fNIRS-based neuropharmacological assessment on children with attention deficit/hyperactivity disorder (ADHD)

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Today's slides are available at:

Just google: dan fnirs
Or visit: brain-lab.jp

Brief introduction of ADHD

Why is fNIRS suitable for ADHD study?

Attention-Deficit Hyperactivity Disorder

ADHD is the most prevalent psychiatric disorder of childhood characterized by heterogeneous phenotypes including

1) Age-inappropriate inattention
2) Impulsivity
3) Hyperactivity

ADHD prevalence rate: 3-7%.

(Polanczyk Am J Psychiatry, 2007)

ADHD symptoms are most often identified during early elementary school years.
Later in school age, ADHD patients tend to suffer from academic difficulties and develop anti-social behaviors.
ADHD persists into adolescence and adulthood in 65% to 85% of cases, leads to impaired educational and vocational performance

Assessment of ADHD

DSM (now 5)
(Diagnostic and Statistical Manual of Mental Disorders)

Inattention: Six or more symptoms of inattention for children up to age 16, or five or more for adolescents 17 and older and adults; symptoms of inattention have been present for at least 6 months, and they are inappropriate for developmental level:

- ◦Often has trouble holding attention on tasks or play activities.
- ◦Often has trouble organizing tasks and activities.
- ◦Often loses things necessary for tasks and activities (e.g. school materials, pencils, books, tools, wallets, keys, paperwork, eyeglasses, mobile telephones).
- ◦Is often easily distracted
- ◦Is often forgetful in daily activities.

Assessment of ADHD, continued

DSM (now 5)
(Diagnostic and Statistical Manual of Mental Disorders)

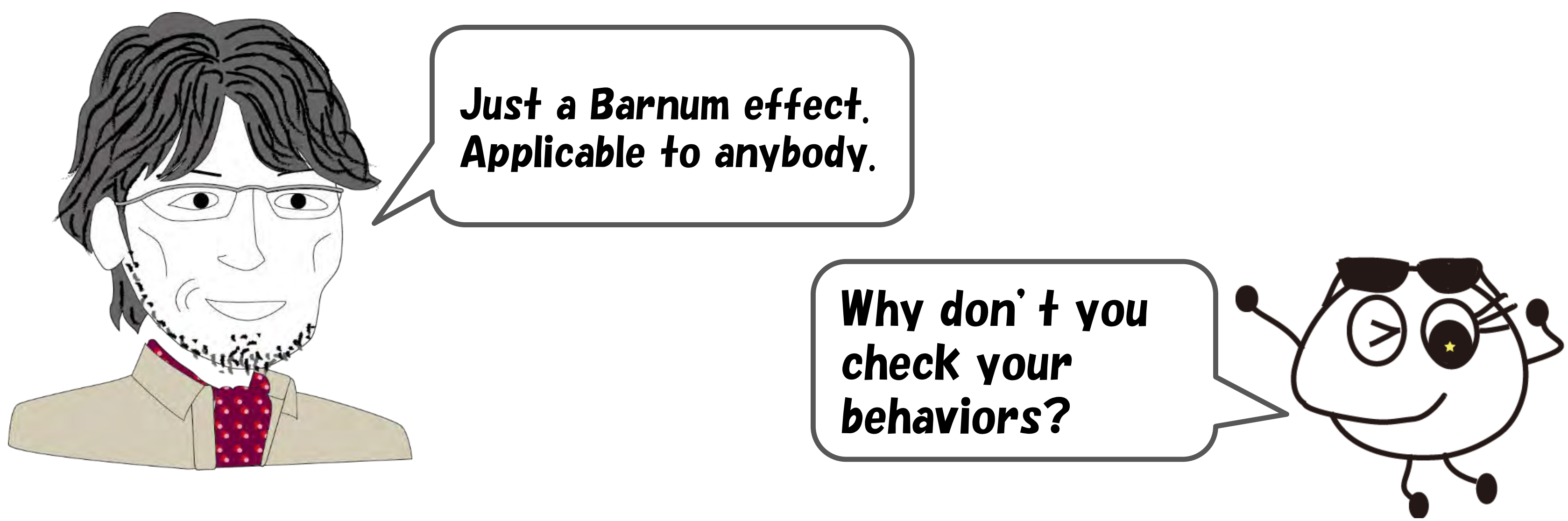
Hyperactivity and Impulsivity: Six or more symptoms of hyperactivity-impulsivity for children up to age 16, or five or more for adolescents 17 and older and adults; symptoms of hyperactivity-impulsivity have been present for at least 6 months to an extent that is disruptive and inappropriate for the person's developmental level:

- Often unable to play or take part in leisure activities quietly.
- Is often "on the go" acting as if "driven by a motor".
- Often talks excessively.
- Often blurts out an answer before a question has been completed.
- Often has trouble waiting his/her turn.

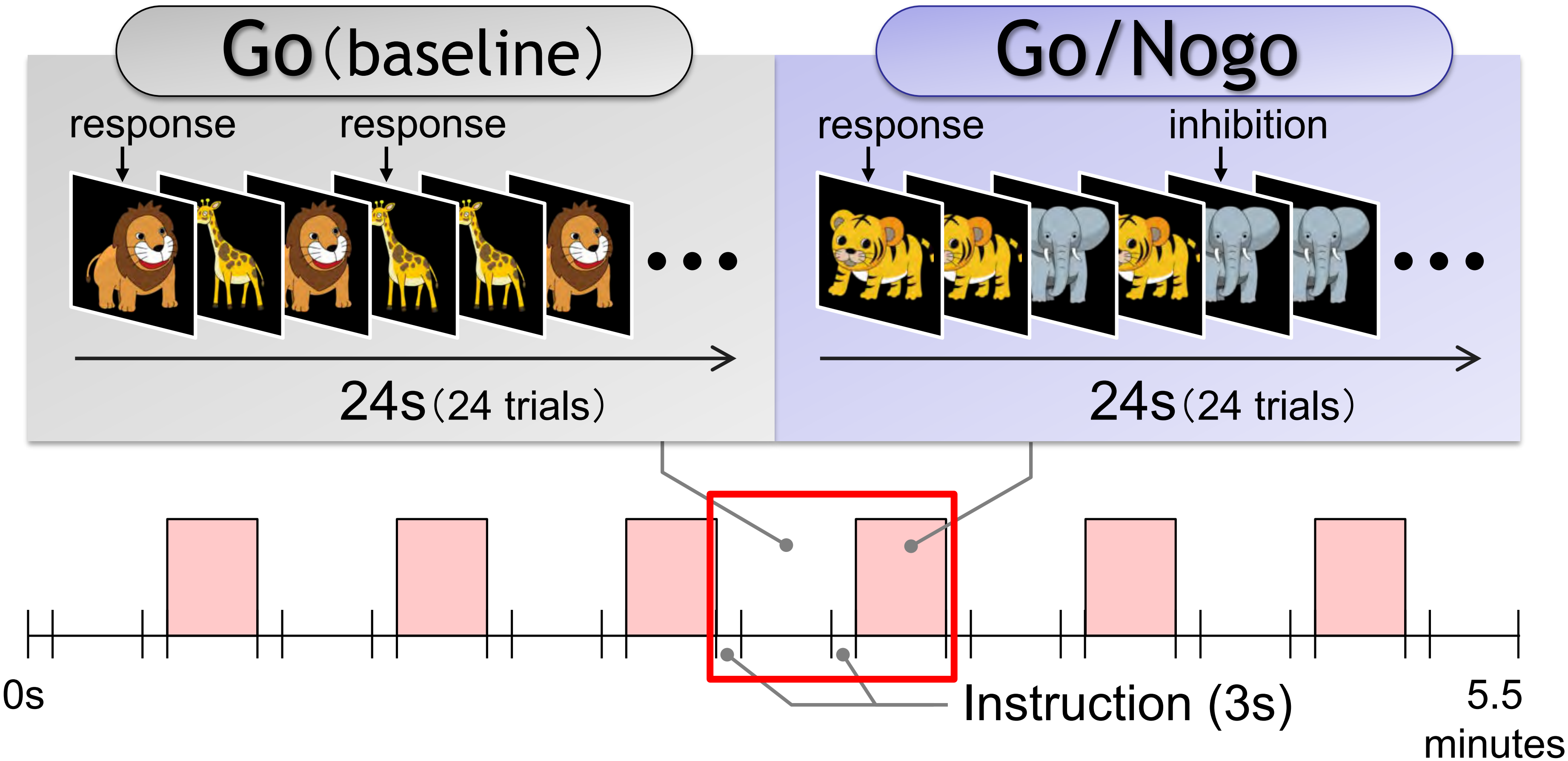
Too subjective, Need for objective measurement

Currently, ADHD diagnosis is heavily dependent on subjective measure.
Assessors are parents, grand parents, teachers etc. They are unexperienced raters.
There are no cut-off criteria.

Objective biomarker is necessary



Go/Nogo task to measure inhibition



Response: Press the button

Inhibition: Not to press the button

Go/no-go task performance data for Typically Developing and ADHD children

	TD		ADHD		ADHD vs TD		
	Mean	SD	Mean	SD	t	p	Sig
RT for correct trials (ms)	421.4	57.5	385.5	96.8	1.275	0.214	n.s.
Accuracy for go trials (%)	96.5	5.5	86.2	21.9	1.829	0.085	n.s.
Accuracy for no-go trials (%)	95.2	4.5	86.6	11.9	2.688	0.014	*

6-14 years old, N=16
*, p<0.05 Bonferroni-corrected; **, p<0.01 Bonferroni-corrected; n.s., not significant.
SD, standard deviation; *t*, *t*-value; *p*, *p*-value; Sig, Statictical significance

Need of examining brain

Behavioral performance data do not always offer clear-cut results

Objective neurobiomarker is wanted

fMRI does not offer an ideal environment for ADHD children

Highly restrictive and ADHD children with hyperactivity cannot stay still in a scanner

fNIRS offers distinct advantages

- Compactness
- Tolerance to body motion
- Accessibility

All these merits contribute towards ADHD studies

Miyai et al.,
NeuroImage (2001)

Okamoto et al.,
NeuroImage (2004)

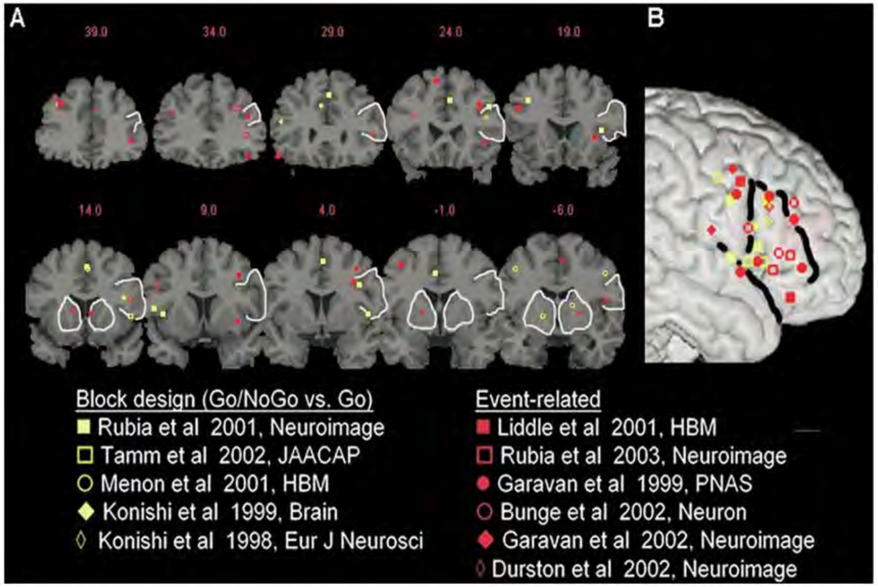
Ono et al.,
NeuroImage (2014)

fNIRS offers an ~~ideal~~ acceptable environment for ADHD children

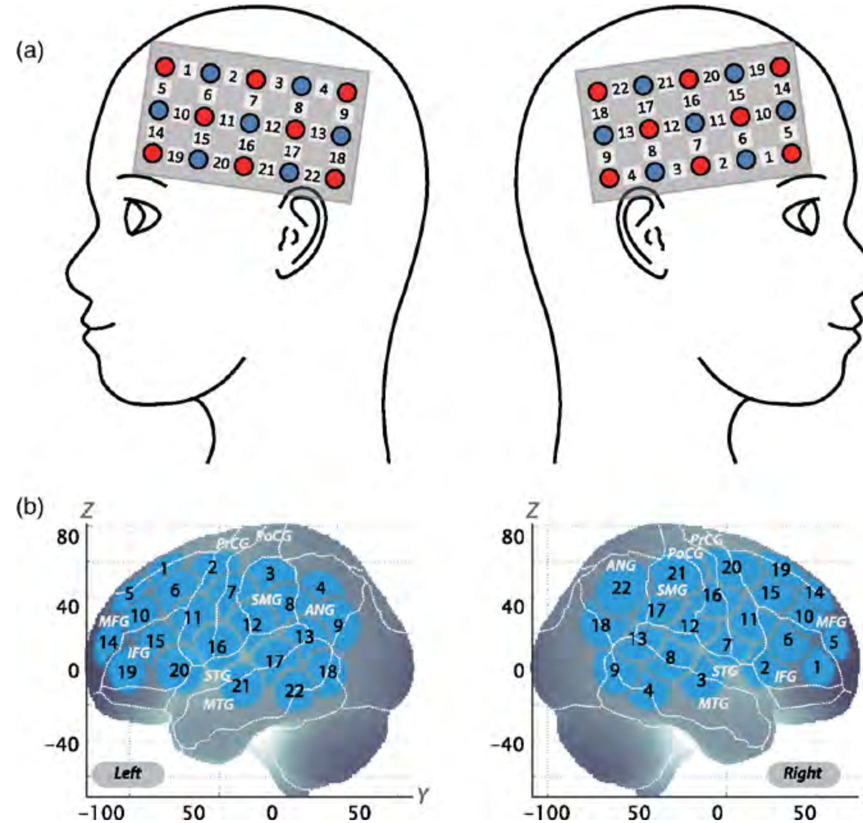
ADHD vs TD

Are they different in cortical representation?
Can they be distinguished?

fNIRS probe placement for Go/Nogo task



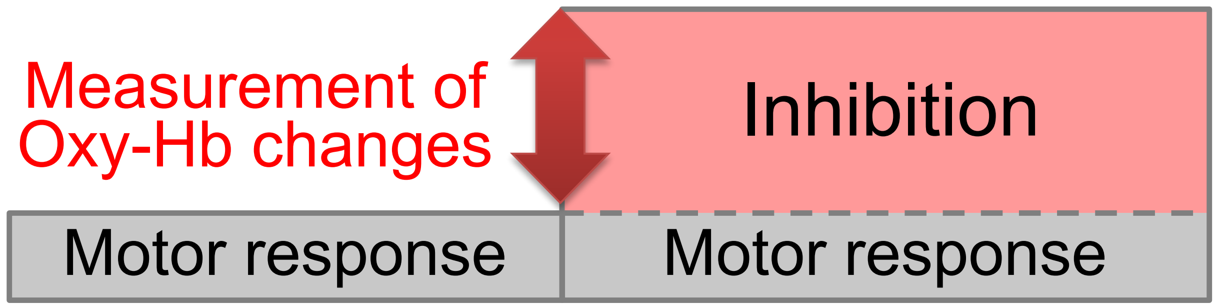
Aron et al., 2005

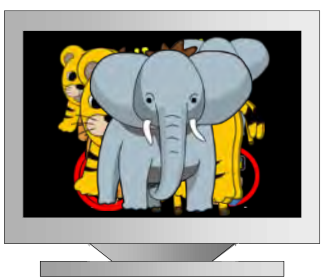


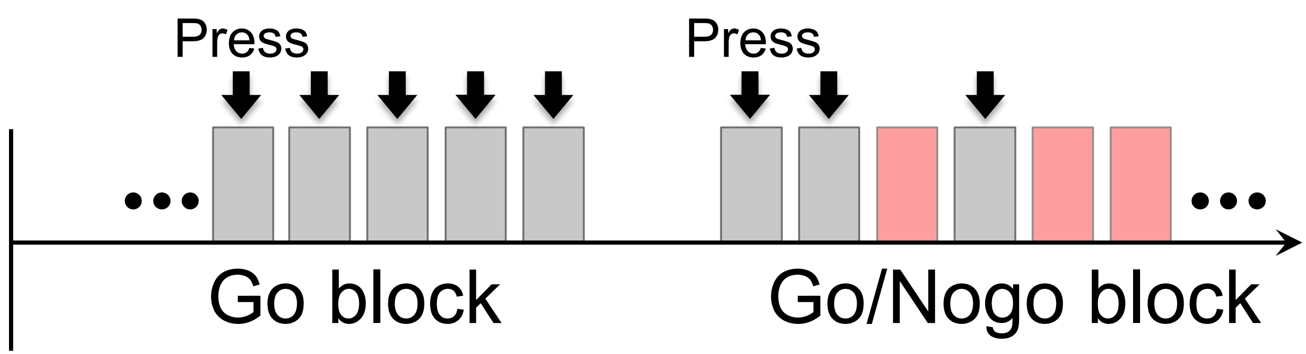
- Channel positions are probabilistically registered to MNI space using 3D digitizer
- MFG, IFG, SMG, AnG are covered

Tsuzuki &Dan, NeuroImage (2014)

fNIRS analysis during Go/Nogo tasks







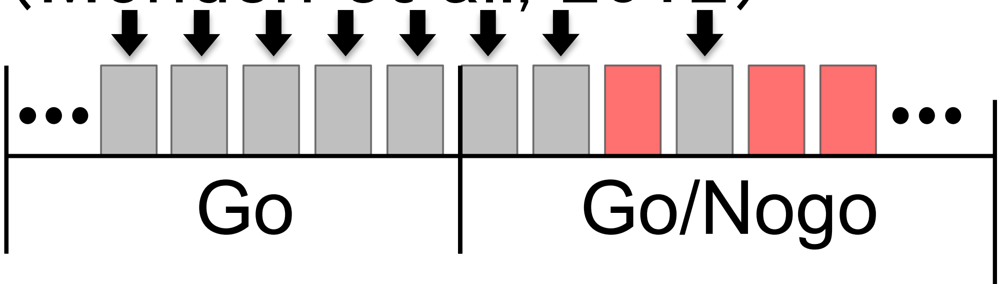
We asked subjects not to press the button when the elephant was displayed.

Monden et al., 2012

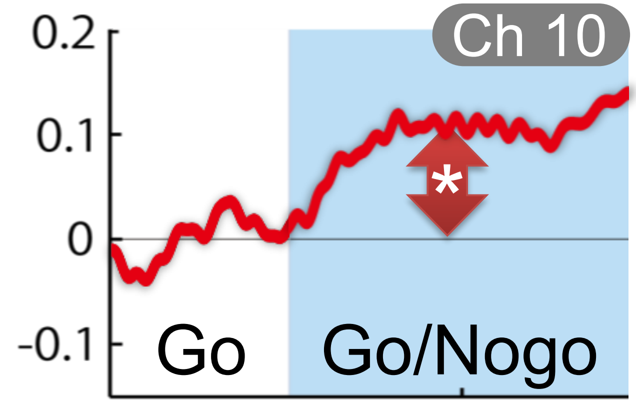
Cortical activation

TD control（n=16）

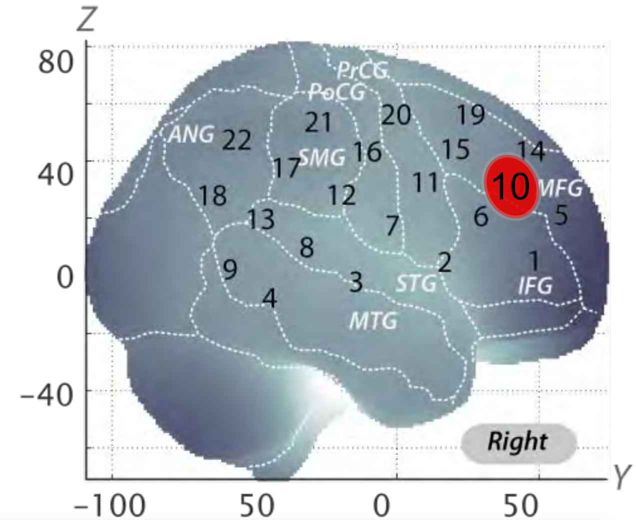
（Monden et al., 2012）



	ES	*P*
Ch 10	1.15	0.0003



Activation



Control subjects exhibited significant brain activation in the right IFG/MFG

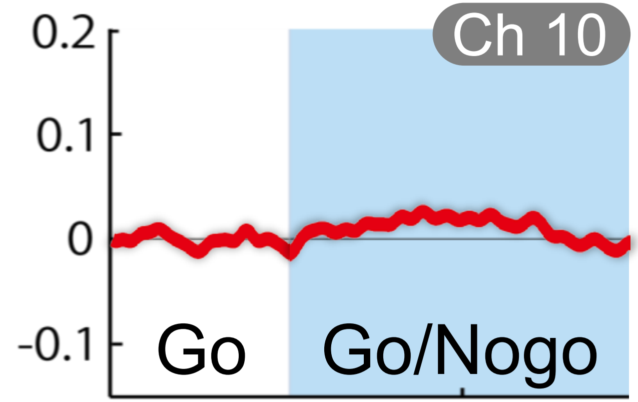
Monden et al., 2012

Cortical activation

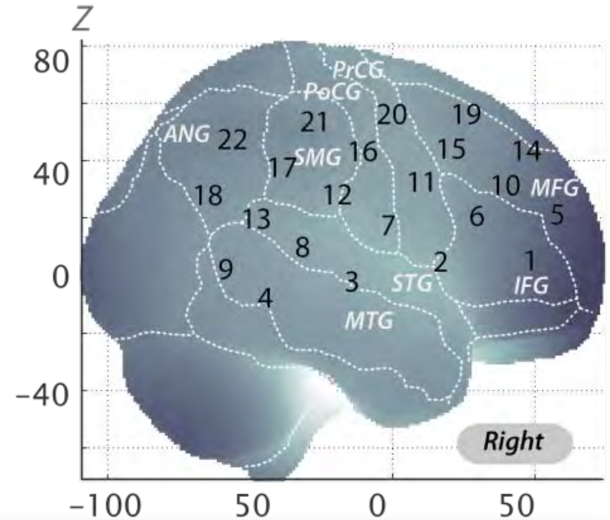
ADHD (n=16, DSM-IV)

(Monden et al., 2012)

	ES	*P*
Ch 10	0.01	0.900



No activation



Pre-medicated ADHD children exhibited reduced brain activation in the right IFG/MFG

Monden et al., 2012

Individual Analysis

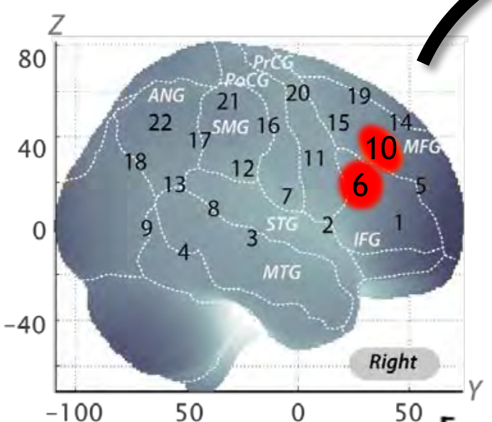
Given such marked activation, fNIRS-based diagnosis may be possible at an individual level

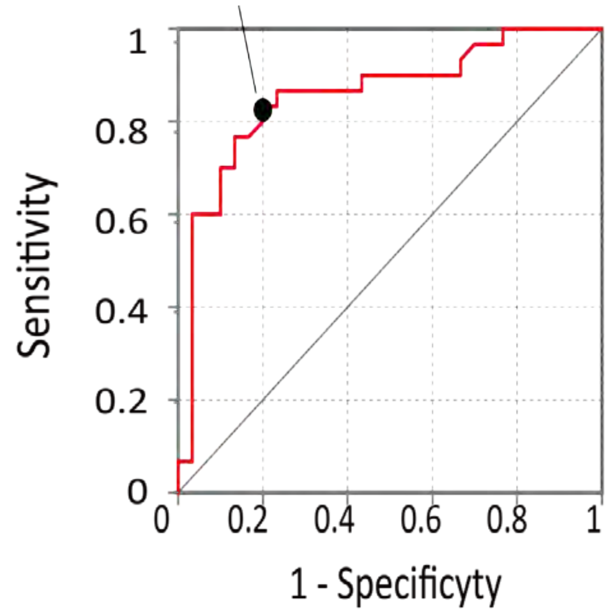
Individual-level analysis may be possible

Cut-off Value: **0.004**

Sensitivity
80%
Specificity
83%

Activation focus
in rPFC



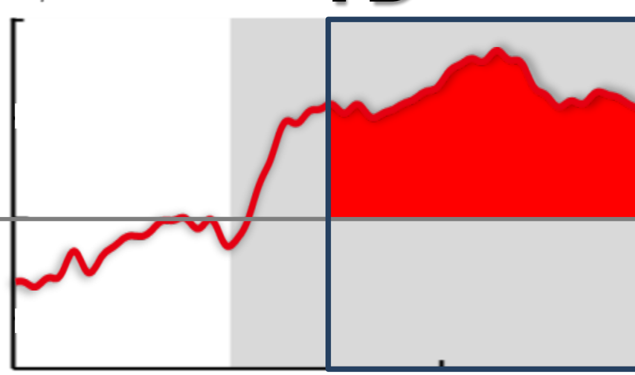


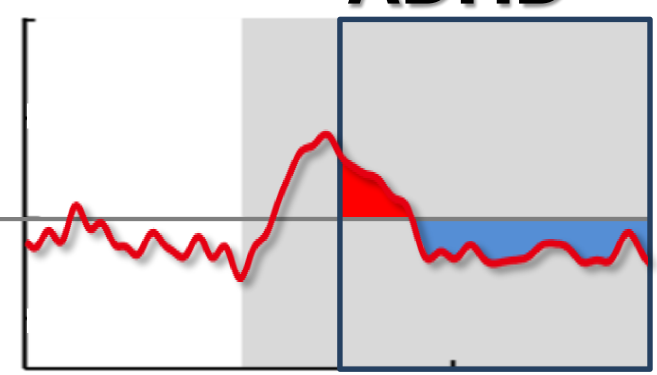
Ch6>0.004
AND
Ch10>0.004
==TD

TD

ADHD

Cut-off
value
0.004
(Mmm





baseline Go/Nogo

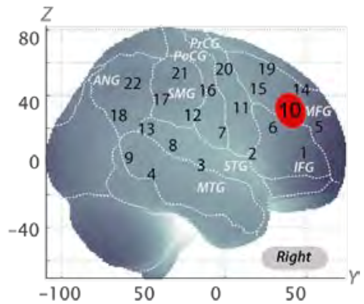
baseline Go/Nogo

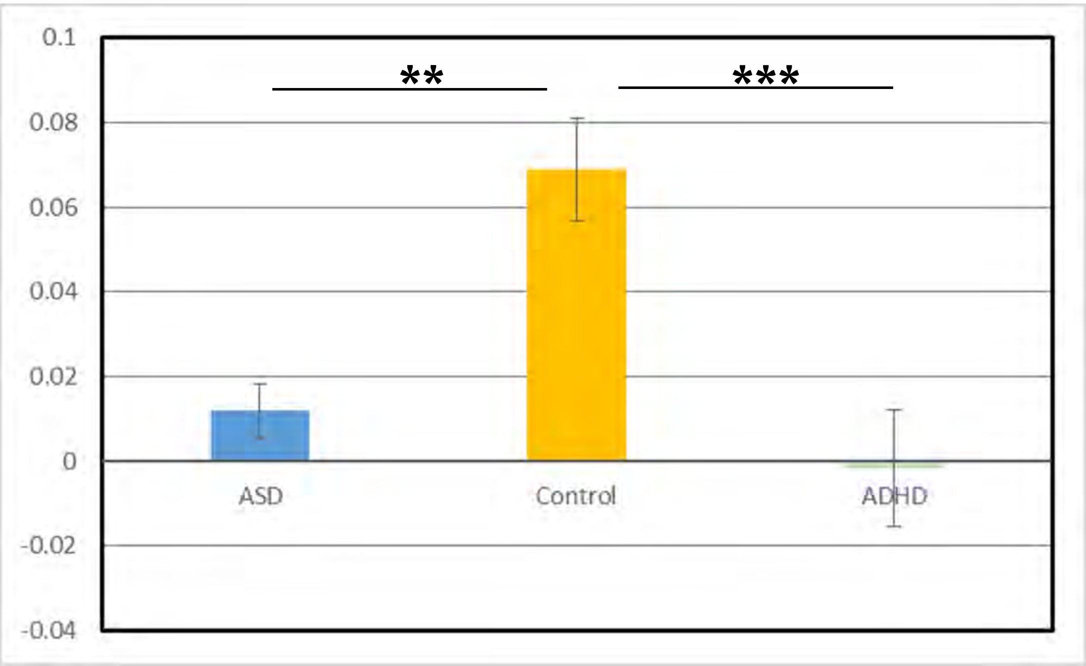
Monden et al., 2015

But, individual-level analysis may be difficult

ASD vs
ADHD vs
TD Cntrl

ASD : 10.5±2.3
ADHD : 10.8±2.2
TD :10.8±1.7
N=17 (M14)





F(2,48)=11.16
(p=0.00)
η^2=0.316

TD vs ASD :
t=4.18(p=0.002) ,
d=1.43
TD vs ADHD :
t=3.83(p=0.000) ,
d=1.32

TD-ADHD distinction may be possible when only they are present.
But ADHD-ASD distinction is difficult.
They are spectral differences.

Tokuda et al. unpublished

fNIRS-based Neuropharmacology

Although fNIRS-based diagnosis is difficult, fNIRS-based neuropharmacology is promising

Conceptual basis of neuropharmacological fNIRS = Behavioral neuropharmacology

Studying effects of drug on behavior.
This area of study has become popular around ‘80.

Basic concept is based on SOR model in neobehaviorism by Hull (1943)

Stimulus	→	Organism	→	Response
Drug administration		Physiological change reflecting health state		Behavioral change and/or Hemodynamical change to be observebed by fNIRS

Another objective of the discipline is to find neurochemical mechanism underlying behaviors.

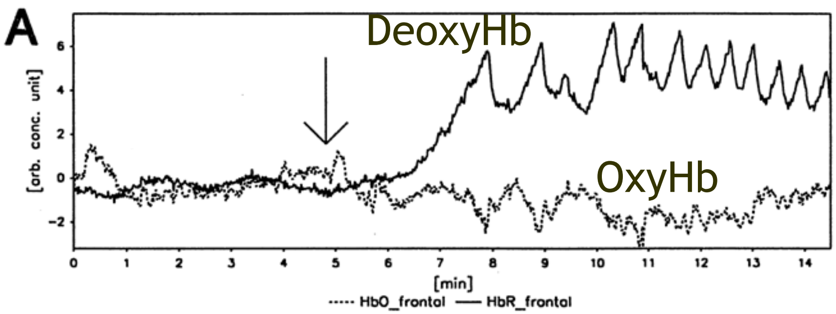
-Behavioural Pharmachology =journal

First stage of neuropharmacological fNIRS

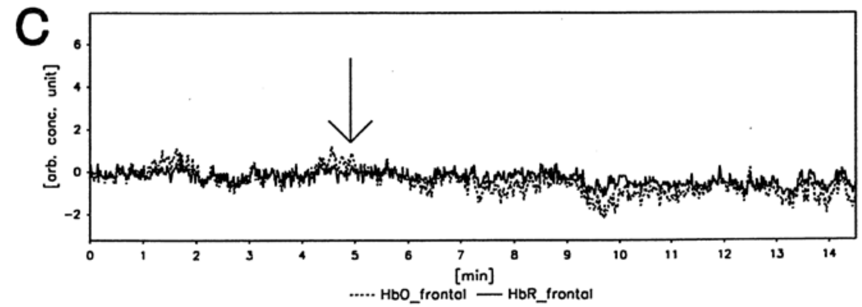
Basic concept: Administrating drug, and see what happens

Intravenous heroin injection. Stohler et al (Drug Alcohol Depend. 1999)

Frontal hemodynamical change



Heroin to heroin-dependent subject



Saline to healthy control

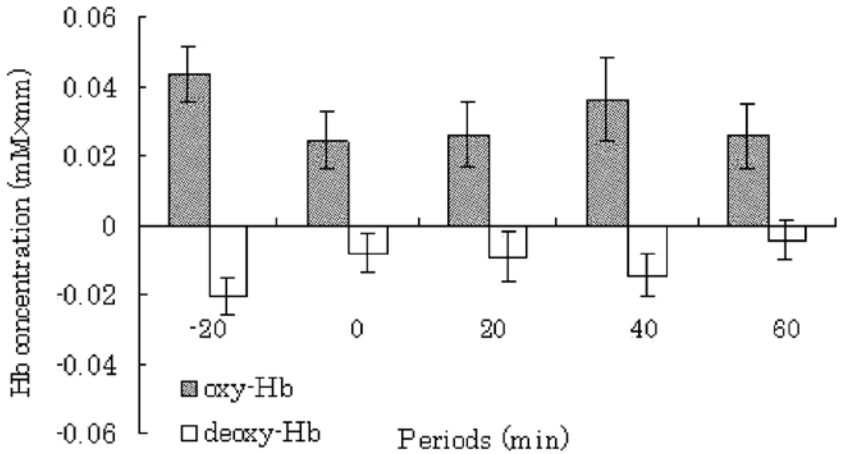
What is the source of such hemodynamic changes?
Cognitive/Perceptual?
Physiological?
Systemic?
Skin blood flow?

Second stage of neuropharmacological fNIRS

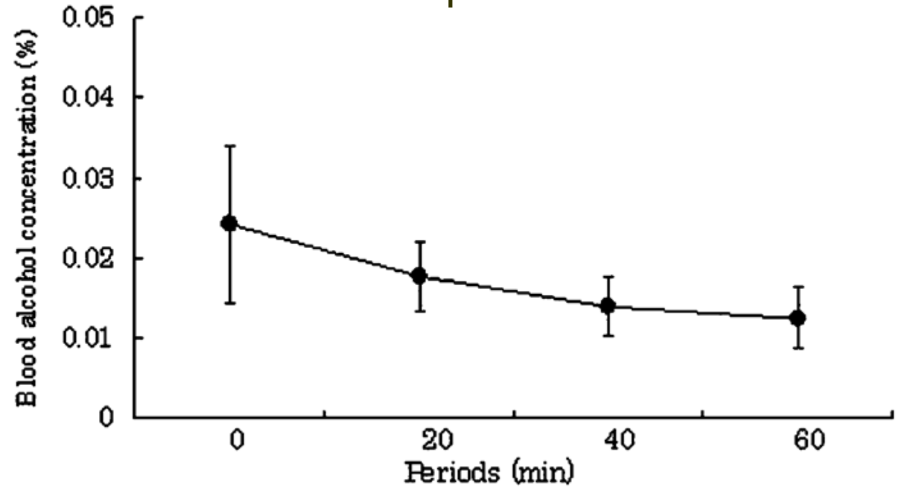
Basic concept: Administrating drug, performing a relevant task, and see what happens

Alcohol (whisky) intake. Obata et al (Phychiatr Res, 2003)

Occipital hemodynamical change
During checker-board flip stimulation



Blood [alcohol] change
Measured in expired air



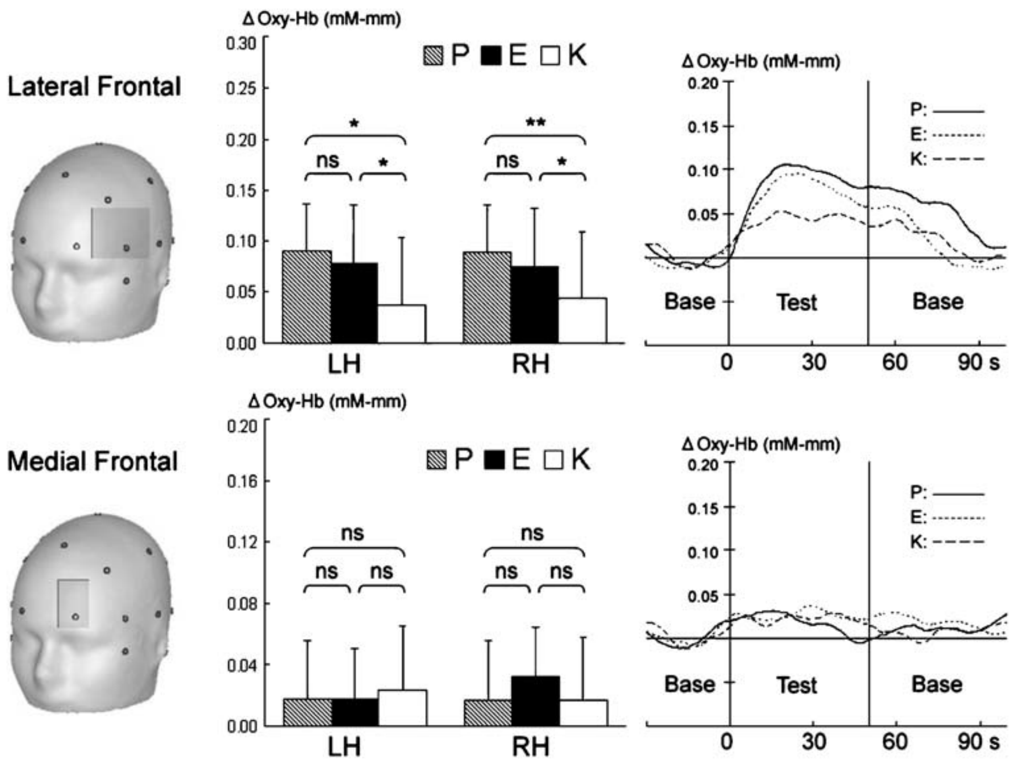
What is the source of such hemodynamic changes?
Cognitive/Perceptual? More likely
Physiological?
Systemic?
Skin blood flow?

Third stage of neuropharmacological fNIRS

Basic concept: Administrating drug, double-blind, placebo-controlled, performing a relevant task, and see what happens

First-generation H1-antagonist (ketotifen) vs Second-generation H1-antagonist (epinastine) vs Placebo (Tsujii et al Psychopharmacology, 2007)

Frontal hemodynamical change
During two-back working memory task



What is the source of such hemodynamic changes?
Cognitive/Perceptual?
Yes
Physiological?
Systemic?
Skin blood flow?
Not likely

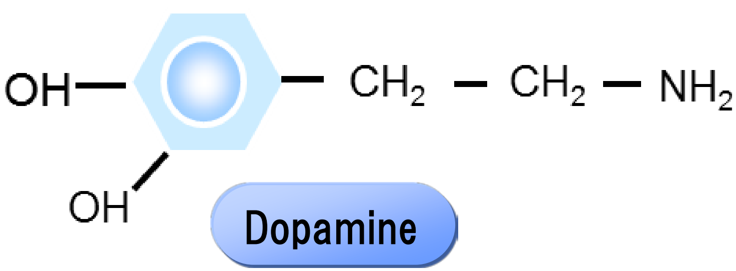
Task-specific activation and no-activation are important indicators of what's happening in brain

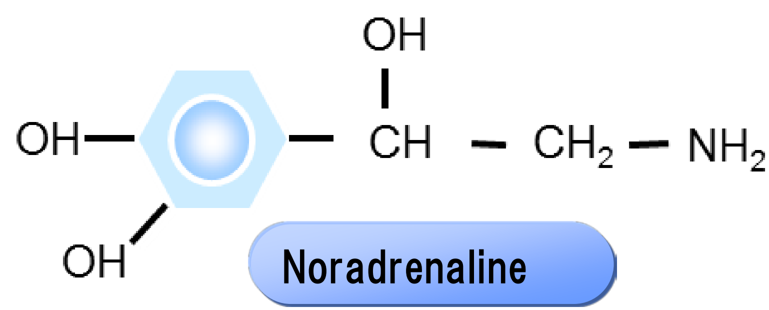
Neuropharmachological fNIRS on ADHD

Are they different in cortical representation?
Can they be distinguished?

Medication for ADHD Children

・Drug treatment is widely practiced:
  -methylphenidate (MPH), dopamine agonist
  -atomoxetine (ATX), noradrenaline agonist
・MPH and ATX inhibit catecholamine reuptake by blocking their transporters
・Each of MPH and ATX is effective for 70% of ADHD children
・High discontinuous rate is problem (30% or more)
  -mainly due to harmful rumors
・Biological marker for objectively assessing their efficacy
fNIRS may be useful

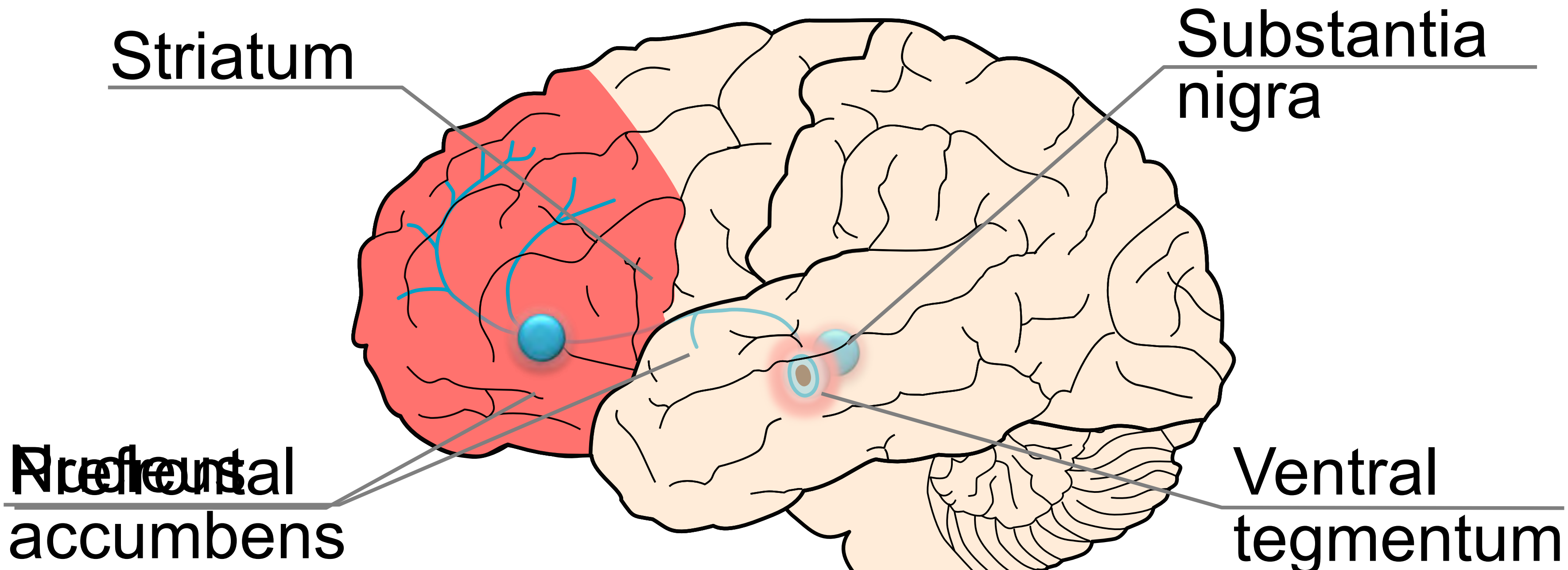




Gatley. et al., Life Sci. (1996) , Aron & Poldrack, Biol. Psychiatr. (2005)

Dopaminergic pathways

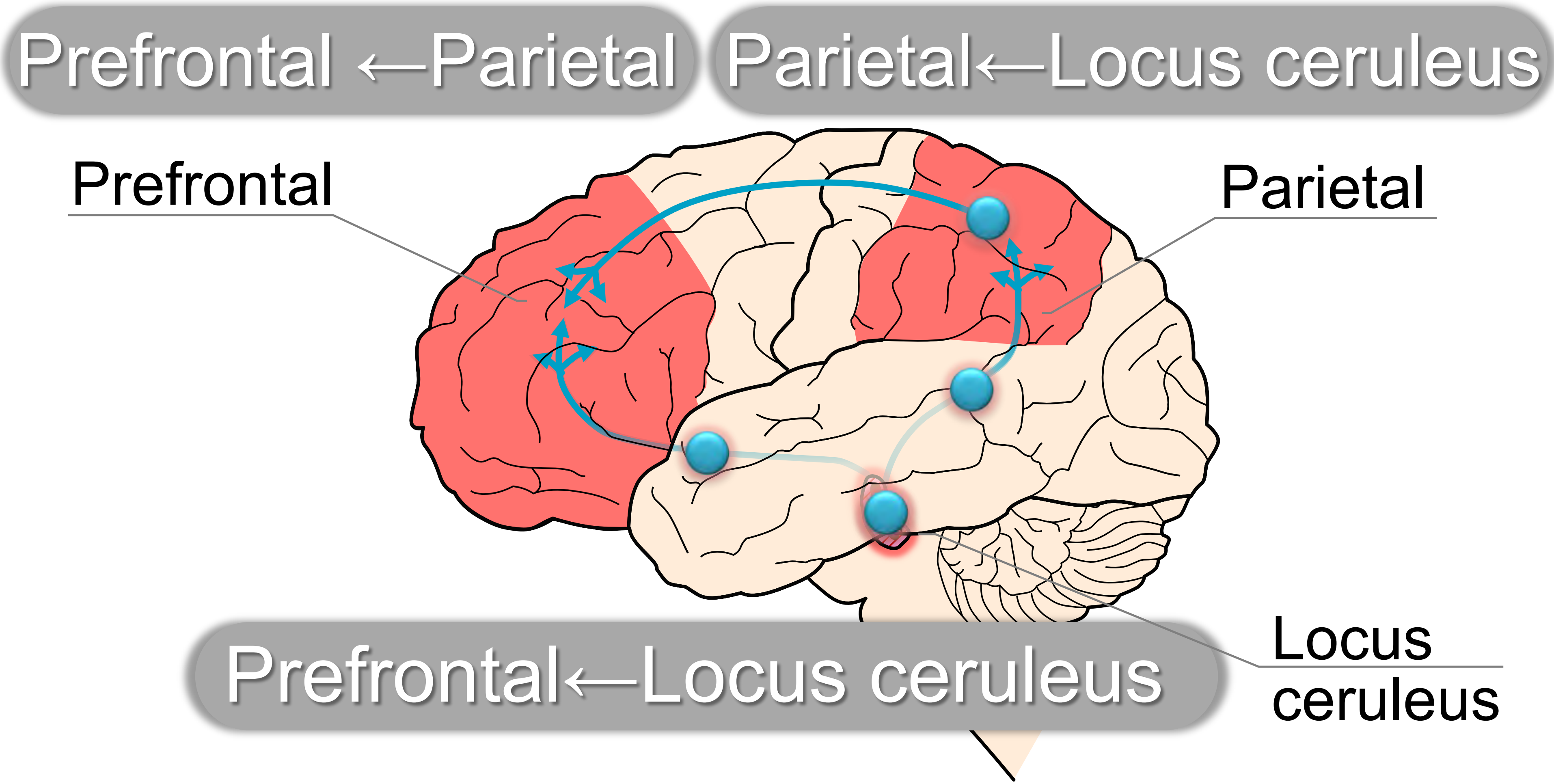
Striatum←Substantia nigra



Nucleus accumbens←Ventral tegmentum

Hyman EH & Nestler EJ.: The Molecular Foundations of Psychiatry: 74-79, 1993.

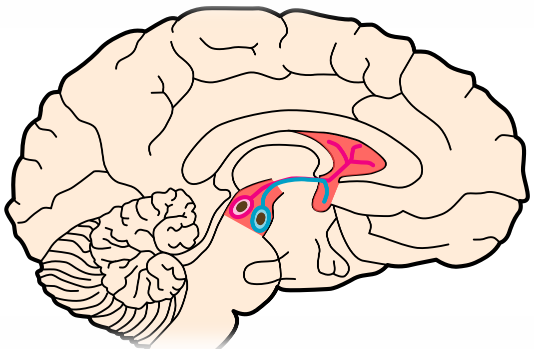
Noradrenergic pathways



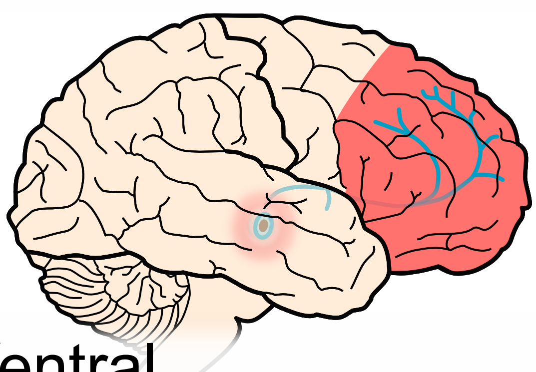
Hyman EH & Nestler EJ.: The Molecular Foundations of Psychiatry: 74-79, 1993.

DA pathways

Substantia nigra→Striatum



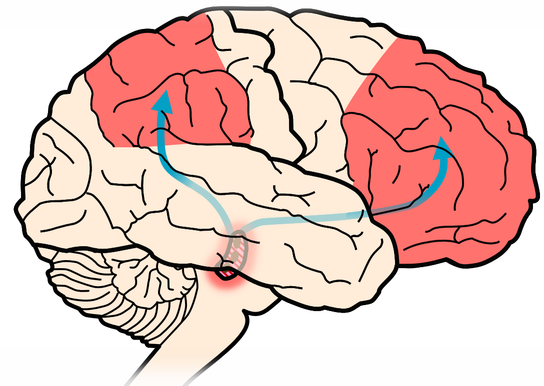
Ventral tegmentam → Nucleus accumbens



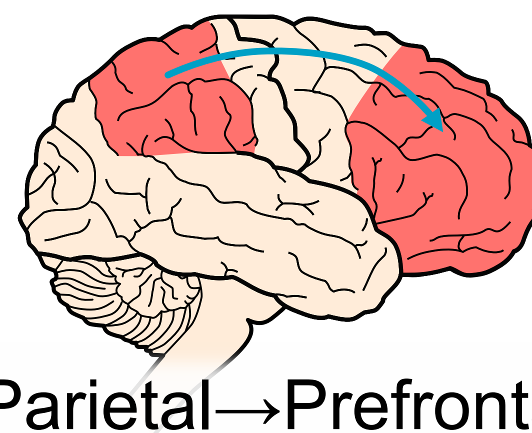
Ventral tegmentam → Prefrontal

NA pathways

Locus ceruleus→Parietal

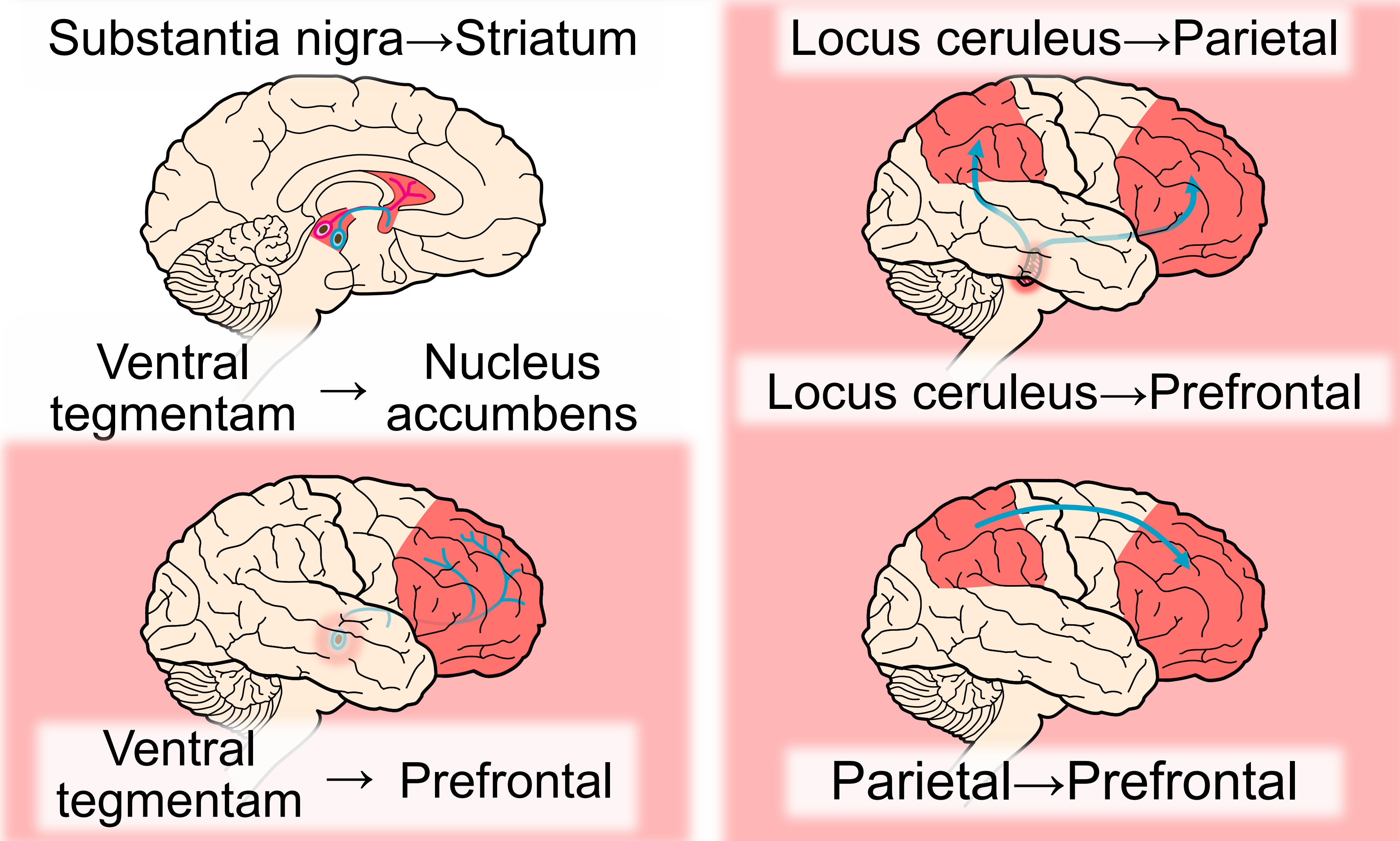


Locus ceruleus→Prefrontal



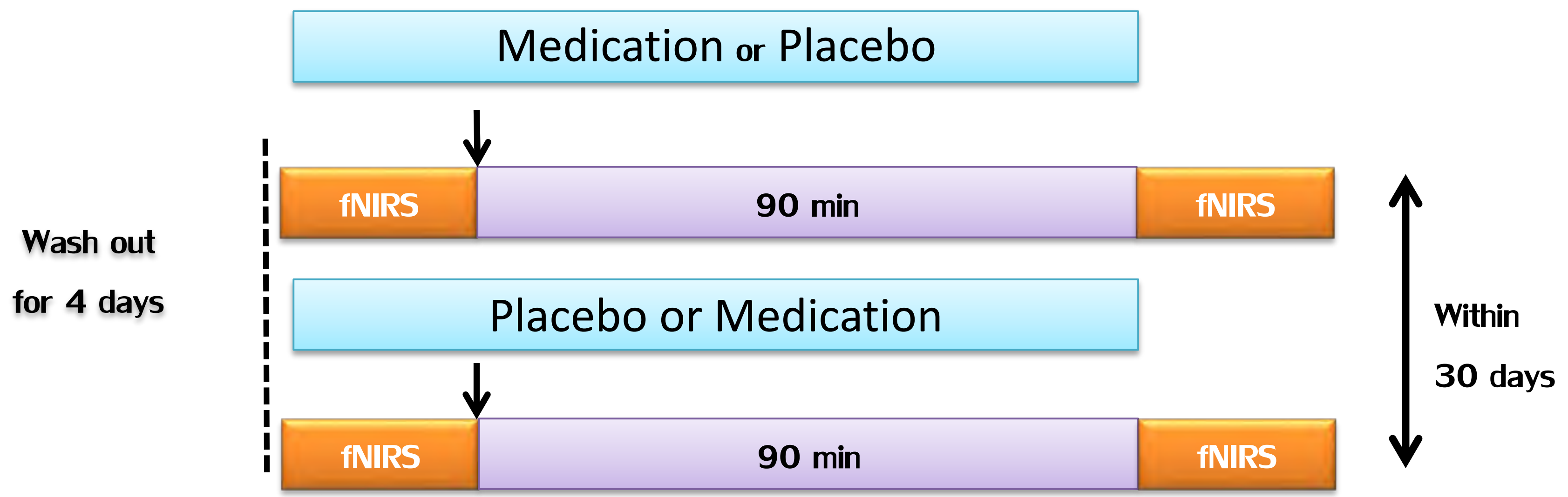
Parietal→Prefrontal

fNIRS system covers Cerebral cortex



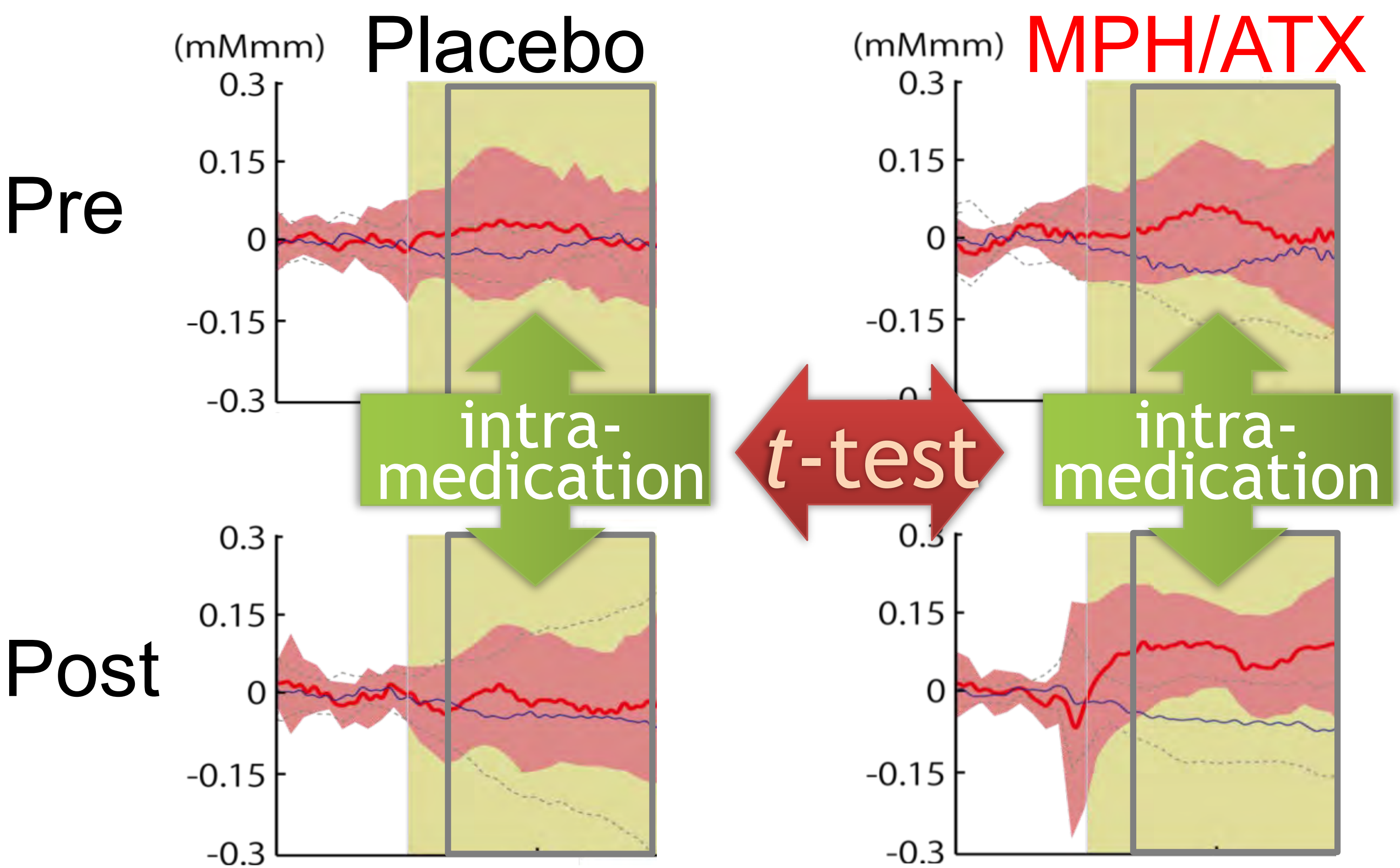
Study design for neuropharmacological assessment of ADHD children

・Assessing effects of MPH or ATX
・On inhibitory (Go/nogo task) or attentional (oddball task) controls
・Randomized, double-blind, placebo-controlled, crossover design
・6-14 years ADHD children (N=69 in total)
・Comparison with unmedicated, age- sex-matched typically-developing control subjects



Neuropharmacological assessment: comparison

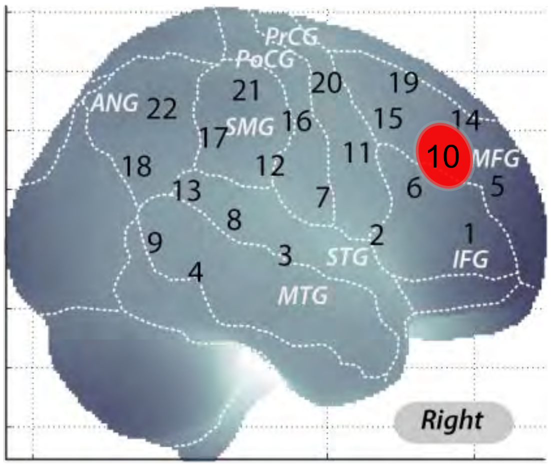
【Inter-medication contrast 】:
Intra-medication vs. intra-placebo



Neuropharmacological assessment: Results

MPH

ADHD N=16

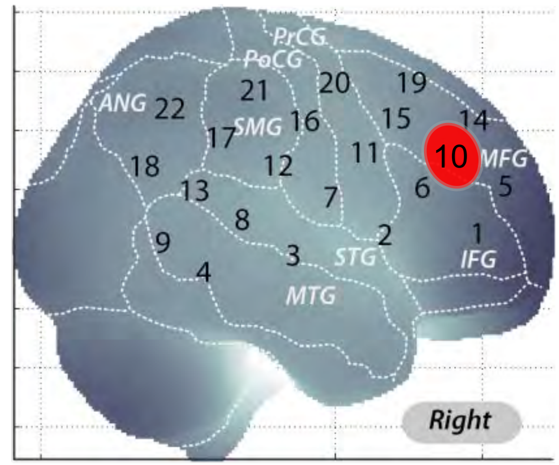


Effect size **0.95**

Monden et al., NeuroImage:Clin (2012)

ATX

ADHD N=16



Effect size **0.68**

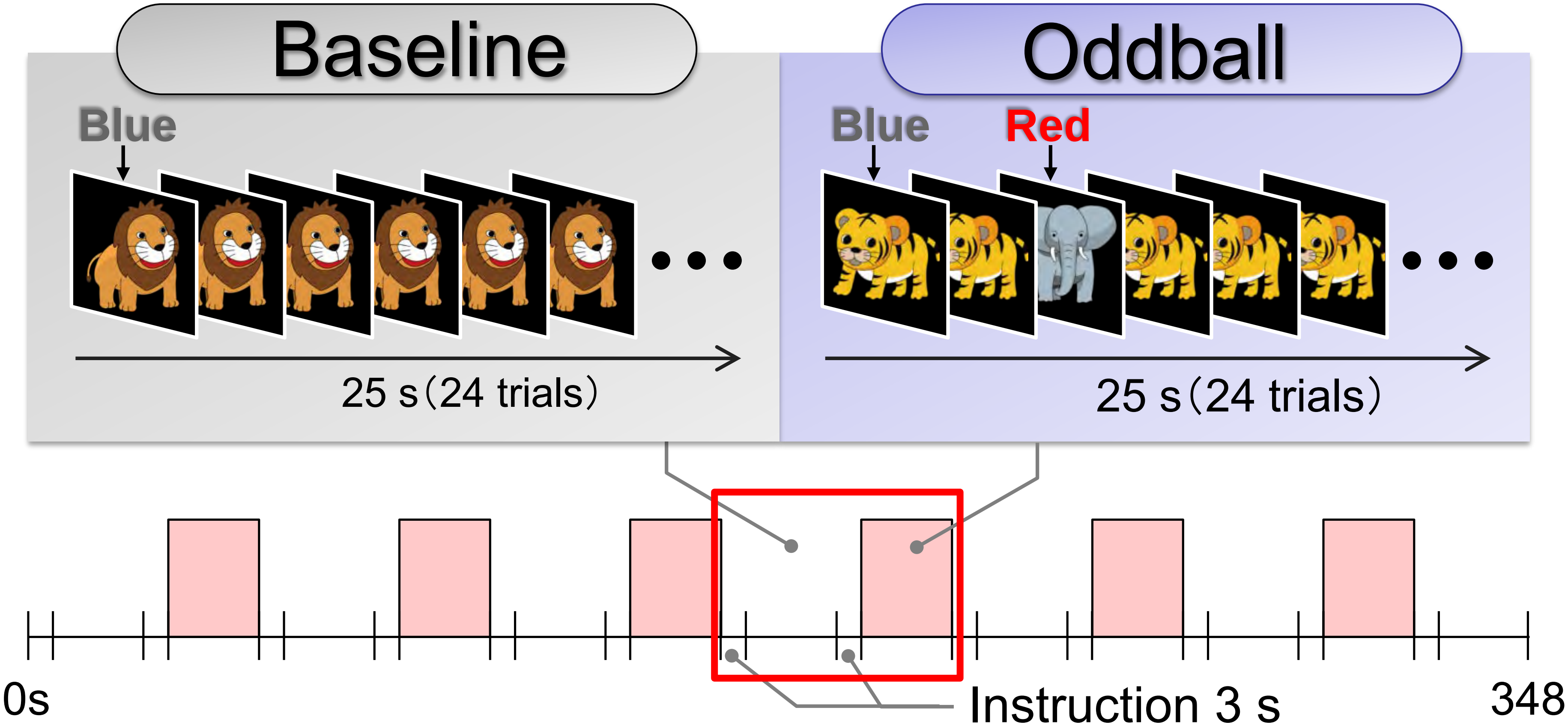
Nagashima et al., Neurophotonics (2014a)

Activation was reduced in pre-medicated ADHD and normalized by MPH and ATX.
rPFC activation = disease state marker

Another aspect of ADHD is made visible

fNIRS-based neuropharmacology is also (or more) effective for assessing attentional dysfunction

Oddball task to assess selective attention



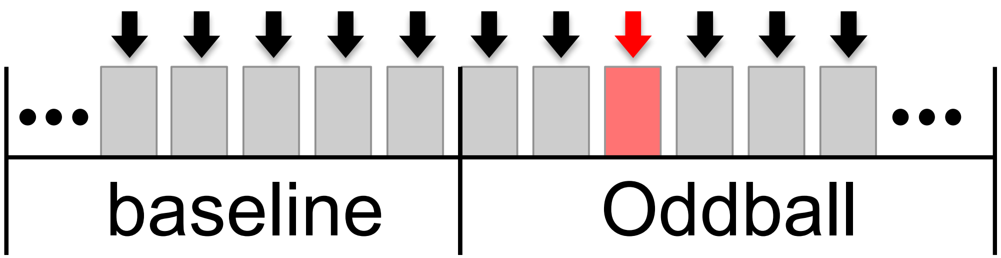
Tiger: Press the blue button

Elephant: Press the red button =target detection

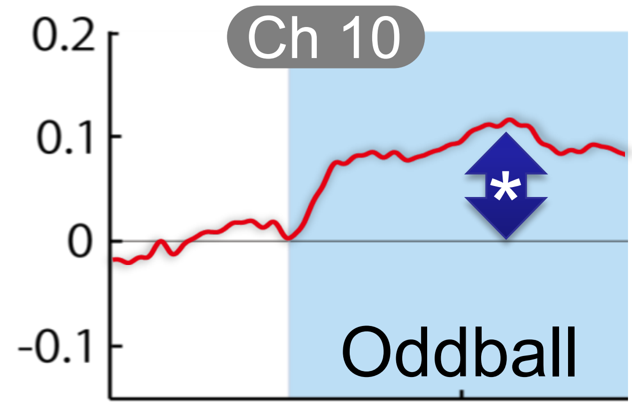
Cortical activation

TD control（n=22）

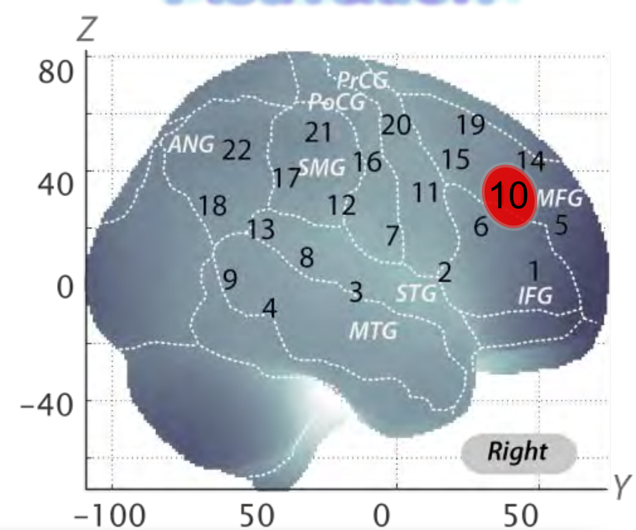
Nagashima et al., Neurophotonics (2014a)



	ES	P
Ch 10	0.98	0.0002



Basal level / Activation

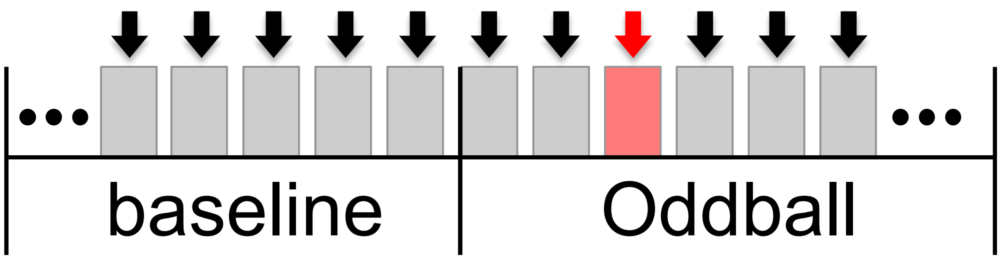


Activation in the right IFG/MFG

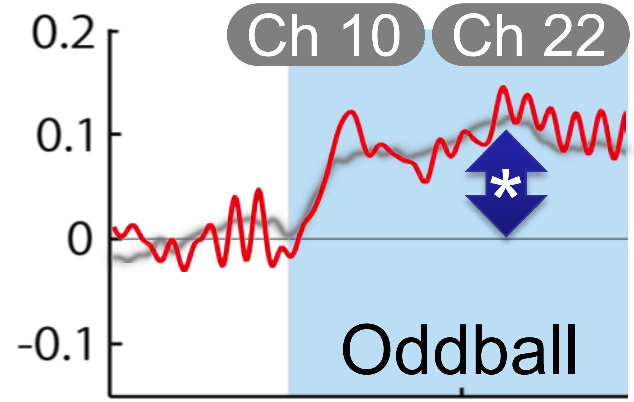
Cortical activation

TD control（n=22）

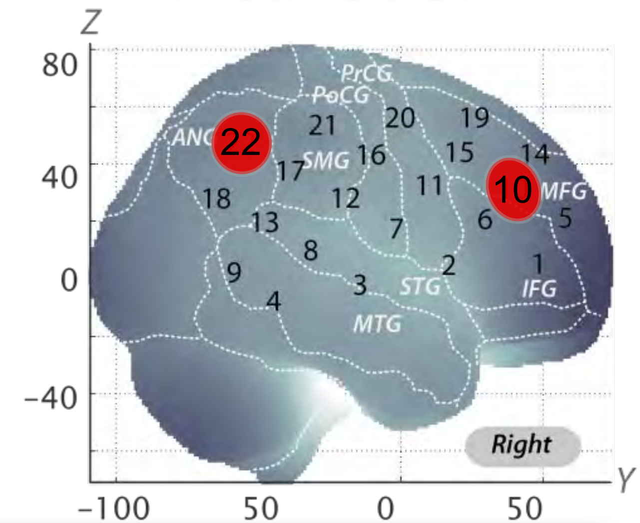
Nagashima et al., Neurophotonics (2014a）



	ES	P
Ch 10	0.98	0.0002
Ch 22	1.01	0.0001



Activation

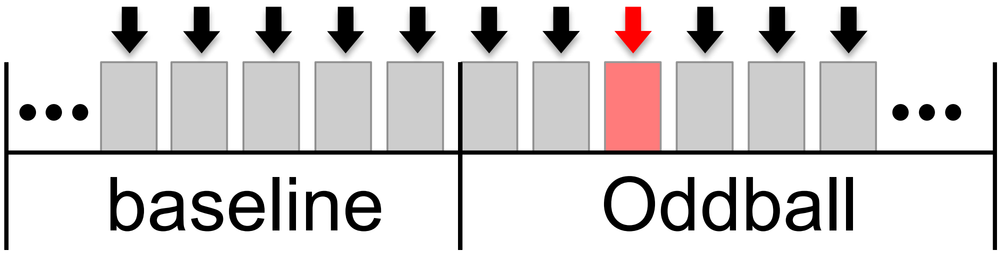


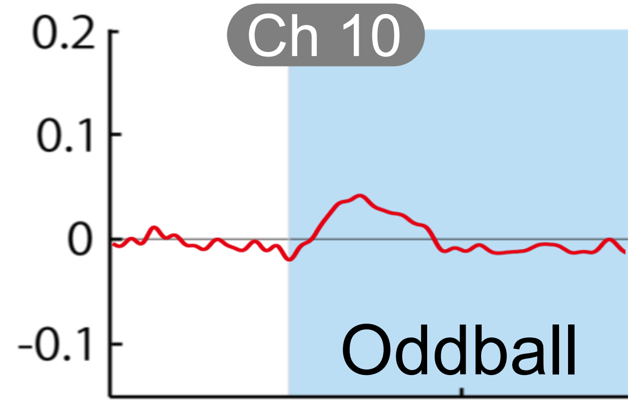
Activation in the right IFG/MFG +Inferior parietal cortex

Activation, oddball task

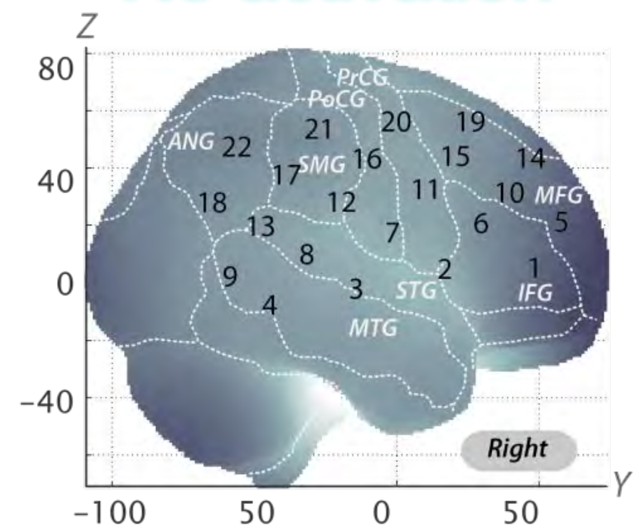
ADHD（n=22）

Nagashima et al., Neurophotonics (2014a）





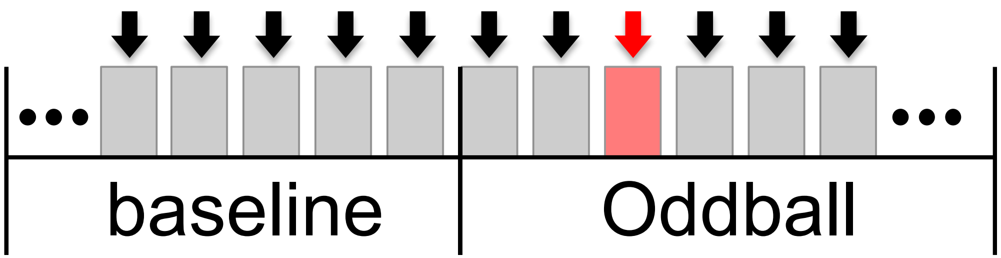
No activation



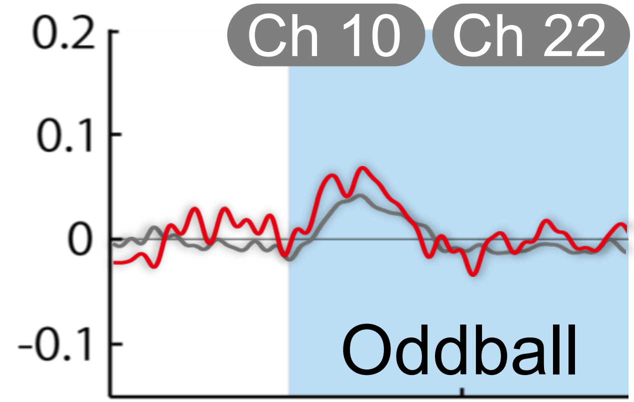
Activation, oddball task

ADHD (n=22)

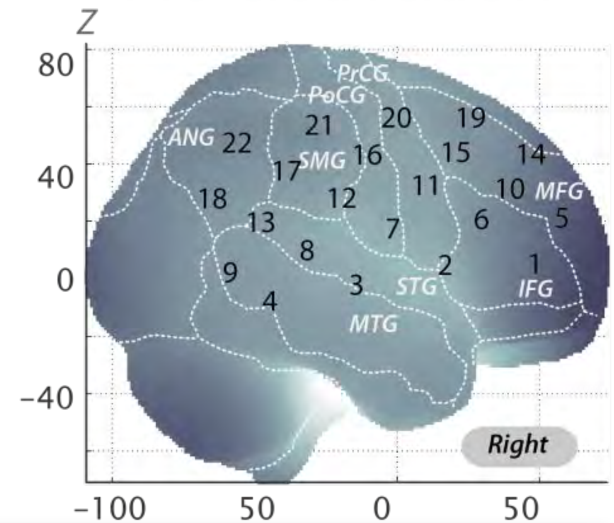
Nagashima et al., Neurophotonics (2014a)



	ES	P
Ch 10	0.21	0.9242
Ch 22	0.02	0.9351



No activation



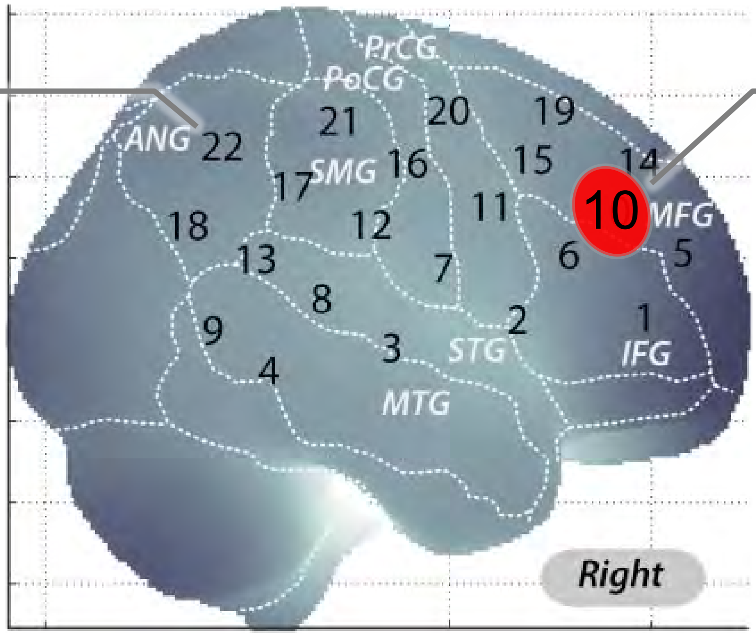
Pre-medicated ADHD children exhibited reduced brain activation in the right IFG/MFG & IPC

Effects of MPH medication: oddball

Ch 22

Effect size
-0.05

P value
0.8108



Ch 10

Effect size
0.70

P value
0.0036

Nagashima et al., Neurophotonics (2014a)

Reduced PFC activation in pre-medicated ADHD was normalized by MPH but not for IPC

Effects of ATX medication: oddball

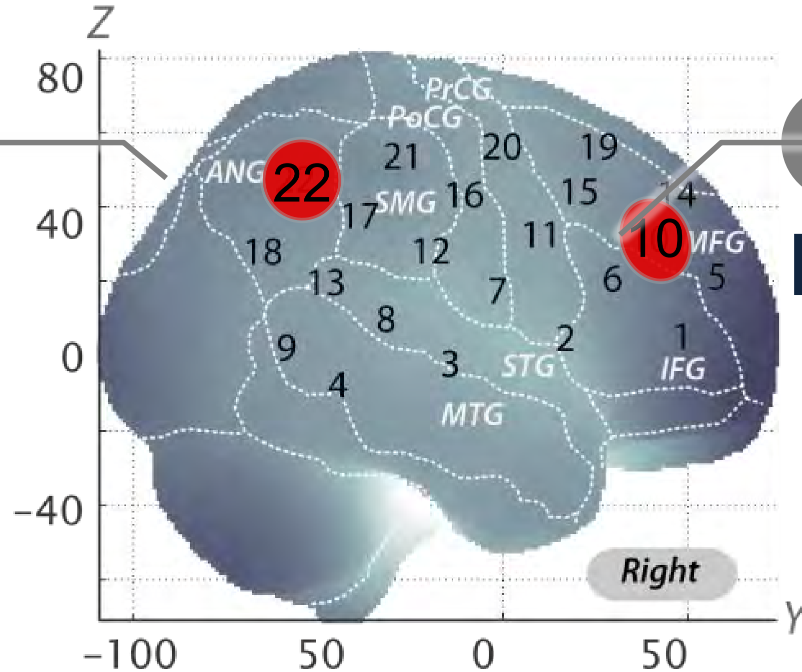
Ch 22

Effect size

0.63

P value

0.028



Ch 10

Effect size

1.03

P value

0.001

Nagashima et al., Neurophotonics (2014b)

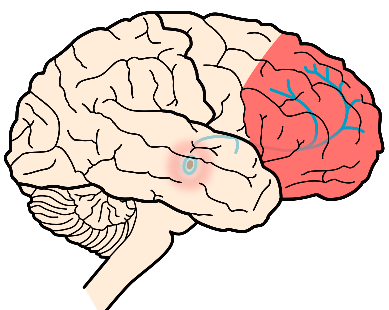
Reduced PFC and IPC activation in pre-medicated ADHD were BOTH normalized by ATX

Interpretation

MPH

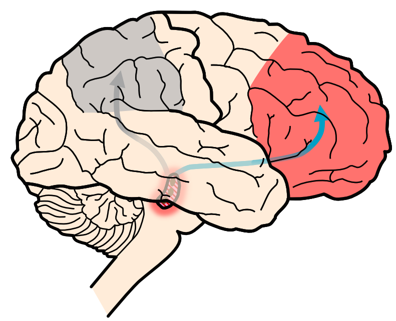
ATX

Dopamine sys.



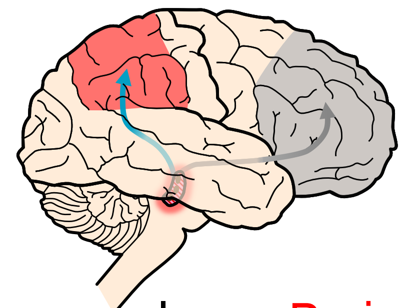
Ventral tegmentam - PFC

Noradrenaline sys.

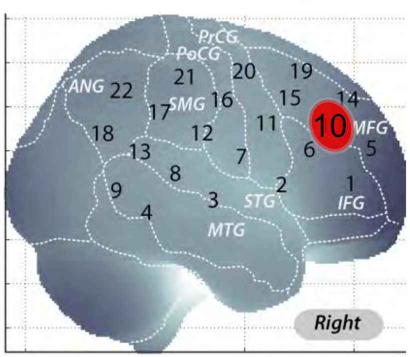


Locus ceruleus - PFC

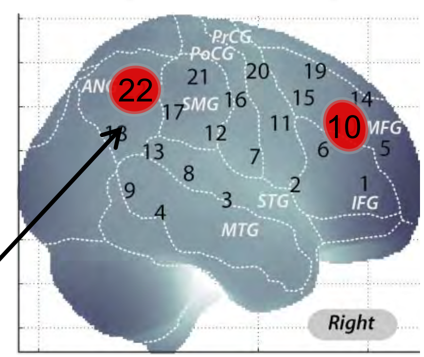
Noradrenaline sys.



Locus ceruleus - Parietal



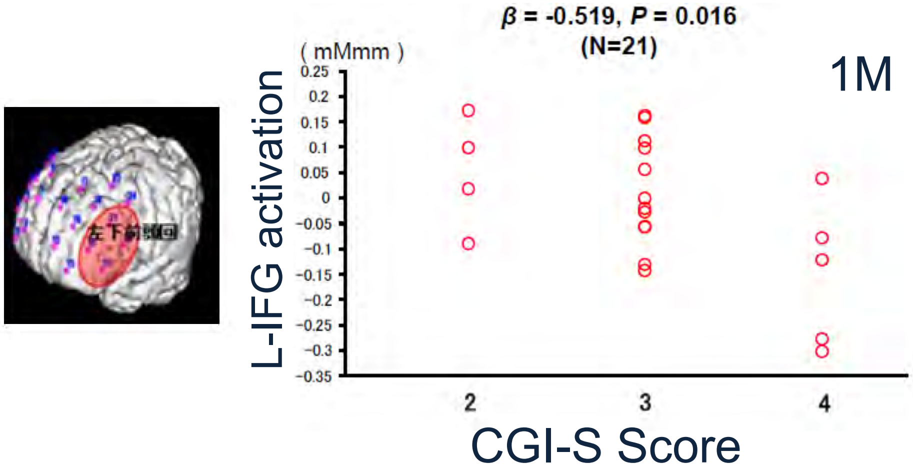
PFC
functional
normalization



Not recruited for
inhibitory control

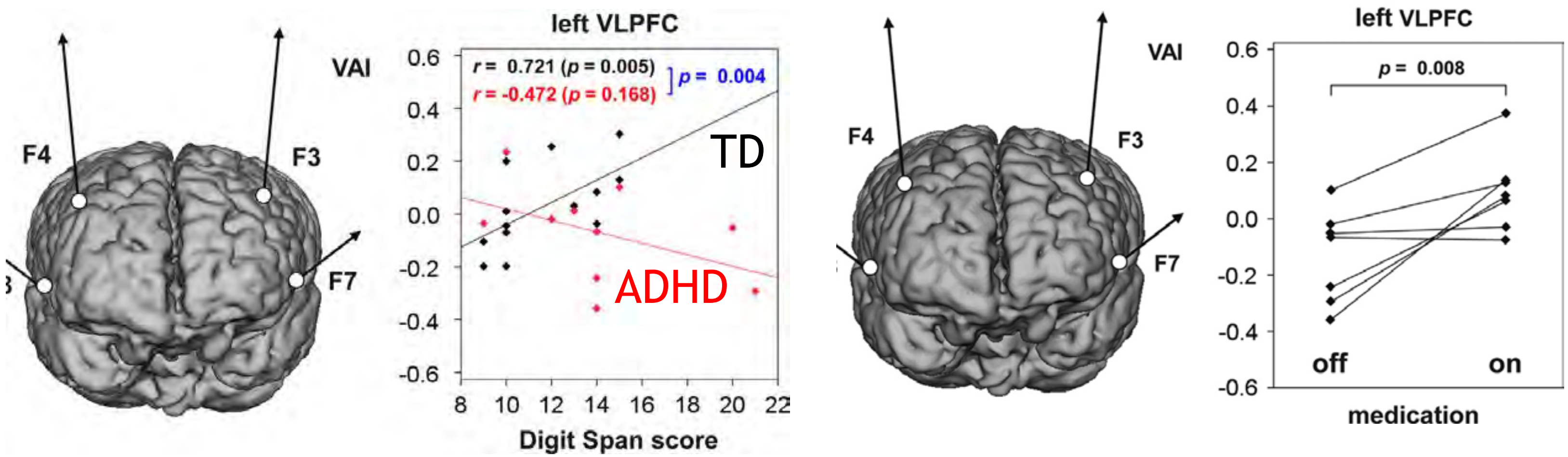
PFC& parietal
functional
normalization

Other neuropharmachological studies



L-IFG activation for stop-signal task (double-blind, placebo-controled, crossover design) is a good predictor of MPH treatment effects on ADHD children after 1M and 1Y.

(Ishii-Takahashi et al. Neuropsychopharmachol, 2015)



Shift to visual from phonological WM (VAI) is visible in VLPFC of TD but not in that of ADHD.

This is recovered by MPH administration.

(Sanefuji et al. NIMG, 2014)

Should be assessed from various facets

Conclusion

fNIRS can detect task-specific, regionally differential neuropharmacological effects of MPH and ATX on ADHD children

- Right prefrontal and inferior parietal activation would serve as biomarkers for MPH & ATX effects
- More robust than behavioral data
- Applicable as early as 6 years old children
- Note that MPH & ATX users were assessed
  - -Not for screening purpose
  - -May be best used to increase medical compliance in ADHD treatment

Effects of drug treatment are made visible by fNIRS

Collaborators

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on behalf of RISTEX ADHD Diagnosis Consortium

Additional discussion

fNIRS-based neuropharmacology is also (or more) effective for assessing attentional dysfunction

Behavior vs Cortical response

Where is neural basis of behavior located?

Stimulus → Organism → Response

Drug administration

Physiological change reflecting health state

Behavioral change

Neural basis of behavior

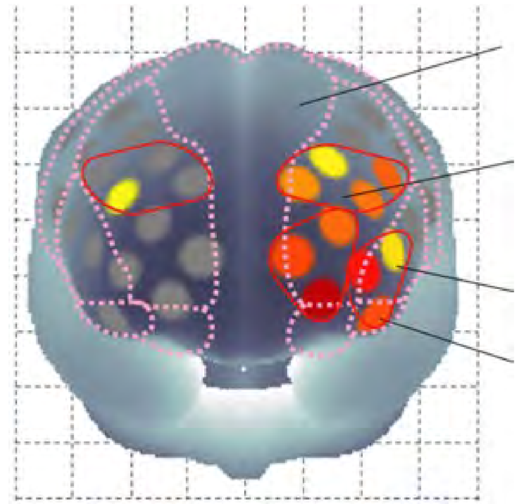
Is there one-to-one relation between behavior and its neural basis?

Example of a happy case

Stroop test

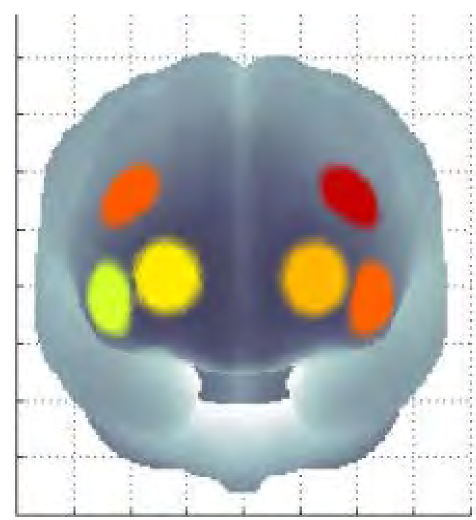
Incongruent	Neutral
Green Blue	XXXX Red

Incongruent - Neutral
= Stroop interference



(Yanagisawa et al. NIMG 2010)

Hemispheric Asymmetry Reduction
in OLDer adults (HAROLD)



(Hyodo et al. Neurobiol. Aging 2012)

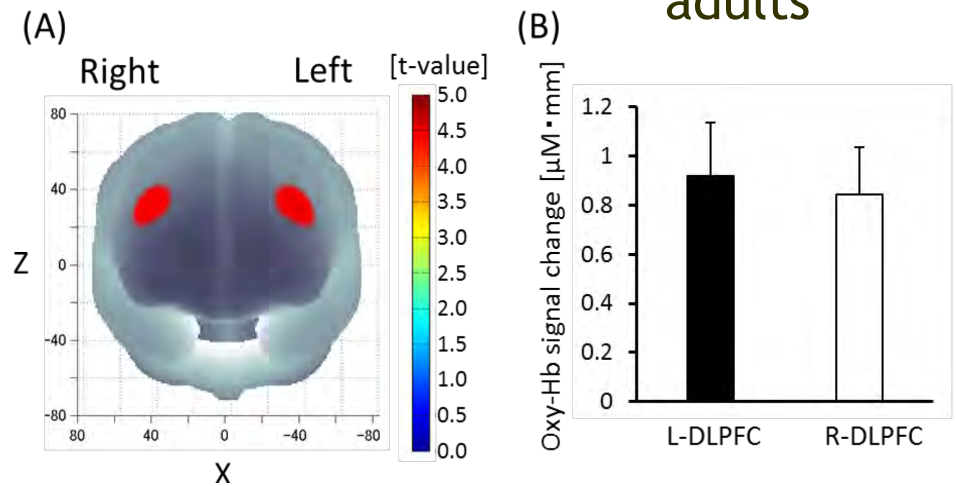
What affects HAROLD?

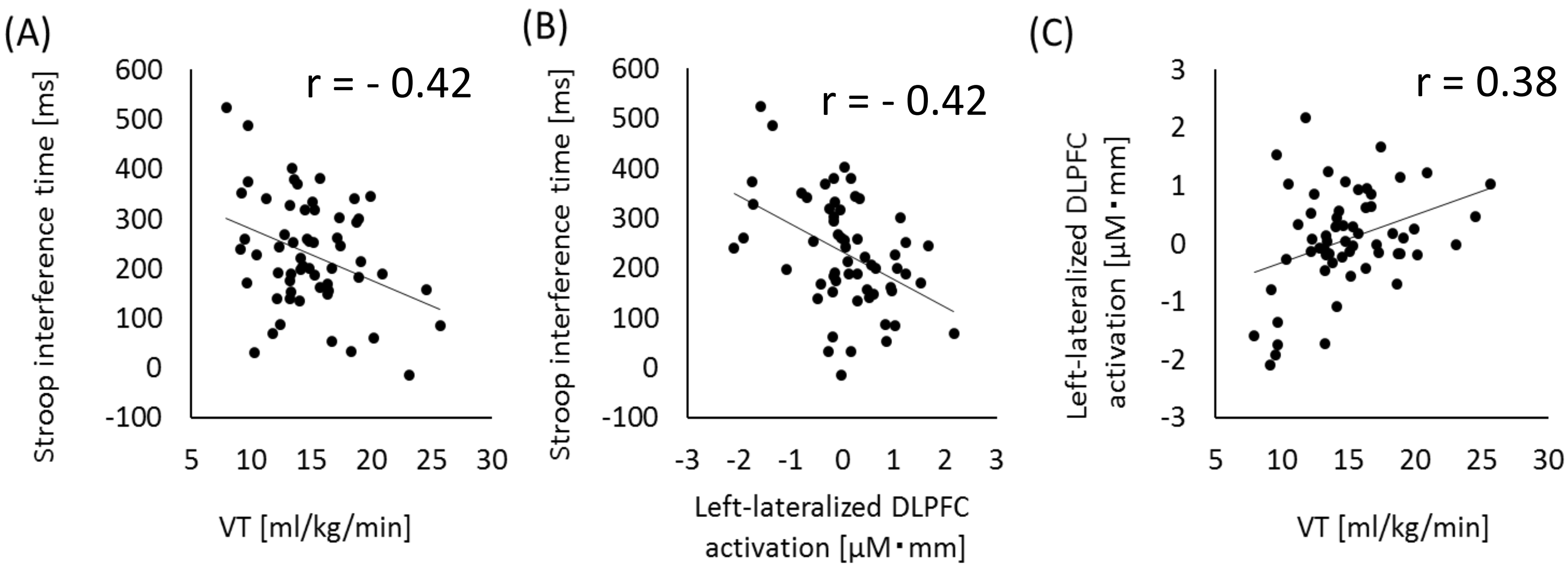
Example of a happy case

DLPFC
Young adults

Ventilation threshold test: Athletic ability

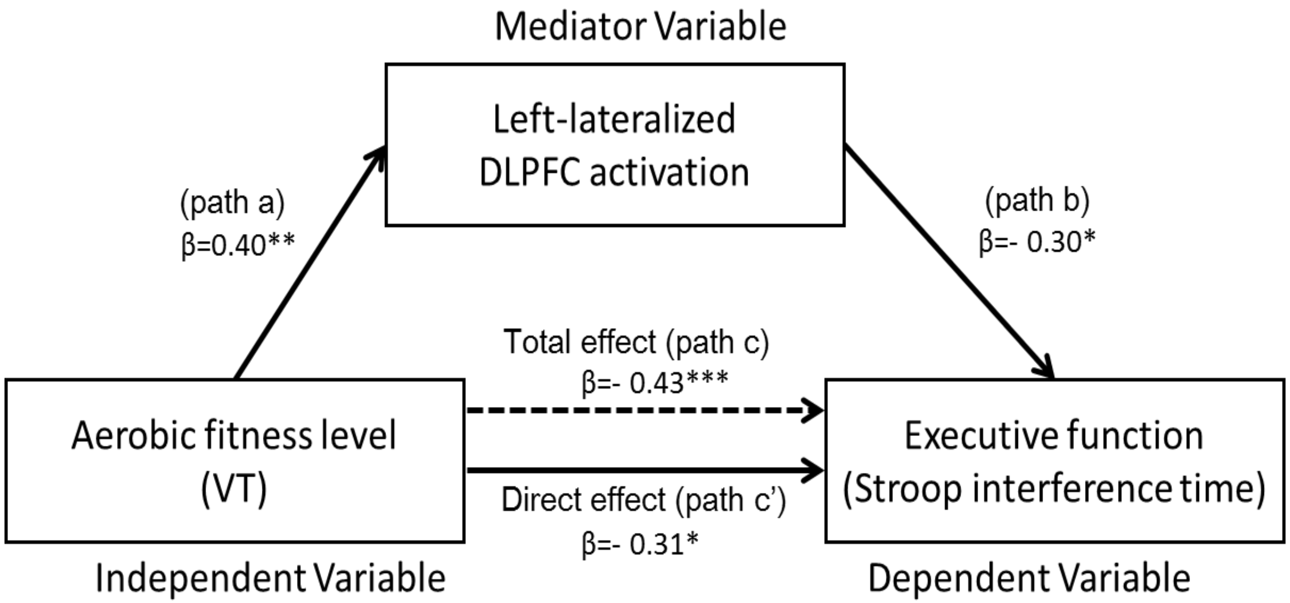
Stroop test: Cognitive ability





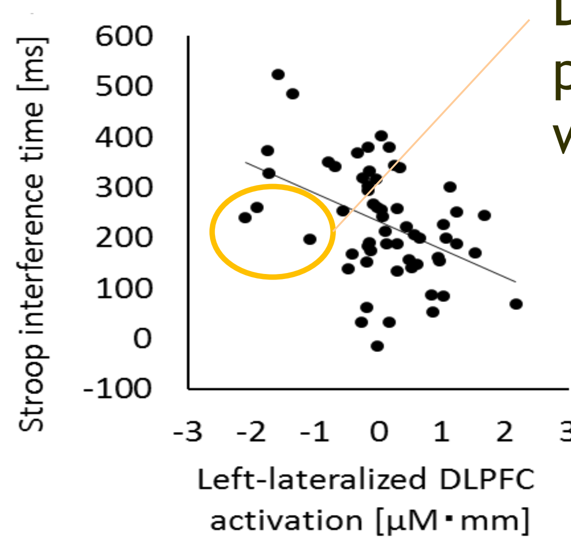
(Hyodo et al. NIMG (2015)

Example of a happy case



Behavioral performance is better interpreted via cortical activation pattern

-Association between cortical activation and behavior is not 100%
-Statement, "neural basis of behavior" is valid when |r|=1



They used right DLPFC and performed well!

Excessive reliance on behavioral parameter should be avoided