Integrating fMRI-based pain biomarkers into a broader neuroscience context

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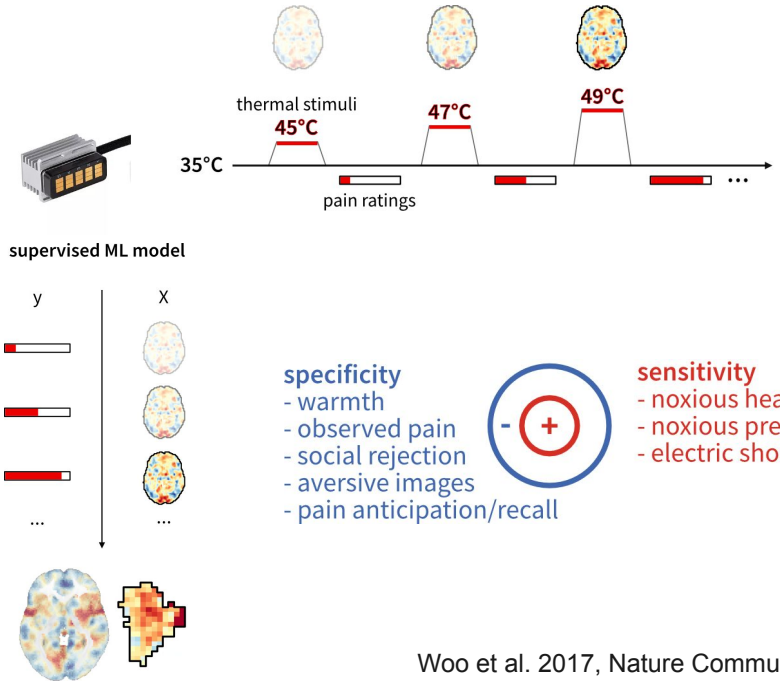
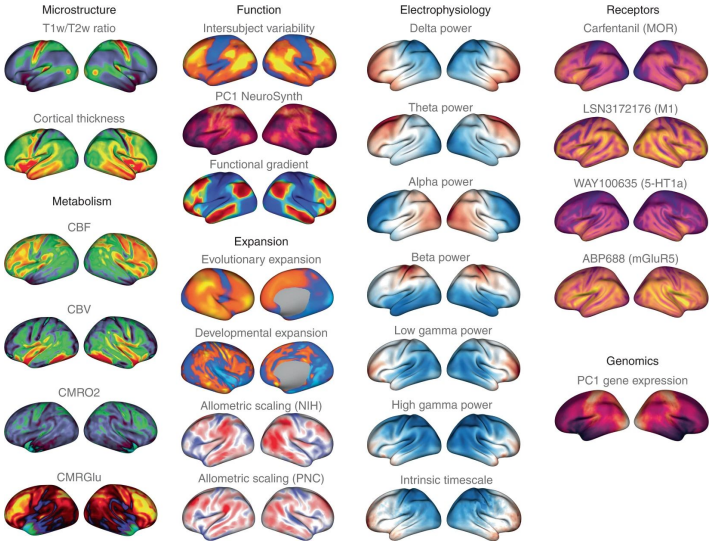
Background (1/2)

outcome: stimulus intensity independent **pain signature**



Woo et al. 2017, Nature Communications

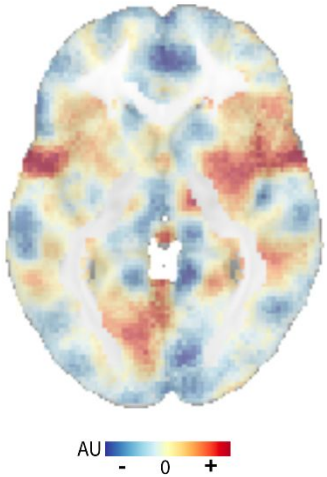
predictors: NeuroMaps, structural and functional



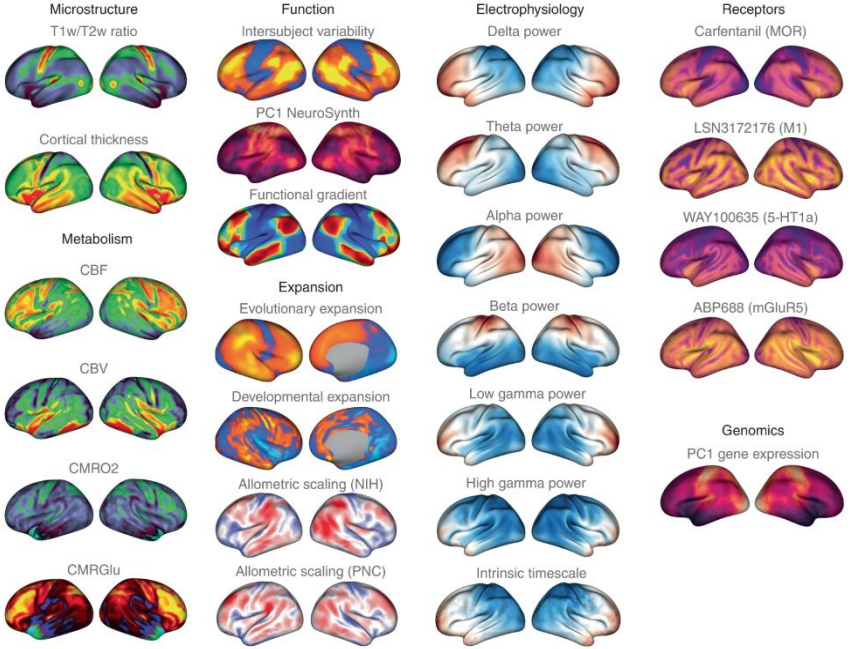
Markello et al. 2022, Nature Methods

Background (2/2)

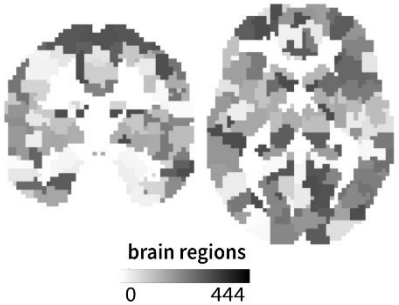
a. Pain Signature: outcome variable



b. Neuromaps: predictor variables

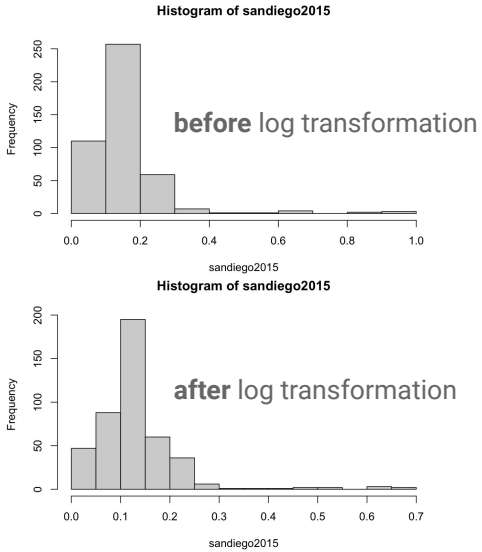


c. Brain Parcellation



Preprocessing

log transformation



dimensionality reduction
principal components

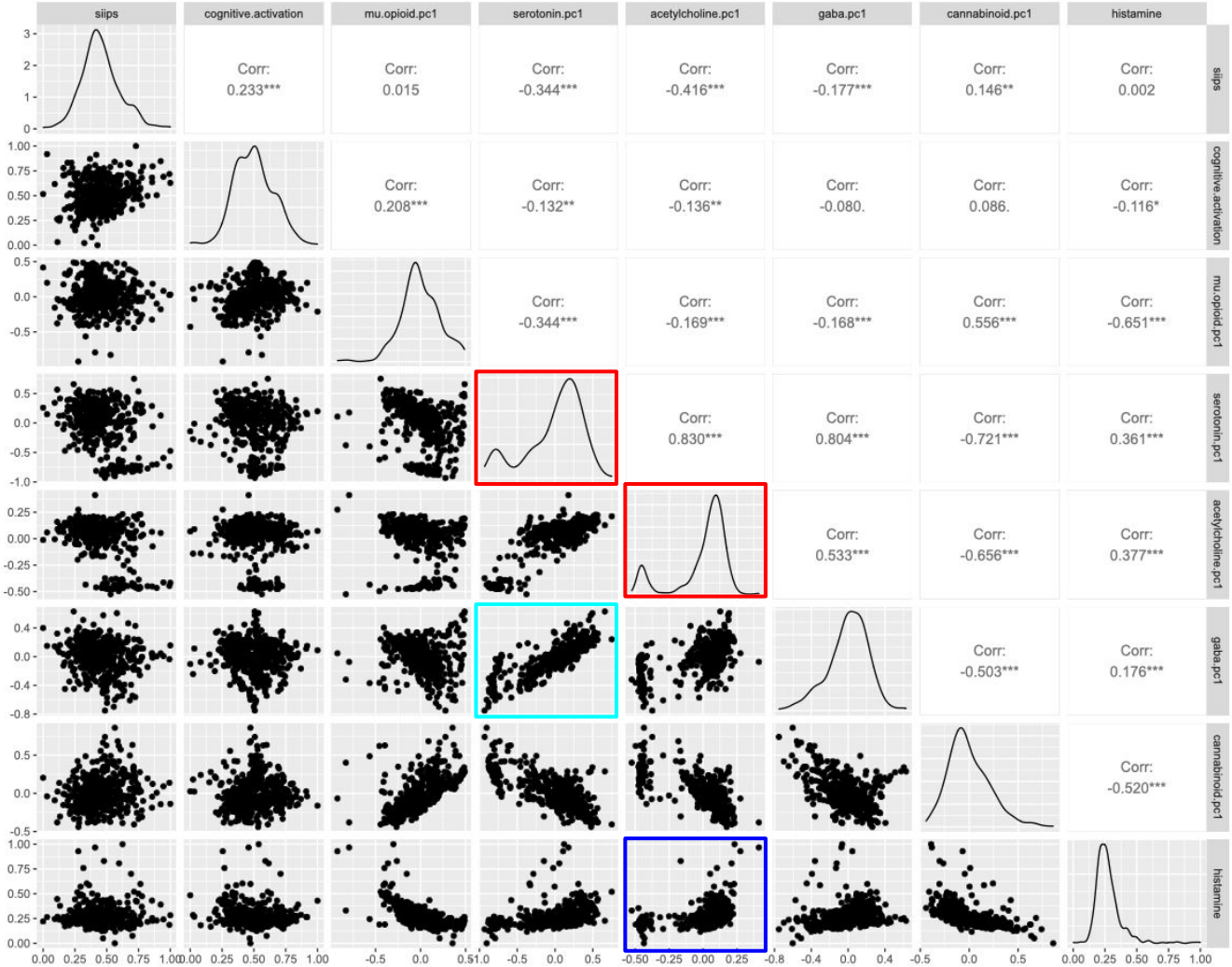
(row)	colname	modality	description
1	neurosynth.cogpc1	fMRI	cognitive.activation
2	satterthwaite2014.meancbf	ASL	cerebral.blood.flow
3	finnema2016.ucbj	PET	synaptic.density
4	turtonen2020.carfentanil	PET	mu.opioid
5	kantonen2020.carfentanil	PET	mu.opioid
6	dukart2018.fpcit	ASL	dopamine
7	jaworska2020.fallypride	PET	dopamine
8	sandiego2015.flb457	PET	dopamine
9	alarkurtti2015.raclopride	PET	dopamine
10	kaller2017.sch23390	PET/MRI	dopamine
11	sasaki2012.fepe2i	PET	dopamine
12	smith2017.flb457	PET	dopamine
13	fazio2016.madam	PET	serotonin
14	gallezot2010.p943	PET	serotonin

... from **34** predictors to **12**

all subsets variable selection
adjusted R^2

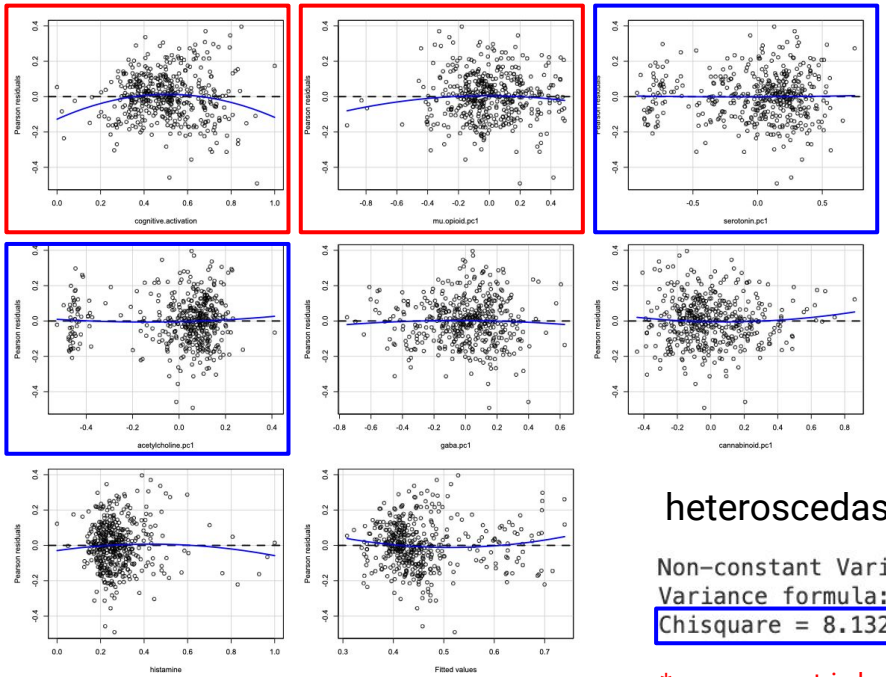
1. **cognitive activation**
2. **mu opioid** distribution PC1
3. **serotonin** distribution PC1
4. **acetylcholine** distribution PC1
5. **GABA** distribution PC1
6. **cannabinoid** distribution PC1
7. **histamine** distribution PC1

from **12** predictors to **7**


siips
cognitive.activation
mu.opioid.pc1
serotonin.pc1
acetylcholine.pc1
gaba.pc1
cannabinoid.pc1
histamine
Corr: 0.233***
Corr: 0.015
Corr: -0.344***
Corr: -0.416***
Corr: -0.177***
Corr: 0.146**
Corr: 0.002
Corr: 0.208***
Corr: -0.132**
Corr: -0.136**
Corr: -0.080.
Corr: 0.086.
Corr: -0.116*
Corr: -0.344***
Corr: -0.169***
Corr: -0.168***
Corr: 0.556***
Corr: -0.651***
Corr: 0.830***
Corr: 0.804***
Corr: -0.721***
Corr: 0.361***
Corr: 0.533***
Corr: -0.656***
Corr: 0.377***
Corr: -0.503***
Corr: 0.176***
Corr: -0.520***

Naive Model

residual plots



nonlinearity

(row)	Test stat	Pr(>|Test stat|)
cognitive.activation	-3.0341	0.0026
mu.opioid.pc1	-1.6227	0.1054
serotonin.pc1	0.2382	0.8119
acetylcholine.pc1	0.7013	0.4835
gaba.pc1	-0.6238	0.5331
cannabinoid.pc1	1.084	0.279
histamine	-1.1978	0.2317
Tukey test	1.9282	0.0538

* add quadratic terms

collinearity

(row)	vif(ols1)
cognitive.activation	1.0884
mu.opioid.pc1	2.8384
serotonin.pc1	10.4786
acetylcholine.pc1	5.3587
gaba.pc1	3.7836
cannabinoid.pc1	3.0159
histamine	2.1033

* remove predictor

heteroscedasticity

```
Non-constant Variance Score Test
Variance formula: ~ fitted.values
Chisquare = 8.132561, Df = 1, p = 0.0043477
```

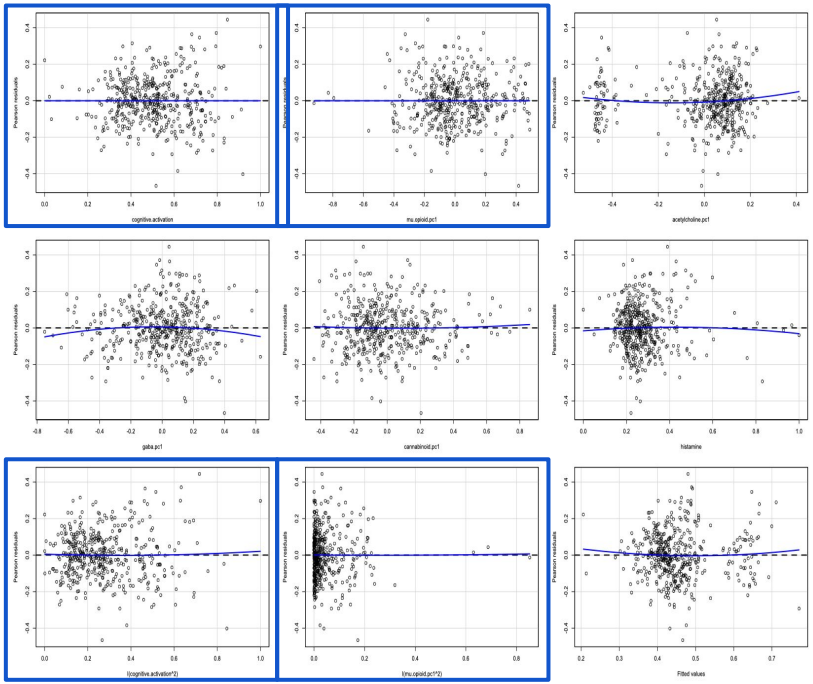
* nonparametric bootstrap

autocorrelation

```
 lag Autocorrelation D-W Statistic p-value
   1      0.01911599      1.961691   0.668
Alternative hypothesis: rho != 0
```

Final Model

residual plots



nonlinearity

(row)	Test stat	Pr(>|Test stat|)
cognitive.activation	1.3599	0.1746
mu.opioid.pc1	-0.0589	0.9531
acetylcholine.pc1	1.3049	0.1926
gaba.pc1	-1.5065	0.1327
cannabinoid.pc1	0.4015	0.6883
histamine	-0.6729	0.5013
I(cognitive.activation^2)	0.6	0.5488
I(mu.opioid.pc1^2)	0.085	0.9323
Tukey test	0.8646	0.3873

anova test: H_0 naive model, H_A final model

Res.Df	RSS	Df	Sum of Sq	F	Pr(>F)
436	7.6417	NA	NA	NA	NA
435	7.4994	1	0.1423	8.2556	0.0043

outlier test

```
No Studentized residuals with Bonferroni p < 0.05
Largest |rstudent|:
     rstudent unadjusted p-value Bonferroni p
177 -3.659496         0.00028381      0.12601
```

final model summary

(row)	Estimate	Std.Error	t.value	p.value
(Intercept)	0.119	0.067	1.783	0.075
cognitive.activation	0.795	0.259	3.069	0.002
mu.opioid.pc1	0.093	0.049	1.91	0.057
acetylcholine.pc1	-0.469	0.058	-8.013	0
gaba.pc1	0.045	0.038	1.202	0.23
cannabinoid.pc1	-0.09	0.053	-1.703	0.089
histamine	0.42	0.097	4.306	0
I(cognitive.activation^2)	-0.616	0.268	-2.298	0.022
I(mu.opioid.pc1^2)	-0.205	0.088	-2.333	0.02

adjusted R^2 = **0.27**

* estimated with nonparametric bootstrap

Conclusions

Six measures of brain function and physiology can explain 27% of the variability in the pain signature

significant predictors of the pain signature:

+ cognitive activation: regions that are activated across a range of experimental stimuli
+ mu opioids: neurotransmitter that modulate pain
+ histamine: neurotransmitter that promotes wakefulness
- acetylcholine: excitatory neurotransmitter

non-significant predictors of the pain signature:

+ GABA: inhibitory neurotransmitter
- cannabinoid receptors: regulation of appetite and pain