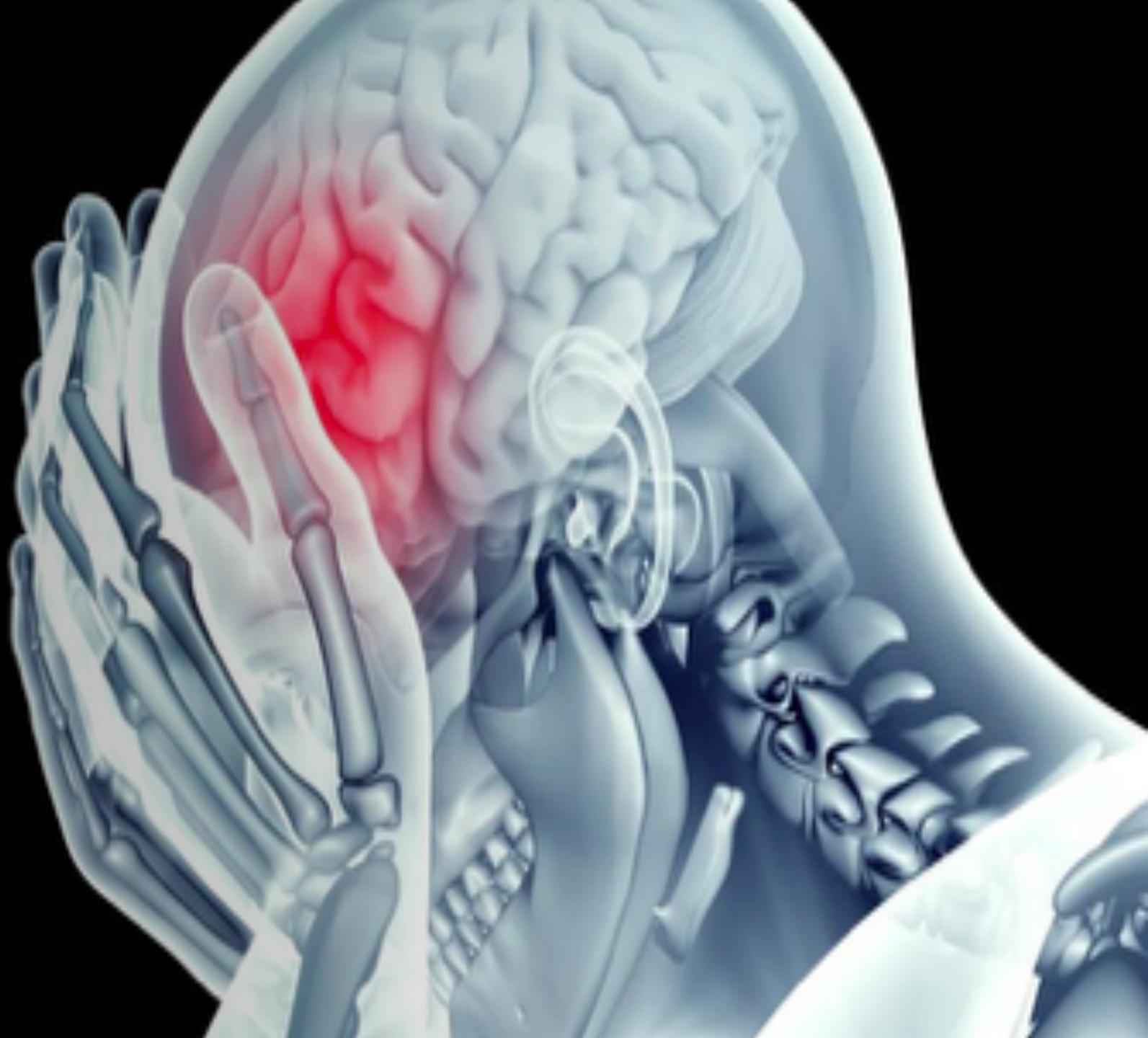


# META-ANALYSIS

Applications to Chronic Pain

Presented on May 18, 2020



# Why Meta-analysis?

## Individual experiment

- Small sample sizes
- Flexibility in analysis pipelines
- Experimental design variability

## Meta-analysis

- More power
- Convergence across experiments
- Can't control literature

## Progress with Meta-analyses

- Applications to neuroscience & psychiatry
- Automated software available (e.g., Neurosynth, Neuroquery)
- **Manual meta-analysis**
  - Search term, database, inclusion
  - Meta-analytic technique

# Steps to a Meta-analysis

1. Decide what to include —> **pre-registration**
  - Question, search strategy, inclusion criteria
2. Database search (and ‘reference chase’)
3. Screen records
  - Abstracts
  - Full-text articles
4. Extract results & synthesize data

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1. Consider the measure of interest
  - fMRI response to pain in chronic pain patients compared to healthy controls
2. Which databases to search?
  - PubMed, EMBASE, Scopus, PsycINFO, Web of Science, Cochrane
  - Supplement with 'reference chase' from previous meta-analyses
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# Inclusion Criteria

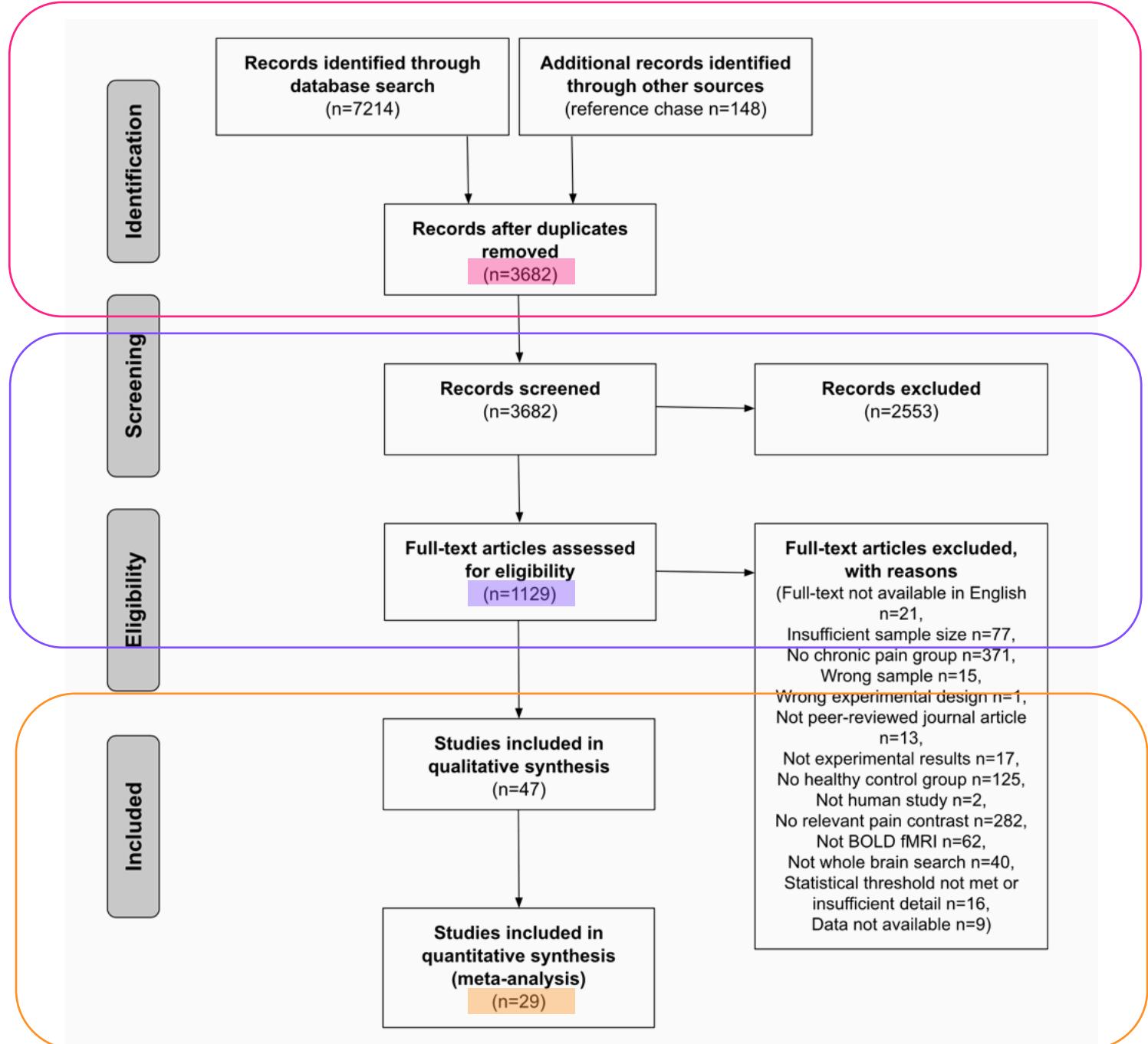
1. Whole-brain analyses
2. Sample sizes 10 or more per group
3. Statistical threshold
  - voxel-height  $p < .001$  uncorrected *or* cluster-corrected  $p < .05$
4. Criteria specific to measure of interest
  - fMRI
  - Chronic pain condition OR pain over 6 months (e.g., PD with pain)
  - Has to include control group
  - Confirmed physical pain stimulus
  - Contrast pain>baseline within-subject
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## Search

- PubMed, Embase, SCOPUS, Web of Science, PsycINFO, Cochrane
- 'Reference chase'
- Generate .ris files

## Screen

- Use Covidence to read .ris files and record
- Abstracts: \*exclude\* if
  - NOT fMRI
  - n<10, <18 age
  - Animal study
  - NO patients
- Full-text inclusion
  - Applied criteria

## Synthesize

- Coordinate data
- ALE

# Extract Data

## Experimental Information

- Pain condition
- Medication inclusion criteria
- Pain stimulus modality
- Pain stimulus location
- Pain diagnosis

## Coordinates (1 set/exp)

- X, Y, Z
- Coordinate space (MNI, Tal)
- Sample size (patients, controls)

**Table 2**

Areas significantly activated in OA Group patients compared to healthy subjects.

Brain region	L/R	MNI coordinates		
		X	Y	Z
Superior frontal cortex	R	24	22	52
	R	20	6	44
	L	-16	44	42
Inferior parietal cortex	L	-26	-86	46
Lingual gyrus	R	30	-74	2
Superior occipital cortex	L	-14	-96	4
Middle occipital cortex	L	-38	-80	32

Brain regions represented as MNI coordinates with activation maxima of experimentally induced P, thresholded at uncorrected  $P < 0.05$ . The pain matrix region is the frontal superior area.

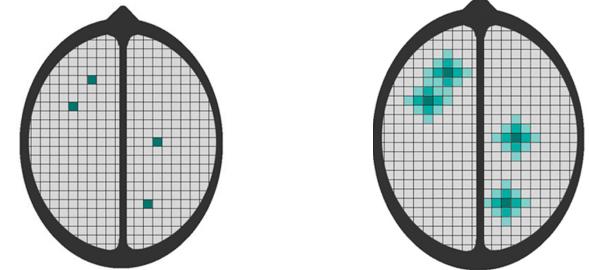
Hiramatsu et al., 2014, *Neuroscience Letters*

# About Our Included Experiments

- Mostly migraine patients ( $n = 7$ ) but also
  - Fibromyalgia ( $n = 5$ ), IBS ( $n = 5$ )
  - Chronic back pain ( $n = 4$ )
  - Complex regional pain syndrome I ( $n = 2$ )
  - Chemotherapy-induced peripheral neuropathy, osteoarthritis, persistent dentoalveolar pain disorder, posttraumatic headache, vulvar vestibulitis, mixed patient group ( $n = 1$ )
- Most used mechanical induction ( $n = 14$ ) but also
  - thermal ( $n = 10$ )
  - electrical ( $n = 4$ )
  - chemical ( $n = 1$ )
- Matched by similar perceptual ratings ( $n = 18$ )

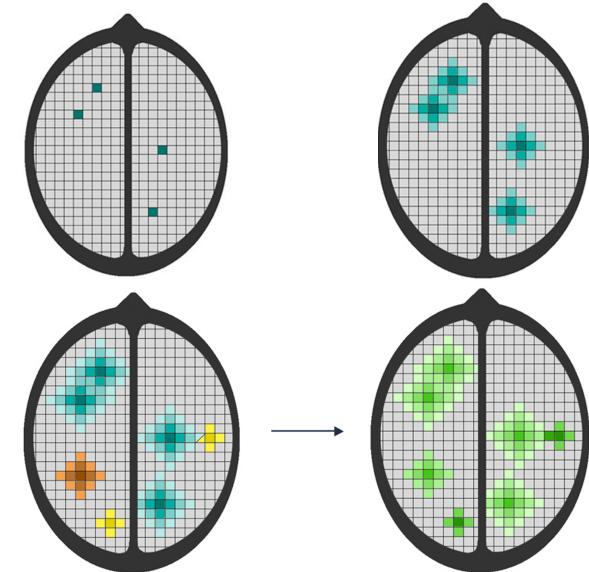
# Activation Likelihood Estimation (ALE)

- **Treat foci as centers of Gaussian distribution**
  - FWHM is determined by  $n$  and spatial template
- **Take voxelwise union to create ALE map**
  - Each voxel represents a z-statistic summarizing probability of activation across experiments
- **Determine significance**
  - Null hypothesis of spatial independence
  - Voxel-level:  $p < .001$  uncorrected
    - Random sampling of grey matter voxels
  - Cluster-level:  $p < .05$  FWE-corrected
    - 10,000 Monte Carlo simulations to determine cluster



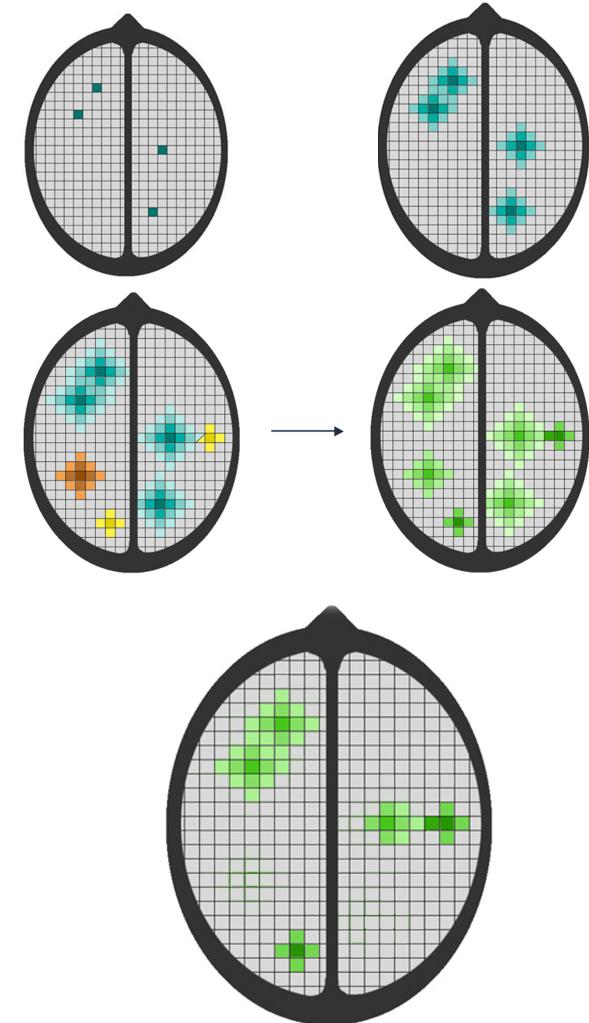
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# Run ALE Scripts

## 1. Coordinate Data

citation	n	x	y	z	space	contrast
Schreiber 20	38	20	2	-24	MNI	abberant
Schreiber 20	38	20	-2	-22	MNI	abberant
Schreiber 20	38	38	18	-42	MNI	abberant
Schreiber 20	38	20	-2	-34	MNI	abberant
Schreiber 20	38	26	-10	-22	MNI	abberant
Schreiber 20	38	40	0	-42	MNI	abberant
Schmid 2015	32	-12	-62	-10	MNI	abberant
	...	...	...	...		...

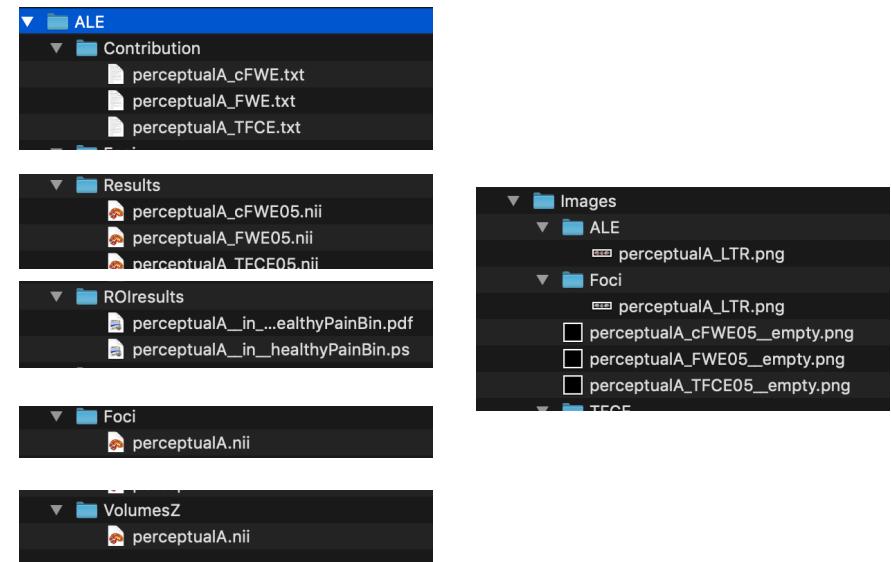
## 2. Define Contrasts

M	perceptualA	perceptualData_2020-01-21.mat	+	+abberant	\$healthyPainBin.nii

## 4. Look at Results

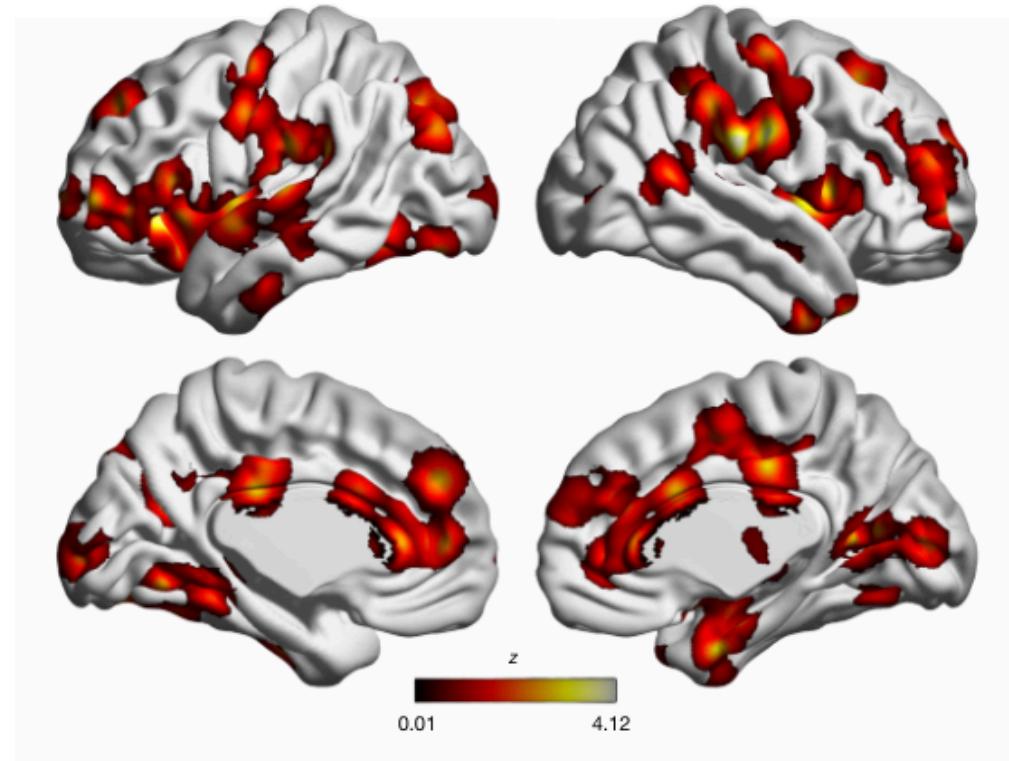
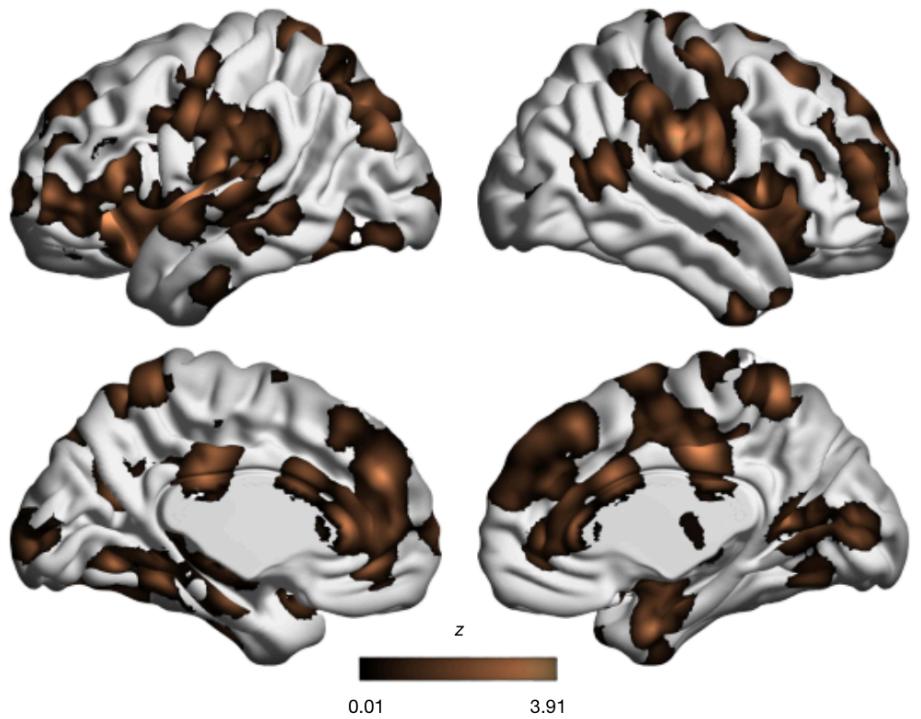
## 3. Run Script

```
% Input  
ale_inputCoords('perceptualData_2020-01-21.xls');  
  
% Compute  
ale_estimateALE('perceptual_20200121.xlsx');
```



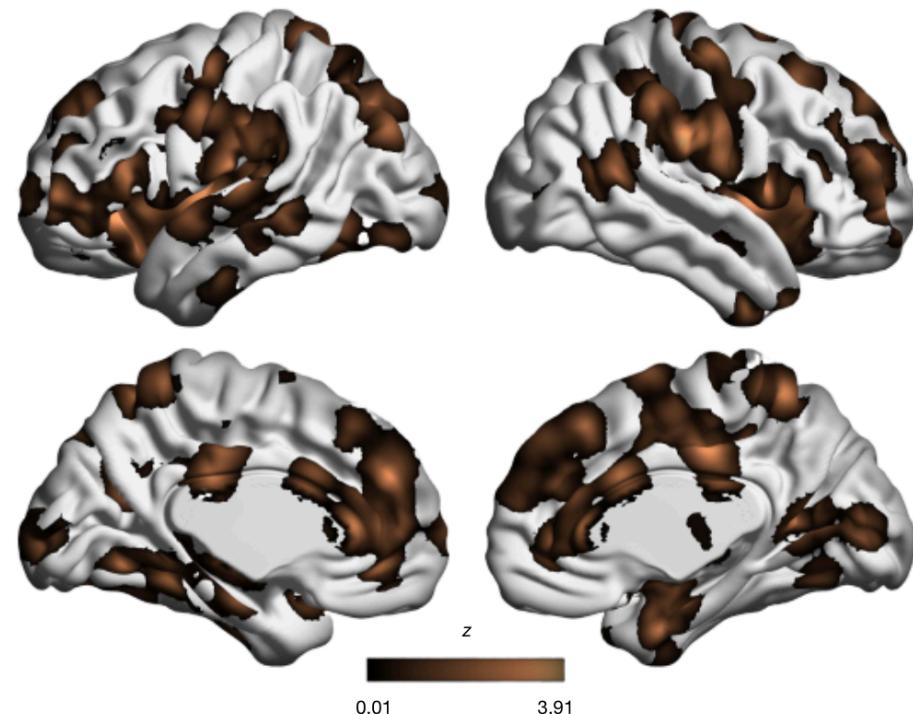
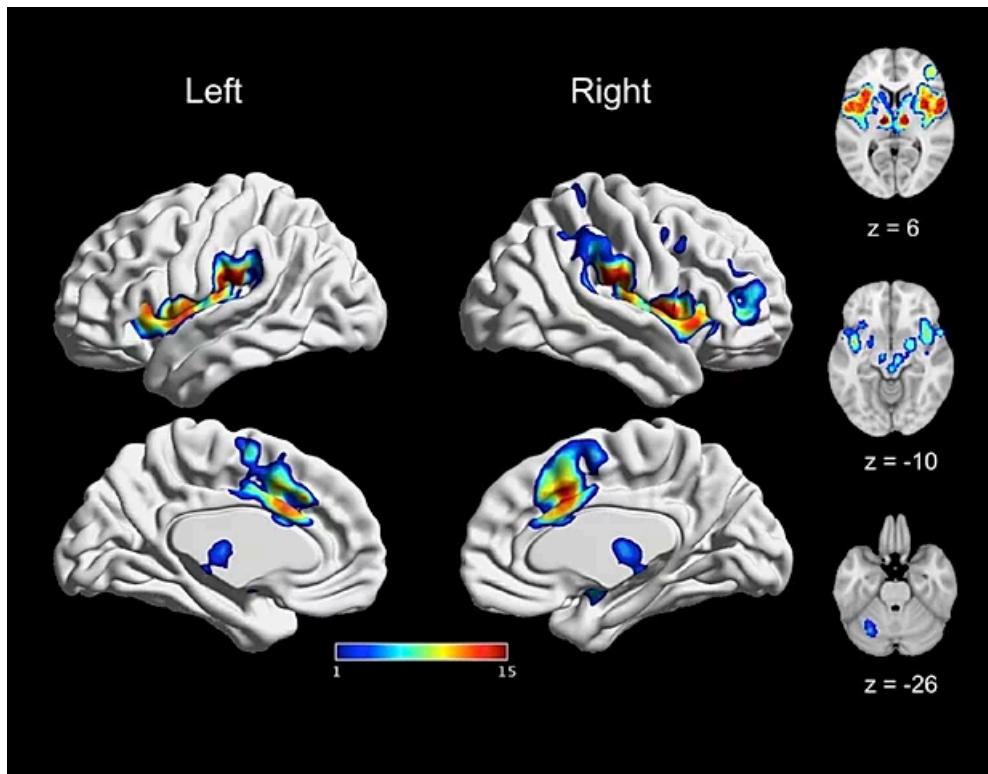
# Null Results from ALE Analyses

- Inconsistencies in regions associated with **aberrant activity**
  - Also true for "**patients > controls**" and match by pain ratings ( $n = 23$ )



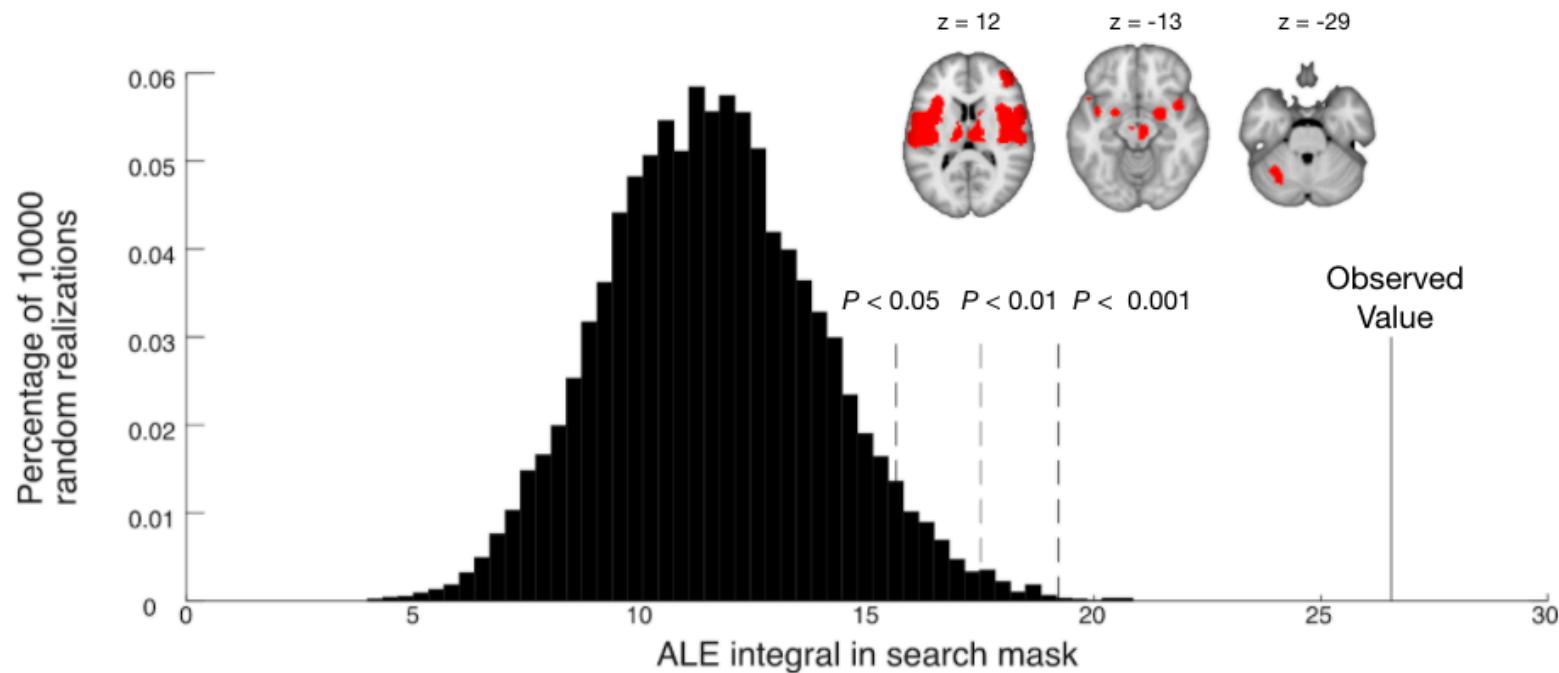
# Compared to Healthy Pain Study...

- Significant convergence across diverse set of exp's ( $n = 222$ )
- Sub-analyses for pain modality, stimulus location



# Exploratory, ROI-based Analyses

- Overall convergence aggregated across pain areas
  - Contrast to whole-brain with inconsistencies in voxel patterns of activation



# **Put It Together: Meta-analysis for Pain**

- Convergent brain regions in response to pain in healthy
- But inconsistencies in regions activated in patients
  - Overall convergence in pain regions
- Not enough experiments for sub-analyses
- Future studies focused on pain meta-analytic map
- Beyond fMRI : structural MRI differences in chronic pain?

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- Beyond fMRI : structural MRI differences in chronic pain?

**Consistent pain-related regions for (1)  
biomarker development and (2) field outlook**

# Future Directions for Meta-analyses

- More applications in psychiatry
- Further biomarker development with meta-analytic maps
  - Test with ML?
- Use of meta-analyses in different fields
  - Experimentally-administered psychedelics
- Technical developments
  - Better meta-analytic algorithms
  - More understanding of properties in different meta-analytic algorithms
  - Better automated meta-analyses?

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