ADHD and Cognition
Learning Objectives

• Identify conceptual definitions of executive function (EF) and examine the role of EF in ADHD
• Address the importance of using scales in the diagnosis of ADHD
• Examine the most effective treatment options for cognitive dysfunction associated with ADHD
"The executive system is responsible for the simultaneous operation of a number of cognitive processes in charge of goal-directed, task-oriented behaviors; self-regulation; and behavior inhibition as well as planning, working memory, mental flexibility, response inhibition, impulse control, and monitoring of action."

Executive Dysfunction: ADHD vs. General Population

Defining Executive Function

• Behavioral rating scales
  - Self, observer, clinician
  - ADHD scales, EF scales, impairment scales

• Neuropsychological testing
  - Which tests?
  - Ecological validity concept

• Neuroimaging/functional connectivity

• Genetics

Operationalized definition determines the construct. Construct relationships may not align.
Diagnostic Overlap

Symptom Diagnosis

ADHD

Intelligence

Learning Disabilities

Executive Function

Neuropsychological Diagnoses
EF Associated With Other Disorders

- ADHD: 30-50% with EF
- Bipolar Disorder
- Schizophrenia
- Major Depression
- General Population: 5-10% with EF
- GAD
- Autism
- Learning Disorders
- Chronic SUD
- Neurological Disorders: TBI, MCI, CVA, CNS tumors, Degenerative
- Genetic Disorder: Klinefelter's (47, XXY)
Neurocircuitry

- Executive Function
  - Prefrontal (dorsolateral and lateral orbital) regions
- Regulation of affect
  - Orbitofrontal and ventromedial regions
- Attention and inhibitory control
  - Frontostriatal structures (ventrolateral prefrontal cortex, dorsal anterior cingulate cortex, caudate, and putamen)

EF Predicts Negative Outcomes

- Childhood EF significantly predicted outcomes in academic achievement and employment status.
- ADHD/low digit span in childhood had lower follow-up reading scores than ADHD/high digit span (not found in controls).
- ADHD/worse ROCF in childhood was associated with suspensions/expulsions.
- Working memory and ROCF were the strongest predictors for young adult outcomes.

ROCF: Rey-Osterrieth Complex Figure
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• Genetics
Executive Function Rating Scales

- Behavior Rating Inventory of Executive Function (BRIEF)\(^1\)
- Behavioral Assessment of the Dysexecutive Syndrome (BADS)\(^2\)
  - 6 subtests, score out of 4
- Dysexecutive Questionnaire (DEX)\(^2\)
  - 20 items on everyday executive problems
- Barkley Deficits in Executive Functioning Scale (BDEFS)\(^3\)
  - 88 items in 5 dimensions of EF

2. Wilson BA. Neuropsychological Rehabilitation 1998;8:213-228
3. Barkley RA. JARD 2010
<table>
<thead>
<tr>
<th>Task Name</th>
<th>EF Construct Assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stop signal reaction time</td>
<td>Response inhibition</td>
</tr>
<tr>
<td>Continuous Performance Test commission errors</td>
<td>Response inhibition</td>
</tr>
<tr>
<td>Continuous Performance Test omission errors</td>
<td>Vigilance</td>
</tr>
<tr>
<td>Wisconsin Card Sorting Test</td>
<td>Set shifting</td>
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<tr>
<td>Trail Making Test Part B</td>
<td>Set shifting</td>
</tr>
<tr>
<td>Tower of Hanoi/London</td>
<td>Planning</td>
</tr>
<tr>
<td>Porteus Maze</td>
<td>Planning</td>
</tr>
<tr>
<td>Rey-Osterrieth Complex Figure Test</td>
<td>Planning/organization</td>
</tr>
<tr>
<td>Working Memory Sentence Span</td>
<td>Verbal working memory</td>
</tr>
<tr>
<td>Digits Backward</td>
<td>Verbal working memory</td>
</tr>
<tr>
<td>Self-Ordered Pointing</td>
<td>Spatial working memory</td>
</tr>
<tr>
<td>CANTAB Spatial Working Memory</td>
<td>Spatial working memory</td>
</tr>
</tbody>
</table>

Willcutt EG. Biol Psychiatry 2005;57:136-1346
Psychometric Approach to Assessing EF Relies on Testing Cold Cognition

EF Constructs Typically Assessed by Tests

- Inhibition and Interference Tasks
  - CPT, Go/No-Go, Stop Signal, Stroop Color and Word Test

- Working Memory Tasks (Verbal and Nonverbal)
  - Digit span, mental arithmetic, n-back, spatial memory, sequence memory, Simon game, Kaufman Hand Movements Test

- Fluency Tasks
  - F-A-S Test, Five-Point Test, ideational fluency

- Planning and Problem Solving Tasks
  - Tower of London, Tower of Hanoi, Wisconsin Card Sorting Task

Slide courtesy of Russell Barkley, PhD
Can EF Tests Detect ADHD?

• These studies examined male and female youth as well as adults and found that most measures of EF have good positive predictive power for ADHD (characterized by adequate sensitivity) but poor negative predictive power (poor specificity)
• That is, abnormal scores on measures of EF are generally predictive of the diagnosis; however, normal scores cannot rule out the diagnosis

Siedman L. Clinical Psychology Review 2006;36:207-226
Problems With the EF Construct

• Lacks any consensus definition (20+ definitions exist)
• Considered to be a meta-construct serving as an "umbrella" term for a set of more specific components (33+)
• Assessment of EF nearly always employs "cold" and relatively brief cognitive psychometric tests

Test limitations
  – Unreliable and often poorly normed
  – Lack ecological validity
    Do not correlate with EF rating scales or observations
  – Do not predict impairment in major domains of life in which EF is important for effective functioning

Slide courtesy of Russell Barkley, Ph.D
Criteria for a Primary Neurocognitive Deficit

- ADHD groups must consistently exhibit weaknesses on EF measures after controlling for confounding variables
- EF weaknesses must account for a substantial proportion of the variance in ADHD symptoms in the population
- EF weaknesses must be present in most individuals with ADHD
- EF weaknesses and ADHD symptoms must be attributable to common etiological influences

Willcutt EG. Biol Psychiatry 2005;57:136-1346
Clinic-Referred Adults With ADHD

WCSD: Wisconsin Card Sorting Test. CPT: Conners' Continuous Performance Test.
Barkley RA & Murphy KR. Impairment in occupational functioning and adult ADHD: The predictive utility of executive function (EF) ratings vs. EF tests. *Archives of Clinical Neuropsychology* 2010;25:157-173
Ecological Validity of EF Tests

- Virtual reality
- Multitasking in a City Test
- Virtual supermarket
- Virtual library
- Multiple Errands Test
- Executive Secretarial Task
Ecological Validity of EF Tests

- 92 mixed etiology neurological patients
- 216 controls
- Assessed 10 neuropsych measures with 6 different tests
- Relatives completed questionnaire about dysexecutive problems
- Factor analysis of symptoms suggested a fractionation of dysexecutive functions into 3 cognitive factors
  - Inhibition, intentionality, working memory

Different tests measure different cognitive processes, and there may be limits to the fractionation of the executive system on the basis of neuropsychological tests
Testing in a Distraction Setting: Adult ADHD vs. Controls


Recall Accuracy %

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Silence</th>
<th>ISE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls (n=32)</td>
<td><img src="image" alt="Bar Chart" /></td>
<td><img src="image" alt="Bar Chart" /></td>
</tr>
</tbody>
</table>

* p > .05
Testing in a Distraction Setting: Adult ADHD vs. Controls

Pelletier MF et al. 2013. Characterisation of Attention and Short Term Memory Processes in Adult ADHD with the Irrelevant Sound Paradigm. Poster Presentation.
Rating Scales vs. Tests: Contribution Variance to Impairment

- **EF scales** predict up to 45% of variance in global self-rated impairment and 20% in other-rated impairment.

- **EF tests** predict up to 6% in global self-rated impairment and 7% in other-rated impairment.

Barkley RA et al. Developmental Neuropsychology 2011;36(2):137-161
• EF tests show their best (albeit weak) relationships with academic achievement tests, but not when IQ is removed
• Overall, EF scales predict 2-20% of variance in work history measures, averaging 11%
• Overall, EF tests predict 2-18% of variance in work history measures, averaging 6.8%
• EF scales predict a wider array of occupational problems than EF tests
• If predicting impairment is an index of validity of measurement, EF scales out-predict EF tests
ADHD Symptoms Correlate Poorly to Impairments

- Average correlation between symptoms and impairment is less than 10% of the variance
- Symptoms never predicted more than 25% of the variance in impairment
- When the measure of impairment was added to symptoms, the sample size shrunk by 77% for an ADHD diagnosis
- Strongest relationship between symptoms and impairment is between inattention and school functioning

Gordon M et al. Symptoms versus Impairments: A Case for Respecting the DSM-IV Criteria
D. J Atten Disord. February 2006;9(3):465-475
Defining Executive Function

• Behavioral rating scales
  – Self, observer, clinician
  – ADHD scales, EF scales, impairment scales
• Neuropsychological testing
  – Which tests?
  – Ecological validity concept
• Neuroimaging
• Genetics
• Evaluate 5 functional SNPs in specific genes related to DA on executive function in a general population
• Use Frontal Assessment Battery (FAB)
• Flexibility subset of FAB was associated with the SNP in COMT after adjusting for confounding variables
• Combination of 2 SNPs in the COMT gene and the dopamine D4 receptor gene had a significant effect on FAB score

Frontal Assessment Battery

FAB composite tool consisting of 6 subtests:
- Categorization
- Flexibility
- Programming
- Resistance to interference
- Inhibitory control
- Forced movement
Genes and ADHD

• Genetic predisposition may be associated with subsequent ADHD symptoms
• Recent study examined the role of glutamate in an animal model for ADHD
• The glutamate transporter GLT1 splice variant, GLT1b was increased, while total GLT1 was reduced in the hippocampus compared to controls
• Pattern is indicative of elevated extracellular glutamate levels
• Glutamate is elevated in the prefrontal cortex of patients with ADHD
• Suggest a role for GLT1 in the pathophysiology of ADHD

What Should Be Treated First?

- alcohol / stimulant / substance abuse
- mood disorders
- anxiety disorders
- ADHD
- nicotine dependence

Goodman DW. In: Biederman J, ed. Across the Life-Span: From Research to Clinical Practice—An Evidence-Based Understanding. Veritas Institute for Medical Education; 2006:227-69;
Pietrzak et al. (2006) provides a meta-analysis of the recent literature on placebo-controlled studies of the effects of MP on a variety of neuropsychological tasks and studies comparing effects for more than 1 clinical dose:

- Higher doses produced greater improvements than lower doses on some tasks (attention, vigilance, memory, and working memory), but no additional improvements on others (planning, cognitive flexibility, inhibitory control, naming, and motor speed).

• In well-controlled studies using batteries, stimulant-related cognitive enhancements were more prominent on tasks without an executive function component (complex reaction time, spatial recognition memory reaction time, and delayed matching to sample) than on tasks with an executive function component (inhibition, working memory, strategy formation, planning, and set shifting).

Understanding the Cognitive Effects of Stimulants

• These reviews marked a watershed in the literature on cognitive deficits in ADHD
  ✓ Pointed out that few children with ADHD showed pervasive deficits across tests
  ✓ Concluded that executive function deficits were not necessary and sufficient causes of ADHD
  ✓ Contributed to the shift from core deficit to multiple deficit theories

• In addition, this approach has uncovered ADHD–control group differences (deficits) on tests of temporal and parietal lobe function (spatial recognition and span, pattern recognition, and delayed matching to sample) as well as frontal lobe function (working memory, planning and strategy formation, and set shifting).

Understanding the Cognitive Effects of Stimulants

• Dose response studies of stimulant medications suggest that the optimal dose varies across individuals and depends somewhat on the domain of function, with high doses tending to produce greater enhancement of some domains (e.g., vigilance) but not others (e.g., planning), without clear evidence of completely correcting the cognitive deficits associated with ADHD

Exercise as Adjunctive Treatment

- Current research status: Physical exercise is beneficial as adjunctive treatment, but there's not enough evidence to suggest that it is a stand-alone treatment.
- Exercise may be particularly effective for youth, potentially preventing or altering the course of ADHD.
- The literature is promising; however, the most challenging complications for these types of studies are: random assignment, blinded raters, and adequate control groups.
- Comparisons have been made between aerobic/nonaerobic, and acute vs chronic exercise on cognitive and behavioral symptoms.
- Exercise has beneficial effects on a variety of cognitive capacities, measured by neuropsychological or EF tasks.
- Systematic exercise appears to have beneficial effects on additional functional domains in ADHD (motor skills, social functioning, behavior, affective/emotional domain).

Exercise as Adjunctive Treatment

Questions that need to be addressed:

- What is the optimal “dose” (individual session duration, frequency, program length)?
- Is there an age during development when exercise could be most effective?
- How does exercise compare to established treatments for ADHD? To medication? To behavioral therapy?
- How long do the beneficial effects of exercise last?
Exercise as Adjunctive Treatment

• Literature review: 25 published studies on exercise and cognition in children with ADHD, 4 studies on adults with ADHD
• Compared 1) exercise type (aerobic vs nonaerobic)
  2) effect type (acute vs chronic)
  3) outcome measure (cognitive/behavioral/socio-emotional, physical/neurophysiological)
• Aerobic exercise appears to be the most effective for improvements in EF
• Both acute and chronic exercise have beneficial effects on behavioral and cognitive measures in children with ADHD
• Cognitive measures: improved response inhibition, cognitive control, attention allocation, cognitive flexibility, processing speed, and vigilance, when assessed immediately after exercise

Heijer et al. Journal of Neurotrauma 2016, 016: 1593-1597
Exercise, Catecholamines, and ADHD

• Exercise may exert its therapeutic effects by raising levels of catecholamines, similar to the effects of medication for ADHD

• Up to 30% of children do not show a beneficial response to stimulants or are unable to tolerate potential side effects

• Physical exercise induces increased levels of norepinephrine (NE), dopamine (DA), and serotonin (5-HT) in the prefrontal cortex, hippocampus, and striatum)

• In a study that compared NE, DA, and epinephrine (Epi) levels in children with ADHD vs controls at baseline, during the last 2 minutes of exercise, 30, and 60 minutes post exercise:
  – Resting NE levels were significantly lower in children with ADHD compared to controls
  – In response to exercise, the increase in NE and Epi were severely blunted, and there was no increase in DA

Exercise, Catecholamines, and ADHD

• There are other medical conditions that can result in a blunted catecholamine response to exercise, such as obesity and type I diabetes
• Gender influences
• Prolonged exercise programs affect not only the acute catecholamine response to individual bouts of exercise, but resting systemic rates of catecholamine secretion
• Training reduces the magnitude of catecholamine response to a comparable exercise challenge; however, it increases the basal resting catecholamine levels
• Thus, future research on the effects of prolonged exercise programs on catecholamine levels in patients with ADHD is needed

Zouhal, Jacob, Delamarche, & Gratas-Delamarche, 2008
Exercise and ADHD

- The findings suggest that an exercise “test” could be a diagnostic tool to measure catecholamine levels, and could serve as a biomarker for children with ADHD.
- Further research is needed to determine the extent to which catecholamine levels are altered in response to exercise in patients with ADHD compared to controls.
- Future studies should examine whether a greater intensity or duration of exercise can increase catecholamine levels in patients not on medication, to the levels that are observed with medication.
- For now, it’s best to view exercise as an effective way of managing ADHD symptoms, but not as a stand-alone treatment.
Conclusions

• Executive function is conceptually understood but operationally ill defined
• Definitional constructs are poorly correlated with each other (scales vs. tests)
• Positive predictive validity for impairments increases further in the presence of executive dysfunction and learning disorders
• Medications seem to have selective effects in ADHD and executive dysfunction, so…
• Don't overdose your patients!
• Explore exercise programs as an adjunctive therapy, particularly in the case of treatment-resistant patients
Executive function is disrupted in approximately 5-10% of the general population, and what % of patients with ADHD?

1. 15-25%
2. 30-50%
3. 80-90%
4. 50-75%
Posttest Question 2

Which of the following may be useful in diagnosing ADHD?

1. Wisconsin Card Sorting Test
2. Trail Making Test Part B
3. Behavior Rating Inventory of Executive Function
4. Digits Backward
5. None of the above
A meta-analysis on the effects of physical exercise for symptom management in children with ADHD, has demonstrated improvement on what cognitive measures?

1. Response Inhibition
2. Visuospatial Tasks
3. Cognitive Flexibility
4. 1 and 3
5. None of the above