University of BRISTOL

Approaches to imaging (epi-) genetics and to life in general

Dr Esther Walton

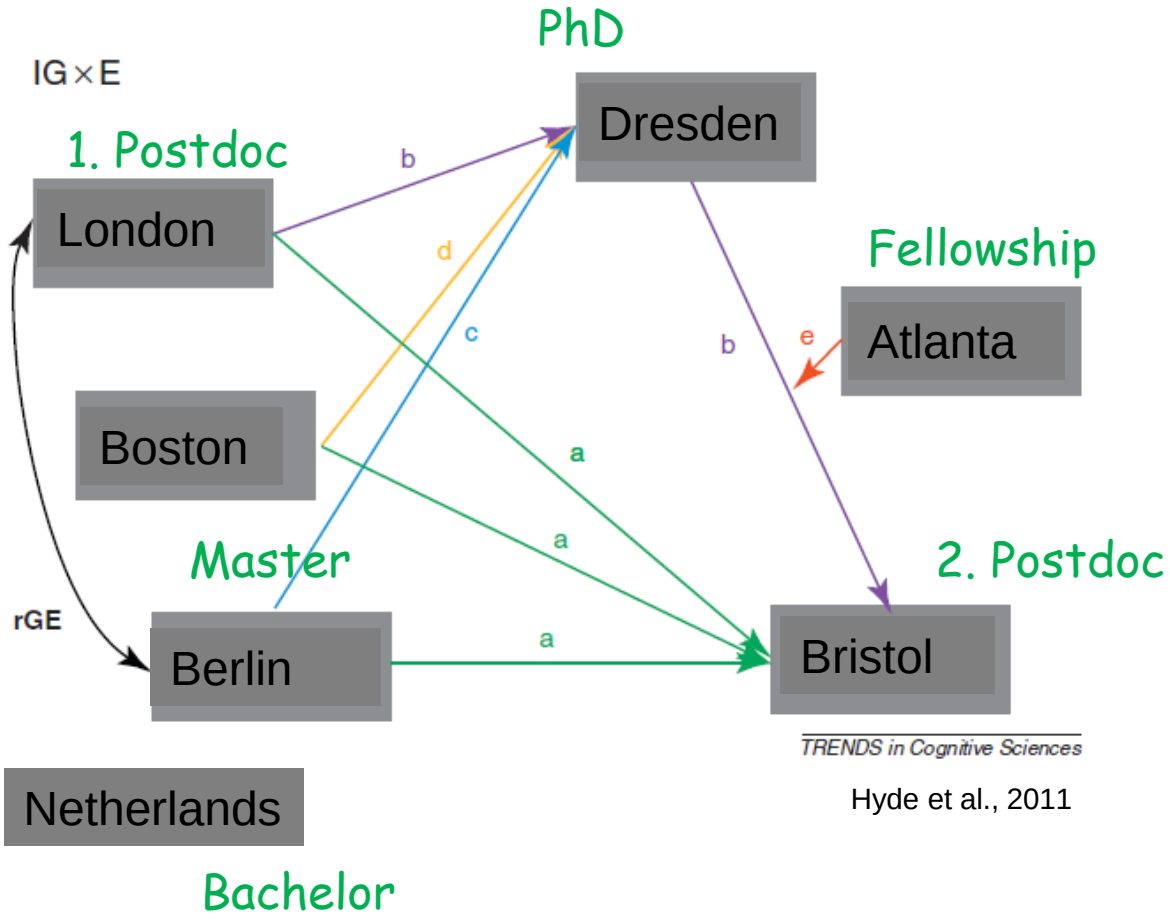
Senior Research Associate in Genetic Epidemiology

MRC Integrative Epidemiology Unit

School of Social & Community Medicine

University of Bristol

Gene – Environment Interactions



Gene – Environment Interactions

A-levels → New Zealand → Bachelor (Maastricht)

Bachelor (Maastricht) → Master in medical neuroscience (Berlin)

Bachelor (Maastricht) → Open University course (online) → Master in medical neuroscience (Berlin)

TIP Discuss all options

TIP Have a back-up plan

Master in medical neuroscience (Berlin) → Masterthesis (Boston) → PhD (Dresden)

TIP Be aware of your own stereotypes

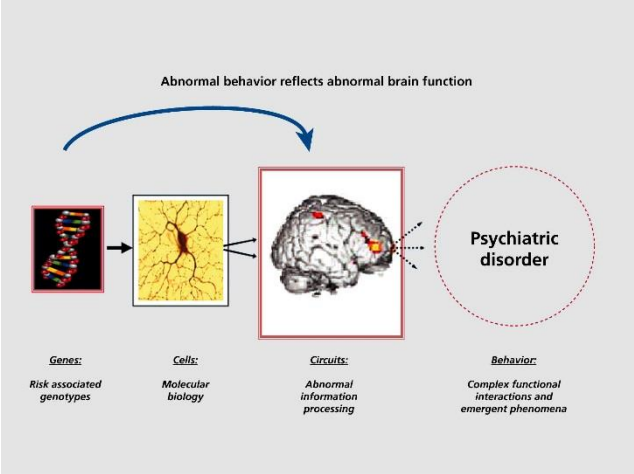
How to align with the partner?

(Some) limitations in psychiatric genetics

- Genetic variants either
  - (too) rare or
  - of small effect or
  - not replicated

  …to explain schizophrenia etiology

  ⇒ Use polygenic scores or/and epigenetics



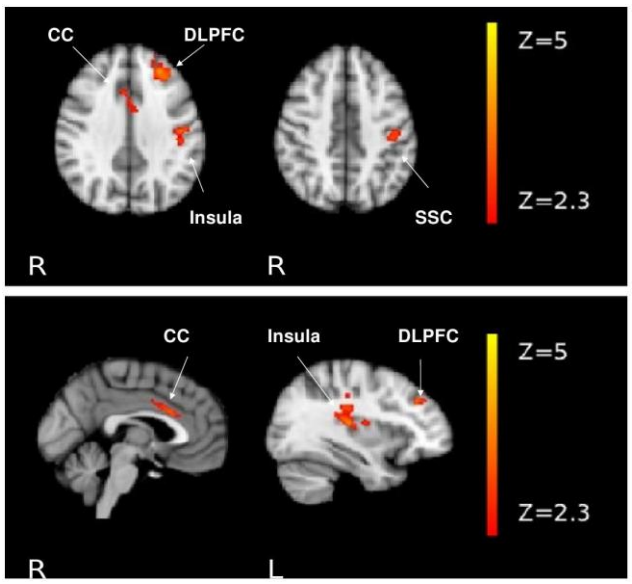
dialogues-cns.org

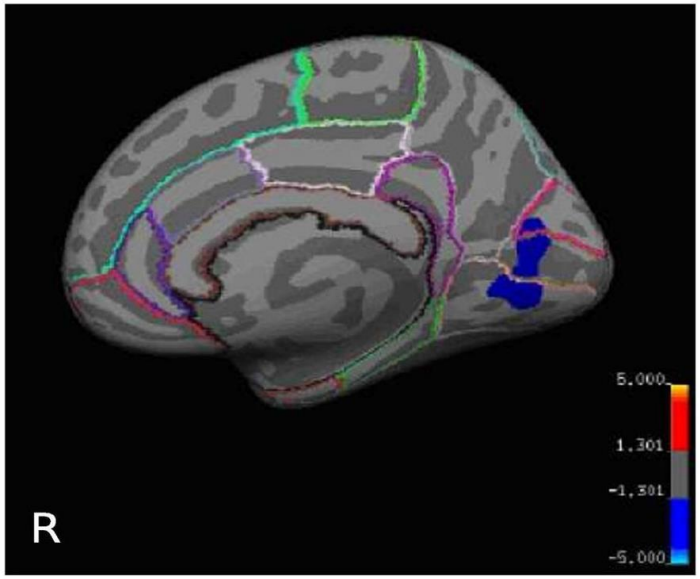
- Dichotomous outcome variable (disease status)
  - Explains little variance
  - Not continuous
  - Does not allow to study risk effect on a brain networks

  ⇒ Use intermediate phenotypes

Neurogranin

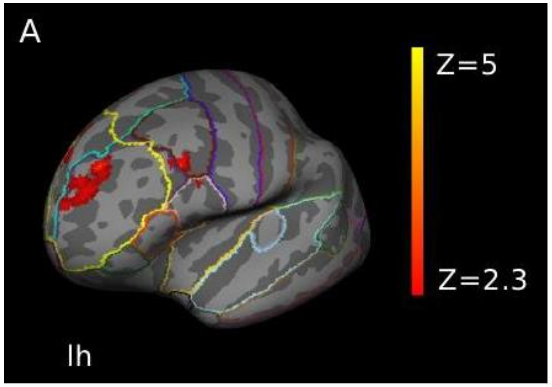
- No genotype effect of either SNP on diagnosis, but on brain function (rs12541) and structure (rs12807809)
- No diagnosis*SNP interaction
- No effect on performance
- => Components in the **NMDA-signalling pathway** contribute to subtle changes in neural functioning and anatomy linked to schizophrenia





Walton et al., 2013a

Polygenic Risk Score



Walton et al., 2013b

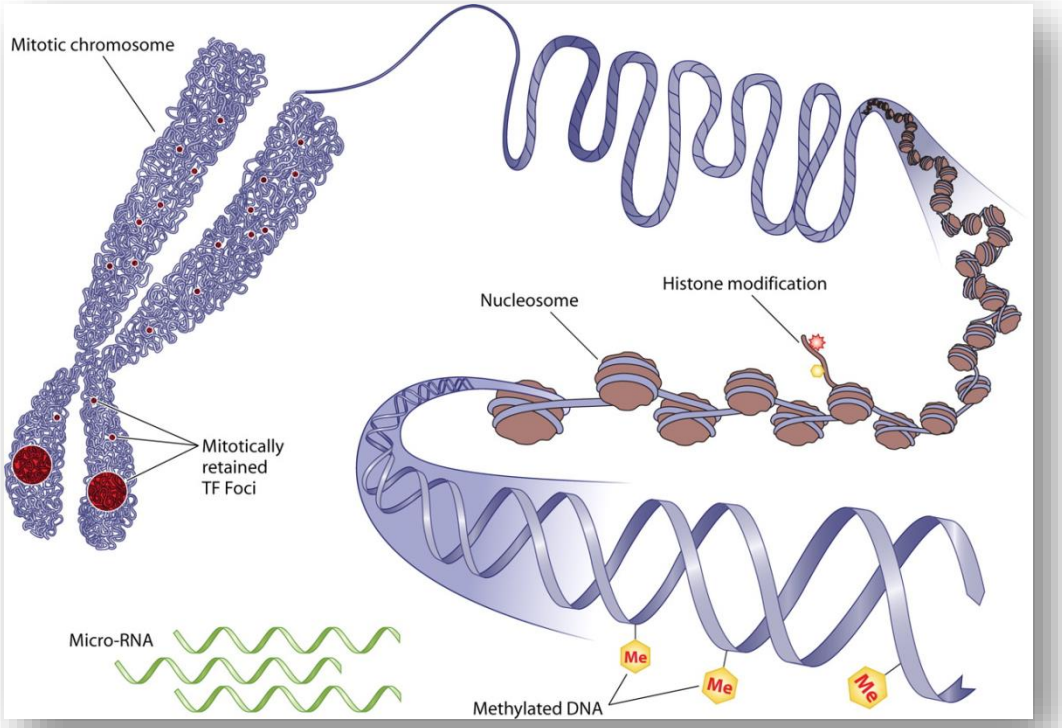
Cluster	Functional annotation	Enrichment score	Number of associated genes
1	axonogenesis	4.58	21
	neuron projection development		
2	ion binding	2.98	73
3	cell motility and migration	2.78	12
4	channel activity	2.32	13
5	GTPase regulator activity	2.23	13

- No PGRS effect on diagnosis, but on brain function
- No PGRS*diagnosis interaction
- No correlation with performance
- Accounted for 4.3% of the total variance
- => combined impact of **many common genetic variants** of small effect reveal etiologic mechanisms of the disorder better than single common genetic variants

DNA methylation

Epigenetic processes

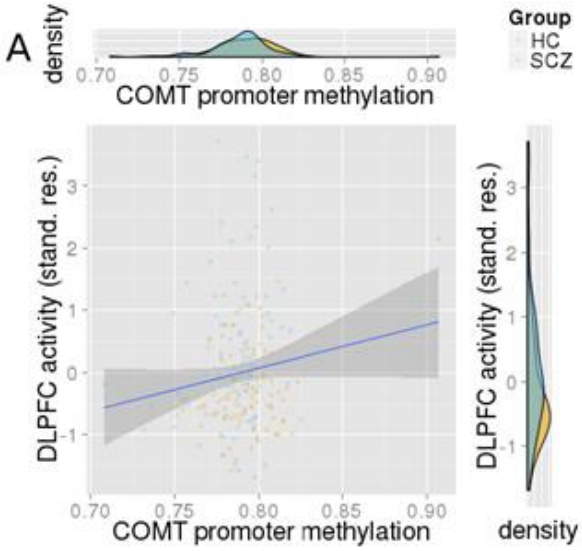
- DNA methylation
- chromatin remodelling
- RNA transcripts
- microRNAs
- prions
- …

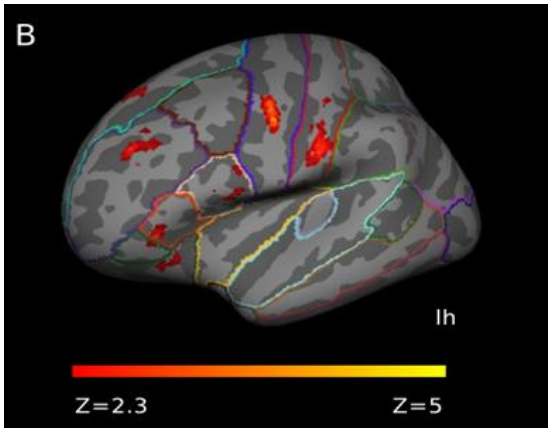


Zaidi et al., 2010

DNA methylation

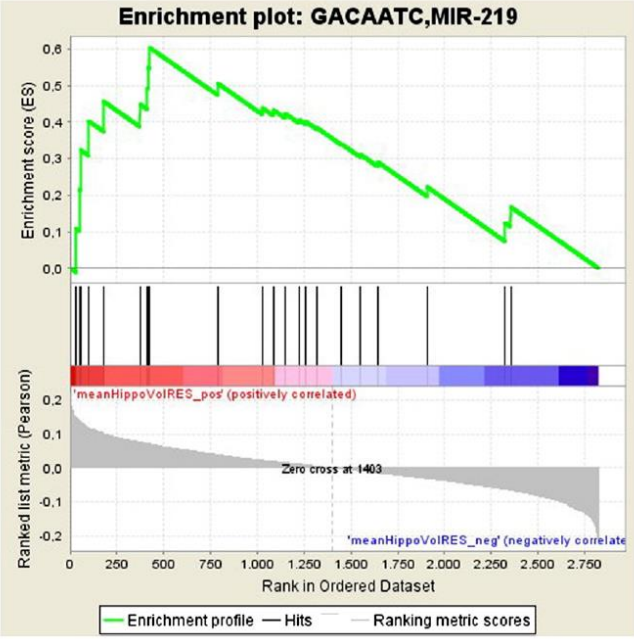
- MB-COMT promoter methylation effects on diagnosis and brain function
- No methylation*diagnosis interaction
- trend correlation with performance (p=0.06)
- => importance of **COMT and epigenetic risk mechanisms** in schizophrenia

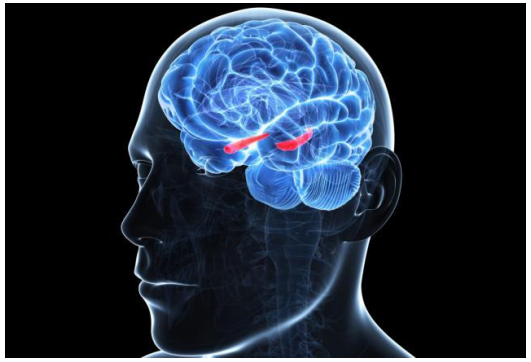




Walton et al., 2014

Gene-set enrichment on hippocampal volume





Hass et al., 2015

- => (dys)regulation of microRNA target genes by epigenetic mechanisms may confer additional risk for developing psychiatric symptoms

Gene – Environment Interactions

A-levels → New Zealand → Bachelor (Maastricht)

TIP Discuss options

Bachelor (Maastricht) → Open University course (online)

Open University course (online) → Master in medical neuroscience (Berlin)

TIP Have a back-up plan

Master in medical neuroscience (Berlin) → Masterthesis (Boston)

Masterthesis (Boston) → PhD (Dresden) → Postdoc (London)

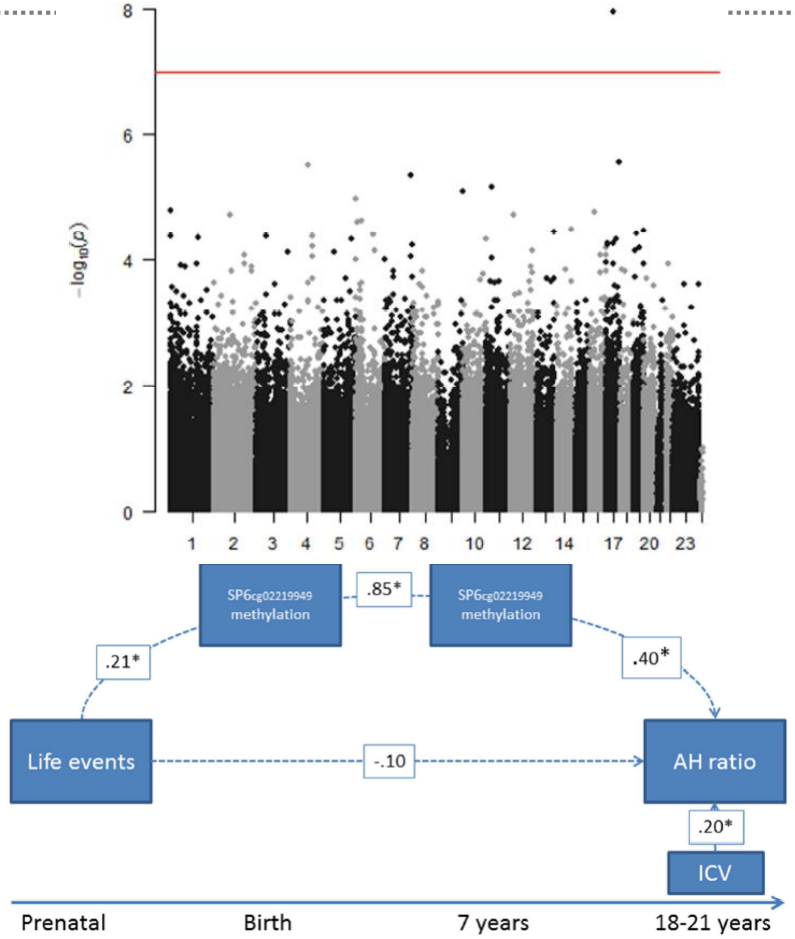
TIP "It's not always men"

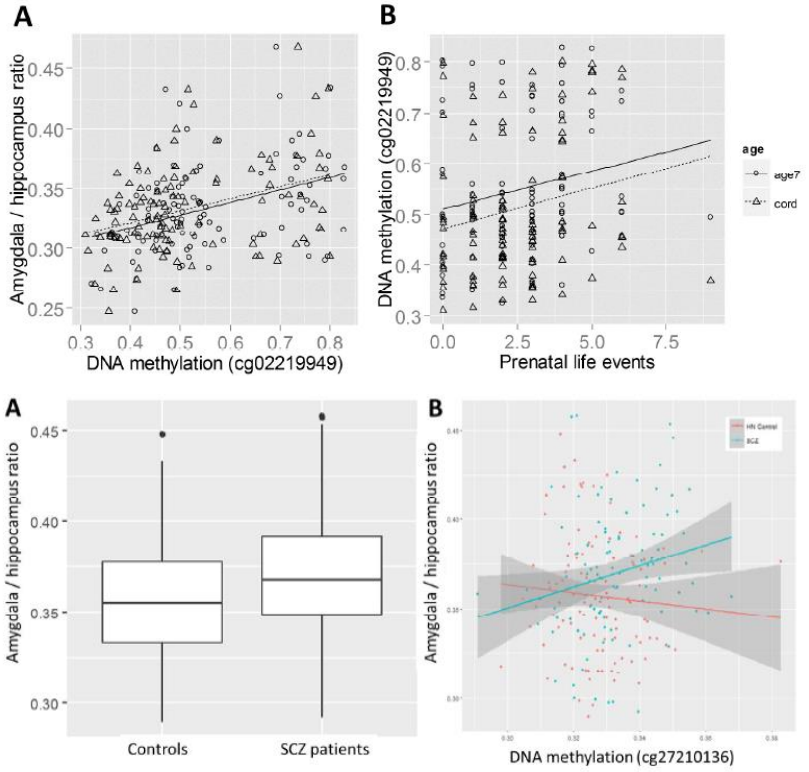
How to align with the partner?

TIP Get a mentor!

How to align with the partner?

Longitudinal EWAS

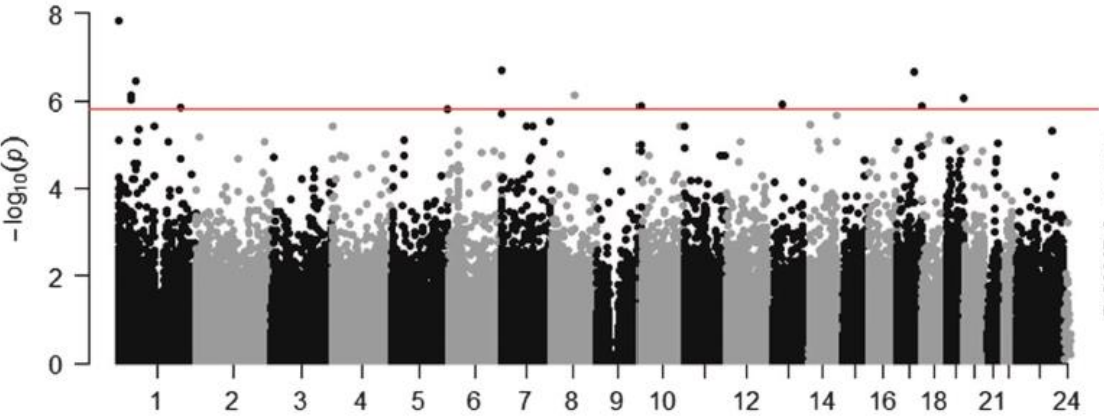


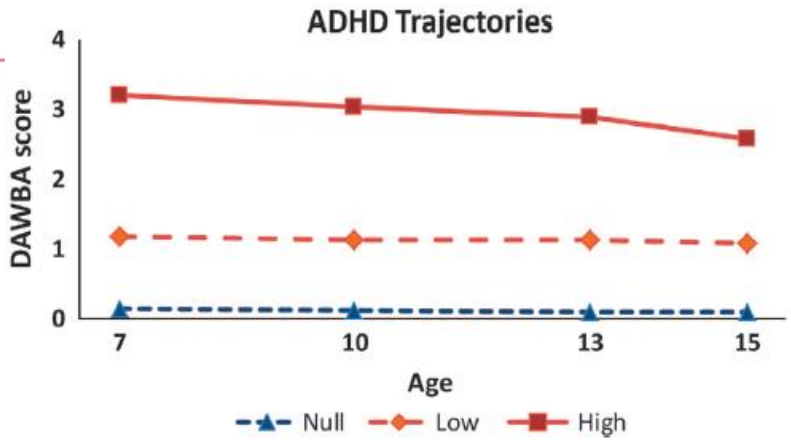


Walton et al., in press

- *SP6* methylation associated longitudinally with higher AH volume ratio

Trajectories

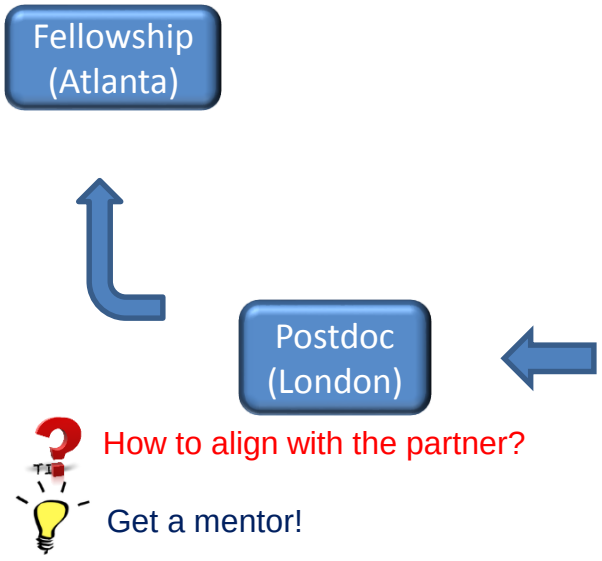




Walton et al., 2016

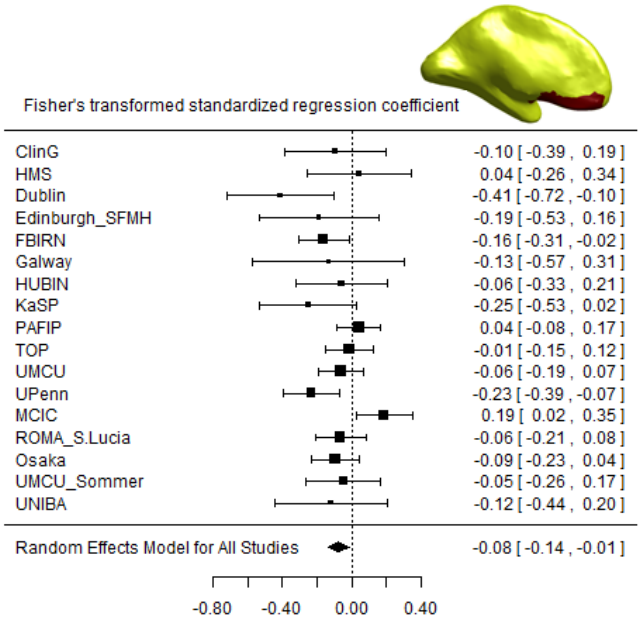
- DNA methylation at birth, but not at age 7, differentiated ADHD trajectories
- probes annotated to
  - SKI (involved in neural tube development)
  - ZNF544 (previously implicated in ADHD),
  - ST3GAL3 (linked to intellectual disability)
  - PEX2 (related to perixosomal processes)

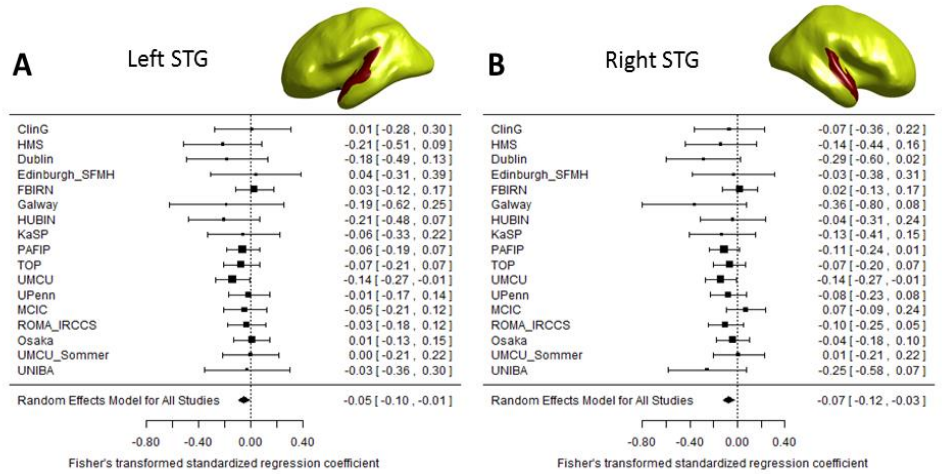
Gene – Environment Interactions



Neural correlates of symptoms in SCZ

- Negative symptoms negatively associated with left, but not right mOFC thickness
- Positive symptoms were negatively related to STG thickness in both hemispheres





Walton et al., under review

Gene – Environment Interactions

2. Postdoc (Bristol)

Changing plans is ok
Have a network

Fellowship (Atlanta)

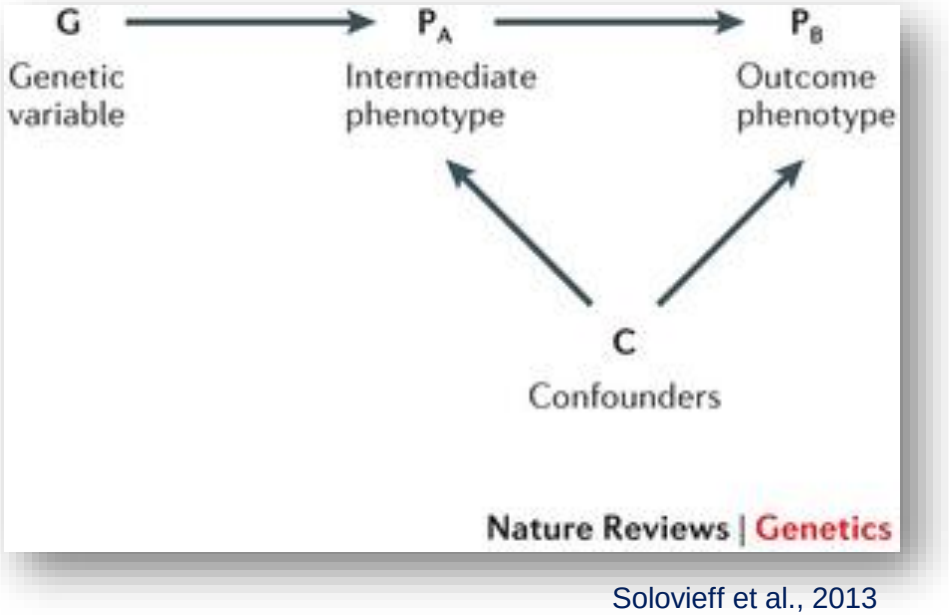
Postdoc (London)

How to align with the partner?

Get a mentor!

Mendelian Randomization

Towards causal associations!

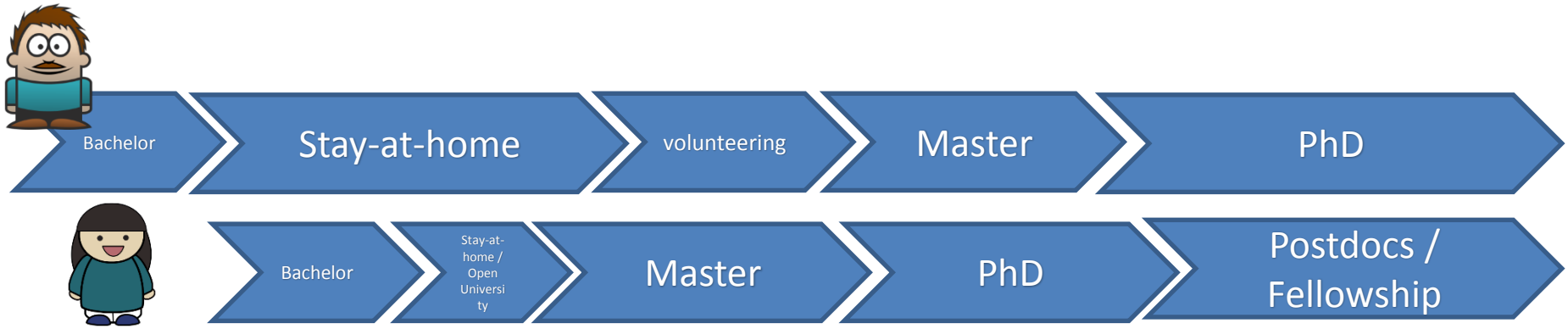


Solovieff et al., 2013

What helped?

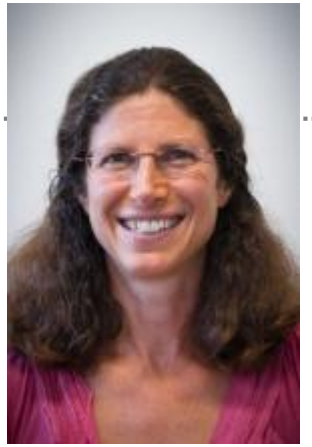
- An open mind (toward people, options and opportunities)
- A supportive partner
- A mentor
- Economic support (government, funding, etc)

- …the shorter straw?



University of BRISTOL






Thank you