Functional Brain Networks Related to Sex, Age, and Alcohol in Adolescence:

Initial Resting-State fMRI Findings from NCANDA

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NCANDA Workshop
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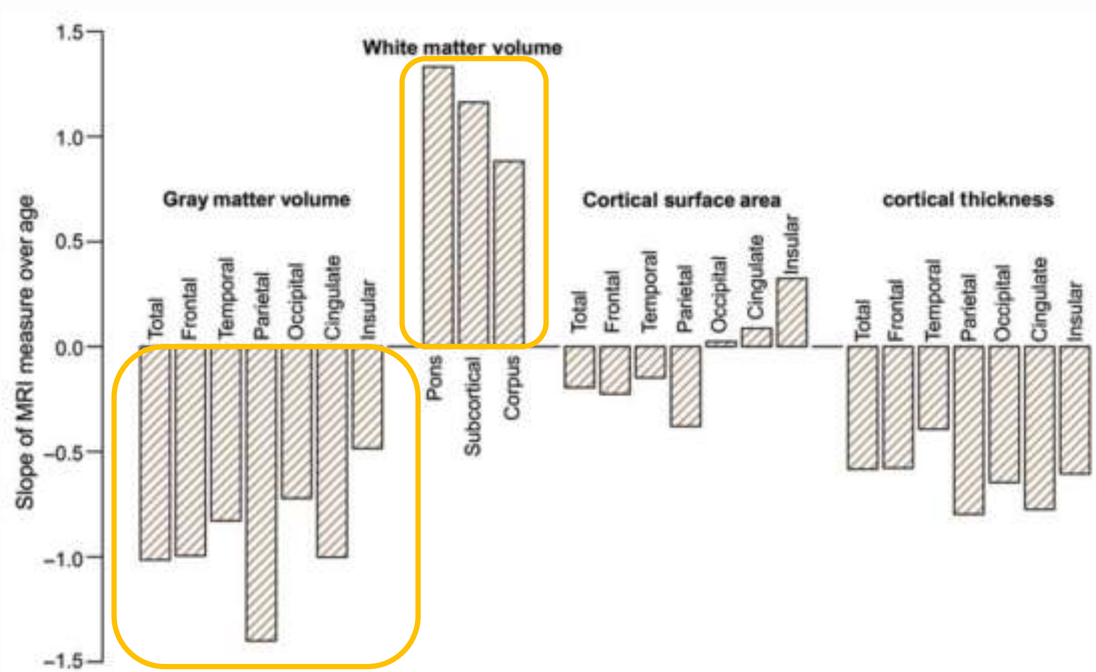
INTRODUCTION

- ➢ Neurodevelopment of brain structure continues throughout adolescence

- ➢ Our cross-sectional analysis of the NCANDA MRI baseline data show age-related differences in brain structural measures:



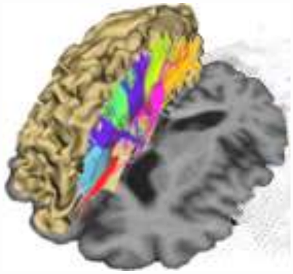
(from: Pfefferbaum et al., 2015, Cerebral Cortex)

- ○ where older adolescents had larger white matter and

- ○ smaller gray matter values than the younger ones,

indicative of development and neuronal pruning.

INTRODUCTION

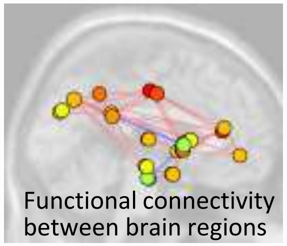


- These processes during adolescence suggest neural rewiring of large-scale cortical and subcortical networks by forming complex fiber connections.

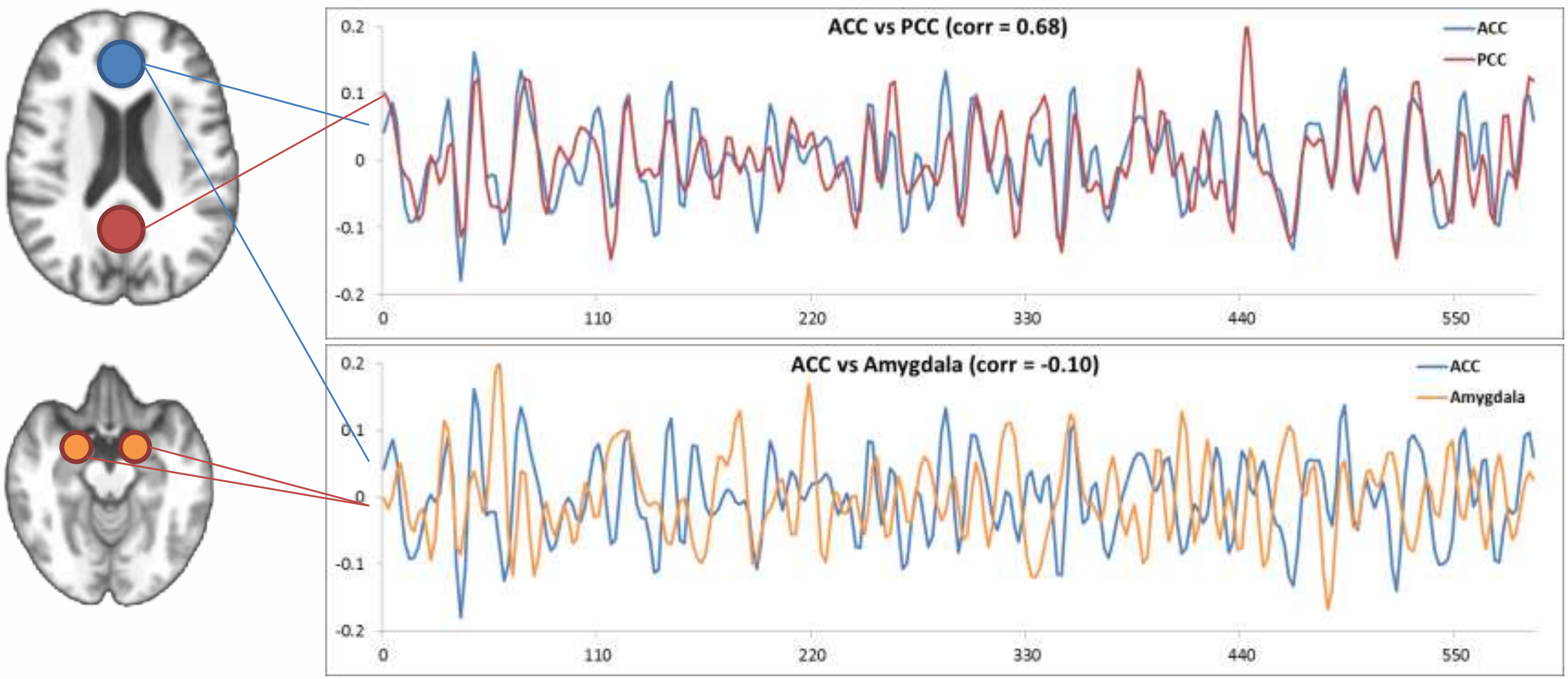
- to support the increasingly sophisticated cognitive abilities, motor performance, self-regulation, and reward-focused processing during adolescent development

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

INTRODUCTION



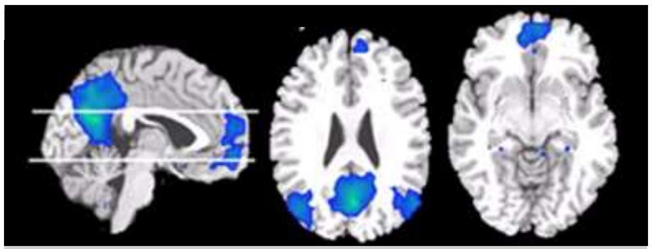
- Neurofunctional characteristics underwriting cognitive, motor, self-reflectory and social-emotional function in adolescence can be captured with whole-brain, resting-state functional MRI (rs-fMRI).



NCANDA S00159; 15 year old girl

INTRODUCTION

Intrinsic connectivity of the DMN

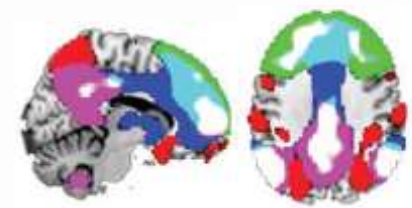


(Menon & Uddin, 2010)

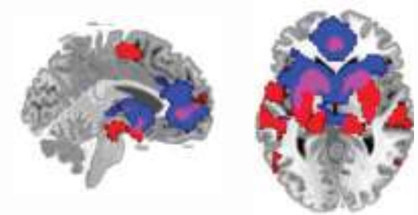
Default mode network (DMN) structures

- are maximally active and functionally coupled during REST
- are typically deactivated and functionally decoupled during TASKS

Self-referential and integrative function



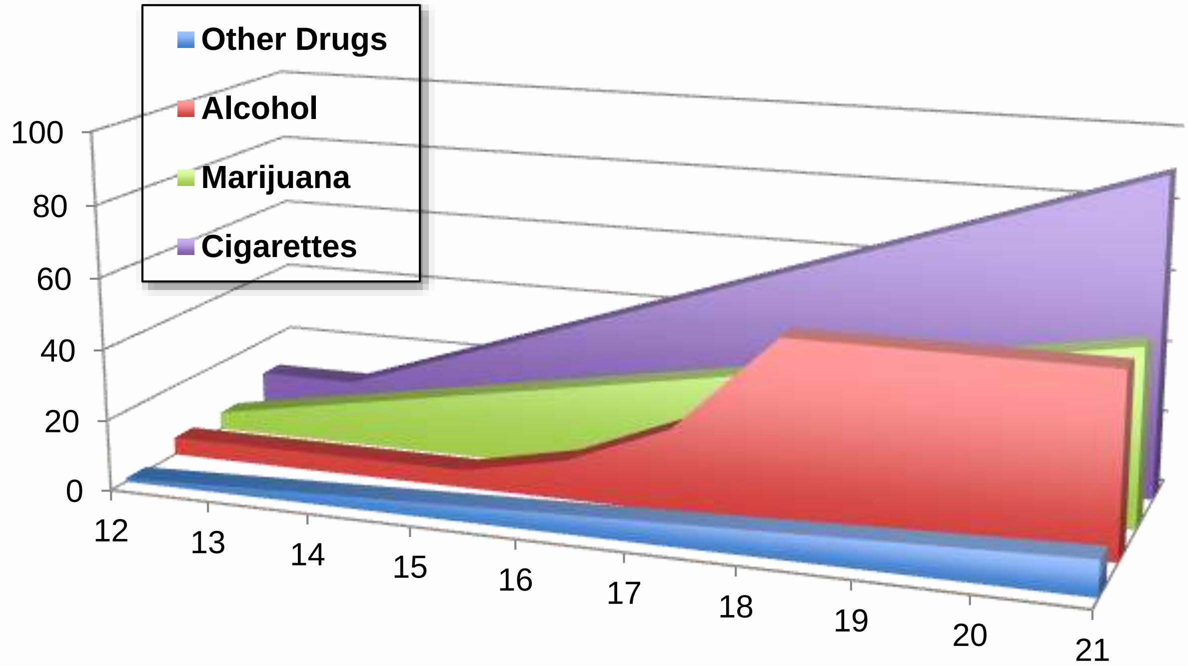
Subcortical emotion and reward function



Müller-Oehring et al., 2014

➢ Using rs-fMRI and functional connectivity analysis, we aimed to test the intrinsic organizing networks underwriting neurodevelopment of selective brain functions
  - at different ages
  - sex differences (boys, girls)
  - alcohol use history.

NCANDA alcohol and drug use criteria



METHODS

Neuroimaging

Resting-state fMRI

Neuropsychological testing

Executive function
Motor function
Emotion function
Reward seeking
General ability

Harmonizing resting-state fMRI collected across five sites, we examined

- **581 adolescents** meeting criteria for no-to-low alcohol or drug consumption and
- **117 recruits exceeding** these criteria.

PARTICIPANTS

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)

Study groups	N *Total*	N *Girls/ Boys*	N *GE / Siemens*	PDS[1]	Parental education (years)	Highest Grade	WRAT[2] *Reading*	WRAT[2] *Math*
No/low alcohol use history								
12-14	231	124/107	161/70	2.7±0.7 (1-4)	16.8±2.5 (6-20)	6.9±0.9 (5-9)	118±18 (82-145)	114±16 (76-145)
15-17	234	120/114	159/75	3.4±0.5 (1.8-4)	17.1±2.4 (6-20)	9.7±1.0 (8-13)	116±16 (80-145)	112±16 (66-145)
18-21	116	62/54	65/51	3.8±0.3 (2.6-4)	16.7±2.3 (6-20)	12.7±1.3 (10-15)	109±13 (84-139)	110±16 (75-143)
Total	**581**	**306/275**	**385/196**	**3.2±0.7 (1-4)**	**16.9±2.4 (6-20)**	**9.2±2.4 (5-15)**	**116±17 (80-145)**	**112±16 (66-145)**
Age (years)	15.9±2.3	15.9/15.9	15.7/16.3					
Exceeds criteria								
12-14	3	2/1	3/0	2.9±1.1 (1.8-4)	17.3±1.2 (16-18)	7.3±1.2 (6-8)	136±14 (120-145)	117±3 (114-120)
15-17	41	19/22	31/10	3.4±0.4 (2.6-4)	17.5±1.82 (14-20)	10.2±0.9 (8-12)	114±164 (87-145)	111±14 (79-139)
18-21	73	41/32	46/27	3.8±0.2 (3.2-4)	17.4±2.3 (12-20)	13.0±1.2 (10-16)	112±12 (85-139)	114±14 (72-143)
Total	**117**	**62/55**	**80/37**	**3.7±0.4 (1.8-4)**	**17.4±2.0 (12-20)**	**11.9±1.9 (6-16)**	**114±14 (85-145)**	**113±14 (72-143)**
Age (years)	18.6±1.9	18.6/18.7	18.5/19.0					

[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

NCANDA fMRI acquisition and preprocessing pipeline

Whole-brain structural and functional MRI data were acquired using

- *3T General Electric (GE) Discovery MR750* at three sites: 180 from UCSD; 132 from SRI; 153 from Duke
- *3T Siemens TIM TRIO scanners* at two sites: 99 from University of Pittsburgh; 134 from Oregon Health & Sciences University

For rs-fMRI: open eyes looking at a gray screen.

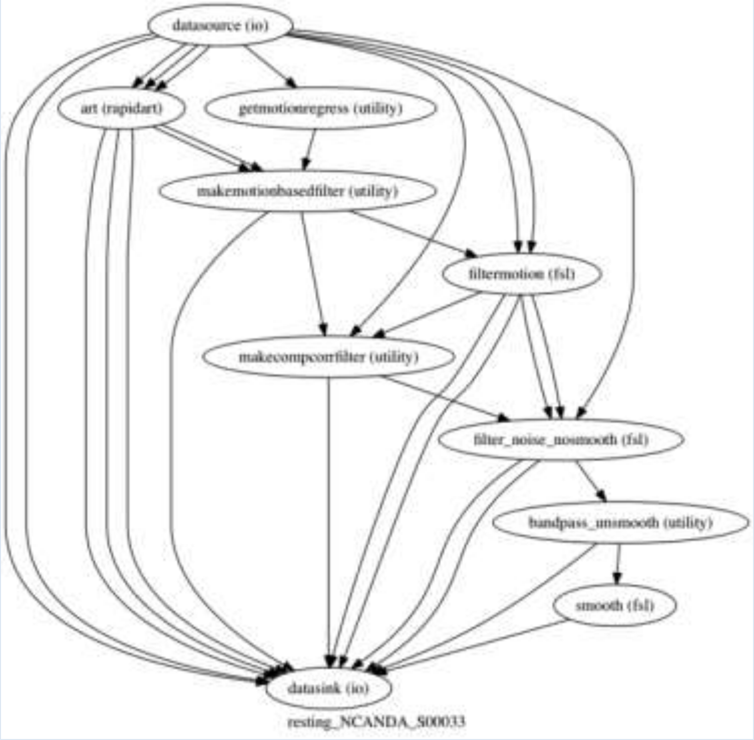
GE: 8-channel head coil

1) ***IR-SPGR*** (slice dimensions=1.2 x 0.9375 x 0.9375mm, 146 slices, acquisition time=7m 16sec); ***CUBE T2*** (slice dimensions=1.2 x 0.9375 x 0.9375mm, 146 slices, acquisition time=3m 26sec),
2) ***field map*** (TE=5/7ms, resolution=2.5 x 2.5 x 2.5 mm, acquisition Time=3m 24sec),
3) ***rs-fMRI*** 2D Axial Gradient-Recalled Echo-Planar (TR=2200ms, 32 slices, resolution=3.75x3.75x5 mm, 275 TRs; acquisition time=10m 03sec).

Siemens: 12-channel head coil

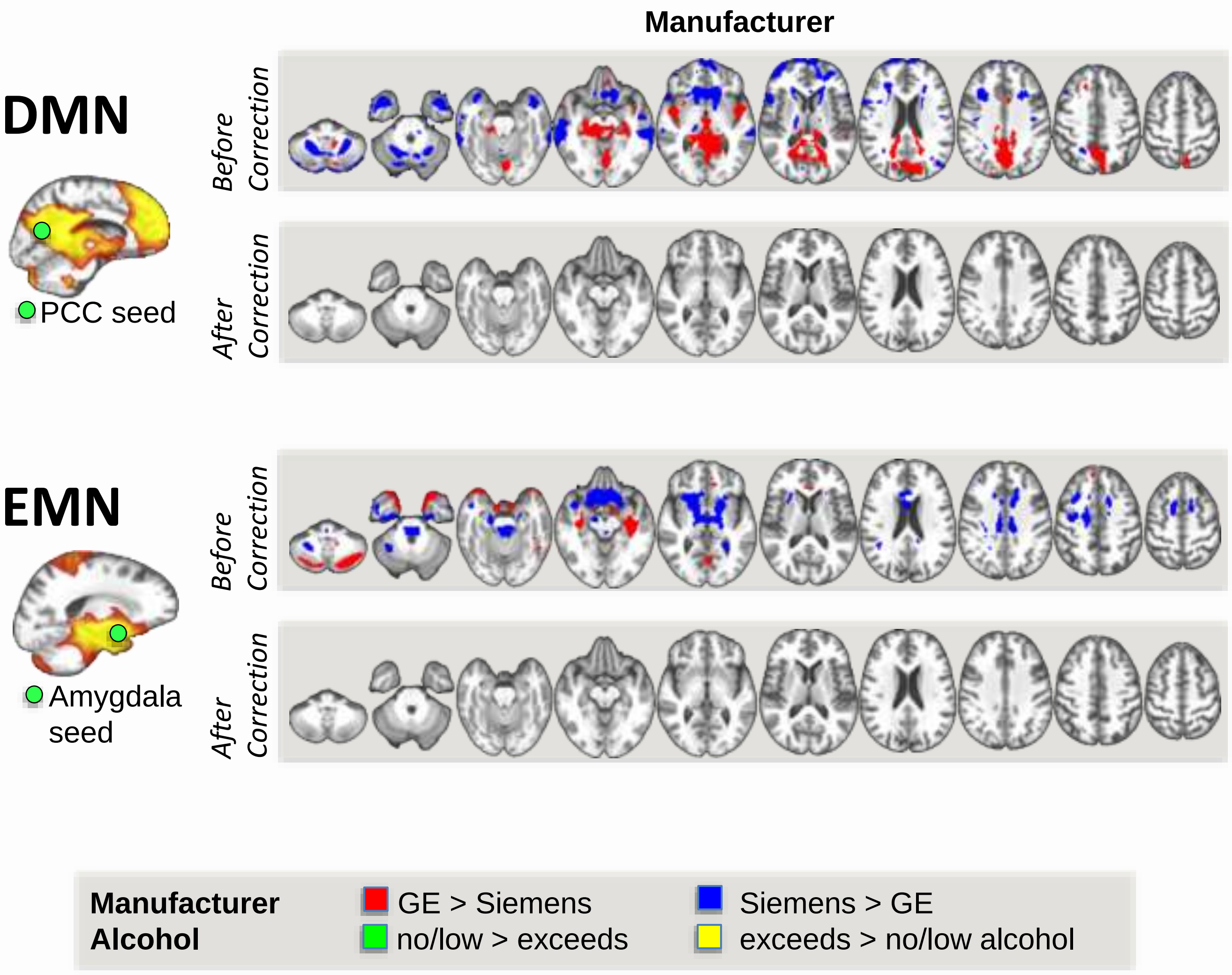
1) ***MPRAGE*** (slice dimensions=1.2 x 0.9375 x 0.9375mm, 160 slices, acquisition time=8m 8sec), ***t2 fse*** (slice dimensions=1.2 x 0.9375 x 0.9375mm, 160 slices, Acquisition Time=4m 18sec),
1) ***field map*** (TE=4.92/7.38ms, resolution=2.5 x 2.5 x 2.5mm, Acquisition Time=2m 16sec)
2) ***rs-fMRI*** 2D Axial Echo-Planar (TR=2200ms, 32 slices, resolution = 3.75x3.75x5mm, 275 TRs; acquisition time=10m 12sec).

rs-fMRI time series:
head motion detection and correction



Compute linear regressor: combined the motion outliers detected by Nipype rapidart with detrending parameters (norm threshold=0.3; intensity Z-threshold=5).
Censoring - interpolate removed frames: apply regressor via FSL GLM.
Physiological noise: detect via Nipype CompCor 19 and correct via FSL GLM.

Correction for Manufacturer Effects: Siemens vs. GE

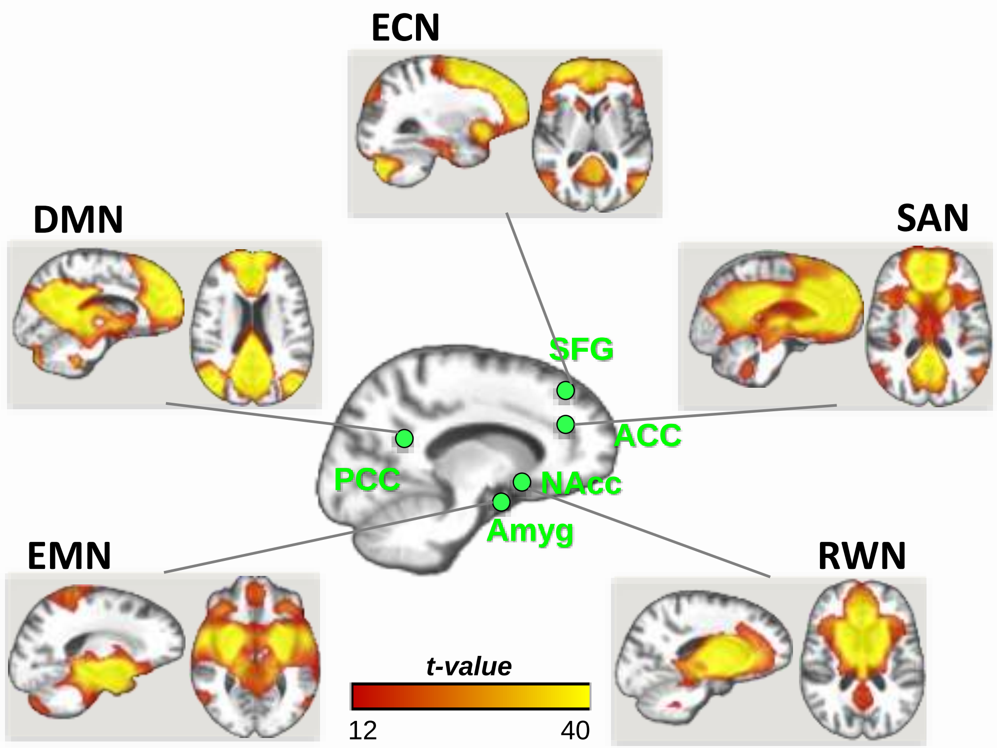


RESULTS

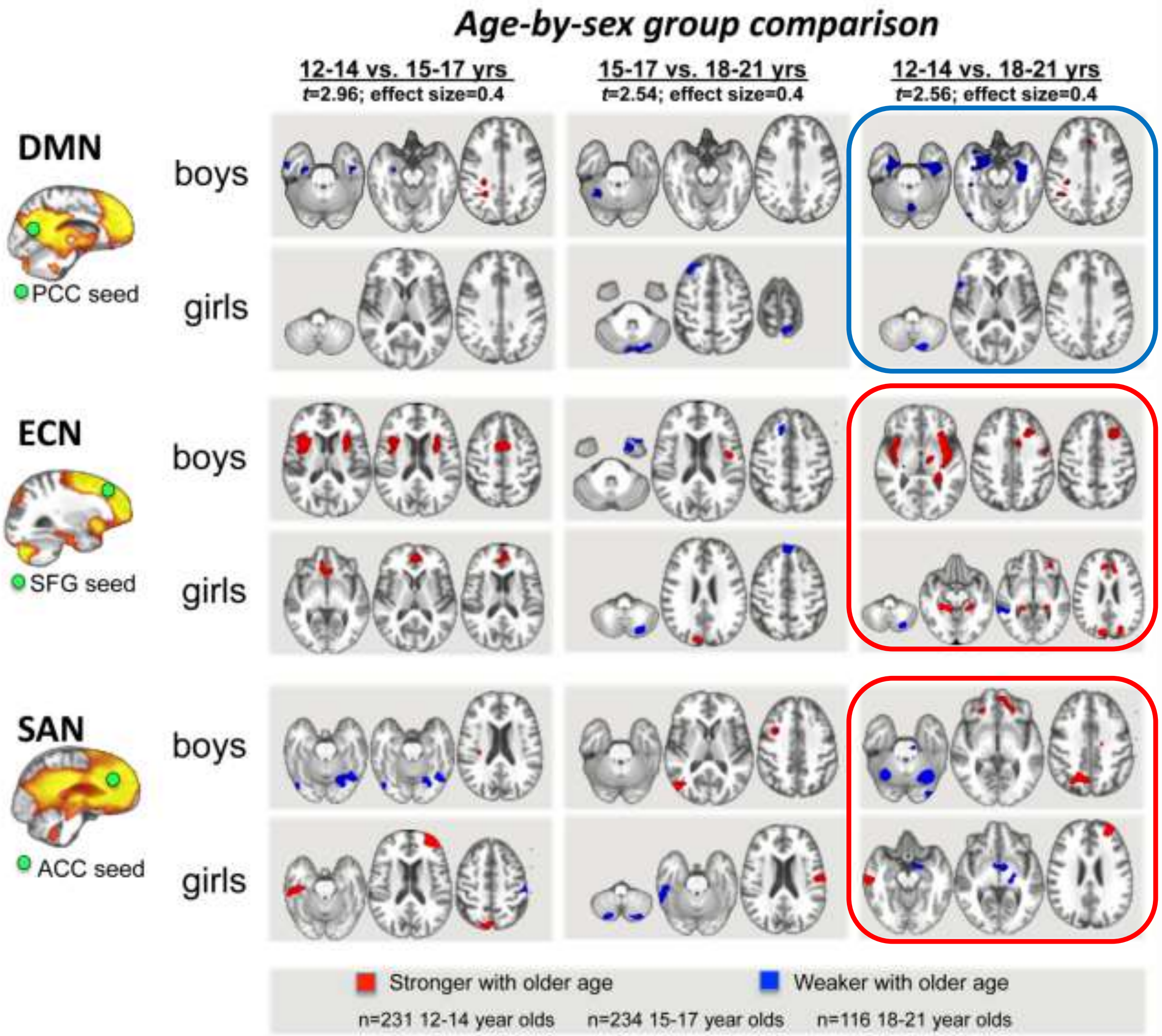
We examined seed-to-voxel functional connectivity for five networks:

1. **Default mode network** (DMN)
   seed: posterior cingulate cortex (PCC)
2. **Executive control network** (ECN)
   seed: superior frontal cortex (SFG)
3. **Salience network** (SAN)
   seed: anterior cingulate cortex (ACC)
4. **Emotion network** (EMN)
   seed: amygdala
5. **Reward network** (RWN)
   seed: nucleus accumbens (Nacc)

Intrinsic functional networks (IFN) in 581 no/low drinking adolescents



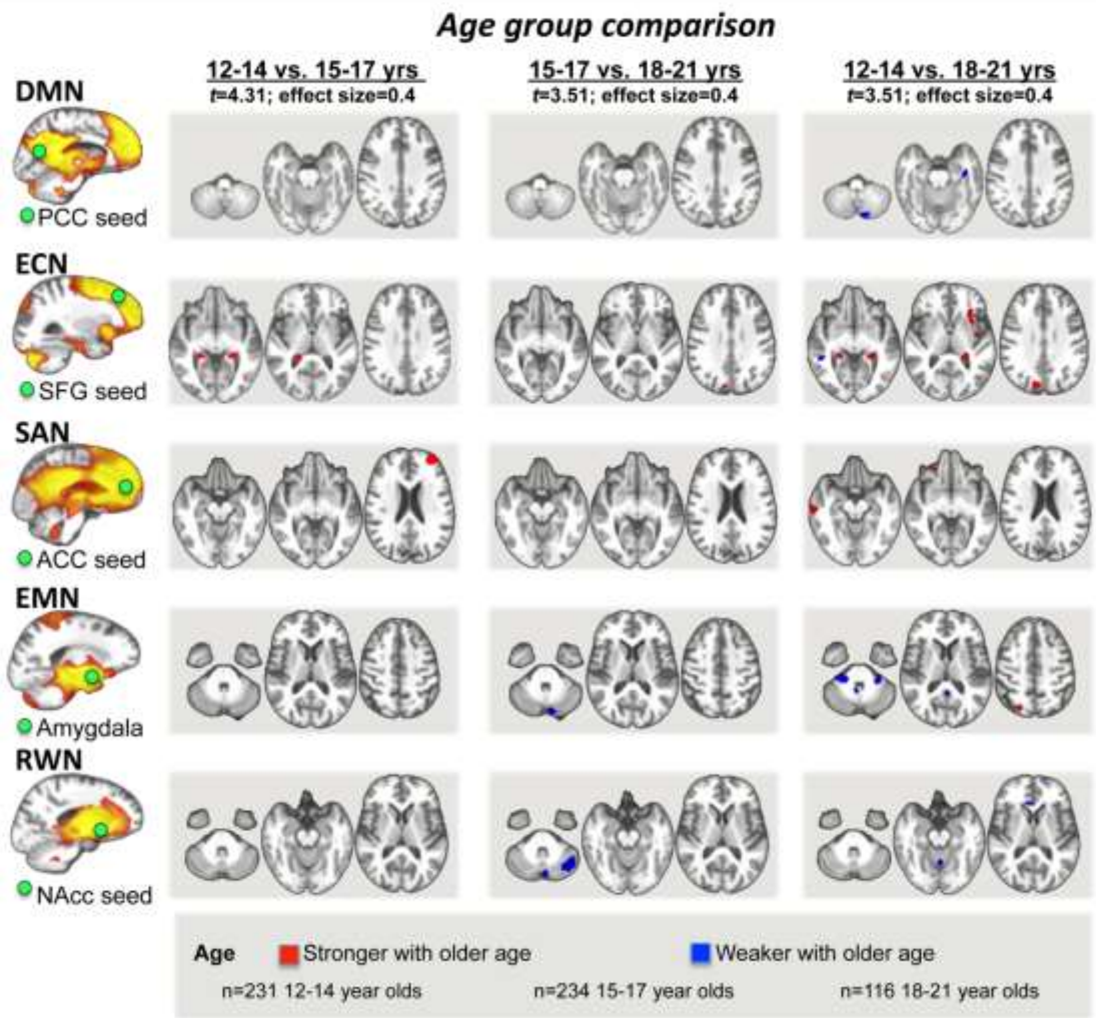
IFN differences between age groups



- Adolescents were categorized into three age groups: 12–14, 15–17, and 18–21 years old http://grants.nih.gov/grants/guide/rfa-files/RFA-AA-12-006.html

Connectivity in the executive and salience networks was stronger and spatially more distributed in older than younger adolescents, with boys showing greater spatial distribution than girls.

IFN differences between age groups

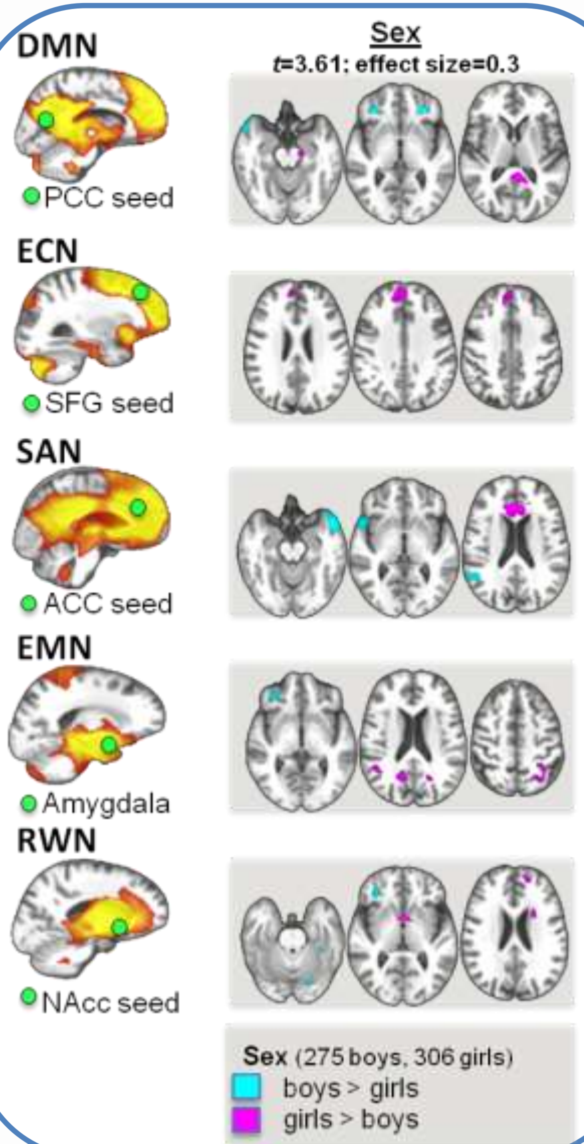


- Similar to structural brain development , ***IFN maturation during adolescence is marked by heterochronicity*** in its development of neurofunctional architecture.

Stronger and more distributed network connectivity in older than younger adolescents was observed for the ECN,
but not the DMN,

possibly indicative of later maturation of the ECN than the DMN.

IFN differences between boys and girls



- Boys showed more spatially distributed connectivity for all IFNs than girls, who exhibited stronger connectivity to regions more proximal to each network seed.

This is consistent with a recent finding from Satterthwaite et al 2015

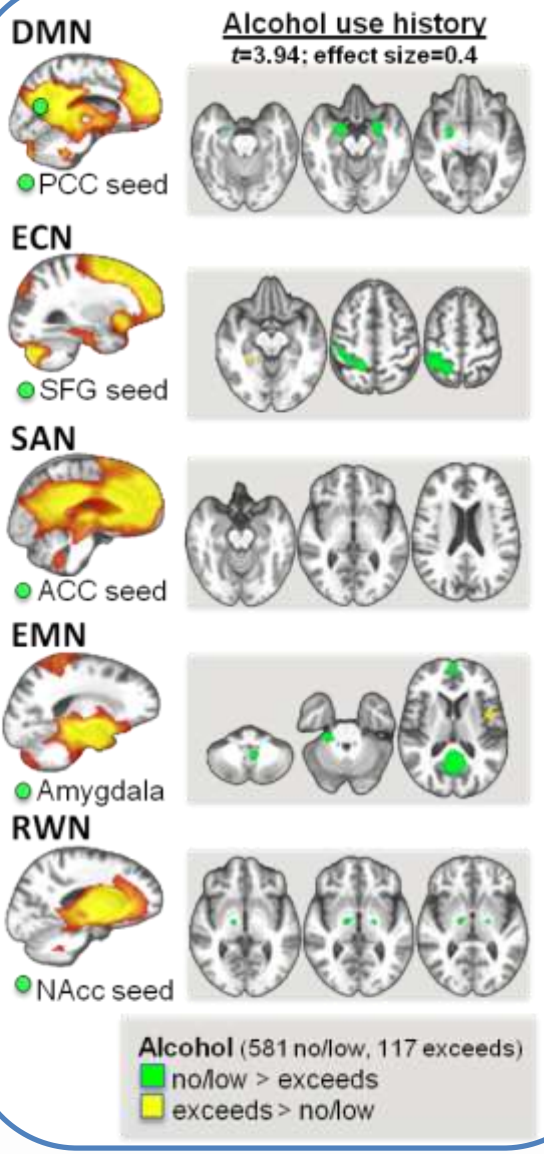
Boys: more between-module connectivity

Girls: within-module connectivity in girls,

Overall, developmental differences did not necessarily occur at a younger age in girls than in boys.

Rather, we observed sexual dimorphism in the patterns of age-related differences in connectivity strength.

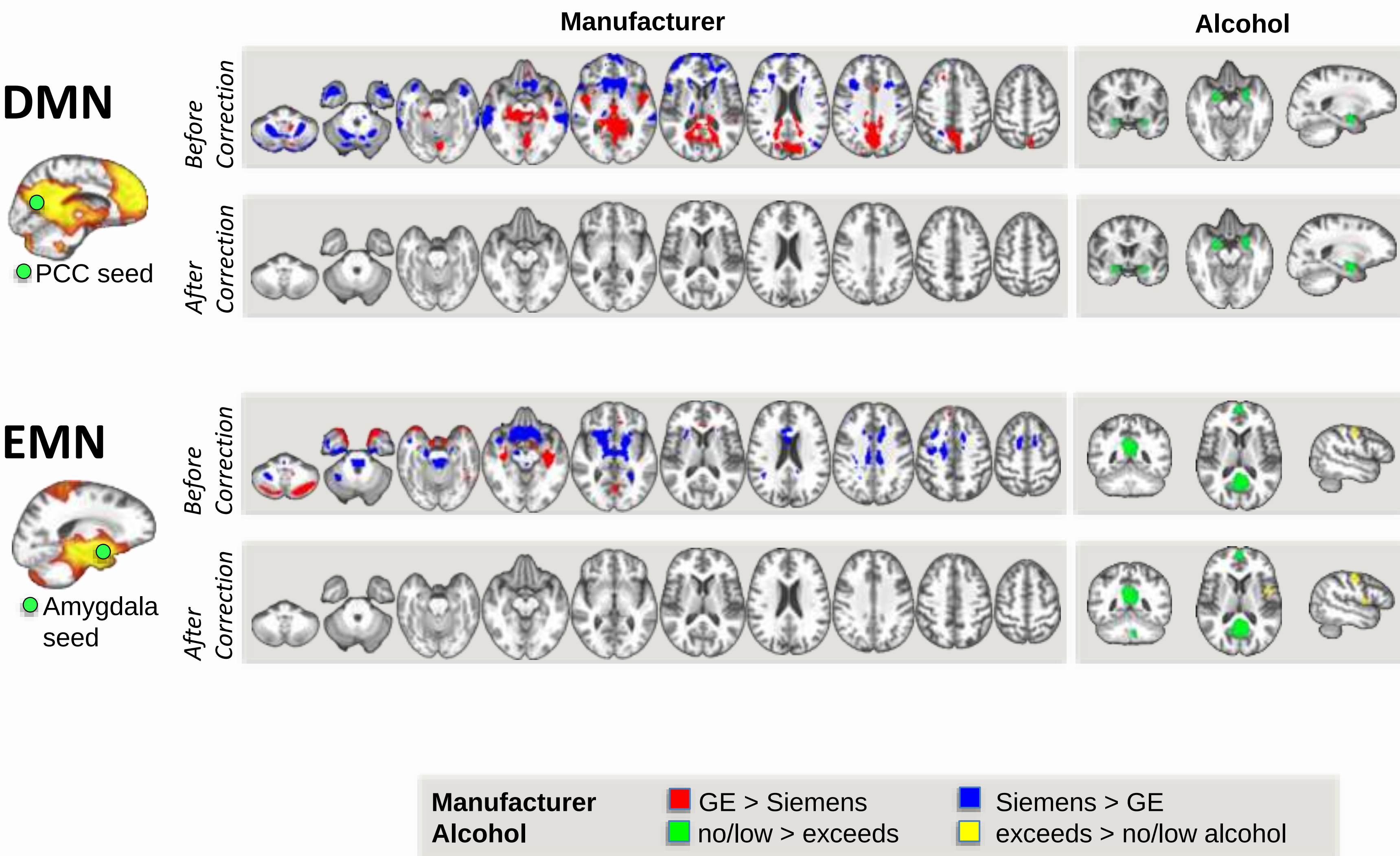
IFN differences between alcohol groups



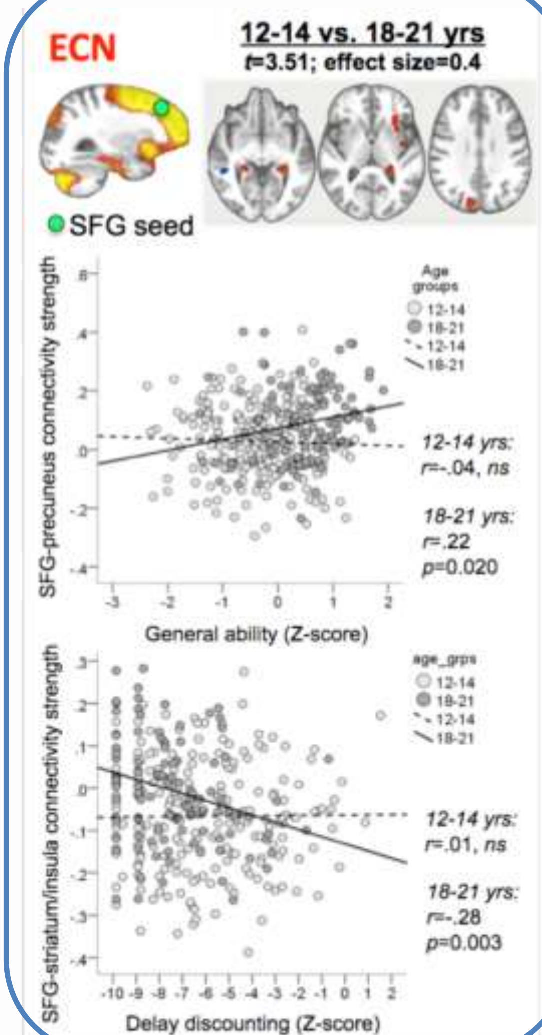
- The effect of alcohol use history was observed mainly in late adolescence as most of the adolescents who exceeded drinking criteria were in the oldest age group.

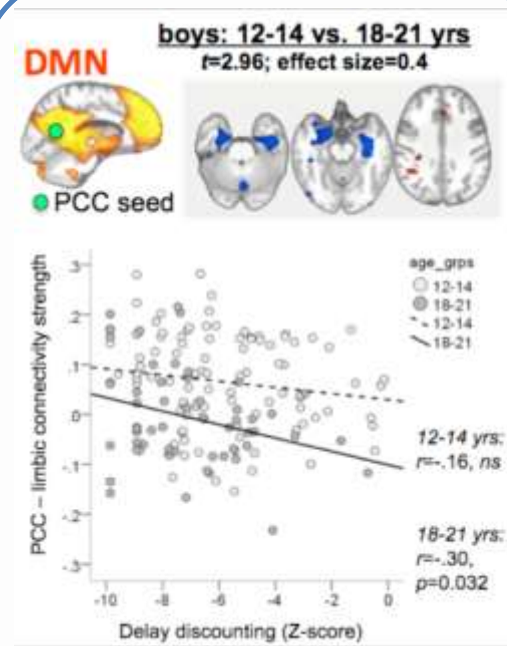
Normal developmental patterns were different in the exceeds-drinking criteria adolescents, particularly in the reciprocal ***limbic-cortical functional synchrony of the emotion (EMN) and default mode networks (DMN).***

Correction for manufacturer effects does not reduce effect size of our group analyses



IFN age differences – Correlation with behavior



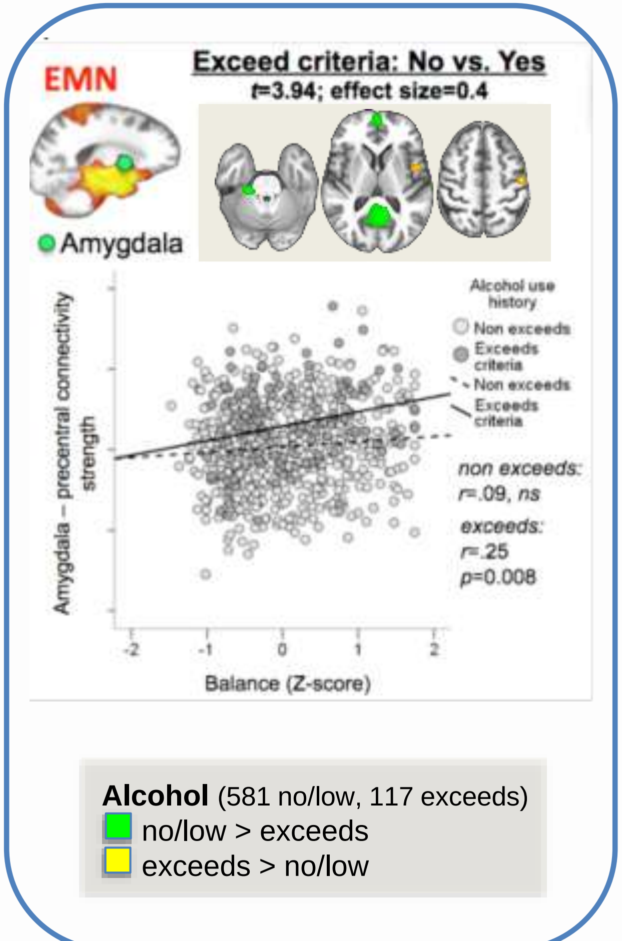


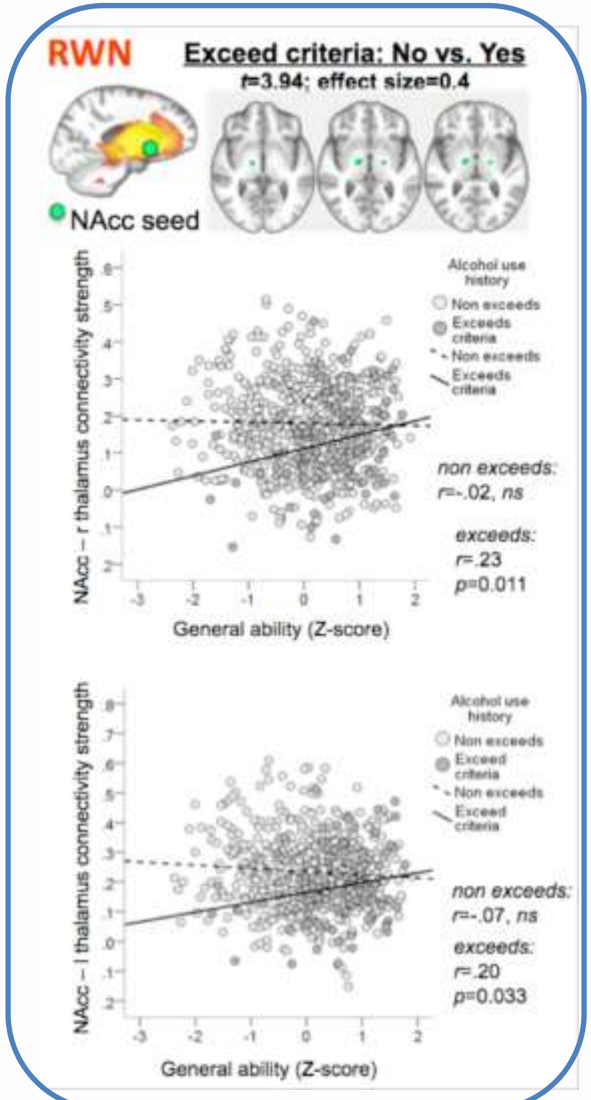
Note:
Delay discounting: negative scores represent better performance, i.e., to withhold responses (larger delay) for greater monetary reward.

- ***Stronger limbic-DMN and ECN connectivity*** to parietal, insular, and striatal regions was associated with ***better performance*** in general ability, and delay discounting by oldest adolescents

This finding further supports the concept that age-related 'rewiring' of the functional architecture is shaped to facilitate cognition.

IFN ‘alc’ differences – Correlation with behavior





In adolescents with a history of alcohol use:

<u>Emotion network (EMN):</u> *weaker motor cortico–limbic connectivity* was related to *poorer balance* in the exceeds-criteria group

<u>Reward network (RWN):</u> *weaker NAcc-thalamic connectivity* was related to *poorer general ability* performance

SUMMARY and CONCLUSION

1) **Age**: Stronger and more distributed network connectivity in older than younger adolescents, specifically for ECN

2) **Sex**: Sexual dimorphism in the patterns of age-related differences in connectivity strength
Developmental differences do not necessarily occur at a younger age in girls than in boys

3) **Alcohol**: Weaker reciprocal connections among the brain's incentive (RWN), affective (EMN), and self-regulatory (DMN) systems

"Functional rewiring" of these networks in adolescents with moderate-to high alcohol use may impede maturation of affective and self-reflection systems and retard ability to regulate emotion and impose behavioral control.

THANK YOU

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