Affective brain patterns as multivariate neural correlates of cardiovascular disease risk

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Background and motivation

- Existing evidence suggests that atherosclerotic cardiovascular disease (CVD) risk may relate to individual differences in the cortical and limbic brain systems that are implicated in encoding, processing, and responding to affective cues and contexts.
- One limitation of most studies of the neural correlates of CVD risk is their small sample sizes, which constrain attempts to cross-validate and replicate candidate brain biomarkers that are (a) stable across individuals and (b) generalize to predict CVD outcomes in new and different samples. Another problematic issue is that few studies have explored the psychometric properties of brain metrics (e.g., activation values) derived from neuroimaging tasks that are then used to predict CVD risk markers in statistical models.

Goal

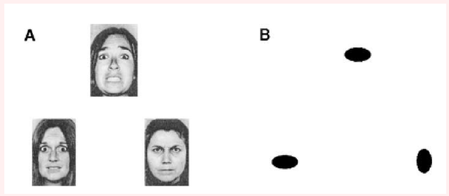
Use of whole-brain and machine-learning methods to test whether individual differences in an indicator of preclinical atherosclerosis and CVD risk (**carotid artery intima-media thickness; CA-IMT**) are reliably associated with distributed brain activity patterns assessed by functional magnetic resonance imaging (fMRI) during affective information processing tasks.

Participants

- Data derived from baseline (cross-sectional) assessments of participants from two studies: the Adult Health and Behavior project - Phase 2 (AHAB-2) and the Pittsburgh Imaging Project (PIP).
- The final total samples were N = 490 (AHAB-2) and N = 331 (PIP).
- Across both cohorts, participants' ages ranged from 30 to 54 years, with an approximate balance of men and women.

FACES fMRI task

- 4 blocks of a facial-expression matching-to-sample condition, interleaved with 5 blocks of a shape-matching (sensorimotor) control condition.
- In the facial-expression matching condition, participants saw 3 same-sex faces in an array for each trial, all expressing either fear or anger. Participants chose 1 of 2 faces at bottom that was identical to a center target at top
- During the control condition, participants also matched-to-sample, but instead used images of circles, vertical ellipses, and horizontal ellipses.



Neuropsychopharmacology 27, 1036-1040

IAPS fMRI task

- Cue of 30 unpleasant and 15 neutral images (15 "Look neutral" trials; 15 "Look negative" trials; 15 "Decrease negative" trials).
- Participants were first trained and then instructed to either (a) "Look" and attend to images or (b) "Decrease" and change their thinking about the image to feel less negative.
- After image viewing, participants rated their emotional state ("How negative do you feel?") on a 5-point Likert-type scale in a 4-sec rating period (1 = neutral, 5 = strongly negative).
- A variable (1-3 sec) rest period preceded each cue.

NeuroImage 23, 483-499

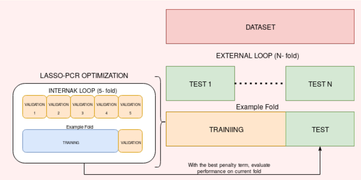
Methodology

CA-IMT (y) was predicted from the evoked responses within gray matter voxels from all participant contrast maps (X) using a principal component regression with a L1 regularization (LASSO-PCR).

LASSO-PCR

1. The predictor matrix X is decomposed into orthogonal components $X = USV^T$.
2. The $Z \equiv US$ matrix is fed onto a lasso regression, $\hat{\vec{\beta}} = \arg\min_\beta ||y - Z\beta||^2 + \lambda||Z||$.
3. This $\hat{\vec{\beta}}$ is projected back to voxel space using V and yielding a weight map $\hat{\vec{w}} = V^T\beta$.
4. This weight map is then used to produce a holdout prediction on $y = \vec{w}x$.

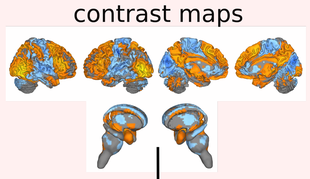
Both model optimization and generalization error estimation have been achieved using a nested cross-validation. For the outer loop, FACES task adopted a 5-Fold cross-validation, whereas IAPS task adopted a 2-Fold cross-validation based on study (PIP and AHAB-2). The inner loop for optimization was a 5-Fold cross-validation for either case.



Ancillary analyses included testing prediction power restricting and excluding the amygdala. Confounding effects were also studied, including age and sex as moderators of associations between predicted and observed CA-IMT, as well as similar tests of age, sex, and components of the metabolic syndrome as covariates.

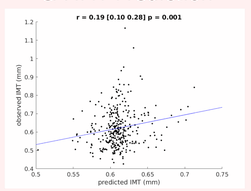
IAPS task results

Look negative vs. Look neutral contrast maps

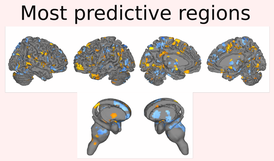


LASSO-PCR and nested cross-validation

CA-IMT Prediction



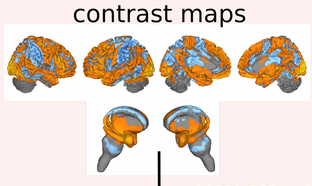
Most predictive regions



- CA-IMT was predicted by a whole-brain multivariate pattern derived from the "Look negative vs. Look neutral" r(336) = 0.19 (95% CI = 0.10 to 0.28, p < 0.001, BF10 = 47.10, BF01 = 0.02).
- Predictive weights within the amygdala were uniformly negative (90 negative vs. 0 positive voxel weights out of 468 possible voxels).
- The internal consistency of the weight map was 0.82.
- After amygdala exclusion, association between predicted and observed CA-IMT across participants is still observed r(336) = 0.19 (95% CI = 0.10 to 0.28, p = 0.001, BF10 = 45.70, BF01 = 0.02), indicating that the amygdala activation might not be necessary to predict CA-IMT across individuals.
- This association was not statistically moderated by age (β = 0.07, SE = 0.05, p = .155, BF10 = BF10 = 0.33, BF01 = 3.03) or sex (β = -0.05, SE = 0.05, p = .384, BF10 = 0.29, BF01 = 3.45).
- Simultaneous adjustment for age, sex, and the composite index of cardiometabolic risk demonstrated that predicted and observed CA-IMT continued to correlate at a conventional threshold of p < 0.05, (β = 0.18, SE = 0.04, t = 4.13, p < 0.001, BF10 = 444.00, BF01 < 0.01).

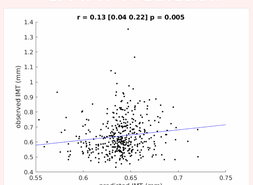
FACES task results

AllFaces vs Shapes contrast maps

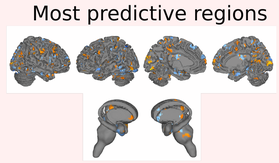


LASSO-PCR and nested cross-validation

CA-IMT Prediction



Most predictive regions



- Predicted CA-IMT by a model trained on the contrast of "Faces vs. Shapes" (inclusive of angry and fearful faces) correlated with observed CA-IMT, r(425) = 0.13 (95% CI = 0.04 to 0.22, p = 0.005, BF10 = 5.16, BF01 = 0.19).
- Predictive contributions of the amygdala were predominately negative (94 negative vs. 17 positive voxel out of 468 possible voxels).
- The internal consistency of this weight map was 0.73.
- Voxels restricted to the amygdala predicted CA-IMT with a smaller effect size, r(425) = 0.10 (95% CI 0.003 to 0.19, p = 0.044, BF10 = 0.84, BF01 = 1.19). In contrast, amygdala exclusion yields an association r(425) = 0.13 (95% CI 0.04 to 0.22, p = 0.007, BF10 = 4.16, BF01 = 0.24.
- This association was not moderated by age (β= 0.04, SE = 0.04, p = 0.340, BF10 = 0.16, BF01 = 6.25) or sex (β = 0.06, SE = 0.05, p = 0.187, BF10 = 0.43, BF01 = 2.33).
- Adjustment for age, sex, and the composite cardiometabolic risk score demonstrated that predicted and observed CA-IMT no longer correlated (β = 0.03, SE = 0.04, t = 0.88, p = 0.378, BF10 = 0.15, BF01 = 6.66).

Conclusion

The present findings underscore the relevance of multivariate and cross-validation methodologies, as well as psychometric characteristics of fMRI tasks, for building predictive models that characterize replicable affective neural correlates of CVD risk. In these regards, the present findings suggest a possible affective neural correlate of preclinical atherosclerosis comprised of multivariate, whole-brain activity evoked by the visual processing of complex affective cues.

Take-home message

We report the first cross-validated evidence in two large samples of adults for a specific and multivariate affective pattern of human brain activity that relates to individual differences in a vascular marker of cardiovascular disease (CVD) risk

References

[1] Gianaros, P. J., & Jennings, J. R. (2018). *Host in the machine: A neurobiological perspective on psychological stress and cardiovascular disease.* American Psychologist, 73(8), 1031-1044.

[2] Gianaros, P. J. *et al* (2008). *Preclinical atherosclerosis covaries with individual differences in reactivity and functional connectivity of the amygdala.* Biol Psychiatry, 65, 943-950