The role of the brain in the direct and indirect genetic transmission of risk for neurodevelopmental disorders in the Generation R cohort

Fin van Uum, Yllza Xerxa, Ryan Muetzel, Alexander Neumann, Charlotte Cecil, Koen Bolhuis, Jean-Baptiste Pingault, Henning Tiemeier, Neeltje van Haren

Funded by the European Union, the Swiss State Secretariat for Education, Research and Innovation (SERI) and the UK Research and Innovation (UKRI) under the UK government's Horizon Europe funding guarantee. Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union, or the European Health and Digital Executive Agency (HADEA), the SERI or the UKRI. Neither the European Union nor the granting authorities can be held responsible for them.

Funded by
the European Union

Project origin

- Started 1 Sep. 2023 as a PhD-student at the Erasmus MC

- Work package 5 – Neuroimaging
- Task 5.4: Explore how genetic and environmental routes of transmission of parental mental health problems to offspring relate to brain features in childhood and adolescence.
- *“Based on WP3 findings, polygenic scores for mental illnesses will be selected, and the triad genetic design from WP3 will be implemented to quantify (i) whether these polygenic scores associate with brain traits that are shared within-family, and (ii) how much of this is due to genetic transmission versus genetic nurture effects”*

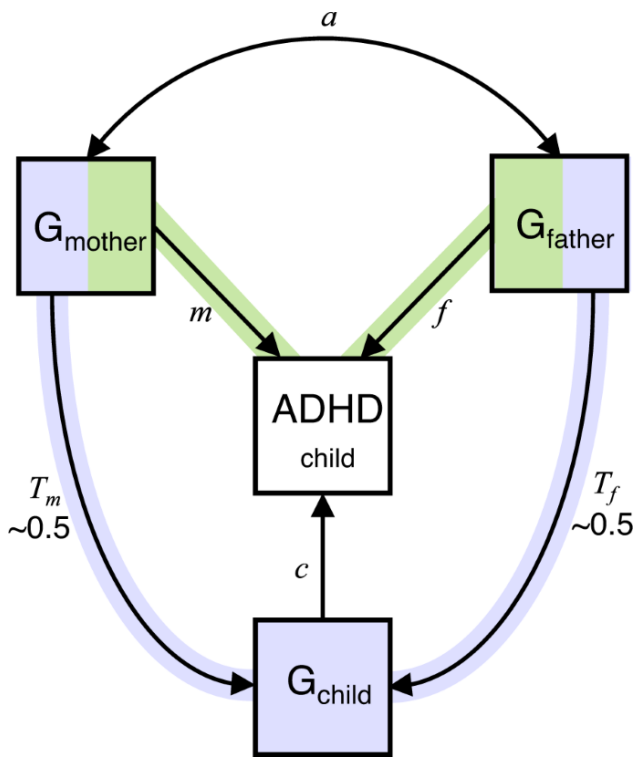
- Today: brief conceptual overview, methods and (discussion about) preliminary results

Funded by the European Union, the Swiss State Secretariat for Education, Research and Innovation (SERI) and the UK Research and Innovation (UKRI) under the UK government’s Horizon Europe funding guarantee. Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union, or the European Health and Digital Executive Agency (HADEA), the SERI or the UKRI. Neither the European Union nor the granting authorities can be held responsible for them.

Funded by
the European Union

Transmission pathways

- Focus current research: **direct genetic transmission** vs **indirect genetic transmission (genetic nurture)** pathways of transmission (and how these relate to neuroimaging variables).

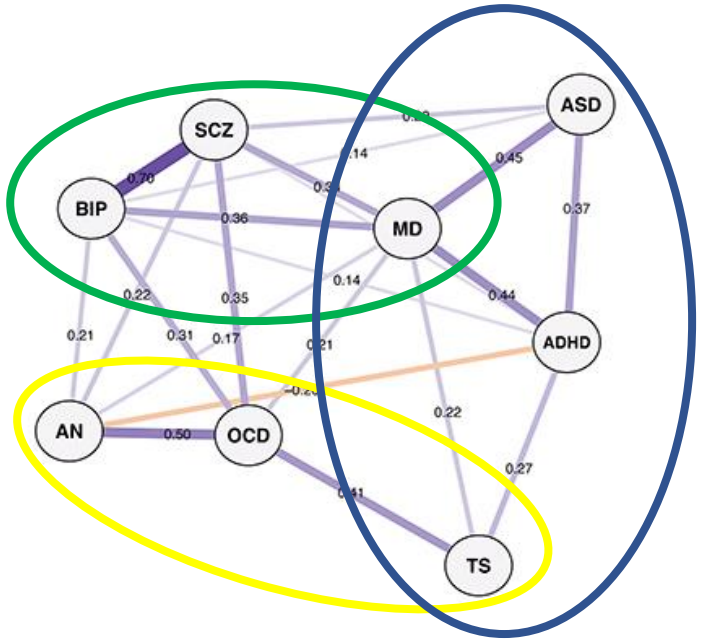


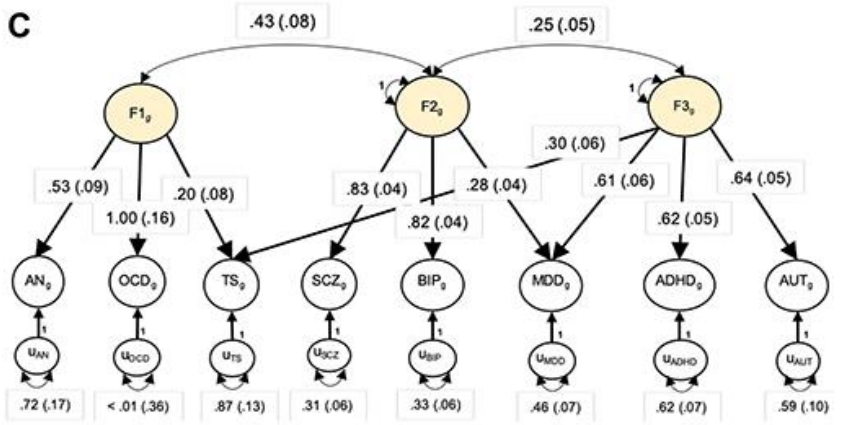
Funded by the European Union, the Swiss State Secretariat for Education, Research and Innovation (SERI) and the UK Research and Innovation (UKRI) under the UK government's Horizon Europe funding guarantee. Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union, or the European Health and Digital Executive Agency (HADEA), the SERI or the UKRI. Neither the European Union nor the granting authorities can be held responsible for them.

Funded by
the European Union

Transdiagnostic polygenic risk operationalization

- Make use of overlap genetic risk across borders psychiatric diagnoses
- EFA has been performed with GWAS data for 8 psychiatric disorders
- Based on genetic correlations, 3 latent factors were derived (**NDev**, OCD/Anxiety, Psychotic)



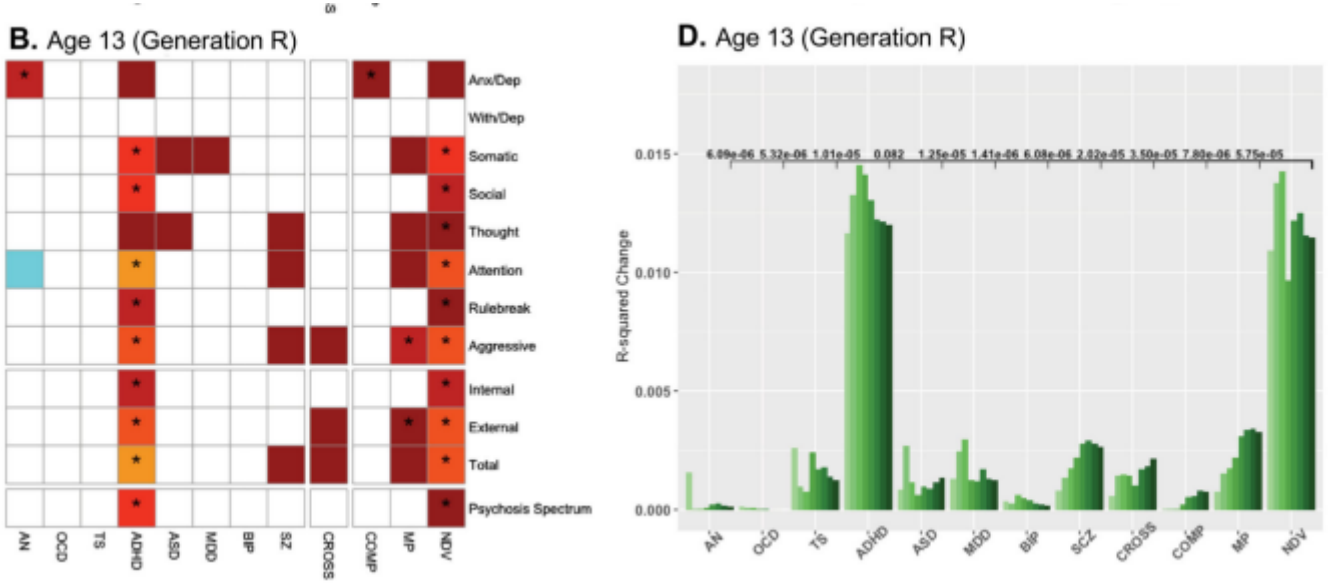


Funded by the European Union, the Swiss State Secretariat for Education, Research and Innovation (SERI) and the UK Research and Innovation (UKRI) under the UK government's Horizon Europe funding guarantee. Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union, or the European Health and Digital Executive Agency (HADEA), the SERI or the UKRI. Neither the European Union nor the granting authorities can be held responsible for them.

Funded by
the European Union

Neurodevelopmental Cluster

- We will use the neurodevelopmental PRS (NDev PRS)
- Strongest predictor of clinical outcomes, and disorders of interest (age GenR)



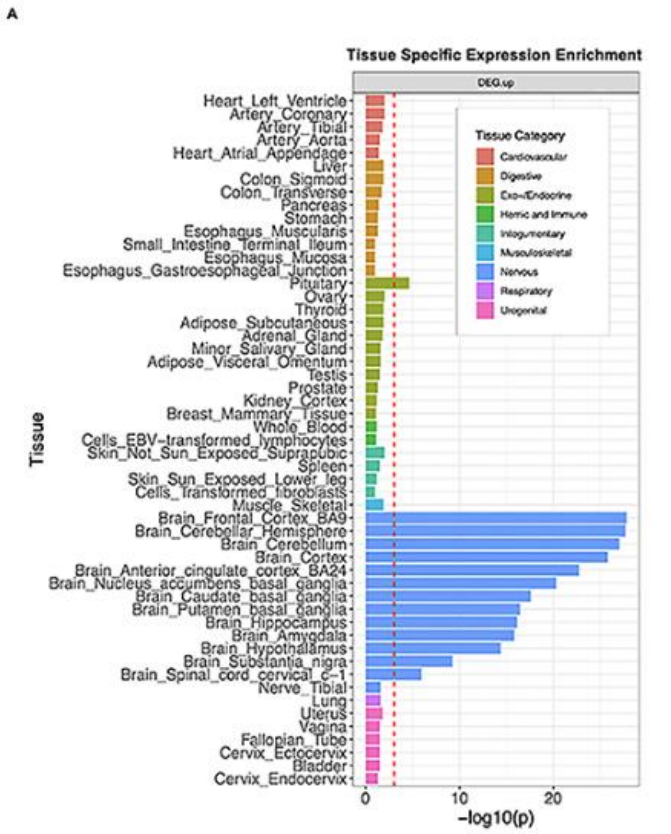
- Outperforms single-trait PRSs in relationship with psychiatric phenotypes
- But, variance highly determined by variance in ADHD PRS

Funded by the European Union, the Swiss State Secretariat for Education, Research and Innovation (SERI) and the UK Research and Innovation (UKRI) under the UK government's Horizon Europe funding guarantee. Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union, or the European Health and Digital Executive Agency (HADEA), the SERI or the UKRI. Neither the European Union nor the granting authorities can be held responsible for them.

Funded by
the European Union

NDev genetic loci tissue expression

- SNP's/genes involved in NDev cluster are **primarily expressed in the brain**



- Moreover, particularly holds for the <u>pleiotropic</u> (75%) genetic loci:

1. Gene *DCC* (involved in all 8 disorders), guides axonal growth during neural development -> expression peaks prenatally
2. Gene *RBFOX1* (involved in 7 disorders), guides neural migration/ synapse formation
3. All 109 pleiotropic risk loci associated with neurogenesis/ development/glutamate signaling, which was not observed for disorder-specific loci

→ <u>Transdiagnostic genetic risk loci for NDev disorders primarily involved in neural development</u>

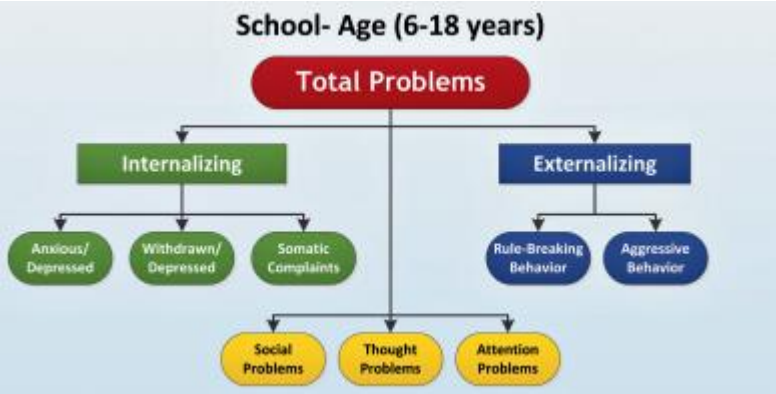
- Suggests (early) brain development as a biological pathway from genetic risk to neurodevelopmental psychological phenotypes -> **neural mediation**

Funded by the European Union, the Swiss State Secretariat for Education, Research and Innovation (SERI) and the UK Research and Innovation (UKRI) under the UK government's Horizon Europe funding guarantee. Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union, or the European Health and Digital Executive Agency (HADEA), the SERI or the UKRI. Neither the European Union nor the granting authorities can be held responsible for them.

Funded by
the European Union

Clinical outcomes

- Clinical outcomes in line with the transdiagnostic nature of the respective genetic risk factors
- Broad syndrome scales: **internalizing problems, externalizing problems, attention, and social problems** (a.o.t. diagnoses)
- Conditional on significant main effects, specific types of behavioural problems (e.g. aggression, withdrawn/depressed) and PRS's (single-disorder PRS's) will be assessed



→

- **Main RQ: How is the transdiagnostic genetic risk for neurodevelopmental disorders transmitted from parent to child, and how is this related to neuroimaging measures?**

Funded by the European Union, the Swiss State Secretariat for Education, Research and Innovation (SERI) and the UK Research and Innovation (UKRI) under the UK government's Horizon Europe funding guarantee. Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union, or the European Health and Digital Executive Agency (HADEA), the SERI or the UKRI. Neither the European Union nor the granting authorities can be held responsible for them.

Funded by
the European Union

Methods

- **Cohort:**
- Generation R

- **Child behavioural outcomes:**
- Youth Self-Report (YSR) – Child self-report internalizing, externalizing, attention, and social symptoms
- Child Behaviour Checklist (CBCL) - Parent-report internalizing, externalizing, attention, and social symptoms
- Behavioural reports at age 14, neuroimaging measures at age 10
- Latent factors over the reporters (YSR/CBCL) are considered

- **Neuroimaging measures:**
- Total cortical surface area, cerebellar cortical volume, subcortical GMV, mean fractional anisotropy (FA)

- **Covariates:**
- Parental age at inclusion, parental education, marital status at baseline, child sex at birth, age, ICV, and genetic principal components (ancestry population structure)

- **Statistical analyses:**
- 1) linear regressions, 2) mediation models, and 3) SEM trio (mediation) models

Funded by the European Union, the Swiss State Secretariat for Education, Research and Innovation (SERI) and the UK Research and Innovation (UKRI) under the UK government's Horizon Europe funding guarantee. Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union, or the European Health and Digital Executive Agency (HADEA), the SERI or the UKRI. Neither the European Union nor the granting authorities can be held responsible for them.

Funded by
the European Union

Preliminary Results (correlations)

- Only with complete data for now!

Pearson's Correlations

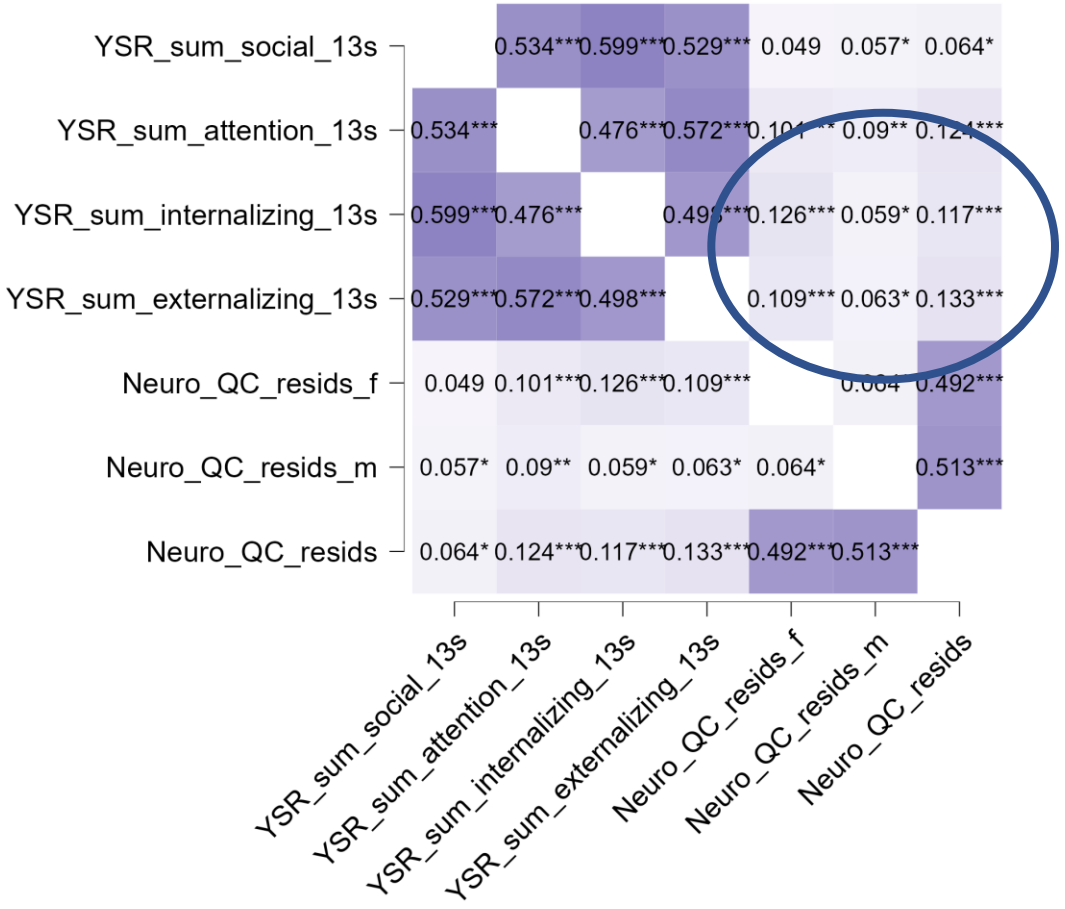
Variable		Neuro_QC_resids	Neuro_QC_resids_m	Neuro_QC_resids_f
1. Neuro_QC_resids	Pearson's r	—		
	p-value	—		
2. Neuro_QC_resids_m	Pearson's r	**0.513** ***	—	
	p-value	< .001	—	
3. Neuro_QC_resids_f	Pearson's r	**0.492** ***	0.064 *	—
	p-value	< .001	0.013	—

* p < .05, ** p < .01, *** p < .001

Funded by the European Union, the Swiss State Secretariat for Education, Research and Innovation (SERI) and the UK Research and Innovation (UKRI) under the UK government's Horizon Europe funding guarantee. Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union, or the European Health and Digital Executive Agency (HADEA), the SERI or the UKRI. Neither the European Union nor the granting authorities can be held responsible for them.

Funded by the European Union

Preliminary Results (correlations) (2)



- Correlations between clinical outcomes and genetic risk seem to be larger for the genetic risk of the father.

Funded by the European Union, the Swiss State Secretariat for Education, Research and Innovation (SERI) and the UK Research and Innovation (UKRI) under the UK government's Horizon Europe funding guarantee. Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union, or the European Health and Digital Executive Agency (HADEA), the SERI or the UKRI. Neither the European Union nor the granting authorities can be held responsible for them.

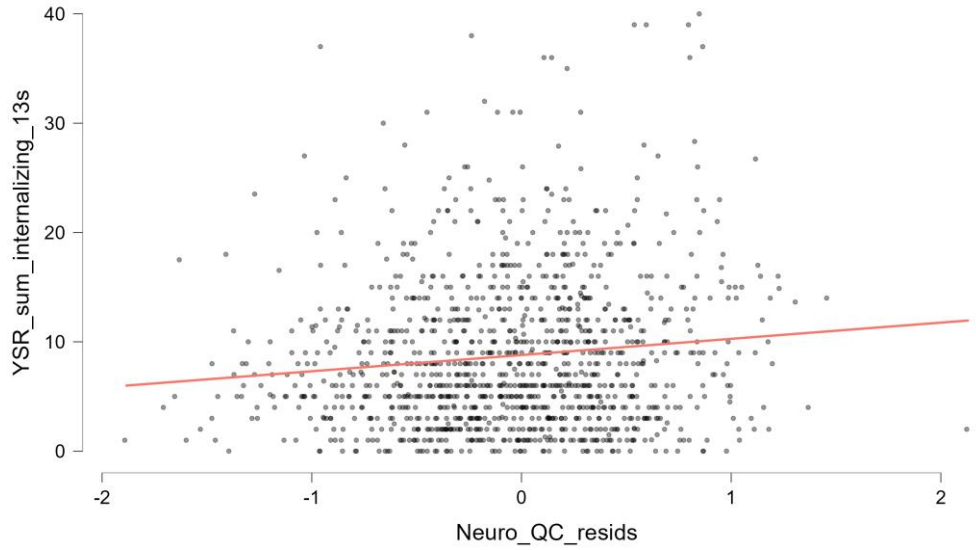
Funded by
the European Union

Preliminary Results (regressions) (1)

- **Aim 1**: To investigate the associations between **child genetic risk** for NDev disorders and child **internalizing**, externalizing, attention, and social problems.

Coefficients

Model		Unstandardized	Standard Error	Standardized[a]	t	p
H_0	(Intercept)	8.707	0.201		43.368	< .001
H_1	(Intercept)	-0.863	7.641		-0.113	0.910
	GENDER (girl)	2.825	0.391		7.229	< .001
	Neuro_QC_resids	1.437	0.359	0.113	3.998	< .001
	YSR_AGECHILD_GR1095	0.606	0.564	0.030	1.074	0.283



Funded by the European Union, the Swiss State Secretariat for Education, Research and Innovation (SERI) and the UK Research and Innovation (UKRI) under the UK government's Horizon Europe funding guarantee. Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union, or the European Health and Digital Executive Agency (HADEA), the SERI or the UKRI. Neither the European Union nor the granting authorities can be held responsible for them.

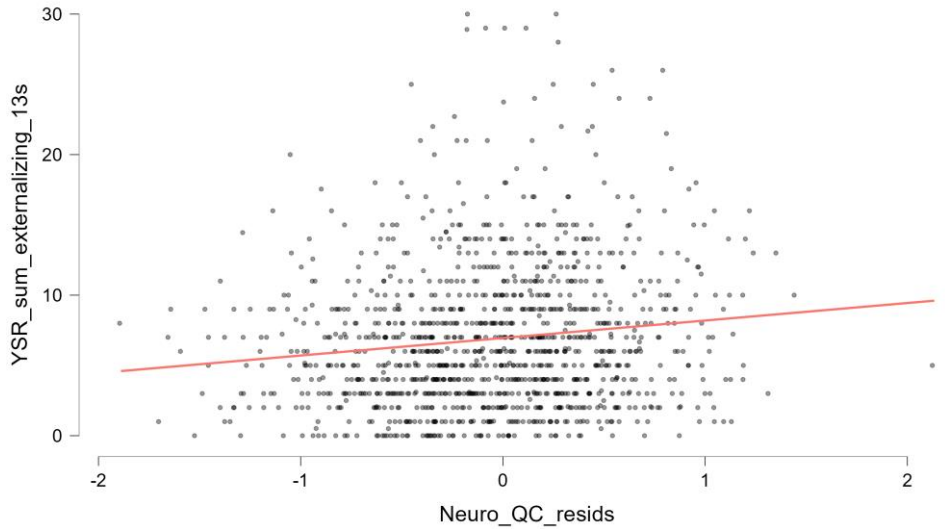
Funded by the European Union

Preliminary Results (regressions) (2)

- **Aim 1**: To investigate the associations between **child genetic risk** for NDev disorders and child internalizing, **externalizing**, attention, and social problems.

Coefficients

Model		Unstandardized	Standard Error	Standardized[a]	t	p
H_0	(Intercept)	6.879	0.149		46.239	< .001
H_1	(Intercept)	-8.565	5.569		-1.538	0.124
	GENDER (girl)	-1.019	0.293		-3.479	< .001
	Neuro_QC_resids	1.258	0.269	0.134	4.670	< .001
	YSR_AGECHILD_GR1095	1.184	0.411	0.083	2.881	0.004



Funded by the European Union, the Swiss State Secretariat for Education, Research and Innovation (SERI) and the UK Research and Innovation (UKRI) under the UK government's Horizon Europe funding guarantee. Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union, or the European Health and Digital Executive Agency (HADEA), the SERI or the UKRI. Neither the European Union nor the granting authorities can be held responsible for them.

Funded by the European Union

Preliminary Results (regressions) (3)

- Modeling genetic risk of both parents instead of child genetic risk:

Coefficients

Model		Unstandardized	Standard Error	Standardized[a]	t	p
H_o	(Intercept)	8.707	0.201		43.368	< .001
H_1	(Intercept)	-0.150	7.629		-0.020	0.984
	YSR_AGECHILD_GR1095	0.554	0.563	0.028	0.984	0.325
	GENDER (girl)	2.840	0.390		7.288	< .001
	Neuro_QC_resids_m	0.741	0.395	0.053	1.875	0.061
	Neuro_QC_resids_f	1.736	0.400	0.123	4.338	< .001

[a] Standardized coefficients can only be computed for continuous predictors.

- Standardized estimates +- 2x as large for paternal (a.o.t. maternal) genetic risk on child internalizing and externalizing symptoms.
- Interpretation?

Funded by the European Union, the Swiss State Secretariat for Education, Research and Innovation (SERI) and the UK Research and Innovation (UKRI) under the UK government's Horizon Europe funding guarantee. Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union, or the European Health and Digital Executive Agency (HADEA), the SERI or the UKRI. Neither the European Union nor the granting authorities can be held responsible for them.

Funded by the European Union

Preliminary Results (regressions) (4)

- Linear relationship brain metrics and clinical outcomes is absent after controlling for relevant variables.

Model		Unstandardized	Standard Error	Standardized[a]	t	p
H_0	(Intercept)	8.707	0.201		43.368	< .001
H_1	(Intercept)	4.870	8.277		0.588	0.556
	avg_Cerebellum_Cortex_Vol	-3.260×10^{-5}	4.724×10^{-5}	−0.026	−0.690	0.490
	GENDER (girl)	2.347	0.465		5.048	< .001
	YSR_AGECHILD_GR1095	0.620	0.568	0.031	1.092	0.275
	eTIV_f09	-2.504×10^{-6}	1.912×10^{-6}	−0.050	−1.309	0.191

Model		Unstandardized	Standard Error	Standardized[a]	t	p
H_0	(Intercept)	8.707	0.201		43.368	< .001
H_1	(Intercept)	3.380	8.109		0.417	0.677
	YSR_AGECHILD_GR1095	0.645	0.568	0.032	1.137	0.256
	eTIV_f09	-4.006×10^{-6}	3.200×10^{-6}	−0.079	−1.252	0.211
	GENDER (girl)	2.439	0.456		5.354	< .001
	avg_WhiteSurfArea_f09	1.547×10^{-5}	5.036×10^{-5}	0.019	0.307	0.759

Model		Unstandardized	Standard Error	Standardized[a]	t	p
H_0	(Intercept)	8.707	0.201		43.368	< .001
H_1	(Intercept)	3.720	8.203		0.454	0.650
	YSR_AGECHILD_GR1095	0.643	0.568	0.032	1.132	0.258
	eTIV_f09	-3.019×10^{-6}	2.516×10^{-6}	−0.060	−1.200	0.230
	GENDER (girl)	2.421	0.452		5.353	< .001
	SubCortGrayVol_f09	-5.731×10^{-6}	7.405×10^{-5}	−0.004	−0.077	0.938

Funded by the European Union, the Swiss State Secretariat for Education, Research and Innovation (SERI) and the UK Research and Innovation (UKRI) under the UK government's Horizon Europe funding guarantee. Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union, or the European Health and Digital Executive Agency (HADEA), the SERI or the UKRI. Neither the European Union nor the granting authorities can be held responsible for them.

Funded by the European Union

Preliminary Results (mediation)

- **Aim 2:** To investigate whether the associations between child genetic risk for NDev disorders with child **internalizing**, externalizing, attention and social problems is **mediated by neuroimaging measures.**

Indirect effects

									95% Confidence Interval	
					Estimate	Std. Error	z-value	p	Lower	Upper
Neuro_QC_resids	→	avg_WhiteSurfArea_f09	→	YSR_sum_internalizing_13s	0.003	0.003	1.065	0.287	-0.002	0.008

Note. Delta method standard errors, normal theory confidence intervals, ML estimator.

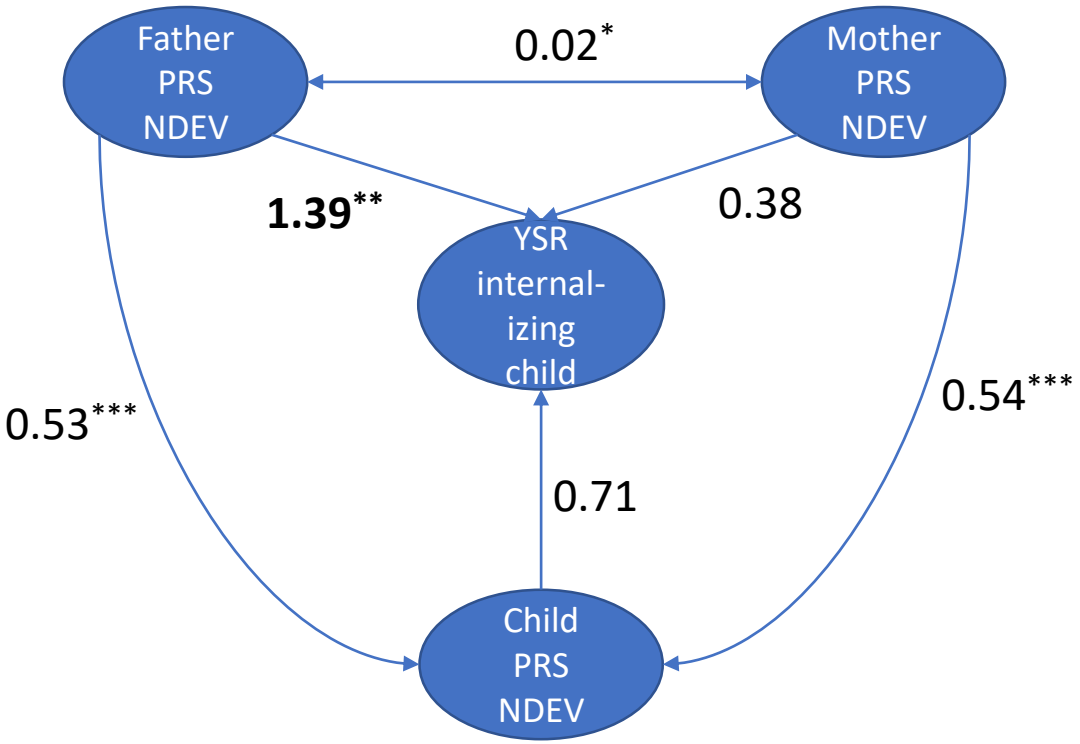
- Effects NDEV PRS on outcomes do not seem to be mediated by the included macro-level neuroimaging variables (both for internalizing and externalizing problems), when controlling for age and gender.

Funded by the European Union, the Swiss State Secretariat for Education, Research and Innovation (SERI) and the UK Research and Innovation (UKRI) under the UK government's Horizon Europe funding guarantee. Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union, or the European Health and Digital Executive Agency (HADEA), the SERI or the UKRI. Neither the European Union nor the granting authorities can be held responsible for them.

Funded by the European Union

Preliminary Results (trio models) (1)

- **Aim 3:** To quantify the **influence of parental genetic** risk for neurodevelopmental disorders in the associations between child genetic risk for neurodevelopmental disorders and child **internalizing**, externalizing, social, and attention problems (genetic transmission vs genetic nurture).



Regression coefficients

Predictor	Outcome	Estimate	Std. Error	z-value	p	95% Confidence Interval Lower	Upper
Neuro_QC_resids_m	Neuro_QC_resids	0.539	0.021	25.716	< .001	0.498	0.580
Neuro_QC_resids_f	Neuro_QC_resids	0.526	0.021	24.538	< .001	0.484	0.568
Neuro_QC_resids	YSR_sum_internalizing_13s	0.707	0.500	1.415	0.157	−0.272	1.686
Neuro_QC_resids_m	YSR_sum_internalizing_13s	0.383	0.485	0.790	0.430	−0.568	1.335
Neuro_QC_resids_f	YSR_sum_internalizing_13s	1.392	0.490	2.840	0.005	0.431	2.352

Residual covariances

Variables		Estimate	Std. Error	z-value	p	95% Confidence Interval Lower	Upper
Neuro_QC_resids_m	Neuro_QC_resids_f	0.015	0.006	2.470	0.014	0.003	0.027

Genetic nurture?
Genetic transmission?
Assortative mating?

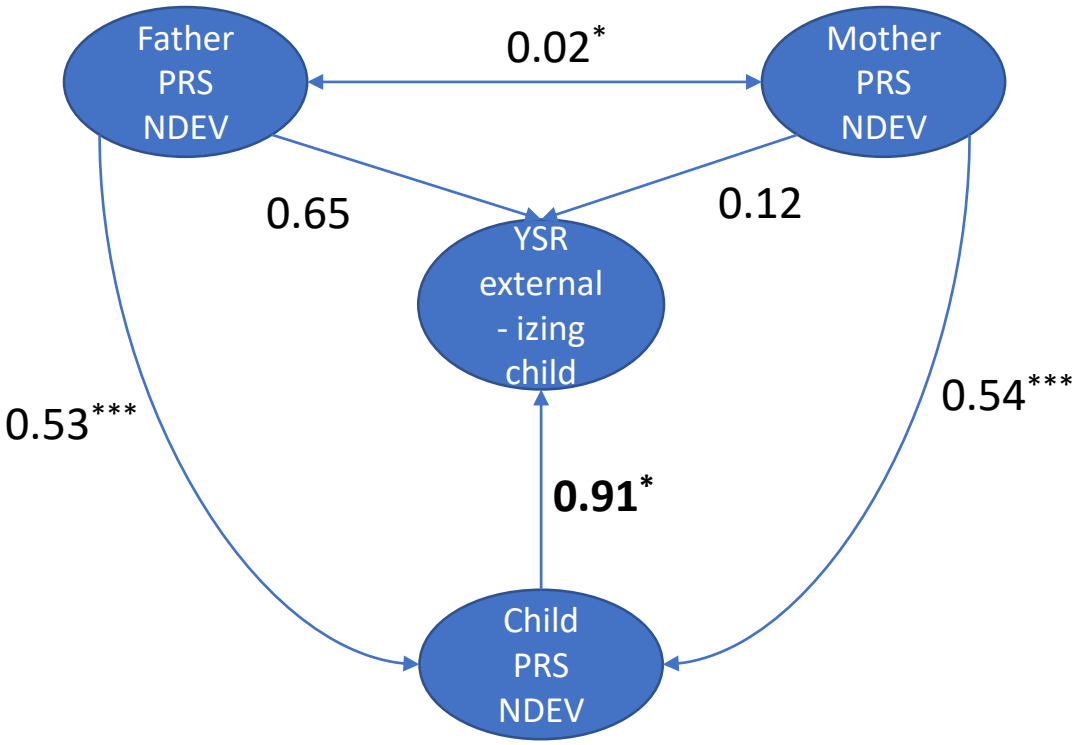
Funded by the European Union, the Swiss State Secretariat for Education, Research and Innovation (SERI) and the UK Research and Innovation (UKRI) under the UK government's Horizon Europe funding guarantee. Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union, or the European Health and Digital Executive Agency (HADEA), the SERI or the UKRI. Neither the European Union nor the granting authorities can be held responsible for them.

Funded by the European Union

Path diagram

Preliminary Results (trio models) (2)

- **Aim 3:** To quantify the **influence of parental genetic** risk for neurodevelopmental disorders in the associations between child genetic risk for neurodevelopmental disorders and child internalizing, **externalizing**, social, and attention problems (genetic transmission vs genetic nurture).



Parameter estimates

Regression coefficients

Predictor	Outcome	Estimate	Std. Error	z-value	p	95% Confidence Interval Lower	Upper
Neuro_QC_resids_m	Neuro_QC_resids	0.539	0.021	25.716	< .001	0.498	0.580
Neuro_QC_resids_f	Neuro_QC_resids	0.526	0.021	24.538	< .001	0.484	0.568
Neuro_QC_resids	YSR_sum_externalizing_13s	0.914	0.370	2.468	0.014	0.188	1.639
Neuro_QC_resids_m	YSR_sum_externalizing_13s	0.115	0.360	0.319	0.750	−0.590	0.820
Neuro_QC_resids_f	YSR_sum_externalizing_13s	0.649	0.363	1.786	0.074	−0.063	1.361

Genetic nurture?
Genetic transmission?

Funded by the European Union, the Swiss State Secretariat for Education, Research and Innovation (SERI) and the UK Research and Innovation (UKRI) under the UK government's Horizon Europe funding guarantee. Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union, or the European Health and Digital Executive Agency (HADEA), the SERI or the UKRI. Neither the European Union nor the granting authorities can be held responsible for them.

Funded by the European Union

Disclaimers

- Not all relevant covariates added yet
- No multiple comparisons corrections yet (although there were not that many)
- Not working with final dataset yet
- Only default settings yet

Funded by the European Union, the Swiss State Secretariat for Education, Research and Innovation (SERI) and the UK Research and Innovation (UKRI) under the UK government's Horizon Europe funding guarantee. Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union, or the European Health and Digital Executive Agency (HADEA), the SERI or the UKRI. Neither the European Union nor the granting authorities can be held responsible for them.

Funded by
the European Union

Questions/ remarks?

Questions or Remarks?

Funded by the European Union, the Swiss State Secretariat for Education, Research and Innovation (SERI) and the UK Research and Innovation (UKRI) under the UK government's Horizon Europe funding guarantee. Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union, or the European Health and Digital Executive Agency (HADEA), the SERI or the UKRI. Neither the European Union nor the granting authorities can be held responsible for them.

Funded by
the European Union