DAY 5 | WEDNESDAY, MAY 24, 2017

8:00 a.m. – 11:00 a.m. | Room 25C, Upper Level | SYMPOSIUM

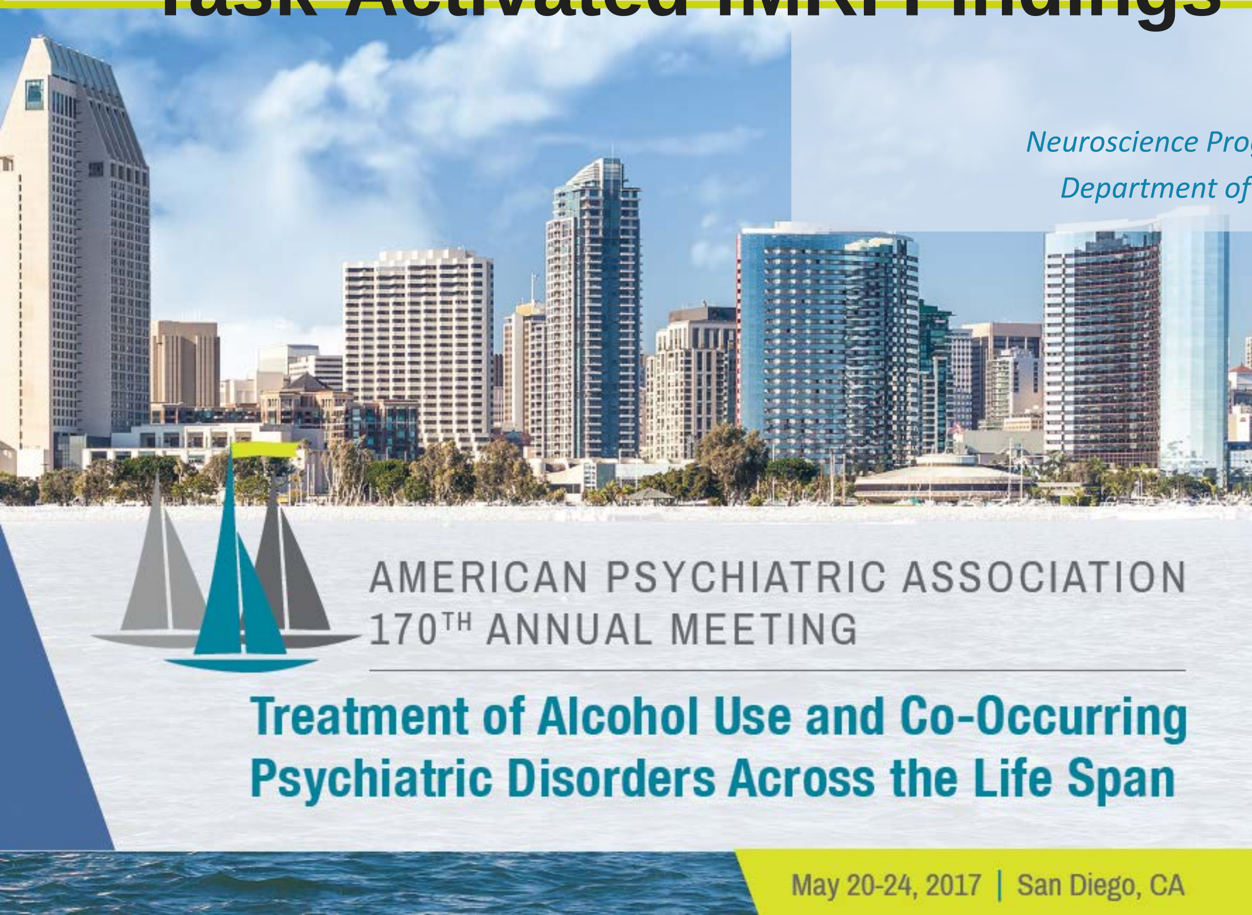
Neuromaturational Consequences and Predictors of Heavy Drinking: Findings from the Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA)

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

Eva M. Müller-Oehring, Ph.D.

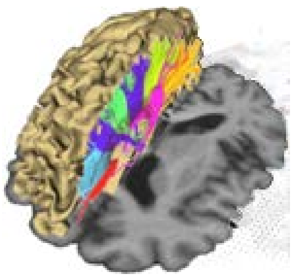
Neuroscience Program, Center for Health Sciences, SRI International

Department of Psychiatry, Stanford University School of Medicine



Financial disclosure:
Nothing to disclose

ADOLESCENT BRAIN DEVELOPMENT



- 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

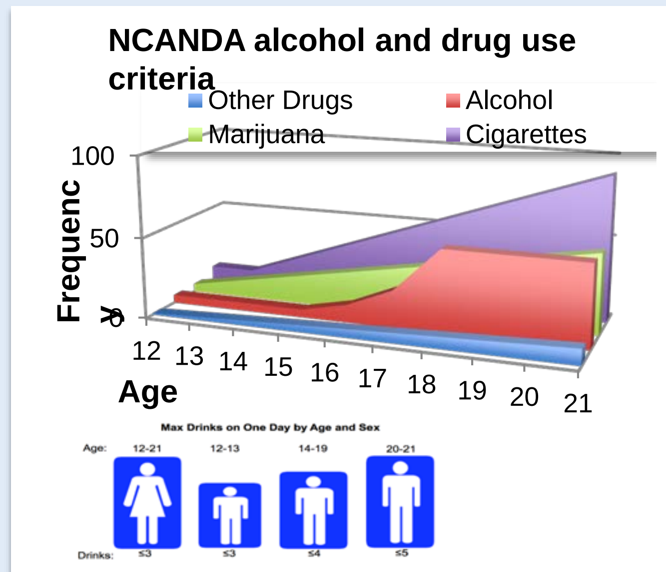
- Healthy neurodevelopment is vulnerable to disruption from environmental insult
such as alcohol consumption
commonly initiated during adolescence.

NCANDA Resting-State fMRI at Baseline

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)

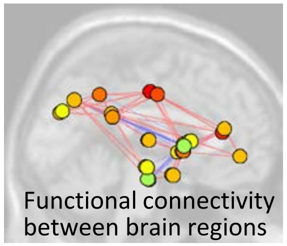
		No/low alcohol use history	Matched groups: *Exceeds-criteria group*	*Matched no/low alcohol use history subgroup*	*Difference between matched groups; p=*
N	*Total*	581	117	117	
	Girls/ Boys	306/275	62/55	62/55	1.0[4]
	GE / Siemens	385/196	80/37	72/45	.27[4]
Age (years)		15.9±2.3 (12-21.9)	18.6±1.9 (13-1.9)	18.4±1.8 (13-21.9)	.39
PDS[1]		3.2±0.7 (1-4)	3.7±0.4 (1.8-4)	3.6±0.4 (2.2-4)	.28
Alcohol use	*Days lifetime*	1.1±4.2	51.6±75.8	3.1±7.2	*<.001*
	Days past year	0.0±2.9	23.7±31.9	1.8±4.9	*<.001*
	Max drinks[3]	0.4±0.9	7.6±4.7	0.8±1.2	*<.001*
	Binges past year	0	12.2±12.2	0	*.004*
Marijuana use	*Days lifetime*	0.6±2.5	10.8±17.7	1.0±3.9	*.004*
	Days past year	0.3±1.6	7.5±16.0	0.6±2.5	*.015*
Parental education (years)		16.9±2.4 (6-20)	17.4±2 (12-20)	17.0±2 (11-20)	.19
Highest Grade		9.2±2.4 (5-15)	11.9±1.9 (6-16)	11.8±1.9 (7-15)	.66
WRAT[2]	*Reading*	116±17 (80-145)	113±14 (85-145)	114±14 (84-145)	.83
	Writing	112±16 (66-145)	113±14 (72-143)	113±167 (75-145)	.73

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

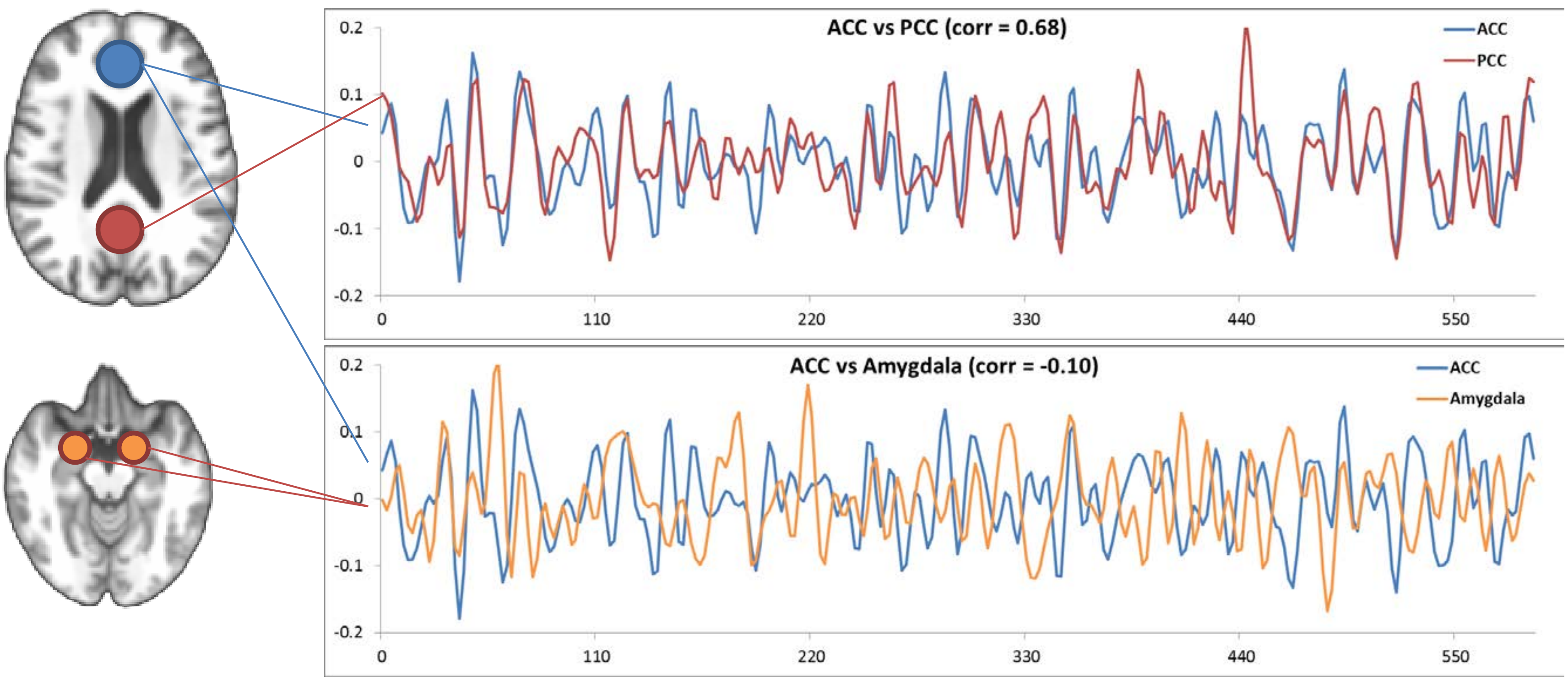


Müller-Oehring et al. 2017. Cerebral Cortex.
Influences of Age, Sex, and Moderate Alcohol Drinking on the Intrinsic Functional Architecture of Adolescent Brains.

Functional Connectivity



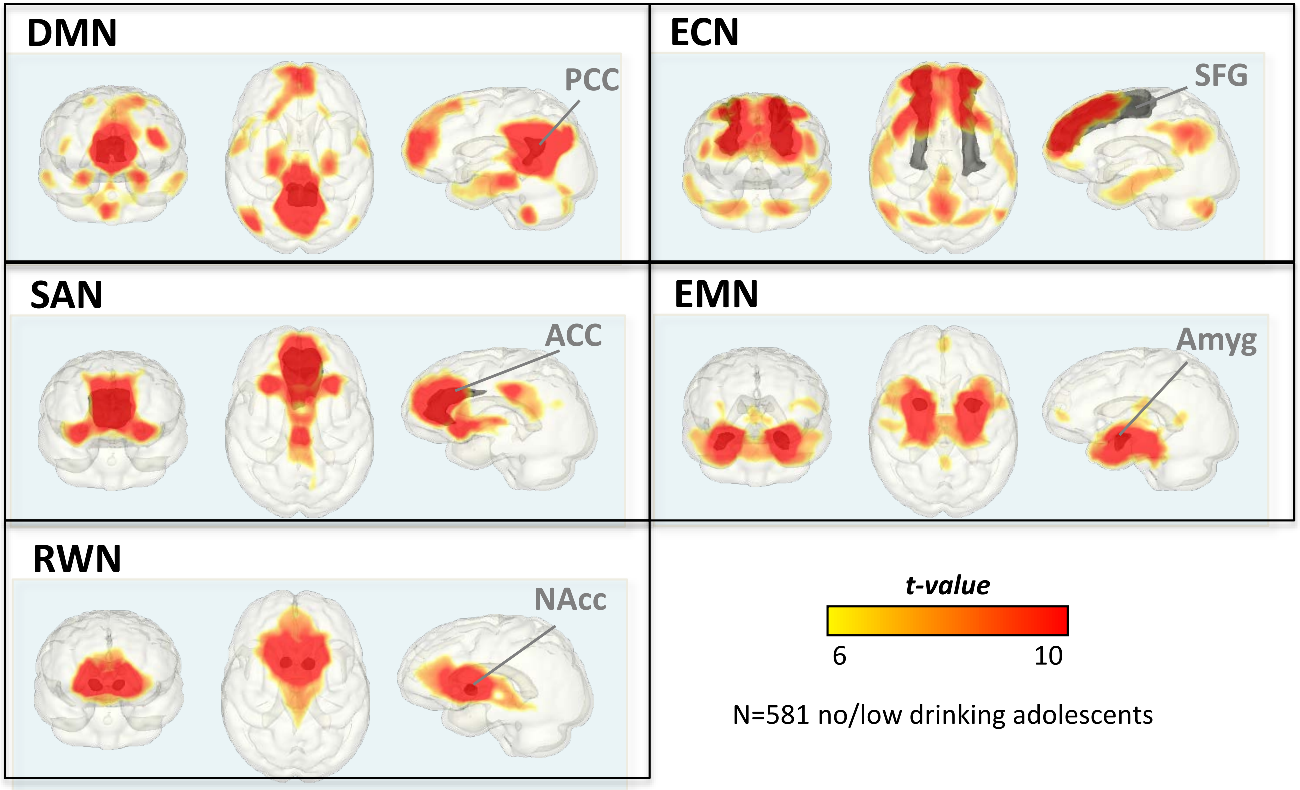
Neurofunctional characteristics underwriting cognitive, motor, self-reflectory and social-emotional function in adolescence can be captured with whole-brain, resting-state functional MRI (rs-fMRI).



NCANDA S00159; 15 year old girl

Resting-State fMRI
Adolescent Intrinsic Network Connectivity

Five Selected Networks:



N=581 no/low drinking adolescents

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

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

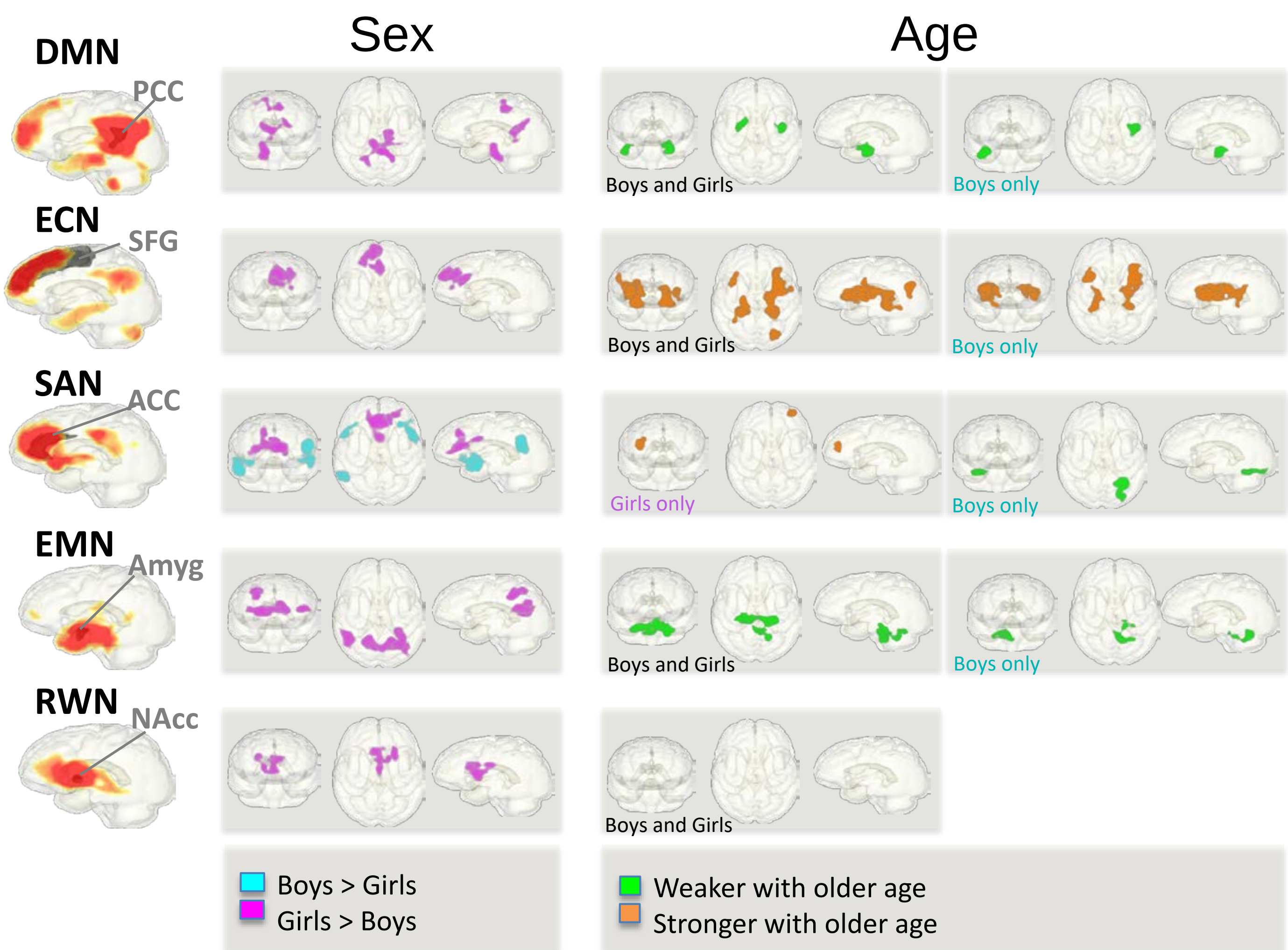
SAN: Salience Network
Seed:
ACC (anterior cingulate cortex)

EMN: Emotion Network.
Seed:
Amyg (amygdala)

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

Müller-Oehring et al. 2017. Cerebral Cortex.

Adolescent Intrinsic Network Connectivity Influences of Sex and Age



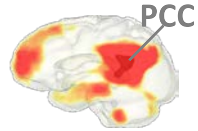
Network rewiring with maturation: with **older age**, connectivity - was stronger in the executive control network (ECN) and spatially more distributed
- was weaker in default mode and emotion networks (DMN, EMN)

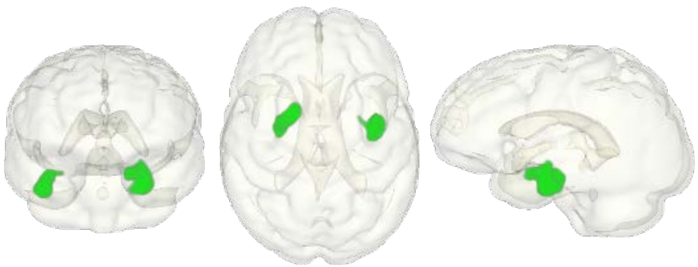
Sexual dimorphism:
- Girls showed stronger connectivity to regions more primal to the seed (SAN,DMN,ECN,RWN)
- Boys showed a more spatially distributed SAN connectivity.

Müller-Oehring et al. 2017. Cerebral Cortex.

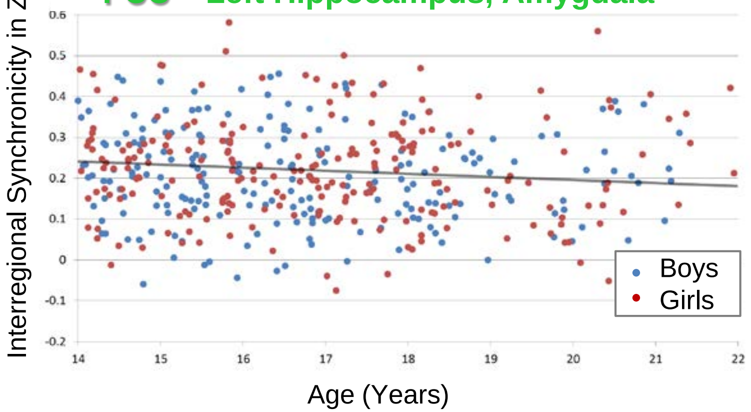
Functional Brain Maturation

Default mode Network

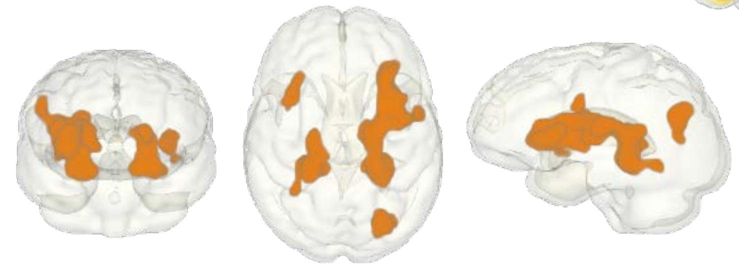




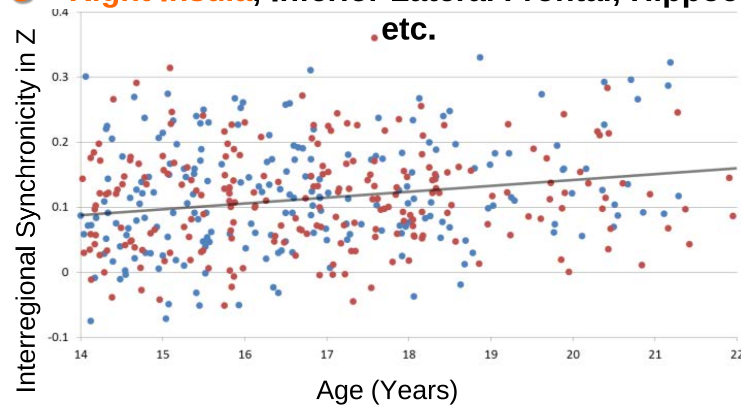
PCC – Left Hippocampus, Amygdala



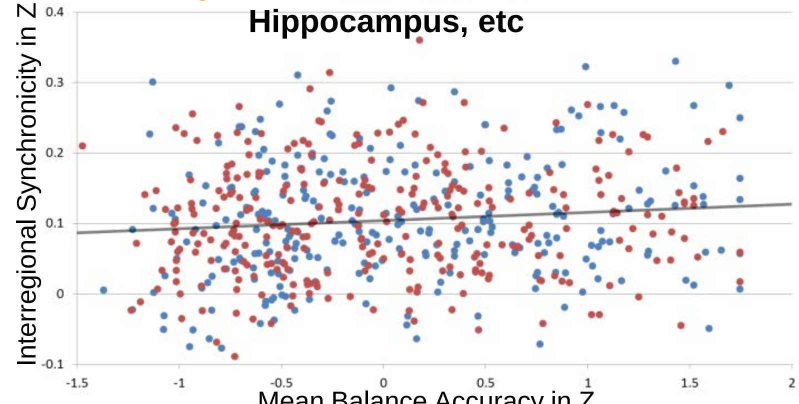
Executive Control Network



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



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

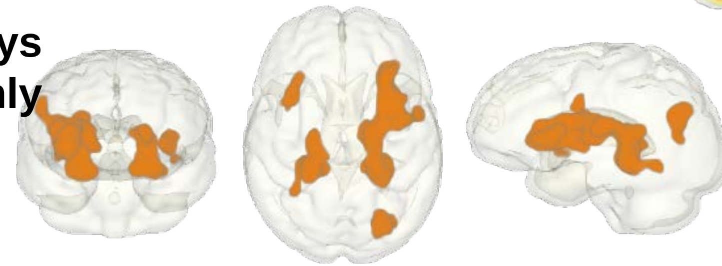


Müller-Oehring et al. 2017. Cerebral Cortex.

Functional Brain Maturation

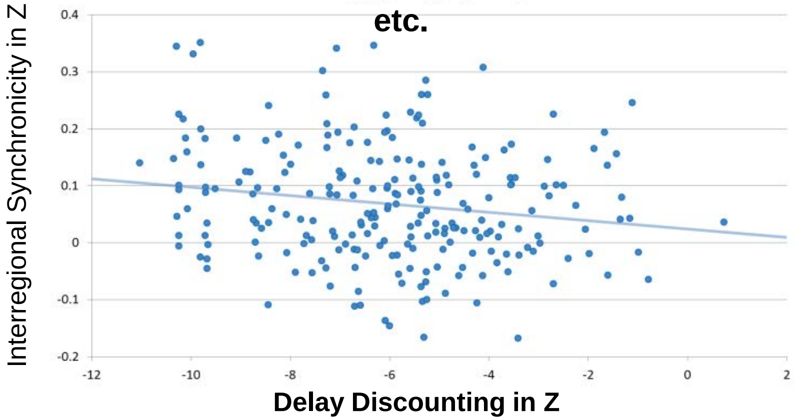
Executive Control Network

Boys only

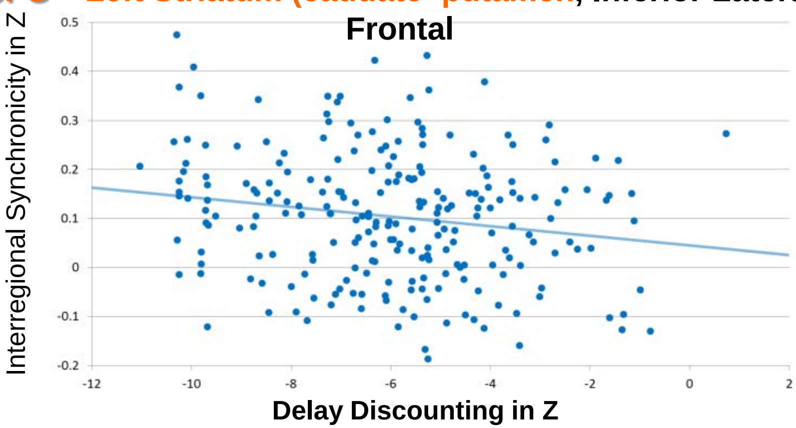


Performance

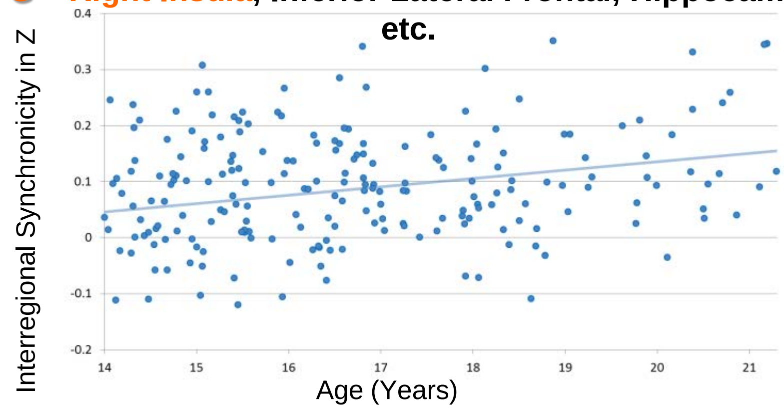
SFG – Right Insula, Inferior Lateral Frontal, Hippocampus, etc.



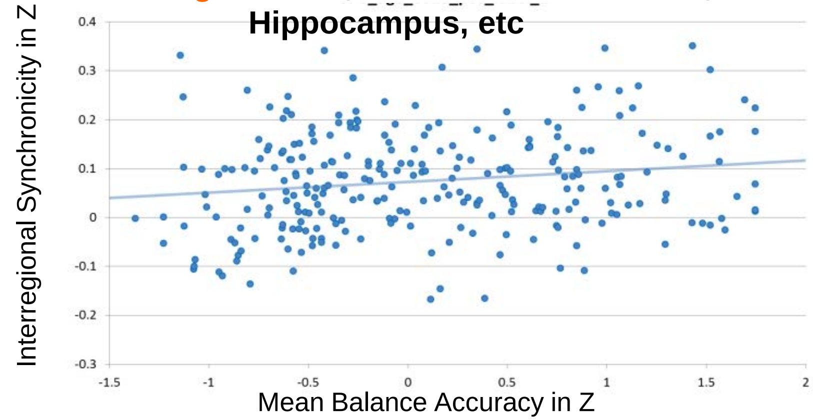
SFG – Left Striatum (caudate+putamen, Inferior Lateral Frontal



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



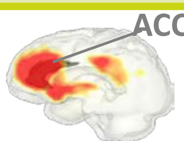
SFG – Right Insula, Inferior Lateral Frontal, Hippocampus, etc



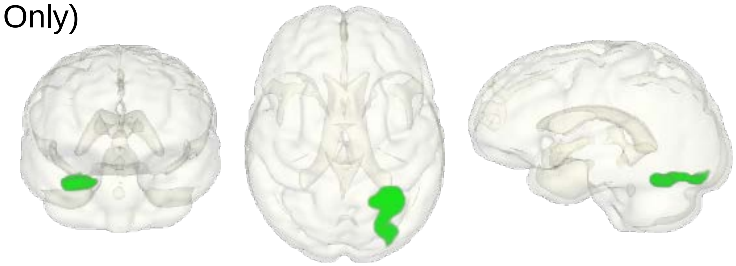
Müller-Oehring et al. 2017. Cerebral Cortex.

Functional Brain Maturation

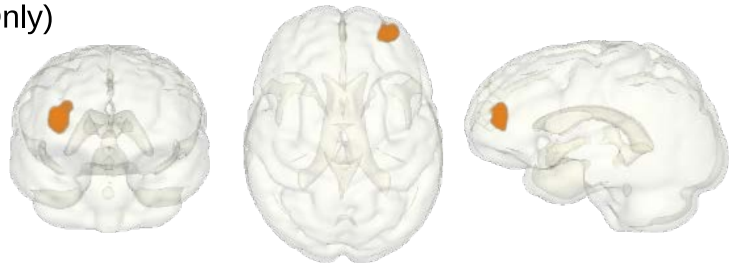
Salience Network

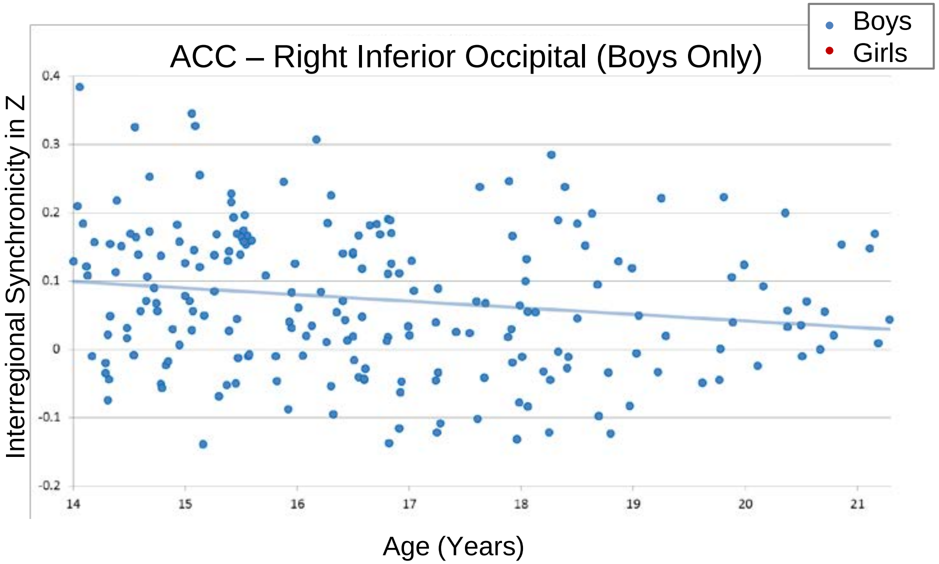


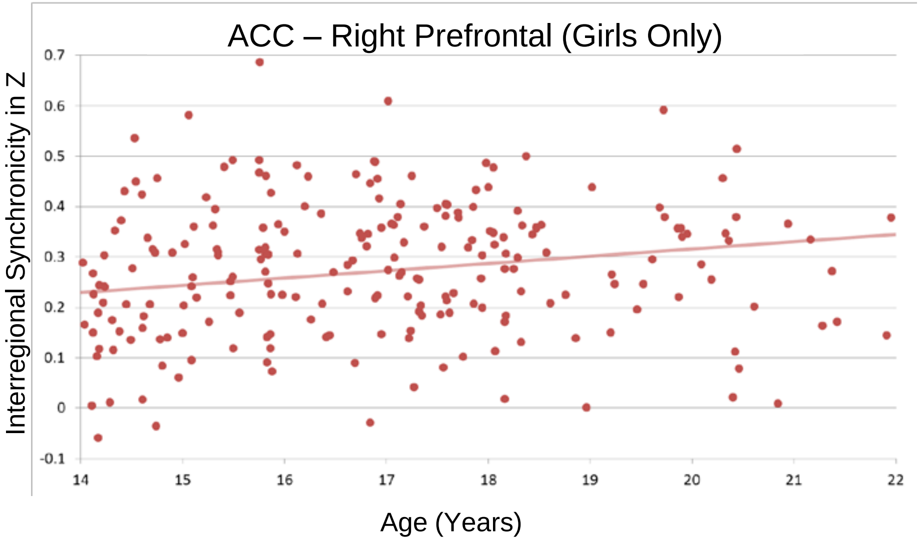
(Boys Only)



(Girls Only)

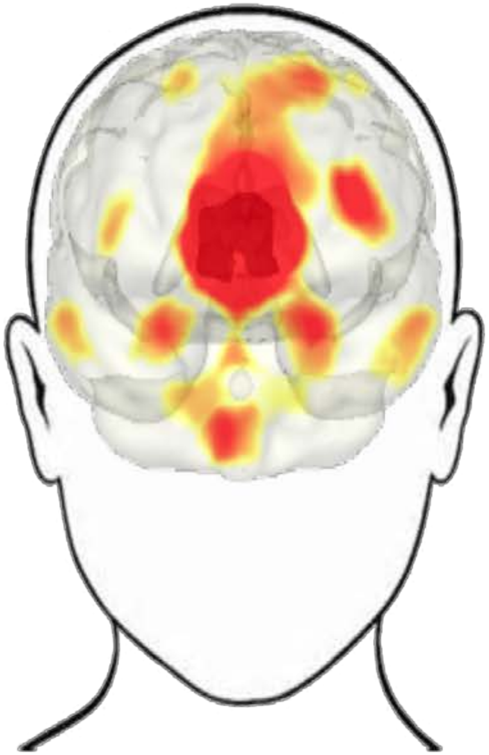


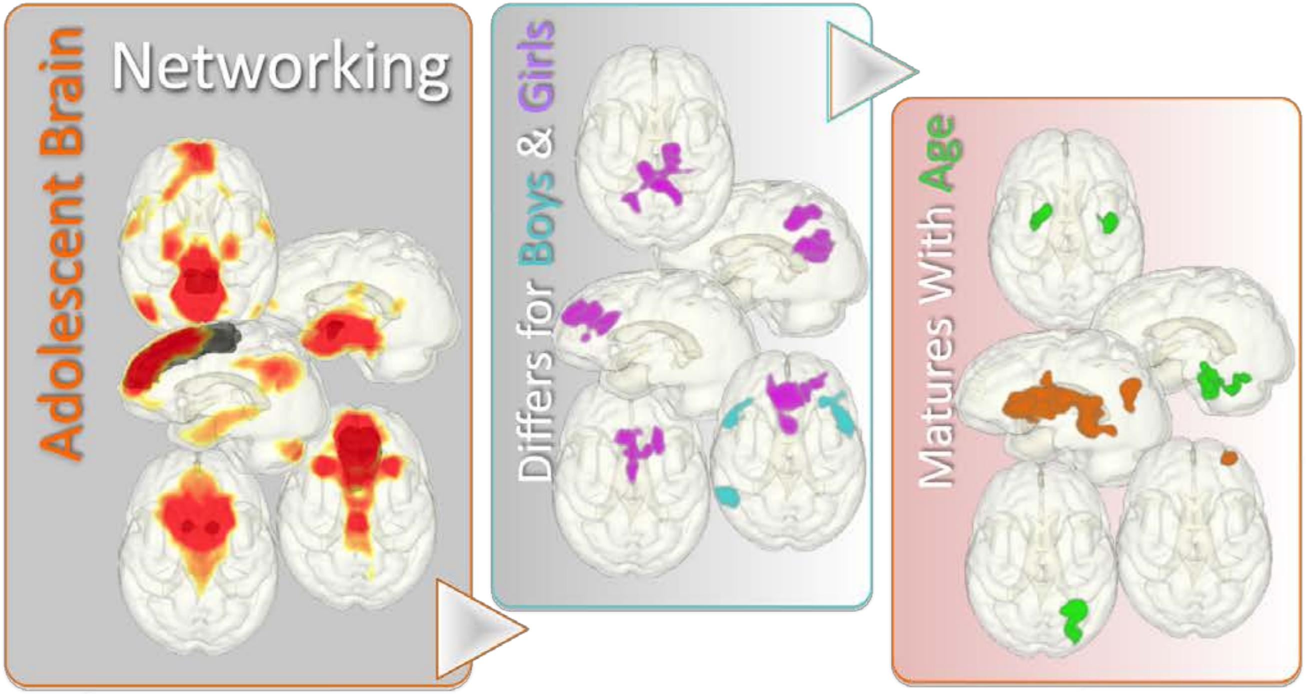




Müller-Oehring et al. 2017. Cerebral Cortex.

Sex and Age
Adolescent Intrinsic Network Connectivity



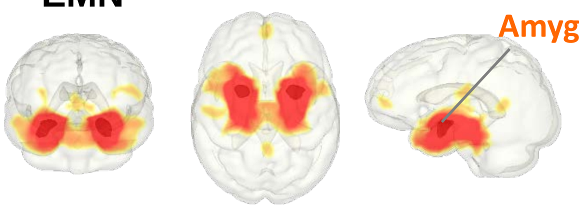


Maturation of adolescents functional brain networks is marked by heterochronicity related to age and sex characterizing “intrinsic network rewiring” to support increasingly sophisticated cognitive abilities, motor performance, self-regulation, and reward-focused processing.

Adolescent Intrinsic Network Connectivity
Alcohol Use History

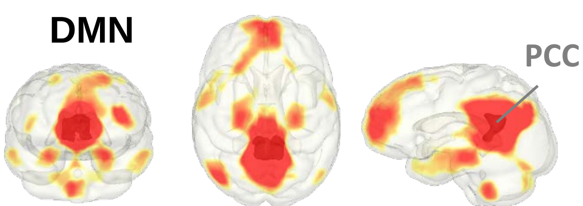
Emotion Network

EMN

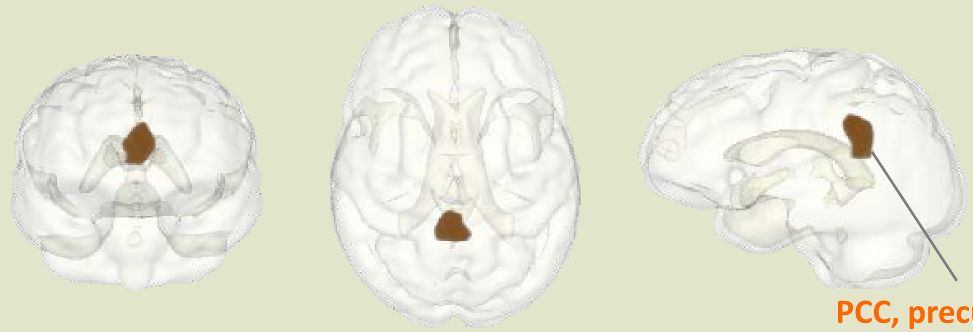


Default mode Network

DMN



Alcohol Use History: No/Low > Exceeds



n=117 adolescents exceeding alcohol/drug use criteria
n=117 no/low alcohol/drug using adolescents matched in age, sex, education, ethnicity, ratio of scanner manufacturer

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.

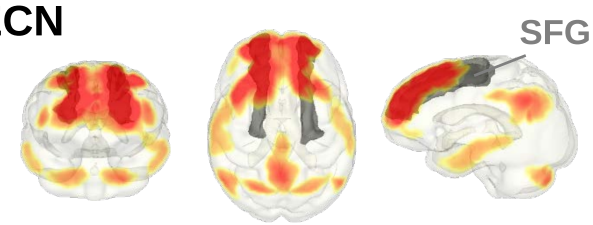
ADOLESCENT BRAIN DEVELOPMENT

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

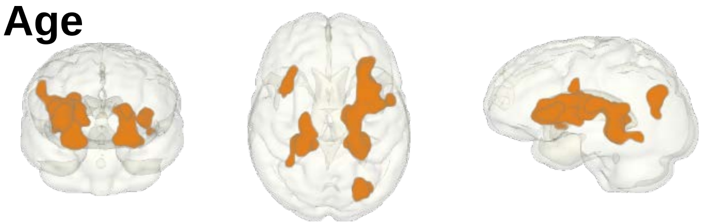
- **inhibitory circuitry during task engagement (executive control ability)**

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

ECN

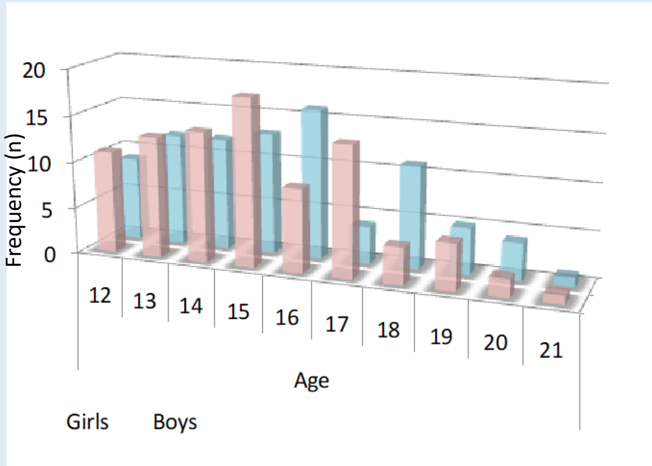


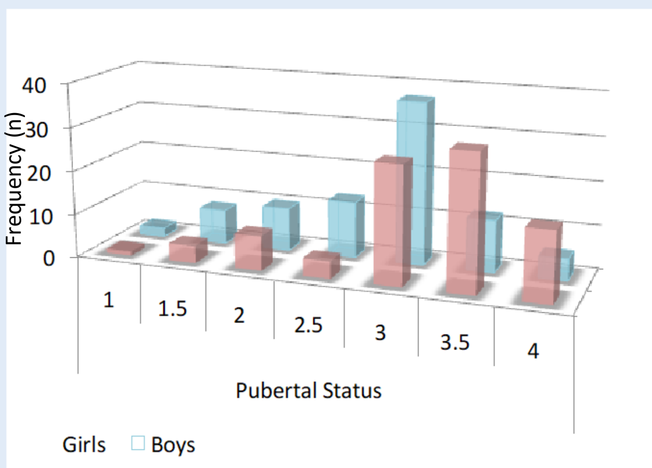
ECN: Age



SFG – Left+Right Insula, Inferior Lateral Frontal, Hippocampus, etc.

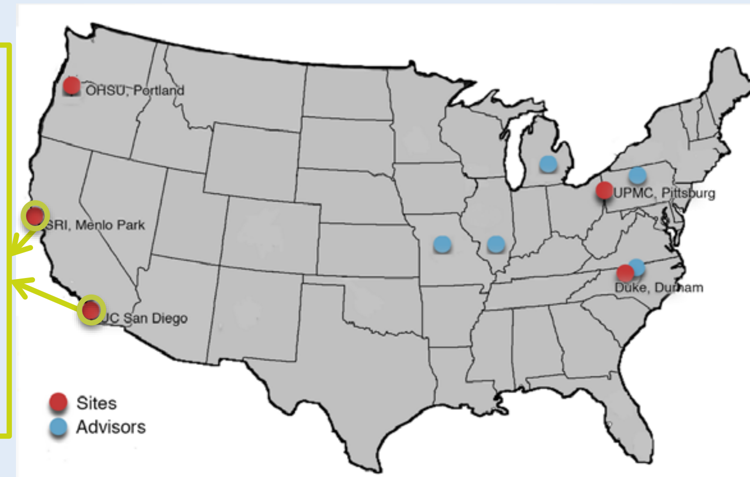
Inhibitory functioning and executive control: Task-Activated fMRI





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)



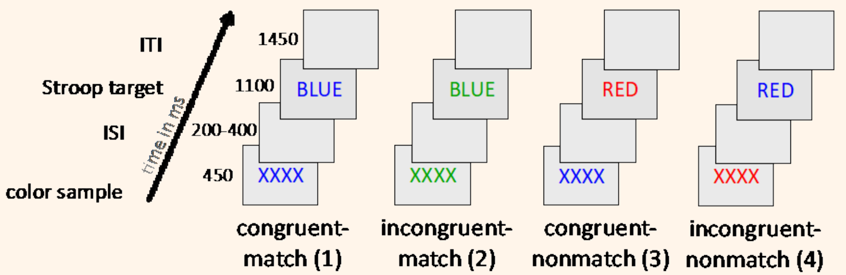
	Boys	Girls	df	p
N	87	91	1	
Age	16±2.34	15.67±2.19	176	.332
Site (UCSD/SRI)	69/18	65/26		.223[a]
PDS[1]	2.93±.7	3.34±.65	176	*.001*
Parent SES	92.06±16.05	90.36±15.15	171	.476
Parent Years of Education	16.76±2.98	16.8±2.46	175	.92
WRAT[2]				
Reading	115.86±16.387	112.97±15.882	176	.233
Math	115.63±15.611	113.32±16.015	176	.331

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).

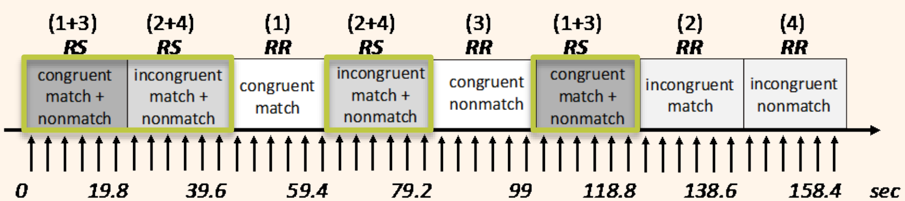
Testing the Inhibitory Circuitry with the Stroop task

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."



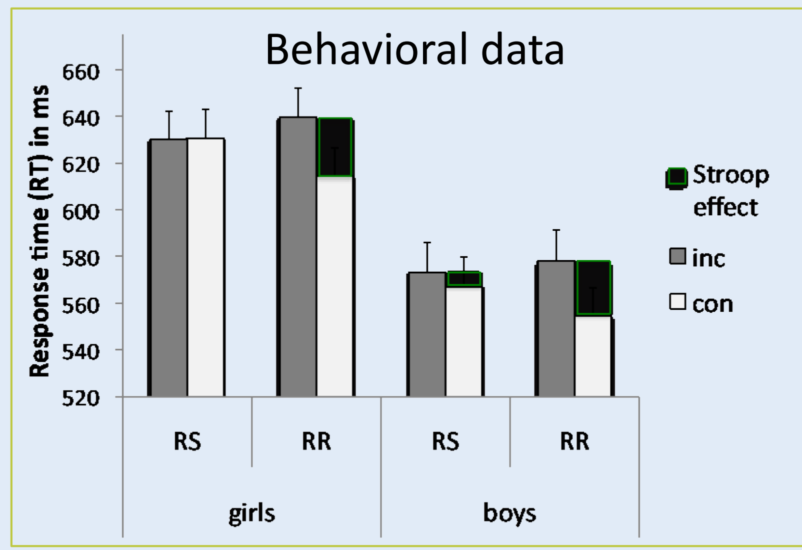
Implicit manipulation of motor responses with a blocked design:
Response switching (RS) versus response repetition (RR)



Cognitive control = Stroop effect (inc vs. con)

BLUE (inc) vs. BLUE (con)

Motor response control = RS vs. RR

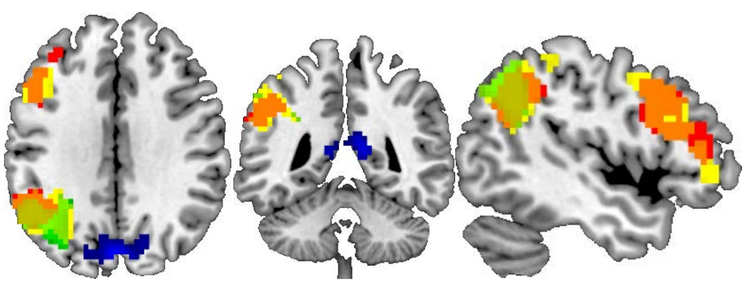


Inhibitory Circuitry

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

Cognitive Control

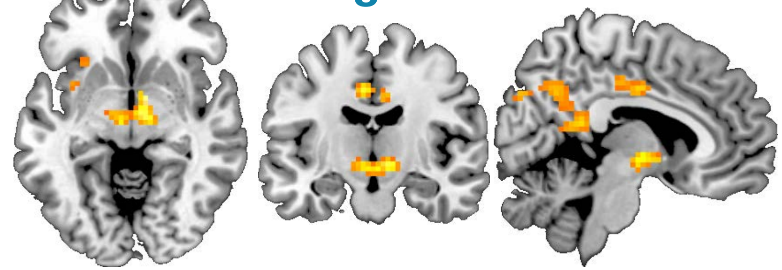
Fronto-parietal regions



dlPFC, SPL/IPL, PCC
Stroop (inc > con)
CTL ALC
CTL (con > inc)

Motor Control

Cerebellar-BG-motor cortical regions



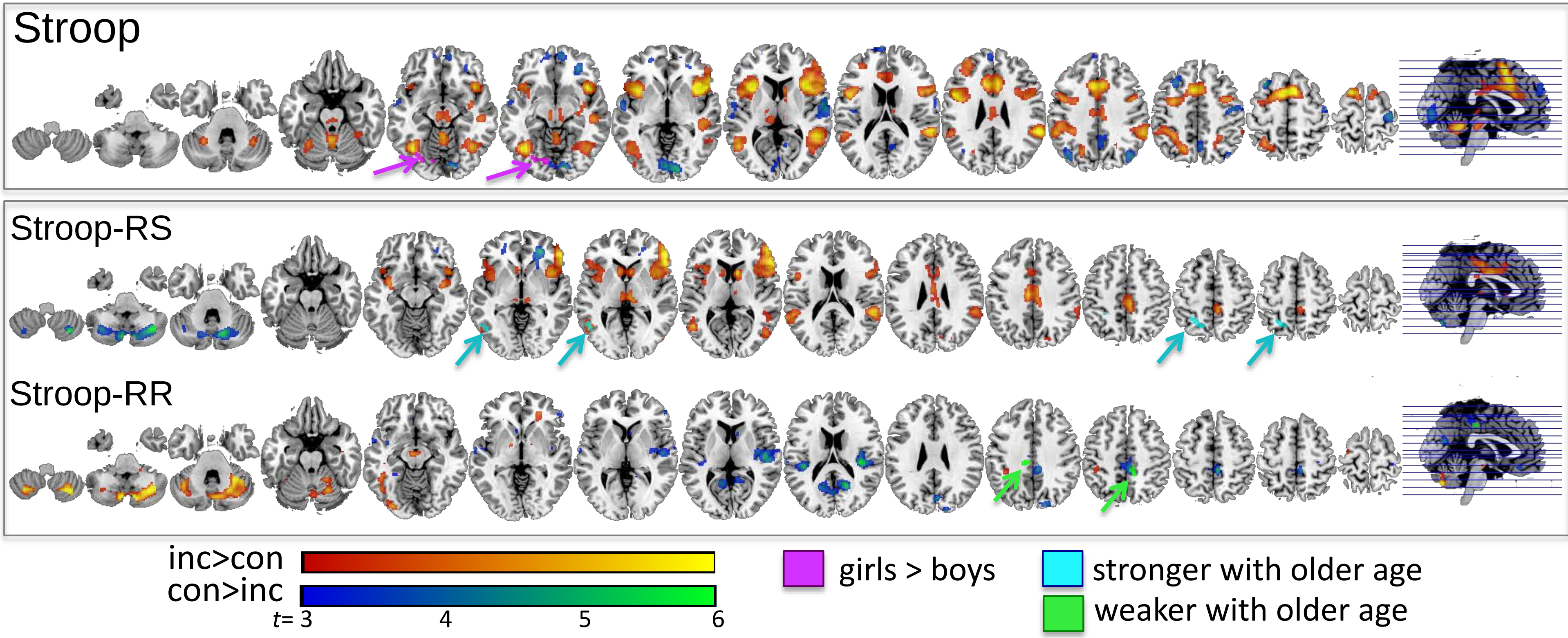
MCC, PCC, midbrain
ALC > CTL for
Stroop-repetition > Stroop-switching

Schulte et al., 2012. Biological Psychiatry

Inhibitory Circuitry in Adolescents

Cognitive Control

Fronto-parietal regions



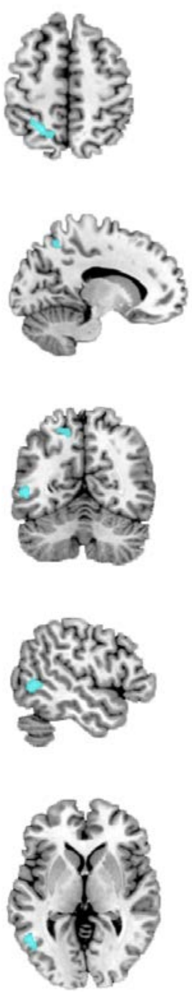
Cognitive control = Stroop effect (inc vs. con)

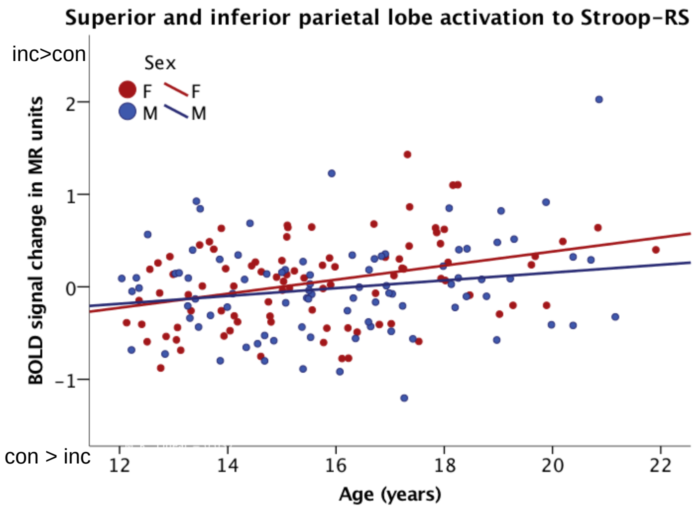
BLUE (inc) vs. BLUE (con)

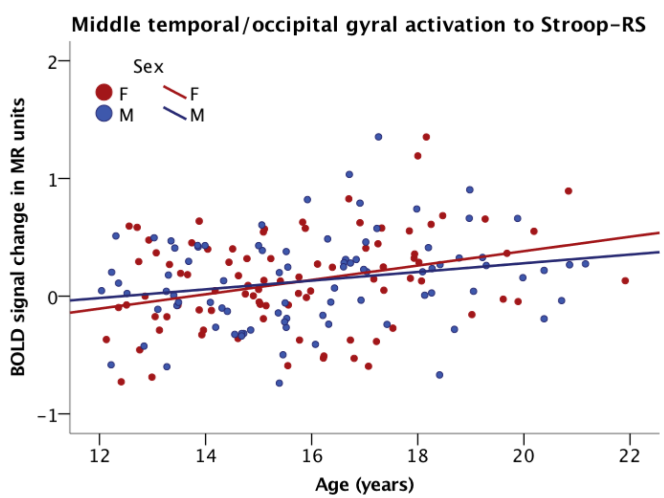
Inhibitory Circuitry: Cognitive control and Age

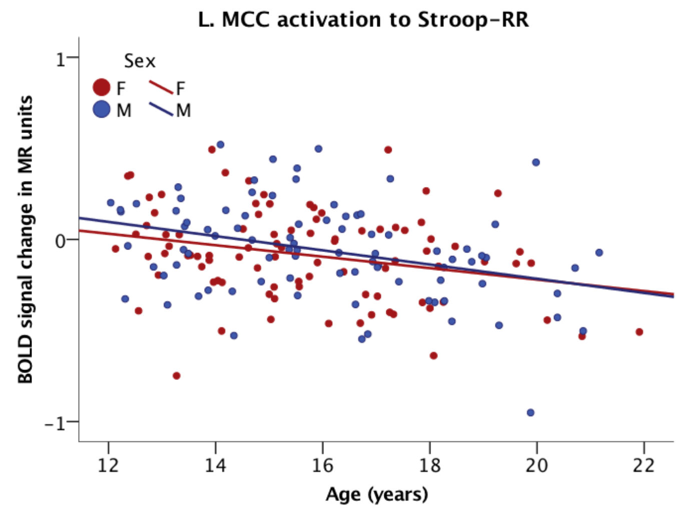
Stroop-RS : parietal, occipital

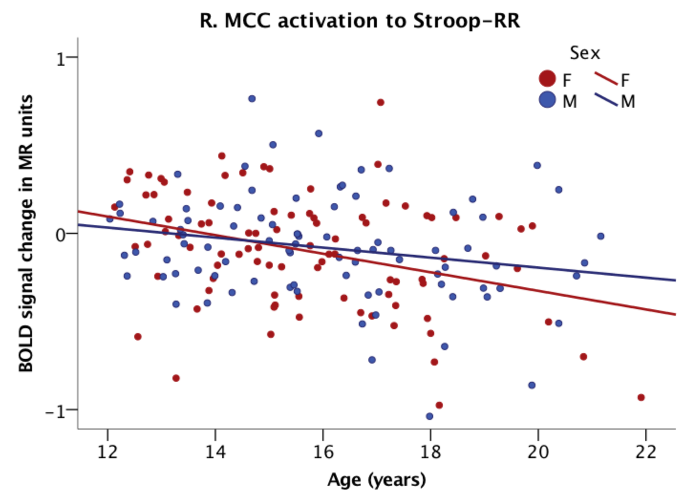
Stroop-RR: middle cingulate cortex (MCC)





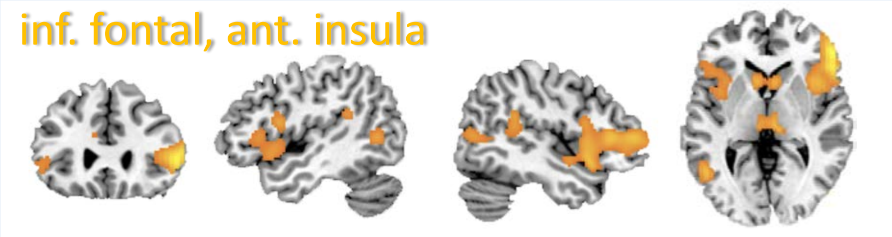


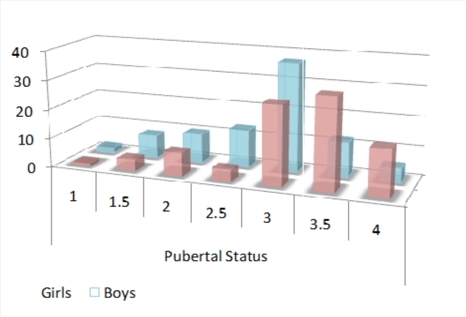


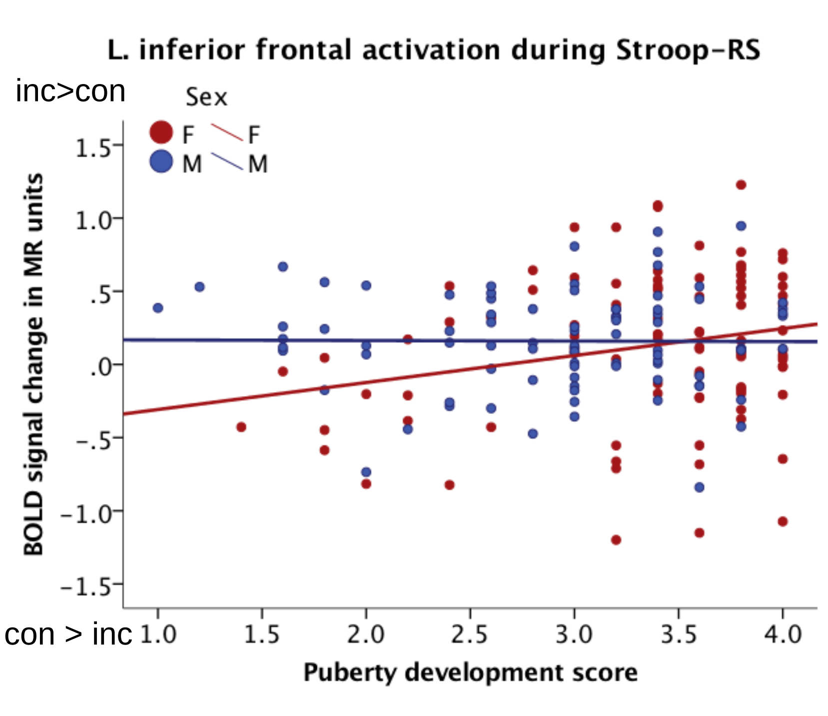


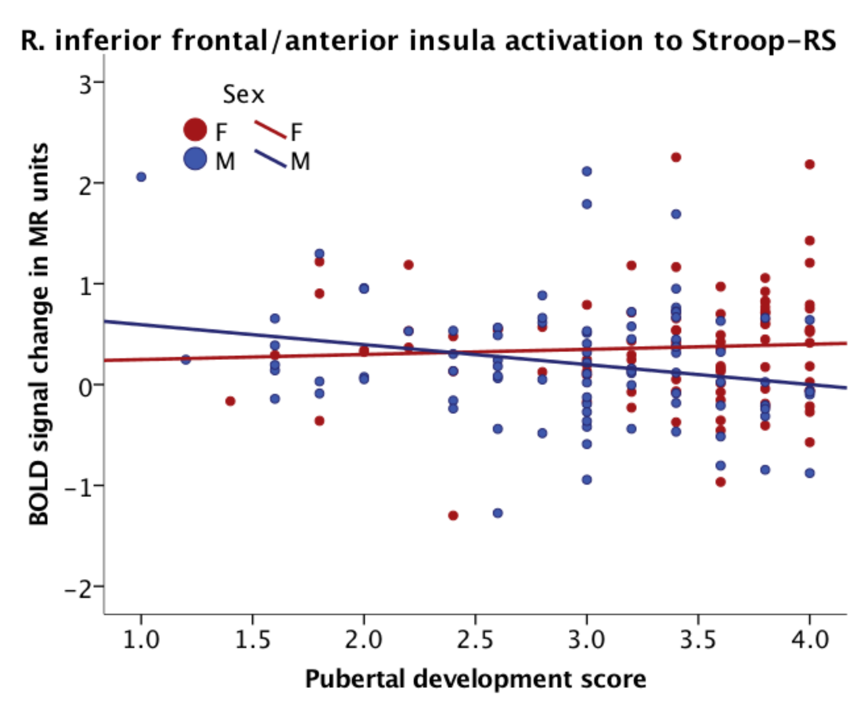
Inhibitory Circuitry:
Cognitive control and Pubertal Development

Stroop-RS









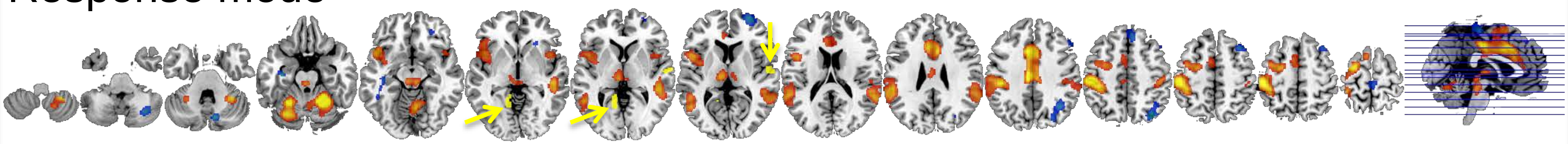
Pubertal development score: 1=puberty not started, 4=puberty completed

Inhibitory Circuitry in Adolescents

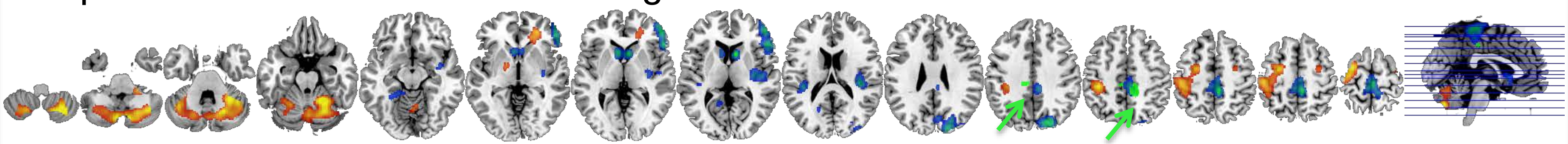
Motor Control

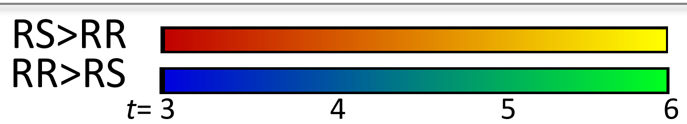
Cerebellar-BG-motor cortical regions

Response mode



Response mode for non-conflict congruent trials

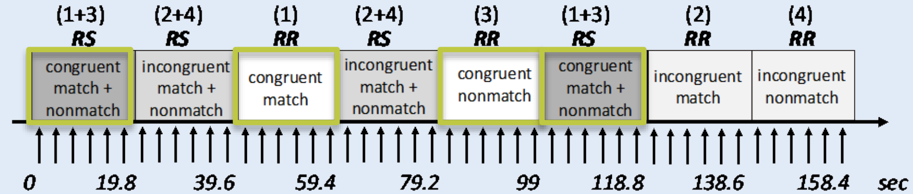




boys > girls

weaker with older age

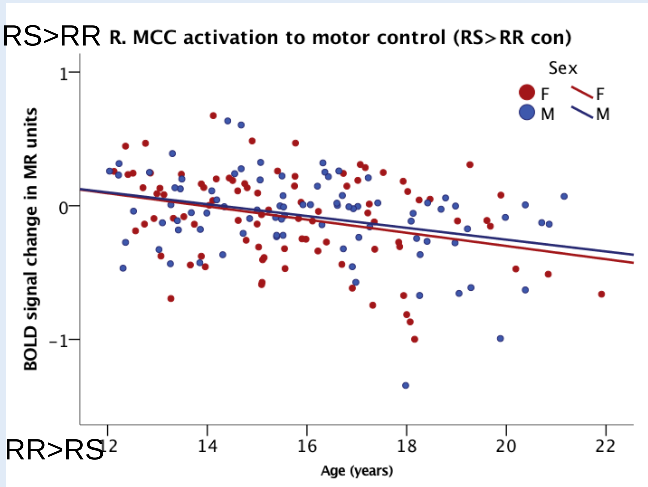
Response Switching vs. Repetition
= RS vs. RR

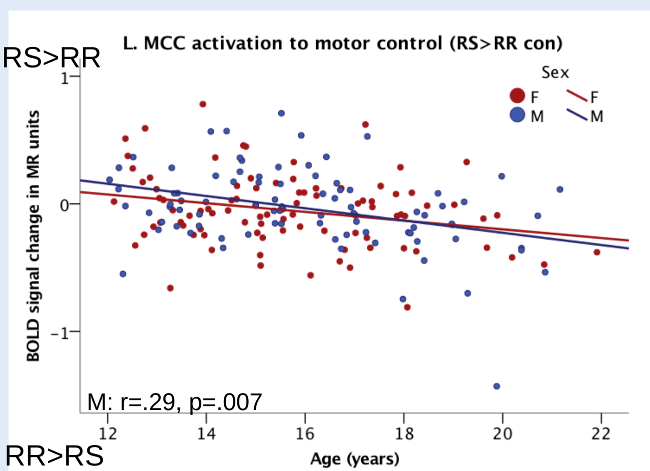


Inhibitory Circuitry:
Motor Control, Age, and Pubertal Development

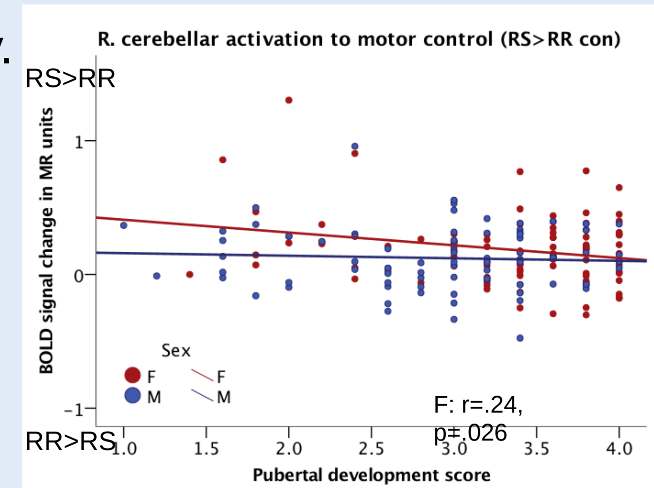
Response Switching vs Repetition (CON trials only: no cognitive conflict)

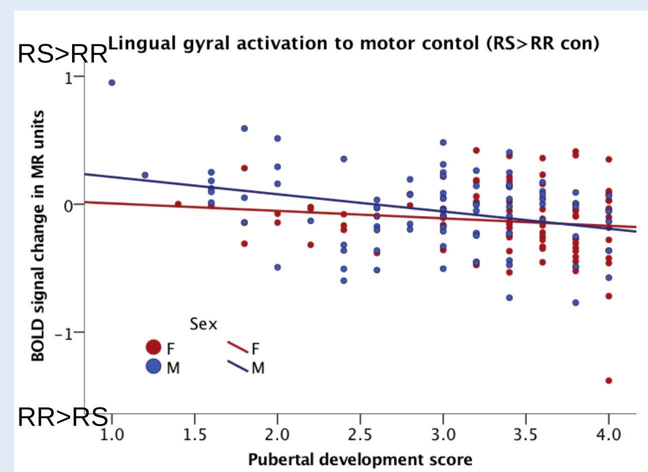
Age





Pubertal Dev.





Summary and Conclusions

‘Neurofunctional Rewiring’ in Adolescence

Sexual dimorphism – pubertal development

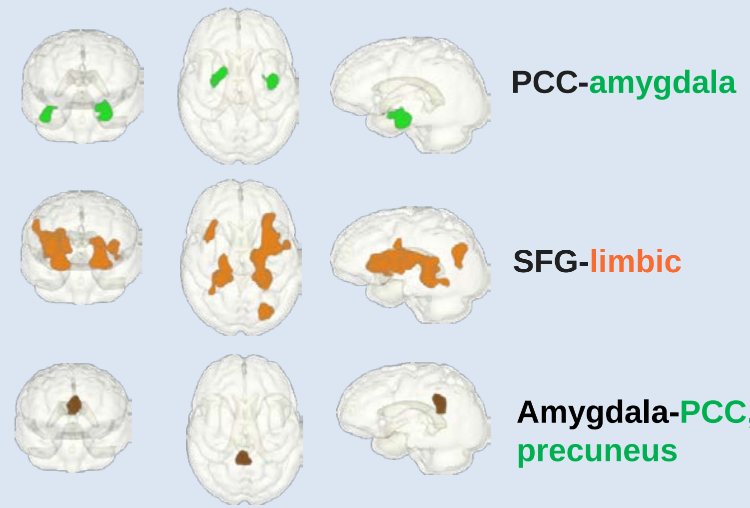
- Boys showed a more spatially distributed SAN connectivity
- Girls showed stronger connectivity to regions more primal to the seed
- Sex differences in frontal, extratriate, and cerebellar activation depending on control demands and related to pubertal development

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

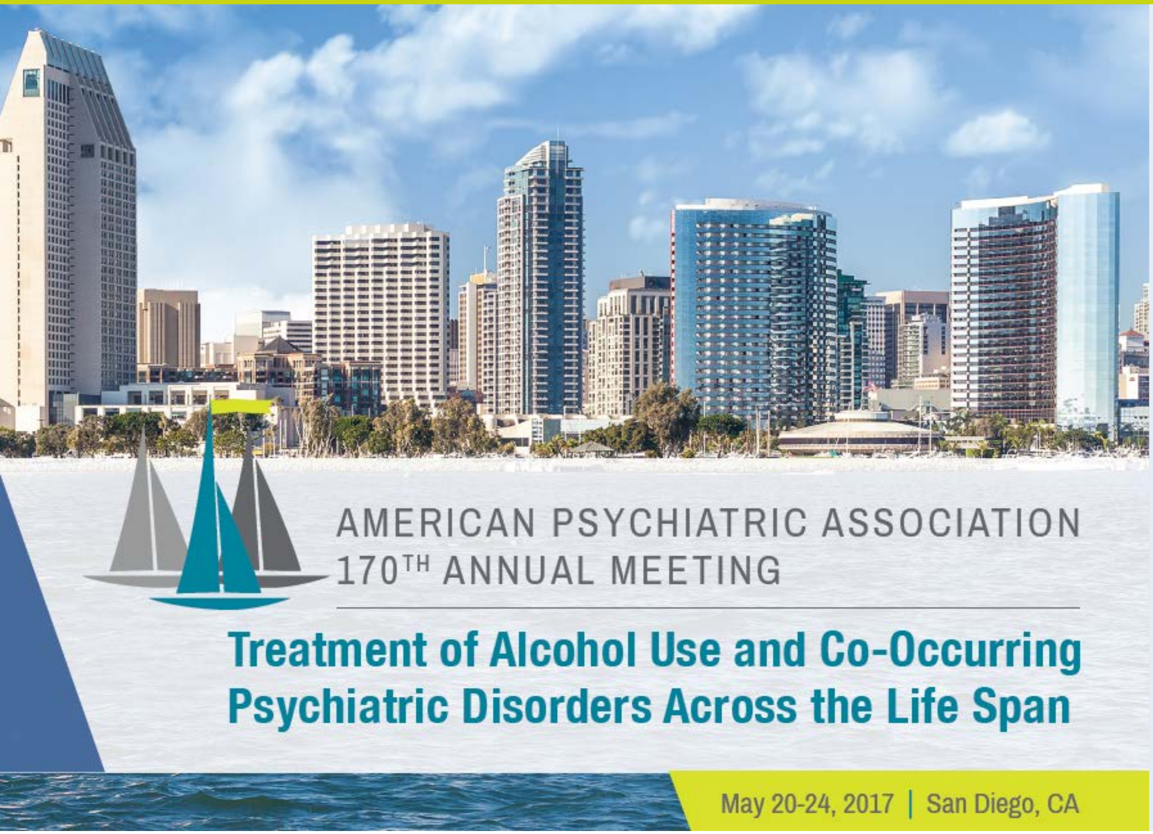
- more parietal, occipital activation for high cognitive & motor control demands
- less MCC activation for low control demands

DAY 5 | WEDNESDAY, MAY 24, 2017

8:00 a.m. – 11:00 a.m. | Room 25C, Upper Level | SYMPOSIUM

Neuromaturational Consequences and Predictors of Heavy Drinking: Findings from the Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA)

THANK YOU



and all NCANDA co-authors

Fiona C. Baker, Sandy A. Brown,
Ty Brumback, Weiwei Chu,
Duncan B. Clark, Ian M. Colrain,
Kevin Cummins, Michael D. De Bellis,
Jui-Yang Hong, Dongjin Kwon,
M.J. Meloy, Bonnie J. Nagel,
Adolf Pfefferbaum, Kilian Pohl,
Devin Prouty, Tilman Schulte,
Edith V. Sullivan, Susan F. Tapert,
J.T. Voyvodic

AM2017 Rotating Slides