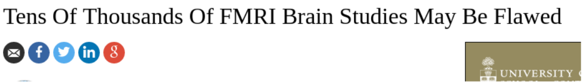
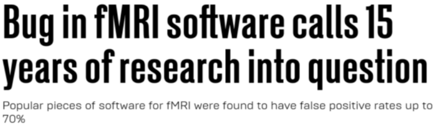
Cluster Failure: Stats Gone Sideways

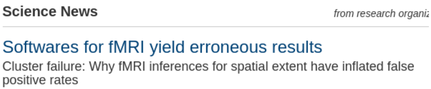
Chris Hammill

September 15, 2016


Tens Of Thousands Of FMRI Brain Studies May Be Flawed


Bug in fMRI software calls 15 years of research into question

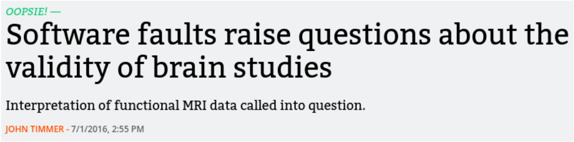
Popular pieces of software for fMRI were found to have false positive rates up to 70%


Science News

from research organiz

Softwares for fMRI yield erroneous results

Cluster failure: Why fMRI inferences for spatial extent have inflated false positive rates


OOPSIE! —

Software faults raise questions about the validity of brain studies

Interpretation of functional MRI data called into question.

JOHN TIMMER - 7/1/2016, 2:55 PM

Cluster failure: Why fMRI inferences for spatial extent have inflated false-positive rates

Anders Eklund[a,b,c,1], Thomas E. Nichols[d,e], and Hans Knutsson[a,c]

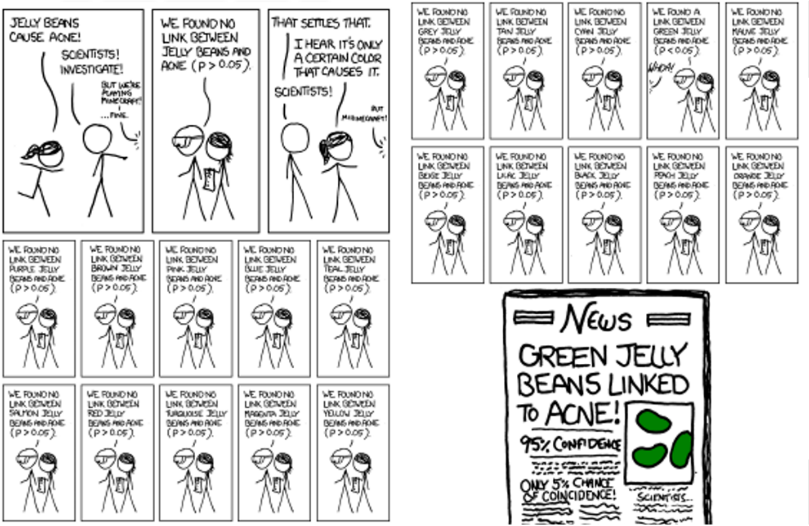
So What Happened

- Eklund, Nichols, and Knutsson demonstrated standard fMRI statistical inference has badly inflated false positives rates
- Makes you wonder if exciting brain region X responding to stimulus Y finding was just a cherry-picked false positive.
- Highlighted that due to non-reproducible workflows, and poor data sharing, many of these finding could never be repeated with valid inference.

How Did We Get Here

- fMRI is challenging to analyze
- Preprocessing steps widely used as black boxes
- Desire to use spatial information to determine signal significance
- Improperly specified models of spatial noise
- Ultimately a multiple testing problem

Multiple Comparisons


JELLY BEANS CAUSE ACNE!
SCIENTISTS! INVESTIGATE!
BUT WE'RE PLAYING MINECRAFT!
...FINE.
WE FOUND NO LINK BETWEEN JELLY BEANS AND ACNE (P > 0.05).
THAT SETTLES THAT.
I HEAR IT'S ONLY A CERTAIN COLOR THAT CAUSES IT.
SCIENTISTS!
BUT MINECRAFT!
WE FOUND NO LINK BETWEEN PURPLE JELLY BEANS AND ACNE (P > 0.05).
WE FOUND NO LINK BETWEEN BROWN JELLY BEANS AND ACNE (P > 0.05).
WE FOUND NO LINK BETWEEN PINK JELLY BEANS AND ACNE (P > 0.05).
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WE FOUND NO LINK BETWEEN RED JELLY BEANS AND ACNE (P > 0.05).
WE FOUND NO LINK BETWEEN TURQUOISE JELLY BEANS AND ACNE (P > 0.05).
WE FOUND NO LINK BETWEEN MAGENTA JELLY BEANS AND ACNE (P > 0.05).
WE FOUND NO LINK BETWEEN YELLOW JELLY BEANS AND ACNE (P > 0.05).
WE FOUND NO LINK BETWEEN GREY JELLY BEANS AND ACNE (P > 0.05).
WE FOUND NO LINK BETWEEN TAN JELLY BEANS AND ACNE (P > 0.05).
WE FOUND NO LINK BETWEEN CYAN JELLY BEANS AND ACNE (P > 0.05).
WE FOUND A LINK BETWEEN GREEN JELLY BEANS AND ACNE (P < 0.05).
WHOA!
WE FOUND NO LINK BETWEEN MAUVE JELLY BEANS AND ACNE (P > 0.05).
WE FOUND NO LINK BETWEEN BEIGE JELLY BEANS AND ACNE (P > 0.05).
WE FOUND NO LINK BETWEEN LILAC JELLY BEANS AND ACNE (P > 0.05).
WE FOUND NO LINK BETWEEN BLACK JELLY BEANS AND ACNE (P > 0.05).
WE FOUND NO LINK BETWEEN PEACH JELLY BEANS AND ACNE (P > 0.05).
WE FOUND NO LINK BETWEEN ORANGE JELLY BEANS AND ACNE (P > 0.05).
NEWS
GREEN JELLY BEANS LINKED TO ACNE!
95% CONFIDENCE
ONLY 5% CHANCE OF COINCIDENCE!
SCIENTISTS...

[1]

[1] Borrowed from XKCD

Multiple Comparisons

- As with most imaging analysis, multiple comparisons is significant concern
- Solutions:

  1. Bonferroni: control your type one error rate by multiplying your p-values by the number of tests. This is equivalent to setting your type one error rate to α/n
  2. FDR (Benjamini-Hochberg): Order your p-values lowest to highest and set $p_{corr} = \frac{pn}{rank(p)}$
  3. FDR (Variants): Assume p-values come from two distributions, a true finding distribution peaked near zero, and a uniform distribution.

- But in low power situations with high covariance between voxels, these can be conservative

Correction To The Paper

> *The authors note that on page 7900, in the Significance Statement, lines 9–11, "These results question the validity of some **40,000** fMRI studies and may have a large impact on the interpretation of neuroimaging results" should instead appear as "These results question the validity of a number of fMRI studies and may have a large impact on the interpretation of weakly significant neuroimaging results."*

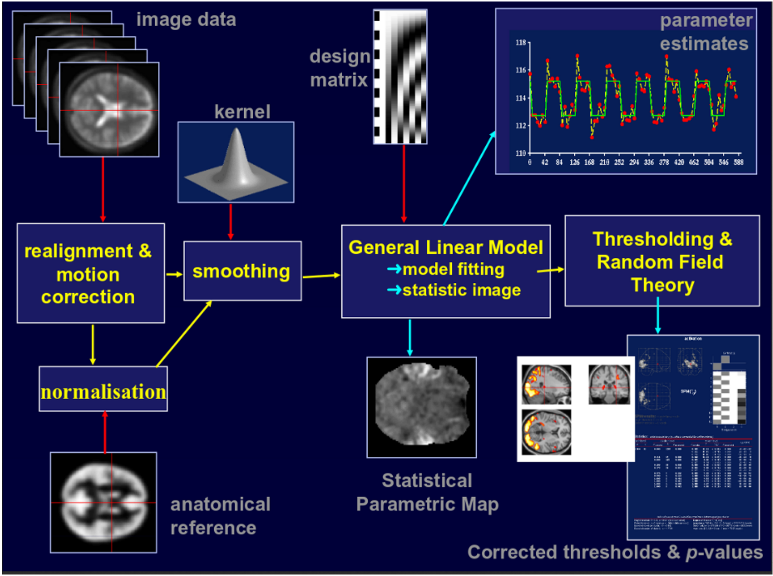
Nichols goes on to say on his blog, the number is closer to 15,000 with an additional 13,000 papers using *no multiple comparison correction at all*

About Group Comparisons Task-Based fMRI

- Most fMRI seeks to measure brain activity by blood flow
- Blood oxygen level dependent (BOLD) contrast
- A time-series of volumes are acquired for each subject
- Stimuli are presented to the subject throughout the time series
- The BOLD signal is modelled as a function of the stimuli
- The statistical associations of the BOLD contrast to the stimuli are compared across groups
- Group comparisons typically simple t-tests and ANOVAs

Why Is This Tough

- Subjects move:
  - within subject each fMRI volume must be aligned to each-other
  - these must be aligned to a corresponding anatomical scan
  - these must be registered to a common space
- BOLD signal is sluggish
  - $\sim$ 2 seconds to start
  - $\sim$ 4-6 to peak
  - $\sim$ 10 to return to baseline so the stimulus time series is convolved with a function to match this behaviour
- Analyzing time series comes with it's own statistical challenges
  - how do we model temporal autocorrelation

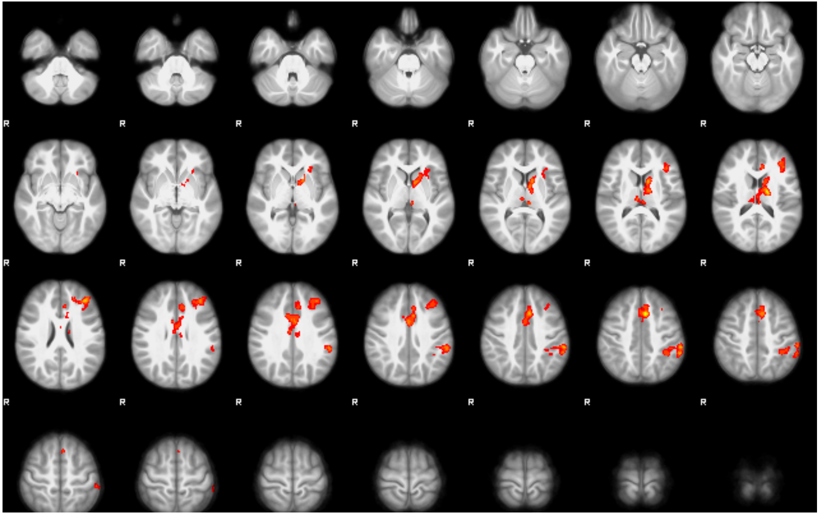


[2]

[2] Borrowed from Nichols (2010)

Enter Spatial Models

- Signals with large spatial extent are probably more likely to be real than individual high intensity
- Question becomes, how do we analyze spatial extent, and how do we correct for multiple comparisons?
- First: Threshold your data at threshold that sounds appealing ($p < .01$, and $p < .001$)
- Then: Use random field theory (RFT) results to assign a p-value to clusters based on their size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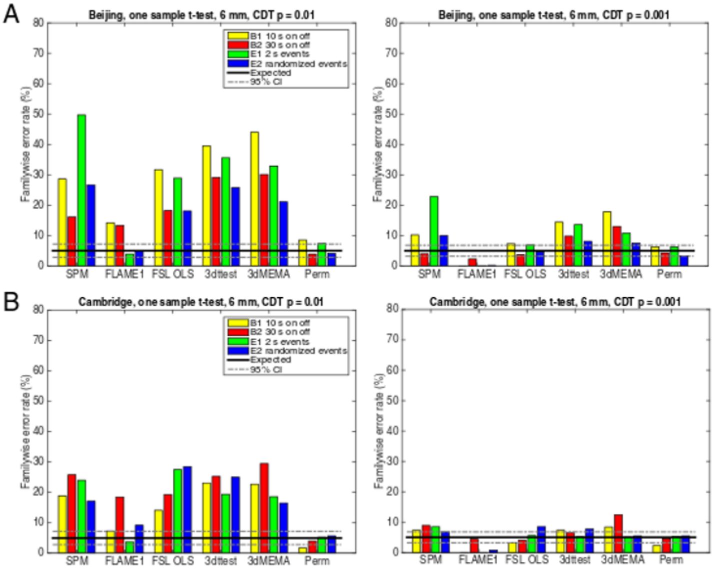
The Problems

- When statistics maps aren't smooth enough, RFT p-values are biased (2003)
- RFT typically assumes a stationary noise distribution (same noise over the brain) which is often invalid (2004)
- Together these problems can lead to 70% FWE rates in single subject analyses (2012)

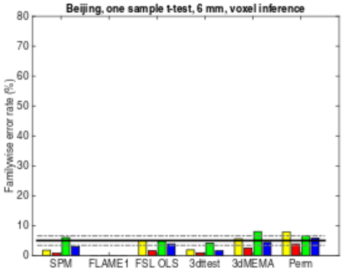
The Paper

- In order to assess how much these problems matter for group comparisons, check the null distribution
- The authors took a large open data set with a pool of neurotypical subjets, and randomly sampled groups to compare
- If after processing and multiple comparison correction any clusters in the brain were significant that test was a false positive (error).
- The distribution for a two group difference should be Student's t distribution, and after bonferroni correction, the expected proportion of errors should be 5%
- Higher error rates imply the multiple comparison correction is insufficient.
- Five analysis functions from the three most popular fMRI software packages were compared to their non-parametric alternative


A
Beijing, one sample t-test, 6 mm, CDT p = 0.01
Beijing, one sample t-test, 6 mm, CDT p = 0.001
B
Cambridge, one sample t-test, 6 mm, CDT p = 0.01
Cambridge, one sample t-test, 6 mm, CDT p = 0.001
Familywise error rate (%)
0
10
20
30
40
50
60
70
80
SPM
FLAME1
FSL OLS
3dttest
3dMEMA
Perm
B1 10 s on off
B2 30 s on off
E1 2 s events
E2 randomized events
Expected
95% CI

The results

- All parametric tools produce FWE higher than 5%
- Situation is more extreme when cluster defining thresholds are high (FWE rates ~20-40)
- Different data sets are affected differently (Beijing less affected than Cambridge)


Beijing, one sample t-test, 6 mm, voxel inference
Familywise error rate (%)
0
10
20
30
40
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70
80
SPM
FLAME1
FSL OLS
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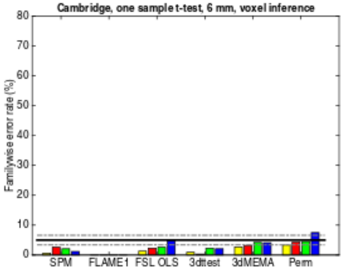
Cambridge, one sample t-test, 6 mm, voxel inference
Familywise error rate (%)
0
10
20
30
40
50
60
70
80
SPM
FLAME1
FSL OLS
3dttest
3dMEMA
Perm

So What To Do

- Give up on cluster inference
- Use a bootstrap/randomization test instead of RFT
  1. Shuffle group membership and covariates between subjects
  2. Refit your model
  3. Create a distribution on largest clusters per sample
  4. Assign p-values to cluster size from this null distribution
- Merge voxel level data with cluster extent (Threshold free cluster enhancement)
  1. Shuffle group membership and covariates between subjects
  2. Refit your model
  3. Perform TFCE
  4. Create a randomization of the cluster enhanced statistics
  5. Assign p-values to voxels from this null distribution
  6. Correct with Bonferroni or FDR

Revisiting The Implications

- 15,000 papers use RFT based cluster inference
- Of these 3,500 use a CDT of p $=$ 0.01, which is only 10% of the literature
- A randomization test may lead to a 2-3 order of magnitude increase in p-value this likely leaves many highly significant results intact.
- So maybe not quite as damning as the sensational headlines suggest

Are We Safe?

- Results show voxel wise results are conservative
- Matches the van Eede *et al.* (2014) results which showed our registration and analysis pipeline were conservative with FDR correction

Questions and Discussion