Predicting health-related quality of life in early adulthood from individual differences in adolescent neurocognitive development

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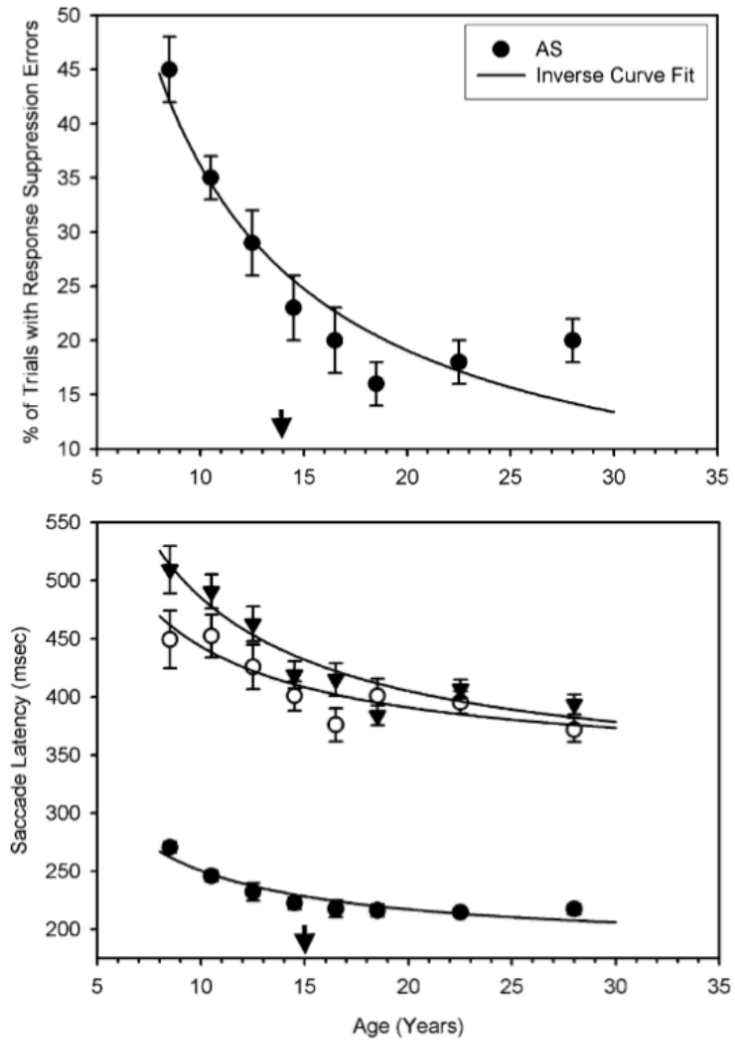
Adolescence

- Unique period of development during which numerous changes take place, including changes in cognitive control
- Cognitive control is of particular interest due to its relationships with risk-taking and psychopathology
- Relatively little work has explored how individual differences in adolescent developmental trajectories may be related to outcomes such as health-related quality of life in early adulthood

Inhibitory control

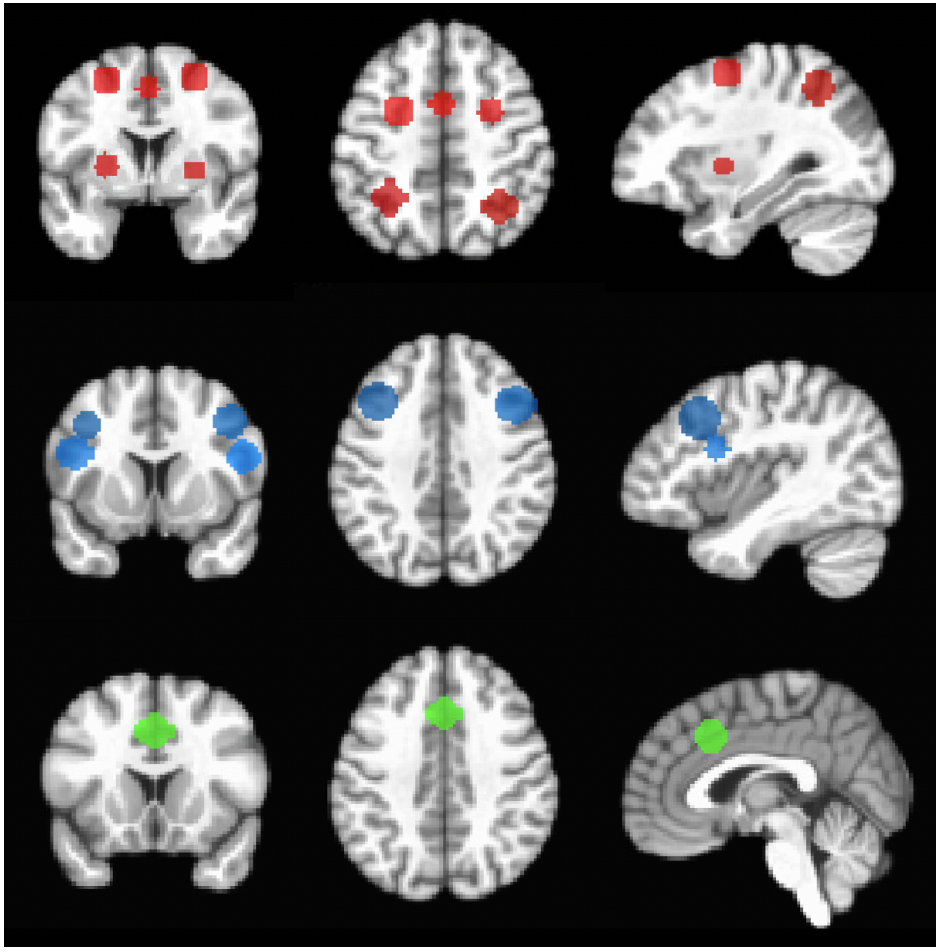
- One of three distinct but overlapping components of cognitive control
- Ability to inhibit a reflexive, goal-irrelevant response in favor of a goal-appropriate response
- Available early in development but undergoes protracted maturation through adolescence



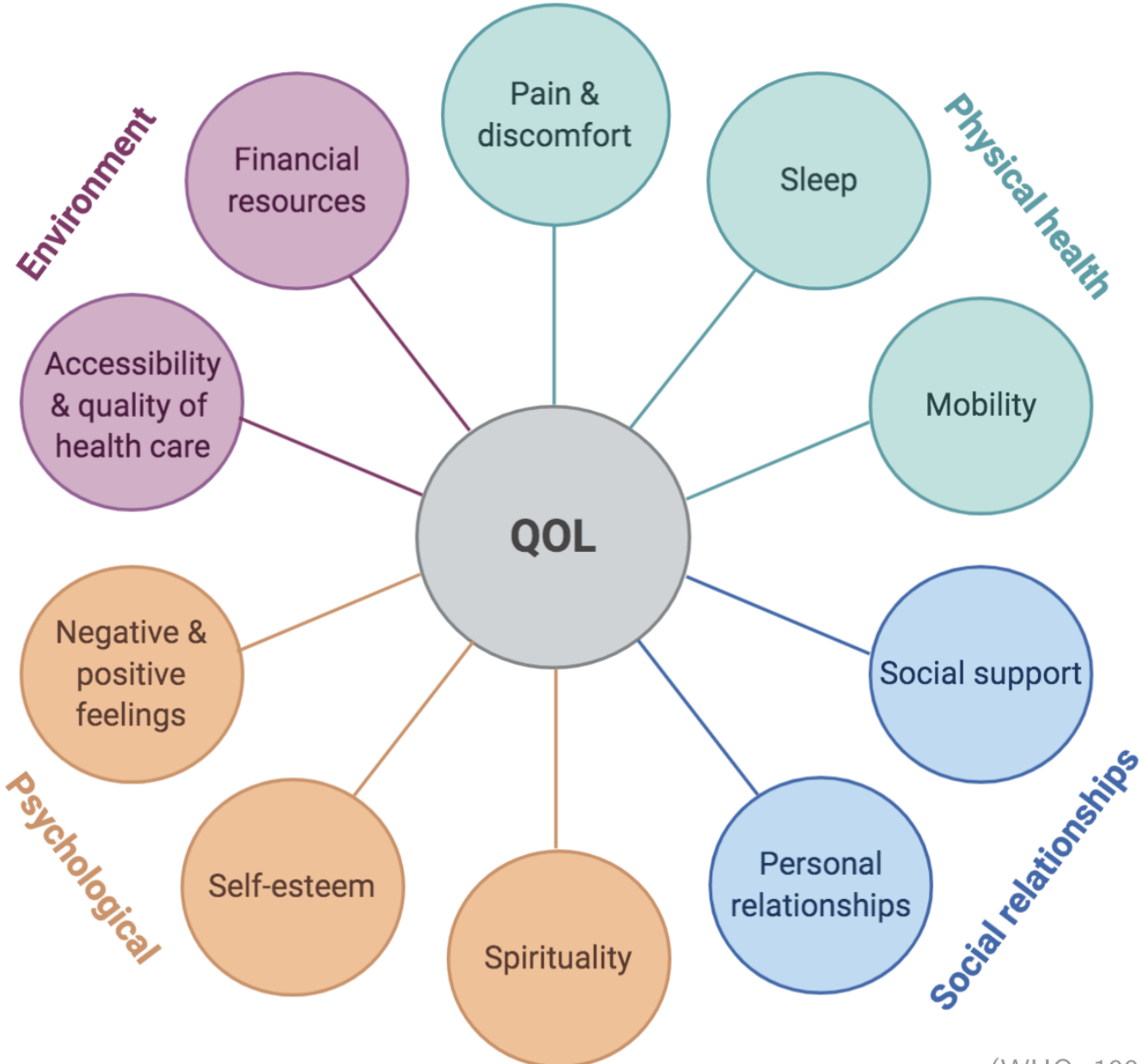
(Luna et al., 2004)

Brain regions supporting inhibitory control

- Motor response regions: little age-related change
- Executive control regions: developmental decreases
- Performance monitoring region: developmental increases



Health-related quality of life (QOL)



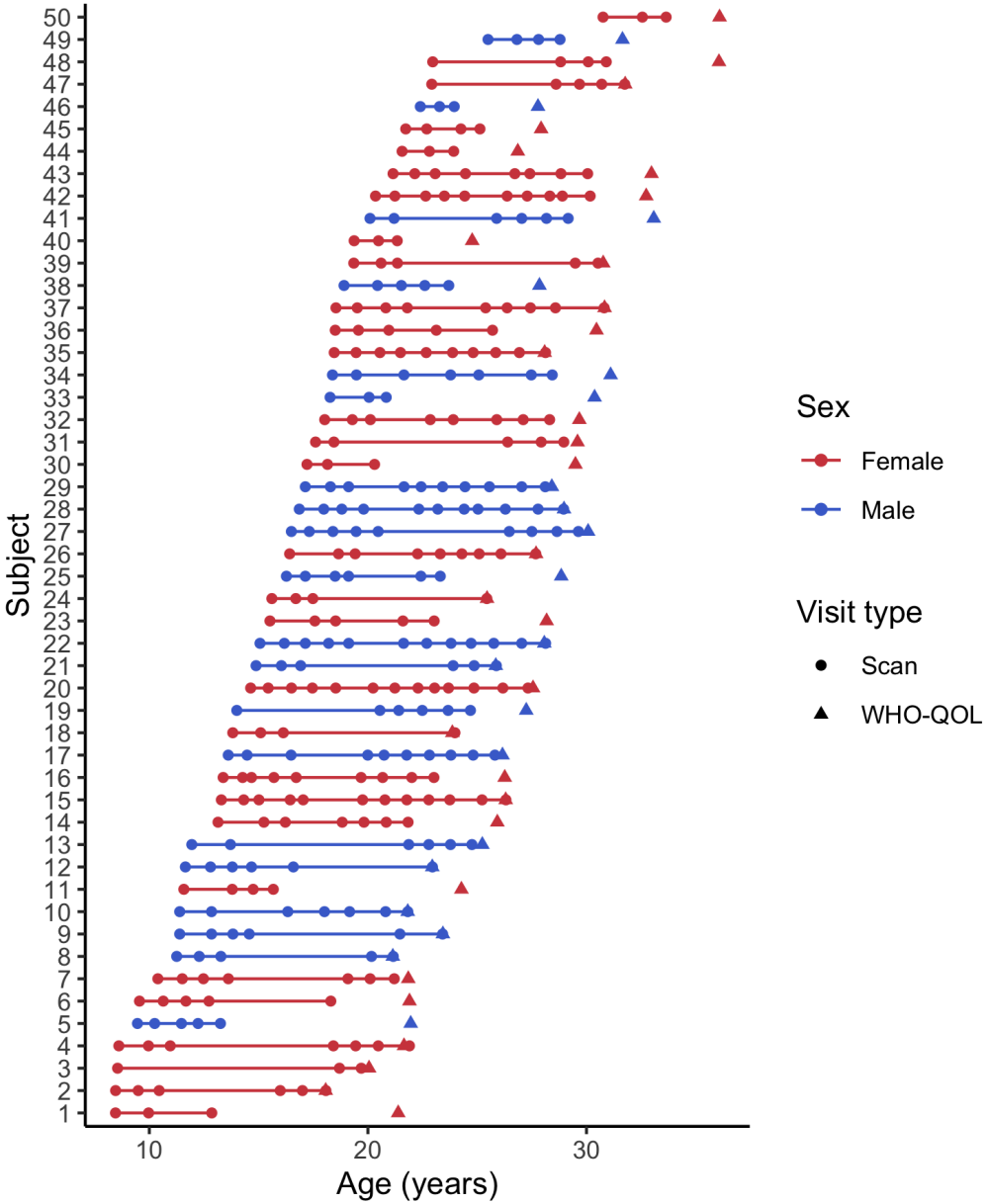
(WHO, 1996)

Objectives

1. To characterize the adolescent development of inhibitory control, both in terms of behavior and activation in motor, executive, and performance monitoring brain regions that support this cognitive process

2. To determine how individual differences in these adolescent developmental trajectories may predict subsequent health-related quality of life in early adulthood

Study and sample



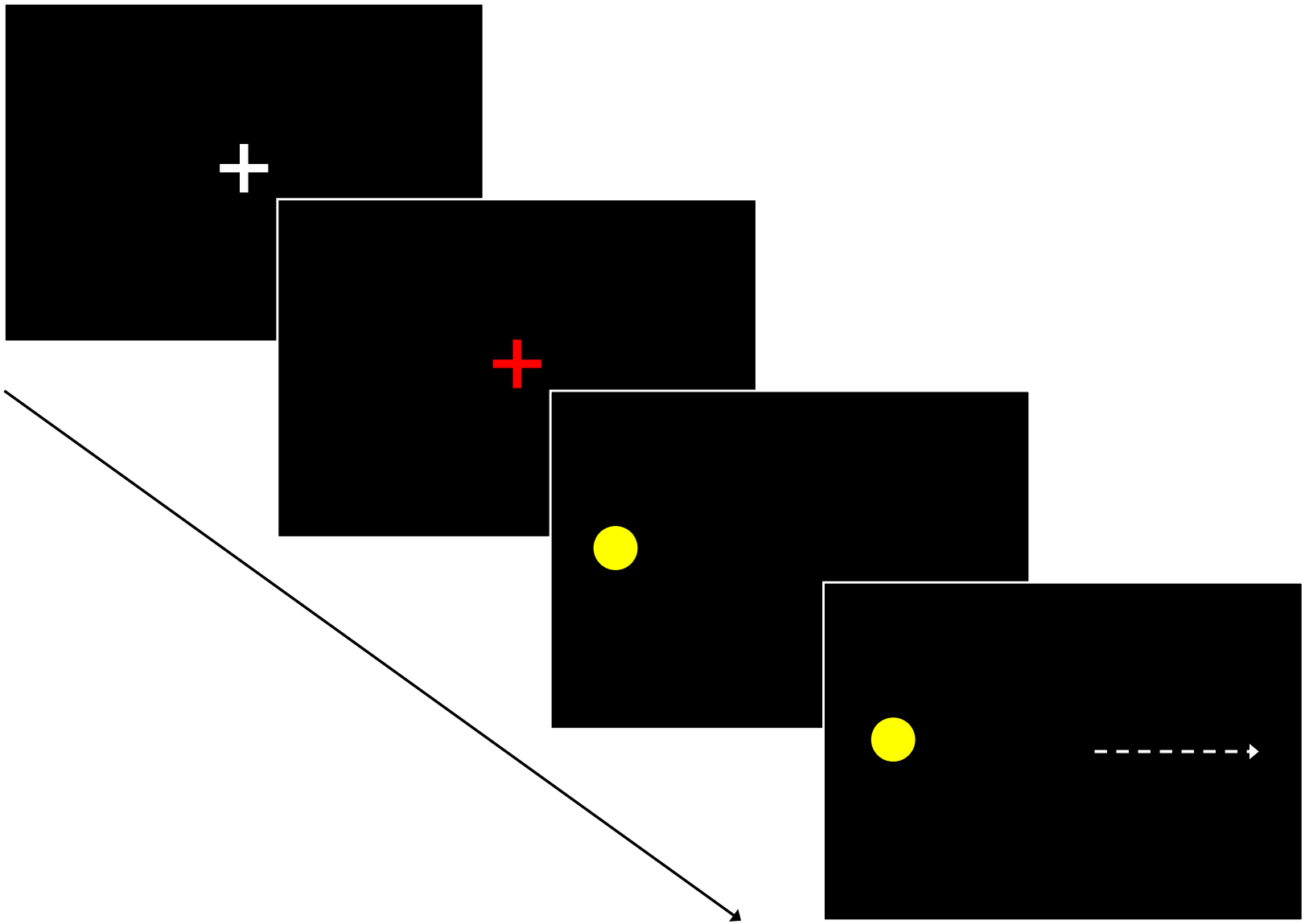
Study design:

- Accelerated longitudinal
- Up to 13 time points

Final sample:

- 50 participants
- 316 scans

Antisaccade task



WHO-QOL questionnaire

- 26 items
- 5-point Likert scale
- Four domains: physical health, psychological health, environment, social relationships

The following questions ask about **how much** you have experienced certain things in the last two weeks.

		Not at all	A little	A moderate amount	Very much	An extreme amount
3 (F1.4)	To what extent do you feel that physical pain prevents you from doing what you need to do?	1	2	3	4	5
4(F11.3)	How much do you need any medical treatment to function in your daily life?	1	2	3	4	5
5(F4.1)	How much do you enjoy life?	1	2	3	4	5
6(F24.2)	To what extent do you feel your life to be meaningful?	1	2	3	4	5

Objective 1: To characterize the adolescent development of inhibitory control in our longitudinal sample

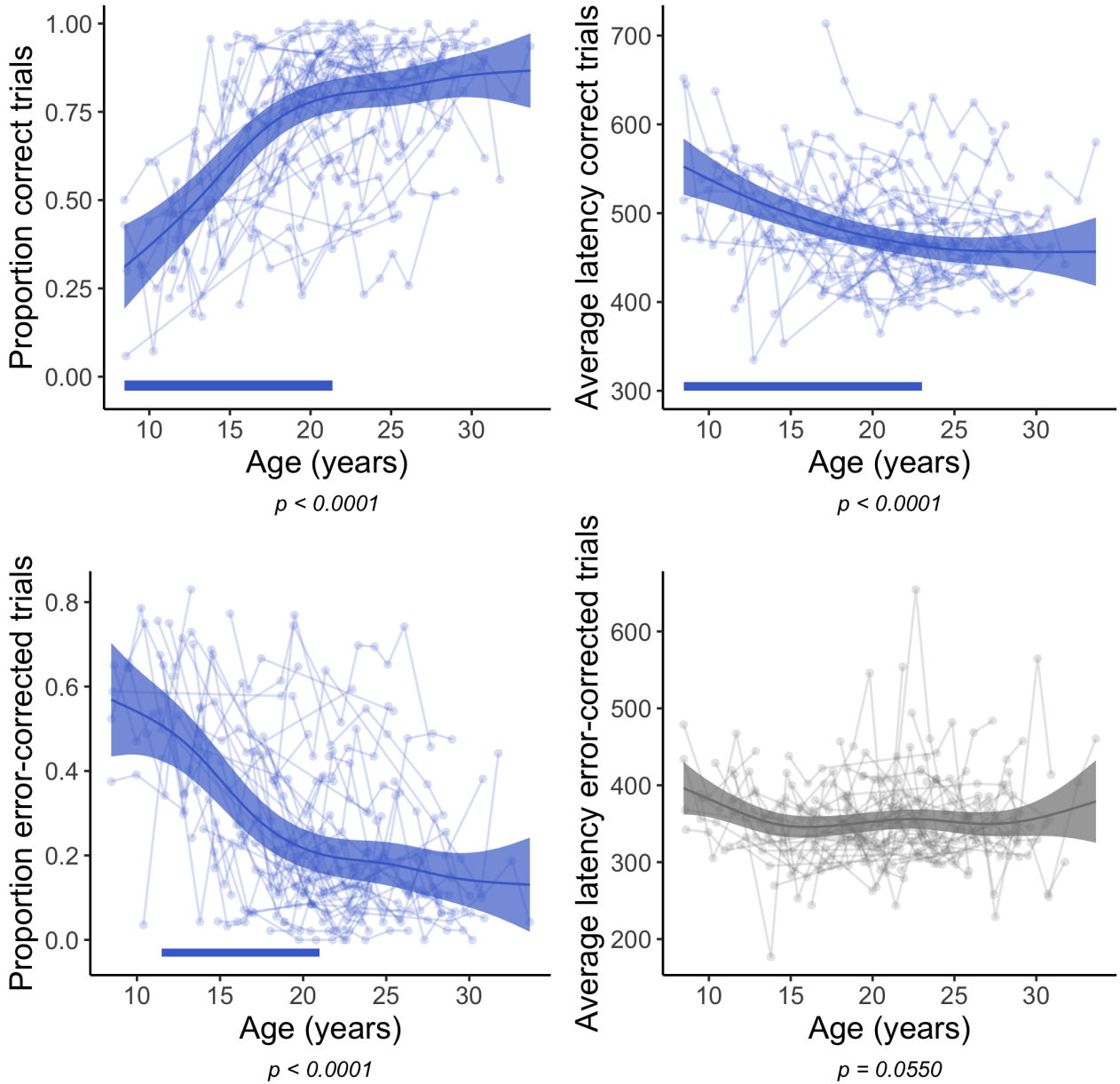
Methods: Generalized additive mixed models (GAMM)

- Flexible, semiparametric method for identifying and estimating nonlinear covariate effects

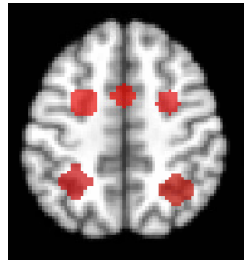
- **Outcomes:**
  - Accuracy and saccade latency
  - Activation in motor response, executive control, and performance monitoring regions during correct trials
  - Activation in performance monitoring region during error-corrected trials
- **Predictor of interest:** Age

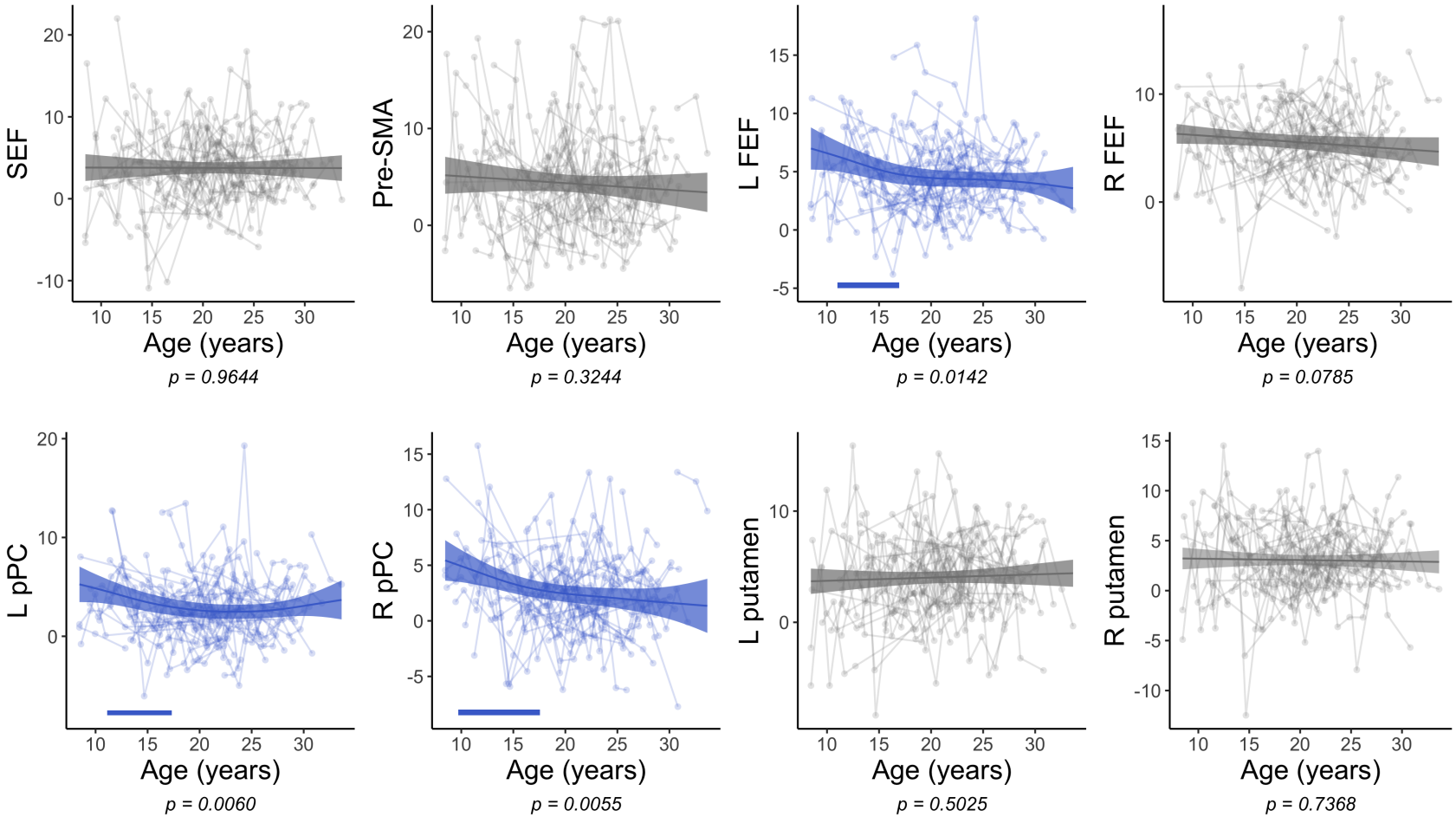
- Post-hoc analysis: approximate derivatives to identify periods of significant developmental change and age of maturation

Results: Accuracy and latency

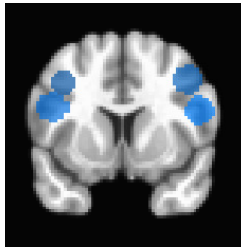


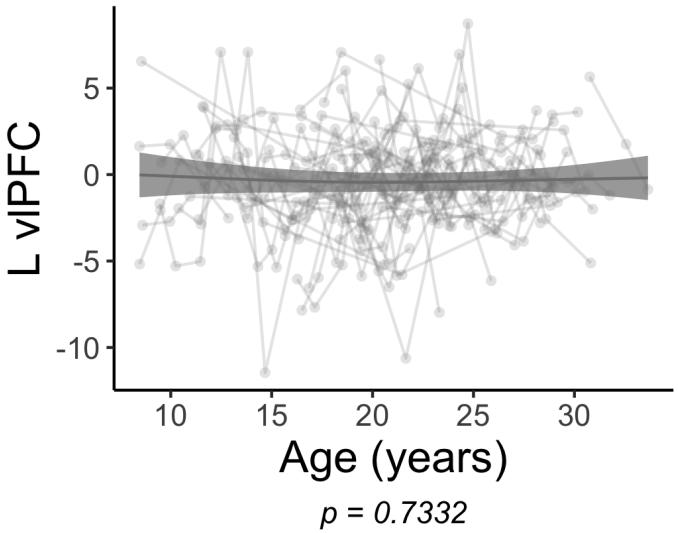
Results: Activation in motor response regions

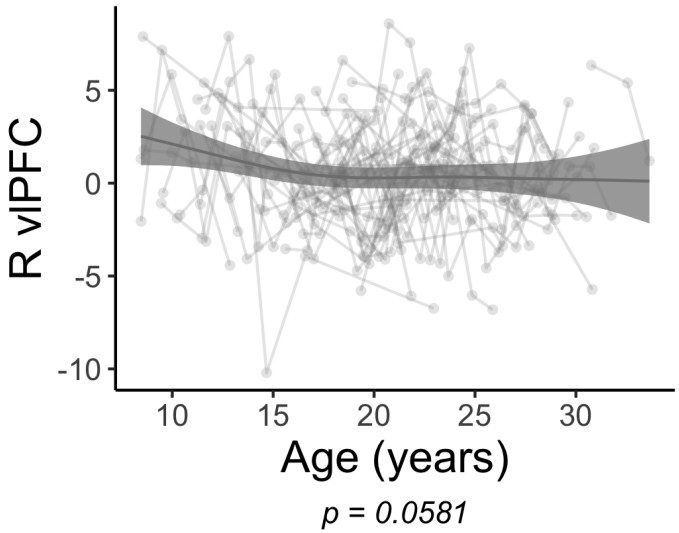


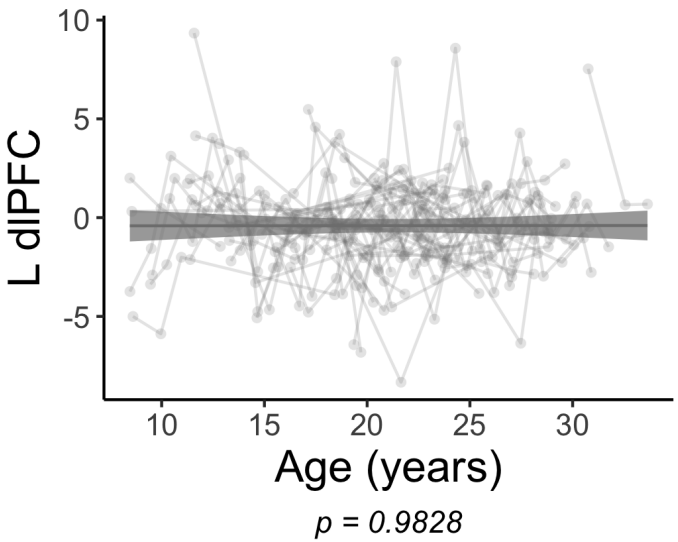


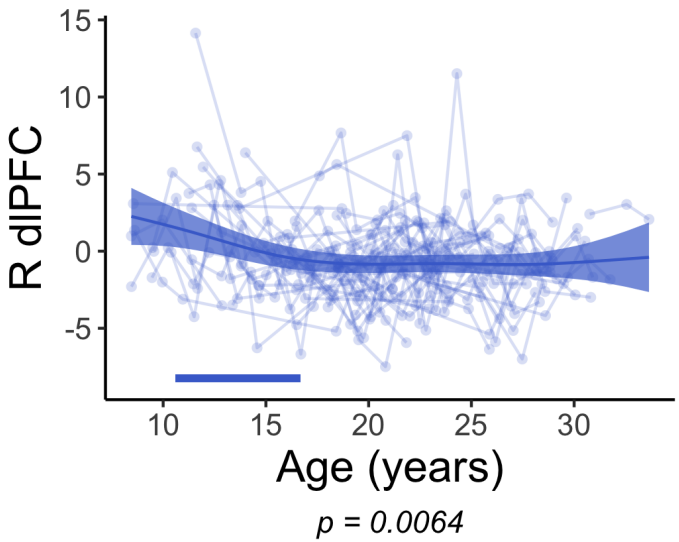
Results: Activation in executive control regions



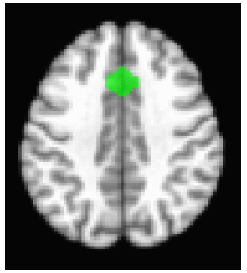


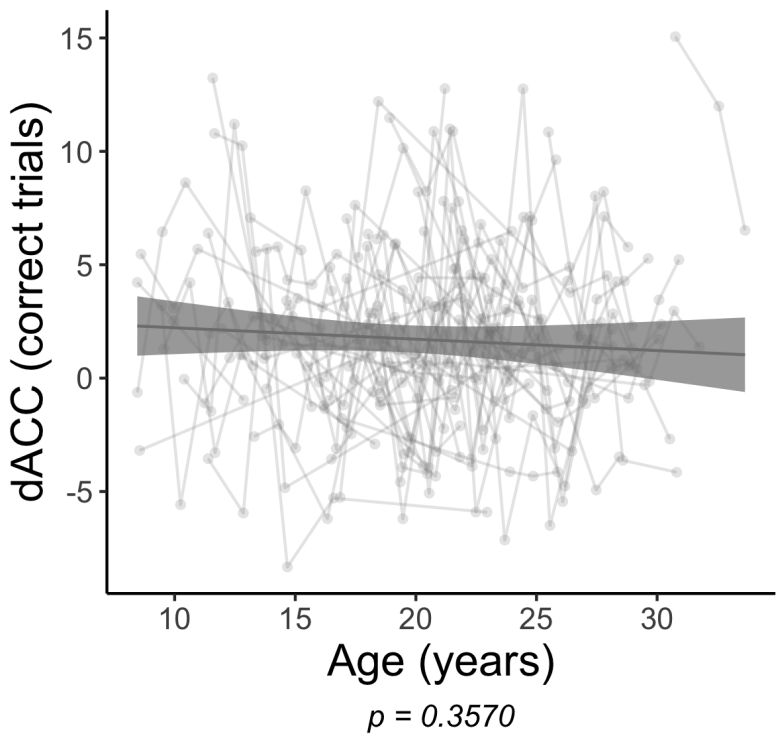


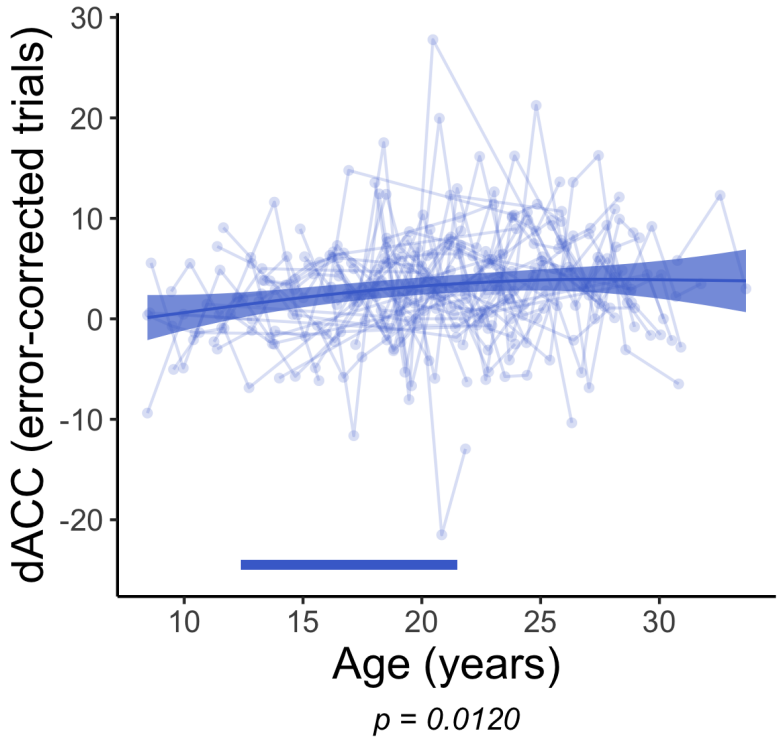




Results: Activation in performance monitoring region







Objective 2: To determine how individual differences in adolescent development of inhibitory control may predict QOL in early adulthood

Methods: Bootstrap-enhanced elastic net regression

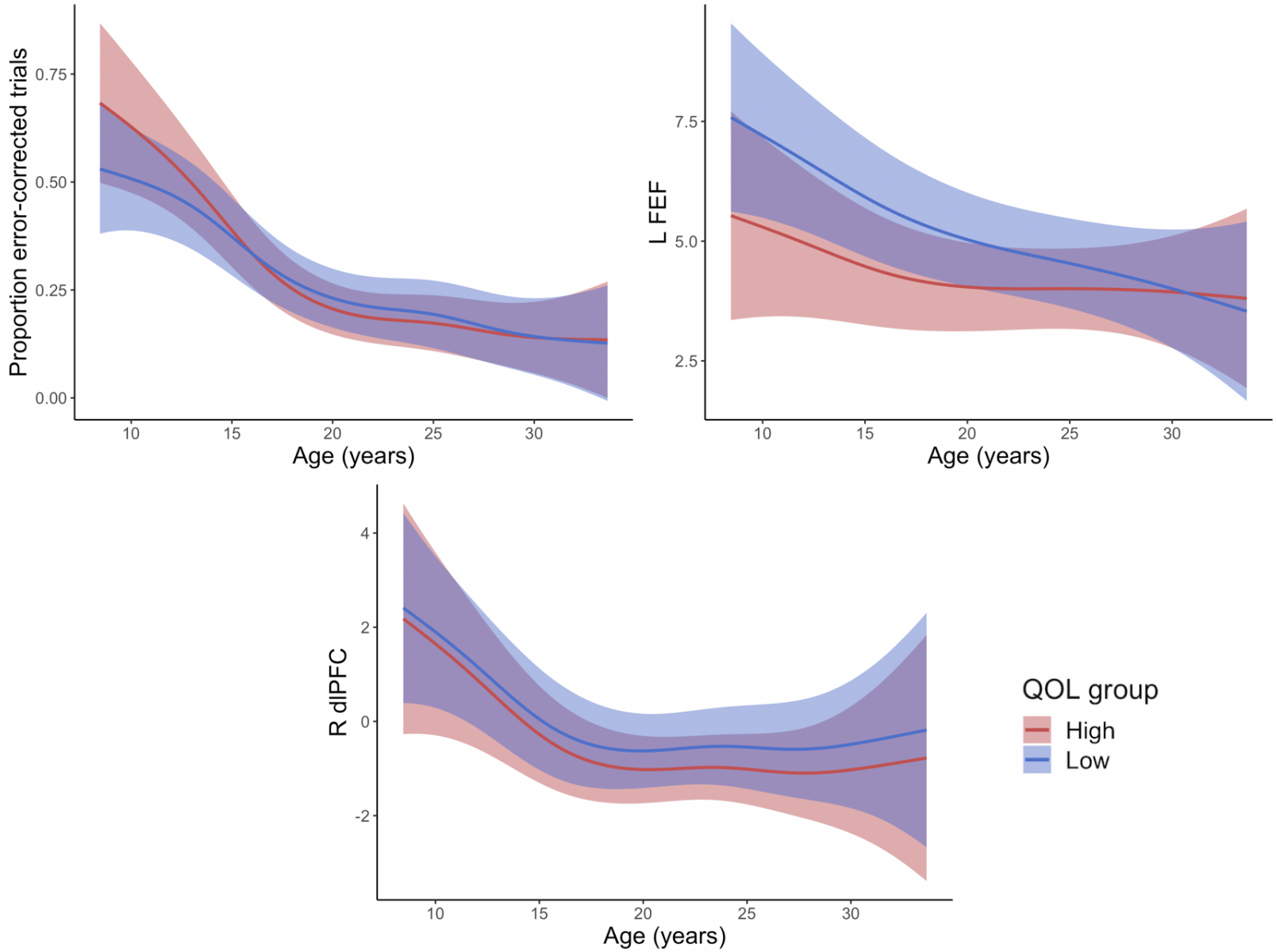
- Performs variable selection and permits inference on the selected model
- Two ways to assess variable importance:
  1. Quantile method
  2. Variable Inclusion Probability (VIP) method
- **Outcome:** Composite WHO-QOL score
- **Predictors:** Random intercepts and slopes extracted from GAMMs with significant age effects

Results: Predicting health-related quality of life

Predictor	$\hat{\beta}$	95% CI	VIP
Proportion correct intercept	0.0286	(-0.0014, 0.1216)	0.6630
Proportion correct slope	0.0225	(0.0000, 0.1012)	0.6216
Proportion error-corrected intercept	-0.0247	(-0.1332, 0.0104)	0.6468
Proportion error-corrected slope	-0.0712	(-0.1500, 0.0000)	0.8200
Average latency intercept	0.0284	(0.0000, 0.1282)	0.6590
Average latency slope	-0.0118	(-0.1647, 0.0305)	0.6178
L FEF activation intercept	-0.0334	(-0.1163, 0.0000)	0.7206
L FEF activation slope	0.0858	(0.0000, 0.1713)	0.8916
L pPC activation intercept	0	(-0.0606, 0.0281)	0.3616
L pPC activation slope	0	(-0.0111, 0.0738)	0.4216
R pPC activation intercept	-0.0735	(-0.1725, 0.0000)	0.7520
R pPC activation slope	0	(-0.1277, 0.0621)	0.5396
R dlPFC activation intercept	-0.0888	(-0.2028, 0.0000)	0.8456
R dlPFC activation slope	0	(-0.1264, 0.0520)	0.4602
dACC activation intercept	0	(-0.0694, 0.0775)	0.4476
dACC activation slope	0	(-0.1004, 0.0462)	0.4746

Model $R^2 = 0.1884$

Results: Predicting health-related quality of life



Summary

- Developmental improvements in inhibitory control behaviorally, with age-related change continuing into young adulthood
- Age-related change in activation in some executive control and motor response regions, continuing into mid-adolescence
- Age-related change in dACC continuing into young adulthood only during error-corrected trials, reflecting its unique role in performance monitoring
- Individual differences in inhibitory control development during adolescence did not significantly predict QOL in early adulthood

Conclusions and public health significance

- Use of a flexible, semiparametric approach provided additional insight into developmental time course of inhibitory control in adolescence, indicating that maturation may occur later than previously reported
- Suggests that there may be a greater window of opportunity during which interventions can be applied to promote optimal adult outcomes
- Relationship between inhibitory control development and QOL remains to be elucidated, though results motivate further investigation

Thank you!

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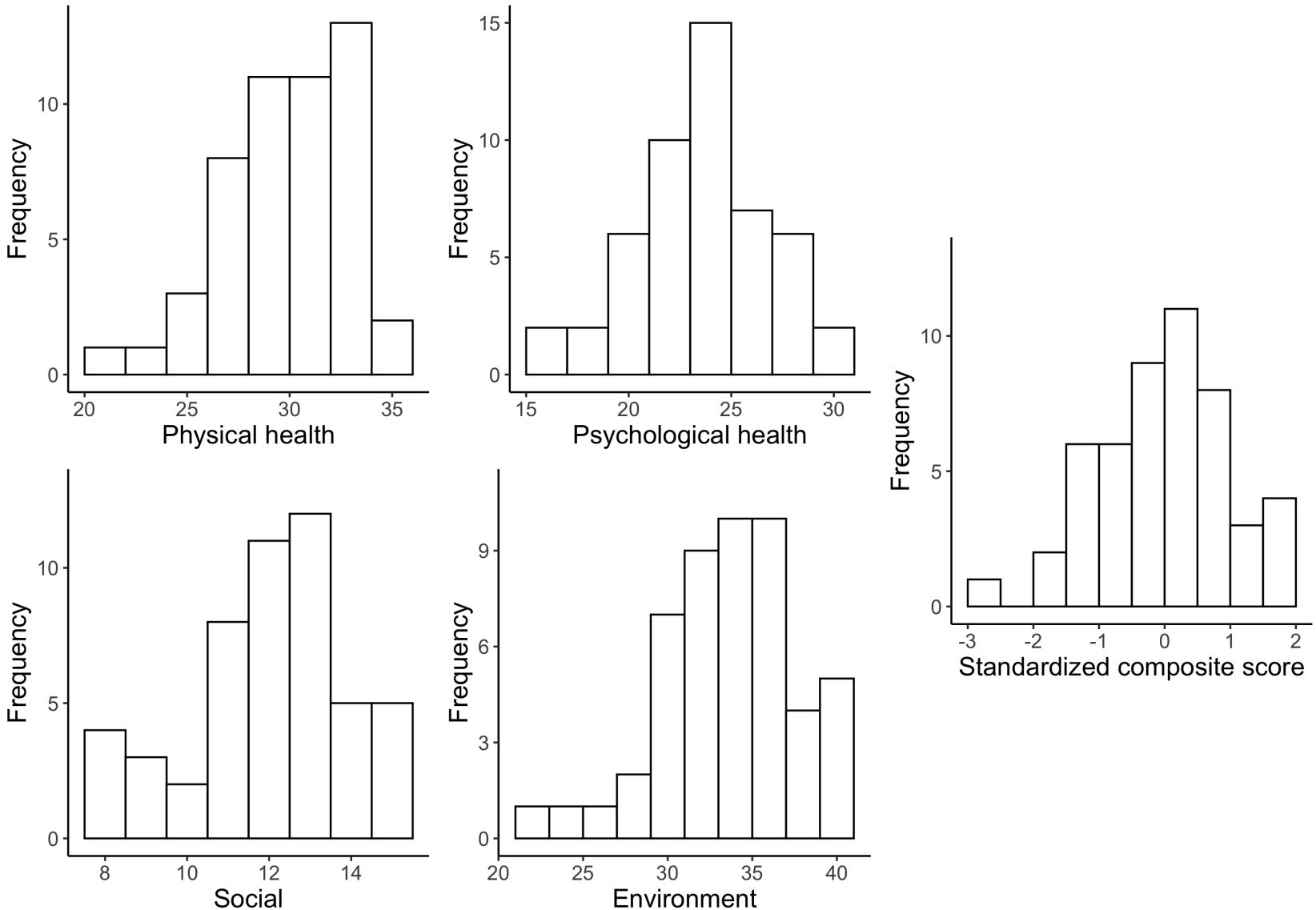
Appendix

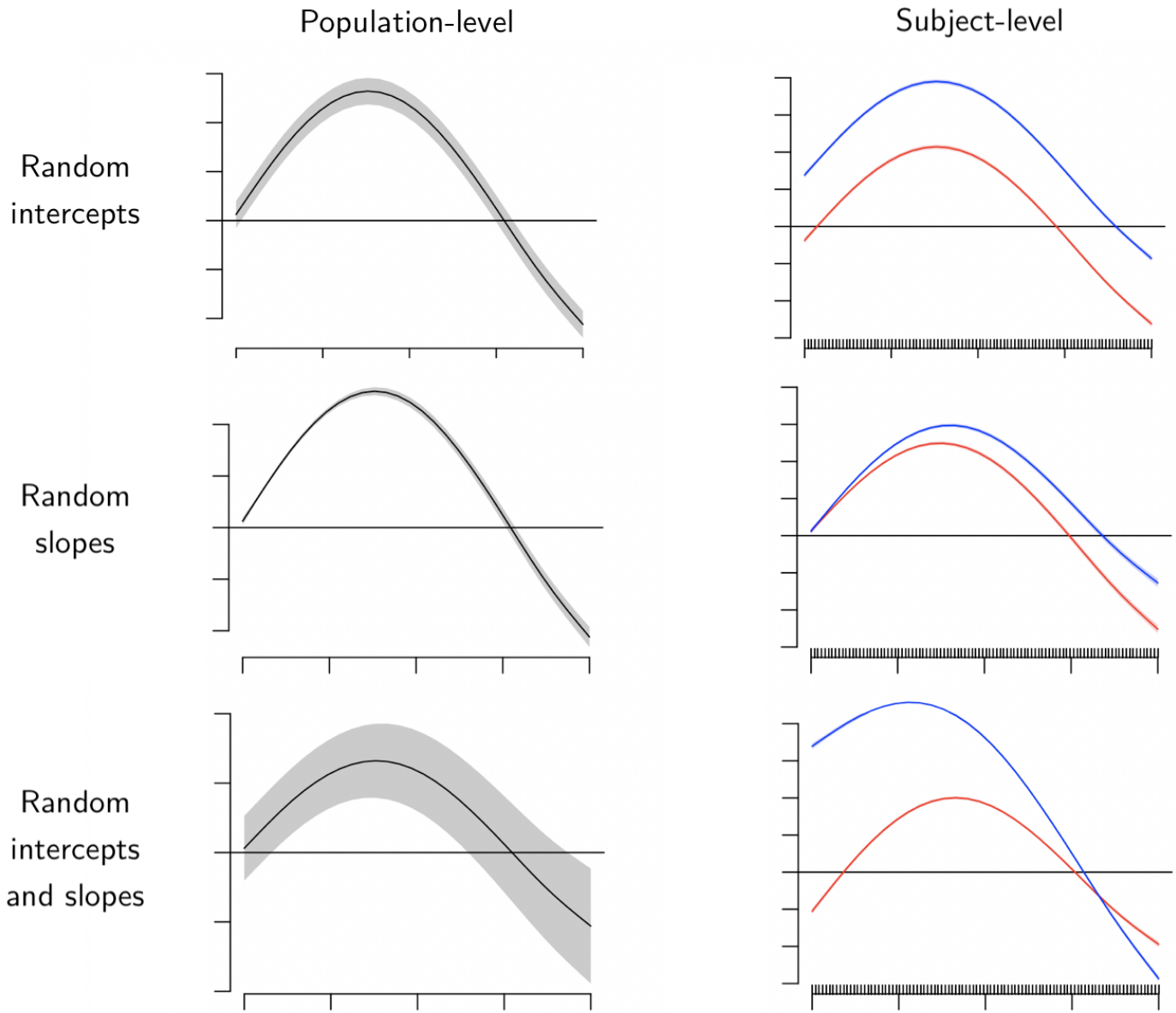
QOL and inhibitory control

Study	Sample	Task	QOL measure	Finding
Jefferson et al., 2006	Older women and men with heart disease	Modified Stroop	Independent functioning in daily activities	No association
Davis et al., 2010	Older but otherwise healthy women	Stroop	QALYs	Positive association
Chamberlain et al., 2019	Young adults who had engaged in gambling at least once in preceding year	Stop signal	Quality of Life Inventory overall score	No association

WHO-QOL score distributions



Random effects in GAMMs



Summary of age effects in GAMMs

Outcome measure	edf	F	p-value	q-value
Proportion correct trials	3.64	24.43	< 0.0001	$< \mathbf{0.0001}$
Proportion error-corrected trials	3.87	17.22	< 0.0001	$< \mathbf{0.0001}$
Average latency correct trials	2.91	12.94	< 0.0001	$< \mathbf{0.0001}$
Average latency error-corrected trials	4.02	2.29	0.0550	0.1046
SEF activation correct trials	1.00	0.00	0.9644	0.9828
Pre-SMA activation correct trials	1.00	0.97	0.3244	0.4867
L FEF activation correct trials	2.67	4.44	0.0142	**0.0320**
R FEF activation correct trials	1.00	3.11	0.0785	0.1285
L putamen activation correct trials	1.00	0.45	0.5025	0.6461
R putamen activation correct trials	1.00	0.11	0.7368	0.8289
L pPC activation correct trials	2.74	4.49	0.0060	**0.0193**
R pPC activation correct trials	2.30	4.63	0.0055	**0.0193**
L dlPFC activation correct trials	1.00	0.00	0.9828	0.9828
R dlPFC activation correct trials	3.15	4.20	0.0064	**0.0193**
L vlPFC activation correct trials	1.54	0.27	0.7332	0.8289
R vlPFC activation correct trials	2.57	2.23	0.0581	0.1046
dACC activation correct trials	1.00	0.84	0.3570	0.4948
dACC activation error-corrected trials	1.51	4.55	0.0120	**0.0309**

Generalized additive models

$$g(\mu) = \beta_0 + s_1(x_1) + ... + s_p(x_p)$$

$g(\cdot)$ represents the link function
$\mu = E(Y)$ is the conditional expectation of the response variable Y
x_j represents the value of the j^{th} of p covariates
$s_j(\cdot)$ represents an unknown smooth function of covariate x_j

Using splines, each smooth function $s_j(x_j)$ can be represented by a sum of basis functions

$$s_j(x_j) = \sum_{k}^{K_j} \beta_{jk} b_{jk}(x_j)$$

Generalized additive mixed models

$$g(\mu_{it}) = \beta_0 + s_1(x_{1it}) + ... + s_p(x_{pit}) + z'_{it} b_i$$

$\mu_{it} = E(Y_{it})$ is the conditional expectation of the response variable Y for subject i, $i = 1, ..., n$ at time t, $t = 1, ..., T_i$

$g(\cdot)$ is the link function

$s_j(\cdot)$ are the unknown smooth functions

x_{jit} is the j^{th} of p covariates associated with fixed effects

z'_{it} is a vector of q covariates associated with random effects

b_i is a vector of random effects

Elastic net regression

Ridge (ℓ_2 penalty)

$$\sum_{i=1}^{n}\left(y_i - \beta_0 - \sum_{j=1}^{p}\beta_j x_{ij}\right)^2 + \lambda\sum_{j=1}^{p}{\beta_j}^2$$

Lasso (ℓ_1 penalty)

$$\sum_{i=1}^{n}\left(y_i - \beta_0 - \sum_{j=1}^{p}\beta_j x_{ij}\right)^2 + \lambda\sum_{j=1}^{p}|\beta_j|$$

Elastic net

$$\sum_{i=1}^{n}\left(y_i - \beta_0 - \sum_{j=1}^{p}\beta_j x_{ij}\right)^2 + \lambda_1\sum_{j=1}^{p}|\beta_j| + \lambda_2\sum_{j=1}^{p}{\beta_j}^2$$

Elastic net reparameterization

$$\sum_{i=1}^{n}\left(y_i - \beta_0 - \sum_{j=1}^{p}\beta_j x_{ij}\right)^2 + \lambda\left(\frac{1-\alpha}{2}\sum_{j=1}^{p}{\beta_j}^2 + \alpha\sum_{j=1}^{p}|\beta_j|\right)$$

$\alpha \in [0, 1]$ is a "mixing" parameter which controls the relative contributions of the ℓ_1 and ℓ_2 penalties

λ controls the overall strength of the elastic net penalty