Improving Reproducibility in Human Neuroimaging

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Scientific Reproducibility Colloquium Series

11 October 2016

Overview

- The Crises of Reproducibility
  - Understanding Ioannidis
  - Evidence of a problem
- Constructive ways forward
  - TOP Principles
  - OHBM COBIDAS

John Ioannidis' Crusade

Open access, freely available online

Essay

Why Most Published Research Findings Are False

John P. A. Ioannidis

Summary

There is increasing concern that most current published research findings are false. The probability that a research claim is true may depend on study power and bias, the number of other studies on the same question, and, importantly, the ratio of true to no relationships among the relationships probed in each scientific field. In this framework, a research finding is less likely to be true when the studies conducted in a field are smaller; when effect sizes are smaller; when there is a

factors that influence this problem and some corollaries thereof.

Modeling the Framework for False Positive Findings

Several methodologists have pointed out [9–11] that the high rate of nonreplication (lack of confirmation) of research discoveries is a consequence of the convenient, yet ill-founded strategy of claiming conclusive research findings solely on the basis of a single study assessed by formal statistical significance, typically

is characteristic of the field and can vary a lot depending on whether the field targets highly likely relationships or searches for only one or a few true relationships among thousands and millions of hypotheses that may be postulated. Let us also consider, for computational simplicity, circumscribed fields where either there is only one true relationship (among many that can be hypothesized) or the power is similar to find any of the several existing true relationships. The pre-study probability of a relationship

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a research claim to be false than true. Moreover, for many current scientific fields, claimed research findings may often be simply accurate measures of the

should be interpreted based only on *p*-values. Research findings are defined here as any relationship reaching

achieving formal statistical significance, the post-study probability that it is true is the positive predictive value, PPV.

- A careful argument for intense skepticism of modern scientific results
- Cited 3562 times (April 2016, Google Scholar)

Ioannidis, J. P. A. (2005). Why most published research findings are false. *PLoS Medicine*, 2(8), e124.

Study Positive Predictive Value

- Sampling Units
  - *Not* a set of subjects
  - A set of research hypotheses!
    - E.g. Hypothesis set in cognitive decline in aging:
      - Vitamin D reduces risk of cognitive decline
      - Exercise reduces risk of cognitive decline
      - Fish oil reduces risk of cognitive decline
      - …
- For a randomly selected study:
  - Given the study is positive, what is the probability the studied hypothesis is true?
  - I.e. what is the study PPV?

PPV Arithmetic

	True Hypothesis H+	False Hypothesis H-
Positive Finding D+	P(D+|H+) *Power* 1-β	P(D+|H-) *FPR* α
Negative Finding D-		
	P(H+)	P(H-)

- Notation
  - $R = N_T / N_F$ *odds of a true hypothesis*
    N_T = # true research hypotheses
    N_F = # false research hypotheses
  - P(H+) *probability of a true hypothesis*
  - Odds vs. probability
    - $P(H+) = N_T /(N_T + N_F) = R / (R+1)$

PPV Arithmetic

	True Hypothesis H+	False Hypothesis H-
Positive Finding D+	P(D+|H+) *Power* 1-β	P(D+|H-) *FPR* α
Negative Finding D-		
	P(H+)	P(H-)

- Bayes Theorem

$$P(H+) = R / (R+1)$$
$$P(H-) = 1 / (R+1)$$

$$PPV = P(H+|D+) = \frac{P(D+|H+)\,P(H+)}{P(D+|H+)\,P(H+) + P(D+|H+)\,P(H+)}$$

$$= \frac{(1-\beta)\,R / (R+1)}{(1-\beta)\,R / (R+1) + \alpha / (R+1)}$$

$$= \frac{(1-\beta)\,R}{(1-\beta)\,R + \alpha}$$

- PPV depends on power (1-β), odds of a true hypothesis (R) & false positive rate (FPR, α)

PPV Arithmetic

- When is PPV > ½?

$$0.5 > PPV = \frac{(1-\beta)\,R}{(1-\beta)\,R + \alpha} \quad \rightarrow \quad (1-\beta)R > \alpha$$

  - Note, (1-β)>α always true for a "unbiased" test
  - If R=1, PPV > ½
  - If R < ½, then PPV might < ½

- PPV & Power

$$PPV = \frac{(1-\beta)\,R}{(1-\beta)\,R + \alpha} = (1-\beta)\,\frac{R}{R + \alpha/(1-\beta)} \approx (1-\beta)$$

  - Lower the PPV, the lower the power

PPV Arithmetic

- PPV & "bias"
  - Suppose fraction *u* of all studies shouldn't have been published but are
    - i.e. won't have been published if no bias
    - Due to "vibration effects"
    - *Not* the α fraction of chance false positive studies
    - *Not* usual estimation bias per se
  - Then…

$$PPV = \frac{(1-\beta)\,R + u\,\beta\,R}{(1-\beta)\,R + u\,\beta\,R + \alpha + u(1-\alpha)}$$

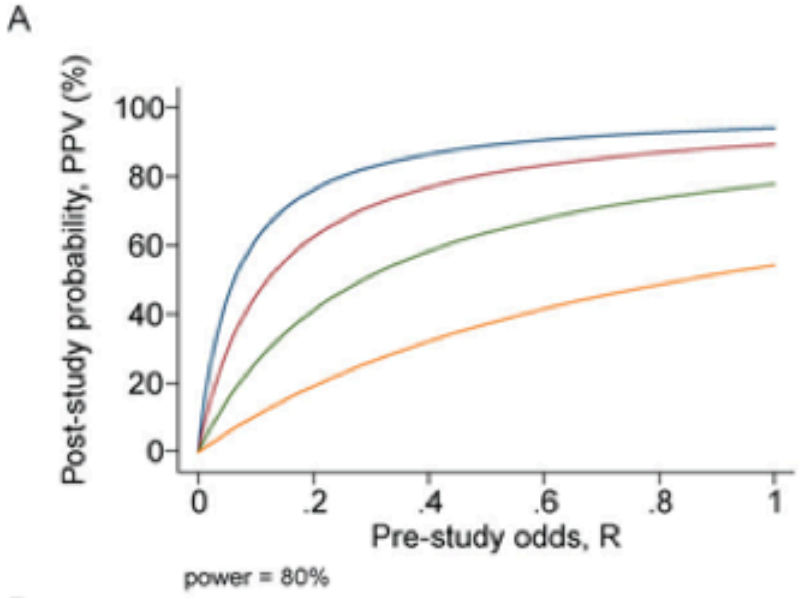
  - As *u* increases, PPV drops

Exploring study PPV

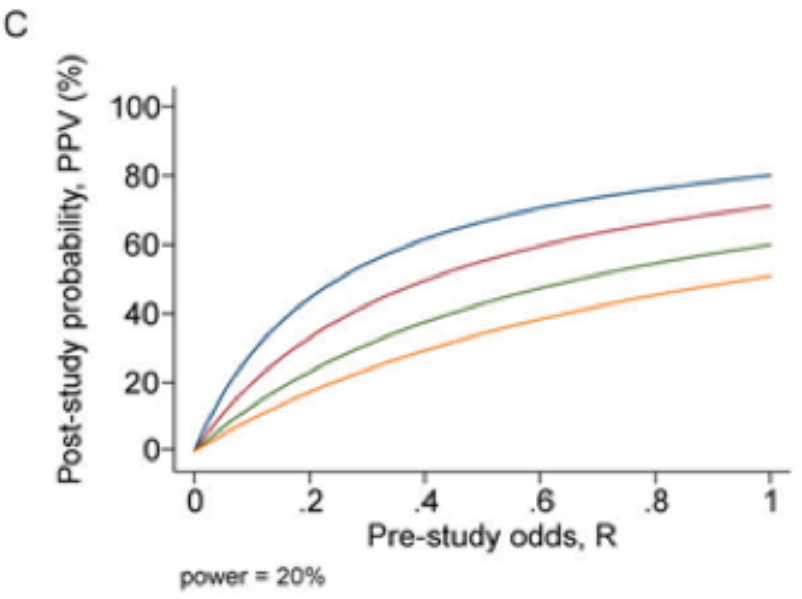
- PPV depends on u & power
  - Skepticism of a discipline (high 'bias' frequency u) translates to lower PPV

PPV vs. R - For different levels of bias *u*

Power = 80%



Power = 20%



u=0.05 u=0.20 u=0.50 u=0.80

Exploring “any” PPV

- Suppose *n* research teams all study a hypothesis
- Define “D+” as one or more of those teams getting a finding
  - They ‘busier’ the discipline, the lower the PPV

PPV vs. R - For number of research teams

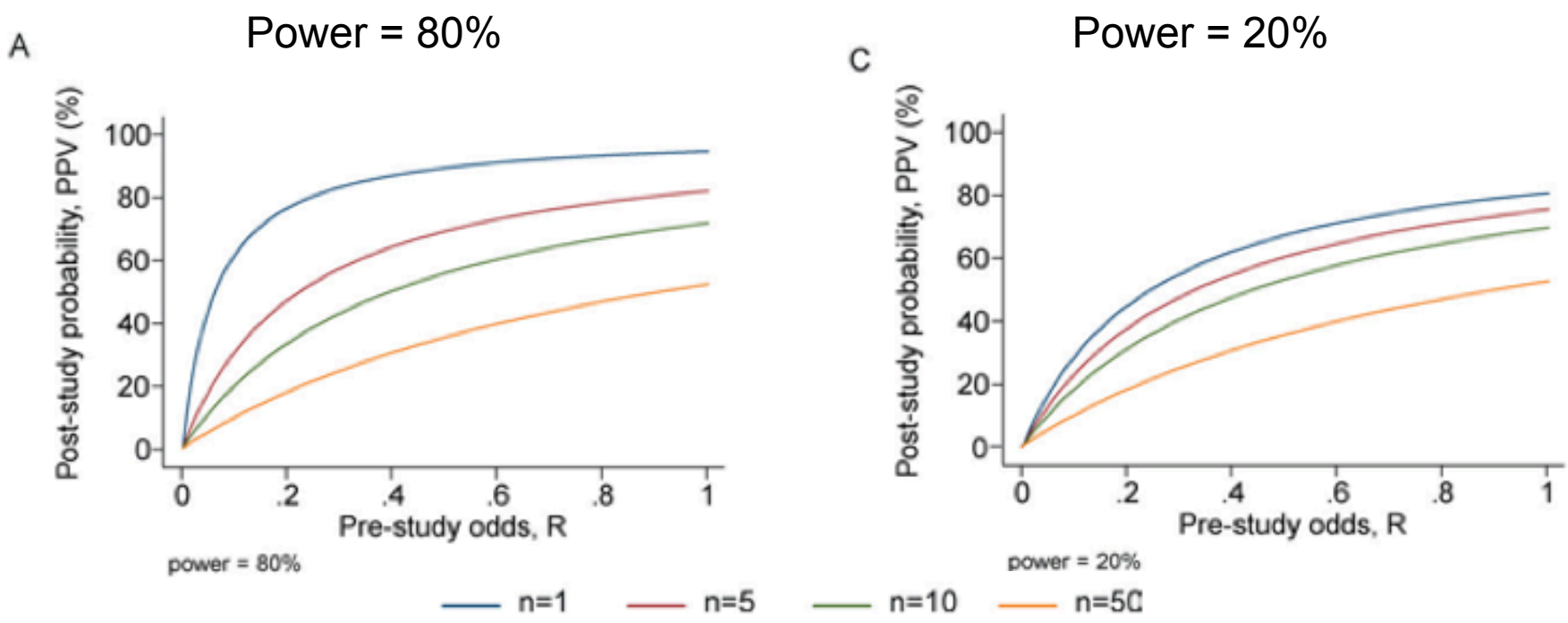


Table 4. PPV of Research Findings for Various Combinations of Power (1 – β), Ratio of True to Not-True Relationships *(R)*, and Bias *(u)*

1 – β	*R*	*u*	Practical Example	PPV
0.80	1:1	0.10	Adequately powered RCT with little bias and 1:1 pre-study odds	0.85
0.95	2:1	0.30	Confirmatory meta-analysis of good-quality RCTs	0.85
0.80	1:3	0.40	Meta-analysis of small inconclusive studies	0.41
0.20	1:5	0.20	Underpowered, but well-performed phase I/II RCT	0.23
0.20	1:5	0.80	Underpowered, poorly performed phase I/II RCT	0.17
0.80	1:10	0.30	Adequately powered exploratory epidemiological study	0.20
0.20	1:10	0.30	Underpowered exploratory epidemiological study	0.12
0.20	1:1,000	0.80	Discovery-oriented exploratory research with massive testing	0.0010
0.20	1:1,000	0.20	As in previous example, but with more limited bias (more standardized)	0.0015

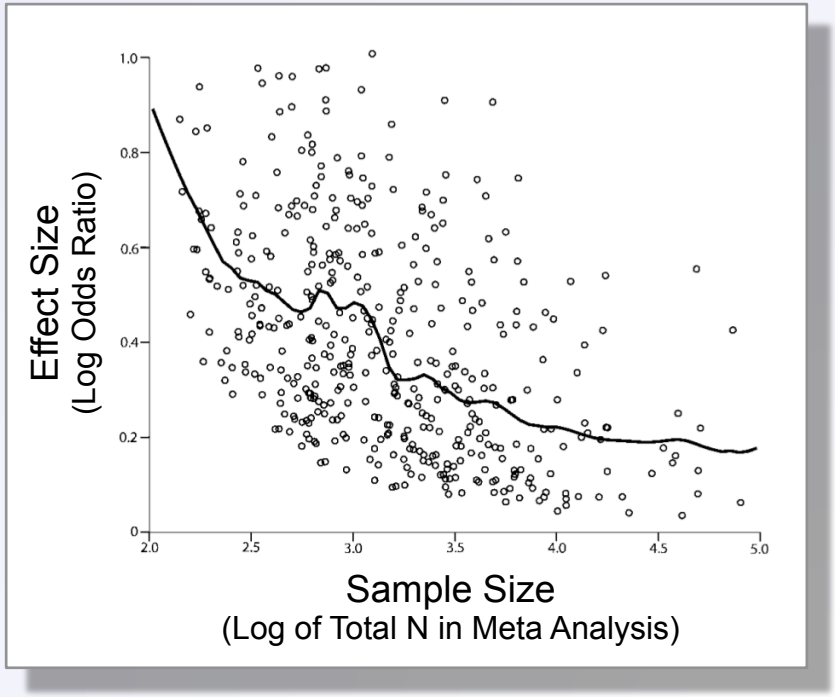
OK, but what's the evidence?

- This is a thought experiment
  - Sampling frame "Research hypotheses"
  - Many studies experience "bias", but this may take P-values from 0.0001 when then should be 0.005
- Is there really a problem here?
  - Canary in the coal mine, or
  - Chicken Little?

Exhibit A: Law of Small numbers

- Or “Winner’s Curse”
  - Small studies over-estimate effect size

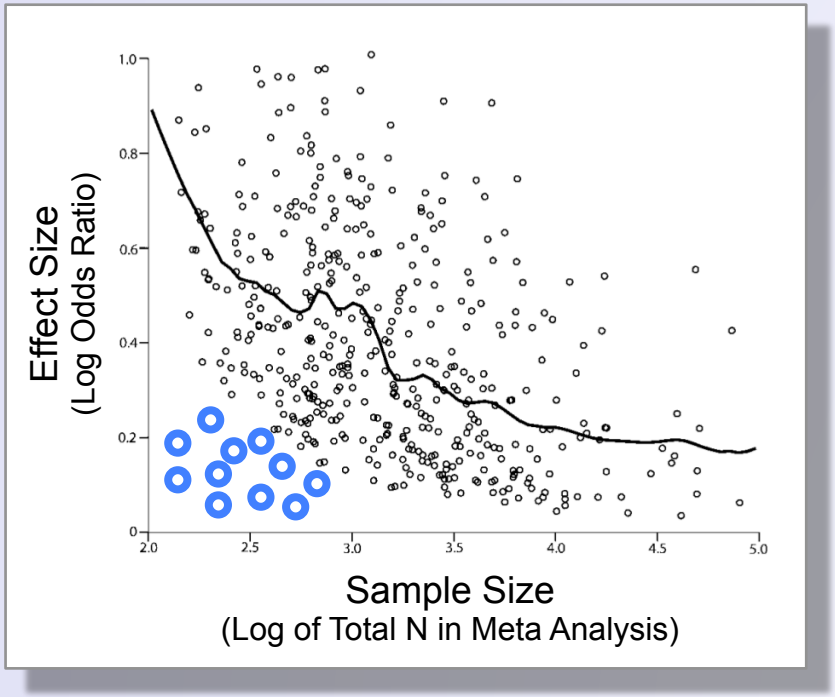
- ☐ 256 meta analyses for a dichotomous effect (odds ratio) from Cochrane database
- ☐ Studies with smallest N have biggest effect size!
  - ☑ Low N studies have low power
  - ☑ Low-power studies rarely succeed, but when they do, is result of randomly high effect or randomly small variance, biasing effect size
- ☐ Explains difficulty with replication



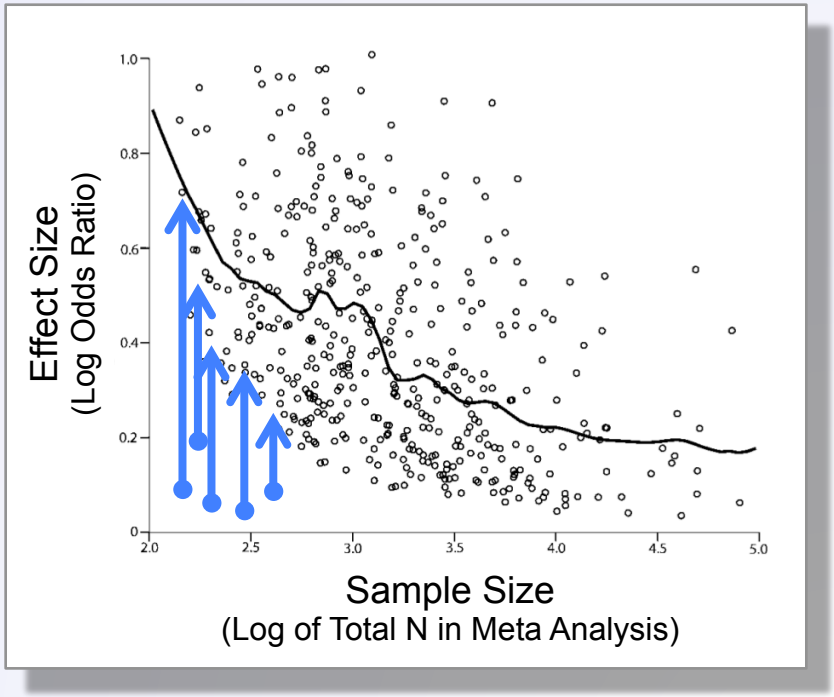
Ioannidis (2008). “Why most discovered true associations are inflated.” *Epidemiology*, 19(5), 640-8.

Two Problems

- Suppressed studies & Biased effects
  - P>0.05 not published
  - Biases that afflict small studies more than large studies



File drawer problem
(Unpublished non-significant studies)



Bias
(Fishing or Vibration Effects)

Vibration Effects

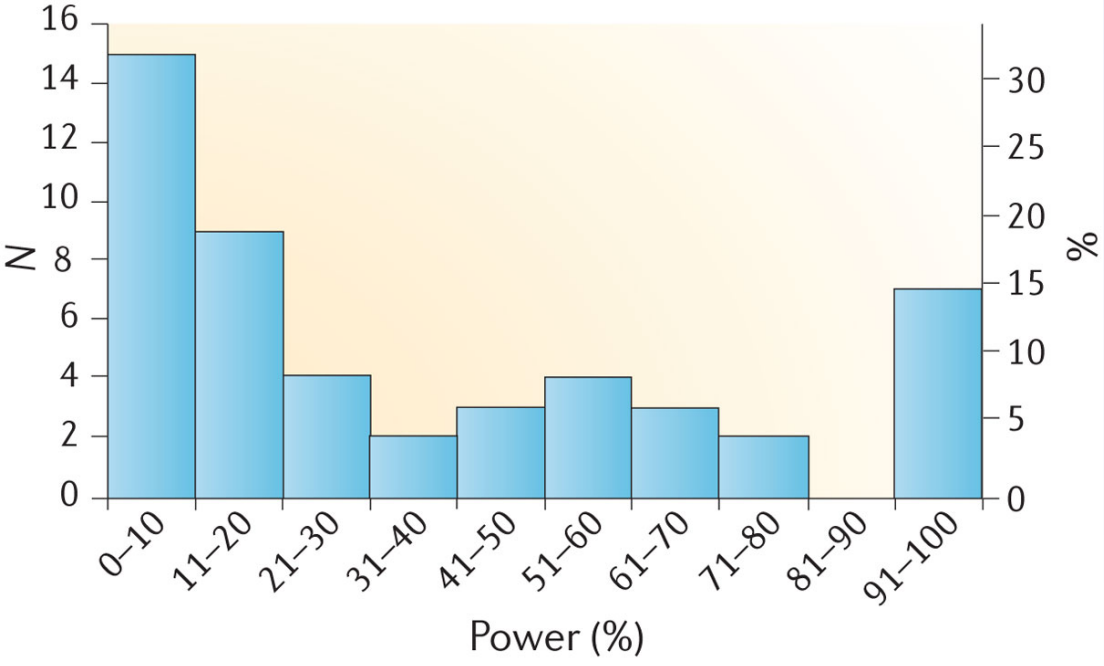
- Sloppy or nonexistent analysis protocols

> "Try voxel-wise whole brain, then cluster-wise, then if not getting good results, look for subjects with bad movement, if still nothing, maybe try a global signal regressor; if still nothing do SVC for frontal lobe, if not, then try DLPFC (probably only right side), if still nothing, will look in literature for xyz coordinates near my activation, use spherical SVC… surely that'll work!"

  - You stop when you get the result you expect
  - These "vibrations" can only lead to inflated false positives
- Afflicts well-intended researchers
  - Modern, "big data" scientific tools have multitude of preprocessing options, modeling choices
    - Pre-modelling normalisation options
    - Even more choices of options, covariates, interactions

Exhibit B: Studies chronically under powered

- Review of 730 neuroscience studies
  - Extracted from 48 meta analyses
  - Power of each of 730 studies calculated
- Median power **21%**
  - For 50% of studies, fewer than 1 in 5 replications will succeed!



Button et al. (2013). Power failure: why small sample size undermines the reliability of neuroscience. Nature Reviews. Neuroscience, 14(5), 365–76.

Exhibit C: Mass replication

- Open Science Collaboration: Psychology
  - Replicated 100 new & classic studies
  - Effort of 270 scientists
- Each replication ‘registered’
  - Carefully powered ($1-\beta \approx 90\%$)
  - Extensive peer review (usually with original authors contributing) in preparing study
  - Complete details of study protocol & analysis publically recorded and fixed

Open Science Collaboration. (2015). PSYCHOLOGY. Estimating the reproducibility of psychological science. Science (New York, N.Y.), 349(6251), aac4716.

Exhibit C: Mass non-replication

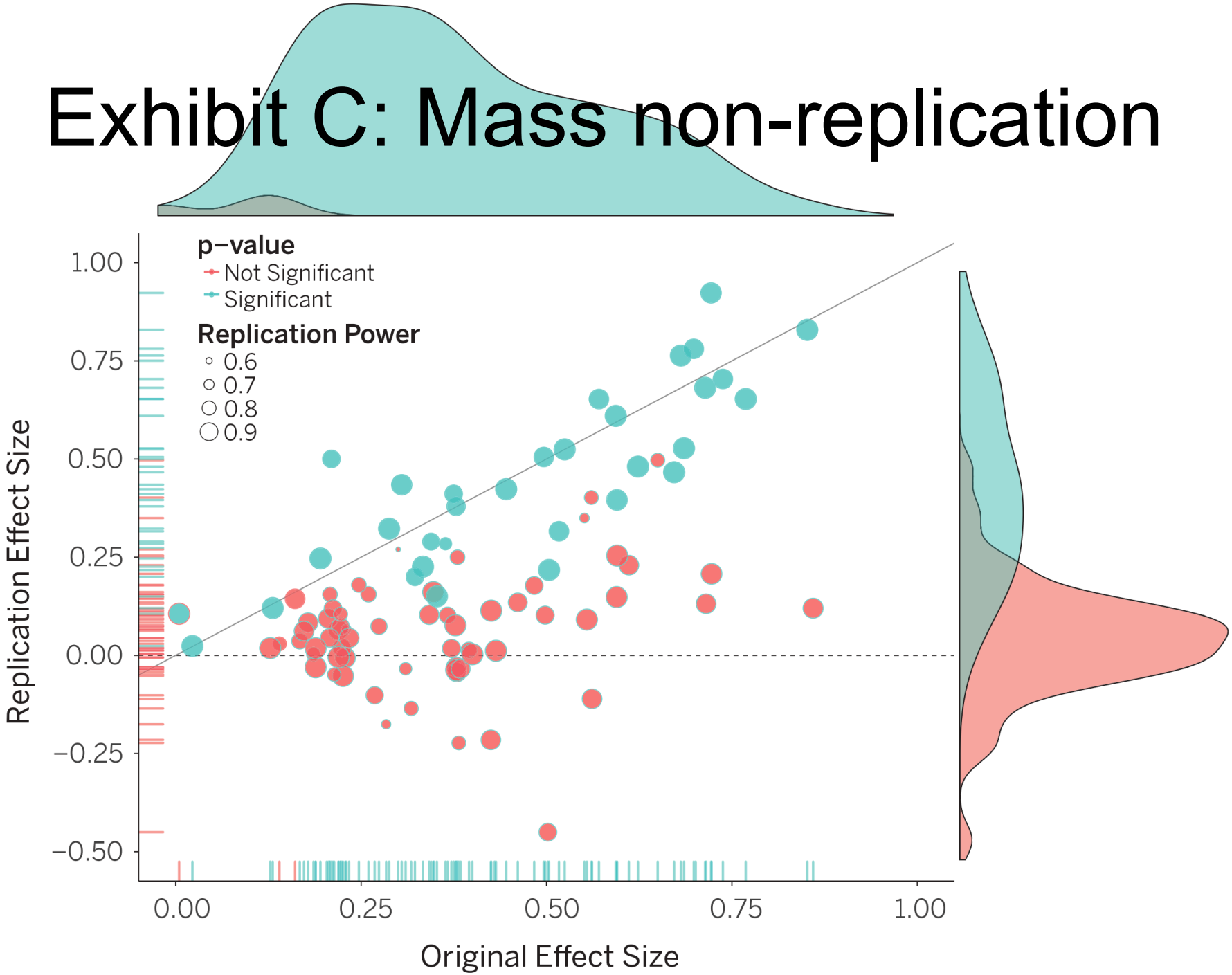


Exhibit C: Mass non-replication

- Mean replication effect size half of original
  - In correlation units: Orig. 0.403 Repl. 0.197
- Most replications not significant
  - P<0.05 significant: Orig. 97% Repl. 36%
- Joint analysis of Orig. & Repl.
  - 68% significant

What can be done?

- TOP – Transparency Openness Promotion
  - Advancing open science goals in service of reproducibly
  - Articulated by
    - Nosek et al. (2015). SCIENTIFIC STANDARDS. Promoting an open research culture. *Science*, 348(6242), 1422–5.
  - Provides 8 areas, 4 levels of success

Summary of the eight standards and three levels of the TOP guidelines

Levels 1 to 3 are increasingly stringent for each standard. Level 0 offers a comparison that does not meet the standard.

	LEVEL 0	LEVEL 1	LEVEL 2	LEVEL 3
Citation standards	Journal encourages citation of data, code, and materials—or says nothing.	Journal describes citation of data in guidelines to authors with clear rules and examples.	Article provides appropriate citation for data and materials used, consistent with journal's author guidelines.	Article is not published until appropriate citation for data and materials is provided that follows journal's author guidelines.
Data transparency	Journal encourages data sharing—or says nothing.	Article states whether data are available and, if so, where to access them.	Data must be posted to a trusted repository. Exceptions must be identified at article submission.	Data must be posted to a trusted repository, and reported analyses will be reproduced independently before publication.

Elements of TOP

- Citation standards
- Data transparency
- Analytic methods (code) transparency
- Research materials transparency
- Design and analysis transparency
- Preregistration of studies
- Preregistration of analysis plans
- Replication

TOP Update (1/2)

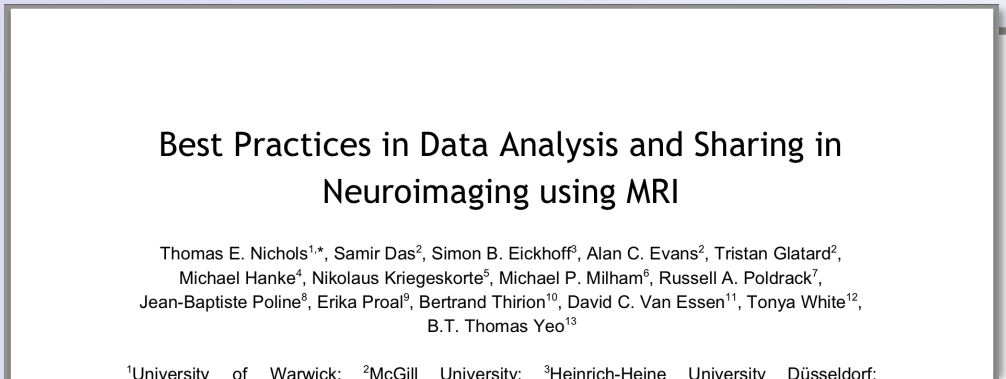
- Citation standards
  - Citation of data, code and materials
  - Level 3: Complete citation of all data, code and materials
    - e.g. New *Science* standard
    - McNutt. (2016). Taking up TOP. Science, 352(6290), 1147–1147
- Data/Code/Materials transparency
  - Availability of data/code/materials
  - Level 3: Before pub., data, code & materials posted to trusted repository; reported analyses independently reproduced
    - e.g. “R” kite-mark in *Biostatistics*

TOP Uptake (2/2)

- Design and analysis transparency
  - Completely described design, following best practice
  - Level 3: Journal requires and enforces adherence to design standards for review and publication
    - Small steps: *Nature* / *Nature Neuroscience* check lists
- Preregistration of Study/Analysis Plan
  - Level 3: Required
- Replication
  - Facilitation of replication studies
  - Level 3: Registered report article type

OHBM **C**ommittee **O**n **B**est **P**ractice In **D**ata **A**nalysis & **S**haring (COBIDAS)

- White paper with checklists of practice & reporting, for all variants of MRI
- Emphasis on comprehensive *reporting*
  - Practice too varied to be prescriptive, except
- Best practice give for 3 areas
  - Statistical modeling, data sharing & reproducibility
- Published bioRxiv doi:10.1101/054262 20 May 2016
  - Commentary commissioned by *Nature Neuroscience*



Best Practices in Data Analysis and Sharing in Neuroimaging using MRI

Thomas E. Nichols[1,*], Samir Das[2], Simon B. Eickhoff[3], Alan C. Evans[2], Tristan Glatard[2], Michael Hanke[4], Nikolaus Kriegeskorte[5], Michael P. Milham[6], Russell A. Poldrack[7], Jean-Baptiste Poline[8], Erika Proal[9], Bertrand Thirion[10], David C. Van Essen[11], Tonya White[12], B.T. Thomas Yeo[13]

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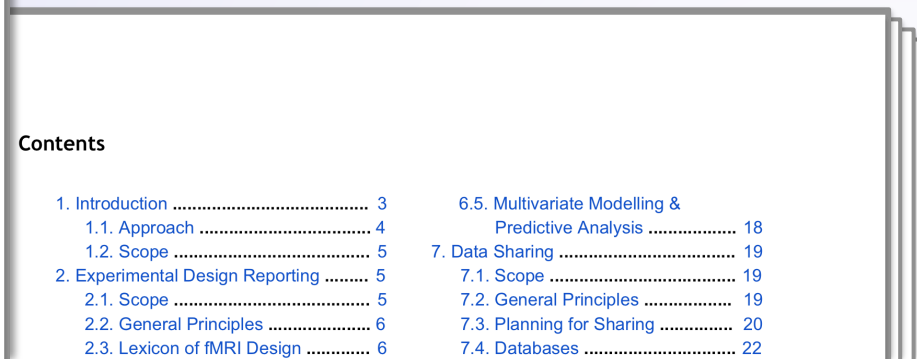


Contents

COBIDAS Structure: 7 Key Areas

Experimental Design Reporting

Subject counts. Inclusion criteria and descriptive statistics. Ethical considerations. Design specifications. Task specification. Power analysis. Behavioral performance.

Acquisition Reporting

Subject preparation. MRI system description. MRI acquisition. Preliminary quality control.

Preprocessing Reporting

General. Temporal/Dynamic. fMRI. Diffusion. Perfusion.

Statistical Modeling & Inference

Mass univariate analyses. Functional connectivity. Multivariate modeling & predictive analysis.

Results Reporting

Mass univariate analysis. Functional connectivity.

Data Sharing

Define data sharing plan early. Database for organized data.

Reproducibility

Documentation. Archiving. Citation.

Reporting items: Experimental Design

Table D.1. Experimental Design Reporting

Aspect	Notes	Mandatory
Number of subjects	*Elaborate each by group if have more than one group.*	
Subjects approached		N
Subjects consented		N
Subjects refused to participate	Provide reasons.	N
Subjects excluded	Subjects excluded after consenting but before data acquisition; provide reasons.	N
Subjects participated and analyzed	Provide the number of subjects scanned, number excluded after acquisition, and the number included in the data analysis. If they differ, note the number of subjects in each particular analysis.	Y
Inclusion criteria and descriptive statistics	*Elaborate each by group if have more than one group.*	
Age	Mean, standard deviation and range.	Y
Sex	Absolute counts or relative frequencies.	Y
Race & ethnicity	Per guidelines of NIH or other relevant agency.	N
Education, SES	Education is essential for studies comparing patient and control groups; complete SES reporting less important for single-group studies, but still useful. Specify measurement instrument used; may be parental SES and education if study has minors.	Y
IQ	Specify measurement instrument used.	N

Discrete , atomic items

Reporting items: Experimental Design

Handedness	Absolute or relative frequencies; basis of handedness-attribution (self-report, EHI, other tests). (Important for fMRI, may be less important for structural studies.)	Y
Exclusion criteria	Describe any screening criteria, including those applied to “normal” sample such as MRI exclusion criteria.	Y
Clinical criteria	Detail the area of recruitment (in- vs. outpatient setting, community hospital vs. tertiary referral center etc.) as well as whether patients were currently in treatment.	Y
Clinical instruments	Describe the instruments used to obtain the diagnosis and provide tests of intra- or inter-rater reliability. Clarify whether a “clinical diagnosis” or “inventory diagnosis” was used (if applicable). State the diagnostic system (ICD, DSM etc) that was used.	Y
Matching strategy	If applicable.	Y
Population & recruitment strategy	Population from which subjects were drawn, and how and where recruitment took place, e.g., schools, clinics, etc. If possible note if subjects are research naïve or have participated in other studies before.	Y
Subject scanning order	With multiple groups, information on ordering and counterbalancing over time; especially report relative to scanner changes/upgrades. (Ideally, use randomized or interleaved order to avoid bias due to scanner changes/upgrades.)	Y
Neurocognitive measures	All measures collected on subjects should be described and reported.	Y
Ethical considerations		
Ethical approval	Describe approval given, including the particular institutional review board, medical ethics committee or equivalent that granted the approval. When data is shared, describe the ethics/institutional approvals required from either the author (source) or recipient.	Y
Informed consent	Record whether subjects provided informed consent or, if applicable, informed assent.	Y

Elaborated, multifaceted items

Reporting items: Experimental Design

Design specifications		
Design type	Task or resting state. Event-related or block design. (See body text for usage of 'block design' terminology.)	Y
Condition & stimuli	Clearly describe each condition and the stimuli used. Be sure to completely describe baseline (e.g. blank white/black screen, presence of fixation cross, or any other text), especially for resting-state studies. When possible provide images or screen snapshots of the stimuli.	Y
Number of blocks, trials or experimental units	Specify per session, and if differing by subject, summary statistics (mean, range and/or standard deviation) of such counts.	Y
Timing and duration	Length of each trial or block (both, if trials are blocked), and interval between trials. Provide the timing structure of the events in the task, whether a random/jittered pattern or a regular arrangement; any jittering of block onsets.	Y
Length of the experiment	Describe the total length of the scanning session, as well as the duration of each run. (Important to assess subject fatigue.)	Y
Design optimization	Whether design was optimized for efficiency, and how.	Y
Presentation software	Name software, version and operating system on which the stimulus presentation was run. When possible, provide code used to drive experiment.	Y
Task specification		
Condition	Enumerate the conditions and fully describe and reference each. Consider using a shorthand name, e.g. AUDSTIM, VISSTIM, to refer to each condition, to clarify the distinction between a specific modeled effect and a psychological construct. Naming should reflect the distinction between instruction periods and actual stimuli, and between single parameters and contrasts of parameters.	Y
Instructions	Specify the instructions given to subjects for each condition (ideally the exact text in supplement or appendix). For resting-state, be sure to indicate eyes-closed,	Y

Reporting items: Experimental Design

	eyes-open, any fixation. Describe if the subjects received any rewards during the task, and state if there was a familiarization / training inside or outside the scanner.	
Stimuli	Specifics of stimuli used in each run. For example, the unique number of stimuli used, and whether/how stimuli were repeated over trials or conditions.	Y
Randomization	Describe block or event ordering as deterministic, or report manner of randomization, in terms of order and timing. If pseudo-randomized, i.e. under constraints, describe how and the criteria used to constrain the orders/timings.	Y
Stimulus presentation & response collection.	Specify the presentation hardware (e.g. back projection, in-room display, goggles, etc), and the response systems (e.g. button boxes, eye tracking, physiology). Note how equipment was synched to the scanner (e.g. scanner TTL, or manual sync.)	Y
Run order	Order in which tasks runs are conducted in the scanner.	Y
Power analysis		
Outcome	Specify the type of outcome used as the basis of power computations, e.g. signal in a pre-specified ROI, or whole image voxelwise (or cluster-wise, peak-wise, etc.).	Y
Power parameters	Specify ● Effect size (or effect magnitude and standard deviation separately). ● Source of predicted effect size (previous literature with citation; pilot data with description, etc). ● Significance level (e.g. uncorrected alpha 0.05 for an ROI, or FWE-corrected significance ● Target power (typically 80%). ● Any other parameters set (e.g., for spatial methods a brain volume and smoothness may be needed to be specified).	Y

Reporting items: Experimental Design

Behavioral performance		
Variables recorded	State number of type of variables recorded (e.g. correct button press, response time).	Y
Summary statistics	Summaries of behavior sufficient to establish that subjects were performing the task as expected. For example, correct response rates and/or response times, summarized over subjects (e.g. mean, range and/or standard deviation).	Y

- Just one area, compare with… CONSORT

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	
	2b	Specific objectives or hypotheses	
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	
	4b	Settings and locations where the data were collected	

Reporting items: Experimental Design

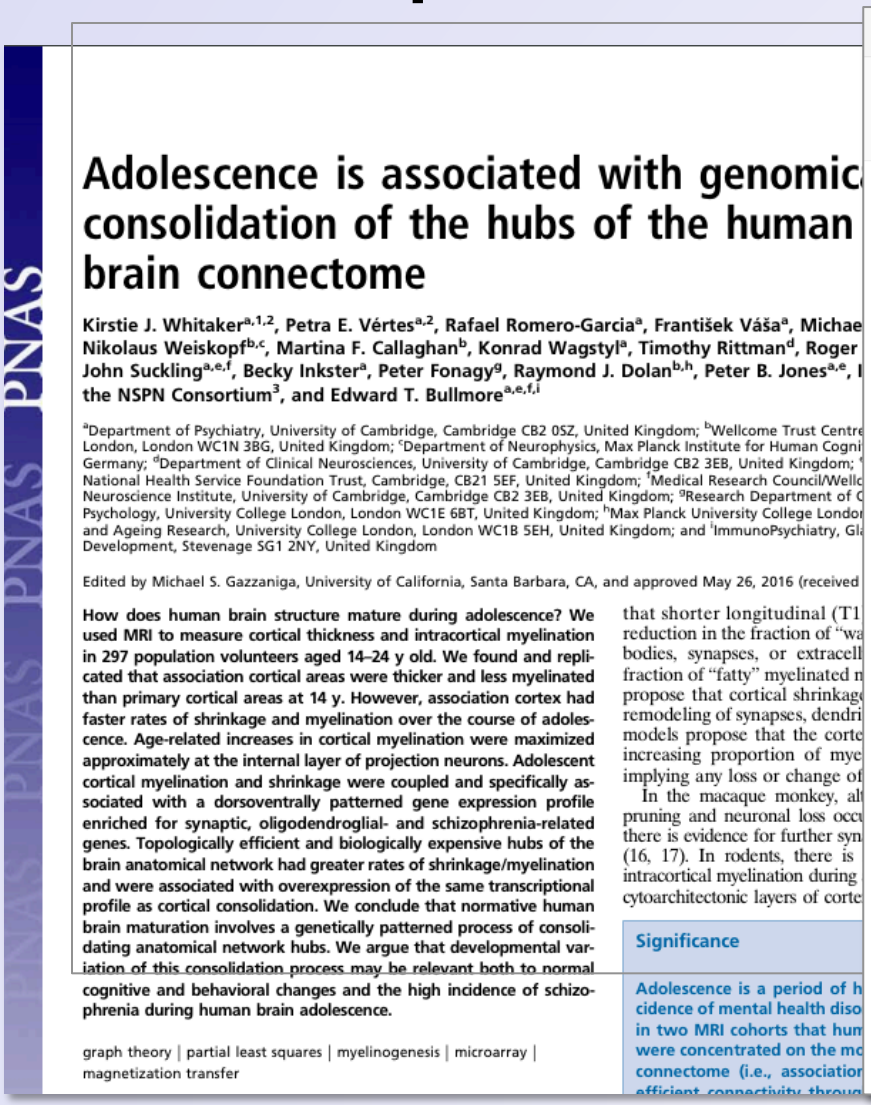
Behavioral performance		
Variables recorded	State number of type of variables recorded (e.g. correct button press, response time).	Y
Summary statistics	Summaries of behavior sufficient to establish that subjects were performing the task as expected. For example, correct response rates and/or response times, summarized over subjects (e.g. mean, range and/or standard deviation).	Y

- Just one area, compare with… Nat. Neuro.

Statistics and general methods

1. Is there a justification of the sample size? If so, how was it justified? Where (section, paragraph #)? Even if no sample size calculation was performed, authors should report why the sample size is adequate to measure their effect size.	We chose the sample size based on literatures in the field.
2. Are statistical tests justified as appropriate for every figure? Where (section, paragraph #)?	The statistics were used based on the properties of the data points, and described in individual figure legends
a. If there is a section summarizing the statistical methods in the methods, is the statistical test for each experiment clearly defined?	Yes, we summarized in the final paragraph of the methods. each statistical test is defined in each fig legend.

Total Transparency: Computational Reproducibility



Adolescence is associated with genomic consolidation of the hubs of the human brain connectome

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How does human brain structure mature during adolescence? We used MRI to measure cortical thickness and intracortical myelination in 297 population volunteers aged 14–24 y old. We found and replicated that association cortical areas were thicker and less myelinated than primary cortical areas at 14 y. However, association cortex had faster rates of shrinkage and myelination over the course of adolescence. Age-related increases in cortical myelination were maximized approximately at the internal layer of projection neurons. Adolescent cortical myelination and shrinkage were coupled and specifically associated with a dorsoventrally patterned gene expression profile enriched for synaptic, oligodendroglial- and schizophrenia-related genes. Topologically efficient and biologically expensive hubs of the brain anatomical network had greater rates of shrinkage/myelination and were associated with overexpression of the same transcriptional profile as cortical consolidation. We conclude that normative human brain maturation involves a genetically patterned process of consolidating anatomical network hubs. We argue that developmental variation of this consolidation process may be relevant both to normal cognitive and behavioral changes and the high incidence of schizophrenia during human brain adolescence.

graph theory | partial least squares | myelinogenesis | microarray | magnetization transfer

that shorter longitudinal (T1
reduction in the fraction of "wa
bodies, synapses, or extracell
fraction of "fatty" myelinated n
propose that cortical shrinkag
remodeling of synapses, dendri
models propose that the corte
increasing proportion of mye
implying any loss or change of
In the macaque monkey, al
pruning and neuronal loss occu
there is evidence for further syn
(16, 17). In rodents, there is
intracortical myelination during
cytoarchitectonic layers of corte

Significance

Adolescence is a period of h
cidence of mental health diso
in two MRI cohorts that hum
were concentrated on the mo
connectome (i.e., associatio
efficient connectivity throug

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KirstieJane / NSPN_WhitakerVertes_PNAS2016 Watch 2 Star 6 Fork 2

Code Issues 1 Pull requests 1 Projects 0 Wiki Pulse Graphs

Data and analysis code to reproduce the NSPN Manuscript "Adolescence is associated with genomically patterned consolidation of the hubs of the human brain connectome". http://kirstiejane.github.io/NSPN_WhitakerVertes_PNAS2016

29 commits 4 branches 1 release 1 contributor MIT

Branch: master New pull request Create new file Upload files Find file Clone or download

KirstieJane Updated help text ... Latest commit 0c049cd 6 days ago

CT_MT_ANALYSES	added RESULTS directory	4 months ago
DATA	added DATA directory	4 months ago
FS_SUBJECTS/fsaverageSubP	added FS_SUBJECTS directory	4 months ago
PRESENTATIONS	ah haaa - I needed to say the cells were slides	a month ago
SCRIPTS	Added two new functions: create_residuals_df and create_corrmat	7 days ago
SUPPLEMENTAL_FILES	Added supplementary files	4 months ago
WRAPPERS	Updated help text	6 days ago
.gitignore		
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brain

tl;dr

If you
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Branch: master NSPN_WhitakerVertes_PNAS2016 / NSPN_CorticalMyelination_AnalysisWrapper.py Find f

KirstieJane added analysis wrapper 55

1 contributor

318 lines (264 sloc) 15.5 KB Raw Blame History

```
#!/usr/bin/env python

'''
This is the analyses wrapper for the NSPN_CorticalMyelination analyses that
are reported in Adolescent Consolidation of Assocation Cortical Hubs of the
Human Brain Connectome.

Created by Kirstie Whitaker in October 2015
Contact kw401@cam.ac.uk
'''

#==============================================================================
# IMPORTS
#==============================================================================
import itertools as it
```

Yes, the sky is falling.

- Many reasons to worry about validity of scientific literature
- Researchers need to…
  - Do power calculations
  - Disclose methods & findings transparently
  - Pre-register your study protocol and analysis plan
  - Make study materials and data available
  - Work collaboratively to increase power and replicate findings
    - Meta-Analyses