Day 2

Fort Lauderdale, Florida 09/2019

Overview

Incomplete remission with TMS treatment of MDD

The Off Label Spectrum:

Sunday
09/29/2019

	Excitatory	Inhibitory
Simple	**10 Hz** 4 s 11 s	1 sec **1 Hz**
Theta Burst	**iTBS** 2sec 8 sec	5/50 Hz **cTBS**

Other Benefits

Cognitive/Executive improvement

Reduction in cravings/self destr

? Prevent Dementia

TMS EFFICACY

Off Label uses

TMS

EFFICACY

Off Label

ADHD
Autism
Bipolar Depression
Chronic Pain
Chronic Traumatic
  Encephalopathy (CTE)
Dementia,

TMS

EFFICACY

Off Label

Executive Function, Working Memory

Head Injury

Parkinson's,

Performance Enhancement etc

Stroke

Tinnitus

Work

Family

Etc

Patient

Continuation Treatment

Physician

Ongoing Clinical Assessment

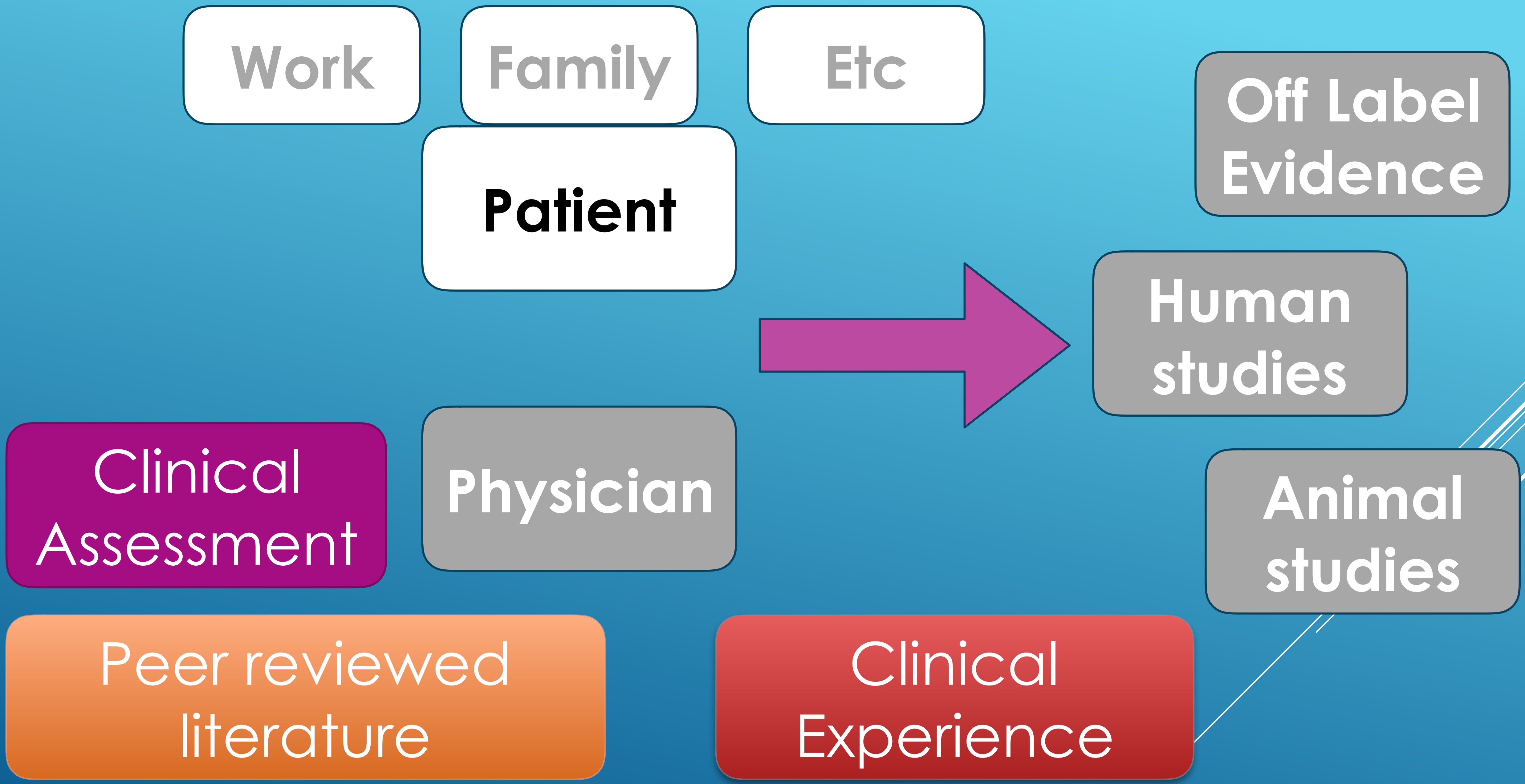
Standard Treatment

Target Engagement

Peer reviewed literature

Digital

Clinical Experience


Work
Family
Etc
Patient
Off Label Evidence
Human studies
Animal studies
Clinical Assessment
Physician
Peer reviewed literature
Clinical Experience

Indication
Other Uses

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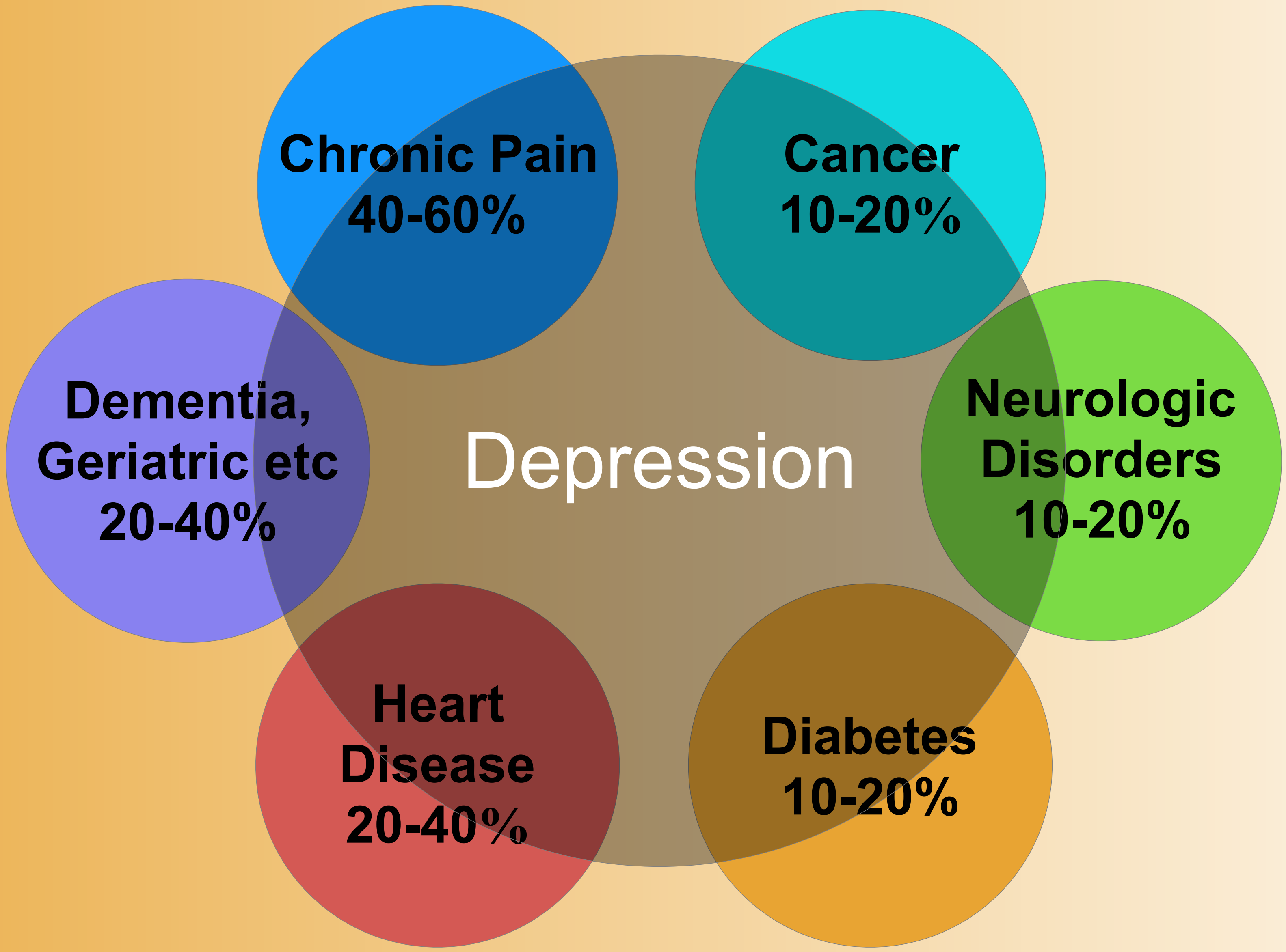
Many Health Problems Co-occur



MDD+
Other Psych or
GMC

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Goulden 2014 The salience network is responsible for switching between the default mode network and the central executive network- Replication from DCM .pdf

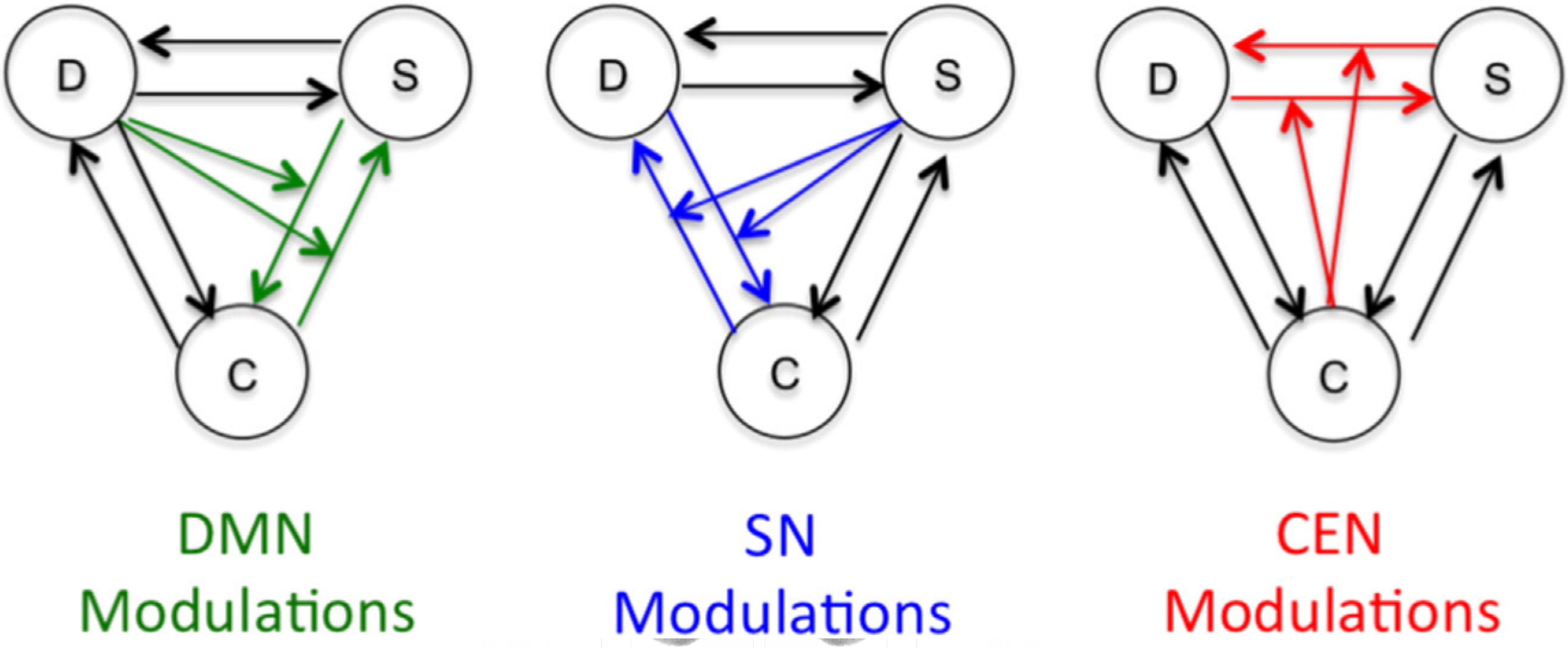

Fig. 2. DCM tests models of connectivity against each other to find the one that has the highest probability of explaining the data. We tested three models in our resting state data. Model 1 has nonlinear modulations by the default mode network (D), and these are indicated with green lines. Model 2 has nonlinear modulations by the salience network (S), and these are in- dicated in blue lines. Model 3 has nonlinear modulations by the central executive network (C), and these are indicated with red lines.

How to think about & discuss Brain

Large Scale Cortical Networks

DMN Default mode network

SN Salience network

ExN Executive network

Large Scale Cortical Networks			
Network	Condition	Stim Target	Other components
Default/Mind Wandering	ADHD, Anxiety, Depression	DLPFC	Posterior Cingulate, Parietal & Rostral VMpfc
Auditory (microstate A)			primary auditory cortex, middle temporal gyrus & left middle frontal gyrus
Visual (microstate B)			primary visual cortex, bilateral inf Occ gyri, middle temporal gyrus, left middle frontal gyrus,, bilateral cuneus, left lingual
Salience/Reward (microstate C)	Addiction	Left OFC	Anterior Cingulate, Anterior Insula, Nucleus accumbens
Salience/Reward (microstate C)	OCD	Right OFC	Anterior Cingulate, Anterior Insula, Nucleus accumbens
Executive/Attention (microstate B)	ADHD, Anxiety, Depression	DLPFC	DLPFC, Dorsal Parietal

Stimulation Site **BA**

10-20 EEG **Network** **Target Disorder Or Problem**

Name	EEG_10_20	BA	Network	Condition	Notes
(T3/P3 1/2	L TPO	40	TOM, Default	Autism	
Tt4/P4)1/2	R TPO	40	TOM, Default	Autism	
L OFC	F1	11	Reward/Salience	Addiction/EtOH	
R OFC	F2	11	Reward/Salience	Obsessions, Ruminative depression	
L-DLpfc	F3	9/46	Executive/Attention	Depression, ADHD, Pain, Parkinsons etc,	
R-DLpfc	F4	9/46	Executive/Attention	Anxiety, Depression, Pain, Parkinsons etc	
M1	Cz	4	Somatomotor	Pain, Parkinsons	
L PT-PO	F7	44/45	Language	Autism	
R PT-PO	F8	44/45	Language	Autism	
SMA	FCz	6	Motor, agency	Parkinsons, Impulsivity, OCD, Tourettes	
DMpfc	Fz	24,32	Reward/Salience	Depression, Autism, anhedonia	

PT-PO = pars triangularis and pars opercularis of the inferior frontal gyrus

TOM = theory of mind

REAL-WORLD CLINICAL PRACTICE

Patient AxisII	MDD + PTSD	TMS Meds	Happy & Resilient

REAL-WORLD CLINICAL PRACTICE ()

Patient

MDD

TMS

Not Ok

Table 1							
Indication	**Location**	**Notes**	**Frequency**	**Train (2)**	**Pause (3)**	**Duration (4)**	**total tim**
ADHD	L-DLPFC(F3)		10 Hz	4	11	20	
Anxiety (GAD)	R-DLPFC(F4)	cTBS 2min on, 1min off, 2min on	1 Hz or cTBS	60	1	20	
Anxiety (Panic)	R-DLPFC(F4)	cTBS 2min on, 1min off, 2min on	1 Hz or cTBS	60	1	20	
Anxiety (Social)	R-DLPFC(F4)						
Autism Spectrum (1)	L-DLPFC(F3)		0.5Hz	40	20	8	once/wee
Autism Spectrum (2)	Individual	According to EEG	Individual				3-5/weel
Bipolar	R-DLPFC(F4)	inhibitory first right side	1 Hz or cTBS	60	1	20	
ChemoBrain	Individual	start with Left DLPFC	10 Hz	4	11	20	
Dementia	Individual	start with Left DLPFC					
Major Dep Disorder F33.2	L-DLPFC(F3)		10Hz	4	11	20	5/week
Epilepsy	Individual	ONLY INHIBITORY	1 Hz or cTBS	60	1	20	
Hallucinations	Left TPO (T3/P3)	cTBS 2min on, 1min off, 2min on	1 Hz or cTBS	60	1	20	
Head Injury	Individual	start with Left DLPFC	10 Hz	4	11	20	
Nicotine Dependence	L-DLPFC(F3), L-OFC(FP1)	DLPFC do Excitatory, L-OFC do Inhibitory	10 Hz	4	11	20	
OCD	R-DLPFC(F4), R OFC, SMA	cTBS 2min on, 1min off, 2min on	1 Hz or cTBS	60	1	20	
Pain Chronic	L-DLPFC(F3), M1	10Hz DLPFC, 20Hz M1 (gentle please)					
Parkinson's	L-DLPFC(F3), M1		10 Hz or 20 Hz				
PTSD	Right F2/F4		20 Hz				
Stroke	Individual	Inhibitory contralat, excitatory penumbra					
Suicide	L-DLPFC(F3)	3X/day X 3 days	10 Hz	5	10	30	
[illegible]	[illegible]	cTBS 2min on, 1min off,	[illegible]	[illegible]	[illegible]	[illegible]	

Protocols			
Indication	**Location**	**Notes**	**Frequency**
ADHD	L-DLPFC(F3)		10 Hz
Anxiety (GAD)	R-DLPFC(F4)	cTBS 2min on, 1min off, 2min on	1 Hz or cTBS
Anxiety (Panic)	R-DLPFC(F4)	cTBS 2min on, 1min off, 2min on	1 Hz or cTBS
Anxiety (Social)	R-DLPFC(F4)		
Autism Spectrum (1)	L-DLPFC(F3)		0.5Hz
Autism Spectrum (2)	Individual	According to EEG	Individual
Bipolar	R-DLPFC(F4)	inhibitory first right side	1 Hz or cTBS

Protocols			
Indication	**Location**	**Notes**	**Frequency**
ChemoBrain	Individual	start with Left DLPFC	10 Hz
Dementia	Individual	start with Left DLPFC	
Major Dep Disorder F33.2	L-DLPFC(F3)		10Hz
Epilepsy	Individual	ONLY INHIBITORY	1 Hz or cTBS
Hallucinations	Left TPO (T3/P3)	cTBS 2min on, 1min off, 2min on	1 Hz or cTBS
Head Injury	Individual	start with Left DLPFC	10 Hz
Nicotine Dependence	L-DLPFC(F3), L-OFC(FP1)	DLPFC do Excitatory, L-OFC do Inhibitory	10 Hz

Protocols			
Indication	**Location**	**Notes**	**Frequency**
OCD	R-DLPFC(F4), R OFC, SMA	cTBS 2min on, 1min off, 2min on	1 Hz or cTBS
Pain Chronic	L-DLPFC(F3), M1	10Hz DLPFC, 20Hz M1 (gentle please)	
Parkinson's	L-DLPFC(F3), M1		10 Hz or 20 Hz
PTSD	Right F2/F4		20 Hz
Stroke	Individual	Inhibitory contralat, excitatory penumbra	
Suicide	L-DLPFC(F3)	3X/day X 3 days	10 Hz
Tourette's	SMA, R OFC, DLPFC	cTBS 2min on, 1min off, 2min on	1 Hz or cTBS

Answering a question.. neuroSynth

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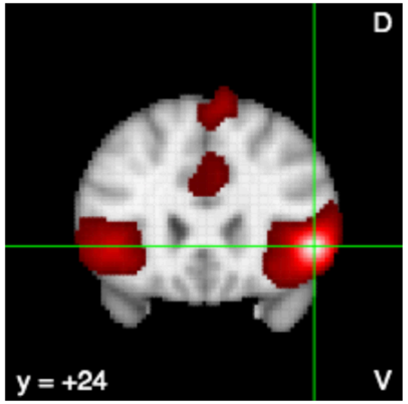
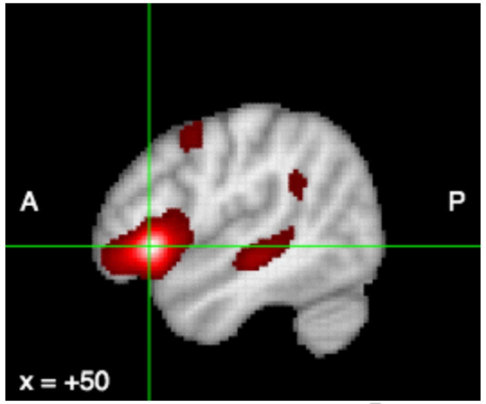
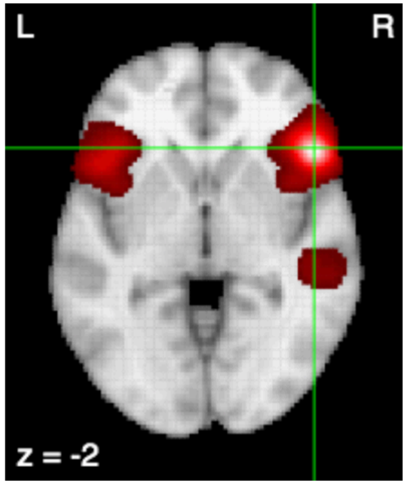
Data for coordinates: 50 24 -2

Maps | Studies | Associations | FAQs

Functional connectivity and coactivation maps







corr. (r): 1

What's here?

X: 0 Y: 0 Z: 0

Description

This image displays resting-state functional connectivity for the seed region in a sample of 1,000 subjects. To reduce blurring of signals across cerebro-cerebellar and cerebro-striatal boundaries, fMRI signals from adjacent cerebral cortex were regressed from the cerebellum and striatum. For details, see Yeo etal (2011), Buckner et al (2011), and Choi et al (2012).

Layers

Fur

Met

ana

Color pal

red

Positive/

positive

Threshol

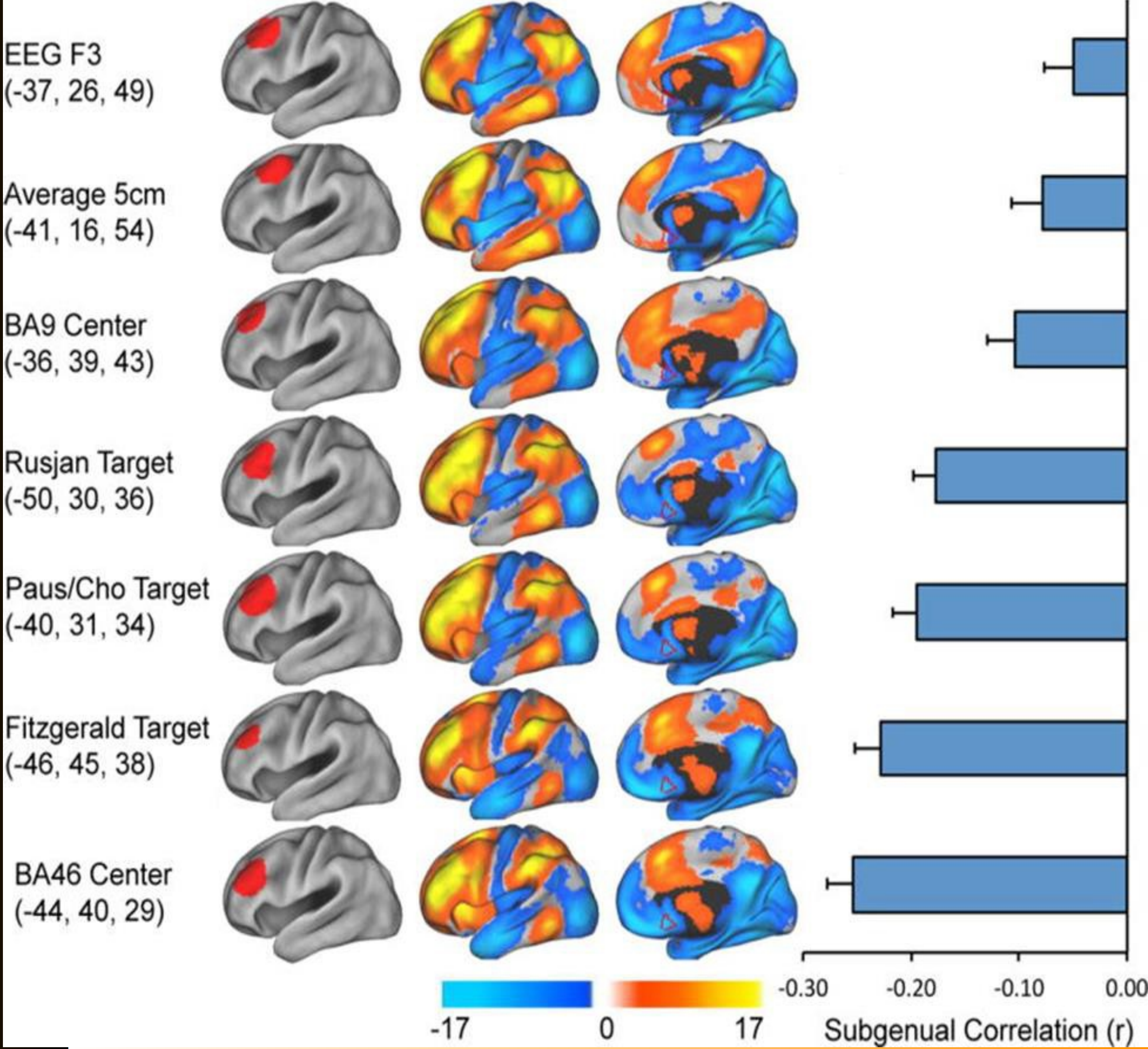
-0.2

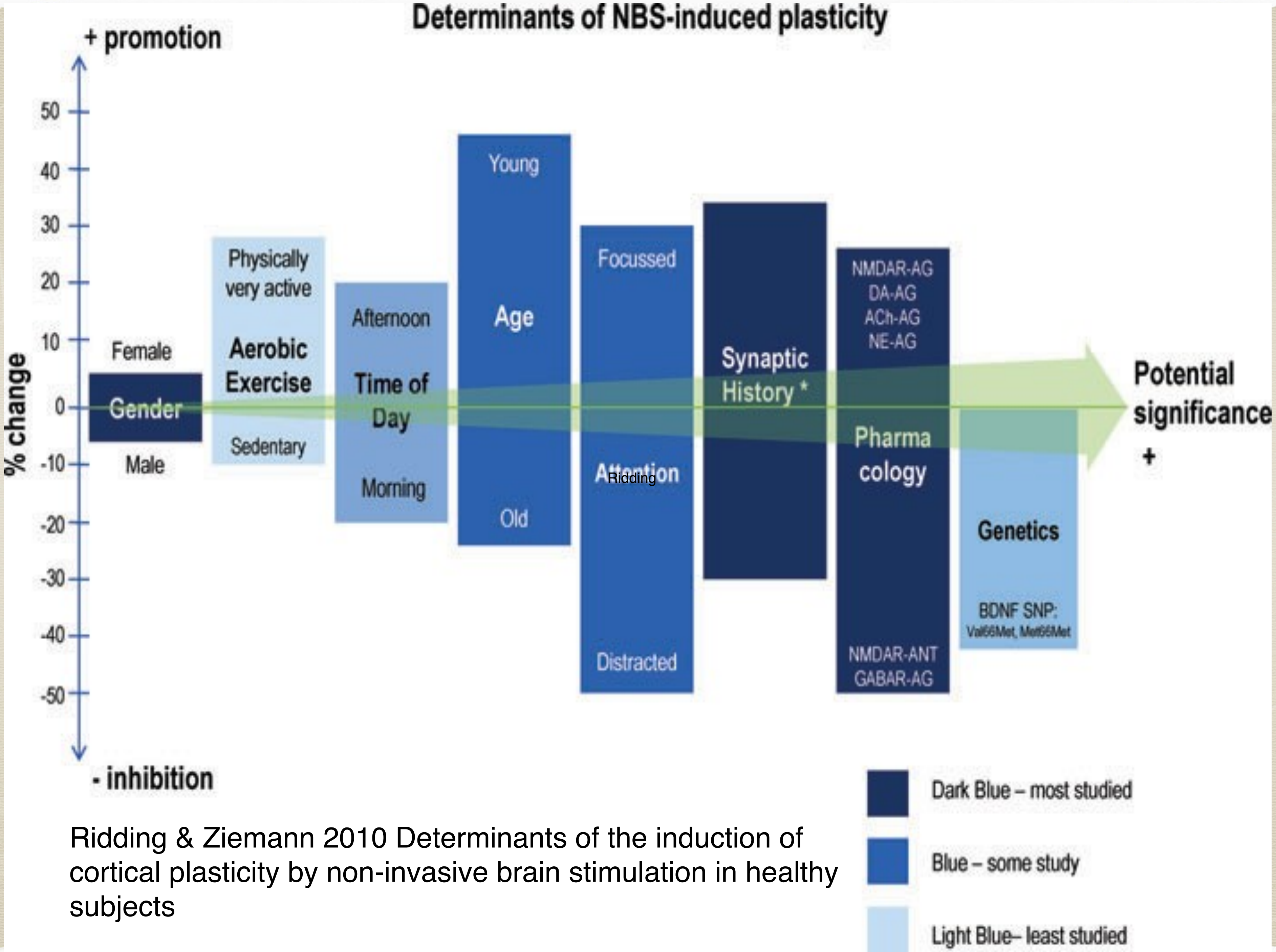
Opacity:

1

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.



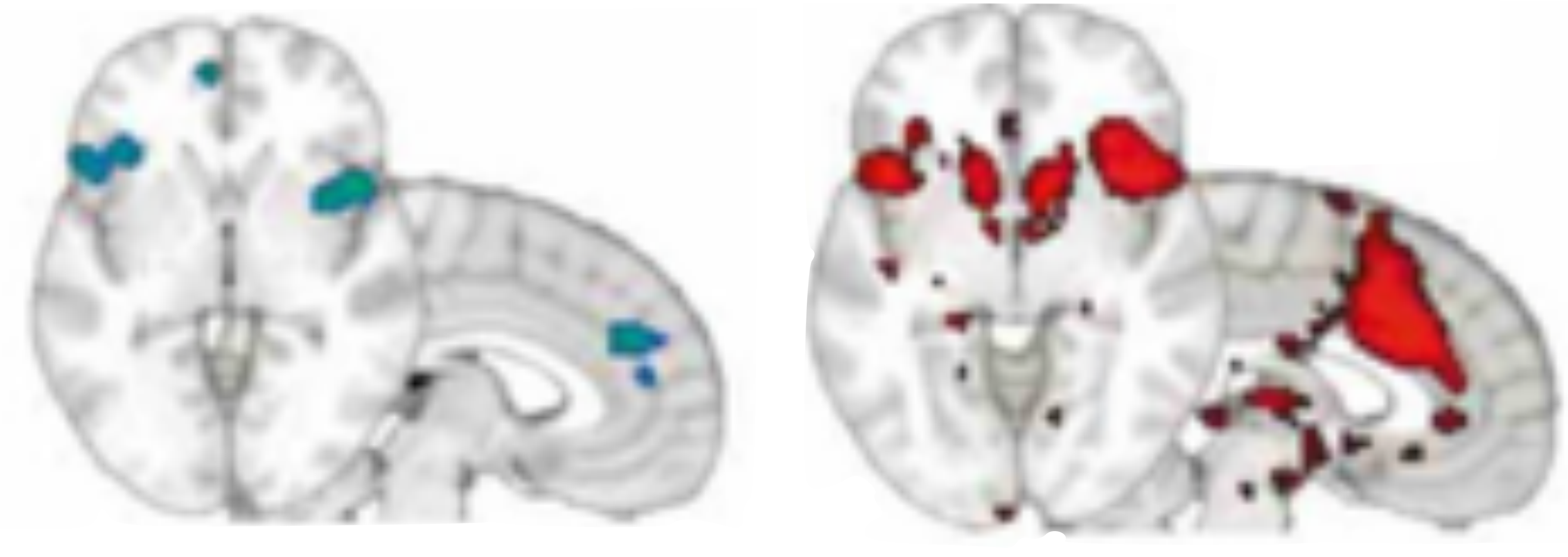


Ridding & Ziemann 2010 Determinants of the induction of cortical plasticity by non-invasive brain stimulation in healthy subjects

Influences on stimulation outcomes: neuroplasticisty

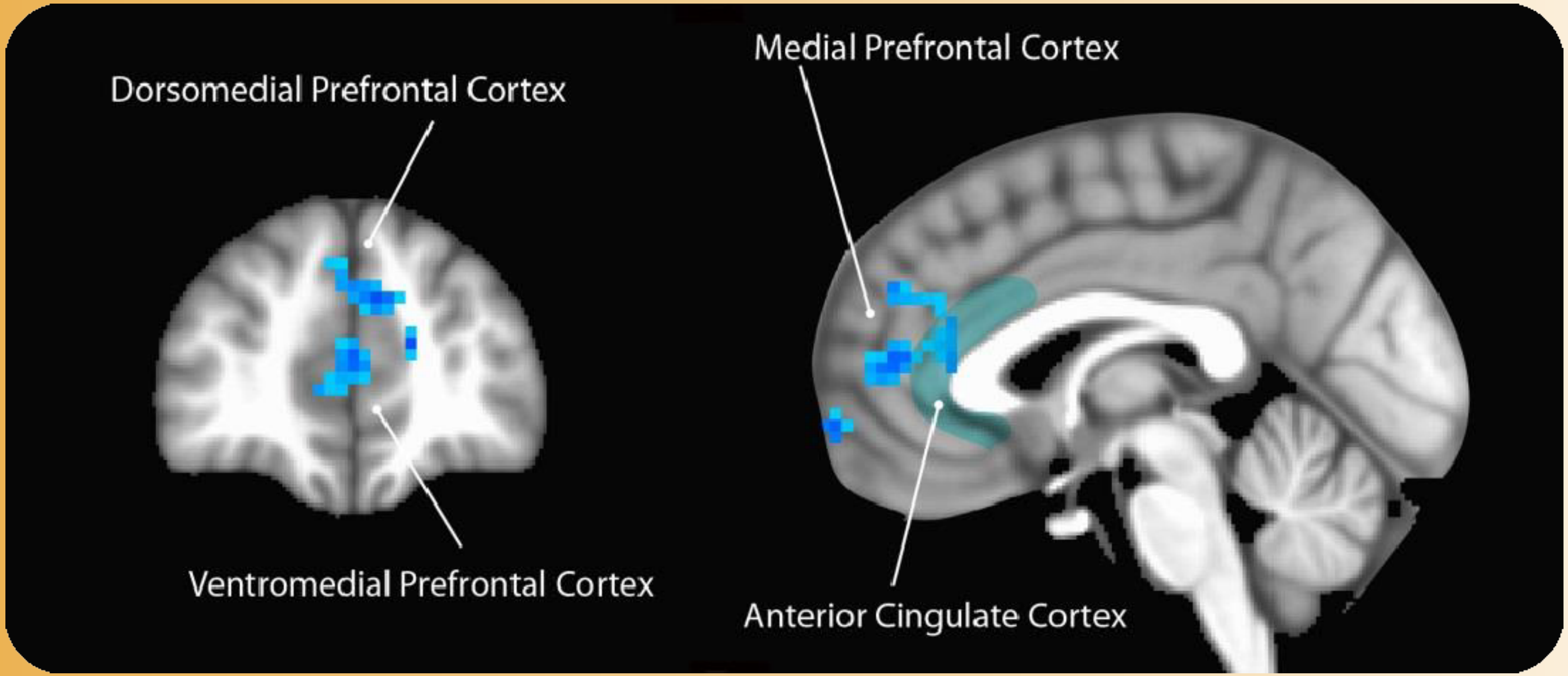
Fort Lauderdale, Florida 09/2019

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

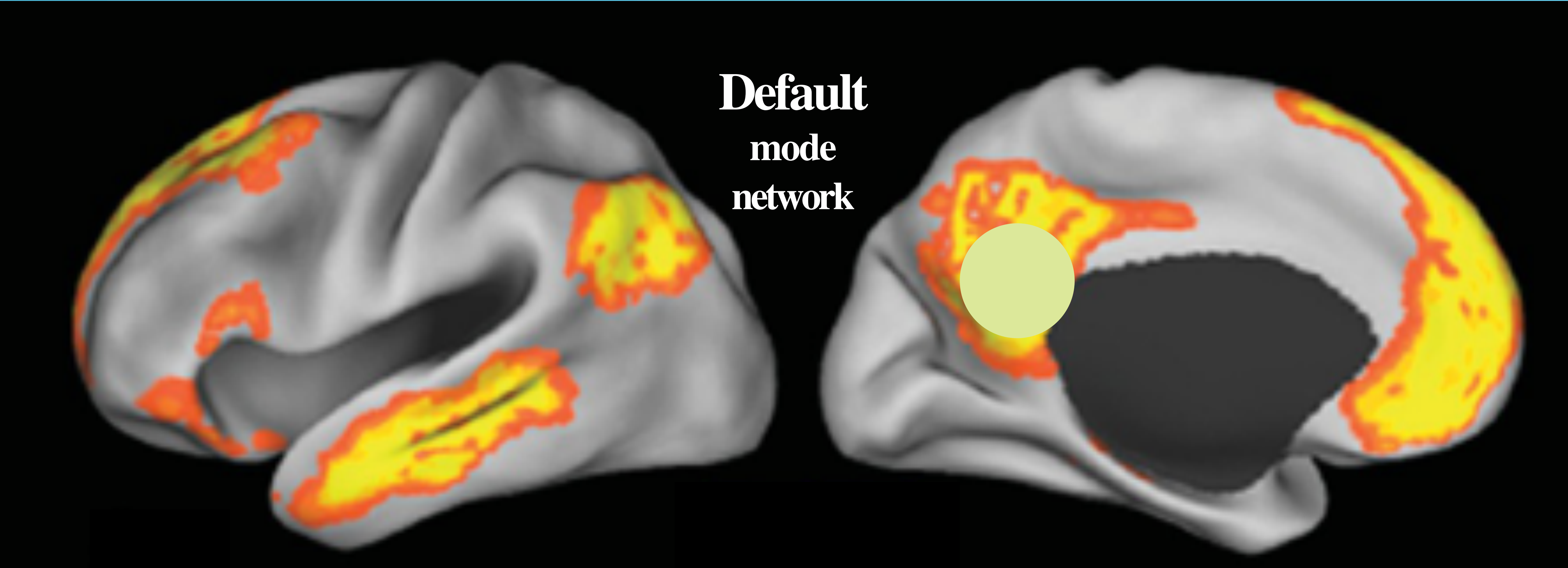


Common substrates of psychiatric illness

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

TMS- UP YOUR GAME

TBI
Stroke

Videos
Brain in general
Prefrontal

NeuroSynth
(Target Planning)

EEG

10/20
Beam
NeuroNavigation

Introduction
Preview
History
Mechanism & the nature of the therapeutic magnetic field
Aspects of the clinician

1. cares, learns & understands
2. Has experience & good outcomes (better a lucky than
   chance favors the prepared mind)
3. Tenacious “I will be with you through this”

Overview

STROKE
TBI

The Procedure

FIND WHERE

FIND HOW MUCH

FIND WHERE

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)

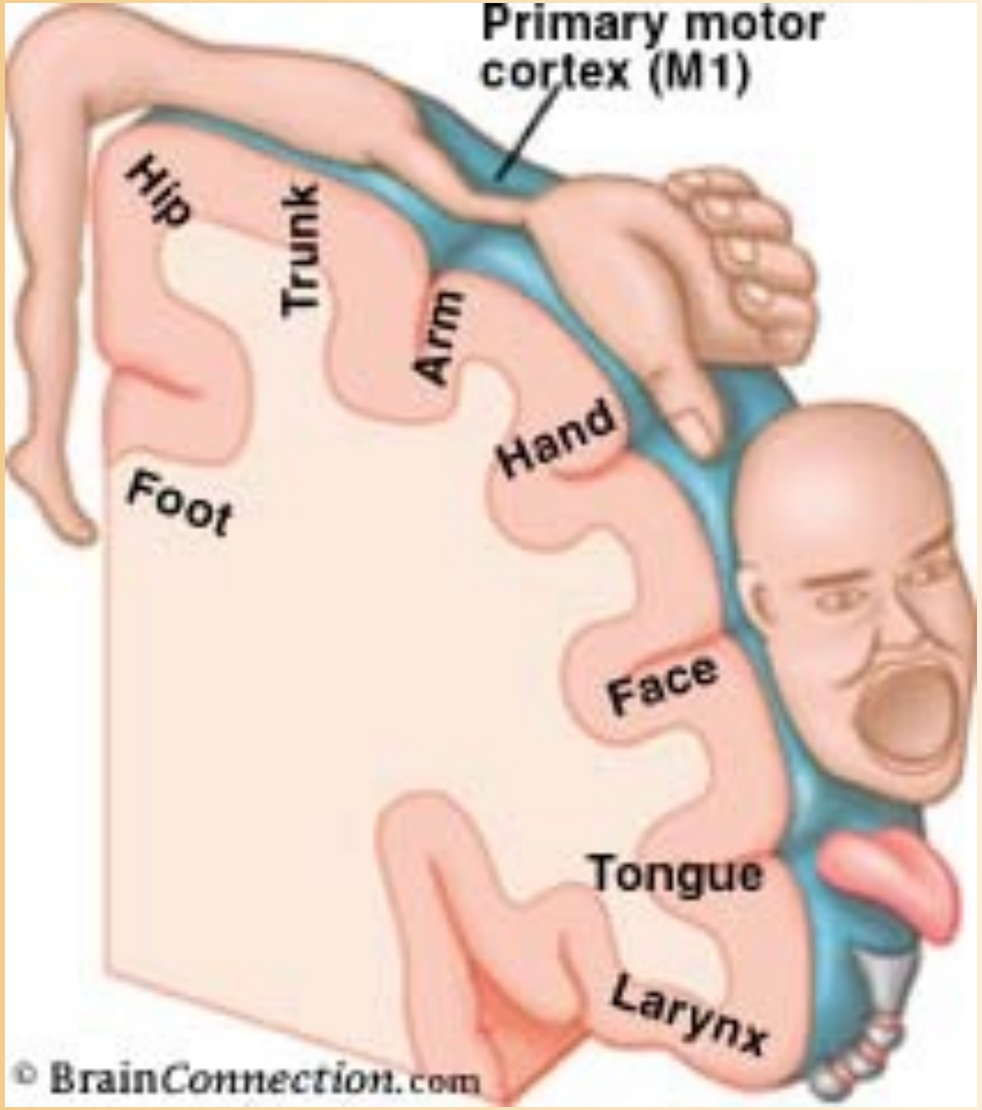
How Much

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...?

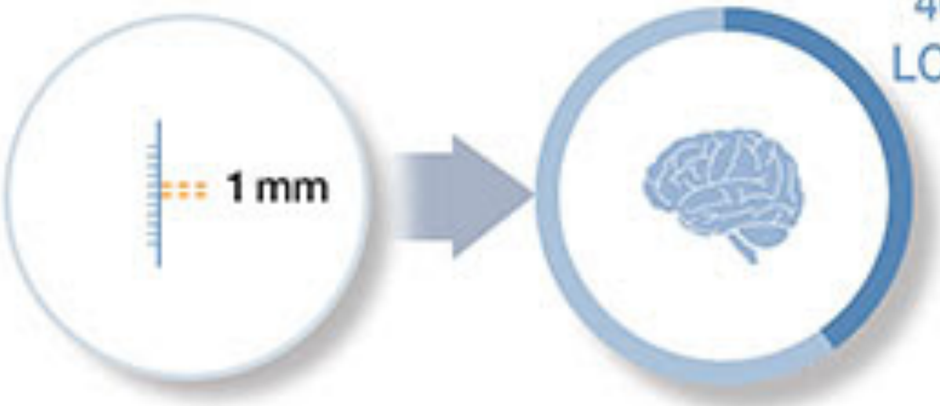
The smallest movements can result in a dramatic loss of the prescribed TMS dose

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

Target Area

Stimulated Area

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]

[1]Institute of Neuroscience and Medicine, INM-1, Research Centre Jülich, Germany, [2]Institute of Neuroscience and Medicine, INM-2, Research Centre Jülich, Germany, [3]Departments of Psychiatry, Psychotherapy, and Psychosomatics, RWTH Aachen University, Aachen, Germany, [4]Institute for Clinical Neuroscience and Medical Psychology, University of Düsseldorf, Germany, [5]JARA-Brain, Translational Brain Medicine, Jülich/Aachen, Germany, [6]C. and O. Vogt Institute for Brain Research, University of Düsseldorf, Düsseldorf, Germany and [7]Research Imaging Institute, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA

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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

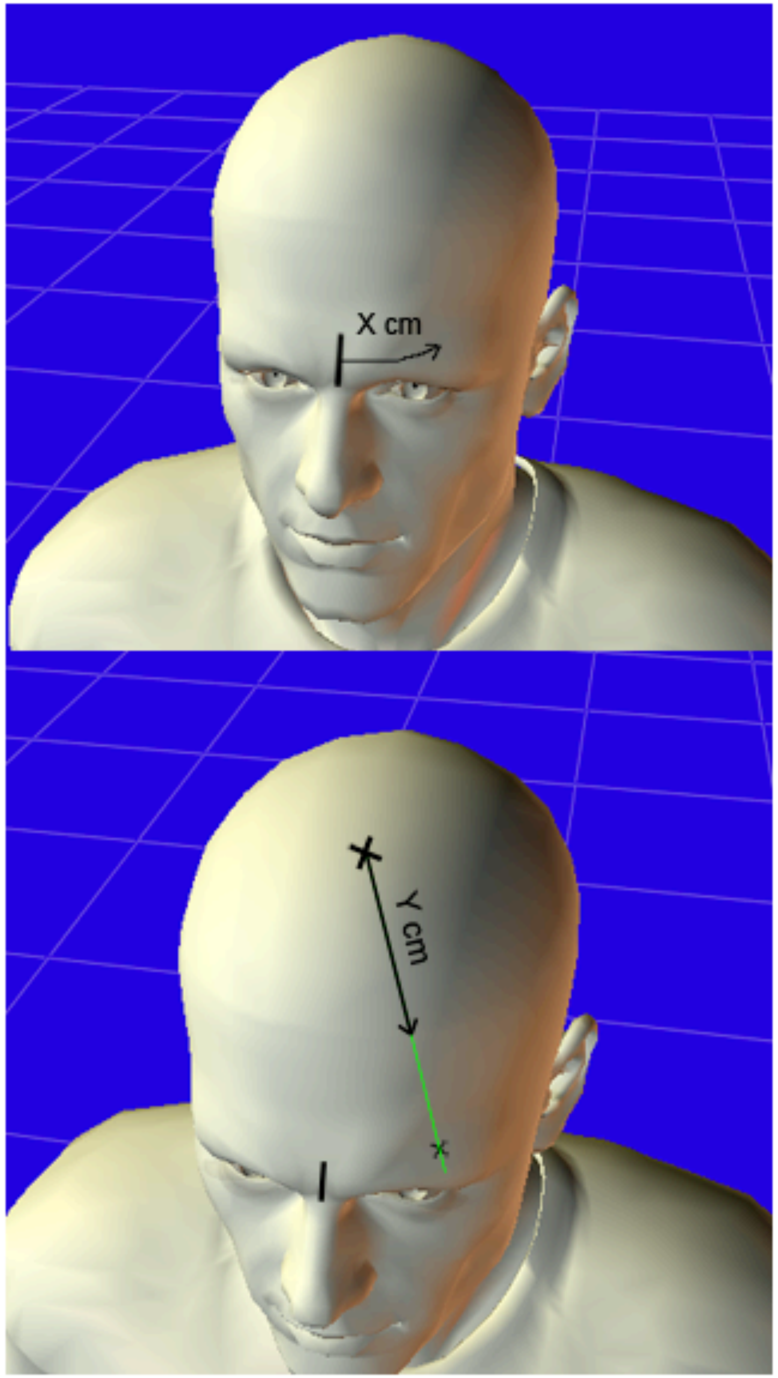
Calculate

Distance along cricumference from midline (X):

?

Distance from Vertex in CM (Y):

?



TMS OVERVIEW

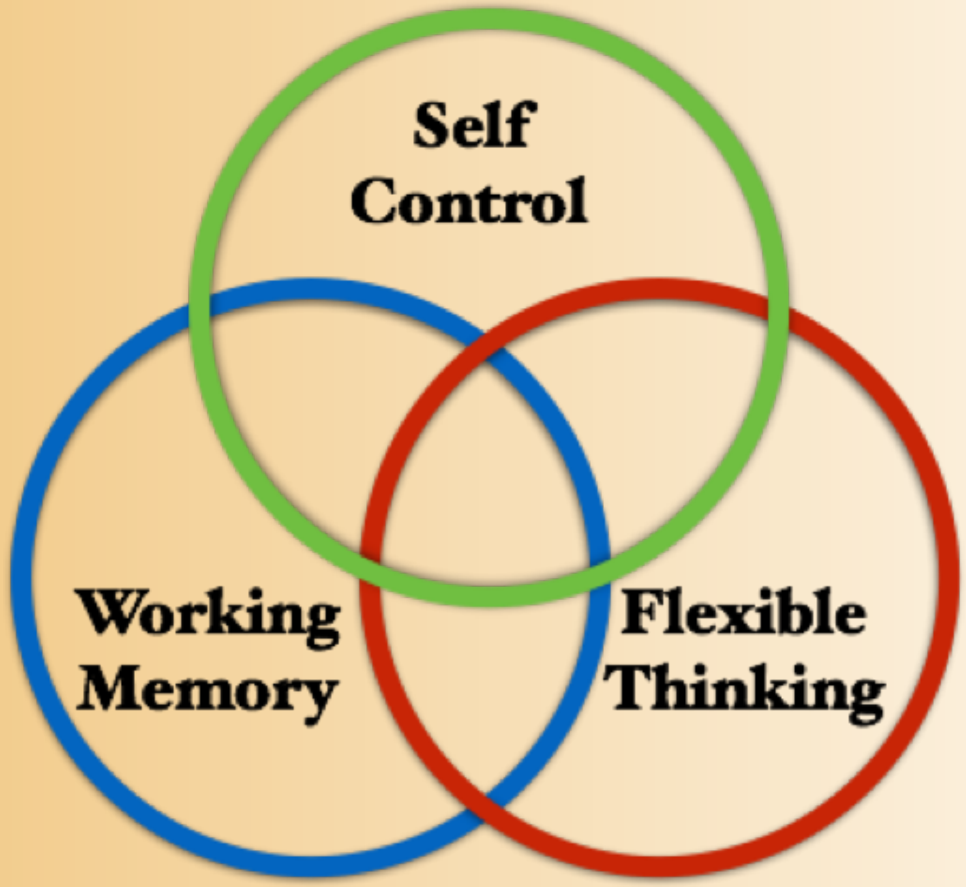
DLPFC

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

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

Striatum

SCA

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.

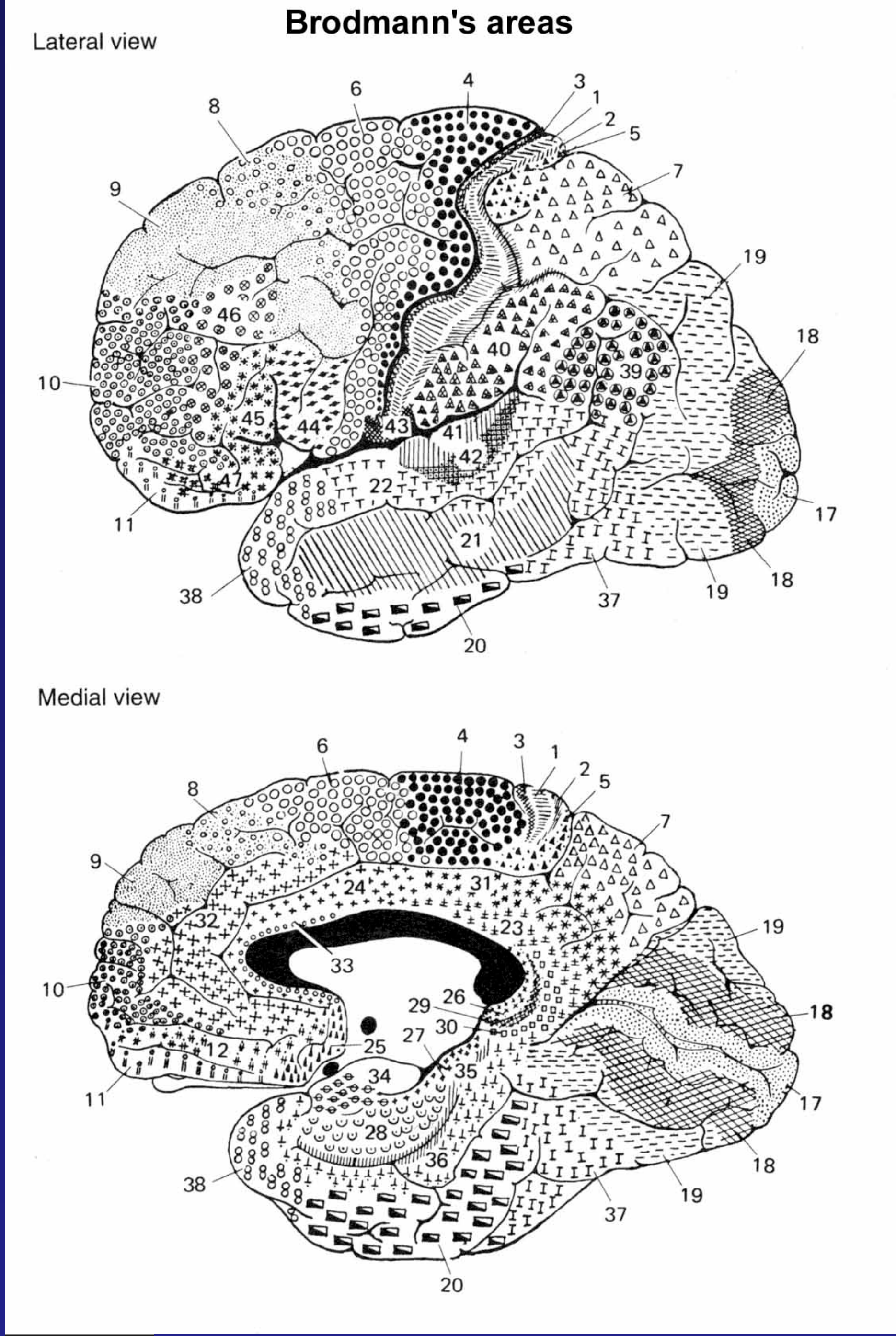
TMS When it hasn’t yet helped

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)

Chapter PRESENTATION

Section

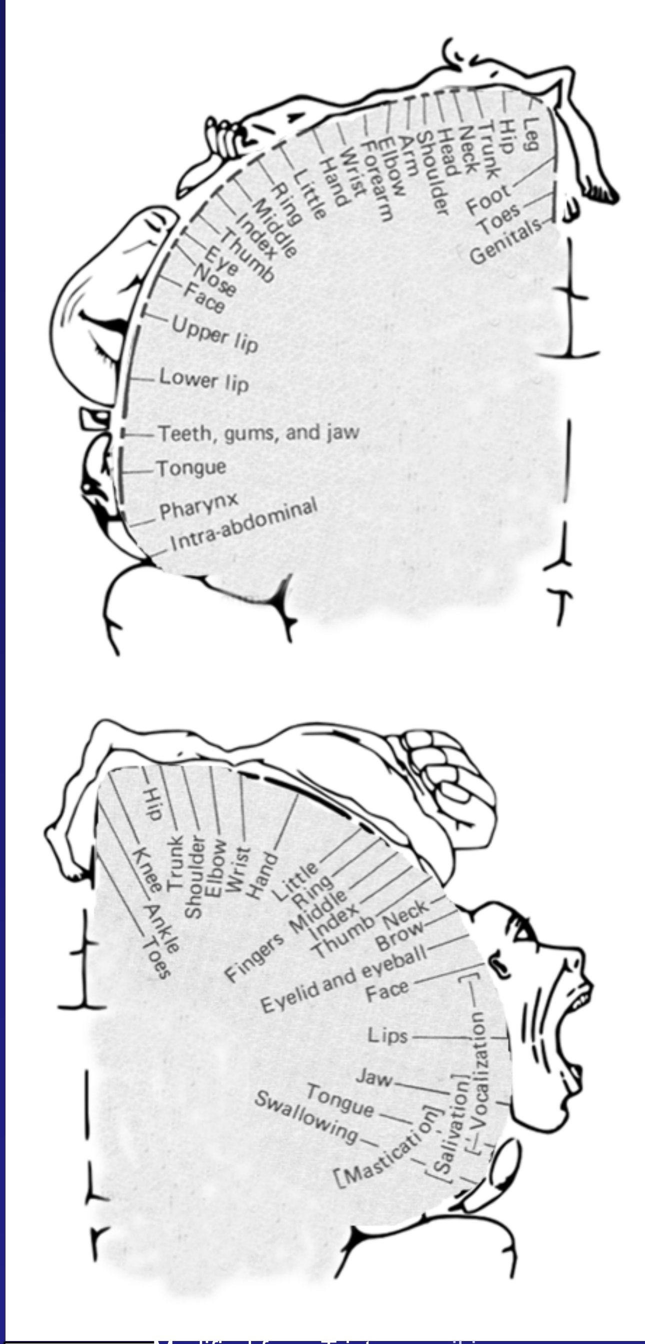
BODY



PD-INEL Brodmann, [wikimedia commons]

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

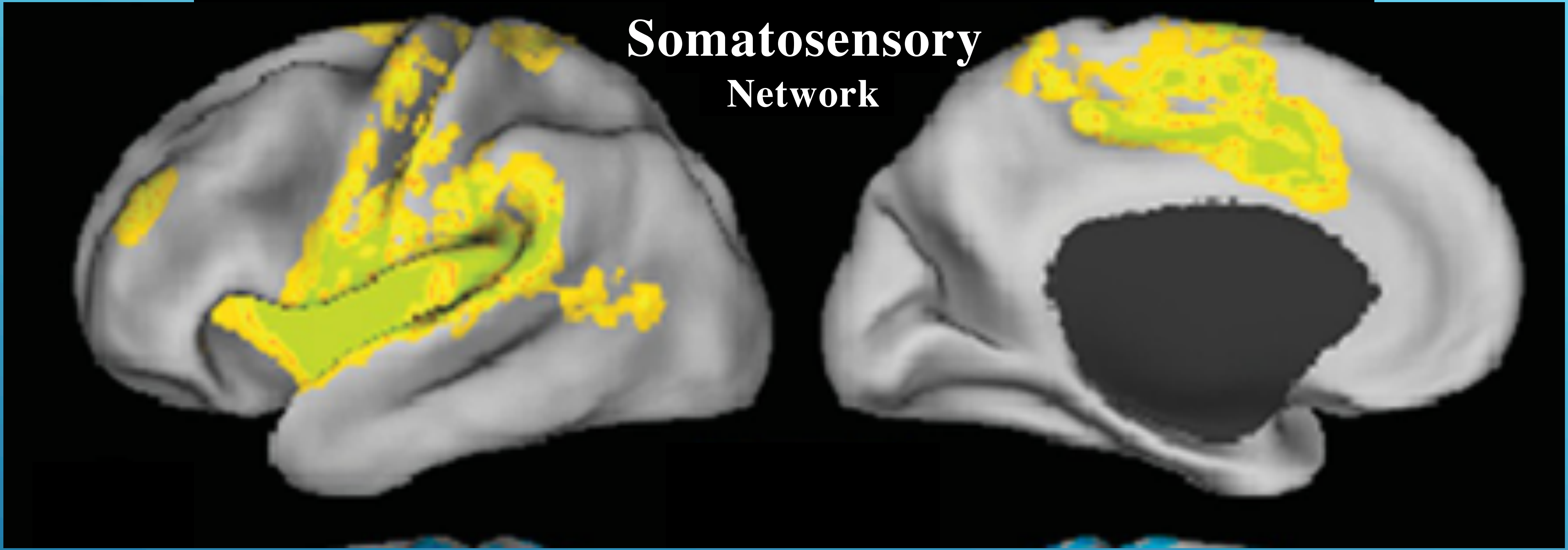
This is the most widely reproduced figure in the fields of neurology and neuroanatomy. Brodmann's nomenclature is still used today, e.g., area 17 is primary visual cortex.



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.

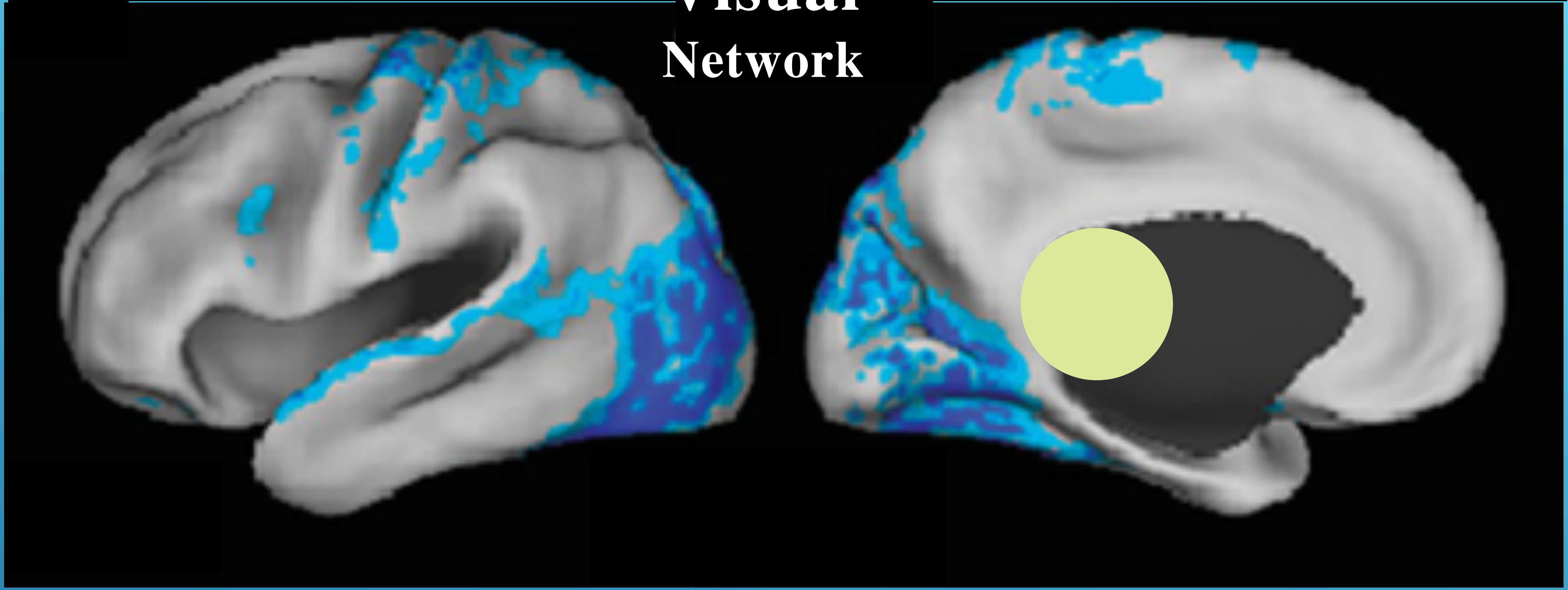
These topographic "maps" are distorted, reflecting sensory specializations of the periphery, such as the fine somatosensory discrimination of the hands and peri-oral regions.

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

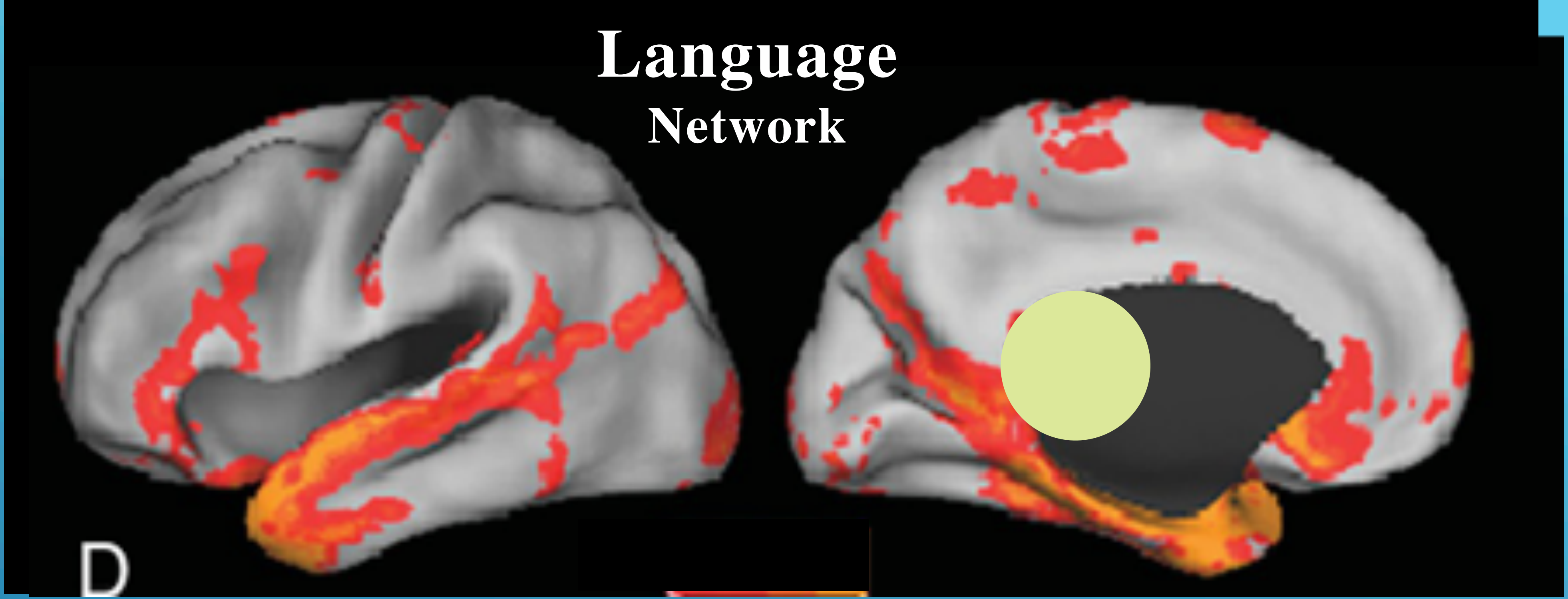


Several other RSNs have been identified. The **somatosensory network**, studied first by Biswal et al,1 includes primary and higher order motor and sensory areas (Fig 1B).

Visual
Network

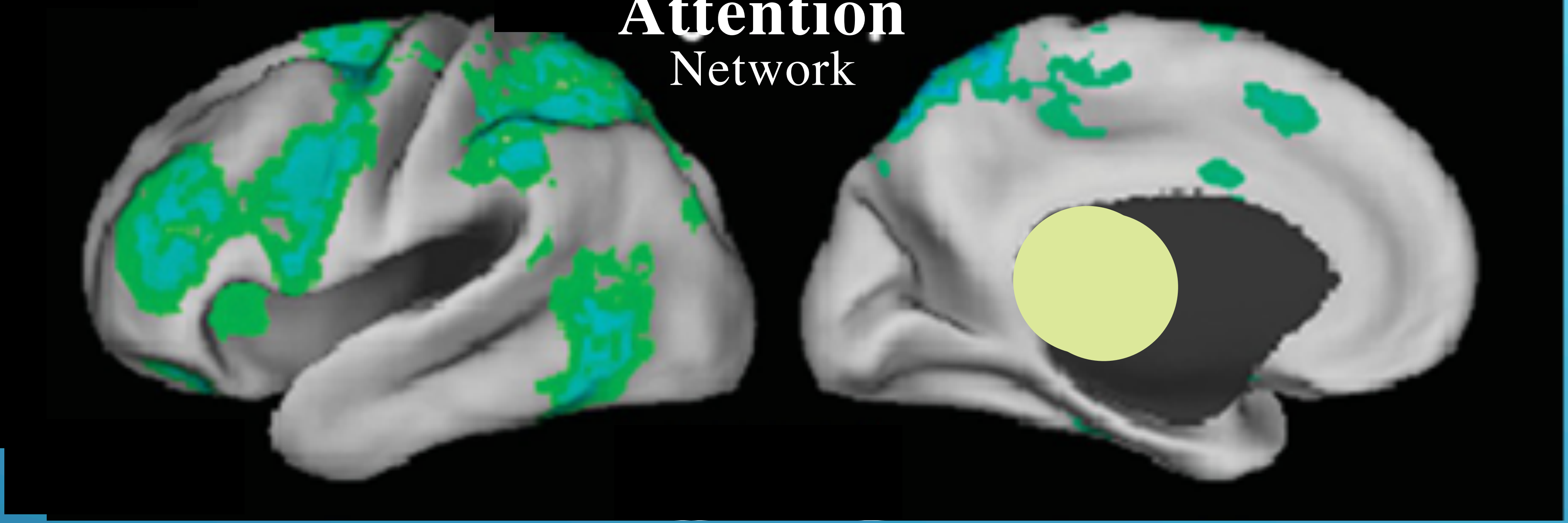


The visual network is highly consistent across various studies and spans much of the occipital cortex (Fig 1C).2-6



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

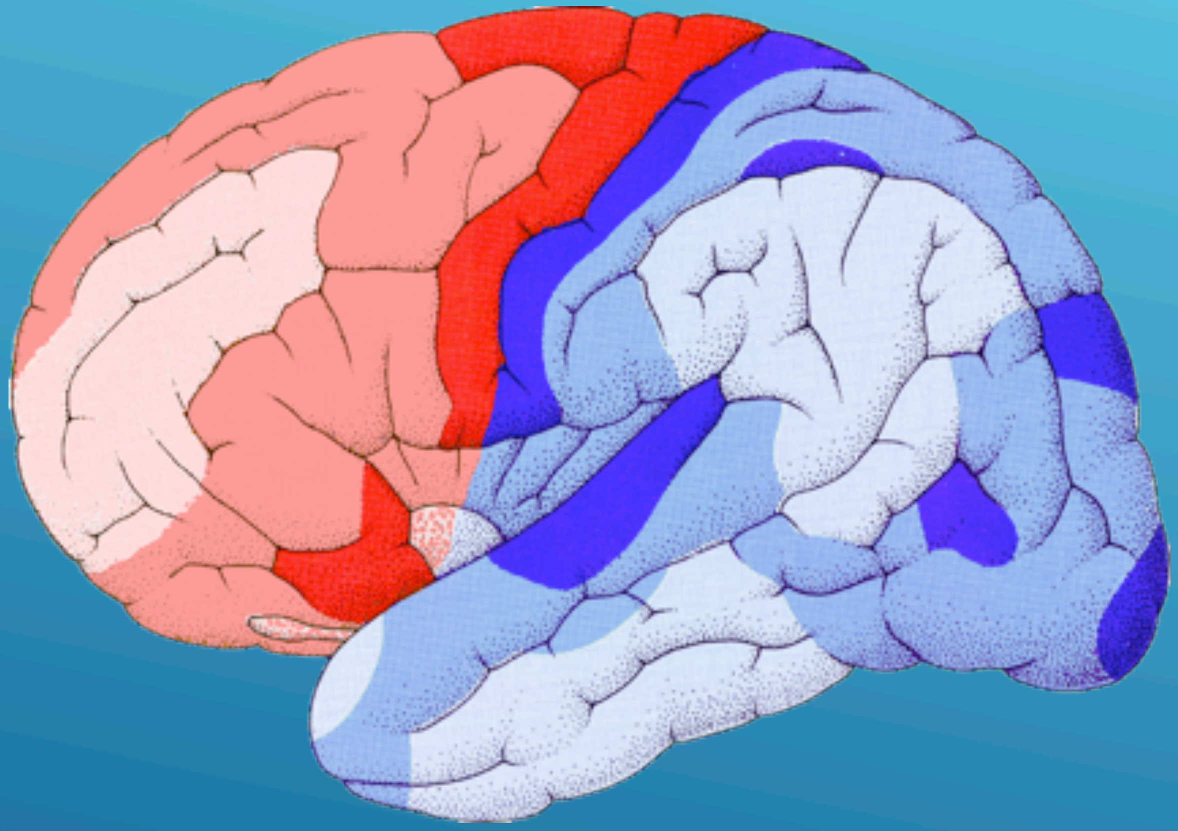
The Dorsal **Attention** Network



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.

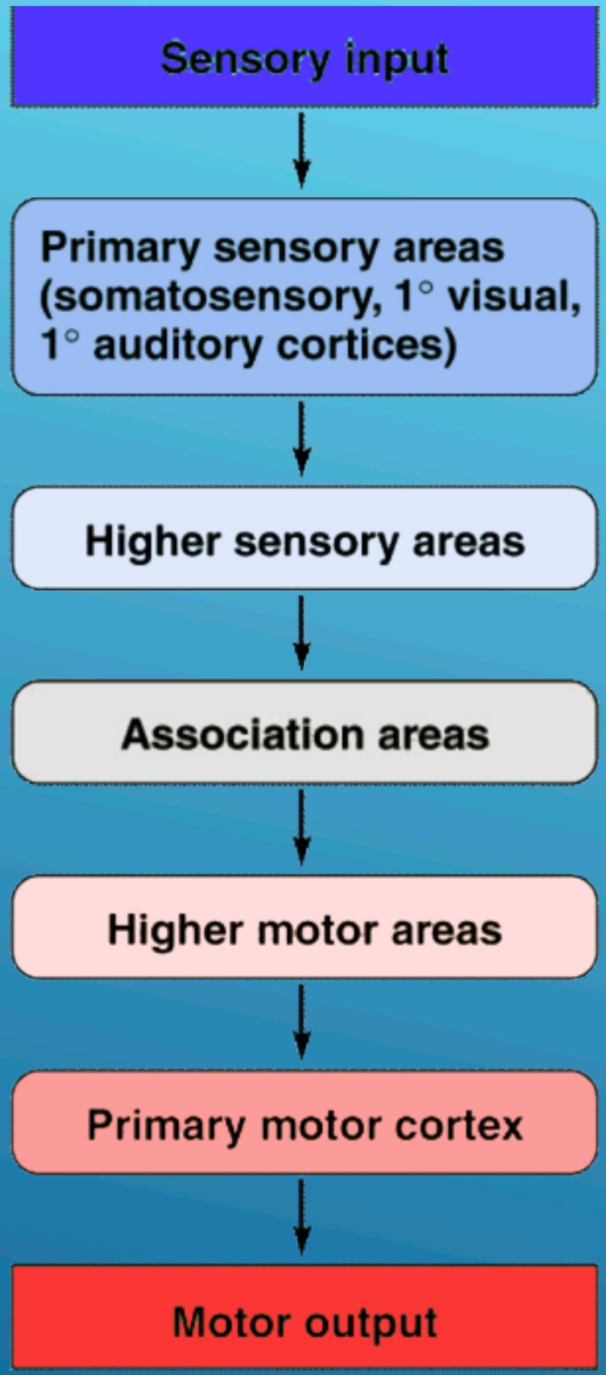
Mapping Cortex

Myelinogenesis

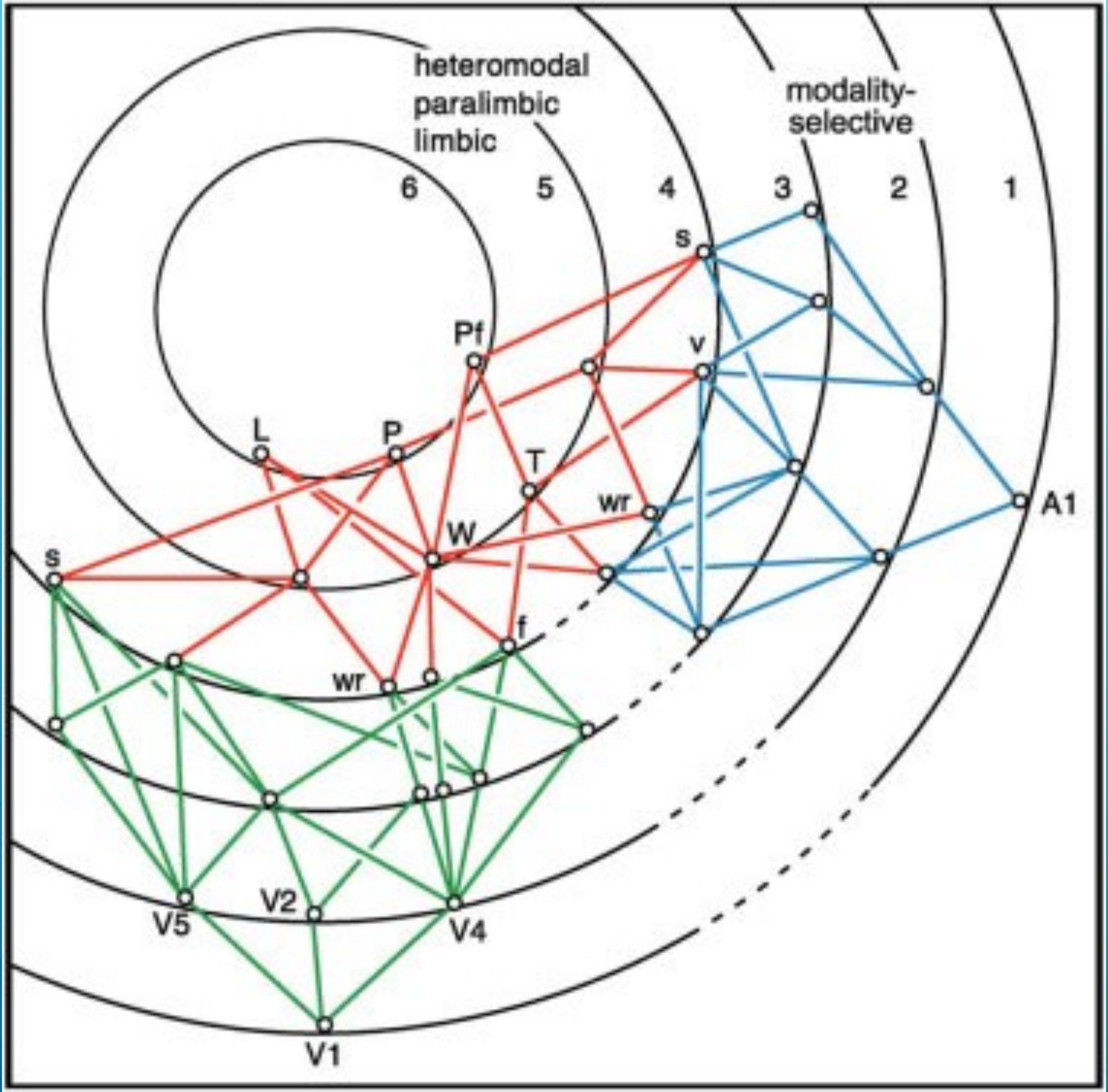


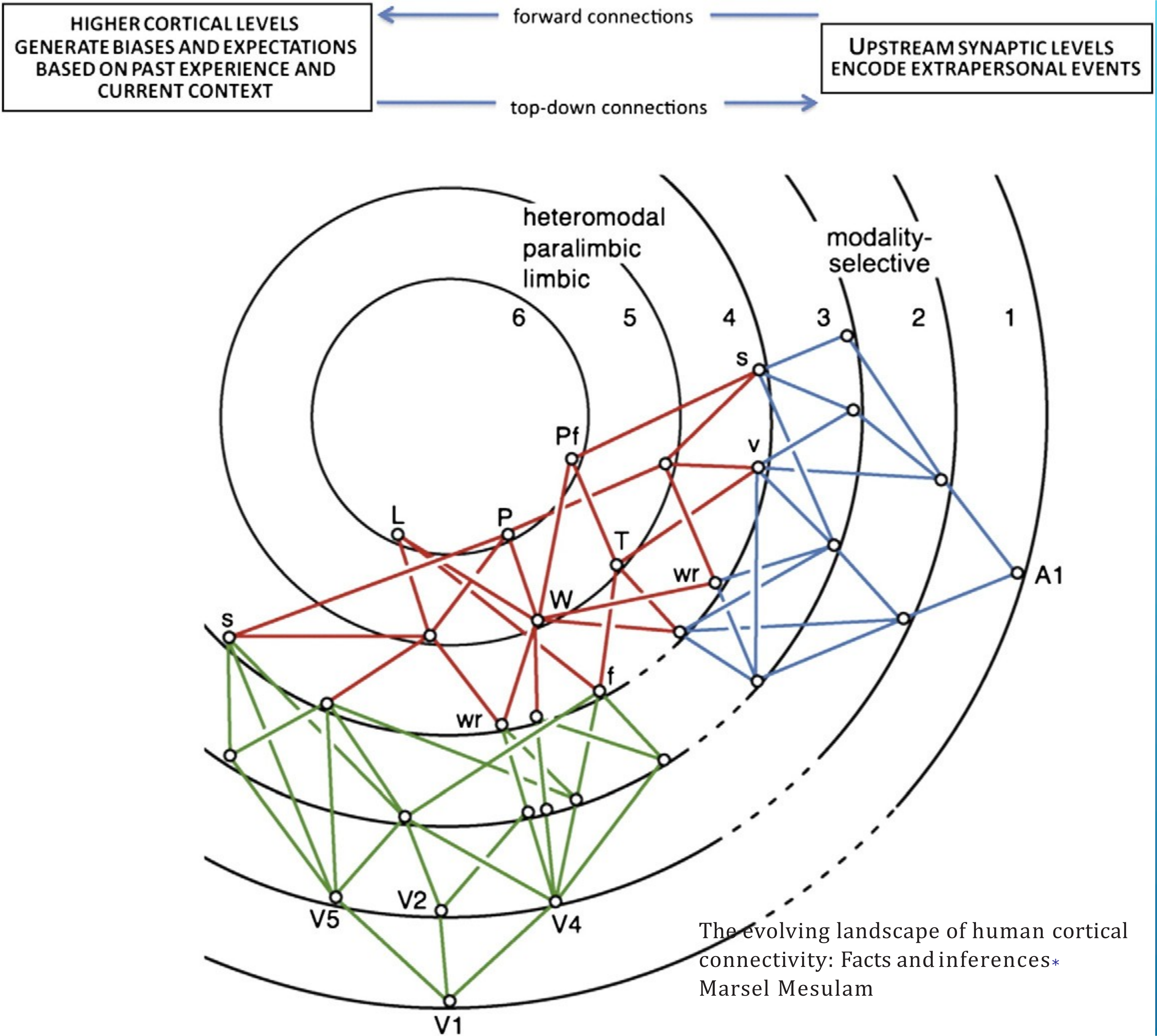
Mapping By Development

Lateral View



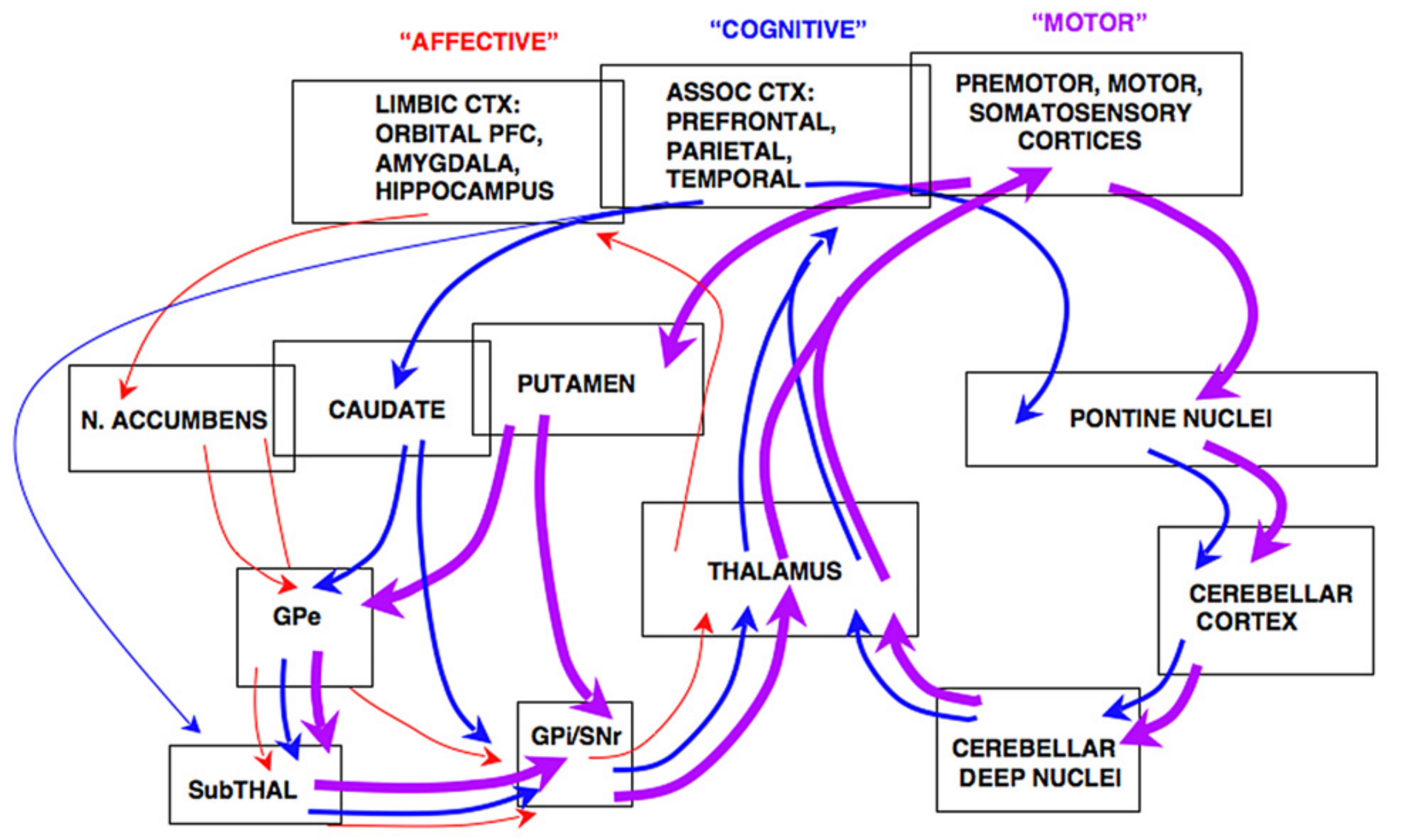
Sensory input
Primary sensory areas (somatosensory, 1° visual, 1° auditory cortices)
Higher sensory areas
Association areas
Higher motor areas
Primary motor cortex
Motor output


heteromodal
paralimbic
limbic
modality-
selective
6
5
4
3
2
1
s
Pf
v
L
P
T
wr
A1
W
s
f
wr
V2
V5
V4
V1



The evolving landscape of human cortical connectivity: Facts and inferences*
Marsel Mesulam

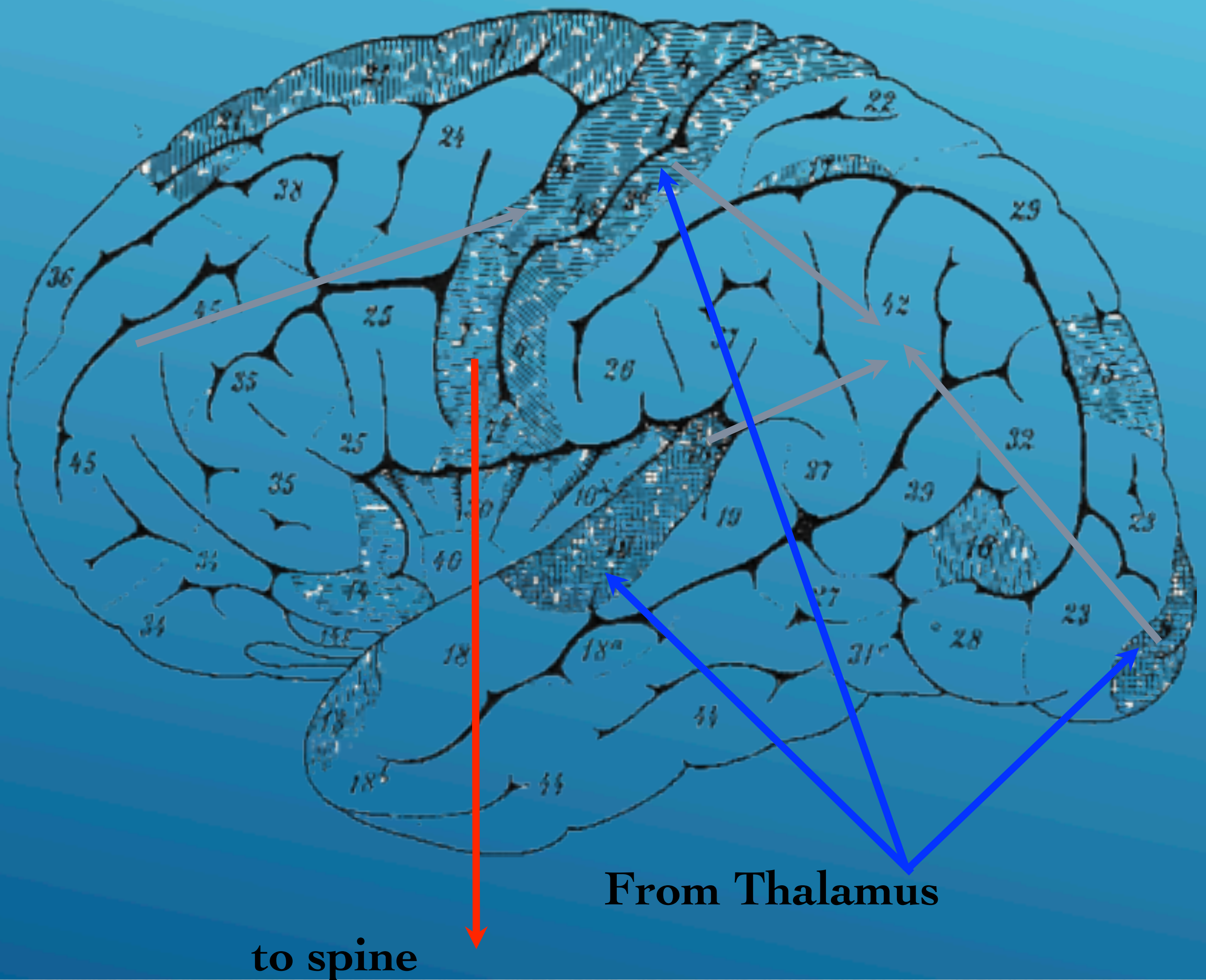
concentric ring represents a different synaptic "level." Any two consecutive levels are separated by at least one unit of synaptic distance. Level 1 is occupied by the primary sensory cortex, levels 2–4 by modality-selective cortices, and levels 5–6 by transmodal cortex. Colored lines represent monosynaptic connections from one synaptic level to another. Visual pathways are shown in green, auditory pathways in blue and transmodal pathways in red. The dashed lines interconnecting visual and auditory pathways in the first four synaptic levels indicate the scarcity of monosynaptic connections between sensory hierarchies belonging to different modalities. Abbreviations: A1—primary auditory cortex, f—area specialized for face encoding, L—the hippocampal– entorhinal or amygdaloid components of the limbic system, P—heteromodal posterior parietal cortex, Pf—lateral prefrontal cortex, s—area specialized for encoding spatial location in

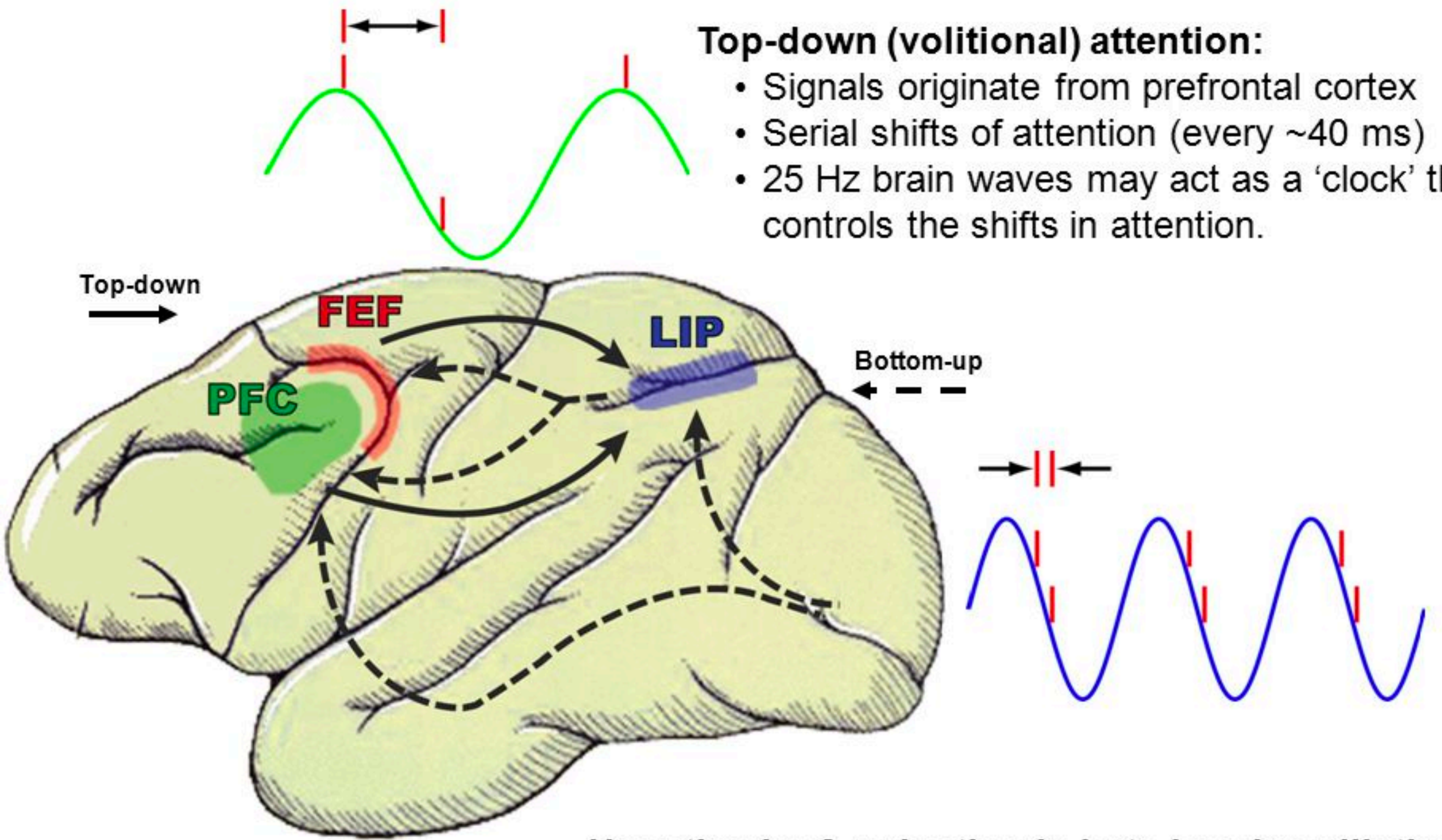


CORTICAL-BASAL GANGLIA CIRCUITS: motor, cognitive, and emotional habits

CORTICAL-CEREBELLAR CIRCUITS: motor and cognitive "gyroscope"

Information FLow
Direction of connections



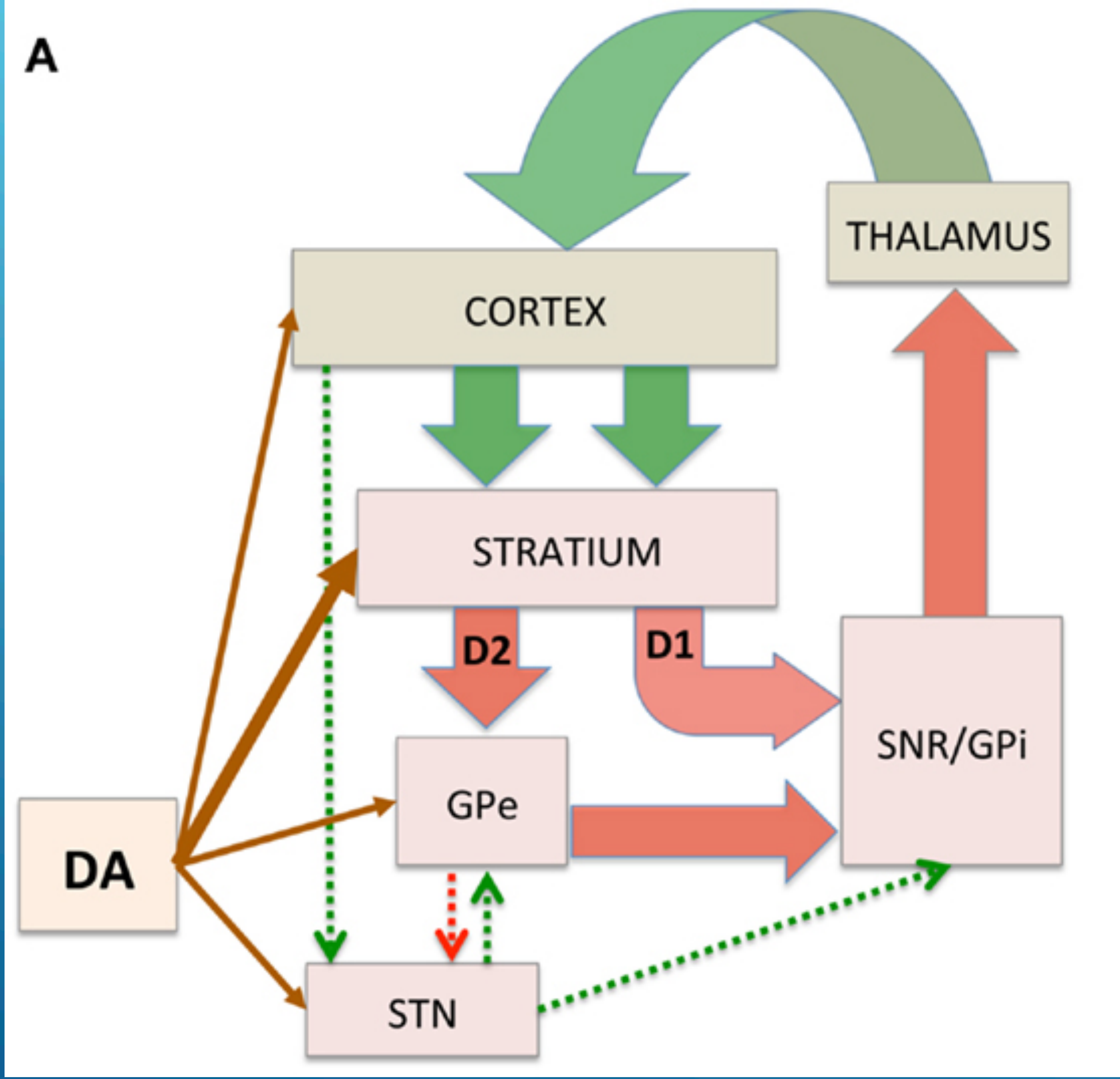


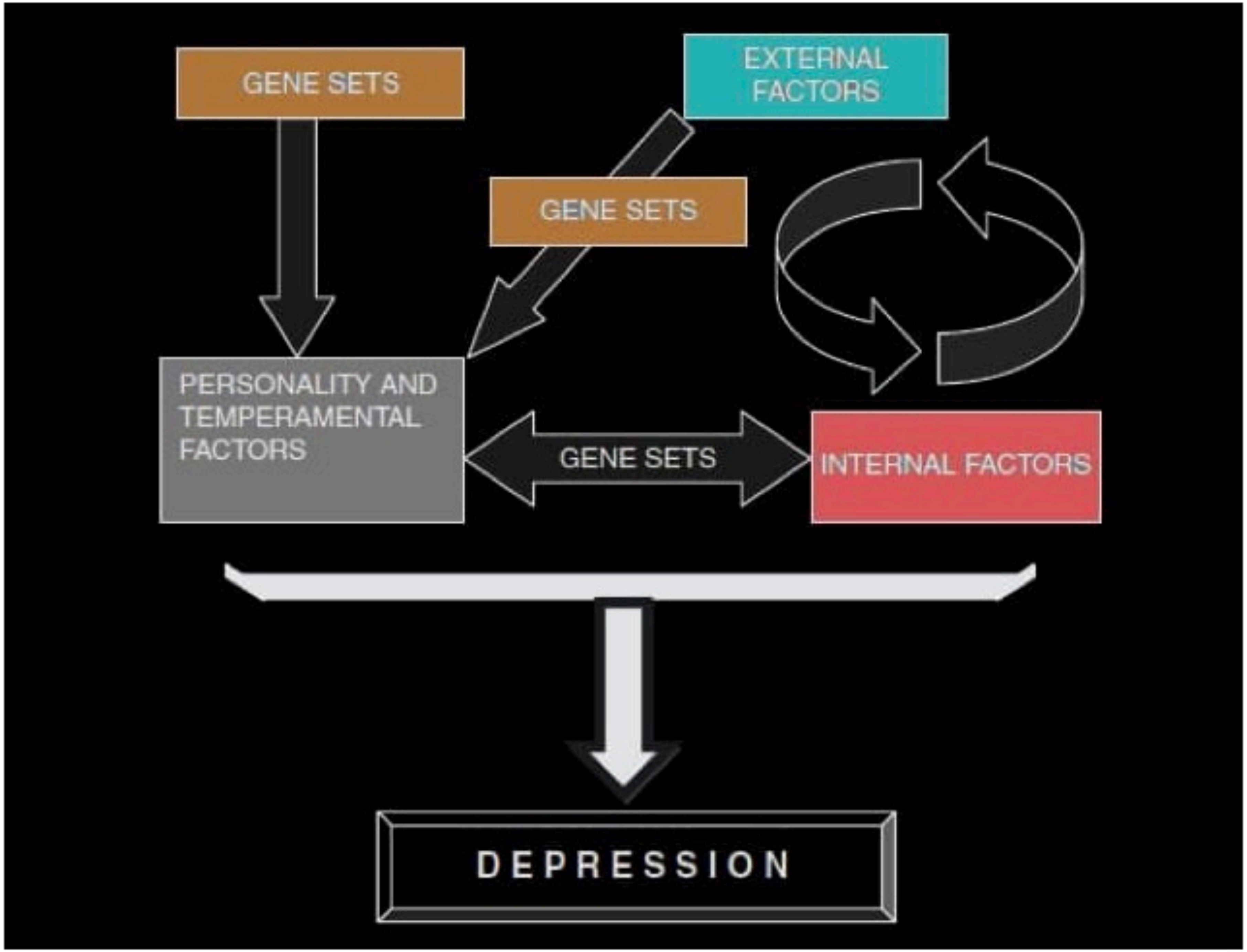
Top-down (volitional) attention:

- Signals originate from prefrontal cortex
- Serial shifts of attention (every ~40 ms)
- 25 Hz brain waves may act as a 'clock' that controls the shifts in attention.

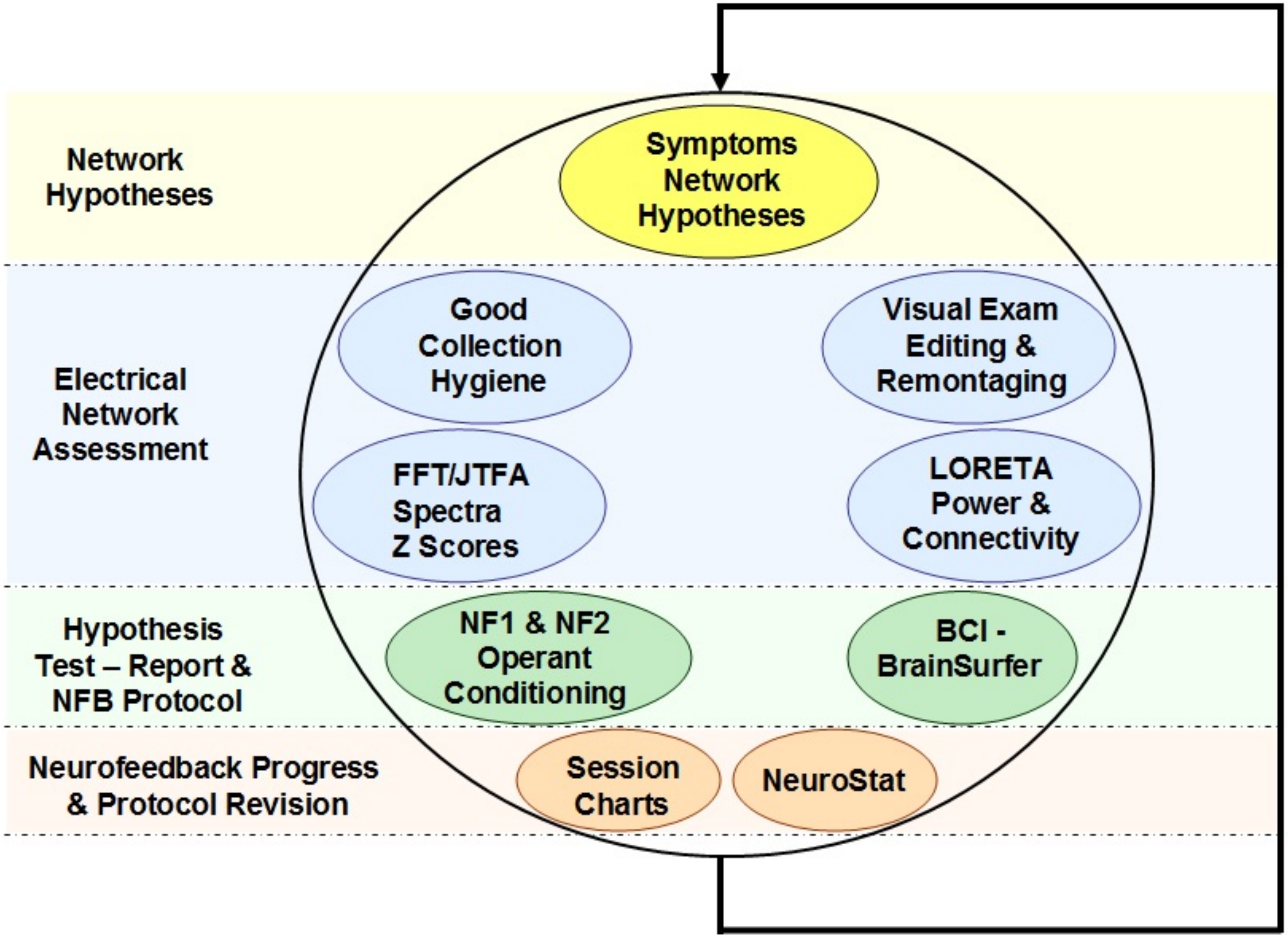
Hypothesis: A reduction in beta-band oscillations might explain why some people have trouble shifting attention away from distracting things.

Buschman and Miller (2007) *Science*
Buschman and Miller (2009) *Neuron*


A
THALAMUS
CORTEX
STRATIUM
D2
D1
SNR/GPi
GPe
DA
STN

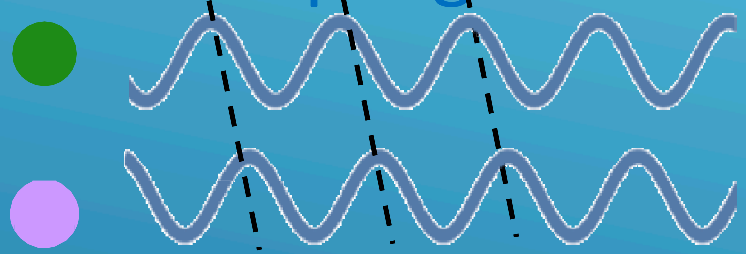

GENE SETS
EXTERNAL FACTORS
GENE SETS
PERSONALITY AND TEMPERAMENTAL FACTORS
GENE SETS
INTERNAL FACTORS
DEPRESSION

Linking Patient’s Symptoms to Patient’s Brain



http://neurosynth.org

Functional Connectivity through Phase Coupling



Fries 2005, 2015

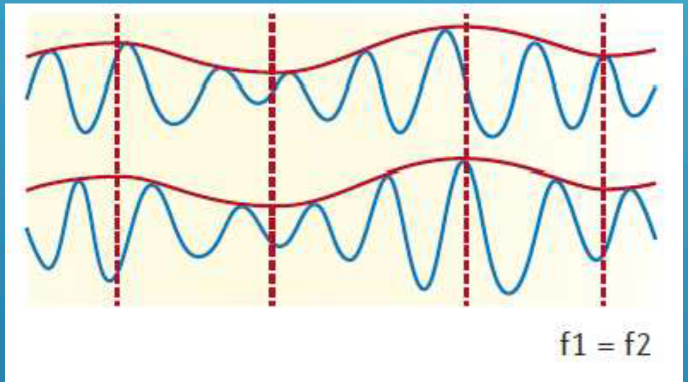
Connectivity requires rhythmic synchronization within pre- and postsynaptic groups , i.e., communication through coherence.

Inputs that consistently arrive at moments of high gain benefit from enhanced connectivity (CTC).

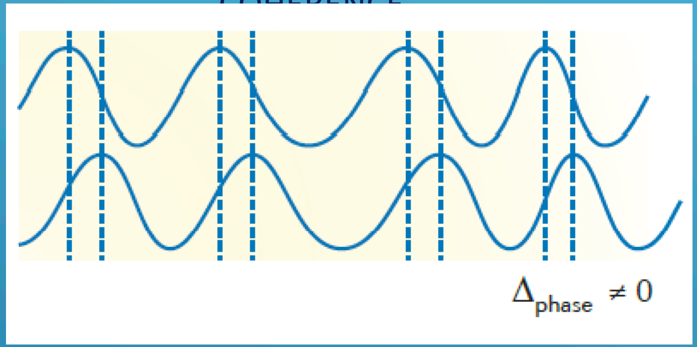
RSNs and MEG: Phase Coherence

A different perspective into brain interactions

AMPLITUDE



PHASE COHERENCE



adapted from Siegel et al., 2012

One possible tool for investigating coupling between cortical populations is to assess the coupling of the respective neuronal oscillations through *Phase Coherence*.

Fettes 2016 Neural correlates of successful orbitofrontal 1 Hz rTMS following unsuccessful dorsolateral and dorsome
rTMS in major depression- A case report 1 Hz right OFC-rTMS.pdf

30 sessions of right OFC-rTMS (positioning per [8]), 5 days/week, Cool-DB80 coil positioned over the Fp2 EEG site, handle vertical and upwards, 360 pulses/session, 1 Hz, 6 × 60 s trains, 30 s interval, as previously employed in a large multicentre trial of right DLPFC-rTMS

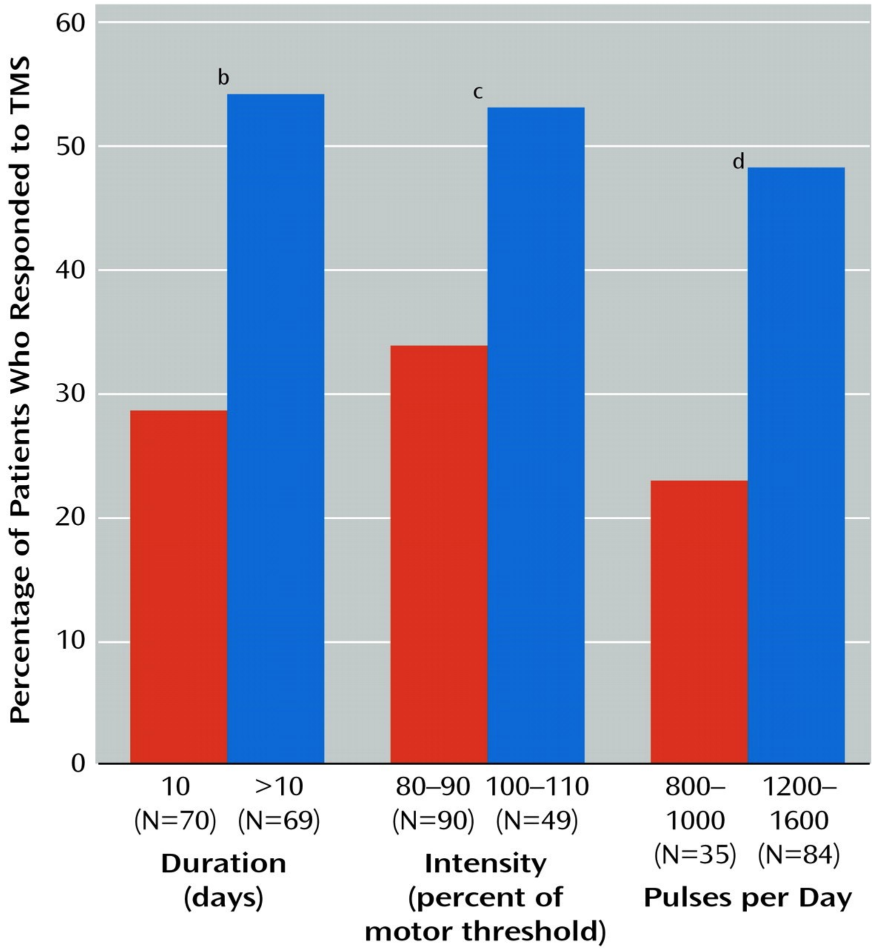
Nauczyciel 2014 80 double cone Deep

The international 10–20 EEG system was used to position the coil over the right OFC, at the right frontopolar 2 (Fp2) electrode
(two per day over 1 week) were administered using the following parameters: 120% motor threshold, 1 Hz, 1200 pulses per sess
OFC.

Brunelin 65 single cone

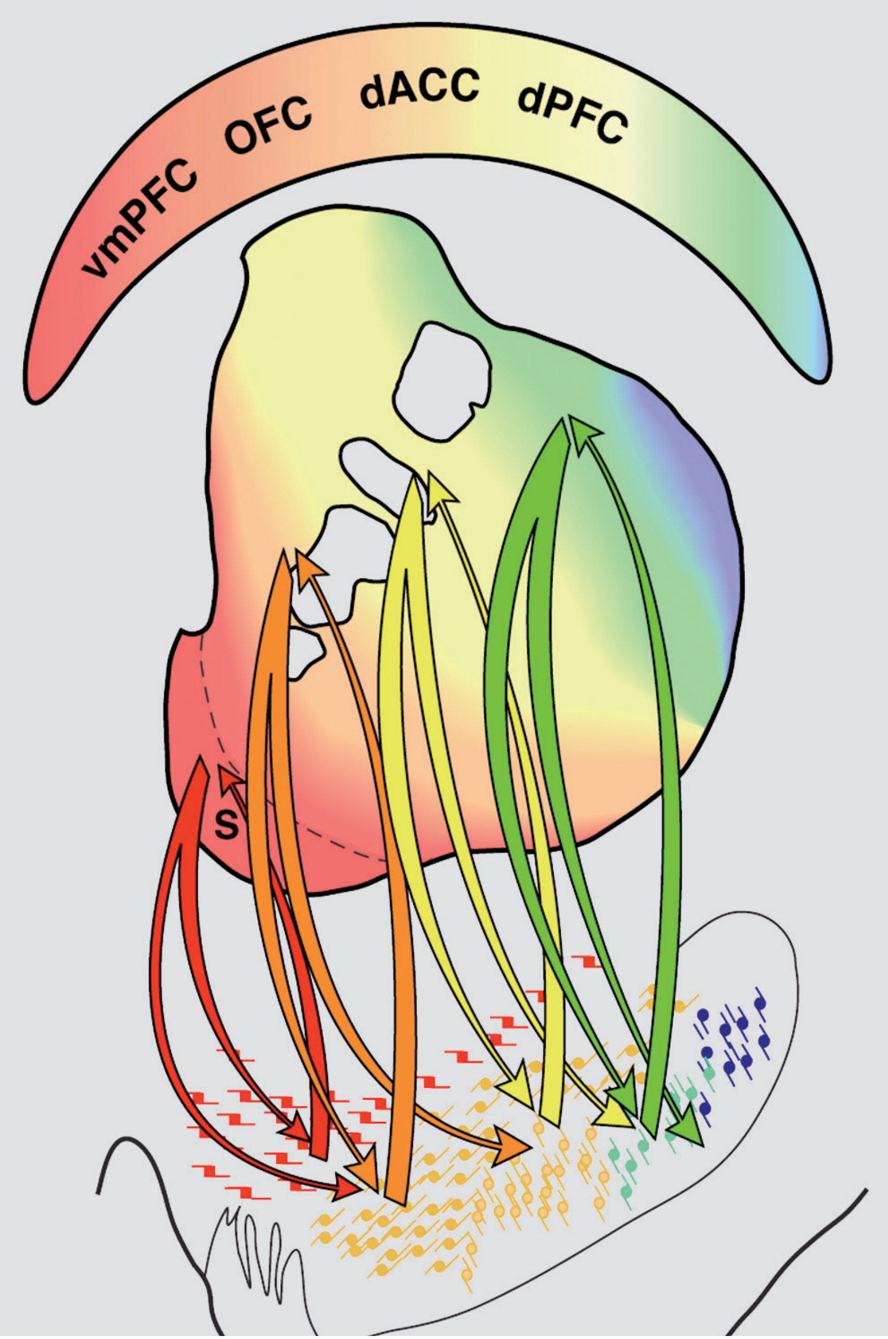
6 trains of 1-min duration separated by 30-sec inter-train "off" periods.

Dose-Response Relationship in Antidepressant Efficacy of TMS



- Stronger antidepressant effects with increased dose:
  - number of sessions
  - stimulation intensity
  - pulses per day
- May underlie increased effect size of recent studies
- Informed design of pivotal trial

Gershon, et al (Am J Psychiatry 2003)



M1
SMA
DLpfc
dACC
OFC
VMpfc

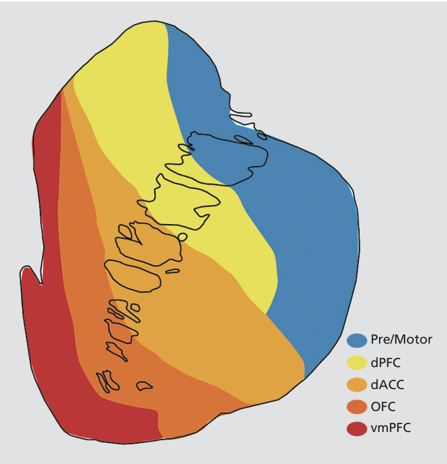
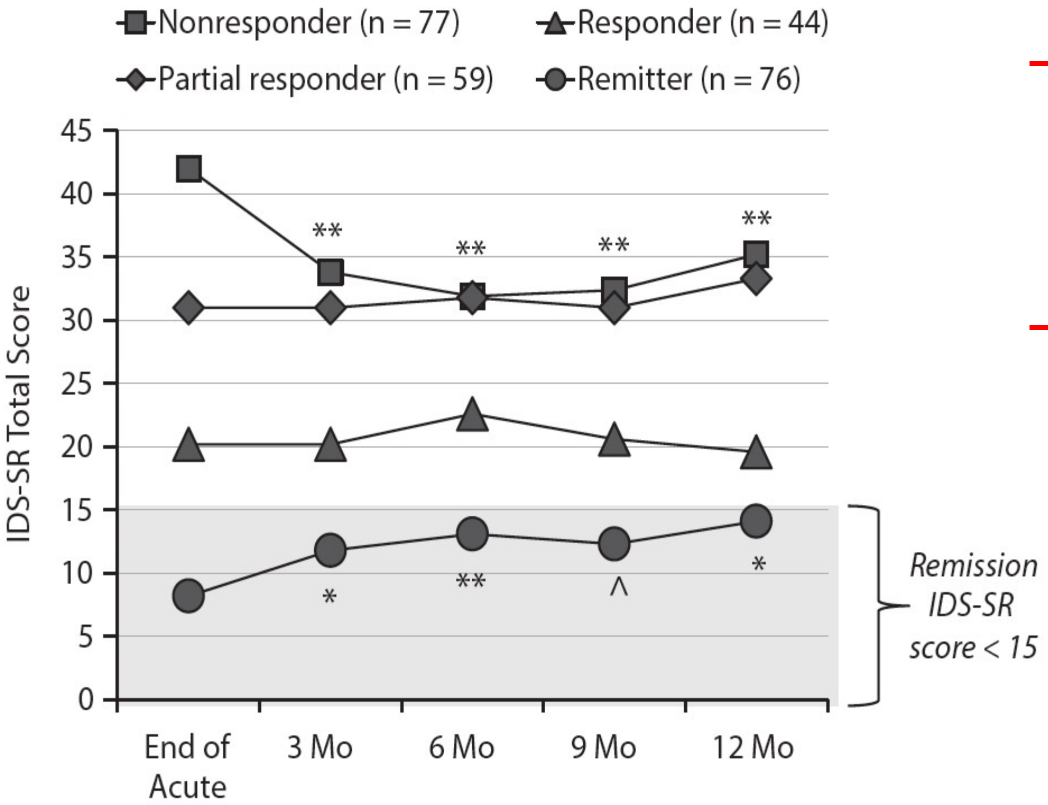


Figure 3. Schematic illustrating the general topography of frontal inputs to the rostral striatum. dACC, dorsal anterior cingulate cortex; dPFC, dorsal prefrontal cortex; OFC, orbitofrontal cortex; vmPFC, ventromedial prefrontal cortex.

How effective is TMS in Practice?

- Dunner et al 2014

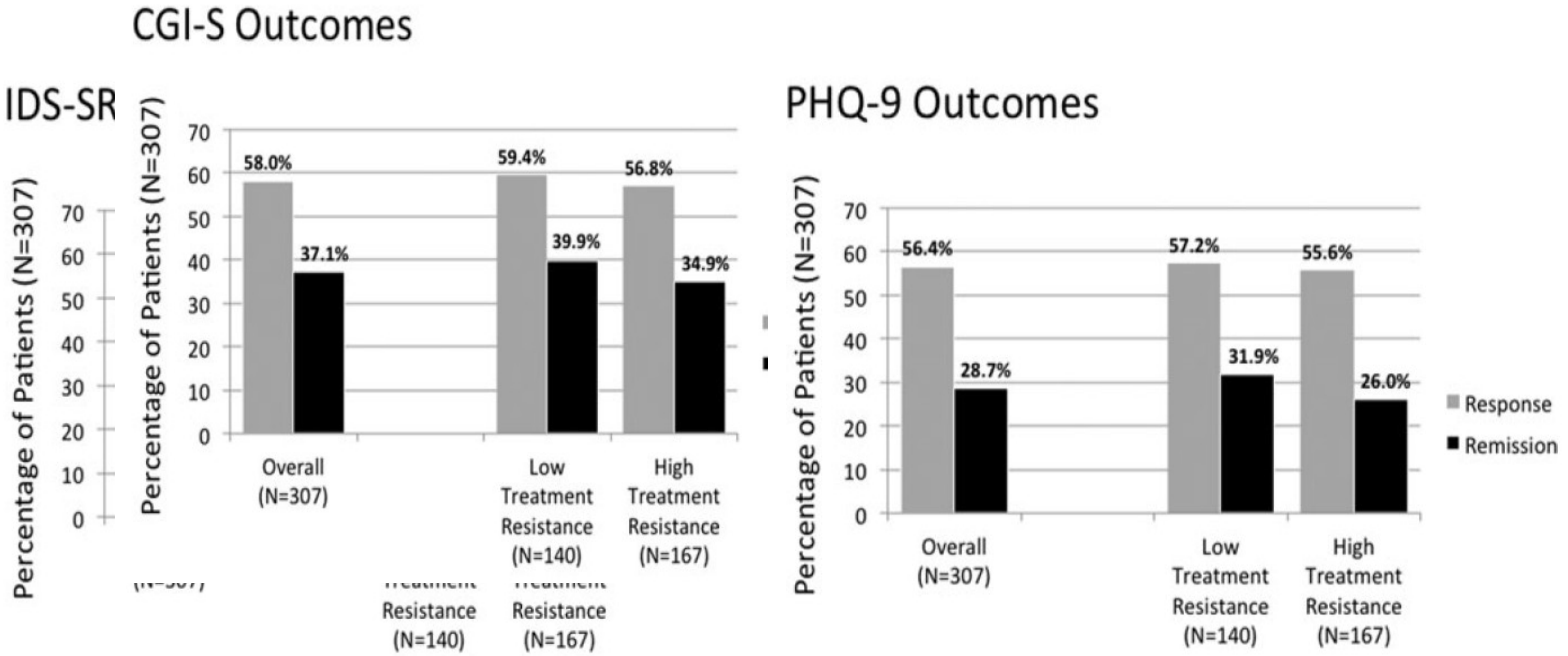
Figure 2. Summary of IDS-SR Total Score Outcomes During Long-Term Follow-Up: Stratification by End of Acute Treatment Clinical Outcome (N = 257)[a]



- – **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

Step 1

FDA Approved Dosage
10 Hz Left DLPFC, 120% MT, 3,000 pulses/day

If ≤25% improvement on QIDS after minimum of 3 wks, consider switch to Step 2

Step 2

Increase Pulses 10 Hz Left DLPFC, up to 6,000 pulses/day

Sequential Bilateral
10 Hz Left + 1 Hz Right DLPFC

MRI Guidance Adjust site and/or intensity to target left DLPFC

1 Hz Right
1 Hz Right DLPFC

If ≤25% improvement on QIDS after minimum of 3 wks, consider switch to Step 3

Step 3

Step 2 Strategy Not Yet Used
Inc. pulses, Bilateral Stim, MRI Guidance, or 1 Hz Right

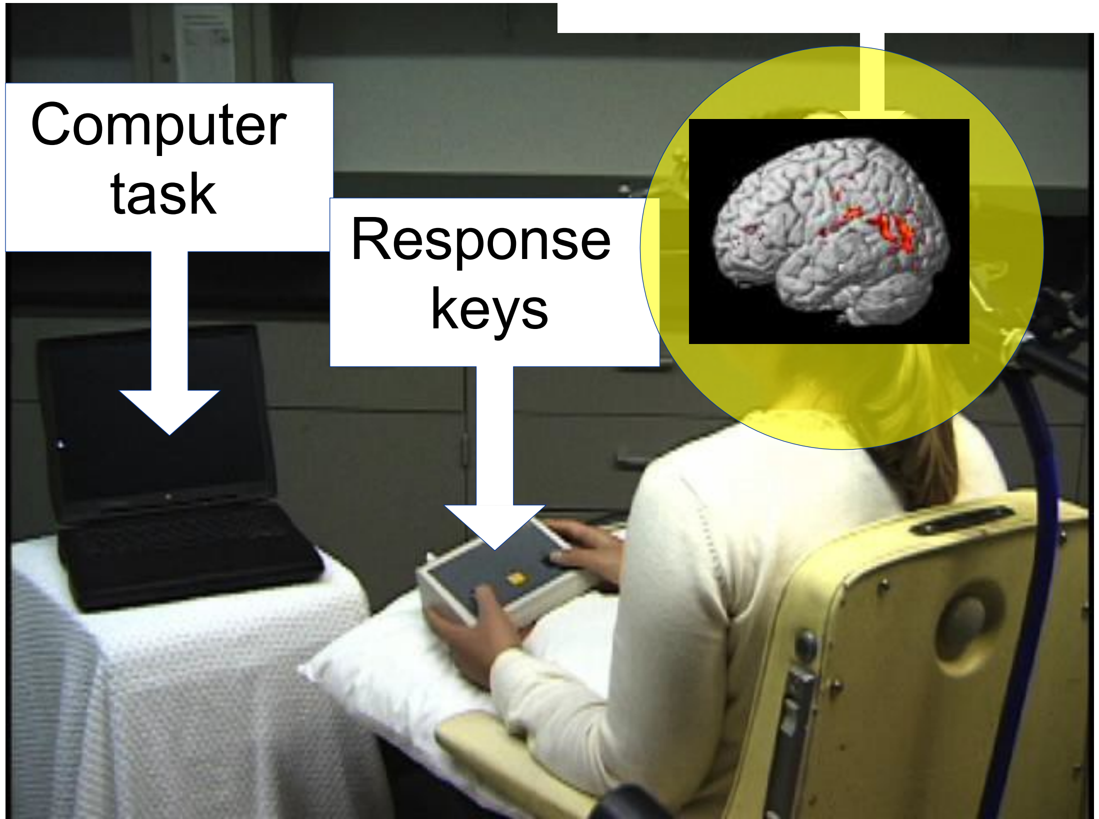
Instructions:
1)Patients who have failed a single antidepressant medication at adequate dose/duration start at Step 1. For more resistant patients, clinician may start at Step 1 (given that efficacy of TMS in such patients on concomitant antidepressant medications is not known), or may chose to start 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?



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

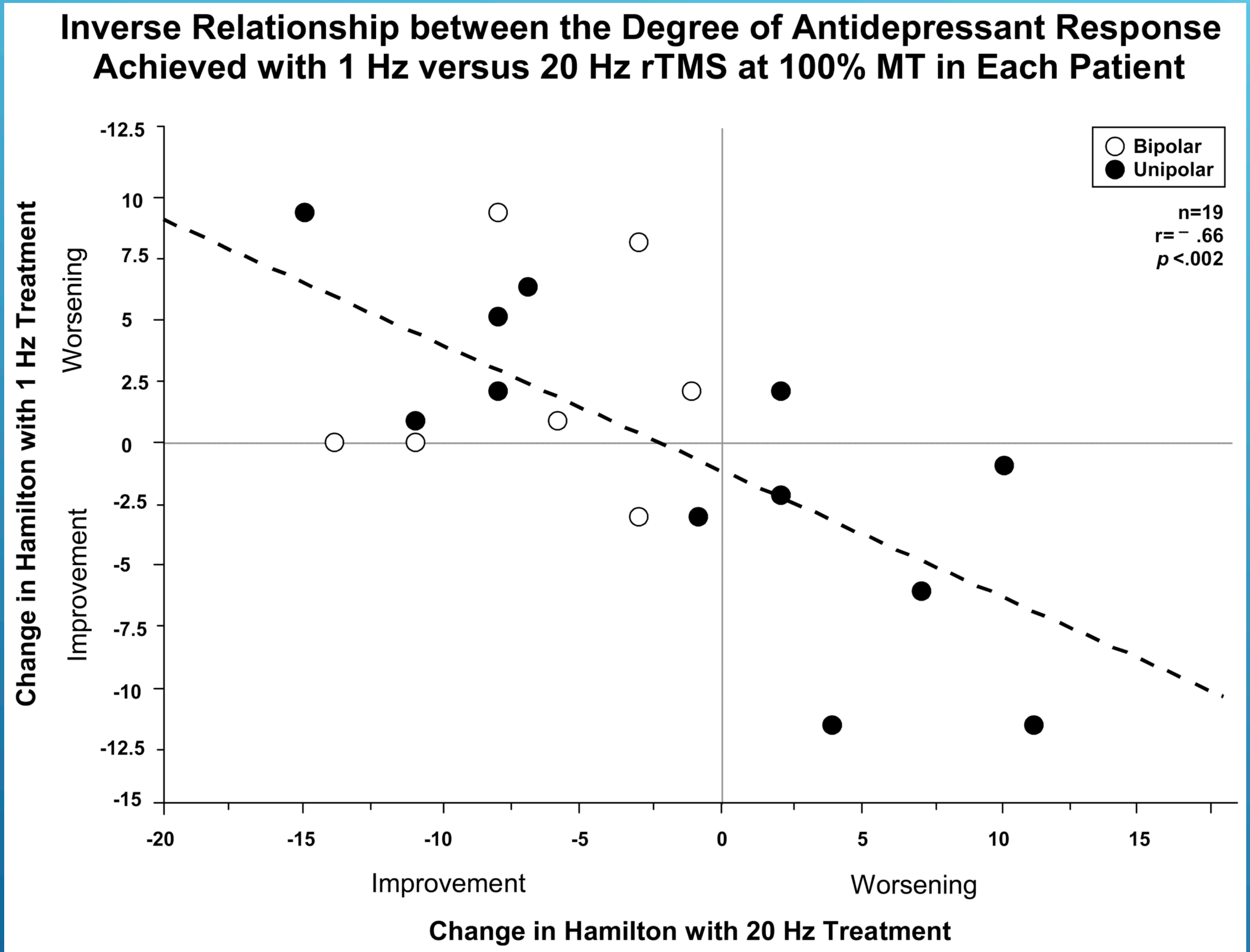


Figure 1.
Inverse relationship (r = −0.66) between the degree of antidepressant response (change in

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

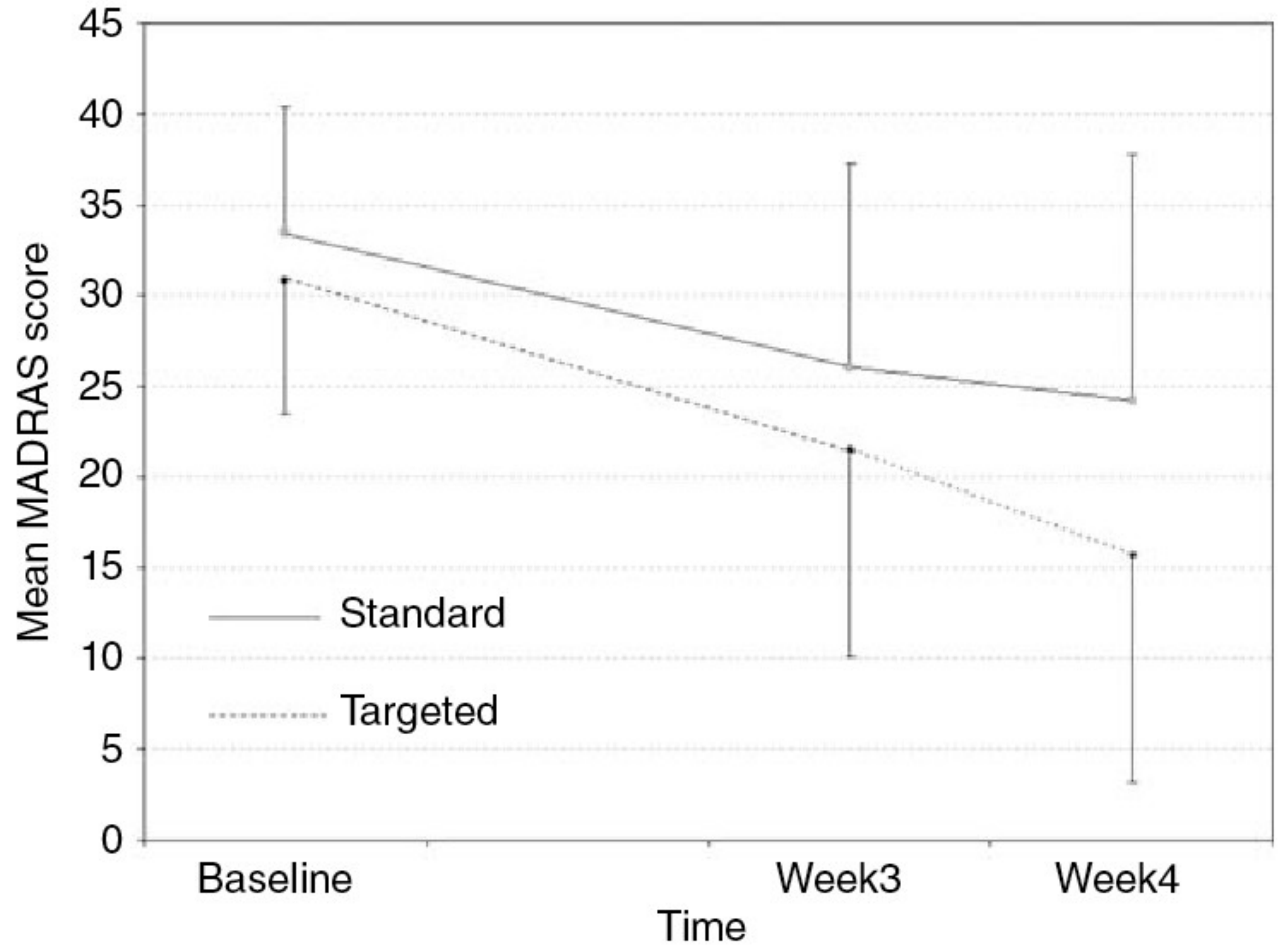


Figure 2 Change in Montgomery–Asberg Depression Rating Scale (MADRS) scores (least square means) over time.

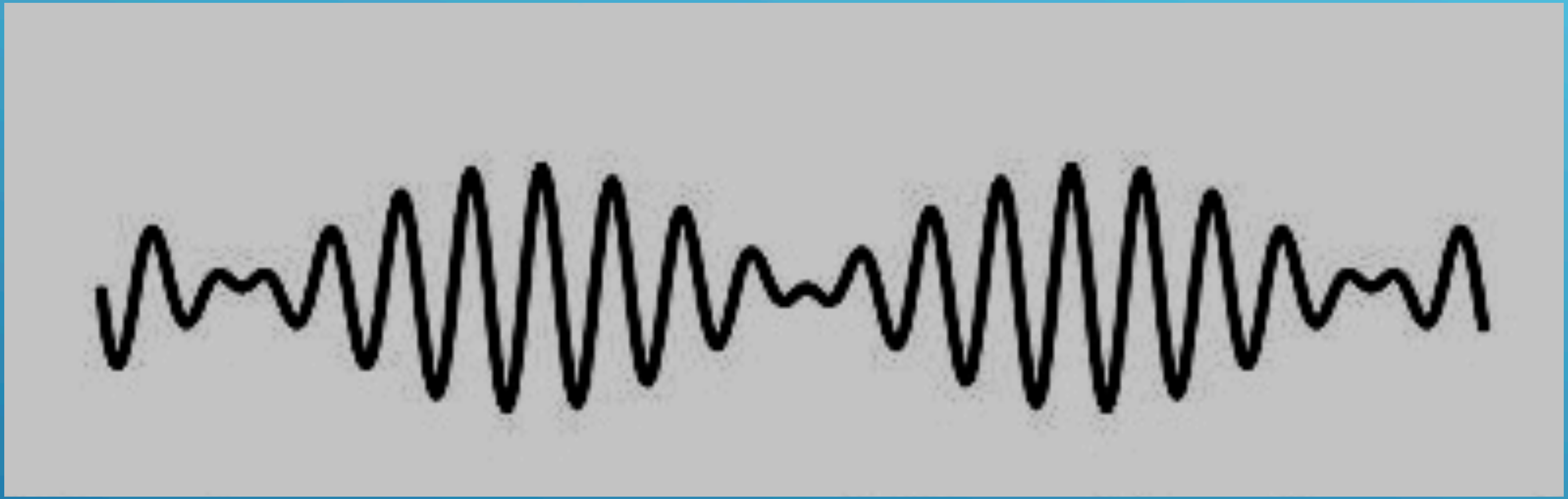
Defining Outcome

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)*

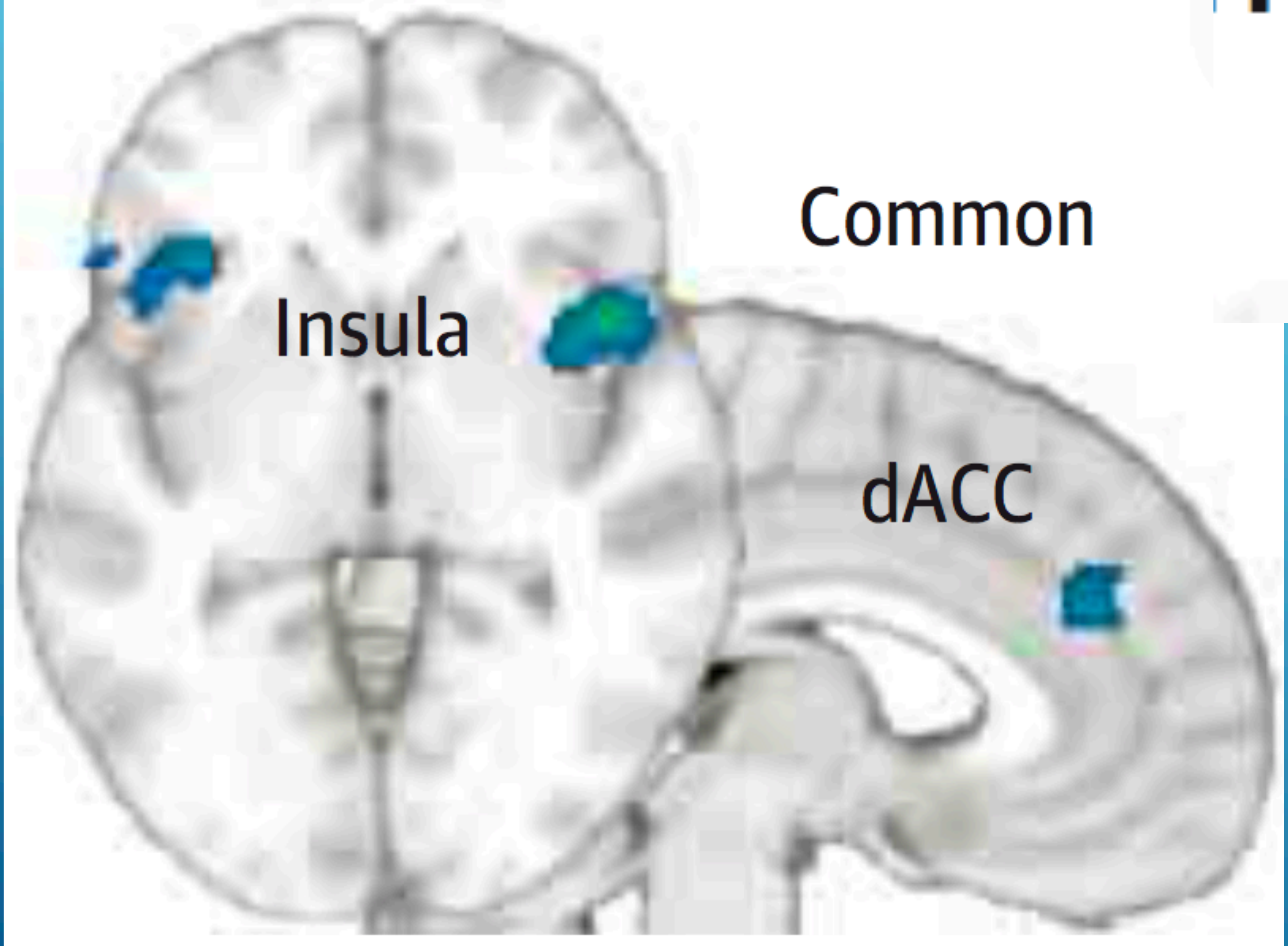
Mann J J. *N Engl J Med*. 2005;353: 1819-1834.

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

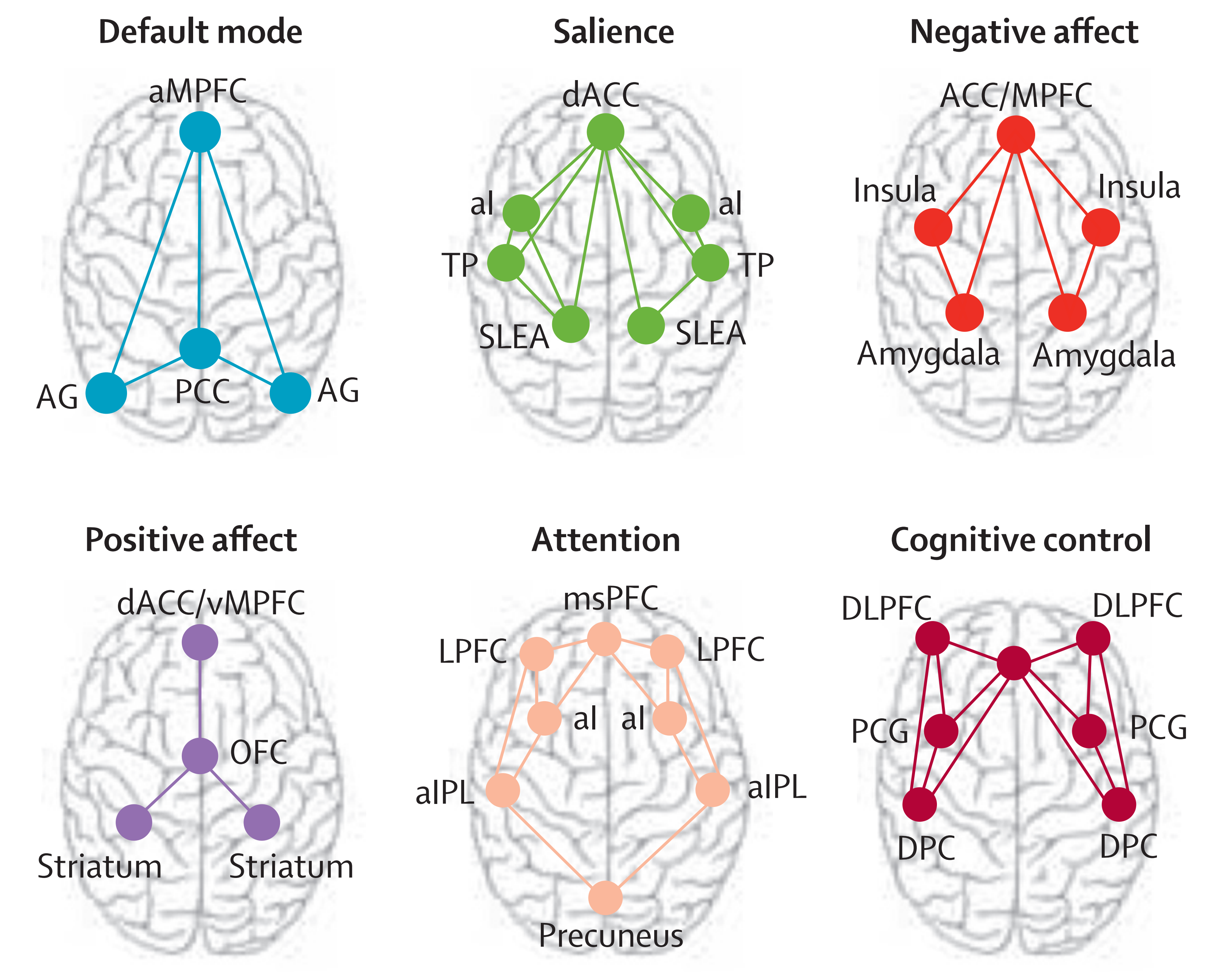

Common
Insula
dACC

Goodkind 2015 Identification of a Common Neurobiological Substrate for Mental Illness

MAIN OUTCOMES AND MEASURES We tested for areas of common gray matter volume increase or decrease across Axis I diagnoses, as well as areas differing between diagnoses. Follow-up analyses on other healthy participant data sets tested connectivity related to regions arising from the meta-analysis and the relationship of gray matter volume to cognition.

RESULTS Based on the voxel-based morphometry meta-analysis of 193 studies comprising
15 892 individuals across
6 diverse diagnostic groups
(**schizophrenia**,
bipolar disorder,
depression,
addiction,
obsessive-compulsive disorder, and
anxiety), we found that gray matter loss converged across diagnoses in 3 regions:
the dorsal anterior cingulate,
right insula, and left insula.
By contrast, there were few diagnosis-specific effects, distinguishing only schizophrenia and depression from other diagnoses. In the parallel follow-up analyses of the 3 independent healthy participant data sets, we found that **the common gray matter loss regions formed a tightly interconnected network** during tasks and at resting and that lower gray matter in this network was associated with **poor executive functioning**.

Effects are influenced in both duration and direction by:
Intensity of Stimulation
Duration of Stimulation
Location of Stimulation
Sensitivity of outcome measure
Time of Day (Sale et al., 2007)
Attention (Stephan et al., 2004)
Hormones (Smith et al., 1999)
Brain State
Inter and intra-individual differences:
1 Hz can be facilitatory in some individuals
Only approximately 50% of individuals respond to PAS
TBS has high intraindividual reliability, PAS does not.



aMPFC=anterior medial prefrontal cortex. AG=angular gyrus. PCC=posterior cingulate cortex (includes precuneus). dACC=dorsal anterior cingulate cortex. aI=anterior insula. TP=temporal pole. SLEA=sublenticular extended amygdala. ACC/MPFC=dorsal medial prefrontal cortex (includes dorsal ACC and vMPFC, including ventral—subgenual and pregenual—and rostral ACC). msPFC=medial superior prefrontal cortex. LPFC=lateral prefrontal cortex. aIPL=anterior inferior parietal lobule. MPFC=medial prefrontal cortex. vMPFC=ventromedial prefrontal cortex. OFC=orbitofrontal cortex. ACC=anterior cingulate cortex. DLPFC=dorsolateral prefrontal cortex (includes anterior prefrontal cortex and inferior frontal cortex). PCG=precentral gyrus. DPC=dorsal parietal cortex.

Figure 1: Large-scale **intrinsic** and **task-evoked circuits** identified in published work

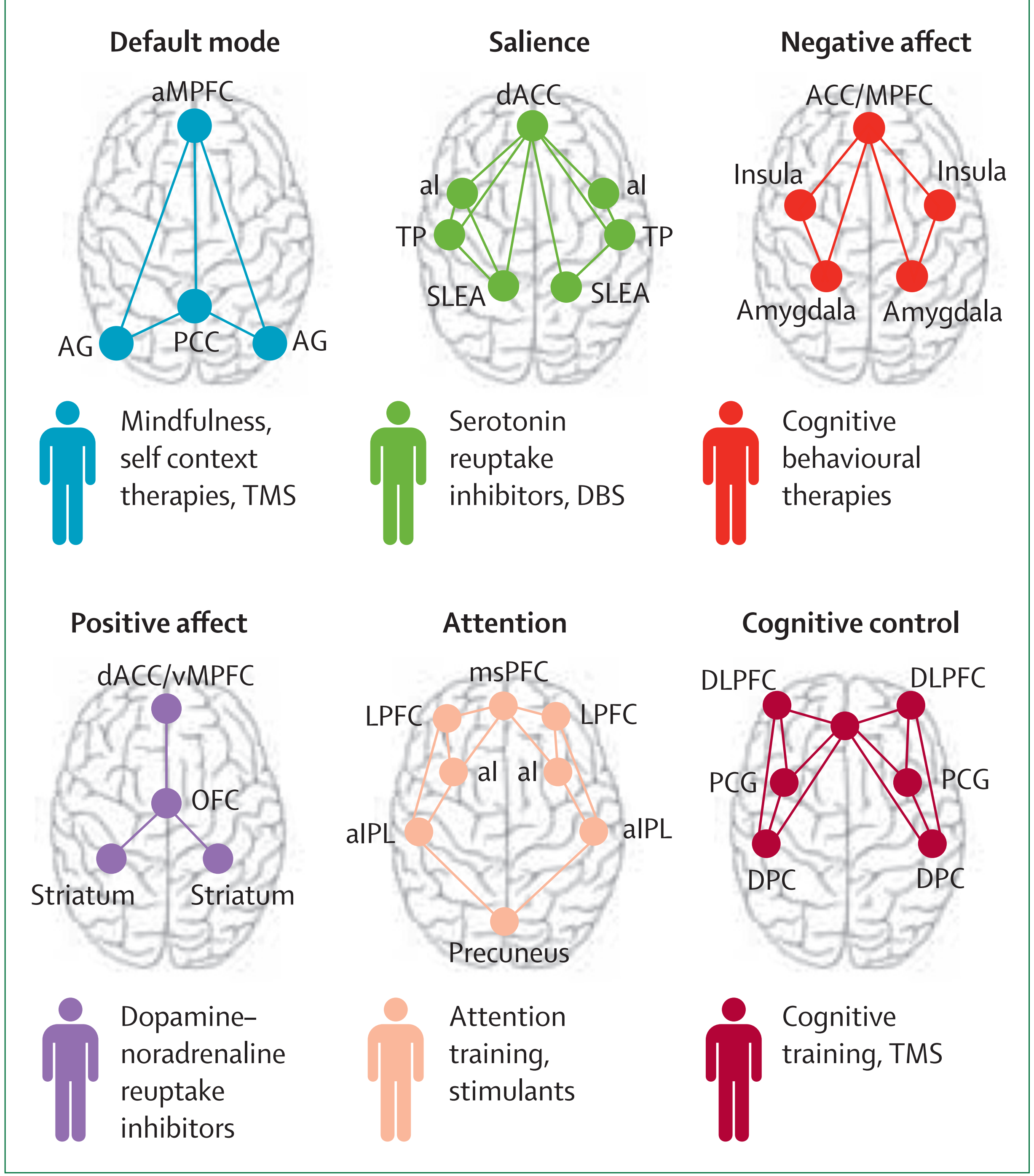
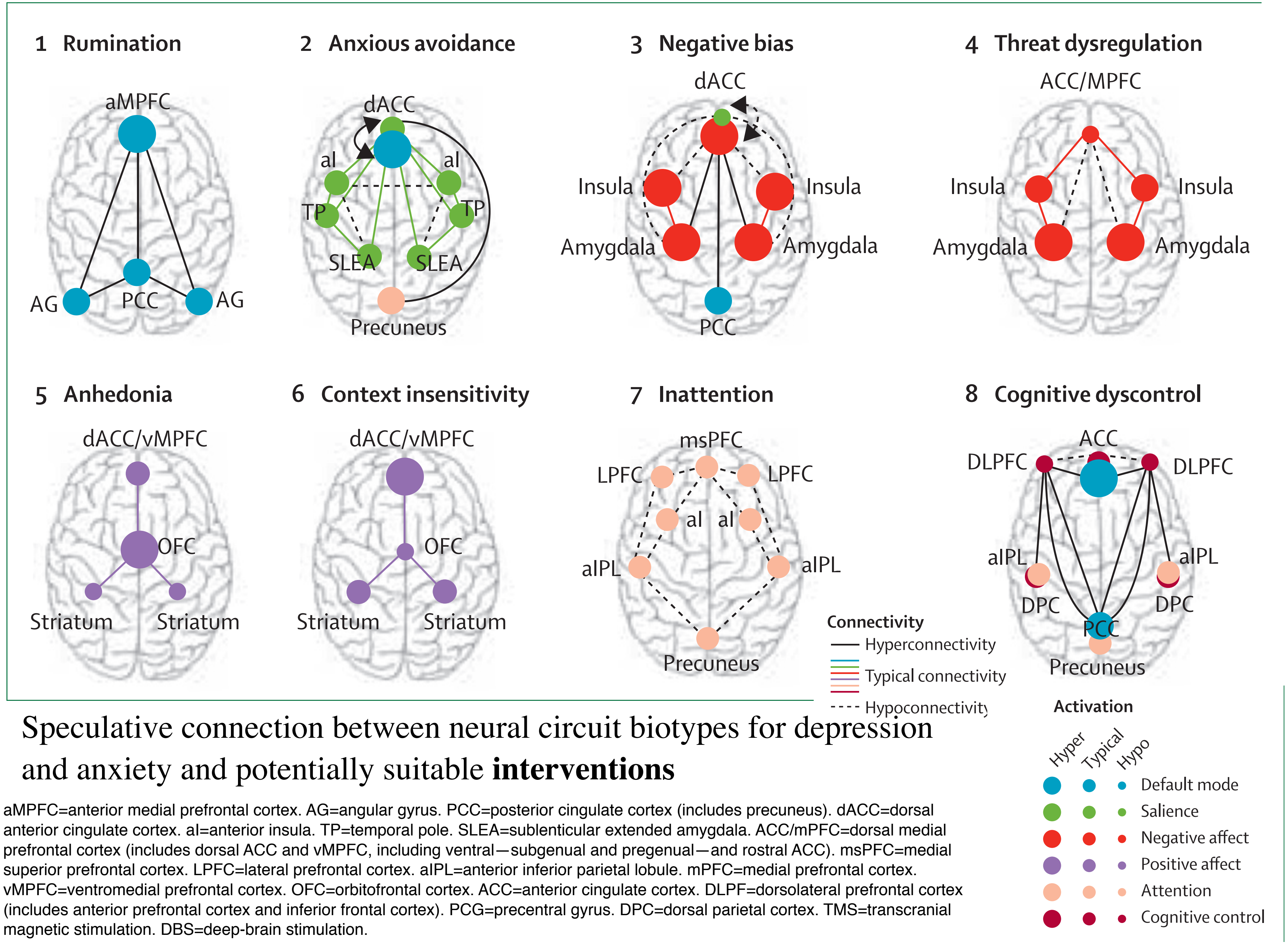


Figure 2: Proposed taxonomy of **putative biotypes of neural circuit dysfunction for depression and anxiety** based on published work

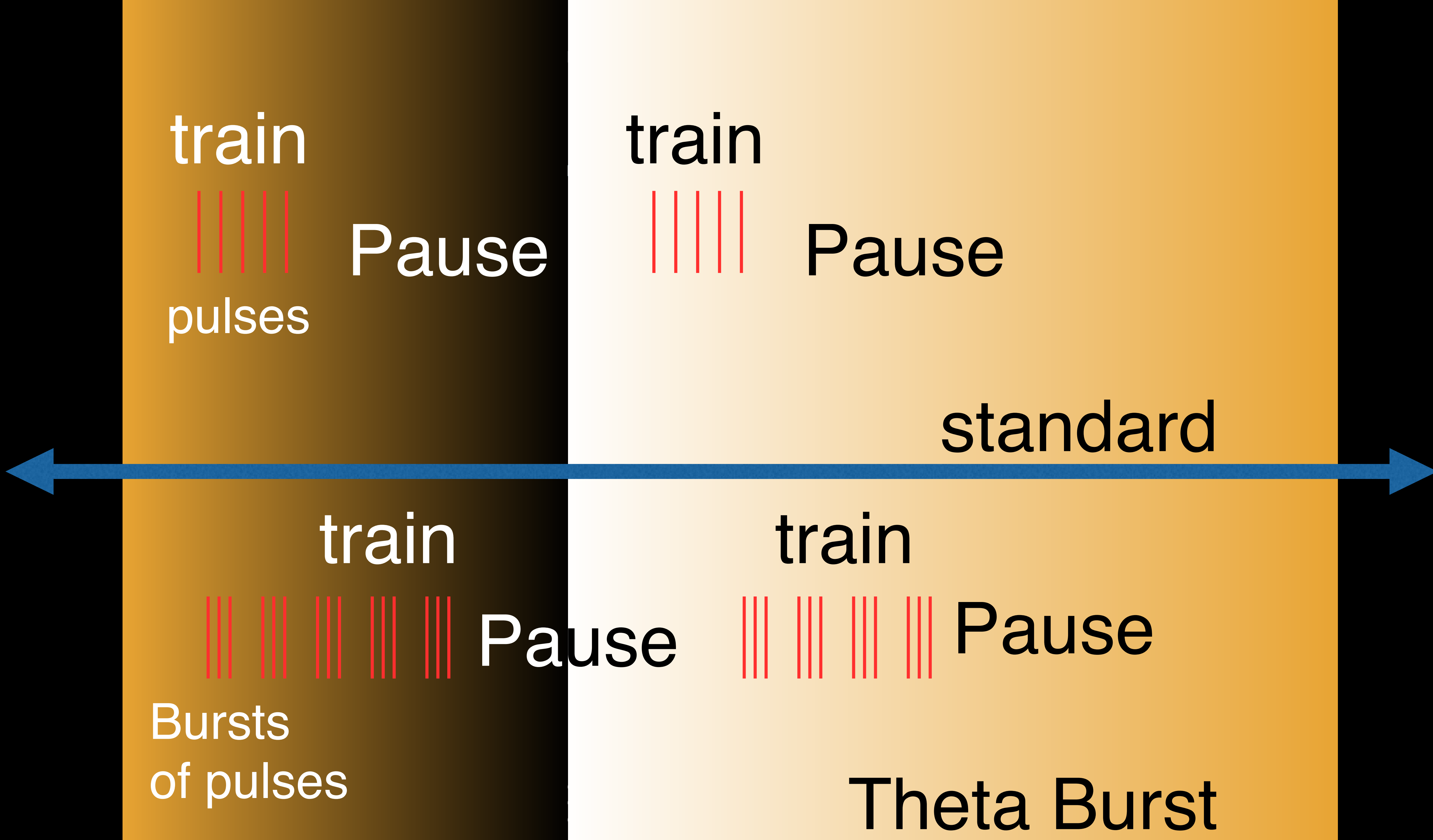
The proposed phenotype associated with each proposed neural dysfunction is mentioned above each type of dysfunction.

aMPFC=anterior medial prefrontal cortex. AG=angular gyrus. PCC=posterior cingulate cortex (includes precuneus). dACC=dorsal anterior cingulate cortex. aI=anterior insula. TP=temporal pole. SLEA=sublenticular extended amygdala. ACC/MPFC=dorsal medial prefrontal cortex (includes dorsal ACC and vMPFC, including ventral—subgenual and pregenual—and rostral ACC). msPFC=medial superior prefrontal cortex. LPFC=lateral prefrontal cortex. aIPL=anterior inferior parietal lobule. MPFC=medial prefrontal cortex. vMPFC=ventromedial prefrontal cortex. OFC=orbitofrontal cortex. ACC=anterior cingulate cortex. DLPF=dorsoateral prefrontal cortex (includes anterior prefrontal cortex and inferior frontal cortex). PCG=precentral gyrus. DPC=dorsal parietal cortex.



Speculative connection between neural circuit biotypes for depression and anxiety and potentially suitable **interventions**

aMPFC=anterior medial prefrontal cortex. AG=angular gyrus. PCC=posterior cingulate cortex (includes precuneus). dACC=dorsal anterior cingulate cortex. aI=anterior insula. TP=temporal pole. SLEA=sublenticular extended amygdala. ACC/mPFC=dorsal medial prefrontal cortex (includes dorsal ACC and vMPFC, including ventral—subgenual and pregenual—and rostral ACC). msPFC=medial superior prefrontal cortex. LPFC=lateral prefrontal cortex. aIPL=anterior inferior parietal lobule. mPFC=medial prefrontal cortex. vMPFC=ventromedial prefrontal cortex. OFC=orbitofrontal cortex. ACC=anterior cingulate cortex. DLPF=dorsolateral prefrontal cortex (includes anterior prefrontal cortex and inferior frontal cortex). PCG=precentral gyrus. DPC=dorsal parietal cortex. TMS=transcranial magnetic stimulation. DBS=deep-brain stimulation.

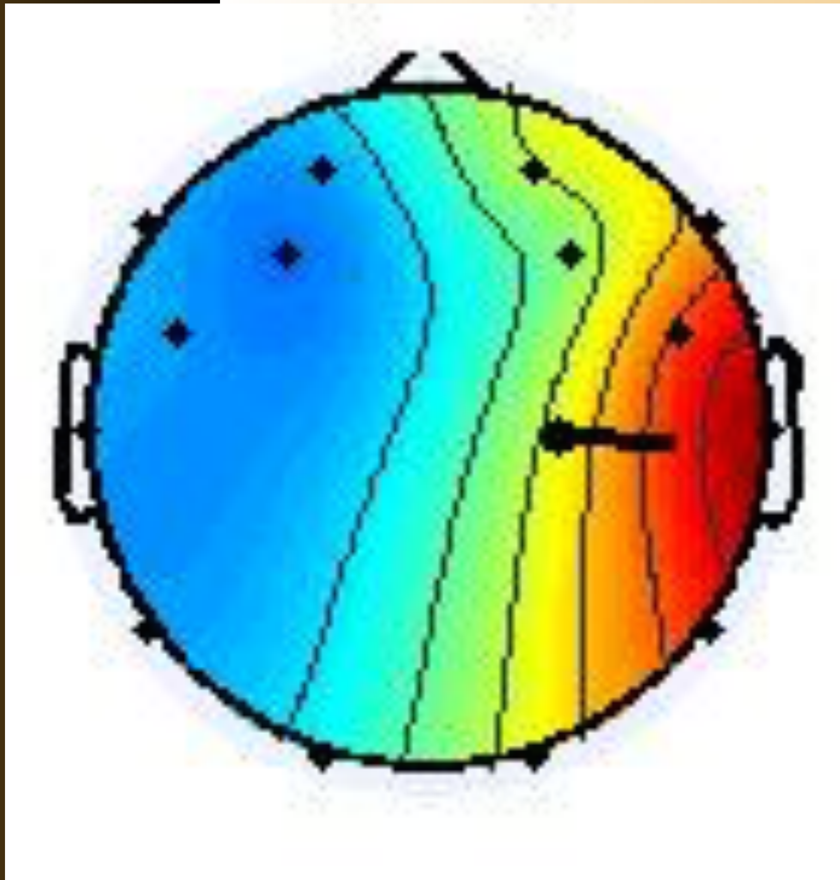

train
pulses
Pause
train
Pause
standard
train
Pause
Bursts
of pulses
train
Pause
Theta Burst

TMS ADVANCED

Left

iTBS

LTP



Right

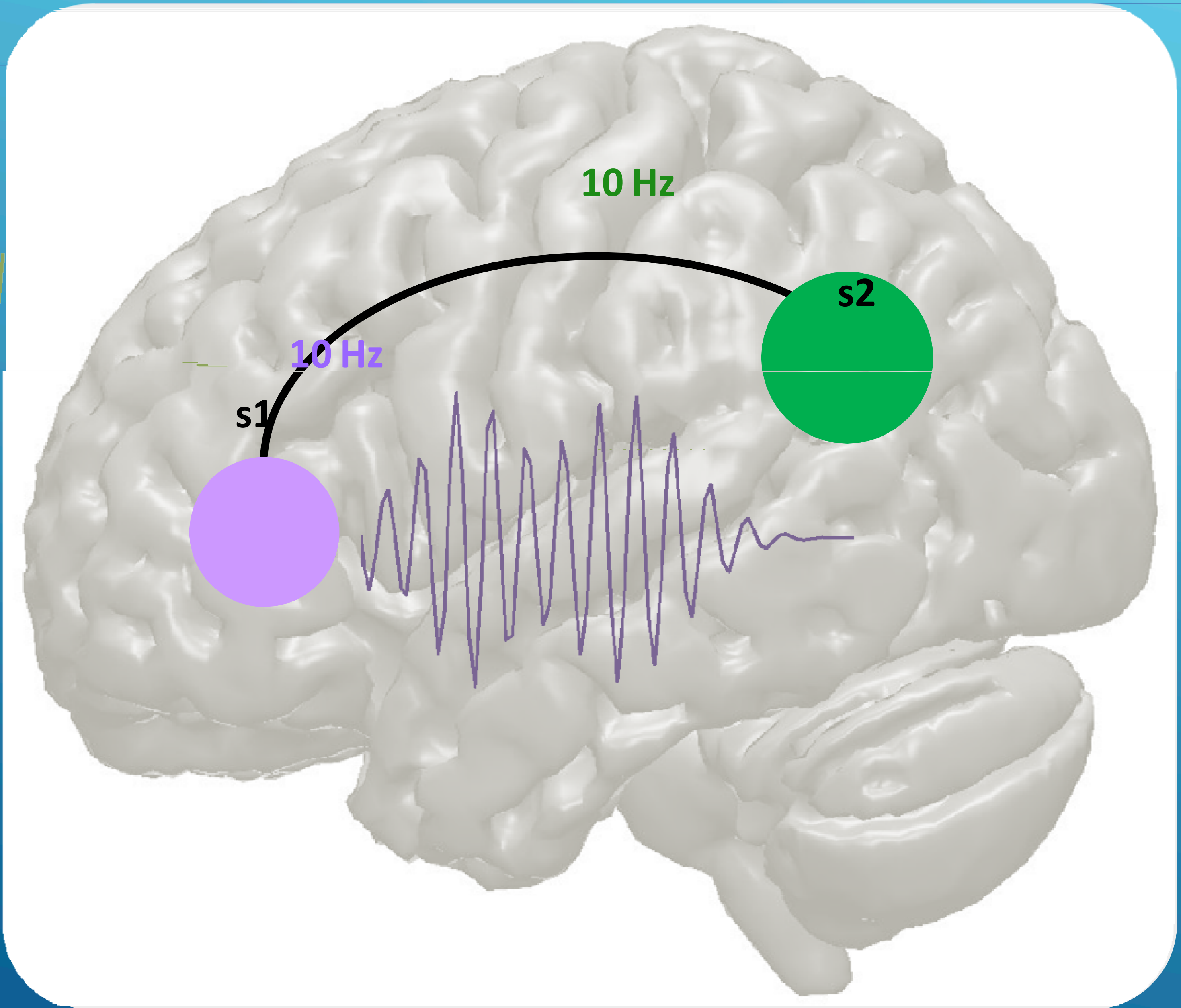
cTBS

LTD

Excitatory

Inhibitory

Functional Connectivity through Amplitude Coupling



Coupling occurs via White matter:
White Matter Matters

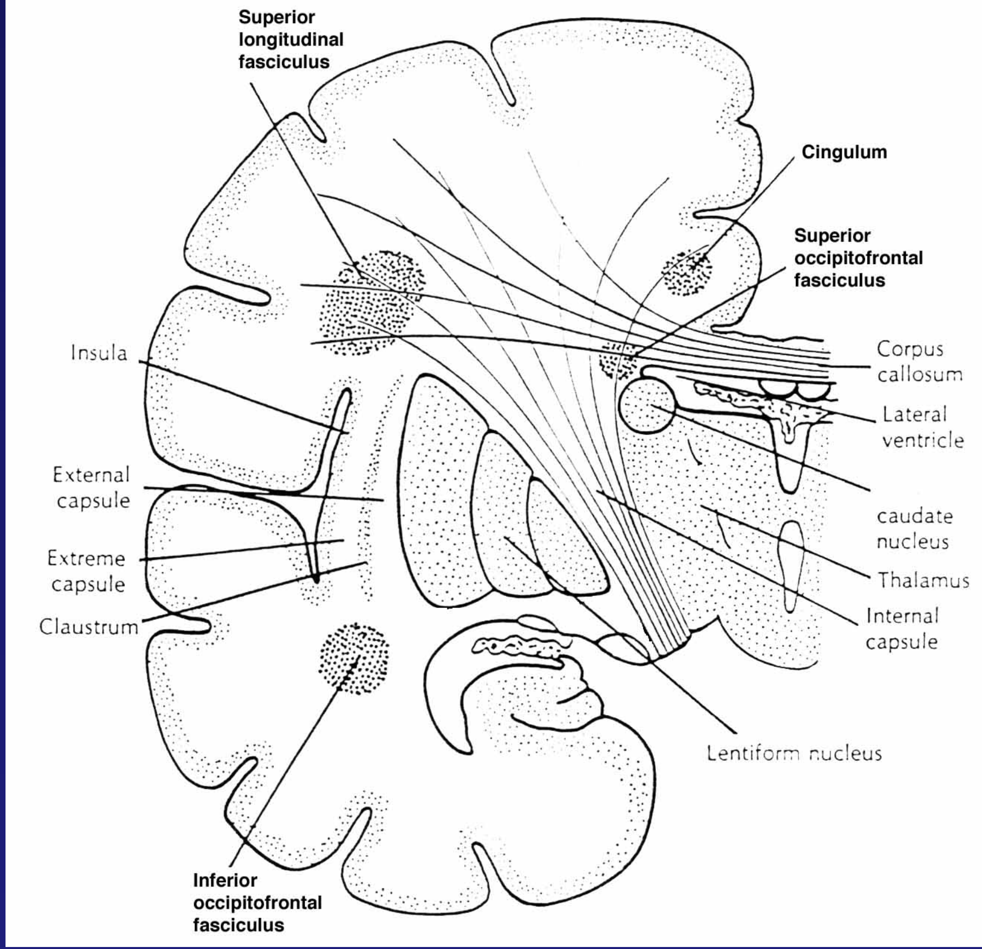
Much of the cerebral hemispheres is occupied by subcortical white matter, which is anatomically organized.

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

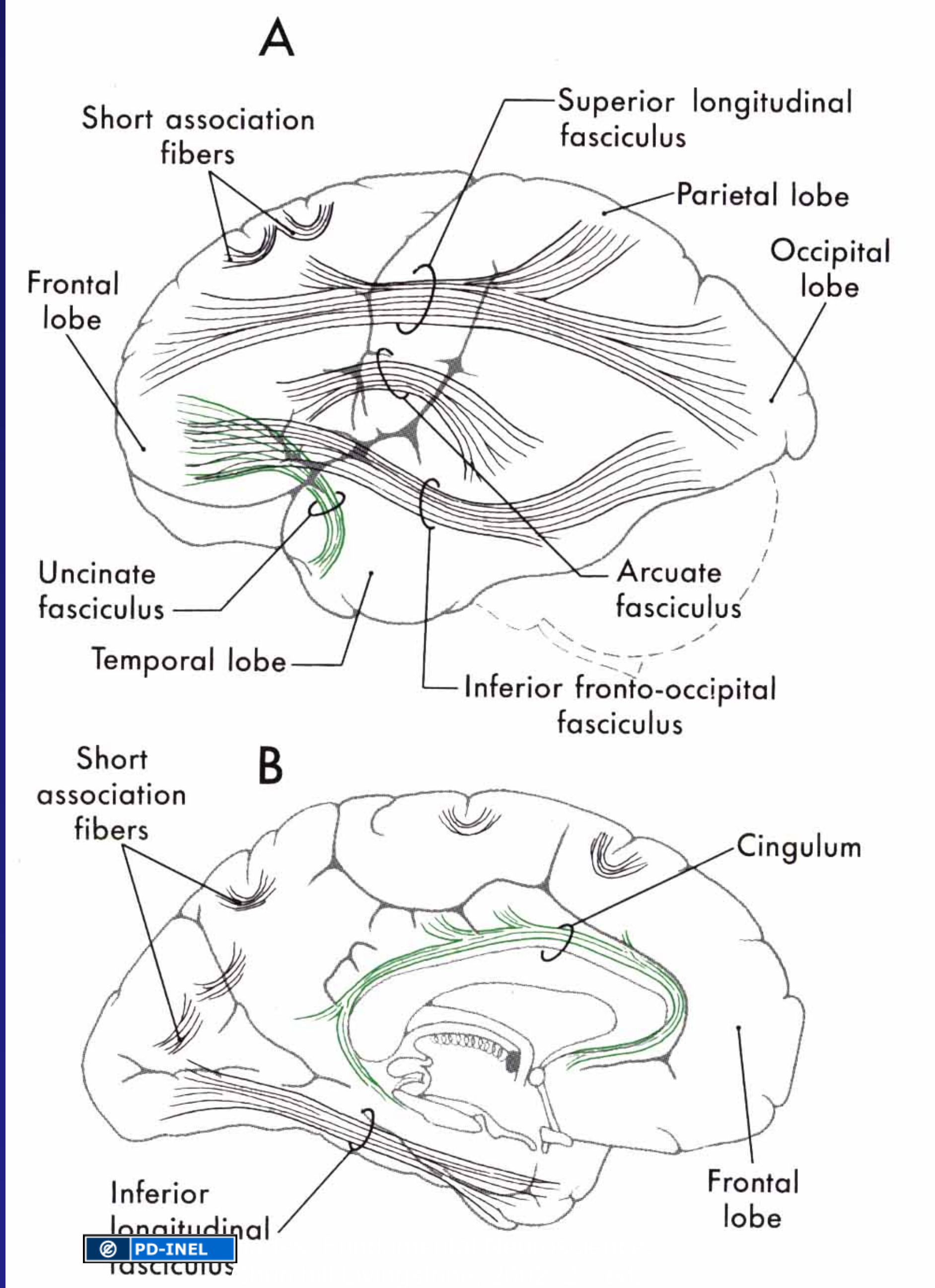
1) projection fibers - leave the hemisphere for subcortical targets

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

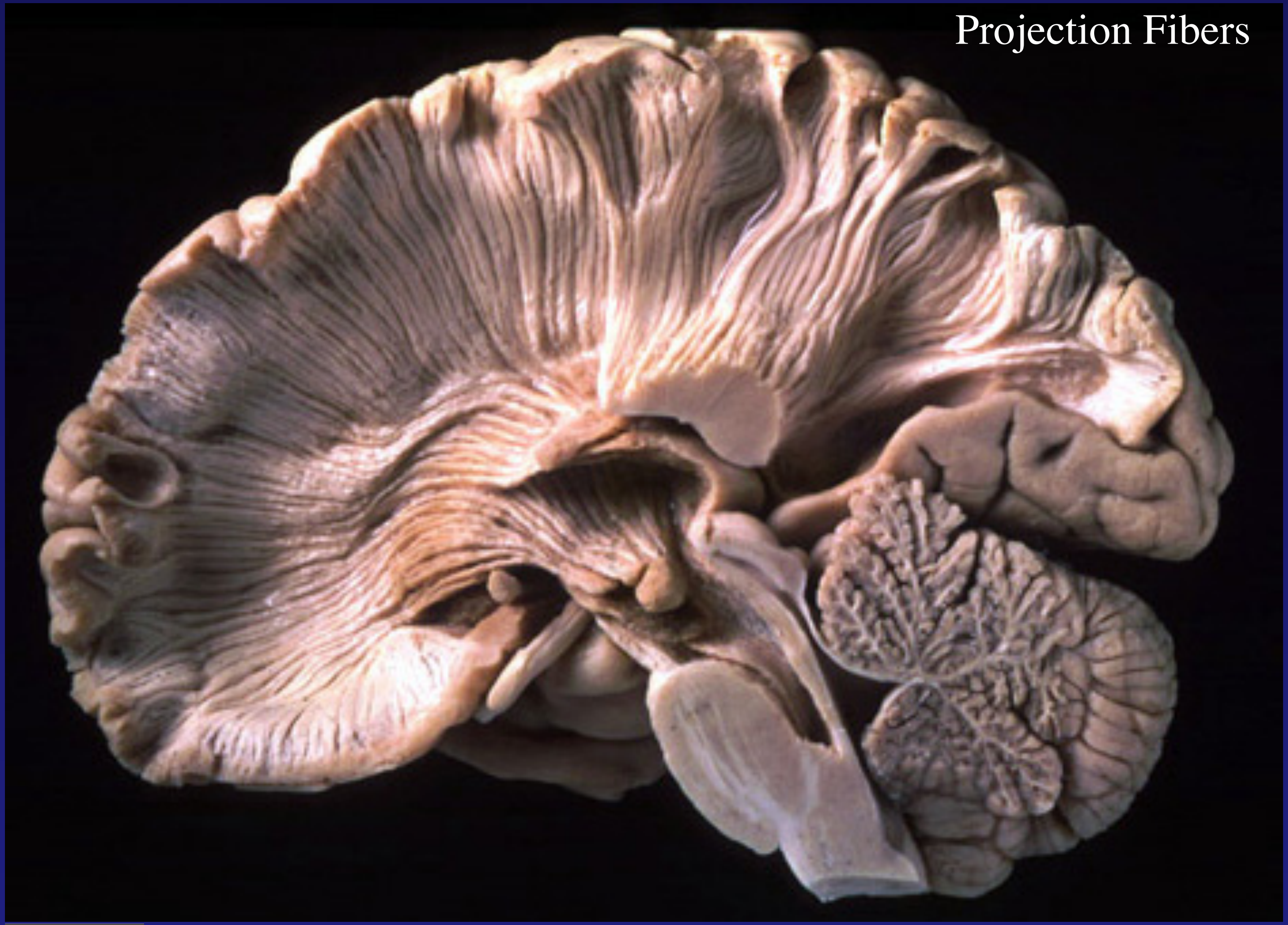
3) **association fibers** (2 types) - interhemispheric connections, L-L and R-R



Superior longitudinal fasciculus
Cingulum
Superior occipitofrontal fasciculus
Insula
Corpus callosum
Lateral ventricle
External capsule
caudate nucleus
Extreme capsule
Thalamus
Claustrum
Internal capsule
Lentiform nucleus
Inferior occipitofrontal fasciculus



A
Short association fibers
Superior longitudinal fasciculus
Parietal lobe
Occipital lobe
Frontal lobe
Uncinate fasciculus
Arcuate fasciculus
Temporal lobe
Inferior fronto-occipital fasciculus
B
Short association fibers
Cingulum
Inferior longitudinal fasciculus
Frontal lobe



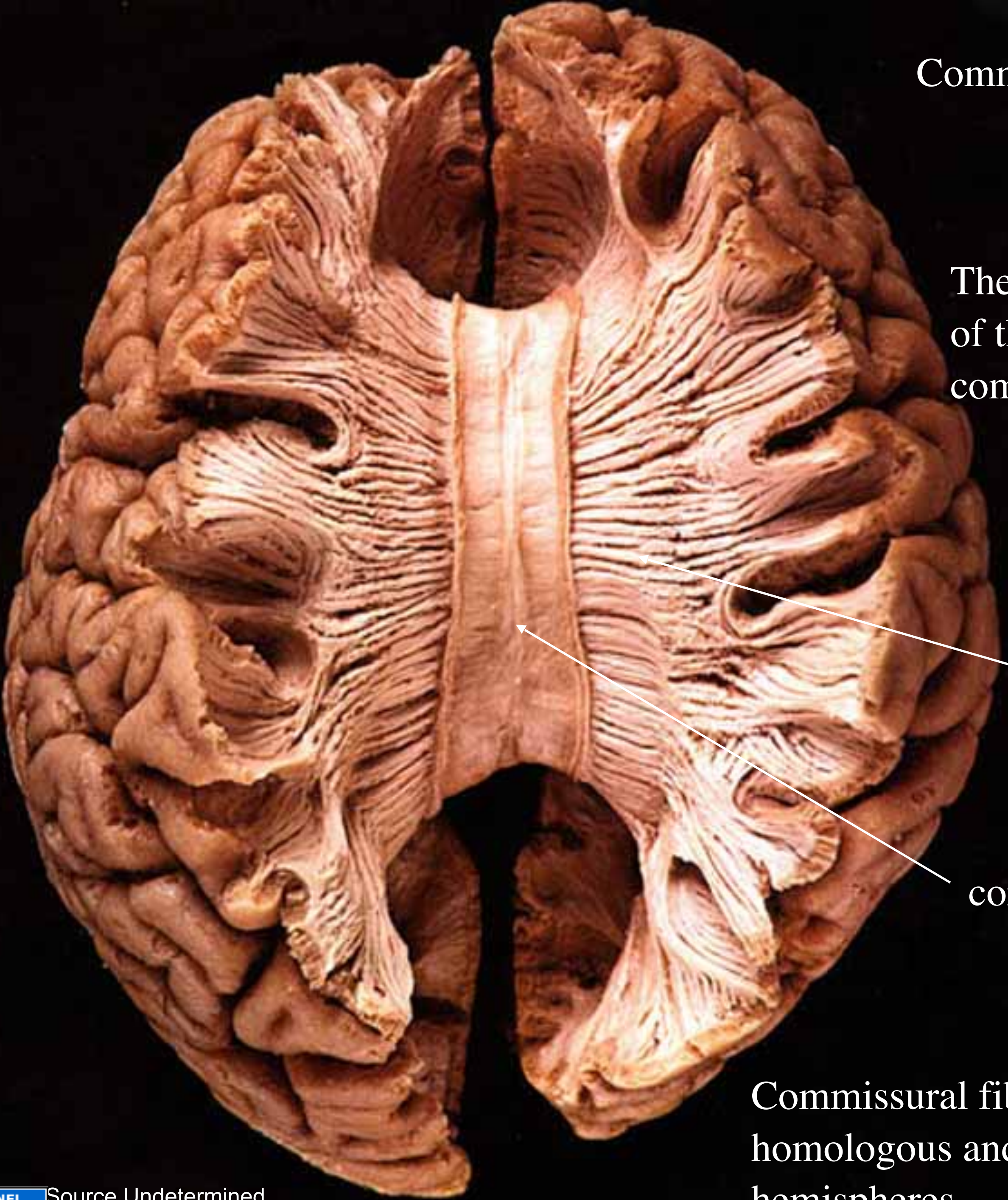
This dissected brain illustrates projection fibers, that innervate subcortical targets, e.g., thalamus, brainstem and spinal cord.

corona radiata

internal capsule

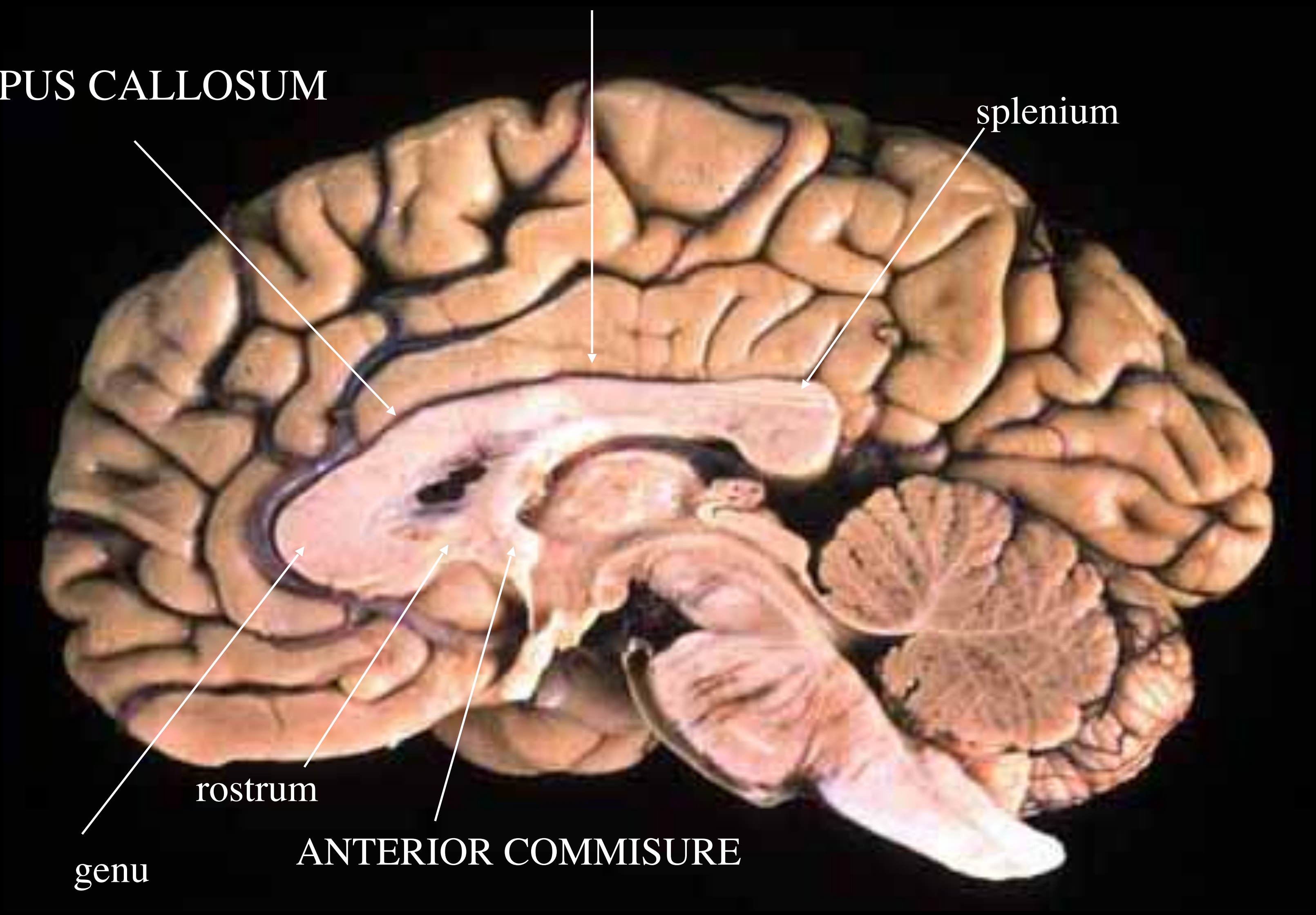
Commissural Fibers

The corpus callosum is the largest of the two structures that contain commissural fibers.

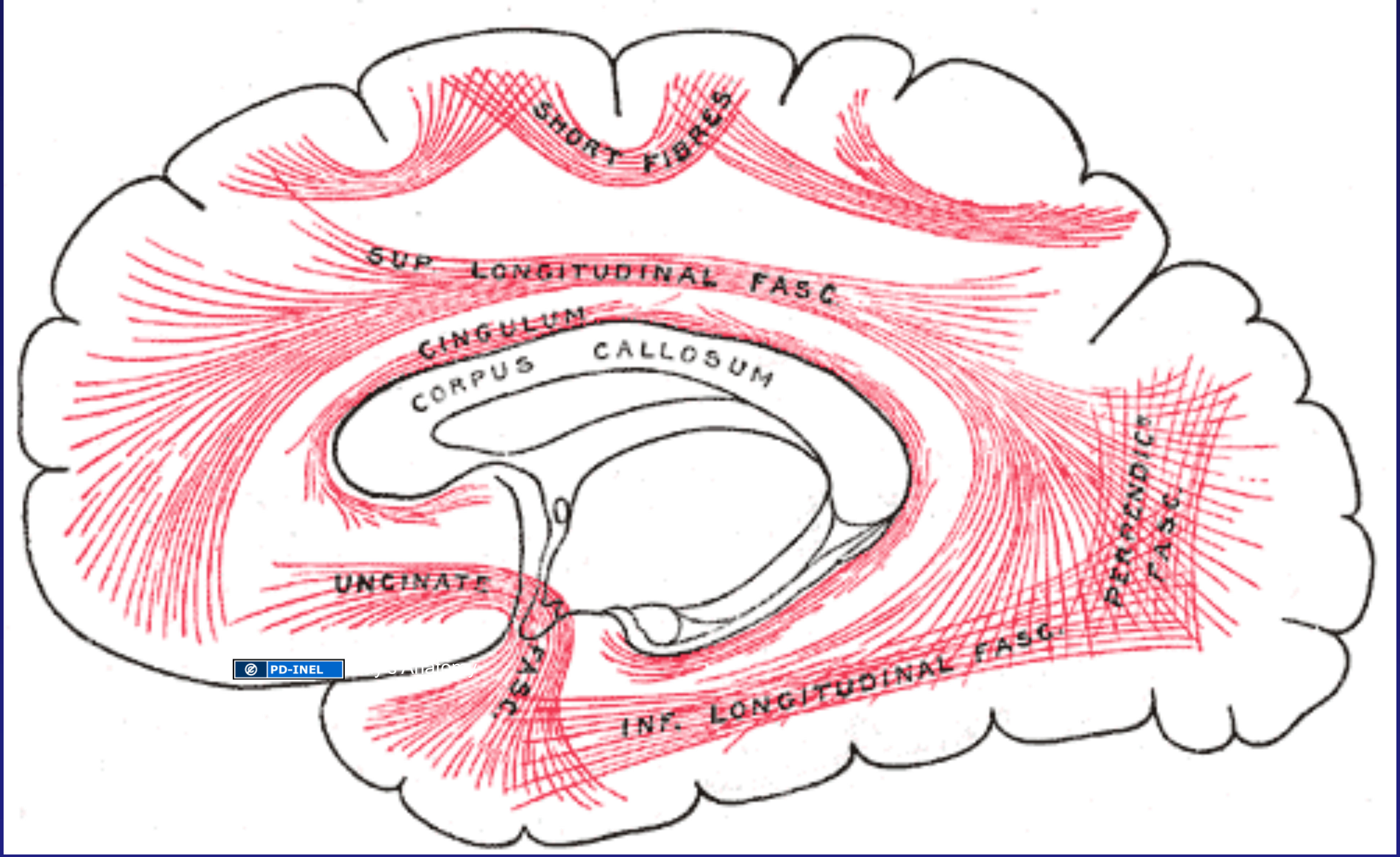


Commissural fibers interconnect both homologous and heterologous areas of the two hemispheres.

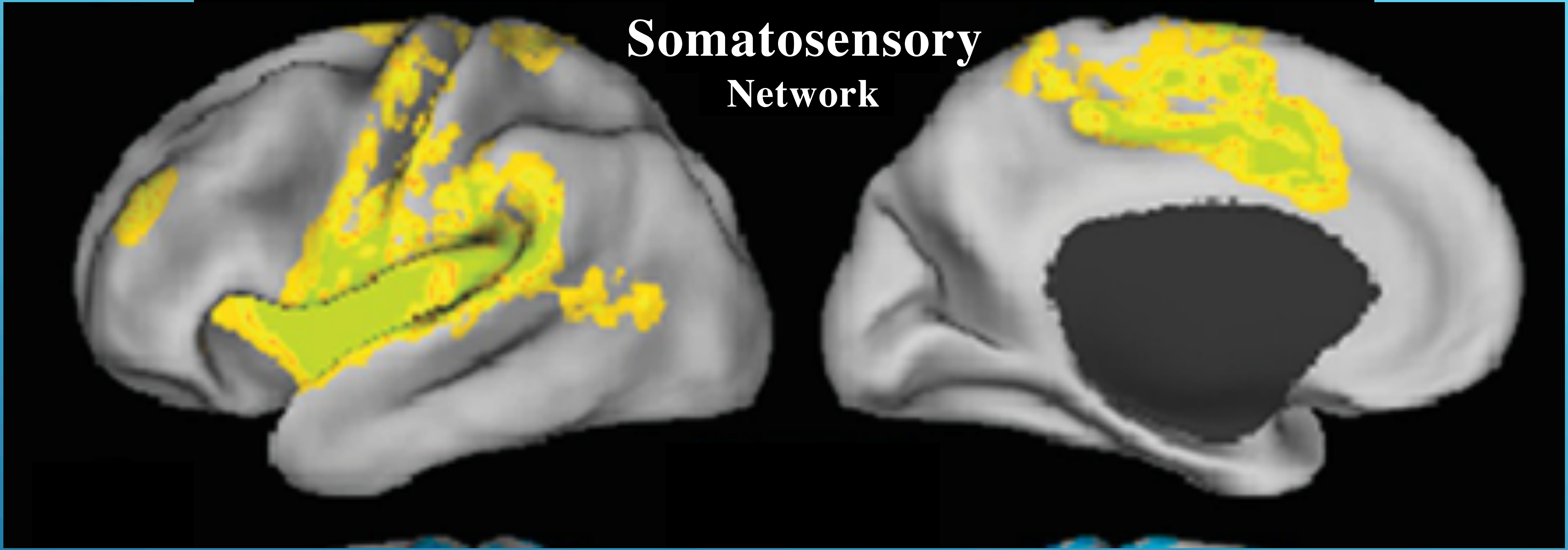
Commissural Fibers



The anterior commisure is the second major structure that contains commissural fibers.

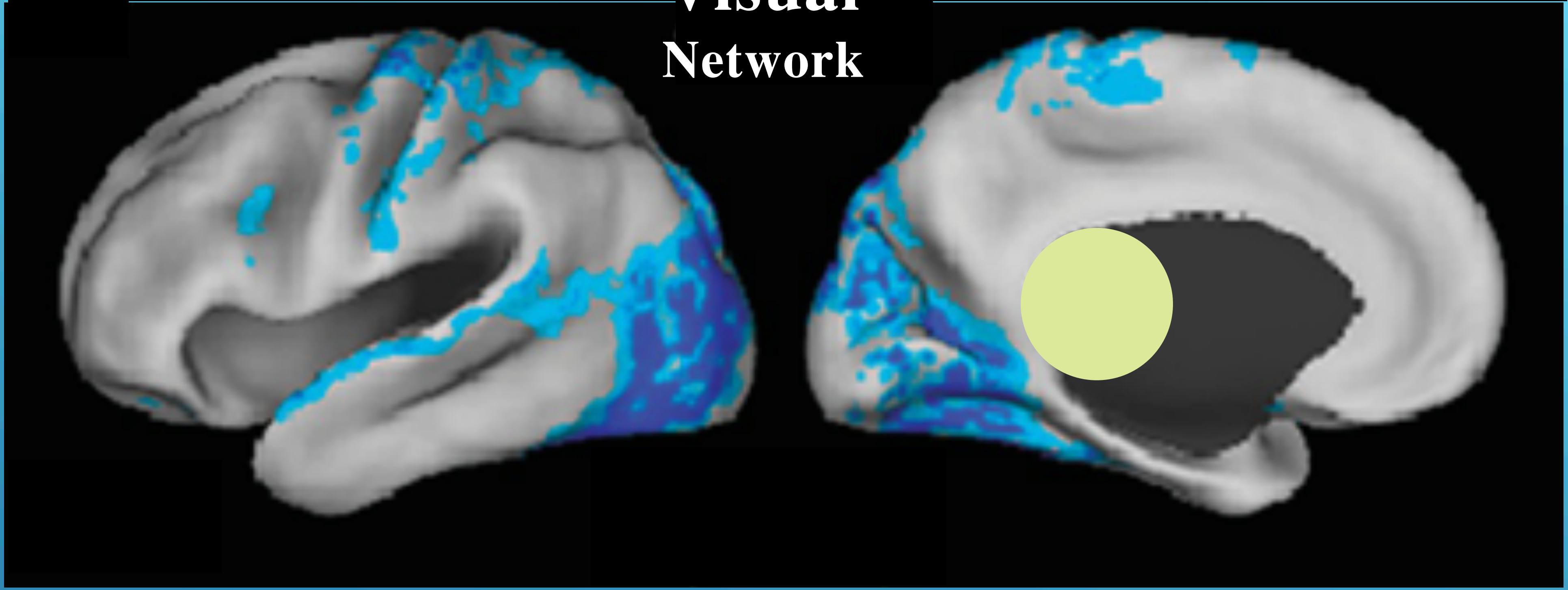


Association fibers do not leave the cerebral hemisphere, and can be classified as either long or short.



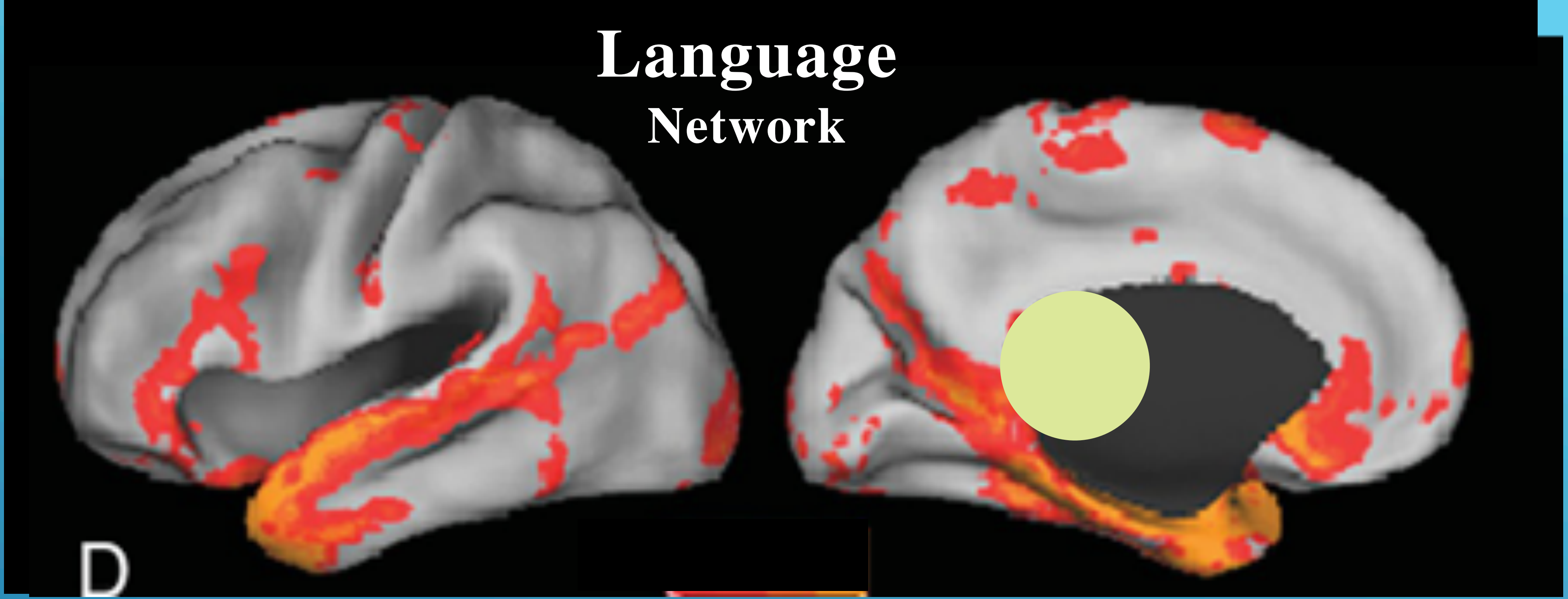
Several other RSNs have been identified. The **somatosensory network**, studied first by Biswal et al,1 includes primary and higher order motor and sensory areas (Fig 1B).

Visual
Network



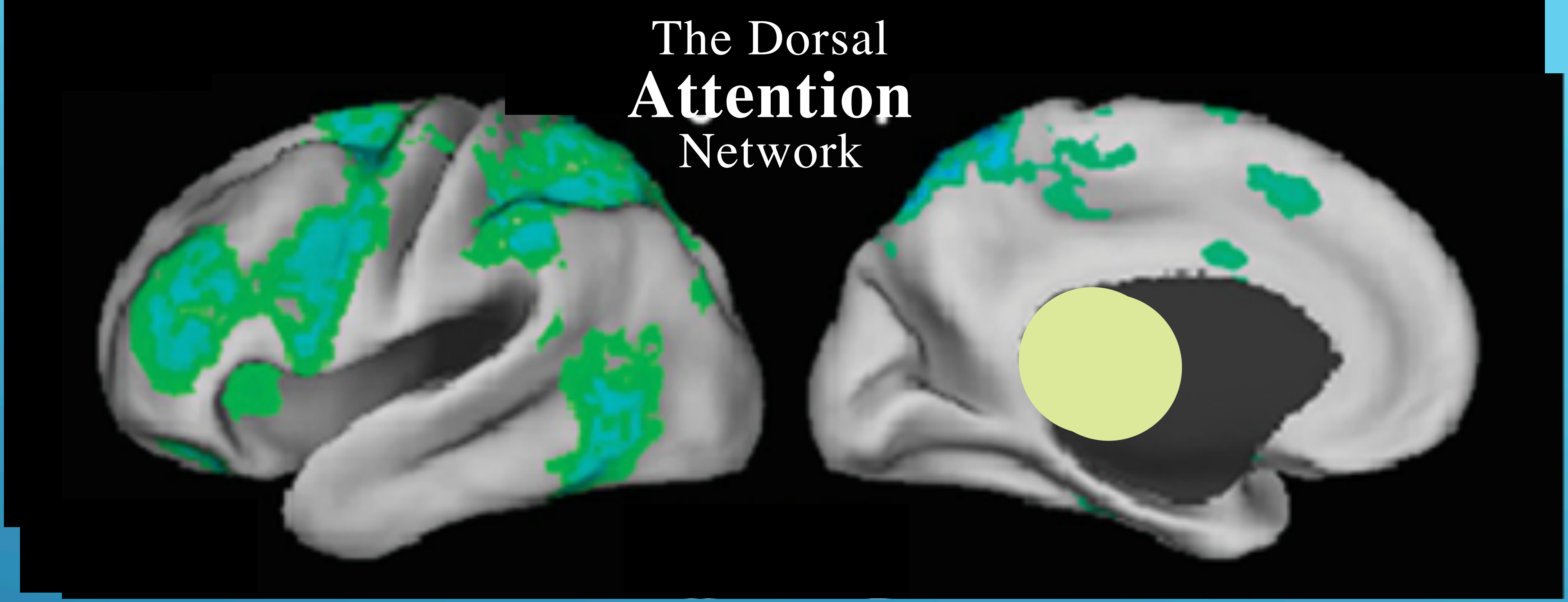
The visual network is highly consistent across various studies and spans much of the occipital cortex (Fig 1C).[2-6]

Language
Network



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

The Dorsal **Attention** Network



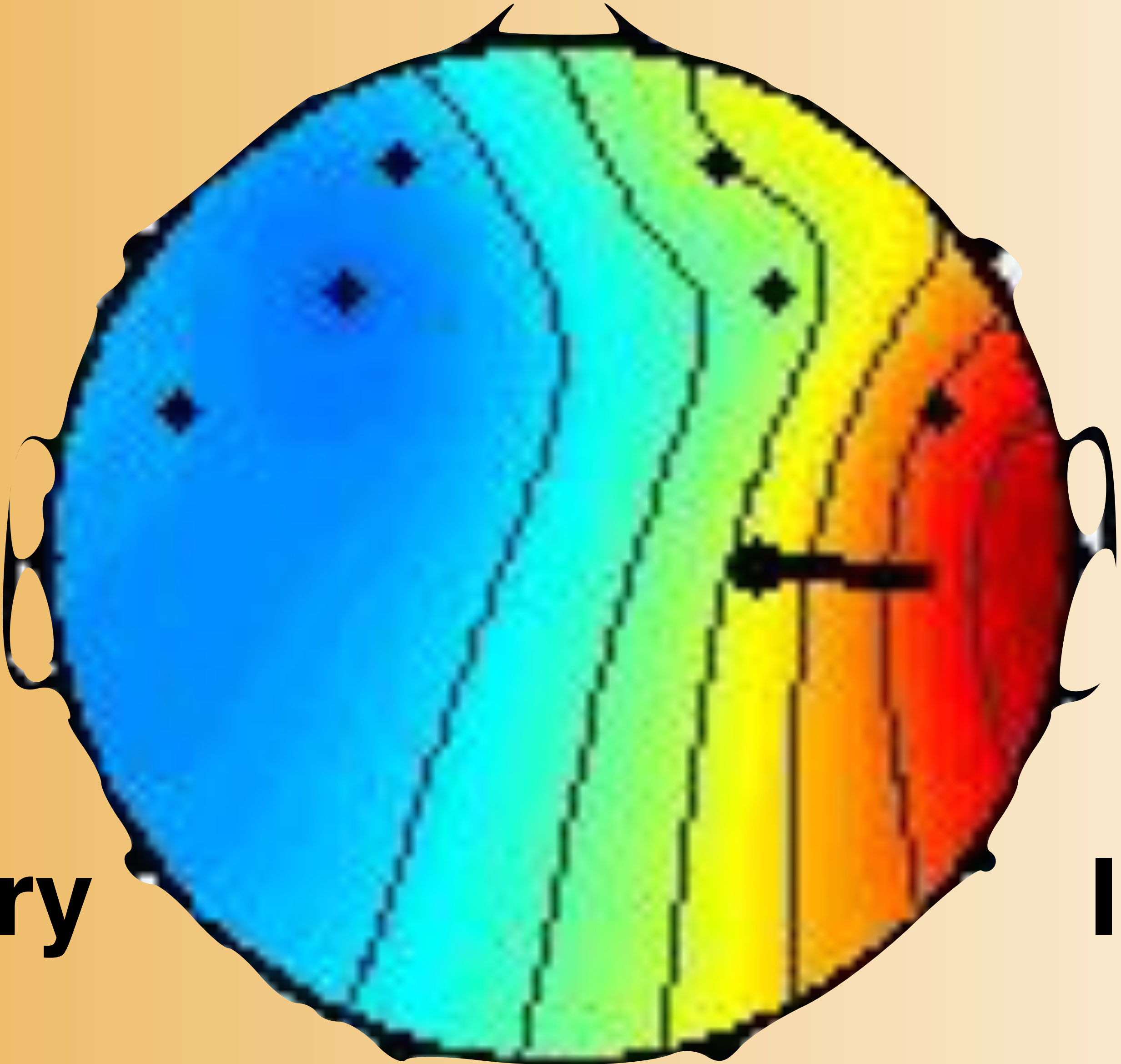
RSNs involved in **attentio**nal modulation and **cognitive control** have also been identified. Two networks identified by using both RS-fMRI and task-based fMRI include the dorsal and ventral attention networks.4,6,17,18 The dorsal attention network (Fig 1E) includes the intraparietal sulcus and the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

Left

iTBS

LTP

Excitatory

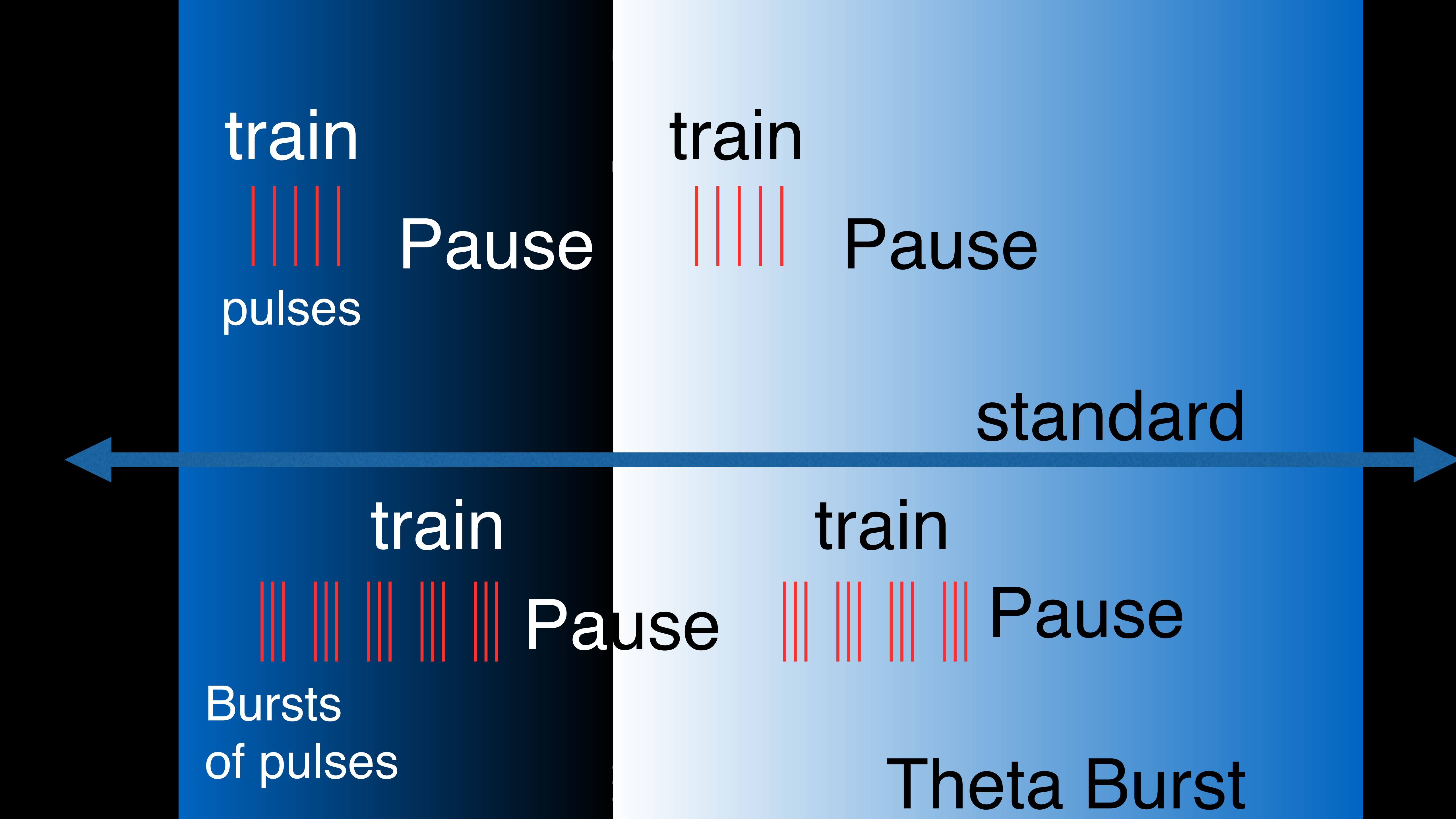


Right

cTBS

LTD

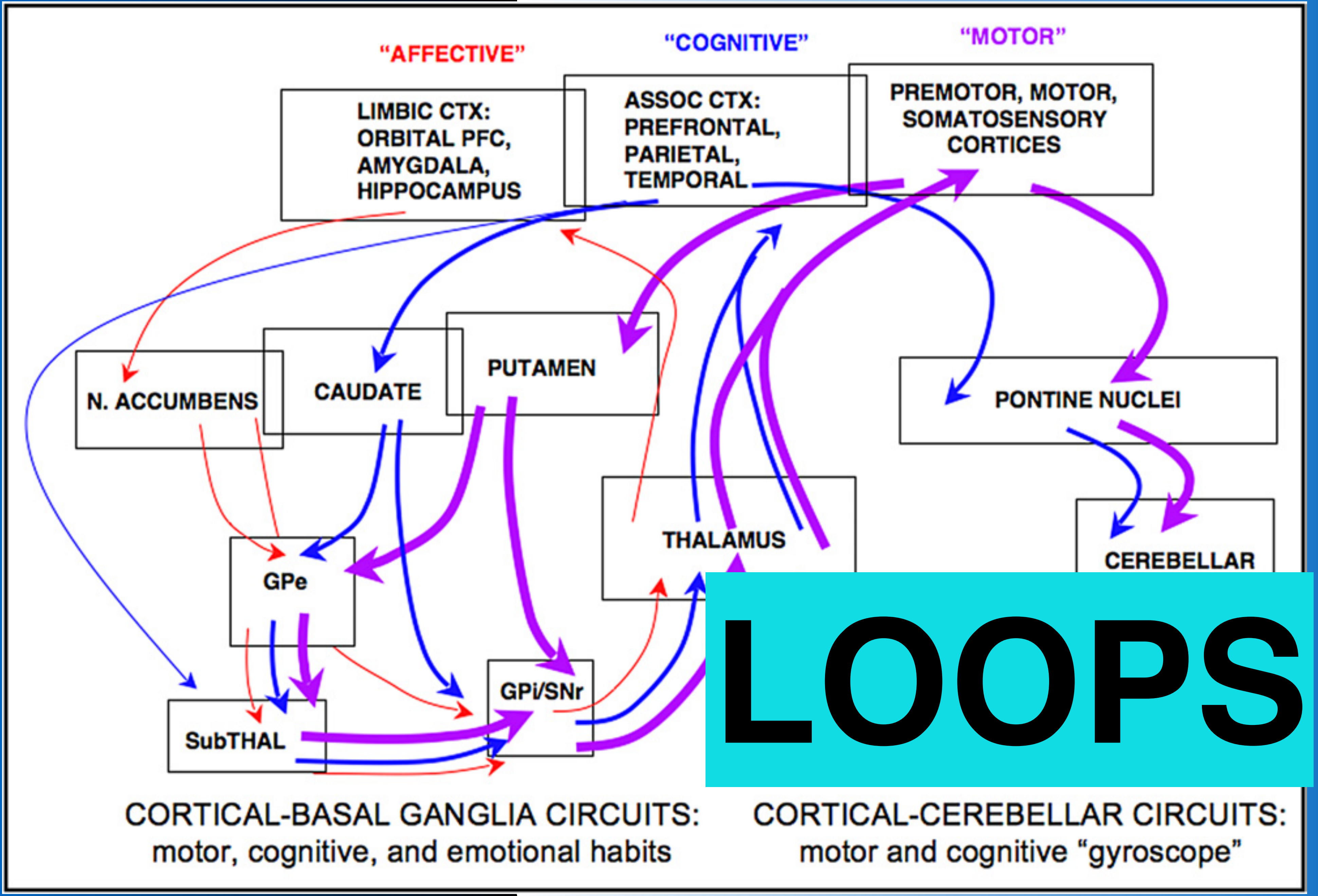
Inhibitory

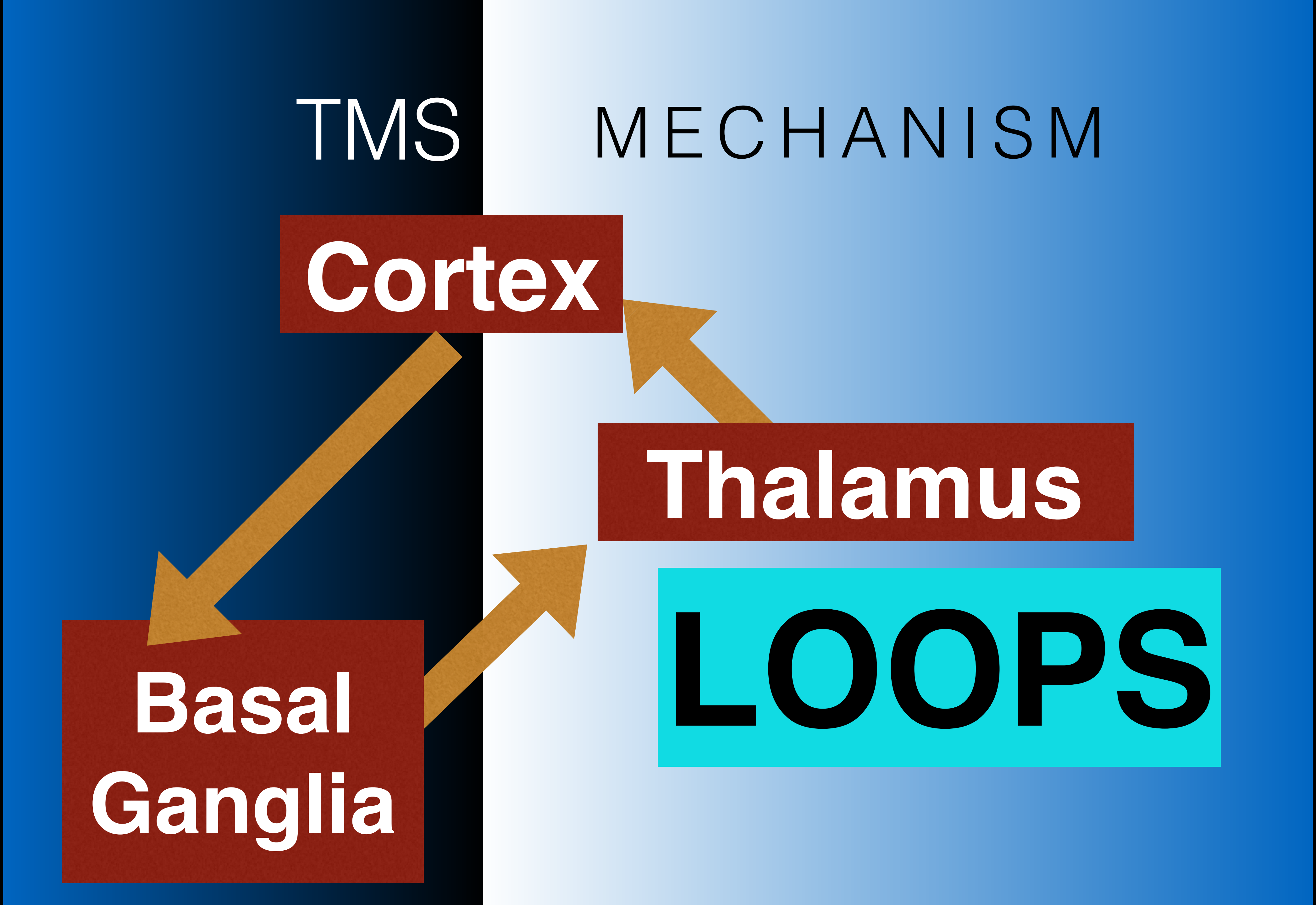

train
pulses
Pause
train
Pause
standard
train
Bursts
of pulses
Pause
train
Pause
Theta Burst

TMS

MECHANISM

Circuits


"AFFECTIVE"
"COGNITIVE"
"MOTOR"
LIMBIC CTX: ORBITAL PFC, AMYGDALA, HIPPOCAMPUS
ASSOC CTX: PREFRONTAL, PARIETAL, TEMPORAL
PREMOTOR, MOTOR, SOMATOSENSORY CORTICES
N. ACCUMBENS
CAUDATE
PUTAMEN
PONTINE NUCLEI
THALAMUS
CEREBELLAR
GPe
GPi/SNr
SubTHAL
CORTICAL-BASAL GANGLIA CIRCUITS: motor, cognitive, and emotional habits
CORTICAL-CEREBELLAR CIRCUITS: motor and cognitive "gyroscope"
LOOPS


TMS
MECHANISM
Cortex
Thalamus
Basal Ganglia
LOOPS

TMS MECHANISM

Default

Salience

Executive

Circuits

Mesulam 1990

NEUROLOGICAL PROGRESS

Large-Scale Neurocognitive Networks and Distributed Processing for Attention, Language, and Memory[1]

M-Marsel Mesulam, MD

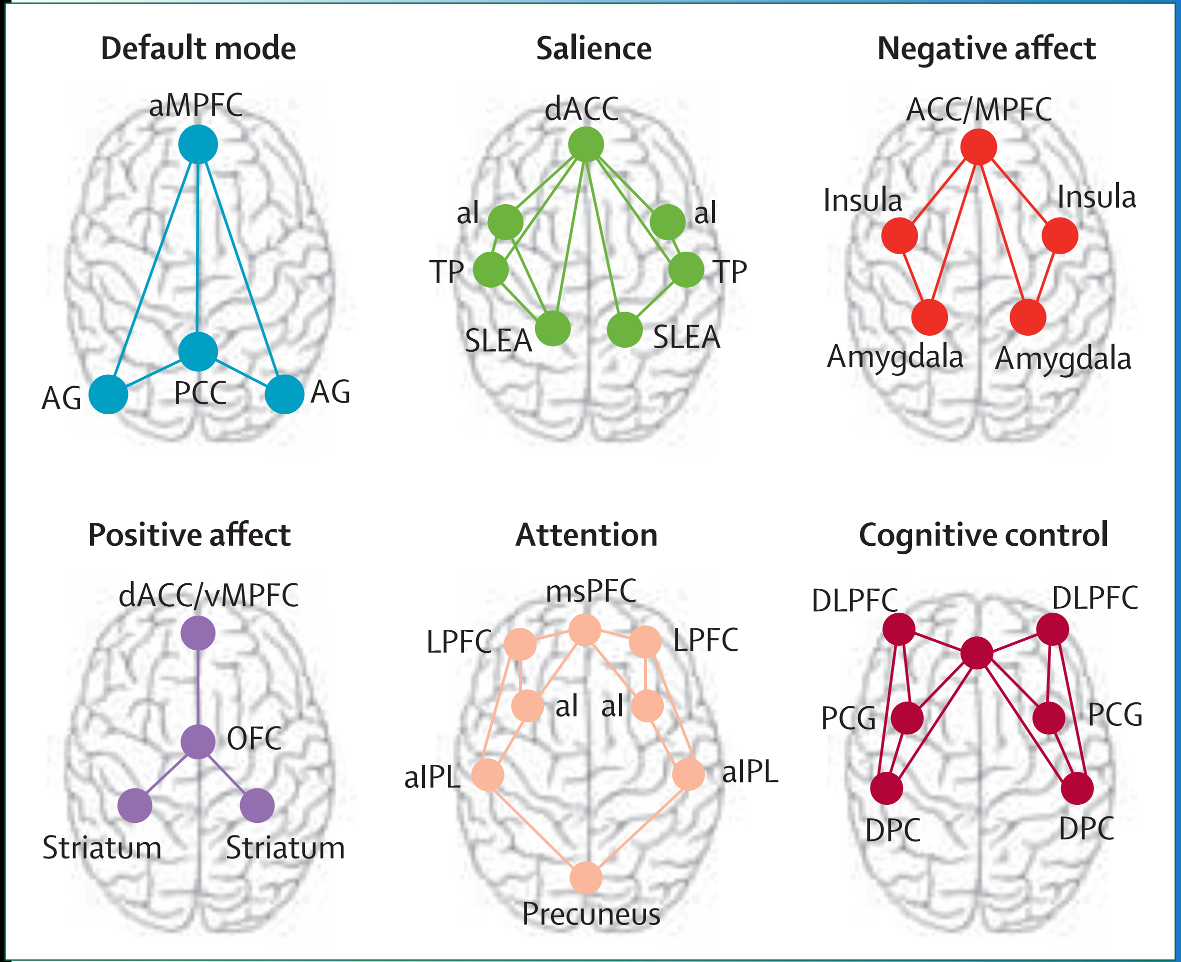
Cognition and comportment are subserved by interconnected neural networks that allow high-level computational architectures including parallel distributed processing. Cognitive problems are not resolved by a sequential and hierarchical progression toward predetermined goals but instead by a simultaneous and interactive consideration of multiple possibilities and constraints until a satisfactory fit is achieved. The resultant texture of mental activity is characterized by almost infinite richness and flexibility. According to this model, complex behavior is mapped at the level of multifocal neural systems rather than specific anatomical sites, giving rise to brain-behavior relationships that are both localized and distributed. Each network contains anatomically addressed channels for transferring information content and chemically addressed pathways for modulating behavioral tone. This approach provides a blueprint for reexploring the neurological foundations of attention, language, memory, and frontal lobe function.

Mesulam M-M. Large-scale neurocognitive networks and distributed processing for attention, language, and memory. Ann Neurol 1990;28:597–613

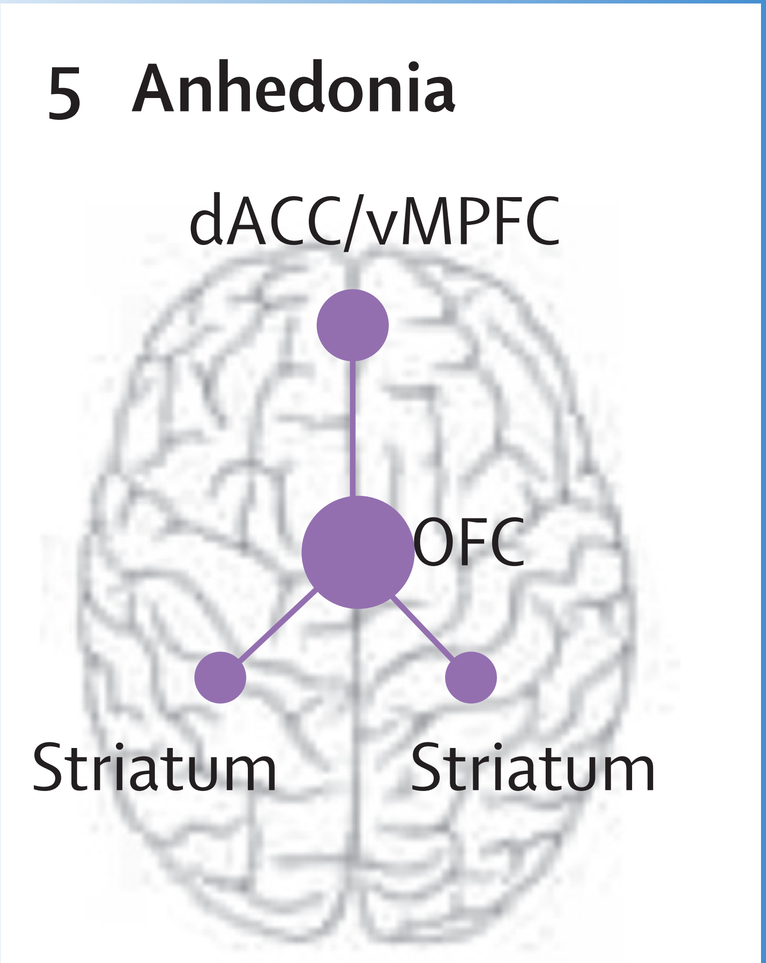
TMS MECHANISM
Williams 2016

Networks:

- Default
- Salience
- Affect (-.+)
- Attention
- Cognitive Control



TMS MECHANISM
Williams 2016



TMS

How does it work?

(Mechanism of action)

MECHANISM

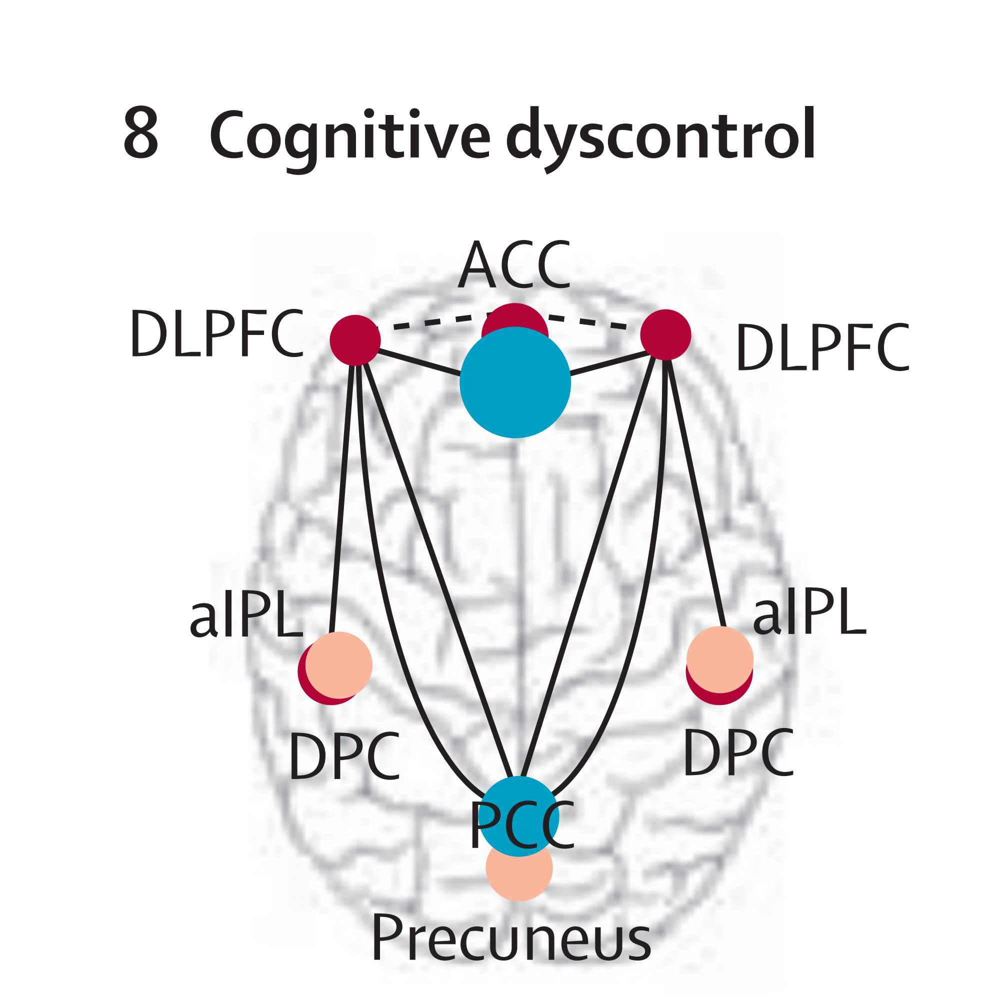
Depolarization of DLPFC Cortical Neurons

Increases Activity of DLPFC Cortical Neurons

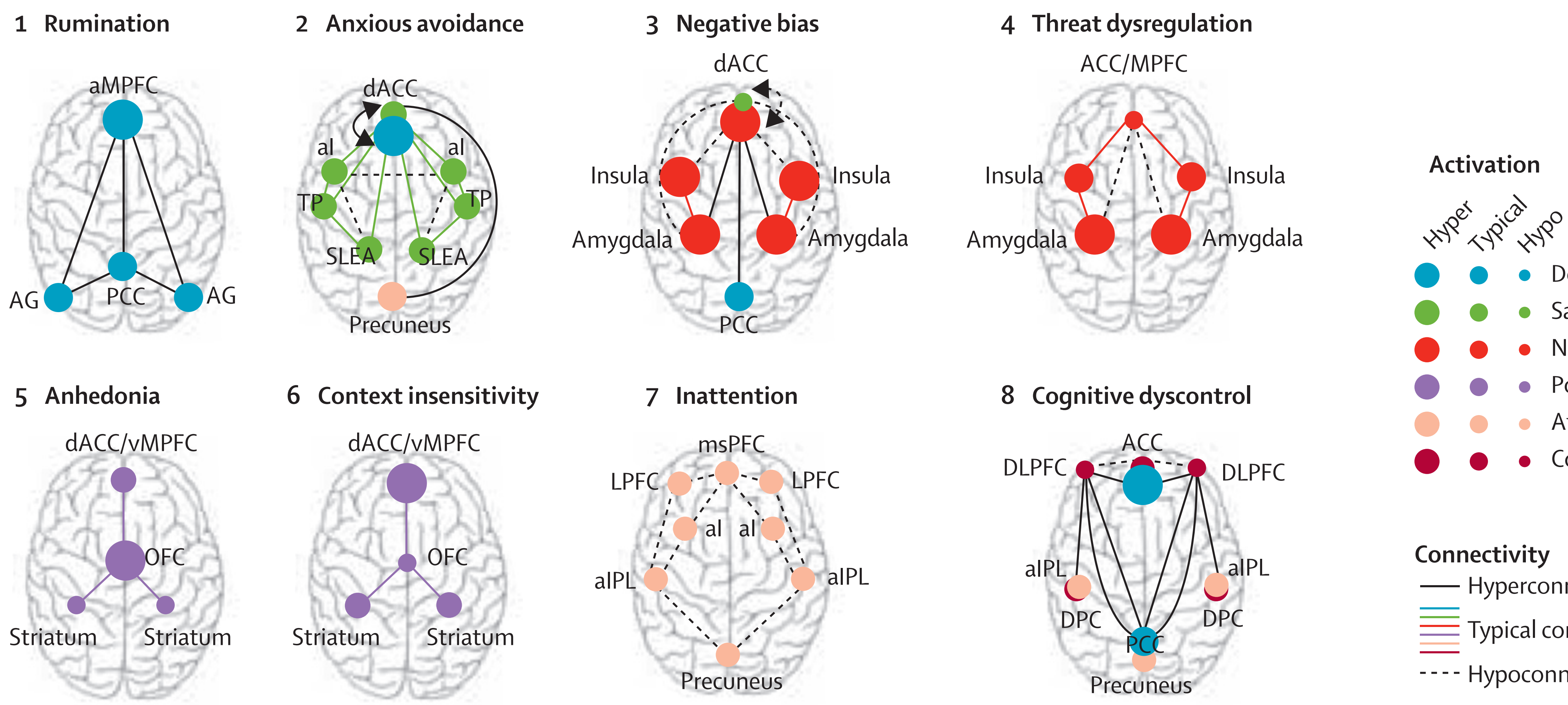
Upregulates BDNF

Increases Dopamine in Prefrontal Cortex

TMS MECHANISM
Williams 2016



TMS MECHANISM
Williams 2016



TMS

How does it work?

(Mechanism of action)

MECHANISM

Increases activity ->

Strengthens

DLPFC

TMS OVERVIEW

DLPFC

why DLPFC?

TMS OVERVIEW

Prefrontal Cortex has Several parts

ACC

(Anterior Cingulate Cortex)

OFC

(Orbitofrontal Cortex)

DLPFC

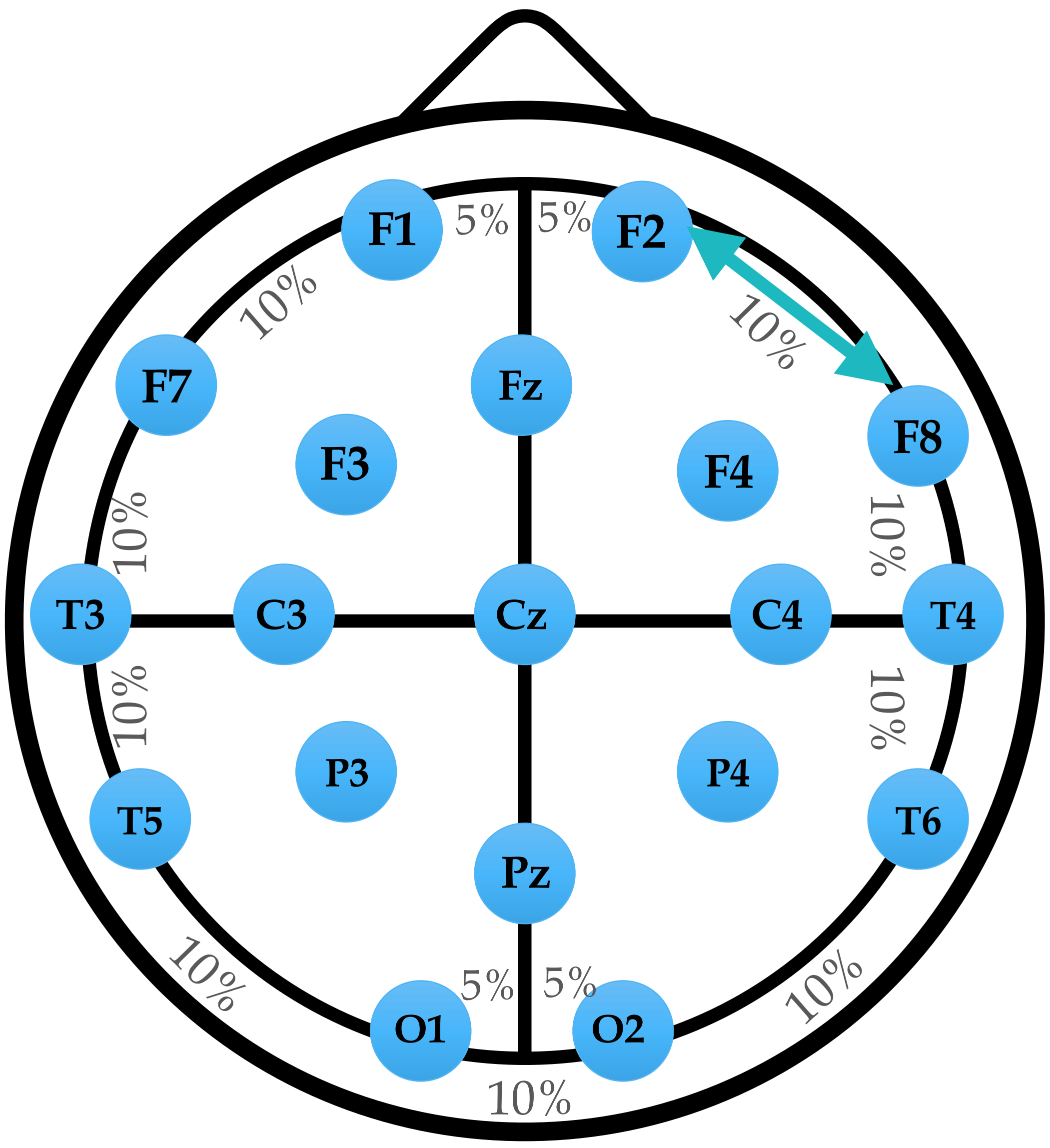
(Dorsolateral Prefrontal Cortex)

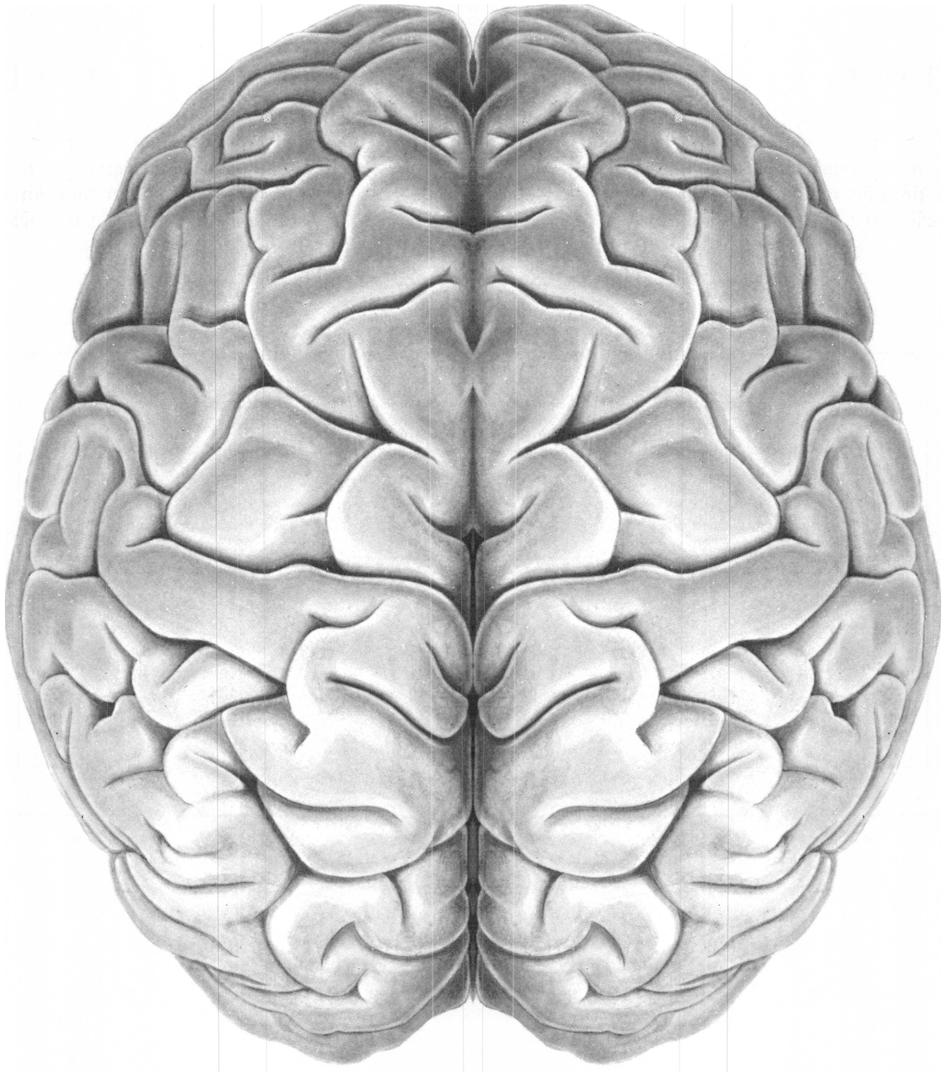
TMS OVERVIEW

DLPFC

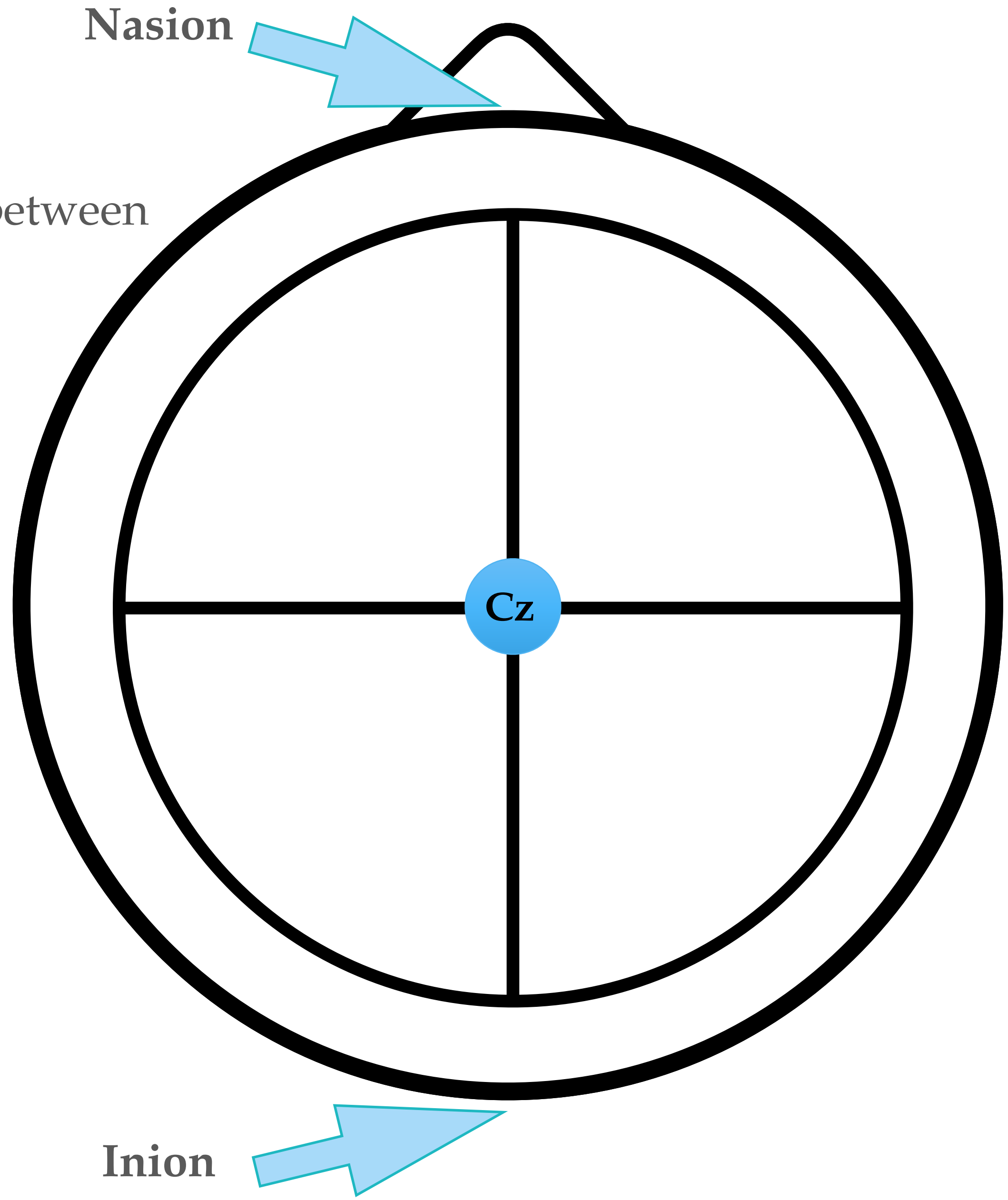
is part of the Prefrontal Cortex

Prefrontal is Association Cortex,
Thalamic inputs are from MedioDorsal not Lateral


F1
5%
5%
F2
10%
10%
F7
Fz
F8
F3
F4
10%
10%
T3
C3
Cz
C4
T4
10%
10%
P3
P4
T5
T6
Pz
10%
10%
5%
5%
O1
O2
10%

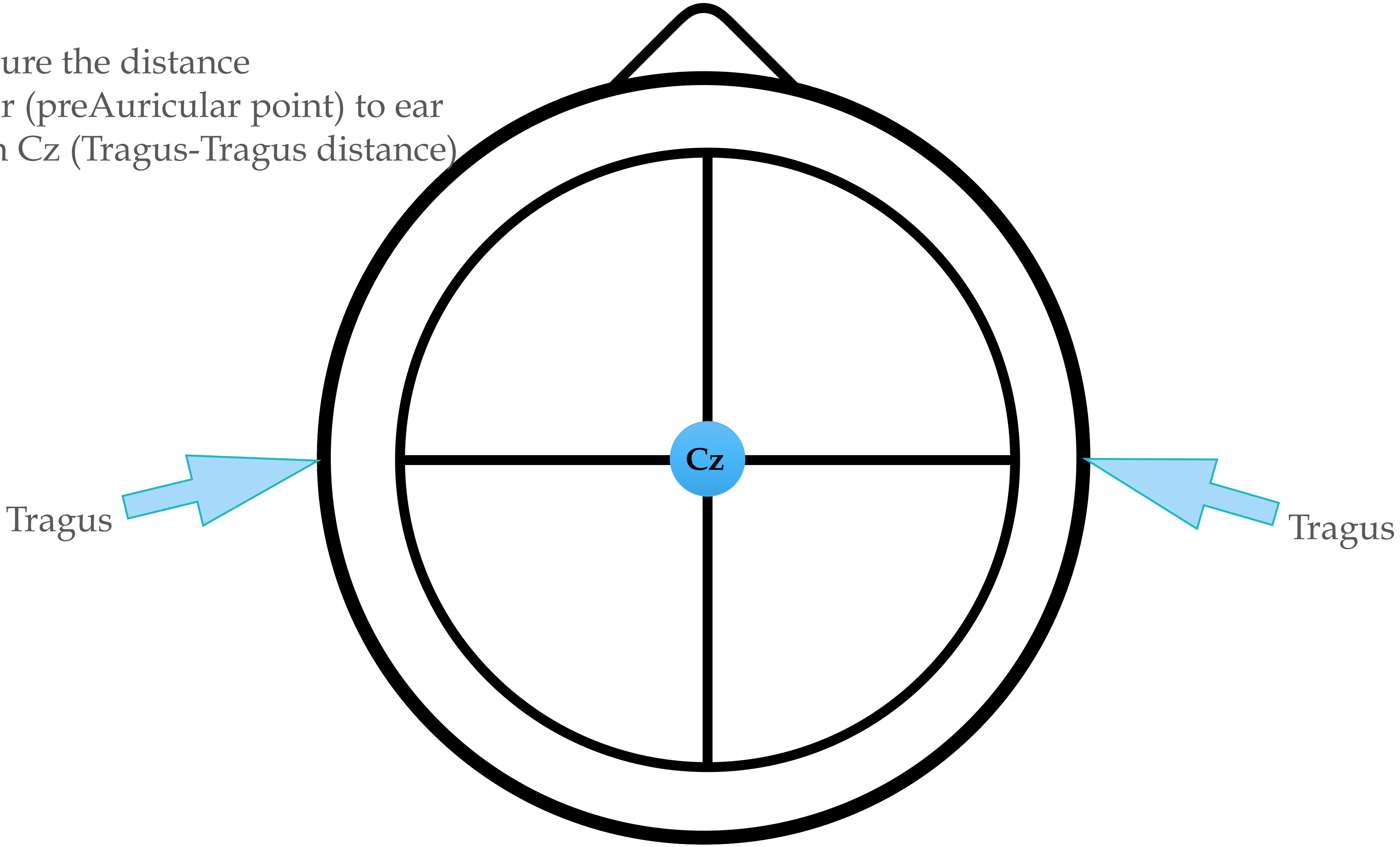


1. Measure the distance
from Nasion to Inion and
2. mark the spot half way between



Cz = 50% distance
Nasion to Inion

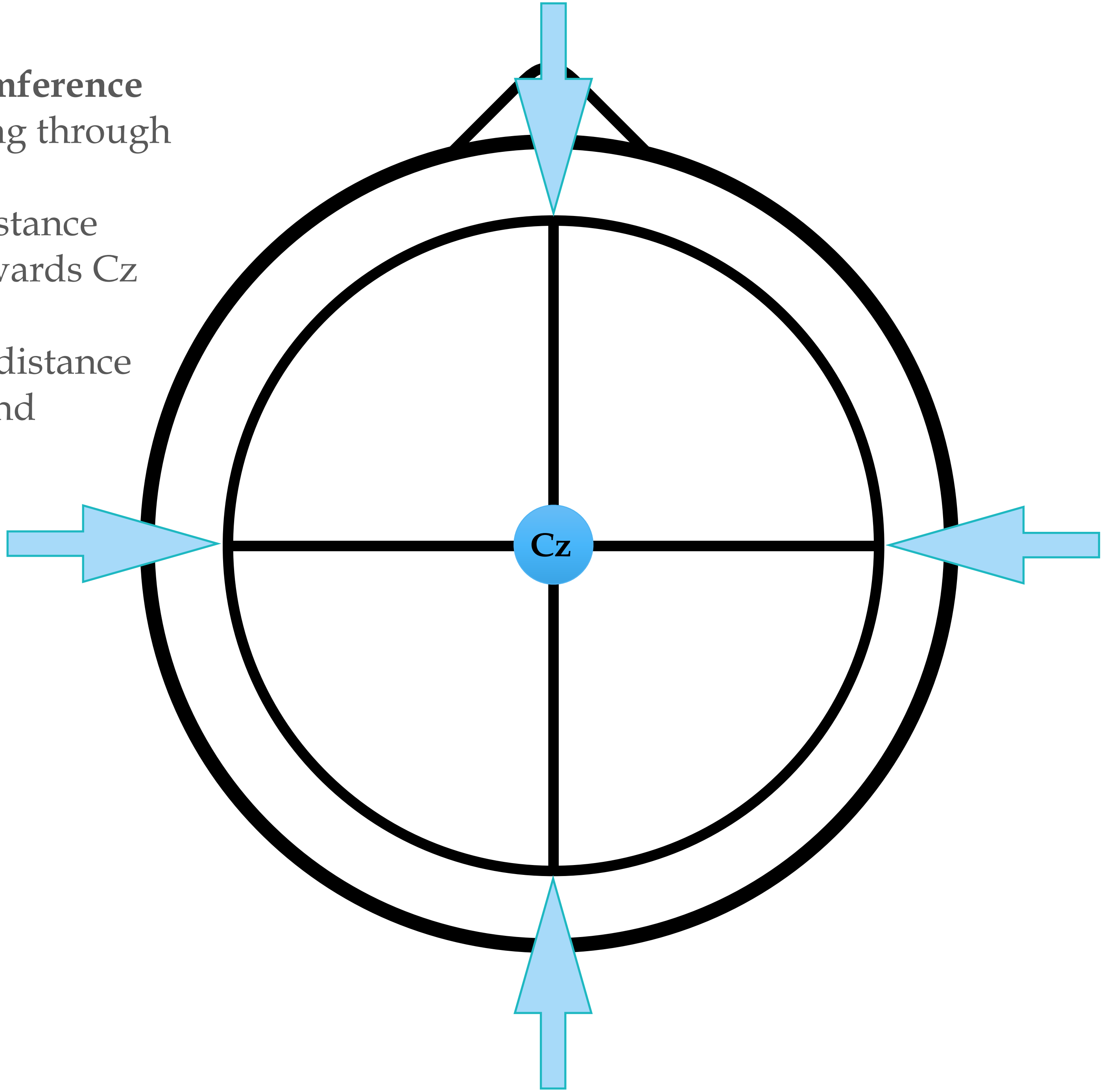
3. Measure the distance
from ear (preAuricular point) to ear
through Cz (Tragus-Tragus distance)



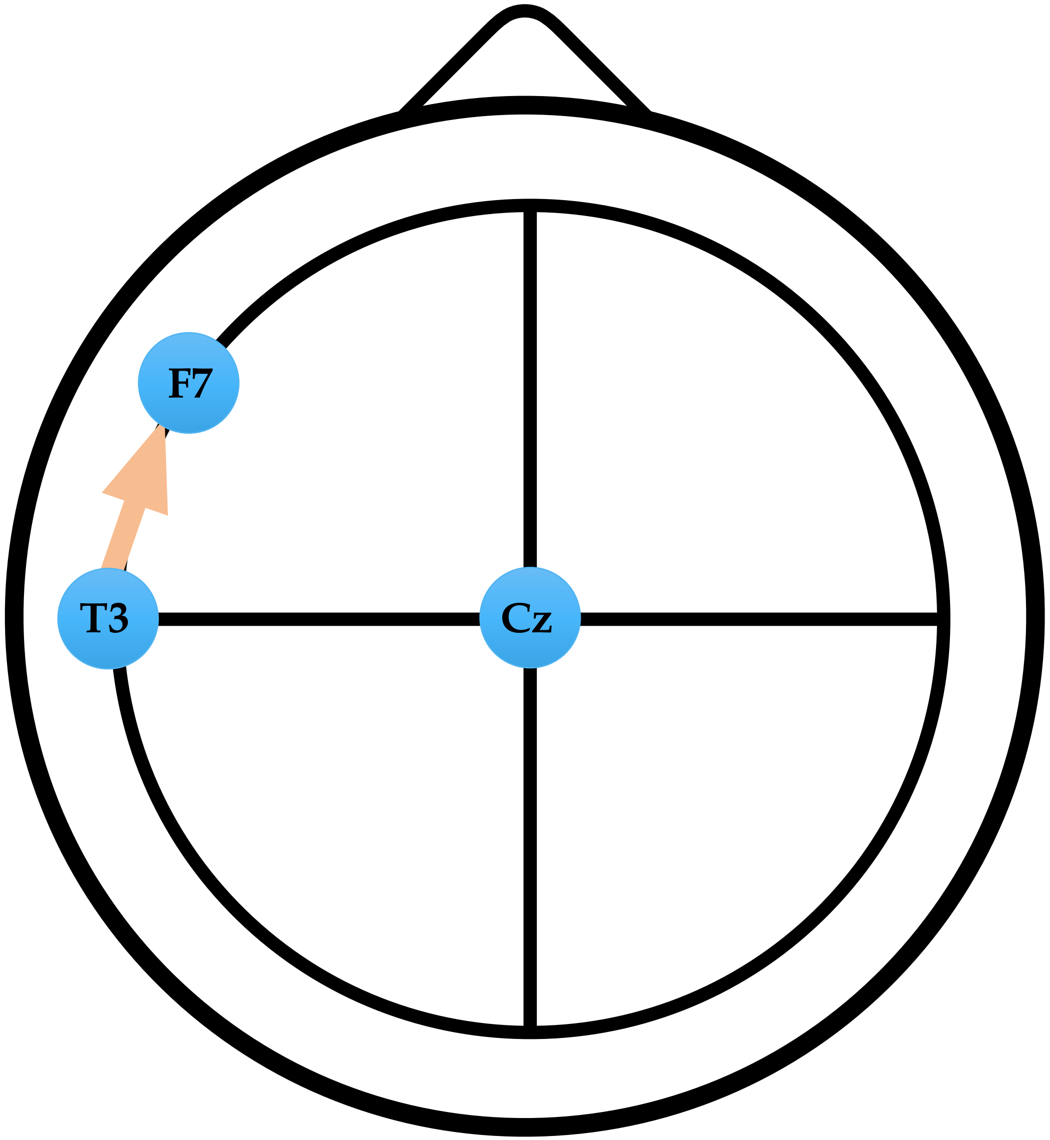
4. Measure the **circumference** around the head going through Four points:

10% tragus-tragus distance From each tragus towards Cz Left & Right tragus

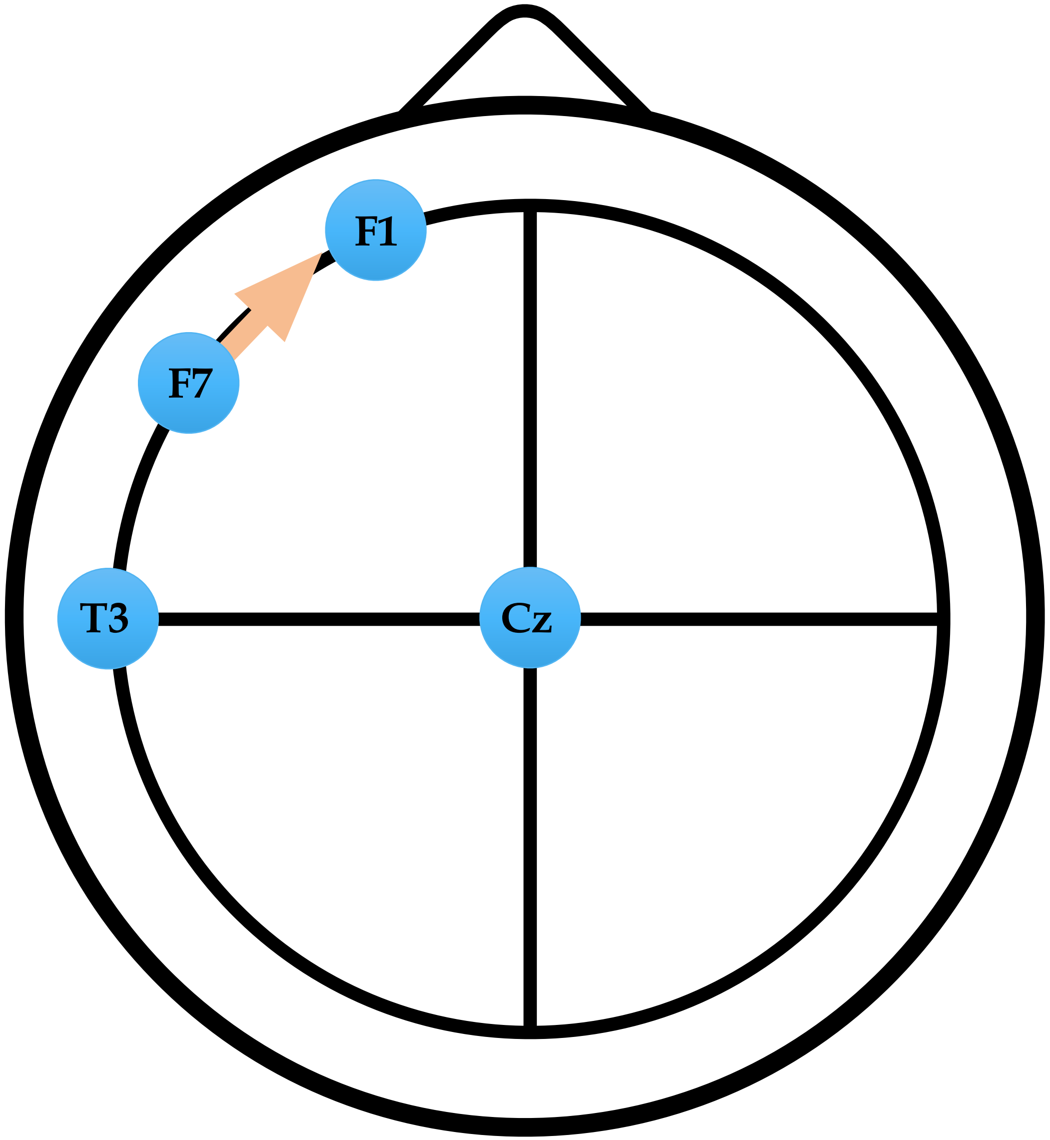
10% Nasion to inion distance From Nasion to Cz and From Inion to Cz



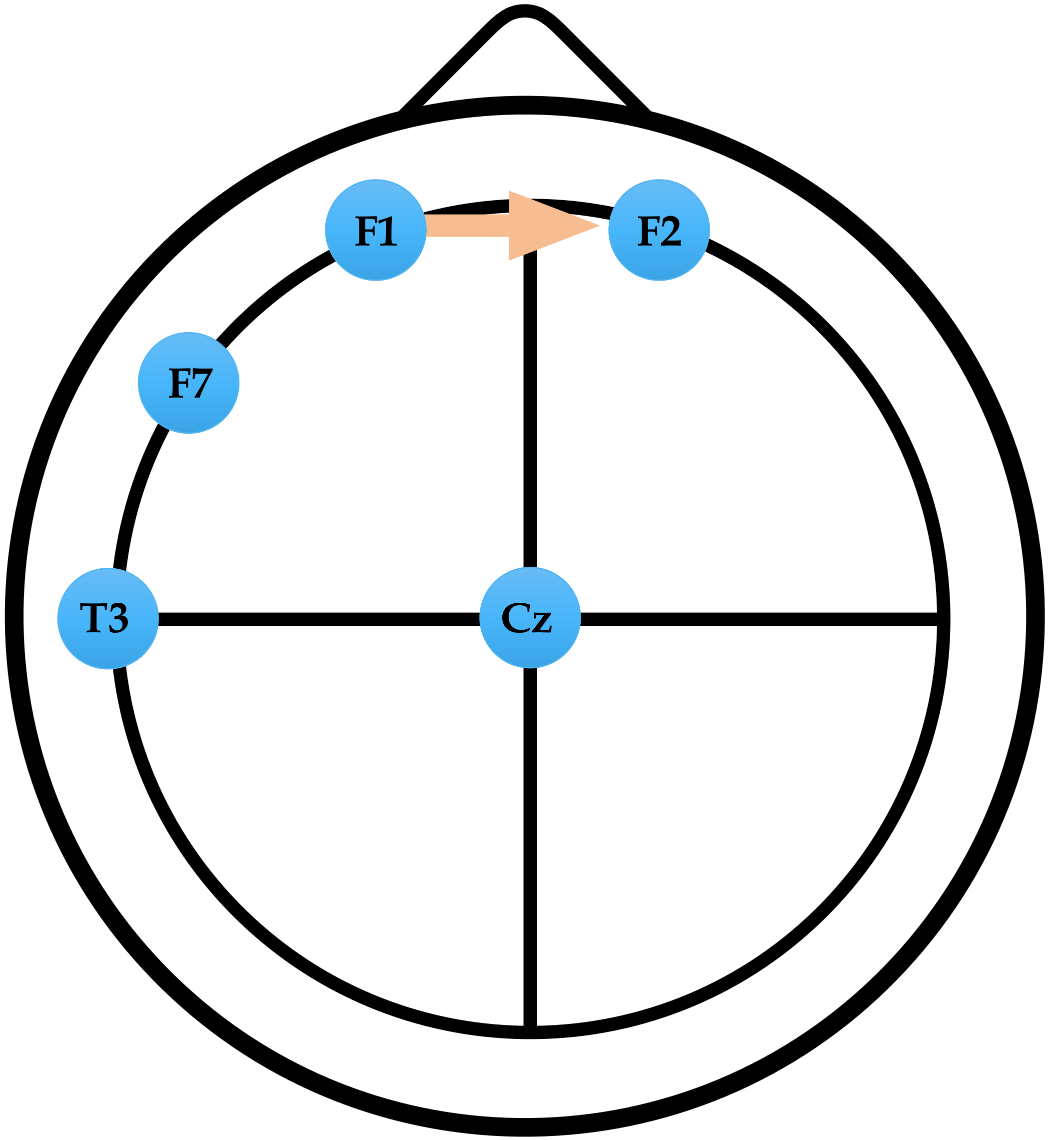
4. Mark increments **10%** of the circumference clock-wise around the head:



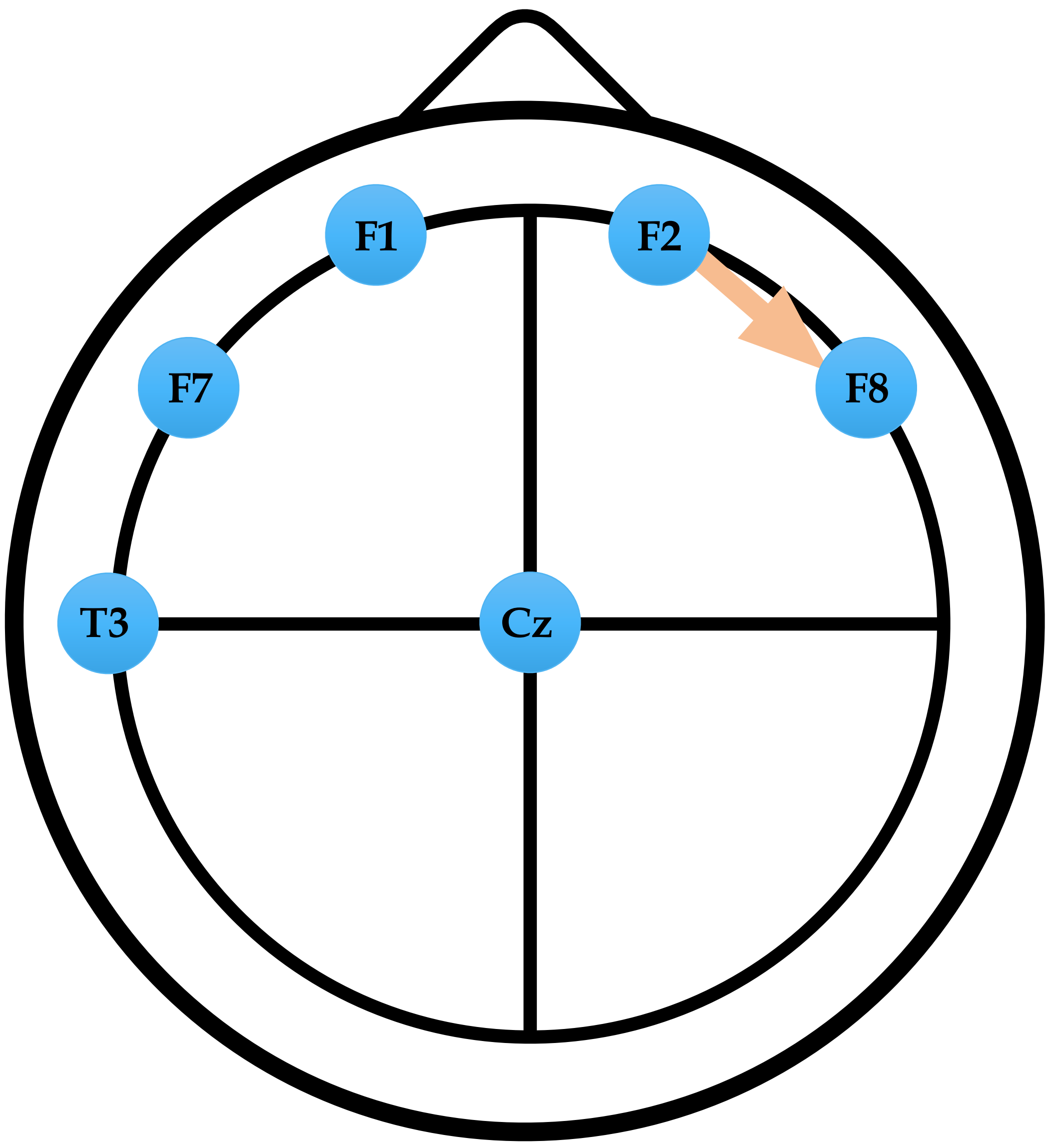
4. Mark increments **10%** of the circumference clock-wise around the head:



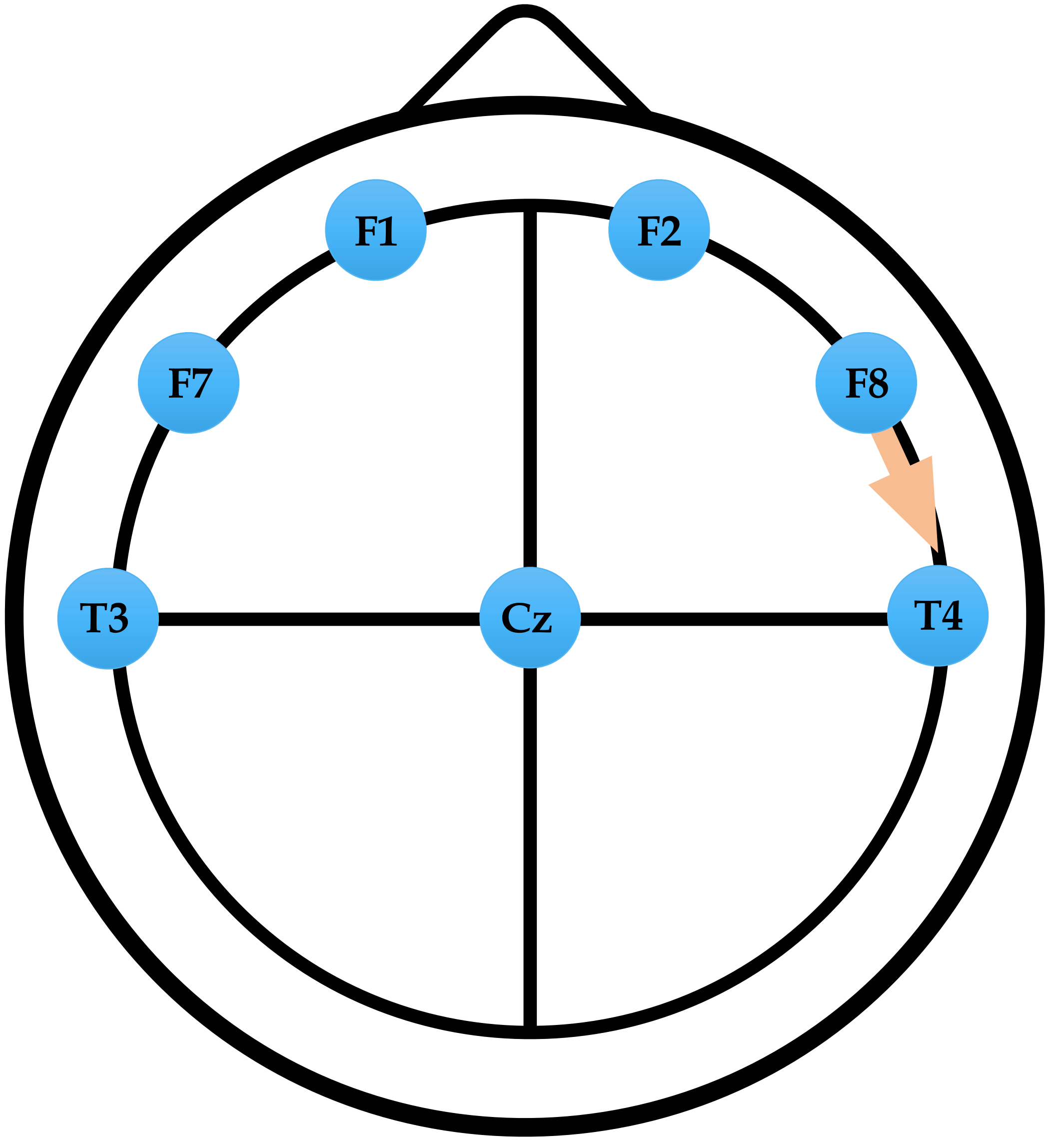
4. Mark increments **10%** of the circumference clock-wise around the head:



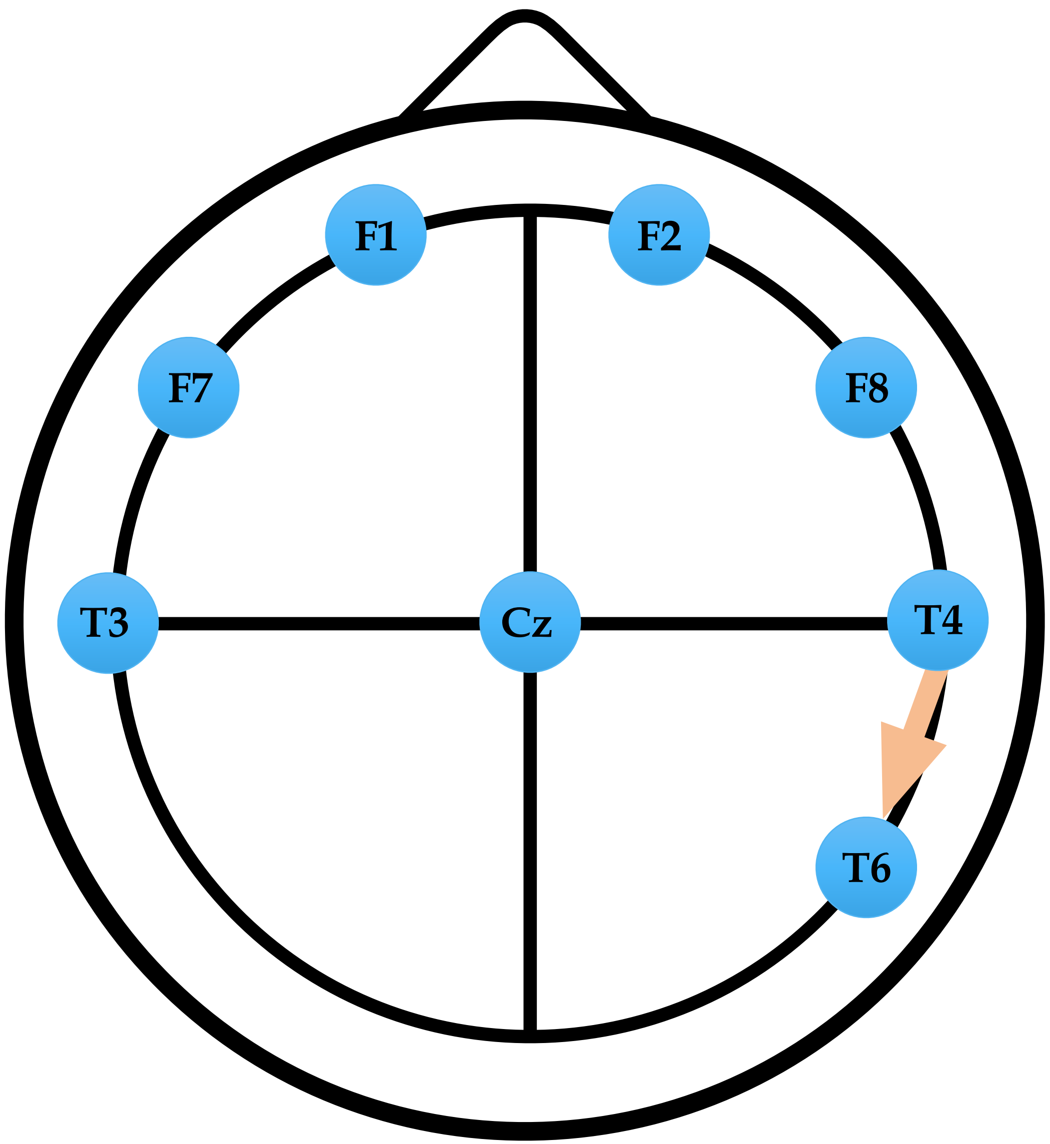
4. Mark increments **10%** of the circumference clock-wise around the head:



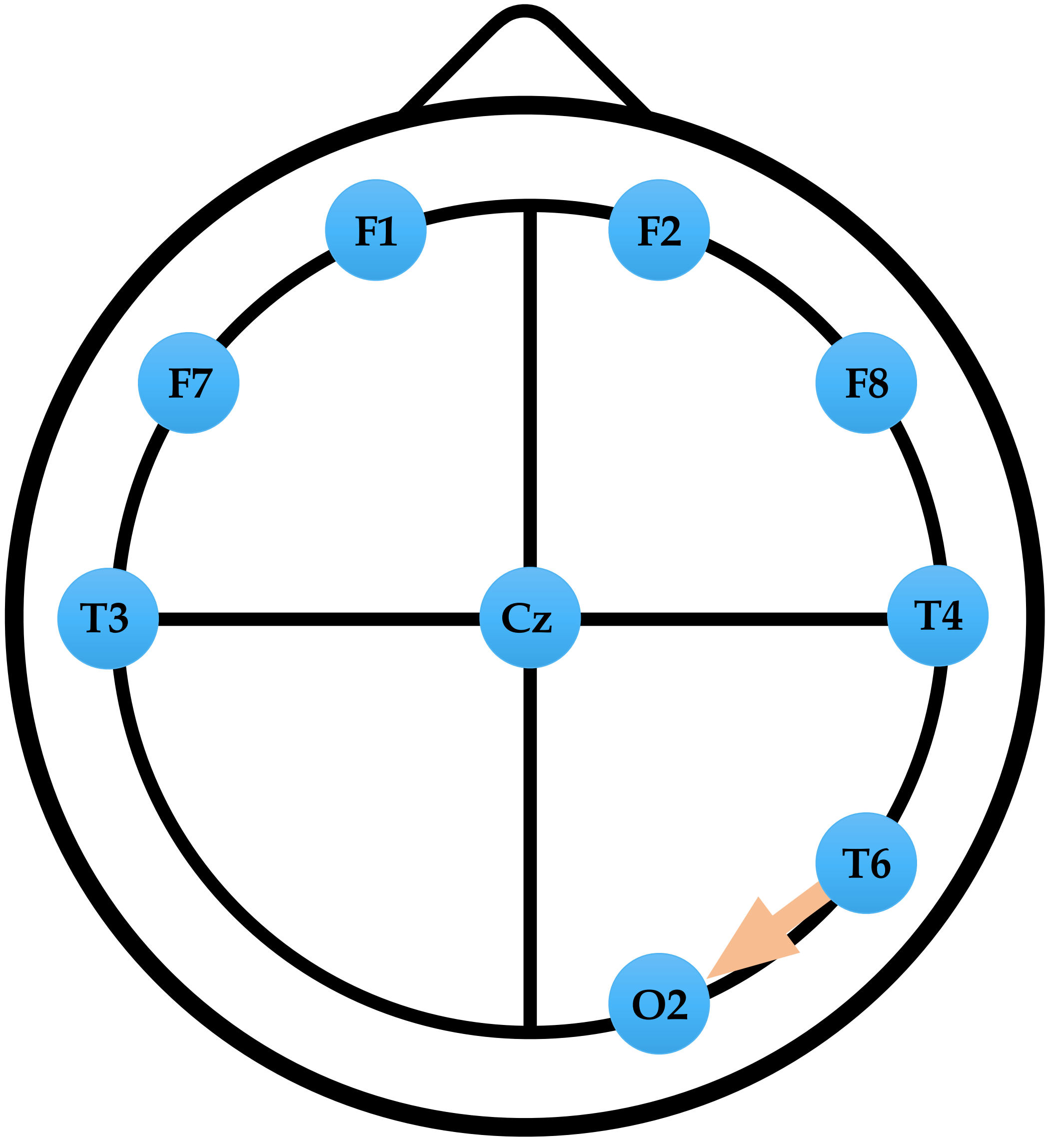
4. Mark increments **10%** of the circumference clock-wise around the head:



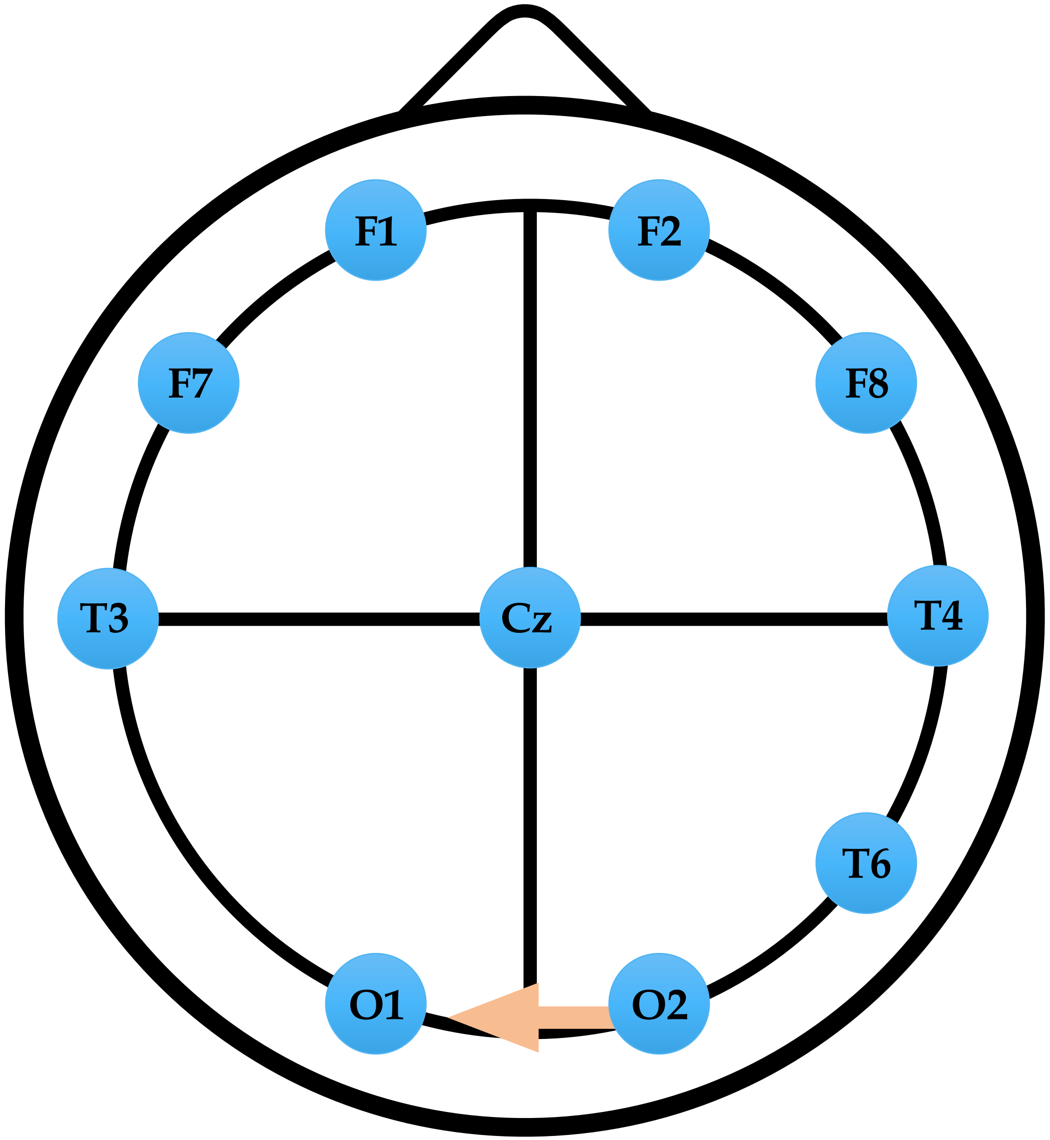
4. Mark increments **10%** of the circumference clock-wise around the head:



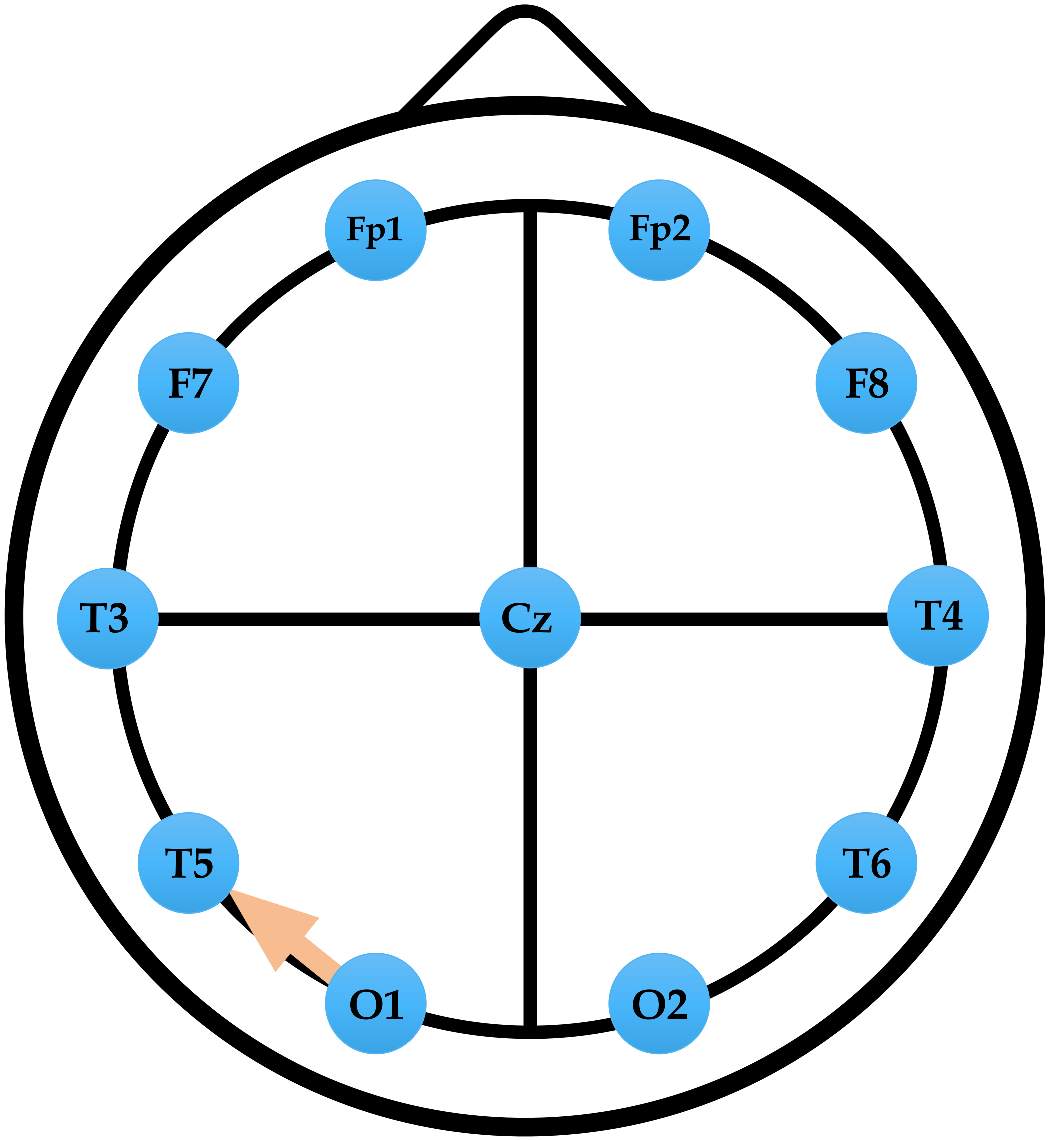
4. Mark increments **10%** of the circumference clock-wise around the head:



4. Mark increments **10%** of the circumference clock-wise around the head:

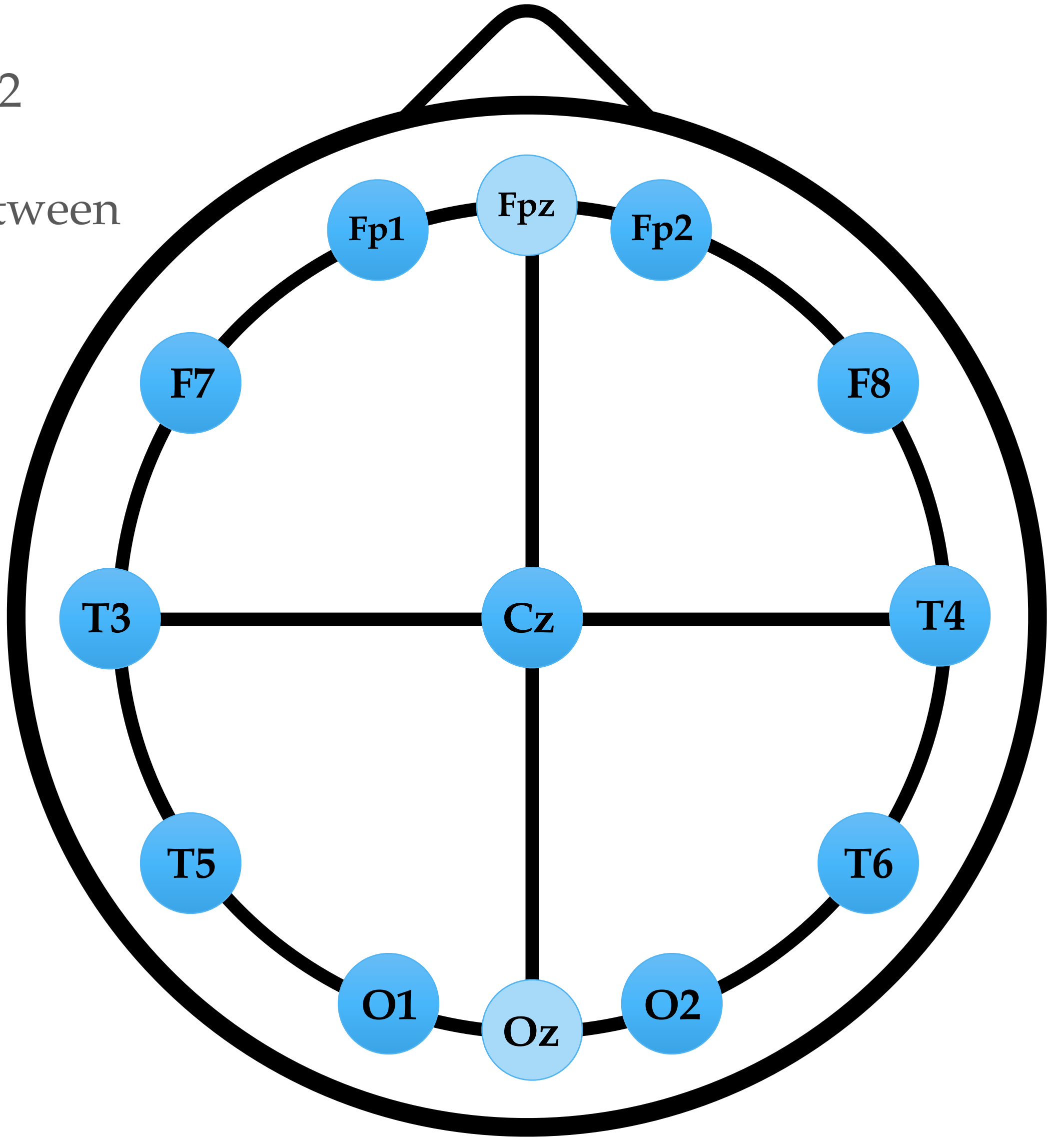


4. Mark increments **10%** of the circumference clock-wise around the head:

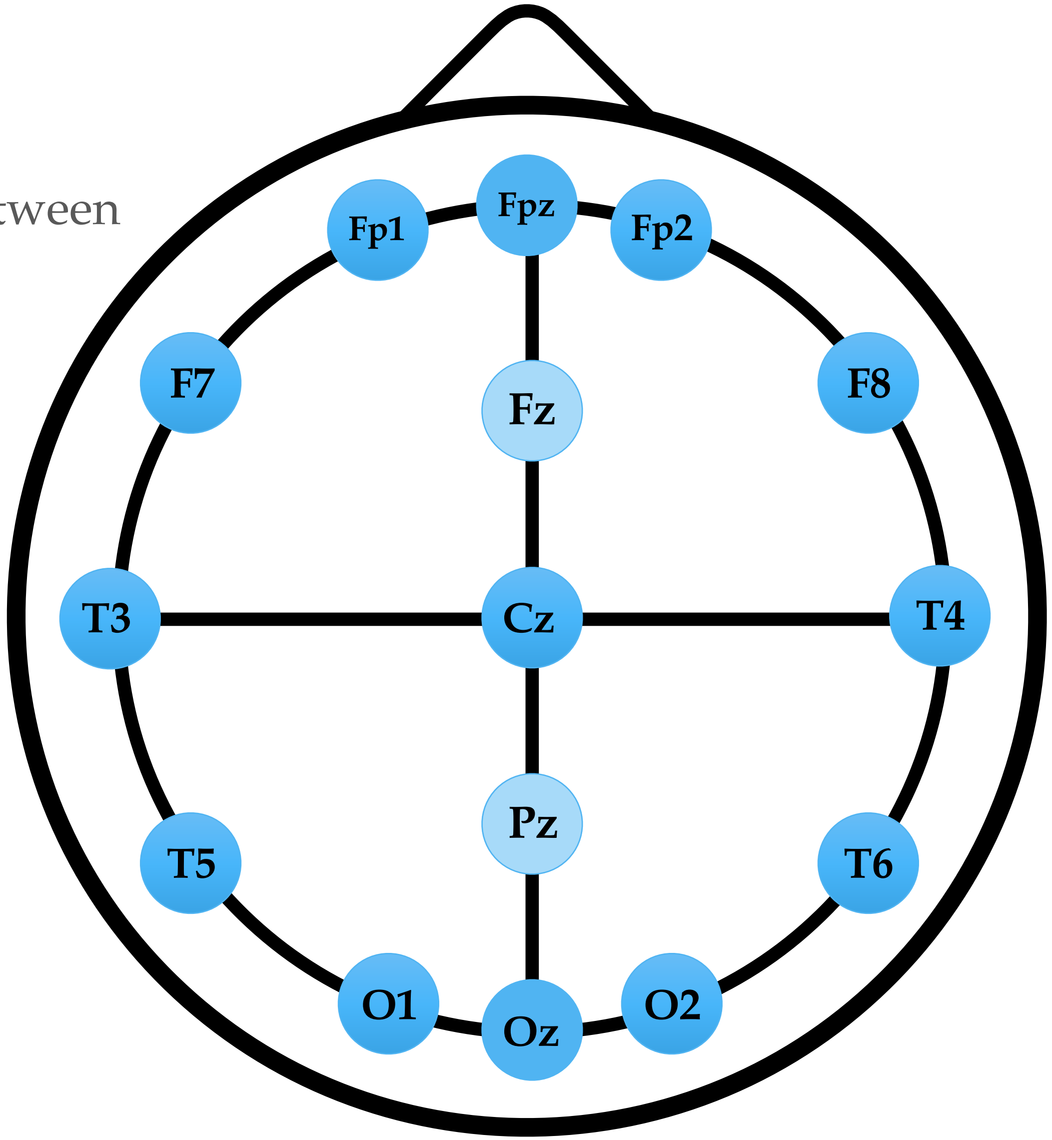


5. Mark the point
half way between Fp1 and Fp2
(Fpz)
and the the point half way between
O1 and O2
(Oz)

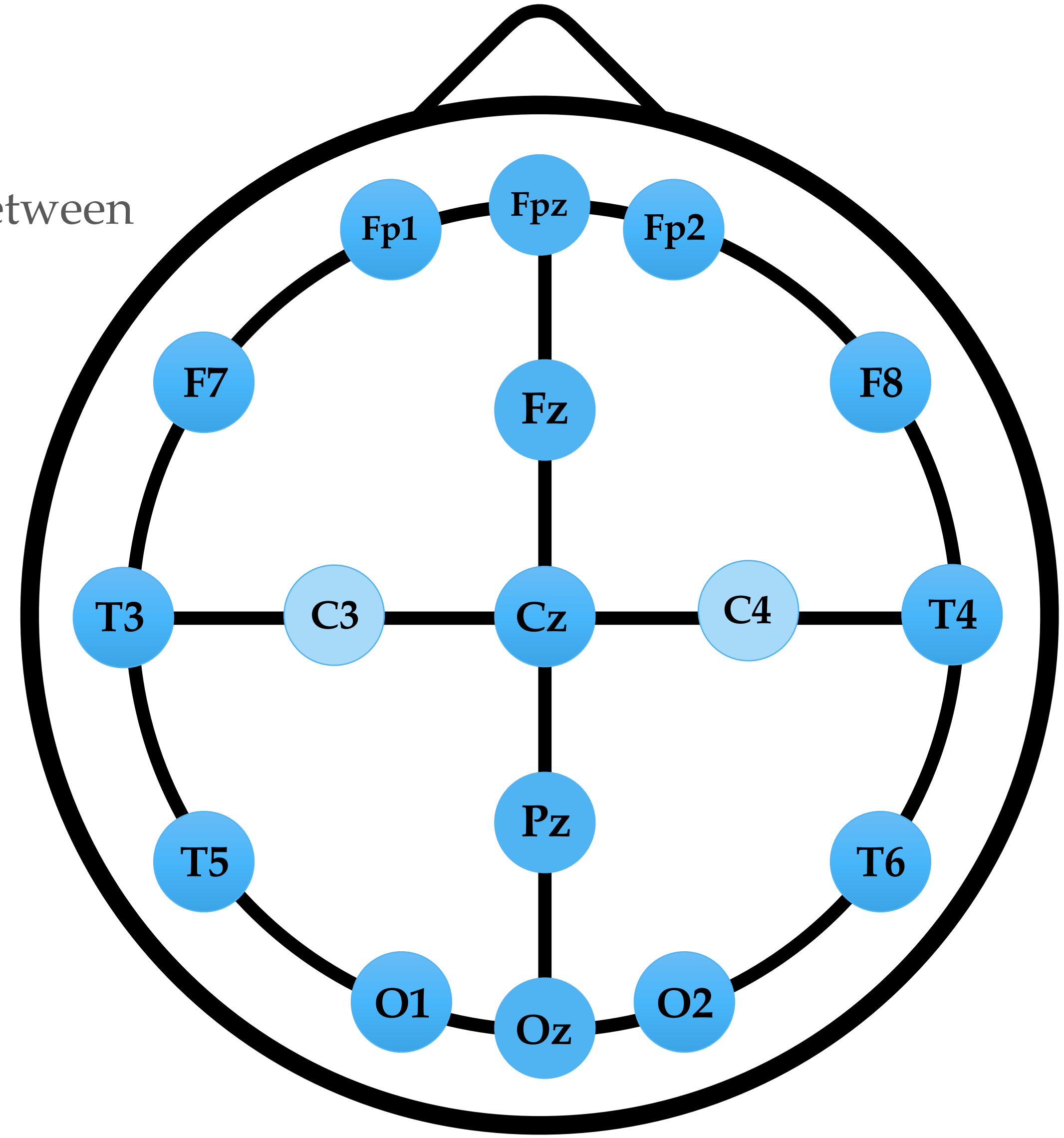
Check that Fpz is also 10%
Of the nasion-Inion distance
From the nasion
And that
Oz is 10%
Of the Nasion-Inion distance
From the inion



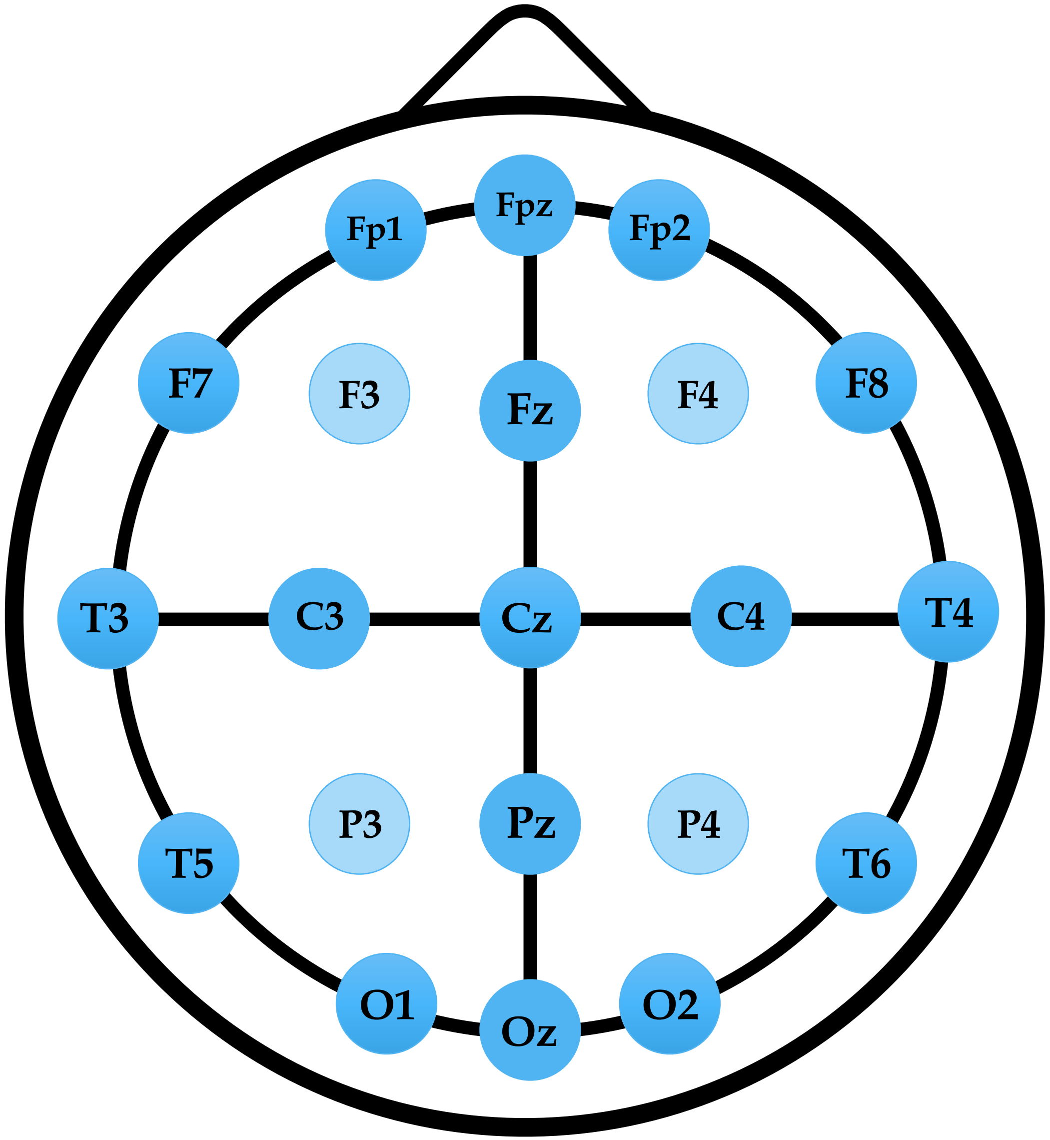
6. Mark the point
half way between Fpz and Cz
(Fz)
and the the point half way between
Oz and Cz
(Pz)



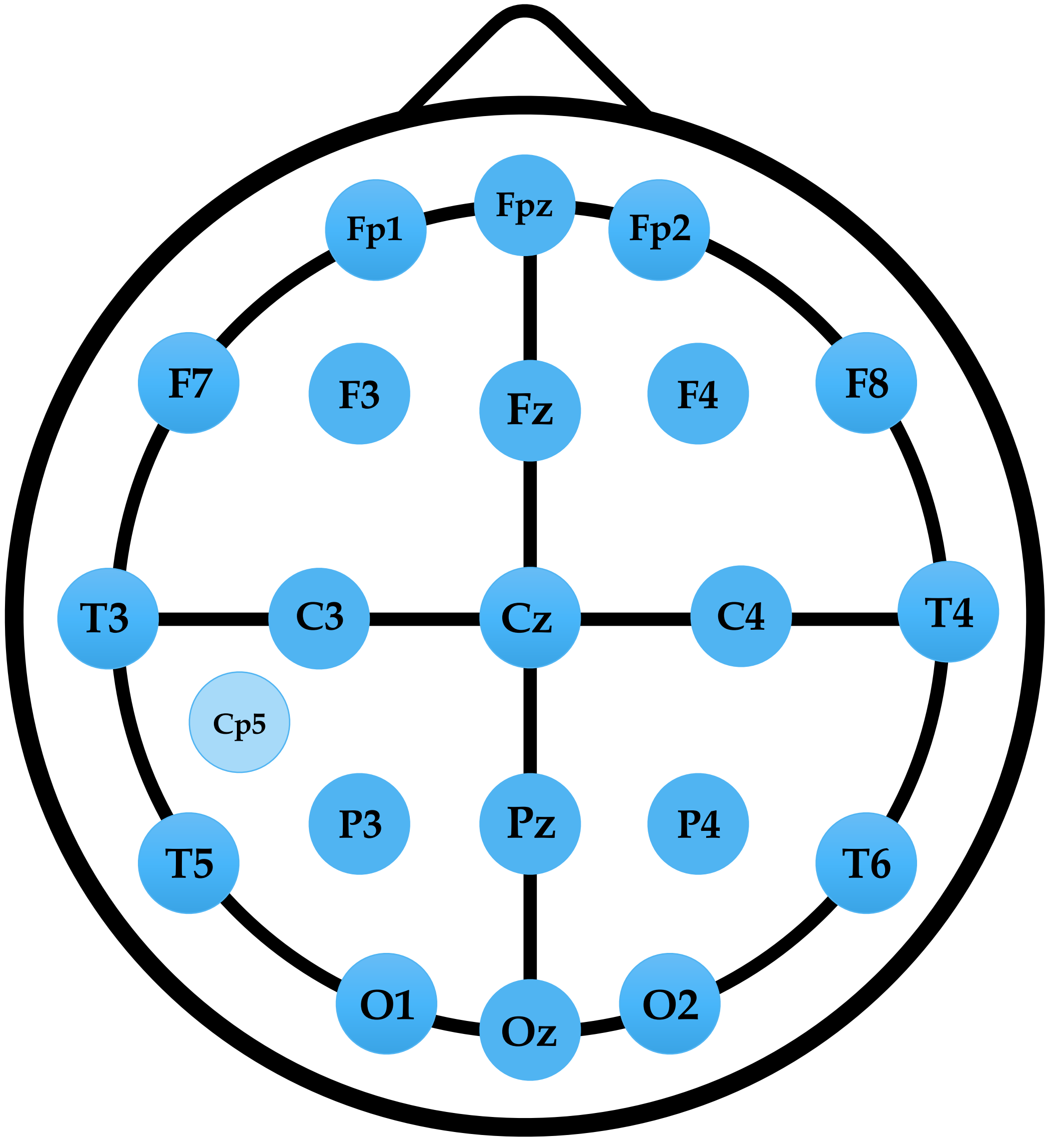
7. Mark the point
half way between T3 and Cz
(C3)
and the the point half way between
T4 and Cz
(C4)



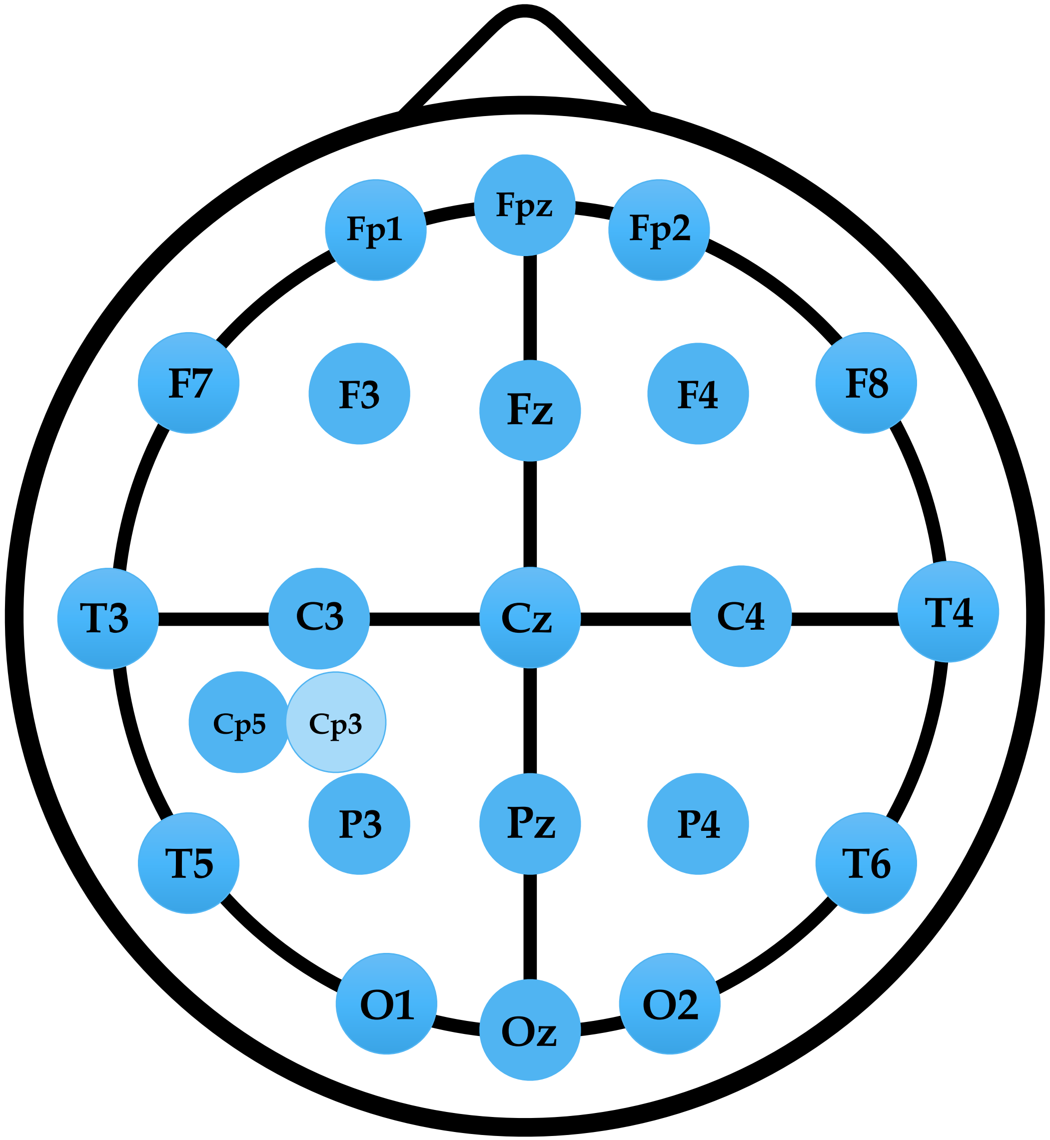
8. Mark the point
half way between F7 and Fz
(F3)
and the point
half way between F8 and Fz
(F4)
and the point
half way between T5 and Pz
(P3)
and the point
half way between T6 and Pz
(P4)



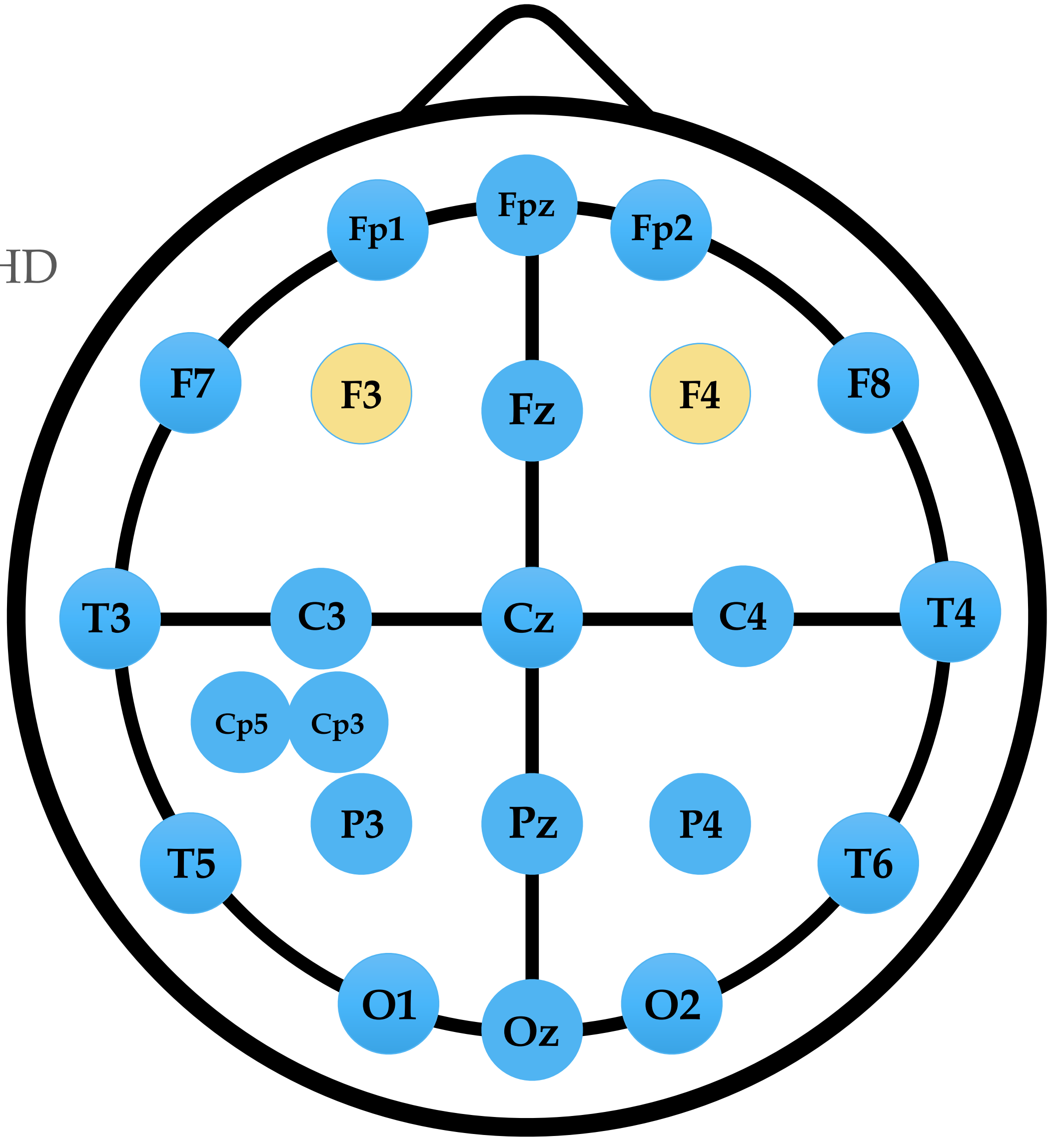
9. Mark the point
half way between P3 and T3
(Cp5)



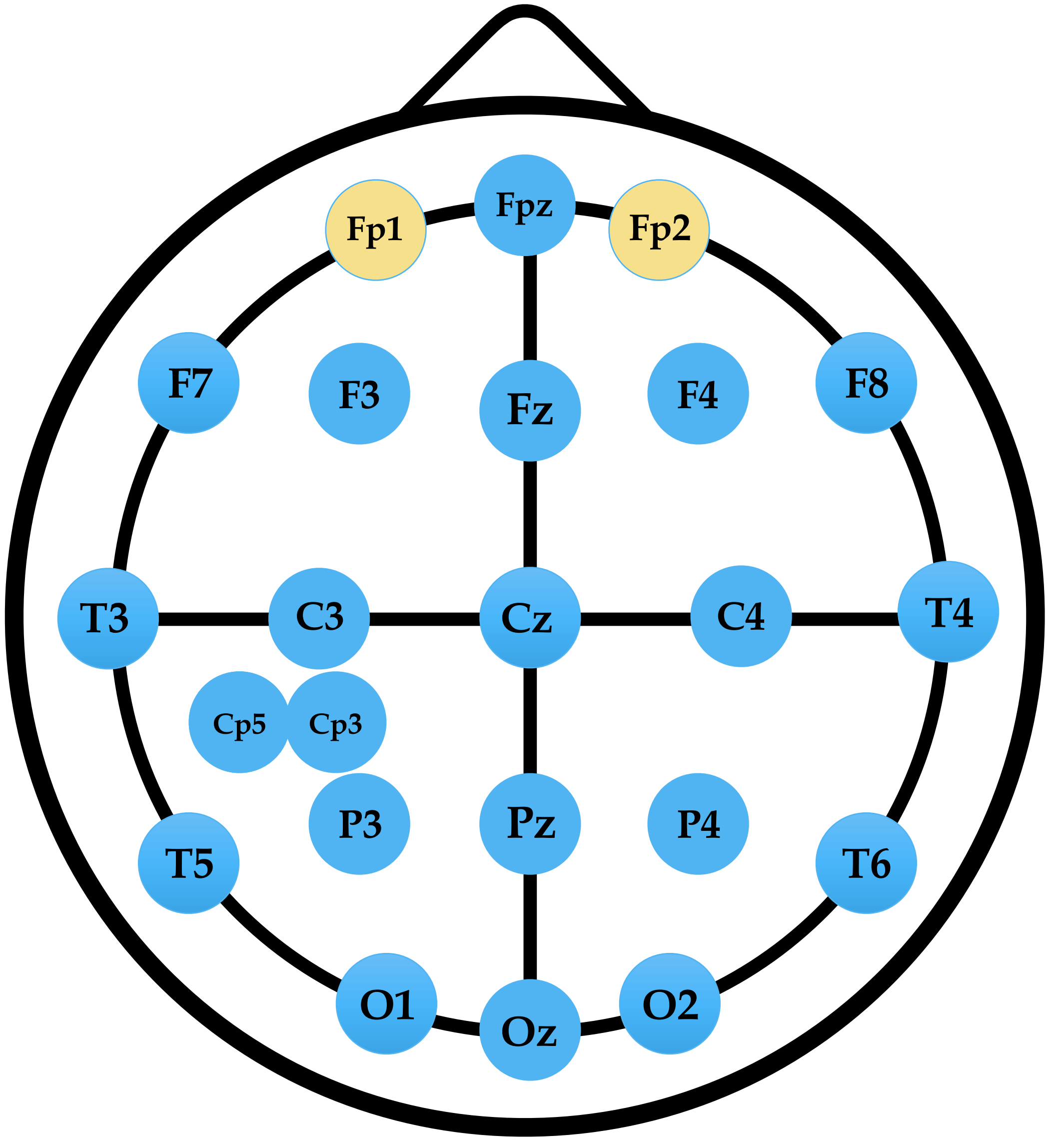
10. Mark the point
half way between P3 and C3
(Cp3)



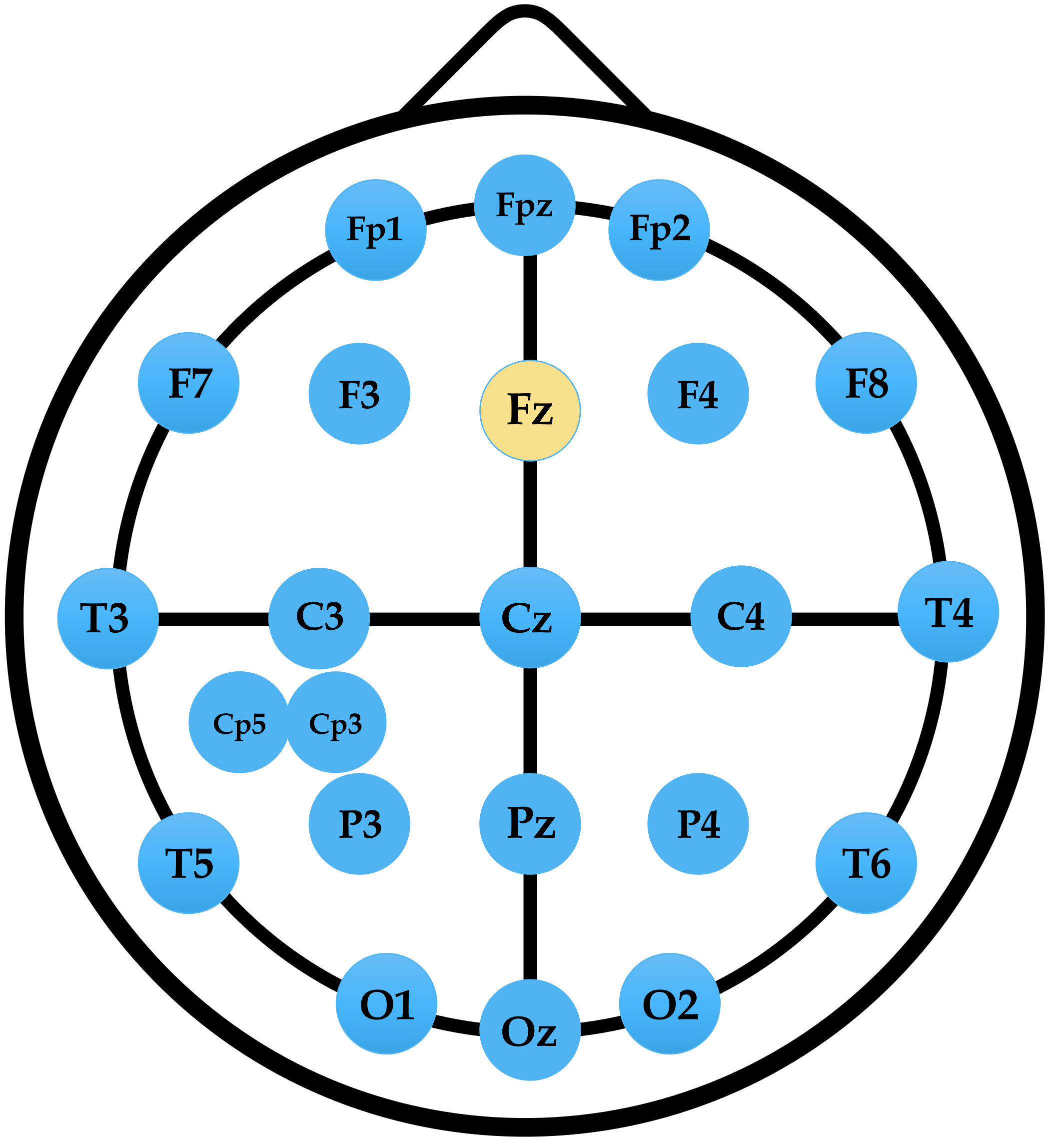
F3 (to target Left DLPFC) and
F4 (to target Right DLPFC)
May be useful to treat
Many conditions including
Depressive Disorder and ADHD



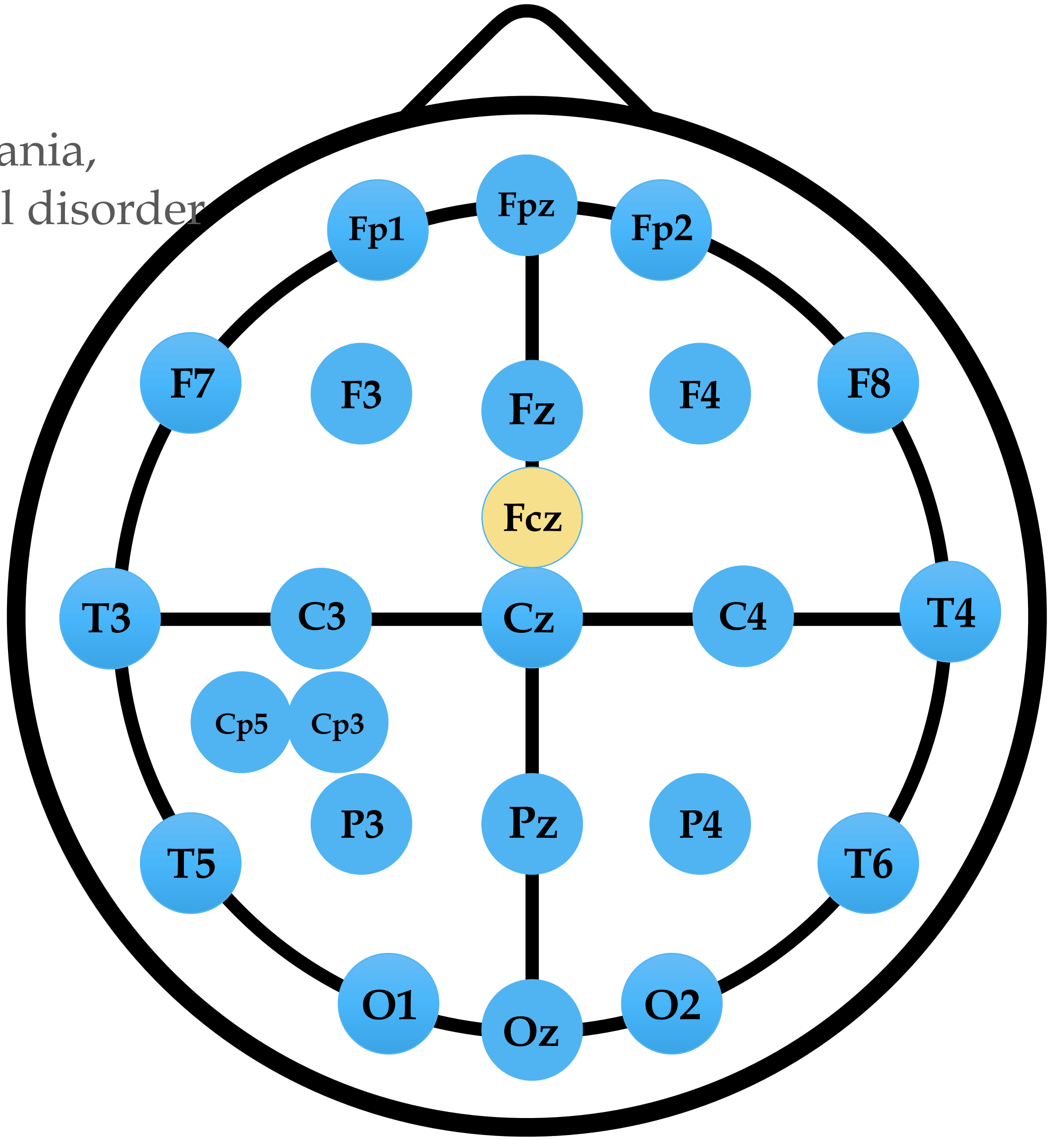
Fp1 (to target Left OFC)
May be useful to treat
Addiction
Fp2 (to target Right OFC)
May be useful to treat
OCD, Anxiety Disorders
and ruminations in
Major Depressive Disorder
(all inhibitory)



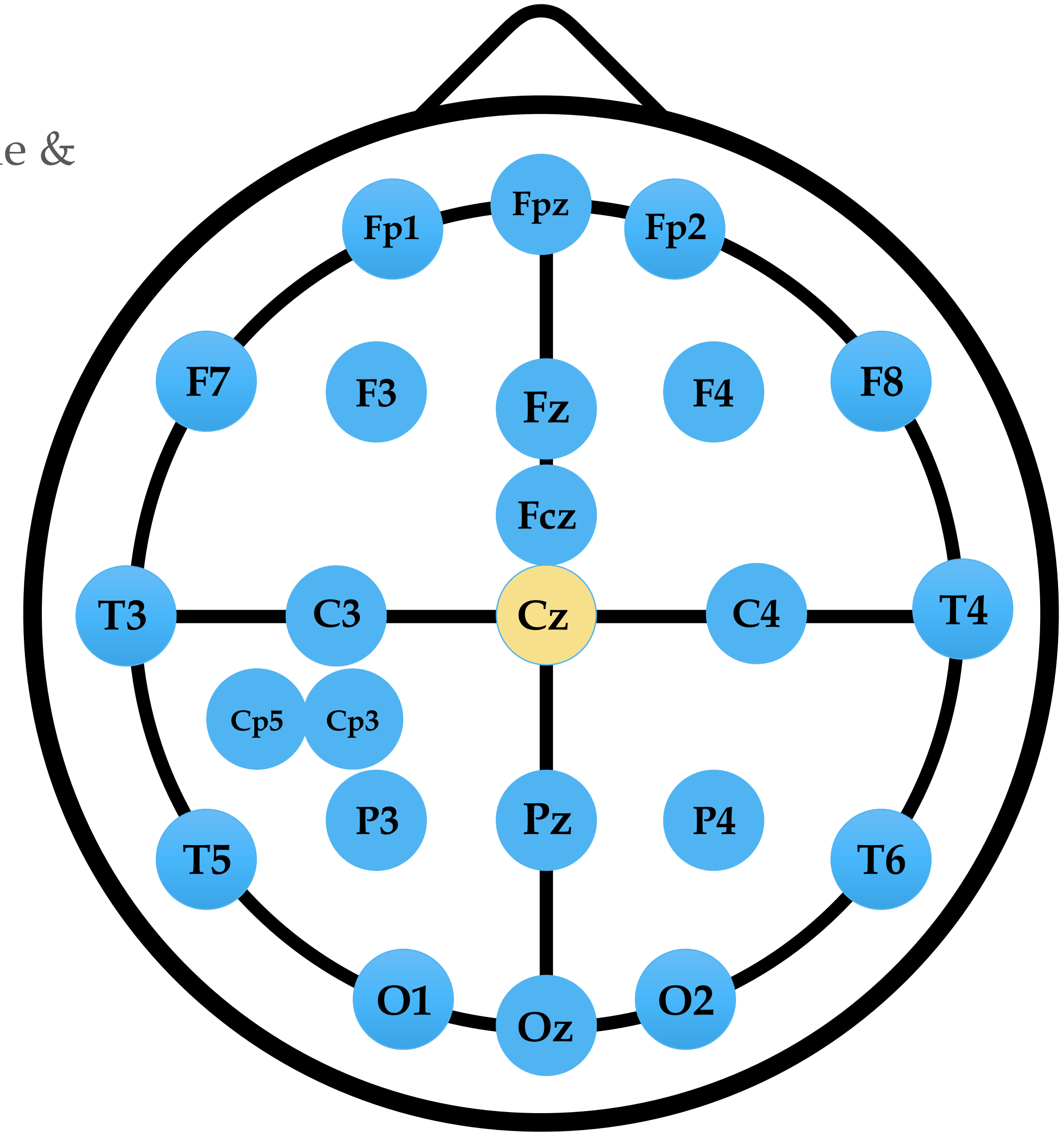
Fz (to target **DM**PFC & ACC)
May be useful to treat
Anhedonia especially
In the absence of anxiety
(excitatory)



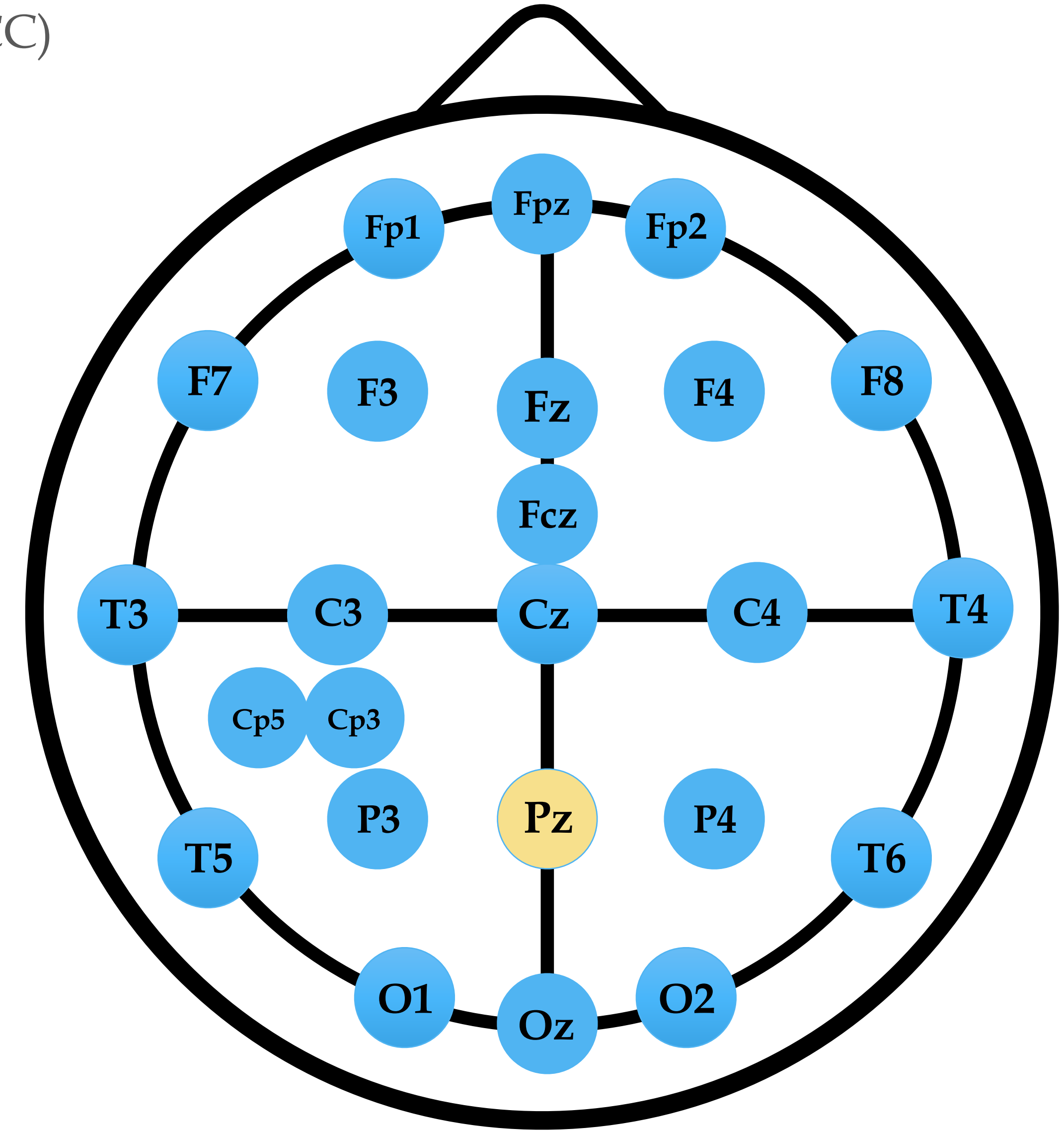
Fcz (to target SMA)
May be useful to treat
OCD, Tourette's, Trichotillomania,
Parkinson's & Impulse control disorder



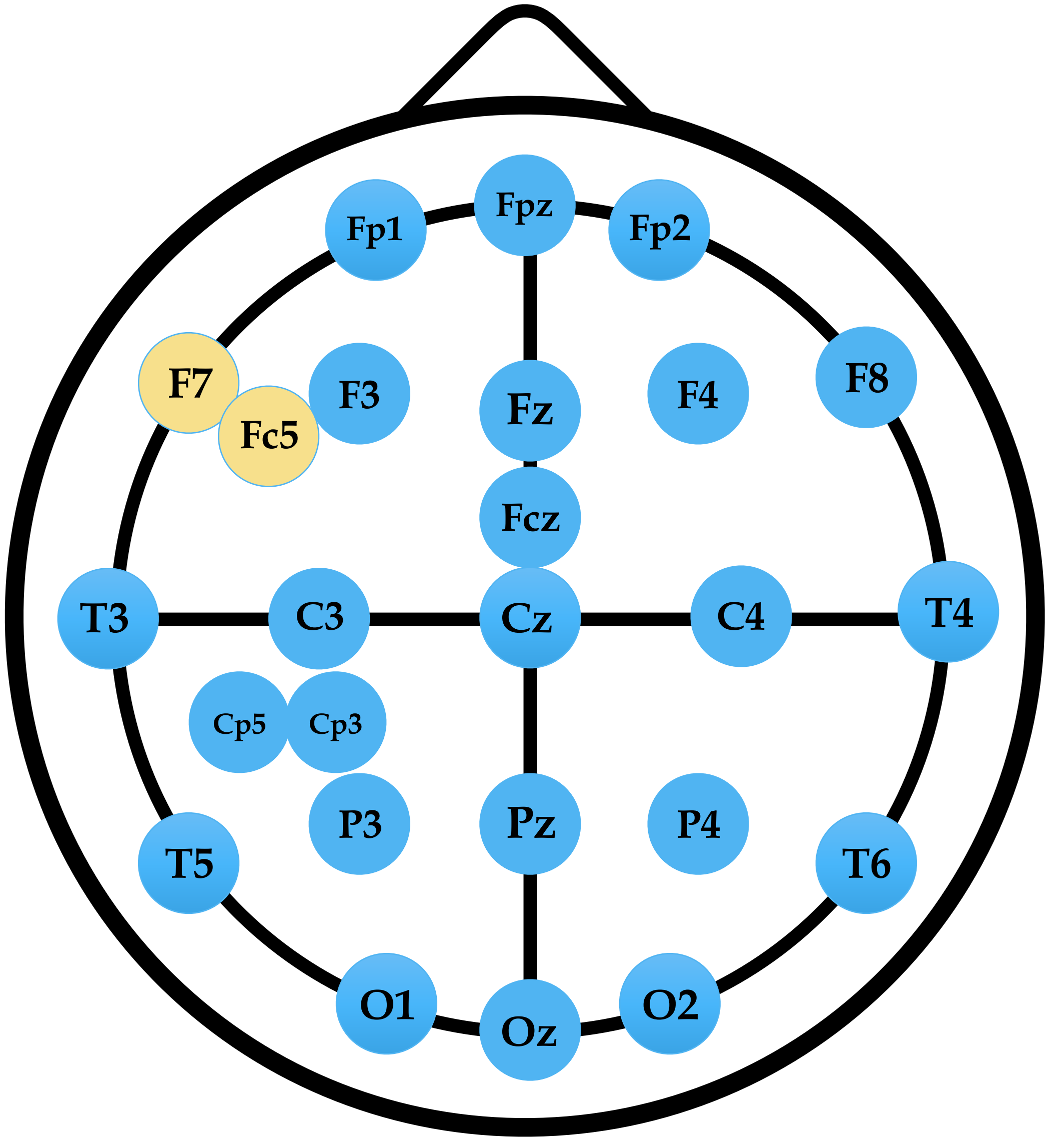
Cz (to target M1)
May be useful to treat
Chronic Pain, Chronic Fatigue &
Parkinson's Disease



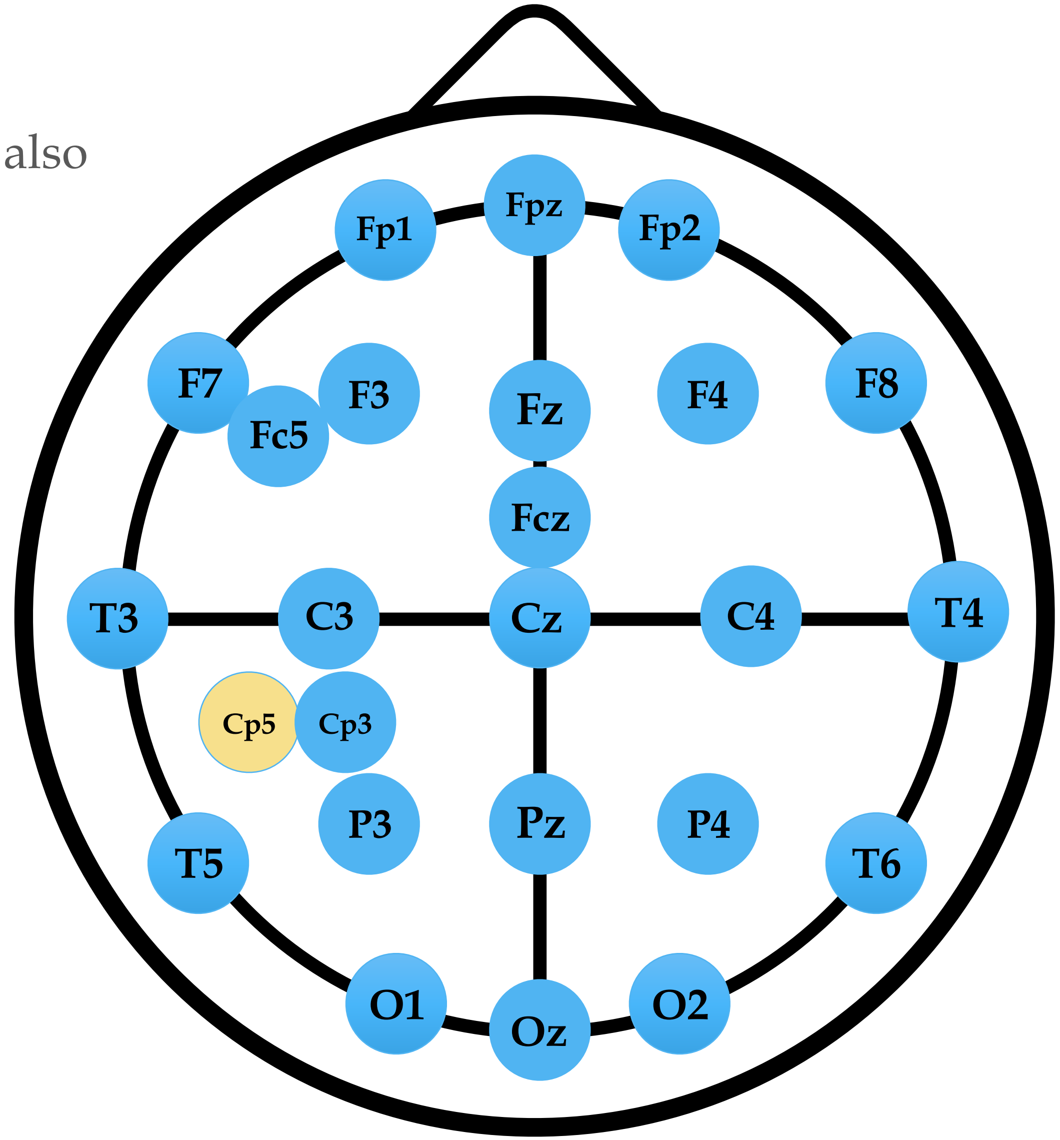
Pz (to target Precuneus & PCC)
May be useful to treat
Certain other conditions



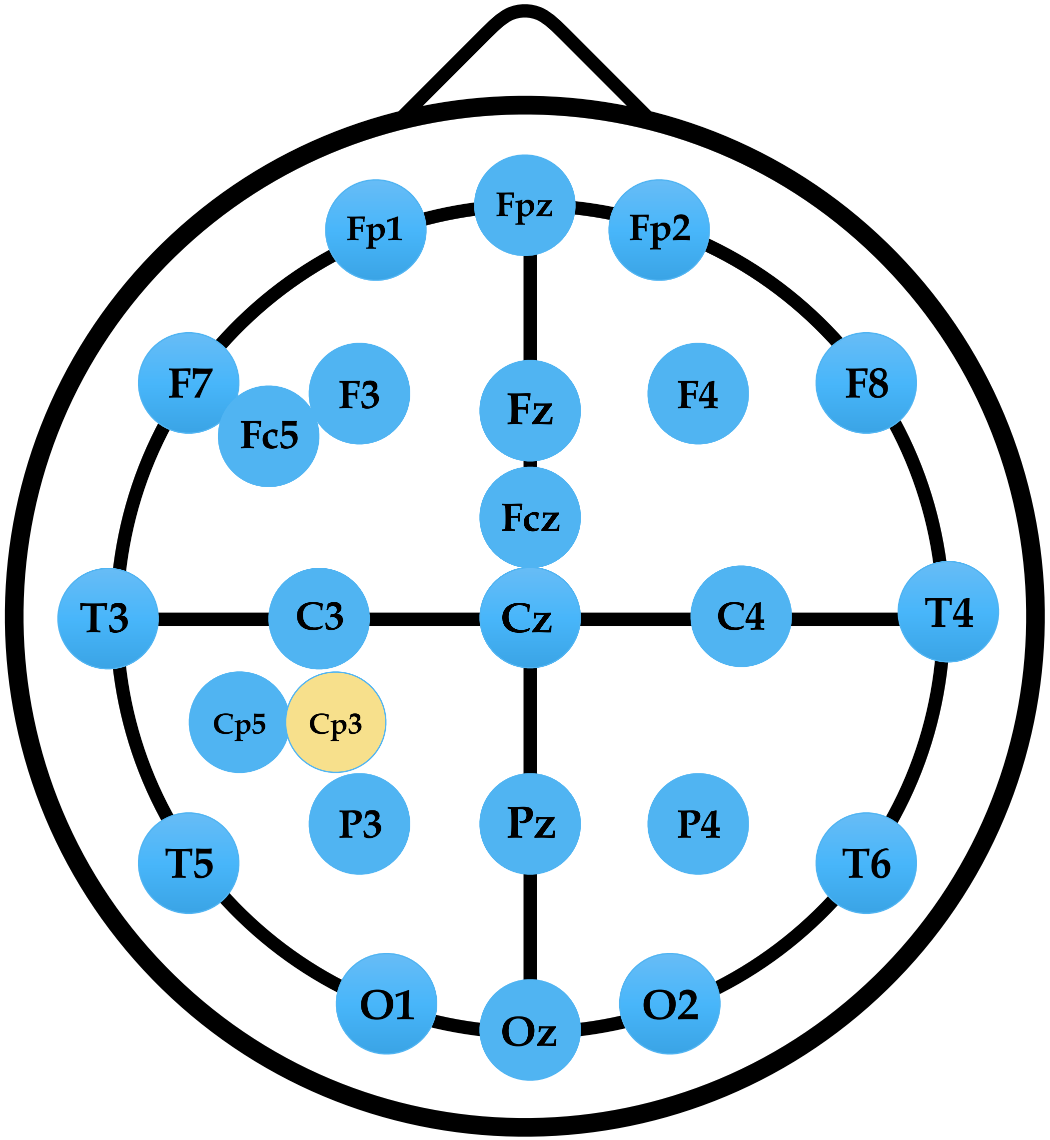
F7/Fc5 (to target IFG)
May be useful to treat
Autism Spectrum Disorders



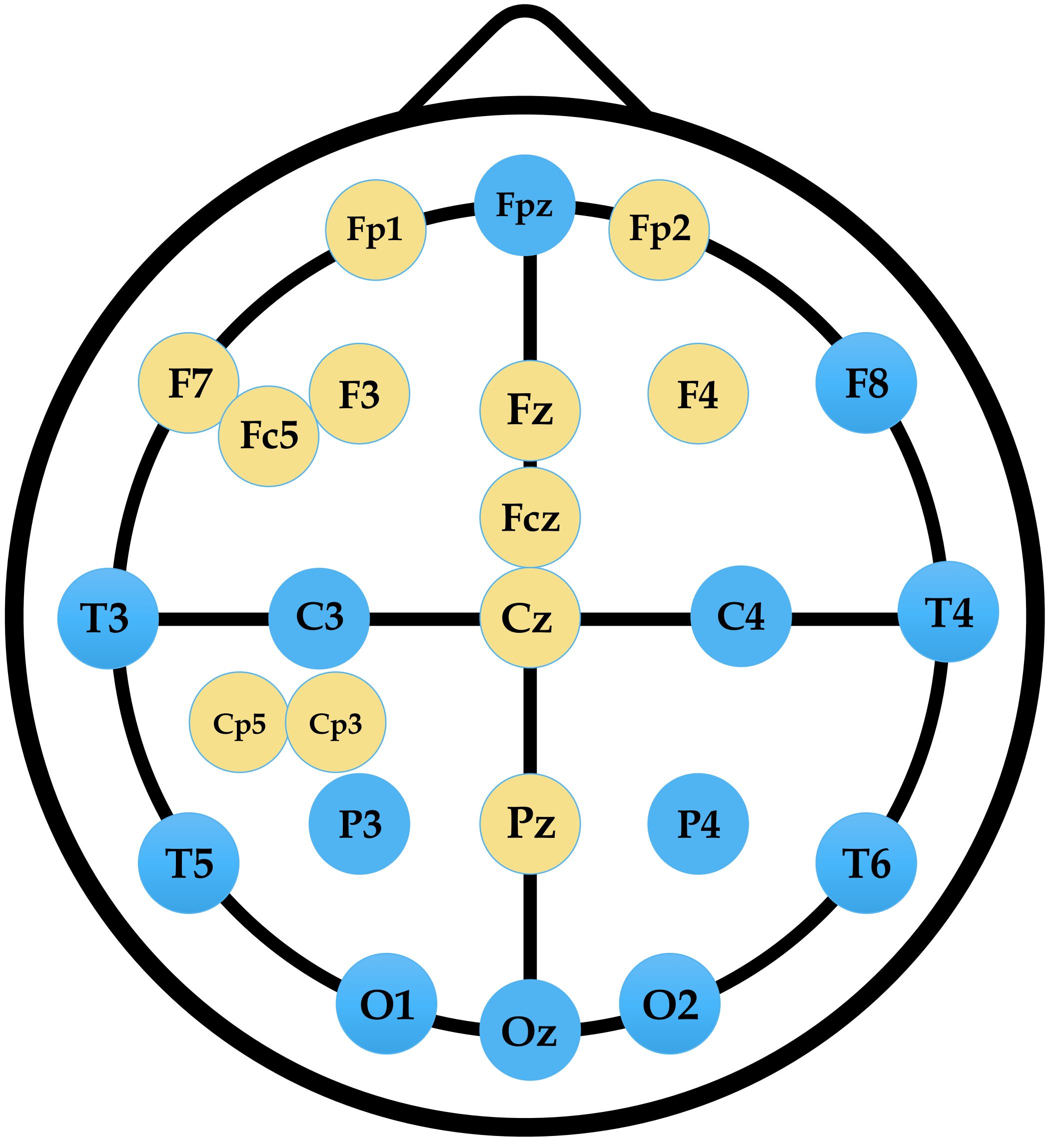
Cp5 (to target **TPO**)
May be useful to treat
Auditory Hallucinations and also
Tinnitus (both inhibitory)



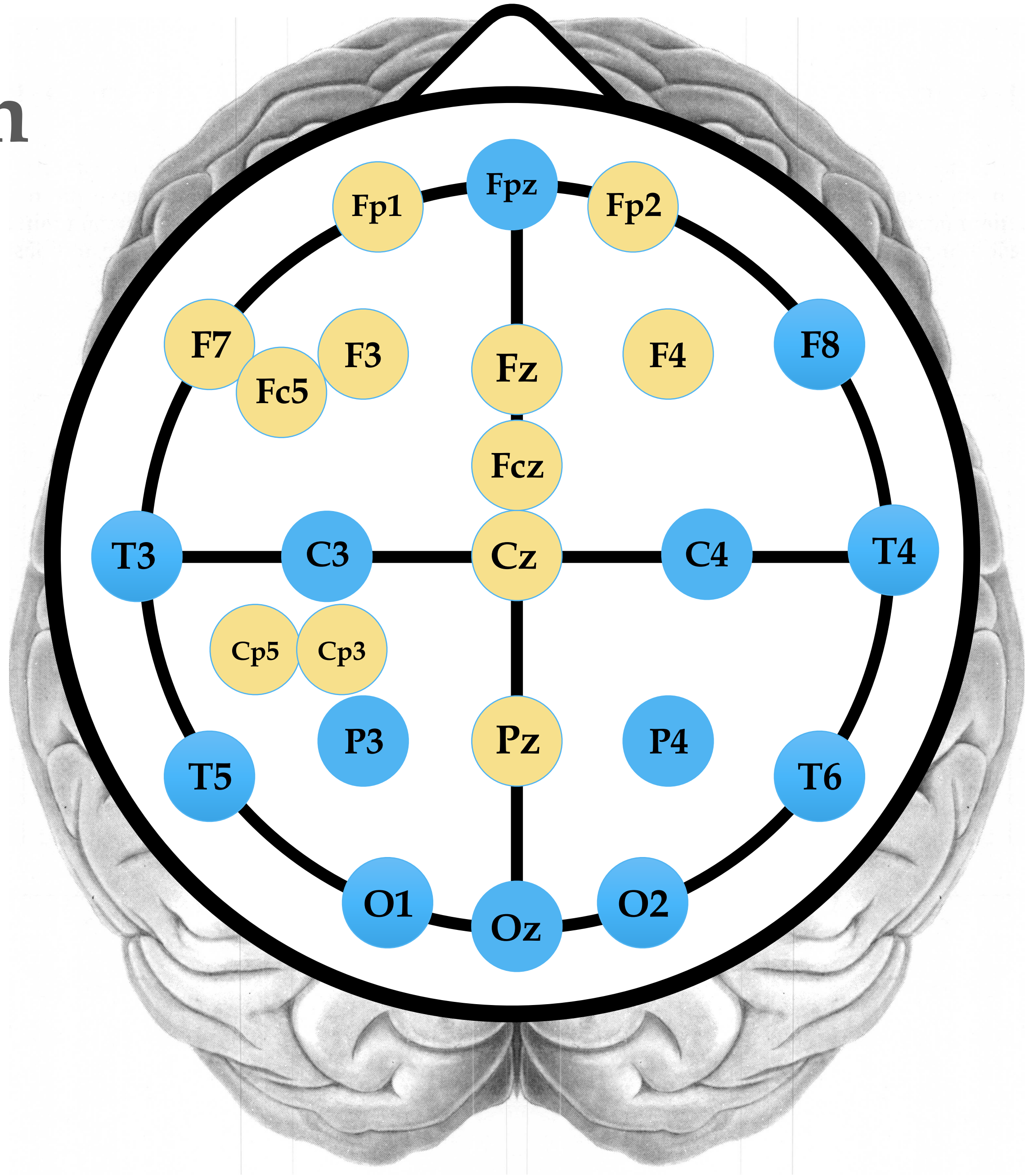
Cp3 (to target **IPC**)
May be useful to treat
Autistic Spectrum Disorders



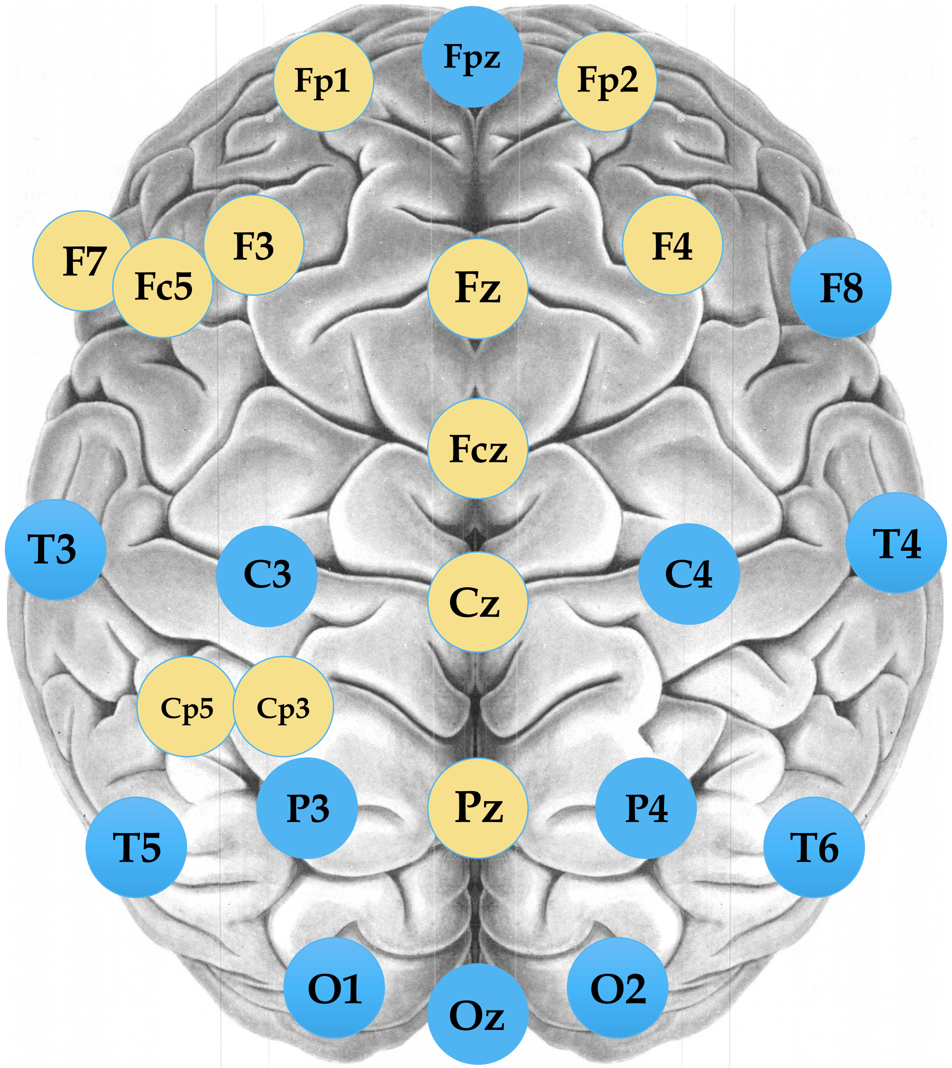
Stimulation Sites



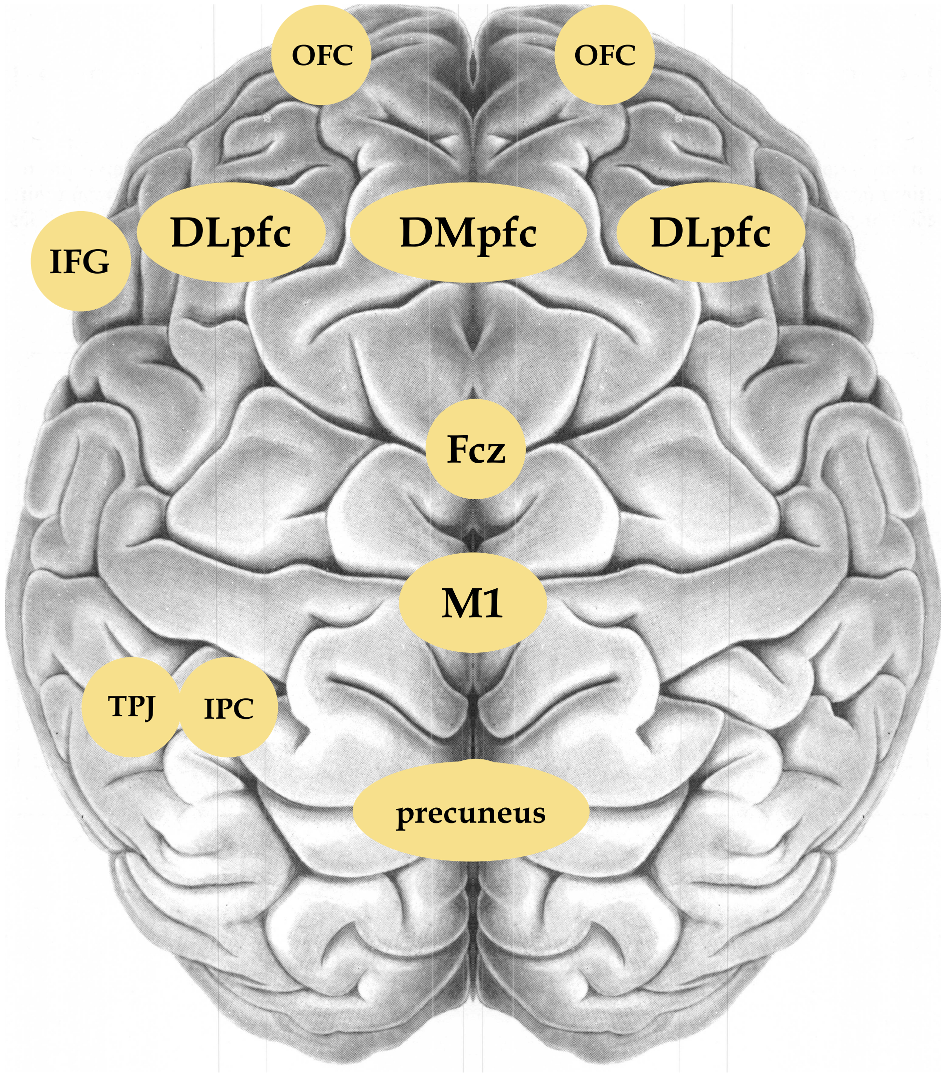
Stimulation Sites



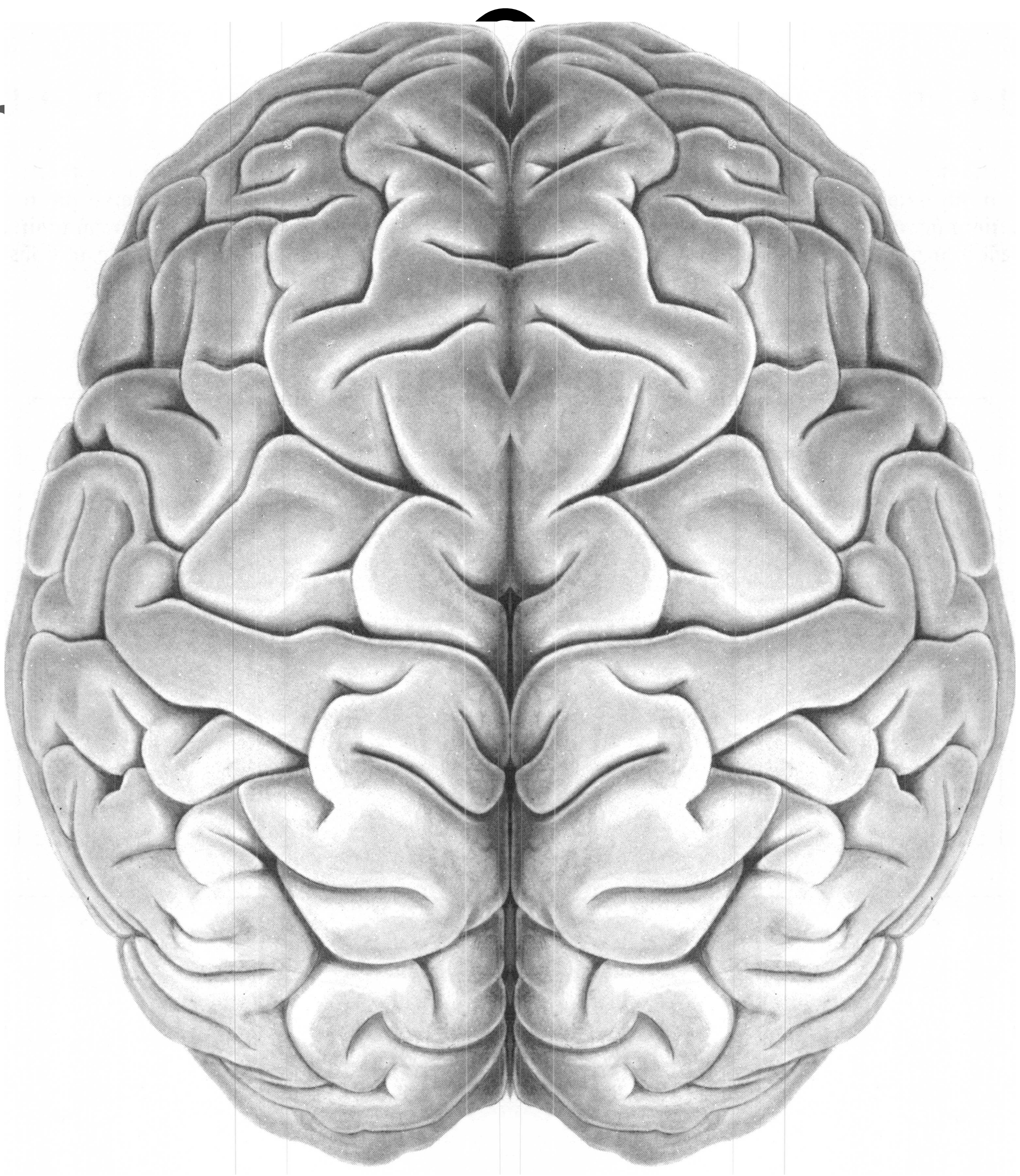
Stimulation Sites



Stimulation Sites



Stimulatior Sites



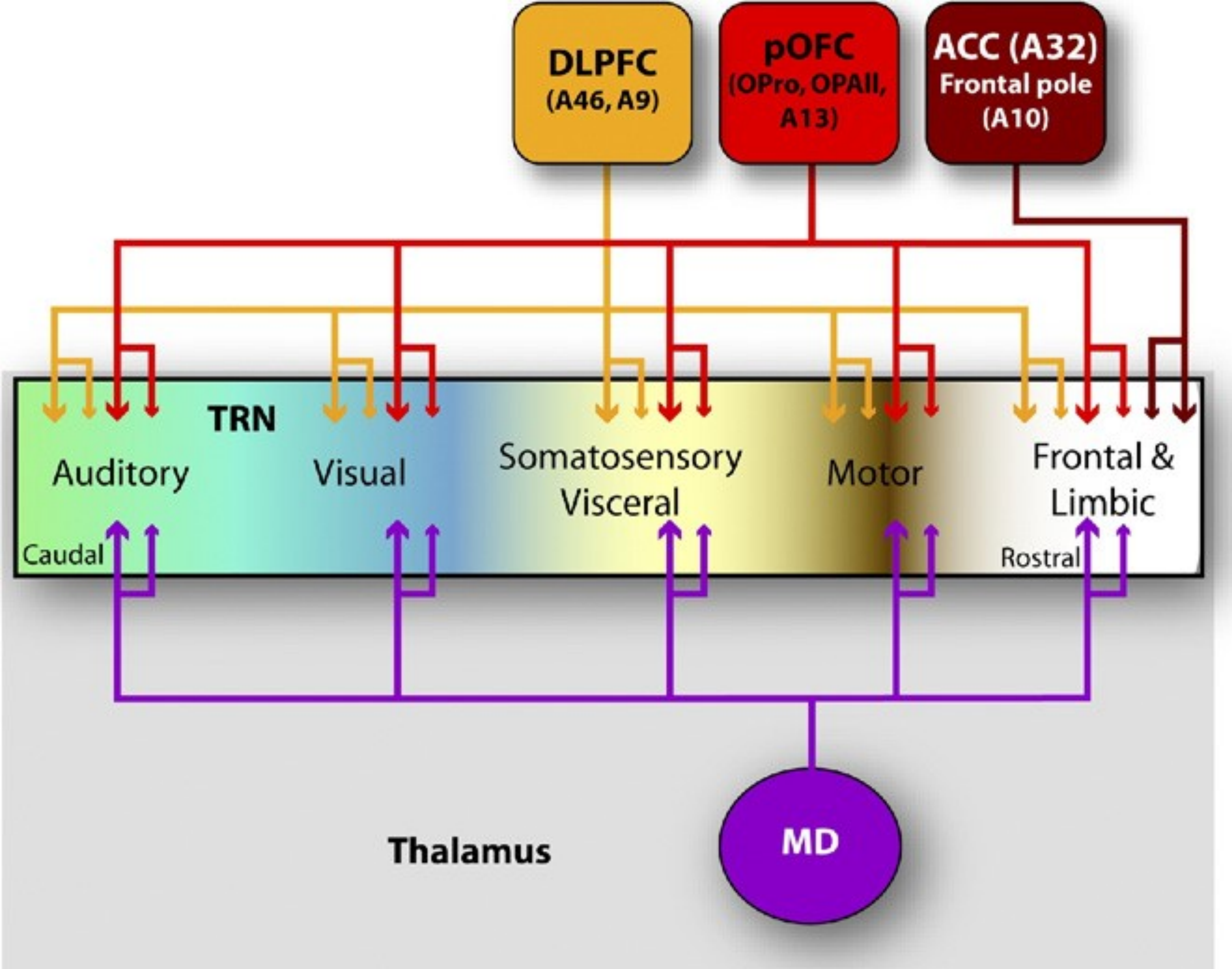
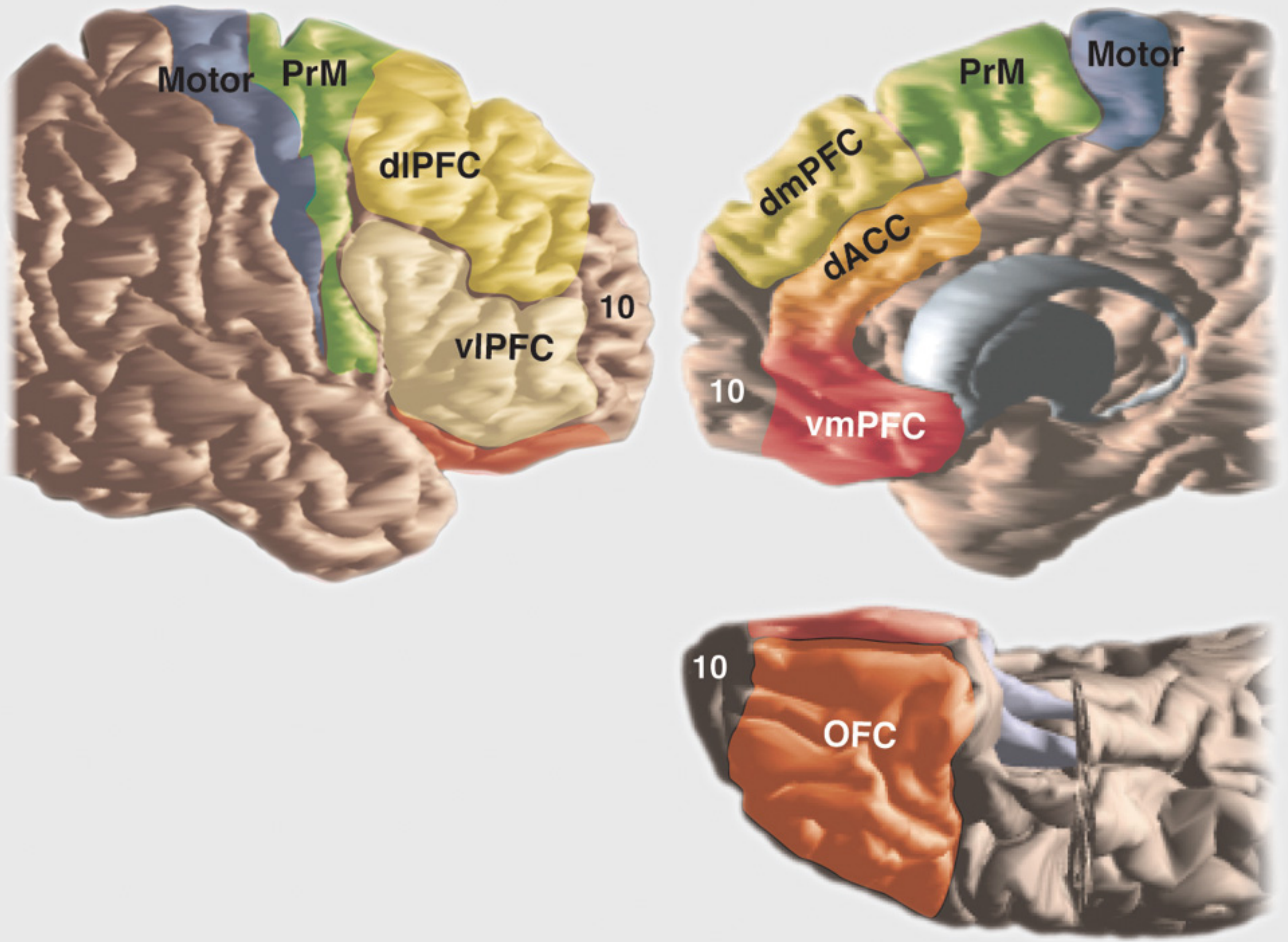


Figure 4. Prefrontal and mediodorsal thalamic projections to the thalamic reticular nucleus (TRN). Different TRN sectors are color-coded based on projections from cortical areas (frontal and limbic: white; mo=tor: brown; somatosensory/visceral: yellow; visual: blue; auditory: green). Projections from all prefrontal cortices and the mediodorsal nucleus in the rhesus monkey are concentrated in the rostral (prefrontal) sector of TRN. However, mediodorsal nucleus, dorsolateral prefrontal (areas 46 and 9), and the posterior orbitofrontal cortex also extend projections to the central and posterior sectors of TRN, potentially influencing the flow of information from sensory and motor thalamic nuclei to the cortex. In addition, prefrontal areas uniquely innervate TRN neurons through a significant (about 10%) proportion of large and potentially more effi=cient terminals (indicated by the size of the arrowheads). ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; MD, mediodorsal nucleus; OPAll, orbital periallocortex; OPro, orbital proisocortex; pOFC, posterior orbitofrontal cortex.

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
Motor
PrM
dmPFC
dACC
10
vmPFC
10
OFC

FIND WHERE

Hands On #1 Locate Stimulation Site

OPTIONS

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

2019 Non-invasive Brain Stimulation for Alcohol Use Disorders: State of the Art and Future Directions

Philip, Sorensen, McCalley & Hanlon

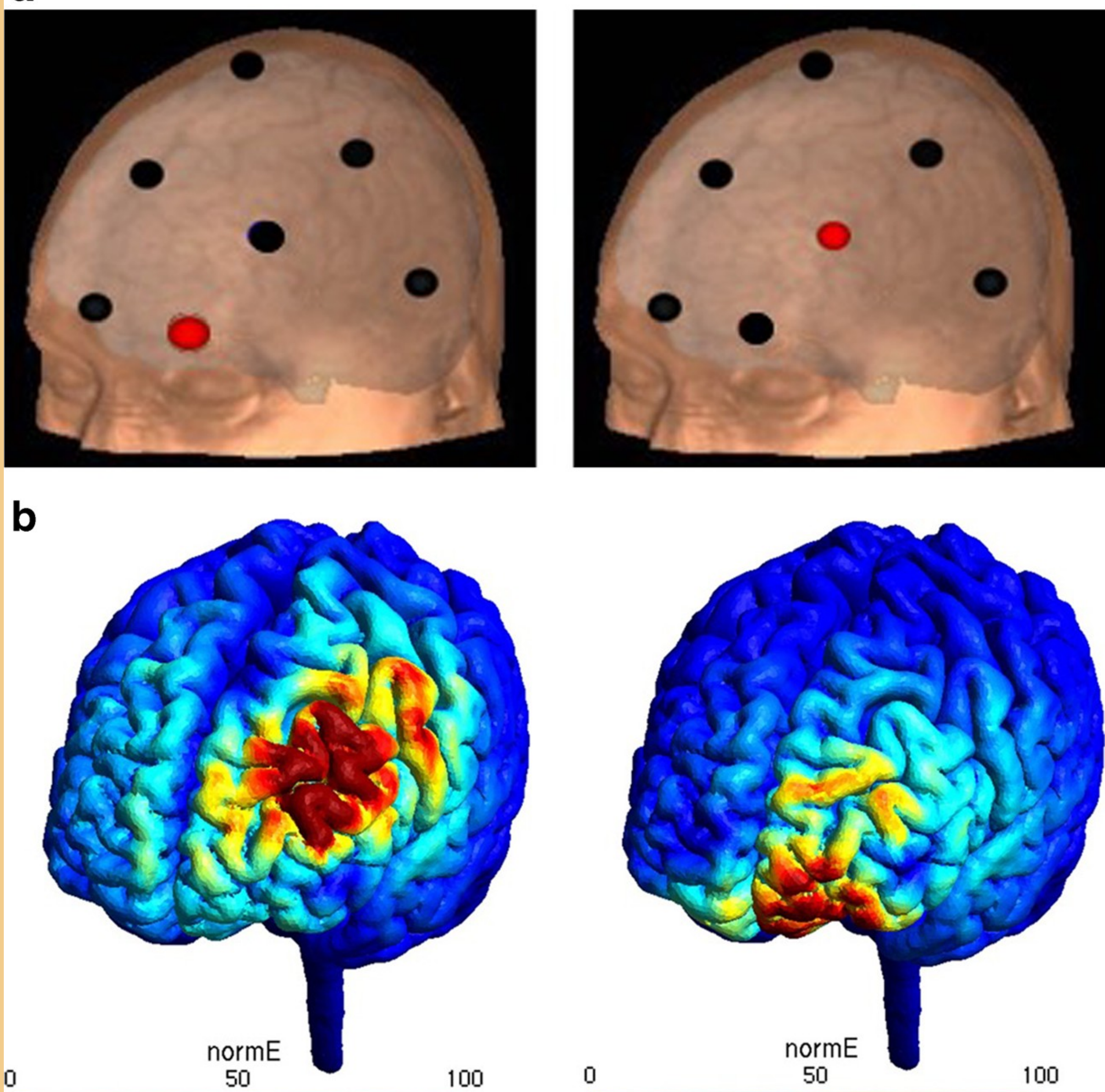


Fig. 1 Electrical effects of transcranial magnetic stimulation to the **dorsolateral prefrontal cortex** and **medial prefrontal cortex**. The DLPFC and the MPFC have been used as TMS treatment targets in individuals with AUD. By placing a standard figure-of-8 coil over the frontal pole (EEG 10–20 system 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]