Genetic risk for psychiatric disorders is associated with psychiatric and cognitive Huntington's disease symptoms

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INTRODUCTION

Huntington's disease (HD) is a destructive and dominantly inherited neurodegeneration caused by a CAG repeat expansion in the Huntingtin gene (*HTT*). The disease is marked by a progressive movement disorder, together with cognitive and psychiatric disturbances. Psychiatric symptoms are especially difficult for patients and their families, but the aetiology of these symptoms remain poorly understood.

We have previously shown that genetic risk for neuropsychiatric traits, captured by polygenic risk scores (PRS), are associated with symptoms reported by HD patients[1]. Here, we extend the analysis to a wider range of motor, cognitive and psychiatric symptoms to identify those most closely associated with polygenic risk for neuropsychiatric disorders. Studying the genetic liability to psychiatric symptoms in HD patients will improve our understanding of the disease.

RESULTS

Fig. 1: The details for the genome-wide association studies (GWAS) for which the polygenic risk scores (PRS) were derived, alongside numbers of cases/controls.

Fig. 2: The 20 most significant associations are shown. "Effect" is the change in phenotype for an increase of one standard deviation of PRS. Phenotypes marked by an asterisk (*) were run as logistic regressions, and "effect" is the log odds-ratio. Associations passing Bonferroni correction are in bold (p<1.85E-5) and nominally significant associations are italicized.

Fig. 3: All significant and nominally significant associations with intelligence PRS are shown. Many of the most significant phenotype associations are cognitive related, but also include functional phenotypes such cUHDRS and total functional capacity (TFC). The dashed line indicates associations passing Bonferroni correction (p<1.85E-5).

Fig. 4: Significant and nominally significant associations with HD phenotypes and Obsessive-Compulsive disorder (OCD) PRS. Several motor-related phenotypes from total motor score (TMS), especially dystonia sub-components, show at least nominal significance. The dashed line indicates associations passing Bonferroni (p<1.85E-5).

Fig. 5: Associations of sub-components of TMS with multiple PRS simultaneously. Luria associates with intelligence, while dystonia associates with obsessive-compulsive disorder (OCD).

Fig. 6: Total functional capacity (TFC) is associated with intelligence PRS across multiple p-value cut-offs. The red line indicates associations passing Bonferroni (p<1.85E-5), whereas the black line indicates nominal significance.

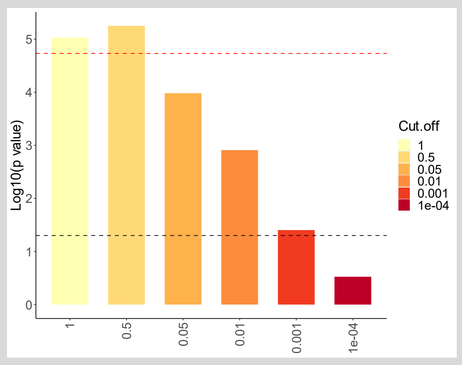

Fig. 6: Total functional capacity (TFC) is associated with intelligence PRS across multiple cut-offs examined.

METHODS

- 5,159 genotyped HD participants[2-3] were taken from the Enroll-HD and Registry-HD studies.
- Polygenic risk scores were calculated for 10 neuropsychiatric traits[1]
- Generalised linear models were constructed using polygenic risk scores and 45 HD phenotypes across motor, cognitive and psychiatric domains.
- Covariates included patient age, *HTT* CAG size and approximate disease duration.

PRS	Cases (N)	Controls (N)	Reference
Suicidality (Meta analysis)	6,569	17,232	Mullins et al., Am J Psychiatry **176** 651-660 (2019).
Intelligence	269,867		Savage et al., Nat Genet **50** 912-919 (2018).
Major Depressive Disorder (MDD)	170,756	329,443	Howard et al., Nat Neurosci **22** 343-352 (2019).
Late onset Alzheimer's disease	17,008	37,154	Lambert et al., Nat Genet **45** 1452-1458 (2013).
Parkinson's disease	26,421	442,271	Nalls et al., Lancet Neurol **18** 1091-1102 (2019).
Bipolar Disorder	20,352	31,358	Stahl et al., Nat Genet **51** 793-803 (2019).
Obsessive-Compulsive Disorder (OCD)	2,688	7,037	Askland et al., Mol Psychiatry **23** 1181 (2017).
Schizophrenia	36,989	113,075	Schizophrenia Working Group of the PGC, Nature **511** 421-427 (2014).
Attention deficit hyperactivity disorder (ADHD)	20,183	35,191	Demontis et al., Nat Genet **51** 63-75 (2019).
Autism Spectrum Disorder (ASD)	18,382	27,969	Grove et al., Nat Genet **51** 431-444 (2019).

Fig 1: Details of the polygenic risk scores (PRS) investigated.

PRS	PRS Cut-off	HD Phenotype	Effect	p-val	N
Intelligence	0.05	Stroop	1.28	**4.88E-13**	3563
Intelligence	0.5	SDMT	1.28	**1.43E-12**	3638
Intelligence	0.5	Luria (TMS)	-0.13	**1.69E-10**	4597
Intelligence	1	MMSE	0.69	**1.24E-08**	1883
Intelligence	1	Trailmaking B	-7.55	**1.46E-08**	2427
Intelligence	0.5	cUHDRS	0.39	**4.96E-08**	3587
Intelligence	0.5	Trailmaking A	-5.95	**1.20E-06**	2517
Intelligence	0.01	Cognitive (CCQ)*	-0.15	**1.36E-06**	4633
Schizophrenia	0.01	Irritability (CCQ)*	0.15	**1.74E-06**	4626
Intelligence	0.5	TFC	0.22	**5.60E-06**	4642
Obsessive-Compulsive Disorder	0.05	Dystonia (TMS)	0.29	**1.72E-05**	4597
Intelligence	0.05	Apathy (CCQ)*	-0.14	**1.84E-05**	4627
Intelligence	0.01	VAB (CCQ)*	-0.13	*1.93E-05*	4630
Depression	0.0001	Irritability (CCQ)*	0.13	*5.25E-05*	4626
Intelligence	0.01	Irritability (CCQ)*	-0.13	*7.06E-05*	4626
Schizophrenia	0.5	Trailmaking B	5.22	*1.13E-04*	2427
Intelligence	0.5	Coordination (TMS)	-0.35	*1.34E-04*	4597
Intelligence	0.01	Depression (HADS)	-0.34	*1.61E-04*	2570
Depression	0.05	Depression (CCQ)*	0.12	*1.89E-04*	4634
Intelligence	0.5	Independence Scale	1.02	*2.15E-04*	4638

Fig 2: Top 20 significant and nominally significant PRS-phenotype associations.

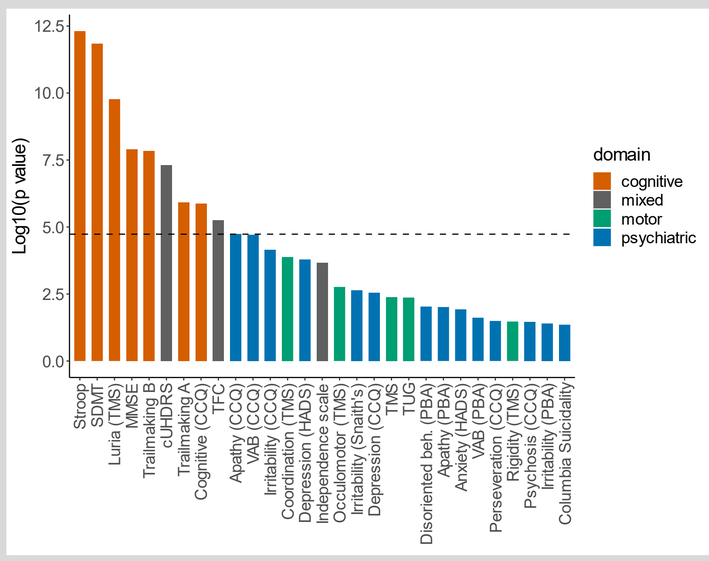

Fig. 3: Intelligence PRS is associated with multiple HD phenotypes.

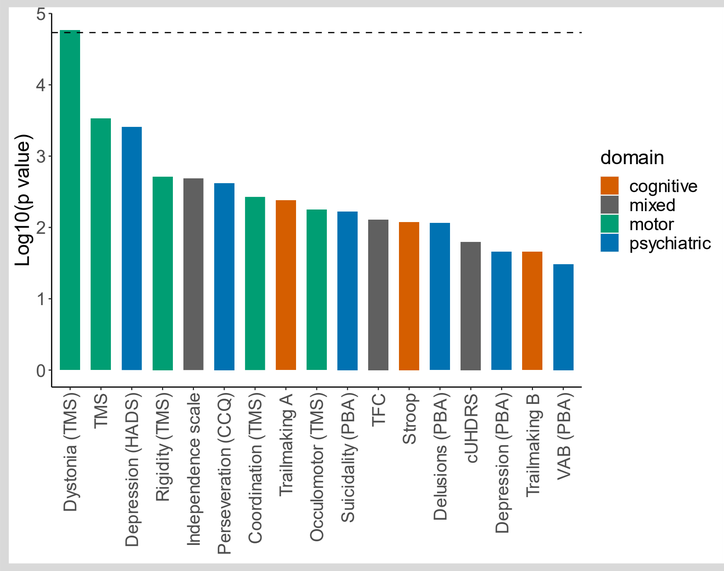

Fig. 4: Obsessive-compulsive disorder PRS has nominal significance with several phenotypes, including dystonia.

Coordination (TMS)			
PRS	PRS Cut-off	Estimate	p-val
Intelligence	0.5	-3.63	*2.89E-04*
Obsessive-Compulsive Dis.	0.05	2.84	*4.47E-03*
Suicidality	0.05	2.43	*1.50E-02*
Autism Spectrum Dis.	0.05	-2.22	*2.68E-02*
Schizophrenia	0.001	1.77	7.76E-02

Dystonia (TMS)			
PRS	PRS Cut-off	Estimate	p-val
Obsessive-Compulsive Dis.	0.05	4.37	**1.27E-05**
Suicidality	0.05	2.74	*6.12E-03*
SEM	1	-2.21	*2.69E-02*
Depression	0.05	-1.73	8.31E-02

Luria (TMS)			
PRS	PRS Cut-off	Estimate	p-val
Intelligence	0.5	-6.18	**6.77E-10**
Autism Spectrum Dis.	0.05	-2.23	*2.60E-02*
Schizophrenia	0.0001	1.96	5.02E-02
Suicidality	0.05	2.06	*3.93E-02*
Parkinson's Disease	0.5	-1.82	6.88E-02

Oculomotor (TMS)			
PRS	PRS Cut-off	Estimate	p-val
Autism Spectrum Dis.	0.05	-3.24	*1.20E-03*
Intelligence	0.5	-3.12	*1.79E-03*
Obsessive-Compulsive Dis.	0.05	2.84	*4.50E-03*
Schizophrenia	0.0001	3.12	*1.83E-03*
Depression	0.001	-2.12	*3.43E-02*
Suicidality	0.05	2.12	*3.41E-02*
SEM	1	-2.37	*1.78E-02*

Fig. 5: Sub-components of total motor score (TMS) are associated with different PRS in multivariate models.

DISCUSSION & FURTHER WORK

- Polygenic risk scores (PRS) for neuropsychiatric traits such as intelligence, obsessive-compulsive disorder and schizophrenia are associated with motor, cognitive and psychiatric phenotypes experienced by HD patients.
- Intelligence PRS is significantly and negatively associated with several phenotypes including total functional capacity (TFC), suggesting intelligence is protective for functional decline in HD patients.
- A surprising association was observed between obsessive-compulsive disorder and total motor score (TMS) sub-components such as dystonia. Further work is needed to understand these associations.
- Future work will use additional genotyped HD individuals, alongside more sophisticated modelling to leverage Enroll's comprehensive longitudinal data.

(1) Ellis et al., *Biol Psychiatry* **87** 857-865 (2020). (2) GeM-HD Consortium, *Cell* **162** 516-126 (2015). (3) GeM-HD Consortium, *Cell* **178** 887-900 (2019).