

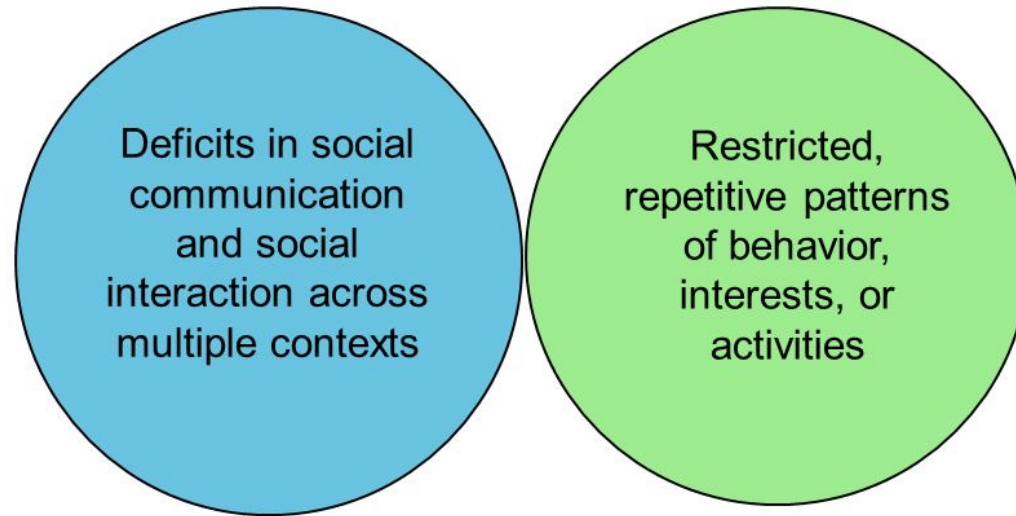
Atypical Functional Connectivity of Amygdala Related to Reduced Symptom Severity in Children with Autism

Inna Fishman et al. J Am Acad Child Adolesc Psychiatry. 2018;57(10):764–774.e3.

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Background

Autism Spectrum Disorder DSM 5 Definition (2013)



Background

Core feature of ASD: social impairments
the neural mechanism supporting human social functioning remains incompletely understood

Amygdala

Established role in social functioning (Brothers L, 1990; Bickart KC et al., 2011; Kanai R et al., 2012)

afferent and efferent connections with neocortex, limbic cortex, and subcortical structures.

- ventromedial prefrontal cortex (social decision making and moral judgment).

- Visual association areas in the ventral temporal cortex (facial expressions)

Background

fcMRI

the synchronization in BOLD signal fluctuations between spatially segregated brain regions

Resting-state fcMRI

Inconsistent findings in rs fc patterns (over- and under FC)

Age-related effects

maturation of the amygdala (volume) in children with ASD

Age-related effects on the amygdala rs iFC in ASD ?

Objective

- A) To determine the amygdala fc in children and adolescents with ASD by utilizing resting-state fcMRI.
- B) To examine age-related changes in amygdala connectivity patterns across childhood and adolescence (7 and 17 years old).

Hypothesis

- A) Children with ASD would exhibit altered fc compared to matched TD controls, and that the atypical connectivity patterns would correlate with autism clinical symptoms.
- B) age-related effects on the amygdala alterations would be found.

Methods

Sample

55 ASD and 50 TD participants (aged 7-17 y)

ASD diagnosis based on DSM-5 criteria

the Autism Diagnostic Interview-Revised (ADI-R)

Social functioning:

the Autism Diagnostic Observation Schedule, 2nd Edition (ADOS-2)

the Social Responsiveness Scale, 2nd Edition (SRS-2)

Cognition (IQ, language):

The Wechsler Abbreviated Scale of Intelligence, 2nd Edition (WASI-II).

Clinical Evaluation of Language Fundamentals, 4th Edition (CELF-4).

Exclusion criteria:

History of autism-related medical conditions (e.g., epilepsy, Fragile-X)

TD participants were personal or family history of autism, and personal history of any other neurological, developmental or psychiatric conditions.

Excessive head motion

Methods

MRI data acquisition

fMRI data preprocessing and fcMRI analyses

Software: AFNI and FSL

Preprocessing:

the first five volumes (10 sec of data) removal

slice timing correlation

temporal bandpass ($.008 < f < .08$ Hz)

mode 1000 normalization

Spatial smoothing (FWHM of 6mm)

rigid body realignment

multiple nuisance parameters (e.g., white matter, cerebrospinal fluid)

regression.

Methods

r were computed between average BOLD time series extracted from each amygdala seed (left and right, separately) and the time courses of all voxels across the brain, for each participant.

The amygdala seeds selection:

from the Harvard-Oxford Subcortical Structural Atlas available in FSL.

The voxel-wise r were converted to z ($z = 0.5 \ln [(1+r)/(1-r)]$)

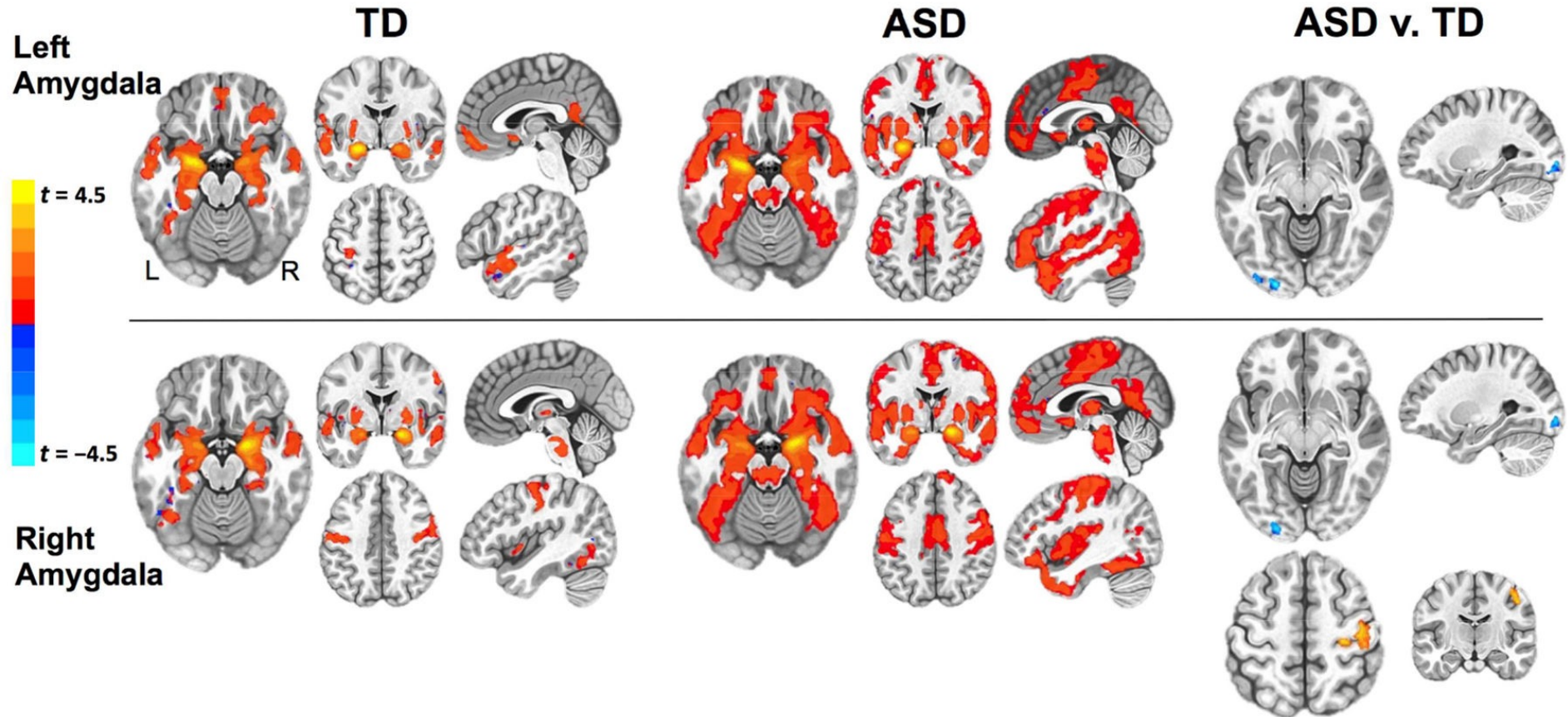
Independent-sample t -tests

Correlational analyses were applied to examine whether fc (average z-scores) between the amygdala and clusters showing significant group differences was associated with cognitive (IQ, language) and social (ADOS-2 and SRS-2) functions.

A post-hoc analysis of subgroups within the ASD cohort was further conducted.

Results

Overall group differences in amygdala fc, independent of age.



Results

Table 2.

Clusters of Significant (uncorr. $p < 0.005$, corr. $p < 0.05$) Group Differences (Autism Spectrum Disorder [ASD] vs. Typically Developing [TD]) in Amygdala Intrinsic Functional Connectivity (iFC)

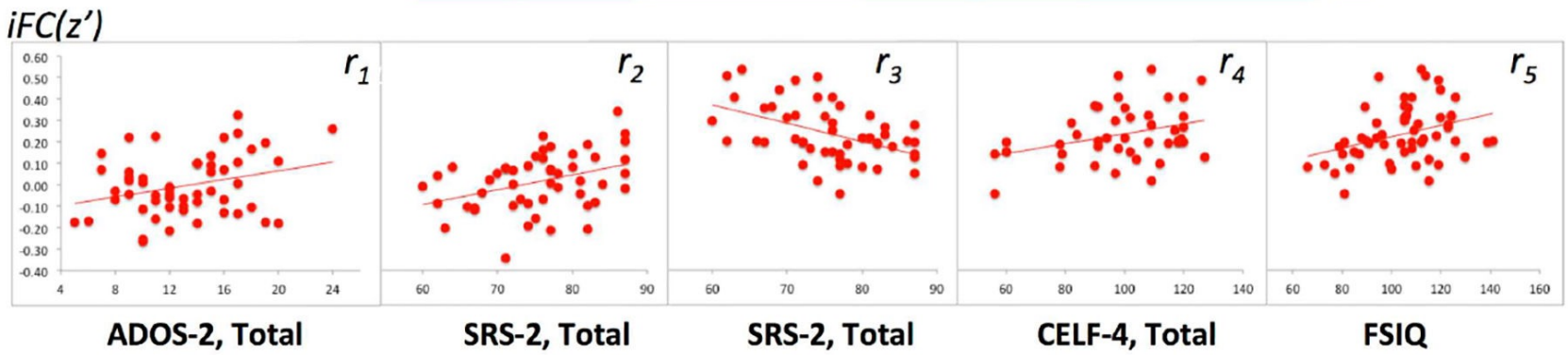
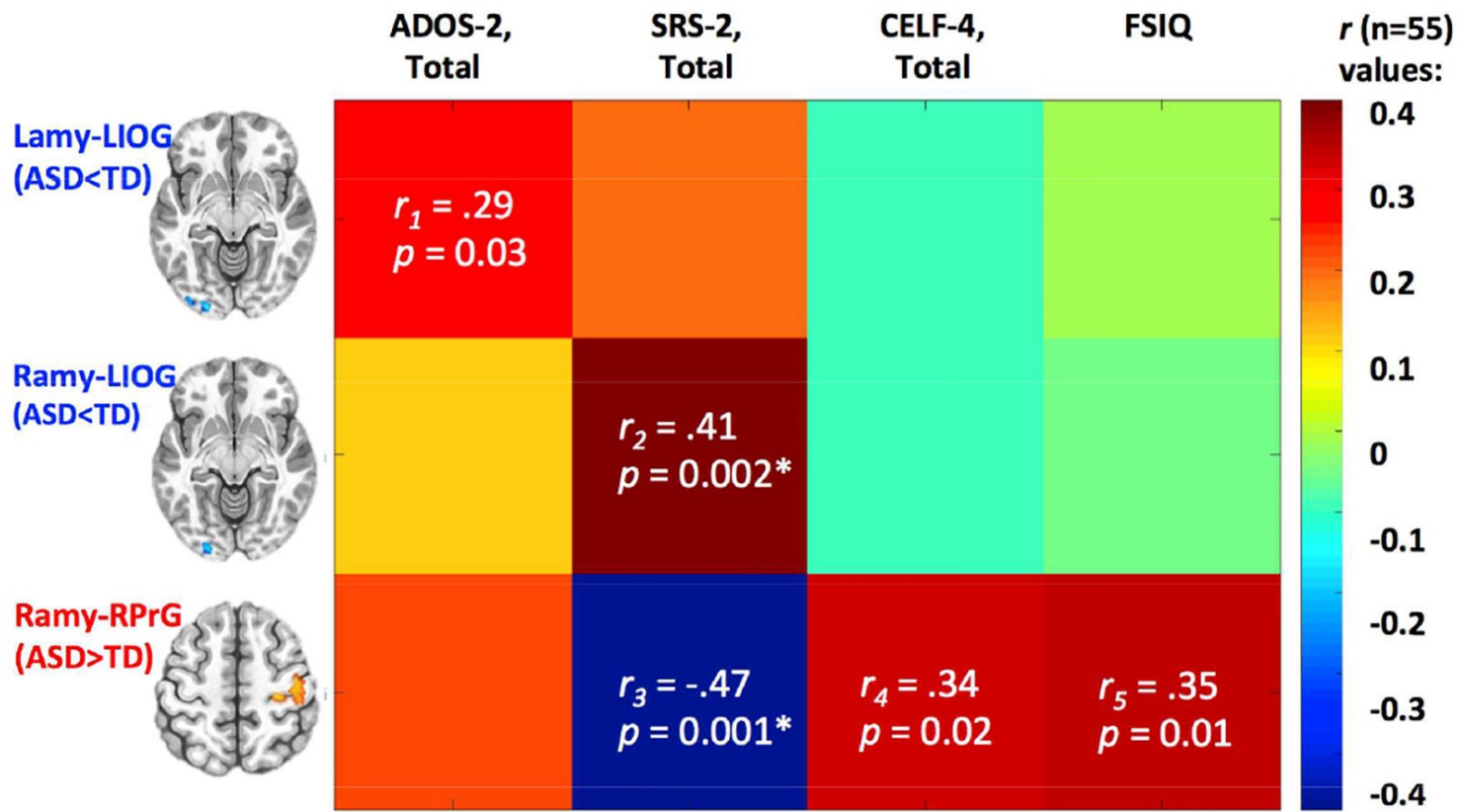
Cluster: Subregions		% of cluster vol.	Vol. (μ l)	t-score*	Cohen's d_s	MNI coordinates		
						x	y	z
<u>Seed: Left amygdala</u>								
L Inferior Occipital Gyrus:	L Middle Occipital Gyrus	49.2%	1350	-4.08	0.92	-37	-95	-16
	L Inferior Occipital Gyrus	41.5%						
<u>Seed: Right amygdala</u>								
R Pre-/Postcentral Gyrus:	R Precentral Gyrus	80.4%	2106	4.61	1.23	48	-21	55
	R Postcentral Gyrus	19.6%						
L Inferior Occipital Gyrus:	L Middle Occipital Gyrus	52.6%	1269	-3.93	0.76	-22	-98	-9
	L Inferior Occipital Gyrus	45.0%						

Note: Cohen's d_s is calculated as standardized mean difference between two groups (of independent observations) for the sample. L: left; R: right.

* Positive t -values denote ASD > TD; negative t -values denote ASD < TD.

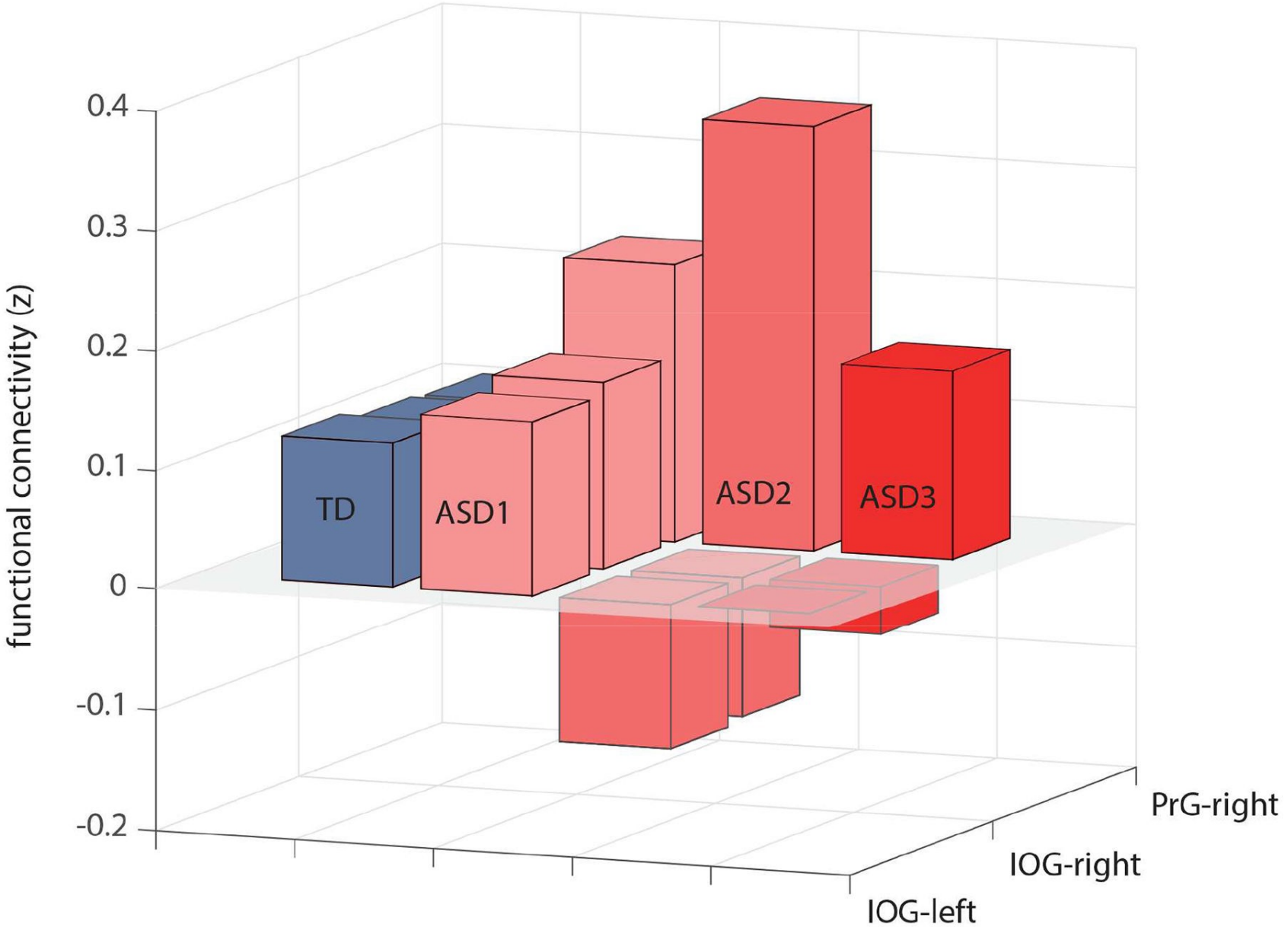
Results

Correlations with social and cognitive impairments.



Results

ASD subgroups



Results

Table 3.

Characteristics of Autism Spectrum Disorder (ASD) Subgroups Determined by the Amygdala Intrinsic Functional Connectivity (iFC) patterns

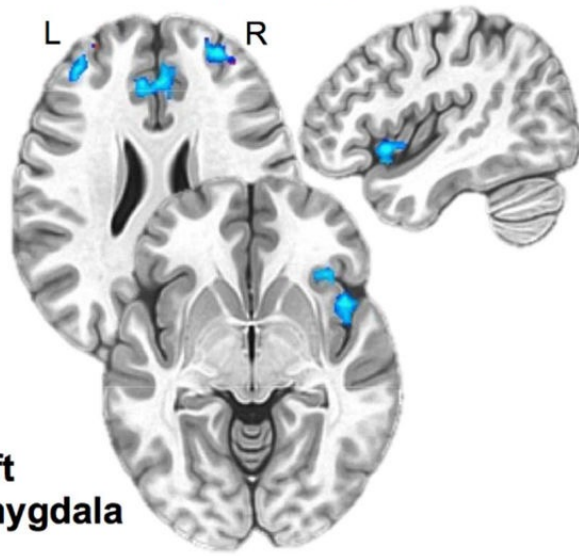
	ASD-1 (n = 16)	ASD-2 (n = 15)	ASD-3 (n = 24)	<i>p</i> value ^a
	<i>M</i> ± <i>SD</i> [range]	<i>M</i> ± <i>SD</i> [range]	<i>M</i> ± <i>SD</i> [range]	
Age (years)	13.7 ± 2.8 [10.0–17.9]	13.8 ± 2.7 [9.0–17.5]	13.7 ± 2.9 [7.4–17.8]	0.96
RMSD (head motion)	0.060 ± 0.026 [0.02–0.11]	0.062 ± 0.024 [0.03–0.11]	0.064 ± 0.028 [0.02–0.11]	0.90
ADOS-2, Total	14.1 ± 5.0 [7–24]	11.9 ± 3.5 [8–20]	13.2 ± 3.5 [5–18]	0.32
ADOS-2, Severity	7.6 ± 2.0 [4–10]	6.5 ± 1.7 [4–10]	7.5 ± 1.8 [4–10]	0.29
SRS-2, Total	84.7 ± 6.7 [75–94]	76.9 ± 9.8 [58–83]	82.3 ± 8.0 [64–94]	0.02
Full-scale IQ	105.4 ± 18.4 [81–141]	110.5 ± 10.4 [89–124]	98.9 ± 19.2 [66–139]	0.11
CELF –4, Core Language	97.9 ± 26.2 [56–127]	103.3 ± 14.7 [82–126]	98.0 ± 13.3 [78–120]	0.74
Rx status, Rx : none	9:7	7:6 (2 unknown)	9:13 (2 unknown)	0.56

Note: Rx status indicates number of participants who were on any psychotropic medications. ADOS-2 = Autism Diagnostic Observation Schedule, 2nd Edition, ADOS-2 Severity, a standardized metric for quantifying ASD symptom severity that is relevantly independent of age and verbal ability; RMSD = root mean square of displacement; SRS-2 = Social Responsiveness Scale

Results

Age-related effects in amygdala iFC

A. Group x Age effects

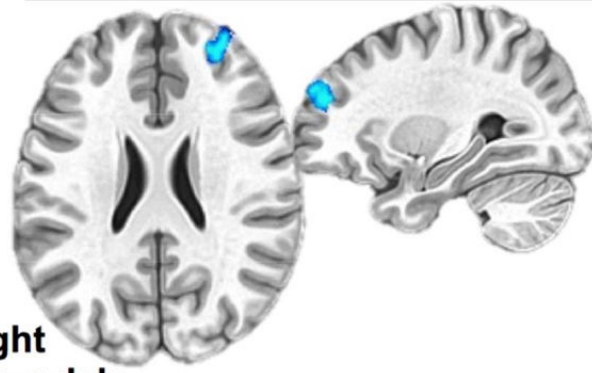
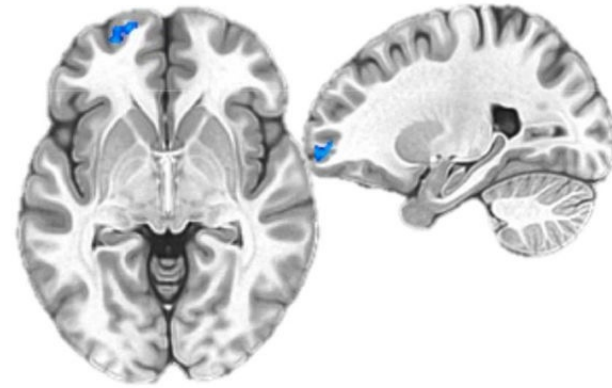


Left
Amygdala

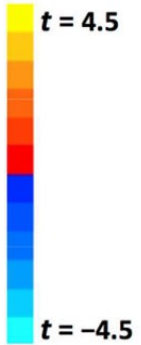
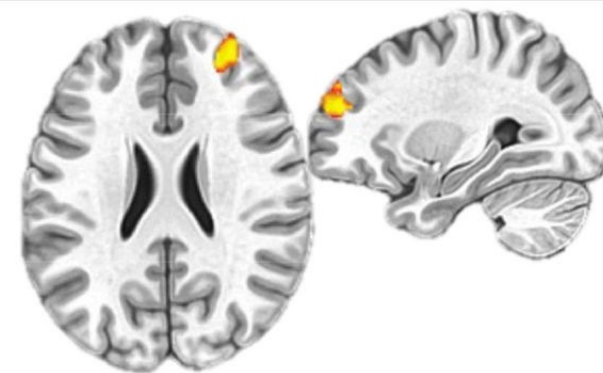
B. Age effects in TD



C. Age effects in ASD



Right
Amygdala



Discussion

- the ASD group had weaker connections between both left and right amygdala and left IOG, but greater connections between right amygdala and right motor /somatosensory cortex.
- the more atypical patterns of amygdala connectivity were unexpectedly associated with more favorable outcomes. This was primarily due to ASD2 subgroup.
- age had differential effect on amygdala iFC in TD and ASD groups, with amygdala-prefrontal and amygdala-insula connectivity increasing from childhood to adolescence in TD participants, while such age-dependent iFC increase was not present in the ASD group, and even reversed trajectories between left amygdala and left prefrontal cortex.

Strengths

- a) Dynamic amygdala iFC patterns from childhood to adolescence
- b) Explain the conflicting evidence of under- and over fc in ASD
- c) Controlling for head motion artifacts
- d) Standard preprocessing steps
- e) TD control group

Limitations

- a) exclusion of low-functioning children with ASDs
- b) use of cross-sectional data in examining age-related effects
- c) lack of pubertal development measures
- d) lack of reliable data on comorbid conditions
- e) Lack of the definition of excessive head motion