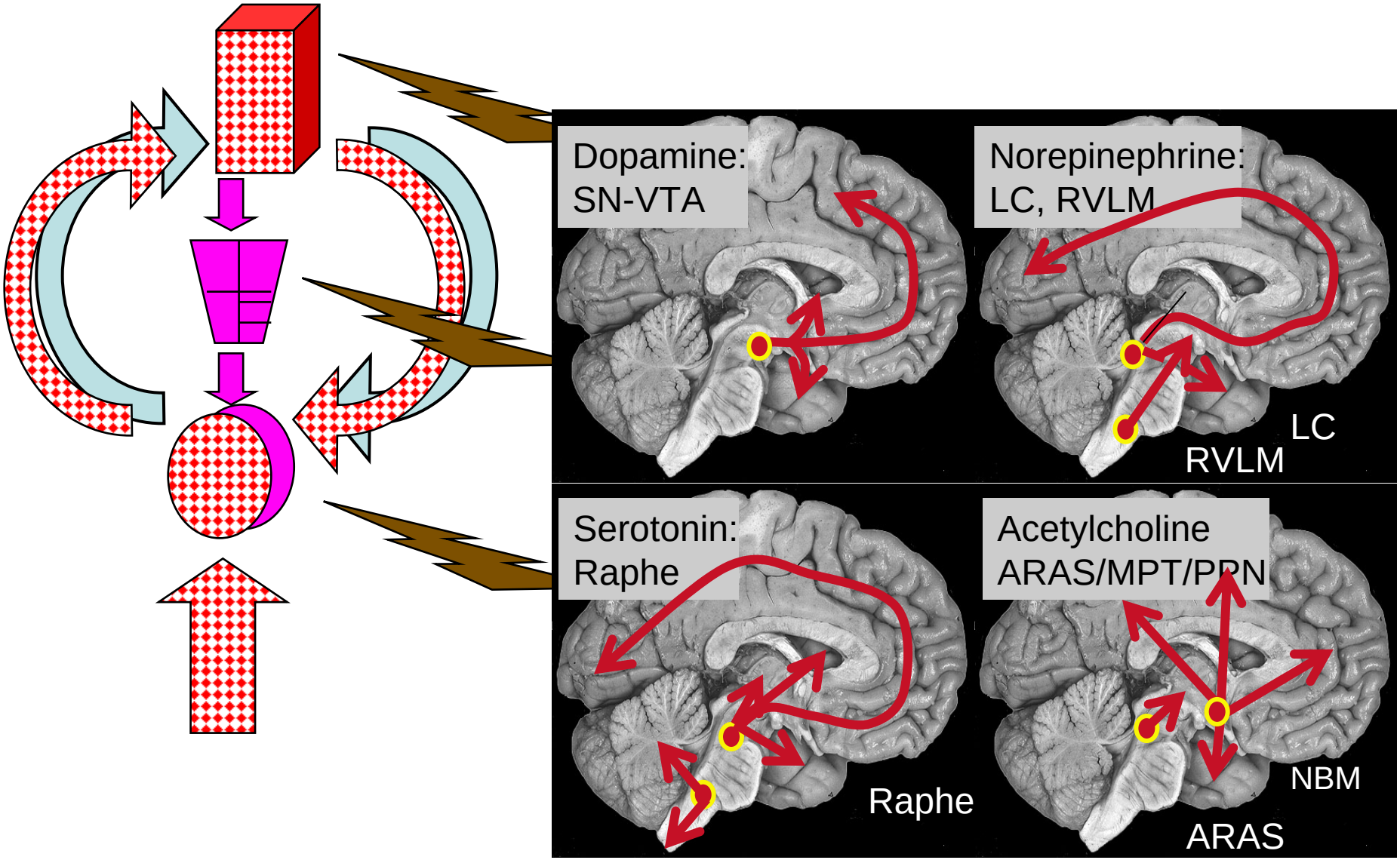
For sensory cortices, this input originates from sense organs

For limbic cortices, this input originates from autonomics, emotions, hormones, association cortices, etc

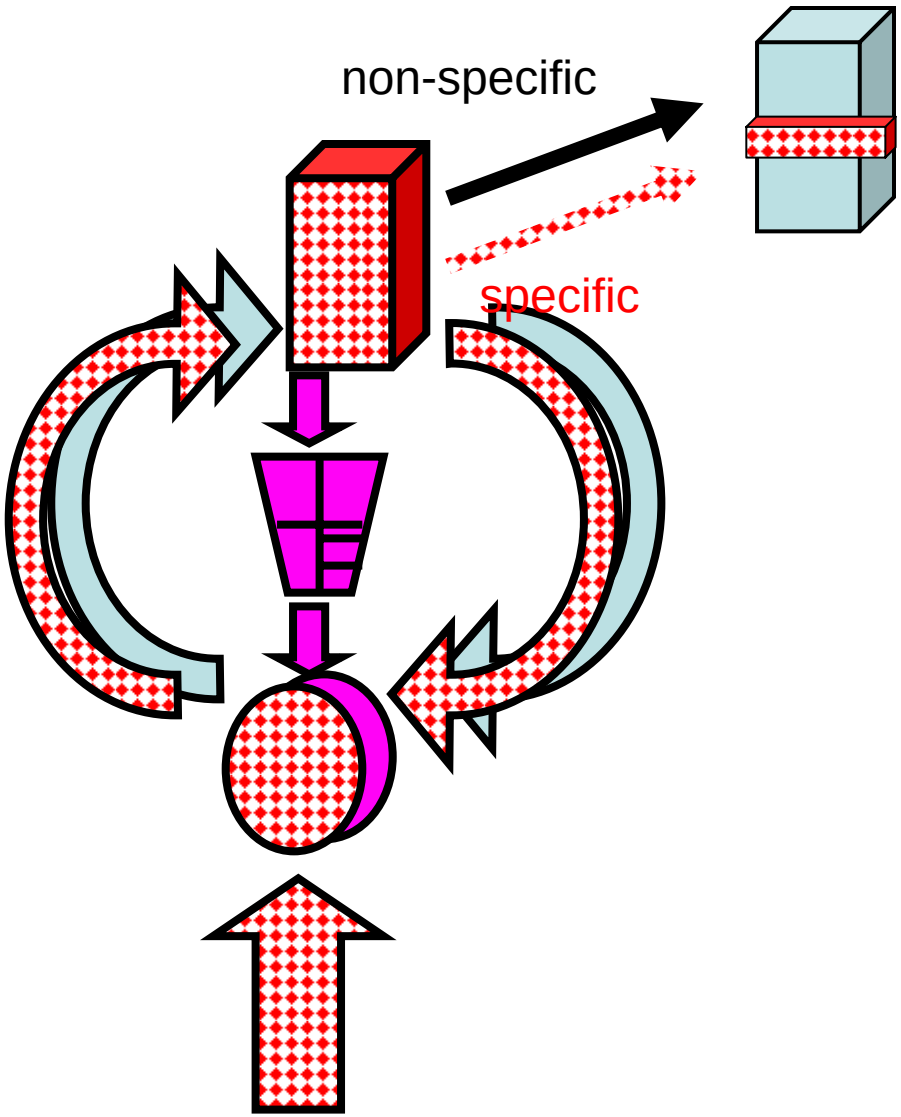

Specific information in the loops
Non-specific information in the loops

Modulatory input/gain from
monoamine systems (DA, NE, 5HT, ACh)

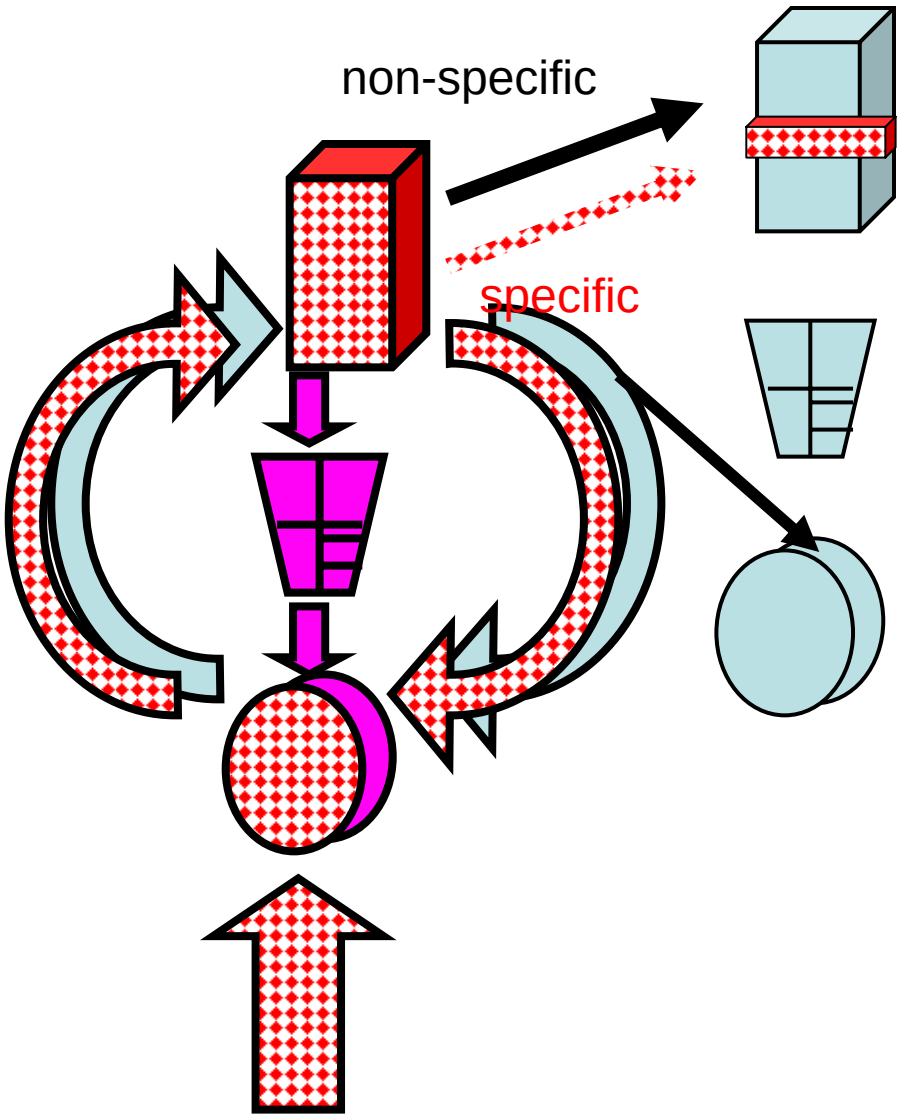
Monoamines increase gain,
signal-noise, impart salience



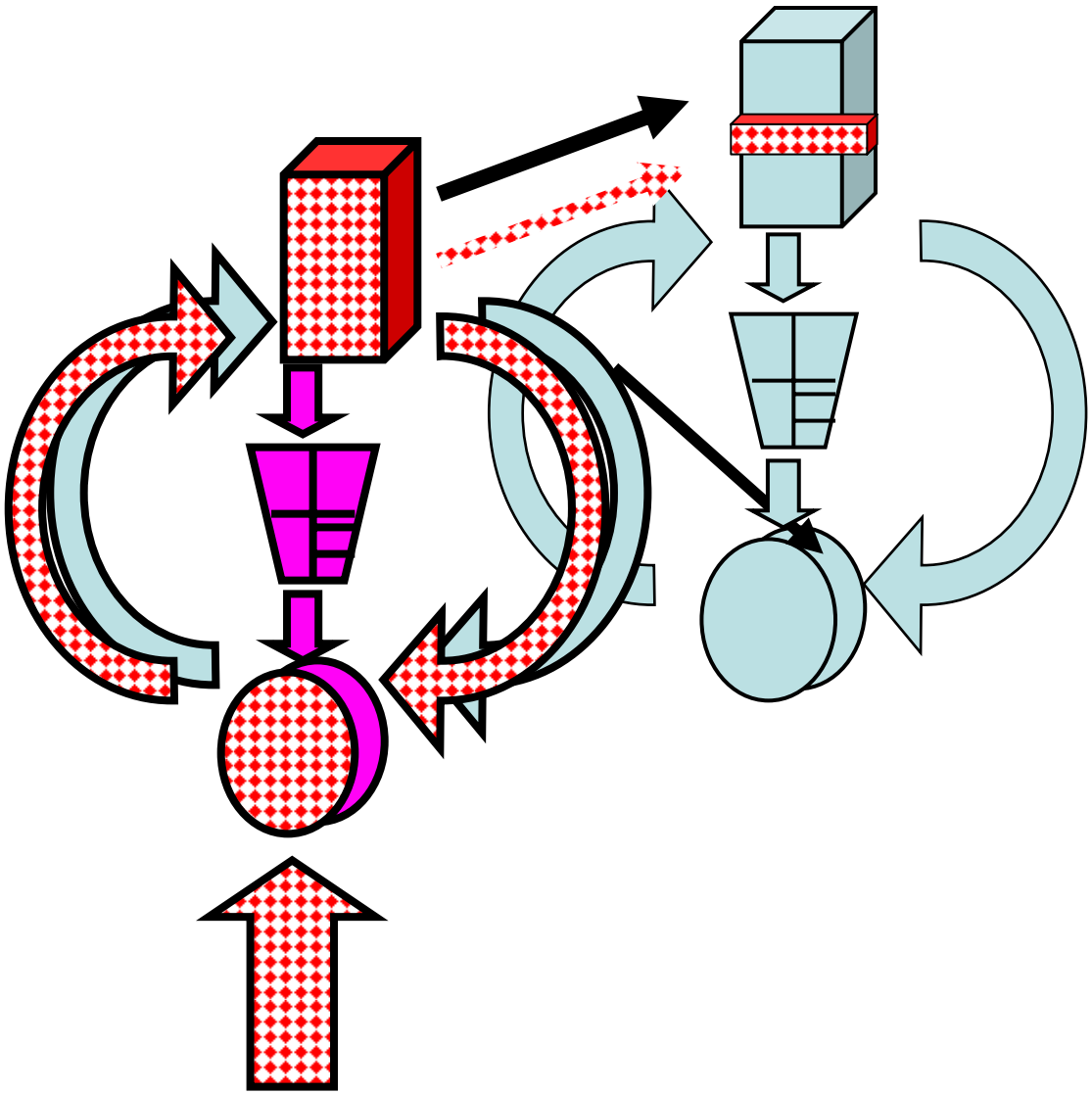
Cortico-cortical projection



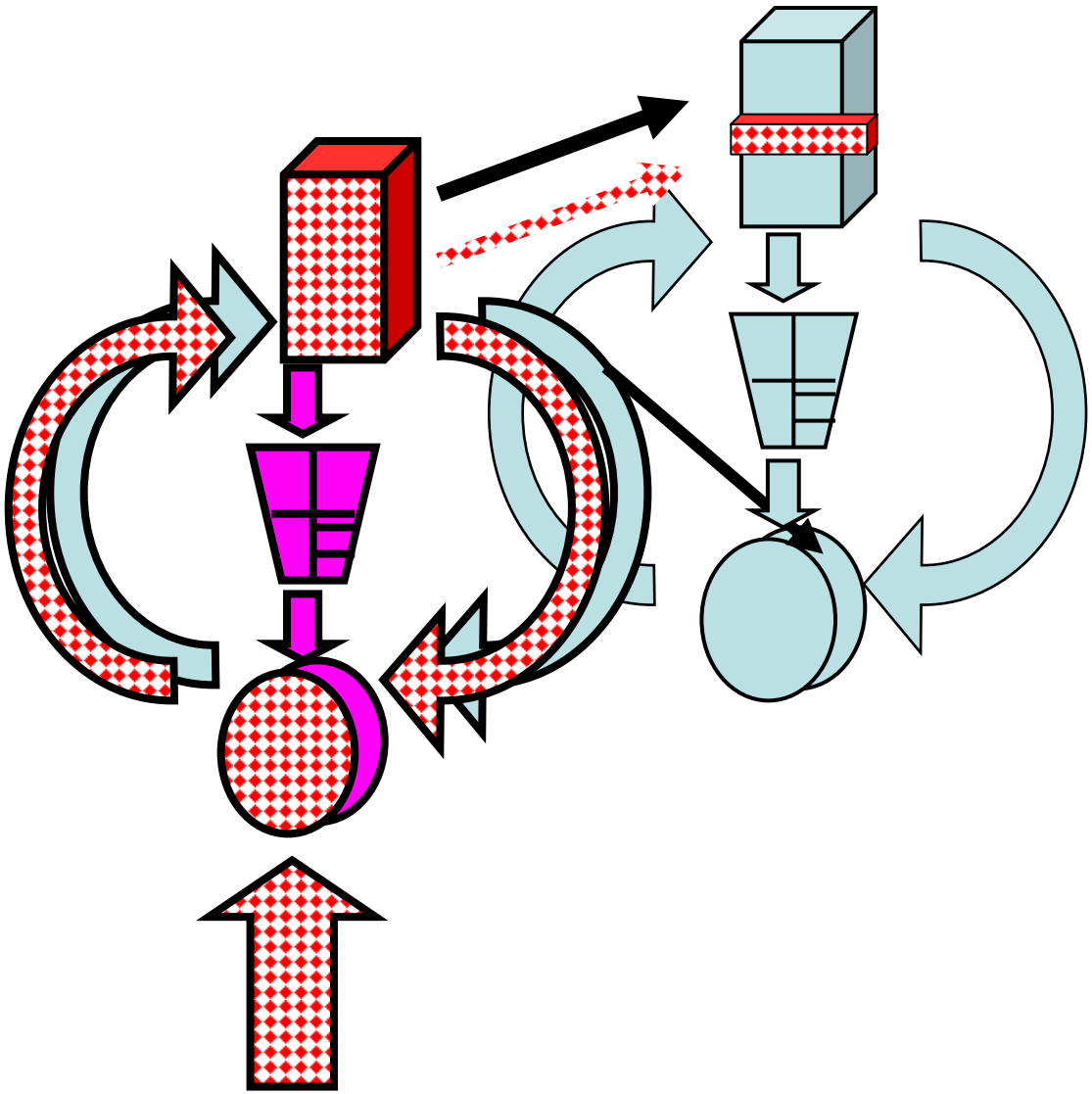
Escape closed loop to access adjacent loop



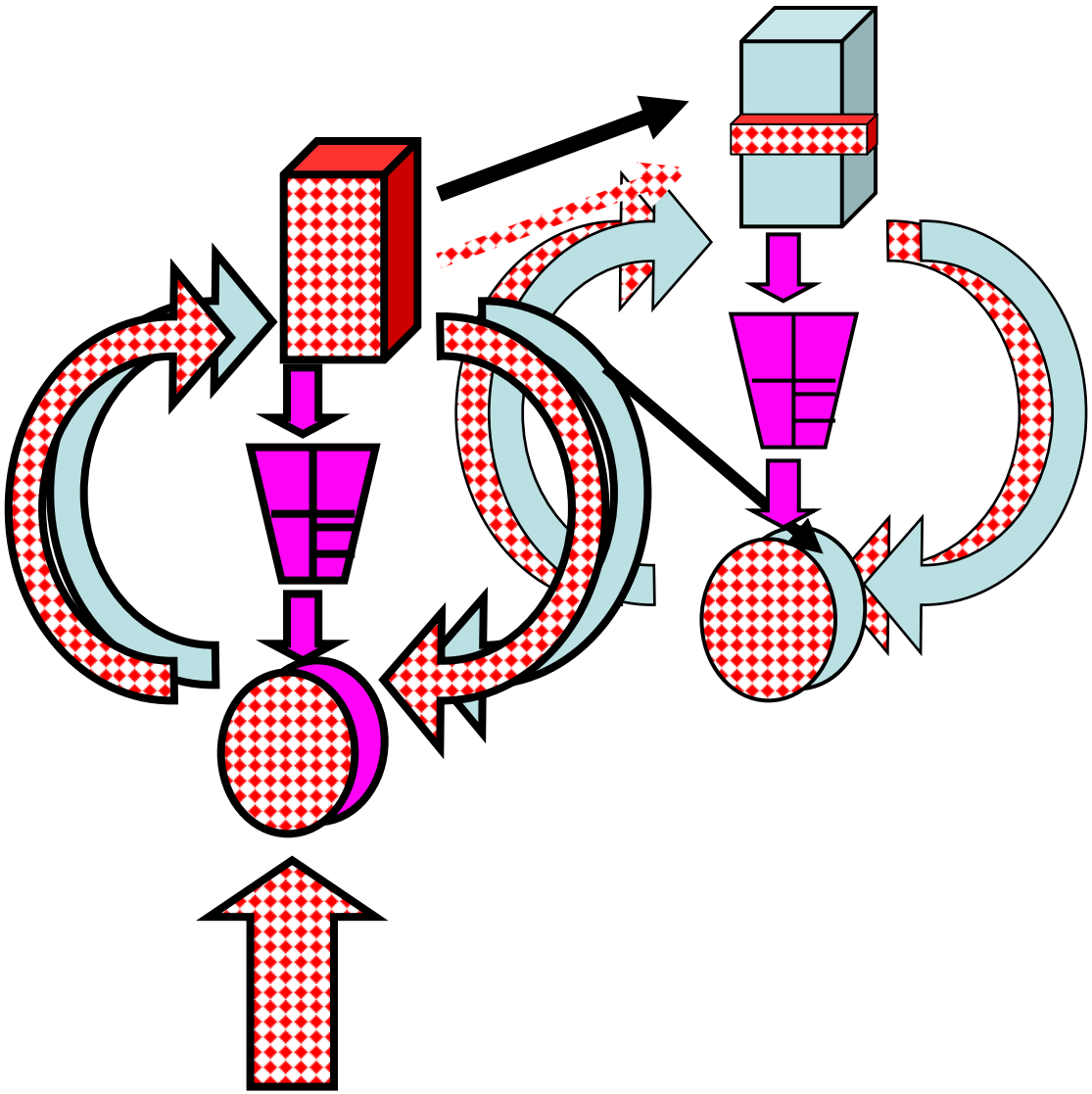
Activate adjacent loop



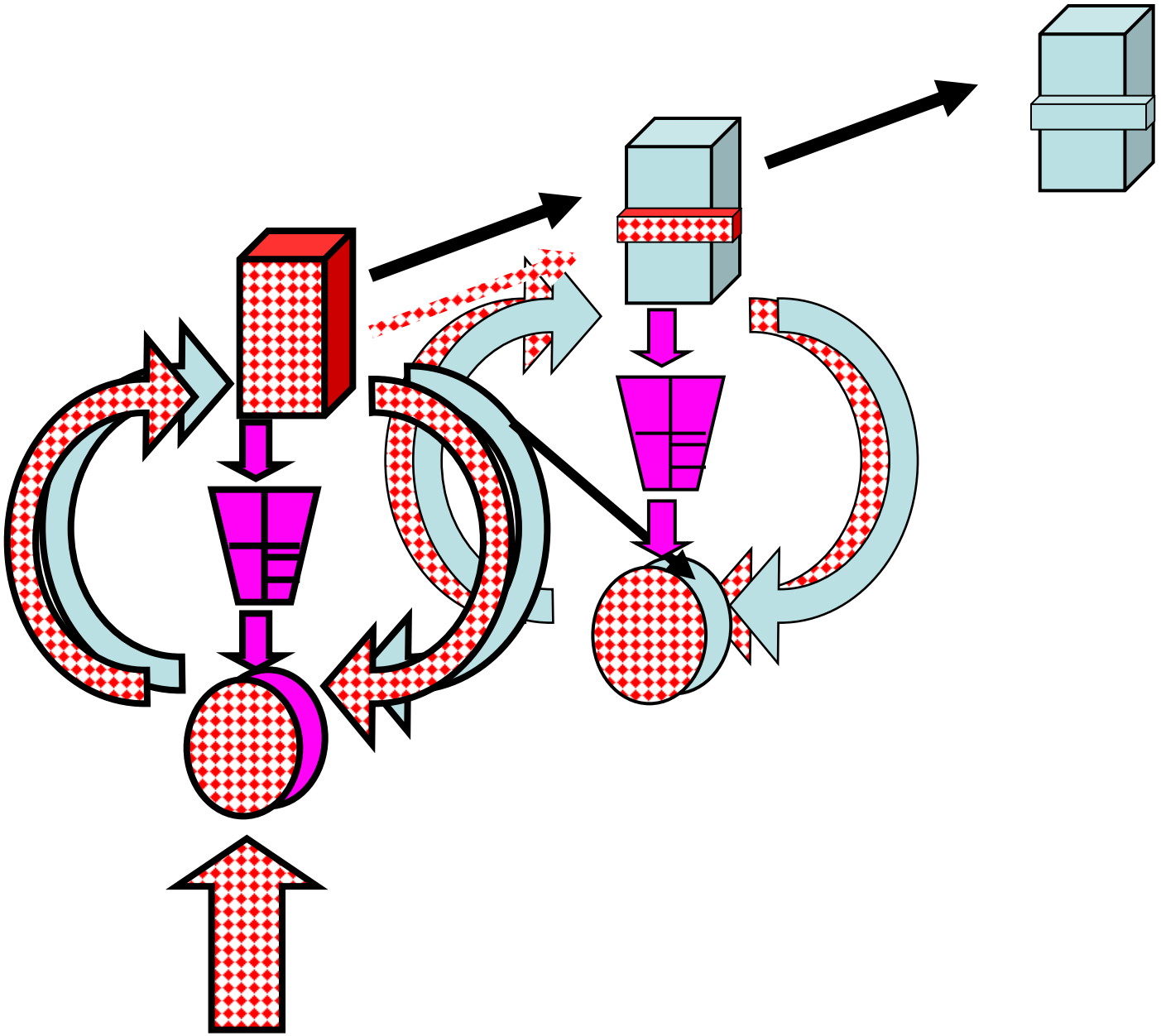
Activate **non-specific**
part of adjacent loop



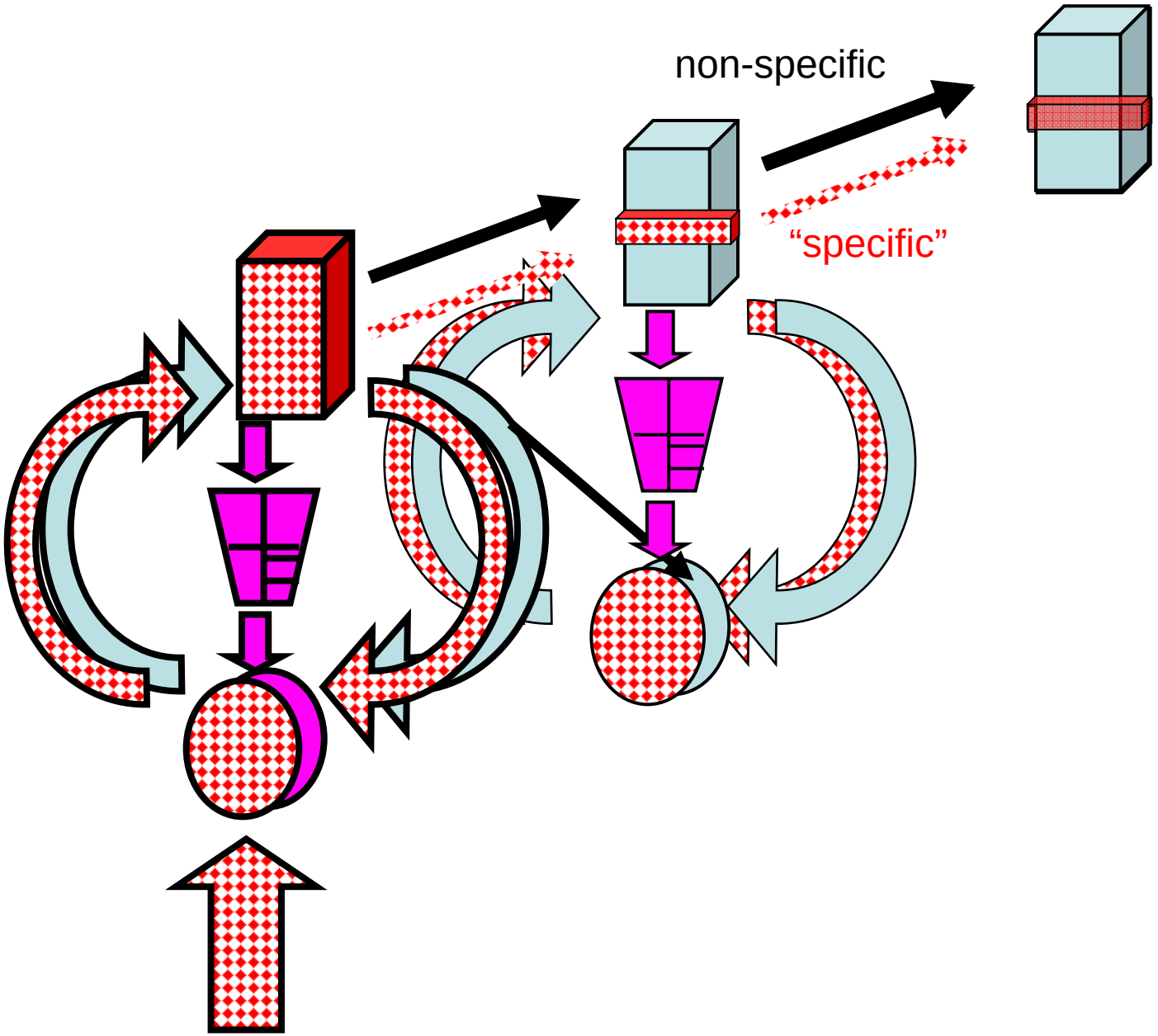
Activate specific
part of adjacent loop



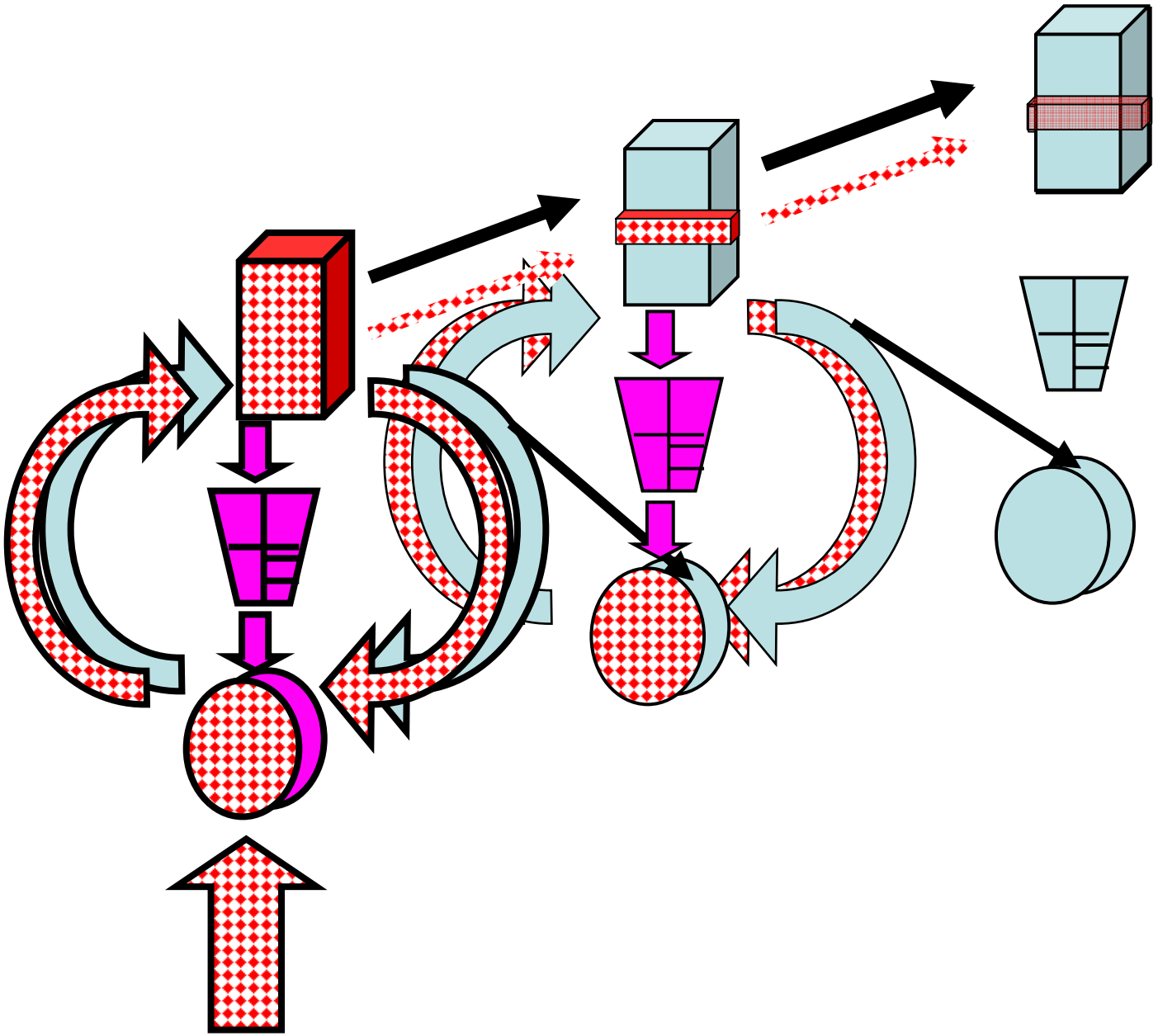
Cortico-cortical projection



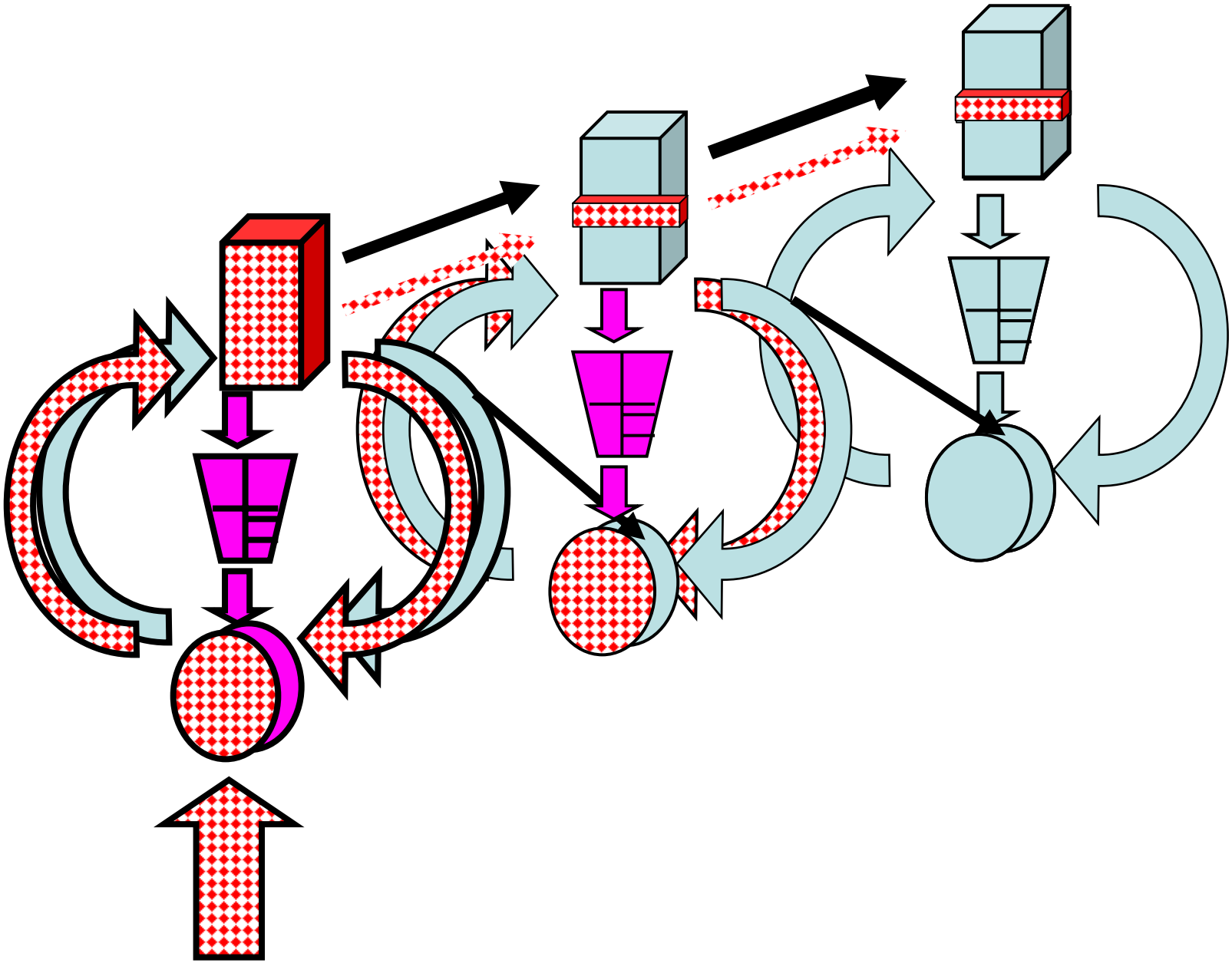
Cortico-cortical projection



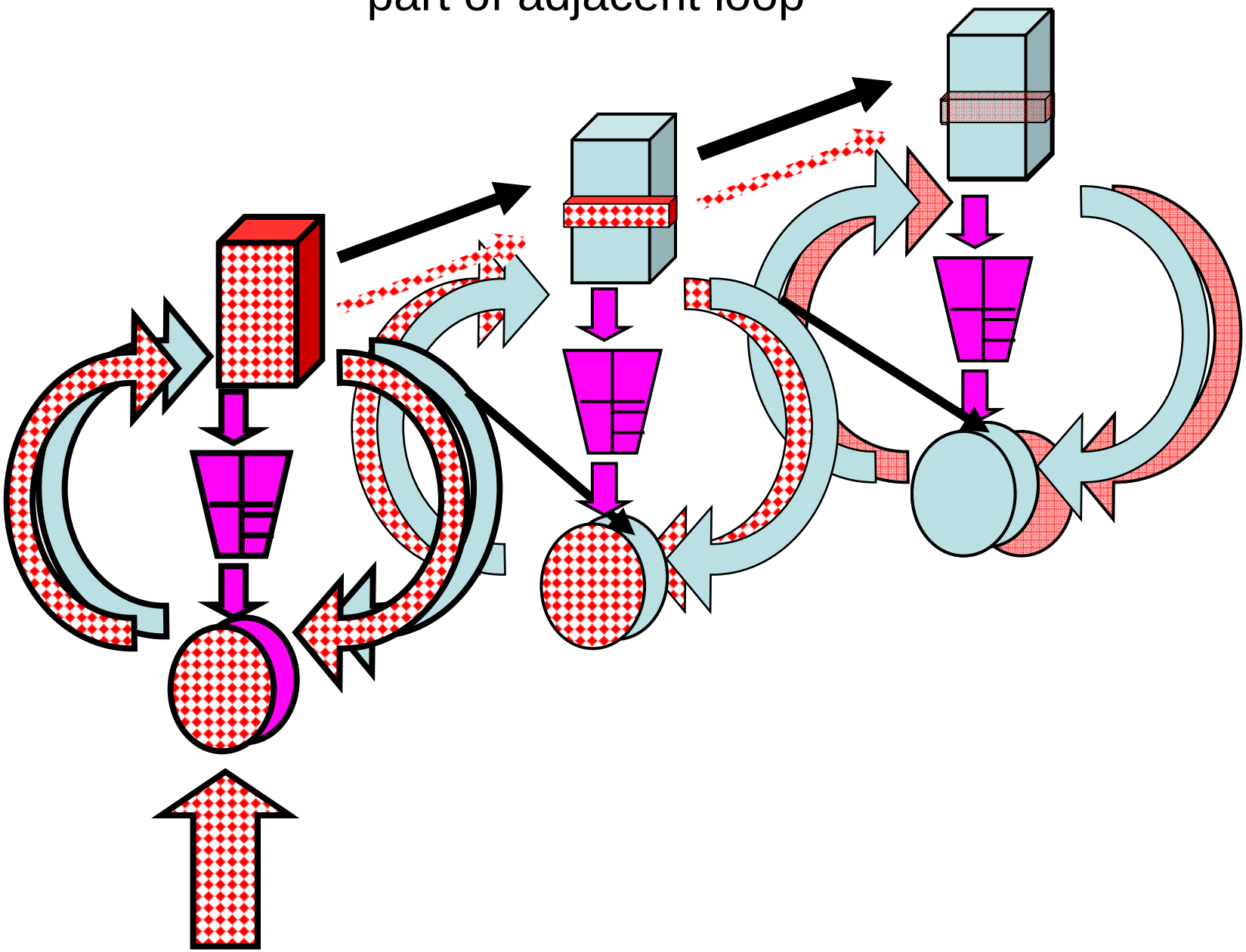
Escape closed loop to access adjacent loop



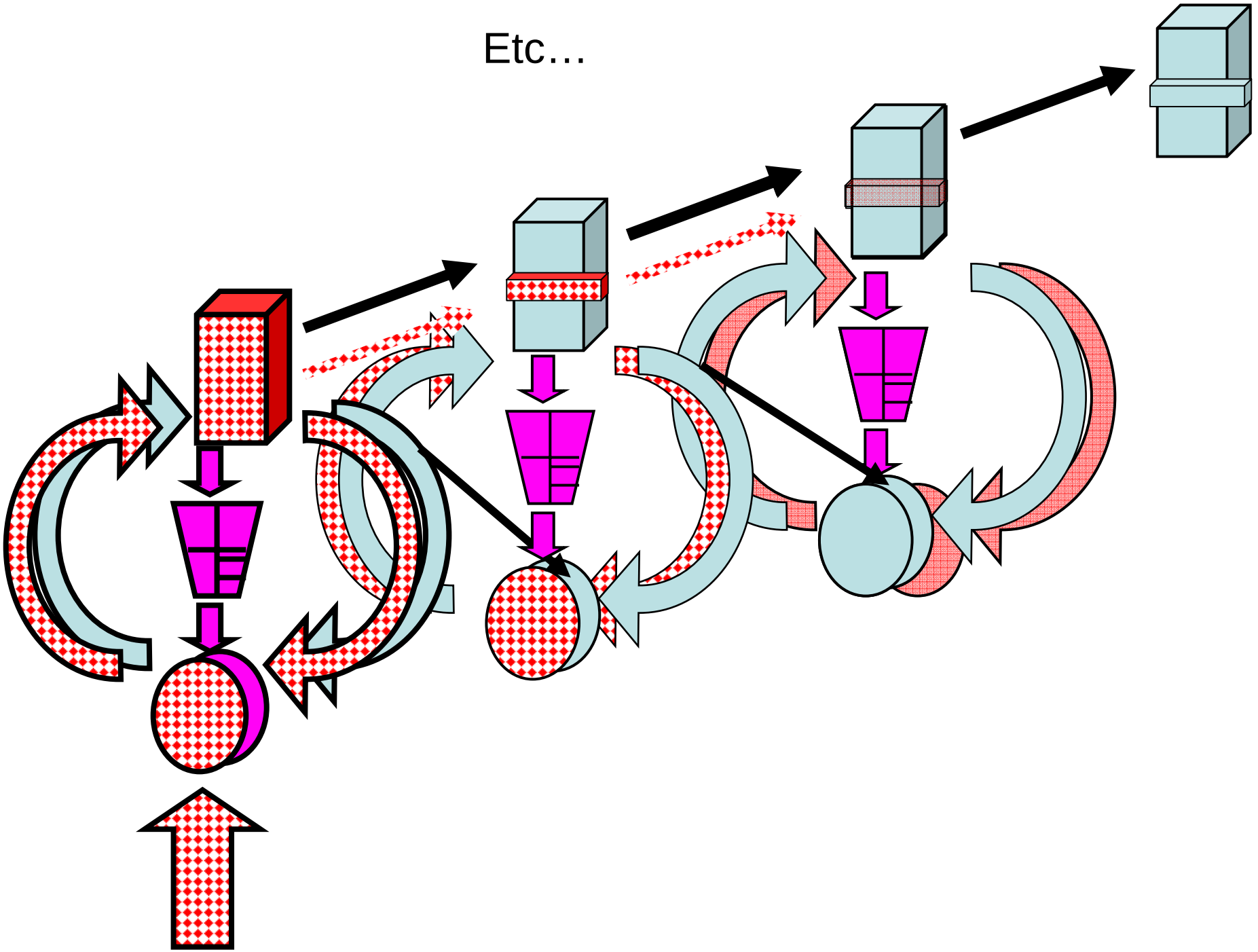
Activate adjacent loop

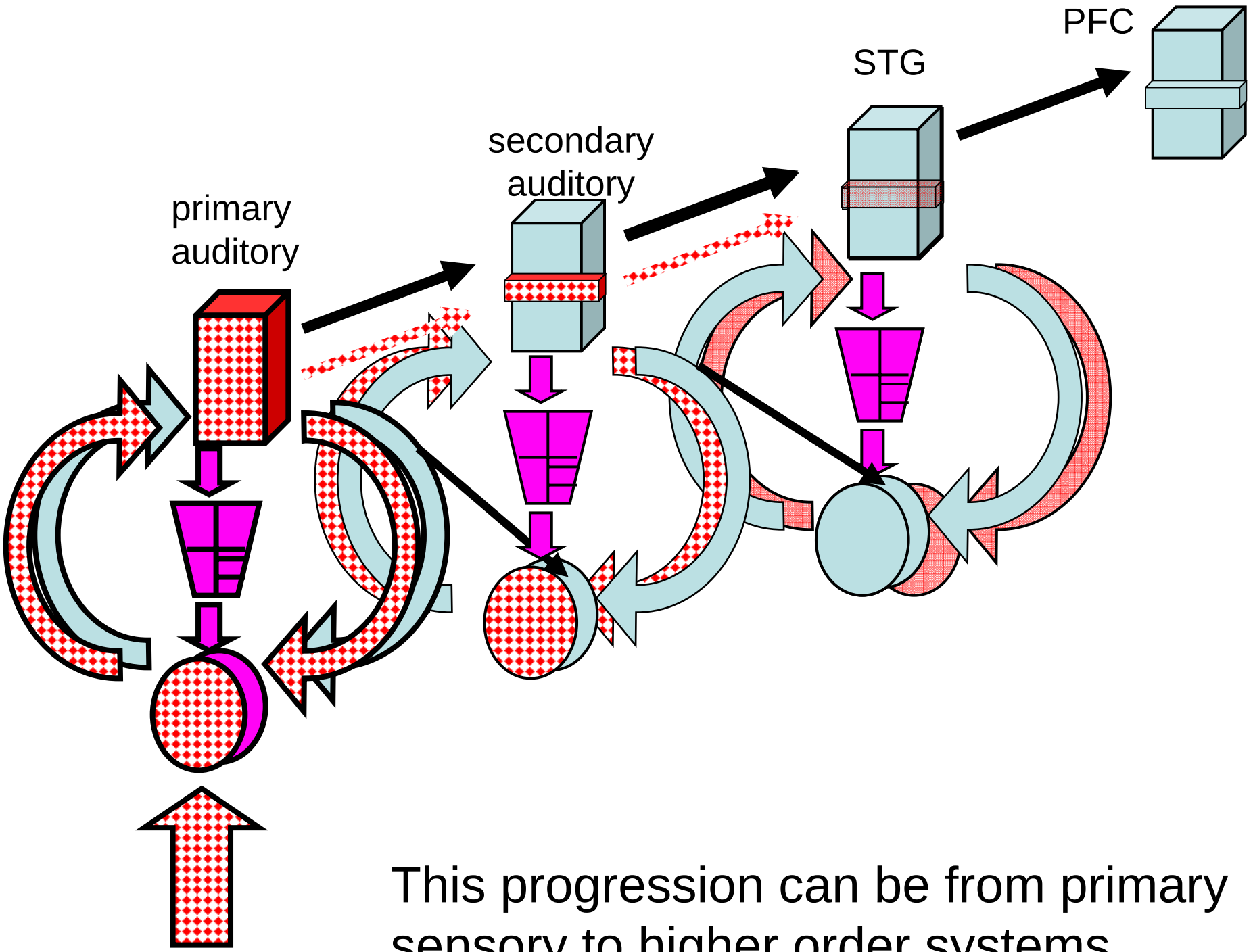


Activate specific
part of adjacent loop

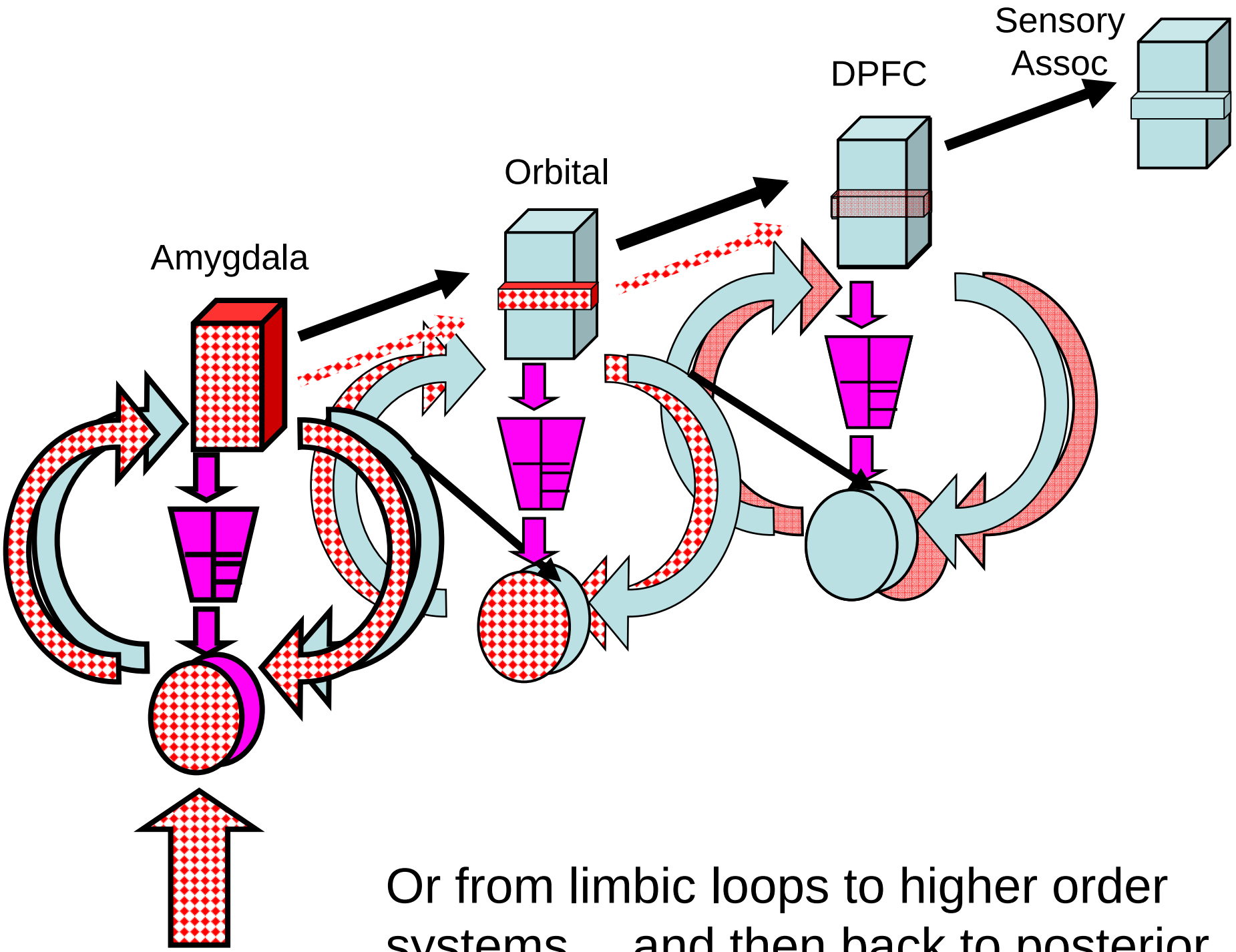


Etc…



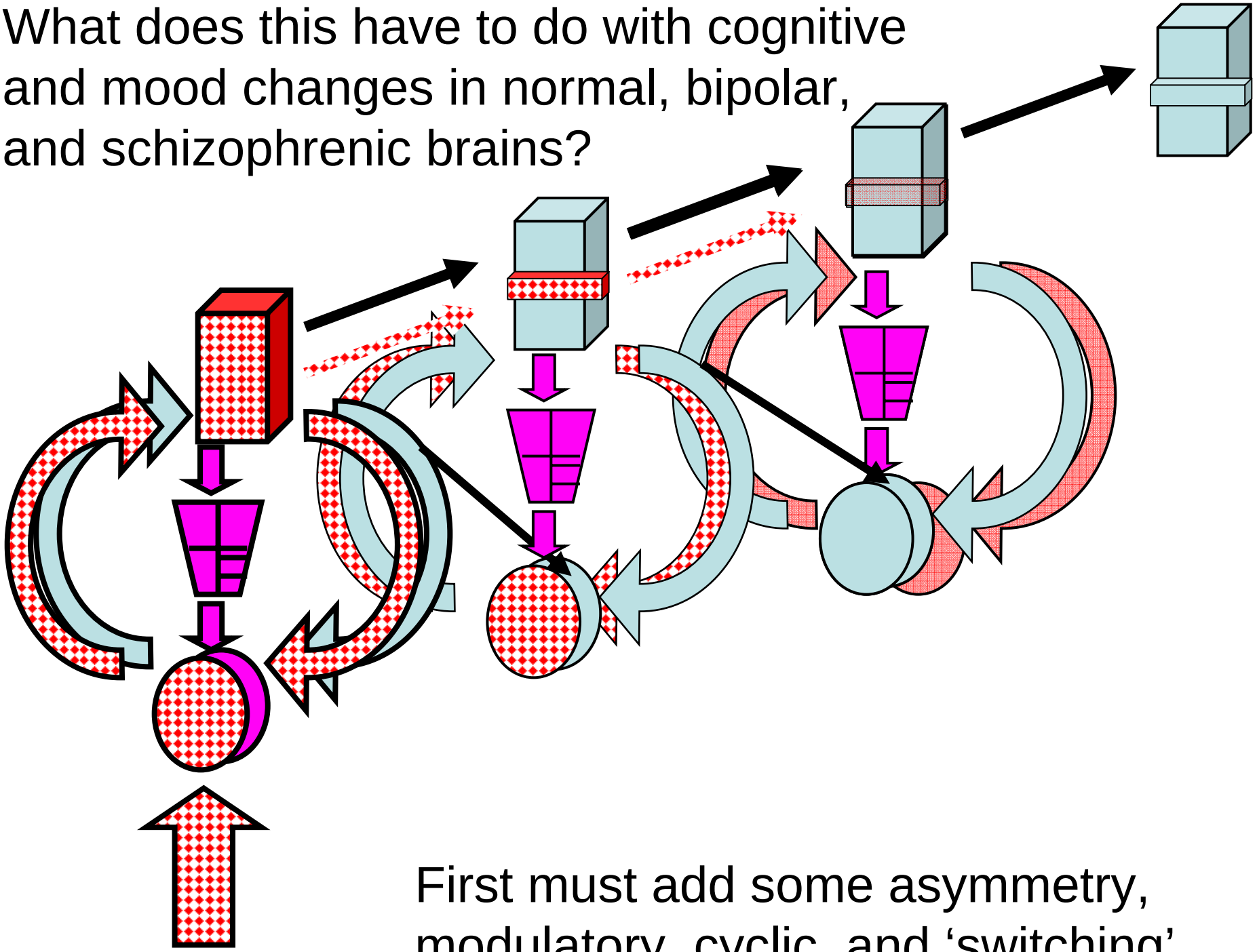


This progression can be from primary sensory to higher order systems….



Or from limbic loops to higher order systems….and then back to posterior sensory association systems

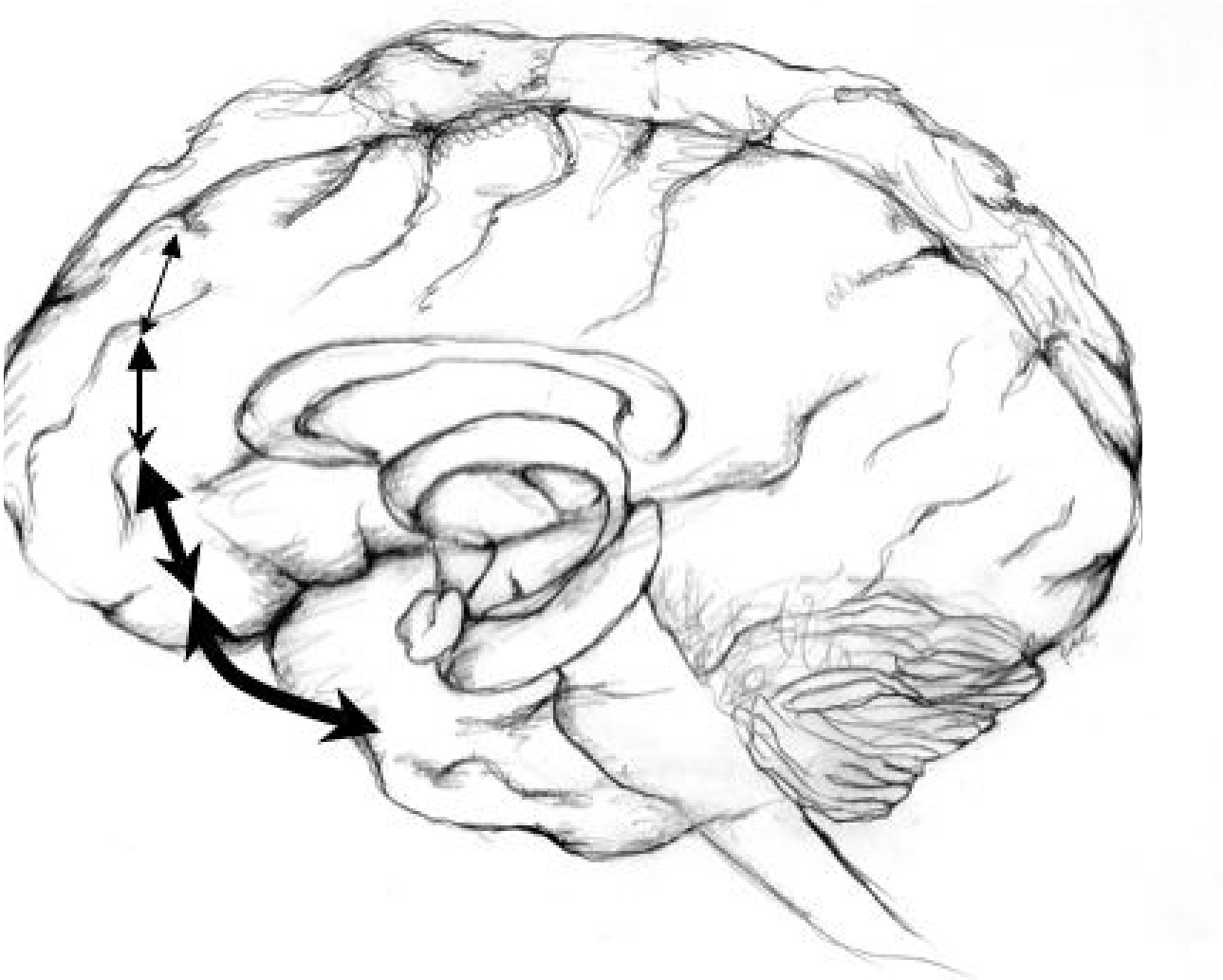
What does this have to do with cognitive and mood changes in normal, bipolar, and schizophrenic brains?

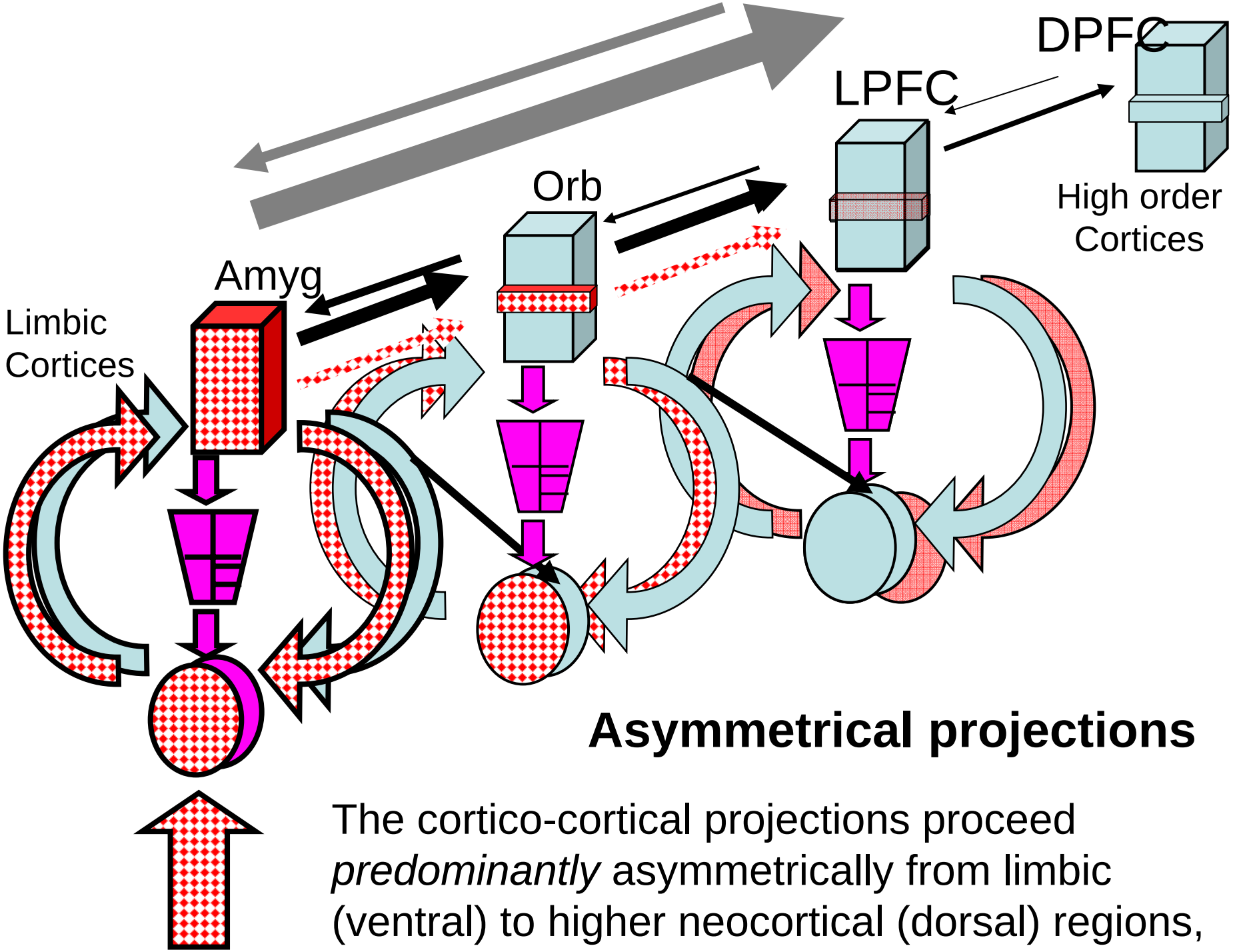


First must add some asymmetry, modulatory, cyclic, and ‘switching’ mechanisms…

Asymmetry of cortico-cortical projections

here there is some interconnectivity, it tends to be from ntral to dorsal areas, and between 'older' (phylog) areas



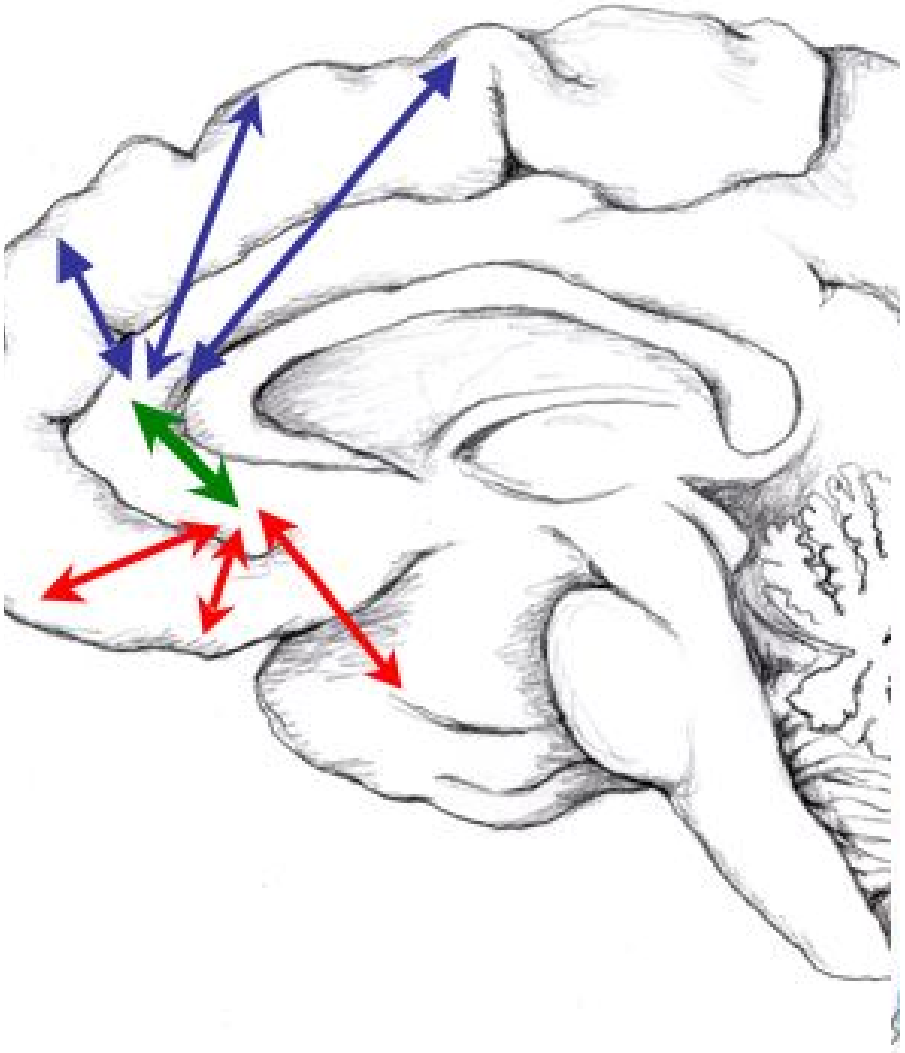


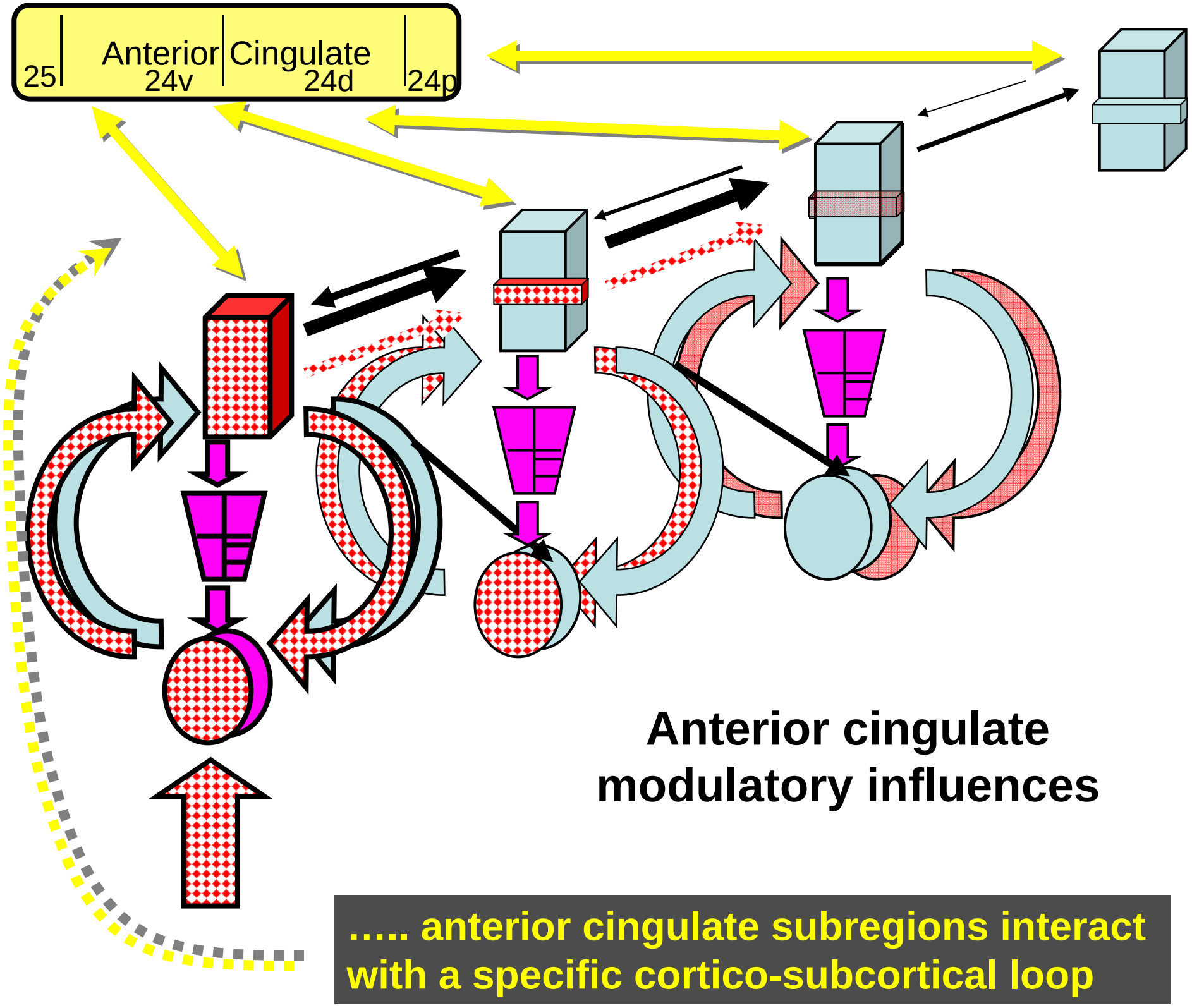
Asymmetrical projections

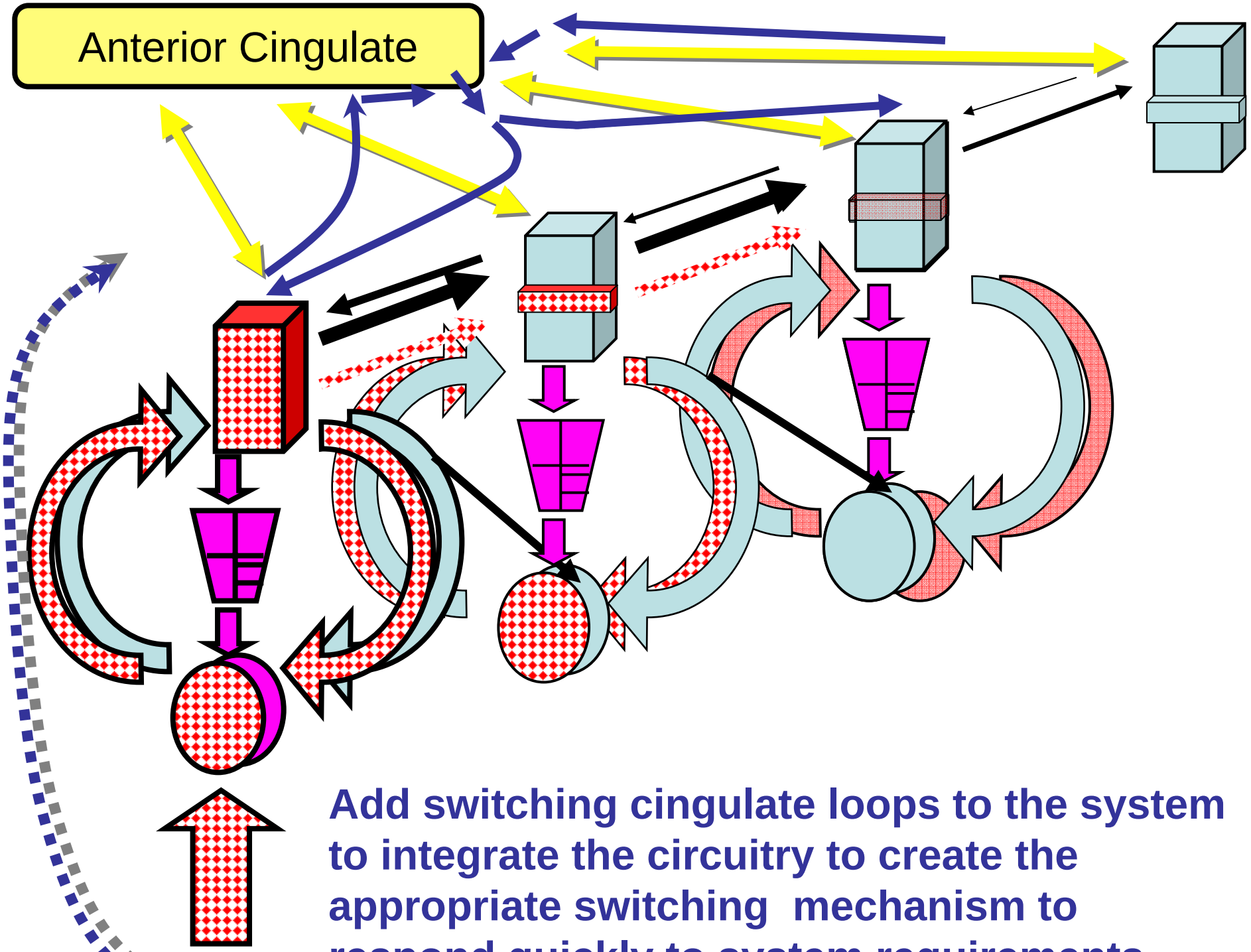
The cortico-cortical projections proceed *predominantly* asymmetrically from limbic (ventral) to higher neocortical (dorsal) regions, i.e., the limbic system trumps the cognitive system from a circuit point of view.

Anterior cingulate modulatory/switch

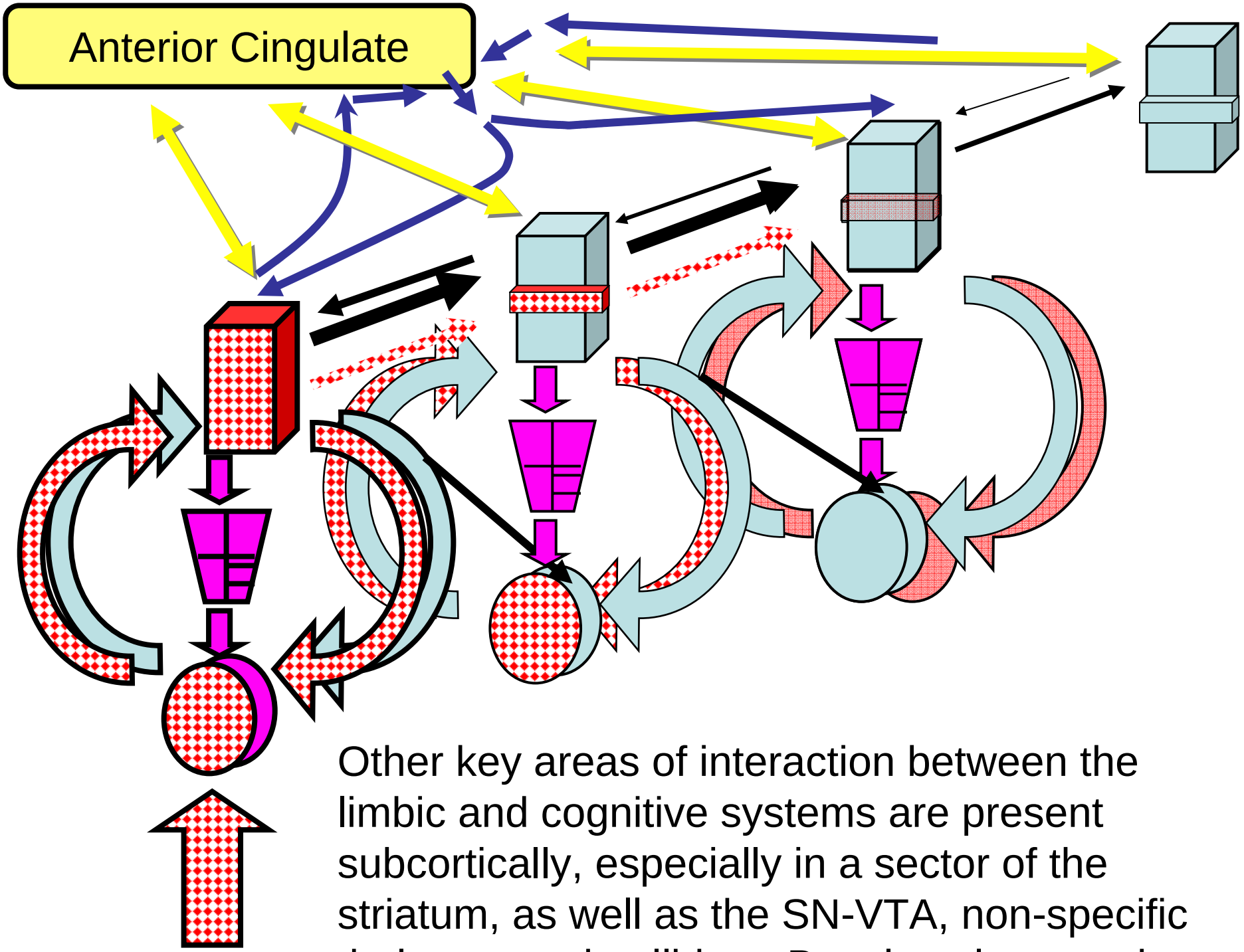
ɜ cortical areas most likely to provide indirect connectivit
ɲe stop shopping) between dorsal and ventral prefrontal
reams are the ventral and dorsal anterior cingulate corti



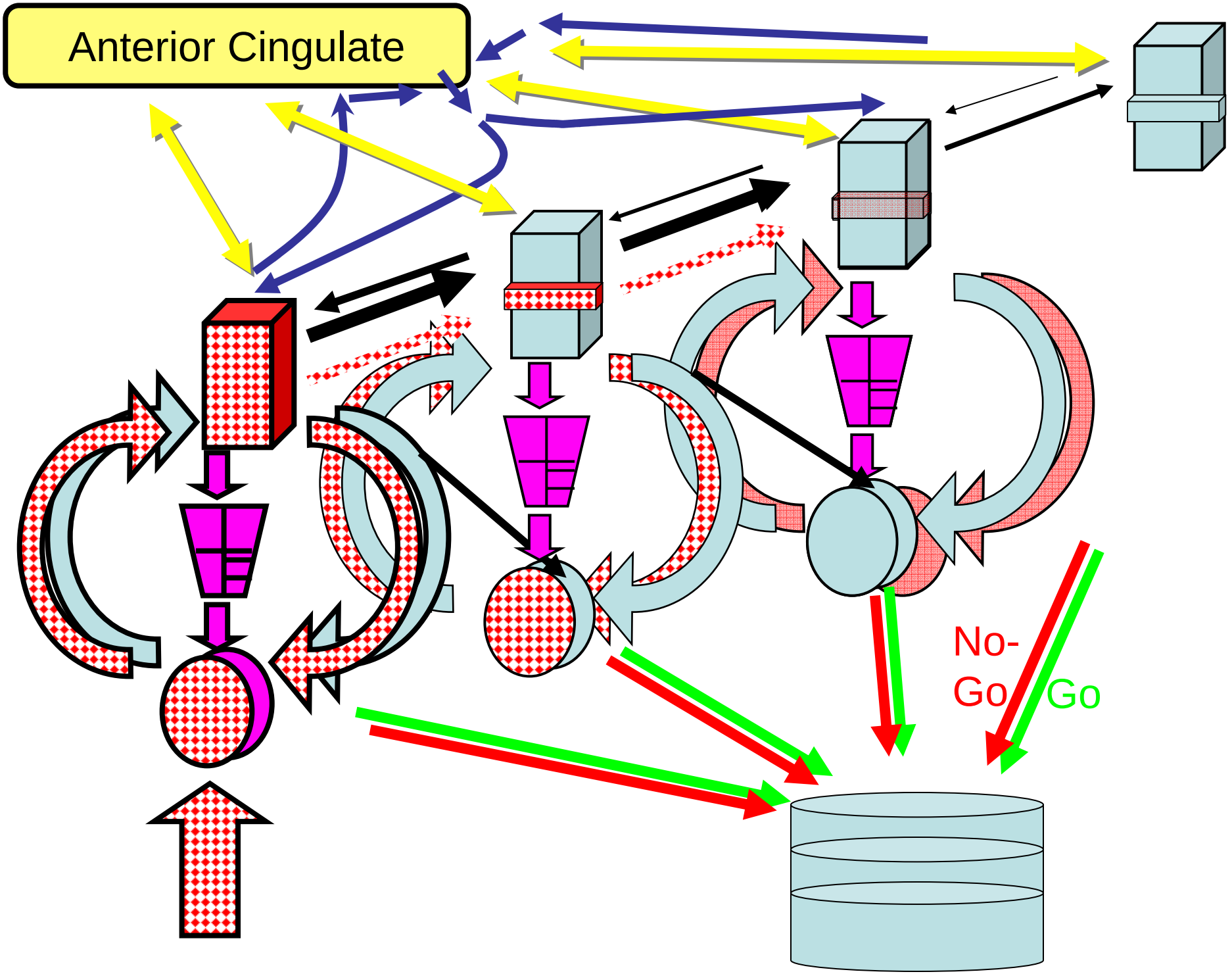

25
Anterior Cingulate
24v
24d
24p
Anterior cingulate
modulatory influences
….. anterior cingulate subregions interact
with a specific cortico-subcortical loop

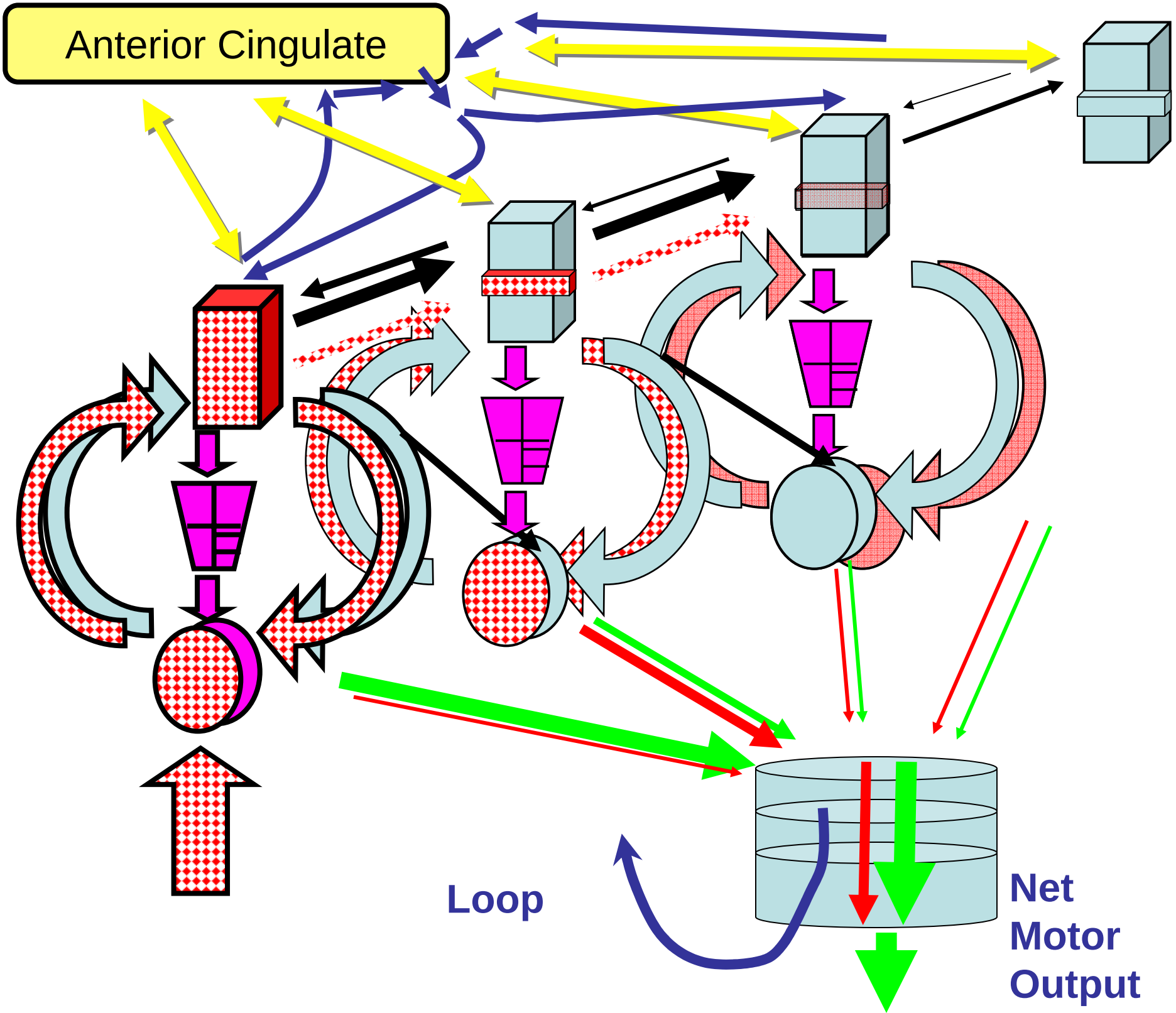


Add switching cingulate loops to the system to integrate the circuitry to create the appropriate switching mechanism to respond quickly to system requirements (eg, thoughts, hormones, emotions)

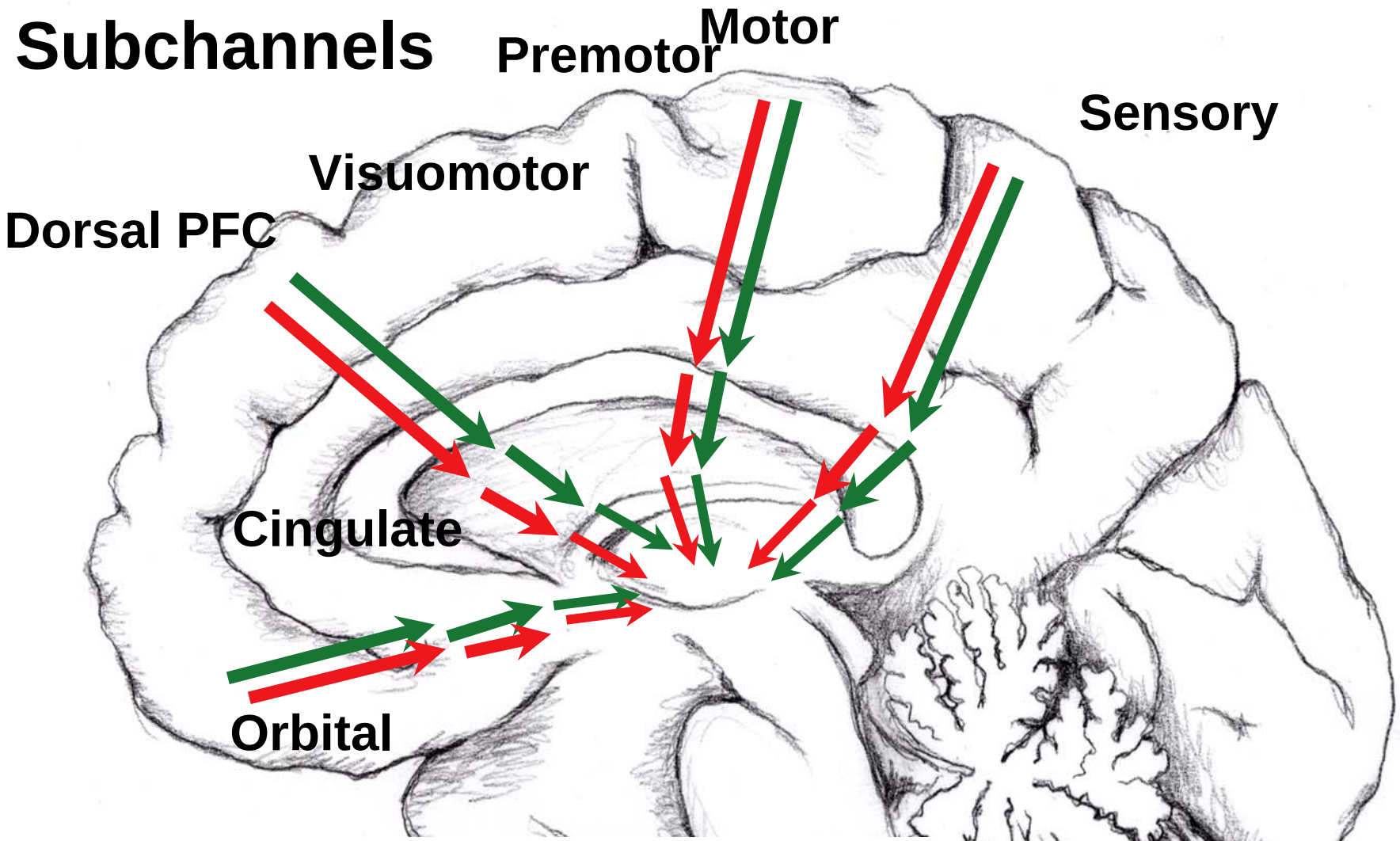


Other key areas of interaction between the limbic and cognitive systems are present subcortically, especially in a sector of the striatum, as well as the SN-VTA, non-specific thalamus and pallidum, Basal nucleus, and Ce/M amygdala


Anterior Cingulate
No-
Go
Go


Anterior Cingulate
Loop
Net
Motor
Output

Subchannels

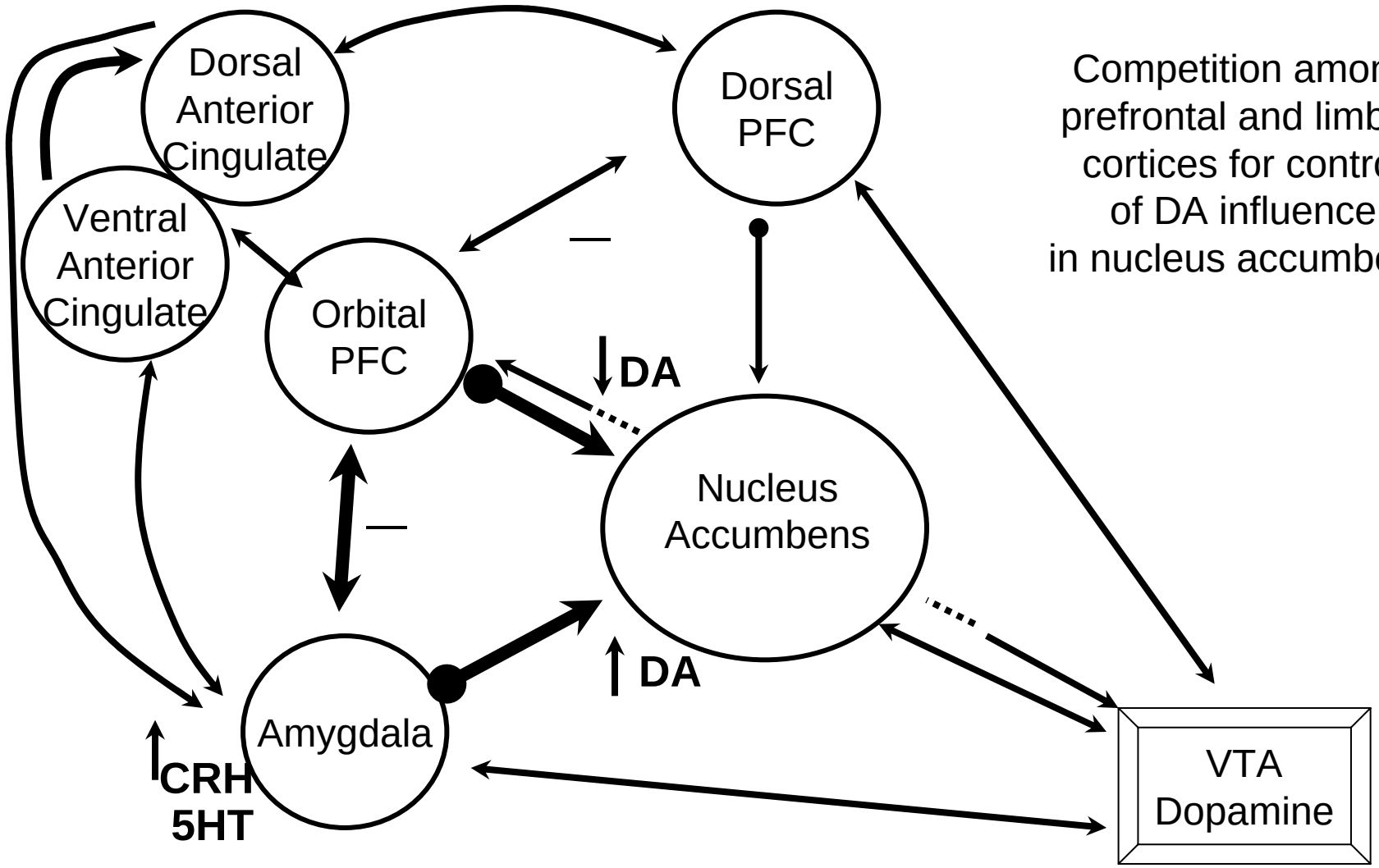


Topographical projection channels
Go/No Go (Do it/Don't Do it) subchannels

Do It- mediated by D1 in striatum (direct pathway)
Don't do it- mediated by D2 in striatum (indirect pathway)

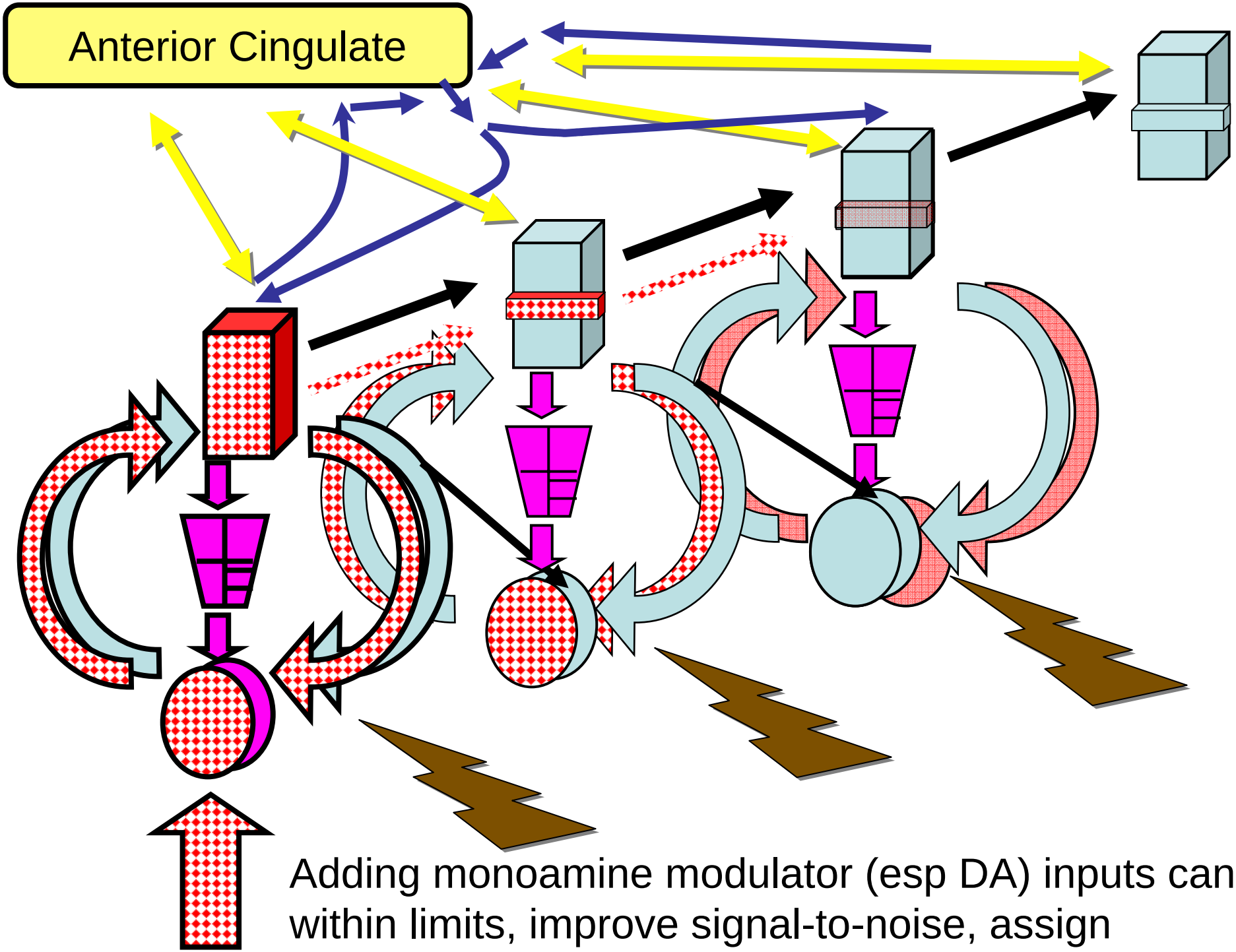
Fallon

Anhedonia in Negative Symptom Schizophrenics

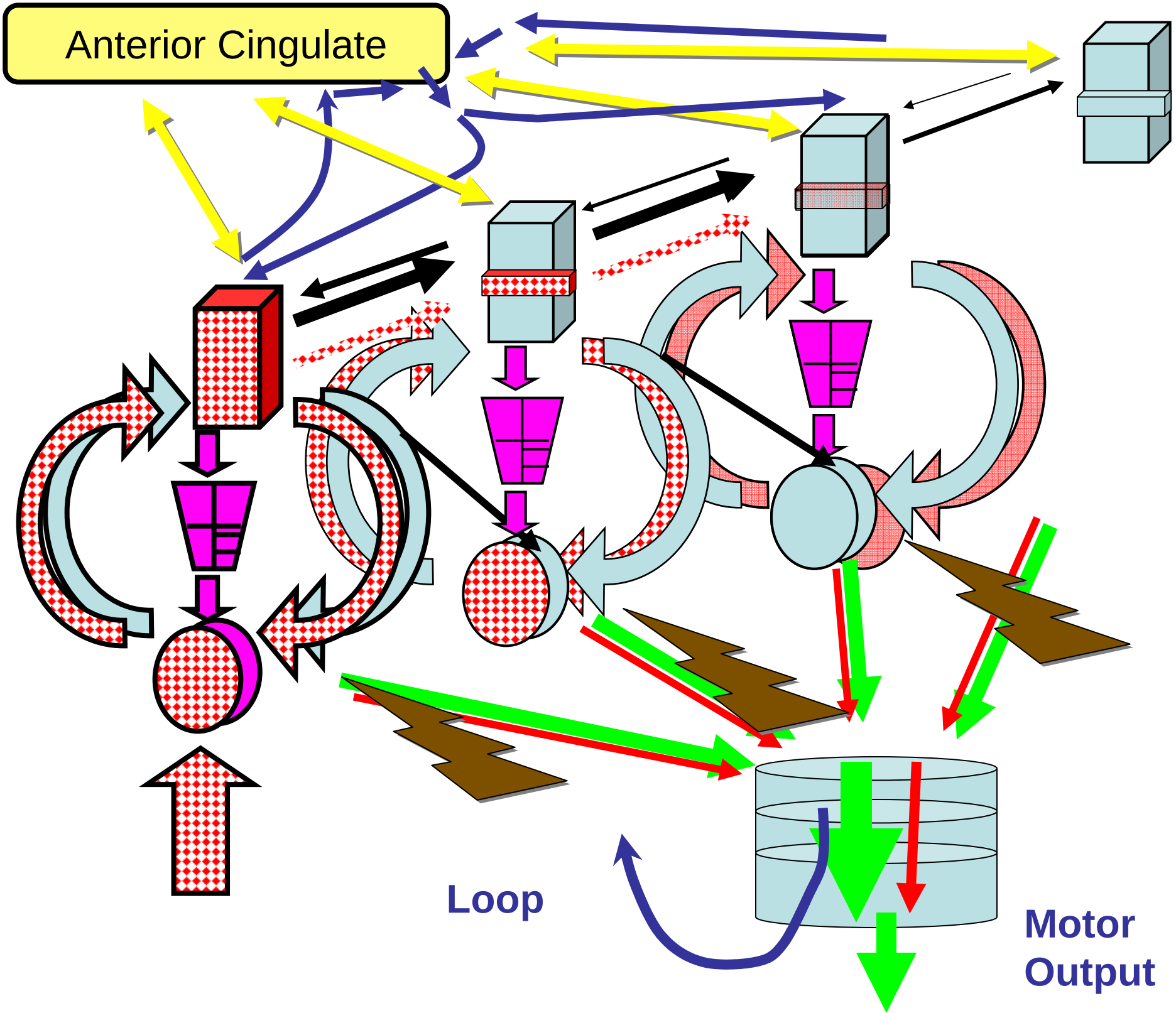


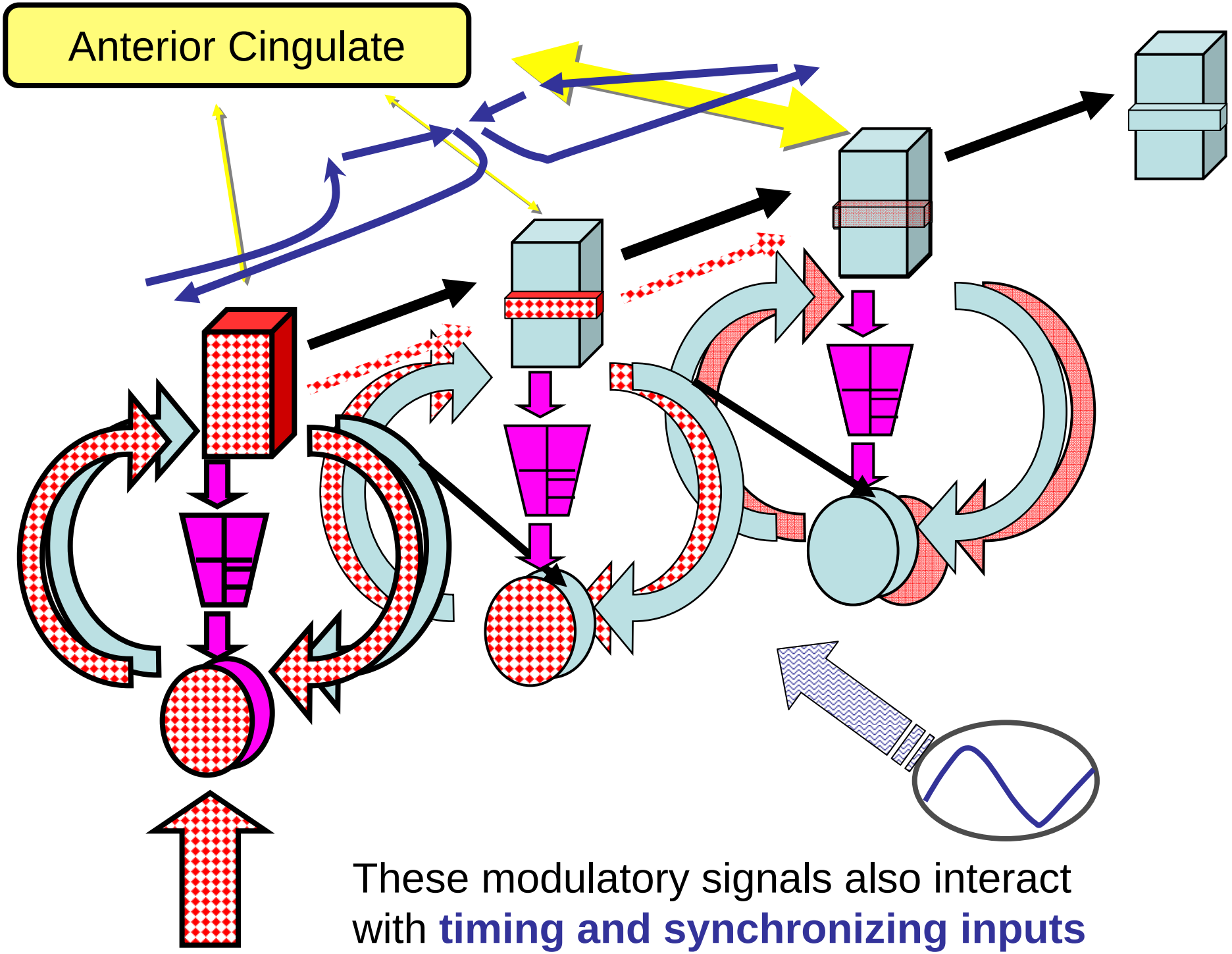
Competition among prefrontal and limbic cortices for control of DA influence in nucleus accumbens

Orbital and Amygdaloid cortices inhibit each others' actions
Amygdala input increases release of DA in nuc accumbens
Orbital and dorsal PFC inputs decrease DA release in nuc accumbens.
Anterior cingulate subsectors act as mediators and indirect connectors



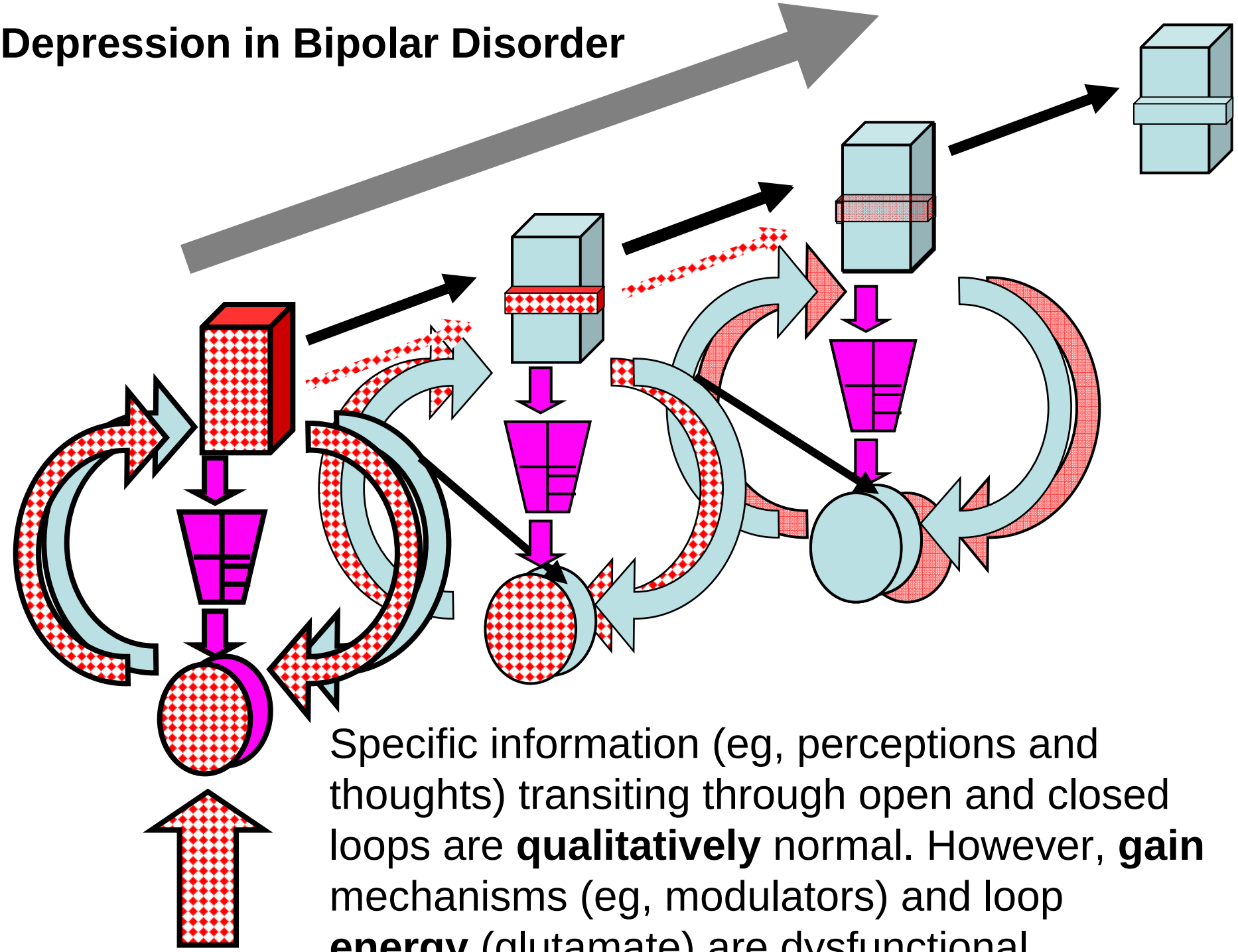
Adding monoamine modulator (esp DA) inputs can. within limits, improve signal-to-noise, assign salience, dampen reverberation, and **quantitatively** increase appropriate motor output


Anterior Cingulate
Loop
Motor
Output

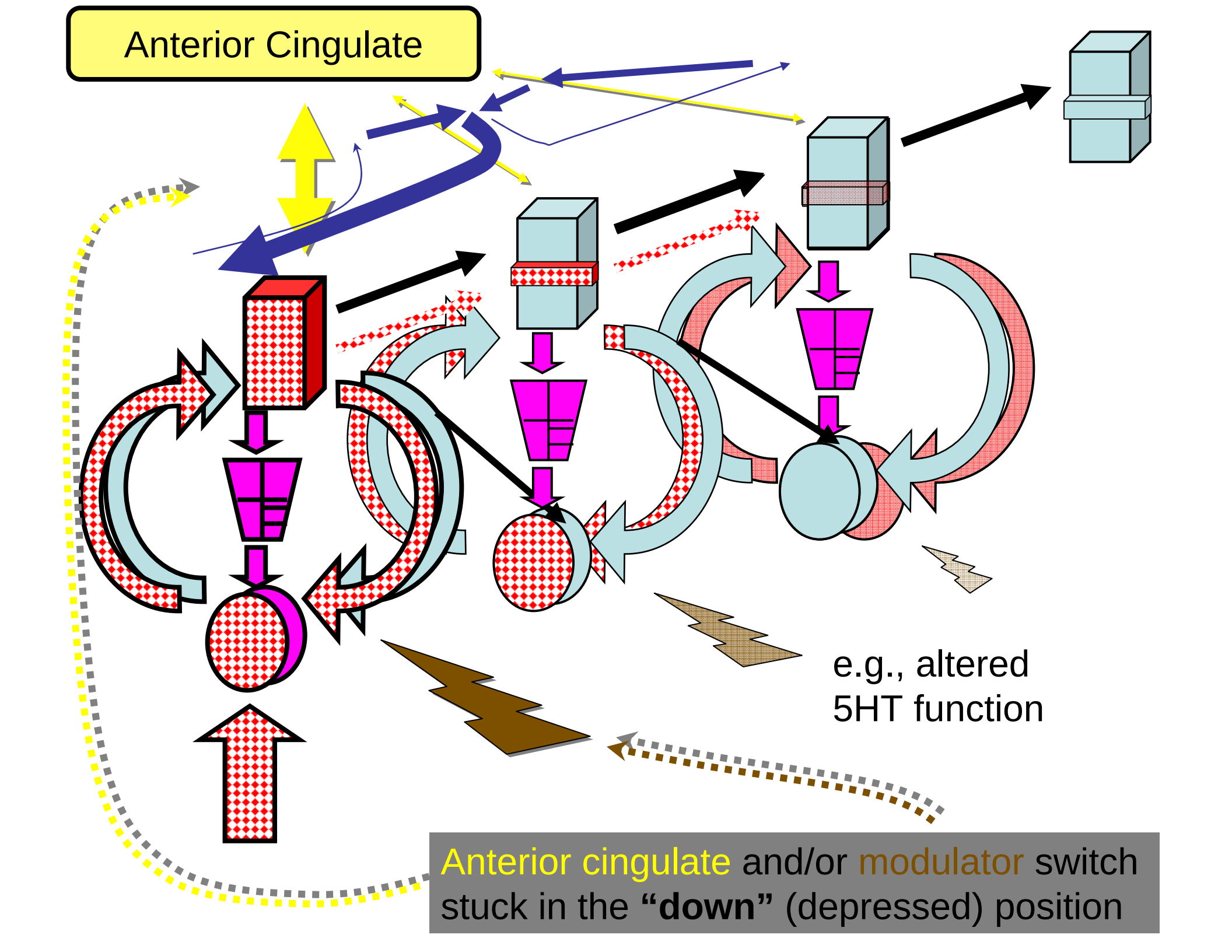


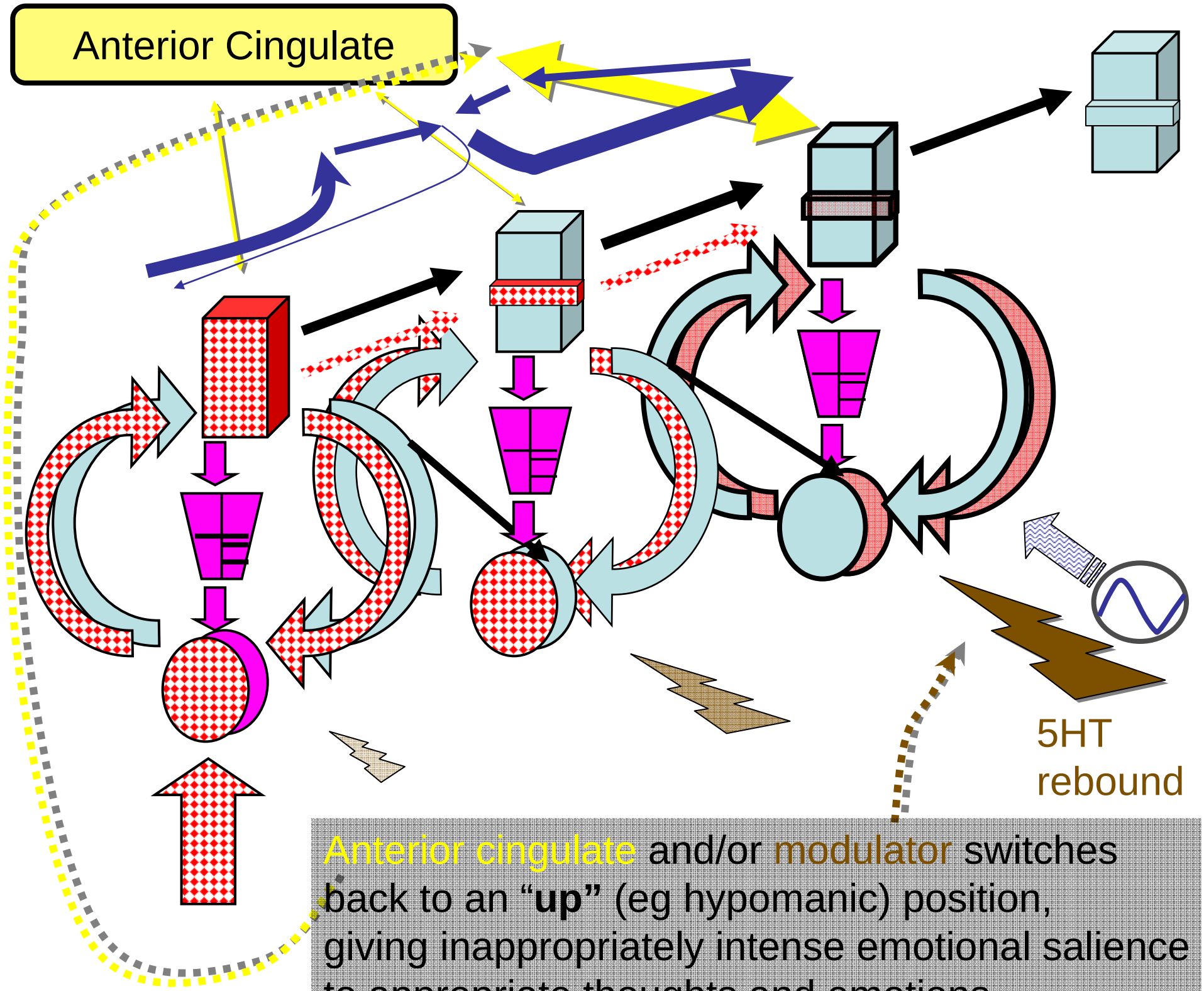
These modulatory signals also interact with **timing and synchronizing inputs** (hormonal, circadian, DA) which can be faulty in depression and bipolar disorder

Depression in Bipolar Disorder



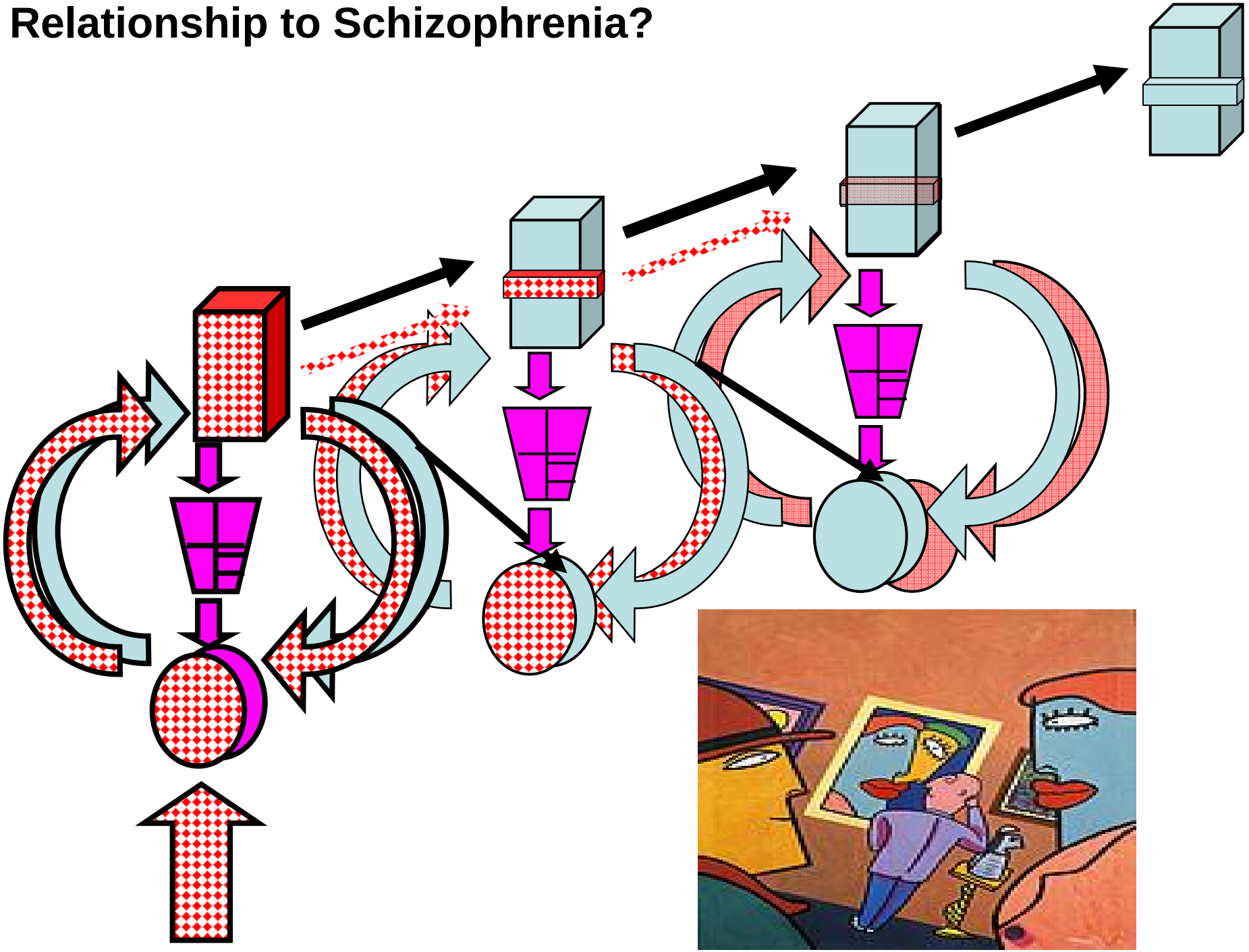
Specific information (eg, perceptions and thoughts) transiting through open and closed loops are **qualitatively** normal. However, **gain** mechanisms (eg, modulators) and loop **energy** (glutamate) are dysfunctional and chronically switched to a down (depression) state, with some cyclic rebounds (mania).


Anterior Cingulate
e.g., altered
5HT function
Anterior cingulate and/or modulator switch
stuck in the **“down”** (depressed) position

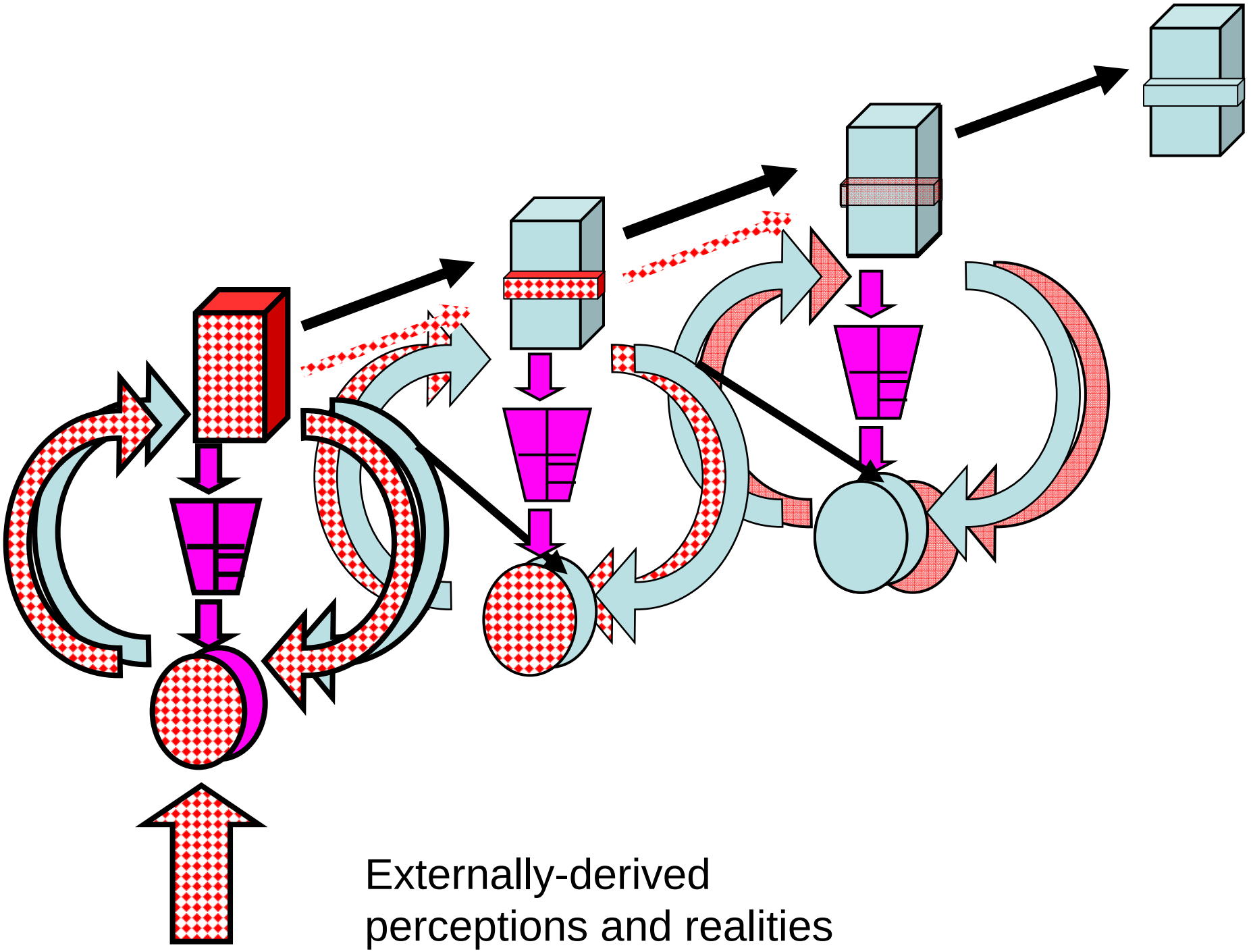


Anterior cingulate and/or modulator switches back to an "**up**" (eg hypomanic) position, giving inappropriately intense emotional salience to appropriate thoughts and emotions

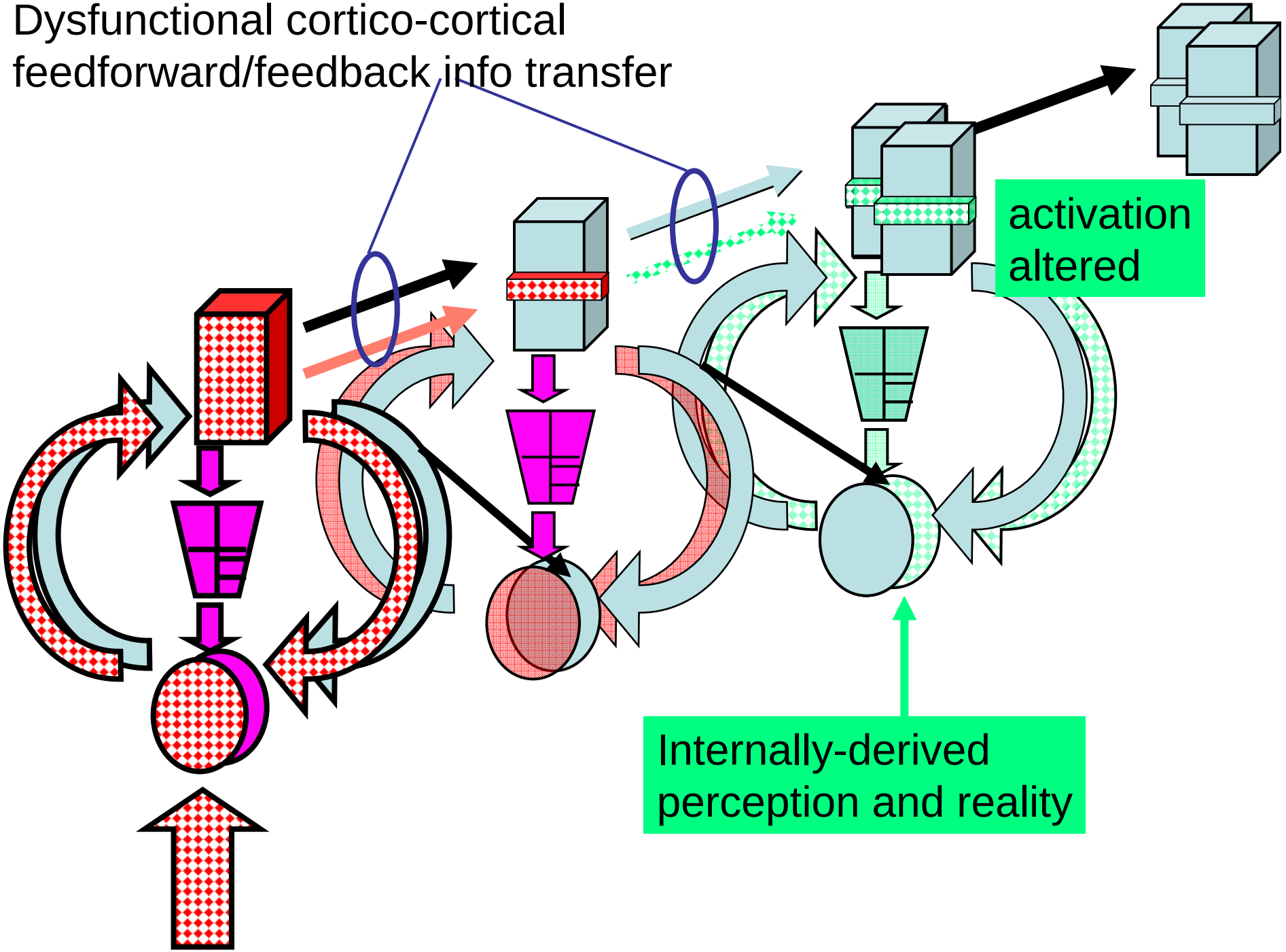
Relationship to Schizophrenia?



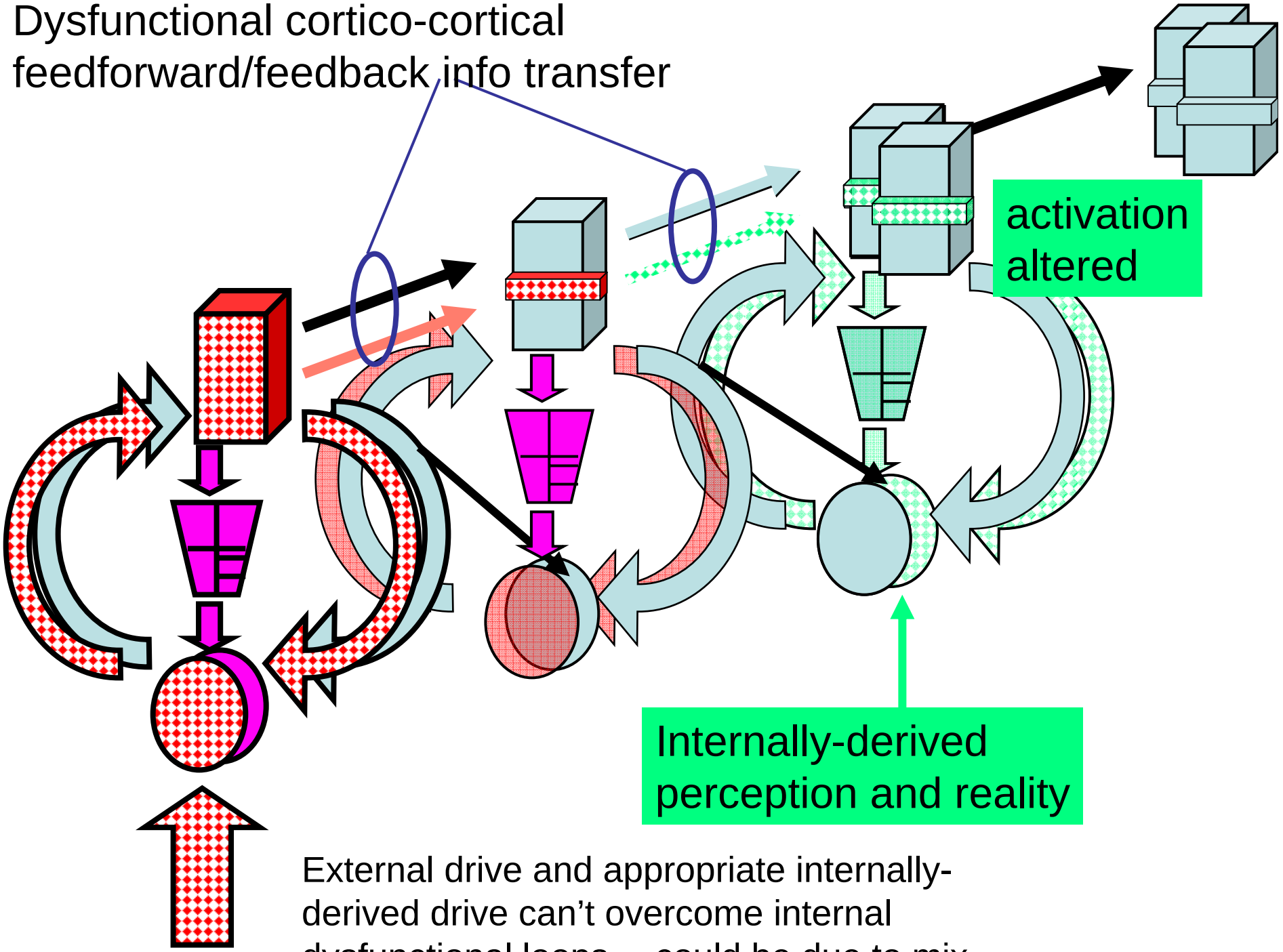
Externally-derived and internally-derived perceptions and realities


Externally-derived
perceptions and realities

Dysfunctional cortico-cortical feedforward/feedback info transfer

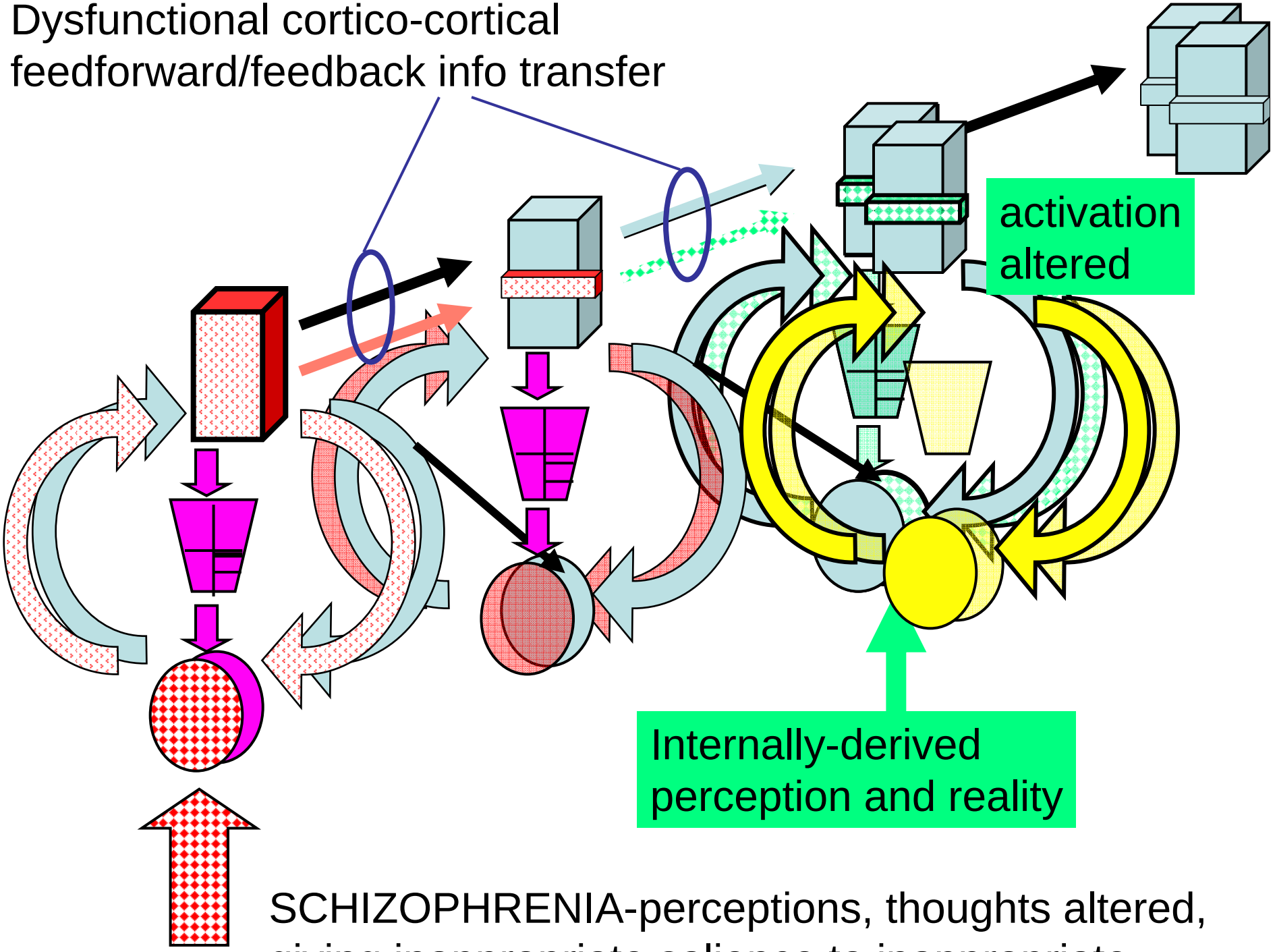


Dysfunctional cortico-cortical feedforward/feedback info transfer



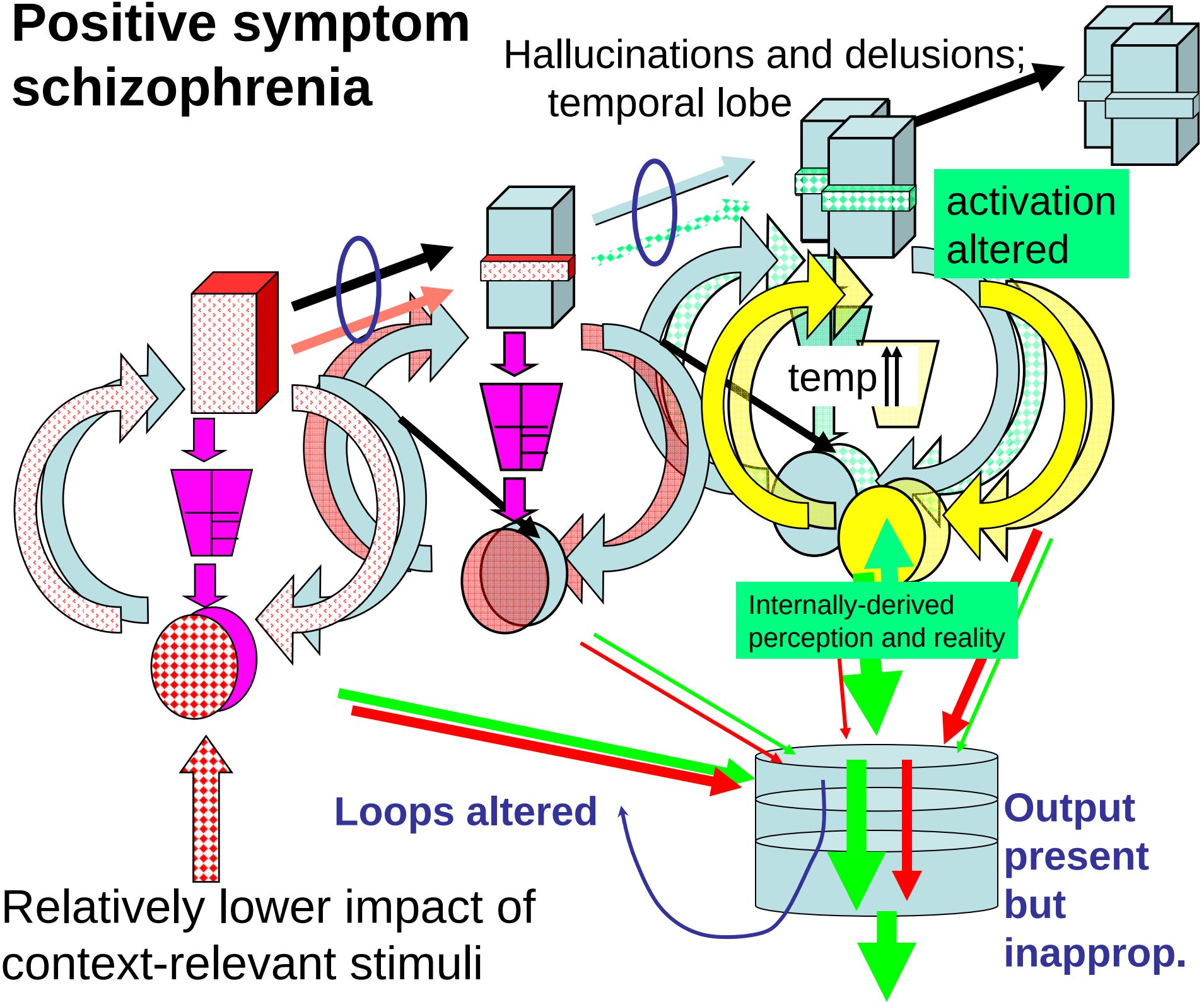
External drive and appropriate internally-derived drive can't overcome internal dysfunctional loops….could be due to mix of altered modulator (DA, NE, 5HT, Ach) and/or neurotransmitter (Glut, GABA) gain

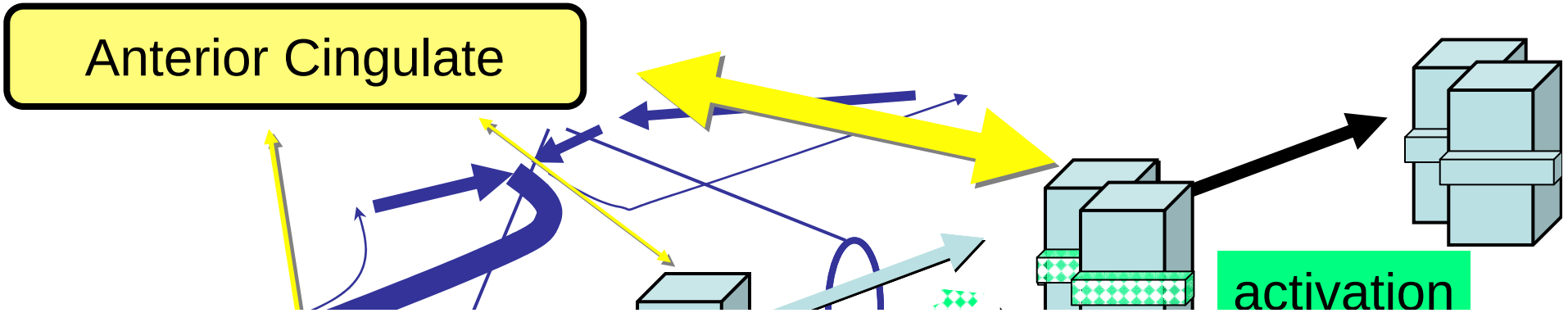
Dysfunctional cortico-cortical feedforward/feedback info transfer



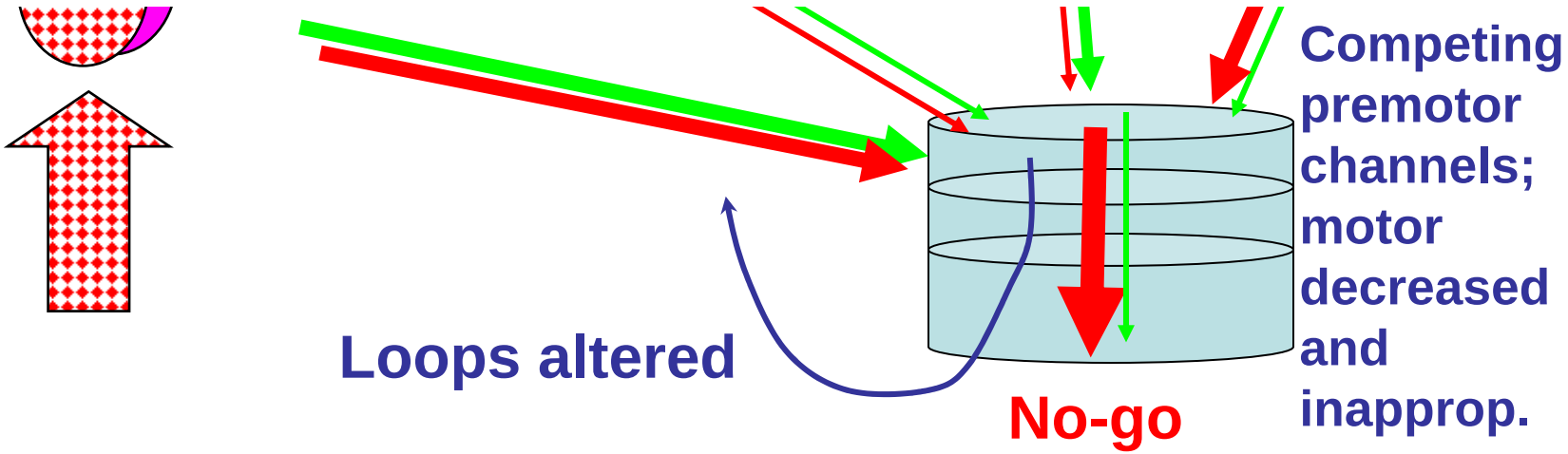
SCHIZOPHRENIA-perceptions, thoughts altered, giving inappropriate salience to inappropriate thoughts, perceptions, and emotions.

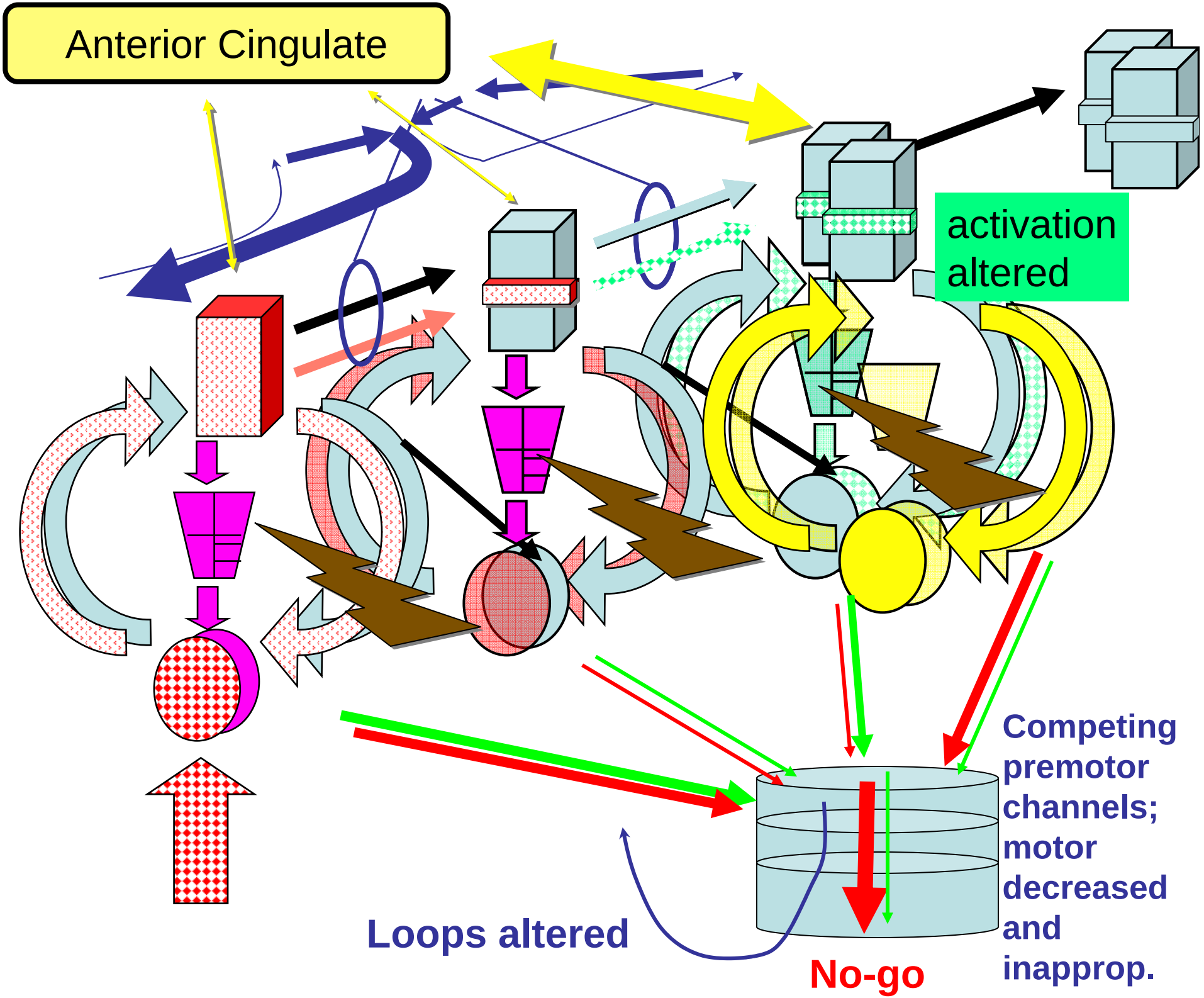
Positive symptom schizophrenia

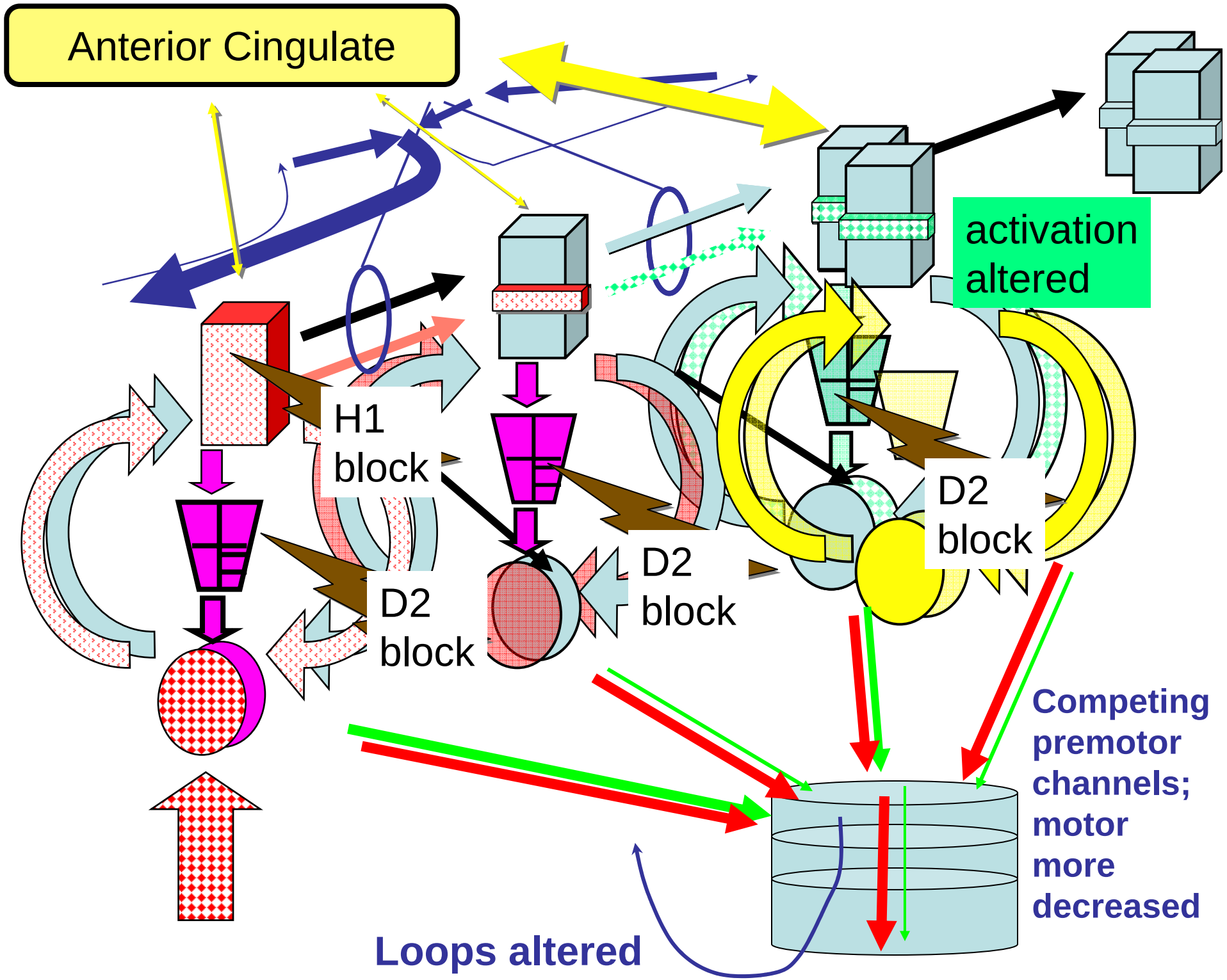




Negative Symptom Schiz differs qualitatively from that in depression; insufficient synaptic drive from layers III/IV through to layers V and VI motor (and II/III) outputs is present because the loops are *both* inappropriately interconnected AND have competing, and therefore, blunted outputs to motor systems.

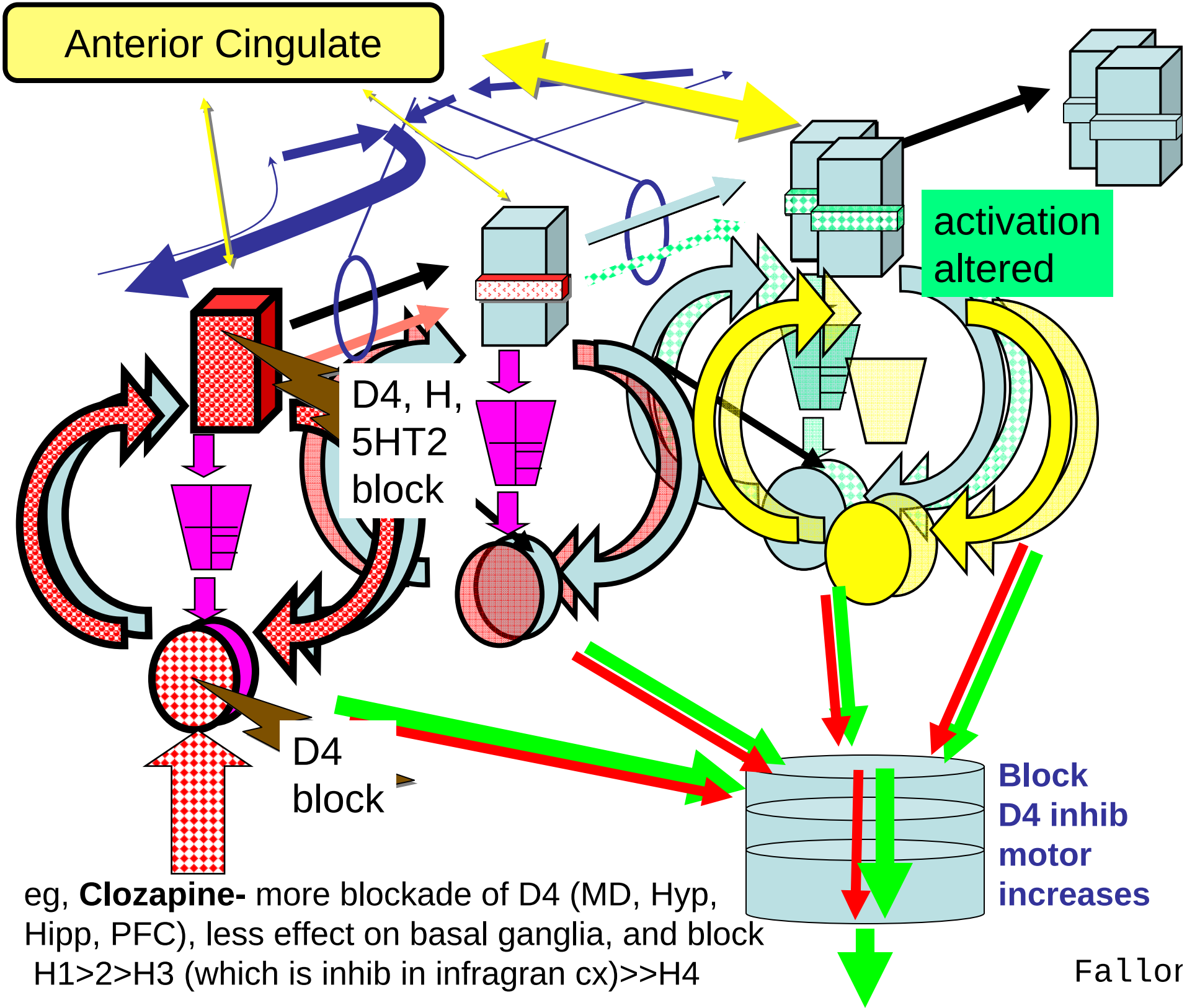



Anterior Cingulate
activation altered
Loops altered
No-go
Competing premotor channels; motor decreased and inapprop.



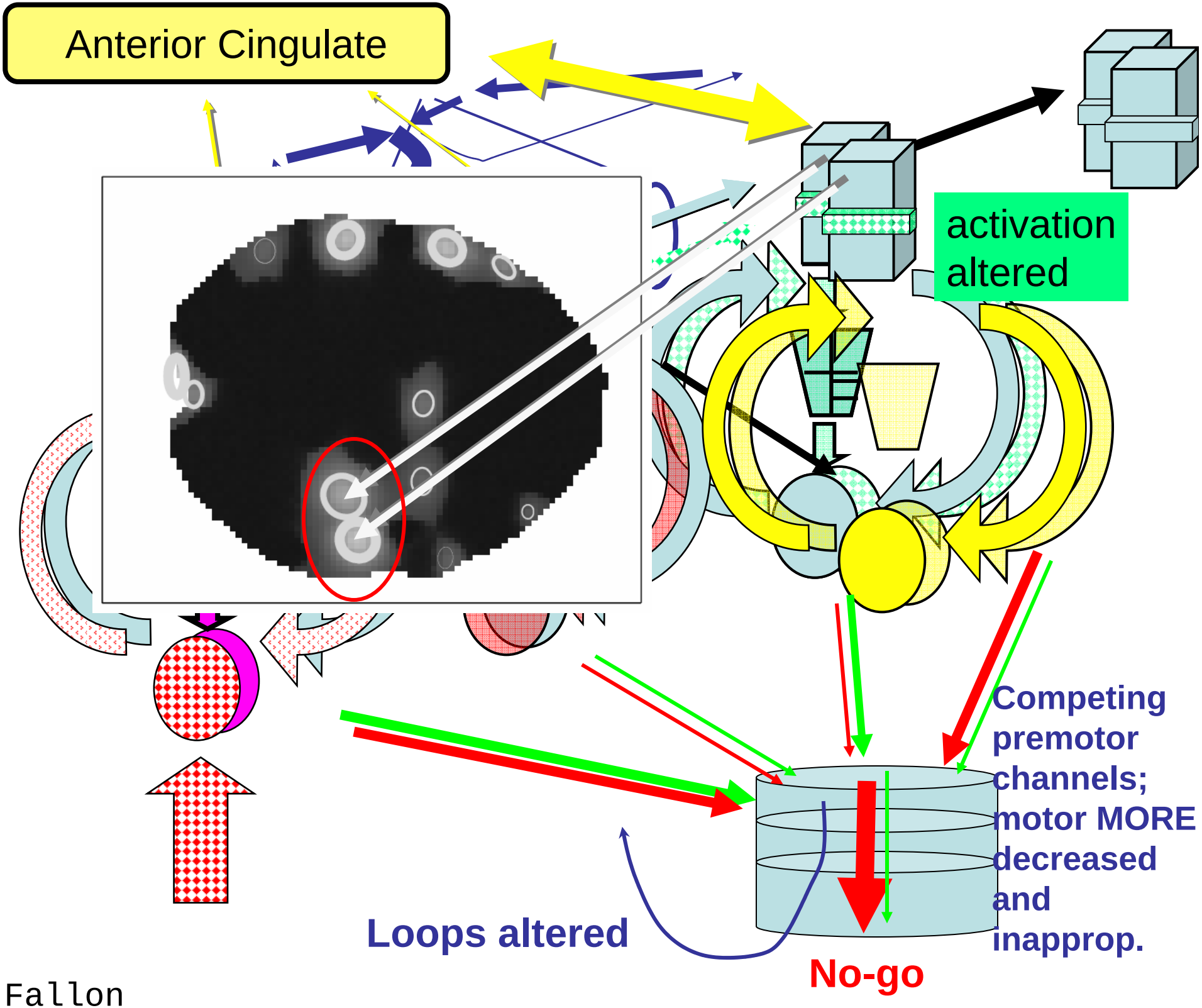
eg, Olanzapine- decrease mania, positive symptoms

Fallor



eg, **Clozapine-** more blockade of D4 (MD, Hyp, Hipp, PFC), less effect on basal ganglia, and block H1>2>H3 (which is inhib in infragran cx)>>H4

Fallor


Anterior Cingulate
activation altered
Competing premotor channels; motor MORE decreased and inapprop.
Loops altered
No-go
Fallon

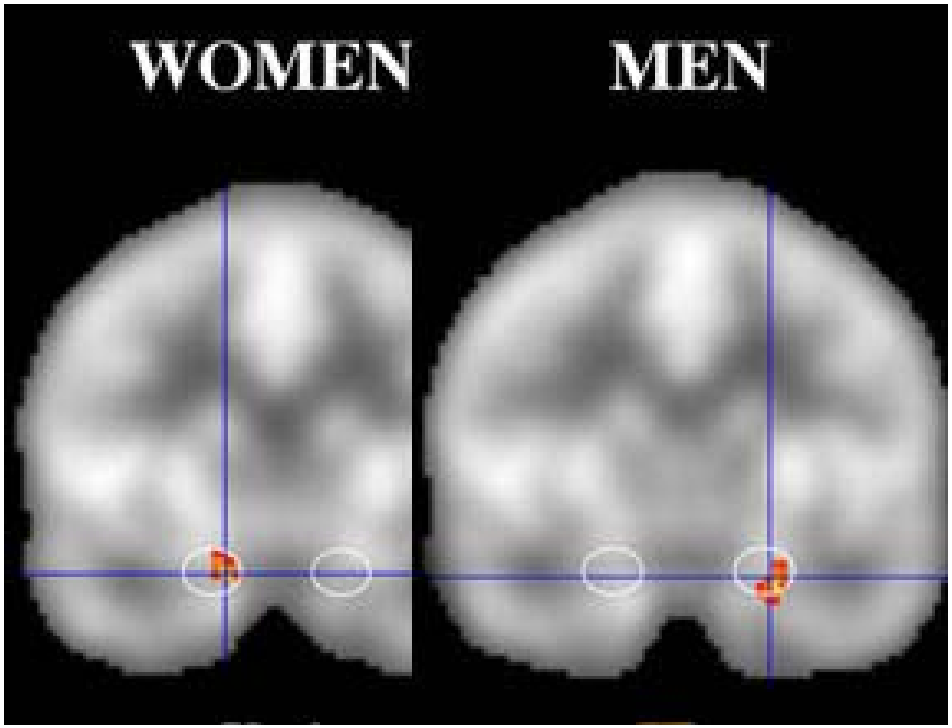
Conclusions

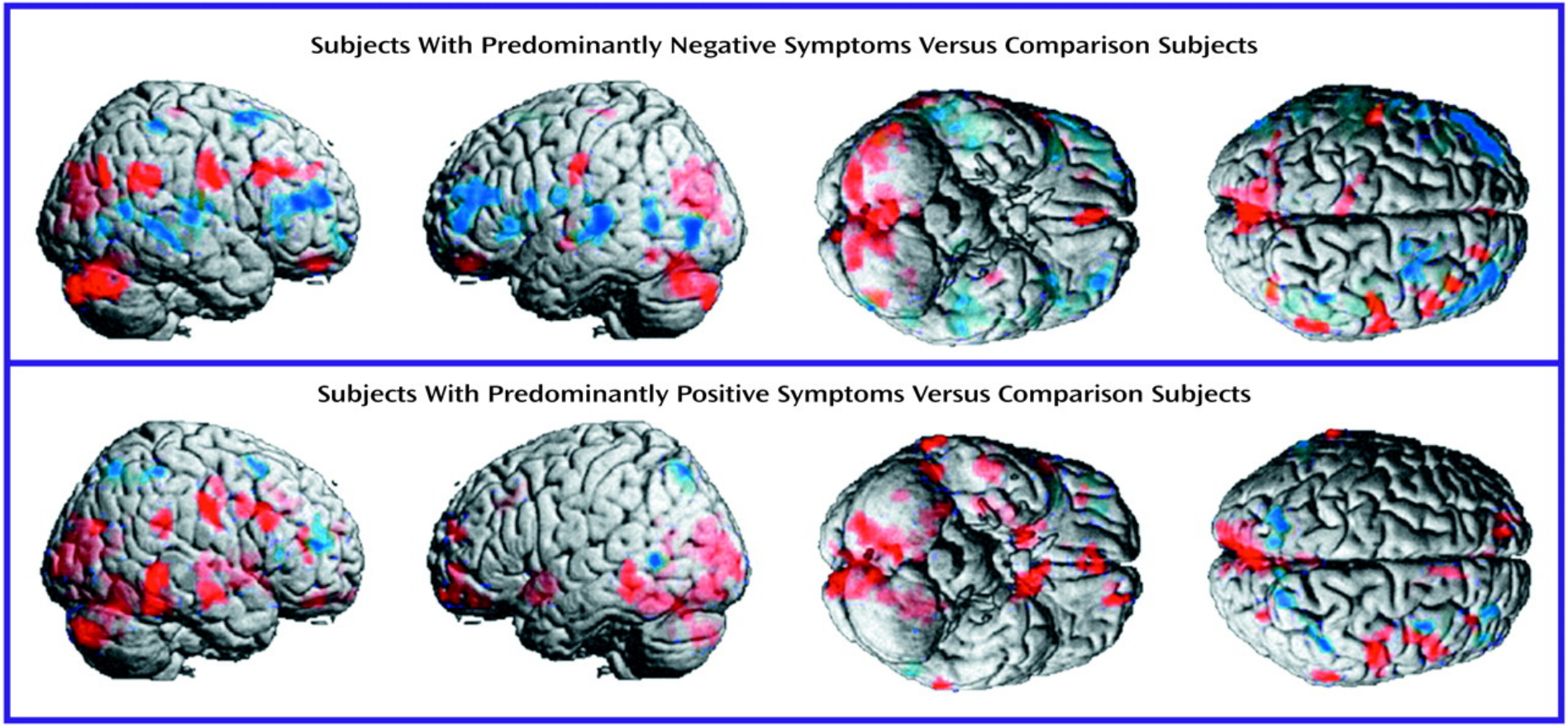
•This model suggests that simply ‘treating’ the supragranular (layers I, II, upper III) and infragranular layers (layers V, VI) with drugs acting on predominantly dopaminergic inputs (or cholinergic, histaminergic) would treat positive symptoms but not negative symptoms.

•It would appear that the homeostasis of the entire cortical column, including specific input layers IV and layer III would benefit negative symptoms.

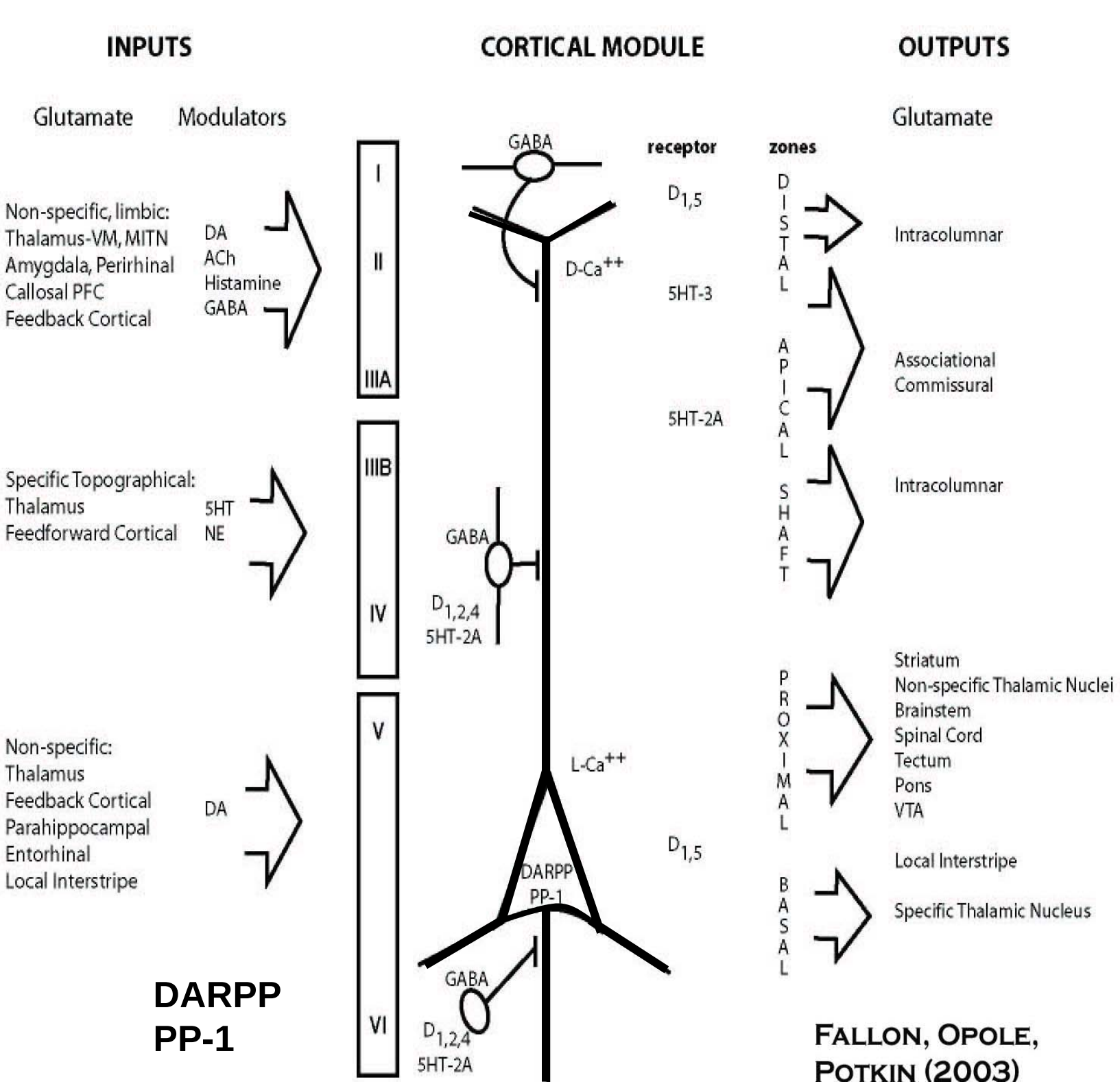
•Thus, enhancing glutaminergic drive and GABA balance in layers IV/lower III, combined with stabilization of noradrenergic & serotonergic tone and stabilization of dopaminergic effects in supragranular layers (to improve signal to noise) and infragranular layers (to stabilize & reverberation & perseveration), and blockade of inhib H3 in deep layers, may be a way to treat patients with predominantly negative symptoms.

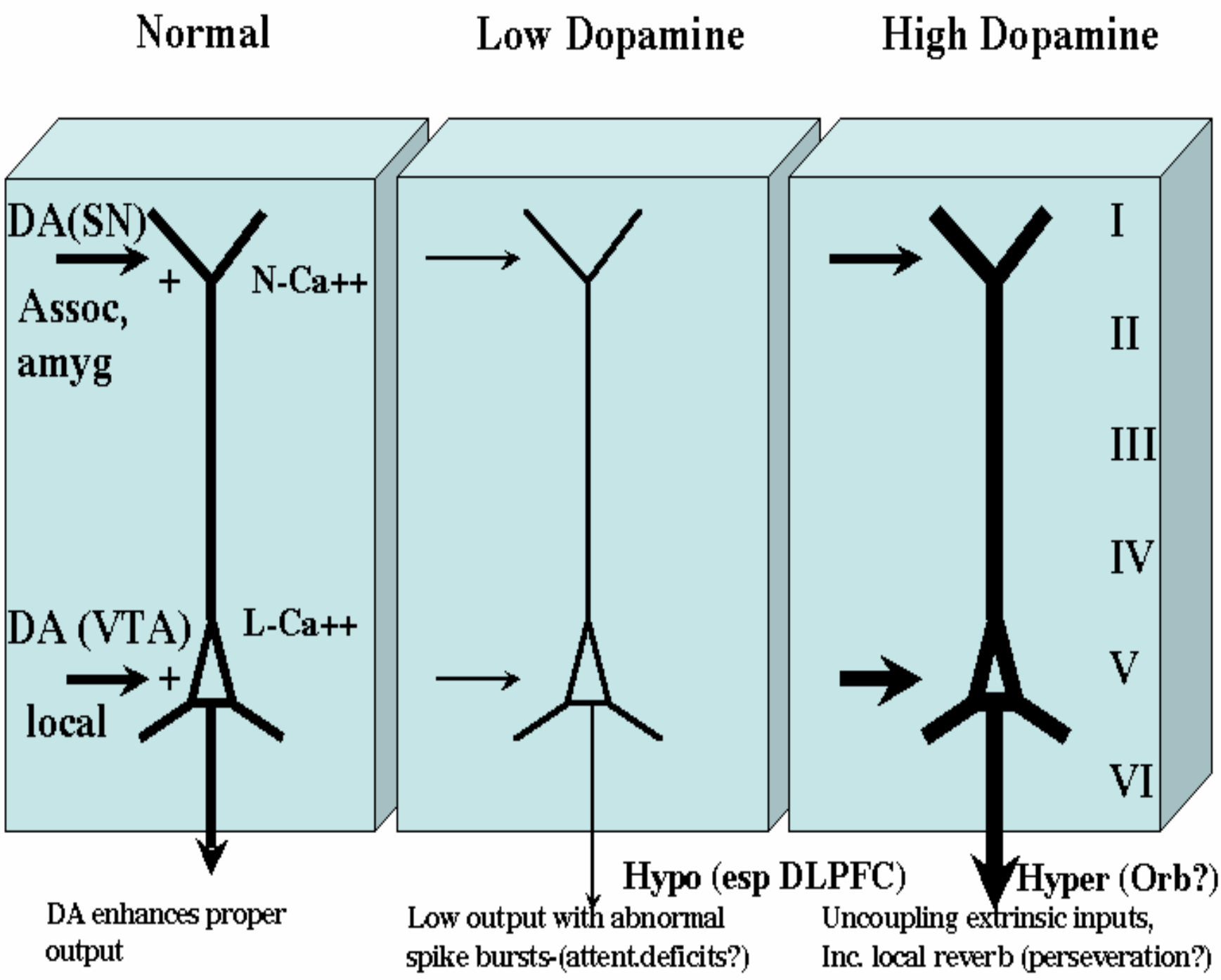
•But one key roadblock appears to be selective regulation of the limbic and right hemispheric prefrontal quadrants of these forebrain loops (e.g., with drugs, *and* focused treatments like RTMS on the right LPFC for negative symptoms?).


WOMEN
MEN



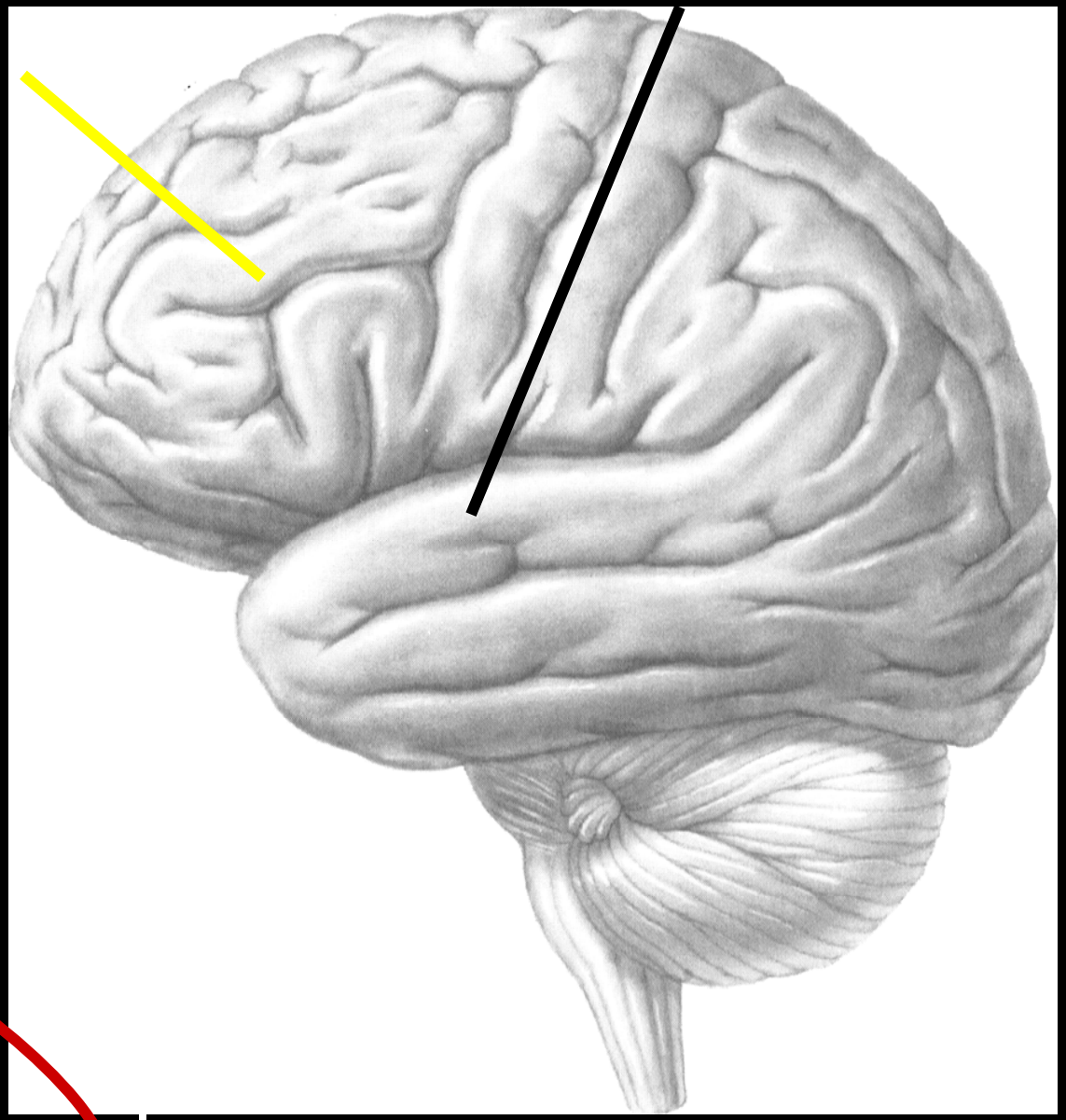
Potkin, Fallon 2002


INPUTS
CORTICAL MODULE
OUTPUTS
Glutamate
Modulators
Glutamate
receptor
zones
Non-specific, limbic:
Thalamus-VM, MITN
Amygdala, Perirhinal
Callosal PFC
Feedback Cortical
DA
ACh
Histamine
GABA
I
II
IIIA
GABA
D1,5
D-Ca++
5HT-3
5HT-2A
DISTAL
Intracolumnar
APICAL
Associational
Commissural
Specific Topographical:
Thalamus
Feedforward Cortical
5HT
NE
IIIB
IV
GABA
D1,2,4
5HT-2A
SHAFT
Intracolumnar
Non-specific:
Thalamus
Feedback Cortical
Parahippocampal
Entorhinal
Local Interstripe
DA
V
VI
L-Ca++
D1,5
DARPP
PP-1
GABA
D1,2,4
5HT-2A
PROXIMAL
Striatum
Non-specific Thalamic Nuclei
Brainstem
Spinal Cord
Tectum
Pons
VTA
BASAL
Local Interstripe
Specific Thalamic Nucleus
DARPP
PP-1
FALLON, OPOLE,
POTKIN (2003)


Normal
Low Dopamine
High Dopamine
DA(SN)
+
N-Ca++
Assoc,
amyg
DA (VTA)
L-Ca++
+
local
I
II
III
IV
V
VI
Hypo (esp DLPFC)
Hyper (Orb?)
DA enhances proper output
Low output with abnormal spike bursts-(attent.deficits?)
Uncoupling extrinsic inputs, Inc. local reverb (perseveration?)

Fallon

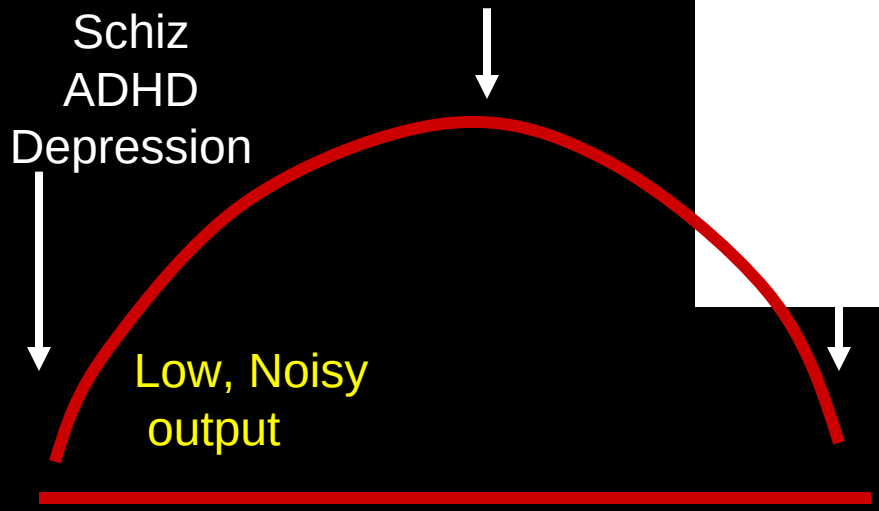
Greatest dopamine effects
in Frontal Lobe



D1 Receptors:
Inverted U-Shaped Curve

Normal behavior

Schiz
ADHD
Depression



Low, Noisy
output

High Output of PFC
But uncoupled from ext.

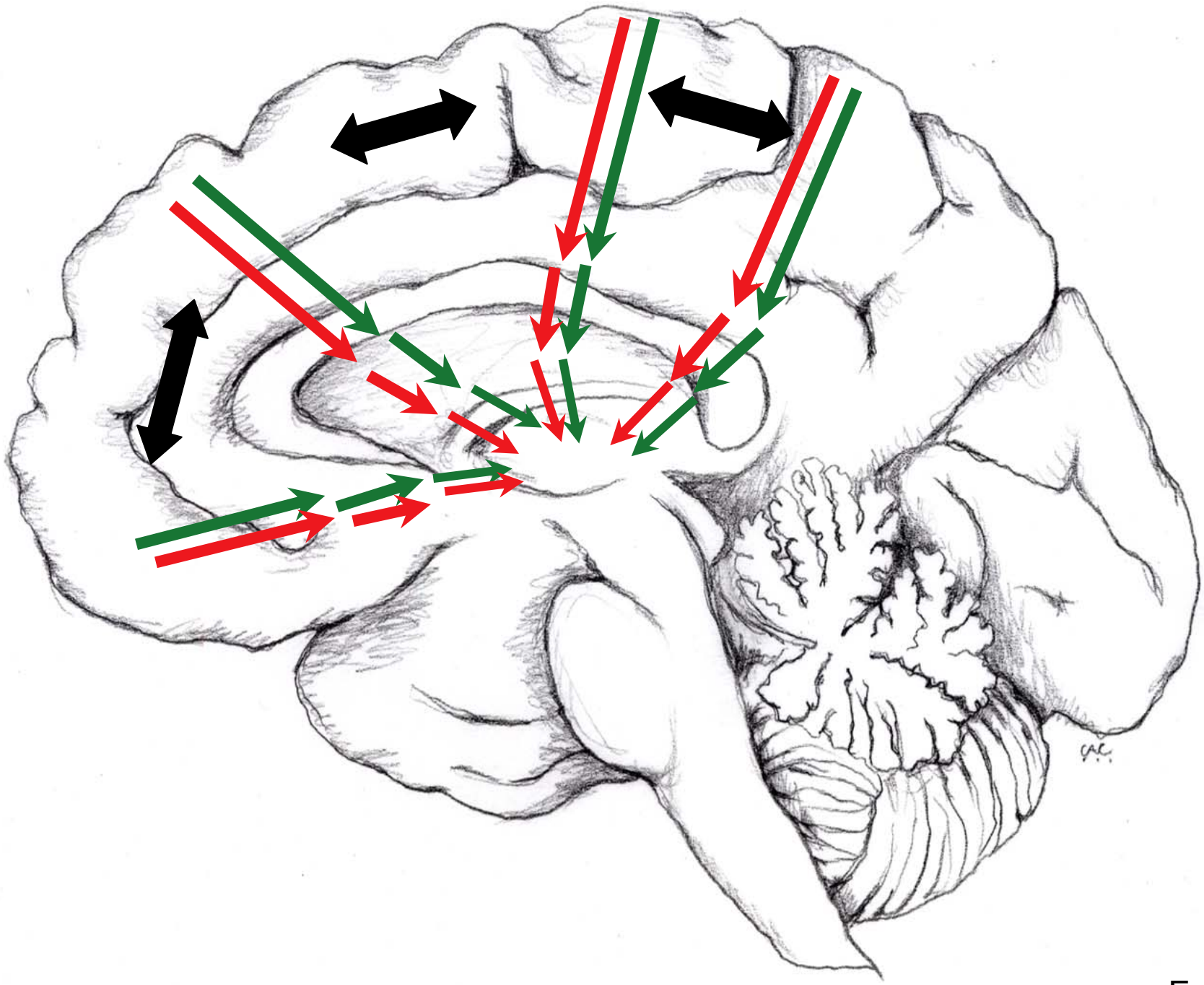
Low DA

High DA

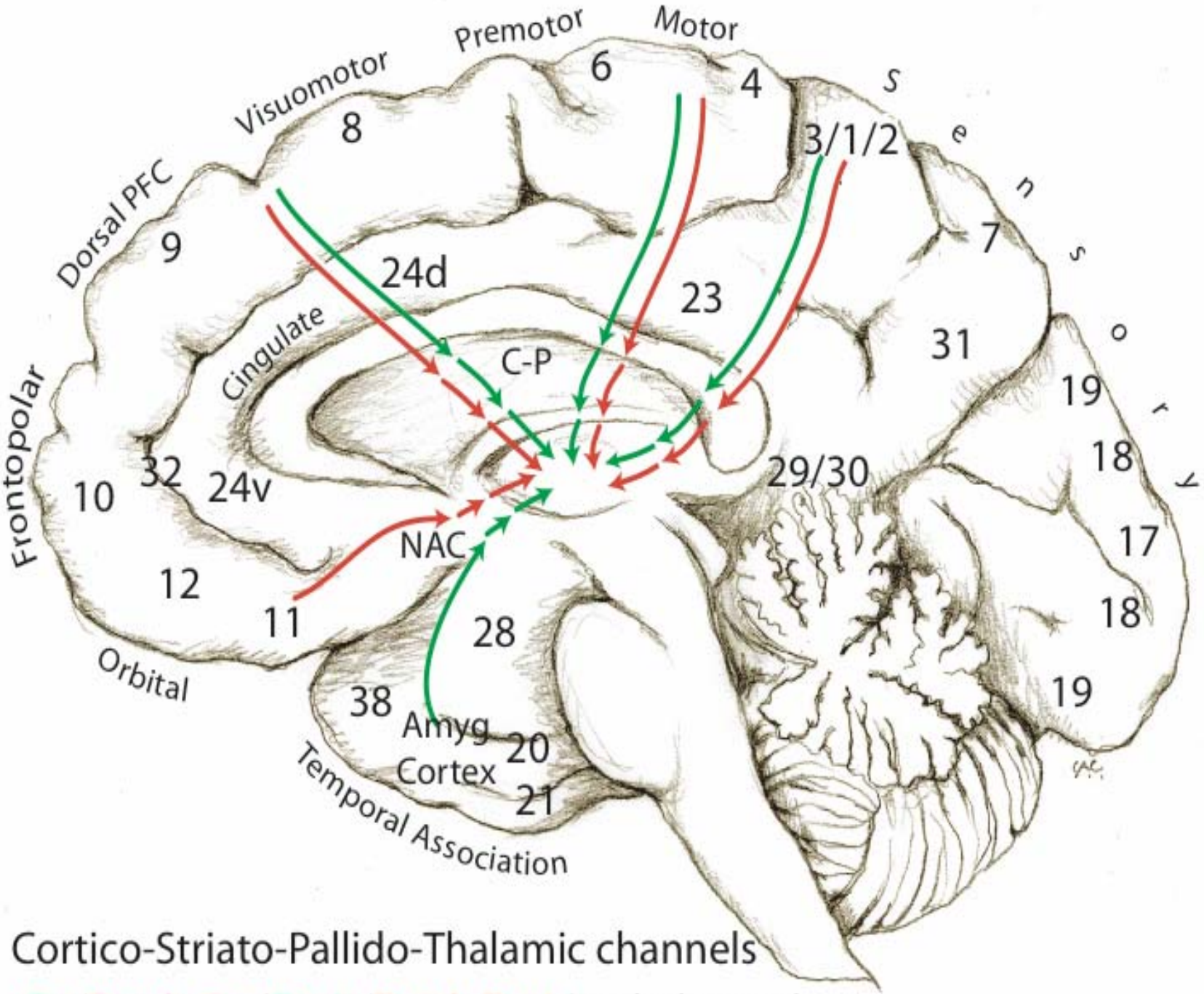
Cf Yerkes-Dodson law)

Fallon

Competition between channels-who dominates thought, beha



Fallon



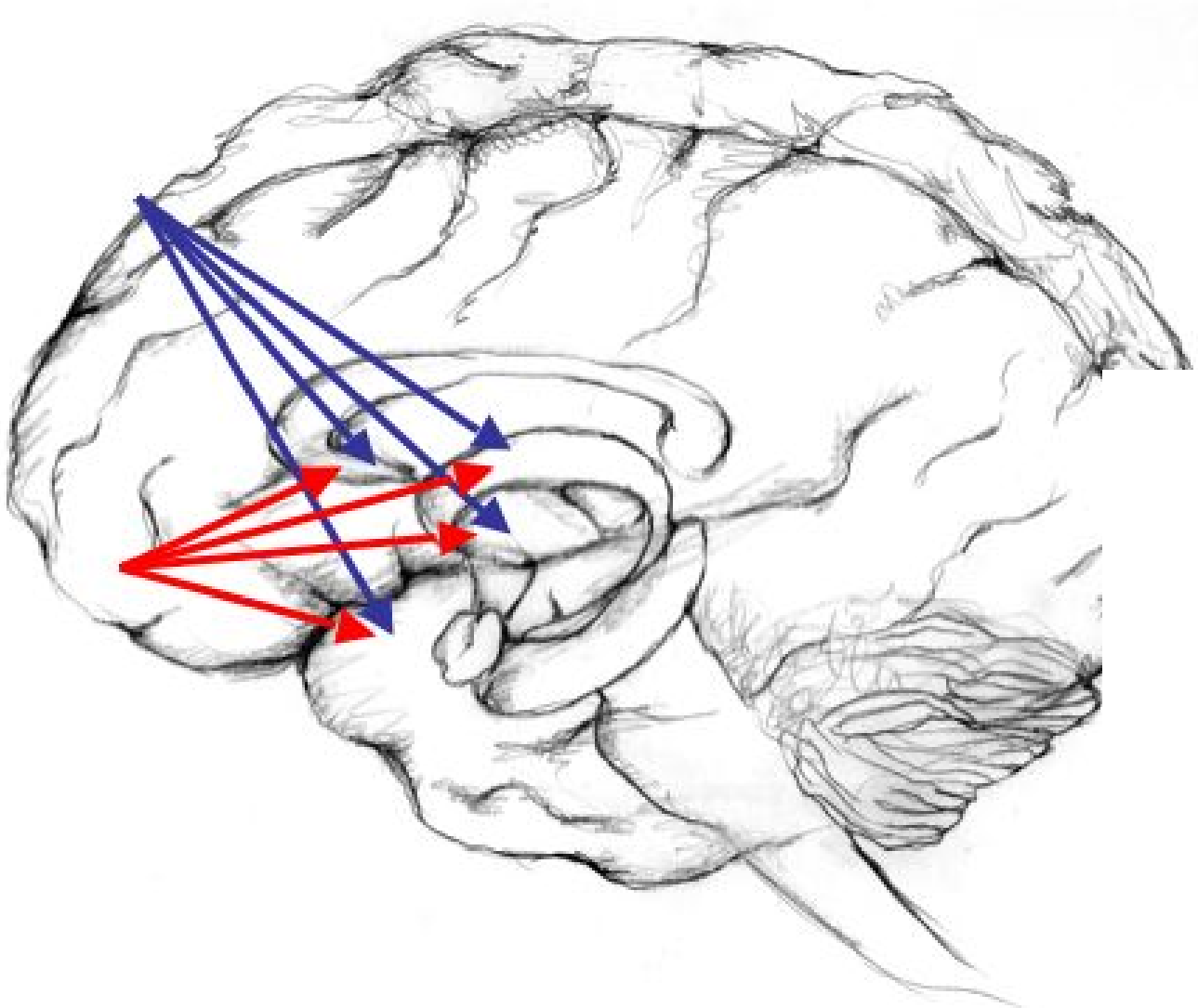
Cortico-Striato-Pallido-Thalamic channels

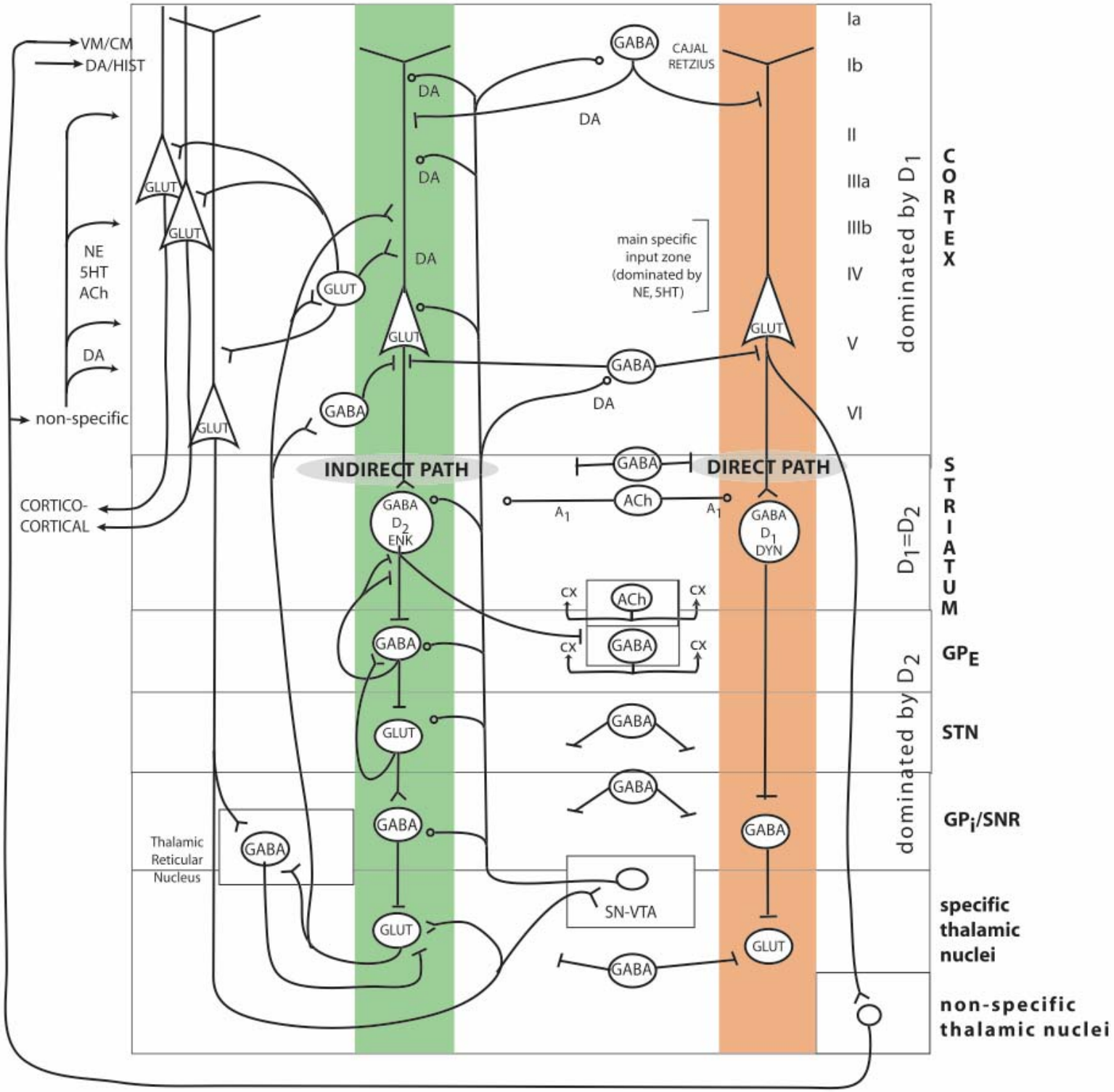
Go/Don't Go (Do It/Don't Do It) subchannels

Fallon et al 2003

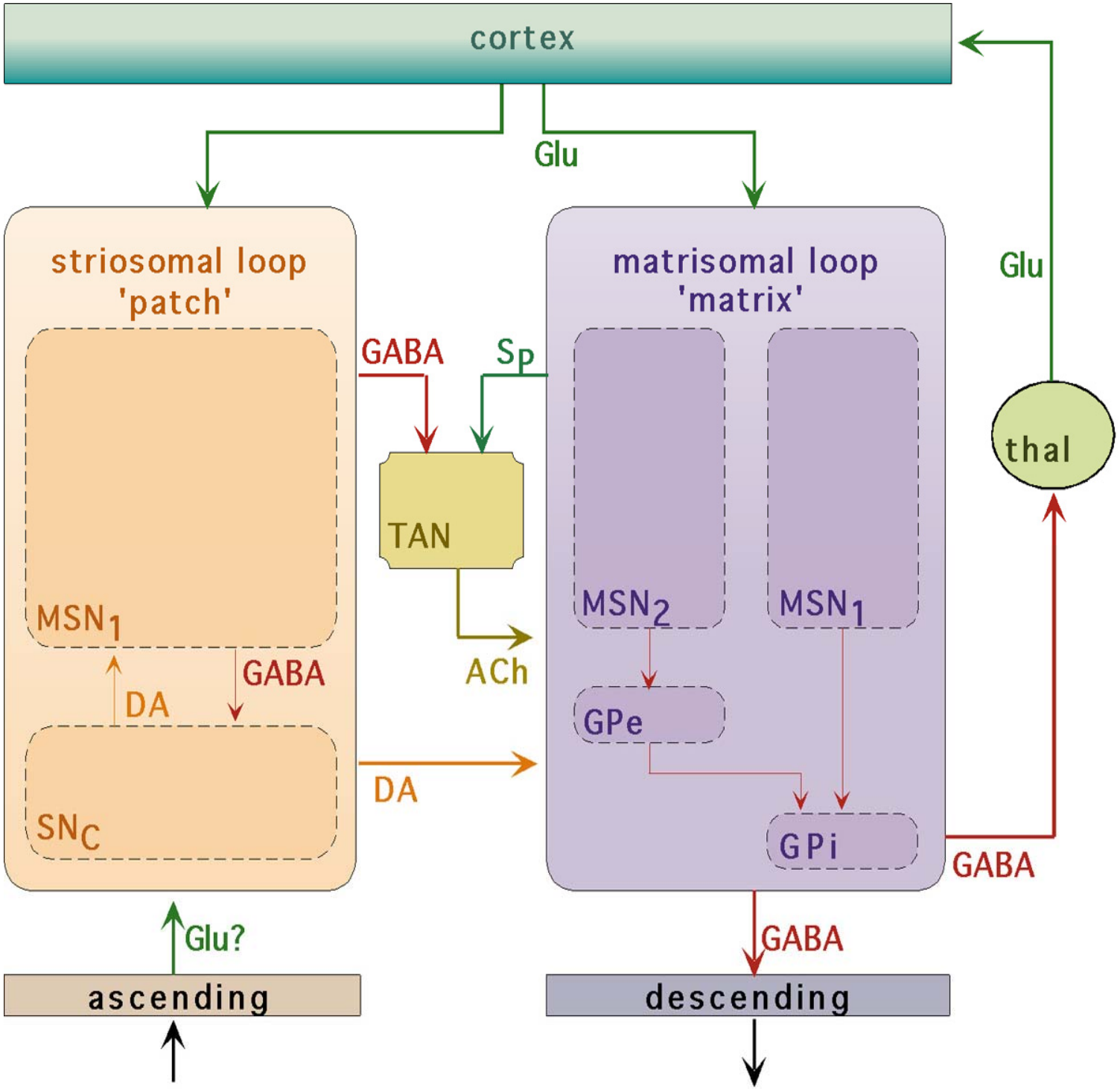
ottom line(s)-

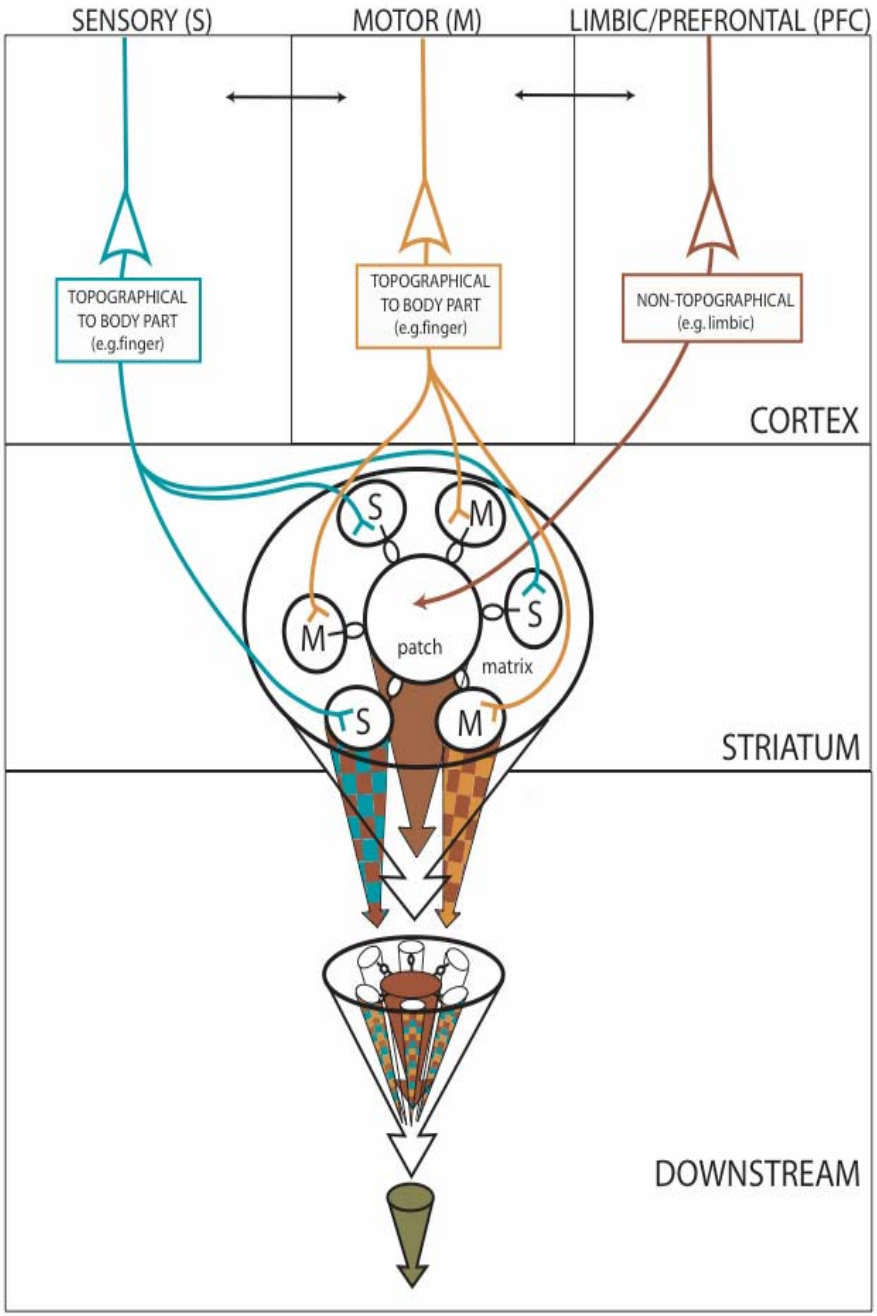
he dorsal and ventral streams most likely interact directl
t subcortical sites such as Ce amygdala/EA, mid-ventral
riatum, SN-VTA, matrix thalamus, and brainstem premotc
eas controlling motor, endocrine, autonomic functions .




VM/CM
DA/HIST
NE
5HT
ACh
DA
non-specific
CORTICO-
CORTICAL
GLUT
GABA
DA
CAJAL
RETZIUS
main specific
input zone
(dominated by
NE, 5HT)
INDIRECT PATH
DIRECT PATH
GABA
D2
ENK
GABA
D1
DYN
ACh
A1
CX
Thalamic
Reticular
Nucleus
SN-VTA
Ia
Ib
II
IIIa
IIIb
IV
V
VI
dominated by D1
D1=D2
dominated by D2
CORTEX
STRIATUM
GPE
STN
GPi/SNR
specific
thalamic
nuclei
non-specific
thalamic nuclei

Striatal complex (basal ganglia) / schematic





Fallon et al 2003

Synopsis:

•The most prevalent neuroanatomical models of faulty circuitry in patients with predominantly n symptoms involve consideration of limbic-cogniti prefrontal system dysfunction, monoamine dysregu especially in the dopaminergic and serotonergic p and a focus on imbalance in the input-output func supragranular and infragranular layers of prefro temporal cortices.

•Another set of faulty prefrontal system throughp especially in negative symptom patients, may also be inferred from the circuitry which factors layers III and IV connectivity and which may resu reduced and asymmetric drive in competing cortico subcortical loops, anterior cingulate switching, and motor outputs of prefrontal systems.