

Meta-Analysis and Combining Information in fMRI

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Outline

- Cochran's Model for One-Way ANOVA
- Likelihood, Profile Likelihood, and ML
- Bayesian Hierarchical Model
- First Example: Sleep Onset Latency and Melatonin
- Multi-Subject fMRI: Spatial Visual Cueing
- fMRI Meta-Analysis
 - The GingerALE Approach
 - Comments and Limitations
 - Some Thoughts on Improvements

Combining Experiments

- Cochran, W.G. (1937). “Problems arising in the analysis of s series of similar experiments”

- Model:

$$x_{ij} = \mu + b_i + \epsilon_{ij}$$

$$b_i \sim N(0, \sigma^2) \quad \epsilon_{ij} \sim N(0, \sigma_i^2)$$

- Experiments indexed by $i = 1, \dots, p$; measurements indexed by $j = 1, \dots, n_i$.
- Heteroscedastic one-way random-effects ANOVA.

Max. Likelihood: Cochran's Publications on Combining Experiments

- (1937), "Problems Arising in the Analysis of a Series of Similar Experiments".
- (1938), "The Analysis of Groups of Experiments", (with F. Yates).
- (1954), "The Combination of Estimates From Different Experiments".
- (1980), "Summarizing the Results of a Series of Experiments".
- (1981), "Estimators for the One-Way Random Effects Model With Unequal Error Variances", (et. al., posthumous).

One-Way Heteroscedastic ANOVA

- Groups $i = 1, \dots, p$; measurements $j = 1, \dots, n_i$ of unknown quantity μ :

$$x_{ij} = \mu + b_i + e_{ij}$$

- Random group effect: $b_i \sim N(0, \sigma^2)$
- Unequal within-group errors: $e_{ij} \sim N(0, \sigma_i^2)$
- Standard errors: $\tau_i^2 \equiv \sigma_i^2/n_i$
- Sufficient statistics ($t_i^2 \equiv s_i^2/n_i$):

$$x_i = \sum_{j=1}^{n_i} x_{ij}/n_i \quad t_i^2 = \sum_{j=1}^{n_i} (x_{ij} - x_i)^2 / (n_i \nu_i)$$

$$x_i \sim N(\mu, \sigma^2 + \tau_i^2) \quad t_i^2 \sim \tau_i^2 \chi_{\nu_i}^2 / \nu_i$$

The Likelihood

Define weights

$$\gamma_i \equiv \frac{\sigma^2}{\sigma^2 + \tau_i^2}$$

The loglikelihood is

$$\begin{aligned} 2\ell &= \sum_{i=1}^p n_i \log \left(\frac{\gamma_i}{\sigma^2} \right) \\ &- \sum_{i=1}^p \frac{\gamma_i}{\sigma^2} \left[(x_i - \mu)^2 + \frac{\nu_i t_i^2}{1 - \gamma_i} \right] \\ &- \sum_{i=1}^p \nu_i \log(1 - \gamma_i) + K. \end{aligned}$$

ML Equations

Differentiate this with respect to parameters μ, σ^2 and $\gamma_i, i = 1, \dots, p$.

$$\mu = \frac{\sum_{i=1}^p \gamma_i x_i}{\sum_i \gamma_i} \quad \sigma^2 = \frac{\sum_{i=1}^p \gamma_i \left[(x_i - \mu)^2 + \frac{\nu_i t_i^2}{1 - \gamma_i} \right]}{\sum_{i=1}^p n_i}$$

$$\gamma_i^3 - (a_i + 2)\gamma_i^2 [(n_i + 1)a_i + (n_i - 1)b_i + 1] \gamma_i - n_i a_i = 0$$

$$a_i \equiv \frac{\sigma^2}{(x_i - \mu)^2} \quad b_i \equiv \frac{t_i^2}{(x_i - \mu)^2}$$

Bayesian Analysis With Between-Group Variability

- Profile likelihood analysis and Bayesian approach:

Vangel, M.G. and A.L. Rukhin (1999). “Maximum-Likelihood Analysis for Heteroscedastic One-Way Random Effects ANOVA in Interlaboratory Studies,” *Biometrics*, 55, 302-313.

- Modified REML:

Rukhin, A.L., B. Biggerstaff, and M.G. Vangel (2000). “Restricted Maximum Likelihood Estimation of a Common Mean and the Mandel-Paule Algorithm,” *Journal of Statistical Planning and Inference*, 83, No. 2, pp. 319-330.

- Modified ML; asymptotic confidence intervals:

Rukhin, A.L. and M.G. Vangel (1998). “Estimation of a Common Mean and Weighted Means Statistics,” *Journal of the American Statistical Association*, 93, 303-309.

Hierarchical Model With Noninformative Priors

$i = 1, \dots, p$ indexes subjects

$j = 1, \dots, n_i$ indexes measurements

$$p(x_{ij} | \delta_i, \sigma_i^2) = N(\delta_i, \sigma_i^2)$$

$$p(\sigma_i) \propto 1/\sigma_i$$

$$p(\delta_i | \mu, \sigma^2) = N(\mu, \sigma^2)$$

$$p(\mu) \propto 1$$

$$p(\sigma) \sim U(a, b)$$

Posterior given $\sigma = 0, p \geq 1$

Given $\sigma = 0$, then the posterior distribution of the consensus mean μ is proportional to a product of scaled t -densities:

$$p(\mu|\{x_{ij}\}|\sigma = 0) \propto \prod_{i=1}^p \frac{1}{t_i} T'_{n_i-1} \left(\frac{x_i - \mu}{t_i} \right)$$

The General Case: $\sigma \geq 0$

In general, $p(\mu|\sigma, \{x_{ij}\})$ is proportional to a *product* of the distributions of the random variables

$$U_i = x_i + \frac{s_i}{\sqrt{n_i}} T_{n_i-1} + \sigma Z,$$

where T_{n_i-1} is a t -distributed random variable with $n_i - 1$ degrees of freedom, Z is distributed $N(0, 1)$, and T_{n_i-1} and Z are independent.

A Useful Probability Density

Let T_ν and Z denote independent Student- t and standard normal random variables, and assume that $\psi \geq 0$ and $\nu > 0$. Then

$$U = T_\nu + Z\sqrt{\frac{\psi}{2}}$$

has density

$$f_\nu(u; \psi) \equiv \frac{1}{\Gamma_{\nu/2}\sqrt{\pi}} \int_0^\infty \frac{y^{(\nu+1)/2-1} e^{-y\left[1+\frac{u^2}{\psi y+\nu}\right]}}{\sqrt{\psi y + \nu}} dy.$$

Posterior of (μ, σ)

- Assume $\delta_i \sim N(\mu, \sigma^2)$, $\sigma \sim p(\sigma)$,
 $p(\mu) \propto 1$, $p(\sigma_i) \propto 1/\sigma_i$.
- Then the posterior of (μ, σ) is

$$p(\mu, \sigma | \{x_{ij}\}) \propto p(\sigma) \prod_{i=1}^p \frac{1}{t_i} f_{\nu_i} \left[\frac{x_i - \mu}{t_i}; \frac{2\sigma^2}{t_i^2} \right].$$

- The posterior of μ given $\sigma = 0$ is a product of scaled t -densities centered at the x_i , since

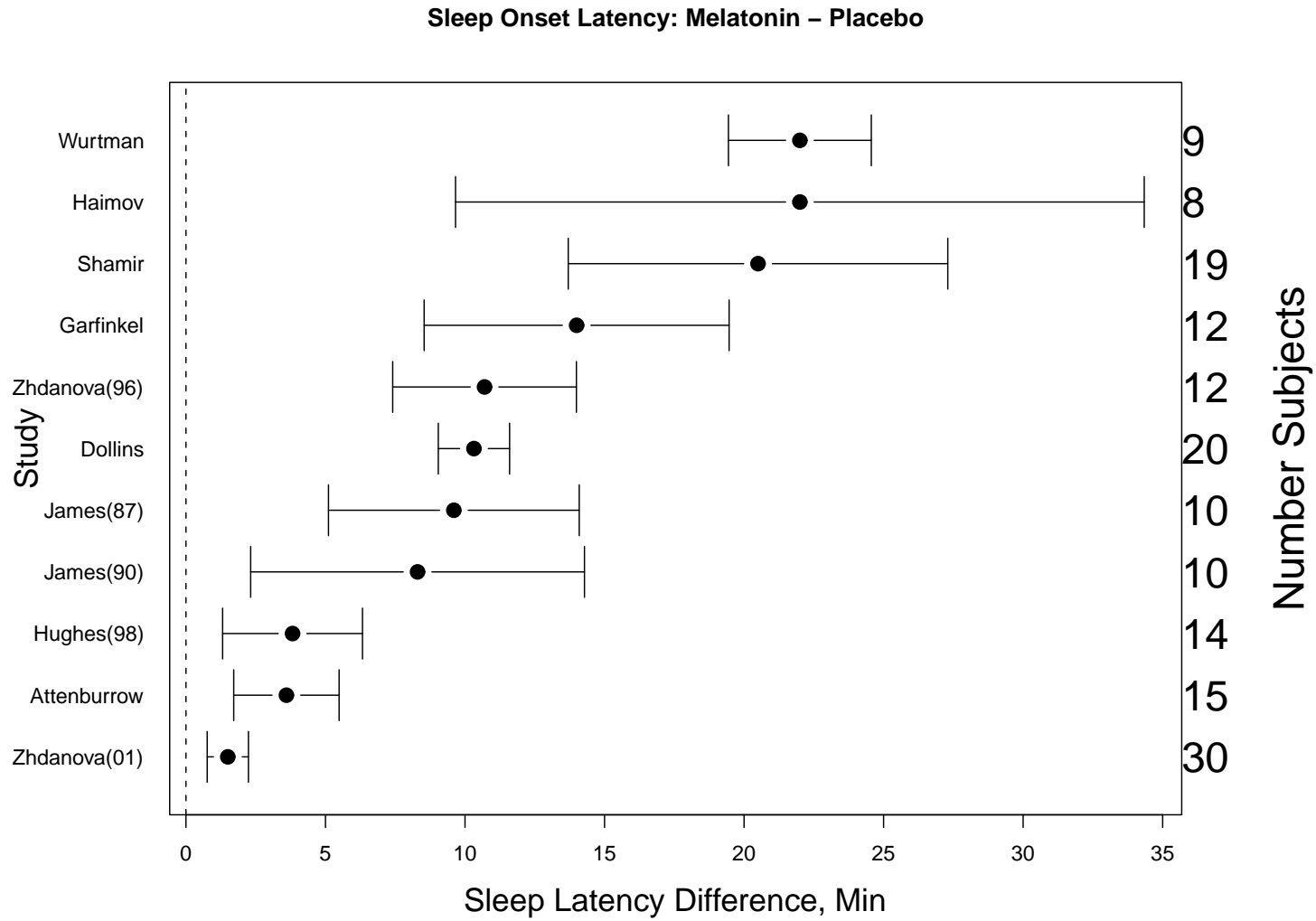
$$\frac{1}{t_i} f_{\nu_i} \left[\frac{x_i - \mu}{t_i}; 0 \right] = \frac{1}{t_i} T'_{\nu_i} \left(\frac{x_i - \mu}{t_i} \right).$$

- We will take $p(\sigma) = K$, a constant, though an arbitrary proper prior does not introduce additional difficulties.

First Example: Melatonin Meta-Analysis

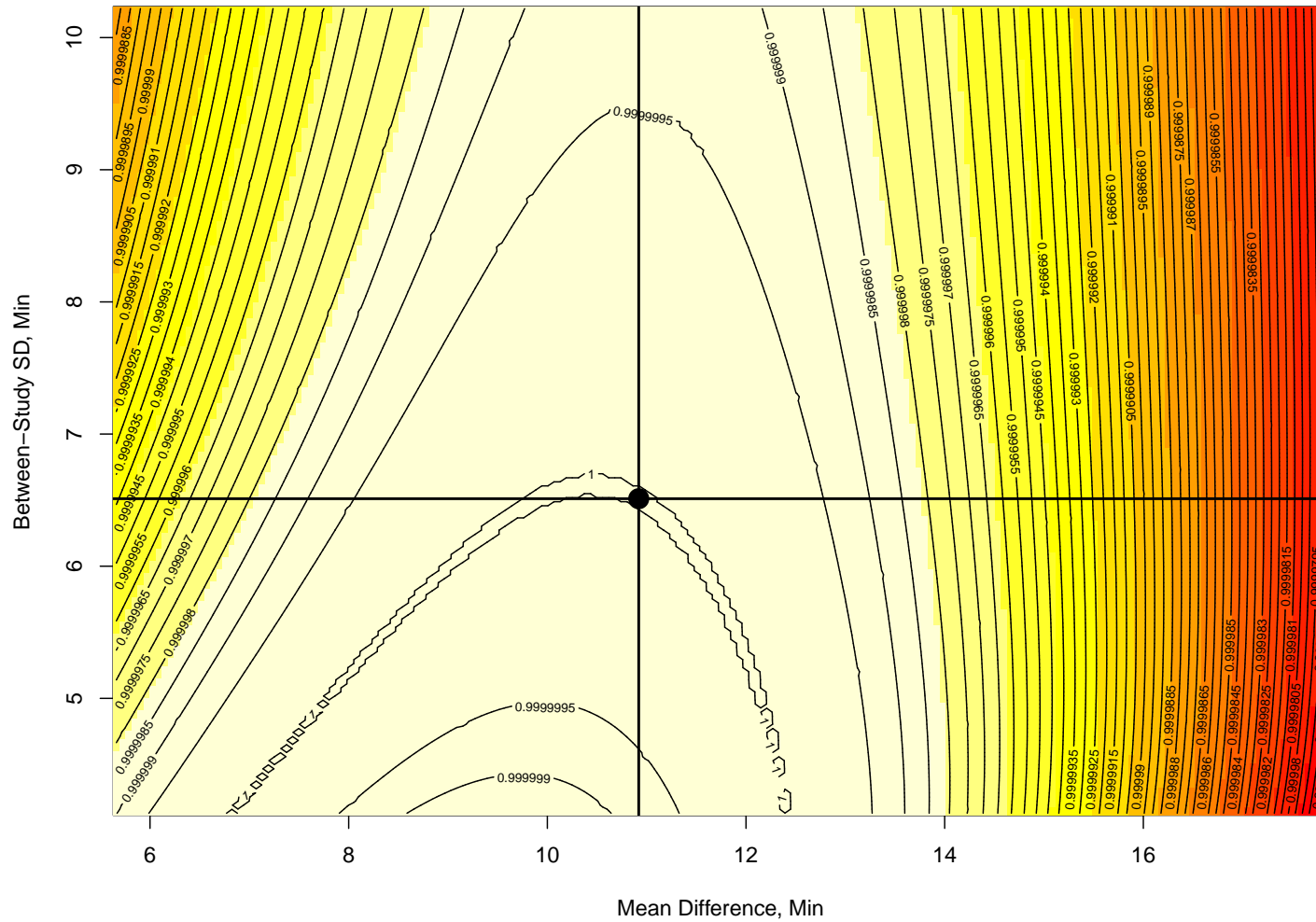
- Brzezinski et al. (2005). Effects of exogenous melatonin on sleep: a meta-analysis. *Sleep Medicine*, 9, 41-50.
- We focus on sleep onset latency
- Eleven blinded, randomized clinical trials , total of 159 subjects
- Each trial compared melatonin with placebo
- Each trial showed some decrease in onset latency

Sleep Onset Latency: 11 RCTs, 159 Subjects

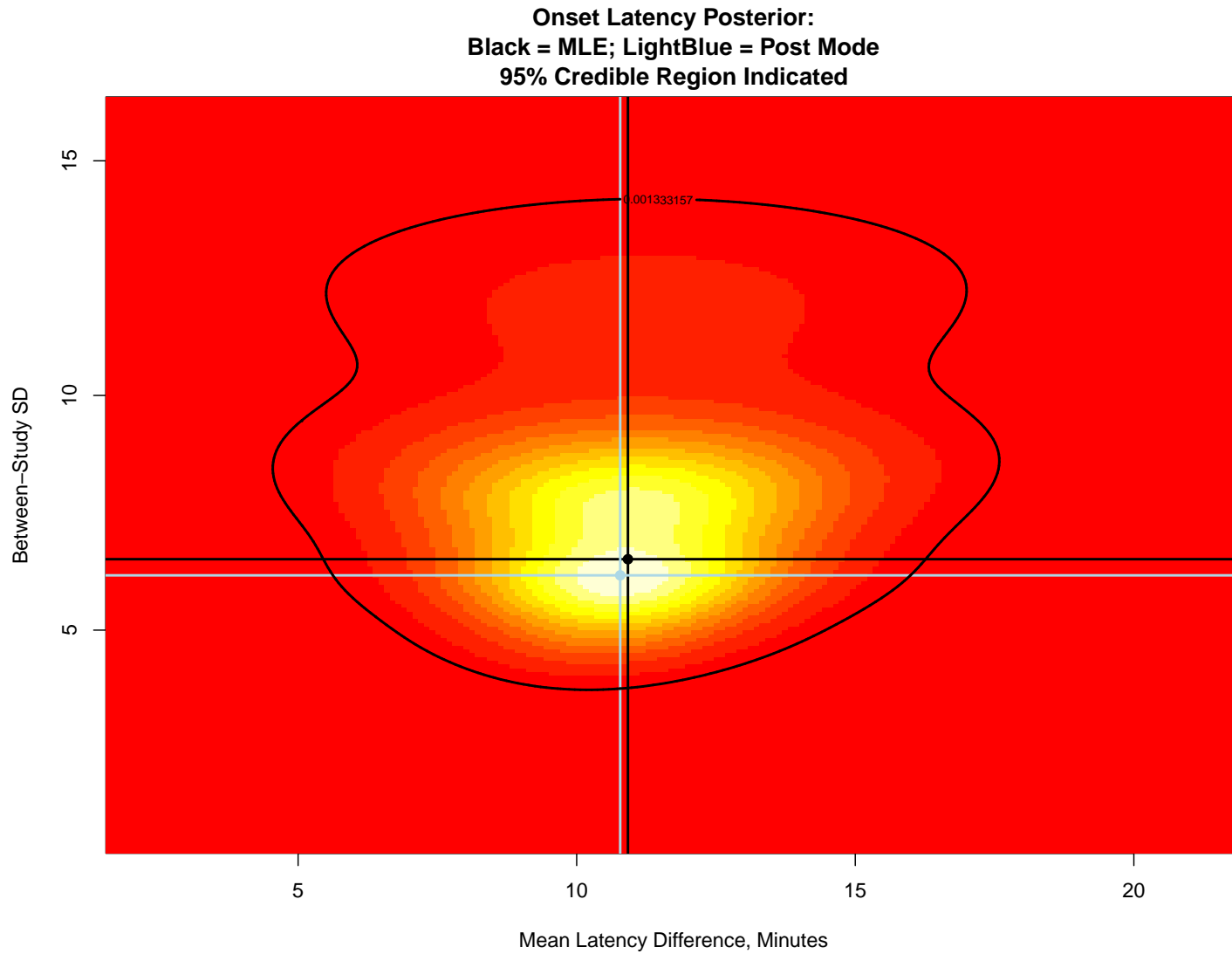


Sleep Onset Latency: Profile Likelihood

Likelihood Surface: Sleep Onset Latency
MLE Indicated

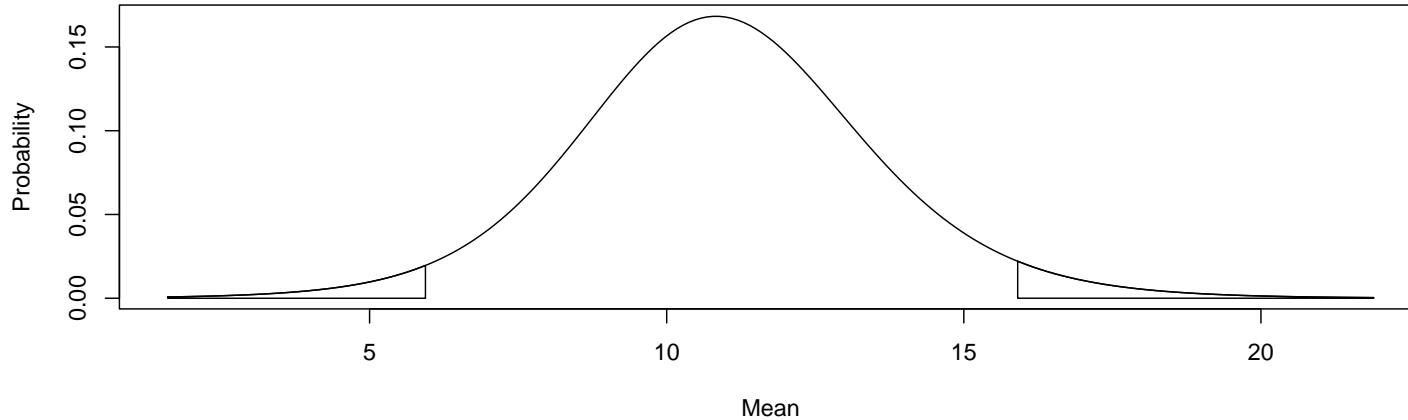


Sleep Onset Latency: Posterior Density



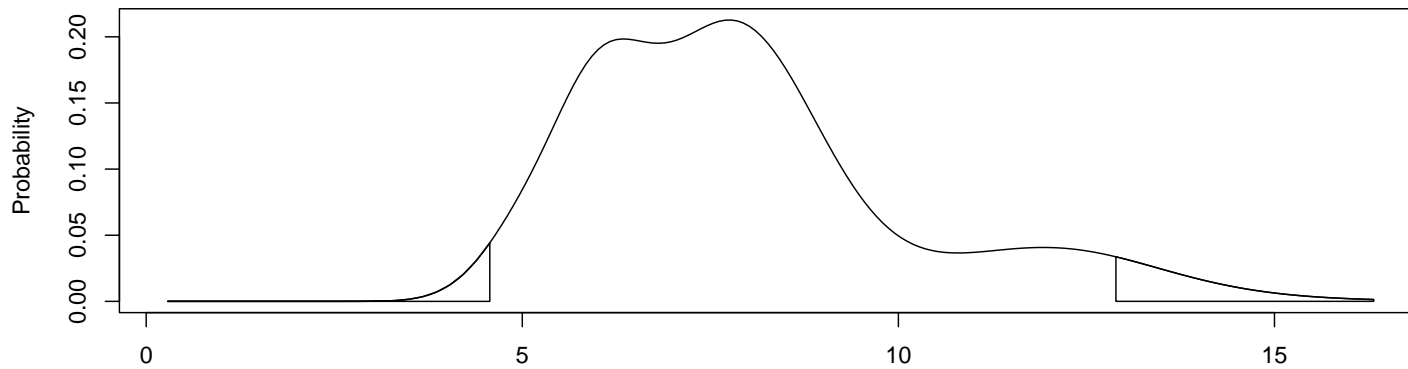
Sleep Onset Latency: Univariate Posteriors

**Marginal Posterior of Onset Latency With
95% HPD Probability Interval**



Post. mean = 10.968 Post. S.D. = 2.57 5.94 < mean < 15.906

**Marginal Posterior of Between Study S.D. With
95% Probability Interval**



Post. mean = 7.944 Post. S.D. = 2.242 4.568 < sigma < 12.892

Nature of fMRI Data

- Noninvasive technique based on a signal which indirectly measures oxygen consumption in the brain.
- Spatial resolution of the order of a few cubic mm.
- Temporal resolution of the order of a few seconds
- Brain is divided into thousands of volume elements called voxels.
- Times series of activation data are collected for each voxel.
- Typically linear models are fit to each time series, and contrasts of interest and their SEs are determined.
- fMRI activation is related to anatomy by structural MRIs on the subjects, which can be related to standard atlases (such as the Talairach atlas).

Example 2: Spatial Visual Cueing

Pollmann, S. and Morillo, M. (2003). “Left and Right Occipital Cortices Differ in Their Response to Spatial Cueing,” *NeuroImage*, 18, 273-283.

Neumann, J. and Lohmann, M. (2003). “Bayesian Second-Level Analysis of Functional Magnetic Resonance Images,” *NeuroImage*, 20, 1346-1355.

Bayesian Analysis of Neumann and Lohmann

- Fit a linear model to each voxel.
- Select a representative voxel in each region of interest from each subject.
- Obtain contrast estimate and standard error.
- Treat the contrast estimates as normal, standard errors as known, use Bayes theorem to get posterior of common mean μ .

Neumann and Lohmann (2003)

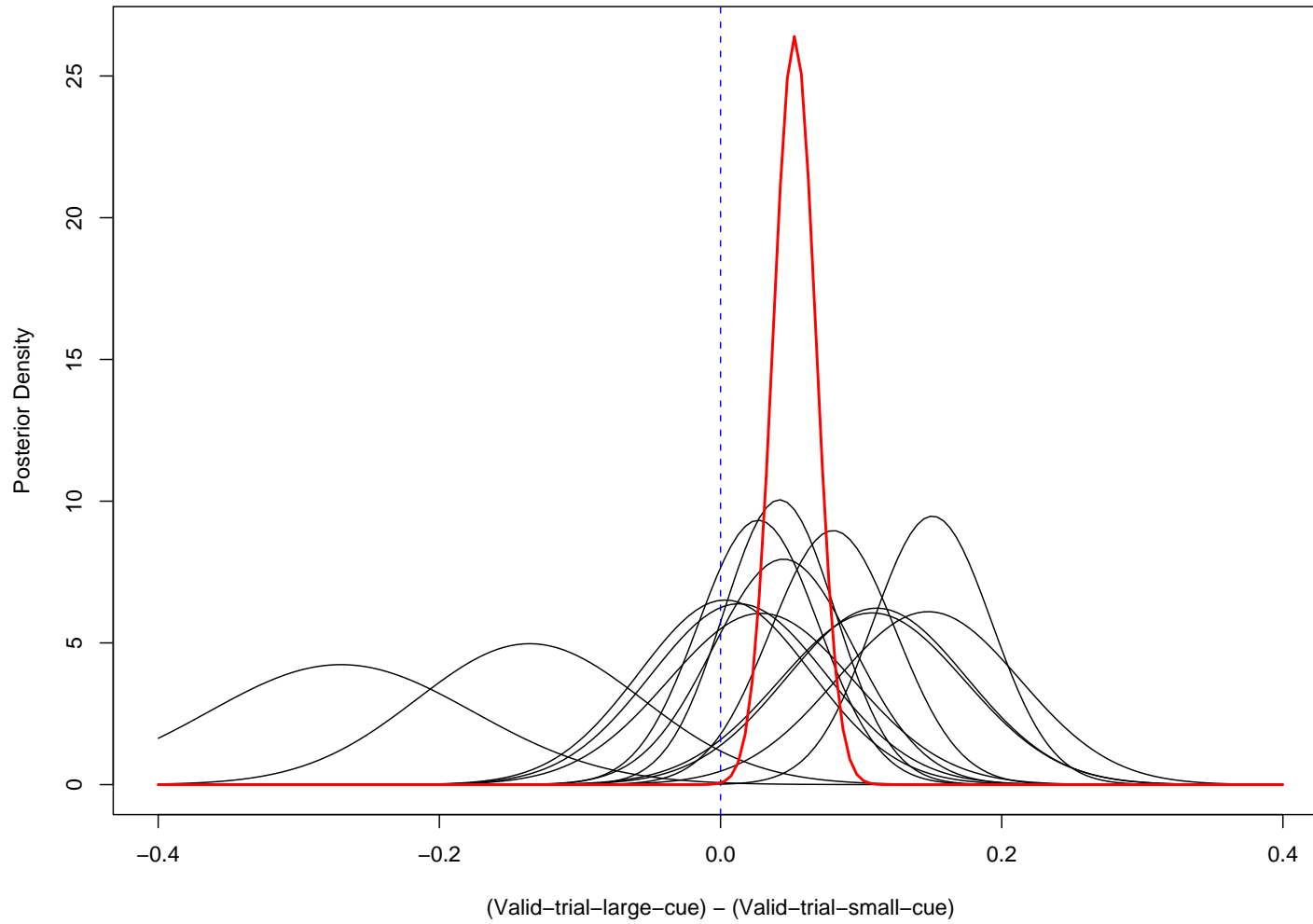
- Contrast estimates $c^T \hat{\beta}_i, i = 1, \dots, p.$
- Estimate μ using variance-weighted mean:

$$\hat{\mu} = \frac{\sum_{i=1}^p c^T \hat{\beta}_i / \tau_i^2}{\sum_{i=1}^p 1 / \tau_i^2} \quad \hat{\tau}^2 = \sum_{i=1}^p 1 / \tau_i^2.$$

- Not such a bad idea. Except –
 1. Standard errors τ_i assumed known (probably not too serious; the ν_i are usually large.)
 2. No between subject variability. *This* omission will make a big difference.

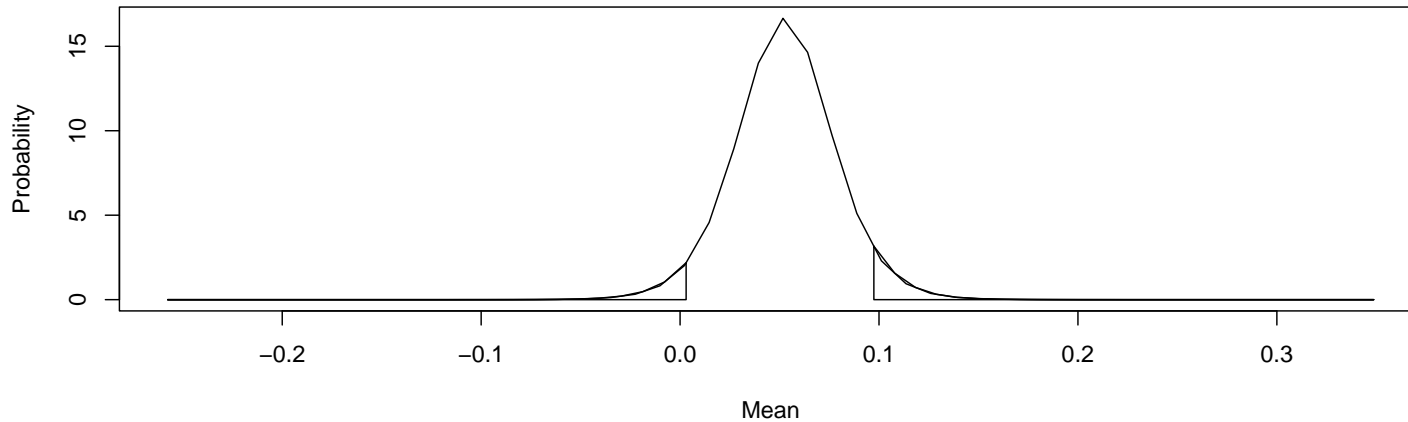
Neumann/Lhomann Model: *valid-small-cue* vs *valid-large-cue*

Neumann Region A Posterior: No Random Effect



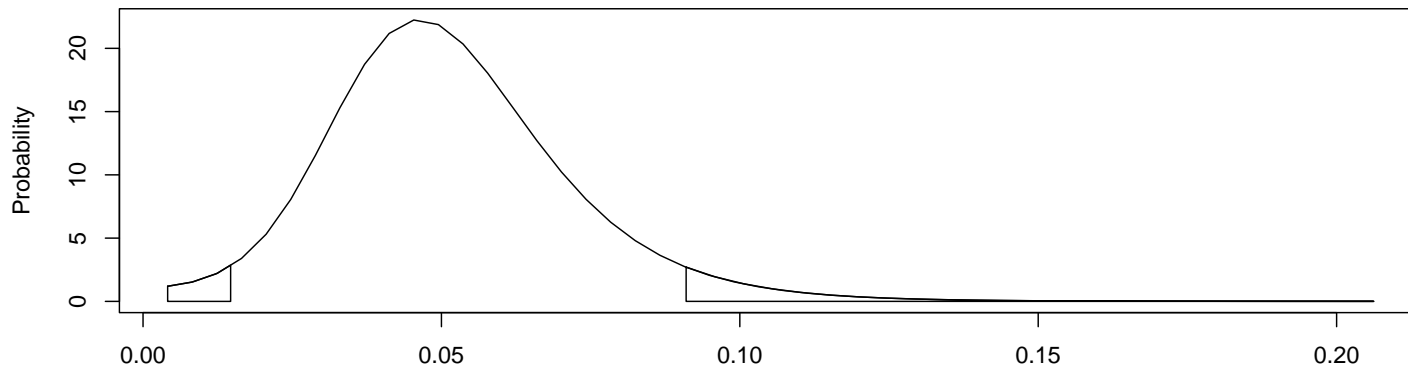
Proposed Model: *valid-small-cue* vs *valid-large-cue*

**Marginal Posterior of Mean With
95% HPD Probability Interval (Neumann-A)**



Post. mean = 0.053 Post. S.D. = 0.026 0.003 < mean < 0.097

**Marginal Posterior of Between-Sub. S.D. With
95% Probability Interval**



Post. mean = 0.052 Post. S.D. = 0.02 0.015 < sigma < 0.091

Comparison With Neumann and Lohmann

- Neuman and Lohmann: Posterior mean for μ : 0.052; standard deviation 0.015.
- Analysis with between-subject variability: Posterior mean for μ : 0.053; standard deviation 0.026.

BrainMap Database www.brainmap.org

- Activation foci from fMRI and PET studies
- Foci and meta-data from over 1000 publications.
- Indexed by experimental paradigm, region of interest, subject population, etc.
- Users can extract foci and add additional publications.

GingerALE Approach to fMRI Meta-Analysis

- Turkeltaub et al. (2002), Meta-analysis of the functional neuroanatomy of single-word reading: Method and validation, *Neuroimage*, 16, 785-780.
- “ALE” is an acronym for Activation Likelihood Estimation
- The data consist of N foci of activation

$$u_i = (x_i, y_i, z_i),$$

all in Talairach coordinates, taken from p fMRI (and/or PET) publications.

- Each focus corresponds to one of k contrasts, where $k \geq p$.
- The foci are modeled as independent isotropic Normal with mean u_i and standard deviation σ .

GingerALE: Continued

- Each focus u_i is thus modeled as Normal in each dimension.
- The SD σ is supplied by the user; 6mm is suggested.
- The probability that at least one focus lies within voxel j is approximated as

$$\hat{P}_j = 1 - \prod_{i=1}^N (1 - p_i \Delta V),$$

where ΔV is the voxel volume; p_i is the density for focus i .

- The hypothesis that the probability map is due to chance is tested by randomly relocating the voxels within the brain, many times.

GingerALE: Comments

- The approximation can, of course, be avoided by expressing the integrals of the densities over a voxel in terms of the normal CDF.
- By letting $\Delta V \rightarrow 0$, we derive

$$f_i(u) = \sum_{i=1}^N \phi\left(\frac{x - x_i}{\sigma}\right) \phi\left(\frac{y - y_i}{\sigma}\right) \phi\left(\frac{z - z_i}{\sigma}\right).$$

Integrating this function over a volume (such a sphere centered on a focus) gives the expected number of foci in that volume.

- Note that the Gaussians are centered at the data, not at unknown locations of foci to be estimated.

GingerALE: Critique

- Why perform a computer-intensive hypothesis test when the model is fully specified?
- No account is taken of between-study and within-study sources of variability.
- *All* of the uncertainty information in the maps which result after extensive computation and simulation come from a single user-supplied value for σ .
- (An attempt to address some of these limitations has been made in a recent paper by Eickhoff [*Human Brain Mapping* (2009)], which I found out about only very recently.)

An Approach to Improving on GingerALE

- (Work in Progress)
- Determine groups of homologous foci from each experiment, and model them using hierarchical modeling techniques, such as the one-way ANOVA approach discussed earlier.
- Explicitly model between-study, within-study spatial variability, and within-subject variability.
- For the most part, I restricted myself to the foci used in the Turkeltaub et al. metaanalysis. This caused difficulties which I'll discuss below.

Within-Study Variability: MIND DLPFC foci

- 21 healthy controls from the MIND multicenter study
- Each with one focus in DLPFC
- Used BA 10 (7-LH, 8-RH) to assess between-subject variability.
- Between-subject SDs:

Hemisphere	X	Y	Z
Left	3.5	5.3	6.7
Right	4.9	5.1	6.3

Turkeltaub: Brodmann Area 6

- 48 Turkeltaub foci in frontal lobes, of which too few overlapped with DLPFC regions from the MIND data.
- So I used the frontal region with the most foci
- Brodmann area 6, with 12 in the left hemisphere; 11 in the right
- Between-Study variability essentially zero.
- Within-Study SDs are

Hemisphere	X	Y	Z
Left	42.7	15.3	15.3
Right	50.2	8.1	8.1

Comments, Difficulties and Future Work

- Very large between-focus variance seems to suggest that BA6 is too large, and probably much of this variability is not noise but due to heterogeneity of function.
- Next step is to collect data on regions among many more publications in the database, and to try to make the regions small enough so that the spatial variation is due to between-study and within-study noise.
- Then I will apply the hierarchical modeling ideas discussed earlier.
- Eickhoff (2009) also needs to be digested and related to the proposed approach above.