Functional Near-infrared Spectroscopy as Natural and Flexible Extension of Conventional Neuroimaging Methods: Applications in Neuropharmacological ~~and Neuromarketing~~ Studies

Ippeita Dan
on behalf of RISTEX ADHD Diagnosis Consortium

Chuo University, Tokyo, Japan

Neuropharmacology in the context of Neuroergonomics

"Neuroergonomics investigates the human brain in relation to behavioral performance in natural environments and everyday settings" Definition by Dr. Ayaz

In everyday lives, we take drugs.
Some affects brain functions, and people use them without knowing the fact
In Japan, common cold drugs typically contain
- Ephedrine: psychostimulant, uppers
- Dihydrocodeine: opiate, downers

This is how you make Japanese work hard when they have cold.

We may want to select drugs based on knowledge on how they affect cognition

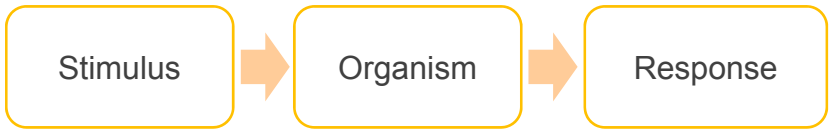
fNIRS-based Neuropharmacology

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)



Drug administration

Physiological change reflecting health state

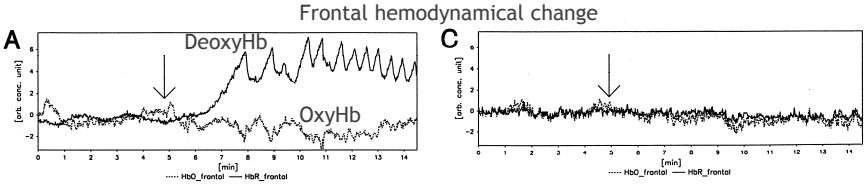
Behavioral change
and/or
Hemodynamical change to be observebed by fNIRS

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

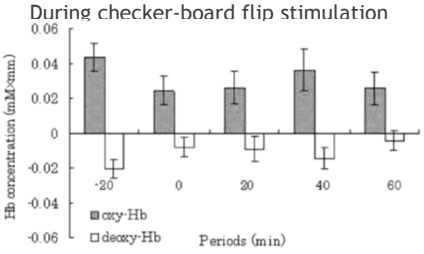
What is the source of such hemodynamic changes?
Cognitive/Perceptual?
Physiological?
Systemic?
Skin blood flow?

Second stage of neuropharmacological fNIRS

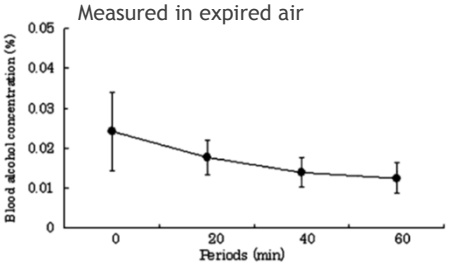
Basic concept: Administrating drug, performing a relevant task, and see what happens

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

Occipital hemodynamical change
During checker-board flip stimulation



Blood [alcohol] change
Measured in expired air



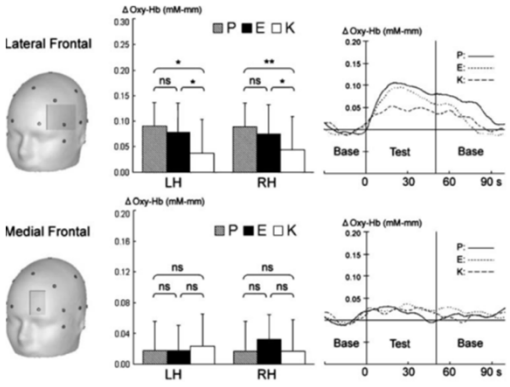
What is the source of such hemodynamic changes?
Cognitive/Perceptual? More likely
Physiological?
Systemic?
Skin blood flow?

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 the brain

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

- Often has trouble organizing tasks and activities.
- Is often forgetful in daily activities. etc.

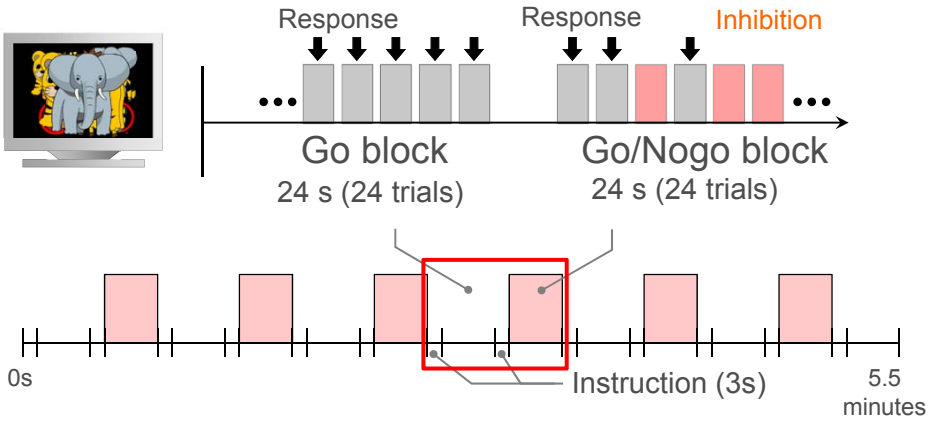
Hyperactivity and Impulsivity

- Is often "on the go" acting as if "driven by a motor".
- Often talks excessively. etc.

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

Objective biomarker is necessary
What about behavior?

Go/Nogo task to measure inhibition



Response: Press the button

Inhibition : Not to press the button

Monden et al., 2012

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

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

Walk and Run

Miyai et al., NeuroImage (2001)

Peel an apple

Okamoto et al., NeuroImage (2004)

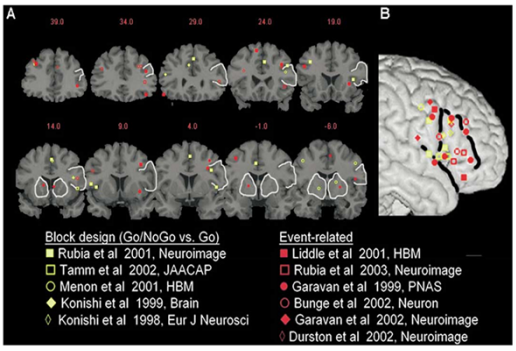
Fly an airplane

Gateaum Ayaz & Dehais Front Hum Neurosci (2018)

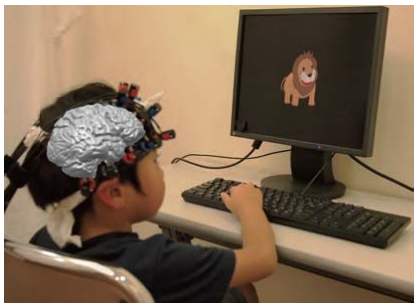
ADHD vs TD

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

Cortical target for Go/Nogo task

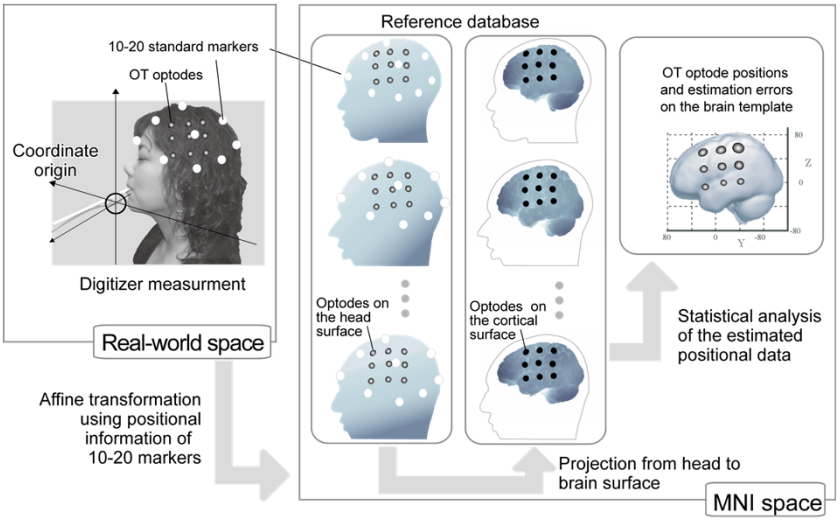


Aron et al., 2005



Where in brain?

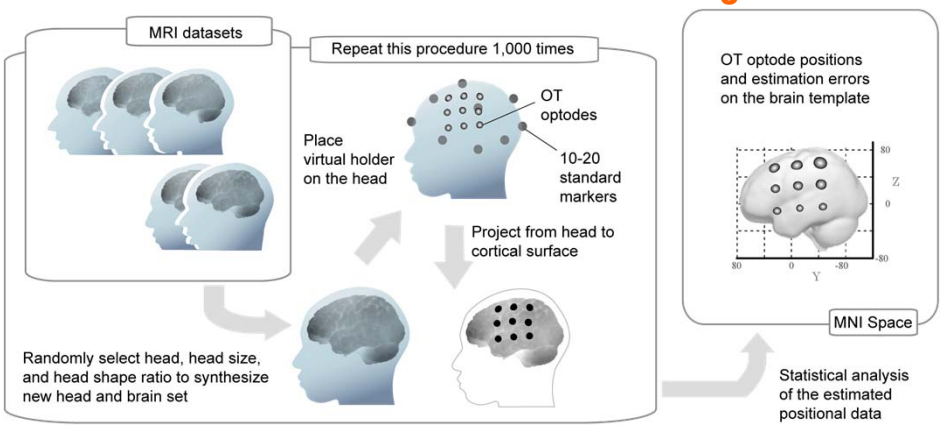
Probabilistic registration using reference database without MRI & with 3D-digitizer



In HOMER2, SPM for fNIRS, POTATO

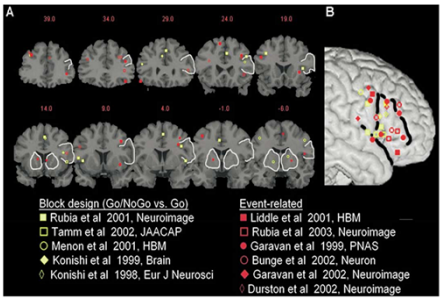
Singh AK et al.
NeuroImage 27,842-851 (2005)

Virtual registration using reference database without MRI & without 3D-digitizer

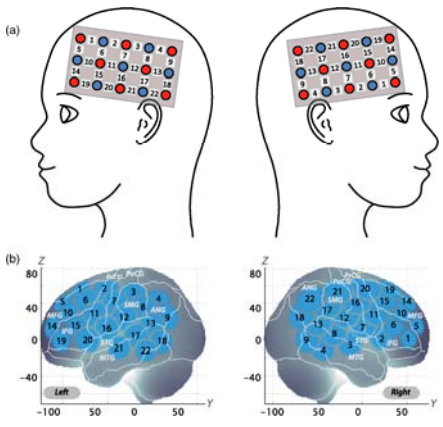


Tsuzuki, D et al. ***NeuroImage*** 34, 1600-1611 (2007)

fNIRS probe placement for Go/Nogo task

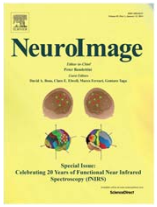


Aron et al., 2005

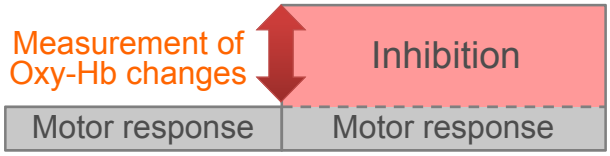


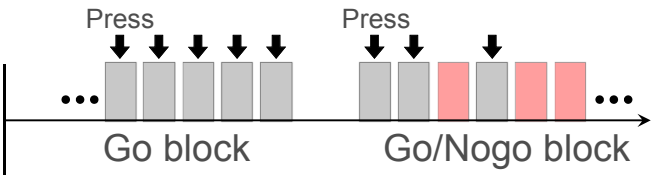
・Channel positions are probabilistically registered to MNI space using 3D digitizer
・MFG, IFG, SMG, AnG are covered

Tsuzuki &Dan, NeuroImage (2014)



fNIRS analysis during Go/Nogo tasks





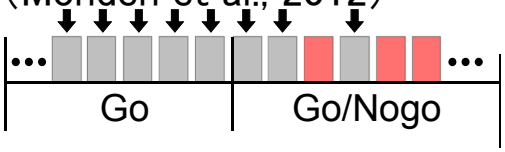
Oxy-Hb difference between Go/Nogo and Go blocks is assessed

Monden et al., 2012

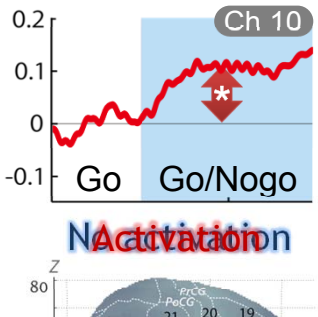
Cortical activation

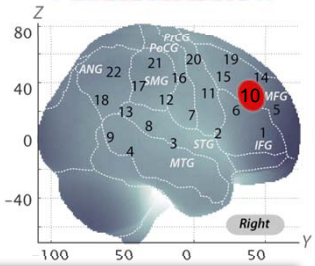
TD control (n=16)

(Monden et al., 2012)



	ES	*P*
Ch 10	1.15	0.0003





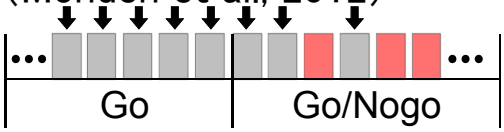
Control subjects exhibited significant brain activation in the right IFG/MFG

Monden et al., 2012

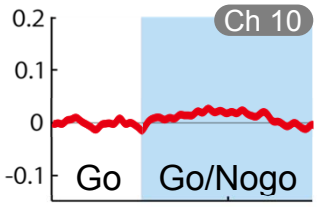
Cortical activation

ADHD (n=16, DSM-IV)

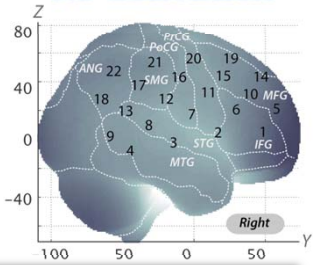
(Monden et al., 2012)



	ES	*P*
Ch 10	0.01	0.900



No activation



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

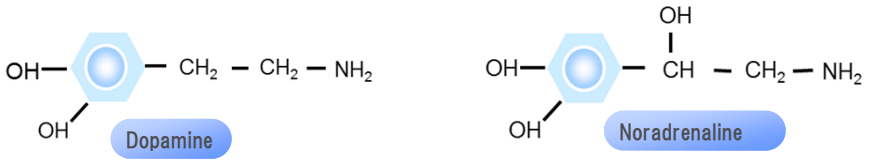
Monden et al., 2012

Neuropharmachological fNIRS on ADHD

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

Medication for ADHD Children

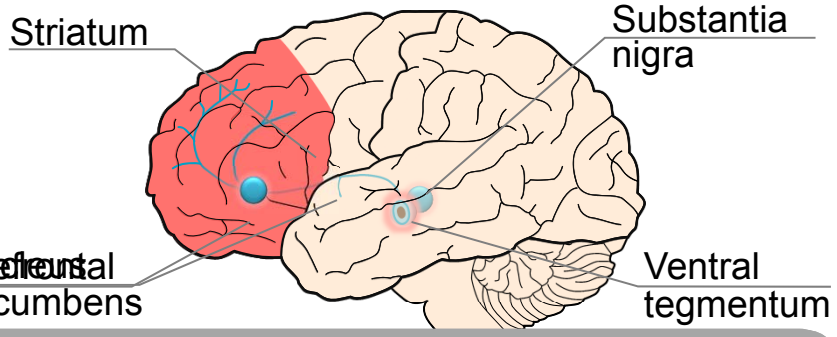
- Drug treatment is widely practiced:
  - -methylphenidate (MPH), dopamine agonist
  - -atomoxetine (ATX), noradrenaline agonist
    - Along with Amphetamines, Methamphetamine, Clonidine, Guanfacine
- Each of MPH and ATX is effective for 70% of ADHD children
- High discontinuous rate is problem (30% or more)
  - -mainly due to harmful rumors
  - -medical compliance is important
- Need biological marker for objectively assessing their efficacy
- fNIRS may be useful for assessing their effects



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

Dopaminergic pathways

Striatum←Substantia nigra



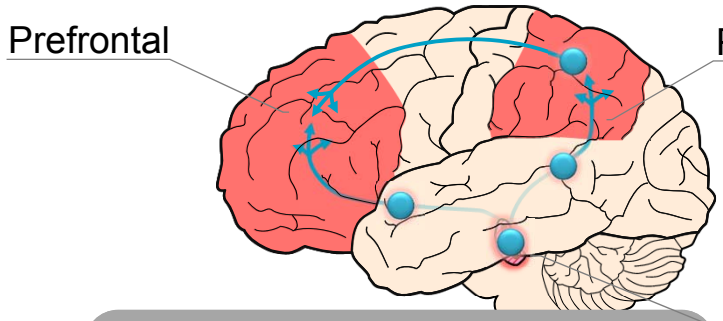
Nucleus accumbens←Ventral tegmentum

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

Noradrenergic pathways

Prefrontal ←Parietal

Parietal←Locus ceruleus



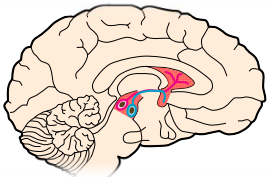
Prefrontal←Locus ceruleus

Locus ceruleus

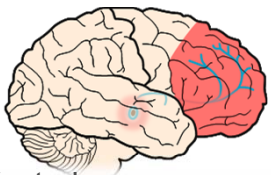
Hyman EH & Nestler EJ.: The Molecular Foundations of Psychiatry: 74-79, 1993.

DA pathways

Substantia nigra→Striatum



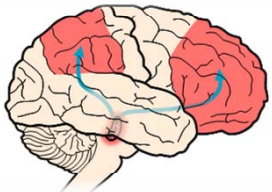
Ventral tegmentam → Nucleus accumbens



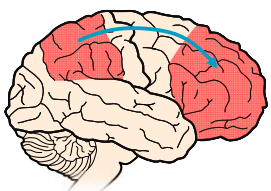
Ventral tegmentam → Prefrontal

NA pathways

Locus ceruleus→Parietal



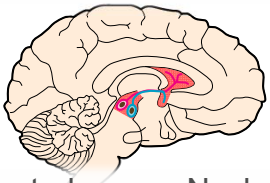
Locus ceruleus→Prefrontal



Parietal→Prefrontal

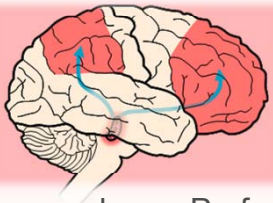
fNIRS system covers Cerebral cortex

Substantia nigra→Striatum

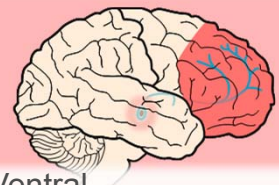


Ventral tegmentam → Nucleus accumbens

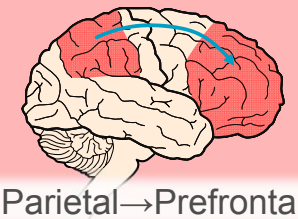
Locus ceruleus→Parietal



Locus ceruleus→Prefrontal



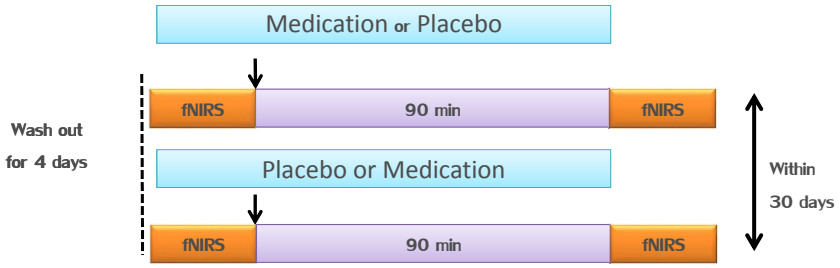
Ventral tegmentam → Prefrontal



Parietal→Prefrontal

Study design for neuropharmachological assessment of ADHD children

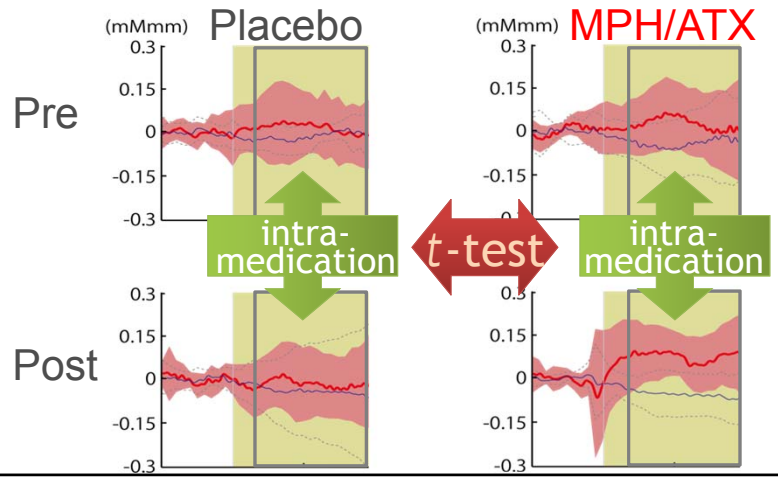
- Assessing effects of MPH or ATX
- On inhibitory (Go/nogo task) or attentional (oddball task) controls
- Randomized, double-blind, placebo-controlled, crossover design
- 6-14 years ADHD children (N=69 in total)
- Comparison with unmedicated, age- sex-matched typically-developing control subjects



Neuropharmacological assessment: comparison

Inter-medication contrast : without placebo effects

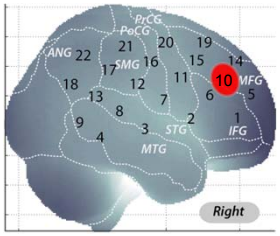
Intra-medication vs. intra-placebo



Neuropharmacological assessment: Results

MPH

ADHD N=16

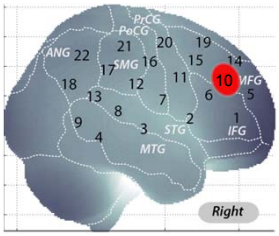


Effect size **0.95**

Monden et al., NeuroImage:Clin (2012)

ATX

ADHD N=16



Effect size **0.68**

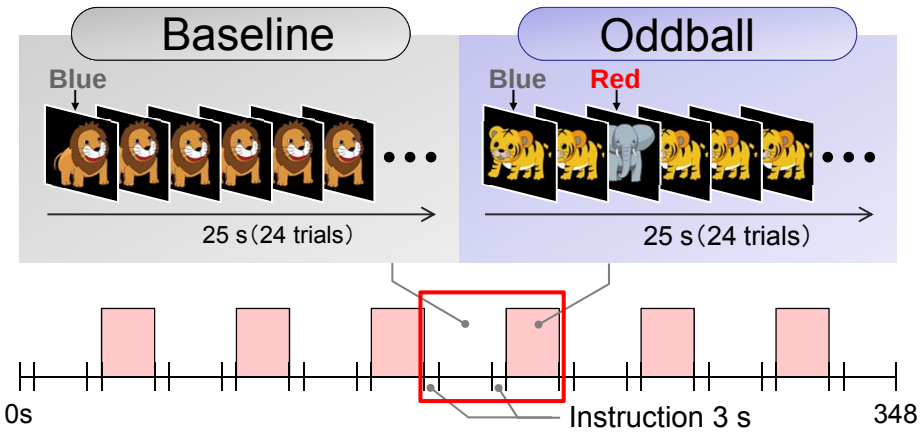
Nagashima et al., Neurophotonics (2014a)

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



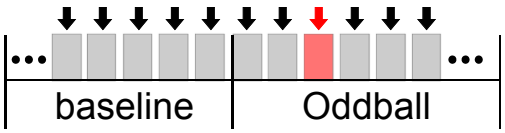
Tiger: Press the blue button

Elephant: Press the red button =target detection

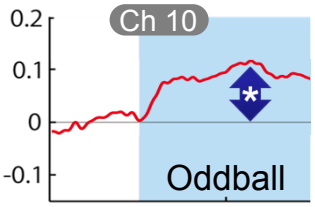
Cortical activation

TD control（n=22）

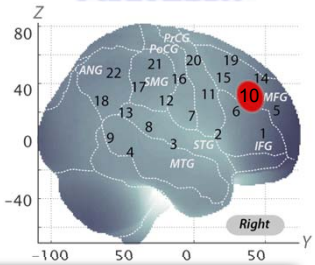
Nagashima et al., Neurophotonics (2014a)



	ES	P
Ch 10	0.98	0.0002



Basal level

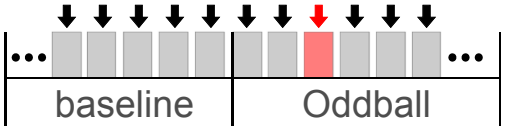


Activation in the right IFG/MFG

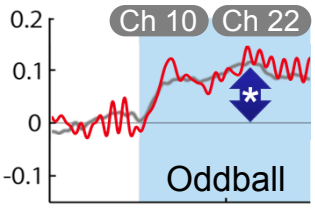
Cortical activation

TD control（n=22）

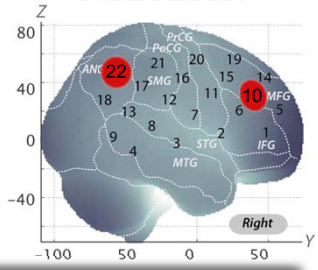
Nagashima et al., Neurophotonics (2014a)



	ES	P
Ch 10	0.98	0.0002
Ch 22	1.01	0.0001



Activation

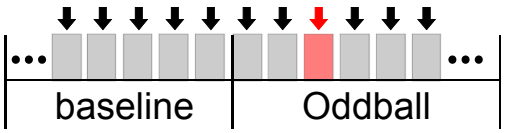


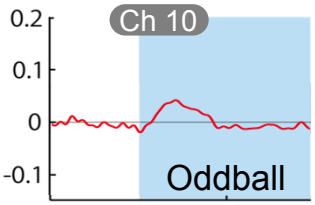
Activation in the right IFG/MFG
+Inferior parietal cortex

Activation, oddball task

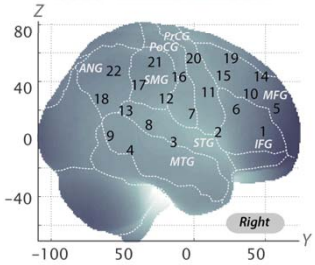
ADHD (n=22)

Nagashima et al., Neurophotonics (2014a)





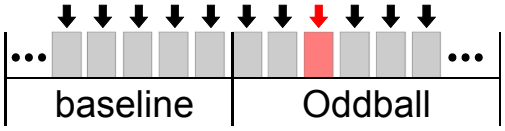
No activation



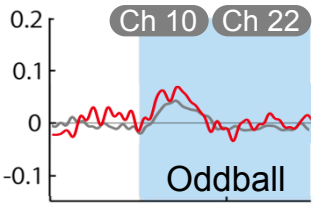
Activation, oddball task

ADHD (n=22)

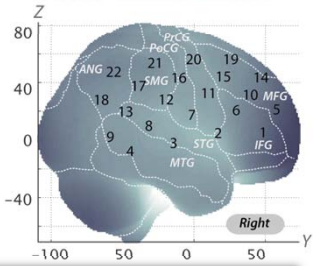
Nagashima et al., Neurophotonics (2014a)



	ES	P
Ch 10	0.21	0.9242
Ch 22	0.02	0.9351



No activation



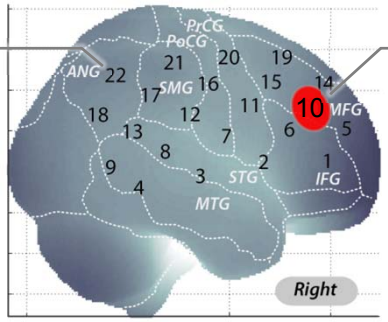
Pre-medicated ADHD children exhibited reduced brain activation in the right IFG/MFG & IPC

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)

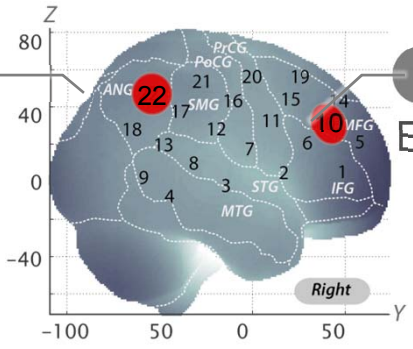
Reduced PFC activation in pre-medicated ADHD was normalized by MPH but not for IPC

Effects of ATX medication: oddball

Ch 22

Effect size
0.63

P value
0.028



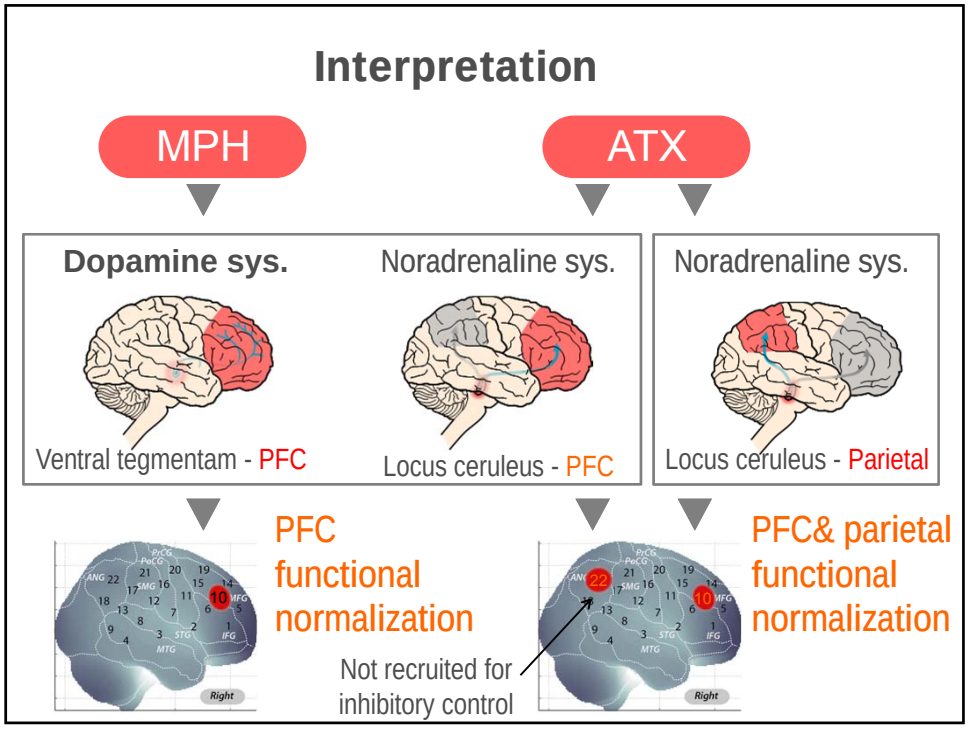
Ch 10

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

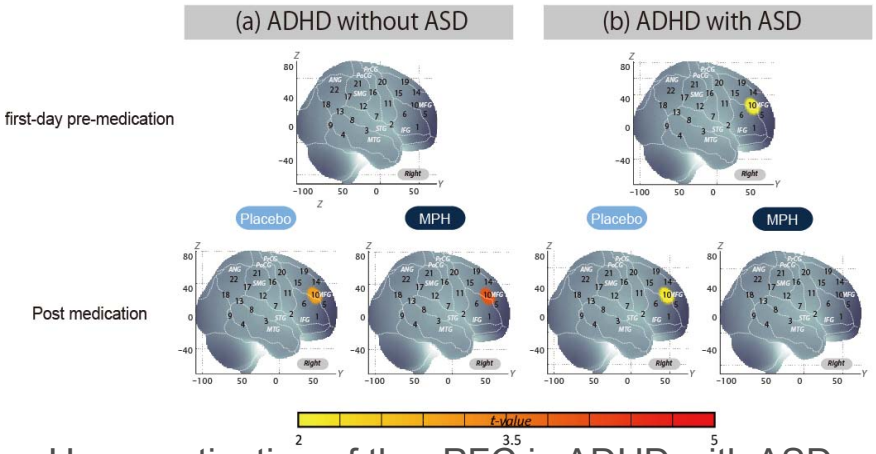


What about ADHD subtypes

fNIRS-based neuropharmacology may visualize differential activation patterns between subtypes of ADHD

ADHD is very often combined with Autism Spectrum Disorder (ASD)

Differential activation patterns between ADHD subtypes: Medication-naïve subjects



- Hyper activation of the rPFC in ADHD with ASD
- MPH may normalize the hyperactivation

Tokuda T, Ikeda T et al. **Neuropsychiatry** (2018)

Conclusion

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

- rPFC and rIPC activations would serve as biomarkers for MPH & ATX effects
- More robust than behavioral data-early indicator?
- Applicable as early as 6 years old children
- May visualize difference between ADHD subtypes
- In future, group analysis ->Individual analysis
- 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

Jichi Medical Univesity
Department of Pediatrics
Yukifumi Monden

Chuo University
Masami K Yamaguchi

Japan Women's Univ.
Dpt of Psychology
So Kanazawa

Dokkyo Medical Univ.
Ryoichi Sakuta

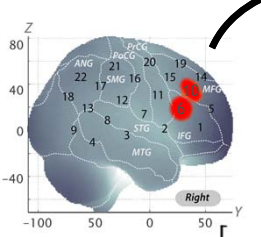
on behalf of RISTEX ADHD Diagnosis Consortium

Individual Analysis

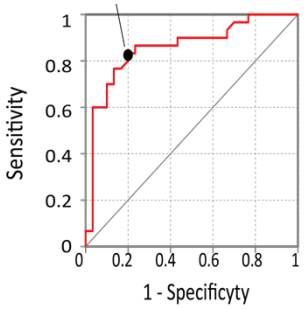
Given such marked activation, fNIRS-based diagnosis may be possible at an individual level

Individual-level analysis may be possible

Activation focus in rPFC

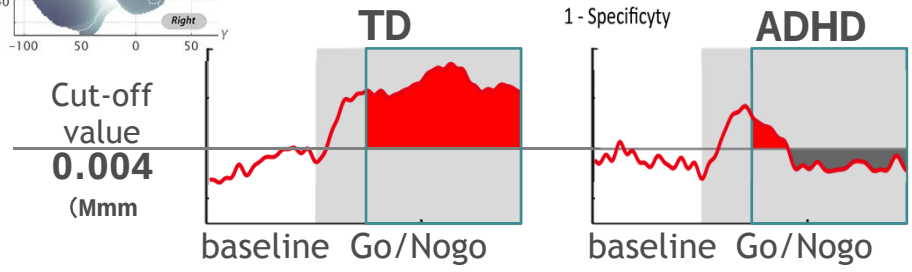


Cut-off Value: **0.004**



Sensitivity 80%
Specificity 83%

Ch6>0.004 AND Ch10>0.004 ==TD

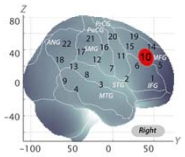


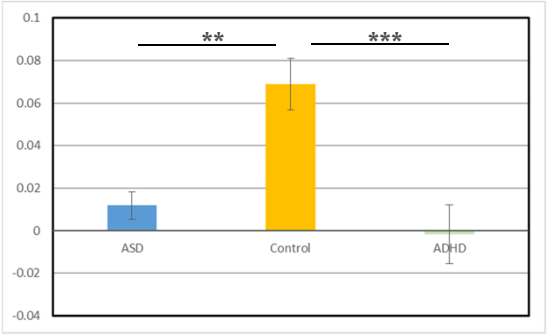
Monden et al., 2015

But, individual-level analysis may be difficult

ASD vs ADHD vs TD

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.

Ikeda, Tokuda et al. Jpn Psychol Res, in press