Subject: RE: Inferential analysis Take 2

From: Dan Hippe - To: ktavabi@uw.edu - Cc: - Date: August 21, 2020 at 17:08, Attachments: image001.png image002.png

Hi Kam,

Responses inline:

From: Kambiz Tavabi [mailto:ktavabi@uw.edu]
Sent: Friday, August 14, 2020 5:01 PM
To: Dan Hippe <dhippe@uw.edu>
Subject: RE: Inferential analysis Take 2

Hi Dan,
See my responses inline.

On August 7, 2020 at 15:24:49, Dan Hippe (dhippe@uw.edu) wrote:

> Hi Kam,
>
> Taking another crack at this now that I've had more time to consider.
>
> **1) AUC_zscore**
>
> What is the AUC_zscore? Is it something like z = sqrt(2)*qnorm(AUC), a transformed version of the AUC? Or a z-score calculated instead of the AUC but corresponding to the same difference? Z = 0 means no difference, Z=1 means 1-SD difference between the type of stimuli? I support the idea of using something like a z-score instead of AUC because a z-score would probably have better behaved distributional properties, just want to be sure I know its meaning so I can interpret the regression coefficients.

Correct! This is your past recommendation in fact. This is the standardized z-score Z(AUC) for the classifier score (AUC) between different stimulus conditions. So bearing in mind the MEG recording is already an electrophysiological index of auditory contrasting, then I'm glad you agree with using z-score standardization as a response measure for differential auditory processing in infant brain.

Phew! Glad my intra-observer variability is not too bad.

> **2) Random effects**
>
> I'd still get rid of the (0+age|sid) term and replace it with (1|sid), but I'd also want to see a version with (1|sid) + (1|scan). In this case, scan would be a unique ID for each scan so that for the infants with 2 scans would have two different IDs. For example, paste(sid, age) would produce a convenient unique ID. The reasoning behind this is that there are actually two levels of clustering. Each infant has 1 or more scans, and within each scan 4 conditions are assessed. However, since the sample size is not huge and many infants have only 1 scan, I'd want to run the models both ways—with (1|sid) only and with (1|sid)+(1|scan)—to see the impact of the second term. It might be more numerically stable to just go with (1|sid), even if (1|sid)+(1|scan) better corresponds to the structure of the data.

Also glad you brought this up! I had actually settled on 1|sid in my latest iteration. As expected the proposal with (1|sid)+(1|scan) does indeed return convergence errors due to degenerate Hessian eigenvalues, I don't know who Hess is, but these random effects test tables also look fishy to me. I was approaching this wrong by grouping by age as category as well to try and account for the discrepancy between repeated & independent samplings: (1|sid) appears to be the more reasonable

partitioning method to account for the within-subject variability. Agree? See (RandEffx.html)

Random Effect LRT

Test	N. par	AIC	LRT	df	p
(1 | sid)	6	2219.63	0.00	1.00	1.000
(1 | scan_id)	6	2219.63	0.00	1.00	1.000

as compared to

Random Effect LRT

Test	N. par	AIC	LRT	df	p
(1 | sid)	5.00	2417.50	199.87	1.00	<.001

I agree with you, those do look suspect. It seems like we can't separate the subject and scan variance, probably not enough with multiple scans. When you compare the variance estimates between the two

Random Components

Groups	Name	SD	Variance	ICC
sid	(Intercept)	0.35	0.12	0.16
scan_id	(Intercept)	0.48	0.23	0.26
Residual		0.81	0.66	

Note. Number of Obs: 852 , groups: sid 70, scan_id 70

0.35 ~ 0.36

Random Components

Groups	Name	SD	Variance	ICC
sid	(Intercept)	0.60	0.36	0.35
Residual		0.81	0.66	

Note. Number of Obs: 852 , groups: sid 70

The residual variance is the same, and the sid + scan_id variance approximately equal the sid variance when that is the only random effect. So putting the two terms in was just splitting the variance attributed to subject, not really adding anything.
So (1|sid) only it is!

3) Age

I think you should just include age in the model, not age + age_grouped. In addition, it would be good to shift and scale age to improve interpretability.

First, what unit is the age variable currently using? Days or months? The regression coefficients related to age are so small (almost zero when rounded to 2 decimal places), so it would be helpful to scale it. If currently days, divide age by (365.25/12) to get age in months.

Second, shift age by 2 months, so that the resulting variable is 0 at 2 months of age. For example, age_scaled = age/(365.25/12) - 2. This shifting has no impact on the age regression coefficients,

but improves the interpretability of the main-effects when you add in the age x condition interaction. Specifically, the condition main-effects would correspond to associations at 2 months of age, instead of when age = 0 as is currently the case.

Based on scaling and shifting age by 2 months (see age_scaledXcondition.html) the parameter estimates indicate stronger AUC scores (0.67 standard deviation) for MMN stimuli (acoustic mismatch) at 2-months relative to deviant AUC scores (phonemic mismatch), however the 0.25 standard deviation increase in AUC score for MMN-deviant with age (modulation of AUC response by age and condition) indicates different rates of acoustic and phonemic processing maturation between 2-6 months.

Would you agree?

Fixed Effects Parameter Estimates

			95% Confidence Interval				
Effect	**Estimate**	**SE**	**Lower**	**Upper**	**df**	**t**	**p**
(Intercept)	0.63	0.55	-0.45	1.71	65.63	1.14	0.257
boy - girl	4.36e-4	0.17	-0.33	0.33	61.41	0.00	0.998
ses	-0.02	0.01	-0.03	0.00	65.60	-1.61	0.112
mmn - deviant	-0.67	0.11	-0.88	-0.45	353.46	-6.09	< .001
headSize	-0.11	0.07	-0.24	0.02	58.82	-1.67	0.100
birthWeight	-0.00	0.01	-0.01	0.01	62.07	-0.19	0.848
age_scaled	-0.25	0.21	-0.66	0.16	63.55	-1.20	0.235
ses ✻ age_scaled	0.01	0.00	-5.73e−4	0.01	63.31	1.80	0.076
mmn - deviant ✻ age_scaled	0.25	0.04	0.17	0.33	353.46	6.33	< .001

Isn't it that MMN stimuli AUC scores are lower than deviant AUC scores at 2 months (mmn – deviant estimate = -0.67)? When age goes from 2 to 6 months (age_scaled increases by 4), the MMN – deviant difference increases by 0.25 x 4 months = 1.00 from -0.67 to 0.33 (-0.67 + 1.00). So the MMN-deviant difference was negative at 2 months and positive at 6 months and the two are significantly different. I don't know what that means biologically, but that is what I can read from the model.

4) Model variables

I would be really helpful to see models with and without the other covariates, and with and without the interaction term, to better understand their impacts on the results. So I suggest fitting the following models

- **Main-effects only:** ~ 1 + condition + age_scaled

- **+Interaction:** ~ 1 + condition + age_scaled + condition:age_scaled

- **+Covariates:** ~ 1 + condition + age_scaled + condition:age_scaled + ses + gender + headSize + birthweight

And fit these models once using (1|sid) as the random effect term and again using (1|sid)+(1|scan), as described in section 2 above. So 6 models total.

I am attaching three outputs here (mainEffx, plusInteraction, plusCovar) for random-effects (1|sid) as (1|sid)+(1|scan) appears to anger Hess. I am curious as to hear how you will determine which is the best model (interaction vs. covariates)? I believe we are converging to good agreement here, tho I've managed to reproduce similar results with lmer in R, I haven't been able to get the exact same GAMLj objects into an ANOVA() to look at the chi-square between models.

The mainEffx file had ~ 1 + condition, not 1 + condition + age_scaled. The latter would still be helpful to see.
Comparing the +interaction and +covariates models, it seems that the covariates are not changing things. I had been wondering if the covariates were inducing any of the age or condition results, but that isn't the case. I think either one is ok to use. One approach would be to present the +interaction results in a table because it is simpler to interpret, but then mention in text that further adjusting for various potential confounders did not impact the results.
I agree that we're converging now. I'm no longer concerned that any of the results are artificial due to model instability or collinearity (mixed models can be tricky beasts, and Hess can sometimes play tricks), so I think the coefficients can be interpreted.

That will really help with understanding what is going on

Thanks,
Dan

From: Dan Hippe
Sent: Tuesday, July 28, 2020 7:22 PM
To: Kambiz Tavabi <ktavabi@uw.edu>
Subject: RE: Inferential analysis Take 2

Hi Kam,

Sorry I'm a bit tied up with this week with various deadlines, but I wanted to give you some initial feedback. Next week I can look into it more thoroughly.

1) In the model specification, the random effect term should include the intercept for subject to account for the repeated assessments for some subjects. I'm not inclined to add a random slope to age unless there is a particular reason. In that case I'd just use (1|sid) as the random effects term

2) Why is both age and age_group included in the model?

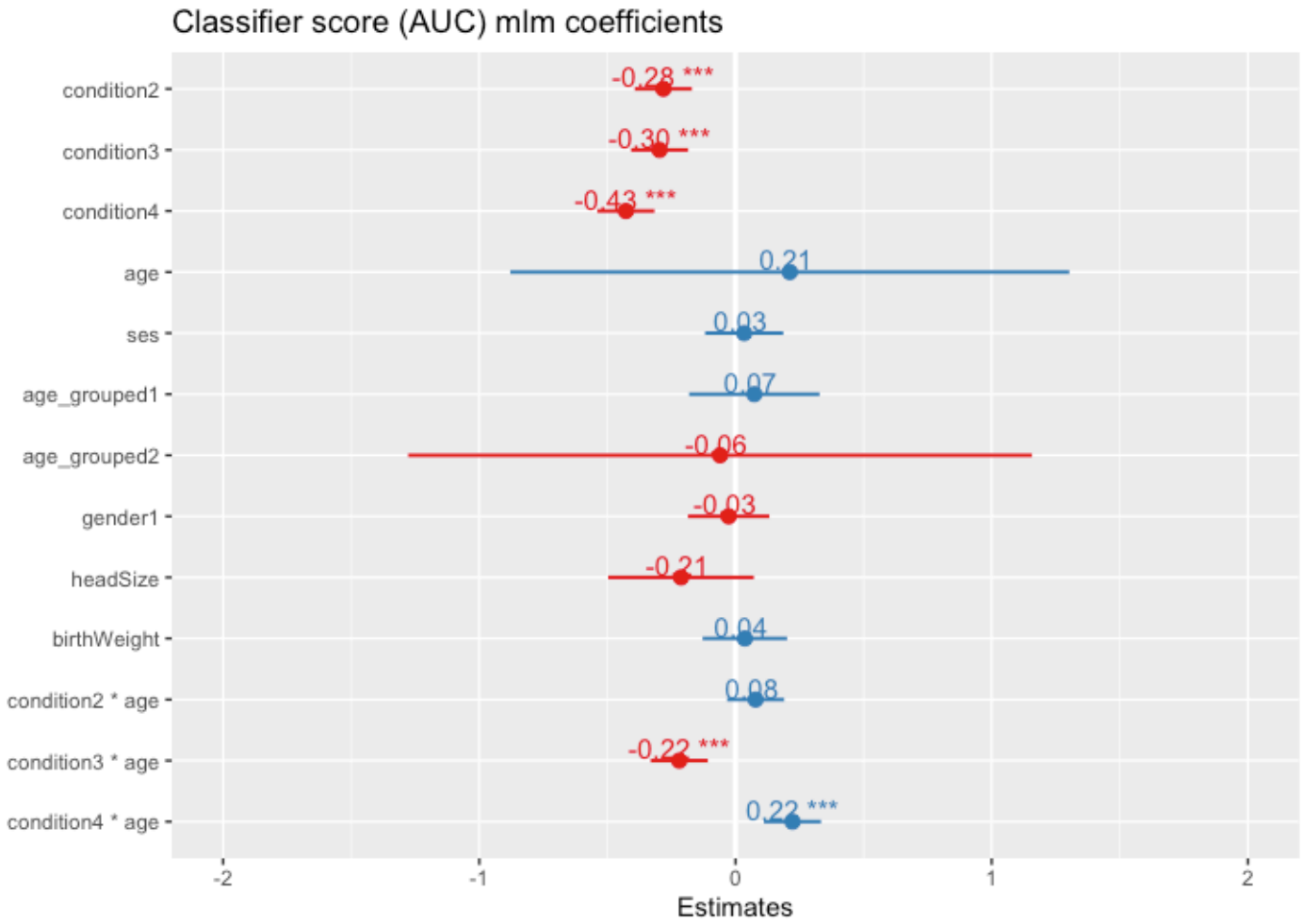
Dan

From: Kambiz Tavabi [mailto:ktavabi@uw.edu]
Sent: Thursday, July 23, 2020 11:01 PM
To: Dan Hippe <dhippe@uw.edu>
Subject: RE: Inferential analysis Take 2

Hi Dan,
Do you mind taking a look at the attached HTML? It contains the mixed effects lmer ANOVA yield for AUC electrophysiology response measure as per suggestions from our previous convo. Results indicate a significant modulation of response by term for interaction between age and condition (4-levels). Makes sense?

I managed to reproduce the results in R studio with direct calls to lmer and produced the following coefficient

estimate plot:



I believe the condition4*age and condition3*age estimates demonstrated the difference I expected in this dataset. I am just not sure how to say so in English and best to visualize it on the data. Thoughts? -Kam

On June 17, 2020 at 10:58:31, Dan Hippe (dhippe@uw.edu) wrote:

> Hi Kam,
>
> Following up on our call:
>
> Here is that code snippet we talked about:
> std = function(x) (x-mean(x,na.rm=T))/sd(x,na.rm=T)
> m1 = lmer((asin(sqrt(vocab/679))) ~ I(cdi_age-18) + std(auc) + SEX + age + ... +
> (1|sid) + ((cdi_age-18)|sid), data=tmp, method="REML")
>
> Also attached are the notes on your responses that we were going over, for reference.
>
> Dan
>
> ---
>
> **From:** Kambiz Tavabi [mailto:ktavabi@uw.edu]
> **Sent:** Tuesday, June 16, 2020 5:16 PM
> **To:** Dan Hippe <dhippe@uw.edu>

Cc: Patricia K Kuhl <pkkuhl@uw.edu>
Subject: Inferential analysis Take 2

Hi Dan,
I'm attaching my responses to issues you've raised. Looking forward to discussing further with you AM.

PS. FYI I am cc'ing PK here only to keep her updated on progress.

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