TMS

How does it work?

(Mechanism of action)

MECHANISM

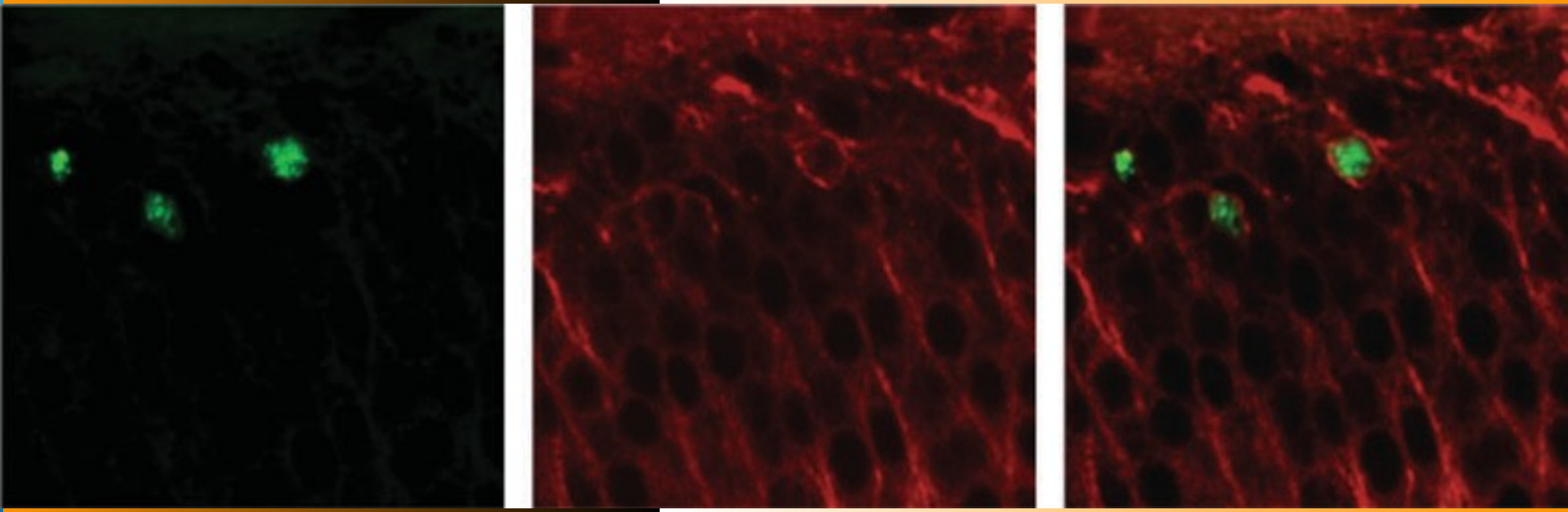
Increased Activity

Increased BDNF

Thicker Cortex

Rb - Downstream & Upstream

Ueyama2011 Chronic repetitive transcranial magnetic stimulation increases hippocampal neurogenesis in rats

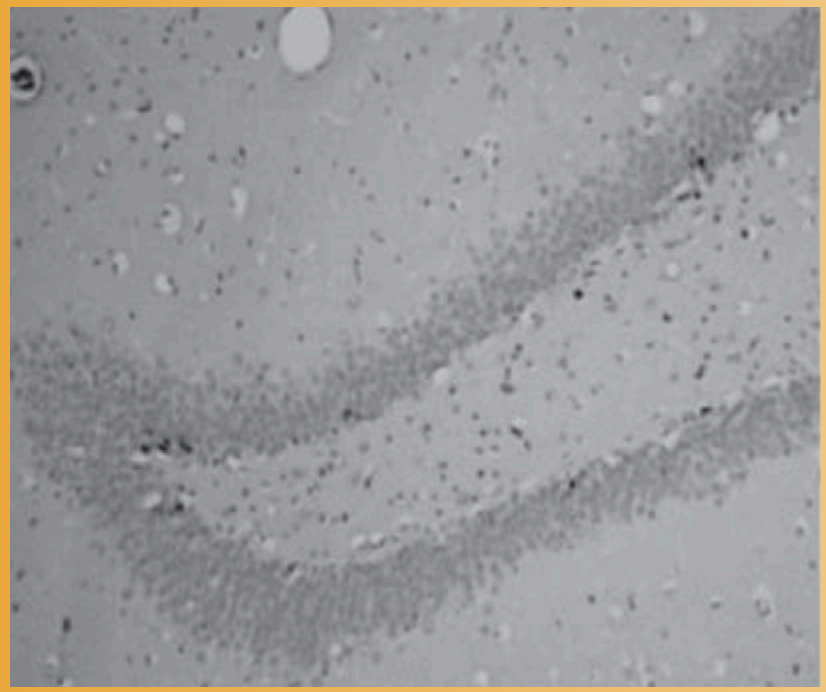


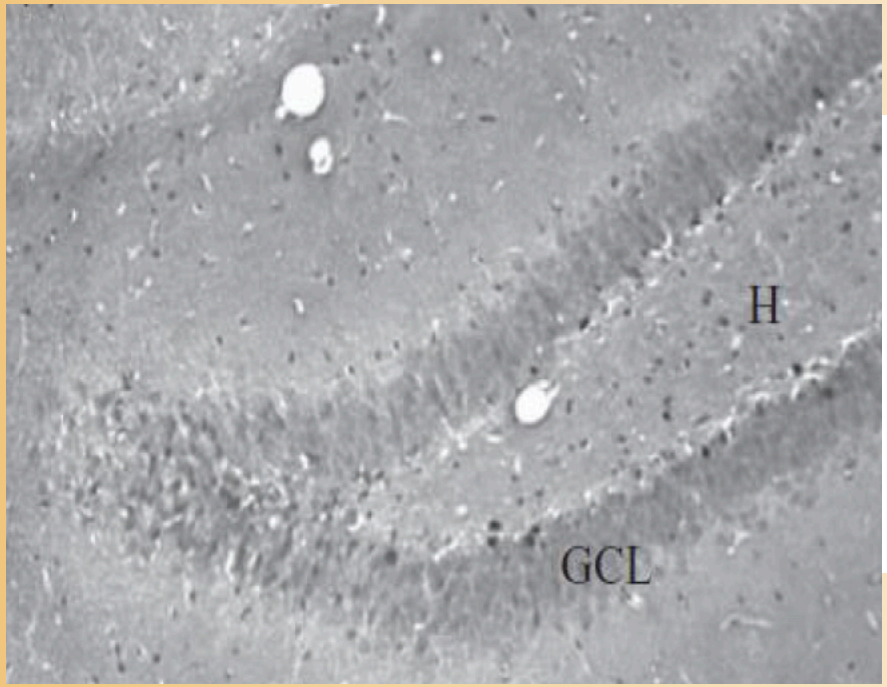
increases hippocampal neurogenesis in rats

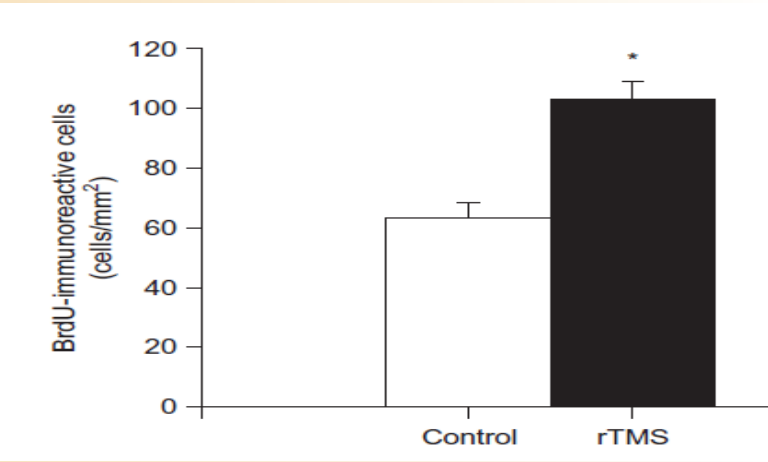
Ueyama E, et al. *Psychiatry Clin Neurosci*. 2011;65(1):77-81.

TMS MECHANISM

Increased Neurogenesis in Hippocampus







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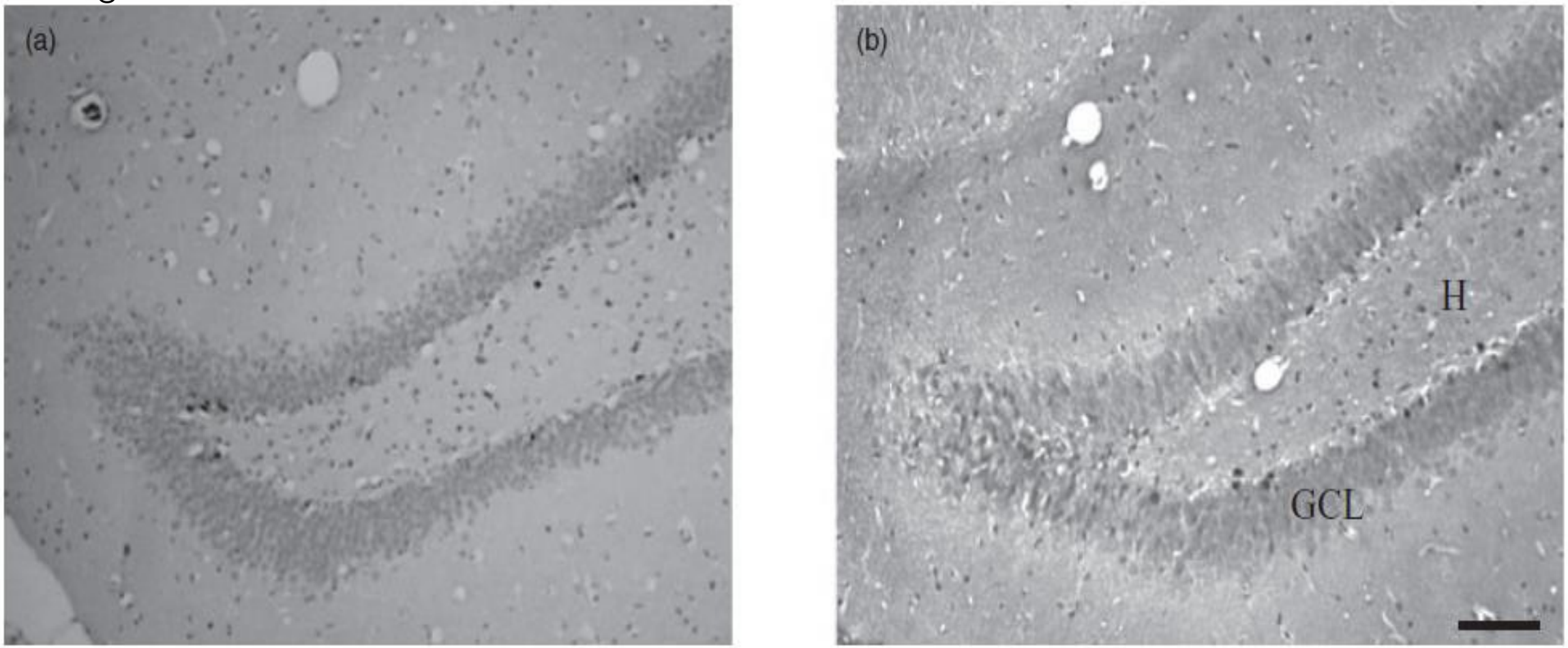


Figure 2. Bromodeoxyuridine-positive cells in the hippocampal dentate gyrus of (a) sham-treated control and (b) repetitive-transcranial-magnetic-stimulation-treated rats. Scale bar: 100 µm. GCL, granule cell layer; H, hilus.

Ueyama E, et al. *Psychiatry Clin Neurosci*. 2011;65(1):77-81.

TMS

How does it work?

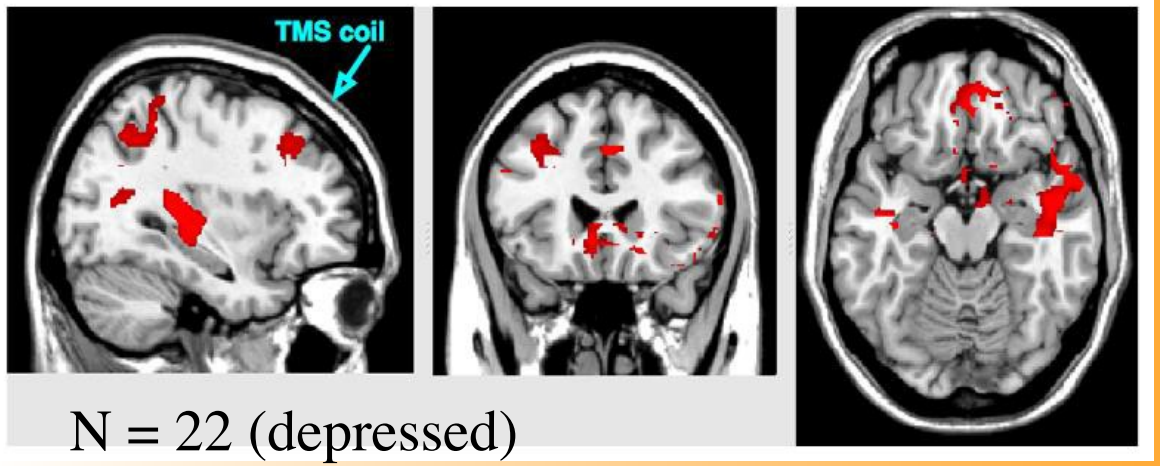
(Mechanism of action)

Li (2004), Teneback(1999)

MECHANISM

Acute Effects

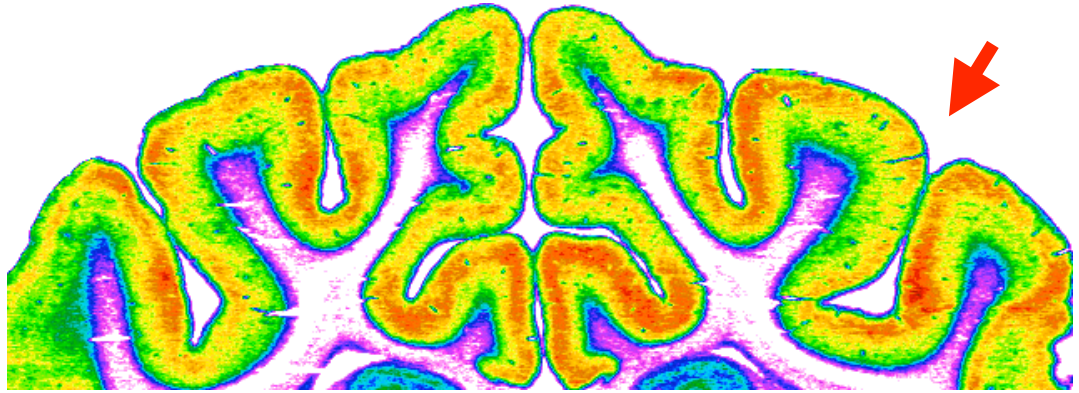
- Induces electric current
- Depolarizes neurons in superficial cortex
- -> trans-synaptic changes in brain activity



N = 22 (depressed)

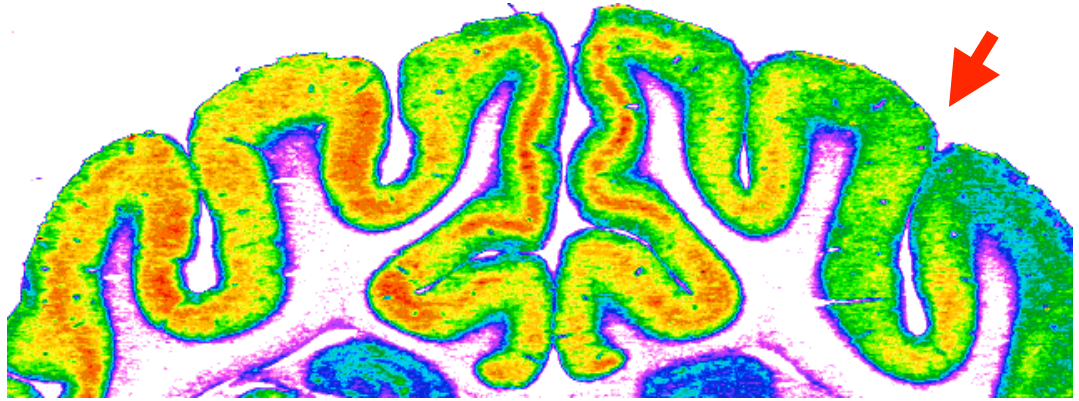
Example: Left prefrontal TMS
Activation demonstrated at site of stimulation and also at synaptically connected cortical and subcortical regions

Sham TMS



control

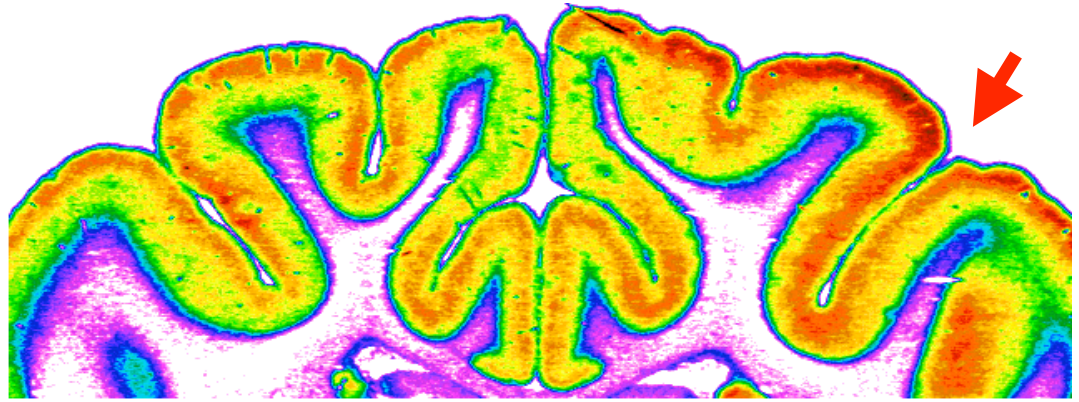
1 Hz TMS



decreased activity

LTD

20 Hz TMS



increased activity

LTP

TMS

How does it work?

(Mechanism of action)

MECHANISM

Brain disorders now viewed as network changes not "chemical imbalance"

CHANGING NETWORK ACTIVITY & CONNECTIVITY

TMS

How does it work?

(Mechanism of action)

MECHANISM

Brain re-growth happens by "axonal sprouting" -

(axons grow new nerve endings & reconnect neurons).

These new connections between nerve cells, increase brain connectivity to improve function.

TMS

How does it work?

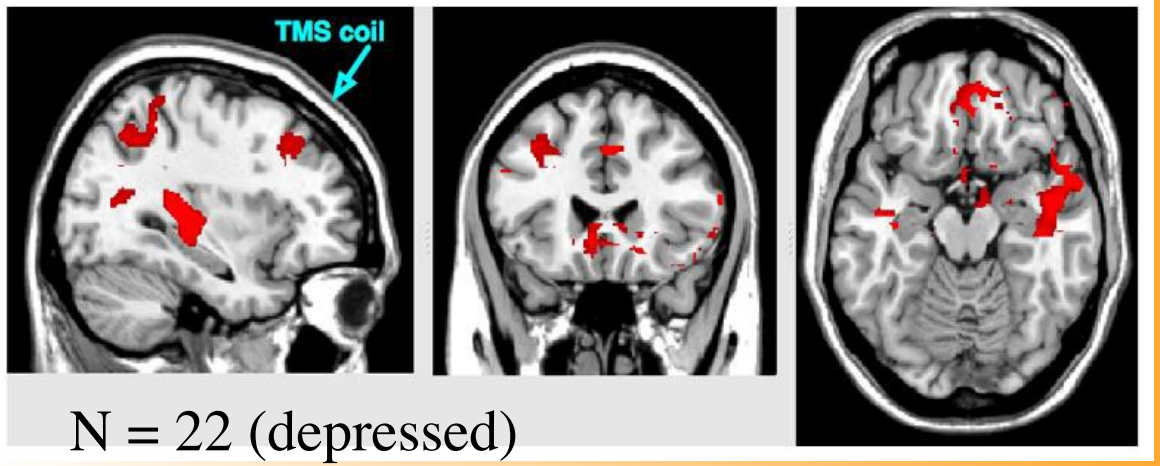
(Mechanism of action)

Li (2004), Teneback(1999)

MECHANISM

Acute Effects

- Induces electric current
- Depolarizes neurons in superficial cortex
- -> trans-synaptic changes in brain activity



N = 22 (depressed)

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Activation demonstrated at site of stimulation and also at synaptically connected cortical and subcortical regions

TMS

How does it work?

(Mechanism of action)

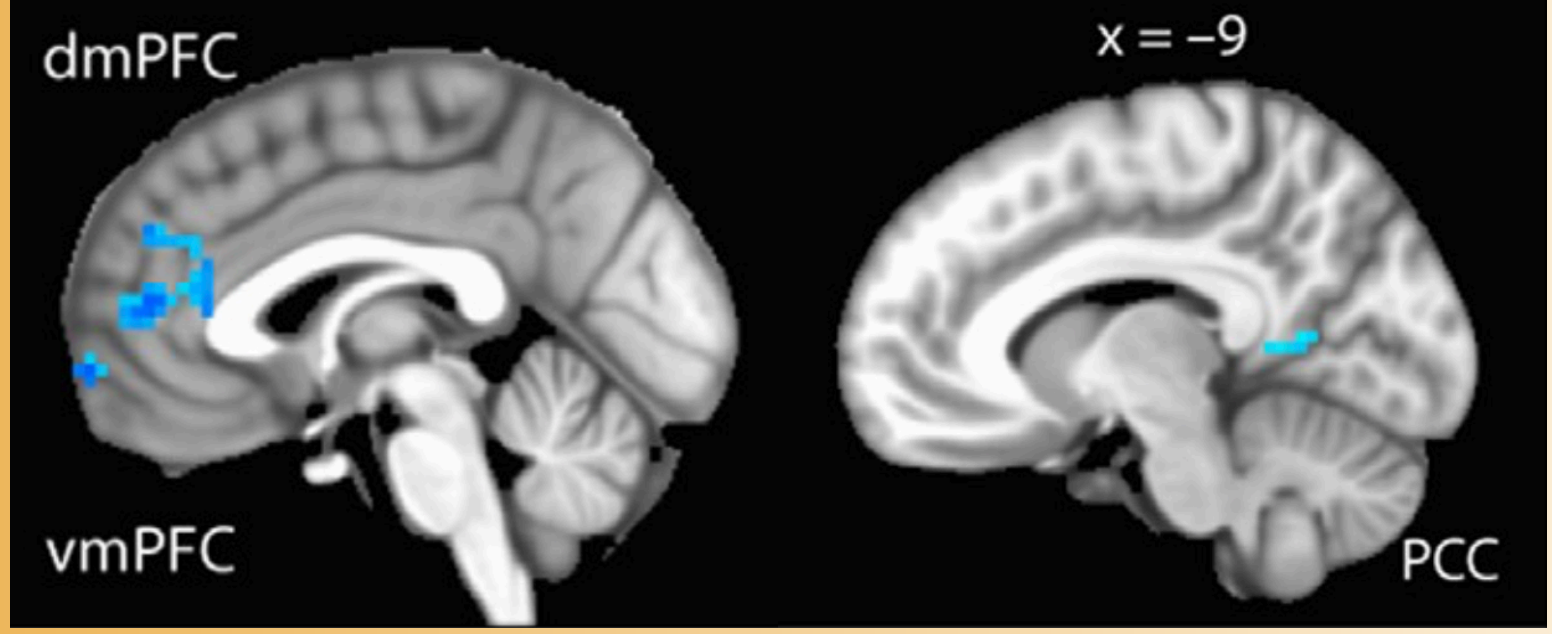
MECHANISM

Increased Activity

Increased BDNF

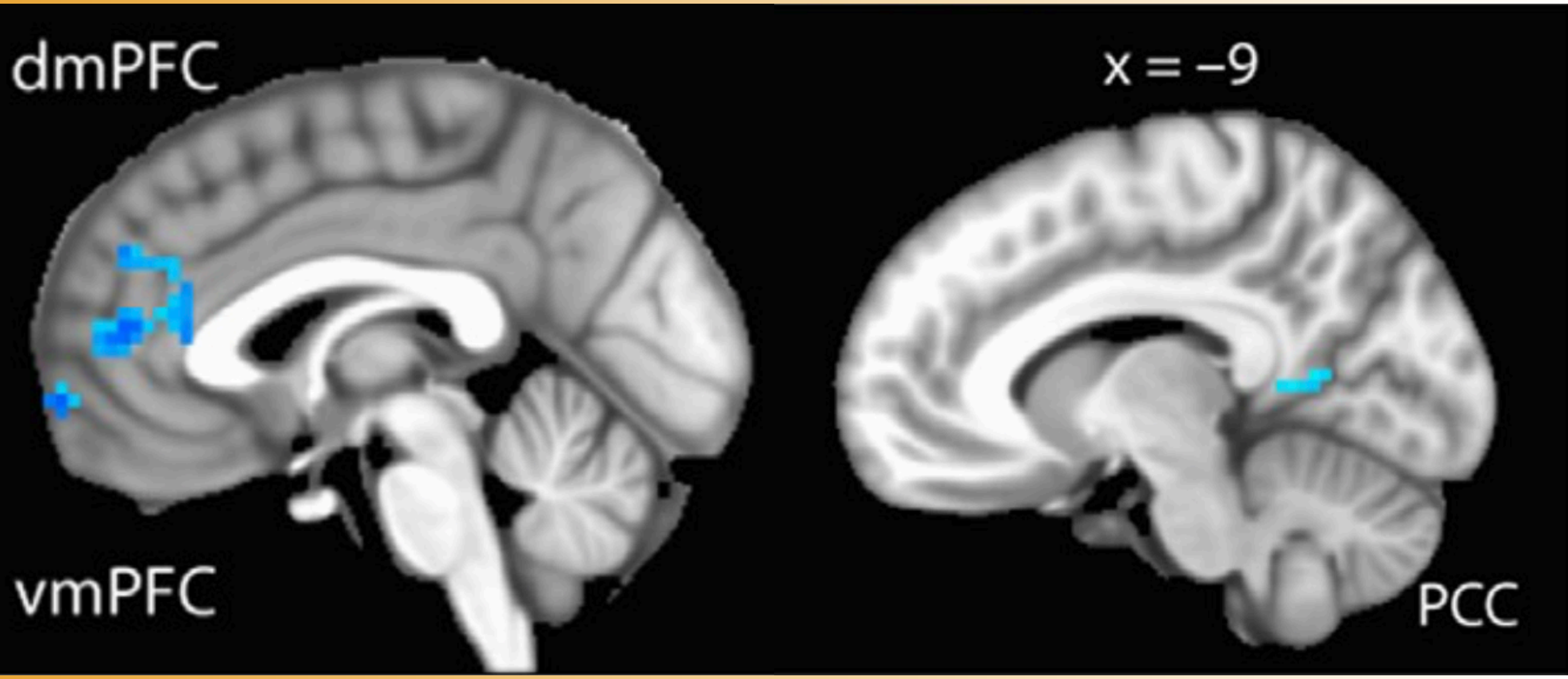
Thicker Cortex

Rb - Downstream & Upstream

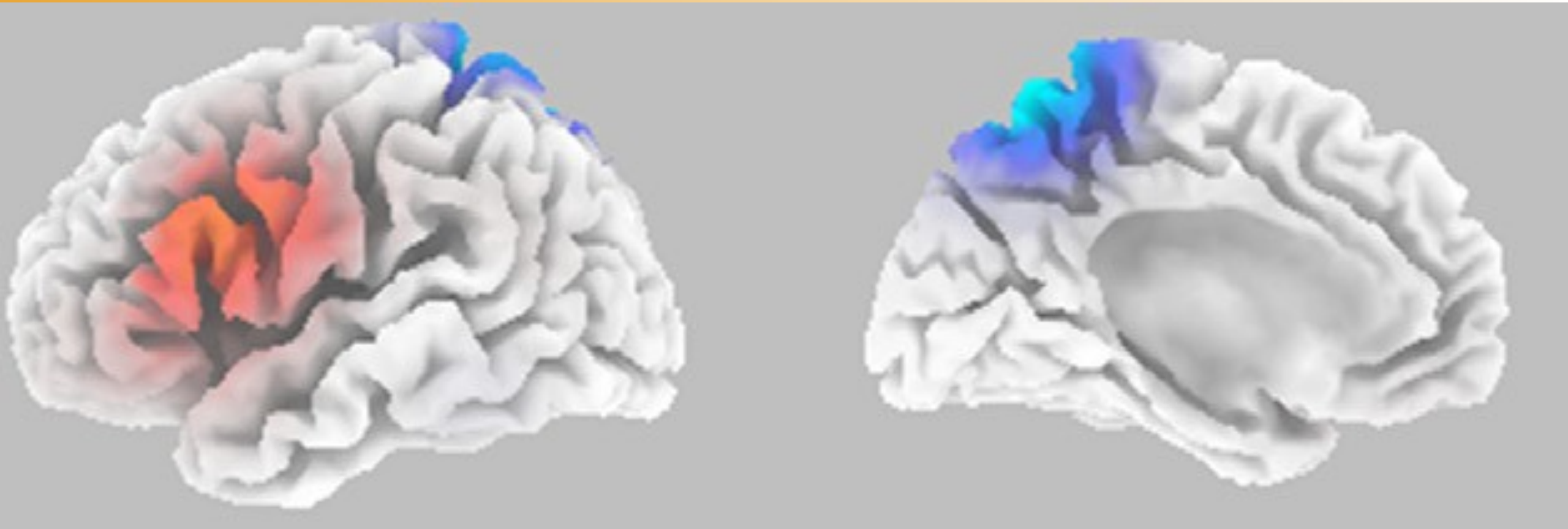


Before treatment, **functional connectivity in depressed patients was abnormally elevated within the DMN and diminished within the CEN**, and connectivity between these two networks was altered. **Transcranial magnetic stimulation normalized depression- related subgenual hyperconnectivity in the DMN** but did not alter connectivity in the CEN. Transcranial magnetic stimulation also induced anticorrelated connectivity between the DLPFC and medial prefrontal DMN nodes. Baseline subgenual connectivity predicted subsequent clinical improvement.

Liston 2014 Default Mode Network Mechanisms of Transcranial Magnetic Stimulation in Depression



Kito 2014 High-frequency Left PFC TMS Modulates Resting EEG **Functional Connectivity for Gamma Band Between the Left Dorsolateral Prefrontal Cortex and Precuneus in Depression**



What can we treat?

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Indication Other Uses

Fort Lauderdale, Florida 09/2019

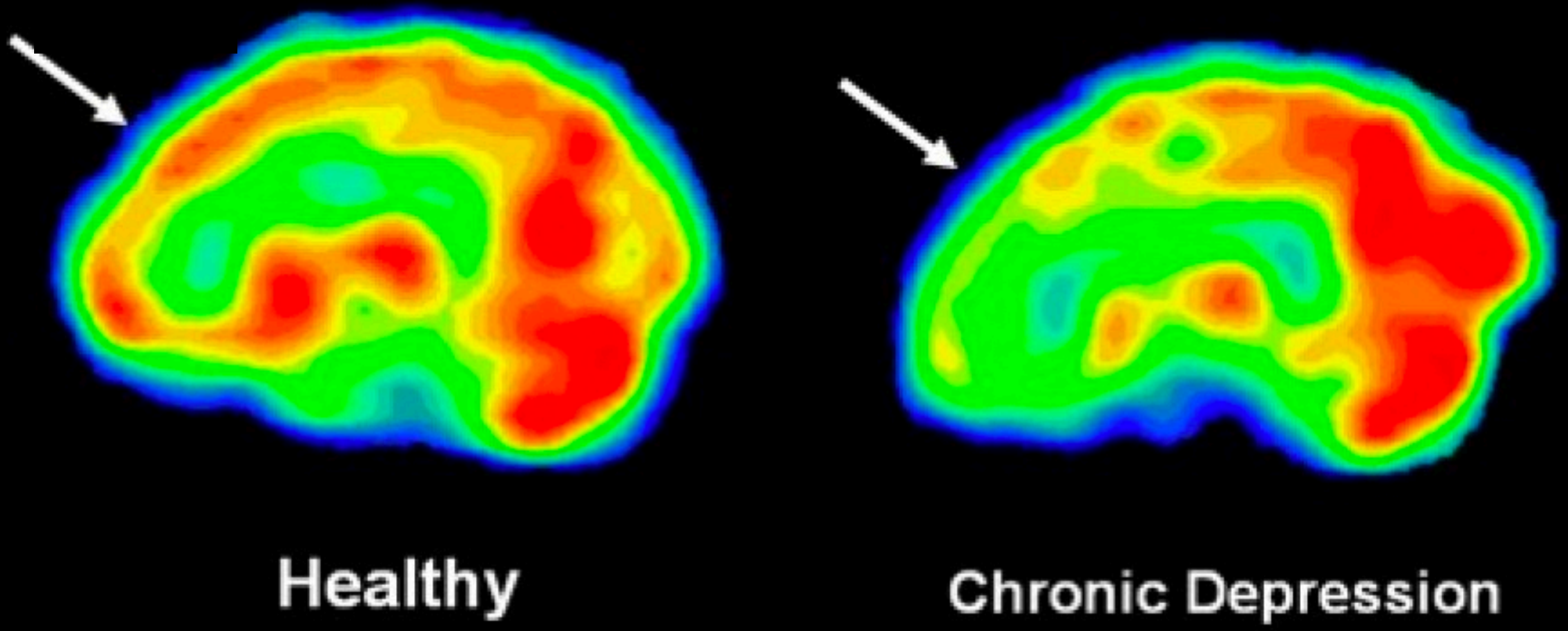
INDICATION:

MAJOR DEPRESSIVE DISORDER

AT LEAST ONE FAILED MEDICATION TRY

NEED BETTER DEPRESSION TREATMENT

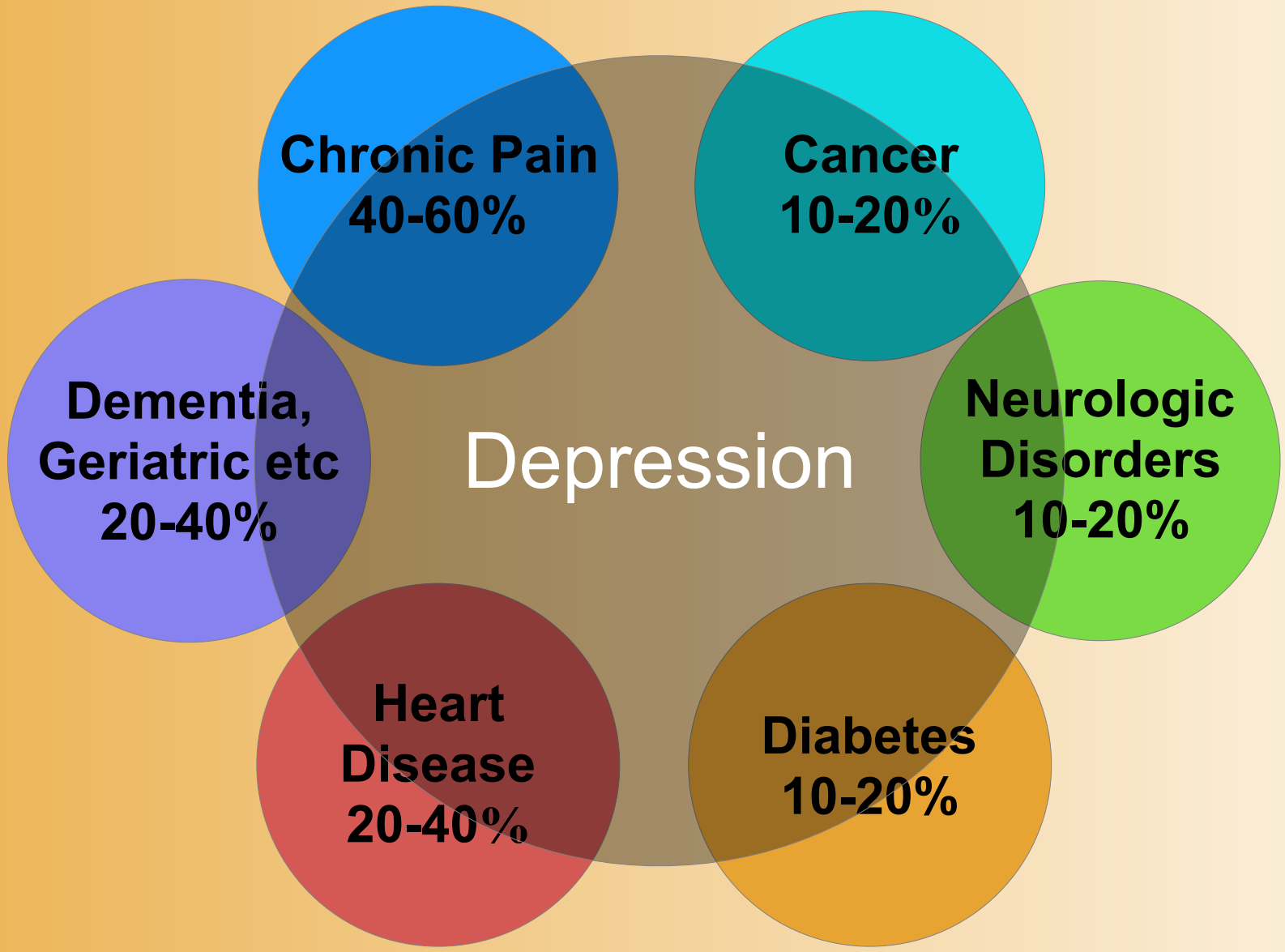
REDUCED FRONTAL LOBE ACTIVITY IN DEPRESSION



Healthy

Chronic Depression

Many Health Problems Co-occur

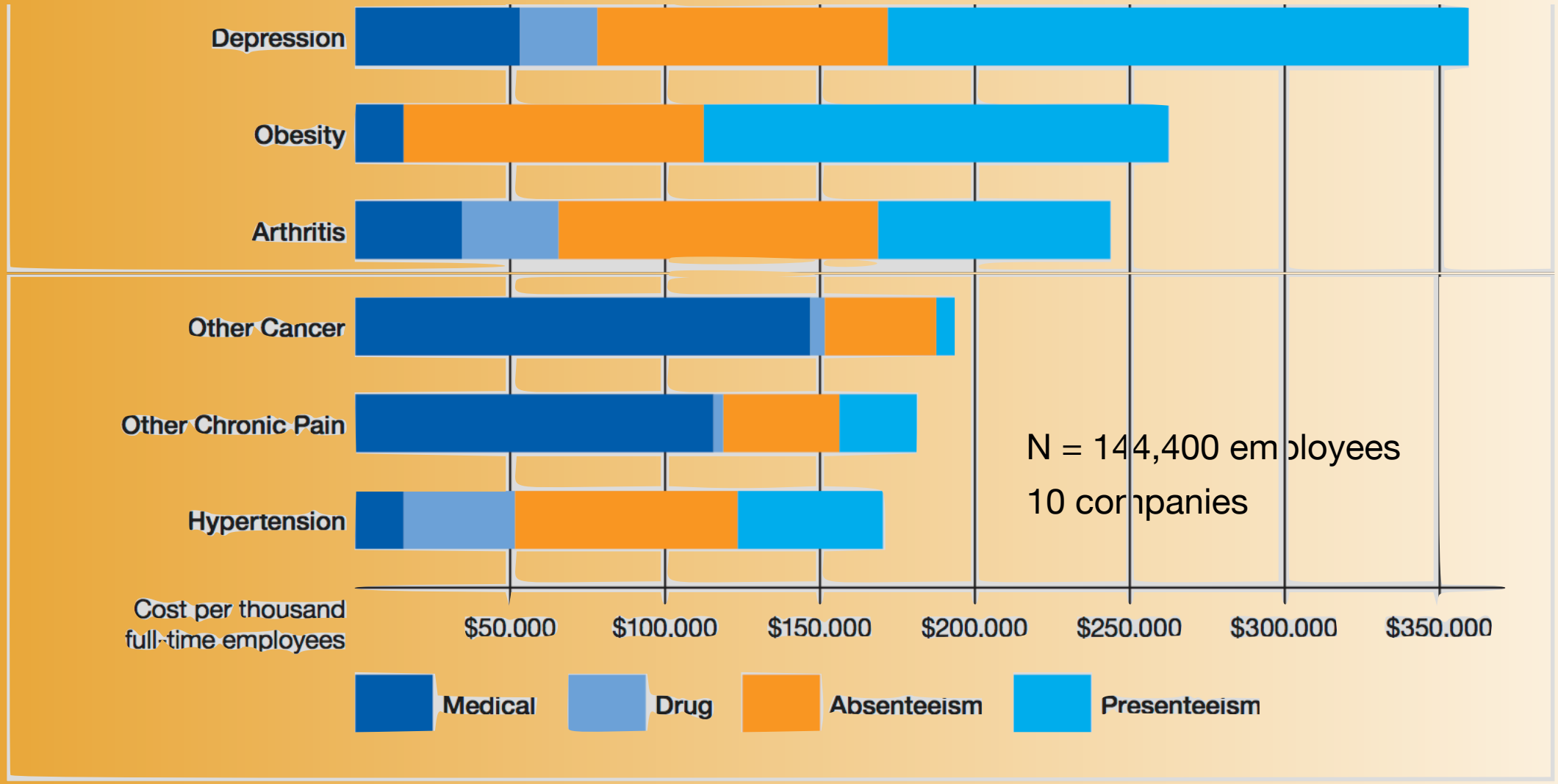


Impact of Treatment Refractory Depression

- **The impact on health resource use is profound**
  - Excess health care visits are for medical evaluation of untreated depression symptoms (eg, chest pain, backache, chronic pain)
  - Excess utilization of health care resources overall
  - Increases are evident on both direct and indirect costs
- **30% of depressed patients attempt suicide**
  - Nearly half of these complete (> 19,000 suicides/year in the United States)

Katon WJ. *Biol Psychiatry*. 2003;54(3):216-226. Rugulies R. *Am J Prev Med*. 2002;23(1):51-61. Fawzy FI, et al. *Arch Gen Psychiatry*. 1993;50(9):681-689. Fawzy FI, et al. *Arch Gen Psychiatry*. 2003;60(1):100-103. Cook JM, et al. *Am J Geriatr Psychiatry*. 2002;10(4):437-446. Eaton WW, et al. *Diabetes Care*. 1996;19(10):1097-1102. American Foundation for Suicide Prevention.

Major Depression Cost at Work



"Even without disability costs being included … the combined medical, pharmacy, absenteeism and presenteeism costs of … depression, and fatigue are far more costly than … previously realized …"

Loeppke R, Results of survey of 10 companies with 144,400 employees from the following business sectors: manufacturing, telecom, hospitality, energy, consulting and insurance.

Cost Impact of Depression on Associated Illnesses

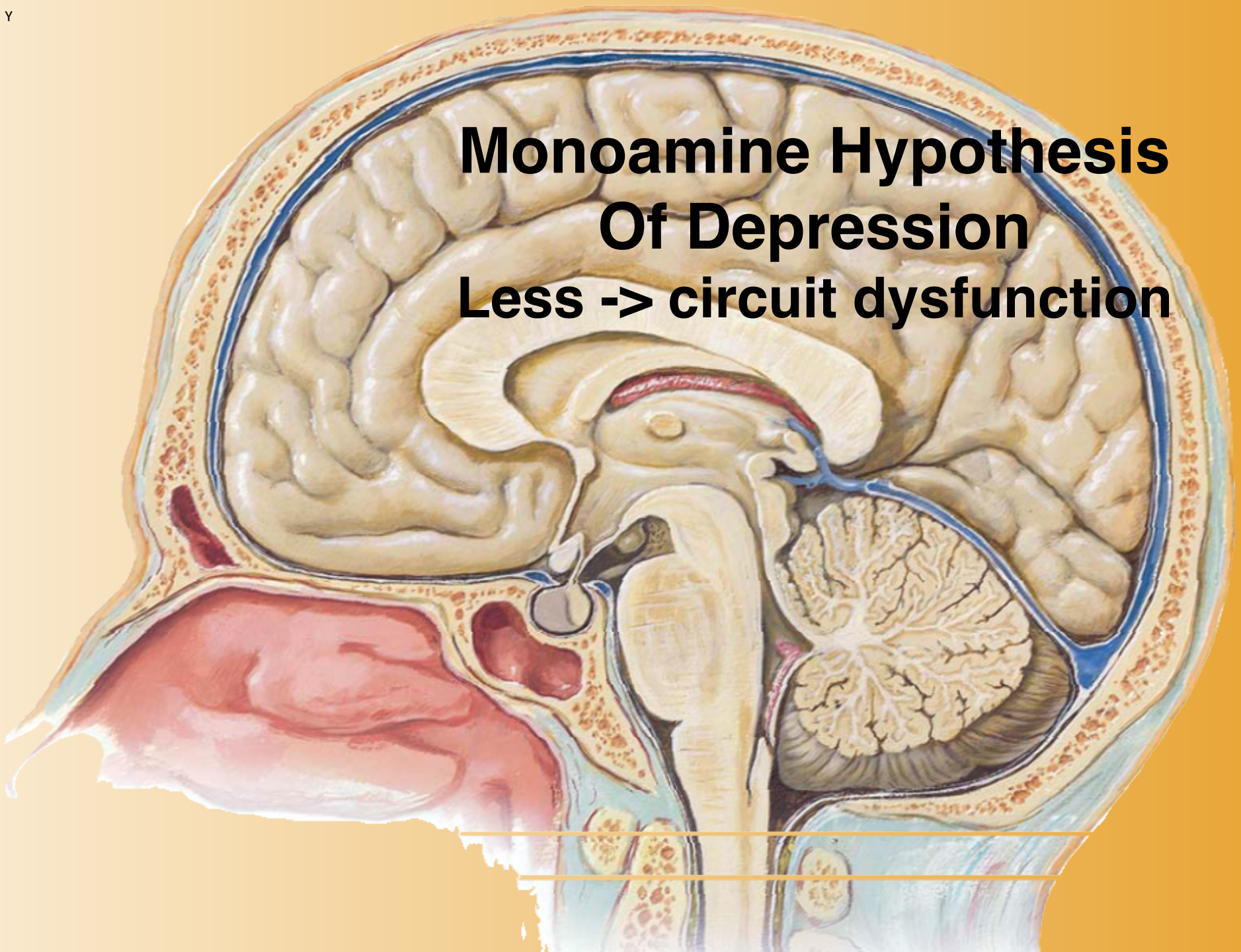
Condition	without Depression	with Depression
Heart failure	2.56	6.74
Allergic rhinitis	3.27	8.46
Asthma	3.73	10.56
Migraine	3.82	15.47
Back pain	11.61	33.25
Diabetes	13.06	27.28
Hypertension	13.38	27.16
Ischemic heart disease	62.40	110.94

Collins RL, et al. *Manag Care*. 2006;15(10 Suppl 9):3-9.

Y

Monoamine Hypothesis Of Depression

Less -> circuit dysfunction



Monoamine Hypothesis Of Depression

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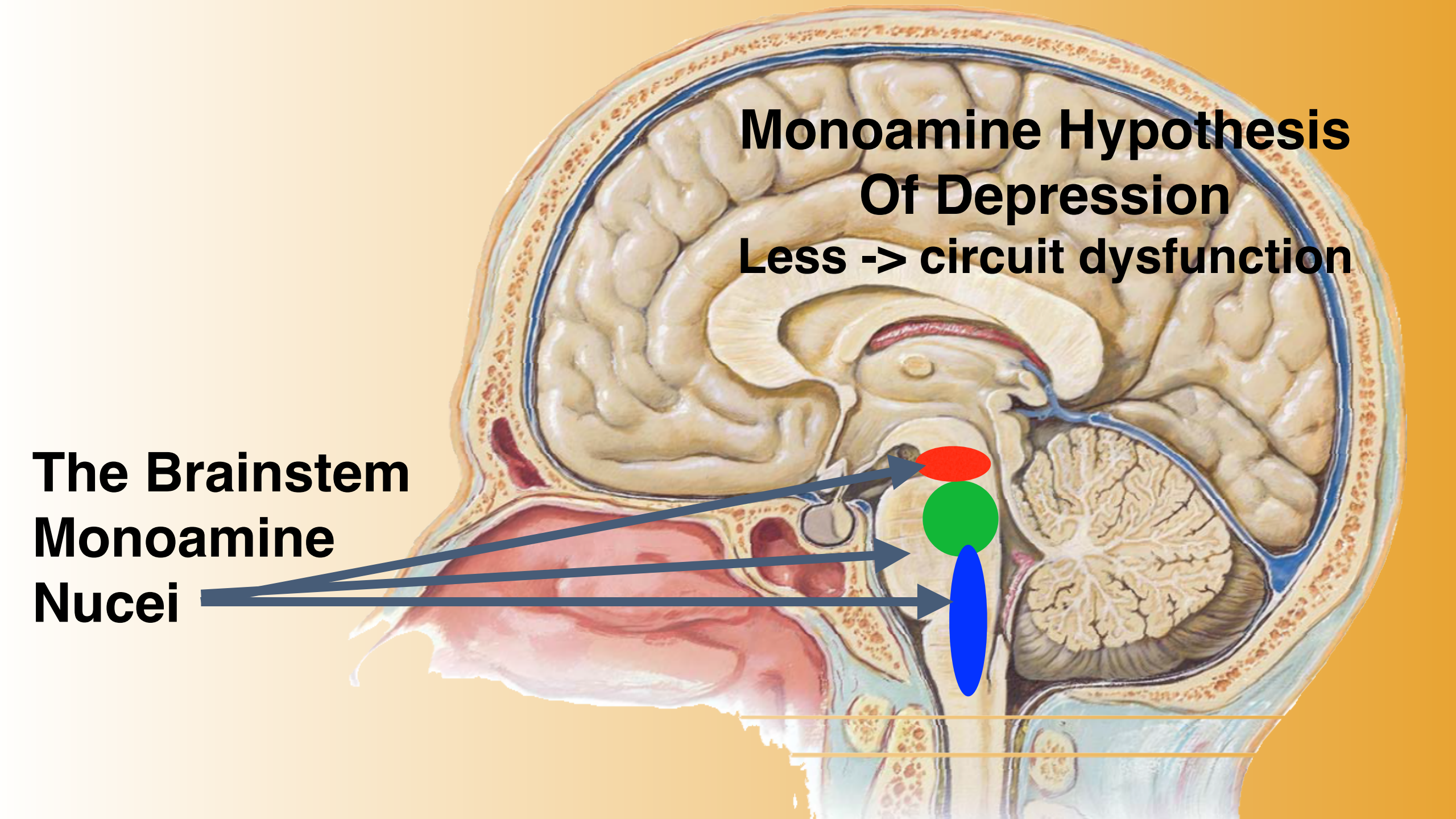
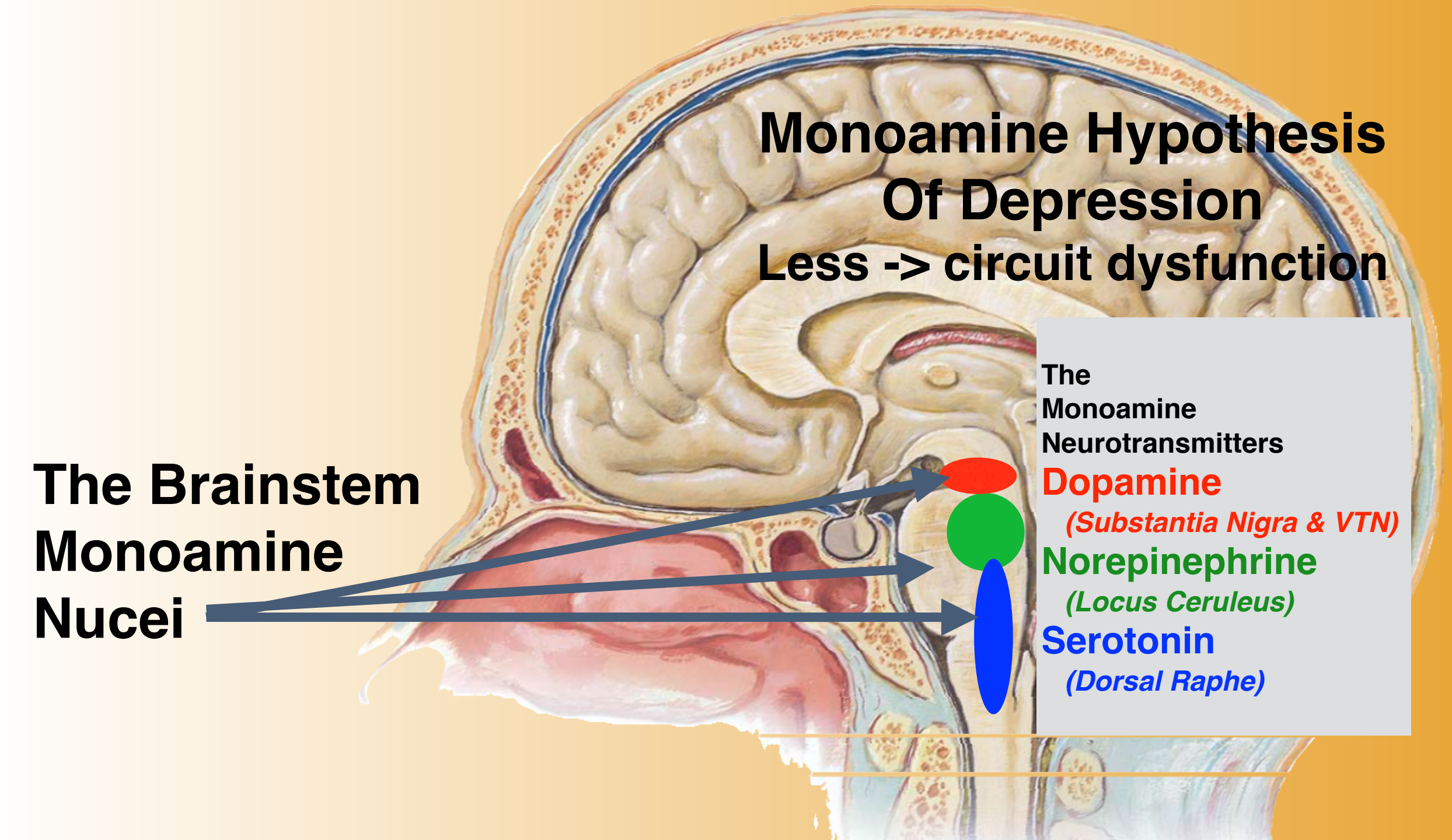


Monoamine Hypothesis Of Depression

Less -> circuit dysfunction



The Brainstem Monoamine Nucei

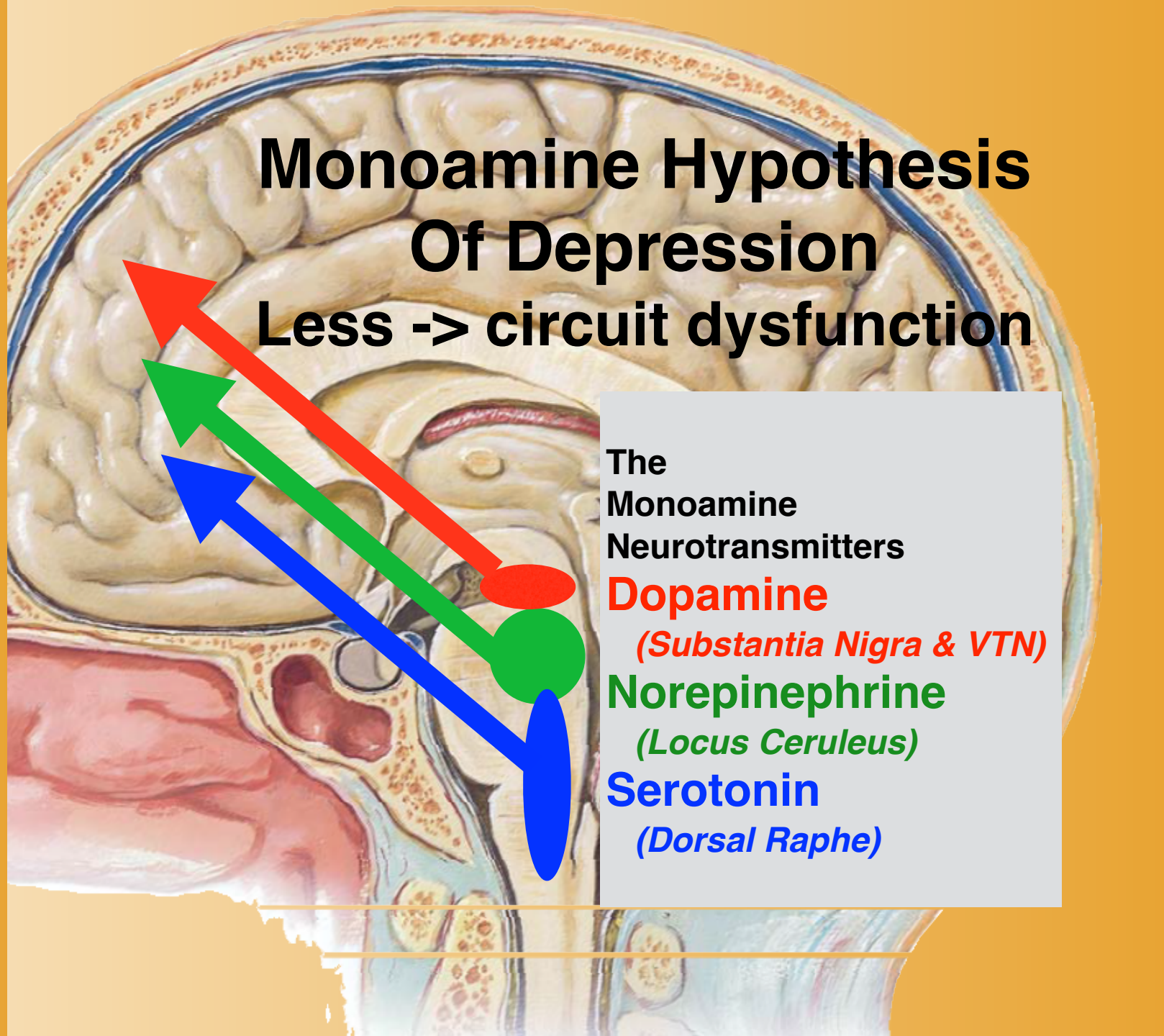
The Monoamine Neurotransmitters

Dopamine
(Substantia Nigra & VTN)

Norepinephrine
(Locus Ceruleus)

Serotonin
(Dorsal Raphe)

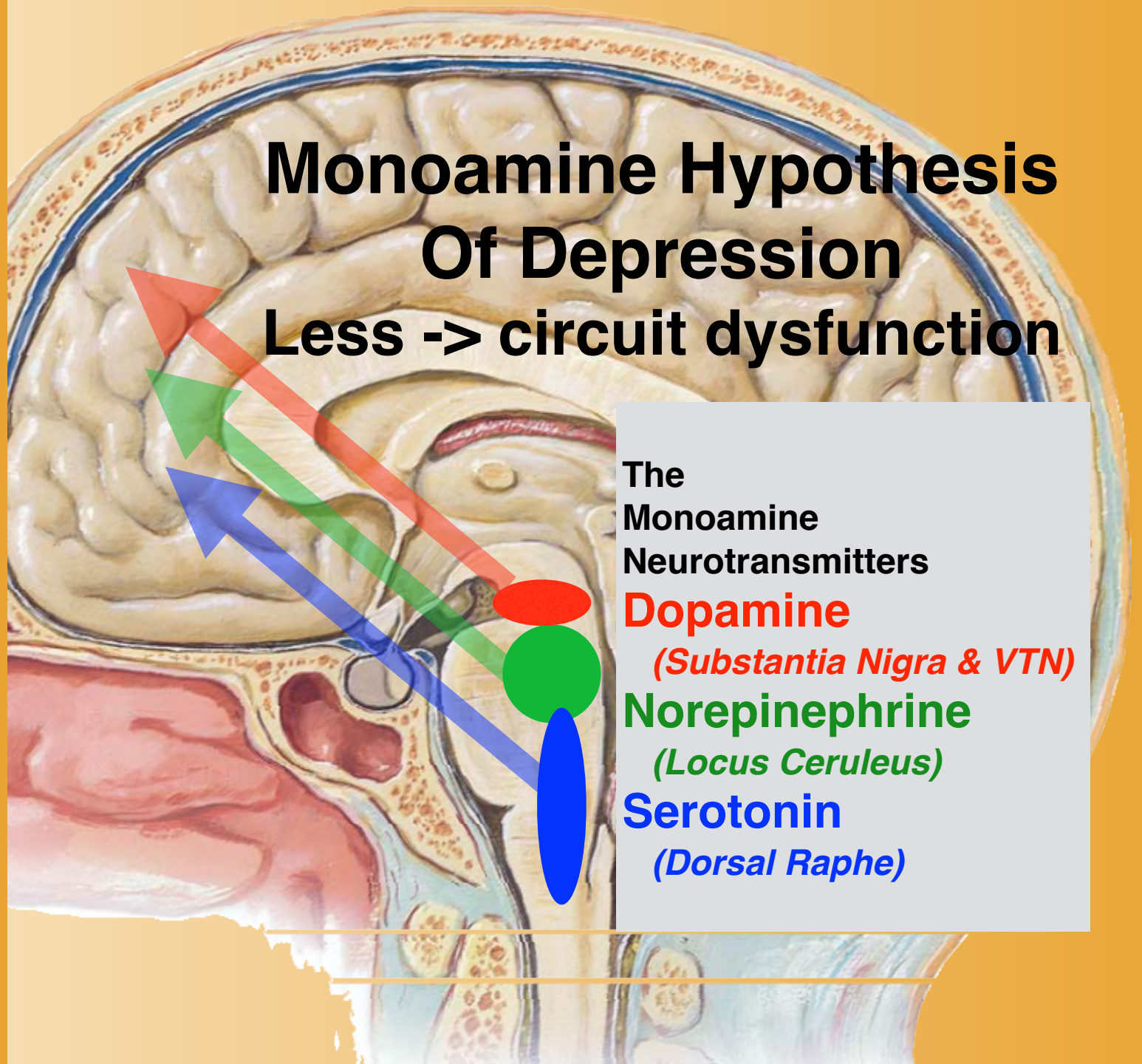
The Brainstem Monoamine Neurotransmitters project to the **Cerebral Cortex** influencing the **Excitatory** ***(Glutamate 70%)*** **& Inhibitory** ***(GABA 25%)*** **synapses**



Lowered Monoamine Neurotransmitters
leads to
Circuit dysfunction
in the
Cerebral Cortex
And other places

Monoamine Hypothesis Of Depression

Less -> circuit dysfunction



The Monoamine Neurotransmitters

Dopamine
(Substantia Nigra & VTN)

Norepinephrine
(Locus Ceruleus)

Serotonin
(Dorsal Raphe)

Monoamine Hypothesis Of Depression

Less -> circuit dysfunction

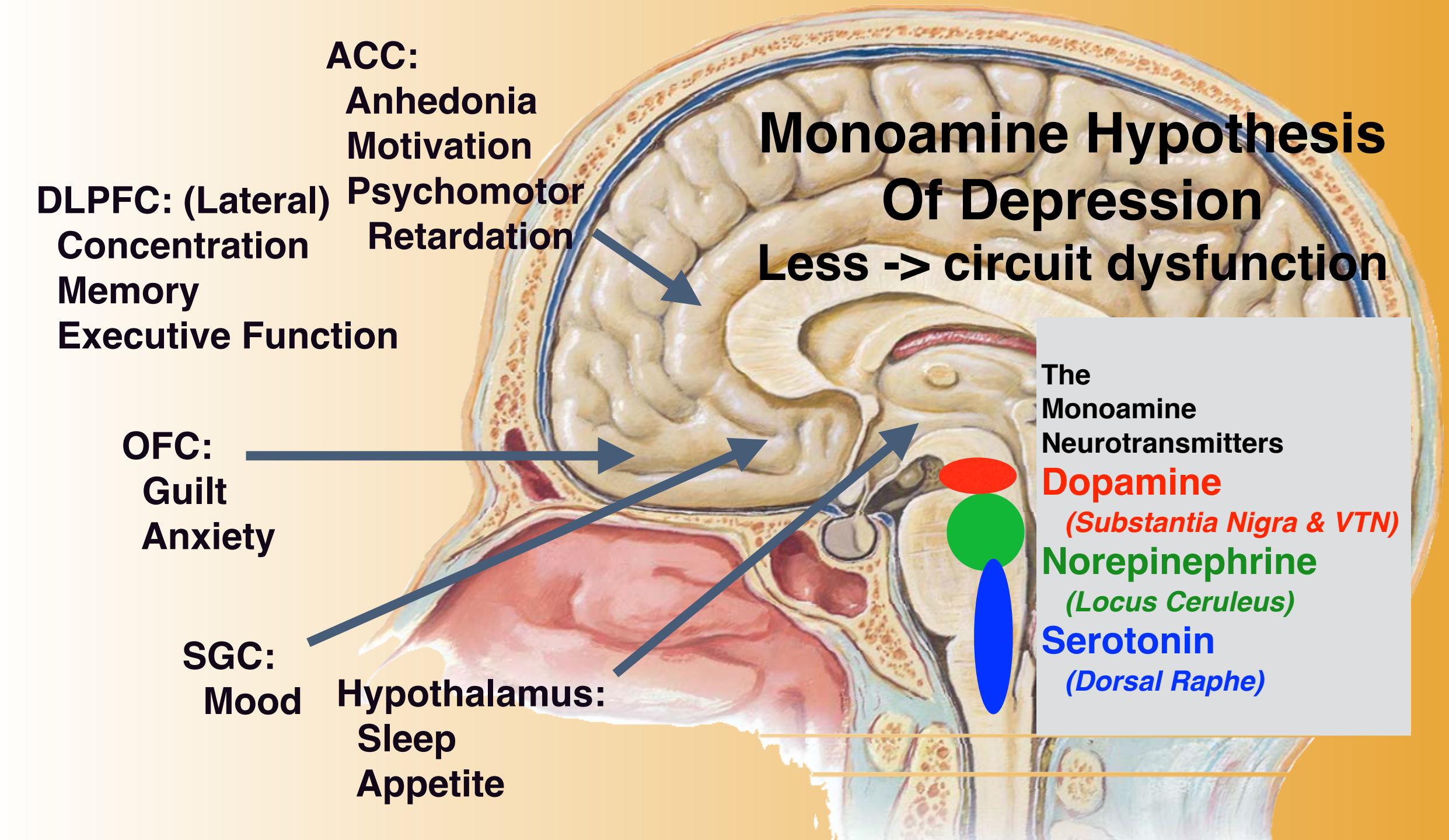
ACC:
- Anhedonia
- Motivation
- Psychomotor Retardation

DLPFC: (Lateral)
- Concentration
- Memory
- Executive Function

OFC:
- Guilt
- Anxiety

SGC:
- Mood

Hypothalamus:
- Sleep
- Appetite



The Monoamine Neurotransmitters

Dopamine
(Substantia Nigra & VTN)

Norepinephrine
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Serotonin
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Welcome

Fort Lauderdale, Florida 09/2019

TMS: History

Fort Lauderdale, Florida 09/2019

TMS: Process

Fort Lauderdale, Florida 09/2019

TMS:
Adverse Effects

Fort Lauderdale, Florida 09/2019

Table 2
Characteristics of reported seizures and subjects.

Seizure description	Frequency	Target	Diagnosis	Medications	Previous TMS
1. "Clinical seizure"	Single/Paired-pulse	Frontal cortex	Epilepsy	Valproate, zonisamide	None
2. Myoclonic	Single/paired-pulse	M1	Myoclonus epilepsy	Antiepileptic(s)	Some (unspecified)
3. Myoclonic	Single/paired-pulse	M1	Myoclonus epilepsy	Antiepileptic(s)	Some (unspecified)
4. Secondary generalized	Single-pulse	M1	Epilepsy	Topiramate, valproate, clobazam	None
5. Partial	Single-pulse	M1	Multiple sclerosis (possible)	None	None
6. Complex partial	Single-pulse	M1	None	None	1 session
7. Partial[†]	Single-pulse	M1	Tumor	Sertraline	2 sessions
8. Partial[*]	Single-pulse	M1	Tumor	Levitiracetam, lamotrigine	1 session
9. Partial	Single-pulse	M1	None	None	None
10. Secondary generalized	Single-pulse	IPS	None	Oral contraceptives	None
11. Generalized	Single-pulse	M1 (round coil at vertex)	Paraparesis	None	None
12. Generalized[*]	Single-pulse	M1	Epilepsy	Clobazam, pregabalin, zonisamide, levetiracetam, valproate, hydantoin	None
13. Not reported	Single pulse	M1	Stroke	Not reported	None
14. Partial	Single-pulse	M1	Arteriovenous malformation	None	None
15. Myoclonic	0.3 Hz	M1 (round coil at vertex)	Myoclonus epilepsy	Valproate, zonisamide, levetiracetam, clobazam	None
16. Generalized	1 Hz	DLPFC	Stroke	Atorvastatin, warfarin	None
17. Partial[*]	7 Hz	M1	Epilepsy	Valproate, eslicarbazepine, lacosamide, levetiracetam	None
18. Partial then generalized	10 Hz	M1	Stroke	Some (unspecified)	Some (Unspecified)
19. Secondary generalized	10 Hz	M1	Stroke	Trifluoperazine	None
20. Secondary generalized	15 Hz	DLPFC	Schizophrenia	Risperidone	4 sessions
21. Secondary generalized	18 Hz	DLPFC	Depression	None	7 sessions
22. Secondary generalized	18 Hz	DLPFC	Depression Alcoholism	None	12 sessions
23. Generalized	18 Hz	DLPFC	Depression/rheumatoid arthritis	Methotrexate	Unreported
24. Secondary generalized	20 Hz	DLPFC	Depression	Mirtazepine	None
25. Secondary generalized	iTBS	M1	Stroke	None	None

Seizures from transcranial magnetic stimulation 2012–2016: Results of a survey of active laboratories and clinics

Adam J. Lerner a,⇑, Eric M. Wassermann b, Diana I. Tamir c,d

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16. Generalized	1 Hz	DLPFC	Stroke	Atorvastatin, warfarin	None
17. Partial*	7 Hz	M1	Epilepsy	Valproate, eslicarbazepine, lacosamide, levetiracetam	None
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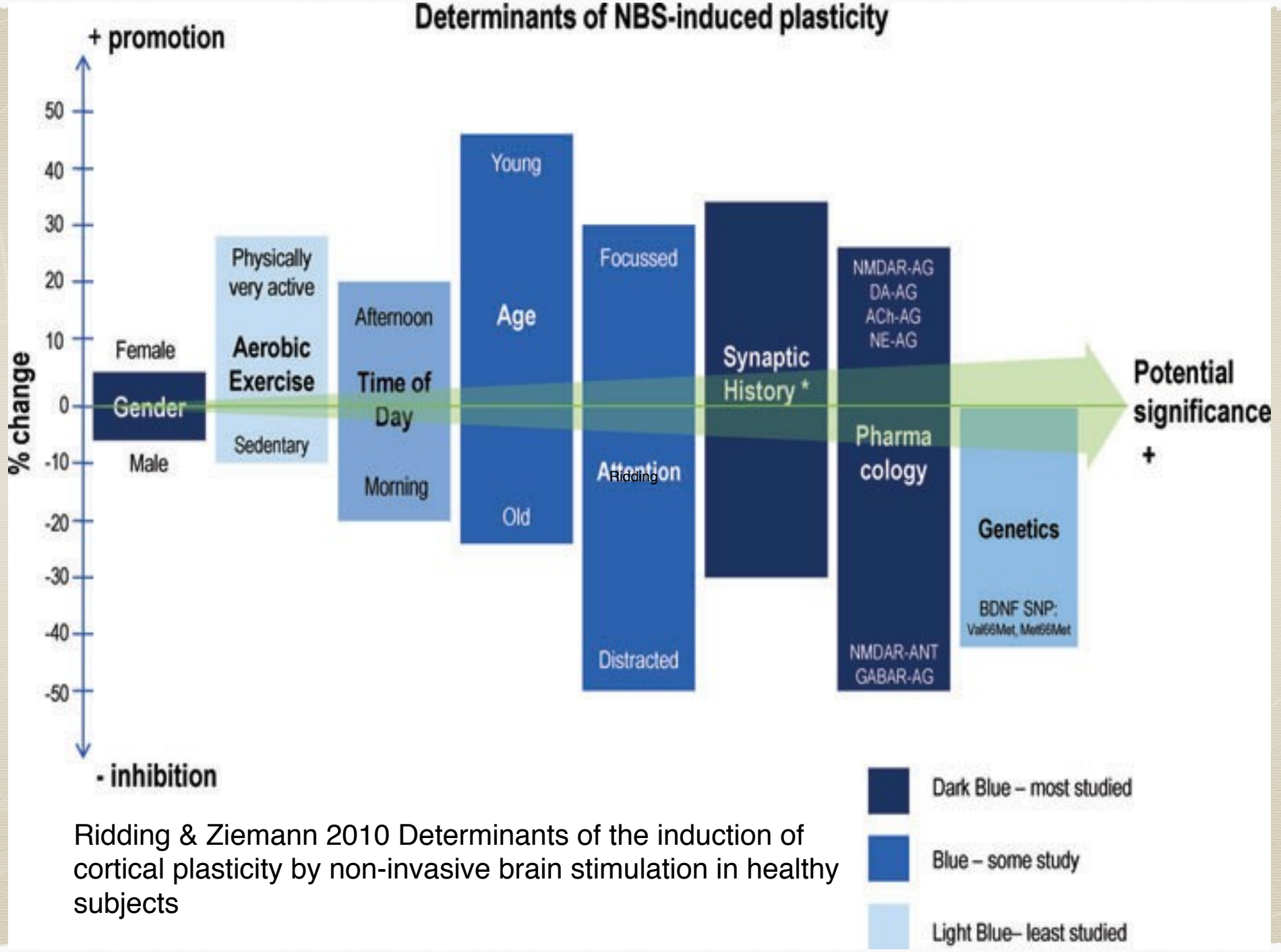
Neuro 17/25
(5 epilepsy)
Psych 5/25



Ridding & Ziemann 2010 Determinants of the induction of cortical plasticity by non-invasive brain stimulation in healthy subjects

Brain:
Cerebral Cortex

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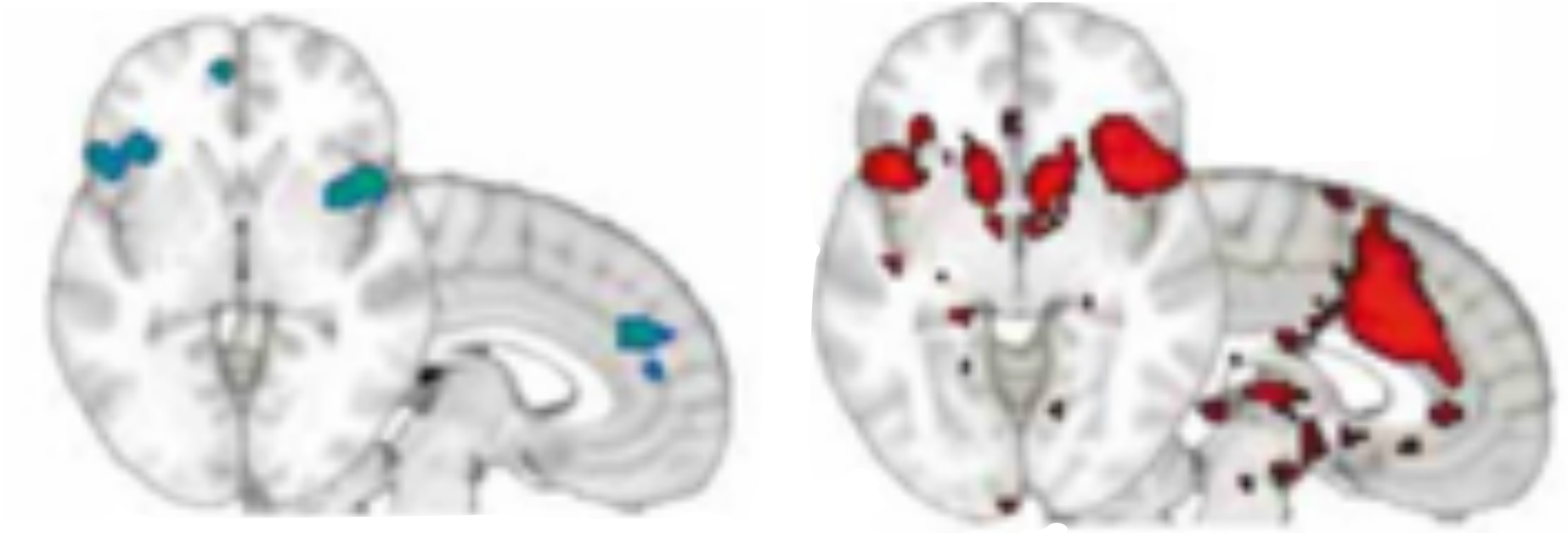
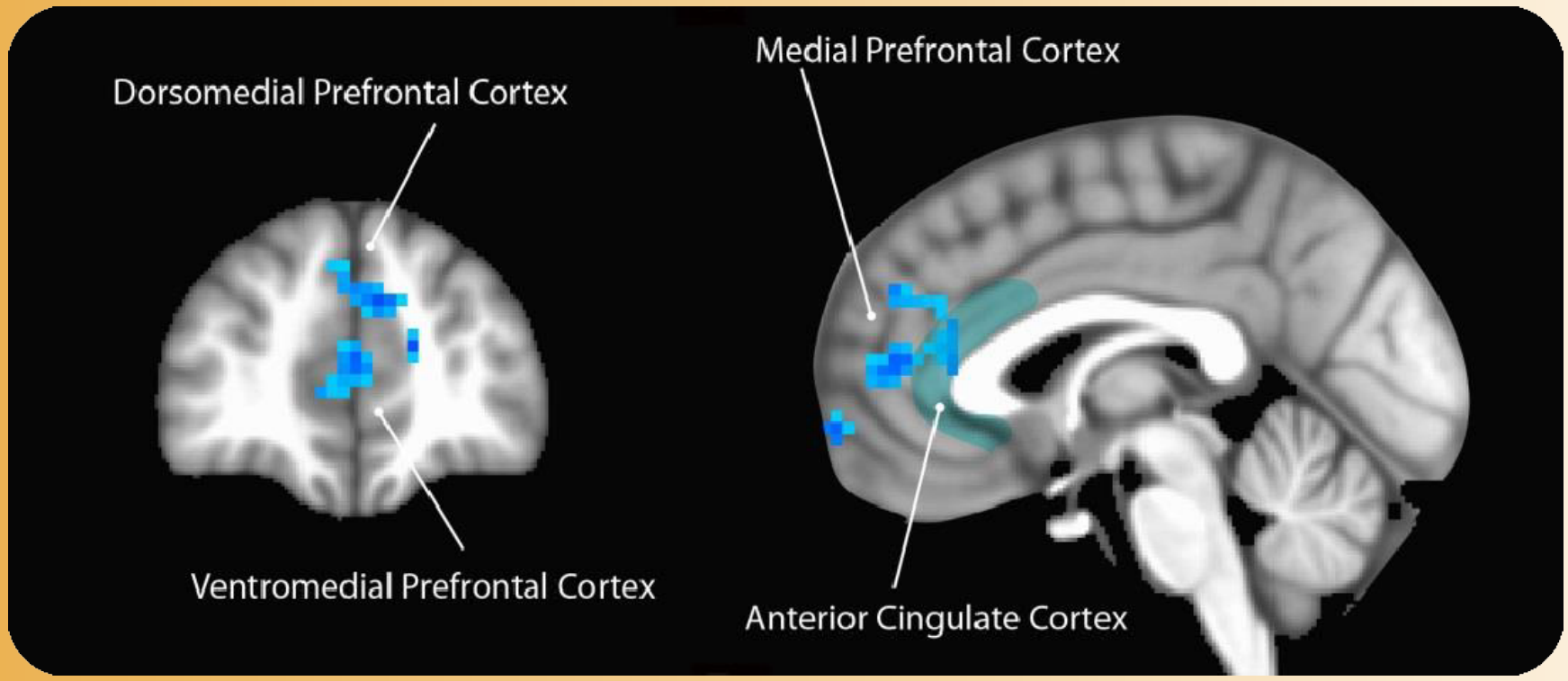
Psychiatric Common Core Regions in the Context of the Functional Architecture of the Human Brain

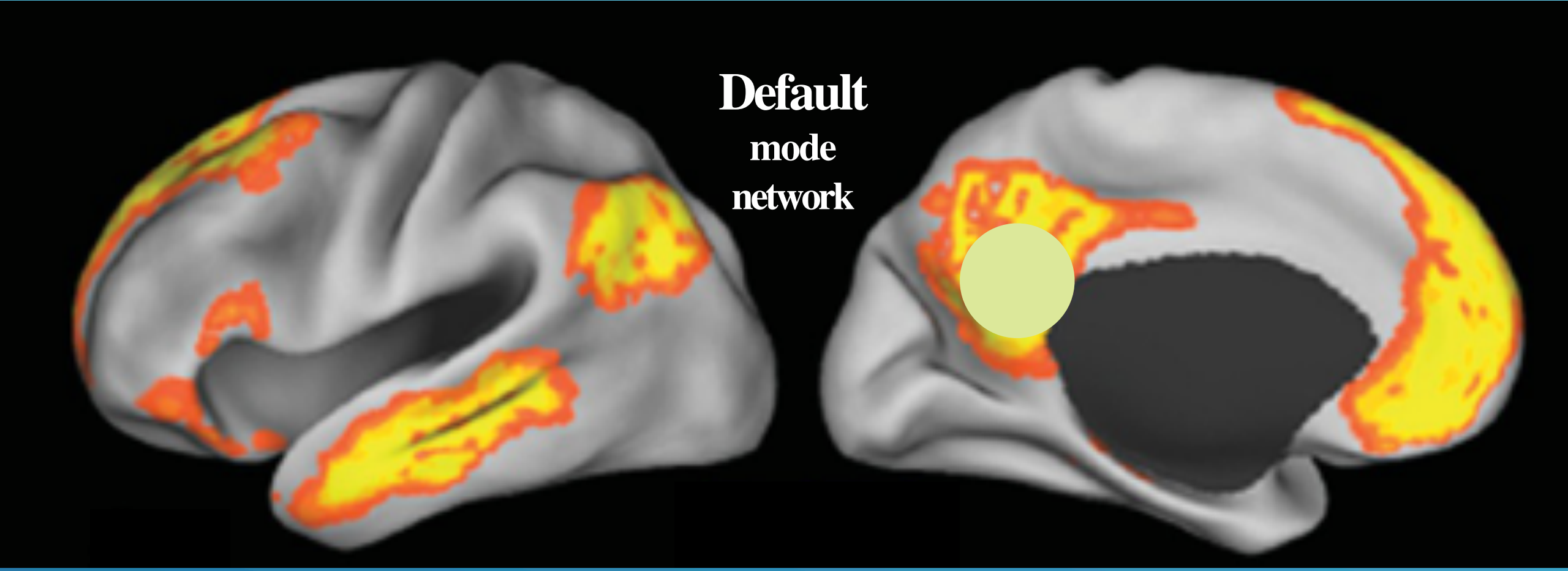


Common substrates of psychiatric illness

Liston 2014 Default Mode Network Mechanisms of Transcranial Magnetic Stimulation in Depression



Treatment with TMS reduces hyperconnectivity within the default mode network (ventromedial prefrontal cortex, pregenual anterior cingulate cortex, thalamus, and precuneus)



Perhaps the most fundamental RSN is the DMN (Fig 1A), first identified from PET data by Raichle et al7 (for further discussion, see Gusnard et al8). In this study, the authors analyzed data from healthy volunteers resting quietly with their eyes closed. They found that consistent regions of the brain were **active at rest but decreased** their **activity** when cognitive **tasks** were performed. The default mode network was identified by Greicius et al9 by using fMRI and was confirmed in many studies by using a variety of analysis methods.2-6,10,11 Studies have hypothesized that **there are 2 large opposing systems** in the brain, one including the **DMN** and the other composed of **attentional or task**-based systems, such as somatosensory, visual, or attention RSNs. Terms used to refer to these systems include "task-positive" and "task-negative"4,12,13 and "intrinsic" and "extrinsic."14,15

Alexander 1986 Parallel Organization Of Functionally Segregated Circuits Linking Basal Ganglia And Cortex

TMS

How does it work?

(Mechanism of action)

MECHANISM

HOW DO WE UNDERSTAND DEPRESSION?

TMS

How does it work?

(Mechanism of action)

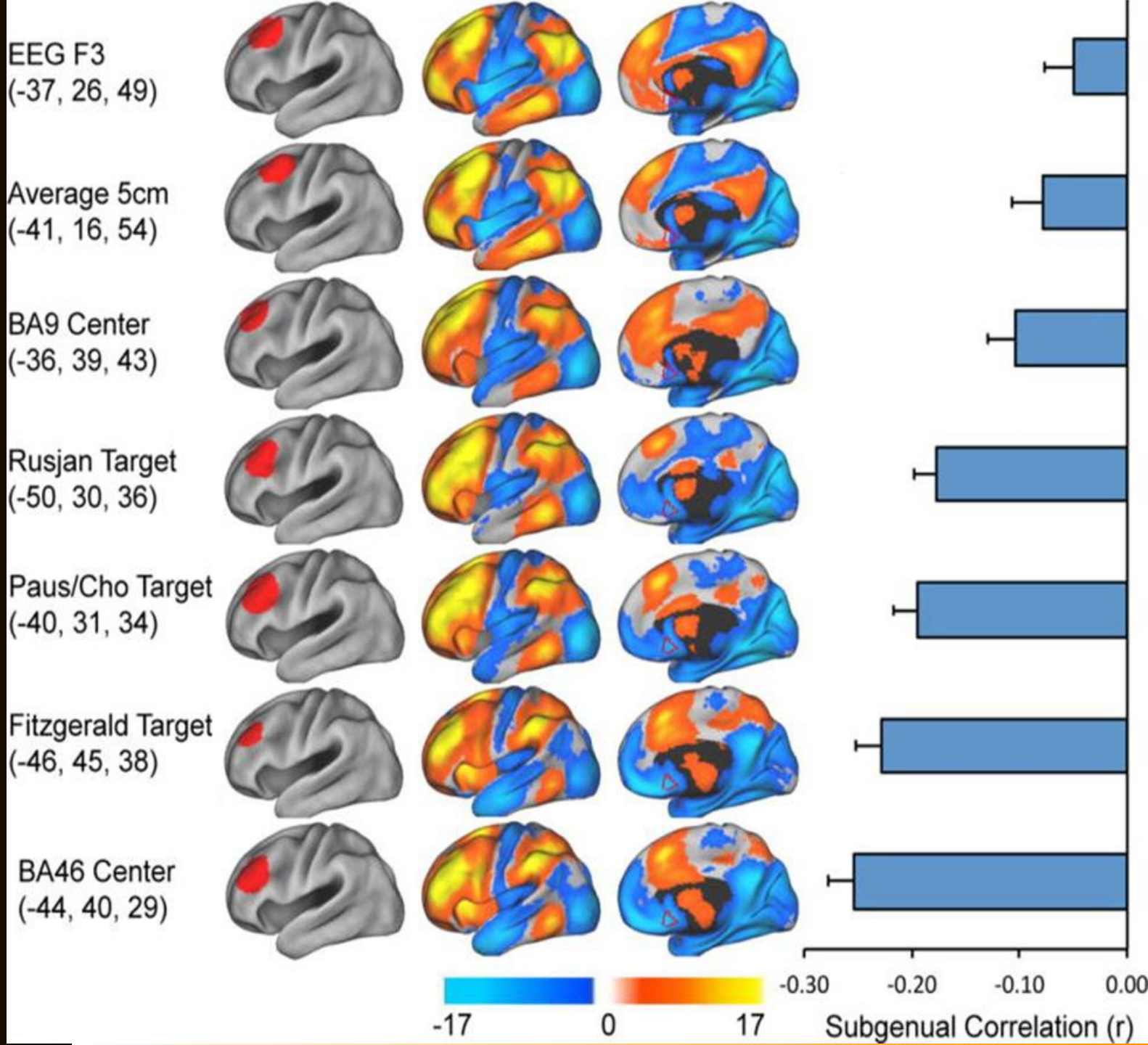
MECHANISM

HOW DO WE UNDERSTAND THE BRAIN?

Haber 2010 The Reward Circuit- Linking Primate Anatomy and Human Imaging

Figure 1. Schematic illustrating key structures and pathways of the reward circuit. Red arrow = input from the vmPFC; dark orange arrow = input from the OFC; light orange arrow = input from the dACC; yellow arrow = input form the dPFC; brown arrows other main connections of the reward circuit. Amy = amygdala; dACC = dorsal anterior cingulate cortex; dPFC = dorsal prefrontal cortex; Hipp = hippocampus; LHb = lateral habenula; hypo = hypothalamus; OFC = orbital frontal cortex; PPT = pedunculopontine nucleus; S = shell, SNc = substantia nigra, pars compacta; STN = subthalamic nucleus.; Thal = thalamus;

1 Some locations are more connected to BA25 (SGC)
2 location influences efficacy
3 MNI numbers can be put into NeuroSynth and you can check



Fox MD, et al. *Biol Psychiatry*. 2012;72(7):595-603.

- Chronic Effects
  - Specific outcome is dependent upon stimulation parameters
  - Alteration of monoamine concentrations
  - β-receptor, serotonin-receptor modulation
  - Induction of neurogenesis genes (eg, BDNF)
  - Plasticity, LTD/LTP effects
  - Local GABA, glutamate effects
  - Stimulation of the DLPFC alters functional activity of the anterior cingulate and deeper limbic regions

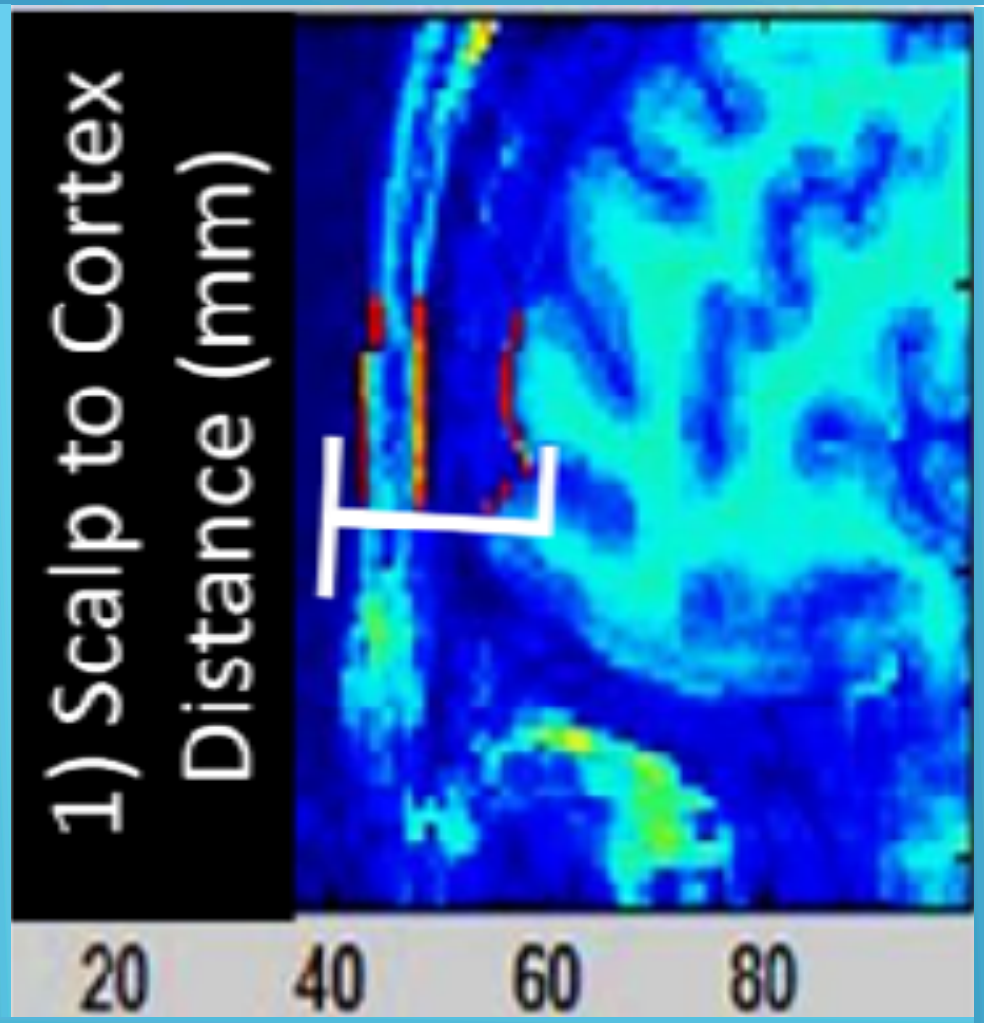
BDNF = brain-derived neurotrophic factor; LTD = long-term depression; LTP = long-term potentiation; GABA = gamma-aminobutyric acid.

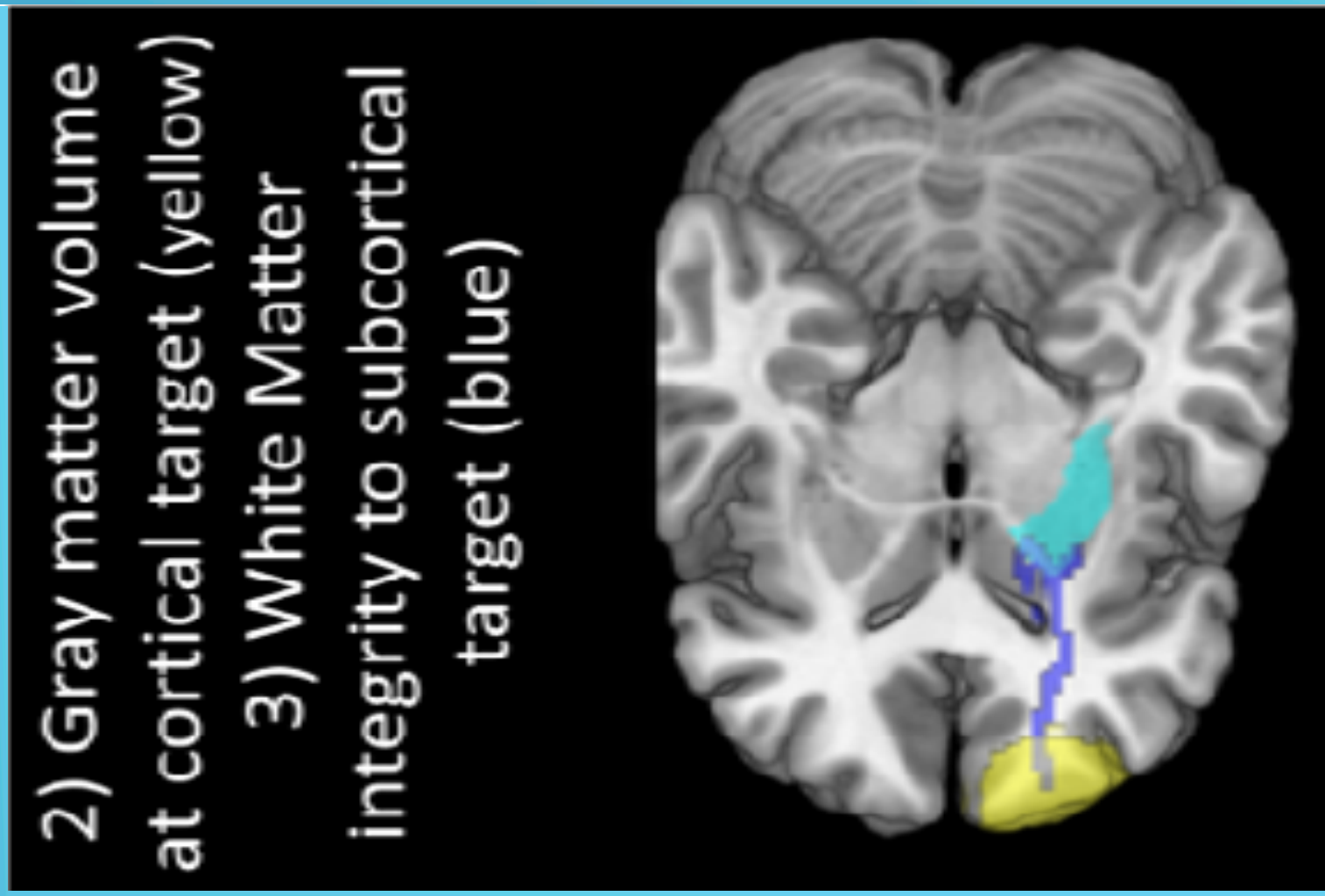
Lisanby SH, et al. *Depress Anxiety*. 2000;12(3):178-187. Kim EJ, et al. *Neurosci Lett*. 2006;405(1-2):79-83. Shajahan PM, et al. *Prog Neuropsychopharmacol Biol Psychiatry*. 2002;26(5):945-954. Teneback CC, et al. *J Neuropsychiatry Clin Neurosci*. 1999;11(4):426-435. Epstein CM, et al. *Neurology*. 1990;40(4):666-670. George MS, et al. *Neuroreport*. 1995;6(14):1853-1856. Post A, et al. *J Psychiatr Res*. 2001;35(4):193-215.

- rTMS produces changes in PFC and paralimbic blood flow with DLPFC stimulation
- Increased output of TSH in association with acute mood change in depression
- Normalization of the DST with rTMS

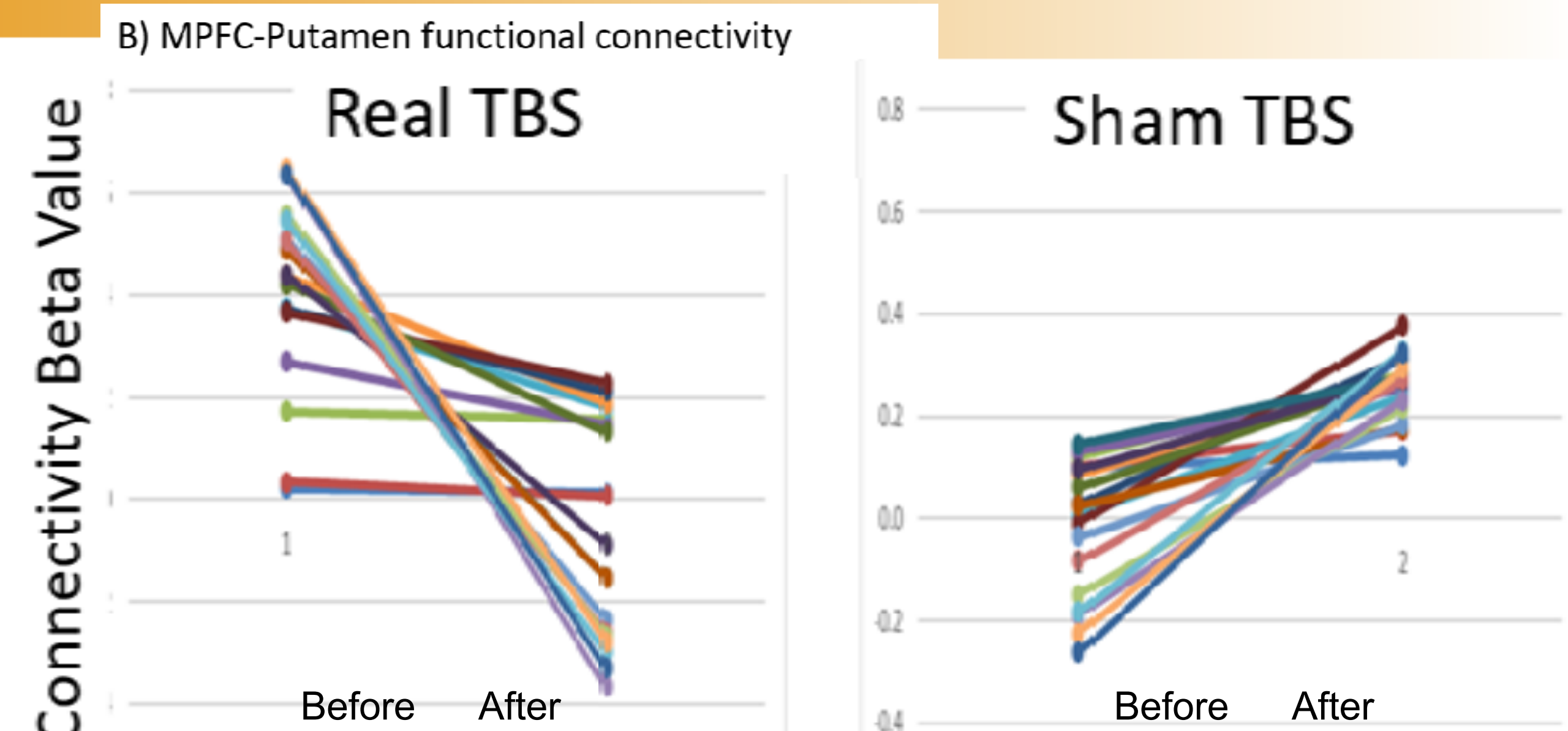
DST = dexamethasone suppression test; DLPFC = dorsolateral prefrontal cortex; PFC = prefrontal cortex; TSH = thyroid-stimulating hormone.

Hanlon 2019 Neural architecture influences rTMS-induced functional change: a DTI and FMRI study of cue-reactivity modulation in alcohol users





Hanlon 2019 Neural architecture influences rTMS-induced functional change: a DTI and FMRI study of cue-reactivity modulation in alcohol users



2019 Non-invasive Brain Stimulation for Alcohol Use Disorders: State of the Art and Future Directions Philip, Sorensen, McCalley & Hanlon

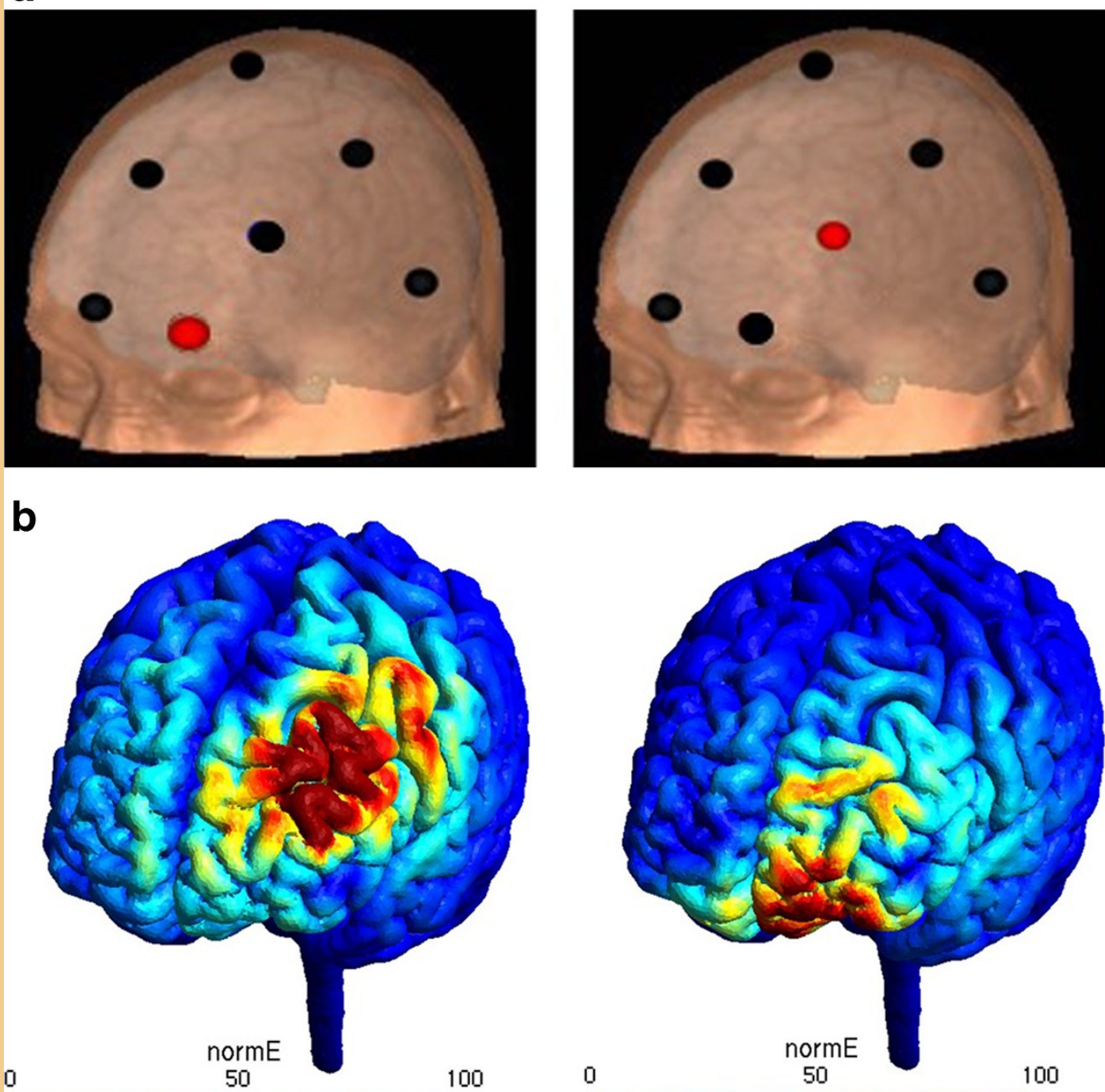
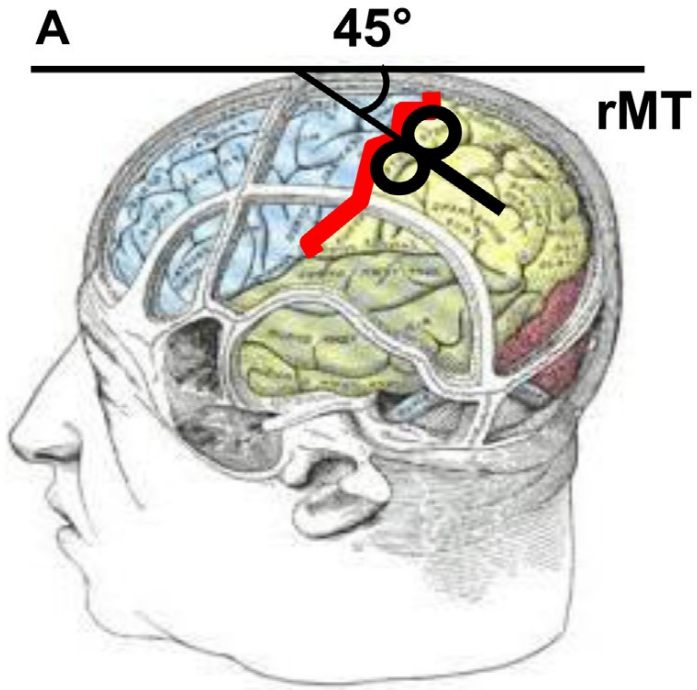
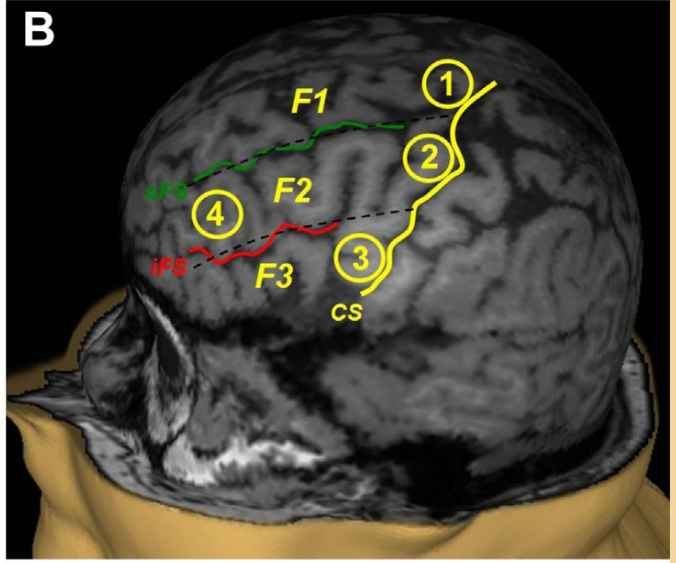
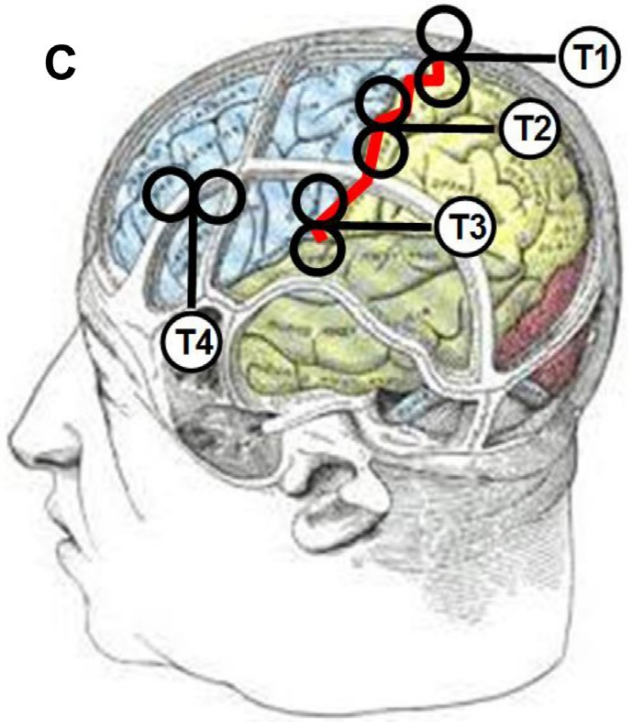
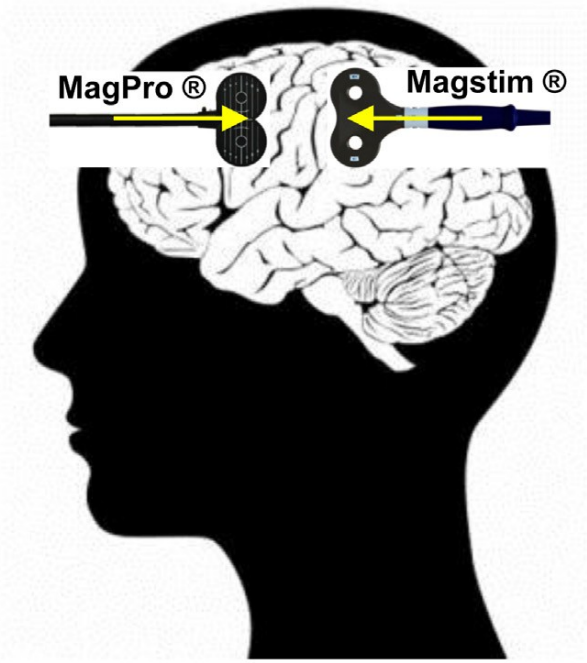


Fig. 1 Electrical effects of transcranial magnetic stimulation to the **dorsolateral prefrontal cortex** and **medial prefrontal cortex**. The DLPFC and the MPFC have been used as TMS treatment targets in individuals with AUD. By placing a standard figure-of-8 coil over the frontal pole (EEG 10–20 system coordinates; (a), an electric field is induced in the orbitofrontal and ventral medial aspects of the prefrontal cortex. Placing a figure-of 8 coil over the DLPFC (F3 coordinate) induces an electric field that extends rostrally towards the anterior PFC and caudally towards the premotor cortex (b). The scale is the induced current strength; modeling image created using SimNIBS [42]

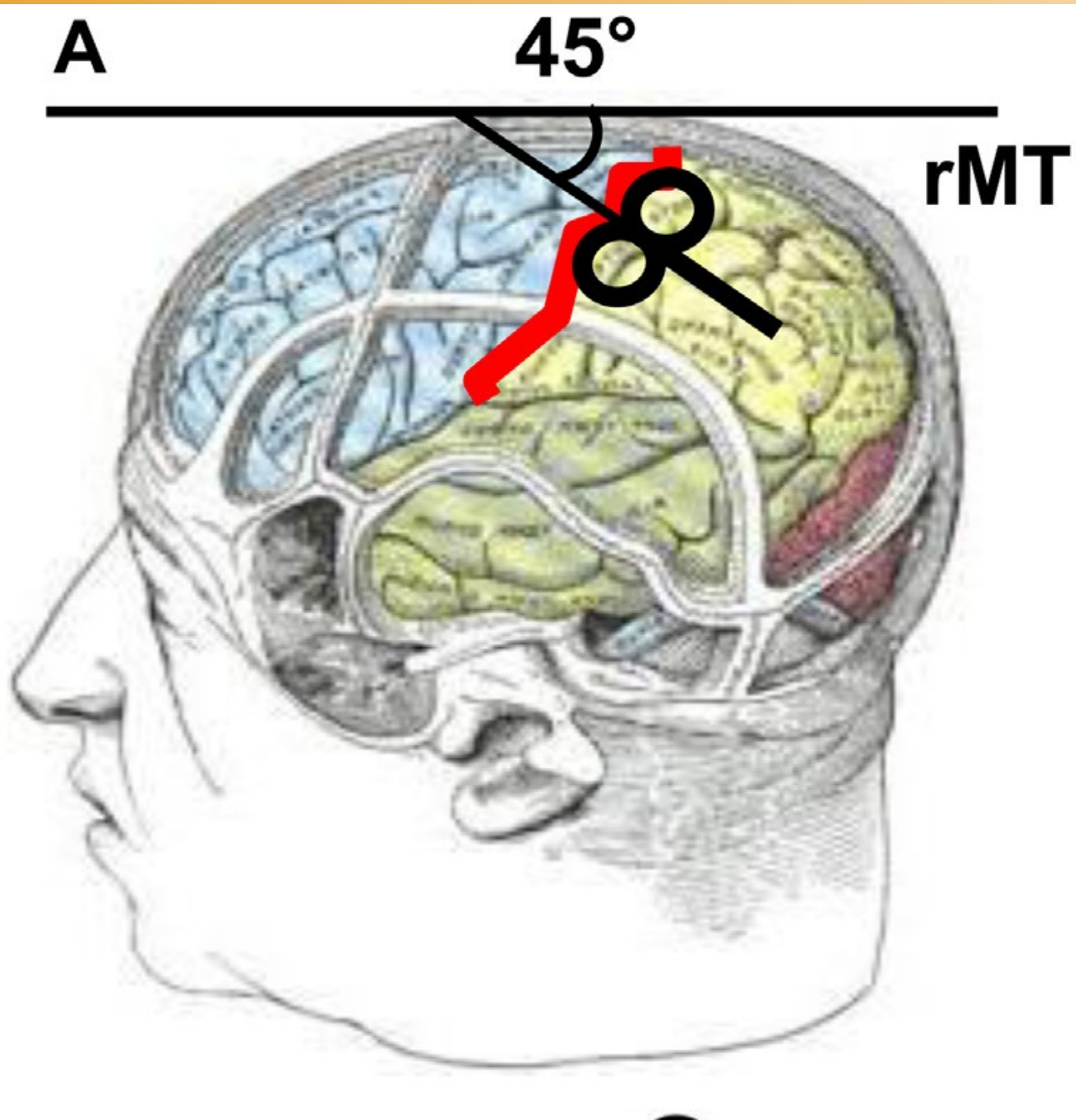

A
45°
rMT

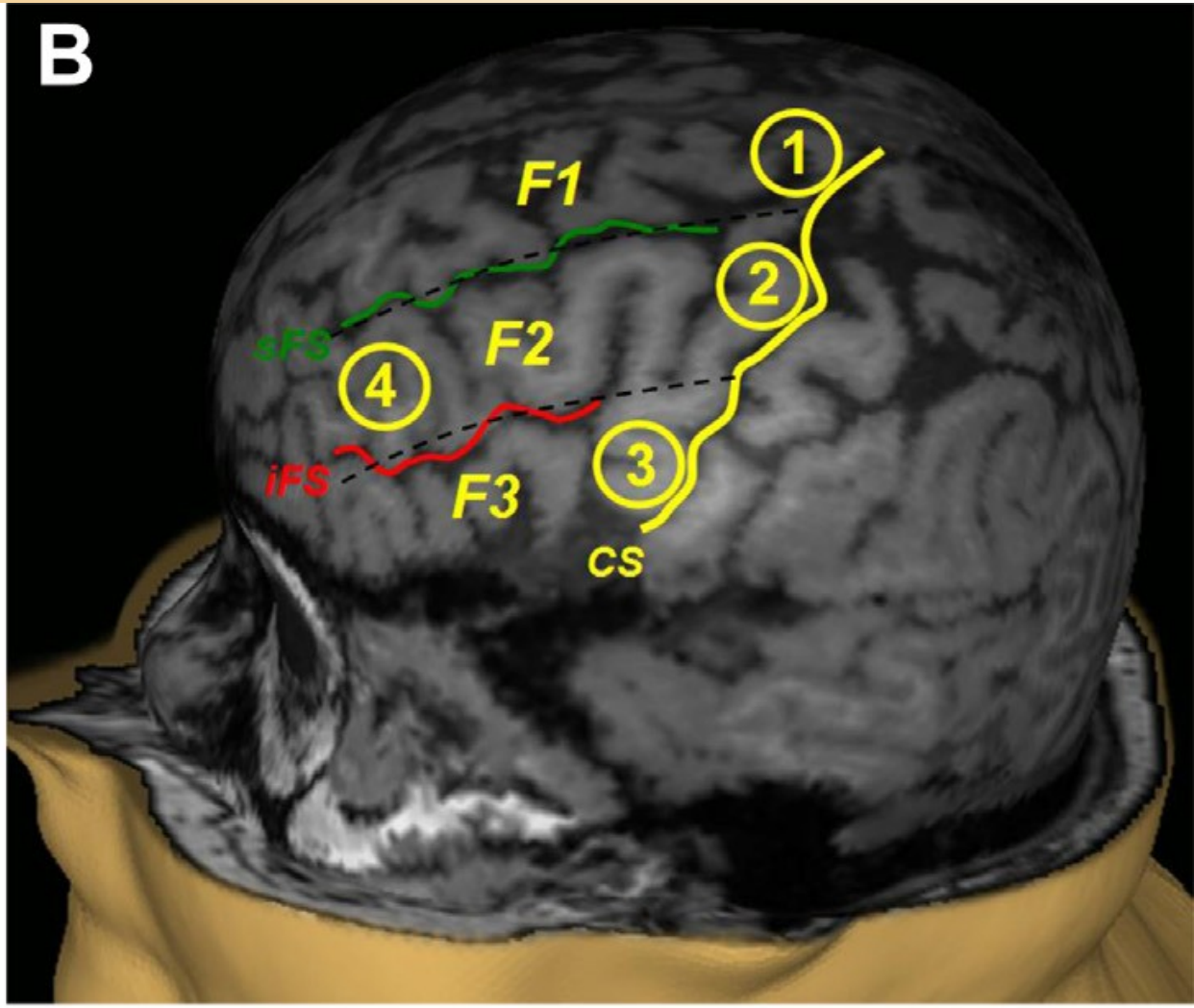

B
F1
aFS
F2
iFS
F3
CS
1
2
3
4


C
T1
T2
T3
T4

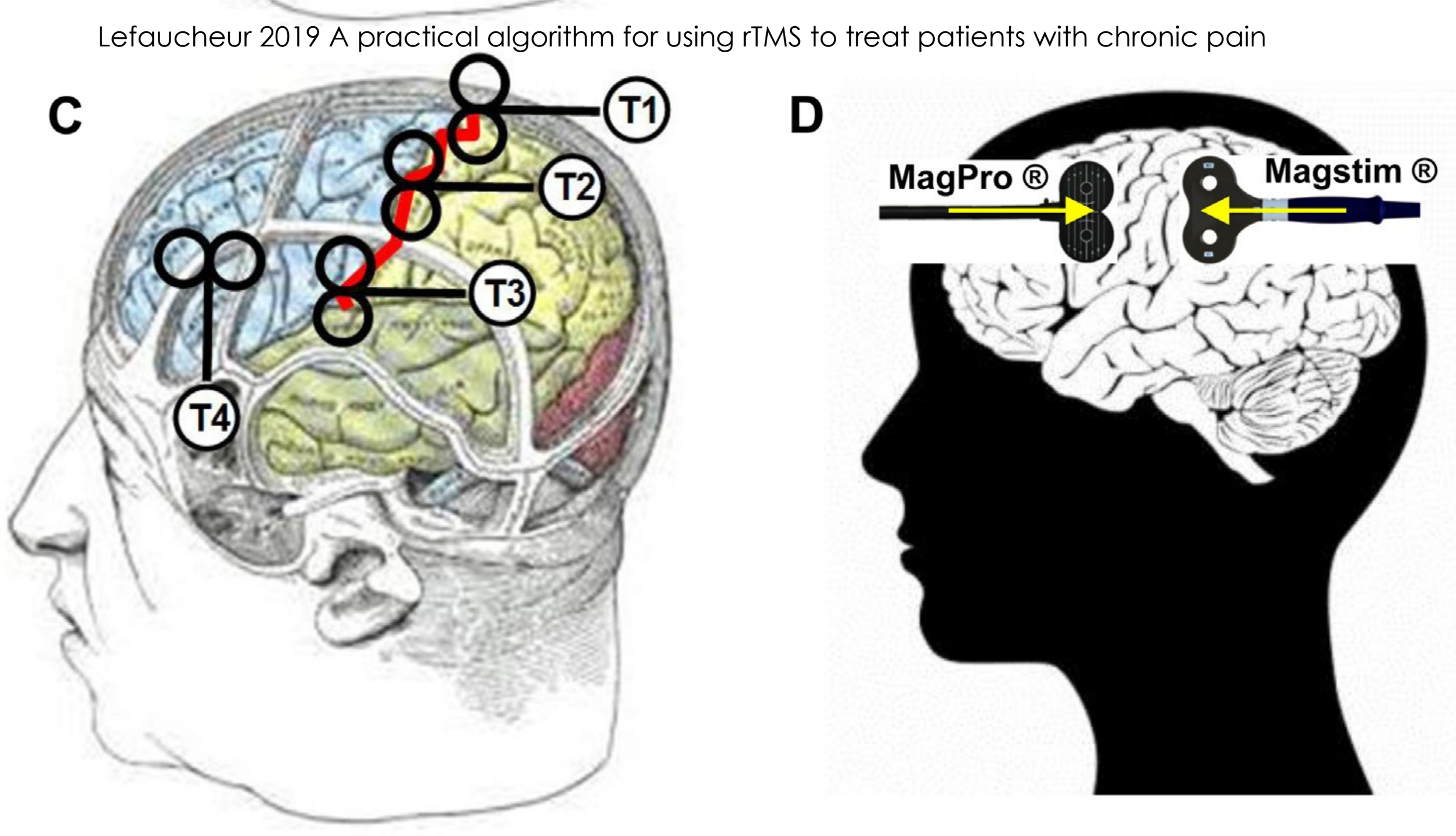

D
MagPro ®
Magstim ®

Lefaucheur 2019 A practical algorithm for using rTMS to treat patients with chronic pain



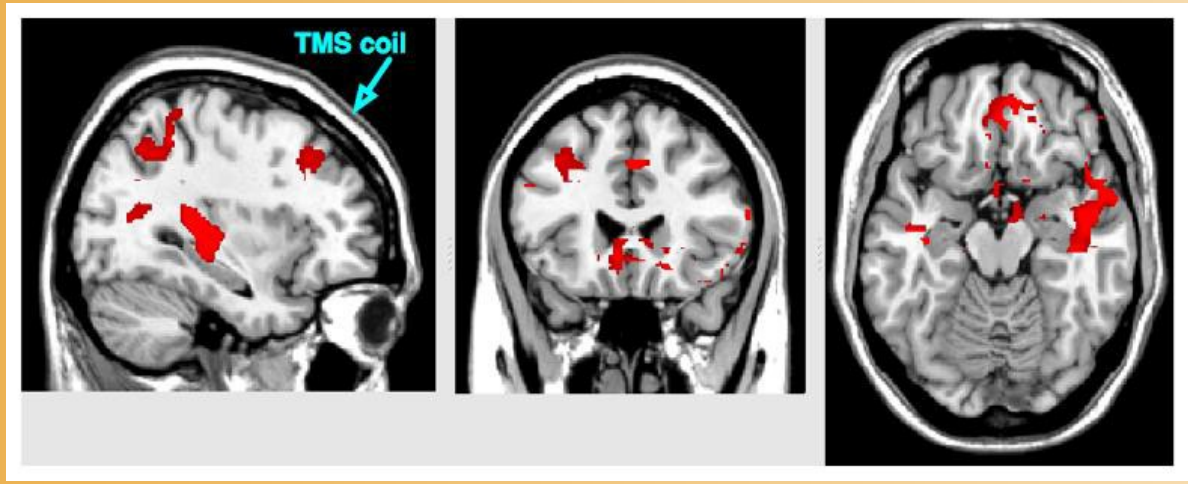


Lefaucheur 2019 A practical algorithm for using rTMS to treat patients with chronic pain



Acute Effects

- Induces electric current
- Depolarizes neurons in superficial cortex
- Leads to local and trans-synaptic changes in brain activity



Example

- **Left prefrontal TMS**
- **22 depressed individuals**
- **Activation demonstrated at site of stimulation and also at synaptically connected cortical and subcortical regions**

Li X, et al. *Biol Psychiatry*. 2004;55(9):882-890. Teneback CC, et al. *J Neuropsychiatry Clin Neurosci*. 1999;11(4):426-435.

Contraindications & Risks

TMS SAFETY

Contraindications

TMS SAFETY

1. History of Seizures/ epilepsy

2. Metal in Head (bullets etc)

TMS SAFETY

SAFETY

TMS

SAFETY

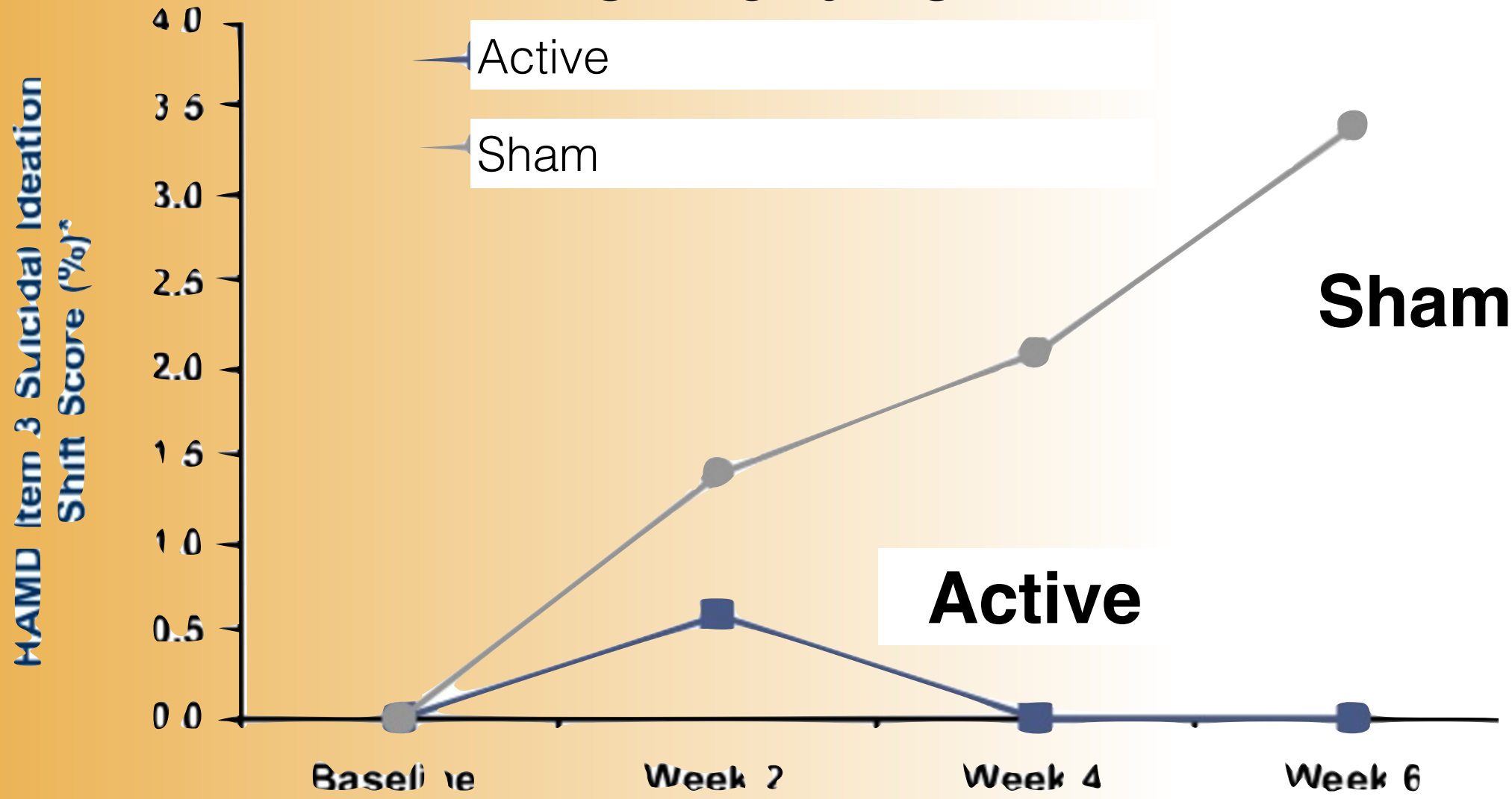
SAFE

- seizures (1/30,000)
- headache .
- stimulation site discomfort
- stimulation site twitching
- <5% of patients discontinued due to adverse events

TMS SAFETY

ECT	TMS
• General Anesthesia	No Anesthesia
• Seizure	No Seizure
• Memory Impairment	Memory **Improvement**
• Inpatient	Outpatient - drive to & from

No Evidence TMS Causes Suicidal Ideation or Behavior



TMS

SAFETY

No Systemic Side Effects

- no weight gain,
- no sexual dysfunction,
- no nausea,
- no dry mouth
- no sedation
- no urinary retension
- No adverse effect on cognition

TMS SAFETY

Tolerability

TMS SAFETY

O'Reardon (2007)

N = 301 patients with refractory depression randomized to active or sham 5X/week -10 pulses/ sec, 120% of motor threshold, 4 – 6 weeks.

TMS was <u>well tolerated,</u> low dropout rate (4.5% in study, 1.5% in practice)

mild headache

transient scalp discomfort or pain.

TMS SAFETY

Adverse Effects

RATIONALE FOR DLPFC

- Based on the hypofrontality found in neuroimaging studies it was rational to use a fo
  stimulation technique to activate neural circuitry in the DLPFC

	Initial Cost	Per Session Fee	Ease of Use	Protocol Flexible ?	Coil Flexible ?	Focal?	Sz	After 100 Patients	Number to break even
NeuroStar	80	100	+	-	-	+	1/ 30,000	820K	9
BrainsWay	180	70	++	?	-	No	1/ 1,000	940K	18
MagStim	60	0	++	+	++	+	1/ 30,000	1,140K	5
MagPro	70	0	+	+	++	+	1/ 30,000	1,130K	6
NeuroSoft	45	0	+++	+	+	+	1/ 30,000	1,195K	4

Overview

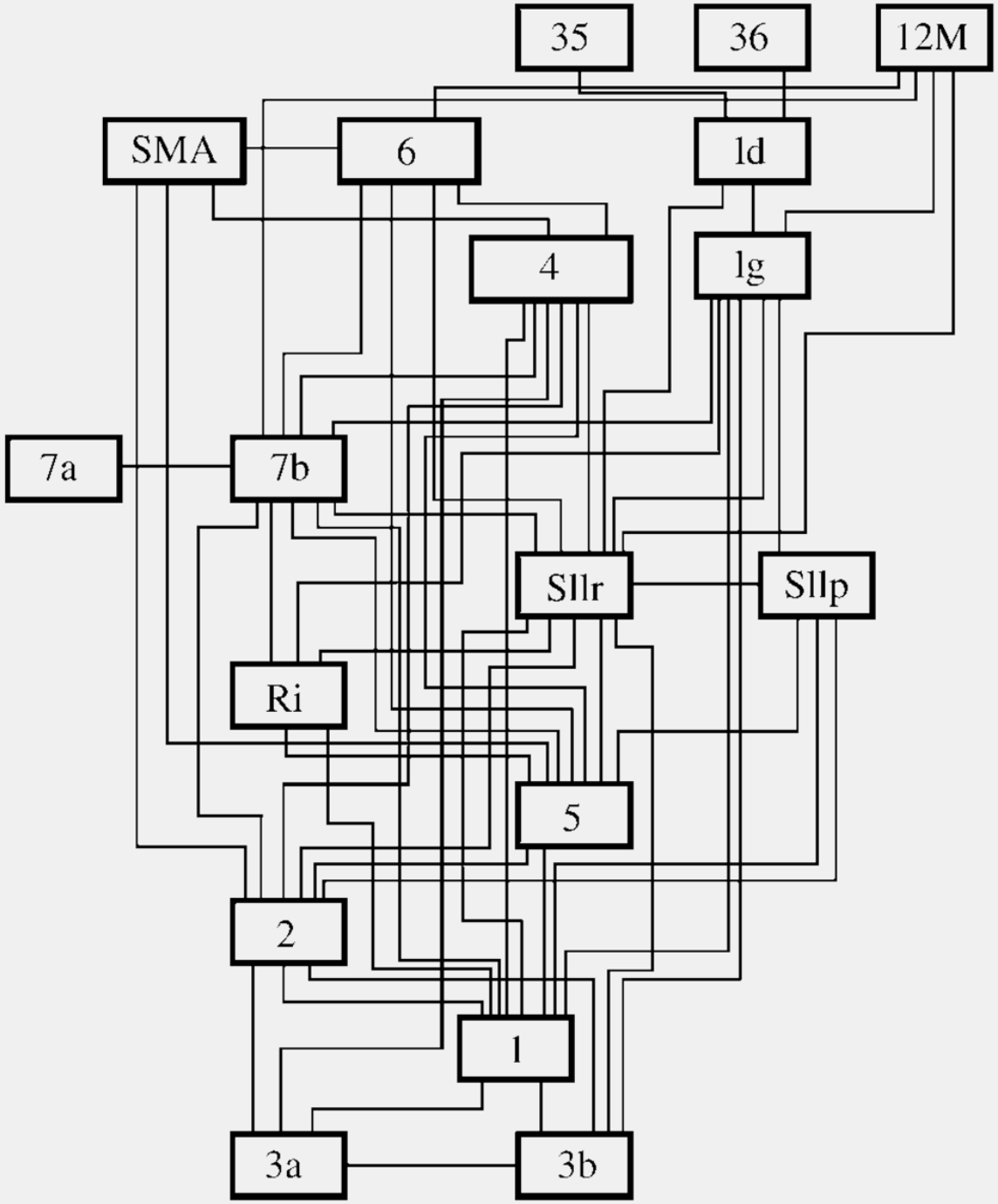
BASICS TMS
BASICS NEUROANATOMY

Overview

STROKE
TBI

Overview

TBI DEFINED BY GASCOW COMA SCALE
1
HOW ELSE?


35
36
12M
SMA
6
ld
4
lg
7a
7b
SIlr
SIlp
Ri
5
2
1
3a
3b

TMS When it hasn't yet helped

DIAGNOSIS
Stop TMS
Recheck Motor Threshold
Increase pulses to >3000
Adjust coil location - anterior, lateral, or both
Increase dose to >120% MT
Increase to >5 sessions per week
Switch to **right sided, low frequency** (1 Hz)

TMS DEVICES & SYSTEMS

The Procedure

TMS THE PROCEDURE

FIND WHERE

FIND HOW MUCH

FIND WHERE

TMS THE PROCEDURE

Hands On #1 Locate Stimulation Site

OPTIONS

1. **Motor Cortex +6.25cm ant**
2. **EEG 10-20**
3. **Beam Protocol**
4. **NeuroNavigation**

TMS THE PROCEDURE

How

1) **Put White Swim Cap on,** *mark center*
2) **Measure a) T-T, b) N-I & c) Circumference**
3) **Calculate: a) distance to the left,** *mark* **& b) from vertex towards it**

Where

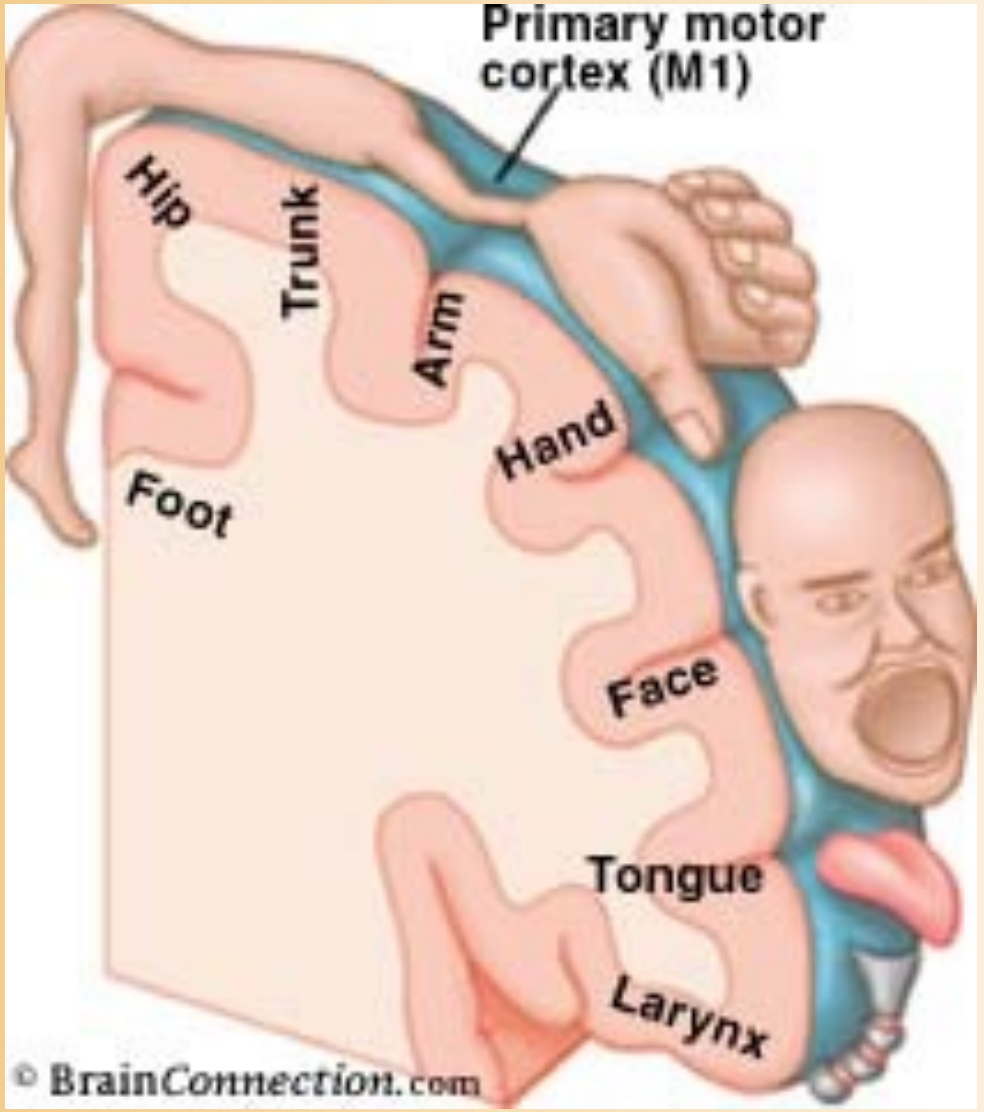
4) **Measure 6cm posterior to find M1 (motor cortex)**

How Much

5) **<u>Motor threshold</u> (MT) determination** *(what % does it require to move the muscles of the right hand?)*
6) **Place coil over DLPFC,** *mark coil location for future use*
7) **Begin Stimulation (at 80% of MT)**
8) **Monitor for discomfort & twitching**

TMS THE PROCEDURE

Motor Cortex



Code	Description
90867	1 Therapeutic Repetitive Transcranial Magnetic stimulation (TMS) **treatment**; initial, including 2 cortical mapping, 3 motor threshold determination, delivery and management (Report only once per course of treatment) (Do not report 90867 in conjunction with 95928, 95929, 90868, 90869)
90868	Subsequent delivery and management, per session
90869	Subsequent motor threshold redetermination with delivery and management

Guidelines Clinical TMS Society

Recommendations

Indicated Patient Population: The labeled indication for use for the TMS therapy states that, "**TMS therapy is indicated for the treatment of Major Depressive Disorder in adult patients who have failed to receive satisfactory improvement from prior antidepressant medication in the current episode.**"

1: TMS therapy is recommended as an **acute treatment for symptomatic relief** of depression in the indicated patient population.

2: TMS therapy is recommended for use as a subsequent option in patients who previously benefited from an acute treatment course and are experiencing a **recurrence** of their illness (continuation or maintenance).

3: TMS therapy can be administered **with or without** the concomitant administration of antidepressant or other psychotropic **medications**.

4: TMS therapy can be used as a continuation or **maintenance treatment** for patients who benefit from an acute course.

5: TMS therapy can be reintroduced in patients who are **relapsing** into depression after initially responding to TMS treatment.

TMS OVERVIEW

DLPFC

Don’t Believe The Hype/FUD

Do you know...?

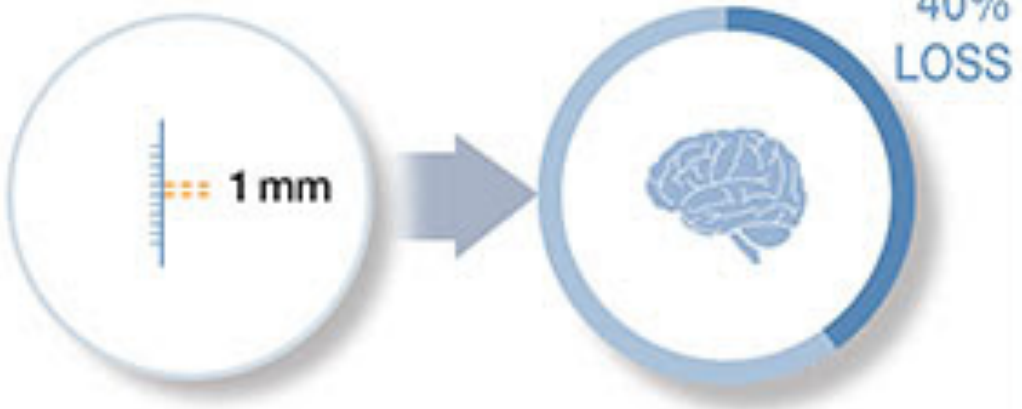
The smallest movements can result in a dramatic loss of the prescribed TMS dose

FIRST DIMENSION

1mm is the equivalent of 3 grains of salt

Proximity to the head

Even 1 mm movement away from the head can result in 40% less of the TMS prescribed dose[1]



Larger movements result in even less stimulation[1]

Movement Off Head	Stimulation Volume
2 mm	70% loss
4 mm	98% loss

The dorsolateral prefrontal cortex (DLPFC) has consistently been implicated in cognitive control of motor behavior. There is, however, considerable variability in the exact location and extension of these activations across functional magnetic resonance imaging (fMRI) experiments. This poses the question of whether this variability reflects sampling error and spatial uncertainty in fMRI experiments or structural and functional heterogeneity of this region. This study shows that the right DLPFC as observed in 4 different experiments tapping executive action control may be subdivided into 2 distinct subregions-an anterior-ventral and a posterior-dorsal one based on their whole-brain co-activation patterns across neuroimaging studies. Investigation of task-dependent and task-independent connectivity revealed both clusters to be involved in distinct neural networks. The posterior subregion showed increased connectivity with bilateral intraparietal sulci, whereas the anterior subregion showed increased connectivity with the anterior cingulate cortex. Functional characterization with quantitative forward and reverse inferences revealed the anterior network to be more strongly associated with attention and action inhibition processes, whereas the posterior network was more strongly related to action execution and working memory. The present data provide evidence that cognitive action control in the right DLPFC may rely on differentiable neural networks and cognitive functions.

Cerebral Cortex November 2013;23:2677–2689
doi:10.1093/cercor/bhs256
Advance Access publication August 23, 2012

Is There "One" DLPFC in Cognitive Action Control? Evidence for Heterogeneity From Co-Activation-Based Parcellation

Edna C. Cieslik[1,2,3,4], Karl Zilles[1,2,5,6], Svenja Caspers[1,2], Christian Roski[1,2], Tanja S. Kellermann[1,2,3], Oliver Jakobs[1,3], Robert Langner[1,2,4], Angela R. Laird[7], Peter T. Fox[7] and Simon B. Eickhoff[1,2,4,5]

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The dorsolateral prefrontal cortex (DLPFC) has consistently been implicated in cognitive control of motor behavior. There is, however, considerable variability in the exact location and extension of these activations across functional magnetic resonance imaging (fMRI) experiments. This poses the question of whether this variability re-

example, the premotor and posterior parietal associative cortices (MacDonald et al. 2000; Koechlin et al. 2003).

In spite of the well-documented role of the DLPFC in regulating aspects of volitional behavior, studies investigating cognitive control had difficulties in delineating functional

More Lateral and Anterior Prefrontal Coil Location Is Associated with Better Repetitive Transcranial Magnetic Stimulation Antidepressant Response

Tal Herbsman, David Avery, Dave Ramsey, Paul Holtzheimer, Chandra Wadjik, Frances Hardaway, David Haynor, Mark S. George, and Ziad Nahas

Background: The left dorsolateral prefrontal cortex (DLPFC) is the most commonly used target for transcranial magnetic stimulation (TMS) in the treatment of depression. The "5-cm rule" is an empiric method used for probabilistic targeting of the DLPFC in most clinical trials. This rule may be suboptimal, as it does not account for differences in skull size or variations in prefrontal anatomy relative to motor cortex location. This study is a post hoc analysis of data from a large repetitive TMS (rTMS) trial in which we examined the variability of coil placement and how it affects antidepressant efficacy.

Methods: Fifty-four depressed subjects enrolled in a randomized, single-site trial received either active rTMS or sham for 3 weeks. Prior to treatment initiation, investigators placed vitamin E capsules at the point of stimulation and used a high-resolution magnetic resonance imaging (MRI) scan to image these fiducials relative to anatomy. We employed a semiautomated imaging-processing algorithm to localize the cortical region stimulated.

Results: Active TMS significantly reduced Hamilton Depression Rating Scale (HDRS) scores. A linear model for this improvement involving the coordinates of the stimulated cortex location, age, and treatment condition was highly significant. Specifically, individuals with more anterior and lateral stimulation sites were more likely to respond.

Conclusions: These results suggest that within the general anatomical area targeted by the 5-cm rule, placing the TMS coil more laterally and anteriorly is associated with improved response rates in TMS depression studies. Controlled studies testing this anatomical hypothesis are needed.

Enter Distance (Tragus to Tragus) in CM:

Enter Distance (Nasion to Inion) in CM:

Enter Head Circumference in CM:

Quit

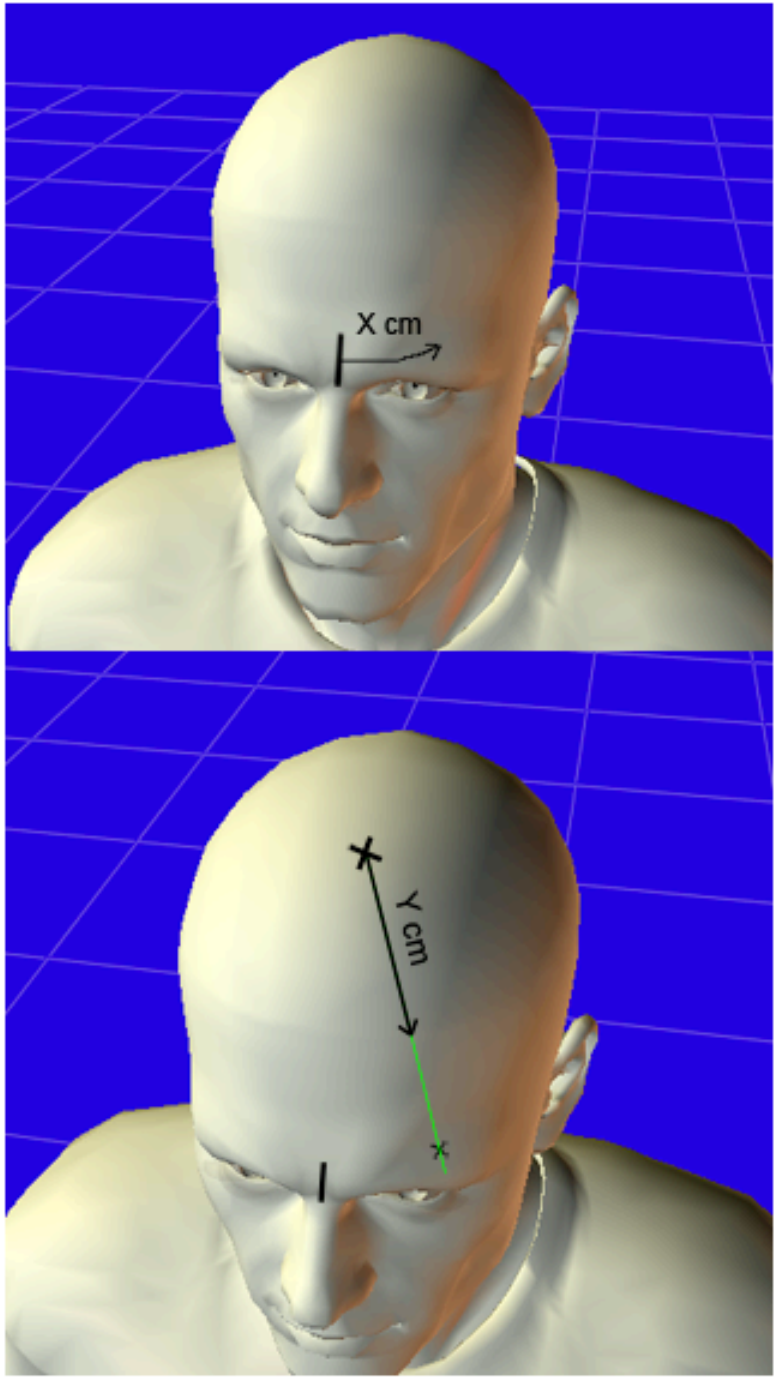
Calculate

Distance along cricumference from midline (X):

?

Distance from Vertex in CM (Y):

?



TMS OVERVIEW

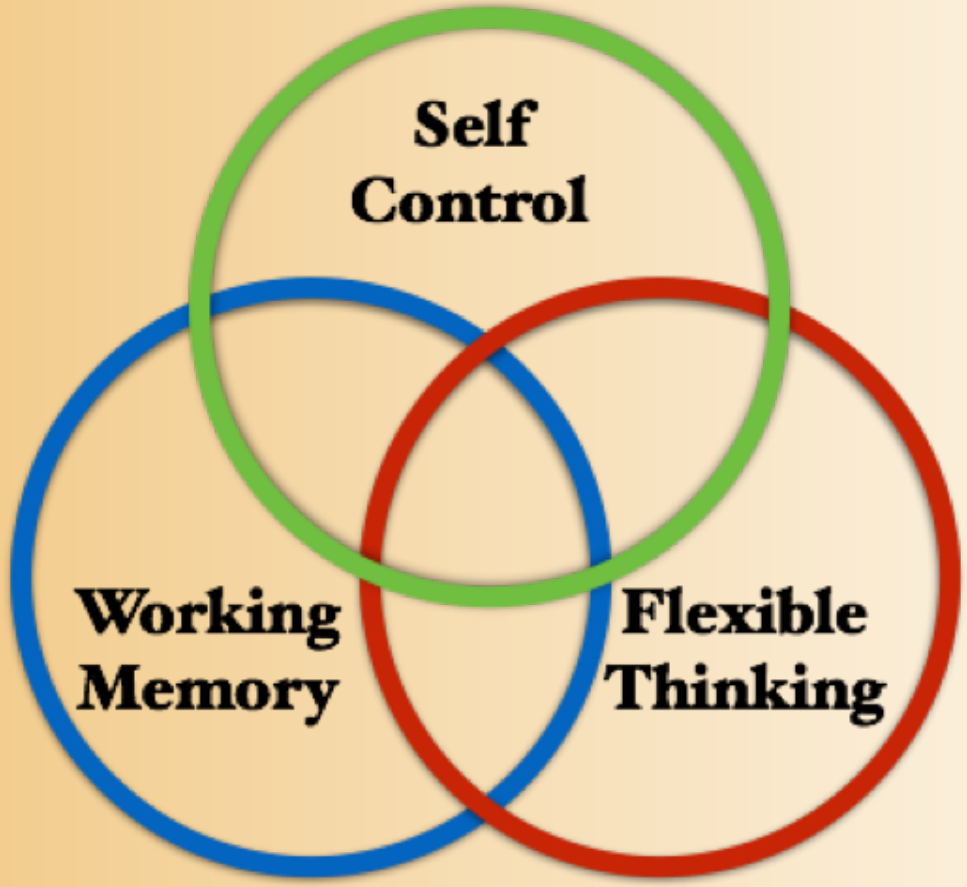
DLPFC

why DLPFC?

TMS OVERVIEW

DLPFC

1) It has lower activity in Depression & Chronic Pain
2) DLPFC inhibits SGC (BA25) which is overactive
3) Stimulating DLPFC improves Executive Function



Executive Function

TMS OVERVIEW

DLPFC

why DLPFC?

TMS OVERVIEW

DLPFC

why DLPFC?

J Neurosci. 2014 Jul 30;34(31):10298-310. doi: 10.1523/JNEUROSCI.4105-13.2014.

Connectivity strength of dissociable striatal tracts predict individual differences in temporal discounting.

1, 2, 3, 4.

Lpfc

Striatum

SCA

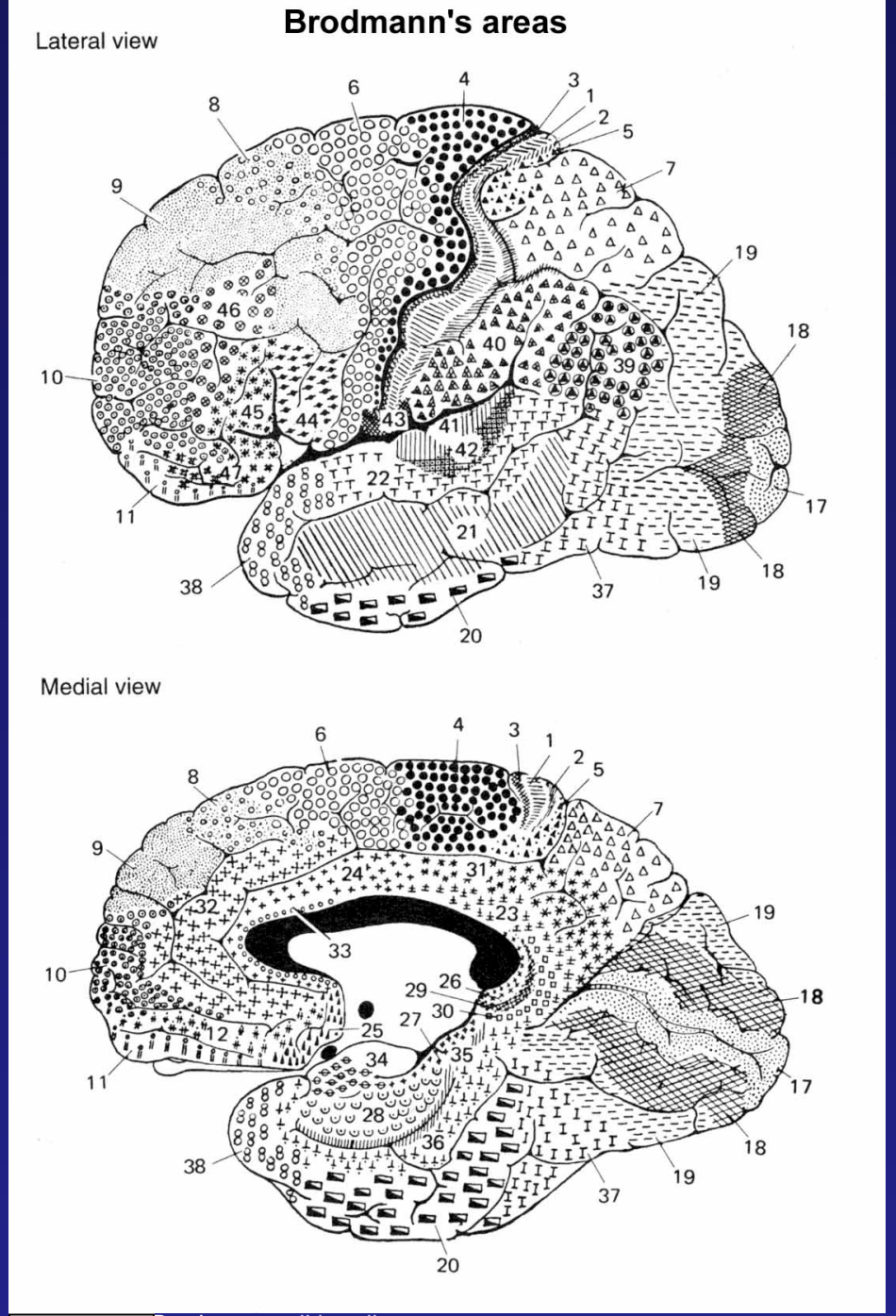
- **Structural and functional connectivity between striatum and lateral prefrontal cortex** was associated with increased *patience*,
- whereas connectivity between subcortical areas and striatum was associated with increased *impulsivity*

Switch to bilateral: left high-frequency and right low-frequency
Switch to alternating sessions of left high-frequency and right high- frequency
Add or increase medications
Add adjunctive therapy: **phototherapy**, CBT, **biofeedback**, exercise, **nutritional supplements**, etc.

Chapter PRESENTATION

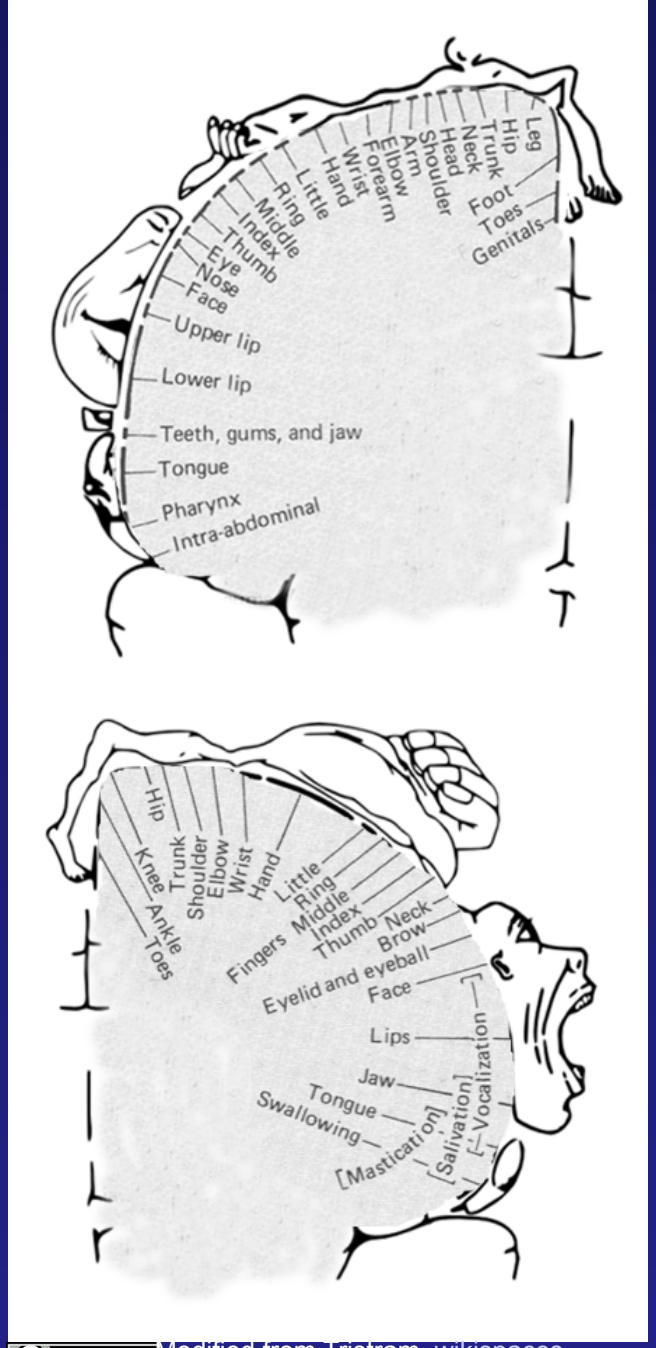
Section

BODY



In a paper published in 1909, Brodmann identified more than 40 cortical areas based on cellular and laminar histology of cerebral cortex.

This is the most widely reproduced figure in the fields of neurology and neuroanatomy. Brodmann's nomenclature is still used today, e.g., area 17 is primary visual cortex.



 Modified from Tristram, wikispaces

The primary sensory and motor areas of the cerebral cortex are precisely topographically organized. This topographic organization reflects the organization of the ascending sensory pathways and nuclei within the dorsal thalamus as well as the descending motor pathways.

These topographic "maps" are distorted, reflecting sensory specializations of the periphery, such as the fine somatosensory discrimination of the hands and peri-oral regions.

The organization of primary cortical areas are species-specific and reflect the specialized use of the sensory and motor periphery.

Tabulated data on the different types of cortex:

neocortex (new cortex) - 6 layers

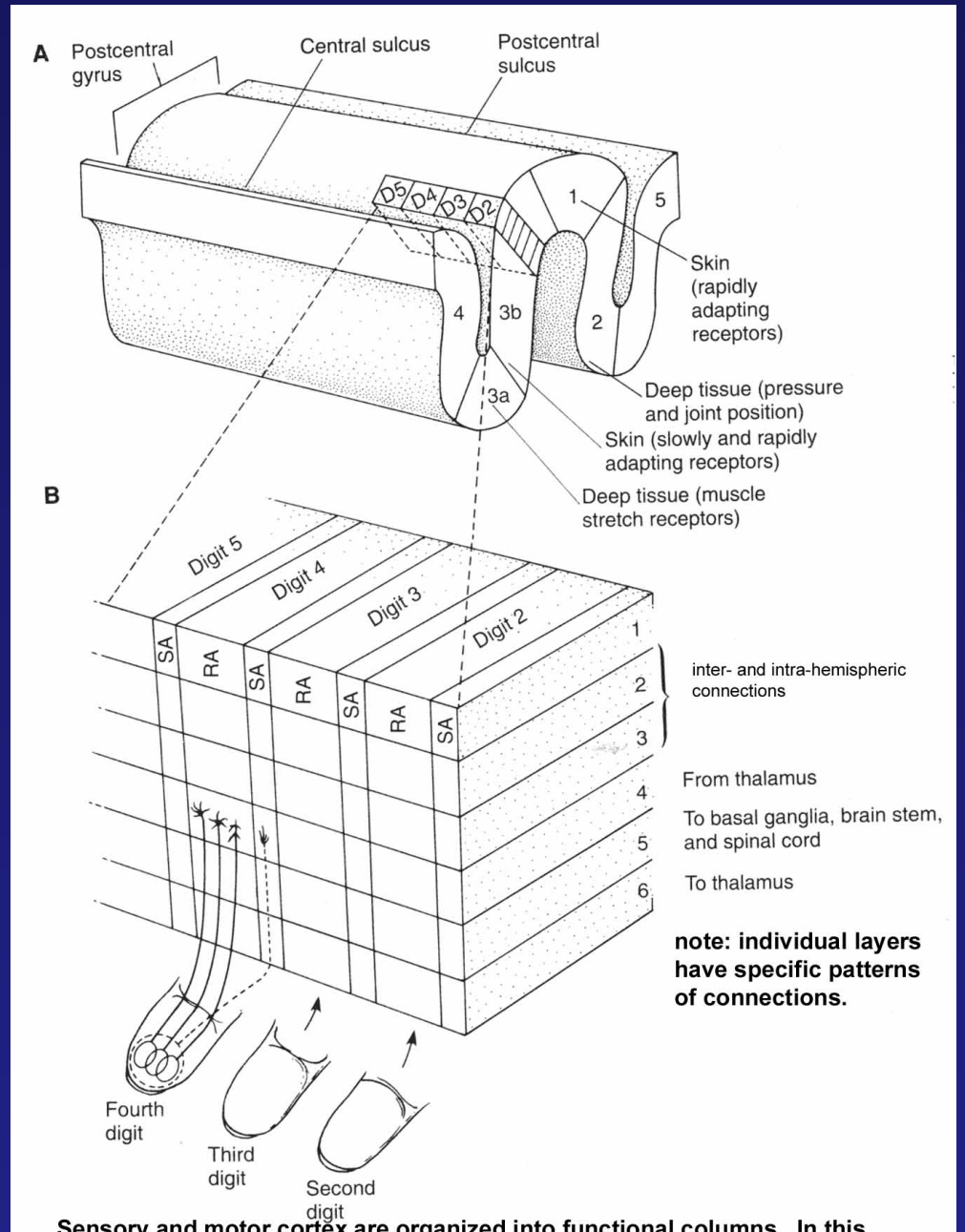
- a. ideotypic cortex - 1° motor and sensory cortex
- b. homotypic cortex - association areas
  1. unimodal association cortex -
  2. multimoldal association cortex -

mesocortex (middle cortex) - 3-6 layers - related to limbic system -

- a. cingulate gyrus
- b. parahippocampal gyrus

allocortex (other cortex) - 3 layers

- **a. archicortex - hippocampal formation**
- **b. paleocortex – piriform cortex**

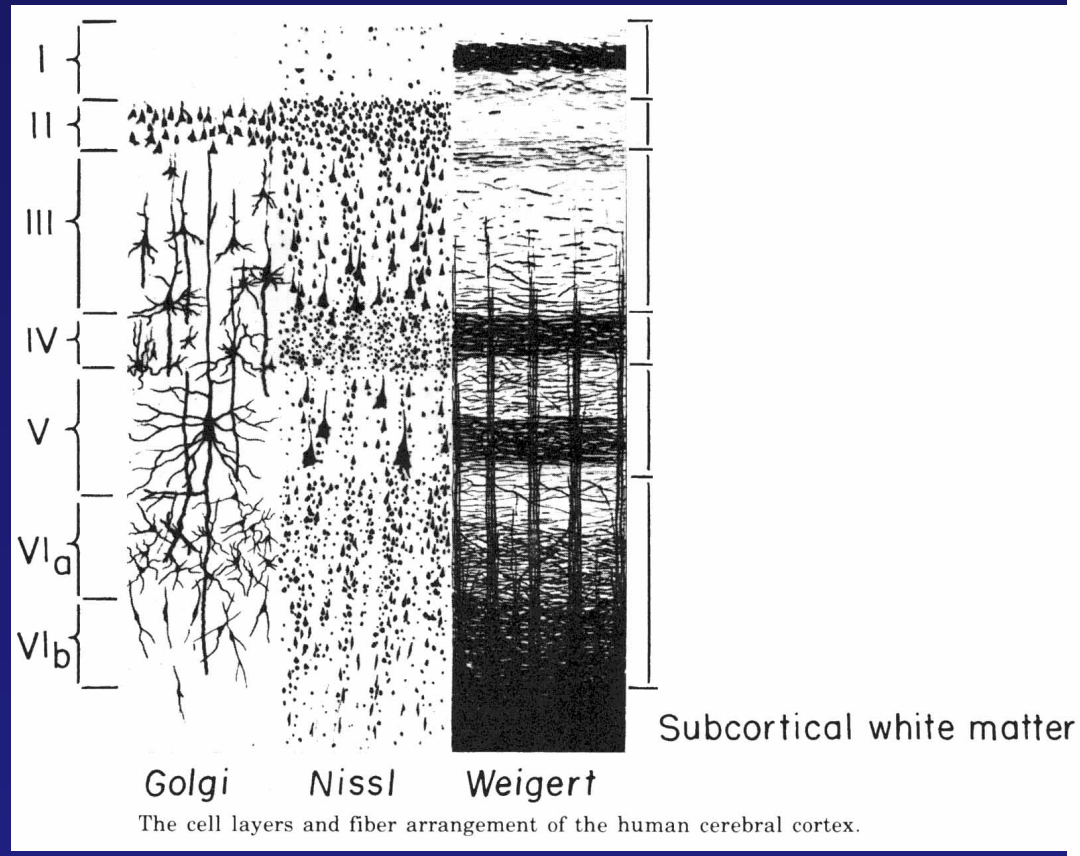


Sensory and motor cortex are organized into functional columns. In this example all neurons in a vertical segment (column) of cortex receive information from the same receptive field.

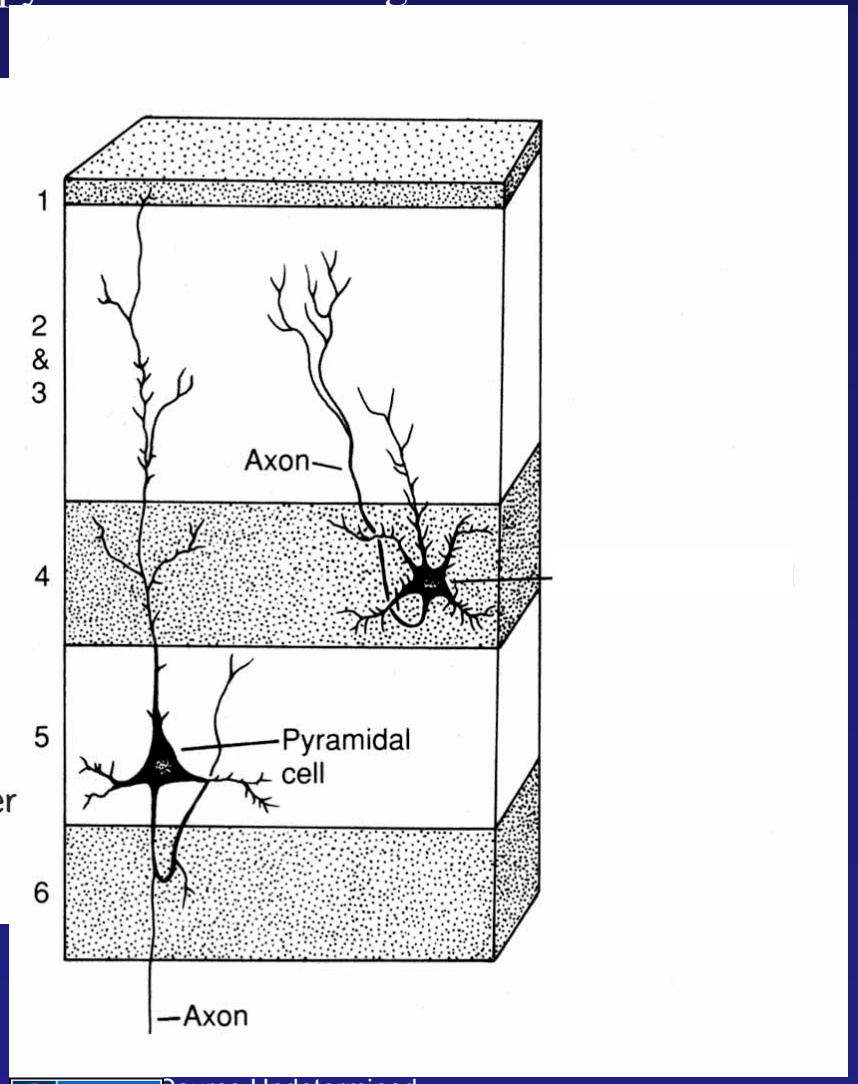
In primary sensory areas, each cortical neuron has a receptive field that corresponds to a location on the sensory sheet (body surface in this instance).

Sensory ‘maps’ extend throughout the depth of the cortex and are functionally organized based on the specificity of the receptors.

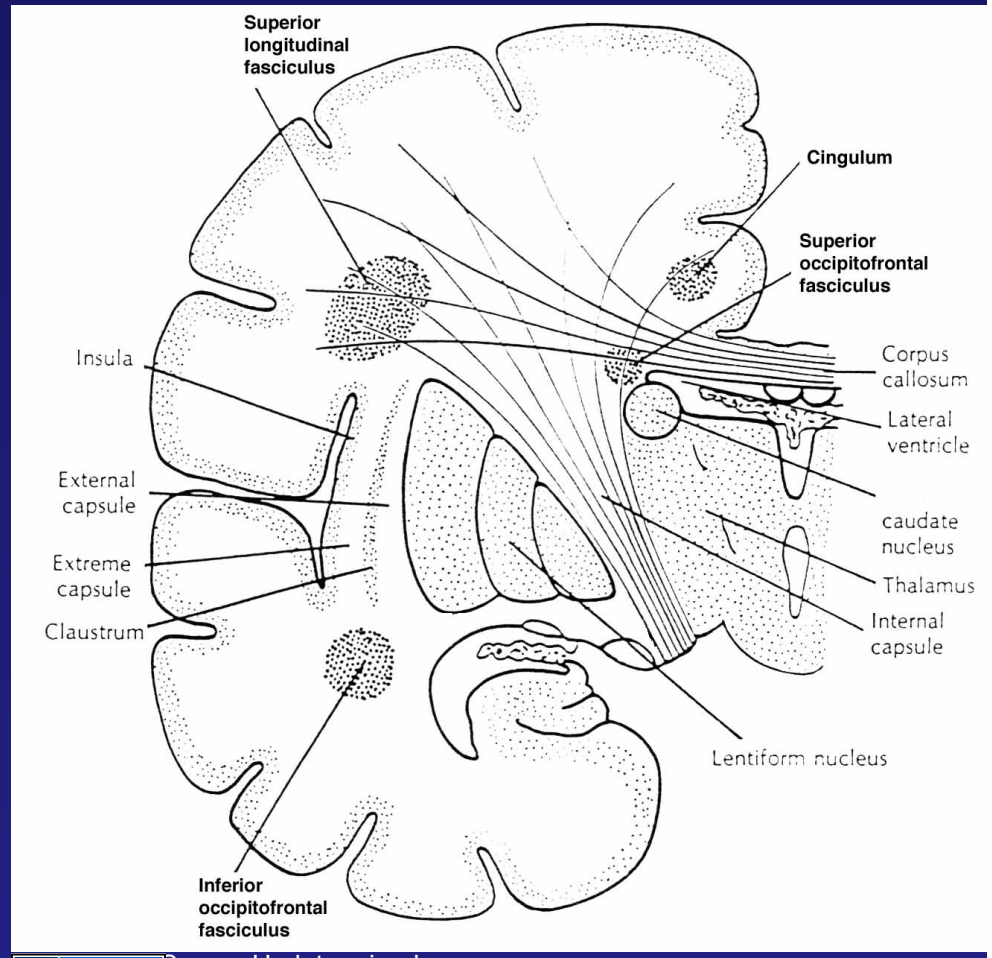
Neocortex constitutes approximately 90% of all cortex and contains 6 identifiable cellular layers. The major neuronal types in neocortex are the pyramidal cells and granule cells.

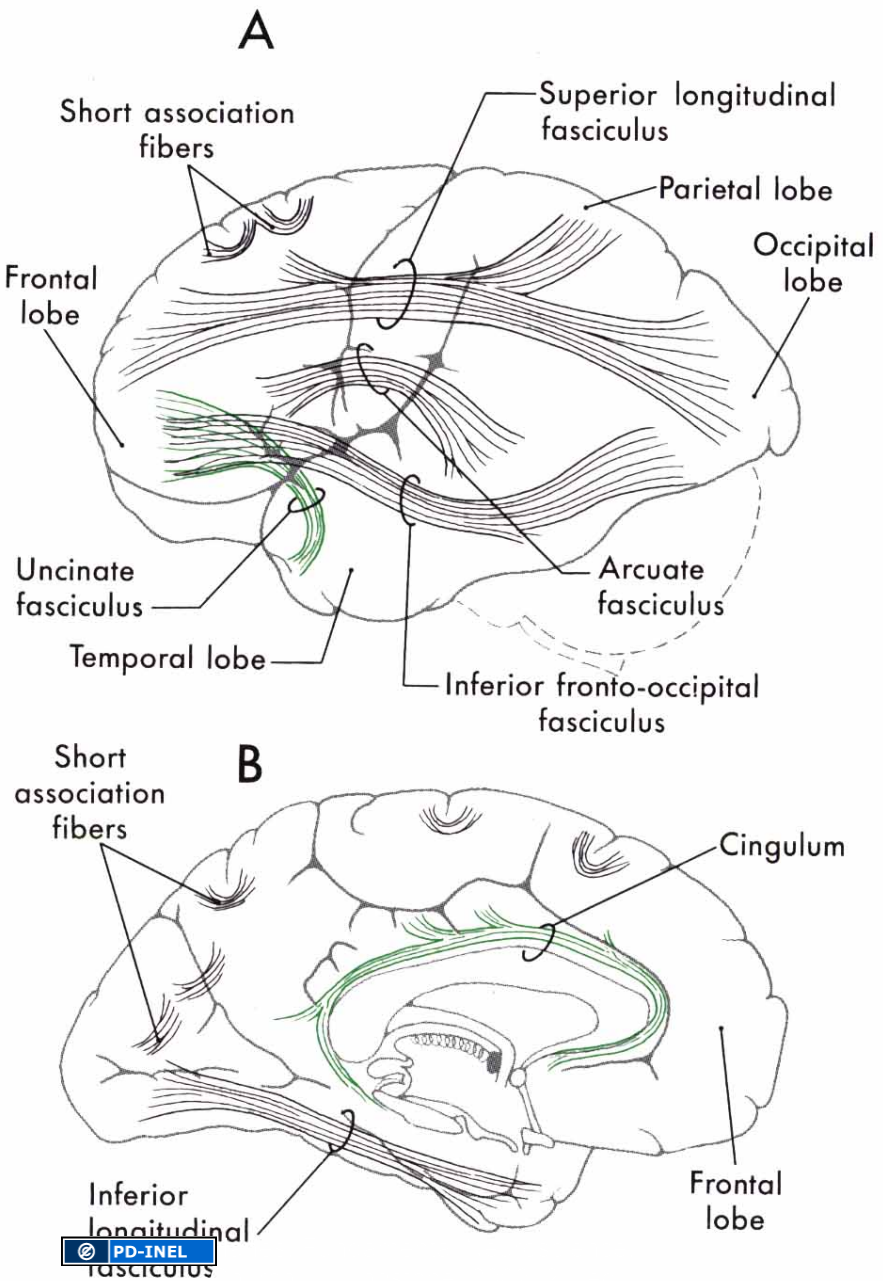


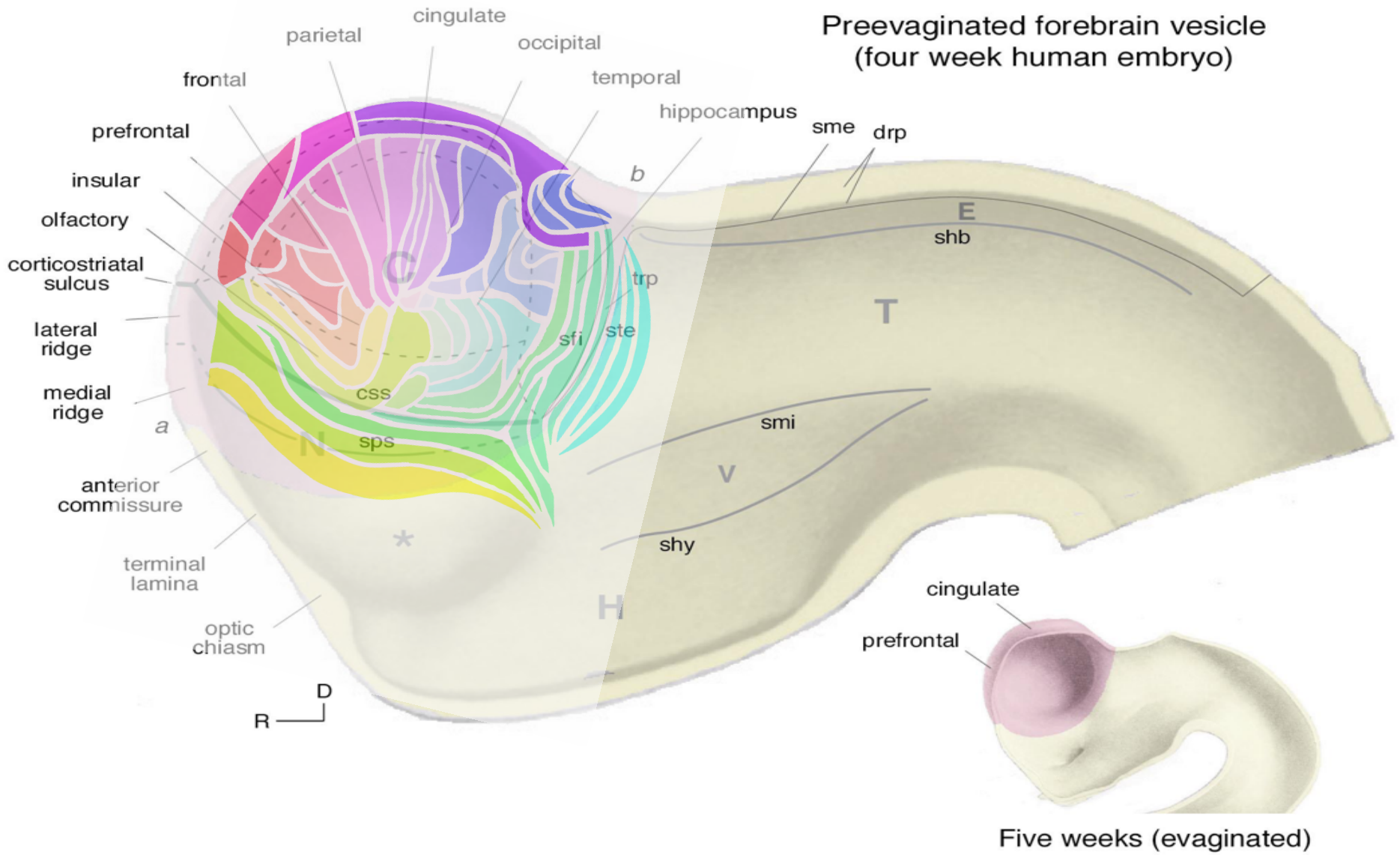
The cell layers and fiber arrangement of the human cerebral cortex.



Layer 4 is the recipient zone of thalamocortical axons. Layers 3, 5 and 6 are the output layers, sending axons to other cortical or subcortical targets. Layer 5 is the principal output layer to subcortical targets.



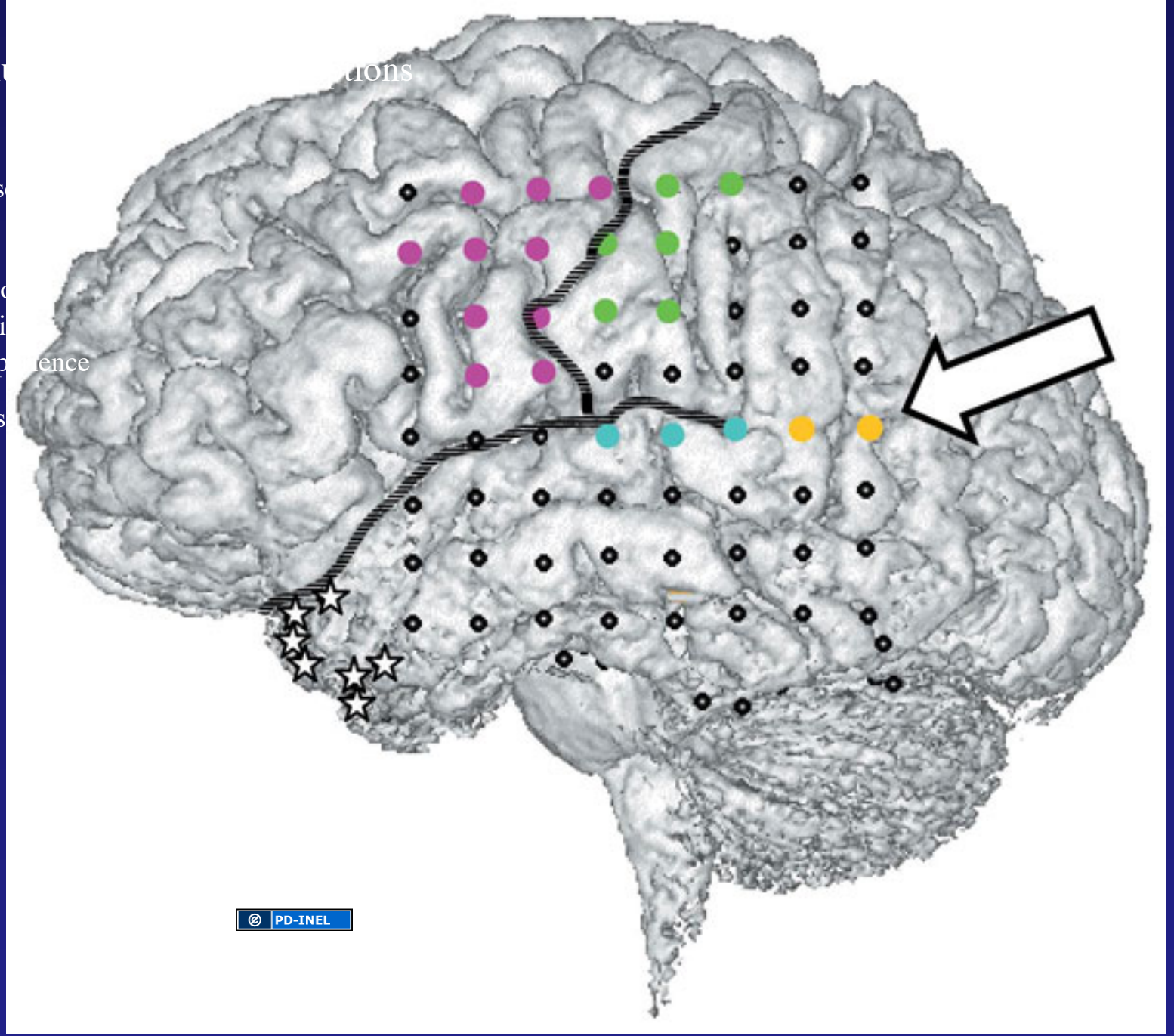



Preevaginated forebrain vesicle
(four week human embryo)
cingulate
parietal
occipital
frontal
temporal
hippocampus
prefrontal
insular
olfactory
corticostriatal sulcus
lateral ridge
medial ridge
anterior commissure
terminal lamina
optic chiasm
sme
drp
b
E
shb
C
trp
T
sfi
ste
css
smi
a
N
sps
V
shy
*
H
D
R
cingulate
prefrontal
Five weeks (evaginated)

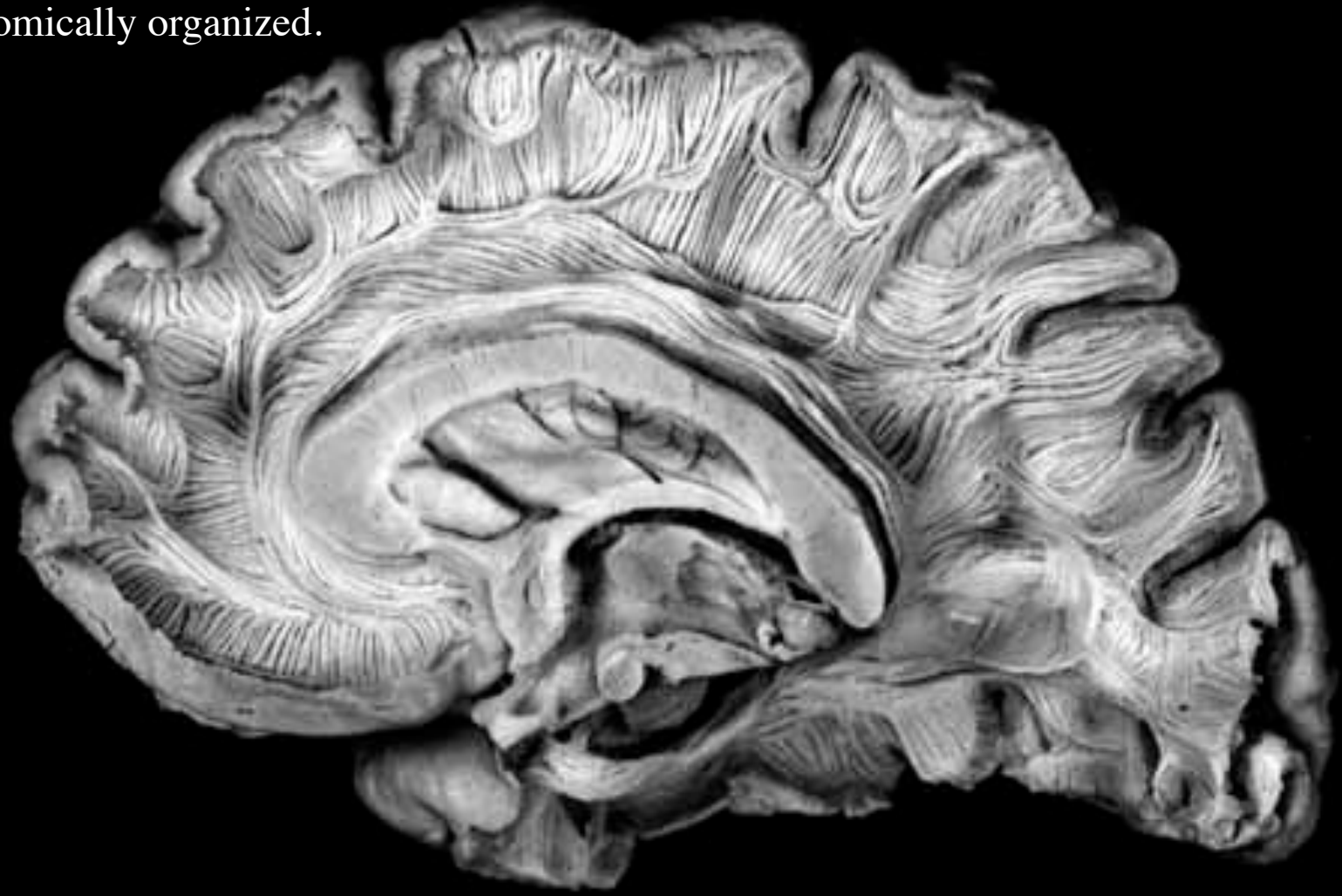
Stimulating illu tions

behavioral respons

- movement
- somatic sensati
- auditory sensati
- out-of body exp ence
- epileptic focus



Much of the cerebral hemispheres is occupied by subcortical white matter, which is anatomically organized.



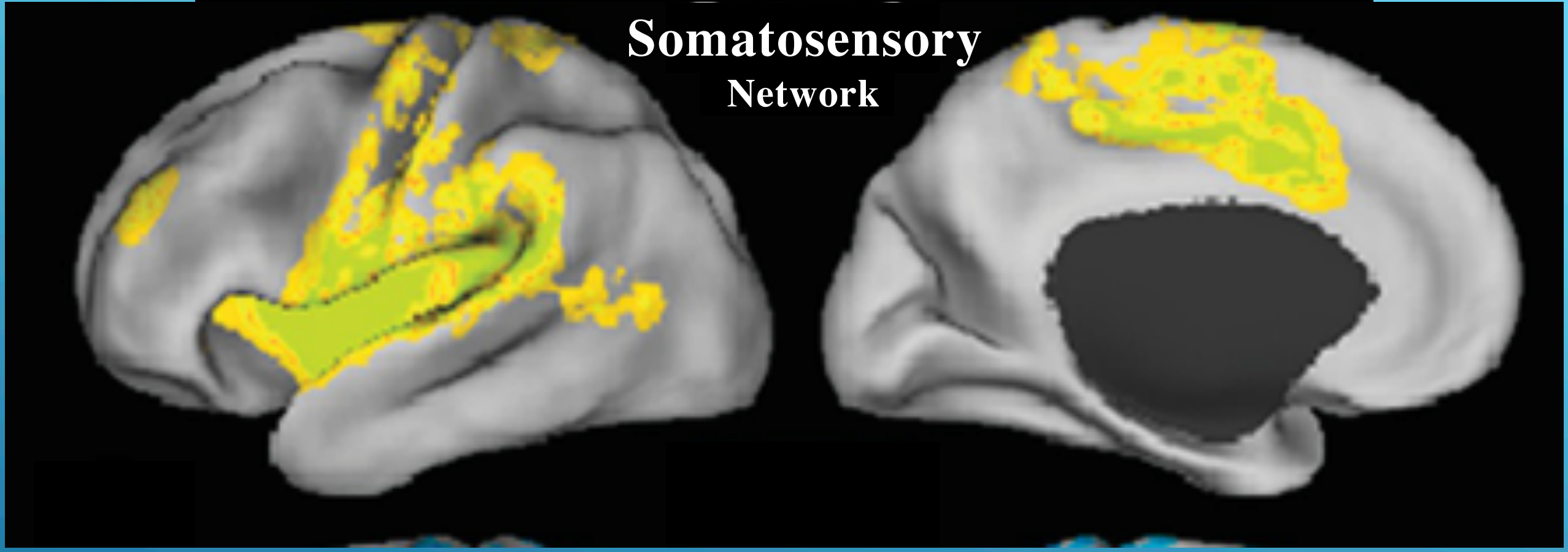
There are three types of fibers in the subcortical white matter:

1) projection fibers - leave the hemisphere for subcortical targets

2) **commissural fibers** - interconnect the two hemispheres, L-R and R-L

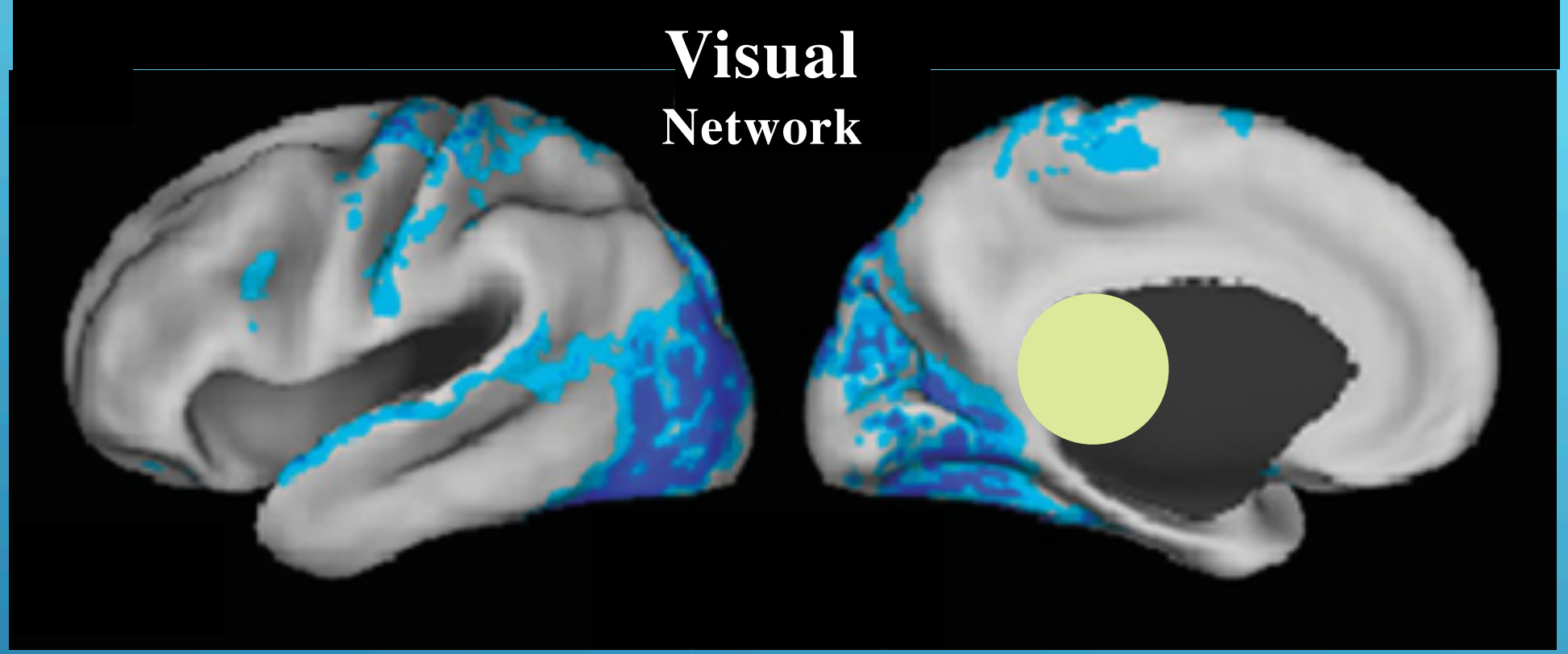
3) **association fibers** (2 types) - interhemispheric connections, L-L and R-R

Somatosensory Network

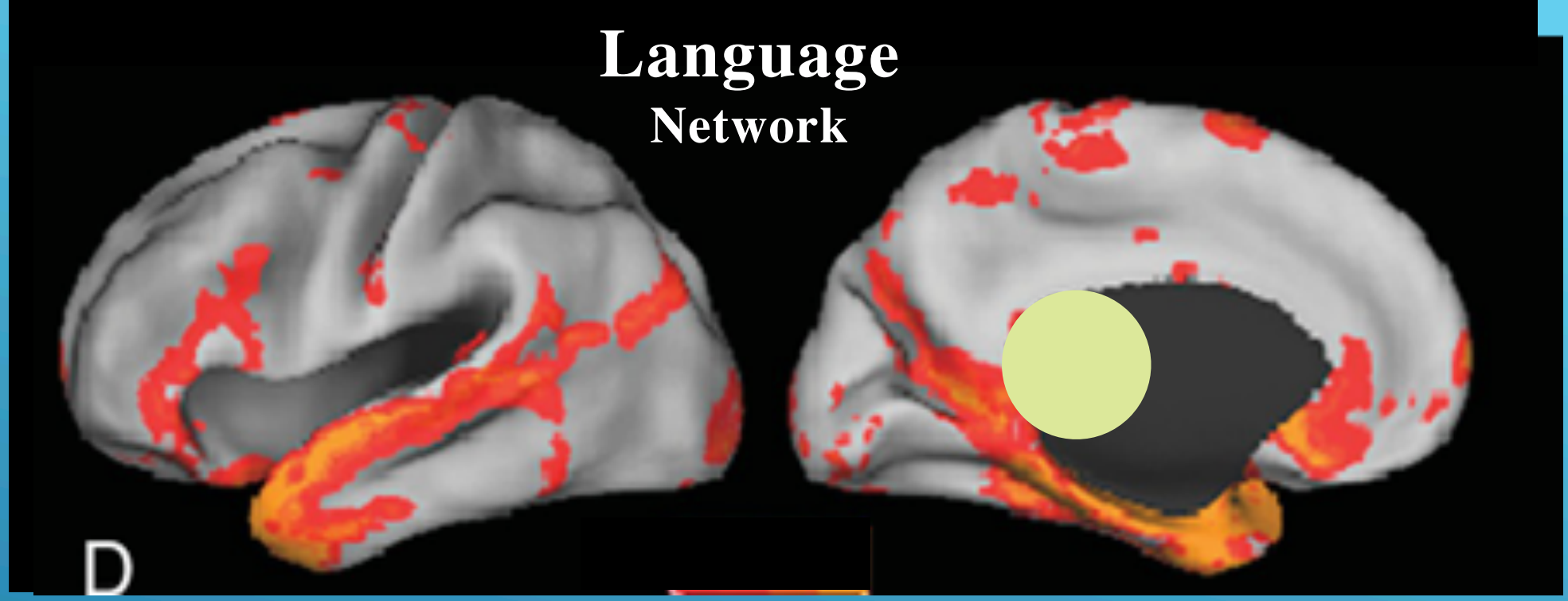


Several other RSNs have been identified. The **somatosensory network**, studied first by Biswal et al,1 includes primary and higher order motor and sensory areas (Fig 1B).

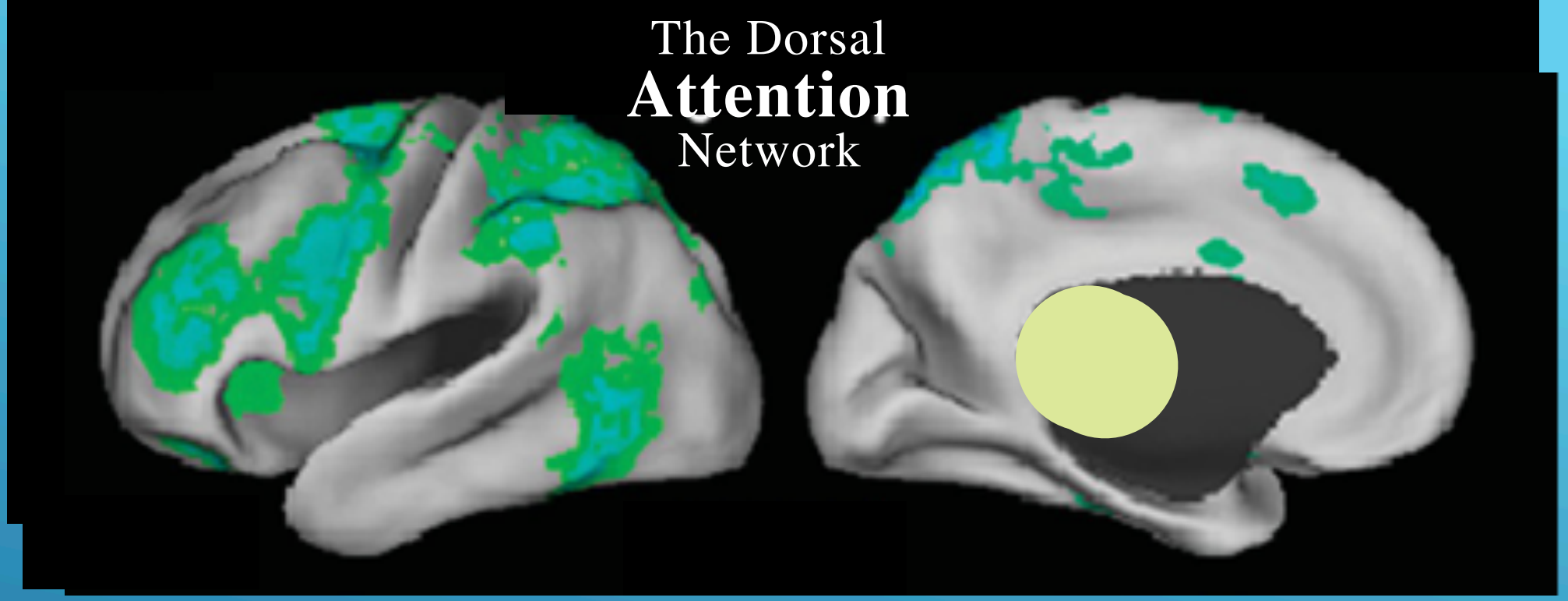
Visual Network



The visual network is highly consistent across various studies and spans much of the occipital cortex (Fig 1C).2-6



An auditory network consisting of the Heschl gyrus, the superior temporal gyrus, and the **posterior insula** has been ident

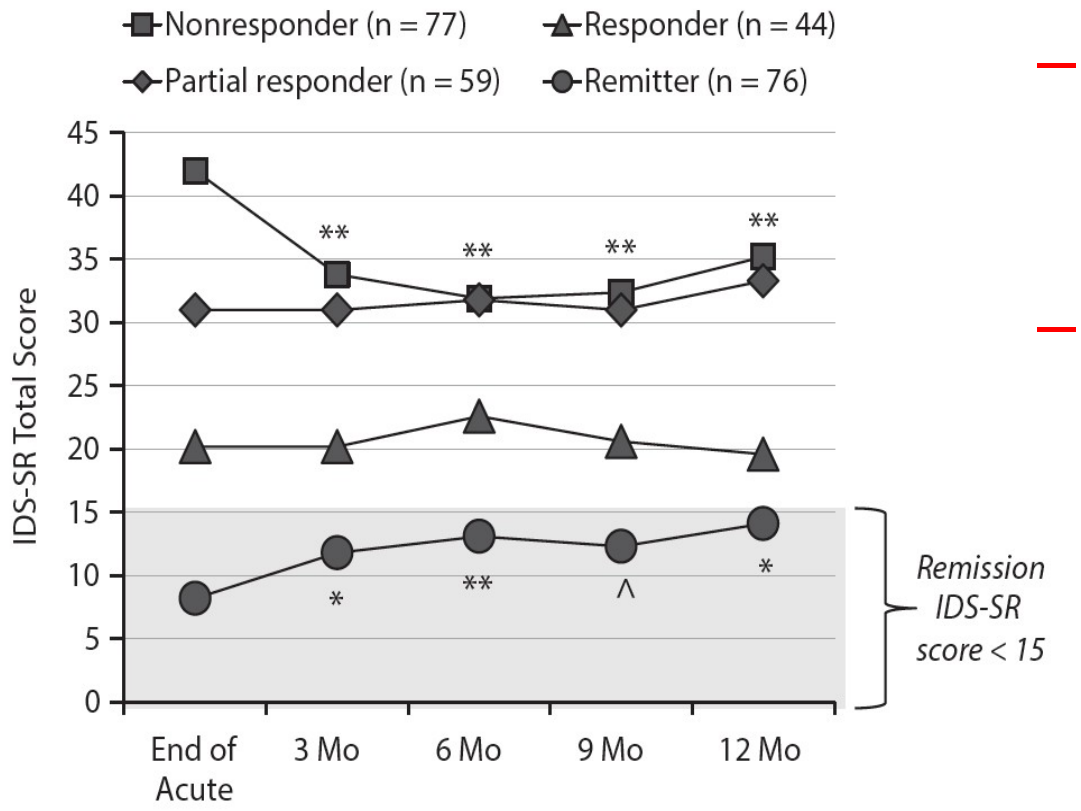


RSNs involved in **attentio**nal modulation and **cognitive control** have also been identified. Two networks identified by using both RS-fMRI and task-based fMRI include the dorsal and ventral attention networks.4,6,17,18 The dorsal attention network (Fig 1E) includes the intraparietal sulcus and the frontal eye field and is involved in the executive control of attention.

How effective is TMS in Practice?

- Dunner et al 2014

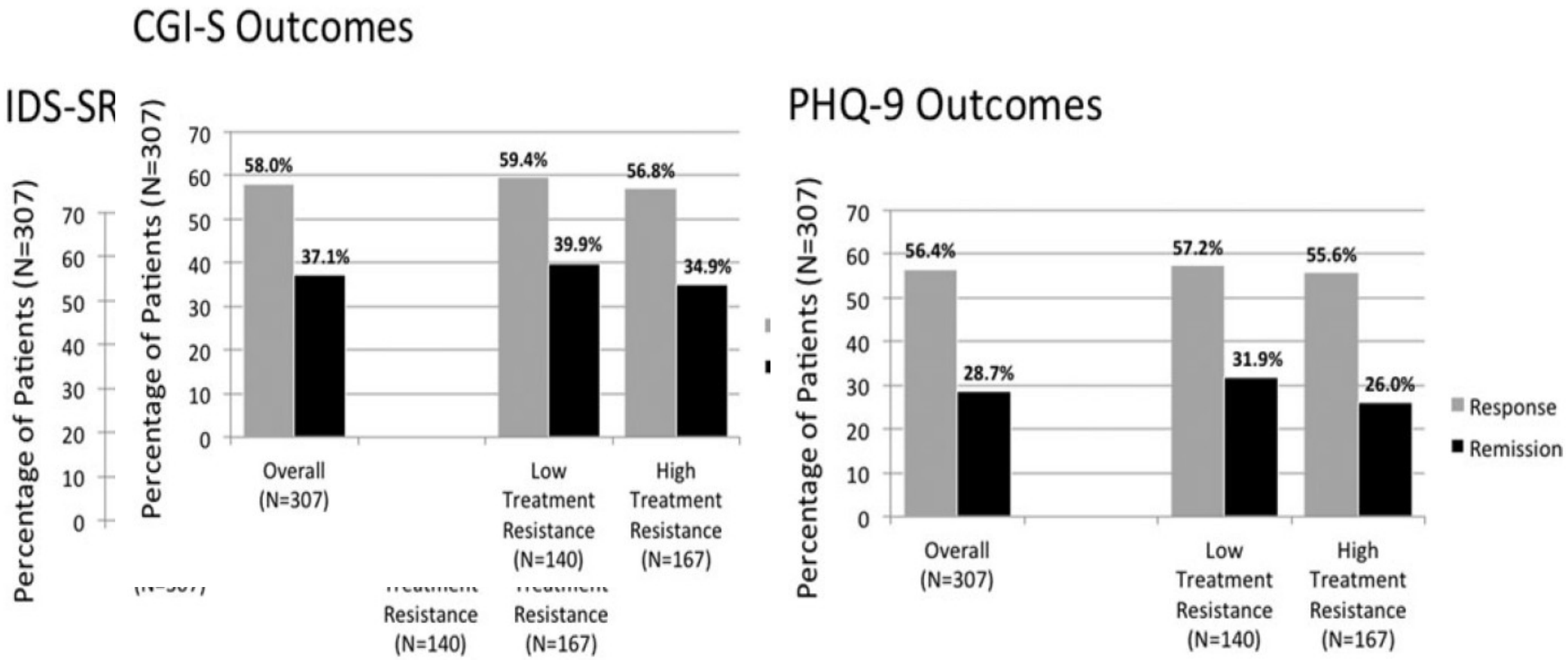
Figure 2. Summary of IDS-SR Total Score Outcomes During Long-Term Follow-Up: Stratification by End of Acute Treatment Clinical Outcome (N = 257)[a]



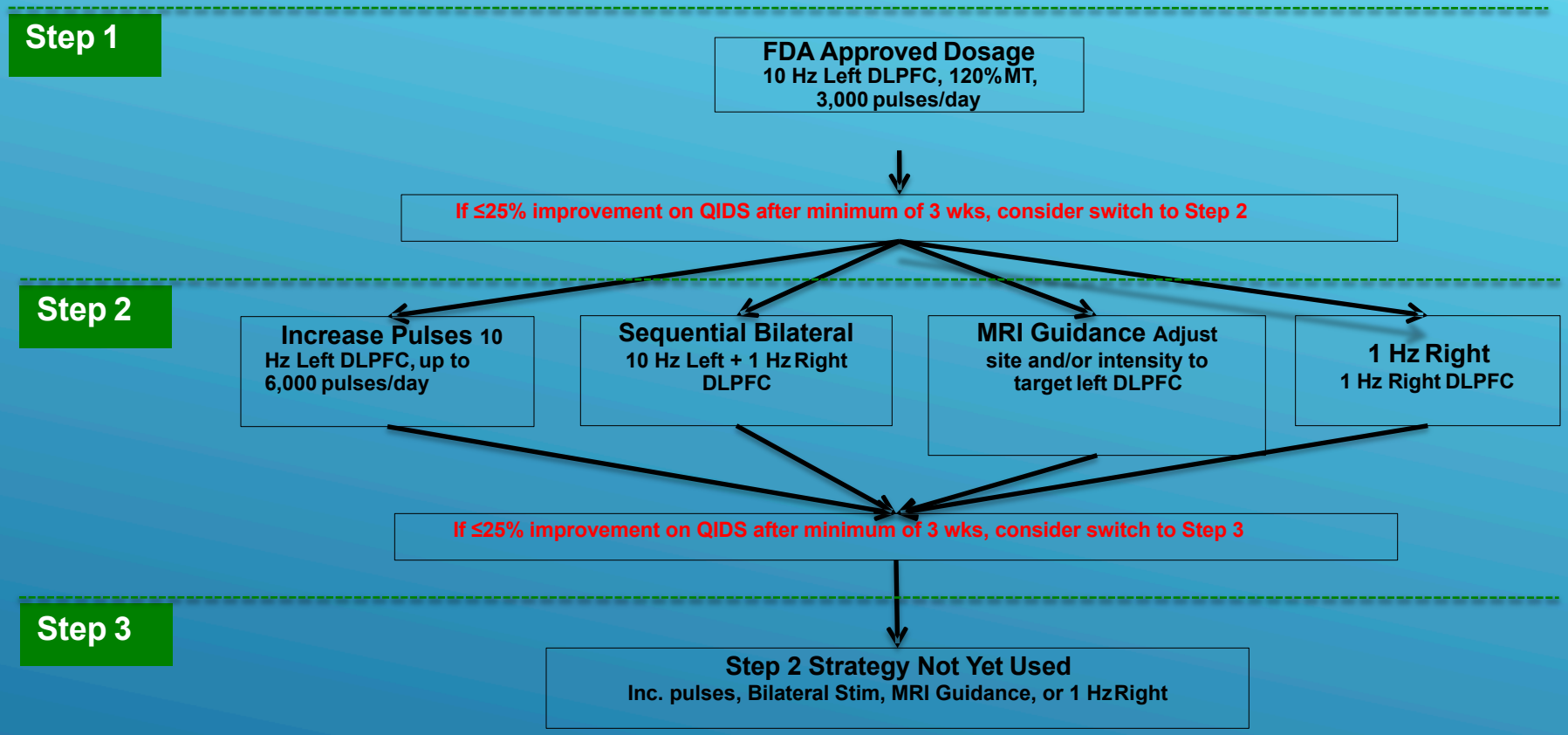
- **N=257 patients with MDD followed for 1 yr**
- **Meds and/or TMS reintroduction provided**
- **62.5% of acute remitters sustained response at 1 yr**

How effective is TMS in Practice?

- Carpenter et al 2012
  - N=307, open label, MDD, on-label dosing



NNDC rTMS Task Group: TMS Dosing Guidelines



Instructions:

1)Patients who have failed a single antidepressant medication at adequate dose/duration start at Step 1. For more resistant patients, clinician may start at Step 1 (given that efficacy of TMS in such patients on concomitant antidepressant medications is not known), or may chose to start at Step 2 if clinically indicated (e.g. extremely resistant, urgent clinical need, etc).

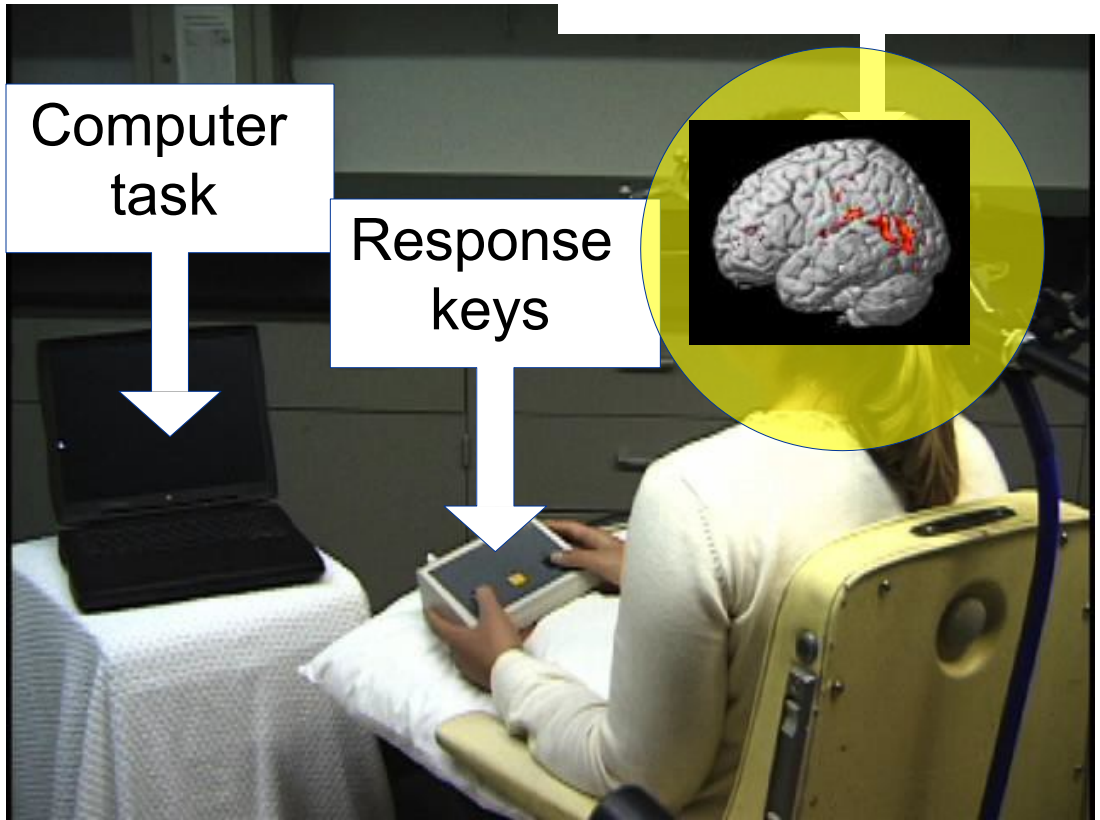
2)Selection at Step 2 depends upon clinician choice, local policy, and availability of MRI. Some clinicians may chose to start at 1Hz Right as an initial strategy if there is a desire to avoid high frequency due to tolerability issues, and if there are comorbidities making right hemispheric treatment attractive (e.g. anxiety symptoms).

3)We advise allowing at least 3 weeks per step before advancing, to see if there is benefit, but we note that maximal remission was seen after 6 weeks, and that nonresponders to the FDA approved dosage benefited from 6 additional weeks of the same dosage. Furthermore, response rate and speed in patients on medications during TMS may differ from what was seen in the trials of unmedicated patients.

The Therapeutic Context ••• Brain State ••• Online before/after

- Brain State
  - – Computer-delivered task

On-line Stimulation



- What is she thinking about, reading, watching, doing?
- Who else is in the room and how are they interacting?
- What medications is she taking?

National Institute of Mental Health

Speer, A.M, Kimbrell, T.A., Wassermann, E.M., Repella, J.D., Willis, M.W., Herscovitch, P., and Post, R.M. (2000) Oppo
high and low frequency rTMS on regional brain activity in depressed patients.pdf

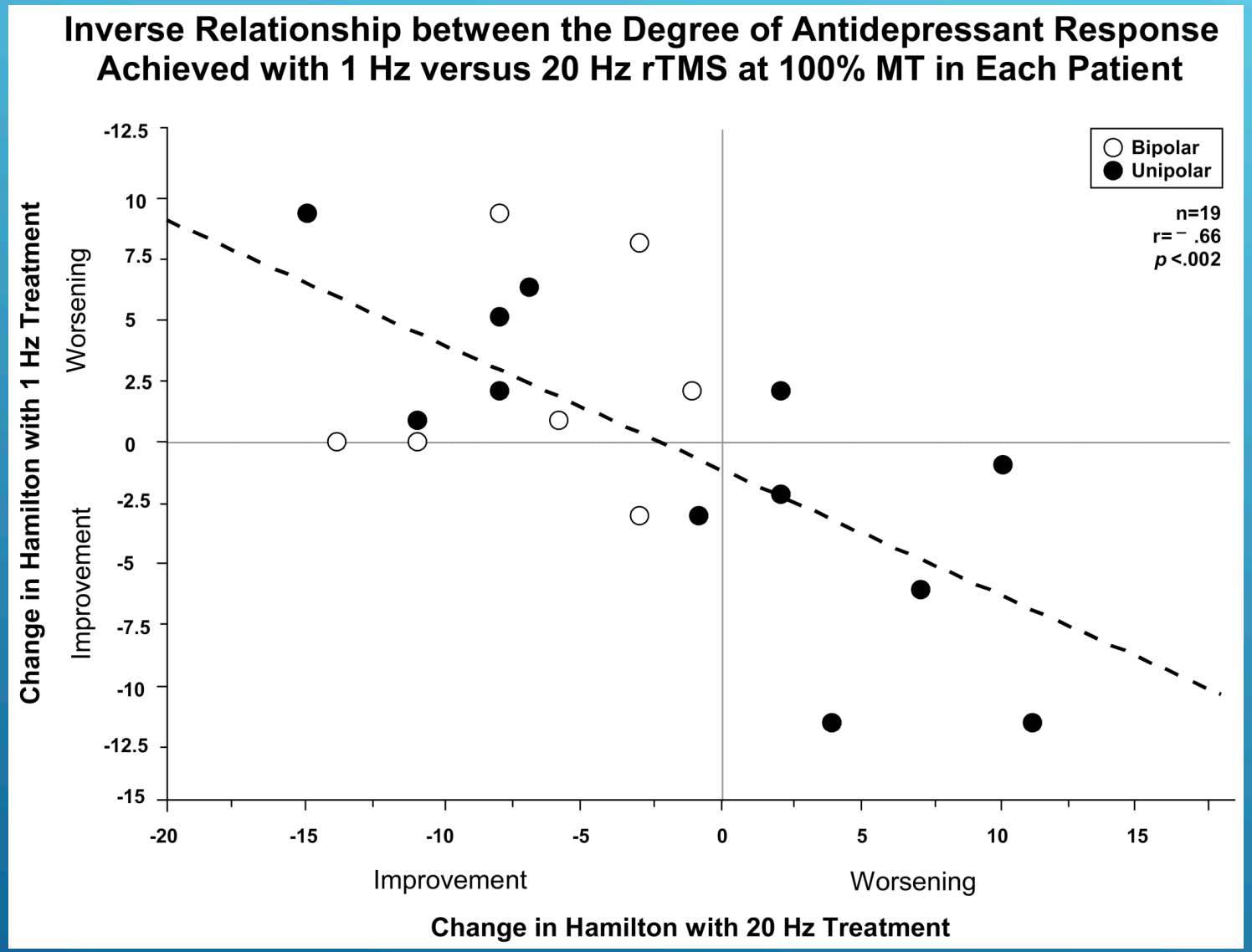


Figure 1.
Inverse relationship (r = −0.66) between the degree of antidepressant response (change in

Fitzgerald 2009

1255–1262

- 10 Hz, 5s, 1500 pulses/day x 4wks
- MDD, failed 2 trials, psych co-morbidities
- TMS added onto meds

- 42% vs 18% response
- 30% vs 11% remission
- No time by group interaction
- Post hoc difference at week 4

- Different drop-out rates: 15 for 5cm group, 7 for MRI group

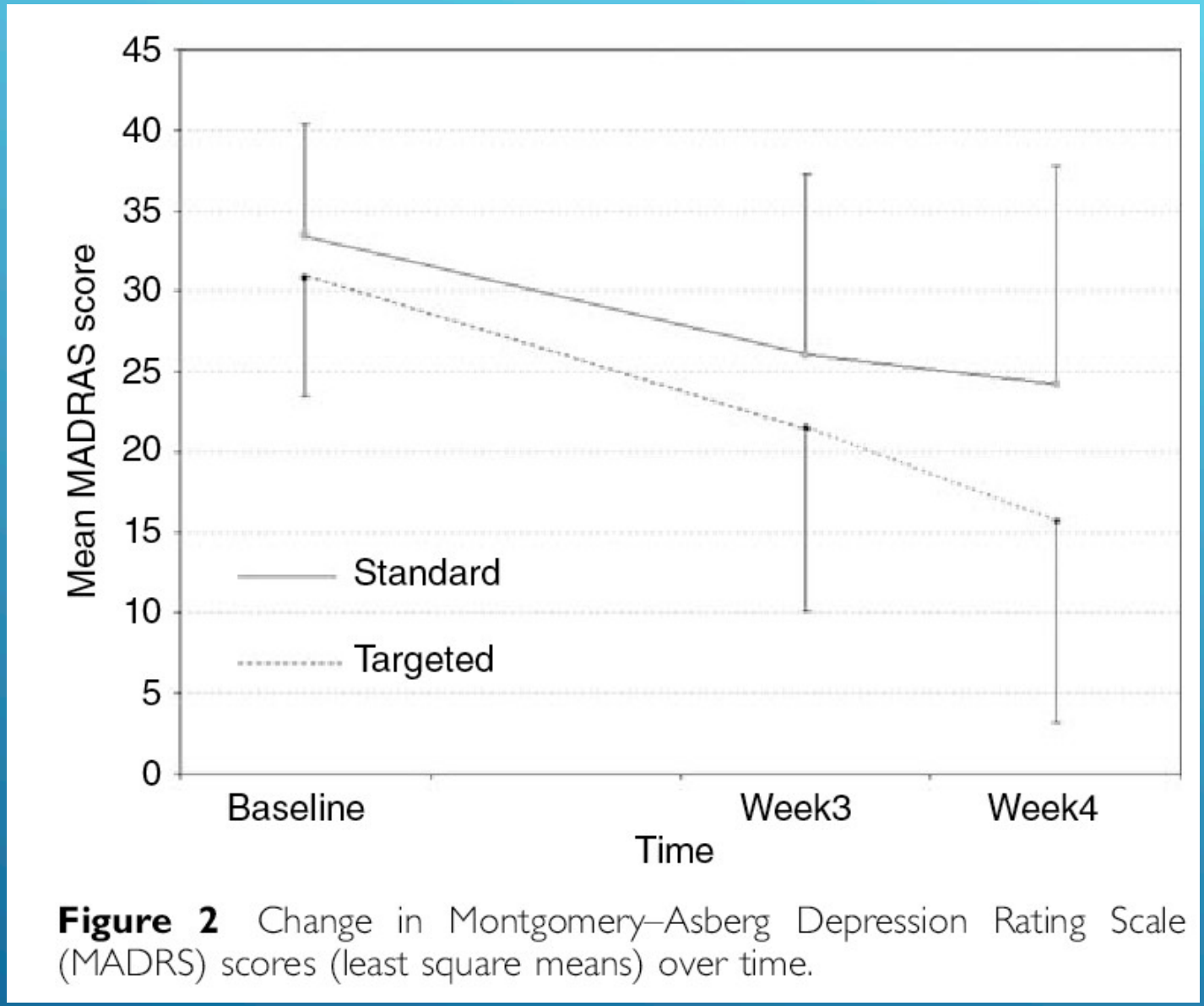


Figure 2 Change in Montgomery–Asberg Depression Rating Scale (MADRS) scores (least square means) over time.

Defining Outcome

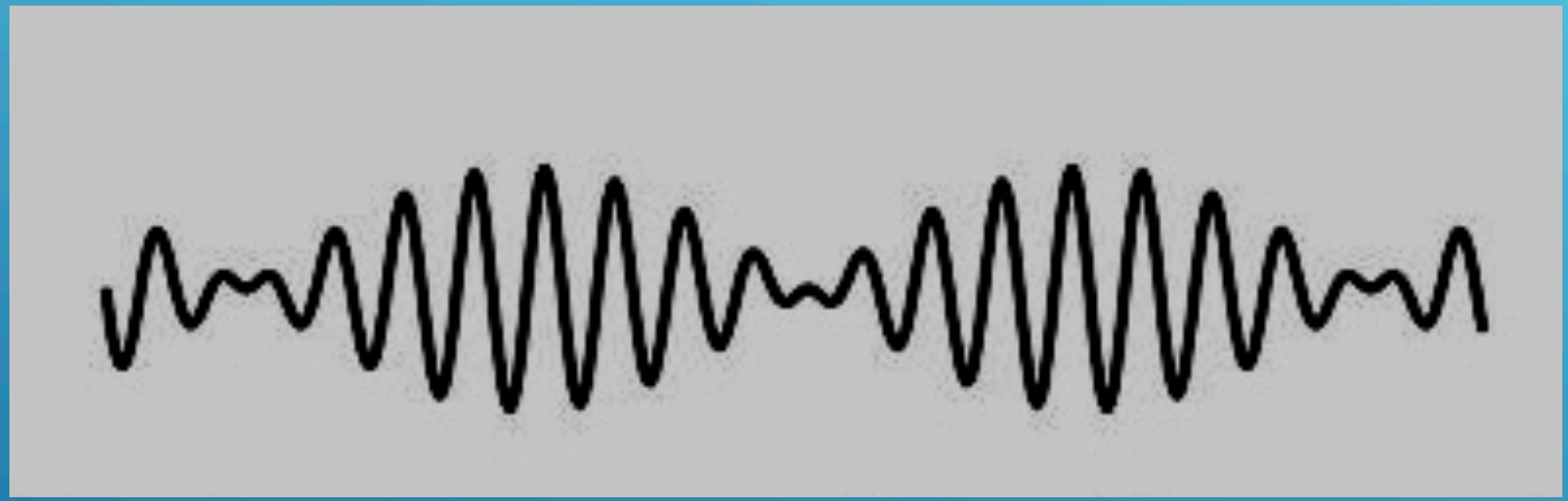
NONRESPONSE	**<25% decrease in baseline severity** *(many residual symptoms still present)*
PARTIAL RESPONSE	**26 to 49% decrease in baseline severity**
RESPONSE	**50% or greater decrease in baseline severity**
REMISSION	**Absence of symptoms** *(minimal residual symptoms present)*

Mann J J. *N Engl J Med*. 2005;353: 1819-1834.

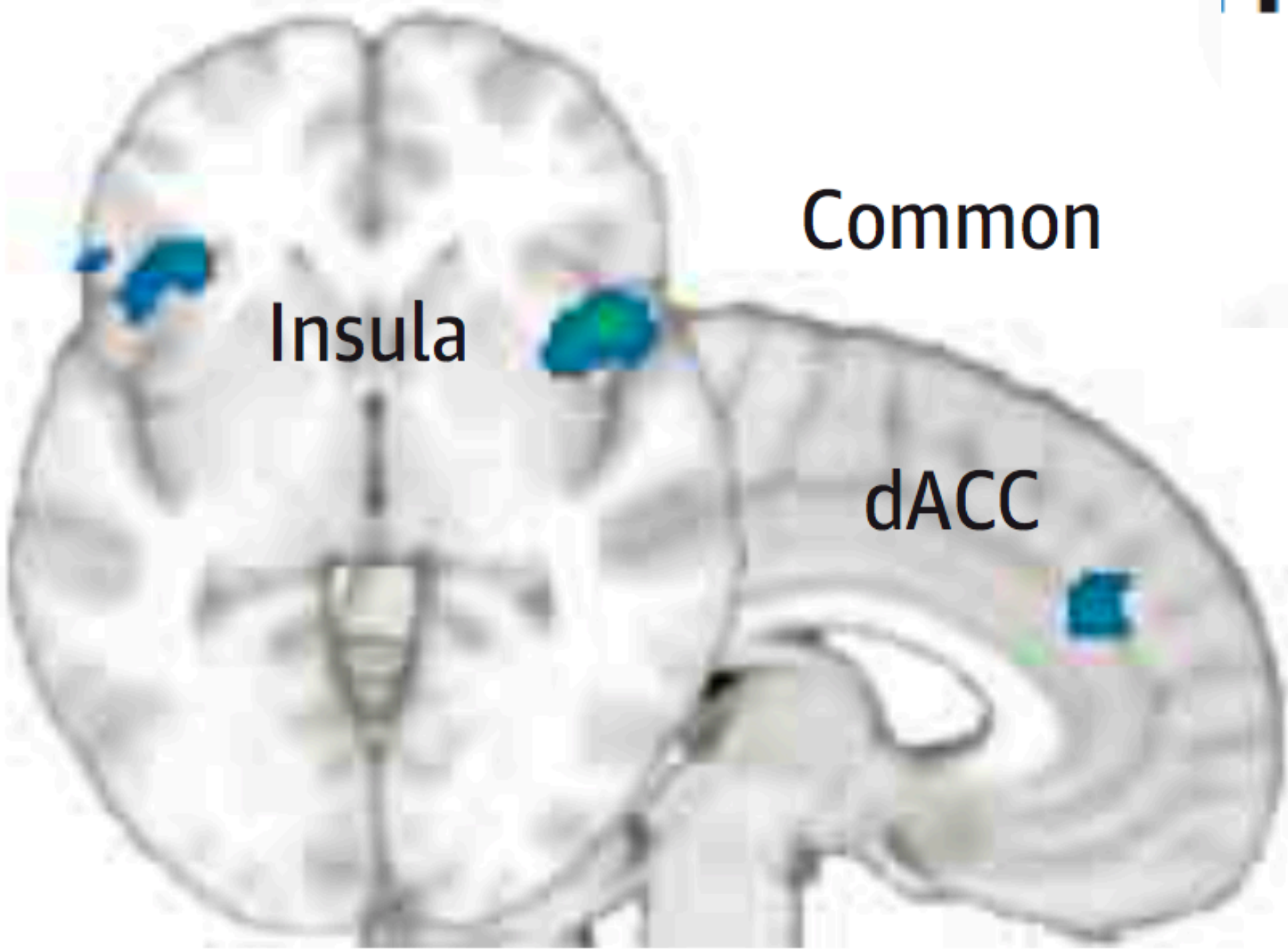
CHANGES IN EEG SIGNAL AFTER 5-HZ DORSOLATERAL PREFRONTAL CORT
(DLPFC) TRANSCRANIAL MAGNETIC STIMULATION IN PATIENTS WITH CO
POSTTRAUMATIC STRESS DISORDER AND MAJOR DEPRESSION

the treatment altered the coherence betv
the stimulated site and those in its imm
vicinity while the longer range connect
remained relatively un=changed.

Phase Amplitude Coupling (PAC)

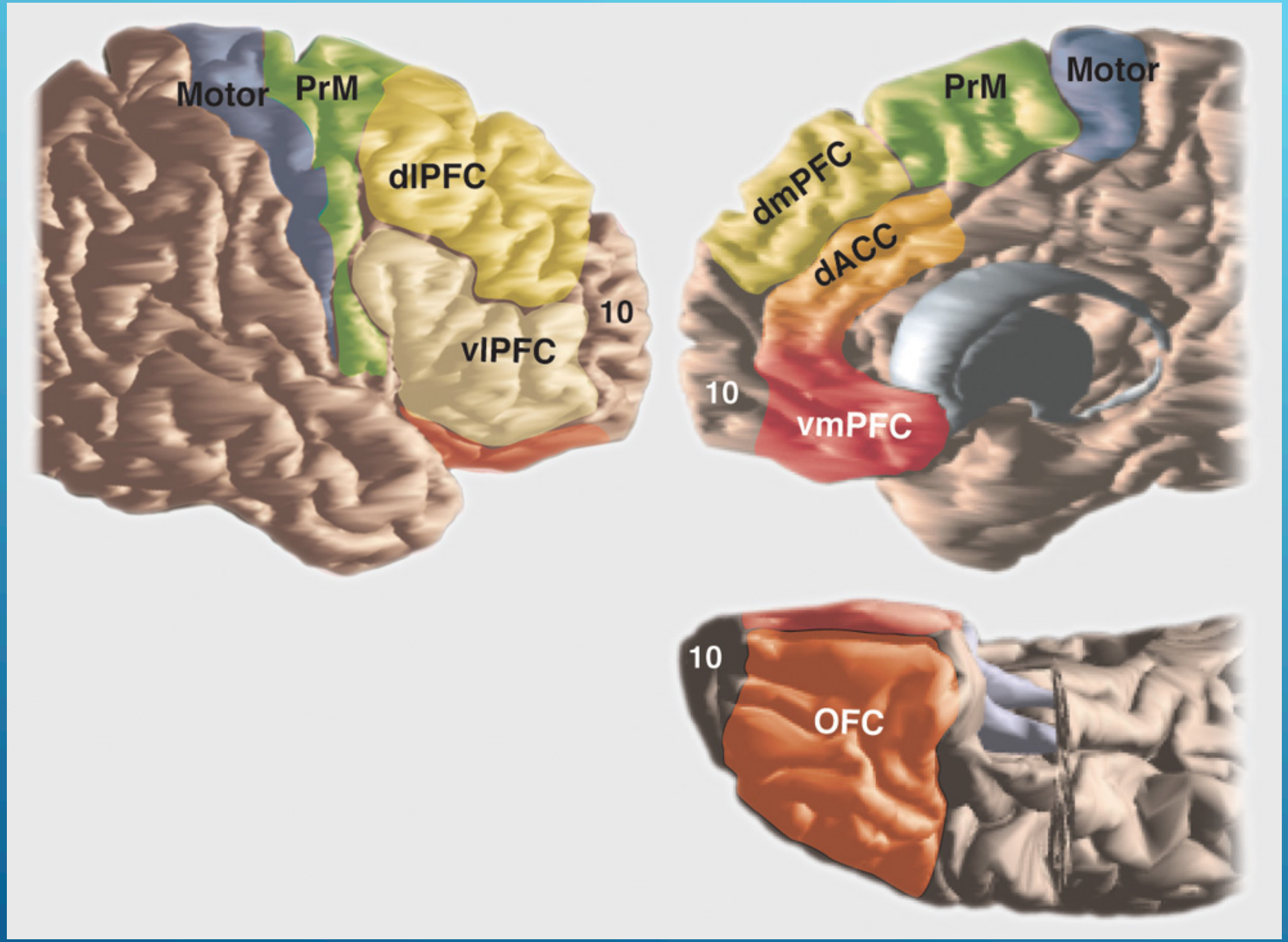


Amplitude of the fast frequency
is modulated by the PHASE of slow frequency

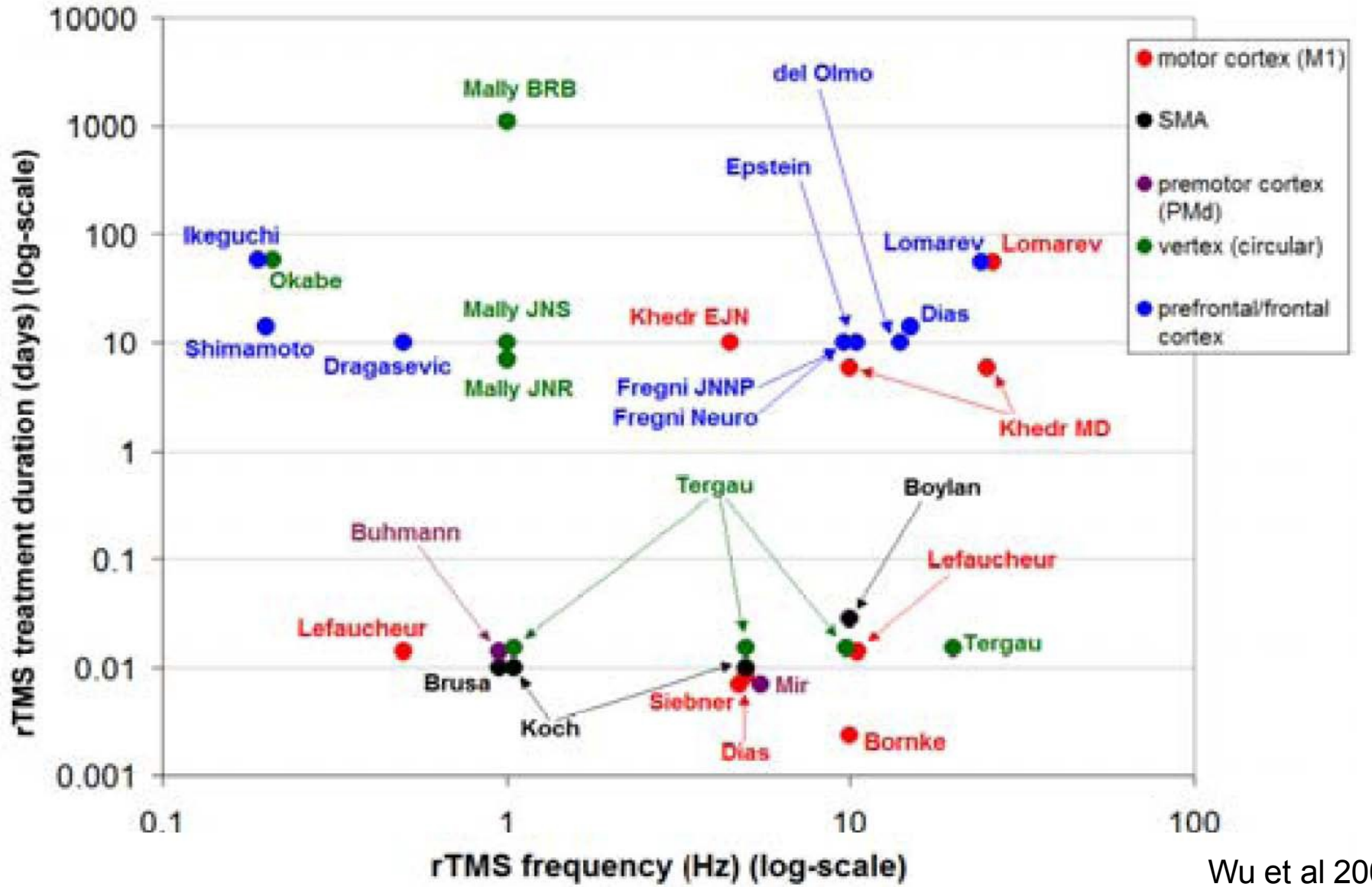

Common
Insula
dACC

Cortical Networks

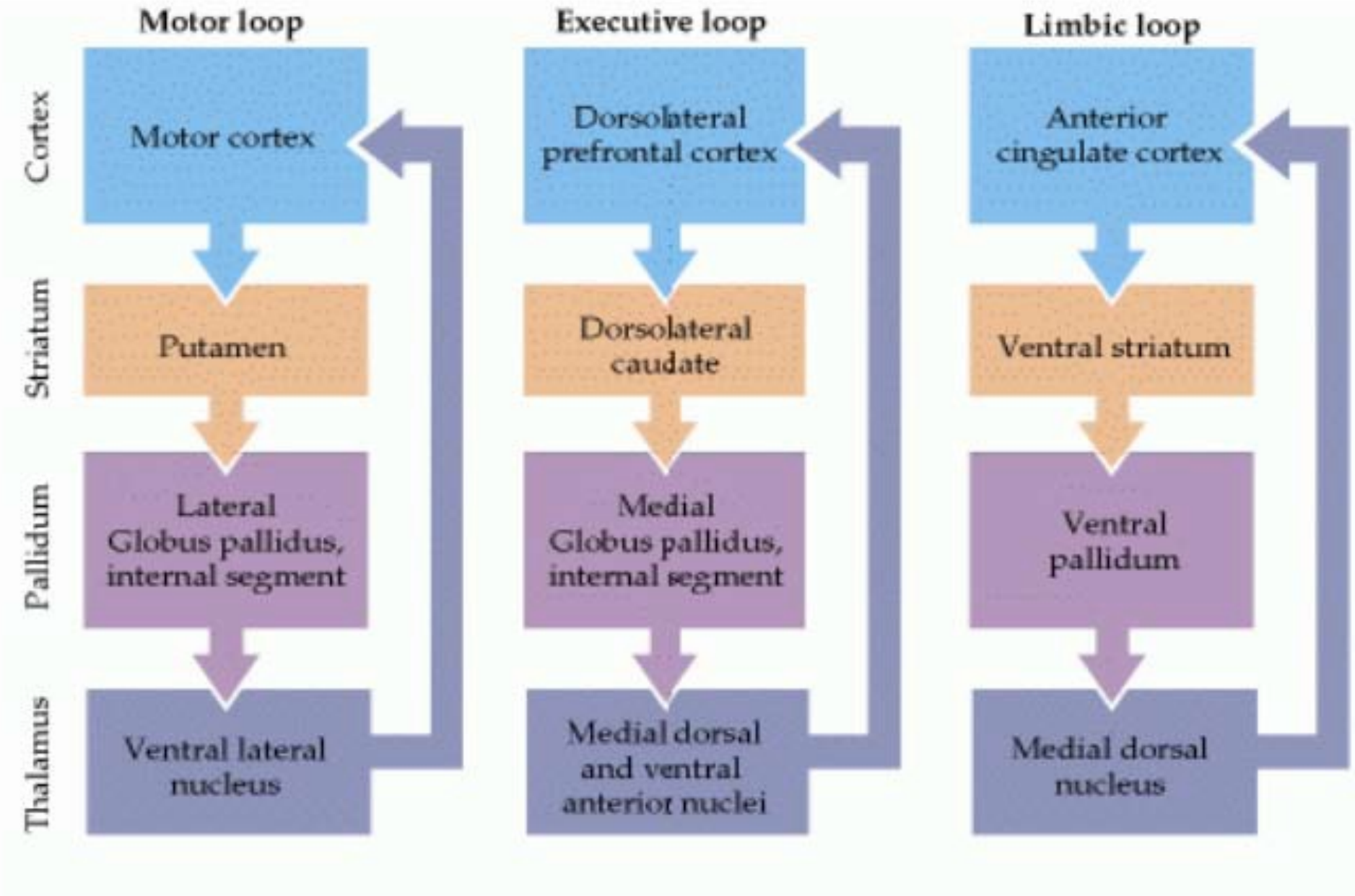
	ICN 1 (limbic and medial-temporal areas) included primary **olfactory** and limbic association cortices (BA 28/34/ 35/36/38), including parahippocampal gyri. This network was strongly associated with discrimination of **emotional** faces and pictures, particularly those that elicited fear, happiness, or humor. In addition, ICN 1 was strongly weighted toward interoceptive processing elicited during air-hunger and, more weakly, olfactory and gustatory responses.
R	• ICN2(subgenual ACC and OFC) included BA25 and BA10/ 11/12 and was loaded toward **olfaction, gustation, and emotion**, with a strong preference for **reward**
	• **ICN 4** (bilateral anterior insula/frontal opercula and the anterior aspect of the body of the cingulate gyrus) encompassed BA 13/16 and BA 24. These regions accounted for a complex set of **language**, **executive function**, **affective**, and **interoceptive**
C	ICN 6 (superior and middle frontal gyri) included the premotor and supplementary motor cortices (SMA; BA 6) and FEFs (BA 8/9) and was related to cognitive control of visuomotor timing and preparation of executed movements. Strongly weighted behavioral domains included **action imagination** and **preparation**
D	**ICN 13** (medial prefrontal and posterior cingulate/precuneus areas) was the component known as the **default mode network** and **strongly corresponded to theory of mind and social cognition tasks**. Weaker correspondence was observed for fixation, episodic recall, imagined scenes, and delay discounting tasks.
	ICN 14 (cerebellum), commonly associated with **action** and somesthesis, demonstrated a distributed range of sensorimotor, autonomic, and cognitive functions. Interestingly, both overt and covert naming showed a preference for cerebellar activity, despite
	ICN 15 (**right-lateralized fronto-parietal regions) included right BA 44/45 and 22/39/40**. This network involved multiple cognitive processes, such as **reasoning, attention, inhibition, and memory, and showed preference for n-back, delay discounting, and divided auditory attention tasks**.
	ICN16(transversetemporalgyri)includedtheprimary auditory cortices (A1; BA 41/42) and was related to **audition**
	ICN 17 (dorsal precentral gyri, central sulci, postcentral gyri, superior and inferior cerebellum) included primary sensorimotor cortices for mouth (M1, S1; BA 4/ 3/1/2) and was associated with action and somesthesis
	ICN 18 (**left-lateralized fronto-parietal regions**) included Broca's (BA 44/45) and Wernicke's (BA 22/39/40) areas and strongly


Motor
PrM
dlPFC
vlPFC
10
PrM
Motor
dmPFC
dACC
10
vmPFC
10
OFC

TMS in Parkinson's Disease



Wu et al 2008


Motor loop
Executive loop
Limbic loop
Cortex
Striatum
Pallidum
Thalamus
Motor cortex
Dorsolateral prefrontal cortex
Anterior cingulate cortex
Putamen
Dorsolateral caudate
Ventral striatum
Lateral Globus pallidus, internal segment
Medial Globus pallidus, internal segment
Ventral pallidum
Ventral lateral nucleus
Medial dorsal and ventral anterior nuclei
Medial dorsal nucleus