BCB 731:

Defense Against the Dark Arts

Introduction

October 2nd, 2023

Prologue: what causes depression?

NHS

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About fluoxetine

Fluoxetine is a type of antidepressant known as a selective serotonin reuptake inhibitor (SSRI). It's often used to treat depression, and sometimes obsessive compulsive disorder and bulimia.

It works by increasing the levels of serotonin in the brain. Serotonin is thought to have a good influence on mood, emotion and sleep.

https://www.nhs.uk/medicines/fluoxetine-prozac/about-fluoxetine/

HOW PROZAC CAN HELP

How it Works

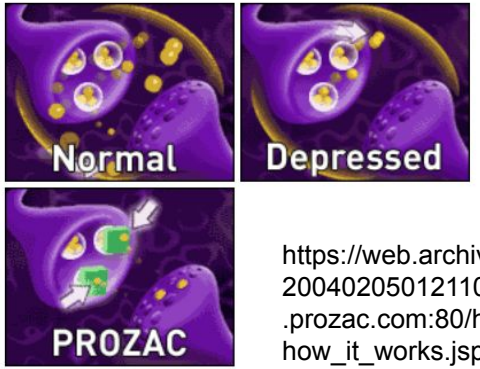
Depression is not fully understood, but a growing amount of evidence supports the view that people with depression have an imbalance of the brain's neurotransmitters, the chemicals that allow nerve cells in the brain to communicate with each other. Many scientists believe that an imbalance in serotonin, one of these neurotransmitters, may be an important factor in the development and severity of depression.

PROZAC may help to correct this imbalance by increasing the brain's own supply of serotonin.

Some other antidepressant medicines appear to affect several neurotransmitters in addition to serotonin. PROZAC selectively affects only serotonin.

While PROZAC cannot be said to "cure" depression, it does help to control the symptoms of depression, allowing many people with depression to feel better and return to normal functioning. [See graphics below]

Below you will find links to animations of the serotonin system within the brain.



https://web.archive.org/web/20040205012110/http://www.prozac.com:80/how_prozac/how_it_works.jsp

...and yet...

Considering the methodological limitations in the evidence base of antidepressants for depression: a reanalysis of a network meta-analysis

Design Reanalysis of a systematic review, with meta-analyses.
Data sources 522 trials (116 477 participants) as reported in the systematic review by Cipriani *et al* and clinical study reports for 19 of these trials.
Analysis We used the Cochrane Handbook's risk of bias tool and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to evaluate the risk of bias and the certainty of evidence, respectively. The impact of several study characteristics and publication status was estimated using pairwise subgroup meta-analyses.
Results Several methodological limitations in the evidence base of antidepressants were either unrecognised or underestimated in the systematic review by Cipriani *et al*. The effect size for antidepressants versus placebo on investigator-rated depression symptom scales was higher in trials with a 'placebo run-in' study design compared with trials without a placebo run-in design (p=0.05). The effect size of antidepressants was higher in published trials compared with unpublished trials (p<0.0001). The outcome data reported by Cipriani *et al* differed from the clinical study reports in 12 (63%) of 19 trials. The certainty of the evidence for the placebo-controlled comparisons should be very low according to GRADE due to a high risk of bias, indirectness of the evidence and publication bias. The mean difference between antidepressants and placebo on the 17-item Hamilton depression rating scale (range 0–52 points) was 1.97 points (95% CI 1.74 to 2.21).
Conclusions The evidence does not support definitive conclusions regarding the benefits of antidepressants for depression in adults. It is unclear whether antidepressants are more efficacious than placebo.

SYSTEMATIC REVIEW OPEN

Check for updates

The serotonin theory of depression: a systematic umbrella review of the evidence

Joanna Moncrieff[1,2]✉, Ruth E. Cooper[3], Tom Stockmann[4], Simone Amendola[5], Michael P. Hengartner[6] and Mark A. Horowitz[1,2]

The serotonin hypothesis of depression is still influential. We aimed to synthesise and evaluate evidence on whether depression is associated with lowered serotonin concentration or activity in a systematic umbrella review of the principal relevant areas of research. PubMed, EMBASE and PsycINFO were searched using terms appropriate to each area of research, from their inception until December 2020. Systematic reviews, meta-analyses and large data-set analyses in the following areas were identified: serotonin and serotonin metabolite, 5-HIAA, concentrations in body fluids; serotonin 5-HT_{1A} receptor binding; serotonin transporter (SERT) levels measured by imaging or at post-mortem; tryptophan depletion studies; SERT gene associations and SERT gene-environment interactions. Studies of depression associated with physical conditions and specific subtypes of depression (e.g. bipolar depression) were excluded. Two independent reviewers extracted the data and assessed the quality of included studies using the AMSTAR-2, an adapted AMSTAR-2, or the STREGA for a large genetic study. The certainty of study results was assessed using a modified version of the GRADE. We did not synthesise results of individual meta-analyses because they included overlapping studies. The review was registered with PROSPERO (CRD42020207203). 17 studies were included: 12 systematic reviews and meta-analyses, 1 collaborative meta-analysis, 1 meta-analysis of large cohort studies, 1 systematic review and narrative synthesis, 1 genetic association study and 1 umbrella review. Quality of reviews was variable with some genetic studies of high quality. Two meta-analyses of overlapping studies examining the serotonin metabolite, 5-HIAA, showed no association with depression (largest $n = 1002$). One meta-analysis of cohort studies of plasma serotonin showed no relationship with depression, and evidence that lowered serotonin concentration was associated with antidepressant use ($n = 1869$). Two meta-analyses of overlapping studies examining the 5-HT_{1A} receptor (largest $n = 561$), and three meta-analyses of overlapping studies examining SERT binding (largest $n = 1845$) showed weak and inconsistent evidence of reduced binding in some areas, which would be consistent with increased synaptic availability of serotonin in people with depression, if this was the original, causal abnormaly. However, effects of prior antidepressant use were not reliably excluded. One meta-analysis of tryptophan depletion studies found no effect in most healthy volunteers ($n = 566$), but weak evidence of an effect in those with a family history of depression ($n = 75$). Another systematic review ($n = 342$) and a sample of ten subsequent studies ($n = 407$) found no effect in volunteers. No systematic review of tryptophan depletion studies has been performed since 2007. The two largest and highest quality studies of the SERT gene, one genetic association study ($n = 115,257$) and one collaborative meta-analysis ($n = 43,165$), revealed no evidence of an association with depression, or of an interaction between genotype, stress and depression. The main areas of serotonin research provide no consistent evidence of there being an association between serotonin and depression, and no support for the hypothesis that depression is caused by lowered serotonin activity or concentrations. Some evidence was consistent with the possibility that long-term antidepressant use reduces serotonin concentration.

Molecular Psychiatry; https://doi.org/10.1038/s41380-022-01661-0

Many published results are not useful

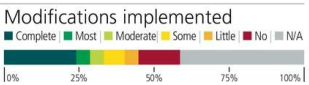
Shown: cancer biology, but many fields similarly full of junk

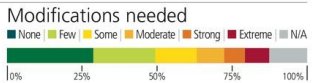
COMPLETED
50 experiments

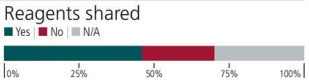
INITIATED
87 experiments

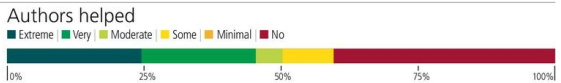
DESIGNED
193 experiments

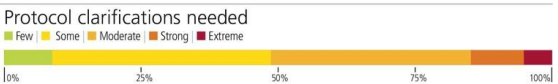
BARRIERS

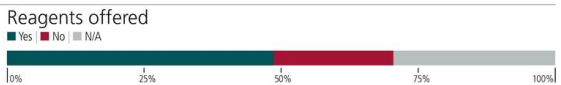


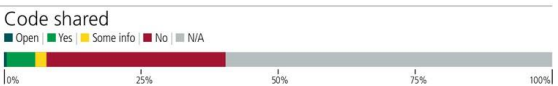


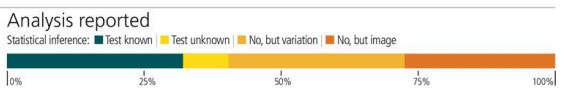


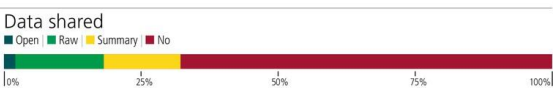


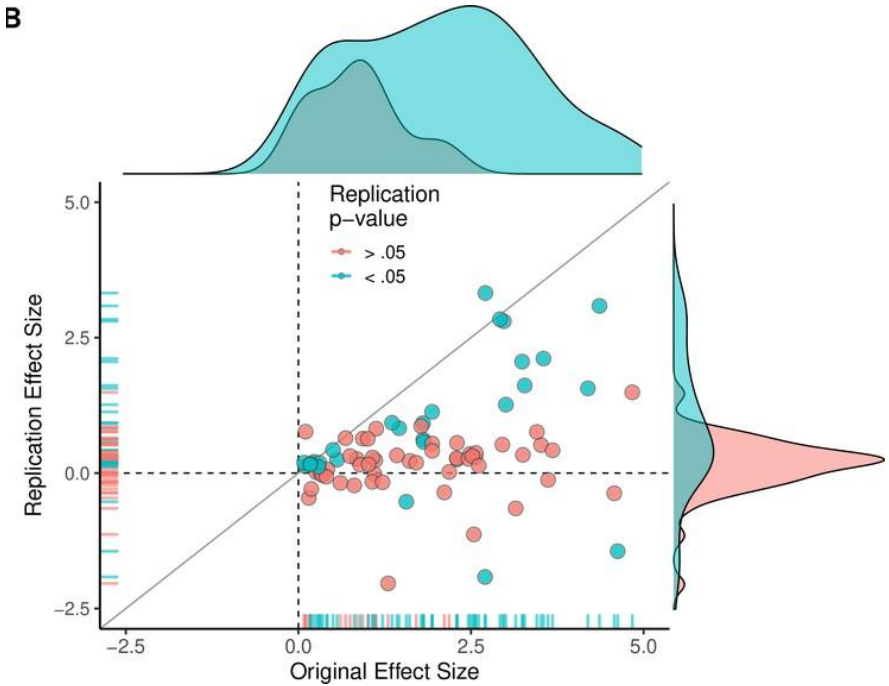








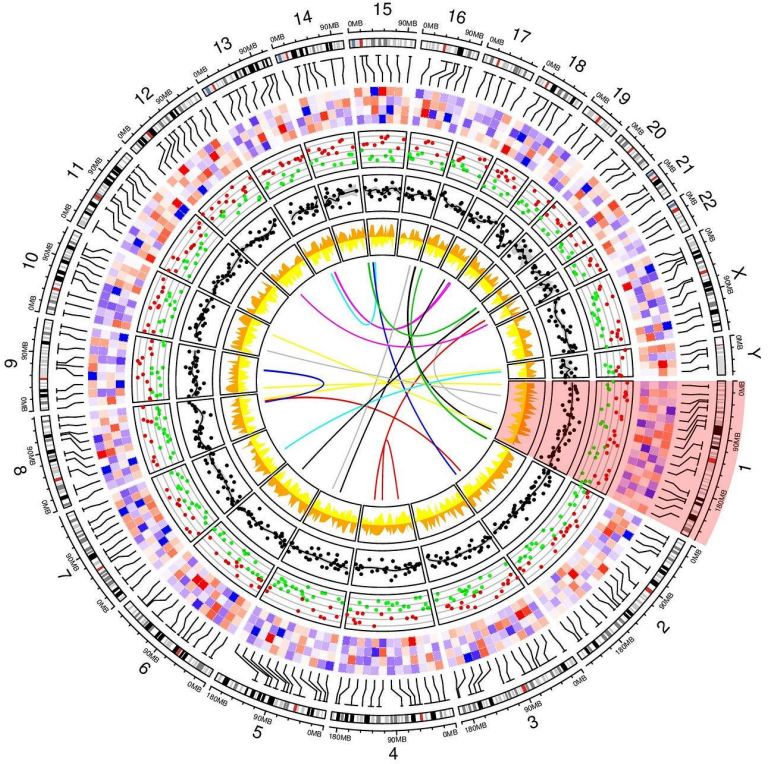




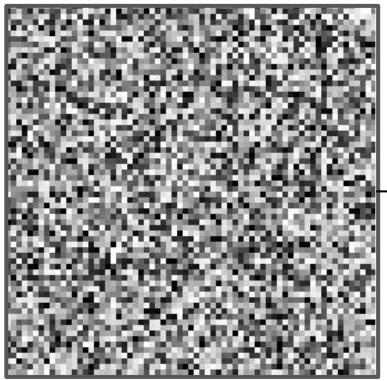
Reproducibility in Cancer Biology: Challenges for assessing replicability in preclinical cancer biology

…and if bench science has a generalizability crisis, wait til you meet its *in silico* cousins…

- There's often nothing to reproduce other than specific figures on specific data used in the paper
  - **…despite making biological claims which sound general…**
- "*Code available upon request*"



What is this class even about?



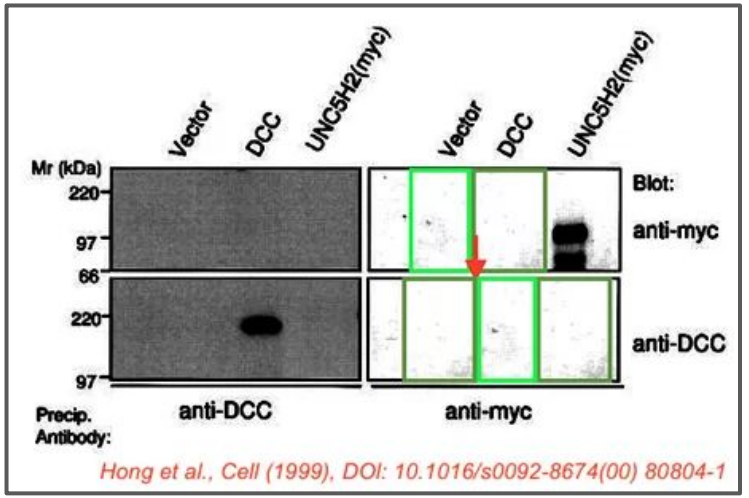
Biological Noise

Dark Arts

"statistically significant"
"predictive model"
"machine learning"

What is this class not about?

- BCB 731 is (mostly) not about:
  - intentional fraud
  - research "misconduct"
    - (in a narrow sense)
  - data fabrication
  - data manipulation / editing



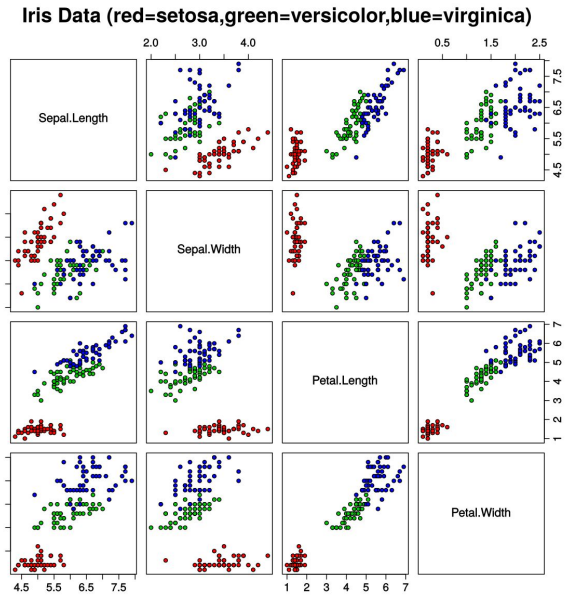
- We will look at a few examples of intentional fraud but **unclear that authors of bad papers know they're doing anything wrong**
  - probably trained to find & rewarded for high impact findings

So, how do mostly honest researchers end up publishing so much junk?

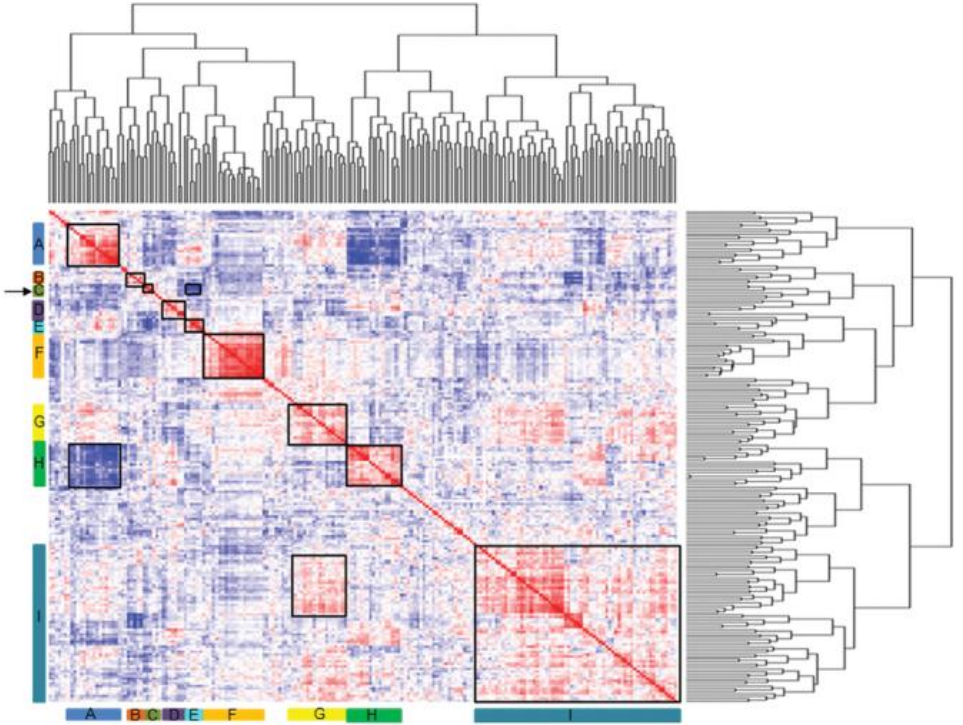
- **High throughput biological assays**
  - ***n*** (number of samples) << ***p*** (number of features)
- **“Garden of forking paths” in data analysis**
  - Researcher Degrees of Freedom
- **Unintentionally doing machine learning**
  - Stats curriculum often doesn’t prepare for dataset (construction, preprocessing, featurization) or evaluating predictive models

The curse of dimensionality

Classical statistics was designed for data like this:



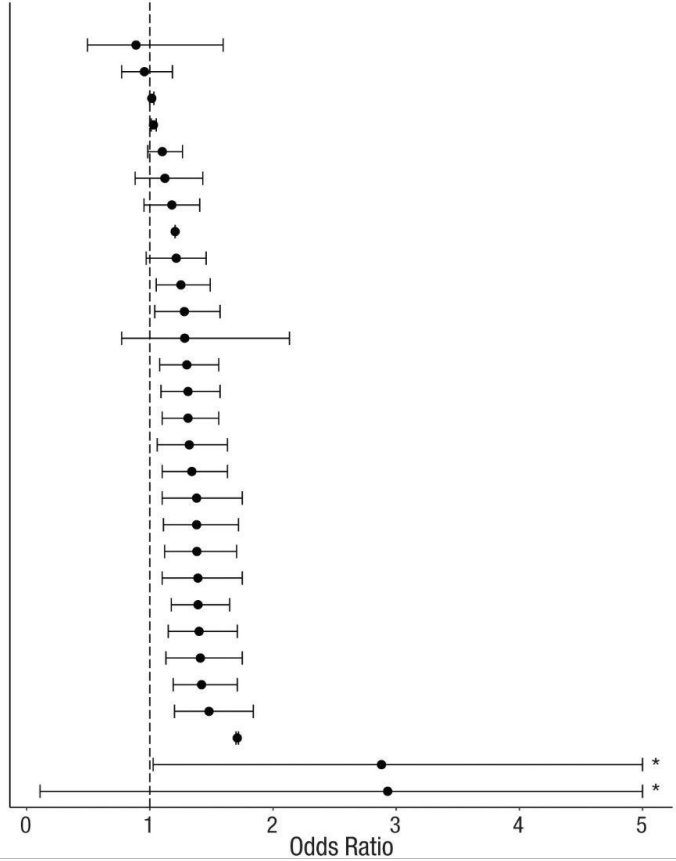
Our data looks like this:



Researcher Degrees of Freedom

Many Analysts, One Data Set: Making Transparent How Variations in Analytic Choices Affect Results

Analytic Approach	Odds Ratio
Zero-Inflated Poisson Regression	0.89
Bayesian Logistic Regression	0.96
Hierarchical Log-Linear Modeling	1.02
Multilevel Regression and Logistic Regression	1.03
Hierarchical Bayes Model	1.10
Logistic Regression	1.12
OLS Regression With Robust Standard Errors, Logistic Regression	1.18
Spearman Correlation	1.21
WLS Regression With Clustered Standard Errors	1.21
Multiple Linear Regression	1.25
Clustered Robust Binomial Logistic Regression	1.28
Linear Probability Model	1.28
Hierarchical Generalized Linear Modeling With Poisson Sampling	1.30
Multilevel Logistic Regression Using Bayesian Inference	1.31
Mixed-Model Logistic Regression	1.31
Hierarchical Poisson Regression	1.32
Linear Probability Model, Logistic Regression	1.34
Generalized Linear Mixed Models	1.38
Multilevel Logistic Regression	1.38
Mixed-Effects Logistic Regression	1.38
Generalized Linear Models for Binary Data	1.39
Negative Binomial Regression With a Log Link	1.39
Cross-Classified Multilevel Negative Binomial Model	1.40
Poisson Multilevel Modeling	1.41
Multilevel Logistic Binomial Regression	1.42
Generalized Linear Mixed-Effects Models With a Logit Link	1.48
Dirichlet-Process Bayesian Clustering	1.71
Tobit Regression	2.88
Poisson Regression	2.93



Objective

- **Learn the red flags!**
  - “Huh, seems like they might be training and testing their predictor on the same data…”
  - “How did they get p<10^{-200} on 23 samples?”
  - “Looks like their model uses test samples as part of feature selection…”
  - “They don’t say why they chose *that* particular gene set, I wonder if they also looked at other ones…”

Class format: role playing

- Every week we'll do a close read of a paper I think has at least one crucial problem
  - I might be wrong! Maybe the analyses are all great, we'll figure that out together.
- Small groups present each paper from two different roles
  - **Optimist**: gullible
  - **Critic:** highlight the core "trick" or misapplied method that helped support a non-generalizable claim


Fin