Relationship between nuclei-specific amygdala connectivity and mental health dimensions in humans

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Nature Human Behavior (2022)

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February 3, 2023
LNCD Journal Club

Takehome

Connectivity of the functionally parcellated amygdala nuclei can predict certain (subclinical) mental health dimensions in human adults

Motivation

Background

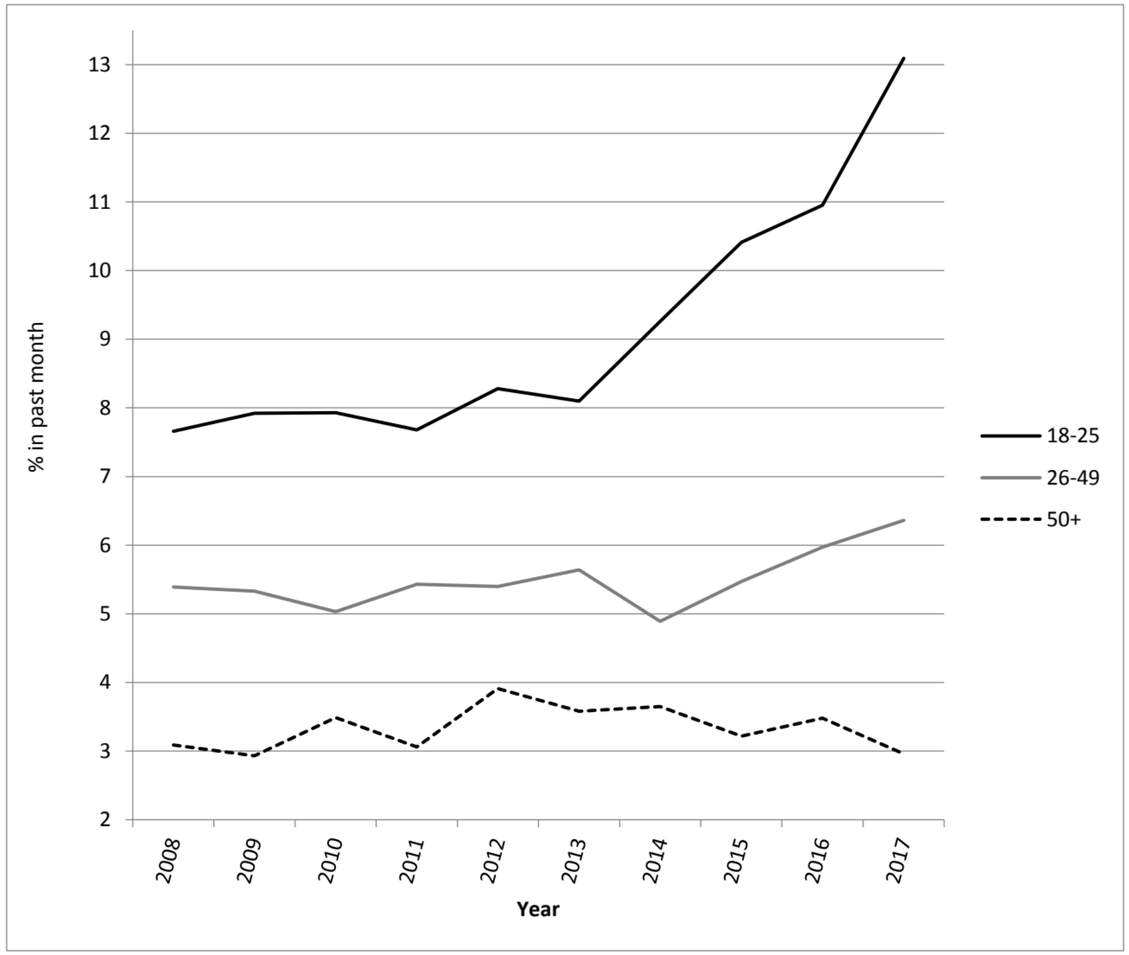
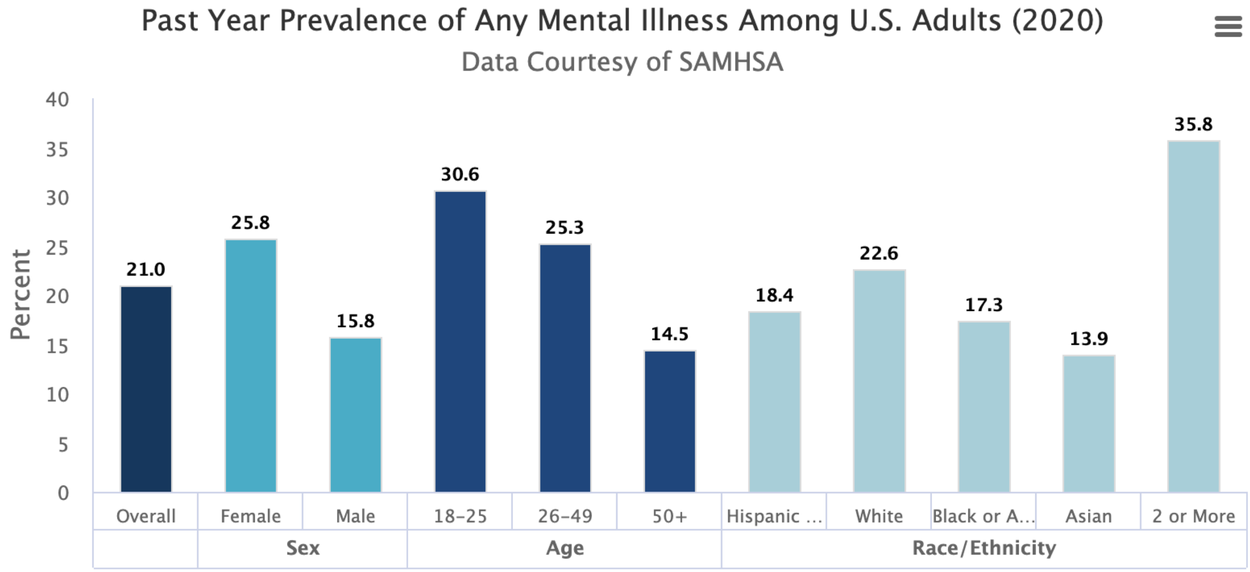


Figure 1: Percent with serious psychological distress in the last month by age group, 2008-2017

Twenge et al., 2019



NIH, 2020

Scientific problem

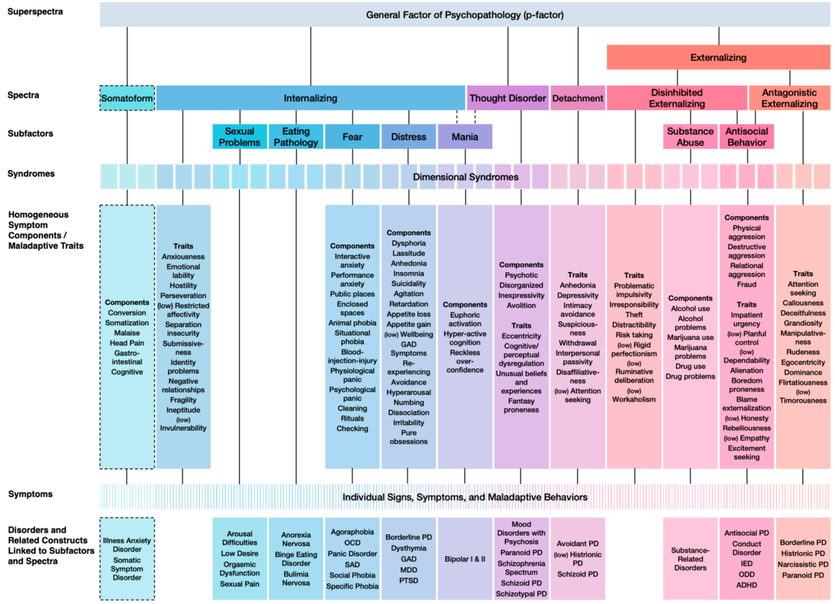
Background

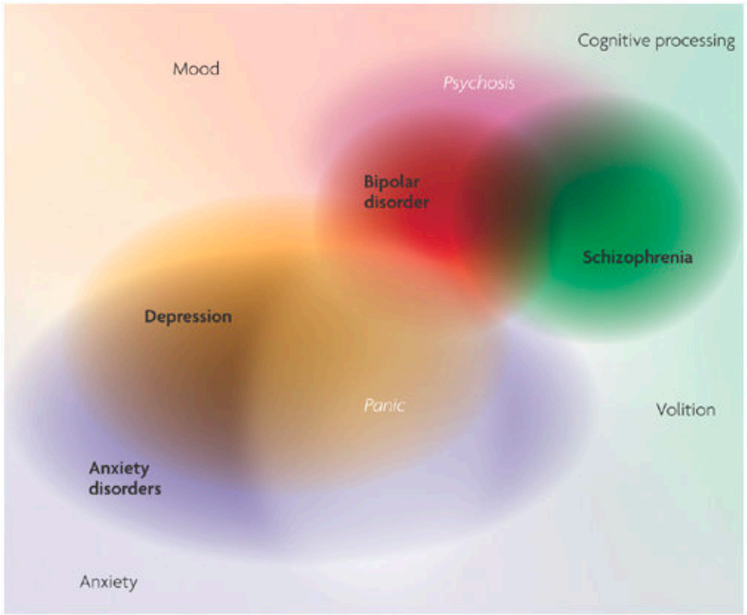
- Humans are complex
- Their brains and behaviors, in particular, are notoriously complex

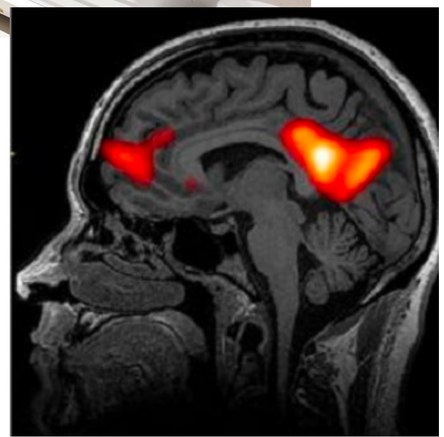
Scientific problem

Background

- Classic approaches in both psychiatry and human neuroscience are lacking







DSM-5 Diagnostic Criteria for Major Depressive Disorder

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. **Note:** Do not include symptoms that are clearly attributable to another medical condition.

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful). (**Note:** In children and adolescents, can be irritable mood.)
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).
3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. (**Note:** In children, consider failure to make expected weight gain.)
4. Insomnia or hypersomnia nearly every day.
5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
6. Fatigue or loss of energy nearly every day.
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

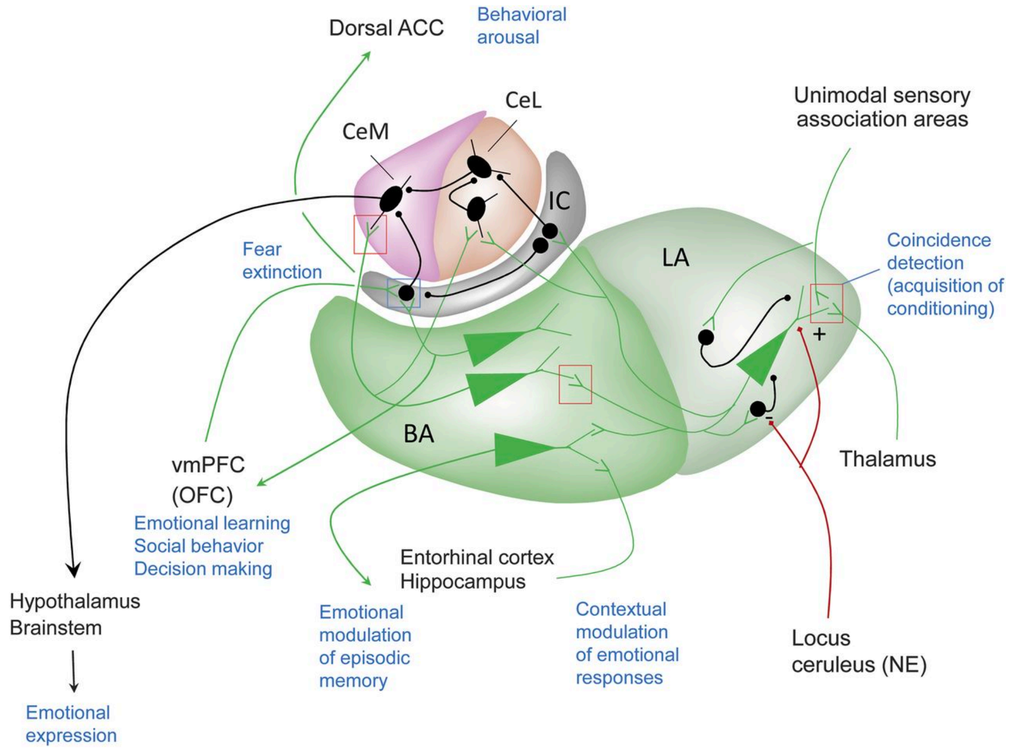
C. The episode is not attributable to the physiological effects of a substance or to another medical condition.

Note: Criteria A–C represent a major depressive episode.

Amygdala circuitry

Background

- The amygdala is implicated across most psychopathologies
- Its subcomponents (nuclei) have distinct structural, functional, and connectional properties



Current concerns

- rsfMRI-based predictors for real-world neuropsychiatric outcomes (diagnosis, treatment response) require lots of (non-specific) brain structures, networks, edges
- Unsupervised decoding methods are often agnostic to anatomical priors
- Amygdala nuclei have specific connections, several of which include the brainstem, where imaging activity has proven difficult
- Psychiatric disorders themselves are poorly characterized and terribly heterogeneous

Study aim

Examine the degree to which it is possible to explain variance in mental well-being across humans in relation to the functional connectivity of identifiable neural circuits centered on the amygdala

Methods

Experimental overview

1. Functionally parcellate the amygdala
2. Replicate the parcellation in 2 additional datasets
3. Identify latent behaviors for mental health dimensions using factor analysis
4. Replicate these latent factors
5. Select best FC predictors for each behavioral dimension
6. Predict mental health variability using FC values in an independent dataset

Methods

Experimental design

- Use rsfMRI from 200 healthy HCP participants to identify reliable functional amygdala nuclei connections with other brain regions for each of the derived mental health (behavioral) dimensions

- Replicate and test in two separate datasets (3T, n = 200; 7T, n = 98) to investigate the extent to which specific amygdala connections predict mental health dimensions

Methods

Participants

	Original set	3T replication	7T replication
n	200	200	98
mean age	29 ± 0.26	28 ± 0.28	29 ± 0.33
age range	22 - 36	22 - 36	23 - 36
sex	54% F	49.5% F	60.2% F
DSM depression	4.25 (12.24)		3.43 (5.73)
ASR total	37.43 (523.82)		31.79 (253.43)

Methods

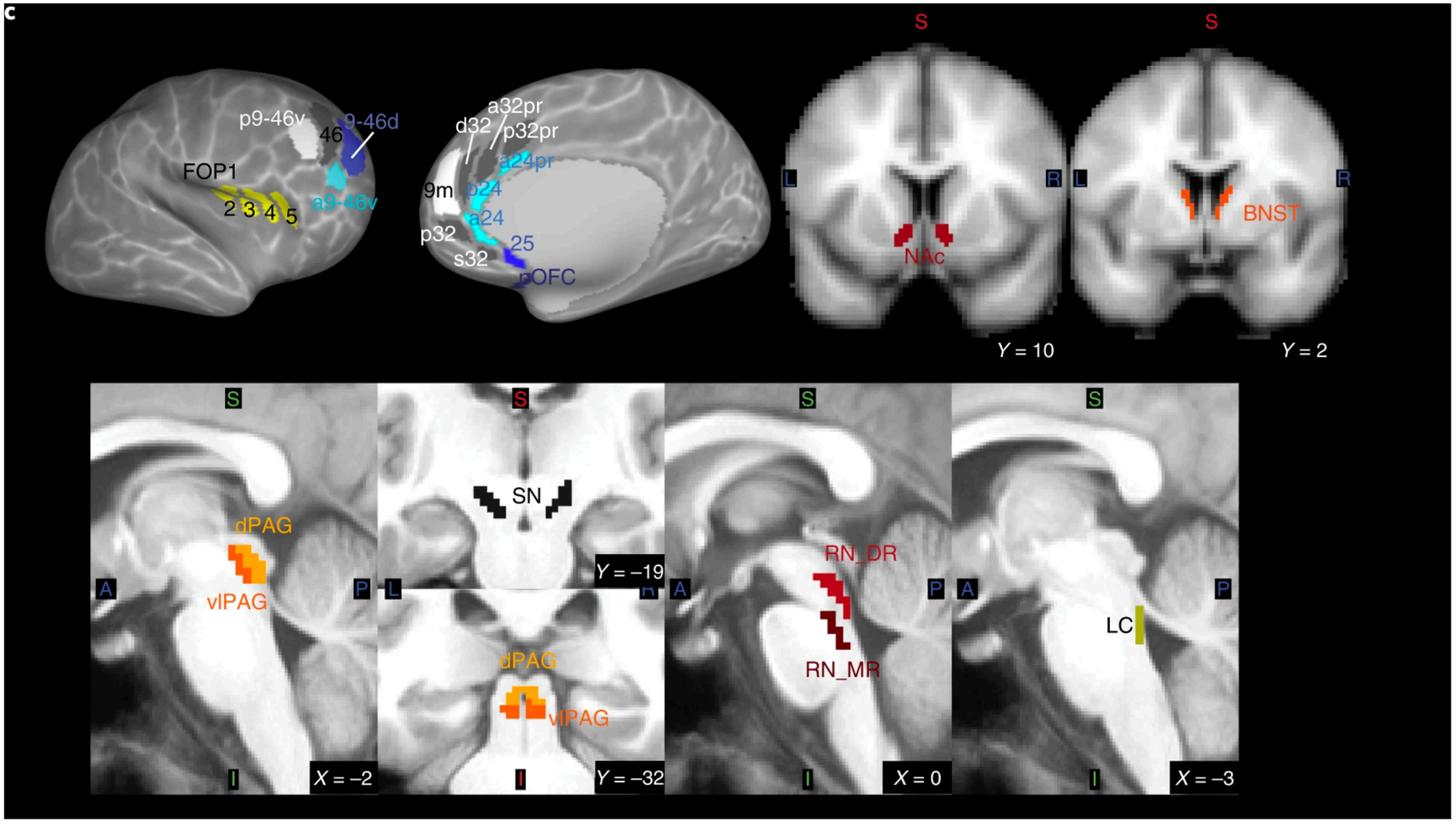
ROI selection

- Criteria: (1) region’s connectivity with the amygdala and (2) implication in mental health pathologies
  - 8 subcortical/brainstem regions
  - 20 cortical regions

Methods

ROIs

- LC = locus coeruleus
- D/MRN = dorsal/medial raphe nucleus
- d/vlPAG = dorsal/ventrolateral periaqueductal grey
- SN = substantial nigra
- BNST = bed nucleus of the stria terminalis
- NAc = nucleus accubens
- pOFC = posterior orbitofrontal cortex
- FOP = frontal operculum



rsfMRI

3T

- Scan length =14.4 minutes
- TR = 720 ms
- TE = 33 ms
- Resolution = 2 mm
- Slices = 72

7T

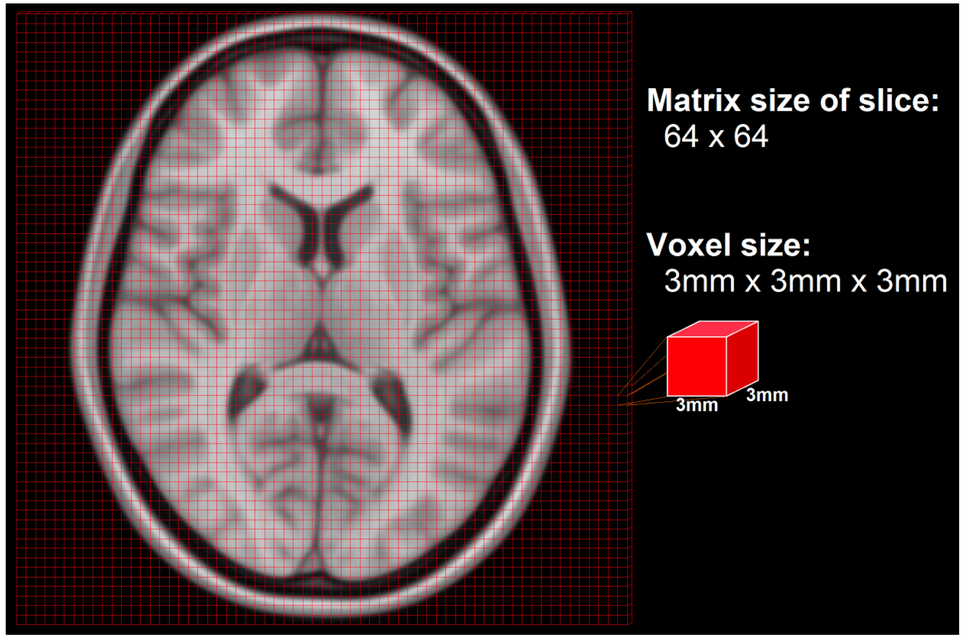
- Scan length = 16 min
- TR = 1 s
- TE = 22.2 ms
- Resolution = 1.6 mm
- Slices = 85

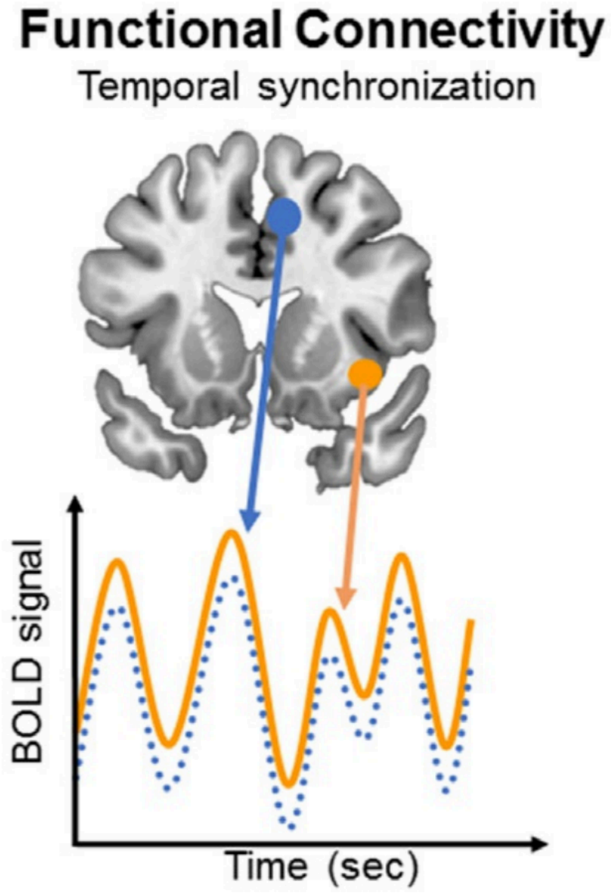
rsfMRI preprocessing

- Distortion-corrected, temporally filtered, projected onto surface reconstruction from T1w, minimally smoothed
- Additional regressors were normalized, high-pass filtered, detrended
  - 33 physiological regressors
  - 24 motion regressors

Methods

Resting-state functional connectivity





Methods

Mental health data (33 “behaviors”)

- 17 measures from NIH toolbox emotion battery
  - 6 measures of negative affect
  - 3 measures of psychological well-being
  - 6 measures of social relationships
  - 2 measures related to stress
- 9 from Pittsburgh Sleep Questionnaire
- 5 factor model of personality
- Penn emotion recognition test

Methods

Behavioral analysis: latent behaviors using factor analysis

- z-scored 33 behavioral measures
- Scree test based on the first 100 participants identified four factors, which replicated in the full (first) dataset of n = 200 participants
  - Social and life satisfaction
  - Negative emotions
  - Sleep
  - Anger and rejection

Methods

Analytic approach

- Robust linear regression models
- Confounds: (1) head motion, (2) weight, (3) height, (4) systolic BP, (5) diastolic BP, (6) hemoglobin A1C, (7) cube-root of total brain volume, (8) cube-root of total ICV

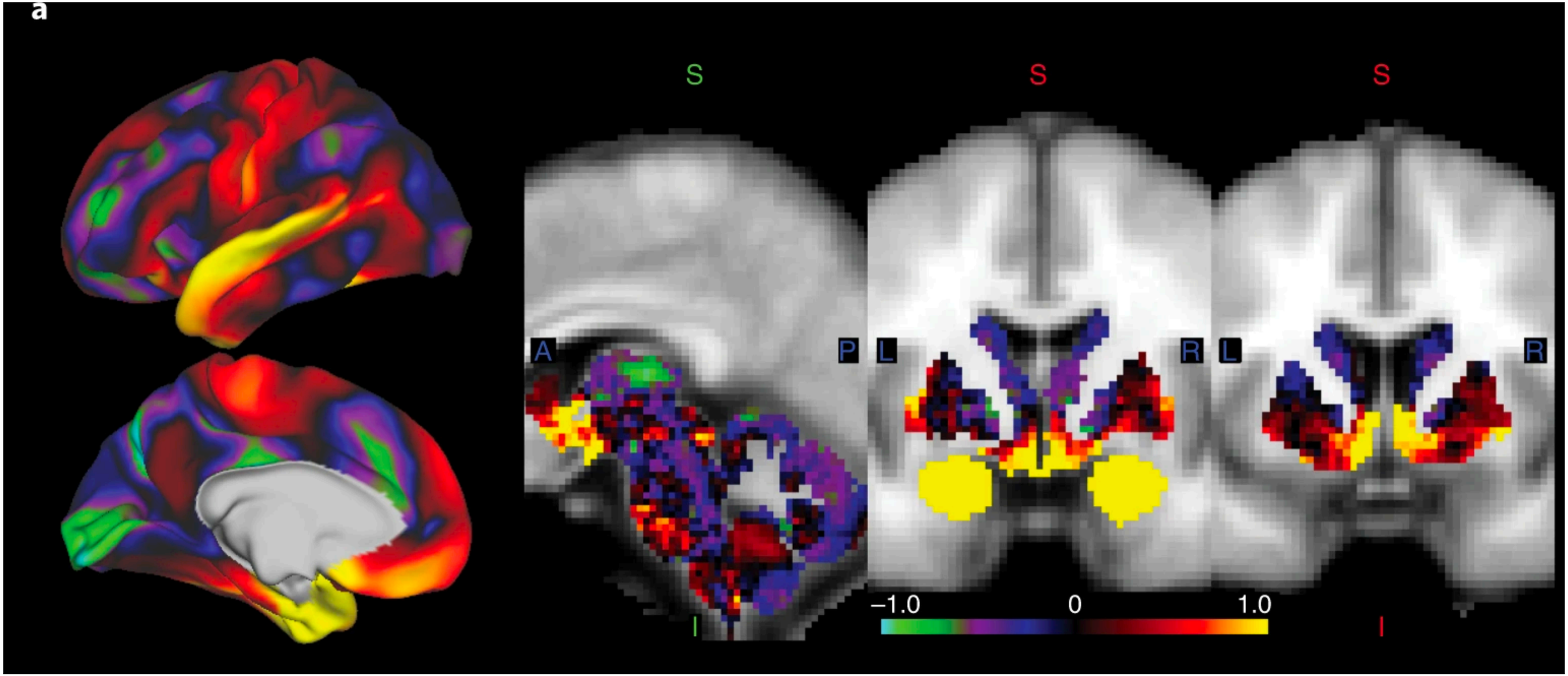
Methods

Analytic approach

- Obtained robust regression weights (for relationships between FC & the four mental health dimensions)
  - Across-dataset replication: similar weights between 3T & 7T?
  - Within-participant replication: similar between two halves of experiment?

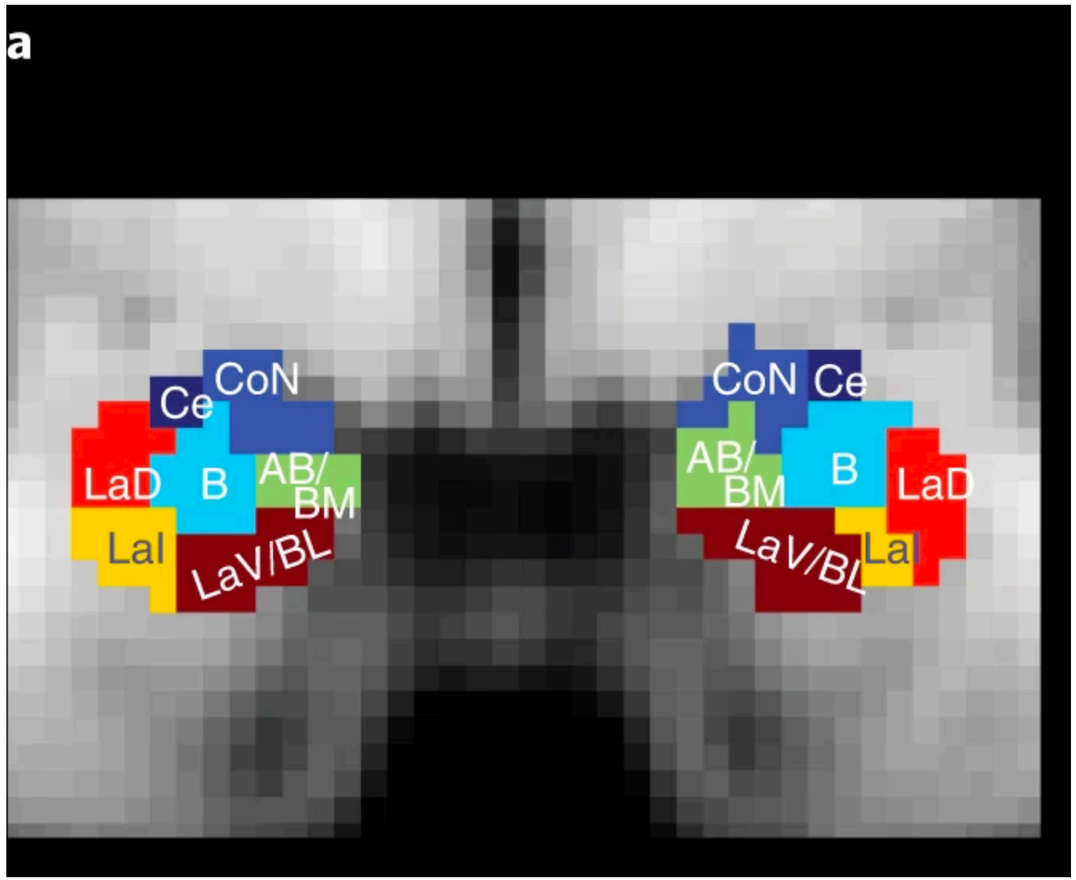
Methods

Functional parcellation



Results

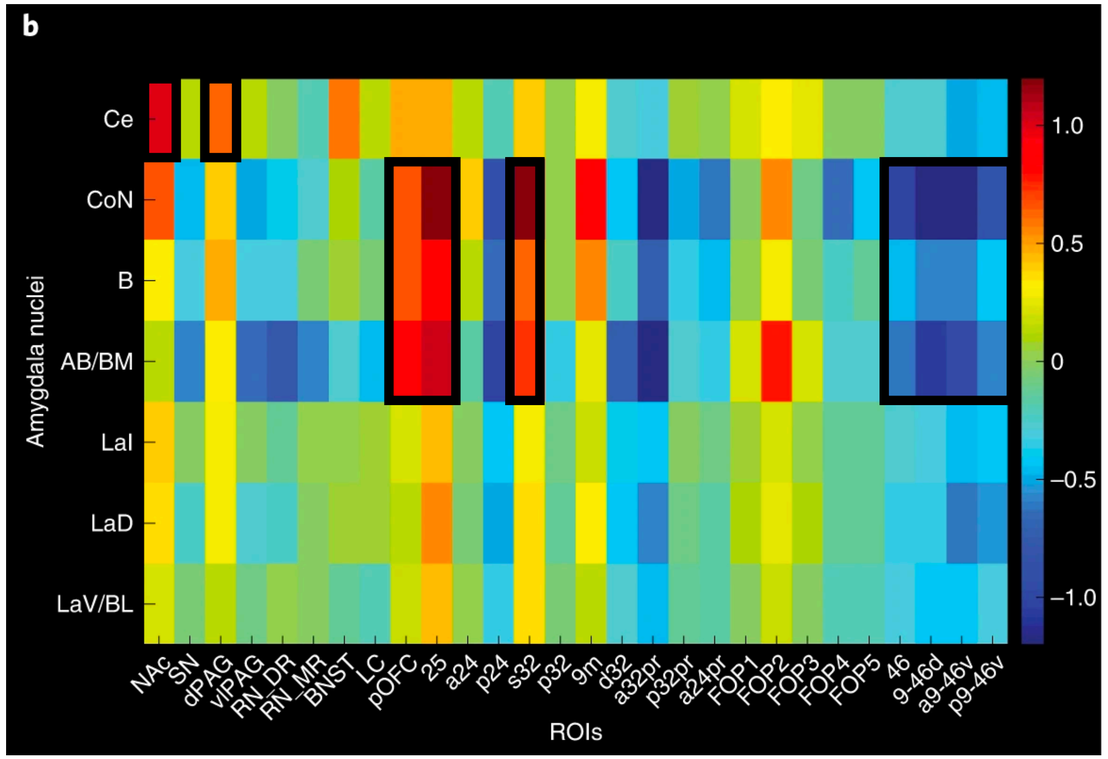
- Ce = central nucleus
- CoN = cortical nucleus
- AB/BM = auxiliary basal / basomedial nucleus
- B = basal nucleus
- LaD = dorsal lateral nucleus
- LaI = intermediate lateral nucleus
- LaV/BL = ventral lateral nucleus



Results

Average connectivity patterns

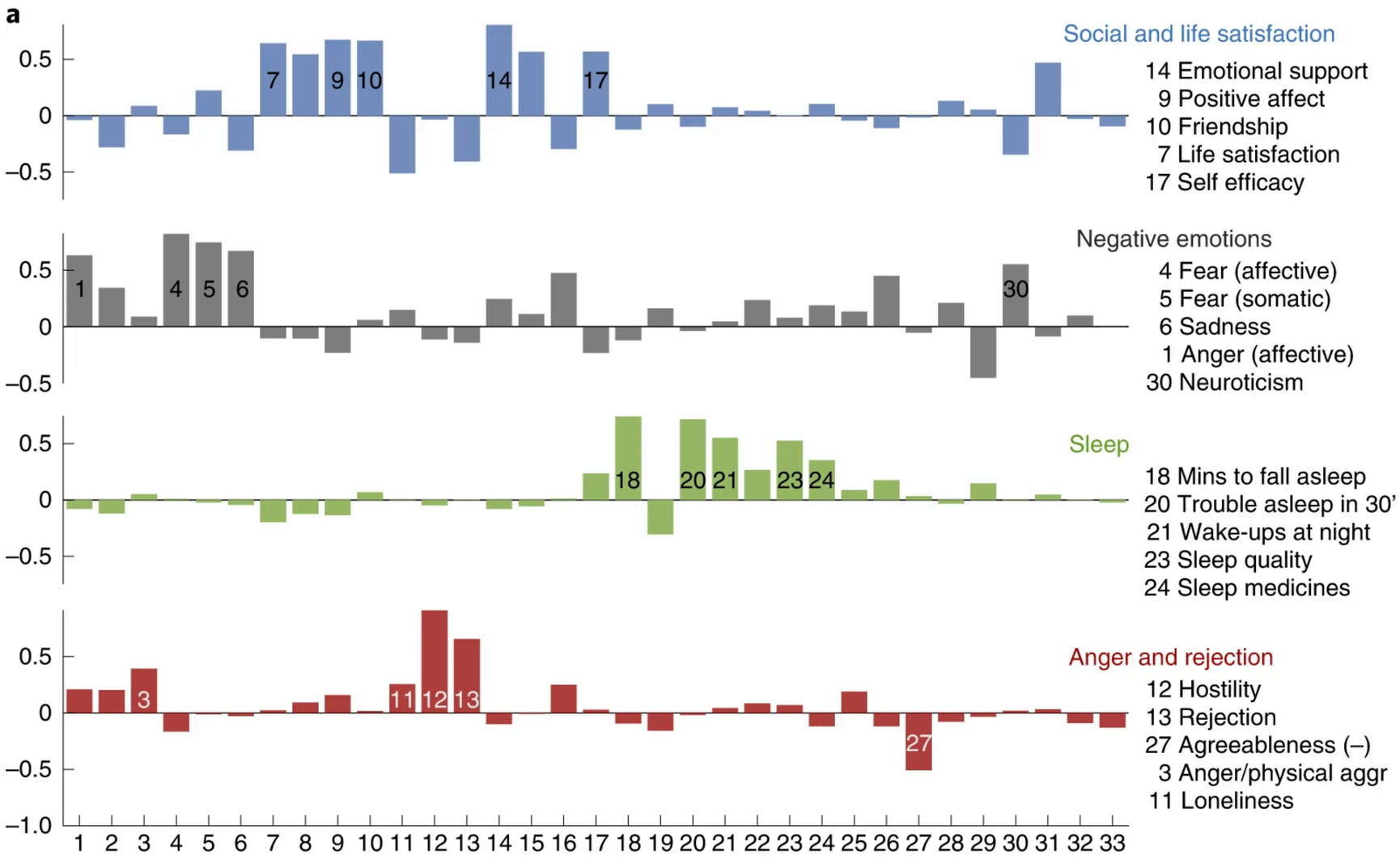
- All amygdala nuclei had strong connectivity with the ventral, caudal, and medial frontal cortex, and caudal OFC: BA 25, pOFC, s32
  - Especially strong for the basal (B, AB/BM), and cortical (CoN) nuclei
  - Negative associations with lateral PFC (46, 9/46)
- Subcortical/brainstem: NAc, dPAG
  - Strongest for central nucleus (Ce)



- Replicated in two separate datasets
  - 3T dataset: $r(194) = 0.968$, $p = 8.832 \times 10^{-119}$, CI = (0.958, 0.976)
  - 7T dataset: $r(194) = 0.884$, $p = 3.92 \times 10^{-66}$, CI = (0.850, 0.912)

Results

Latent mental health dimensions



Results

Amygdala FC ~ mental health dimensions

- Life satisfaction: **B & LaD amygdala — frontal regions**
- Negative emotions: **LaD amygdala — LC, NAc, pOFC**
- Sleep: **several amygdala nuclei — SN, dPAG, LC, NAc, p32**
- Anger: **CoN & LaD — several ROIs**

- Ce = central nucleus
- CoN = cortical nucleus
- AB/BM = auxiliary basal / basomedial nucleus
- B = basal nucleus
- LaD = dorsal lateral nucleus
- LaI = intermediate lateral nucleus
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- LC = locus coeruleus
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- pOFC = posterior orbitofrontal cortex
- FOP = frontal operculum

Out-of-sample prediction

Amygdala FC ~ mental health dimensions

- Can we predict individual participants' behavioral scores in a separate dataset using regression coefficients estimated from the original dataset?
  - Yes: life satisfaction $r(95) = 0.187, p = .0335$, negative emotions $r(95) = 0.219, p = .0.0155$, anger $r(95) = 0.226, p = .0143$
  - No: sleep $r(95) = 0.05, p = .31$
- Can we predict behavioral scores within-participants (first-half vs second-half of rsfMRI) using regression coefficients rather than across-datasets?
  - Yes $r(488) = 0.47, p = .014$

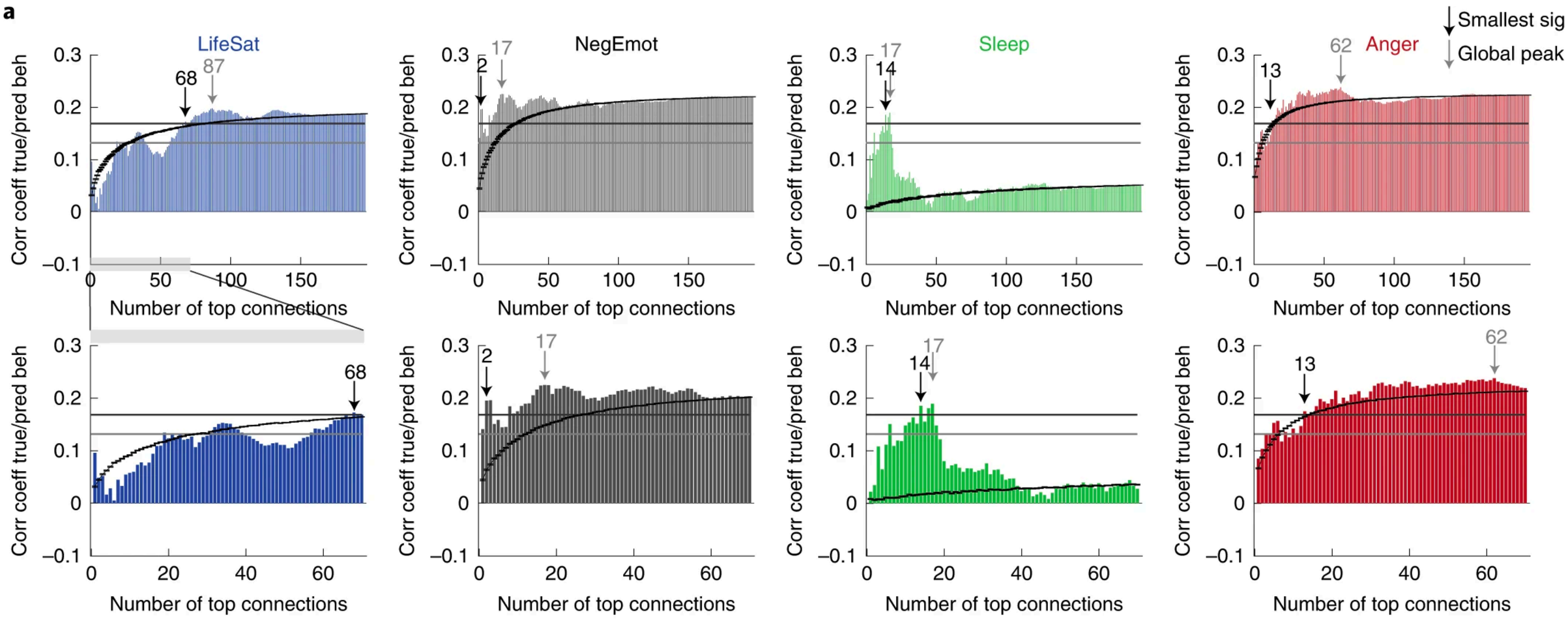
Results

Iterative inclusion of FC values

- Does adding FC edges iteratively (1 to 196) based on regression coefficients in the 3T dataset allow prediction in a separate 7T dataset?
- Generated two null distributions, shuffling behavioral scores
  - for the smallest number of edges to reach significance
  - for Pearson's *r* at the overall best prediction expected

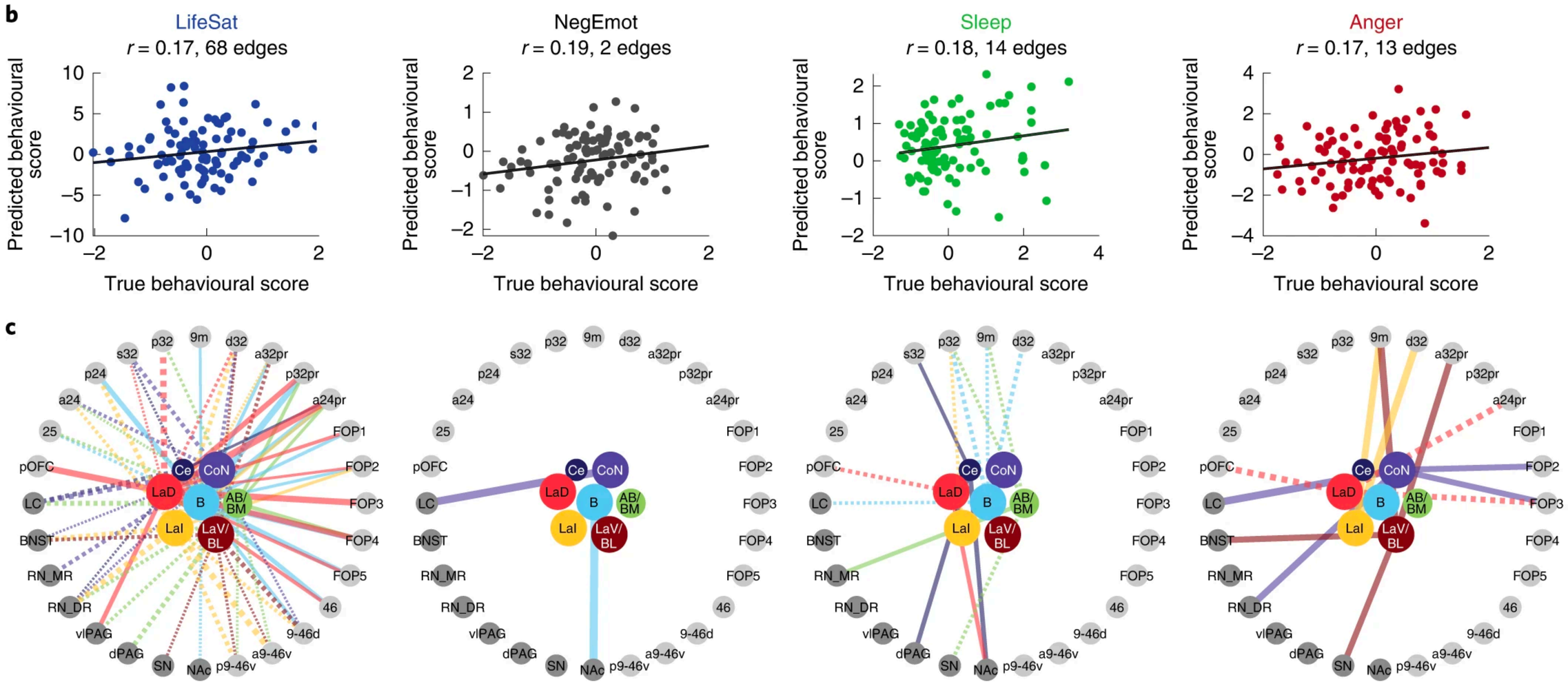
Results

Iterative inclusion of FC values



Results

Iterative inclusion of FC values



Results

- Amygdala as a singular ROI?
  - Parcellation performs significantly better
- Overall depression score?
  - Latent behaviors work better

Discussion

Main takeaways

- For three of the four behavioral dimensions, FC in < 15 connections was sufficient to predict behavioral scores in an independent dataset
- Variations in nuclei-specific amygdala FC were better associated with mental health dimensions than when treating the amygdala as a single ROI
- Amygdala nuclei FC was better at predicting behavioral dimensions than aggregate depression scores

Pros & Cons

Pros

- Data-driven

Cons

- Functional parcellation of amygdala nuclei

NeuroImage 155 (2017) 370–382

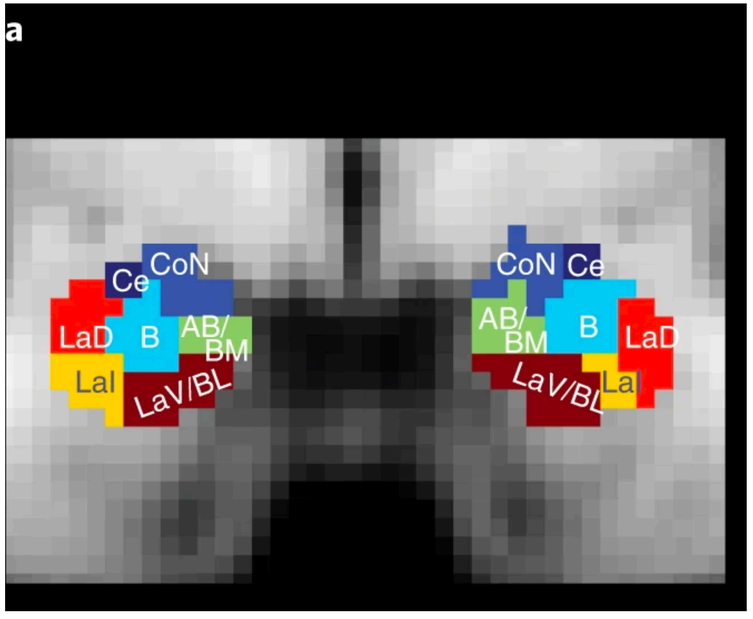
Contents lists available at ScienceDirect

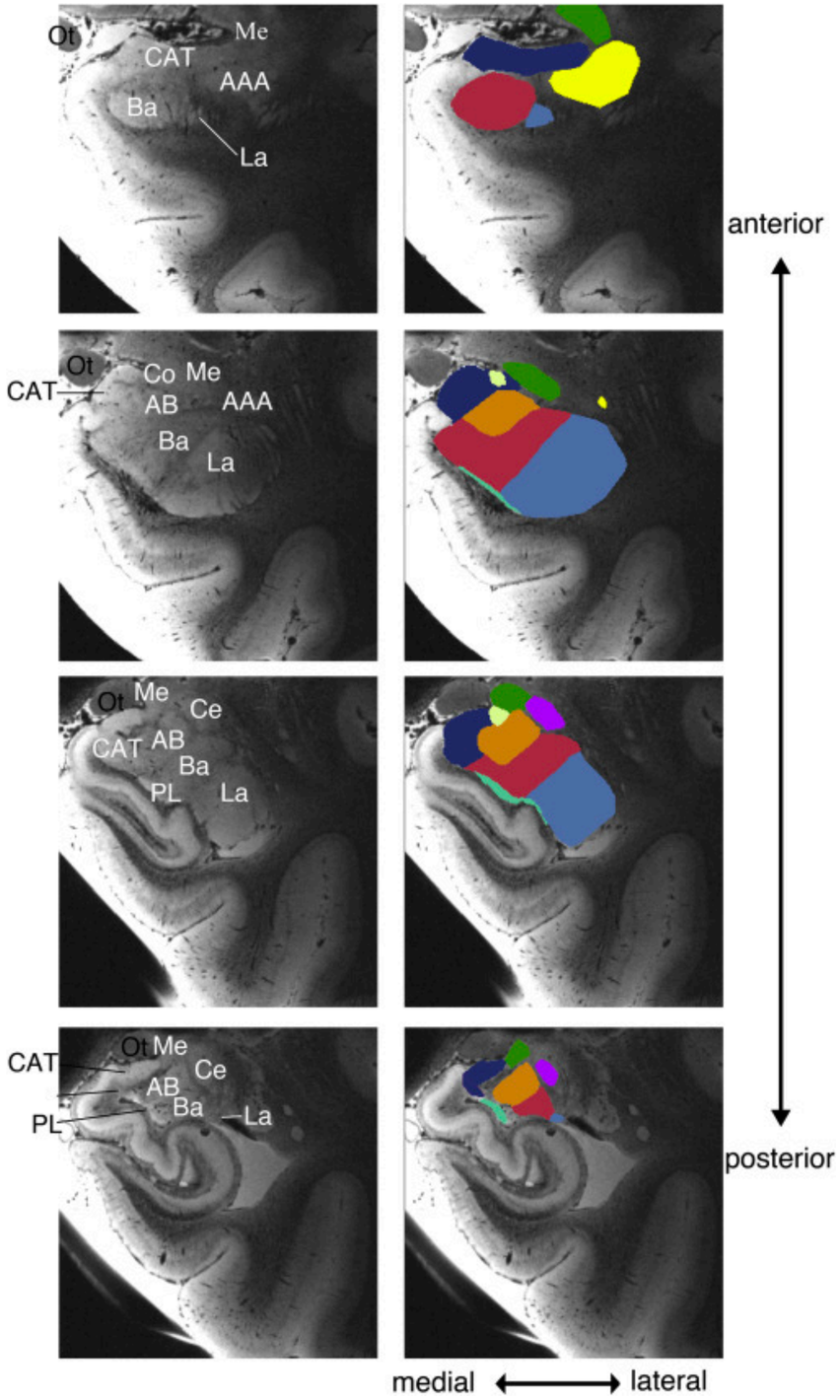
NeuroImage

journal homepage: www.elsevier.com/locate/neuroimage

High-resolution magnetic resonance imaging reveals nuclei of the human amygdala: manual segmentation to automatic atlas

Z.M. Saygin[a,b,*,1], D. Kliemann[a,b,1], J.E. Iglesias[c,d], A.J.W. van der Kouwe[b], E. Boyd[b], M. Reuter[b], A. Stevens[b], K. Van Leemput[b,e], A. McKee[f,g], M.P. Frosch[h], B. Fischl[b,i], J.C. Augustinack[b], for the Alzheimer's Disease Neuroimaging Initiative[2]





Pros & Cons

Pros

- Data-driven
- Validation of principles using replication datasets

Cons

- Functional parcellation of amygdala nuclei

Pros & Cons

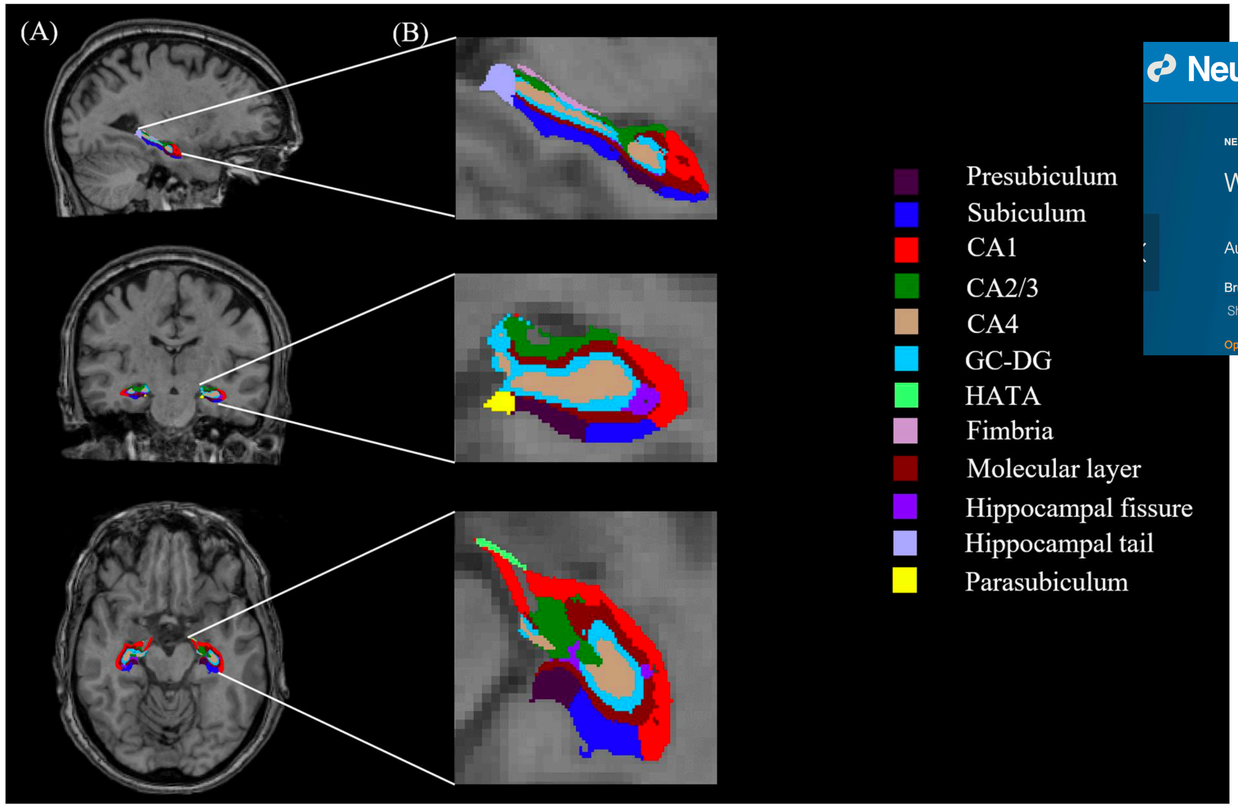
Pros

- Data-driven
- Validation of principles using replication datasets

Cons

- Functional parcellation of amygdala nuclei
- Hippocampus & hypothalamus excluded because it was hard to parcellate them :(

YOU CAN DO IT.



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Whole Brain Segmentation

Automated Labeling of Neuroanatomical Structures in the Human Brain

Bruce Fischl • David H. Salat • Evelina Busa • ... Nikos Makris • Bruce Rosen • Anders M. Dale

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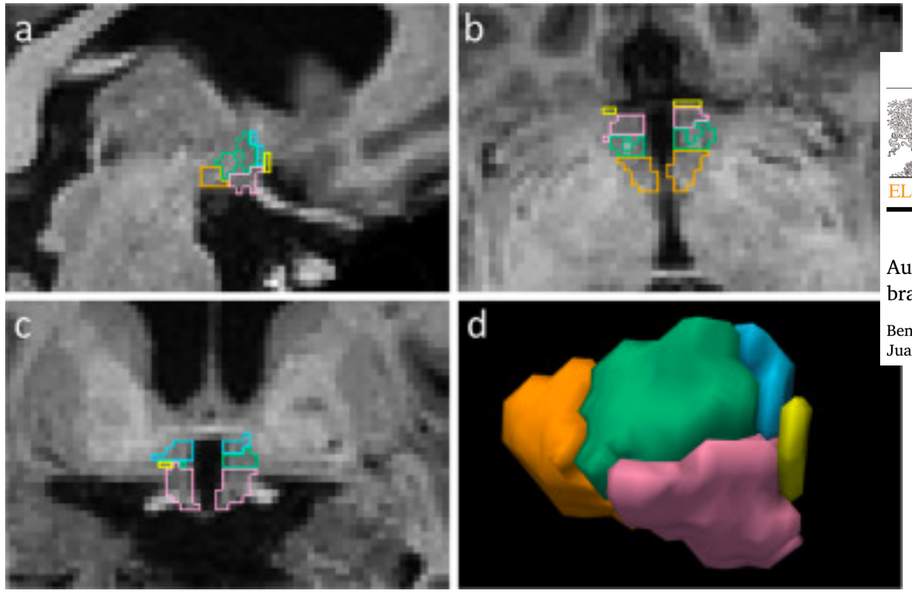

NeuroImage 223 (2020) 117287

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Automated segmentation of the hypothalamus and associated subunits in brain MRI☆

Benjamin Billot[a,*], Martina Bocchetta[b], Emily Todd[b], Adrian V. Dalca[c,d], Jonathan D. Rohrer[b], Juan Eugenio Iglesias[a,c,d]

Pros & Cons

Pros

- Data-driven
- Validation of principles using replication datasets
- Dimensional & subclinical symptoms
- Anatomically motivated

Cons

- Functional parcellation of amygdala nuclei
- Hippocampus & hypothalamus excluded because it was hard to parcellate them :(

Pros & Cons

Pros

- Data-driven
- Validation of principles using replication datasets
- Dimensional & subclinical symptoms
- Anatomically motivated

Cons

- Functional parcellation of amygdala nuclei
- Hippocampus & hypothalamus excluded because it was hard to parcellate them :(
- Limited mental health variability (questionnaire score + clinical populations)
- Exclusive use of (robust) linear models
- No directionality of connections or consideration of extended circuitry
- Cross-sectional data in a modest sample size of adults

Questions?