Today

- HW 1: due February 7, 2 pm.
- Data preparation: reading and neuroscience study
- Generalized linear models: over-dispersion, examples
- In the News: a serendipitous experiment

Neuroscience – reading and resting state FMRI

"Short- and long- term effects of a novel on connectivity in the brain", Berns, G.S. et al. (2013) Brain Connectivity **3**, 590–600

Reading material

Each participant was subject to 19 consecutive days (July 18, 2011–August 5, 2011) of resting-state scans that consisted of a total appointment time of less than 30 min at the same time each day. The first 5 days and last 5 days were "wash-in" and "washout" sessions, respectively. Each of the middle 9 scans was preceded by reading approximately 1/9th of the novel (*Pompeii: A Novel*, by Robert Harris, Fawcett, 2003). This novel was chosen because it was based on true events but written as historical fiction and conveyed in a classic narrative arc (Freytag, 1900). During the "washin" and "washout" sessions, the participants did not perform any other tasks except for the resting-state scan (Fig. 1). For each of the other 9 days, the story days, the participants performed the resting-state scan after taking a quiz and self-report about the effect of the material presented in the portion of the novel that was assigned for the previous night and included a five-point rating scale of how arousing the reading was (see Supplementary Data for quizzes; Supplementary Data are available online at www.liebertpub.com/brain). Through repeated scans, each participant served as his or her own control to measure changes in resting-state connectivity after the consumption of the novel.

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Preprocessing

All of the preprocessing was performed using the 1000 Functional Connectomes Scripts available from NITRC (www.nitrc.org). The only modification to these scripts was the addition of an iterative loop to cycle through the 19days of data. The scripts performed the following preprocessing procedures using FSL (Analysis Group, FMRIB) and AFNI (NIMH). First, the anatomical image was deobliqued and reorientated to the coordinate space that is compatible with FSL. Next, the image was skull stripped.

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The resting-state functional images were preprocessed through a multi-step procedure. The images were deobliqued and reoriented similarly to the anatomical images. A mean functional image was computed to serve as a target for motion correction. Using 3dvolreg, the functional images were then aligned to the mean image using two-pass Fourier interpolation. To decrease edge artifacts from Fourier interpolation, a zero pad of four voxels was added around the edges and stripped off after motion correction. The images were then skull stripped to create a mask that was then applied to the motion-corrected data. To allow for full magnetization and settling on any startle responses from the onset of the scanning, the eighth volume was used for registration to the anatomical image. Spatial smoothing was performed using a 6-mm Gaussian kernel. Grand mean scaling was performed with an intensity normalization to 10,000. A low-pass filter of 0.1 Hz and a high-pass filter of 0.005 Hz were applied for temporal filtering. The images were detrended by calculating the mean of the temporally filtered image and detrending with the addition of Legendre polynomials of an order up to and including two. An image that was the addition of both the mean and detrended image was created.

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Three separate registration alignments were performed. The functional (using the eighth image acquisition as a template) to anatomical alignment was produced using a trilinear interpolation (six degrees of freedom). The anatomical to standard brain (MNI152_T1) was created again using a trilinear interpolation (12 degrees of freedom). The transformation matrices of both of these steps were saved. A third matrix, for the ability to transform between functional to standard, was created by concatenating the matrices of the previous two steps. The inverse of each of these matrices

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Segmentation was performed to create individual images for each tissue type and individual probability maps. The tissue types recognized as cerebrospinal fluid (CSF) and white matter (WM) were masked. These masks were used to control for nuisance signals. We utilized the global signal, WM and CSF segmentation masks, and the six motion parameters to adjust the functional signals for the effects of physiological noise and motion (Yan et al., 2013). Although adjustment for global signals is controversial, we opted to take a conservative approach and control for physiological noise (Fox et al., 2009). This approach may protect against false positives but may introduce spurious negative correlations (Murphy et al., 2013; Weissenbacher et al., 2009), so our analysis focused only on changes in positive correlations.

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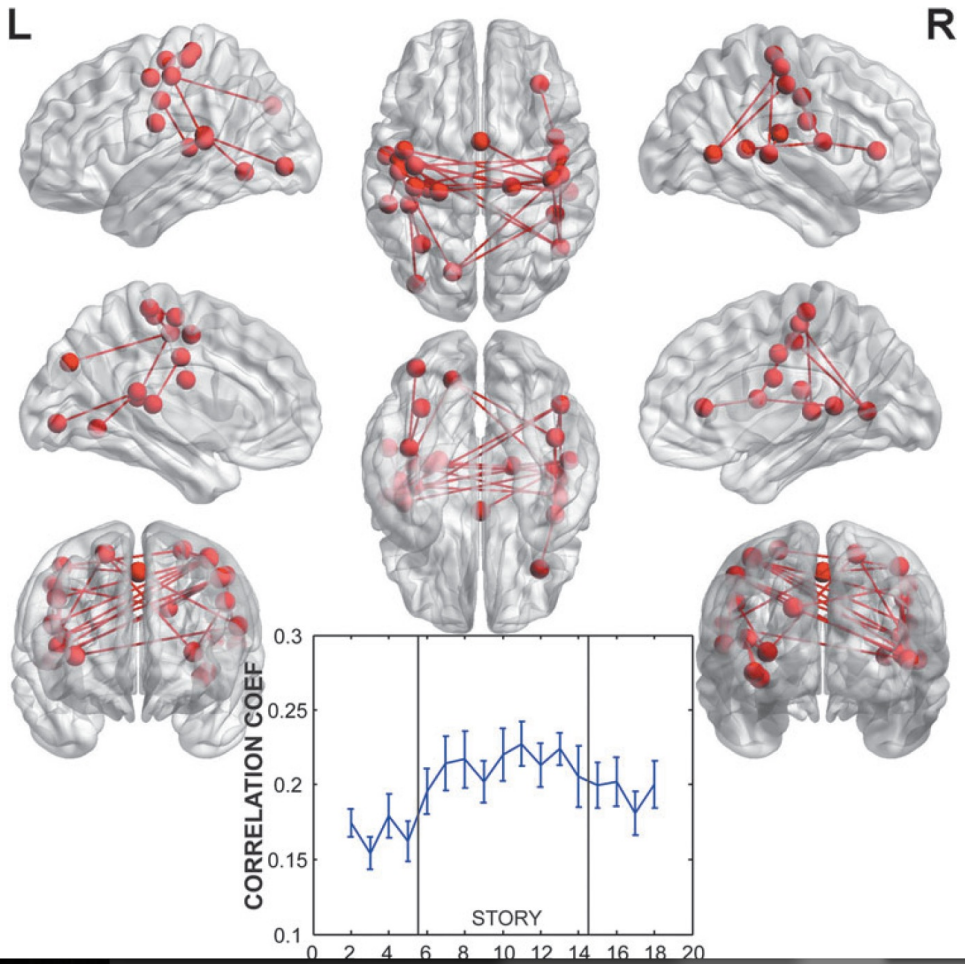


FIG. 6. Network ($p = 0.001$ corrected for FWER) of nodes and connections with significantly increased correlation during story days and that persisted beyond the story. This network was located bilaterally around the central sulcus with sparse connections to the insula and occipital regions. The timecourse of correlations across days showed a gradual rise beginning on the first post-story day that was sustained beyond the end of the novel.

Generalized linear models: recap

- $$f(y_j; \mu_j, \phi_j) = \exp\{\frac{y_j\theta_j - b(\theta_j)}{\phi_j} + c(y_j; \phi_j)\}$$
- $\mathrm{E}(y_j \mid x_j) = b'(\theta_j) = \mu_j$ defines μ_j as a function of θ_j
- $g(\mu_j) = x_j^T\beta = \eta_j$ links the n observations together via covariates
- $g(\cdot)$ is the link function; η_j is the linear predictor
- $\mathrm{Var}(y_j \mid x_j) = \phi_j b''(\theta_j) = \phi_j V(\mu_j)$
- $V(\cdot)$ is the variance function

... recap

- in most cases, either ϕ_j is known, or $\phi_j = \phi a_j$, where a_j is known
- Normal distribution, $\phi = \sigma^2, a_j = 1$
- Binomial distribution $\phi = 1, a_j = 1/m_j$
- Gamma distribution, $\phi = 1/\nu, a_j = 1$
- Poisson distribution, $\phi = 1, a_j = 1$
- maximum likelihood estimate of ϕ may be poor (by analogy with normal theory linear model)
- $$\hat{\phi} = \frac{1}{n-p} \sum_{j=1}^{n} \frac{(y_j - \hat{\mu}_j)^2}{a_j V(\hat{\mu}_j)}$$

... recap

- $\ell(\beta) = \sum_j \ell_j\{\eta_j(\beta); y_j, \phi_j\}$
- $\frac{\partial \ell(\beta)}{\partial \beta} = X^{\mathrm{T}} u(\beta), \quad X = \frac{\partial \eta}{\partial \beta^{\mathrm{T}}}, \quad u_j = \frac{(y_j - \mu_j)}{\phi_j g'(\mu_j) V(\mu_j)}$
- $\hat{\beta} = (X^T \widehat{W} X)^{-1} X^T \widehat{W} (X\hat{\beta} + \widehat{W}^{-1}\hat{u})$
- $w_j = w_j(\beta) = 1/\{g'(\mu_j)^2 \phi_j V(\mu_j)\}, \quad W = \mathrm{diag}(w_j)$
- $z = X\beta + W^{-1}u$
- $z_j = x_j^{\mathrm{T}}\beta + w_j^{-1}u_j = x_j^{\mathrm{T}}\beta + g'(\mu_j)(y_j - \mu_j)$
- $I(\beta) = \mathrm{E}\{-\partial^2 \ell(\beta)/\partial\beta\partial\beta^{\mathrm{T}}\} = X^{\mathrm{T}} W X$
- $\mathrm{a.var}(\hat{\beta}) \doteq (X^{\mathrm{T}} \widehat{W} X)^{-1}$

... recap

- $\ell(\beta) = \sum_j \ell_j\{\eta_j(\beta); y_j\}$
- $\frac{\partial \ell(\beta)}{\partial \beta} = X^{\mathrm{T}} u(\beta), \quad X = \frac{\partial \eta}{\partial \beta^{\mathrm{T}}}, \quad u_j = \frac{(y_j - \mu_j)}{\phi_j g'(\mu_j) V(\mu_j)}$
- $\frac{\partial^2 \ell(\beta)}{\partial \beta \partial \beta^{\mathrm{T}}} = X^{\mathrm{T}} \frac{\partial u(\beta)}{\partial \beta^{\mathrm{T}}}$
- $$\frac{\partial u_j(\beta)}{\partial \beta_b} = \frac{-(\partial \mu_j / \partial \beta_b)\phi_j g'(\mu_j) V(\mu_j) + (y_j - \mu_j)\phi_j\{g''(\mu_j) V(\mu_j) + g'(\mu_j) V'(\mu_j)\}}{\{\phi_j g'(\mu_j) V(\mu_j)\}^2}$$
- $\partial \mu_j / \partial \beta_b = x_{jb} / g'(\mu_j)$
- $I(\beta) = \mathrm{E}\{-\partial^2 \ell(\beta) / \partial \beta \partial \beta^{\mathrm{T}}\} = X^{\mathrm{T}} W X$

Over-dispersion §10.6

- over-dispersion means Var(Y) is larger than expected under the Poisson or Binomial model
- which specify Var(Y) $= \mu$, or $v(\mu) = \mu(1-\mu)/m$
- where does over-dispersion come from? possibly multiplicative "noise", see p. 511 for Poisson, (10.34) for Binomial
- likelihood analysis computes marginal density, averaged over noise – e.g. Poisson $\rightarrow$ Negative Binomial (Ex. 10.26)
- alternative analysis based on "quasi-likelihood" uses analogy with least squares
- recall that if $E(Y) = X\beta$, Var(Y) $= \sigma^2 I$, then $\hat{\beta}$ is best linear unbiased estimator of β, even if Y is not normally distributed (Gauss-Markov theorem)
- there could be better nonlinear estimators of β

... overdispersion

- if $E(Y) = X\beta$ and $\text{Var}(Y) = V$, then $\hat{\beta} =$ unbiased for β
- $\text{Var}(\hat{\beta}) =$ (8.19)
- if we knew V, replace $\hat{\beta}$ by weighted least squares estimator; otherwise, use $\hat{\beta}$ and adjust confidence intervals by some estimate of V, see p.377

... overdispersion

- estimation of β in a generalized linear model depends only on the specification of the mean function
- and the variance function
- suggests using the same estimating equation for β, but allow inflation of the variance function by an unknown dispersion parameter
- e.g. $E(y_j) = \mu_j, \quad \text{Var}(y_j) = \phi\mu_j$ –
- e.g. $E(y_j) = \mu_j, \quad \text{Var}(y_j) = \phi\pi_j(1-\pi_j)/m$ –
- estimating equation for β is unchanged

... overdispersion

- $$\sum_{j=1}^{n} x_j \frac{y_j - \mu_j}{g'(\mu_j) V(\mu_j)} = 0$$
- this is an unbiased estimating function $g(y; \beta)$; satisfies $E\{g(Y; \beta)\} = 0$
- under some regularity conditions the solution of $g(y; \beta) = 0$ is consistent, asymptotically normal
- a. $\text{Var}(\tilde{\beta}) = \phi(X^T \tilde{W} X)^{-1}$; $\tilde{W}$ is diagonal with the same w_j, but **without** the ϕ_j
- from general theory on unbiased estimating functions

$$E\left\{-\frac{\partial g(Y;\beta)}{\partial \beta}\right\}^{-1} Var\{g(Y;\beta)\} E\left\{-\frac{\partial g(Y;\beta)}{\partial \beta}\right\}^{-1}$$

Example 10.29

City	Rain	r/m	City	Rain	r/m	City	Rain	r/m	City	Rain	r/m
1	1735	2/4	11	2050	7/24	21	1756	2/12	31	1780	8/13
2	1936	3/10	12	1830	0/1	22	1650	0/1	32	1900	3/10
3	2000	1/5	13	1650	15/30	23	2250	8/11	33	1976	1/6
4	1973	3/10	14	2200	4/22	24	1796	41/77	34	2292	23/37
5	1750	2/2	15	2000	0/1	25	1890	24/51			
6	1800	3/5	16	1770	6/11	26	1871	7/16			
7	1750	2/8	17	1920	0/1	27	2063	46/82			
8	2077	7/19	18	1770	33/54	28	2100	9/13			
9	1920	3/6	19	2240	4/9	29	1918	23/43			
10	1800	8/10	20	1620	5/18	30	1834	53/75			

Table 10.19 Toxoplamosis data: rainfall (mm) and the numbers of people testing positive for toxoplasmosis, r, our of m people tested, for 34 cities in El Salvador (Efron, 1986).

Terms	df	Deviance
Constant	33	74.21
Linear	32	74.09
Quadratic	31	74.09
Cubic	30	62.63

Table 10.20 Analysis of deviance for polynomial logistic models fitted to the toxoplasmosis data.

- incidence of toxoplasmosis as a function of rainfall
- residual deviances approximately twice the degrees of freedom

... example 10.29

```
> data(toxo)
  rain  m  r
1 1620 18  5
2 1650 30 15
3 1650  1  0
4 1735  4  2
> toxo.glm0 = glm(cbind(r,m-r) ~ rain + I(rain^2) + I(rain^3), data = toxo,
family = binomial)

> anova(toxo.glm0)
 ...
          Df Deviance Resid. Df Resid. Dev
NULL                         33     74.212
rain       1   0.1244        32     74.087
I(rain^2)  1   0.0000        31     74.087
I(rain^3)  1  11.4529        30     62.635
> toxo.glm1 = glm(cbind(r,m-r) ~ poly(rain,3), data = toxo, family = binomial)

> summary(toxo.glm1)
...
Coefficients:
                        Estimate Std. Error z value Pr(>|z|)
(Intercept)              0.02427    0.07693   0.315 0.752401
poly(rain, degree = 3)1 -0.08606    0.45870  -0.188 0.851172
poly(rain, degree = 3)2 -0.19269    0.46739  -0.412 0.680141
poly(rain, degree = 3)3  1.37875    0.41150   3.351 0.000806 ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

(Dispersion parameter for binomial family taken to be 1)

    Null deviance: 74.212  on 33  degrees of freedom
Residual deviance: 62.635  on 30  degrees of freedom
```

... example 10.29

```
> toxo.quasi2 <- glm(cbind(r,m-r) ~ rain +I(rain^2)+I(rain^3),
+ data = toxo, family = quasibinomial)

> summary(toxo.quasi2)

Call:
glm(formula = cbind(r, m - r) ~ rain + I(rain^2) + I(rain^3),
    family = quasibinomial, data = toxo)

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-2.7620  -1.2166  -0.5079   0.3538   2.6204

Coefficients:
             Estimate Std. Error t value Pr(>|t|)
(Intercept) -2.902e+02  1.215e+02  -2.388   0.0234 *
rain         4.500e-01  1.876e-01   2.398   0.0229 *
I(rain^2)   -2.311e-04  9.616e-05  -2.404   0.0226 *
I(rain^3)    3.932e-08  1.635e-08   2.405   0.0225 *
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for quasibinomial family taken to be 1.940446)

    Null deviance: 74.212  on 33  degrees of freedom
Residual deviance: 62.635  on 30  degrees of freedom
> (74.212-62.635)/3/1.940446
[1] 1.988718
> pf(1.988718,3,30,lower=F)
[1] 0.1368842
```

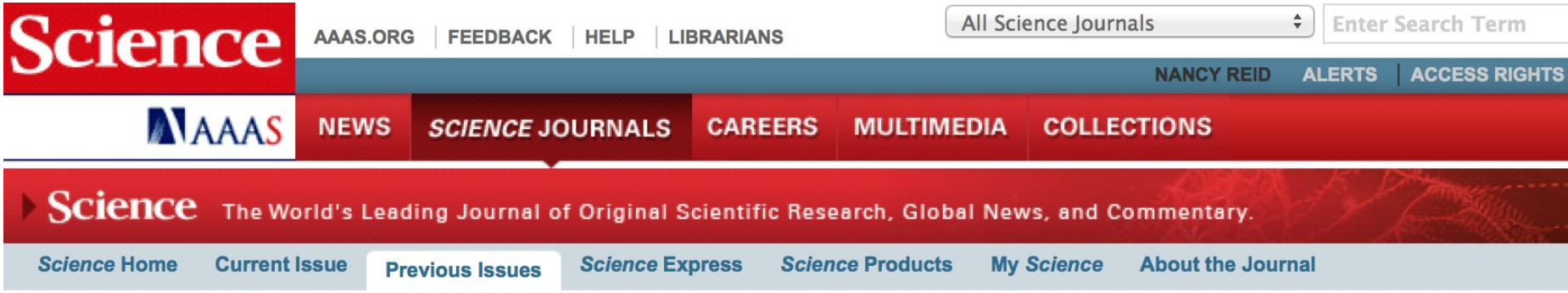
... inference

- $\hat{\phi} = \dfrac{1}{n-p} \displaystyle\sum_{j=1}^{n} \dfrac{(y_j - \hat{\mu}_j)^2}{V(\hat{\mu}_j)}$
- $\widehat{\text{Var}}(\tilde{\beta}_j) = \hat{\phi}\, \widehat{\text{Var}}(\hat{\beta}_j)$, $\quad \widehat{\text{Var}}(\hat{\beta}_j)$ from `glm` fit
- comparison of models: $A \subset B$ $D_A - D_B \dot{\sim} \chi^2_{p_B - p_A}$
- changes to

$$\frac{(D_A - D_B)/(p_B - p_A)}{\hat{\phi}} \dot{\sim} F_{p_B - p_A, p_B}$$

- $\hat{\phi}$ estimated under the larger model, B

In the News



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Published Online January 2 2014
Science 17 January 2014:
Vol. 343 no. 6168 pp. 263–268
DOI: 10.1126/science.1246183

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RESEARCH ARTICLE

Medicaid Increases Emergency-Department Use: Evidence from Oregon's Health Insurance Experiment

Sarah L. Taubman[1,*], Heidi L. Allen[2], Bill J. Wright[3], Katherine Baicker[1,4], Amy N. Finkelstein[1,5]

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ABSTRACT EDITOR'S SUMMARY

In 2008, Oregon initiated a limited expansion of a Medicaid program for uninsured, low-income adults, drawing names from a waiting list by lottery. This lottery created a rare opportunity to study the effects of Medicaid coverage by using a randomized controlled design. By using the

... in the News

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In 2008, Oregon initiated a limited expansion of a Medicaid program for uninsured, low-income adults, drawing names from a waiting list by lottery. This lottery created a rare opportunity to study the effects of Medicaid coverage by using a randomized controlled design. By using the randomization provided by the lottery and emergency-department records from Portland-area hospitals, we studied the emergency department use of about 25,000 lottery participants over about 18 months after the lottery. We found that Medicaid coverage significantly increases overall emergency use by 0.41 visits per person, or 40% relative to an average of 1.02 visits per person in the control group. We found increases in emergency-department visits across a broad range of types of visits, conditions, and subgroups, including increases in visits for conditions that may be most readily treatable in primary

have less than $2000 in assets. OHP Standard provides relatively comprehensive medical benefits (including prescription drug coverage) with no consumer cost sharing and low monthly premiums (between $0 and $20, based on income), provided mostly through managed care organizations.

Oregon conducted eight lottery drawings from a waiting list for this Medicaid program between March and September 2008. Among the individuals randomly selected by lottery, those who completed the application process and met the eligibility criteria were enrolled (fig. S1). The lottery process and the insurance program are described in more detail elsewhere (*11*). Multiple institutional review boards have approved the Oregon Health Insurance Experiment research.

Our prior work on the Oregon Health Insurance Experiment used the random assignment of the lottery to study the impacts of the first 2 years of Medicaid coverage (*11*–*13*). We found that


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Happy Chinese New Year!