Effects of Methylphenidate on Default Mode, Dorsal Attention, and Frontoparietal Neural Networks among Children with Attention-Deficit/Hyperactivity Disorder

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Abstract

Current research on methylphenidate treatment for Attention-Deficit/Hyperactivity Disorder (ADHD) highlights modulation of functional connectivity within and between neural networks, such that patterns of network communication appear closer to individuals without ADHD. This study sought to examine the modification of network functional connectivity by methylphenidate, and utilized resting-state and cognitive-state fMRI neuroimaging and a double-blind, randomized administration of short-acting methylphenidate and placebo to drug-naïve children with ADHD (*n*=20). An ROI approach was used to estimate functional connectivity in three networks: the default mode (DMN), the frontoparietal (FPN), and the dorsal attention (DAN). Graph theory metrics (i.e., segregation and integration) were used to compare network topology with either acute methylphenidate treatment or placebo. Methylphenidate was associated with a reduction in segregation of the DMN during the resting-state and also of the DAN during the cognitive control task. These findings provide a model for how methylphenidate may exert functional effects by reducing segregation of actively recruited networks.

Background

Attention-Deficit/Hyperactivity Disorder (ADHD)

- Neurodevelopmental disorder with symptoms of inattention, hyperactivity, and impulsivity (APA, 2013)
- Affects 5-10% of youth worldwide (WHO, 2019)
- Functional impairments (right) lead to economic burden of $143 B in the US/year (Doshi et al., 2012)
- Treated with stimulant or non-stimulant medication and/or behavior therapy
  - Methylphenidate (brand name: Ritalin) most prescribed and researched stimulant for ADHD (NIH, 1998)

Neural Networks of Interest

Default Mode Network (DMN)

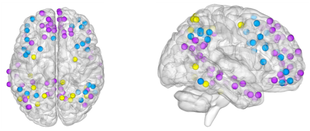
- **"Task-negative"** = more active during "rest," wakeful state without cognitive demands
- Implicated in daydreaming, recovering memories, envisioning the future, and assessing others' perspectives (Buckner et al., 2008)

Fronto-Parietal Network (FPN)

- **"Task-positive"** = more active during focused attention and cognition
- Responsible for central executive control, higher-level thinking

Dorsal Attention Network (DAN)

- "Task-positive"
- Voluntary attention



Typically, task-positive and task-negative networks are anti-correlated, active at opposite times (Fox et al., 2005)

Default Mode Intrusion Hypothesis of ADHD:

DMN active (interfering) during cognition

Suppressed with methylphenidate

(An et al., 2013, Liddle et al., 2011)

Methods

Participants

- 20 children with ADHD, ages 8-12 years (M = 9.79; SD = 1.20; 11 males, 9 females)
- IQ > 85 (WISC-V)
- All were medication naïve
- Pre-pubescent
- Ethnicity: 85.0% White, 5.0% African American, and 10.0% having more than one racial/ethnic background

Procedures

Screening

- Telephone screening to determine eligibility
- Administer Diagnostic Interview Schedule for Children (DISC) to assess ADHD and other childhood psychiatric disorders

Baseline Behavioral Day

- Wechsler Intelligence Scale for Children (WISC-V)
- Mock scan

Two separate fMRI scanning days

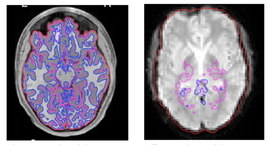
- Placebo controlled (Placebo pill on one scan day; 0.3 mg/kg methylphenidate (rounded to the nearest 5mg tablet) on the other scan day)
- Double-blind, randomized (counter-balanced) drug administration
- Two 5-minute resting state scans (participants stare at fixation cross, instructed to stay awake and keep eyes open)
- Go/No-go Task
  - Inhibitory control task
  - Indicator of neural network organization in the presence of attention demands and a moderate cognitive load (Gomez, Ratcliff, & Perea, 2007).

Neuroimaging Processing

Preprocessing

- fMRI Prep software used to map high-resolution anatomical image onto low-resolution functional image

fMRIPrep Output



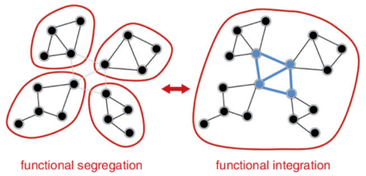
Anatomical image Functional image

Postprocessing

- Whole brain atlas (Seitzman et al., 2020) used to extract ROIs for default mode, dorsal attention, and frontoparietal networks

Analyses

- Measured segregation (within-network connectivity) and integration (between-network connectivity)
- Used graph theory metrics Within-Module Degree (WD) to measure segregation and Participation Coefficient (PC) to measure integration
- Paired t-tests, not controlling for covariates



(Sporns, 2013)

Results

Resting-State Results

		Within-Module Degree (WD)					Participation Coefficient (PC)				
		Placebo	MPH	*t*	*p*	CI	Placebo	MPH	*t*	*p*	CI
DMN	*Mean*	10.01	8.57	2.82	*.011	[.37, 2.5]	.93	.92	.61	.55	[-.01, .01]
	SD	2.16	1.04				.01	.01			
FPN	*Mean*	5.11	4.83	1.02	.32	[-.3, .87]	.92	.90	-.19	.85	[-.01, .01]
	SD	1.10	1.00				.01	.01			
DAN	*Mean*	2.37	2.23	.79	.44	[-.23, .51]	.90	.90	-1.24	.23	[-.01, 0]
	SD	.79	.51				.02	.02			

- Methylphenidate (MPH) only significantly decreased DMN WD, meaning decreased segregation during rest
- Expected increased DMN segregation based on this being found in adults with ADHD (Picon et al., 2020)

Cognitive-State (i.e., go/no-go task) Results

		Within-Module Degree (WD)					Participation Coefficient (PC)				
		Placebo	MPH	*t*	*p*	CI	Placebo	MPH	*t*	*p*	CI
DMN	*Mean*	7.96	7.56	1.4	.18	[-.21, 1.02]	.91	.91	.01	.99	[-.01, .01]
	SD	1.01	.94				.02	.02			
FPN	*Mean*	5.02	4.84	.85	.41	[-.26, .62]	.91	.91	.45	.66	[-.01, .01]
	SD	.86	1.18				.02	.02			
DAN	*Mean*	2.01	1.73	2.27	*.04	[.02, .56]	.84	.84	.7	.45	[-.01, .02]
	SD	.47	.59				.05	.04			

- Methylphenidate only significantly decreased DAN WD, meaning decreased segregation during rest
- First finding, to my knowledge, of methylphenidate altering DAN segregation during a cognitive task

Conclusions

Age related differences in methylphenidate actions on default mode?

Segregation of resting-state brain systems differs across the lifespan (Wig, 2017)

Methylphenidate only acting on recruited networks?

Changes observed only in task-negative during rest and task-positive during task

No changes in network's integration

Maybe methylphenidate does not alter between-network connectivity, BUT measured integration using PC, which represents level of outside-network connections so distribution levels of each network may not have changed, but significant reconfigurations could have occurred

Limitations

- Did not control for covariates (e.g., age, sex, IQ, intercranial volume)
- Restrictive age range (8-12 years)
- Did not measure specific interactions between networks
- ADHD severity may be relatively low in a drug-naïve sample
- Small dose of methylphenidate
- No non-ADHD controls

Future Directions

- Compare ADHD and non-ADHD children to determine methylphenidate effects on ADHD-specific functional connectivity deficits
- Evaluate all networks
- Sex differences
  - Greater connectivity dysfunction between task-positive and task-negative networks in males (Mills et al., 2018)
- Vary task difficulty and context
  - High incentive conditions are associated with FC changes similar to methylphenidate (Liddle et al., 2011)
- Interactions between methylphenidate effects and ADHD presentations

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