

Latest Treatments & Related Issues for Tourette Syndrome and Co-Morbid Disorders

Donald Gilbert, MD MS

Assoc. Professor of Pediatric Neurology

Director, Tourette Syndrome & Movement Disorders
Clinics

Cincinnati Children's Hospital Medical Center

tics@cchmc.org

Disclosure

- Nothing to disclose
- Off label uses of medications will be discussed

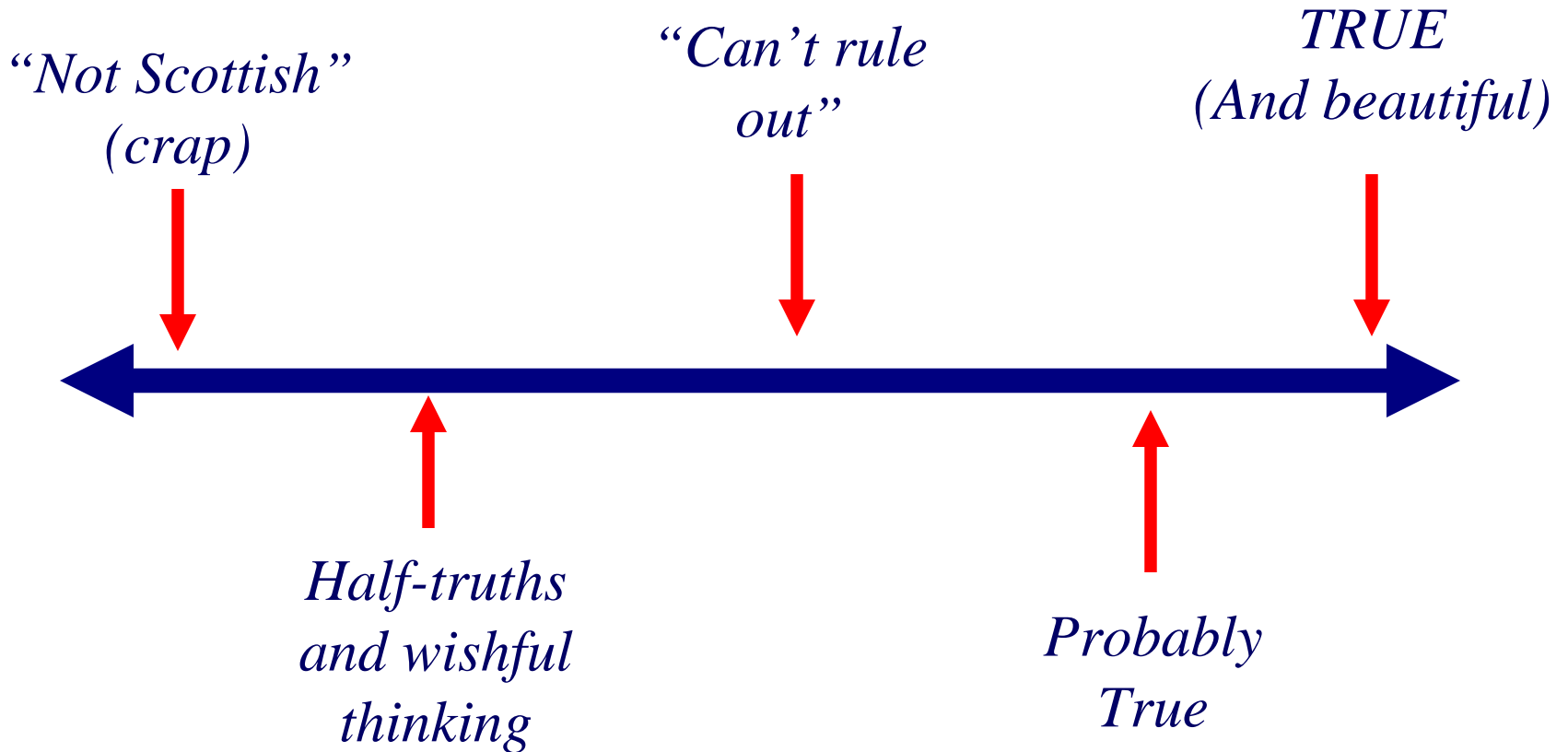
Objectives of this talk

- Discuss recent information on medical treatment of Tourette-associated symptoms
- Provide Tools for keeping yourself informed and judging the value of information that you read

Tools

1. Assess the spectrum of evidence – how can we trust what we read on the internet?

Information Metric v.1



What makes brains tic?

Tics are like normal movement –
so the question is –
What makes us move at all?

We are wired to move quickly

- Patterned Movements are learned and remain in the brain as a network ready to be activated
- A deep part of the brain, the striatum, is involved in a braking mechanism
- We are constantly filtering sensory information online through another deep structure, the thalamus

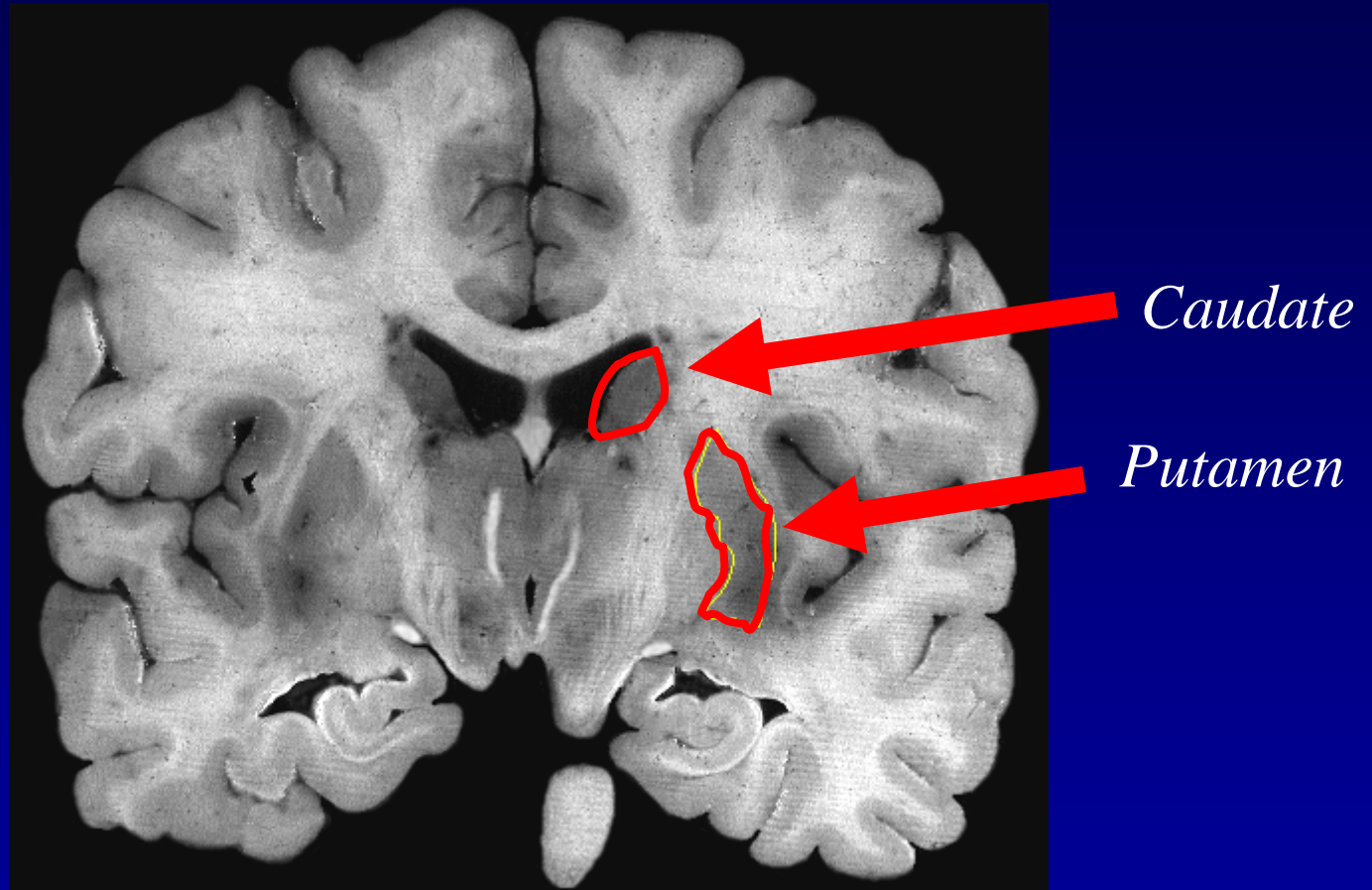
Purposeful movement

- The brakes are on until you automatically or voluntarily release them, then you move
- When the brakes short-circuit or leak motor programs slip through (involuntarily, semi-voluntarily)
- When the filter leaks, itches or urges enter awareness and may cause aggravation or an urge to tic in a certain way

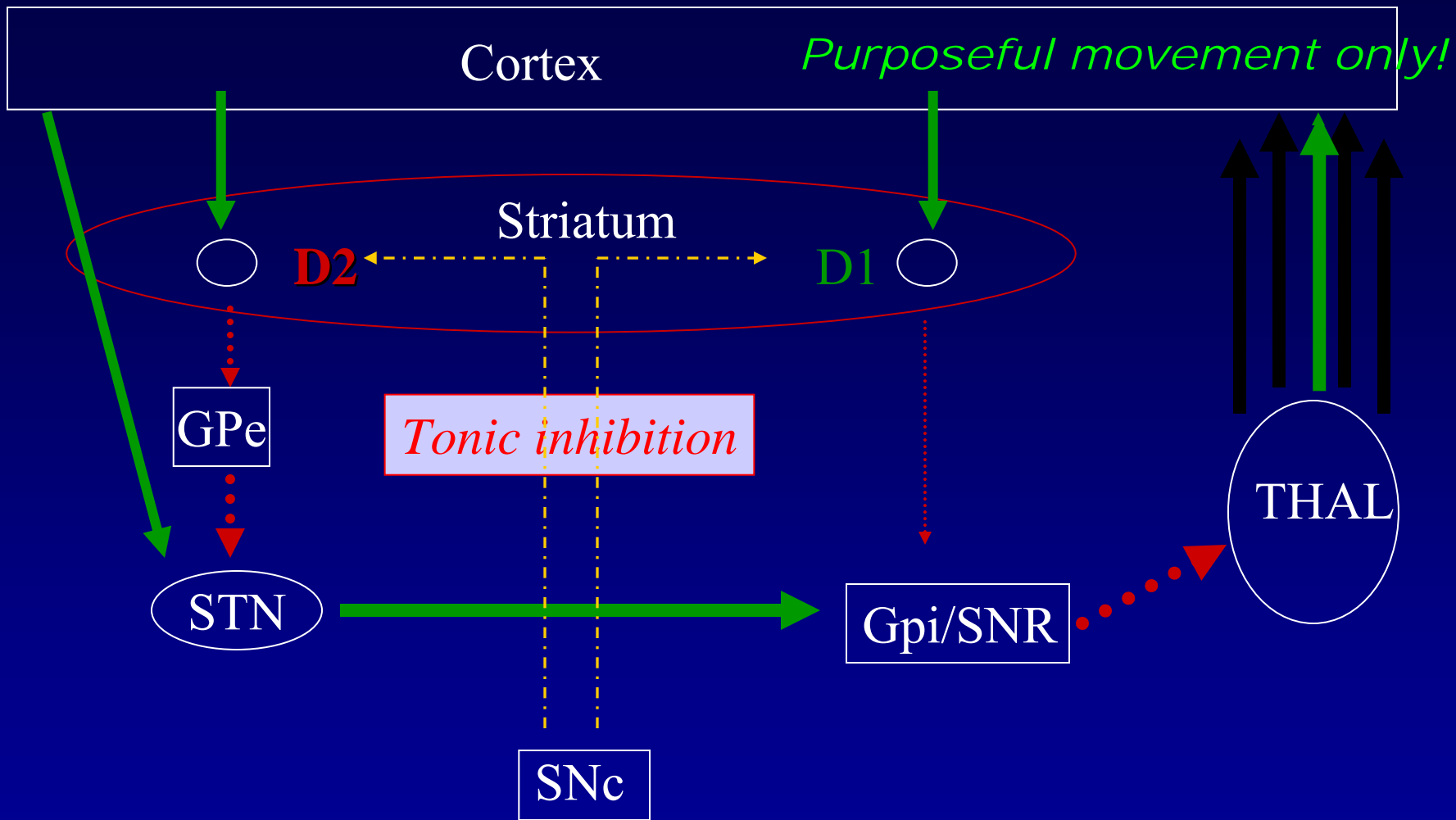
The brakes

An important general concept for understanding Tourette Syndrome

The Brakes

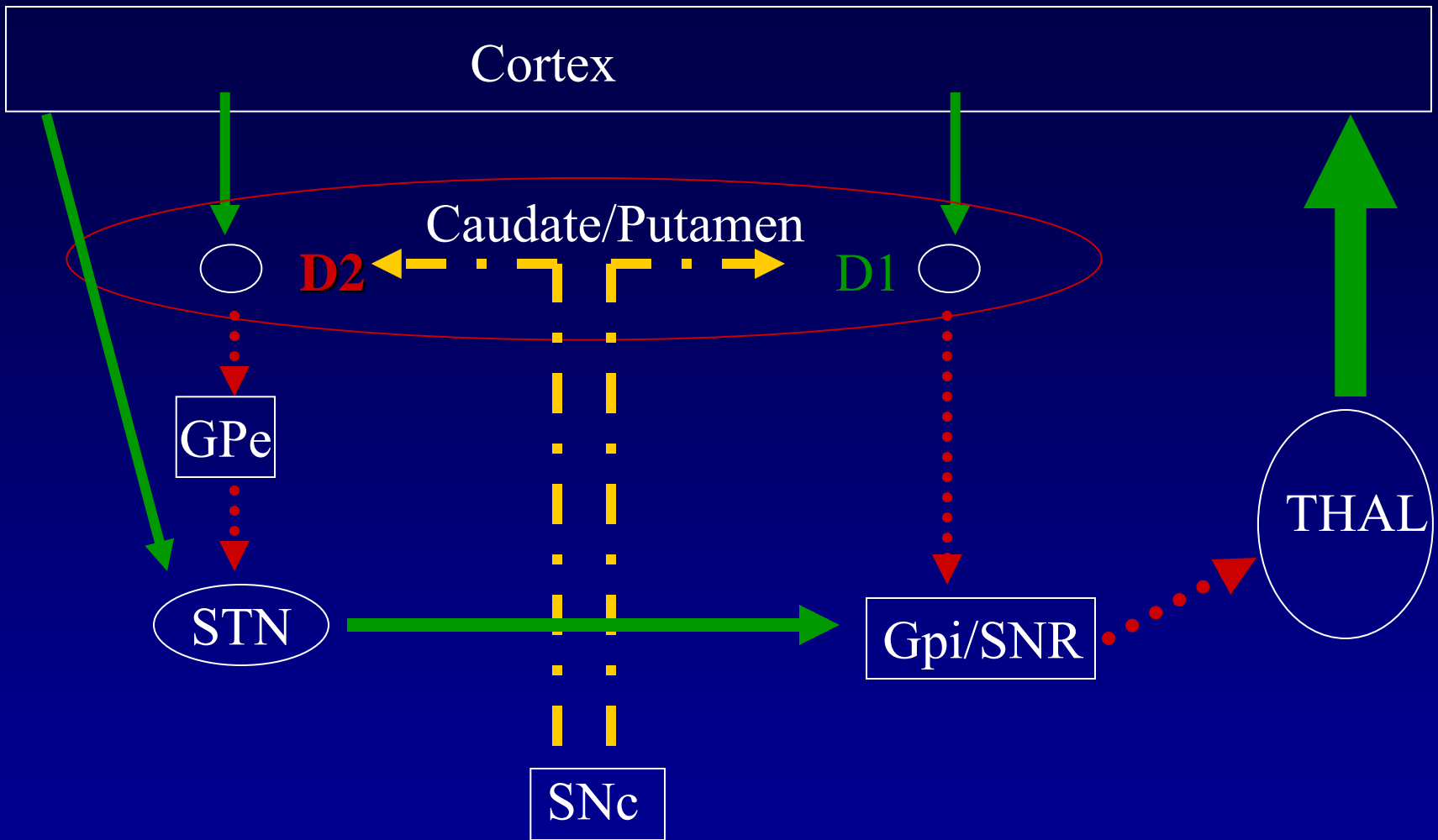


University of Washington Digital Anatomist Program



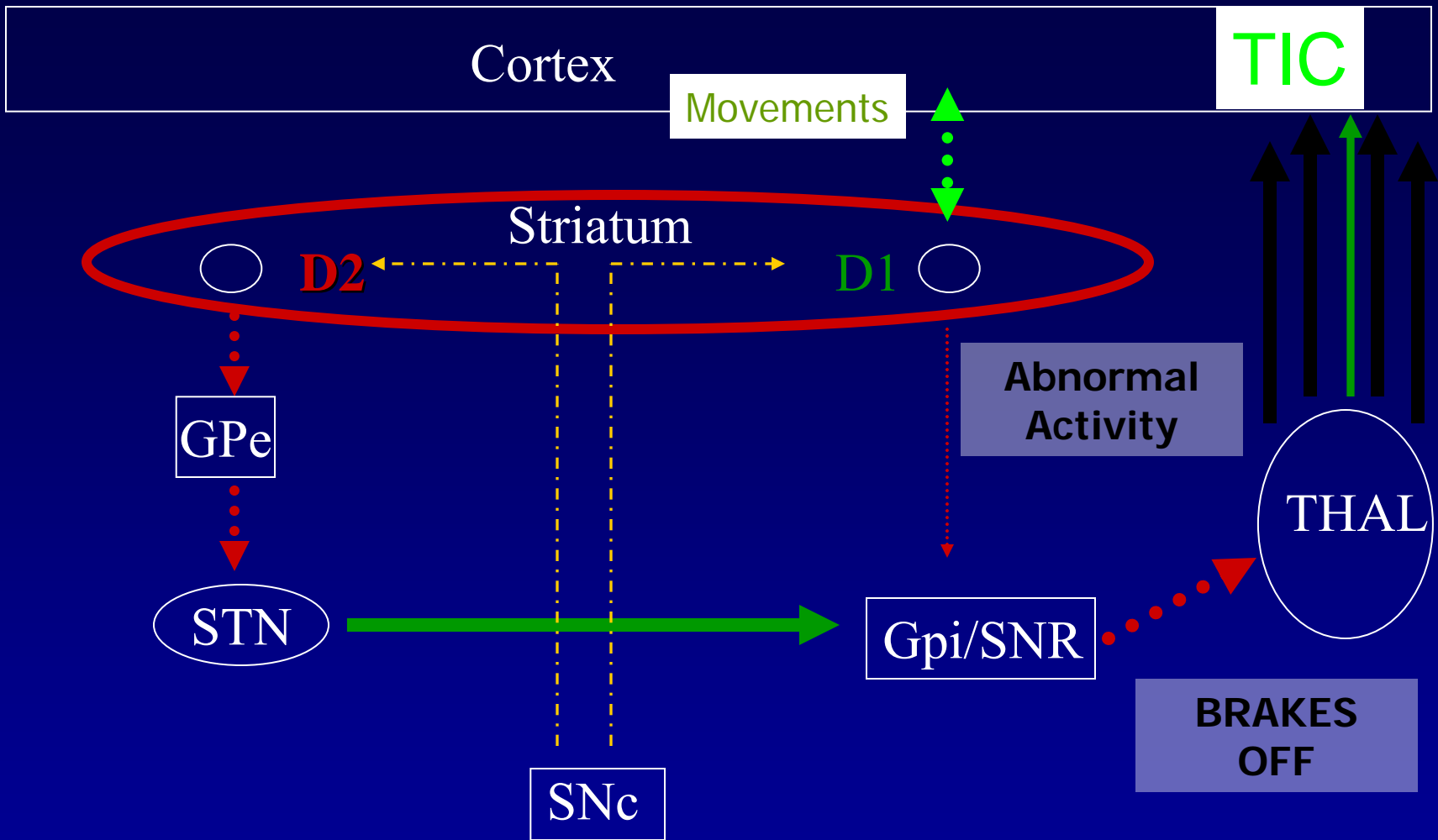
Model for purposeful movement

Brain structures connected by excitatory (Glutamate)
and inhibitory (GABA) signals

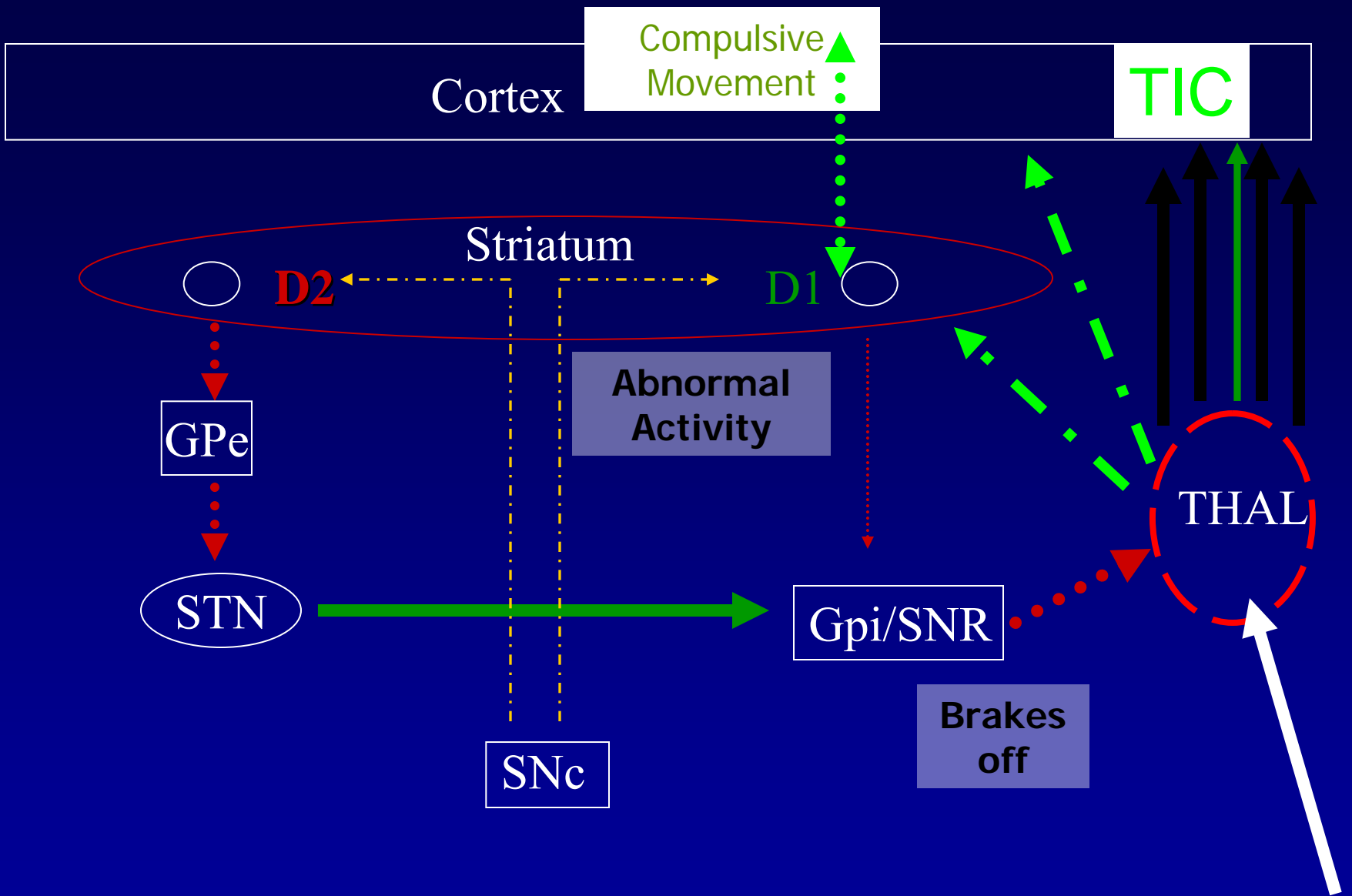


**Dopamine From the SNc to the Striatum
Drives Movement**

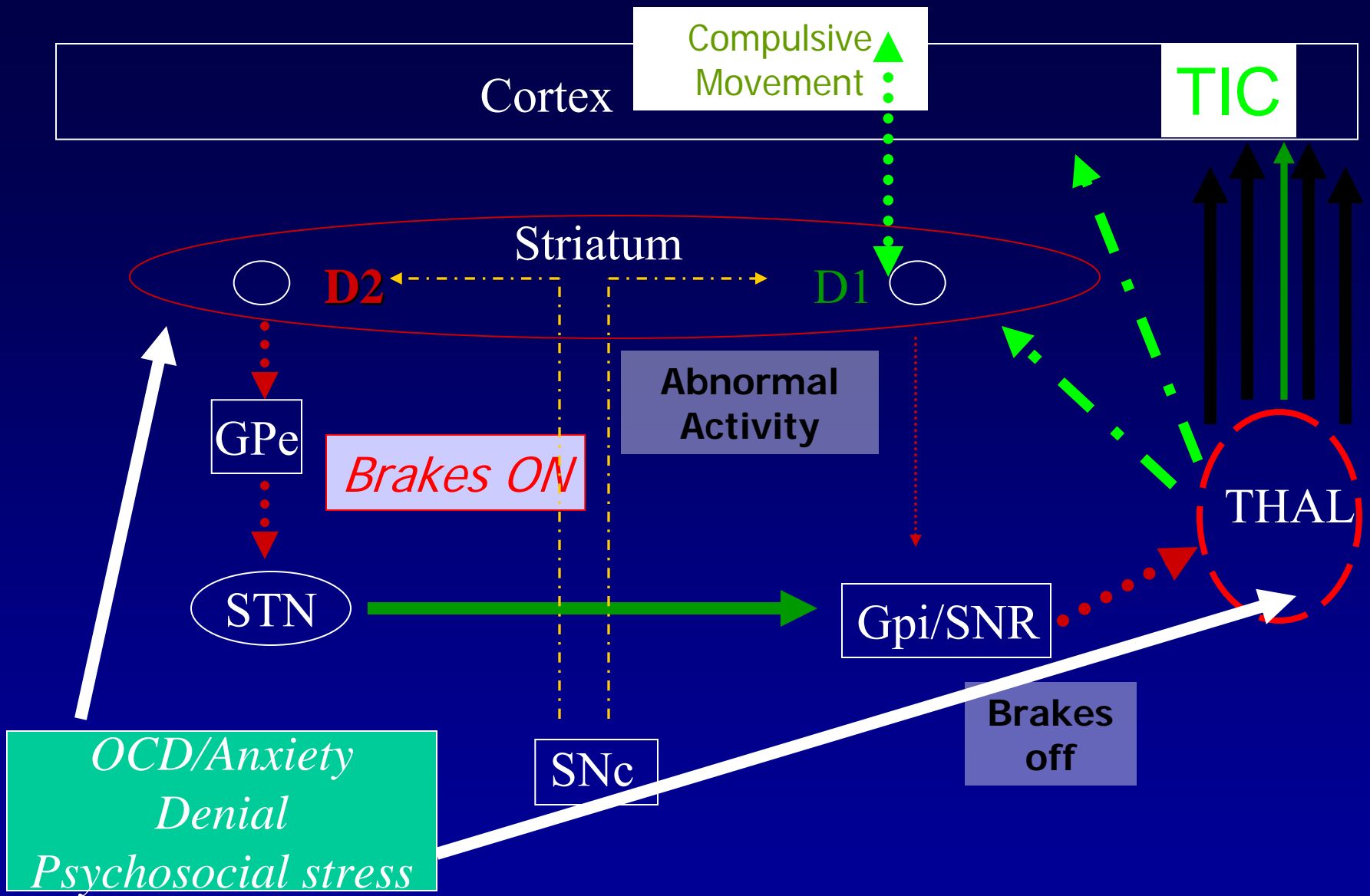
The ticcing brain



Involuntary tic model – facilitated cortico-striatal pathway



Semi-voluntary tic model – ticcing due to itches/urges



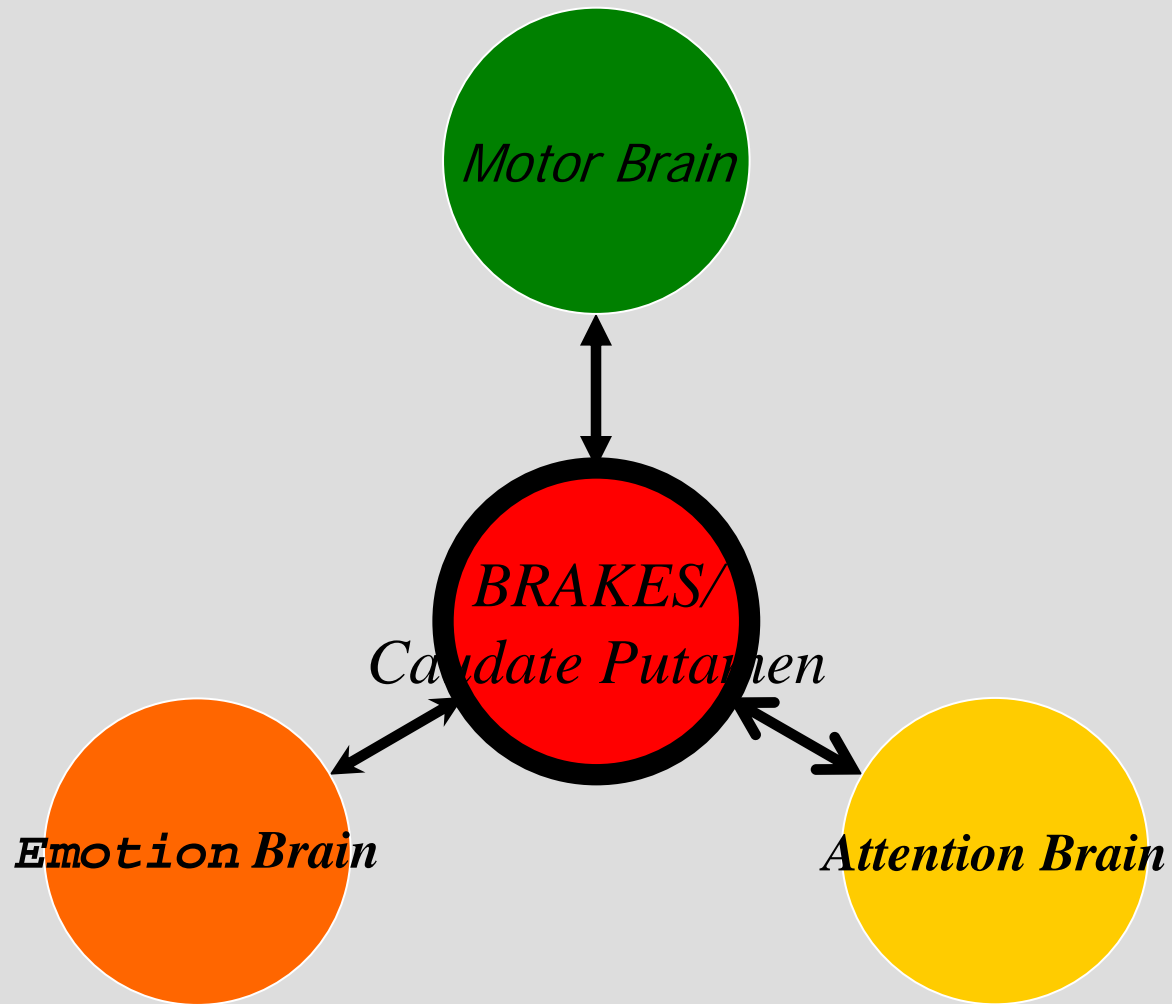
Tics worsen during stress

Regulators/ Brakes

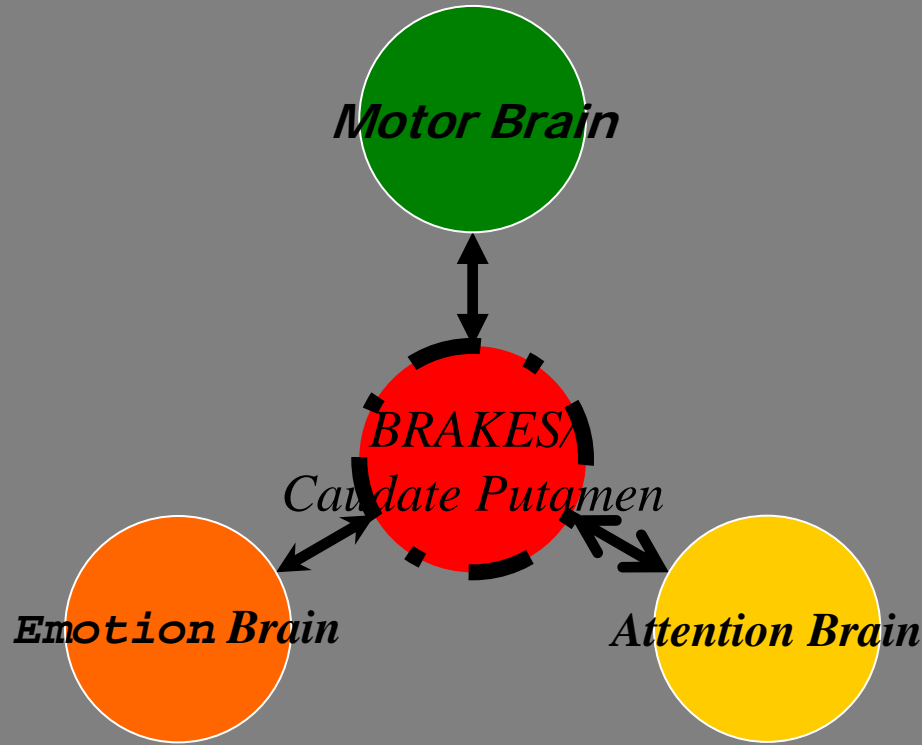
Motor

Distraction filter

Emotional response regulator



TICS



Anxiety

Disinhibition

In addition to tics:

Impulsive

Disruptive

Can't stay on task

Stuck

On thoughts

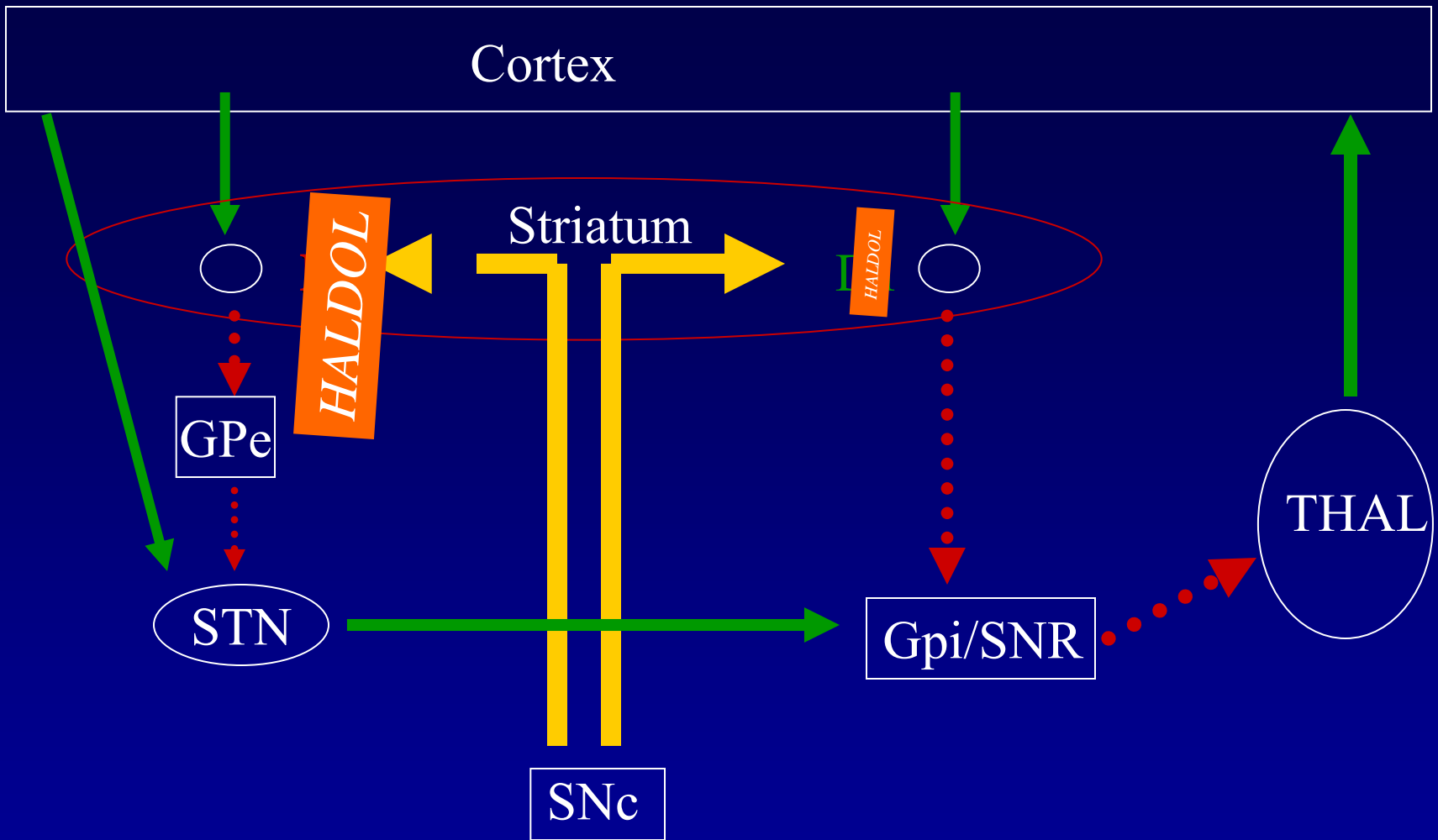
And worries

*Hyper-
sensitive*

Tic Treatments – how might they act?

- BLOCK MOVEMENT SYSTEM/ ACTIVATE THE BRAKING SYSTEM
- ENHANCE COGNITIVE CONTROL SYSTEM
- TREAT ANXIETY
- ENHANCE THE SENSORY FILTERS

BLOCKING: Dopamine blockers



Tourette's Syndrome – Dopamine 2 blocker treatment

Names of Dopamine Blockers

- Dopamine receptor blocking agents
- Neuroleptics
- Antipsychotics
- Atypical Antipsychotics

Examples of Dopamine Blockers

- TYPICAL: Haldol, Orap, Prolixin
- Semi-TYPICAL: Risperdal
- ATYPICAL: Seroquel, Zyprexa, Geodon
- Unique: Abilify, Tetrabenazine

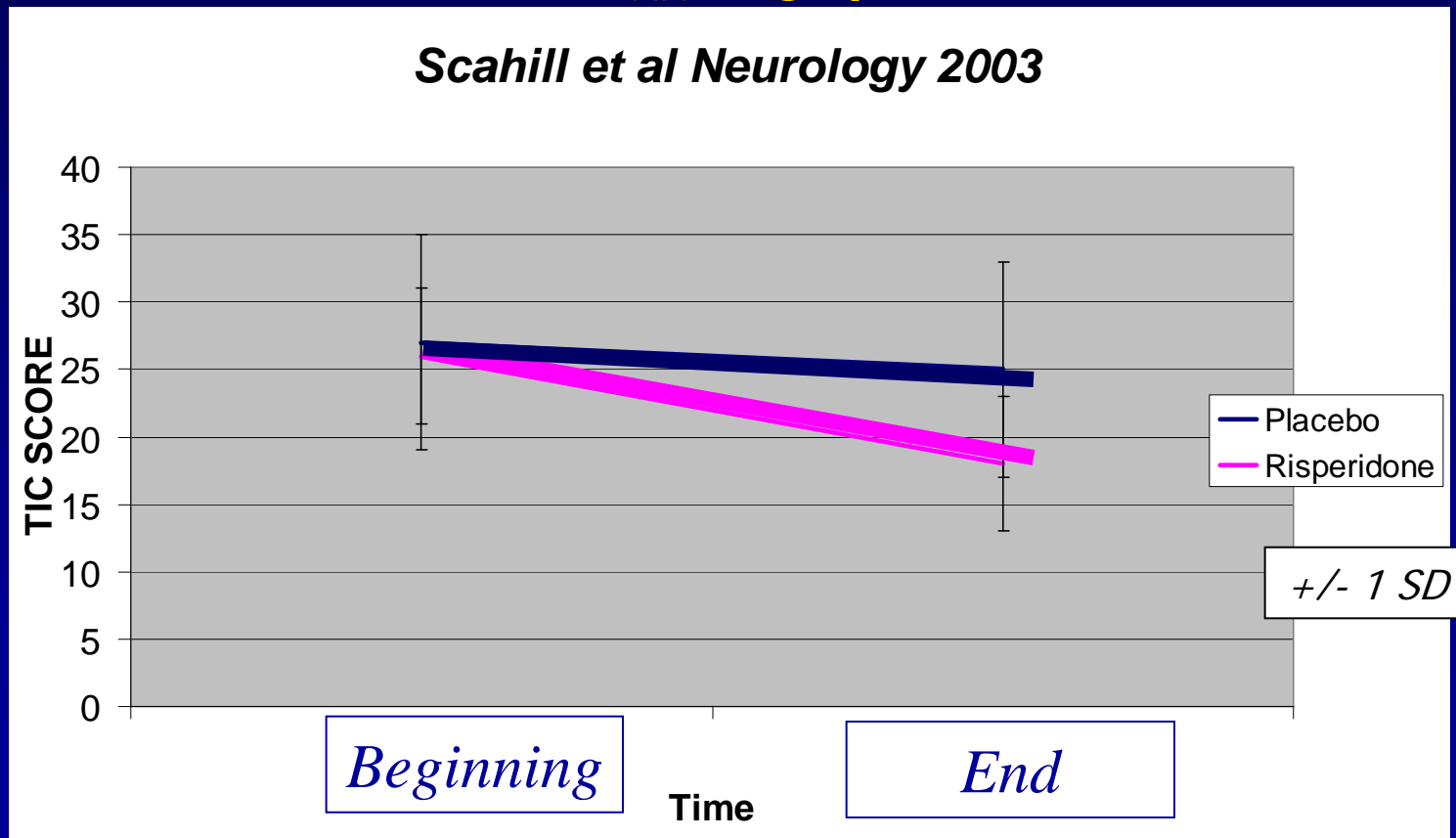
Tools

1. The spectrum of evidence
2. Study design –
randomized controlled
trials are the gold
standard

How do we know if a treatment really works?

- Our best estimate of whether something really works is from Randomized Controlled Clinical Trials – look for this when you are on the internet seeking new treatments

Example - Clinical Trial: Risperidone vs. placebo at 8 weeks, n = 34

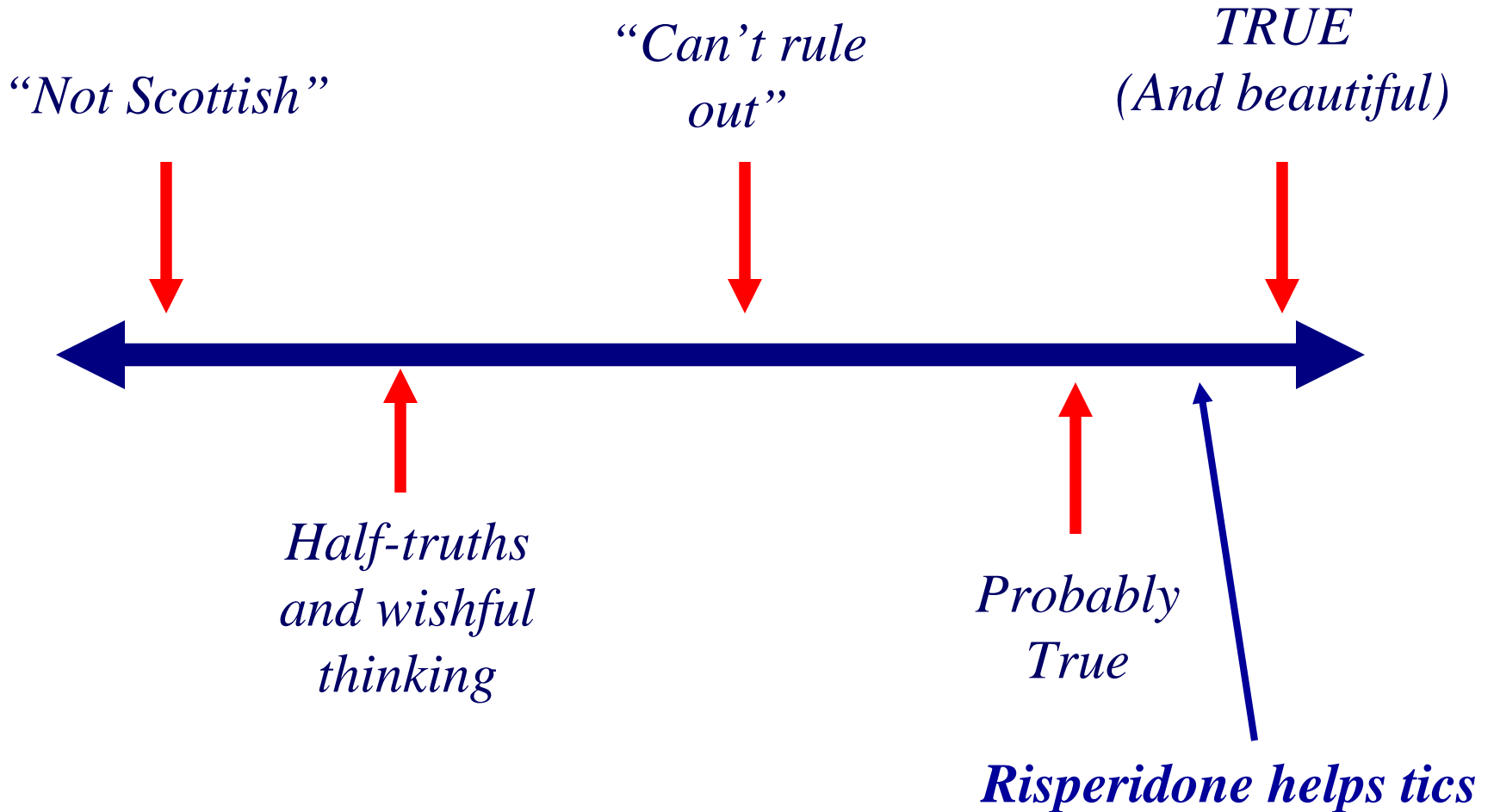


Does risperdal help with tics?

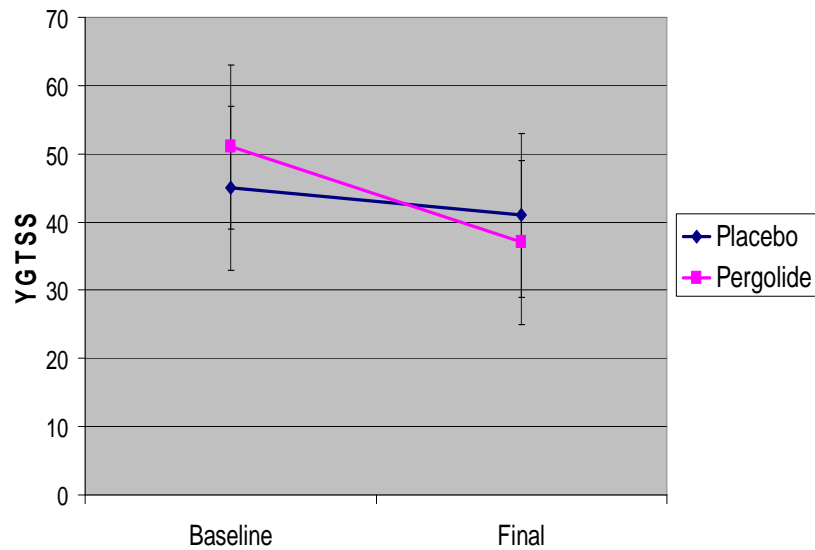
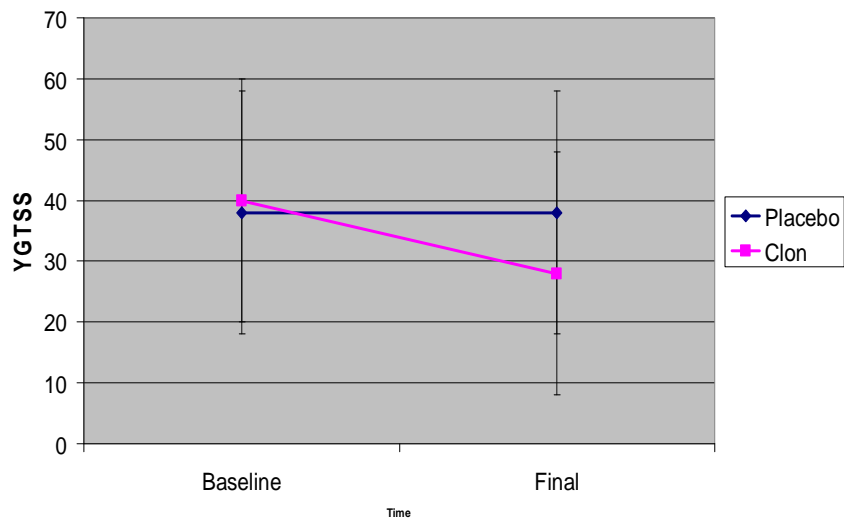
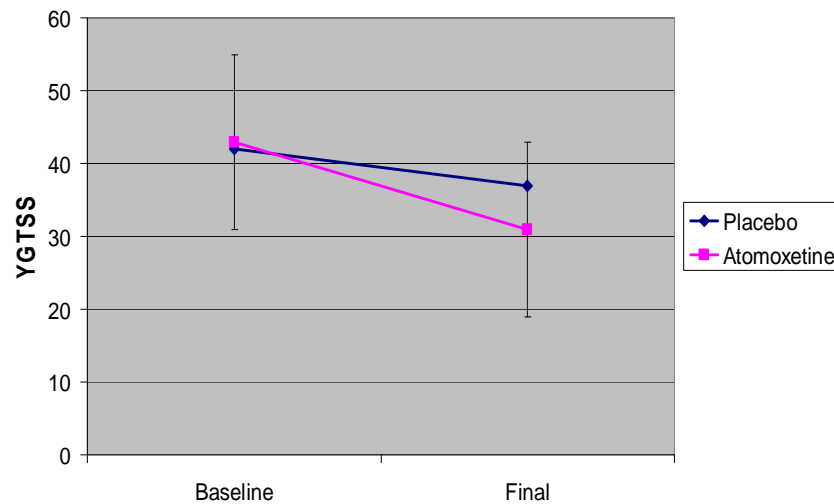
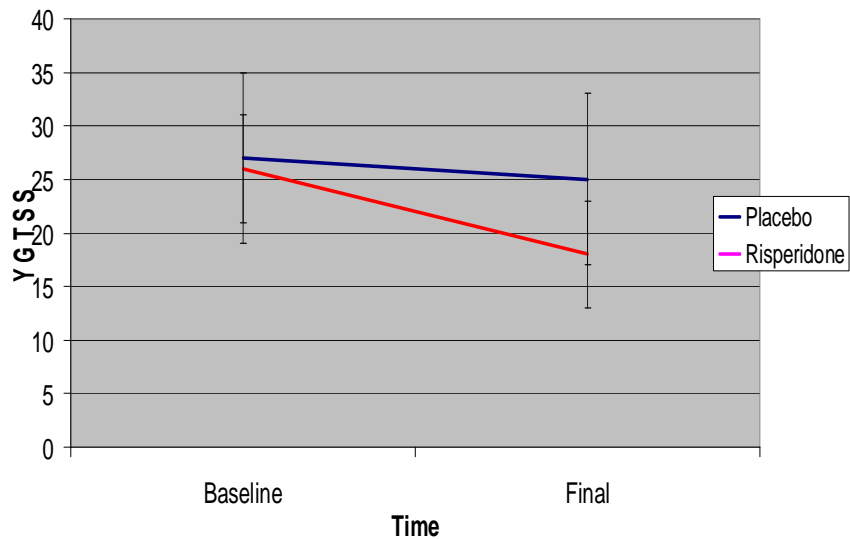
Tics and Dopamine Blockers - Use with caution

- Neurologic side effects – restlessness, stiffness
- Sedation
- *Weight gain*
- Mood changes, panic/anxiety/depression
 - Separation anxiety
 - Stomach aches before school
- Sexual dysfunction

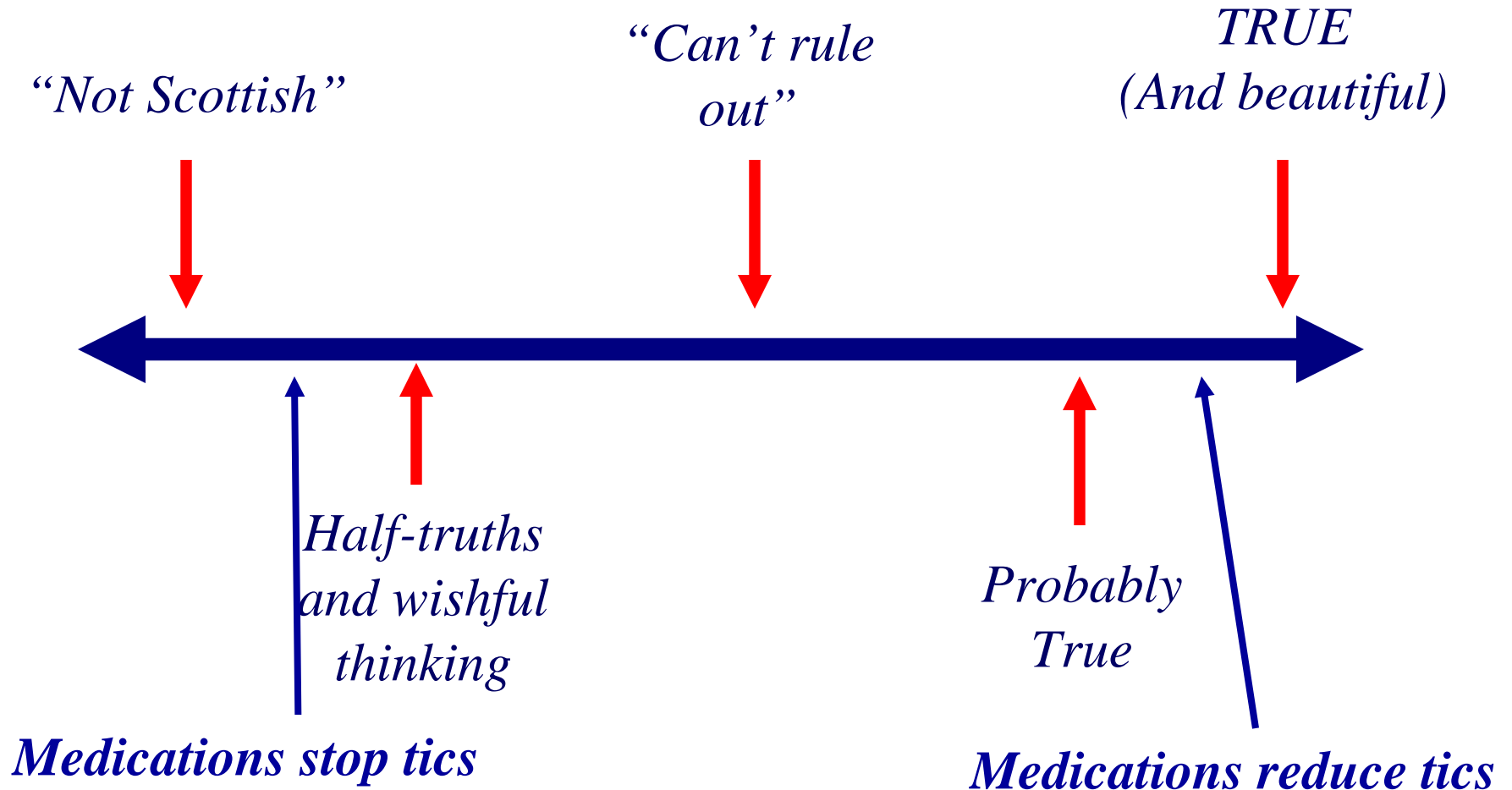
Information Metric v.1



*Examples of 4 clinical trials showing that medications reduce tics:
Although tics are reduced, the amount of improvement is only about 25%*



Information Metric v.1



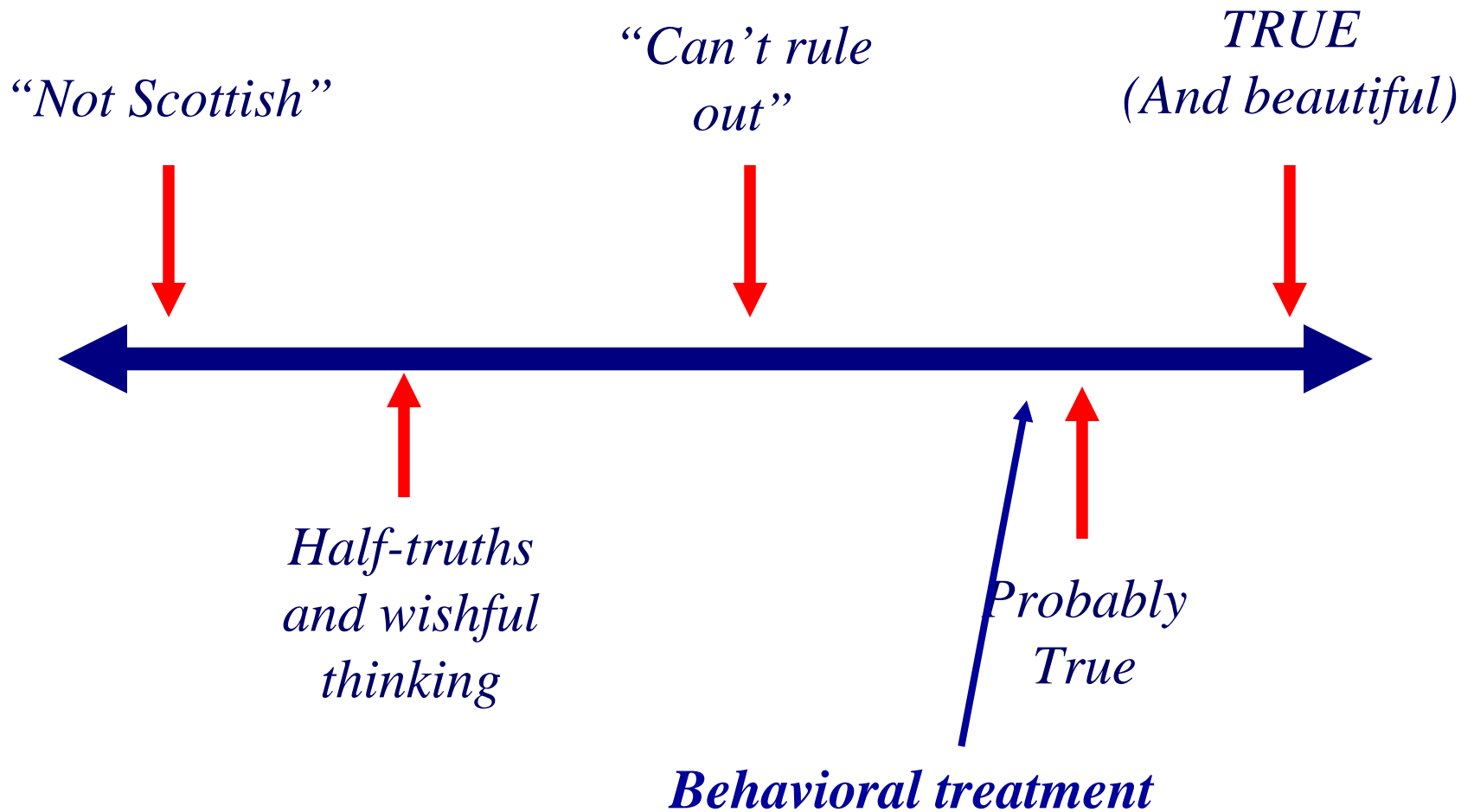
Enhance Cognitive Control

- Behavioral therapies – Habit reversal therapy
- Motor Control – Music, sports – train the body and mind to a high level of skill

Sensory filters

- Behavioral therapy to augment the sensory filter?
- New medications?

Information Metric v.1



Treatment approach implications

- No one approach helps all problems
- No one medication improves everything in all persons with Tourette Syndrome (or ADHD or OCD...)
- Every child or adult is unique in terms of their pattern of involvement and responses to treatments

Medications aren't everything

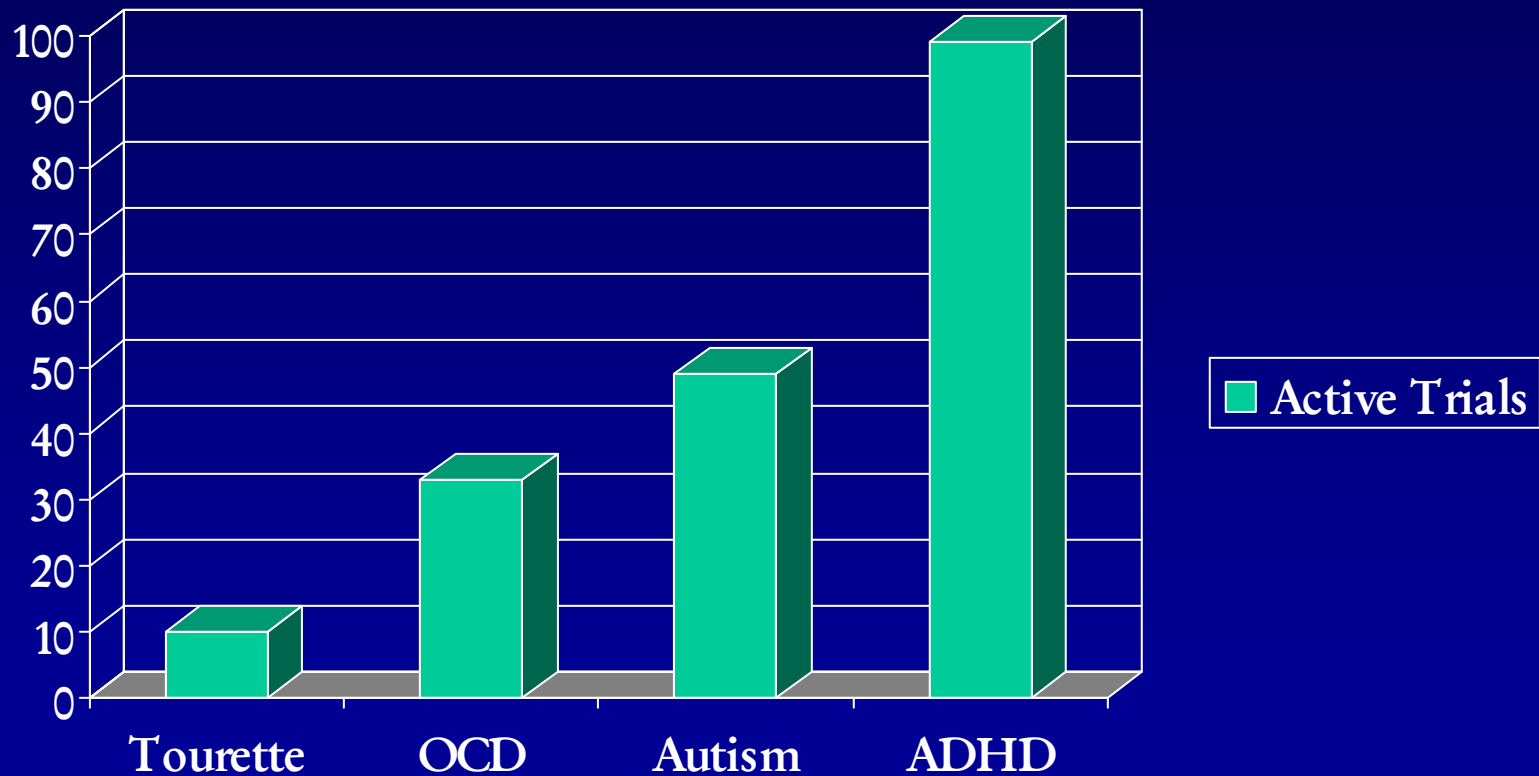
- All new problems do not have a biological basis, nor do they necessarily have a medical solution
- Medicines move the brain in a helpful direction (at best), the rest is up to us humans

Getting to new Treatments

Tools

1. The spectrum of evidence
2. Study design –
randomized controlled
trials are the gold
standard
3. [ClinicalTrials.gov](https://clinicaltrials.gov)

ClinicalTrials.gov as of April 2008



Found 99 studies with search
of:

ADHD | Open Studies | Interventional
Studies

1 Recruiting [Open-Label Pilot Study of Namenda in Adult Subjects With ADHD and ADHD NOS](#)

Conditions: ADHD; ADHD NOS

Intervention: Drug: memantine hydrochloride

2 Recruiting [Randomized, Double-Blind, Placebo-Controlled Study of Mixed Amphetamine Salts \(Adderall-XR\) for the Treatment of Adult Attention Deficit Hyperactivity Disorder \(ADHD\) and Cocaine Dependence](#)

Conditions: Adult Attention Deficit Hyperactivity Disorder;
Cocaine Dependence

Interventions: Drug: Placebo; Drug: Adderall-XR;
Drug: Adderall-XR

3 Recruiting [Cognitive Behavioral Therapy for Treatment of Adult Attention Deficit Hyperactivity Disorder](#)

Condition: Attention Deficit Disorder With Hyperactivity

Interventions: Behavioral: Cognitive Behavioral Therapy;
Behavioral: Relaxation techniques and
education about ADHD

Attention Deficit Hyperactivity Disorder and Disruptive Behavior Disorders

Treatment of ADHD in children with
tics



Are stimulants safe for kids with
tics?

Hoekstra PJ, Steenhuis MP, Troost PW, Korf J,
Kallenberg CG, Minderaa RB.

Relative contribution of
attention-deficit hyperactivity disorder,
obsessive-compulsive disorder,
and tic severity
to social and behavioral problems in tic
disorders.

Journal of Developmental & Behavioral Pediatrics
2004;25(4):272-9.

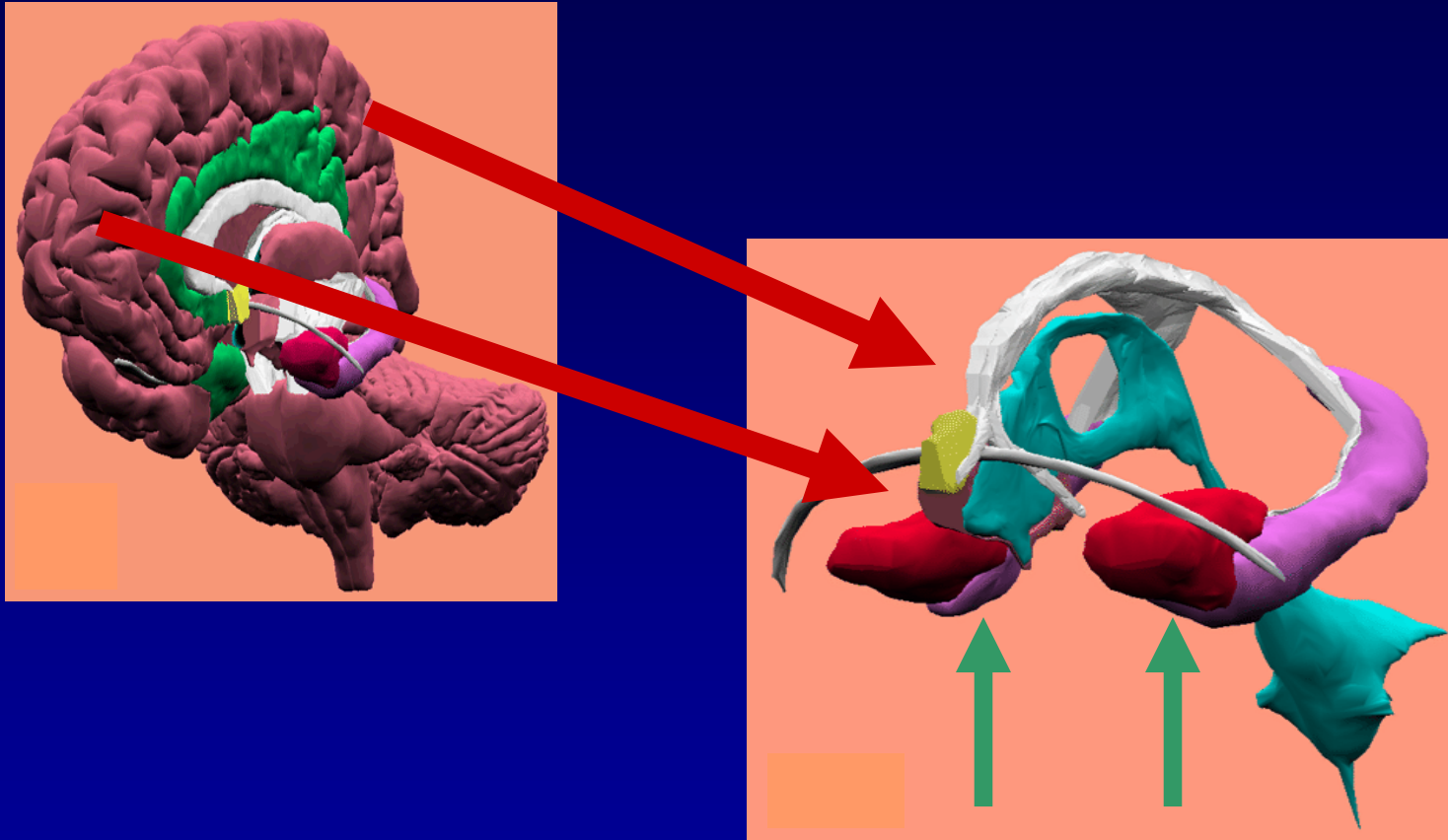
Pelham WE, Jr., Lang AR, Atkeson B, et al.

Effects of deviant child behavior on parental alcohol consumption. Stress-induced drinking in parents of ADHD children.

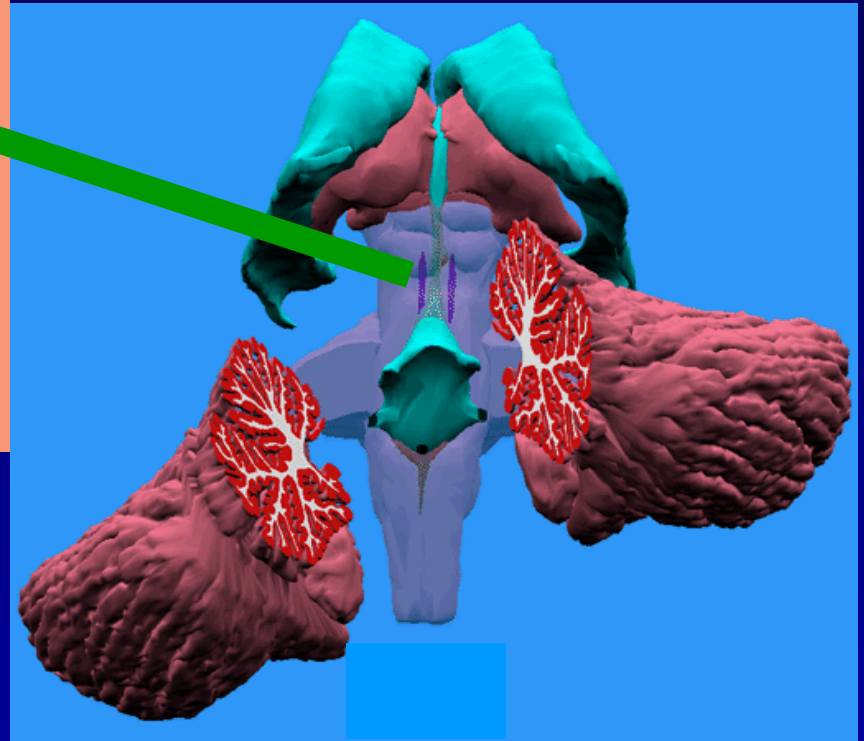
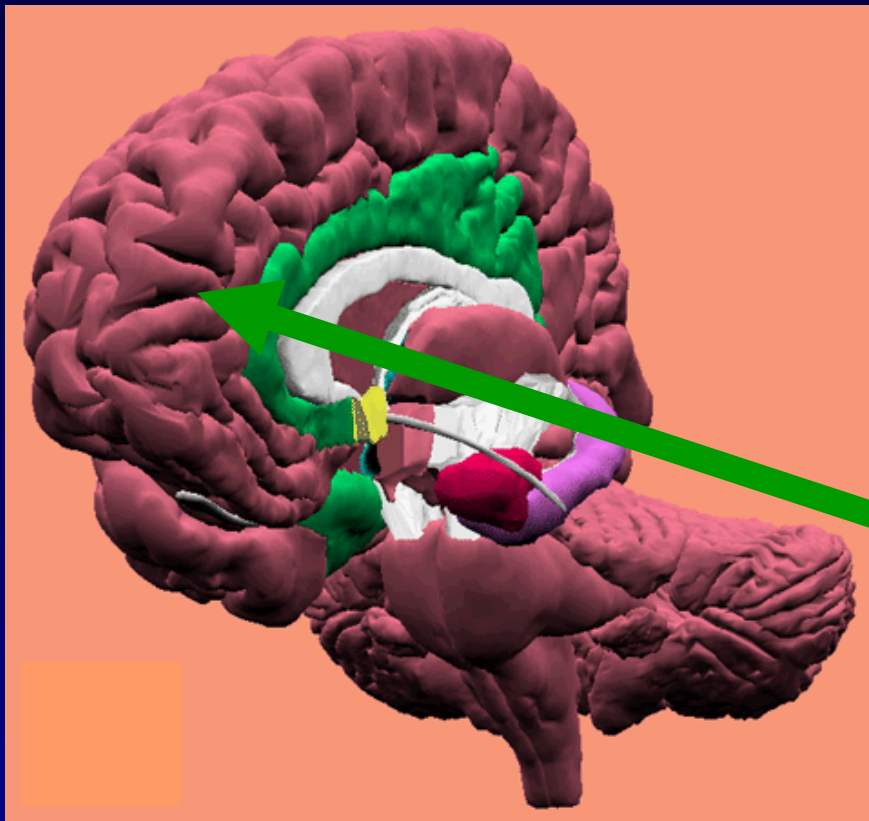
American Journal on Addictions

1998;7(2):103-14

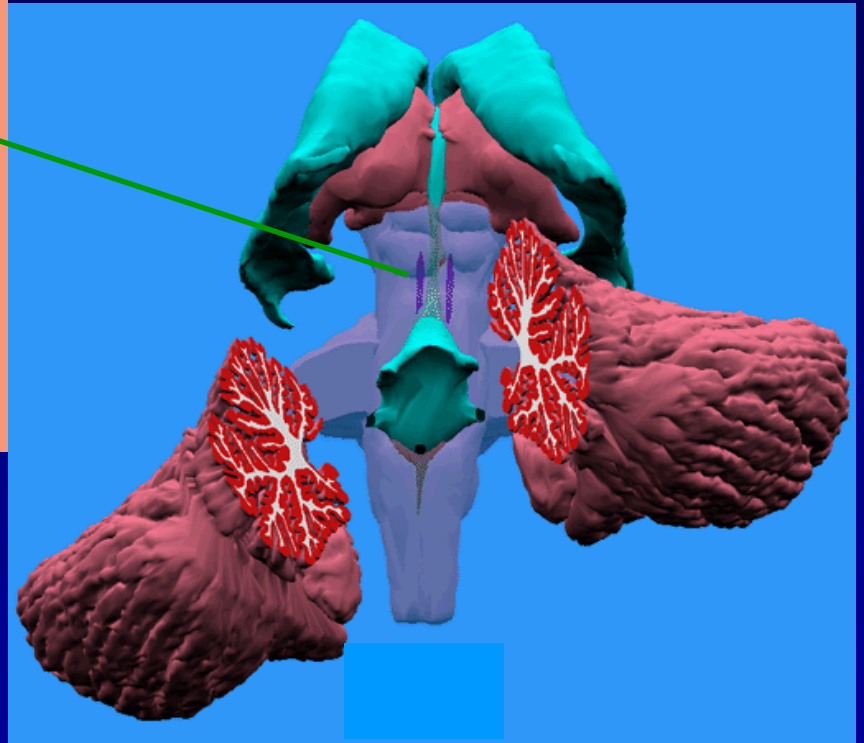
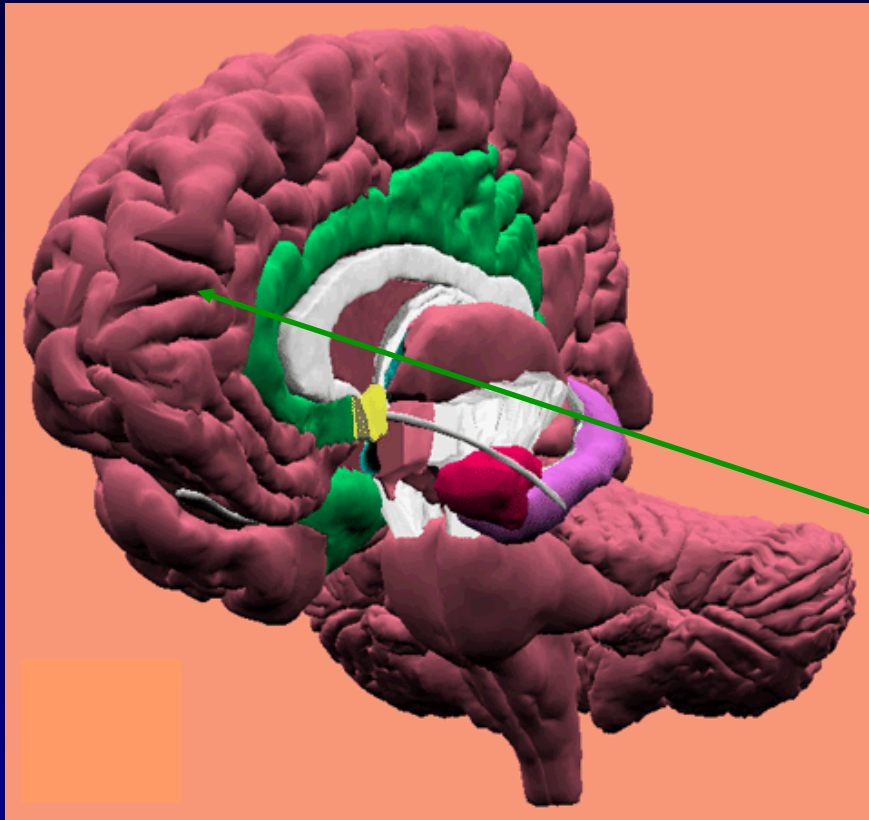
Model of the human limbic system



Emotional input



Dopamine and Norepinephrine

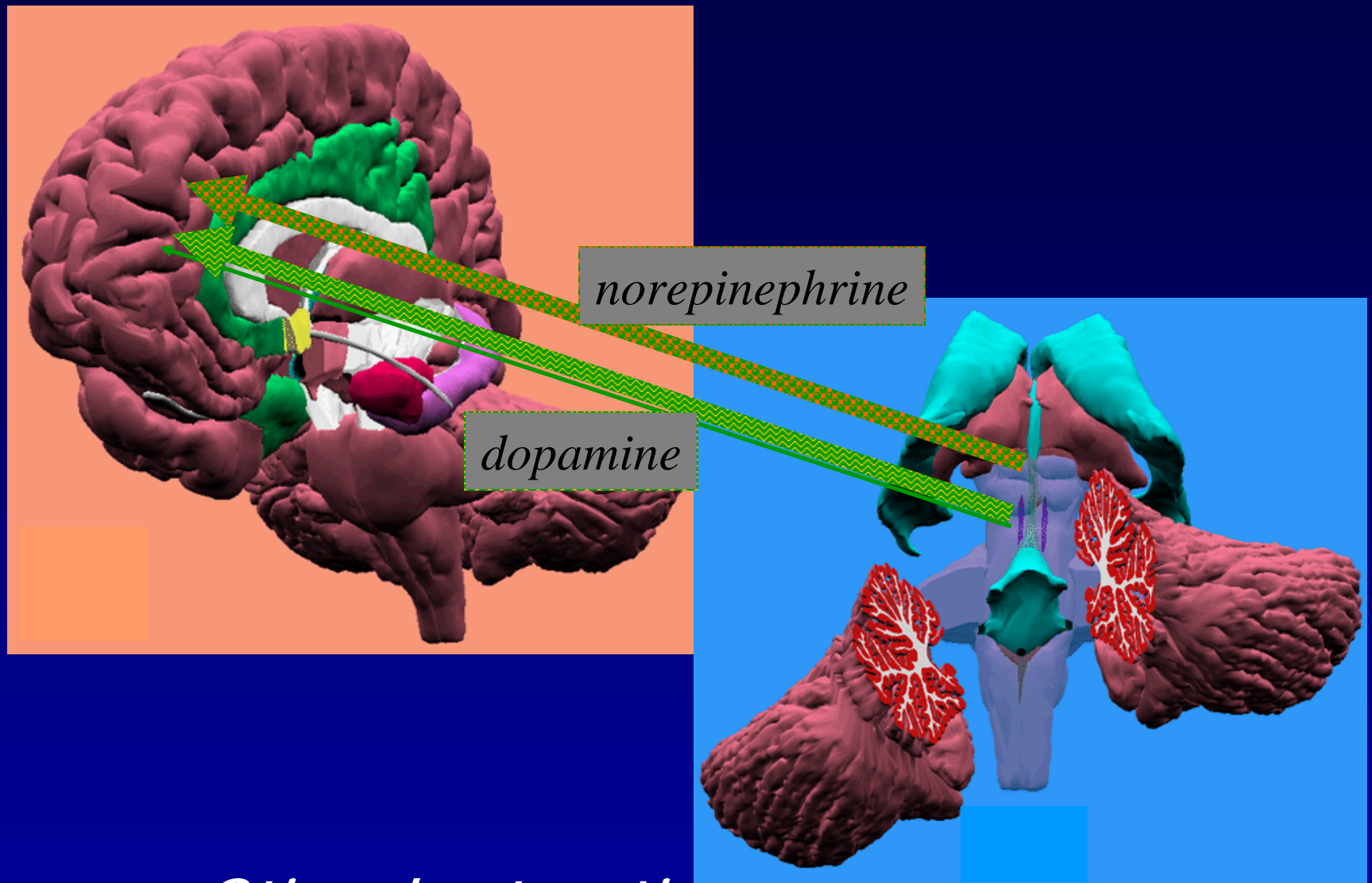


ADHD

Less signal to activate the frontal lobes

Medical options for treatment of ADHD

- Short acting: Ritalin, Methylin, Dexedrine, Dextrostat, Focalin
- Intermediate acting: Ritalin-SR, Metadate ER, Methylin ER, Metadate CD, Adderall, Dexedrine Spansule
- Long acting: Concerta, Adderall XR



Stimulant action

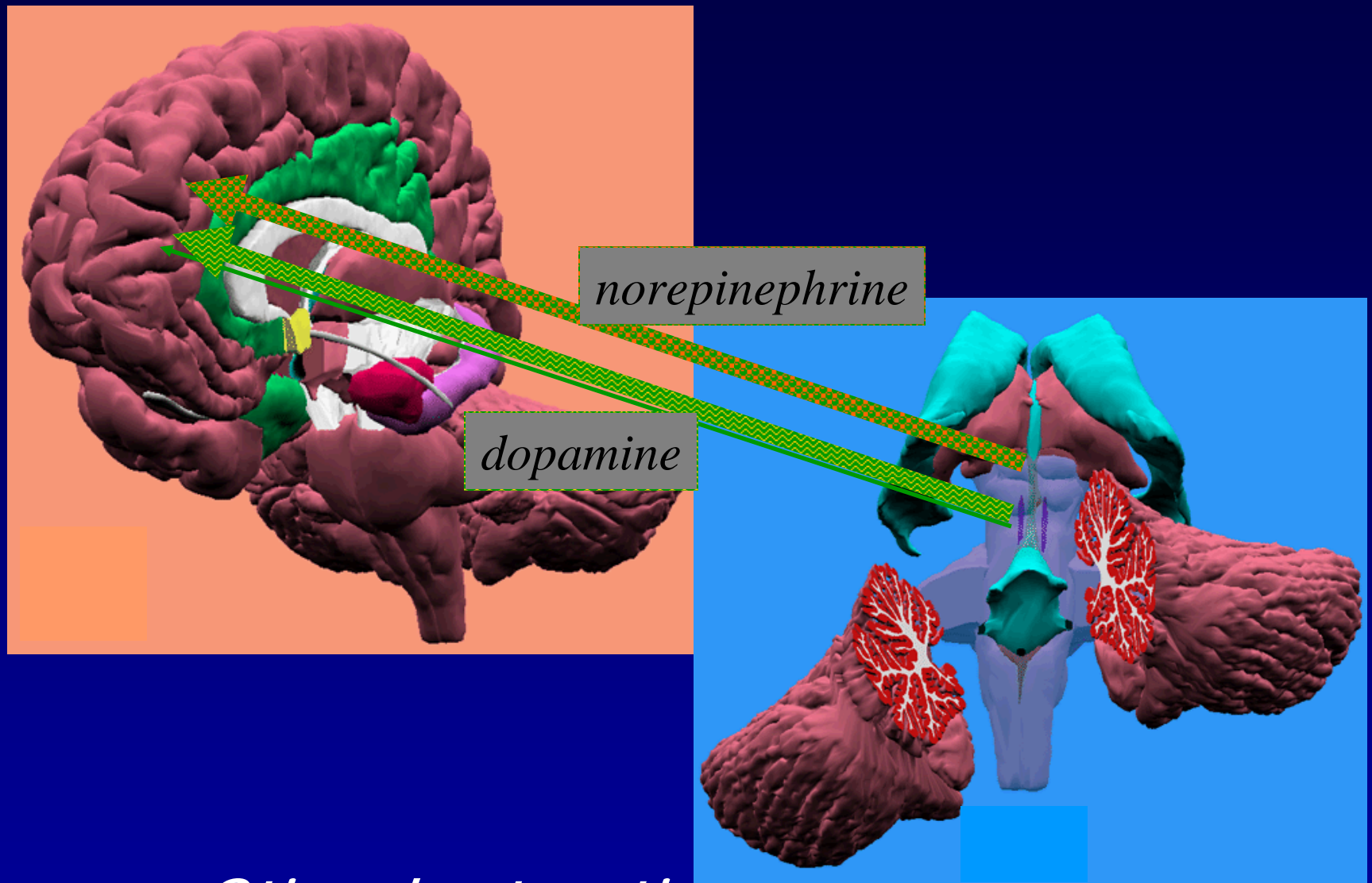
Shaw, P., *et al.* 2007. Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. *Proc Natl Acad Sci, USA.*

New Study of ADHD brains

- 223 ADHD kids, 223 typical kids
- 824 MRI scans
- Thickness measured in 40,000 locations

RESULTS

- Maturation progressed in a similar manner regionally in both children with and without ADHD.
- However, there was a marked, 3 year delay in ADHD in attaining peak thickness throughout most of the cerebrum:
- The delay was most prominent in prefrontal regions important for control of cognitive processes including attention and motor planning.



Stimulant action

Treatment of ADHD in Children With Tics

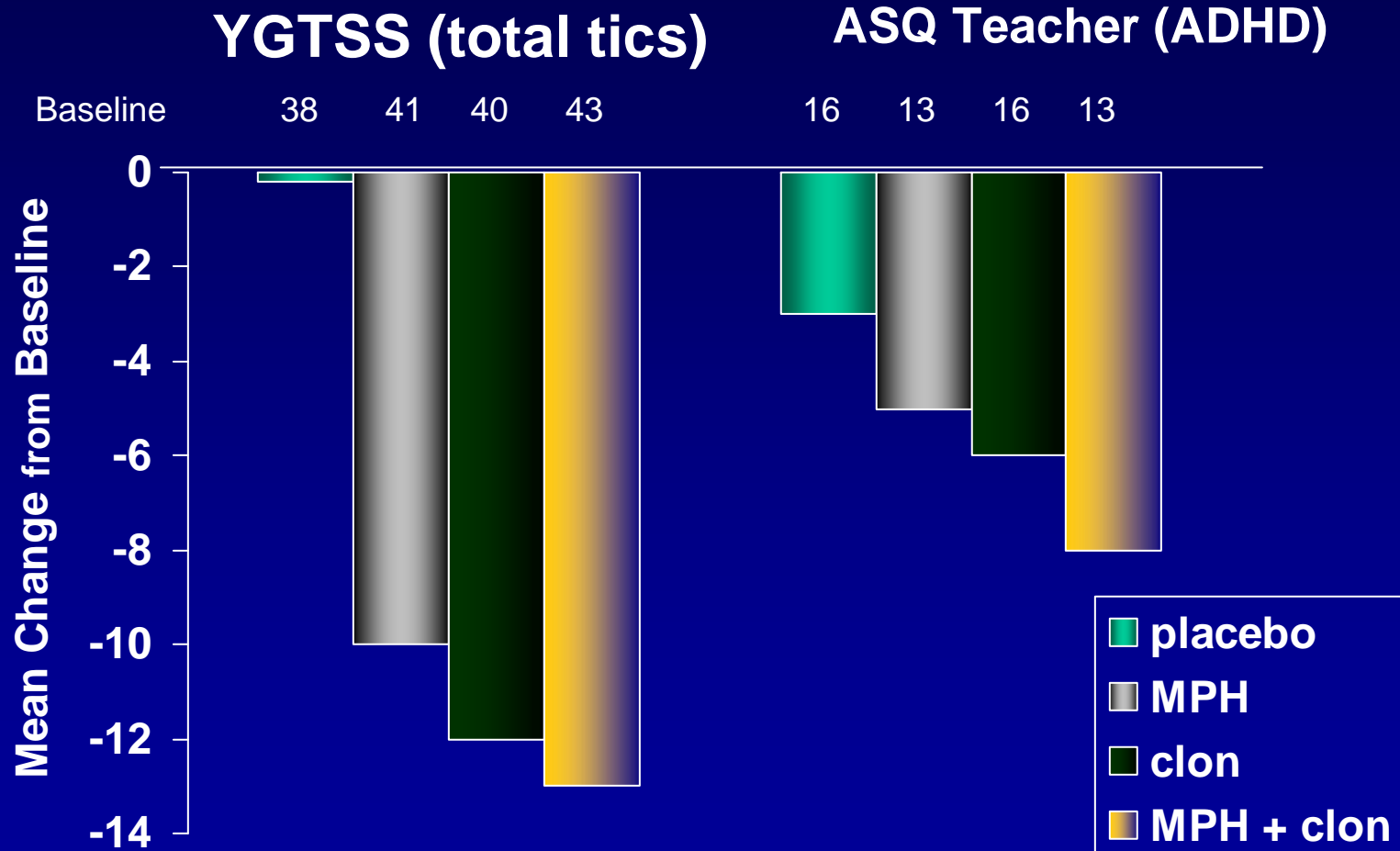
Tourette Syndrome Study Group

Neurology 2002

TACT Study – your tax \$ at work

- 4 groups: clonidine, methylphenidate, BOTH, or placebo, n = 136, 16 weeks
- ADHD results: all groups improved. Combined group did the best.
- Tic results: All groups but placebo improved. Even MPH group alone had fewer tics

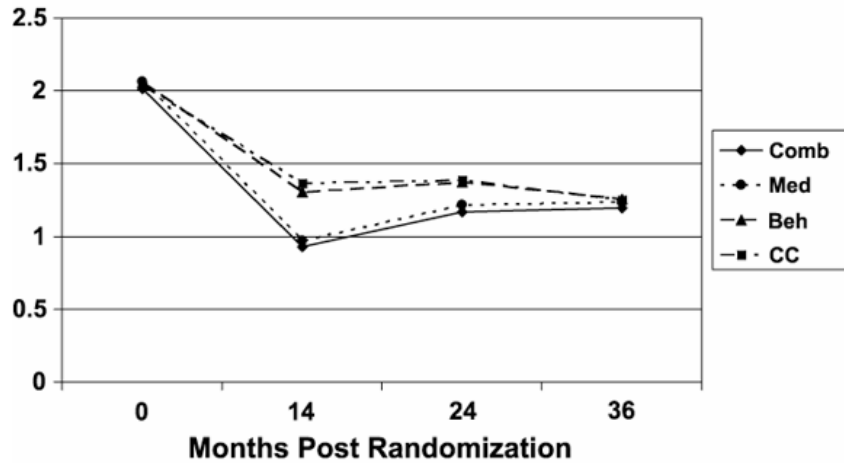
Changes in tics and ADHD



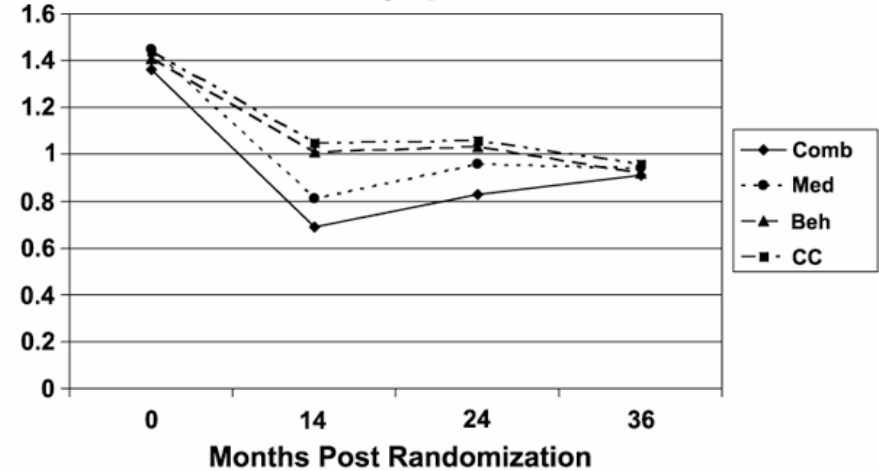
Long term ADHD treatment?

- MTA Study 1999: Landmark study for treatment of ADHD – compares intensive but limited behavioral treatment and medication
- At 12 months – medication is the winner for main problems with attention and hyperactivity

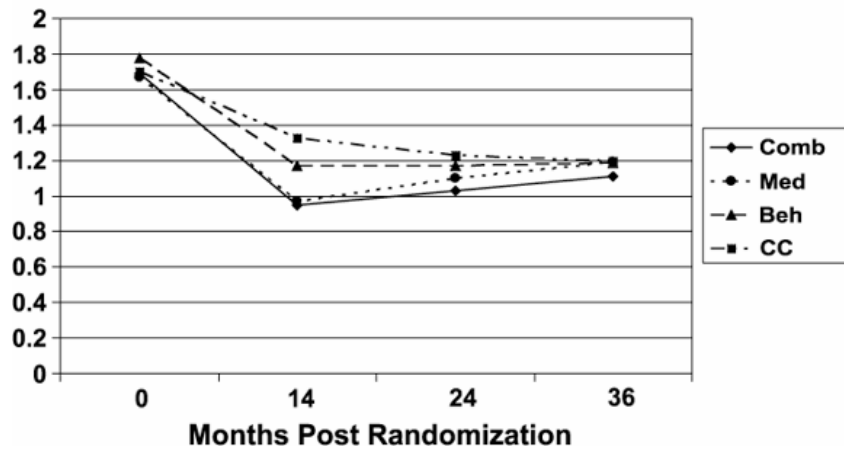
ADHD Symptoms



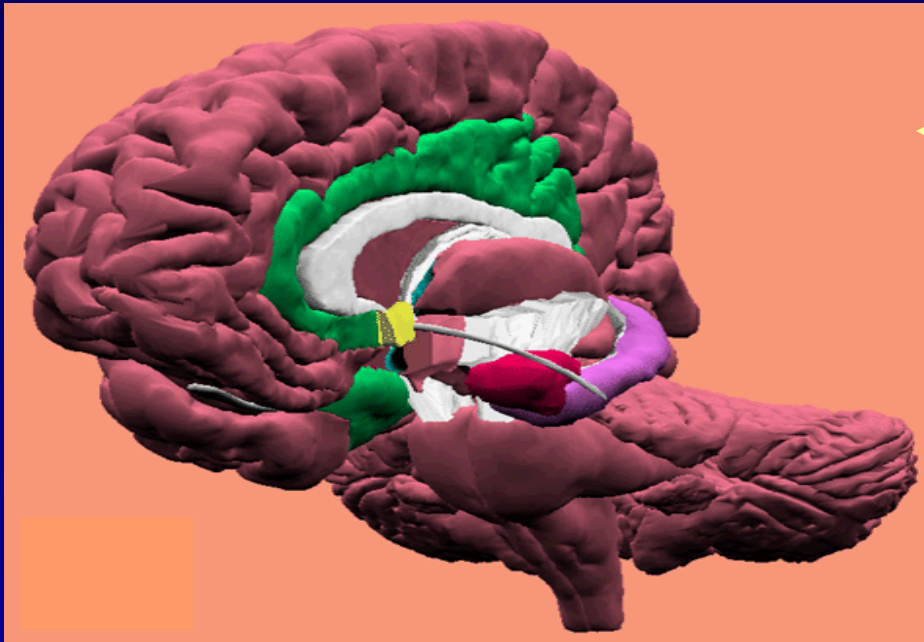
ODD Symptoms



Columbia Impairment Scale



Jensen PS et al. Journal of the American Academy of Child & Adolescent Psychiatry. 46(8):989-1002, 2007 Aug.



Medication

When medication works

It is usually just a beginning, not an ending or solution

The Human Cortex

*Parents,
teachers:*

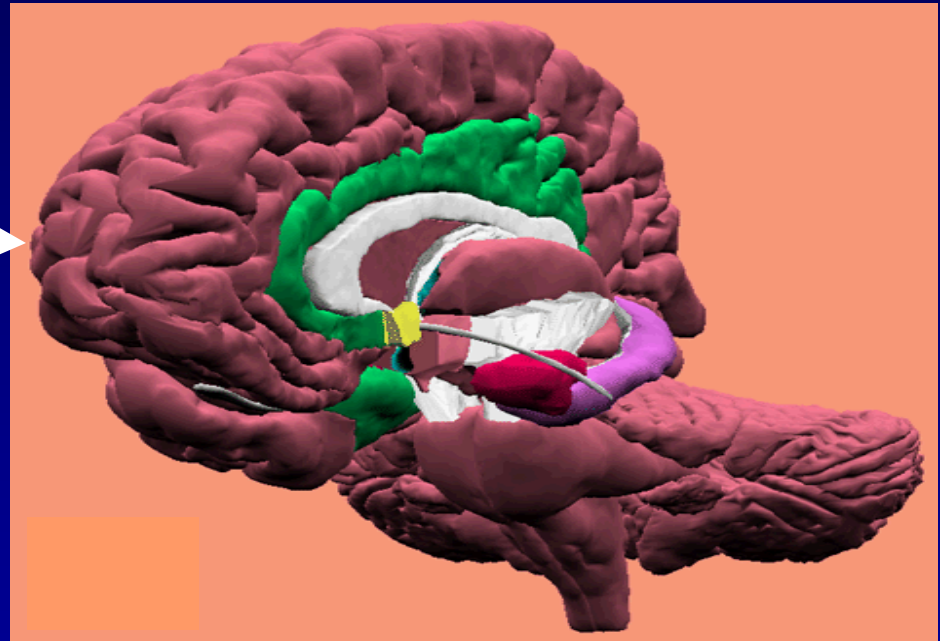
*The content
in this
area is our
job*



The Human Cortex

*Your job is
not
intuitive.
You may
need:*

*Psychology
Good
psychology
books*





PANDAS

Pediatric Autoimmune Neuro-
Psychiatric Disorders Associated
with Streptococcal infection

Singer HS, Hong JJ, Yoon DY, Williams
PN.

Serum autoantibodies do not differentiate
PANDAS and Tourette syndrome from
controls.

Neurology 2005



PANDAS

Who has it?

Identifying who might have strep related tics or OCD remains a major problem

PANDAS and Group A Strep

- Perrin (Arch Ped Adol 2004): Prospective cohort study of ~400 GABHS infected, ~200 ill but GABHS-negative, and ~200 non-infected 4-11 y.o.
 - Questionnaire at baseline, 2 and 12 weeks
 - At baseline, ill children (with or without GAS) had more frequent behavioral symptoms than well children, but
 - No ↑ risk of new onset PANDAS symptoms in the 400 with GAS over follow-up period

PANDAS and Group A Strep

- 9 center cohort study with 40 PANDAS and 40 matched tic/OCD controls followed for 25 mo.
- Monthly TC, ASO, Anti-DNAse B, and symptom evals
- RESULTS:
 - 65 exacerbations (40 PANDAS, 25 controls), RR 1.8, $p = 0.07$
 - 43 GAS infections (31 PANDAS, 12 controls). (RR=2.8, $p=0.002$)
 - 5 PANDAS exacerbations (0 in controls) were temporally related to GAS.

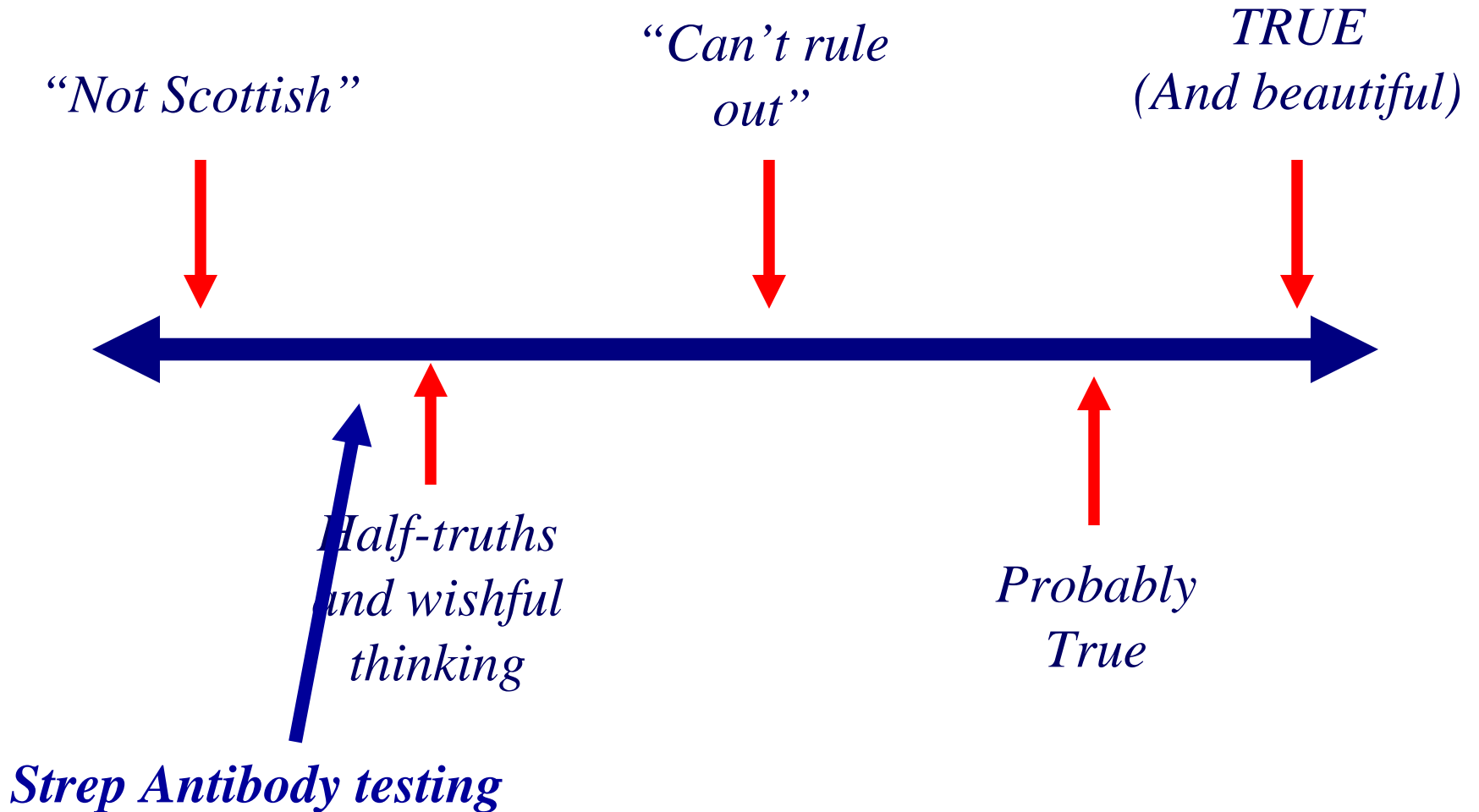
PANDAS – the bottom line

- Perhaps GABHS is just one of several infections that can induce exacerbation of TS/OCD
- Longitudinal studies show stressful events influence tics more than infections
- At present, there is insufficient basis to recommend long-term anti-streptococcal prophylaxis or plasmapheresis, exchange transfusion, or IVIG for children with these neurologic features

PANDAS – the bottom line

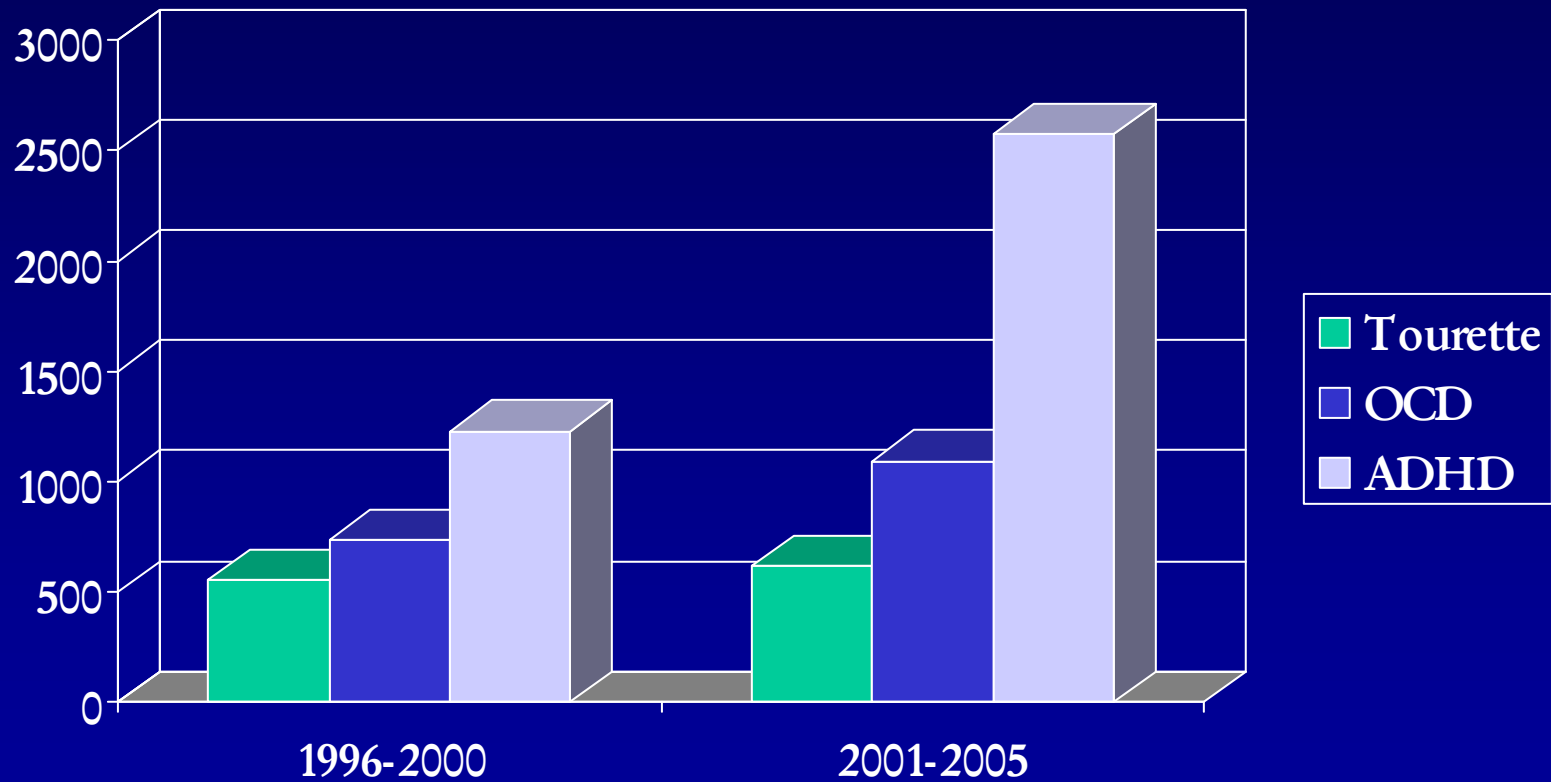
- An exciting hypothesis
- The evidence is still circumstantial
- Tonsillectomies, chronic antibiotics, and immune modulating therapies do not have proven value
- Antibody blood tests – see next slide
- NINDS/NIMH longitudinal study is in progress, so stay tuned

Information Metric v.1



*Tools for
keeping
yourself
informed*

Publications 1996-2005



Tools

1. The spectrum of evidence
2. Study design – randomized controlled trials are the gold standard
3. ClinicalTrials.gov
4. Journal Impact Factor

Sources

PRETTY STRONG

- New England Journal of Medicine, JAMA, LANCET, NEUROLOGY
- TSA Website

NOT SCOTTISH

- Some Psychiatry journals
- Journals your doctor has never heard of
- CNN, FOX

Really interesting research to come

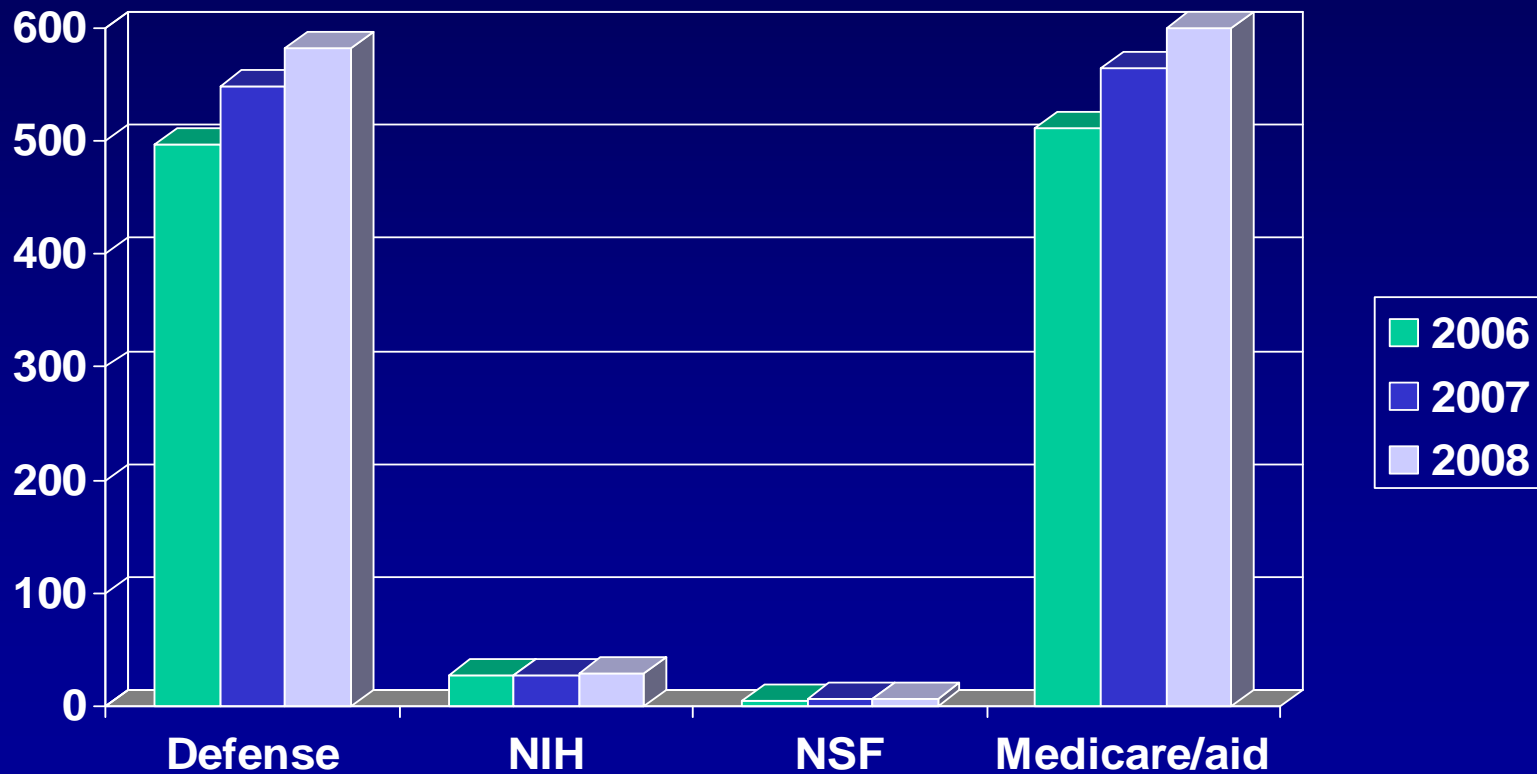
- Probably will include genetic research
- May not be on new medications
- May be on therapy, on brain training

Research funding

Tools for ensuring we are better
informed in the future than we are
now

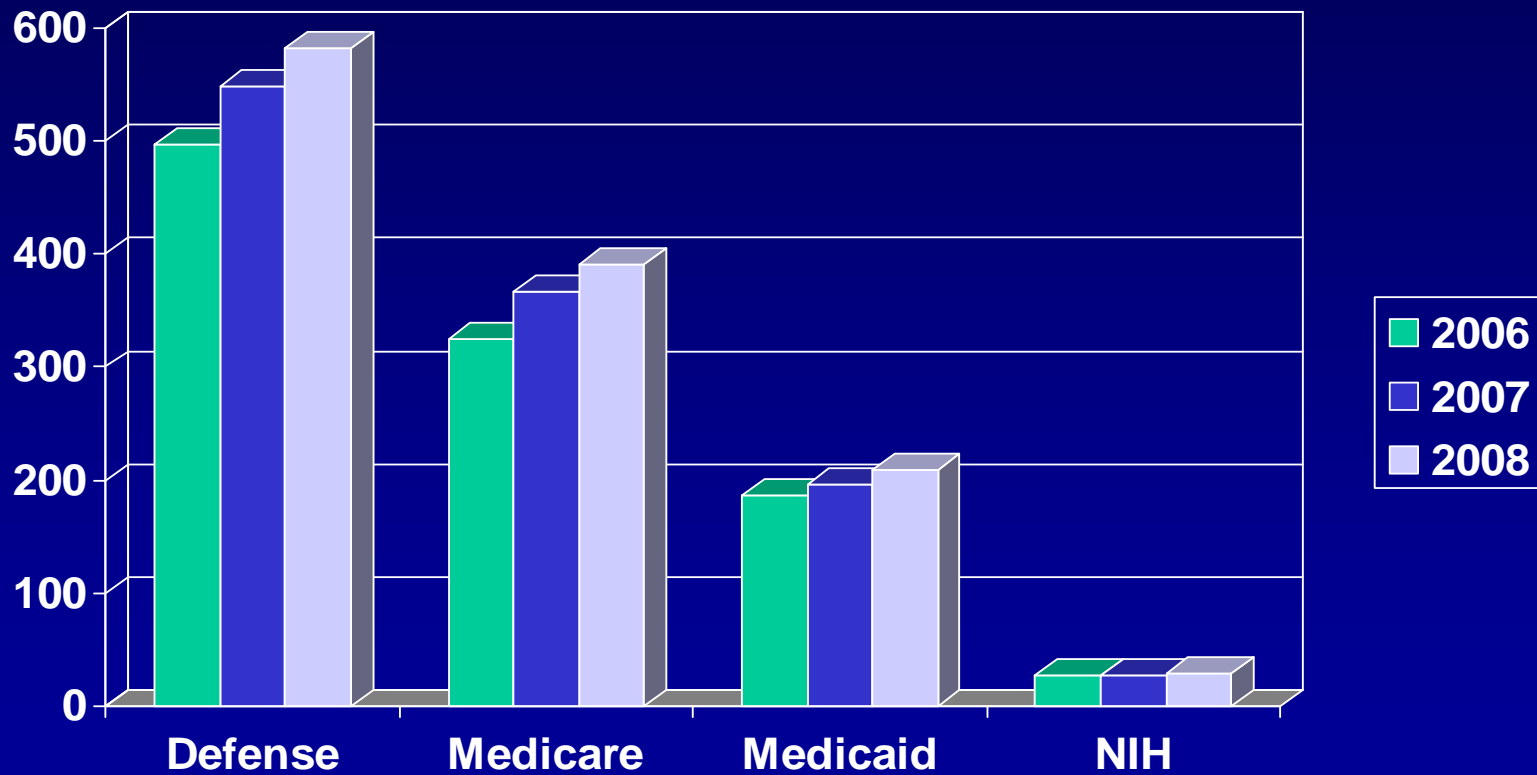
Federal Funding for Patient Care and Research

US Budget (Billions of \$)

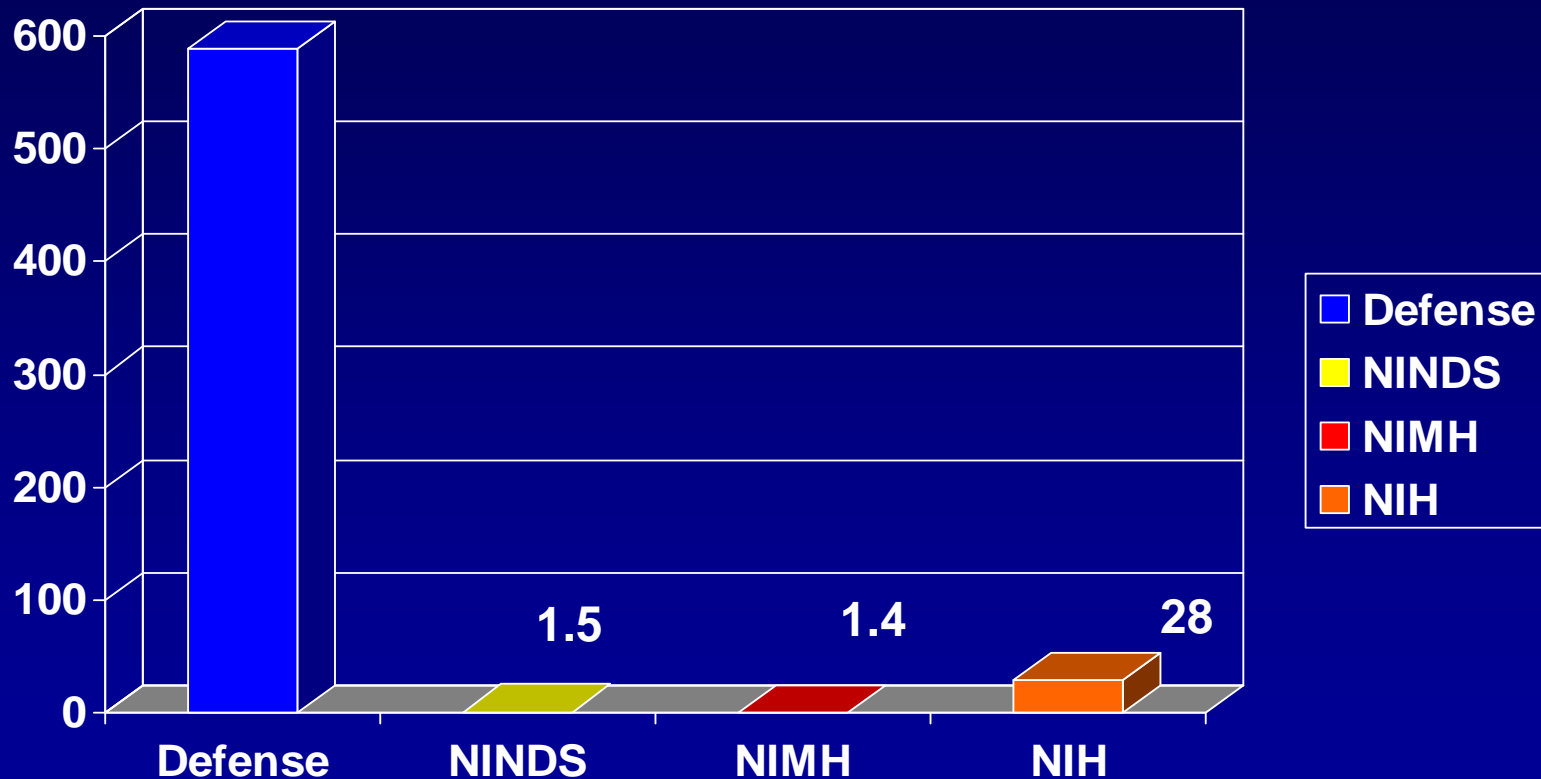


NIH = National Institutes of Health; NSF = National Science Foundation

US Budget (Billions of \$)

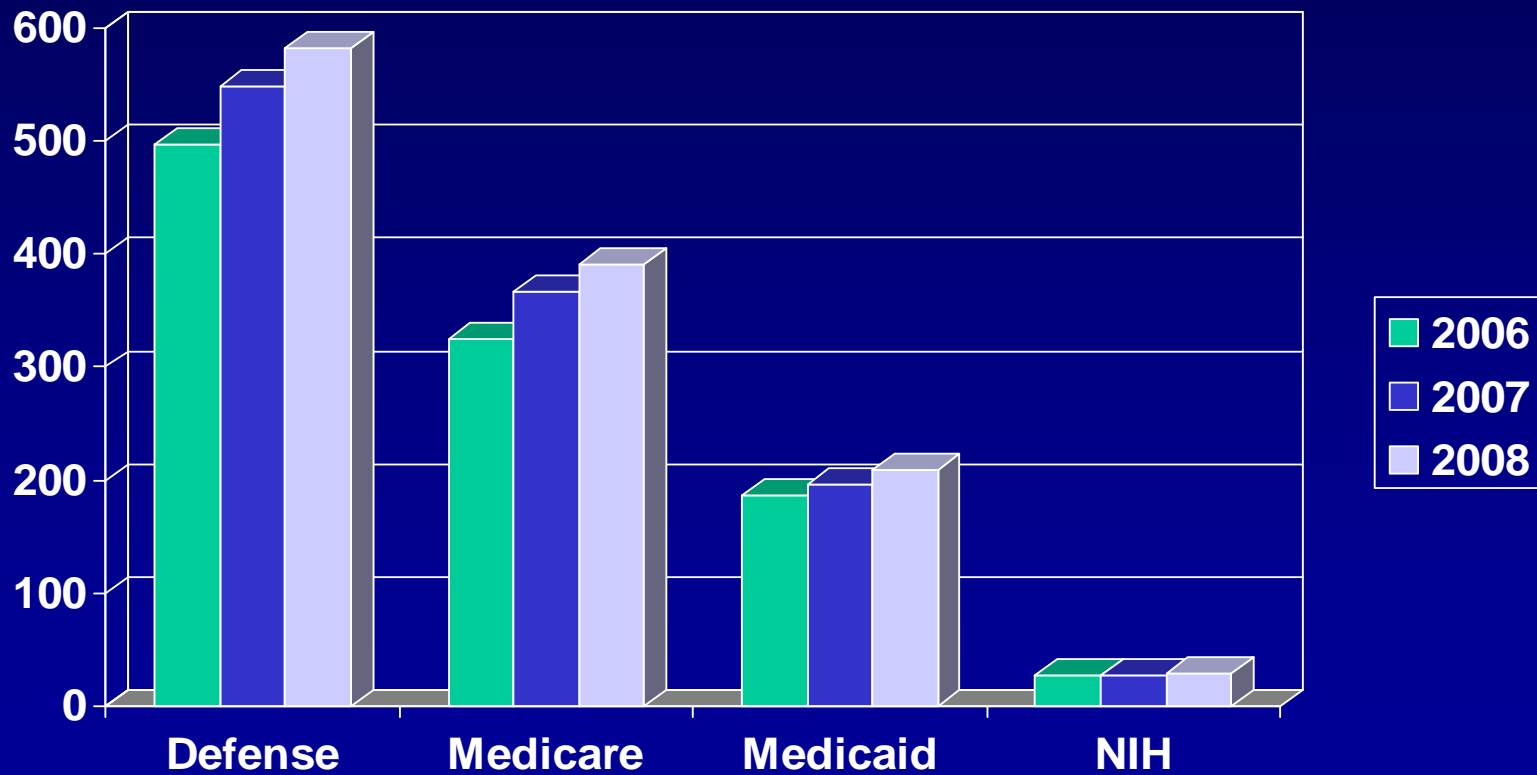


US 2008 Budget (Billions of \$)



NINDS = National Institute of Neurological Disorders and Stroke;
NIMH = National Institute of Mental Health

US Budget (Billions of \$)



Tools

1. The spectrum of evidence
2. Study design – randomized controlled trials are the gold standard
3. ClinicalTrials.gov
4. Journal Impact Factor
5. Advocate for Research (and consider participating)