Meta-analytic approaches to mapping the brain, its functions and connectivity

Simon Eickhoff

Institut für Neurowissenschaften und Medizin (INM-1)

Institut für klinische Neurowissenschaften

HEINRICH HEINE UNIVERSITY DÜSSELDORF
Background

Why meta-analytic approaches?
Limitation of neuroimaging data

Small samples
Compred to other fields of cognitive and social science and particularly to clinical research

Indirect measures of neuronal activity
Reliability is limited by biological, technical and methodological confounds

Publication of isolated findings
Due to logistic expenses, additional experiments for confirmation and extension are rare

Generalisation of context-specific findings
Inference on brain function and pathomechanisms is based on a specific observed difference between two conditions
Advantages of neuroimagigig data

There are many studies

Recent estimate
14,000 fMRT and PET Paper
>1200 Articles on Schizophrenia, Depression und Autism

All report standardised results!

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Derrfuss & Mar 2009
Image based meta analyses

Mega-analyses
jointly analyze the raw data of all experiments

Multi-Study Conjunctions
Overlap between significant effects

Third-level analyses
Statistical test on the between-experiment effects

Compilation of original data rarely feasible, usually accompanied with strong biases

Coordinate based meta-analyses

Based on published maxima-coordinates
Sparse representation of results
May integrate the entire literature
The “where” approach
Meta-Analyses
Activation likelihood estimation (ALE)

189 neuroimaging experiments on working memory

Location of activation foci

Where do these foci converge?
Activation likelihood estimation (ALE)

The reported coordinates are not treated as points but centres of probability distributions.

The “true” location of each reported activation is modelled by a 3D Gaussian.

Empirical model of spatial uncertainty associated with neuroimaging data

FWHM
Activation likelihood estimation (ALE)

ALE defined by the union over all experiments

Which of these values are significant?

Permutation procedure testing null-hypothesis of random spatial association

Eickhoff et al., Hum Brain Mapp 2009
Eickhoff et al., Neuroimage 2012
Meta-analytic contrasts

Where is the convergence for set A higher than for set B?
Is A more likely to result in activation at this voxel than B?

n-back vs. Sternberg

The choice of task may bias your results!

Rottschy et al., Neuroimage 2012
The “what” approach

Functional characterization
The problem of functional inference

- Visual search
  - Manjaly 2003

- Motor imagery
  - Binkofski 2000

- Action observation
  - Vogt 2007

- Mental Algebra
  - Wu 2009

- Lexical decisions
  - Heim 2006

- Spatial mapping
  - Grol 2007
The BrainMap database

BrainMap Paradigm Classes

- Action Observation
- Acupuncture
- Anti-Saccades
- Braille Reading
- Breath-Holding
- Classical Conditioning
- Counting/Calculation
- Cued Explicit Recognition
- Deception Task
- Deductive Reasoning
- Delayed Match to Sample
- Divided Auditory Attention
- Drawing
- Eating
- Encoding
- Episodic Recall
- Face Monitor/Discrimination
- Film Viewing
- Finger Tapping
- Fixation
- Flanker Task
- Flashing Checkerboard
- Flexion/Extension
- Free Word List Recall
- Go/No-Go
- Grasping
- Imagined Movement
- Imagined Objects/Scenes
- Isometric Force
- Mental Rotation
- Micturition Task
- Music Comprehension/Production n-back
- Naming (Covert)
- Naming (Overt)
- Non-Painful Electrical Stimulation
- Non-Painful Thermal Stimulation
- Oddball Discrimination
- Olfactory Monitor/Discrimination
- Orthographic Discrimination
- Pain Monitor/Discrimination
- Paired Associate Recall
- Passive Listening
- Passive Viewing
- Phonological Discrimination
- Pitch Monitor/Discrimination
- Pointing
- Posner Task
- Reading (Covert)
- Reading (Overt)
- Recitation/Repetition (Covert)
- Recitation/Repetition (Overt)
- Rest
- Reward Task
- Saccades
- Semantic Discrimination
- Sequence Recall/Learning
- Simon Task
- Spatial/Location Discrimination
- Sternberg Task
- Stroop Task
- Syntactic Discrimination
- Tactile Monitor/Discrimination
- Task Switching
- Theory of Mind Task
- Tone Monitor/Discrimination
- Transcranial Magnetic Stimulation
- Vibrotactile Monitor/Discrimination
- Visual Distraction/Visual Attention
- Visual Pursuit/Tracking
- Wisconsin Card Sorting Test
- Word Generation (Covert)
- Word Generation (Overt)
- Word Stem Completion (Covert)
- Word Stem Completion (Overt)
- Writing

BrainMap Behavioral Domains

- Action
  - Execution
  - Speech
  - Imagination
  - Inhibition
  - Motor Learning
  - Observation
  - Preparation
  - Rest
- Cognition
  - Attention
  - Language
  - Orthography
  - Phonology
  - Semantics
  - Speech
  - Syntax
  - Memory
  - Explicit
  - Implicit
  - Working
  - Music
  - Reasoning
  - Soma
  - Space
  - Time
- Perception
  - Audition
  - Gustation
  - Olfaction
  - Somesthesia
  - Pain
  - Vision
  - Color
  - Motion
  - Shape
- Pharmacology
  - Alcohol
  - Amphetamines
  - Caffeine
  - Capsaicin
  - Cocaine
  - Ketamine
  - Marijuana
  - Nicotine
  - NSAIDs
  - Psychiatric Medications
    - Anti-Depressants
    - Anti-Psychotics
    - Steroids and Hormones
- Emotion
  - Anger
  - Anxiety
  - Disgust
  - Fear
  - Happiness
  - Humor
  - Sadness
Forward inference

How likely is a particular type of experiments to activate this region?

Identify all experiments in BrainMap that activate in the ROI

222 Experiments in BrainMap (2944 subjects, 3445 foci)

Proportion of experiments from domain X activating ROI vs. a priori probability of activating ROI

Were experiments of a given domain more likely to activate this ROI than chance? Is the number of activations higher than expected?
Reverse inference

How likely was a particular domain present when the ROI activates?

Inference on domain-specificity

Decoding of functional recruitment

Depends on forward probability and base rate of the domain

$$P(\text{Domain|Activation}) = \frac{P(\text{Activation|Domain}) \times P(\text{Domain})}{P(\text{Activation})}$$

Dependent on the a priori probability for the given domain
168 experiments reported activation in left M1

Probability for experiments using this task vs. probability of any experiment in BrainMap

For activating this ROI

Were experiments using a particular task more likely to activate this ROI than chance?

Forward inference

\[ P(\text{Activation} \mid \text{Task}) \]

Probability for paradigms

\[ P(\text{Activation} \mid \text{Paradigm}) \]

For activating this ROI

Action.Execution

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Likelihood ratio
168 experiments reported activation in left M1

**Reverse inference**

\[ P(\text{Task} \mid \text{Activation}) \]

\[ P(\text{Domain} \mid \text{Activation}) \]

\[ P(\text{Paradigm} \mid \text{Activation}) \]

Depends on forward probability and baserate of the task.

What was the chance that a particular task is present given activation in that ROI?
The “with whom” approach
Meta-Analytic Connectivity Modelling
The ~2431 activation foci reported in the 168 experiments activating left M1

Experiments are only identified by the fact that they feature activation in the seed
Meta-analytic connectivity modeling

Activation likelihood estimation for each voxel based on uncertainty associated with each focus

Probabilistic representation of co-activations

How likely is it that experiment activating the seed region also activates any other voxel
 Activation likelihood estimation for each voxel based on uncertainty associated with each focus

Probabilistic representation of co-activations

How likely is it that experiment activating the seed region also activates any other voxel
Co-activation of left M1

Meta-Analysis on finger tapping (73 experiments)

fMRI study on finger tapping (21 subjects)
Fusion
Meta-analytic Brain Mapping
Ispi- vs. contralateral responses

Random vs. predictable responses

Probabilistic learning

Motor WM: 6 vs 4 items

Jakobs, Wang, Dafotakis, Grefkes, Zilles, Eickhoff
NeuroImage 2009

Eickhoff, Pomjanski, Jakobs, Zilles, Langner
Cerebral Cortex 2011

Kellermann, Sternkopf, Schneider, Habel, Turetsky, Zilles, Eickhoff
Soc Cogn Affect Neurosci 2012
**Co-activation based parcellation**

Cortical regions show distinct connectivity-profiles

Computation of each voxel’s interactions

Clustering based on these profiles

Eickhoff, Bzdok, Laird, Roski, Caspers, Zilles, Fox; *Neuroimage* 2011

**BrainMap Database**

- 12,000 Neuroimaging experiments
- Coordinates for local maxima
- Meta-Data on tasks etc

**Approach (per voxel)**

Identification of all experiments featuring activation at that voxel

Computation of across-experiment convergence of co-activations accommodating spatial uncertainty

Eickhoff, Bzdok, Laird, Kurth, Fox; *Neuroimage* 2012

Cieslik, Zilles, Caspers, Roski, Kellermann, Jakobs, Langner, Laird, Fox, Eickhoff, *Cerebral Cortex. ePub* 2012
Co-activation based parcellation

Whole-brain connectivity per voxel

Computation of cross-correlation

Similarities in the co-activation patterns

Identify groups via multivariate cluster-analyses

Eickhoff, Bzdok, Laird, Roski, Caspers, Zilles, Fox; Neuroimage 2011
Differential co-activations and RS-connectivity

Cieslik, Zilles, Caspers, Roski, Kellermann, Jakobs, Langner, Laird, Fox, Eickhoff
Cerebral Cortex. ePub 2012

Action, Working memory
Attention, Inhibition, Conflict

Random vs. predictable responses

Motor WM: 6 vs 4 items

Ipsi- vs. Contralateral responses

Probabilistic learning

Functional decoding using the BrainMap meta-data

Cieslik, Zilles, Kurth, Eickhoff
J Neurophysiol 2010

Eickhoff, Pomjanski, Jakobs, Zilles, Langner
Cerebral Cortex 2011
The present and future of MACM-CBP

Mapping cortical segregation, connectivity and functions

Quantitative evaluation of each parameter

Clos et al., Neuroimage in revision
Insight from each individual neuroimaging study is limited by inherent drawbacks.

High degree of standardization pooling of results allows inference on converging evidence.

Coordinate-based meta-analyses provide a statistical tool for the objective integration of findings.

Database driven functional decoding allows objective forward and reverse inference.

Meta-analytic connectivity modelling offers a new approach to task-based functional connectivity.

Co-activation based parcellation enables to identify cortical modules in a data-driven fashion.