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)

- **Stimulus**: Drug administration
- **Organism**: Physiological change reflecting health state
- **Response**: Behavioral change and/or Hemodynamical change to be observed 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


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?
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

<table>
<thead>
<tr>
<th></th>
<th>TD</th>
<th>ADHD</th>
<th>ADHD vs TD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>RT for correct trials</td>
<td>421.4</td>
<td>57.5</td>
<td>385.5</td>
</tr>
<tr>
<td>(ms)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accuracy for go trials</td>
<td>96.5</td>
<td>5.5</td>
<td>86.2</td>
</tr>
<tr>
<td>(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accuracy for no-go</td>
<td>95.2</td>
<td>4.5</td>
<td>86.6</td>
</tr>
<tr>
<td>trials (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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, Statistical 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


Fly an airplane

Gateaum Ayaz & Dehais Front Hum Neurosci (2018)
fNIRS offers an ideal acceptable environment for ADHD children

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

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


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


fNIRS probe placement for Go/Nogo task

Aron et al., 2005
fNIRS analysis during Go/Nogo tasks

Measurement of Oxy-Hb changes

Inhibition

Motor response

Motor response

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)

Go block

Go/Nogo block

Press

Press

Go block

Go/Nogo block

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)

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

Neuropharmachological fNIRS on ADHD

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

Monden et al., 2012
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

Dopaminergic pathways

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: without placebo effects
Intra-medication vs. intra-placebo

MPH/ATX

Pre
Post

Placebo MPH/ATX

Effect size MPH: 0.95
Effect size ATX: 0.68

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)

<table>
<thead>
<tr>
<th></th>
<th>baseline</th>
<th>Oddball</th>
</tr>
</thead>
<tbody>
<tr>
<td>ES</td>
<td>Ch 10 0.98</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.0002</td>
<td></td>
</tr>
</tbody>
</table>

Activation in the right IFG/MFG

Cortical activation
TD control (n=22)
Nagashima et al., Neurophotonics (2014a)

<table>
<thead>
<tr>
<th></th>
<th>baseline</th>
<th>Oddball</th>
</tr>
</thead>
<tbody>
<tr>
<td>ES</td>
<td>Ch 10 0.98</td>
<td>Ch 22 1.01</td>
</tr>
<tr>
<td>P</td>
<td>0.0002</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Activation in the right IFG/MFG
+ Inferior parietal cortex
### Activation, oddball task

**ADHD** (n=22)  
Nagashima et al., Neurophotonics (2014a)

<table>
<thead>
<tr>
<th></th>
<th>baseline</th>
<th>Oddball</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ch 10</td>
<td>ES 0.21</td>
<td>P 0.9242</td>
</tr>
<tr>
<td>Ch 22</td>
<td>ES 0.02</td>
<td>P 0.9351</td>
</tr>
</tbody>
</table>

Pre-medicated ADHD children exhibited reduced brain activation in the right IFG/MFG & IPC
Effects of MPH medication: oddball

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

Effects of ATX medication: oddball

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

(a) ADHD without ASD  (b) ADHD with ASD

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


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 University
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

TD

ADHD

Cut-off value 0.004 (Mmm)

baseline Go/Nogo

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

TD

ADHD

Cut-off value 0.004 (Mmm)

baseline Go/Nogo

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)
η²=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