EINSTEIN
Albert Einstein College of Medicine

An introduction to Multivoxel pattern analysis (MVPA), machine learning, & fMRI

Instructor: Marianne Reddan, PhD
PRIME Center for Health Equity at Montefiore Einstein

March 2024

Research significance is determined by:

A. Statistical thresholds (e.g., p-values)
B. Effect sizes (e.g., Cohen's *d*)
C. Model accuracy, as validated on external datasets
D. Reproducibility of effect
E. Social, political, and clinical impact

?

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E. Social, political, and clinical impact
F. **All of the above** *(with the lowest emphasis on A)*

Call for neuroimaging 'biomarkers'

PERSPECTIVE

Why has it taken so long for biological psychiatry to develop clinical tests and what to do about it?

S Kapur[1], AG Phillips[2] and TR Insel[3]

2012 Molecular Psychiatry

CellPress

Neuron
Article

Attenuating Neural Threat Expression with Imagination

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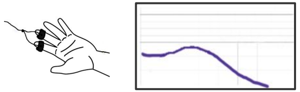
https://doi.org/10.1016/j.neuron.2018.10.047

Pavlovian threat conditioning



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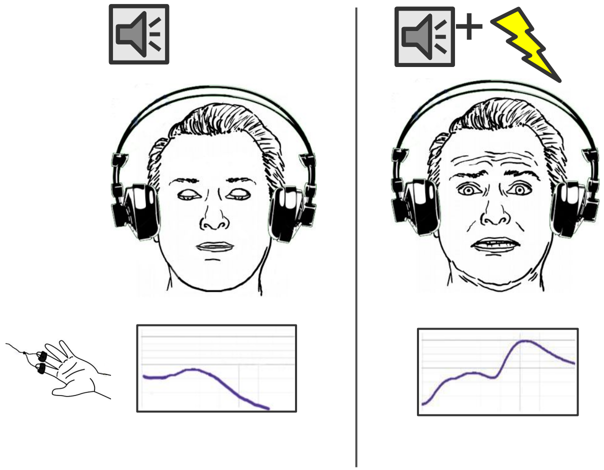

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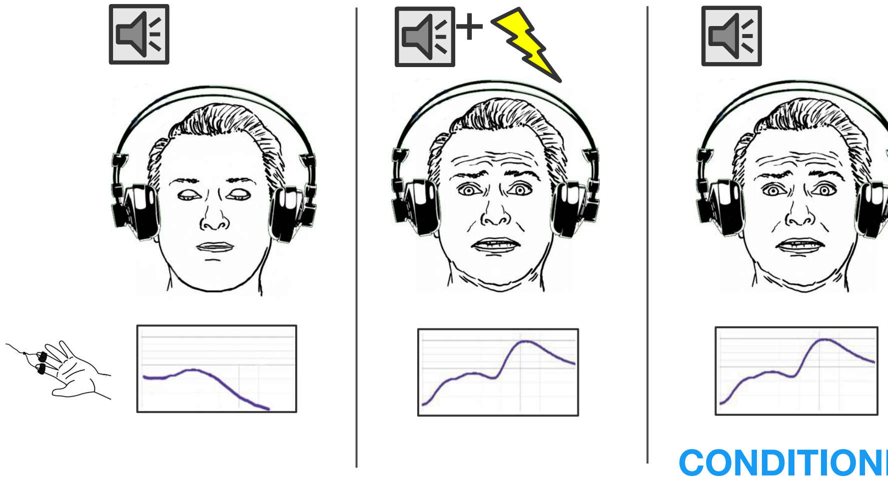
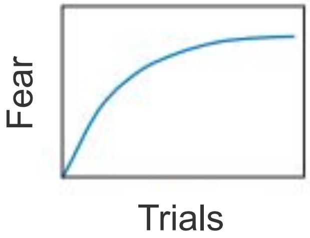


CONDITIONED
SKIN CONDUCTANCE
RESPONSE (SCR)

Fear Conditioning



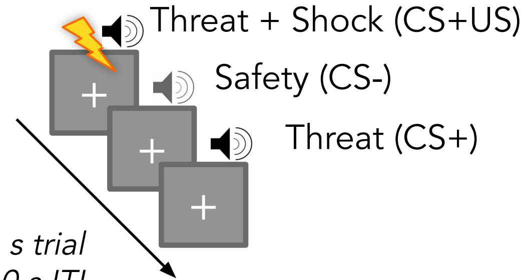
Vervliet, Craske, & Hermans (2013)

Subjects

N = 68 (45 Female)
Mean Age = 29.64 (15.89 STD) years
neurotypicals in NYC

Reddan, Wager, & Schiller (2018)

Phase 1
Acquisition
all subjects
N = 68
33% reinforcement rate



4 s trial
10 s ITI
8 trials per stimulus

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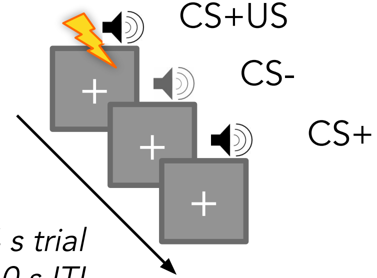

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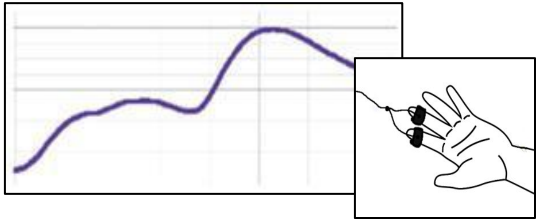
Dependent Measures



Skin Conductance (SCR)

+

3T Siemens Allegra

Reddan, Wager, & Schiller (2018)

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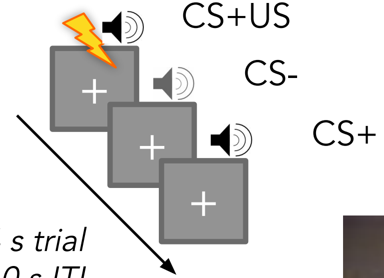

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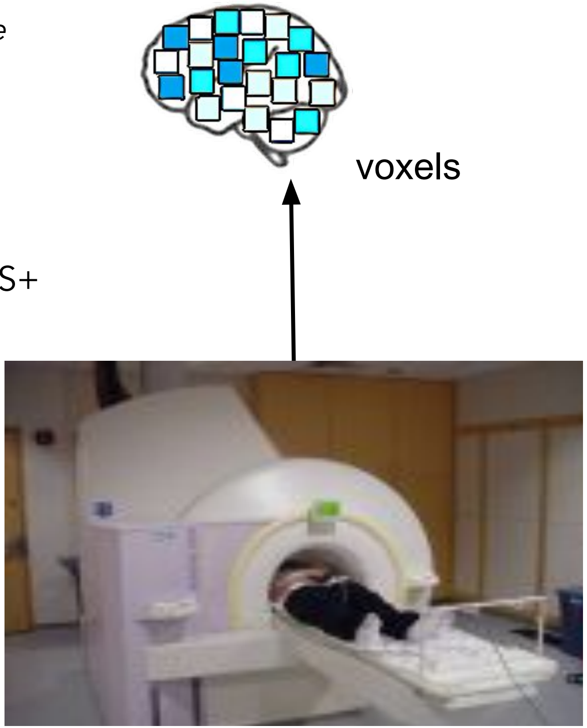

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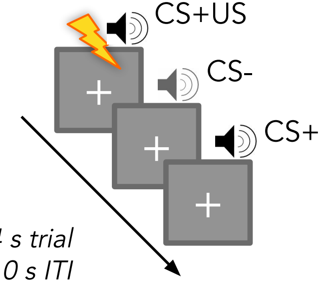

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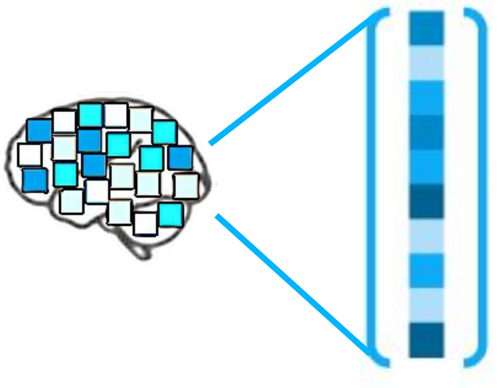
Voxel Time Series



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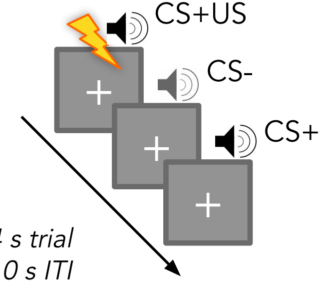

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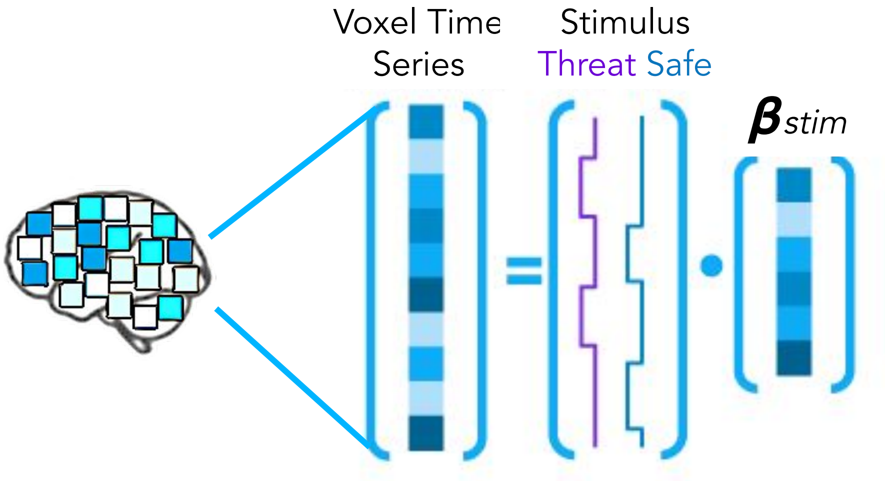

Linear Regression:
subject-level GLM with threat & safety stimuli as predictors

Reddan, Wager, & Schiller (2018)

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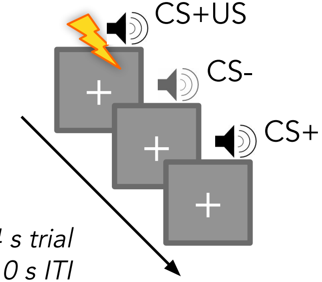

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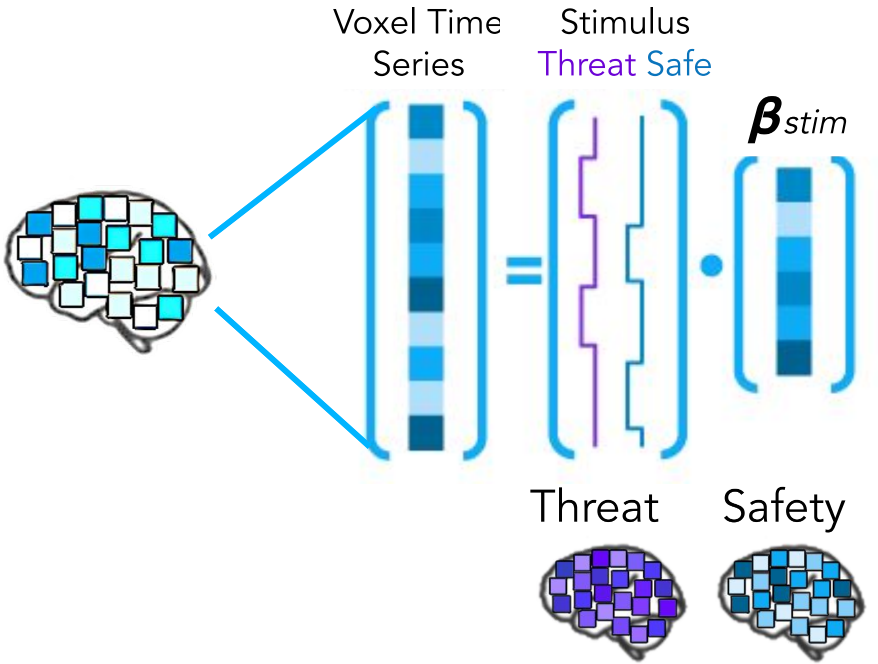

Reddan, Wager, & Schiller (2018)

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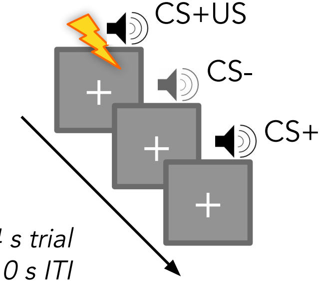

4 s trial
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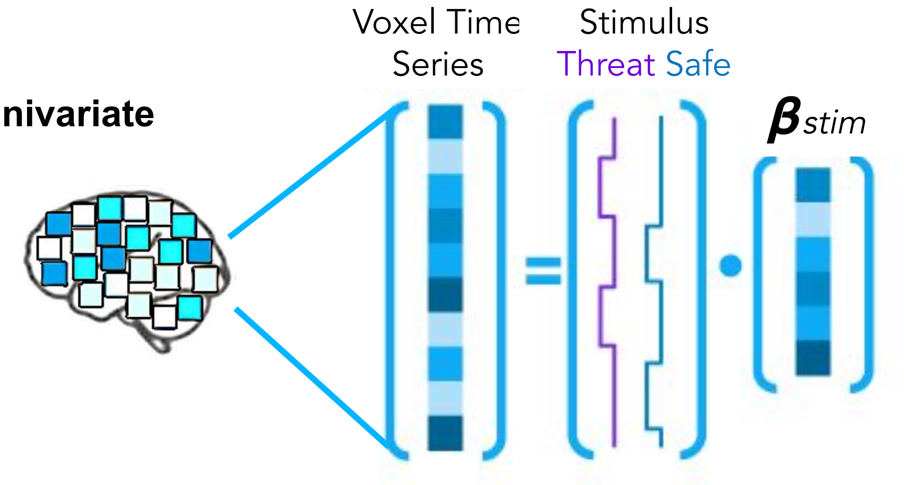
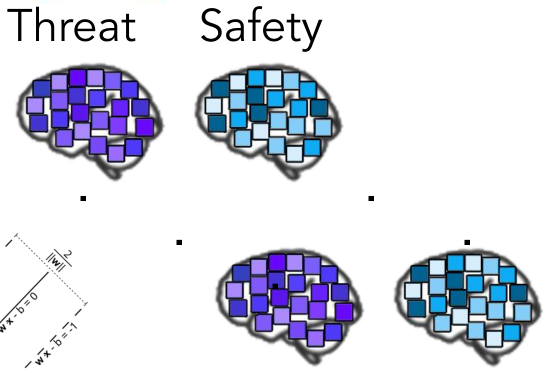
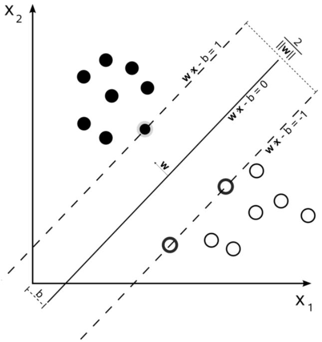
univariate



Classifier Training:
linear SVM (C =1)



multivariate

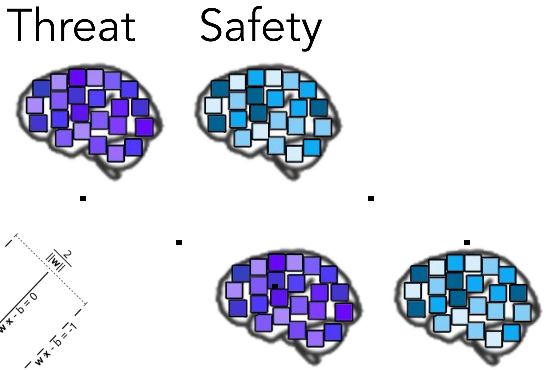


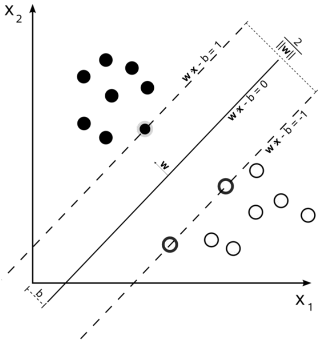
Reddan, Wager, & Schiller (2018)

Putting all the voxels into one model is known as “MVPA”

Multi-Voxel Pattern Analysis capitalizes on the covariance structure of the whole brain to uncover patterns of activity indicative of some event.

Classifier Training:
linear SVM (C =1)



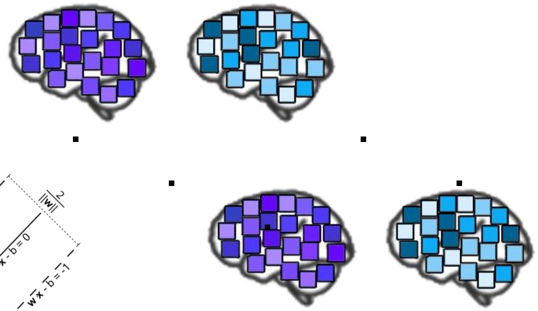


Reddan, Wager, & Schiller (2018)

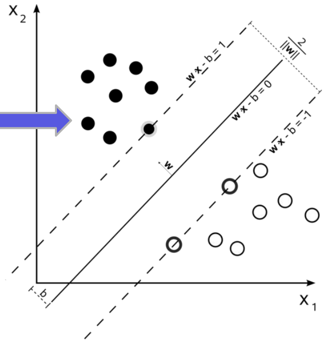
But where are all the voxels??

Classifier Training:
linear SVM (C =1)

Threat Safety



Isn't that dot a subject?



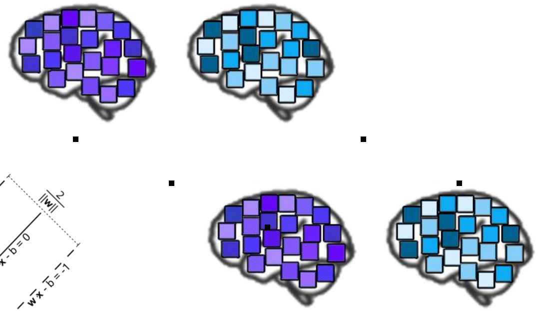
Reddan, Wager, & Schiller (2018)

But where are all the voxels??

It sure is, but this is a 2 dimensional feature space… it's just a picture, not the actual behind-the-scenes math

Classifier Training:
linear SVM (C =1)

Threat Safety



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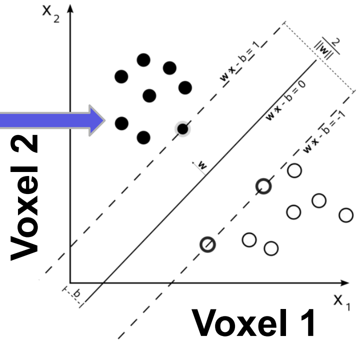
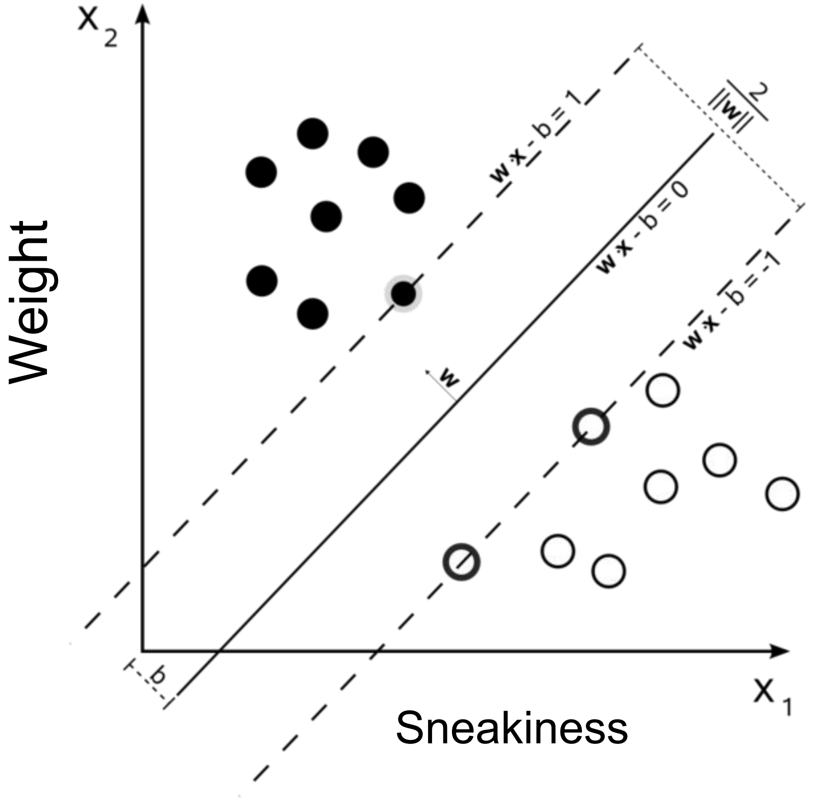


Reddan, Wager, & Schiller (2018)

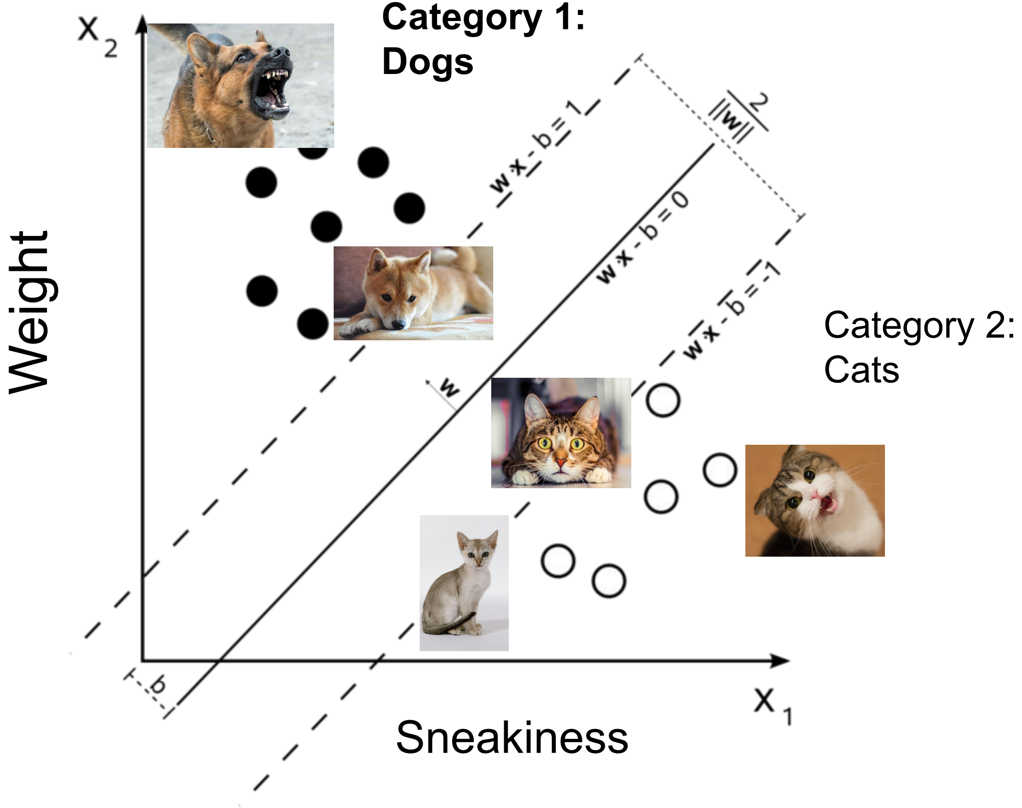
But where are all the voxels??



But where are all the voxels??

But cats and dogs aren't fully defined by their weight and sneakiness…
They have other dimensions!

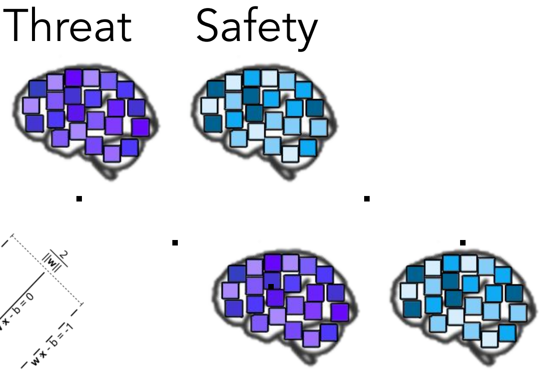
- Time awake
- Diet
- Pack size
- Claw length
- Eye color
- And more!!!!!

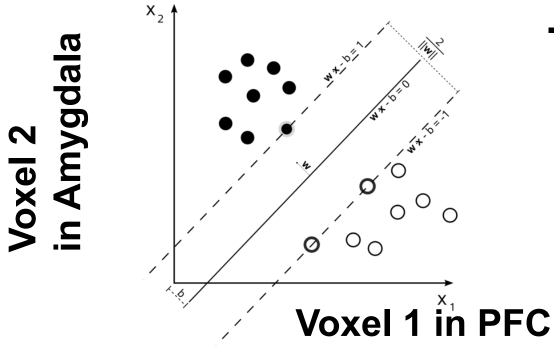


But where are all the voxels??

Likewise, threat and safety have more dimensionality in the brain than two voxels. But if say voxel 1 here is in the amygdala and voxel 2 is in the PFC, maybe we can see this plot.

Classifier Training:
linear SVM (C =1)





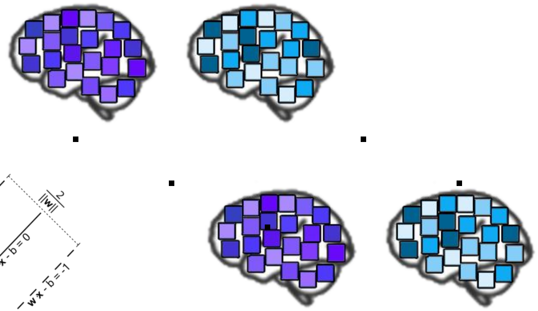
Reddan, Wager, & Schiller (2018)

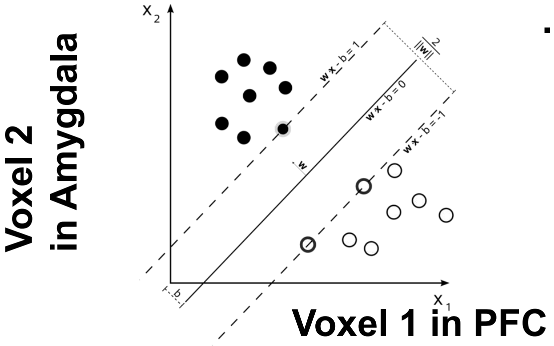
But where are all the voxels??

But we won't know this without assessing the whole brain, and then learning which voxels were most important.

Classifier Training:
linear SVM (C =1)

Threat Safety



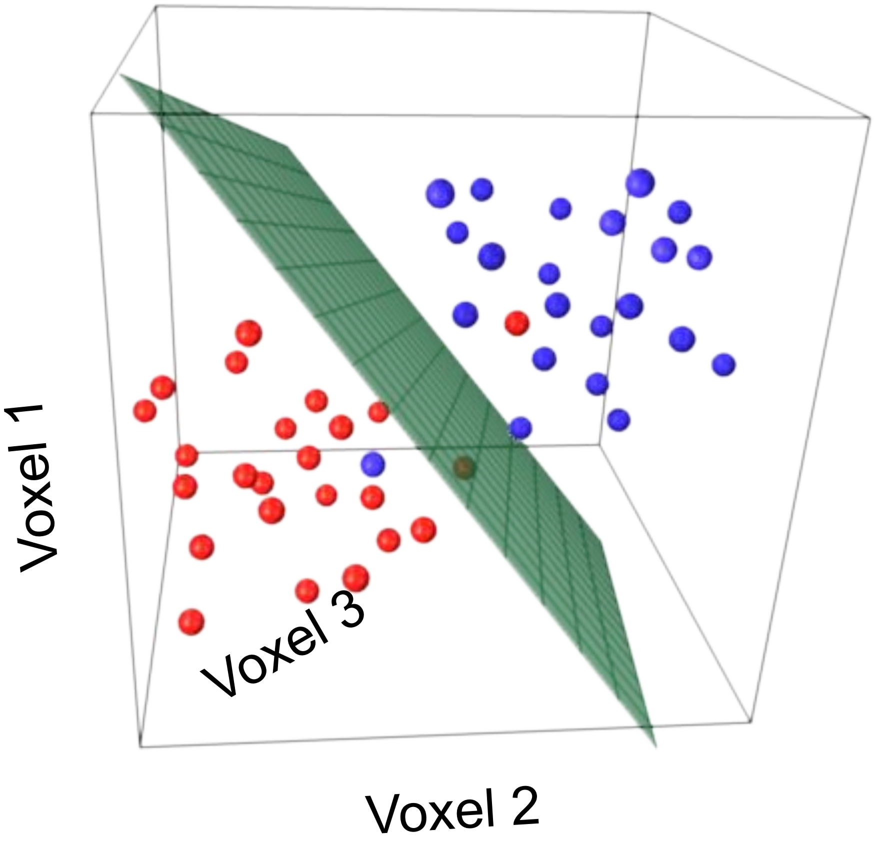


Reddan, Wager, & Schiller (2018)

But where are all the voxels??

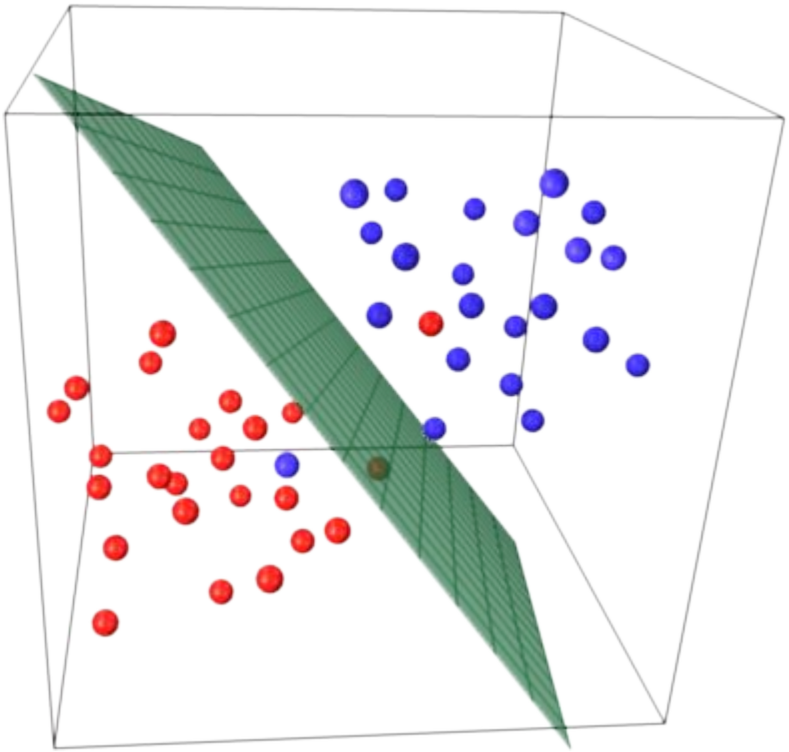
The high-dimensionality of brain data creates a very high-dimensional feature space. Here we see only **3 dimensions**.

Imagine 350,000.



The high-dimensionality of brain data creates a very high-dimensional feature space. Here we see only 3 dimensions.

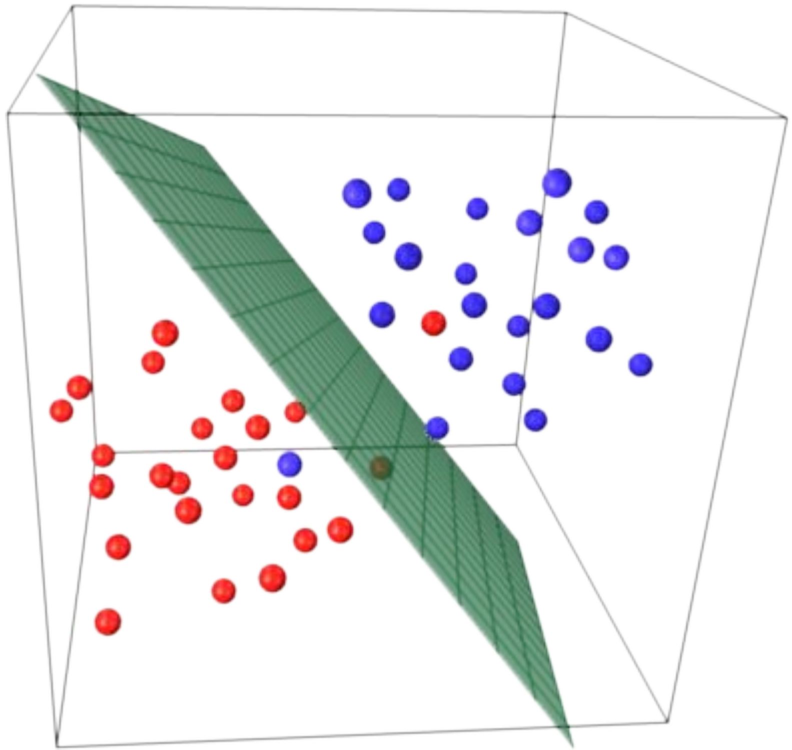
Imagine 350,000. You can't.



The high-dimensionality of brain data creates a very high-dimensional feature space. Here we see only 3 dimensions.

Imagine 350,000. **You can't.**

But a support vector machine can!



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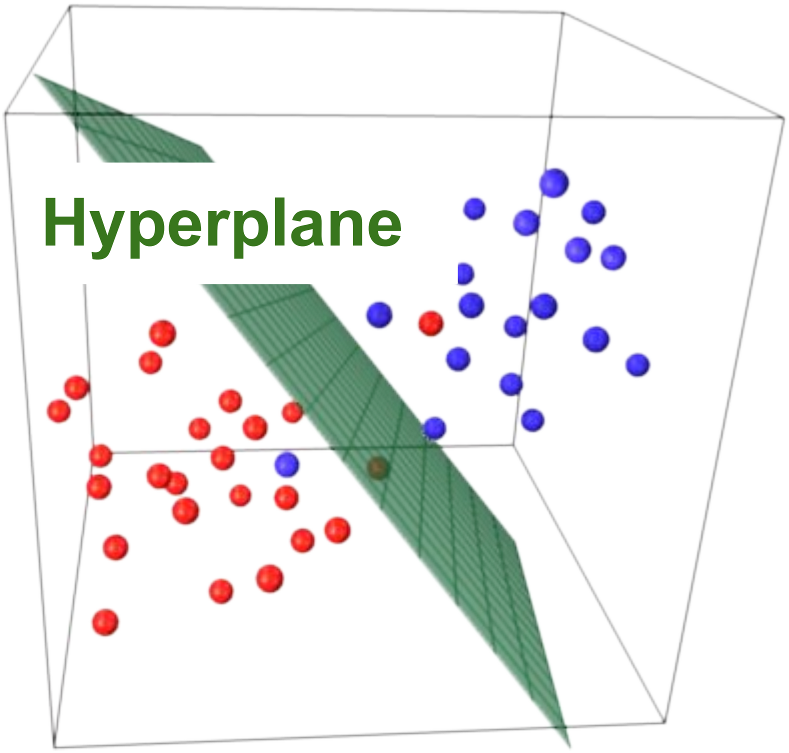
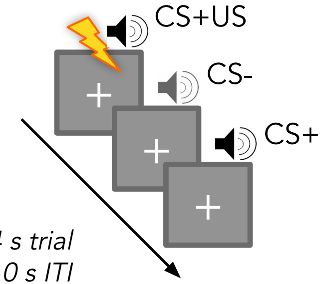


Phase 1
Acquisition

all subjects
N = 68

33% reinforcement rate



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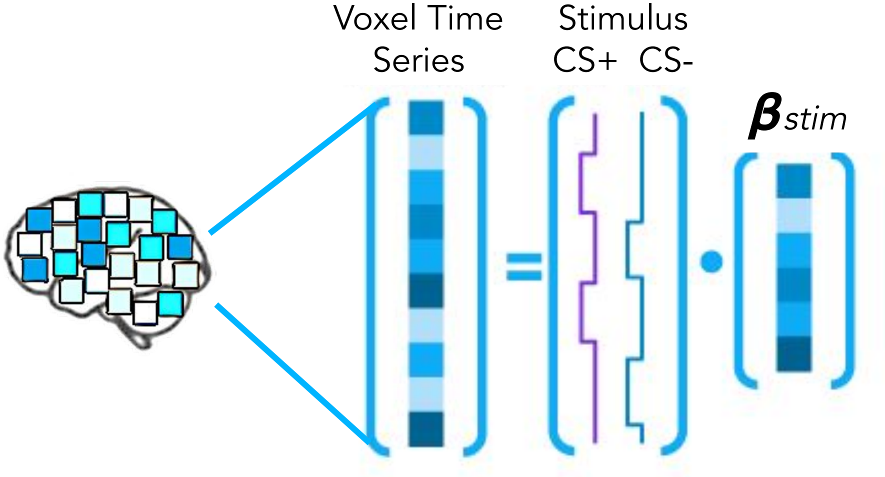
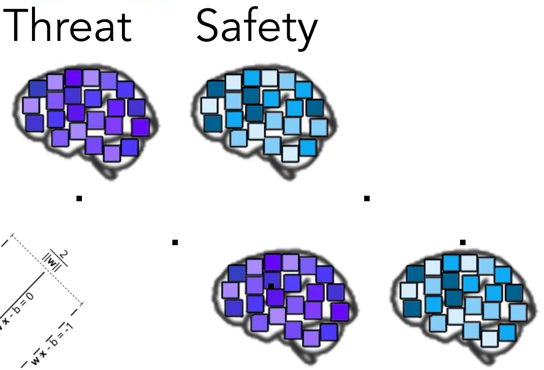
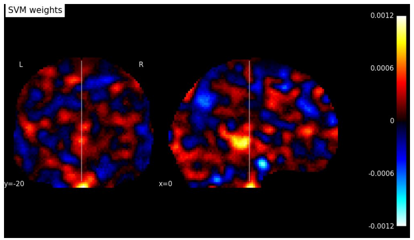
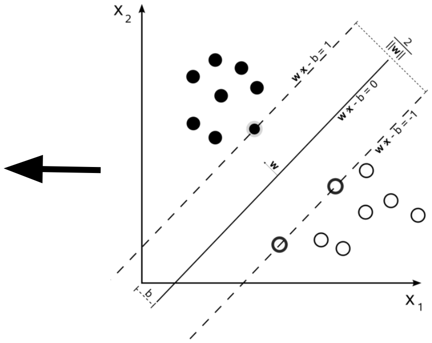


Classifier Training:
linear SVM (C =1)



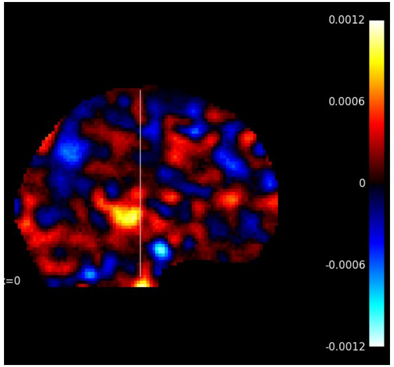
Whole-brain SVM weights



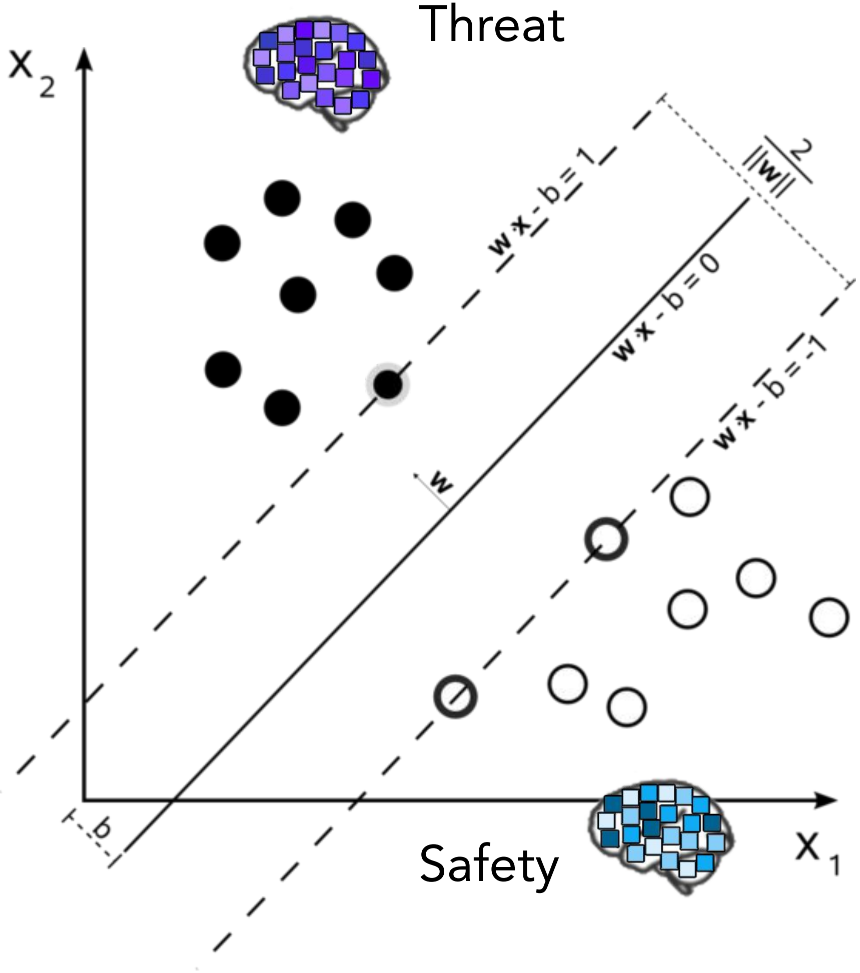


Reddan, Wager, & Schiller (2018)

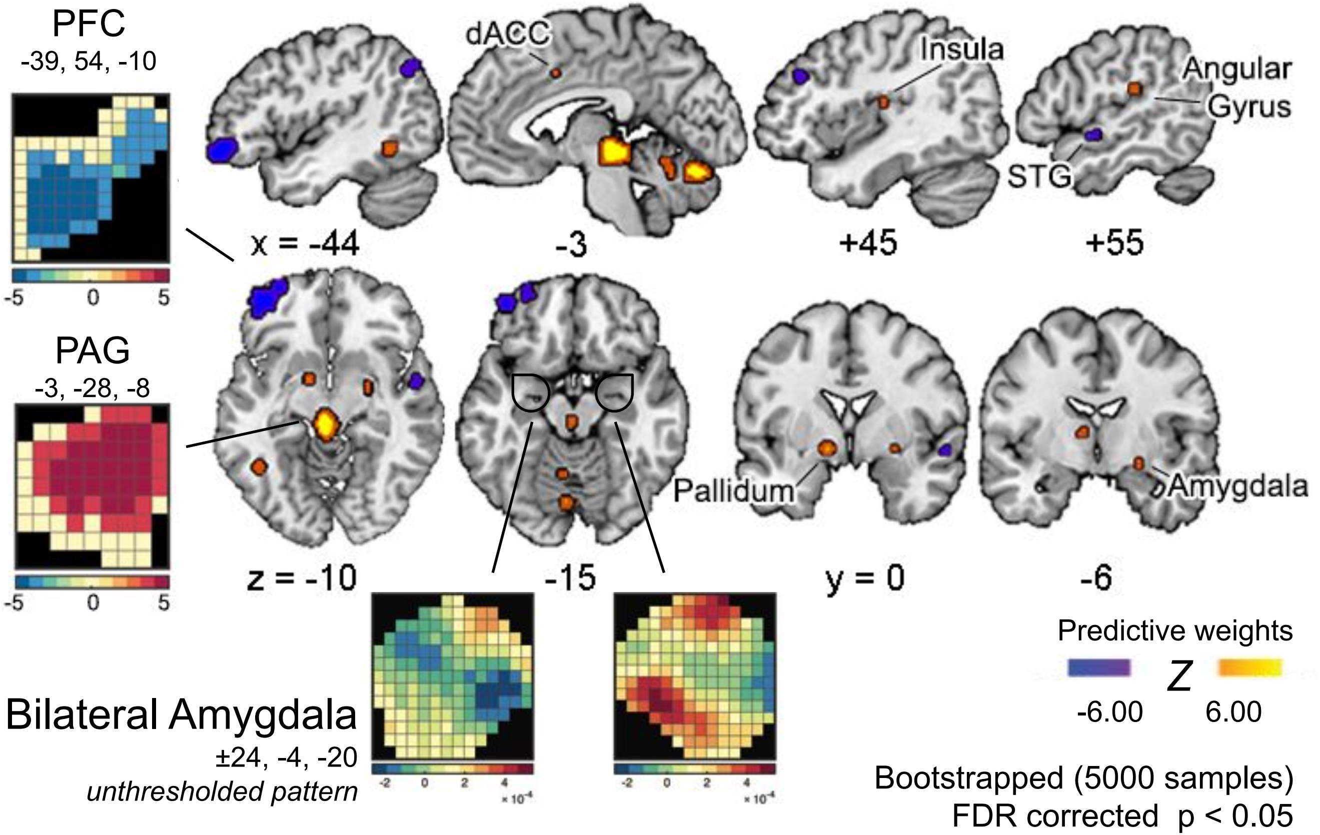
SVM outputs a set of weights, one for each feature, whose linear combination predicts the value of *y*.



SVM predictive weight map



Neural Biomarker of Threat

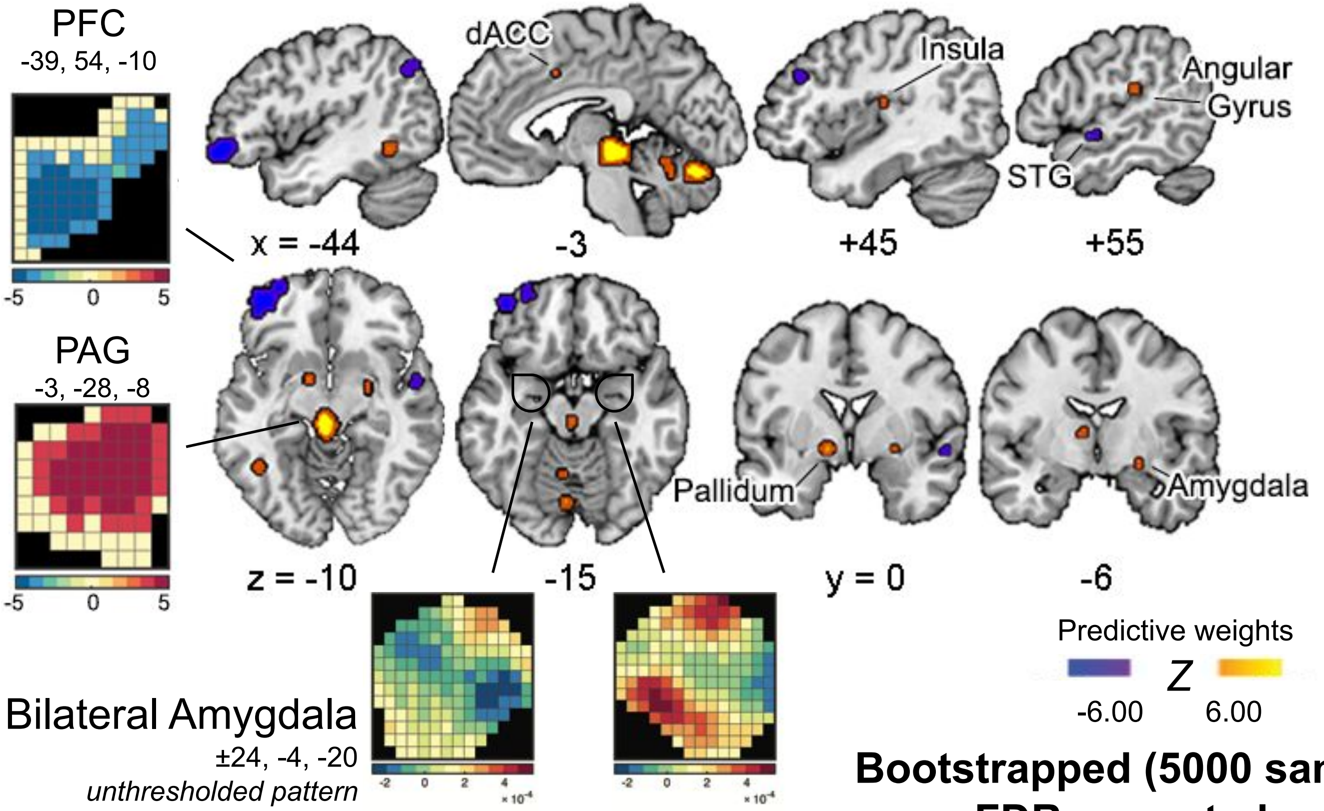


linear SVM (C=1)

trained on
unreinforced threat vs.
safety acquisition trials

Reddan, Wager, & Schiller (2018)

Neural Biomarker of Threat



linear SVM (C=1)

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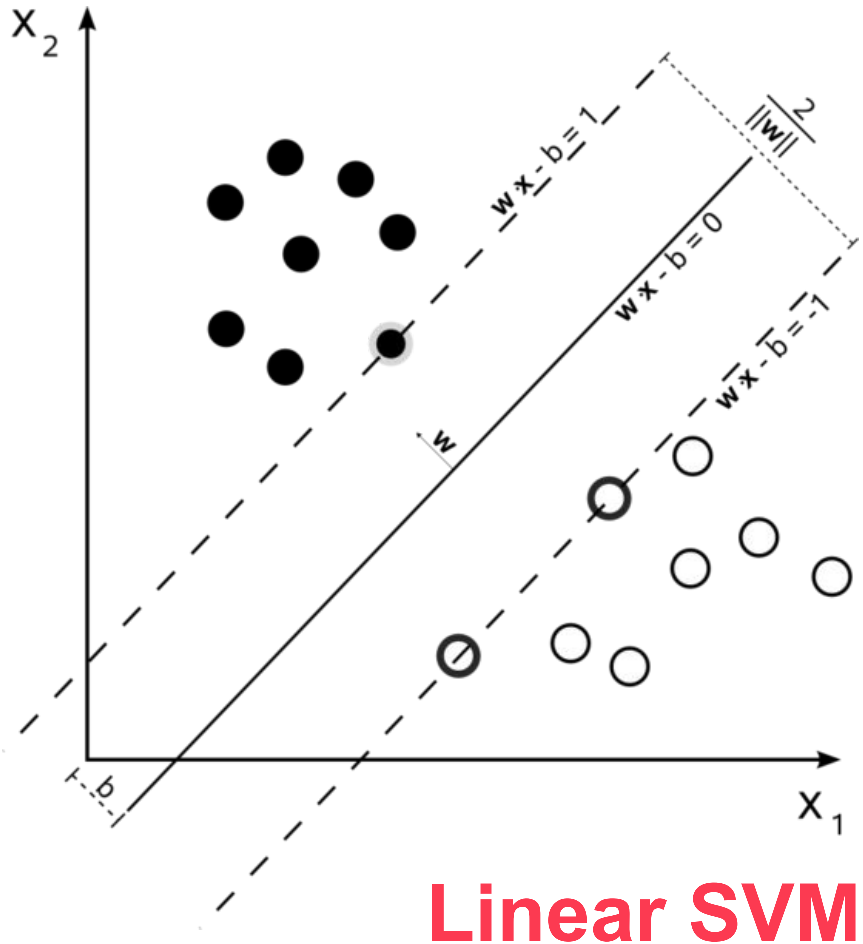
Bootstrapped (5000 samples)
FDR corrected $p < 0.05$

Reddan, Wager, & Schiller (2018)

How do we know if that model is any good?

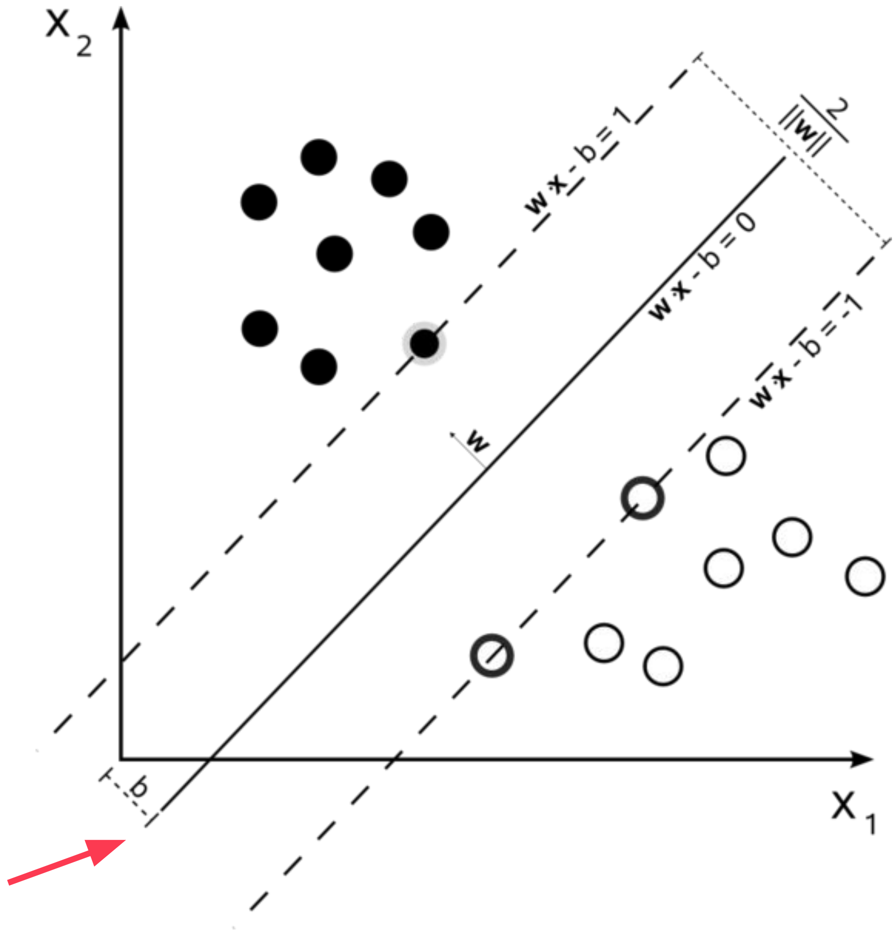
Accuracy is how well the classifier separated the data.



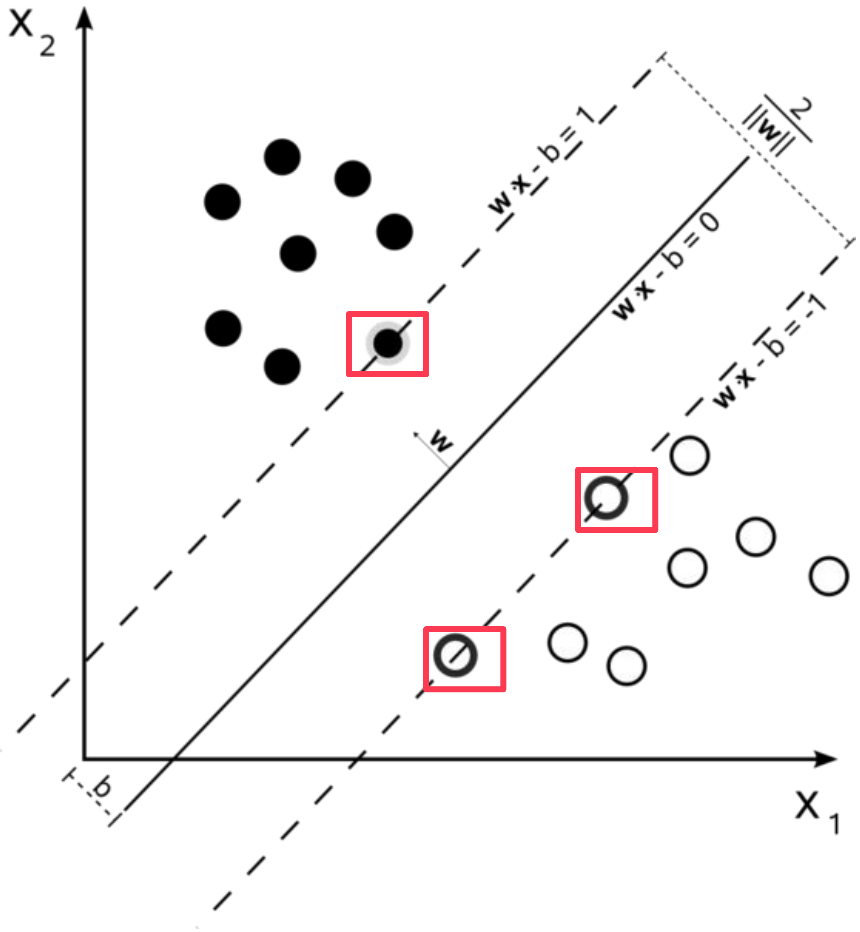
Linear SVM

What is *accuracy*?

SVMs draw a **decision boundary** which maximally separates two labeled classes of data.

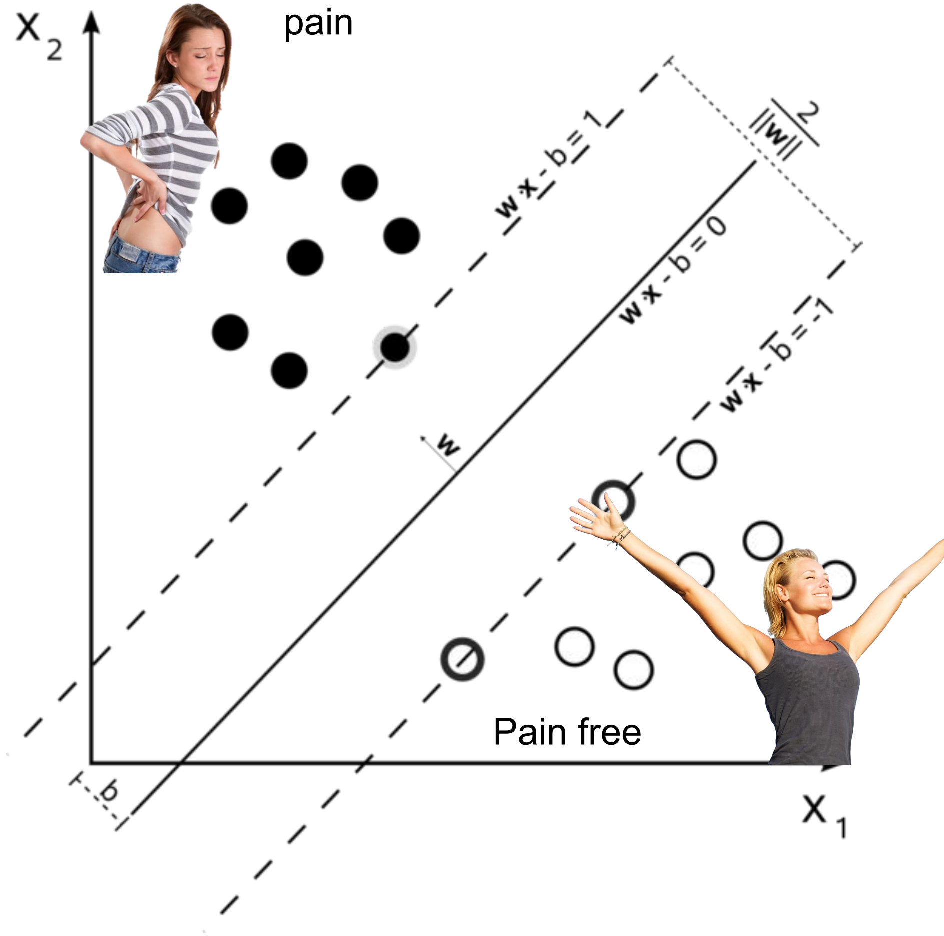


SVM is efficient because it only stores the points which are most difficult to classify, called **support vectors**.



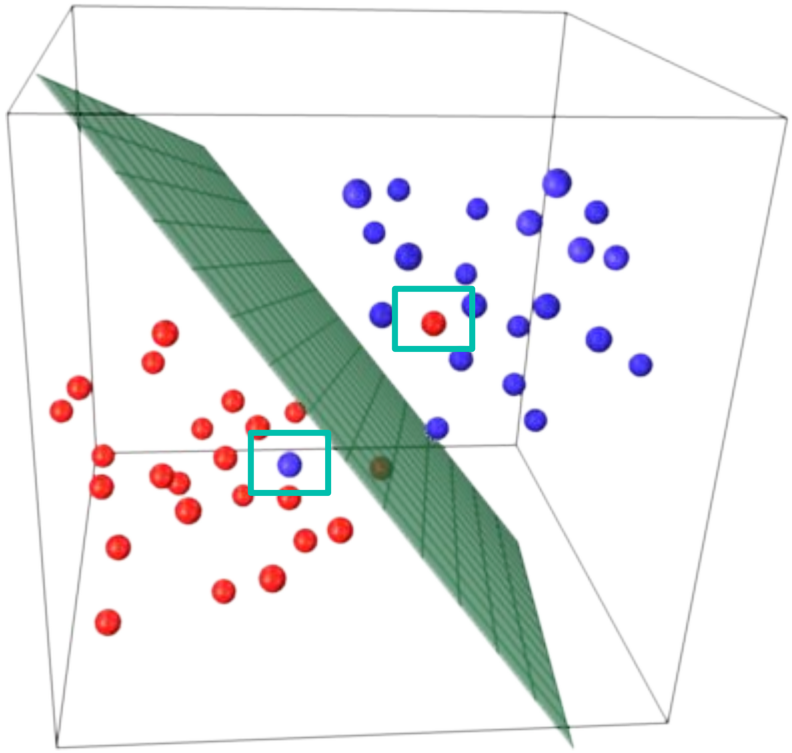
SVM is *large margin classifier*

Every point is a **subject in a known class (condition)**.



You can allow some error, by changing the capacity (C).

Misclassified data points are called **slack variables.**



Typically C=1

Smaller values of C allow for more error (smoother decisions surface)

Larger values of C produce more complex surfaces

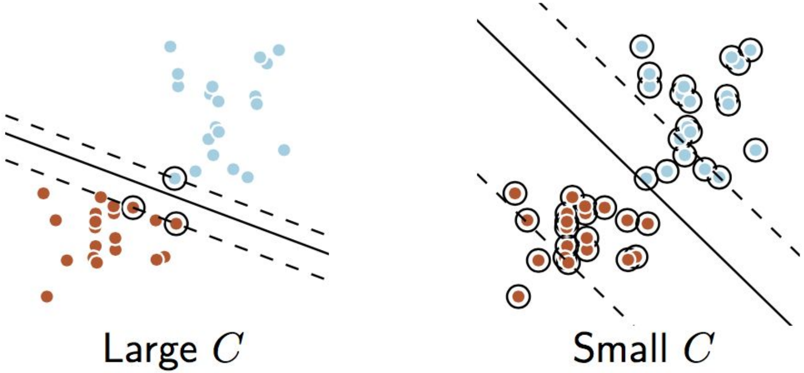
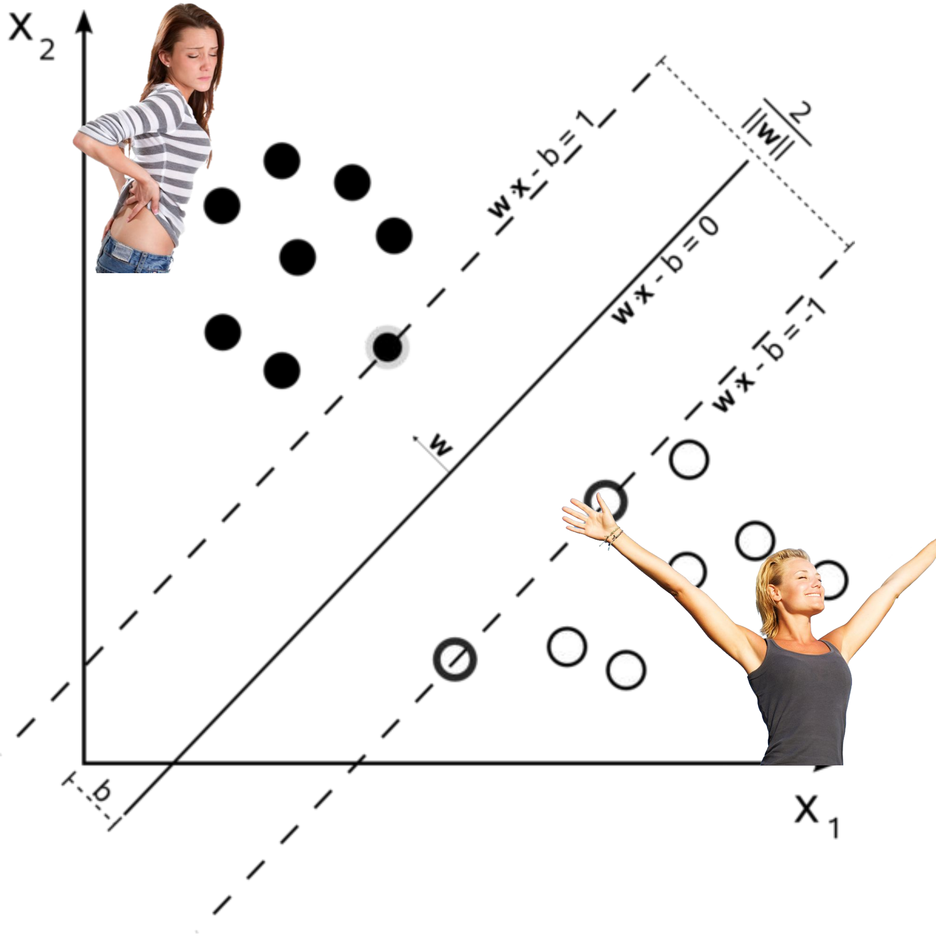
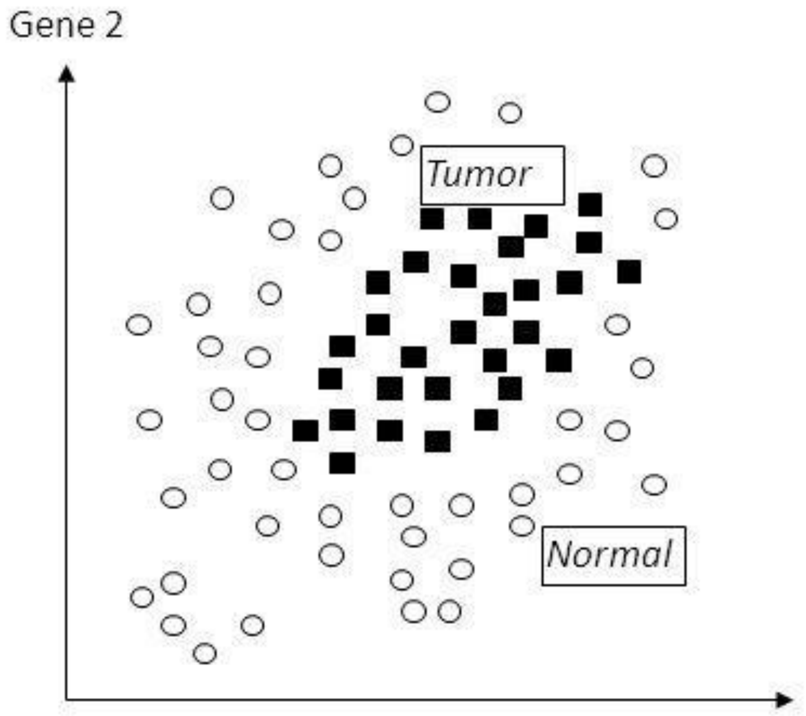


Figure from: Varoquaux et al (2016)

These data are **linearly separable.**



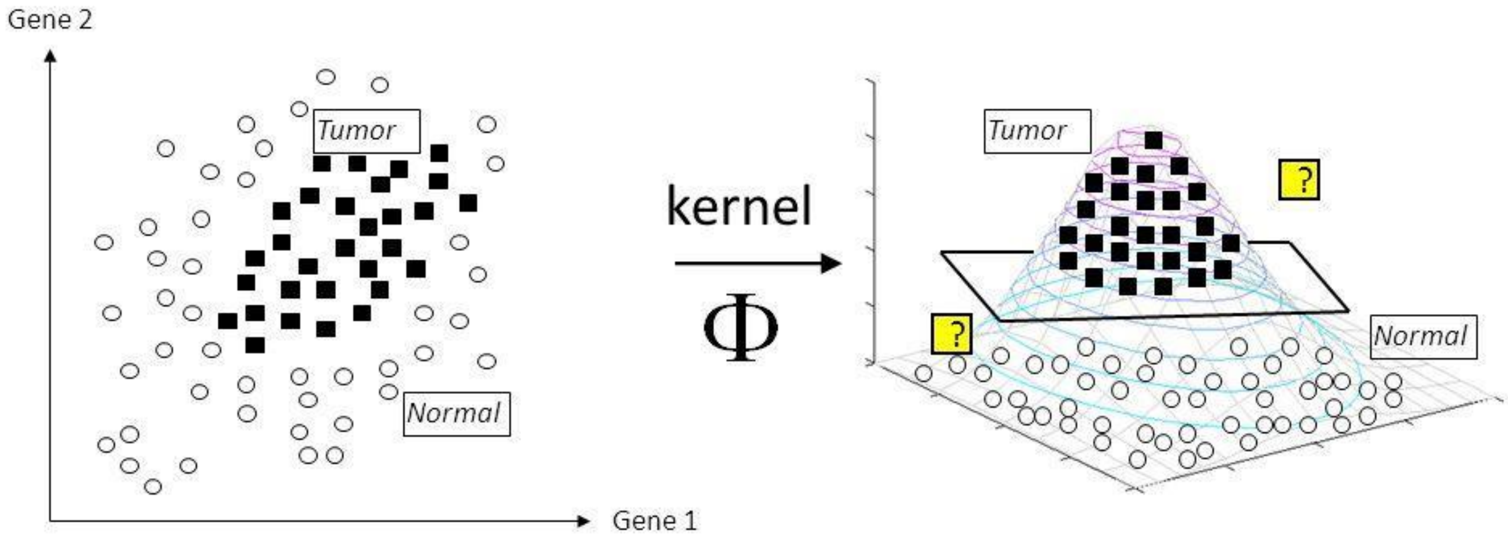
What if they weren’t?



Nonlinear decision boundary

Nonlinear decision space

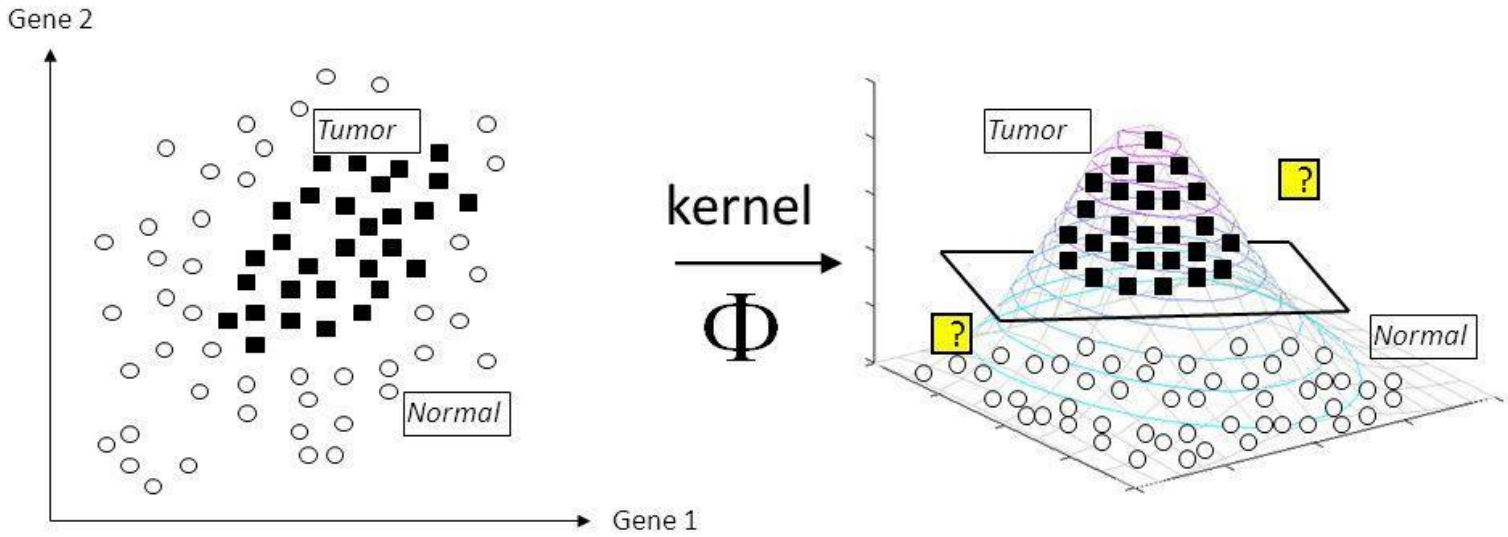
(e.g., Radial basis function (RBF), Polynomials)



http://www.oneweirdkerneltrick.com/

Psychology tends to *only* use linear classifiers

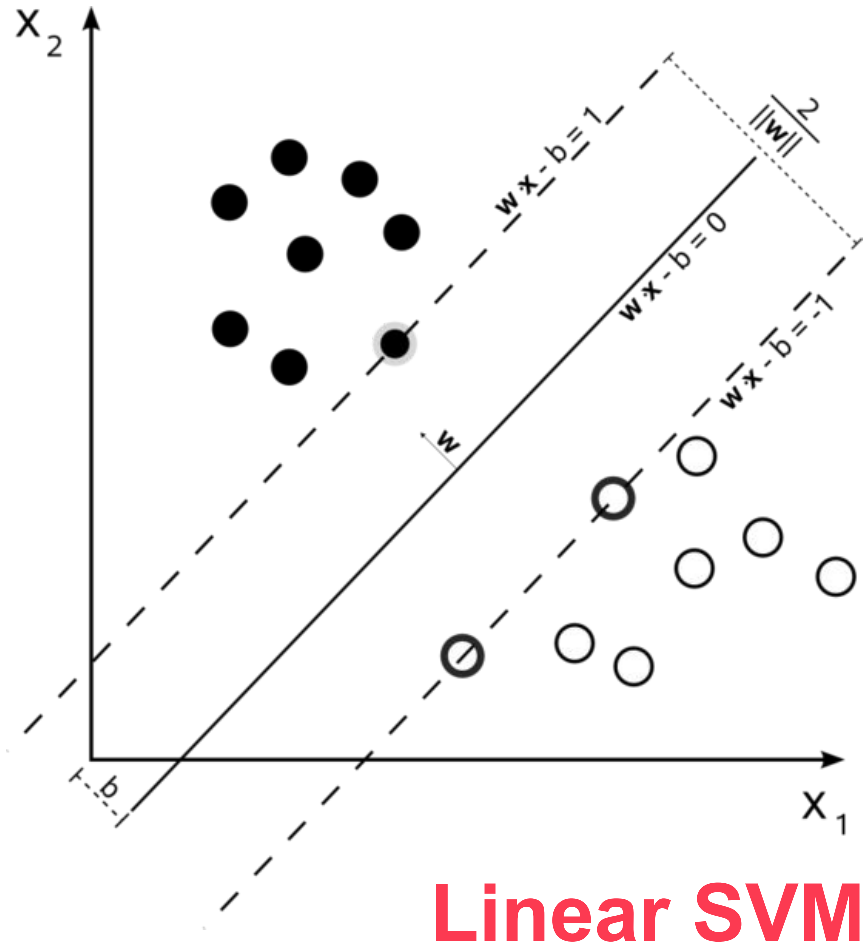
(1) Risk of overfitting with kernels
(2) Lack of interpretability



http://www.oneweirdkerneltrick.com/

Accuracy is how well the classifier separated the data.

Training accuracy tells us how well the decision boundary separated the classes of data in our training sample.

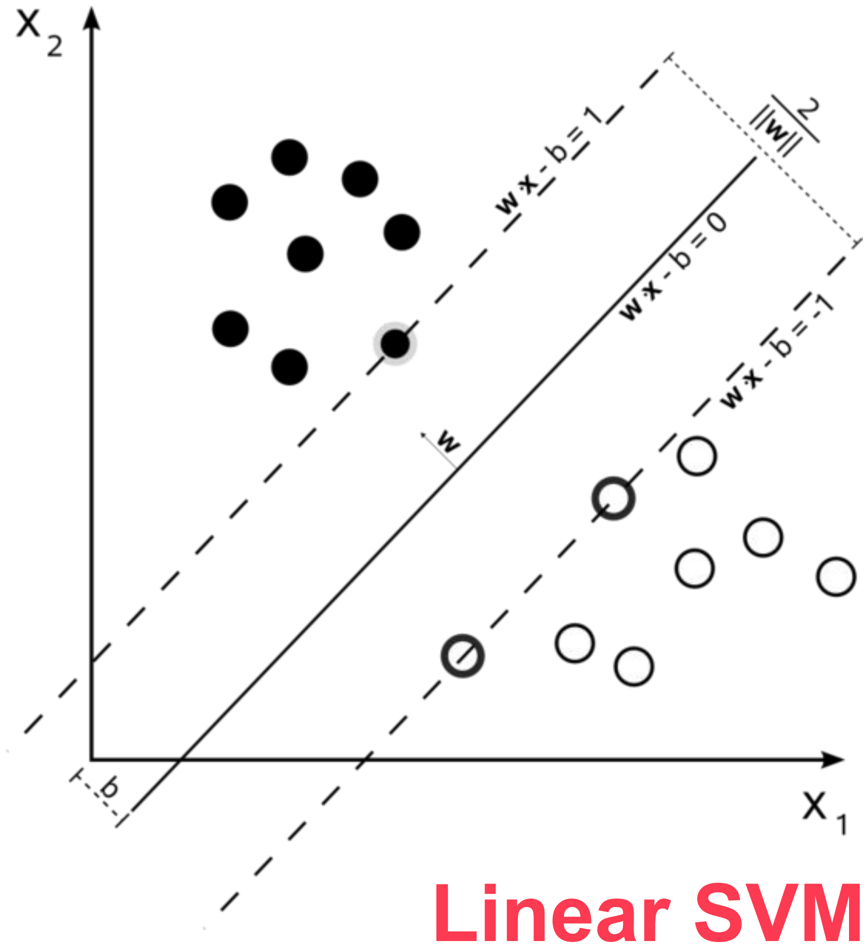


Linear SVM

Accuracy is how well the classifier separated the data.

Training accuracy tells us how well the decision boundary separated the classes of data in our training sample.

Testing accuracy tells us how well the classifier performs on *new* data.



Linear SVM

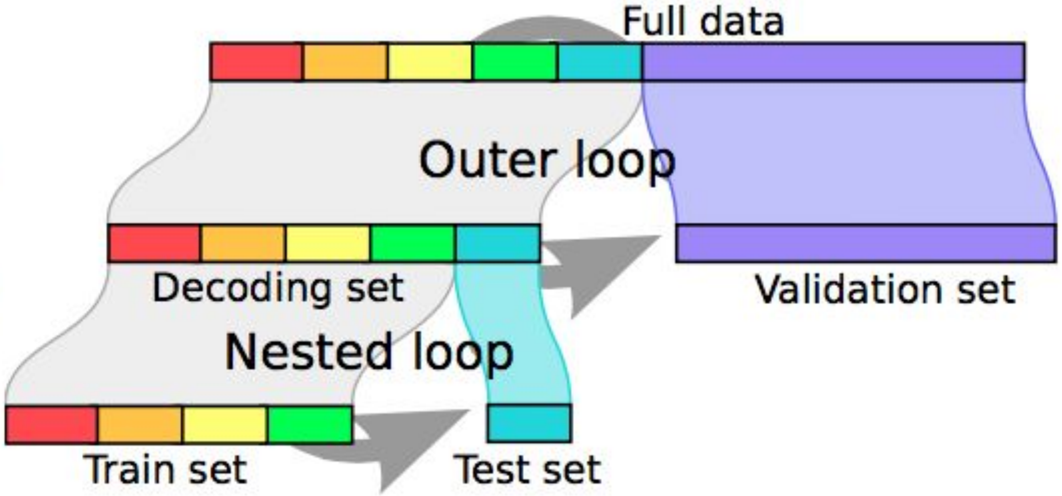
Machine Learning requires (though imagers get away with not doing this):

Training data set (largest proportion of data that you train the model on)

Test data set (you can peak to tweak)

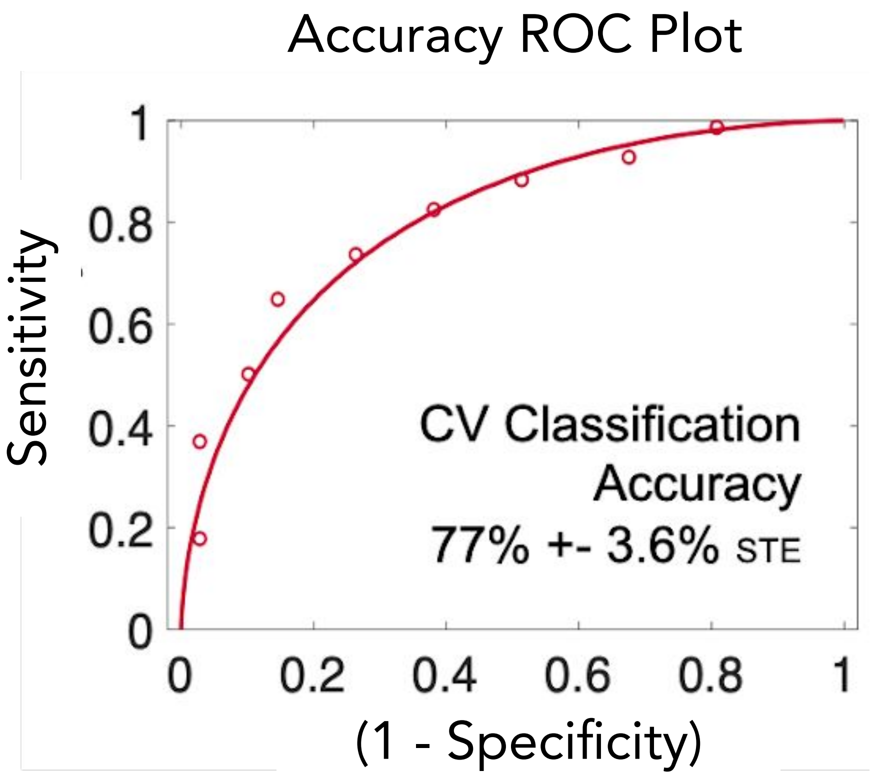
Validation set (no peaking!! unbiased)

So in the end you should have 3 different types of accuracies.



Varoquaux et al (2016)

Neural Biomarker of Threat



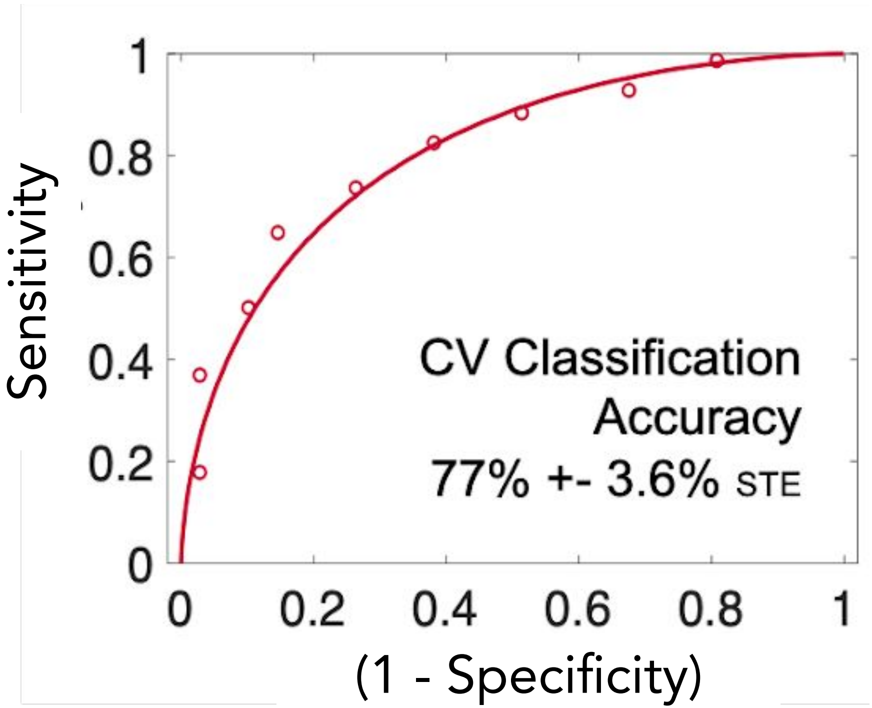
Receiver Operating Characteristic is a graph showing the performance of a classification model at all classification thresholds. This curve plots two parameters:

- True Positive Rate
- False Positive Rate

Reddan, Wager, & Schiller (2018)

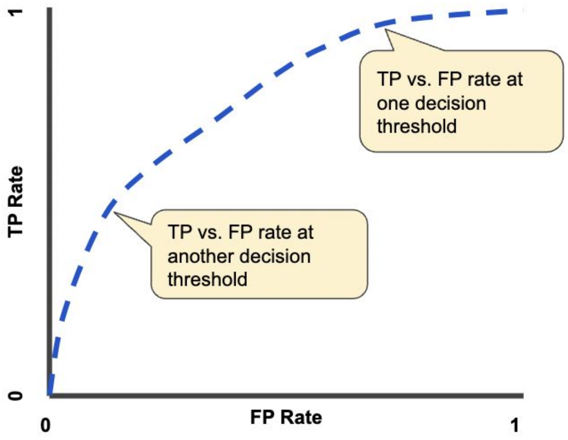
Neural Biomarker of Threat

Accuracy ROC Plot



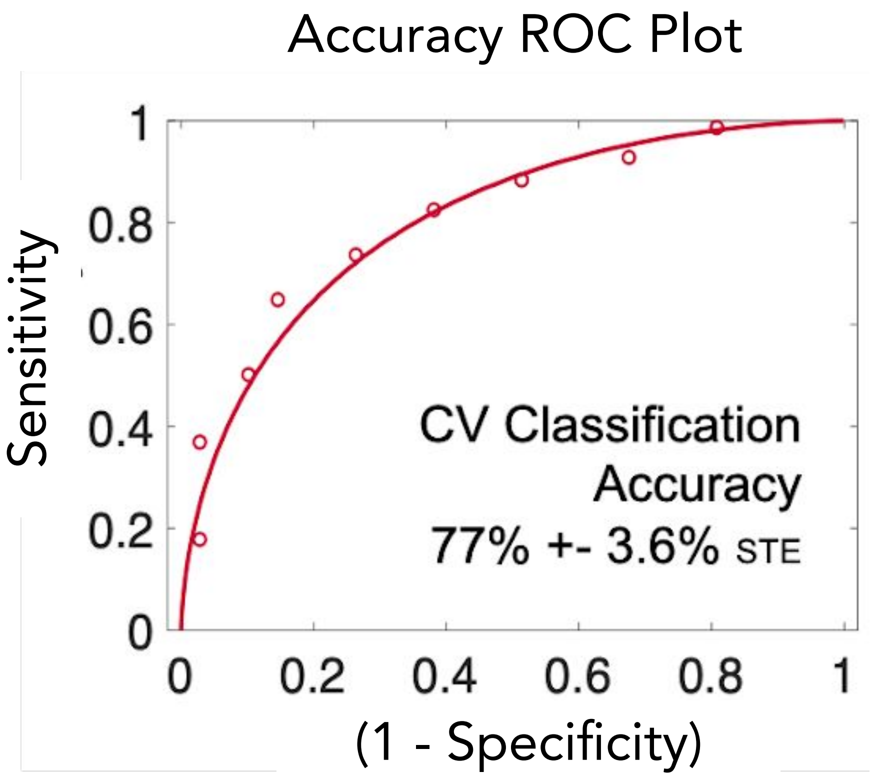
Receiver Operating Characteristic

An ROC curve plots TPR vs. FPR at different classification thresholds. Lowering the classification threshold classifies more items as positive, thus increasing both False Positives and True Positives. The following figure shows a typical ROC curve.



Reddan, Wager, & Schiller (2018)

Neural Biomarker of Threat



AUC stands for "Area under the ROC Curve." That is, AUC measures the entire two-dimensional area underneath the entire ROC curve (think integral calculus) from (0,0) to (1,1).

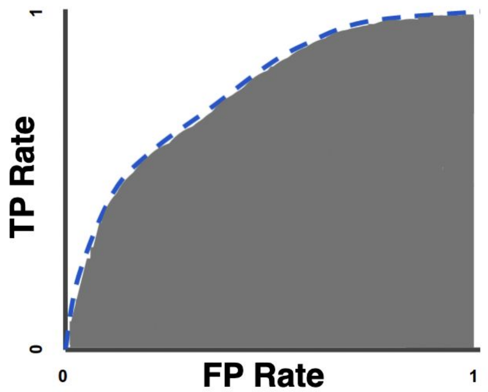


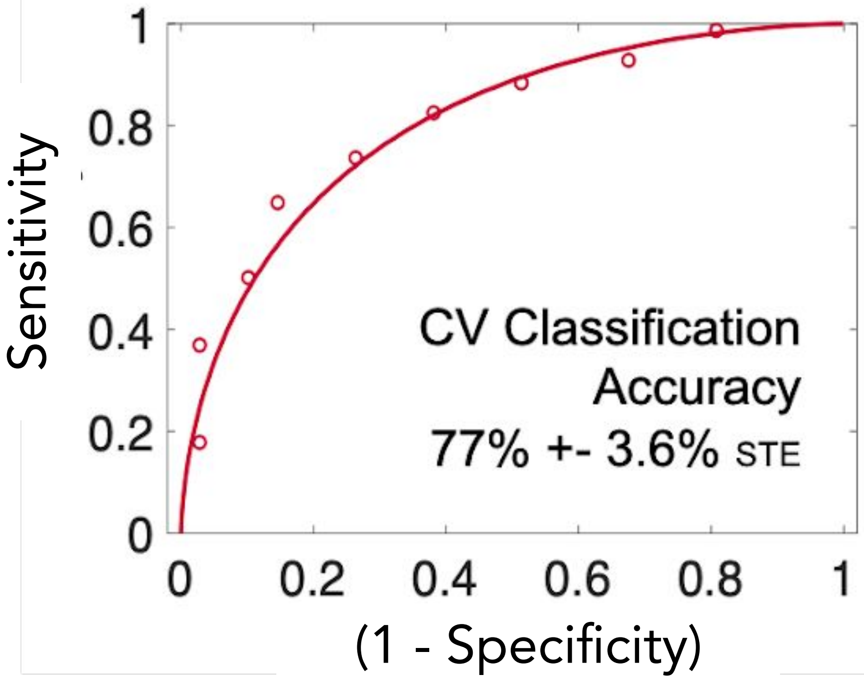
Figure 5. AUC (Area under the ROC Curve).

Read more

Reddan, Wager, & Schiller (2018)

Neural Biomarker of Threat

Accuracy ROC Plot



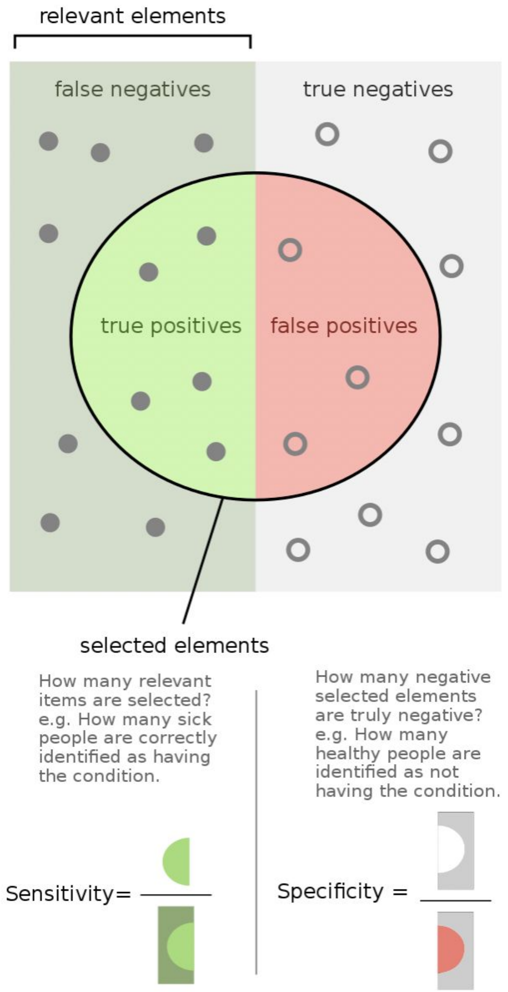
Area under the curve = 0.82

Leave-3-subj-out cross-validation

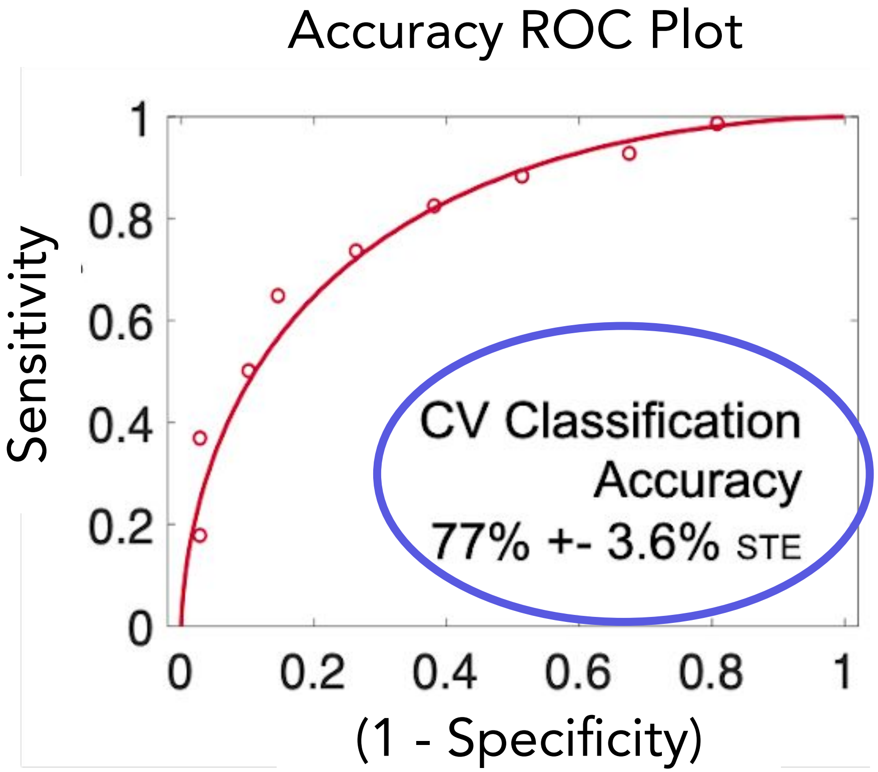
Reddan, Wager, & Schiller (2018)

Sensitivity (true positive rate) refers to the probability of a positive test, conditioned on truly being positive.

Specificity (true negative rate) refers to the probability of a negative test, conditioned on truly being negative.

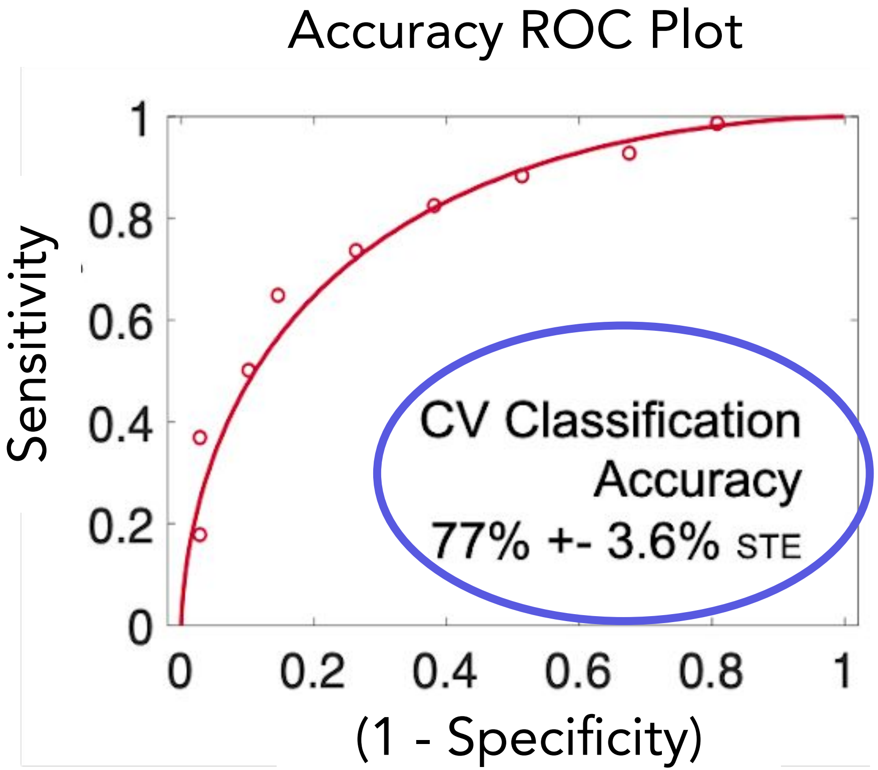


Neural Biomarker of Threat

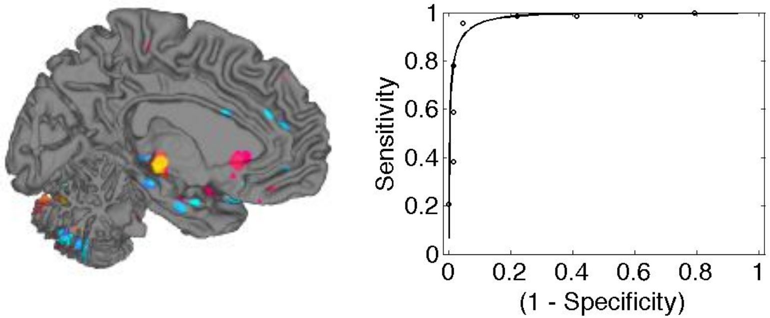


Reddan, Wager, & Schiller (2018)

Neural Biomarker of Threat



Aside:
In a separate project, I used feature engineering to boost the classification accuracy to **93.5%**, but that classifier is not used here because we wanted to study the entire brain.



Reddan, Wager, & Schiller (2018)

Accuracy is NOT enough

because you can overfit to your training data, or rely on poor training data, & produce a classifier that has little real-world utility or ***stability***.

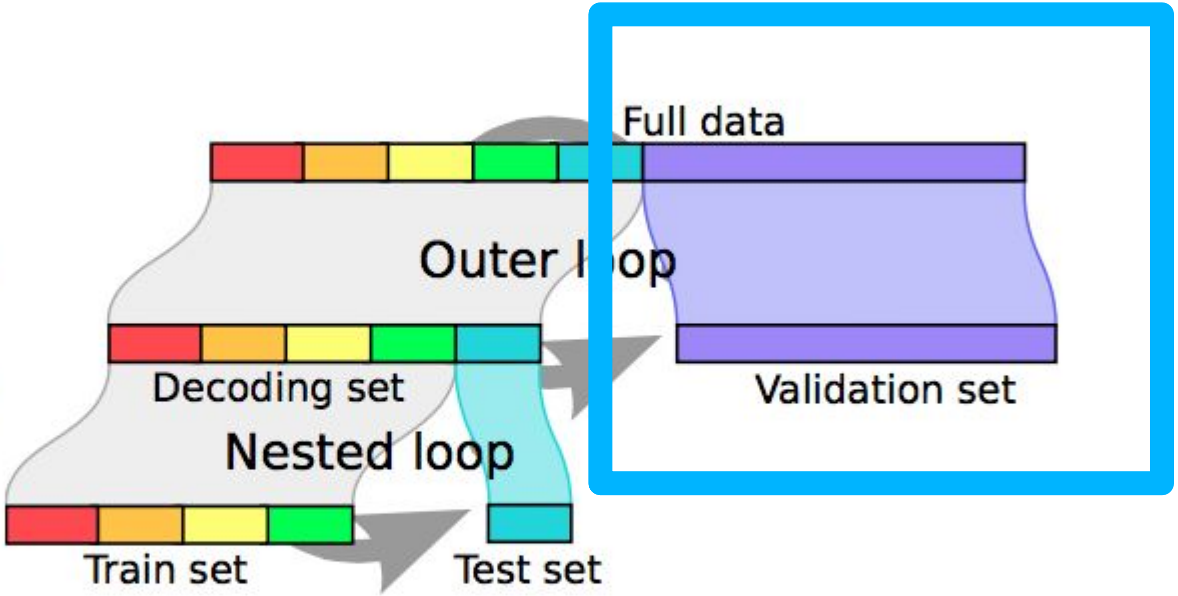
Accuracy is NOT enough

because you can overfit to your training data, or rely on poor training data, & produce a classifier that has little real-world utility or ***stability***.

How do you validate your accuracy's stability?

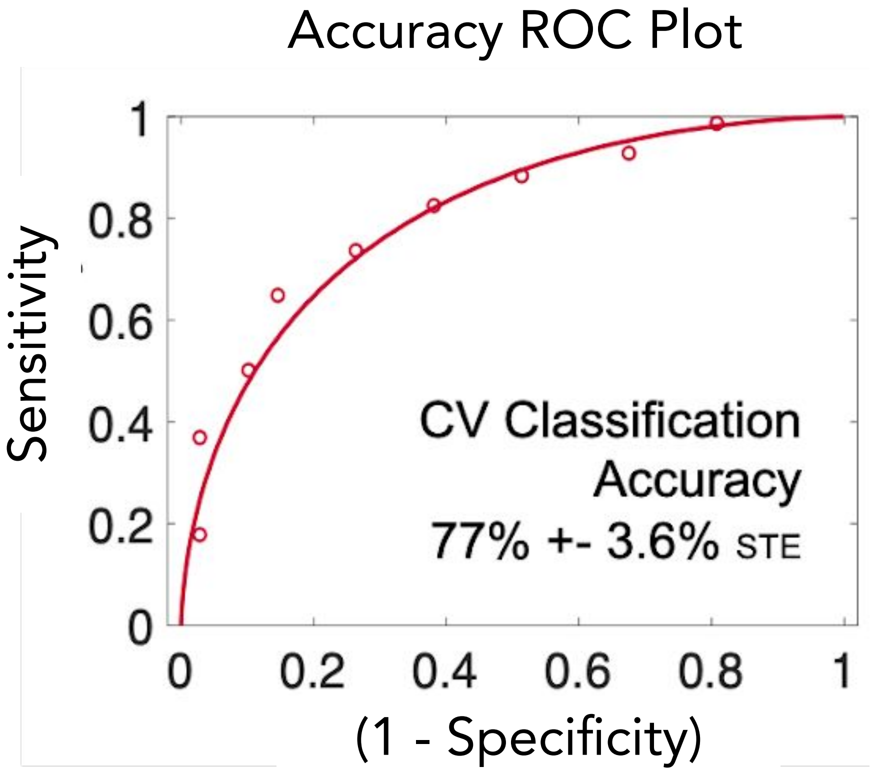
validating your biomarker

Because of limitations on sample size, the way we validate neuroimaging classifiers can sometimes be a little creative and involve multiple studies, sites, and phenomena.



Varoquaux et al (2016)

Neural Biomarker of Threat



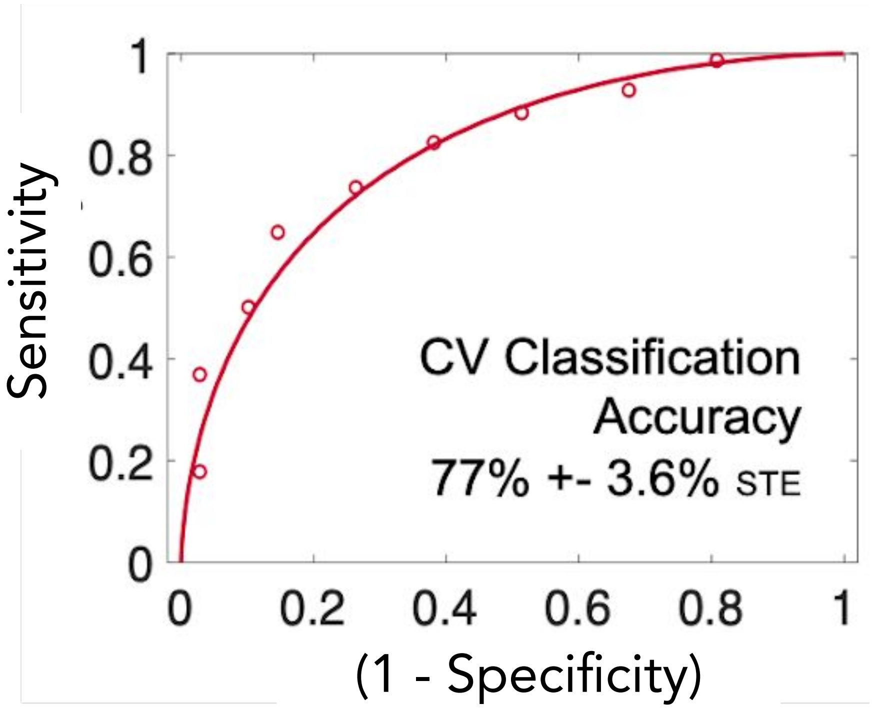
Signature validated in two independent *visual* threat-conditioning datasets:

Zhou et al. (2019) 87.93% Accuracy
Zhou et al. (2020) 93 ∓ 3.3% Accuracy

Reddan, Wager, & Schiller (2018)

Neural Biomarker of Threat

Accuracy ROC Plot



Signature validated on two independent *visual* threat-conditioning datasets:

Zhou et al. (2019) 87.93% Accuracy
Zhou et al. (2020) 93 ∓ 3.3% Accuracy

Signature validated on an independent *visual* emotion induction dataset:

Kragel, Reddan, LaBar, & Wager (2019)

Reddan, Wager, & Schiller (2018)

THREAT mean ‘threat level’ rating = 42.29 (+/-12.82), N = 84

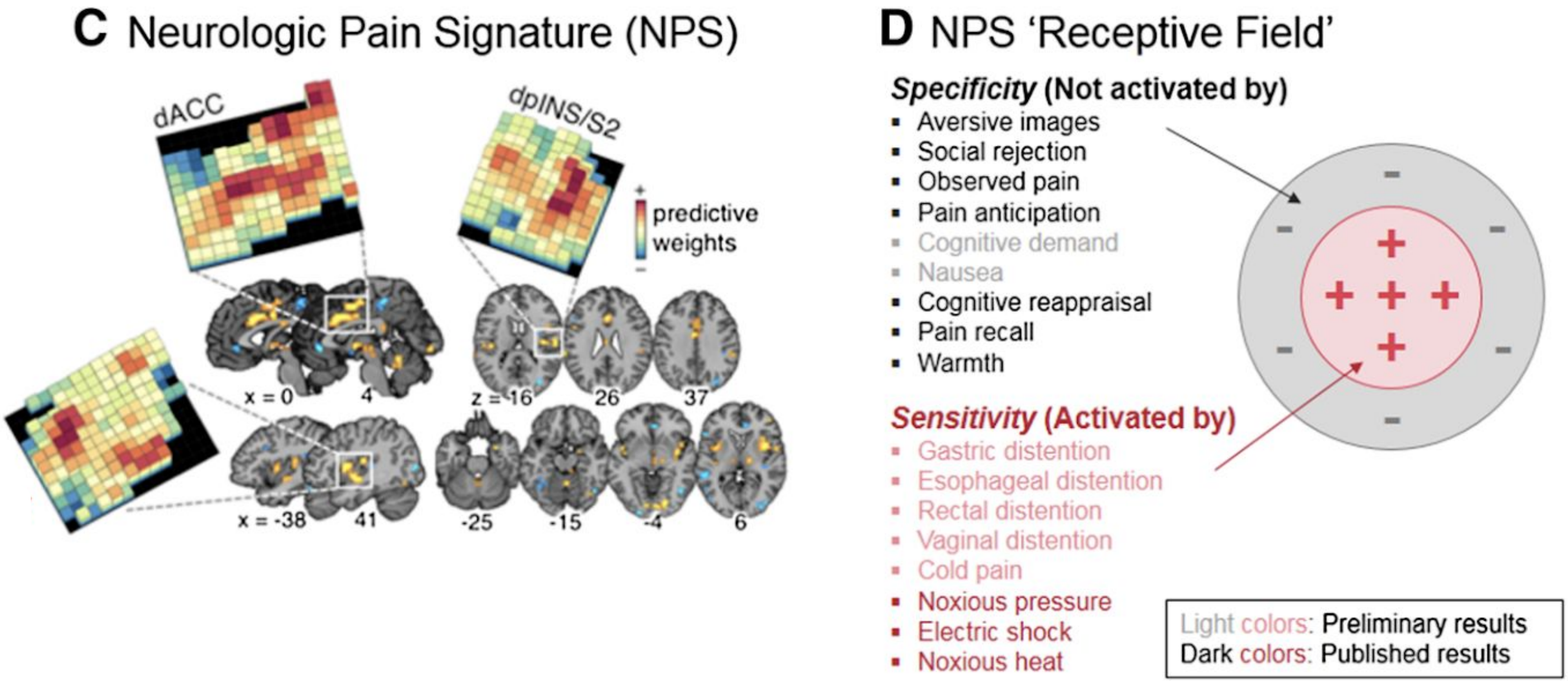
THREAT mean ‘threat level’ rating = 42.29 (+/-12.82), N = 84




SAFE mean ‘threat level’ rating = 4.1 (+/- 0.94), N = 84




Reddan, Kragel, Chang & Wager (in prep)

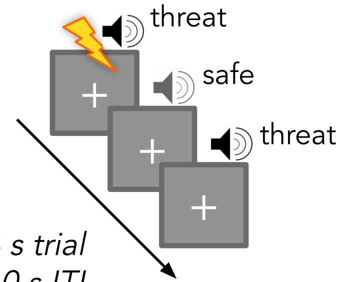


Beyond accuracy validation, there is 'concept' validation.

applying your biomarker

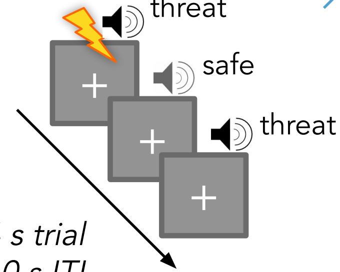
Phase 1
Acquisition
all subjects
N = 68

Phase 2
Extinction
three groups



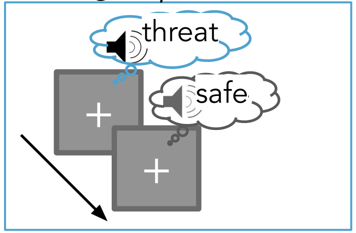
4 s trial
10 s ITI
8 trials per stimulus

Phase 1
Acquisition
all subjects
N = 68



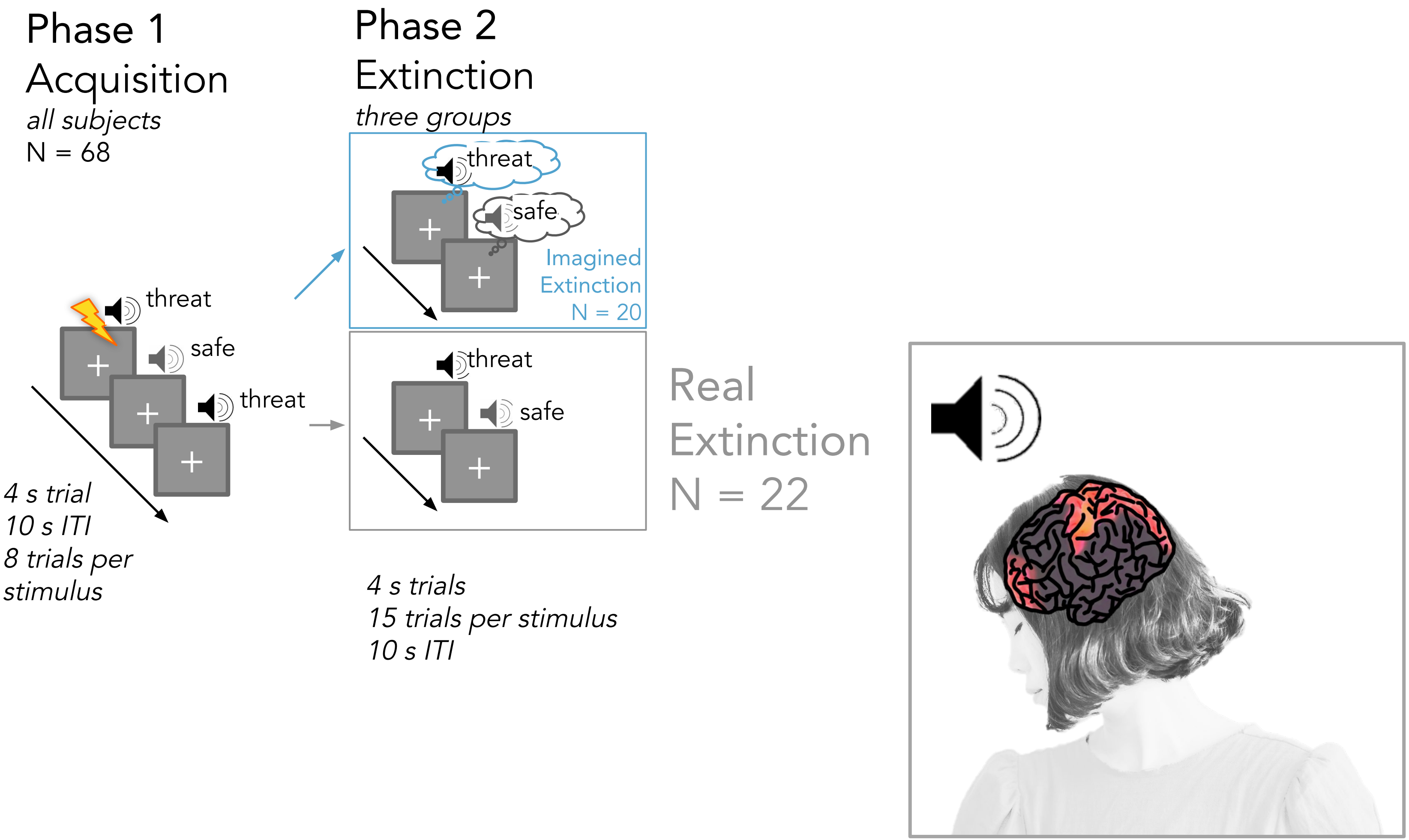
4 s trial
10 s ITI
8 trials per stimulus

Phase 2
Extinction
three groups

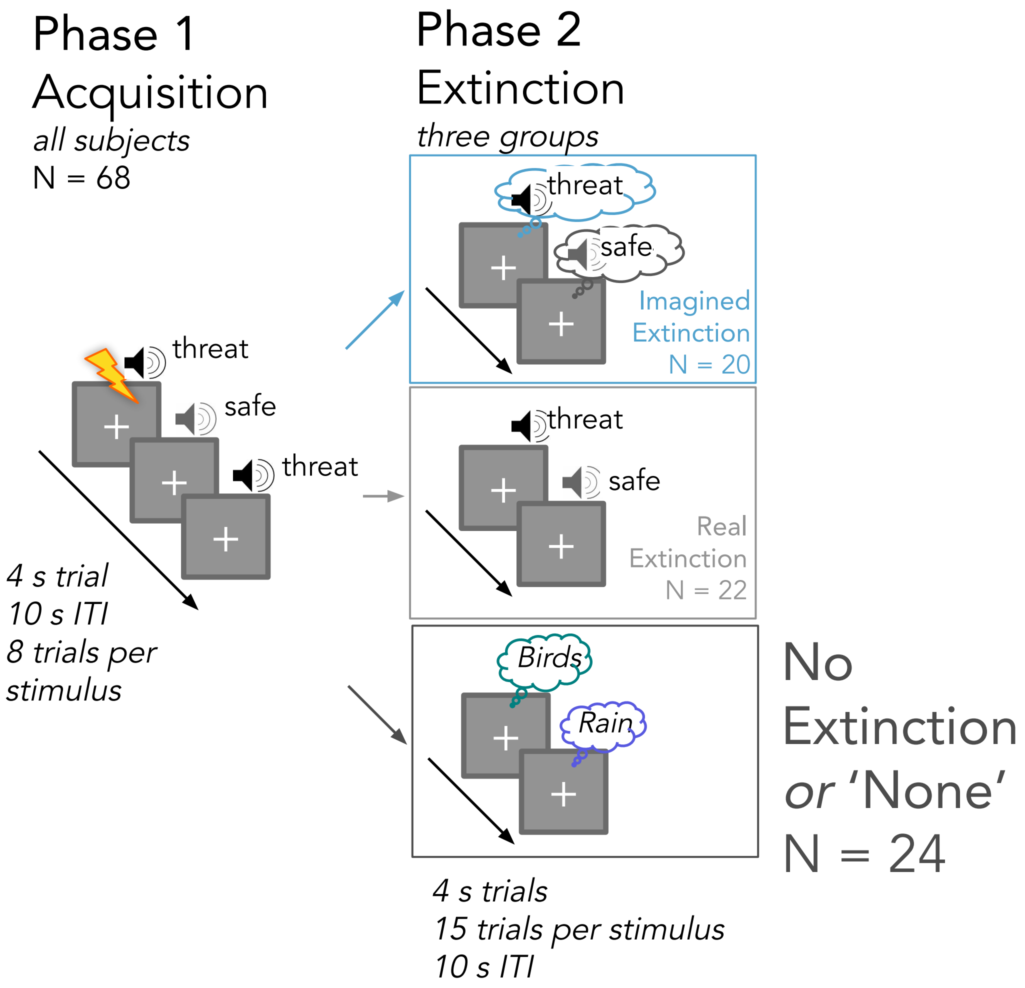


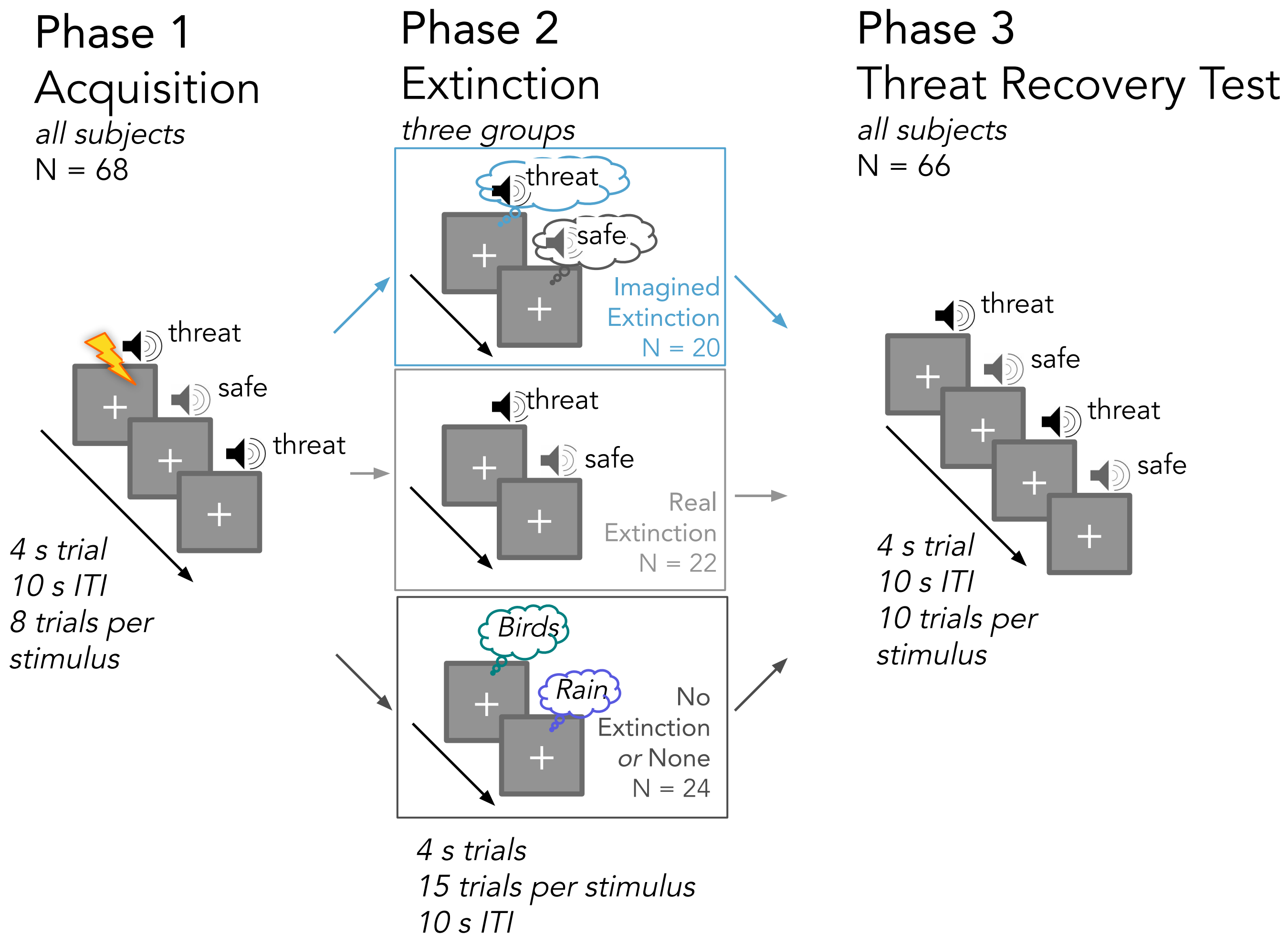
4 s trials
15 trials per stimulus
10 s ITI

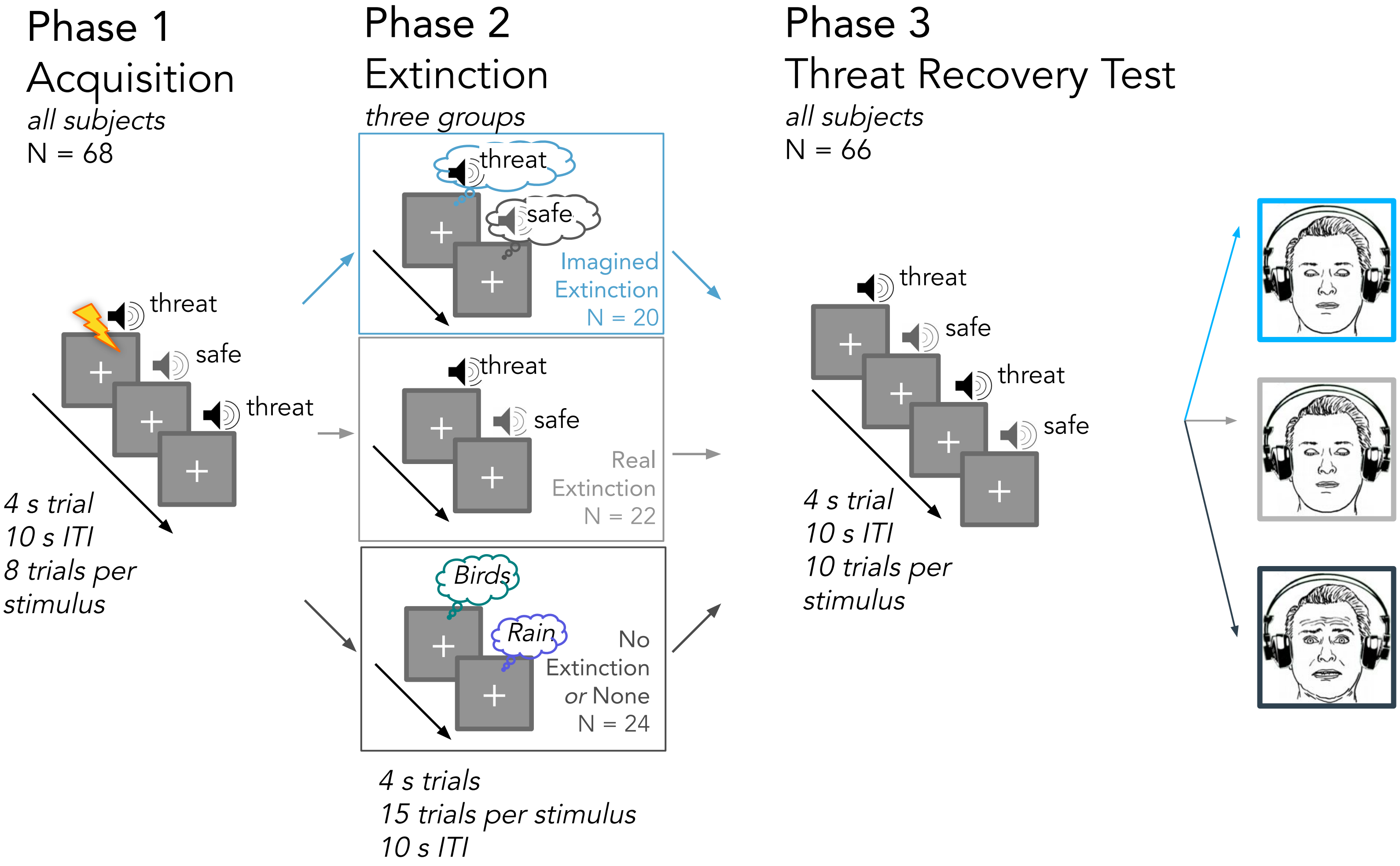
Imagined Extinction
N = 20

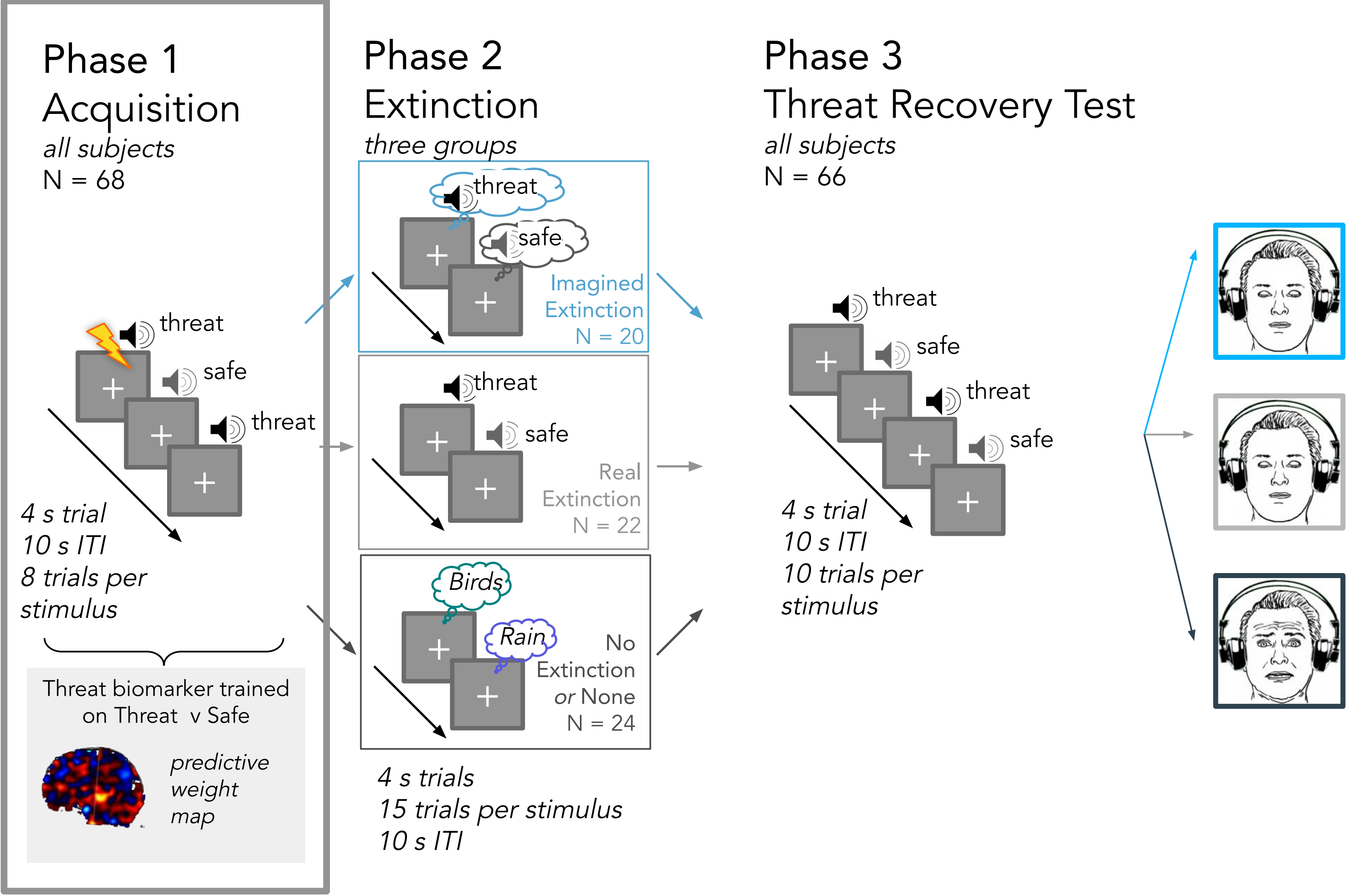


Phase 1
Acquisition
all subjects
N = 68
threat
safe
threat
4 s trial
10 s ITI
8 trials per stimulus
Phase 2
Extinction
three groups
threat
safe
Imagined Extinction
N = 20
threat
safe
4 s trials
15 trials per stimulus
10 s ITI
Real Extinction
N = 22


Phase 1
Acquisition
all subjects
N = 68
threat
safe
threat
4 s trial
10 s ITI
8 trials per stimulus
Phase 2
Extinction
three groups
threat
safe
Imagined Extinction
N = 20
threat
safe
Real Extinction
N = 22
Birds
Rain
No Extinction
or 'None'
N = 24
4 s trials
15 trials per stimulus
10 s ITI

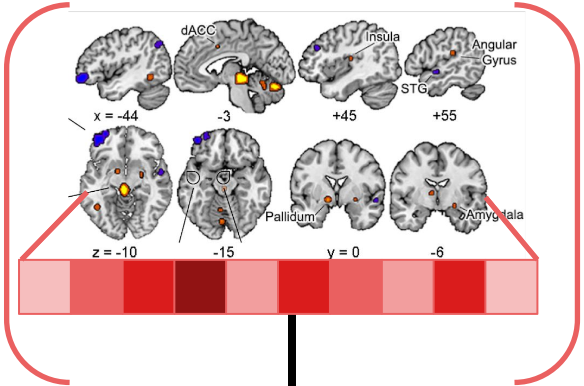

Phase 1
Acquisition
all subjects
N = 68
threat
safe
threat
4 s trial
10 s ITI
8 trials per stimulus
Phase 2
Extinction
three groups
threat
safe
Imagined Extinction
N = 20
threat
safe
Real Extinction
N = 22
Birds
Rain
No Extinction or None
N = 24
4 s trials
15 trials per stimulus
10 s ITI
Phase 3
Threat Recovery Test
all subjects
N = 66
threat
safe
threat
safe
4 s trial
10 s ITI
10 trials per stimulus


Phase 1
Acquisition
all subjects
N = 68
threat
safe
threat
4 s trial
10 s ITI
8 trials per
stimulus
Phase 2
Extinction
three groups
threat
safe
Imagined
Extinction
N = 20
threat
safe
Real
Extinction
N = 22
Birds
Rain
No
Extinction
or None
N = 24
4 s trials
15 trials per stimulus
10 s ITI
Phase 3
Threat Recovery Test
all subjects
N = 66
threat
safe
threat
safe
4 s trial
10 s ITI
10 trials per
stimulus


Phase 1
Acquisition
all subjects
N = 68
threat
safe
threat
4 s trial
10 s ITI
8 trials per stimulus
Threat biomarker trained on Threat v Safe
predictive weight map
Phase 2
Extinction
three groups
threat
safe
Imagined Extinction
N = 20
threat
safe
Real Extinction
N = 22
Birds
Rain
No Extinction or None
N = 24
4 s trials
15 trials per stimulus
10 s ITI
Phase 3
Threat Recovery Test
all subjects
N = 66
threat
safe
threat
safe
4 s trial
10 s ITI
10 trials per stimulus

Threat Biomarker Pattern

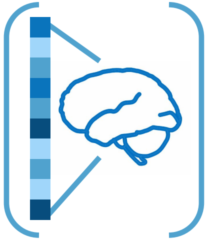
non-thresholded SVM Classifier Weights



$\underline{w} = (w_1, \ldots. w_v)$

Brain Activity during Threat Recovery Test

GLM Beta Maps (threat > safety)



Imagined Extinction Group

$\underline{x} = (x_1, \ldots. x_v)$

Dot-product

Threat Pattern Expression

Biomarker Response

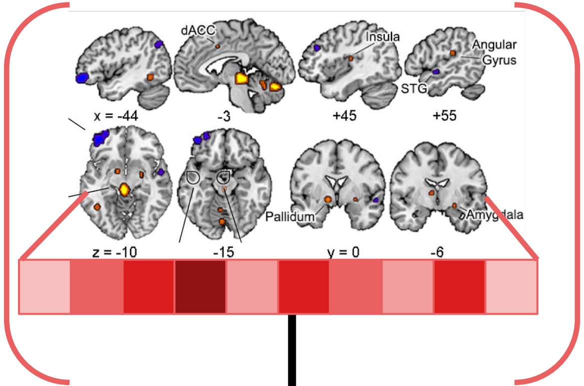
-0.3

$y = \underline{w}^T \underline{x}$

adapted from Lindquist & Wager (2015)

Threat Biomarker Pattern

non-thresholded SVM Classifier Weights



$\underline{w} = (w_1, \ldots . w_v)$

Brain Activity during Threat Recovery Test

GLM Beta Maps (threat > safety)

Real Extinction Group

$\underline{x} = (x_1, \ldots . x_v)$

→ Dot-product →

Threat Pattern Expression

Biomarker Response

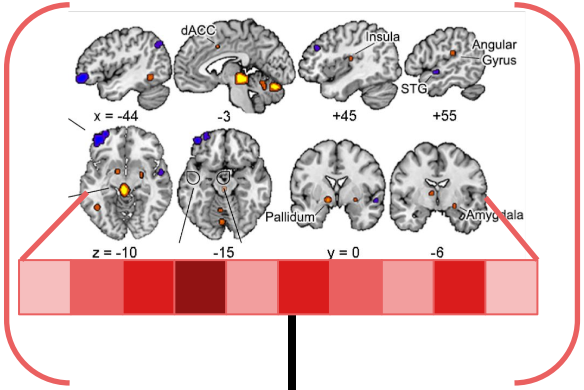
-0.2

$y = \underline{w}^T \underline{x}$

adapted from Lindquist & Wager (2015)

Threat Biomarker Pattern

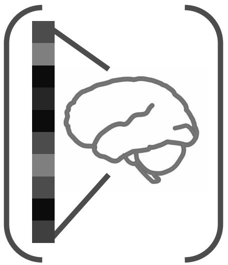
non-thresholded SVM Classifier Weights



$\underline{w} = (w_1, \ldots. w_v)$

Brain Activity during Threat Recovery Test

GLM Beta Maps (threat > safety)



None or 'No extinction' Group

$\underline{x} = (x_1, \ldots. x_v)$

Dot-product

Threat Pattern Expression

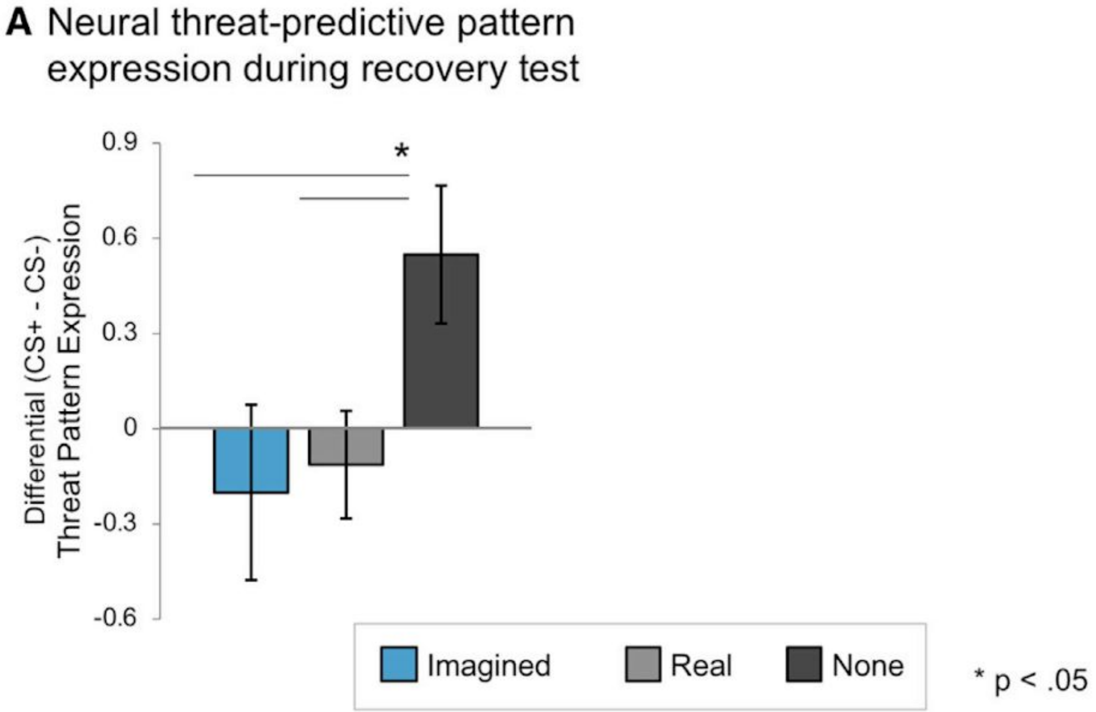
Biomarker Response

.9

$y = \underline{w}^T \underline{x}$

adapted from Lindquist & Wager (2015)

Imagined and real extinction decreased expression of the biomarker



Reddan, Wager, & Schiller (2018)

Let’s do an example