Functional Brain Networks Related to Sex, Age, and Alcohol Use in Adolescence: Resting-State and Task-Activated fMRI Findings from NCANDA

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Brain structural changes during adolescence suggest neural rewiring of large-scale cortical and subcortical networks by forming complex fiber connections.

to support the increasingly sophisticated cognitive abilities, motor performance, self-regulation, and reward-focused processing during adolescent development

Healthy neurodevelopment is vulnerable to disruption from environmental insult such as alcohol consumption commonly initiated during adolescence.
Demographic characteristics of adolescent study groups for those meeting no/low alcohol use history criteria and those exceeding criteria for at-risk alcohol consumption:
N=subject count; Mean ± SD (range)

<table>
<thead>
<tr>
<th></th>
<th>No/low alcohol use history</th>
<th>Matched groups</th>
<th>Difference between matched groups; p=</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Exceeds-criteria group</td>
<td>Matched no/low alcohol use history subgroup</td>
</tr>
<tr>
<td>Total</td>
<td>581</td>
<td>117</td>
<td>117</td>
</tr>
<tr>
<td>Girls/Boys</td>
<td>306/275</td>
<td>62/55</td>
<td>62/55</td>
</tr>
<tr>
<td>GE/Siemens</td>
<td>385/196</td>
<td>80/37</td>
<td>72/45</td>
</tr>
<tr>
<td>Age (years)</td>
<td>15.9±2.3</td>
<td>18.6±1.9</td>
<td>18.4±1.8</td>
</tr>
<tr>
<td>(12-21.9)</td>
<td>(13-1.9)</td>
<td>(13-1.9)</td>
<td></td>
</tr>
<tr>
<td>PDS¹</td>
<td>3.2±0.7</td>
<td>3.7±0.4</td>
<td>3.6±0.4</td>
</tr>
<tr>
<td>(1-4)</td>
<td>(1-8-4)</td>
<td>(2-2-4)</td>
<td></td>
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<tr>
<td>Alcohol use</td>
<td>Days lifetime</td>
<td>1.1±4.2</td>
<td>51.6±75.8</td>
</tr>
<tr>
<td></td>
<td>Days past year</td>
<td>0.0±2.9</td>
<td>23.7±31.9</td>
</tr>
<tr>
<td></td>
<td>Max drinks³</td>
<td>0.4±0.9</td>
<td>7.6±4.7</td>
</tr>
<tr>
<td>Binges past year</td>
<td>0</td>
<td>12.2±12.2</td>
<td>0</td>
</tr>
<tr>
<td>Marijuana use</td>
<td>Days lifetime</td>
<td>0.6±2.5</td>
<td>10.8±17.7</td>
</tr>
<tr>
<td></td>
<td>Days past year</td>
<td>0.3±1.6</td>
<td>7.5±16.0</td>
</tr>
<tr>
<td>Parental education (years)</td>
<td>16.9±2.4</td>
<td>17.4±2</td>
<td>17.0±2</td>
</tr>
<tr>
<td></td>
<td>(6-20)</td>
<td>(12-20)</td>
<td>(11-20)</td>
</tr>
<tr>
<td>Highest Grade</td>
<td>9.2±2.4</td>
<td>11.9±1.9</td>
<td>11.8±1.9</td>
</tr>
<tr>
<td></td>
<td>(5-15)</td>
<td>(6-16)</td>
<td>(7-15)</td>
</tr>
<tr>
<td>WRAT²</td>
<td>Reading</td>
<td>116±17</td>
<td>113±14</td>
</tr>
<tr>
<td></td>
<td>(80-145)</td>
<td>(85-145)</td>
<td>(84-145)</td>
</tr>
<tr>
<td></td>
<td>Writing</td>
<td>112±16</td>
<td>113±14</td>
</tr>
<tr>
<td></td>
<td>(66-145)</td>
<td>(72-143)</td>
<td>(75-145)</td>
</tr>
</tbody>
</table>

¹Pubertal Development Score (PDS): score ranges between 1=“puberty not started” and 4=“puberty completed” ²Wide Range Achievement Test (WRAT): Standard scores are reported with an expected mean±SD of 100±15 ³Maximum number of drinks at one occasion in the past year; ⁴Chi-square test

Neurofunctional characteristics underwriting cognitive, motor, self-reflectory and social-emotional function in adolescence can be captured with whole-brain, resting-state functional MRI (rs-fMRI).
Resting-State fMRI
Adolescent Intrinsic Network Connectivity

Five Selected Networks:

**DMN**: Default Mode Network
Seed: PCC (posterior cingulate cortex)

**ECN**: Executive Control Network
Seed: SFG (superior frontal gyrus)

**SAN**: Salience Network
Seed: ACC (anterior cingulate cortex)

**EMN**: Emotion Network
Seed: Amyg (amygdala)

**RWN**: Reward Network
Seed: NAcc (nucleus accumbens)

N=581 no/low drinking adolescents

Müller-Oehring et al. 2017. Cerebral Cortex.
Adolescent Intrinsic Network Connectivity Influences of Sex and Age

Network rewiring with maturation: with older age, connectivity - was stronger in the executive control network (ECN) and spatially more distributed - was weaker in default mode and emotion networks (DMN, EMN).

Sexual dimorphism:
- Girls showed stronger connectivity to regions more primal to the seed (SAN,DMN,ECN,RWN)
- Boys showed a more spatially distributed SAN connectivity.

Müller-Oehring et al. 2017. Cerebral Cortex.
Functional Brain Maturation

Default mode Network

- PCC – Left Hippocampus, Amygdala

![Brain Image 1]

Executive Control Network

- SFG – Right Insula, Inferior Lateral Frontal, Hippocampus, etc.

![Brain Image 2]

Graphs showing interregional synchronicity in Z with age (years) for boys and girls.

- PCC: Interregional Synchronicity in Z

- SFG: Interregional Synchronicity in Z

Müller-Oehring et al. 2017. Cerebral Cortex.
Functional Brain Maturation

Performance

**SFG** – Right Insula, Inferior Lateral Frontal, Hippocampus, etc.

Interregional Synchronicity in Z

Delay Discounting in Z

**SFG** – Left Striatum (caudate+putamen, Inferior Lateral Frontal

Mean Balance Accuracy in Z

Executive Control Network

Boys only

**SFG** – Right Insula, Inferior Lateral Frontal, Hippocampus, etc.

Age (Years)

Mean Balance Accuracy in Z
Functional Brain Maturation

Salience Network

ACC – Right Inferior Occipital (Boys Only)

ACC – Right Prefrontal (Girls Only)

Interregional Synchronicity in Z

Age (Years)

Müller-Oehring et al. 2017. Cerebral Cortex.
Maturation of adolescents' functional brain networks is marked by heterochronicity related to age and sex, characterizing "intrinsic network rewiring" to support increasingly sophisticated cognitive abilities, motor performance, self-regulation, and reward-focused processing.
Adolescents in the exceed drinking group had attenuated connectivity between the emotion network seed of the amygdala and default mode network regions of the PCC/precuneus.

Müller-Oehring et al. 2017. Cerebral Cortex.
the increasingly sophisticated **cognitive abilities**, **motor performance, self-regulation, and reward-focused processing** during adolescent development

**inhibitory circuitry during task engagement** (executive control ability)

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**At rest**, the Executive Control Network was the only of 5 intrinsic networks with expanded connectivity during Adolescent Maturation:

**ECN**

**SFG**

**ECN: Age**

**SFG – Left+Right Insula, Inferior Lateral Frontal, Hippocampus, etc.**
Inhibitory functioning and executive control: Task-Activated fMRI

- **fMRI task count N=178 with no/low alcohol (87 boys, 91 girls)**
  - N=266 task-fMRI
  - n=37 exceed criteria
  - n=229 no/low alcohol
  - (exclude n=44 (19%) motion exclude n=7 with unusable behavioral data)

<table>
<thead>
<tr>
<th>Boys</th>
<th>Girls</th>
<th>df</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>87</td>
<td>91</td>
<td>1</td>
</tr>
<tr>
<td>Age</td>
<td>16±2.34</td>
<td>15.67±2.19</td>
<td>176</td>
</tr>
<tr>
<td>Site</td>
<td>69/18</td>
<td>65/26</td>
<td>.223*</td>
</tr>
<tr>
<td>PDS¹</td>
<td>2.93±.7</td>
<td>3.34±.65</td>
<td>176</td>
</tr>
<tr>
<td>Parent SES</td>
<td>92.06±16.05</td>
<td>90.36±15.15</td>
<td>171</td>
</tr>
<tr>
<td>Parent Years of Education</td>
<td>16.76±2.98</td>
<td>16.8±2.46</td>
<td>175</td>
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<tr>
<td>WRAT²</td>
<td></td>
<td></td>
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<tr>
<td>Reading</td>
<td>115.86±16.387</td>
<td>112.97±15.882</td>
<td>176</td>
</tr>
<tr>
<td>Math</td>
<td>115.63±15.611</td>
<td>113.32±16.015</td>
<td>176</td>
</tr>
</tbody>
</table>

Age and PDS were more strongly correlated in boys than girls (age/pds: boys \( r=.81 \), girls \( r=.639 \), \( z=-2.43 \), \( p=0.0151 \)).
Testing the Inhibitory Circuitry with the Stroop task

Stroop Match-to-Sample Task
“Match the color of the XXXX to the font color of the word, press YES for matches and NO for non-matches.”

Implicit manipulation of motor responses with a blocked design:
Response switching (RS) versus response repetition (RR)

Cognitive control = Stroop effect (inc vs. con)
BLUE (inc) vs. BLUE (con)

Motor response control = RS vs. RR

Behavioral data

Response time (RT) in ms

Stroop effect
inc
con

RS
RR
RS
RR

Girls
Boys
BACKGROUND: Using the Stroop Match-to-Sample task, we previously observed in healthy adults and chronic alcoholics:

Cognitive Control

Fronto-parietal regions

dIPFC, SPL/IPL, PCC

- Yellow: Stroop (inc > con)
- Red: CTL
- Green: ALC
- Blue: CTL (con > inc)

Motor Control

Cerebellar-BG-motor cortical regions

MCC, PCC, midbrain

- Green: ALC > CTL for
- Stroop-repetition > Stroop-switching

Schulte et al., 2012. Biological Psychiatry
Cognitive Control

Inhibitory Circuitry in Adolescents

Stroop

Stroop-RS

Stroop-RR

Cognitive control = Stroop effect (inc vs. con)

BLUE (inc) vs. BLUE (con)
Inhibitory Circuitry: Cognitive control and Age

Stroop-RS: parietal, occipital

Stroop-RR: middle cingulate cortex (MCC)
Inhibitory Circuitry: Cognitive control and Pubertal Development

Stroop-RS

Pubertal development score: 1=puberty not started, 4=puberty completed

L. inferior frontal activation during Stroop-RS

R. inferior frontal/anterior insula activation to Stroop-RS
Response mode for non-conflict congruent trials

RS > RR
RR > RS

t = 3 4 5 6

boys > girls weaker with older age

Response Switching vs. Repetition
= RS vs. RR
Inhibitory Circuitry: Motor Control, Age, and Pubertal Development

Response Switching vs Repetition (CON trials only: no cognitive conflict)

Age

RS>RR  R. MCC activation to motor control (RS>RR con)

Pubertal Dev.

RS>RR  R. cerebellar activation to motor control (RS>RR con)

Inhibitory Circuitry: Motor Control, Age, and Pubertal Development

Response Switching vs Repetition (CON trials only: no cognitive conflict)
Summary and Conclusions

‘Neurofunctional Rewiring’ in Adolescence

Sexual dimorphism – pubertal development
- Boys showed a more spatially distributed SAN connectivity
- Girls showed stronger connectivity to regions more primal to the seed
- Sex differences in frontal, extratriate, and cerebellar activation depending on control demands and related to pubertal development

Age-related “functional rewiring”
- Weaker DMN-limbic connectivity
- Stronger ECN fronto-limbic connectivity

Alcohol use history in adolescents
- Weaker EMN-DMN connectivity

Age-related activation during an executive control task
Older age
- more parietal, occipital activation for high cognitive & motor control demands
- less MCC activation for low control demands
and all NCANDA co-authors
