Genetic risk underlying psychiatric and cognitive symptoms in Huntington's Disease

Authors: Natalie Ellis[1,*], Amelia Tee[1,*], Branduff McAllister[2], Thomas Massey[2], Duncan McLauchlan[2,3] Timothy Stone[2], Kevin Correia[4], Jacob Loupe[5], Kyung-Hee Kim[4,6], Douglas Barker[4], Eun Pyo Hong[4,6], Michael J. Chao[4,6], Jeffrey D. Long[7], Diane Lucente[4,6], Jean Paul G. Vonsattel[8], Ricardo Mouro Pinto[4,6], Kawther Abu Elneel[4], Eliana Marisa Ramos[4], Jayalakshmi Srinidhi Mysore[4], Tammy Gillis[4], Vanessa C. Wheeler[4,6], Christopher Medway[9], Lynsey Hall[2], Seung Kwak[10], Cristina Sampaio[10], Marc Ciosi[11], Alastair Maxwell[11], Afroditi Chatzi[11], Darren G. Monckton[11], Michael Orth[12^], G. Bernhard Landwehrmeyer[12^], Jane S. Paulsen[13], Ira Shoulson[14], Richard H. Myers[15], Erik van Duijn[16,17,$], Hugh Rickards[18,$], Marcy E. MacDonald[4,6,19], Jong-min Lee[4,6], James F. Gusella[4,19,20,21], Lesley Jones[2], Peter Holmans[2].

Affiliations:

[1] Cardiff University School of Medicine, UHW Main Building, Heath Park, Cardiff CF14 4XN, United Kingdom

[2] Medical Research Council (MRC) Centre for Neuropsychiatric Genetics and Genomics, Division of Psychological Medicine and Clinical Neurology, School of Medicine, Cardiff University, Cardiff, United Kingdom

[3] Cardiff University Brain Research Imaging Centre, Cardiff University, Maindy Road, Cardiff CF24 4HQ, United Kingdom

[4] Molecular Neurogenetics Unit, Center for Genomic Medicine, Massachusetts General Hospital, Boston MA 02114, USA

[5] HudsonAlpha Institute for Biotechnology, Huntsville, AL 35806, USA

[6] Department of Neurology, Harvard Medical School, Boston MA 02115, USA

[7] Department of Biostatistics, College of Public Health, and Department of Psychiatry, Carver College of Medicine, University of Iowa, Iowa City 52242, USA

[8] Department of Pathology and Cell Biology and the Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Columbia University Medical Center, New York, NY 10032, USA.

[9] All Wales Medical Genetics Service, Institute of Medical Genetics, University Hospital Wales, Cardiff CF14 4XW, United Kingdom

[10] CHDI Foundation, Princeton NJ 08540 USA

[11] Institute of Molecular, Cell and Systems Biology, College of Medical, Veterinary and Life Sciences,

University of Glasgow, Glasgow G12 8QQ, United Kingdom

[12] Department of Neurology, University of Ulm, Oberer Eselsberg 45/1, 89081 Ulm, Germany

[13] Departments of Psychiatry and Neurology, University of Iowa Roy and Lucille Carver College of Medicine, Iowa City IA 52242, USA

[14] Department of Neurology, University of Rochester Medical Center, Rochester NY 14642, USA

[15] Department of Neurology and Genome Science Institute, Boston University School of Medicine, Boston MA 02118, USA

[16] Leiden University Medical Centre, Department of Psychiatry, PO Box 9600, 2300 RC Leiden, Netherlands

[17] Mental Health Care Centre Delfland, PO Box 5016, 2600 GA Delft, Netherlands

[18] National Centre for Mental Health, BSMHFT, Birmingham and College of Medical and Dental Sciences, University of Birmingham, Birmingham B15 2TT, United Kingdom.

[19] Medical and Population Genetics Program, the Broad Institute of M.I.T. and Harvard, Cambridge MA 02142, USA

[20] Department of Pathology and Cell Biology and the Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Columbia University Medical Center, New York, NY 10032, USA.

[21] Department of Genetics, Blavatnik Institute, Harvard Medical School, Boston MA 02115, USA

*equal contributions

^ on behalf of the European Huntington's Disease Network (EHDN) Registry investigators

[$] on behalf of the EHDN Behavioral Phenotype Working Group

Corresponding author:

Professor Peter Holmans
MRC Centre for Neuropsychiatric Genetics and Genomics
School of Medicine, Cardiff University
Hadyn Ellis Building
Maindy Road
Cardiff CF24 4HQ, UK
Tel: +44 2920 688427
holmanspa@cardiff.ac.uk

Abstract

Huntington's disease (HD) is an inherited neurodegenerative disorder caused by an expanded CAG repeat in the *HTT* gene. It is diagnosed following a standardized exam of motor control and often presents with cognitive decline and psychiatric symptoms. Recent studies have detected genetic loci modifying the age at onset of motor symptoms in HD, but genetic factors influencing cognitive and psychiatric presentations are unknown. We tested the hypothesis that psychiatric and cognitive symptoms in HD are influenced by the same common genetic variation as in the general population by constructing polygenic risk scores from large genome-wide association studies of psychiatric and neurodegenerative disorders, and of intelligence, and testing for correlation with the presence of psychiatric and cognitive symptoms in a large sample (n=5160) of HD patients. Polygenic risk score for major depression was associated specifically with increased risk of depression in HD, as was schizophrenia risk score with psychosis and irritability. Cognitive impairment and apathy were associated with reduced polygenic risk score for intelligence. In general, polygenic risk scores for psychiatric disorders, particularly depression and schizophrenia, are associated with increased risk of the corresponding psychiatric symptoms in HD, suggesting a common genetic liability. However, the genetic liability to cognitive impairment and apathy appears to be distinct from other psychiatric symptoms in HD. No associations were observed between HD symptoms and risk scores for other neurodegenerative disorders. These data provide a rationale for treatments effective in depression and schizophrenia to be used to treat depression and psychotic symptoms in HD.

Introduction

Huntington's disease (HD) is an inherited neurodegenerative disorder caused by an expanded CAG repeat in *HTT*. A clinical diagnosis is typically made via a movement disorder, but nearly all participants experience progressive cognitive decline, and many exhibit behavioural and psychiatric symptoms (1). Depression, irritability, obsessive and compulsive symptoms, apathy and psychosis all occur at rates higher than seen in the non-HD population, though they are not universal in HD (2). Psychiatric symptoms are often present before motor symptoms become manifest. Age at motor onset of HD is determined both by the length of the CAG repeat tract in *HTT* and by other genetic variants in the genome (3–5). Despite the fact that age at motor onset measures only one specific facet of the pathological process (1), it has been widely used to identify genetic modifiers in HD whilst genetic influences on behavioural and neuropsychiatric symptoms in HD have not been systematically investigated. Small studies have shown familial aggregation of psychosis in HD (6, 7) with weak evidence for the influence of specific candidate genes (8).

Common genetic variation contributes to the risk of developing schizophrenia (SCZ) (9), bipolar disorder (BPD) (10), major depressive disorder (MDD) (11) and attention deficit hyperactivity disorder (ADHD) (12). There is significant shared genetic risk between these psychiatric disorders (13).

Increased general intelligence (*g*) – a measure of cognitive function - has been shown to be genetically correlated with reduced risk of Alzheimer's disease (AD), ADHD and schizophrenia (14). As in HD, there are substantially increased levels of psychiatric symptoms in many neurological diseases. For instance 50% of those with AD (15), and up to 75% of those with Parkinson's disease (PD) develop psychotic symptoms (16, 17). In dementia with Lewy bodies visual hallucinations are a core clinical feature seen in 80% of patients (18). AD with psychosis is heritable (19, 20), though

increasing polygenic risk score for schizophrenia was associated with reduced risk of psychosis in PD and AD (21).

Given the increased frequency of neuropsychiatric and cognitive symptoms in HD, it is of interest to test for genetic overlap of these symptoms with psychiatric and neurodegenerative disorders and intelligence. This was done by constructing polygenic risk scores using the latest available genome-wide association studies for these disorders and testing these for correlation with the presence of neuropsychiatric and cognitive symptoms in HD.

Materials & Methods

HD participants and phenotypes

The HD participants in this analysis were part of the European REGISTRY study (22) or its successor, the international Enroll-HD (23) observational study of HD. REGISTRY was a multisite, prospective, observational study, which collected phenotypic data (2003–13) for more than 13000 participants, mostly HD gene carriers with manifest disease. Enroll-HD is an expanded and modified version of the REGISTRY study and is international: to date it has over 16000 participants (some of whom rolled over from REGISTRY) from 19 nations. All experiments were performed in accordance with the Declaration of Helsinki, ethical approval for the REGISTRY and Enroll-HD studies including written informed consent of all participants was obtained. This study was approved by Cardiff University School of Medicine Research Ethics Committee.

There were 6278 individuals with manifest HD defined by motor onset from REGISTRY (n=4986) and Enroll-HD (n=1292) with appropriate quality-controlled genome-wide association study (GWAS) data as described in (5). We examined seven symptoms: depression, irritability, psychosis, apathy, violent/aggressive behaviour, perseverative/obsessive behaviour and cognitive impairment, from the clinical characteristics questionnaire (CCQ) in REGISTRY and Enroll-HD. The clinical characteristics questionnaire asks if a sign or symptom has ever been experienced by a subject, (see Supplementary Information Appendix A). At least one CCQ symptom endorsement (positive or negative) was recorded in 5854 participants (4563 REGISTRY, 1291 Enroll-HD). We removed 133 individuals with a comorbid diagnosis of bipolar disorder, schizophrenia, schizotypy or schizoaffective disorder (since these are likely to share risk genes for psychiatric disorders independently of their HD status). We also removed one member (561 individuals) of each pair of first or second degree relatives (IBD>0.25) to minimise the correlation between individuals due to cryptic relatedness. This left 5160 participants in the final analysis (**Supplementary Figure 1)**.

Genetic analysis

For each individual in the HD dataset, their genetic risk for each psychiatric/neurodegenerative disorder was captured by a polygenic risk score (PRS) (24). A PRS is defined as the sum of the number of minor alleles across a set of SNPs, each weighted by the corresponding risk of that allele for the psychiatric/neurodegenerative disorder observed in a “training” GWAS. The set of SNPs used to calculate the PRS was chosen to be present in both the training GWAS and the HD dataset, to be in approximate linkage equilibrium, and to capture as much of the association signal in the training GWAS as possible. Following the procedure outlined by the Psychiatric Genomics Consortium (9), this was achieved by taking the most significant SNP in the training GWAS, removing all SNPs within 500kb that are in linkage disequilibrium (r^2>0.1) with it, then moving to the next most significant

remaining SNP and repeating the process. Analysis was restricted to SNPs with minor allele frequency >0.01 that were well imputed (r^2 between allele dosages and the unknown true genotypes >0.9) in the HD dataset and (where this information was available) in the training GWAS. SNPs were selected for inclusion into the PRS by applying criteria to their p-values in the training set. Since the optimal criterion was not known *a priori,* we applied six different p-value cutoffs (p<0.0001, p<0.001, p<0.01, p<0.05, p<0.5, p<1). Effects of population stratification were removed by regressing the PRS on 20 principal components. The residuals from this regression were standardised, to enable comparison of effect sizes across cutoffs.

Nine large publicly available sets of GWAS summary statistics were used for training (**Table 1**). These comprised five GWAS of psychiatric disorders from the Psychiatric Genomics Consortium (PGC): schizophrenia, bipolar disorder (BPD), attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD) and obsessive compulsive disorder (OCD) (9, 10, 12, 25, 26), a meta-analysis of the PGC and UK Biobank major depressive disorder (MDD) samples (11), two neurodegenerative disorders: late-onset Alzheimer's disease (AD) (27), and Parkinson's disease (PD) (28, 29), and a large GWAS of *g*, a measure of general intelligence (14). The major histocompatibility complex (MHC) region was removed from the schizophrenia GWAS due to a strong schizophrenia signal and long-range linkage disequilibrium potentially biasing the PRS (9). Summary statistics for the Psychiatric Genomics Consortium GWAS are available from https://www.med.unc.edu/pgc/results-and-downloads, those from the PGC and UK Biobank MDD meta-analysis from https://datashare.is.ed.ac.uk/handle/10283/3203, those for the AD and intelligence GWAS from https://www.ebi.ac.uk/gwas/downloads/summary-statistics, and the PD GWAS (omitting 23 and Me samples) from https://drive.google.com/drive/folders/10bGj6HfAXgl-JslpI9ZJIL_JIgZyktxn.

Associations were tested between all 9 PRS and all 7 symptoms at each PRS cutoff. The following p-value criteria were used to define significance correcting for multiple testing: 7.94×10^{-4} (Bonferroni corrected for 7 symptoms tested on 9 disease PRS, a total of 63 tests), 1.32×10^{-4} (Bonferroni corrected for 63 tests x 6 PRS cutoffs)

We also defined 27 PRS-symptom comparisons as primary hypotheses of interest, reflecting prior associations in the general population between the phenotypes and the diseases from which the PRS were derived. These were:

- MDD with depression, irritability and apathy
- BPD with depression and irritability
- Schizophrenia with depression, irritability, psychosis, apathy and violent/aggressive behaviour
- ADHD with irritability, violent & aggressive behaviour and cognitive impairment
- ASD with irritability, psychosis and perseverative/obsessive behaviour
- OCD with perseverative/obsessive behaviour
- AD with depression, irritability, apathy, violent/aggressive behaviour and cognitive impairment
- PD with depression, irritability, apathy and cognitive impairment
- Intelligence with cognitive impairment

Results

The frequency of each symptom in the 5854 HD participants with at least one endorsed symptom (positive or negative) varied from 10.8% (psychosis) to 66.0% (depression), and differed significantly by sex for depression, which was more common in women, and irritability and violent/aggressive behaviour which were both more common in men (**Table 2**). Symptoms were significantly (positively) correlated with each other (**Supplementary Table 1**), resulting in individuals exhibiting multiple symptoms.

We approximated disease duration as the age at the most recent observation available minus age at motor onset for REGISTRY and Enroll-HD individuals. Mean duration of HD was significantly lower in Enroll-HD, at 6.54 years, than REGISTRY, at 8.14 years ($p=6.55x10^{-21}$). The effects of CAG length, age at motor onset, sex and disease duration on symptom presence, were tested simultaneously via logistic regression (**Table 3**), along with potential differences in symptom frequency between REGISTRY vs Enroll-HD. Increased disease duration was significantly correlated with symptom presence for all symptoms except depression. These associations remained significant when age at most recent visit was included in the model (to account for increasing frequency of symptoms with increasing age) instead of age at motor onset (results not shown). Thus, the increased frequency of symptoms with disease duration cannot simply be attributed to age. Perseverative/obsessive behaviour was seen substantially more frequently in Enroll-HD than REGISTRY participants ($p = 5.72x10^{-10}$), otherwise there were no significant differences.

Table 4 lists the PRS-symptom associations reaching nominal ($p<0.05$) significance, with only the PRS cutoff giving the most significant result being shown. Full PRS-symptom analyses are shown in **Supplementary Tables 2- 10.** The schizophrenia PRS showed significant associations with psychosis, irritability and violent and aggressive behaviour after correction for both the number of PRS-symptom tests and the six PRS cutoffs, as did the MDD PRS with depression, irritability and violent and aggressive behaviour. The associations of schizophrenia PRS with depression and perseverative/obsessive behaviour were significant after correction for the number of PRS-symptom tests, as was the association between BPD PRS and depression. Of the primary hypotheses, the following nominally significant associations were also observed: MDD PRS with apathy, ADHD PRS with violent and aggressive behaviour, PD PRS with cognitive impairment and (interestingly, given the relatively small training GWAS) OCD PRS with perseverative/obsessive behaviour. In each case, increased PRS was associated with an increased risk of the symptom (as shown by odds ratios >1 in **Table 4**). Associations of the intelligence PRS with violent and aggressive behaviour, apathy and cognitive impairment were significant after correction for both the number of PRS-symptom tests and the 6 PRS cutoffs, while the association between intelligence PRS and irritability was significant after correction for the number of PRS-symptom tests. The associations with intelligence PRS have OR <1 in Table 2, indicating that decreased PRS (*i.e.* reduced intelligence) is associated with increased risk of the symptom. In general, PRS-symptom associations in **Table 4** surviving correction for multiple testing of symptom-PRS comparisons showed at least nominally significant association over a range of PRS cutoffs **(Figures 1, 2 and 3, Supplementary Tables 2,3,10**) thus increasing confidence that these results are robust. Conversely, the association between PD PRS and cognitive impairment was only significant for PRS cutoff $p<0.0001$ (**Supplementary Table 9**), making it likely that this is a false positive. This is also the case for the apparent association between psychosis and AD PRS (**Supplementary Table 8**). It can be seen from **Table 4** that the proportion of symptom

variance accounted for by the PRS, as measured by the Nagelkerke R^2, is small (<1%). Likewise, the ability of the PRS to predict symptom presence, as measured by the AUC, is limited (AUCs <0.55). For comparison, the Psychiatric Genomics Consortium (9) observed that schizophrenia PRS accounted for ~7% of variance in schizophrenia liability, with AUC around 0.7. AUC of 0.8 is generally required for a clinically useful predictor (30).

Since sex, CAG length, age at motor onset and disease duration were found to correlate significantly with symptom risk (**Table 3**), the association analyses between PRS and symptom were repeated conditioning on the effects of the factors found to be significantly associated with symptom presence. This made little difference to the significance of the PRS-symptom associations (results not shown). Together, these factors give AUC of 0.57-0.64 (**Table 3**), and adding the PRS makes little difference to this (results not shown).

For symptoms with a significant association with sex (depression, irritability and violent and aggressive behaviour) and PRS with a significant association in the whole sample, the PRS-symptom association analyses were run in males and females separately (**Supplementary Table 11**). There were no significant differences in OR between males and females.

PRS for schizophrenia, MDD, BPD and intelligence are associated with multiple symptoms in **Table 4**. Since these symptoms are correlated (**Supplementary Table 1**), it is unclear which symptom is driving the association. Likewise, symptoms are often associated with multiple PRS in **Table 4**. These PRS will be correlated, due to genetic overlap between psychiatric disorders (13). We therefore performed logistic regression of each symptom on all the significant PRS from **Table 4** simultaneously, including the six other symptom diagnoses as covariates (**Supplementary Table 12**). This analysis highlighted specific associations between MDD PRS and depression, schizophrenia PRS and both psychosis and irritability, BPD PRS and violent/aggressive behaviour and intelligence PRS and cognitive decline. AD PRS and PD PRS were significantly associated with psychosis and cognitive impairment respectively, but these are likely to be false positives, as discussed above.

The number of symptoms seen in any individual can be regarded as a surrogate for disease severity, and might be expected to correlate with PRS. A linear regression of PRS on symptom count (0-7) was therefore performed, (**Supplementary Table 13**). Significant associations with symptom count were observed for schizophrenia ($p=4.45\times10^{-9}$), intelligence ($p=5.78\times10^{-8}$), MDD ($p=4.17\times10^{-8}$) and BD ($p=0.00268$), with the latter being attributable to correlation with the other PRS. To test whether association of PRS with individual symptoms can be explained by the general association with symptom count, the number of other symptoms was included as a covariate in the regression of PRS on symptom presence. Psychosis and irritability were found to be associated with schizophrenia PRS independently of other symptoms (**Supplementary Table 14**). Depression was associated with MDD PRS across all cutoffs (**Supplementary Table 15**), as was cognitive impairment with intelligence PRS (**Supplementary Table 16**). These results corroborate the specific PRS-symptom associations from the previous paragraph.

Discussion

We show significant genetic overlaps between psychiatric disorders and psychiatric symptoms in HD, along with genetic overlap between intelligence and cognitive symptoms in HD. There is little overlap between the two neurodegenerative disorders and neuropsychiatric symptoms or cognition in HD. While the overall pattern of individual associations is complex, reflecting the genetic

relationships between the disorders, (see **Figure 4** for a graphical overview), we were able to identify that MDD PRS is specifically associated with depression, schizophrenia PRS with psychosis and irritability, BPD PRS with violent/aggressive behaviour and intelligence PRS with cognitive impairment.

Our results are consistent with observations of shared genetic risk amongst psychiatric disorders but no overlap between the individual neurological disorders and no overlap with neuropsychiatric symptom risk in neurodegenerative disorders (13, 21, 29). By contrast, common genetic variation is associated with behavioural phenotypes (such as autistic behaviour and developmental delay) in severe monogenic neurodevelopmental disorders, with similar effect sizes (R^2 of 0.6-0.8%) to those observed here (31). These results, along with ours, indicate that even in diseases previously assumed to be entirely attributable to single genetic variants, there is a contribution of polygenic risk in influencing phenotypic presentation (31).

Schizophrenia PRS is associated with psychosis (and irritability) independently of other symptoms and is the only PRS to predict HD psychosis. While psychosis in HD is around ten times more common than in the general population, it is seen in only a minority of cases (2), as in the participants studied here (11%). There are also reports of clustering of psychotic symptoms in HD families (6, 7), implying a genetic contribution to these symptoms. Previously, Tsuang *et al.* (8) tested for association of psychosis in HD with a set of 214 SNPs chosen from candidate genes for schizophrenia, HD or psychosis in neurodegenerative disorders. None of their associations survived correction for multiple testing, possibly due to the small sample size (47 HD cases with psychosis, 126 without psychosis). Of the SNPs tested by Tsuang *et al.*, 183 were available in our data; a polygenic risk score generated from these (with effect sizes taken from the PGC schizophrenia GWAS) showed no association with psychosis in our HD sample (OR=0.97, p=0.536). The highly significant association between schizophrenia PRS and psychosis observed in our sample shows the benefits of a large sample size of HD patients, along with a larger set of SNPs systematically selected for association with schizophrenia in a powerful schizophrenia GWAS. The schizophrenia PRS is also the most significantly associated with perseveration, one of the most characteristic behavioural problems in HD. The PRS for OCD also influences the presence of perseverative/obsessive behaviour **(Table 4, Supplementary Table 12)**, despite the OCD PRS having been derived from a much smaller and less powerful sample than that for schizophrenia.

Schizophrenia may be regarded as a neurodevelopmental disorder with origins in foetal development that manifest in symptoms most usually in early adulthood (32), whereas psychotic symptoms in HD generally manifest later in life (2, 33). The genes that contribute to the schizophrenia PRS are preferentially expressed in the medium spiny neurons of the striatum (34), which are the most vulnerable cell types in HD: by the time HD motor symptoms are manifest up to half of these neurons have died (35). Susceptibility to psychiatric symptoms in surviving cells is influenced by the schizophrenia polygenic risk, and provides a potential explanation for the increased rates of psychotic symptoms observed in HD patients.

Cognitive decline and dementia are part of HD progression, with executive and psychomotor function often the first deficits noted, with memory problems later in disease (2). Longer CAG repeat tracts are associated with increased risk of cognitive deficits in our sample: the previous data on this relationship have been inconsistent (2, 36). Recent studies have shown that poorer performance in the symbol digit modality test was associated with longer *HTT* CAG repeat lengths (37), and poorer

cognitive function was seen with increasing repeat lengths in the disease causing range (38). The clinical characteristics questionnaire used to assess symptoms for this study seeks an integrated measure of cognitive decline by asking about problems that might interfere with performing everyday functions and is relatively crude, though this will be partly offset by the larger size of our study (1000s rather than 100s of participants).

It is notable that neither apathy nor cognitive dysfunction in HD are correlated with PRS for psychiatric or neurodegenerative disorders apart from nominal associations between apathy and MDD, schizophrenia and BPD PRS, which become non-significant when accounting for the presence of other symptoms (see **Supplementary Table 12**). However, both are significantly correlated with a PRS measuring intelligence. This suggests that apathy in HD should be considered as a cognitive, rather than psychiatric, symptom (unlike depression), and is also consistent with apathy being the only psychiatric symptom to correlate with disease progression (39). Higher PRS for intelligence is associated with later cognitive decline in HD, as it is in AD (14). The genes associated with intelligence are highly expressed in medium spiny neurons of the striatum and pyramidal neurons of the CA1 hippocampus (14), early targets of degeneration in HD and AD respectively, potentially contributing to the severe cognitive decline seen in these diseases. Surprisingly, there is no significant association between the presence of cognitive deficits in HD and genetic risk for AD, though AD PRS predicts memory decline and poorer cognitive performance in healthy children and adults well before the age of risk for AD (40, 41). In children, *HTT* CAG repeat length itself shows a J-shaped relationship with cognition, with maximum cognition at 40-41 repeats (38). Since higher intelligence is associated with better health and increased well-being (42), there may thus be a selective advantage of longer *HTT* CAG repeat length, below the threshold for HD, in the wider population.

Depression is very common in HD and more common in females (2). MDD PRS is specifically associated with increased risk of depression in HD, and the converse is also true (**Supplementary Table 12**). However, there were no significant sex differences in these associations (**Supplementary Table 11**). There is a significant correlation in our sample of increased likelihood of depression with shorter CAG repeat lengths in the disease-causing allele in *HTT* (**Table 3**), along with an association with earlier age at motor onset. The reason for these associations is unclear; the obvious explanation that longer disease duration makes depression more likely is not the case in our sample (**Table 3**). In fact, the apparent associations between depression and both age at motor onset and CAG repeat length are explained by the residual of age at motor onset after correction for CAG length (see (5) for how this is derived). Participants with an earlier than expected age at onset (given their CAG length) are more likely to have depression. This could be due to increased environmental stress among individuals with earlier motor onset, and also that some genetic modifiers of age at motor onset may also be associated with depression in HD. The few previous studies, each examining less than 100 participants, detected no relationship between CAG length and presence of depression (43–45). In the non-disease causing range, longer *HTT* CAG length from 24 to 38 repeats was associated with an increased likelihood of depression (46).

Irritability, like depression, is very common in HD and has a significantly reduced risk with longer CAG length (**Table 3**) but unlike depression, longer duration of disease makes irritability more likely. This association is not explained by increased age. Schizophrenia PRS is associated with increased risk of irritability (**Table 4, Supplementary Table 12**). Violent/aggressive behaviour can be

considered to be an extreme manifestation of irritability, and is associated with PRS for bipolar disorder (**Supplementary Table 12**), with the apparently more significant associations with schizophrenia, intelligence and MDD PRS (**Table 4**) attributable to correlations between violent/aggressive behaviour and other symptoms. As in the wider population violence and aggressive behaviour is more common in men (2).

The study presented here has a number of limitations. As noted, the clinical characteristics questionnaire is a relatively crude instrument. The larger size of this study compared with previous studies partly mitigates its limitations, and these initial findings provide a platform for more detailed studies using specific psychiatric instruments. We note that all Enroll-HD participants now undergo a short problem behaviours assessment battery (PBA), which may account for the increased frequency of perseverative/obsessive behaviour observed in Enroll-HD relative to REGISTRY. It would be useful to investigate further the predictive power of the PRS using more detailed clinical data, including age at onset, on the psychiatric symptoms in HD. It would also be interesting to explore the overlap of multiple symptoms and the psychiatric and cognitive PRS to attempt to establish directions of causation.

It is notable that the PRS for psychiatric diseases associate with increased risk of developing parallel phenotypic behavioural and psychiatric symptoms in HD participants. The data available in the ongoing Enroll-HD study will provide for a much more detailed analyses of these symptoms, their aetiology and treatment and may in turn inform the psychiatric diseases. The lack of genetic overlap with other neurodegenerative disorders, consistent with the Brainstorm study (13), implies different underlying pathways leading to degeneration in the different neurodegenerations that may relate to the disease-specific characteristic differential neuronal vulnerabilities to degeneration. Striatial medium spiny neurons are most vulnerable in HD, dopaminergic neurons of the substantia nigra in PD and hippocampal and entorhinal cortical neurons in AD. The differential vulnerability may relate to pathways essential to the survival and continued function of each specific cell type and these are likely to be different in different neurodegenerations (47). Thus, psychiatric symptoms may be mediated by common dysfunctional pathways in surviving cells whereas cognitive and neurodegenerative symptoms are likely due to specific regional cellular populations degenerating via different pathways. These data provide a rationale for treatments used in the wider population for depression and psychotic symptoms, to be used for these symptoms in HD.

Acknowledgements

This work was supported by the CHDI Foundation, the National Institutes of Health USA (U01NS082079, R01NS040068, R01NS091161, P50NS016367, and R01NS049206) and the Medical Research Council (UK; MR/L010305/1). Dr. Massey received a fellowship from the MRC (MR/P001629/1) and Mr. McAllister received a studentship from the Cardiff University School of Medicine. The Enroll-HD and REGISTRY, studies would not be possible without the vital contribution of the research participants and their families. Individuals who contributed to the collection subject data can be found at https://www.enroll-hd.org/acknowledgments/ for Enroll-HD, and in Supplementary Information Appendix B for REGISTRY. Members of the EHDN Behavioral Phenotype Working Group are listed in Supplementary Information Appendix C.

Disclosures

Drs Gusella and Wheeler have a financial interest in Triplet Therapeutics, Inc., a company developing new therapeutic approaches to address triplet repeat disorders such Huntington's Disease and Myotonic Dystrophy. Drs Gusella and Wheeler's interests were reviewed and are managed by Massachusetts General Hospital and Partners HealthCare in accordance with their conflict of interest policies.

Dr. Long is a paid advisory board member for F. Hoffman-La Roche Ltd, Wave Life Sciences USA Inc, Huntington Study Group (for uniQuire biopharma B.V.), and Mitoconix Bio Limited. Dr. Long is also a paid consultant for Vaccinex Inc and Azevan Pharmaceuticals Inc.

Dr. Monckton has been a scientific consultant and/or received an honoraria or stock options from Biogen Idec, AMO Pharma, Charles River, Vertex Pharmaceuticals, Triplet Therapeutics, LoQus23, BridgeBio and Small Molecule RNA, and had a research contract with AMO Pharma.

Dr. Landwehrmeyer has provided consulting services, advisory board functions, clinical trial services and/or lectures for Allergan, Alnylam, Amarin, AOP Orphan Pharmaceuticals AG, Bayer Pharma AG, CHDI Foundation, GlaxoSmithKline, Hoffmann-LaRoche, Ipsen, ISIS Pharma, Lundbeck, Neurosearch Inc, Medesis, Medivation, Medtronic, NeuraMetrix, Novartis, Pfizer, Prana Biotechnology, Sangamo/Shire, Siena Biotech, Temmler Pharma GmbH and Teva Pharmaceuticals. He has received research grant support from the CHDI Foundation, the Bundesministerium für Bildung und Forschung (BMBF), the Deutsche Forschungsgemeinschaft (DFG), the European Commission (EU-FP7, JPND). His study site Ulm has received compensation in the context of the observational Enroll-HD Study, TEVA, ISIS and Hoffmann-Roche and the Gossweiler Foundation. He receives royalties from the Oxford University Press and is employed by the State of Baden-Württemberg at the University of Ulm.

Dr. van Duijn has provided consulting services to Azevan Pharmaceuticals and Teva Pharmaceutical Industries Ltd., and advisory board service for Lundbeck.

Dr. Paulsen has provided consulting services and advisory board functions for Wave Life Sciences, Lundbeck, and Roche.

Dr. Rickards has performed consultancy work for Roche.

Dr. McLauchlan is currently employed as a clinical fellow in clinical trials funded in part by CHDI, UCB Pharma and Roche. He holds a Welsh Assembly Government funded WCAT fellowship and has received grant funding from the MRC and Cardiff University.

Drs Ellis, Tee, McAllister, Stone, Correia, Loupe, Kim, Barker, Hong, Chao, Lucente, Vonsattel, Pinto, Abu Elneel, Ramos, Mysore, Gillis, Medway, Hall, Kwak, Sampaio, Ciosi, Maxwell, Chatzi, Orth, Shoulson, Myers, MacDonald, Lee, Jones and Holmans report no potential conflicts of interest.

References

1. Bates GP, Dorsey R, Gusella JF, Hayden MR, Kay C, Leavitt BR, *et al.* (2015): Huntington disease. *Nat Rev Dis Prim*. 1: 15005.

2. Craufurd D, Snowden J (2014): Neuropsychiatry and Neuropsychology. In: Bates GP, Tabrizi SJ, Jones L, editors. *Huntington's Dis*, 4th ed. New York: Oxford University Press, pp 36–65.

3. Huntington's GM of, Disease Consortium (GeM-HD) (2015): Identification of Genetic Factors that Modify Clinical Onset of Huntington's Disease. *Cell*. 162: 516–526.

4. Holmans PA, Massey TH, Jones L (2017): Genetic modifiers of Mendelian disease: Huntington's disease and the trinucleotide repeat disorders. *Hum Mol Genet*. . doi: 10.1093/hmg/ddx261.

5. Lee J-M, Correia K, Loupe J, Kim K-H, Barker D, Hong EP, *et al.* (2019): Huntington's disease onset is determined by length of uninterrupted CAG, not encoded polyglutamine, and is modified by DNA maintenance mechanisms. *bioRxiv*. 529768.

6. Lovestone S, Hodgson S, Sham P, Differ AM, Levy R (1996): Familial psychiatric presentation of Huntington's disease. *J Med Genet*. 33: 128–131.

7. Tsuang D, Almqvist EW, Lipe H, Strgar F, DiGiacomo L, Hoff D, *et al.* (2000): Familial aggregation of psychotic symptoms in Huntington's disease. *Am J Psychiatry*. 157: 1955–1959.

8. Tsuang DW, Greenwood TA, Jayadev S, Davis M, Shutes-David A, Bird TD (2018): A Genetic Study of Psychosis in Huntington's Disease: Evidence for the Involvement of Glutamate Signaling Pathways. *J Huntingtons Dis*. 7: 51–59.

9. Biological insights from 108 schizophrenia-associated genetic loci. (2014): *Nature*. 511: 421–427.

10. Stahl EA, Breen G, Forstner AJ, McQuillin A, Ripke S, Trubetskoy V, *et al.* (2019): Genome-wide association study identifies 30 loci associated with bipolar disorder. *Nat Genet*. 51: 793–803.

11. Howard DM, Adams MJ, Clarke TK, Hafferty JD, Gibson J, Shirali M, *et al.* (2019): Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. *Nat Neurosci*. 22: 343–352.

12. Demontis D, Walters RK, Martin J, Mattheisen M, Als TD, Agerbo E, *et al.* (2019): Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. *Nat Genet*. 51: 63–75.

13. Anttila V, Bulik-Sullivan B, Finucane HK, Walters RK, Bras J, Duncan L, *et al.* (2018): Analysis of shared heritability in common disorders of the brain. *Science (80-)*. 360. doi: 10.1126/science.aap8757.

14. Savage JE, Jansen PR, Stringer S, Watanabe K, Bryois J, de Leeuw CA, *et al.* (2018): Genome-wide association meta-analysis in 269,867 individuals identifies new genetic and functional links to intelligence. *Nat Genet*. 50: 912–919.

15. Murray PS, Kumar S, Demichele-Sweet MAA, Sweet RA (2014): Psychosis in Alzheimer's disease. *Biol Psychiatry*. 75: 542–552.

16. Barrett MJ, Smolkin ME, Flanigan JL, Shah BB, Harrison MB, Sperling SA (2017): Characteristics, correlates, and assessment of psychosis in Parkinson disease without dementia. *Parkinsonism Relat Disord*. 43: 56–60.

17. Ravina B, Marder K, Fernandez HH, Friedman JH, McDonald W, Murphy D, *et al.* (2007): Diagnostic criteria for psychosis in Parkinson's disease: report of an NINDS, NIMH work group.

Mov Disord. 22: 1061–1068.

18. McKeith IG, Boeve BF, Dickson DW, Halliday G, Taylor J-P, Weintraub D, *et al.* (2017): Diagnosis and management of dementia with Lewy bodies. *Neurology*. 89: 88 LP – 100.

19. Hollingworth P, Hamshere ML, Holmans PA, O'Donovan MC, Sims R, Powell J, *et al.* (2007): Increased familial risk and genomewide significant linkage for Alzheimer's disease with psychosis. *Am J Med Genet B Neuropsychiatr Genet*. 144B: 841–848.

20. Sweet RA, Bennett DA, Graff-Radford NR, Mayeux R (2010): Assessment and familial aggregation of psychosis in Alzheimer's disease from the National Institute on Aging Late Onset Alzheimer's Disease Family Study. *Brain*. 133: 1155–1162.

21. DeMichele-Sweet MAA, Weamer EA, Klei L, Vrana DT, Hollingshead DJ, Seltman HJ, *et al.* (2018): Genetic Risk for Schizophrenia and Psychosis in Alzheimer Disease. *Mol Psychiatry*. 23: 963–972.

22. Orth M, Handley OJ, Schwenke C, Dunnett SB, Craufurd D, Ho AK, *et al.* (2010): Observing Huntington's Disease: the European Huntington's Disease Network's REGISTRY. *PLoS Curr*. 2: RRN1184.

23. Walker T, Ghosh B, Kipps C (2017): Assessing Decline: Visualising Progression in Huntington's Disease using a Clinical Dashboard with Enroll-HD Data. *J Huntingtons Dis*. . doi: 10.3233/JHD-170234.

24. Purcell SM, Wray NR, Stone JL, Visscher PM, O'Donovan MC, Sullivan PF, *et al.* (2009): Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature*. . doi: 10.1038/nature08185.

25. Grove J, Ripke S, Als TD, Mattheisen M, Walters RK, Won H, *et al.* (2019): Identification of common genetic risk variants for autism spectrum disorder. *Nat Genet*. 51: 431–444.

26. (OCGAS) IOCDFGC (IOCDF-G and OCDCGAS, Arnold PD, Askland KD, Barlassina C, Bellodi L, Bienvenu OJ, *et al.* (2017): Revealing the complex genetic architecture of obsessive–compulsive disorder using meta-analysis. *Mol Psychiatry*. 23: 1181.

27. Lambert JC, Ibrahim-Verbaas CA, Harold D, Naj AC, Sims R, Bellenguez C, *et al.* (2013): Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. *Nat Genet*. 45: 1452–1458.

28. Nalls MA, Pankratz N, Lill CM, Do CB, Hernandez DG, Saad M, *et al.* (2014): Large-scale meta-analysis of genome-wide association data identifies six new risk loci for Parkinson's disease. *Nat Genet*. 46: 989–993.

29. Nalls MA, Blauwendraat C, Vallerga CL, Heilbron K, Bandres-Ciga S, Chang D, *et al.* (2018): Parkinson's disease genetics: identifying novel risk loci, providing causal insights and improving estimates of heritable risk. *bioRxiv*. .

30. Schummers L, Himes KP, Bodnar LM, Hutcheon JA (2016): Predictor characteristics necessary for building a clinically useful risk prediction model: a simulation study. *BMC Med Res Methodol*. 16: 123.

31. Niemi MEK, Martin HC, Rice DL, Gallone G, Gordon S, Kelemen M, *et al.* (2018): Common genetic variants contribute to risk of rare severe neurodevelopmental disorders. *Nature*. 562: 268–271.

32. Clifton NE, Hannon E, Harwood JC, Di Florio A, Thomas KL, Holmans PA, *et al.* (2019): Dynamic expression of genes associated with schizophrenia and bipolar disorder across development. *Transl Psychiatry*. 9: 74.

33. Eddy CM, Parkinson EG, Rickards HE (2016): Changes in mental state and behaviour in Huntington's disease. *The lancet Psychiatry*. 3: 1079–1086.

34. Skene NG, Bryois J, Bakken TE, Breen G, Crowley JJ, Gaspar HA, *et al.* (2018): Genetic identification of brain cell types underlying schizophrenia. *Nat Genet*. 50: 825–833.

35. Vonsattel JP, DiFiglia M (1998): Huntington disease. *J Neuropathol Exp Neurol*. 57: 369–384.

36. Podvin S, Reardon HT, Yin K, Mosier C, Hook V (2019): Multiple clinical features of Huntington's disease correlate with mutant HTT gene CAG repeat lengths and neurodegeneration. *J Neurol*. 266: 551–564.

37. Tabrizi SJ, Scahill RI, Owen G, Durr A, Leavitt BR, Roos RA, *et al.* (2013): Predictors of phenotypic progression and disease onset in premanifest and early-stage Huntington's disease in the TRACK-HD study: analysis of 36-month observational data. *Lancet Neurol*. 12: 637–649.

38. Lee JK, Conrad A, Epping E, Mathews K, Magnotta V, Dawson JD, Nopoulos P (2018): Effect of Trinucleotide Repeats in the Huntington's Gene on Intelligence. *EBioMedicine*. 31: 47–53.

39. Thompson JC, Harris J, Sollom AC, Stopford CL, Howard E, Snowden JS, Craufurd D (2012): Longitudinal Evaluation of Neuropsychiatric Symptoms in Huntington's Disease. *J Neuropsychiatry Clin Neurosci*. 24: 53–60.

40. Marden JR, Mayeda ER, Walter S, Vivot A, Tchetgen Tchetgen EJ, Kawachi I, Glymour MM (2016): Using an Alzheimer Disease Polygenic Risk Score to Predict Memory Decline in Black and White Americans Over 14 Years of Follow-up. *Alzheimer Dis Assoc Disord*. 30: 195–202.

41. Axelrud LK, Santoro ML, Pine DS, Talarico F, Gadelha A, Manfro GG, *et al.* (2018): Polygenic Risk Score for Alzheimer's Disease: Implications for Memory Performance and Hippocampal Volumes in Early Life. *Am J Psychiatry*. 175: 555–563.

42. Wraw C, Deary IJ, Gale CR, Der G (2015): Intelligence in youth and health at age 50. *Intelligence*. 53: 23–32.

43. Weigell-Weber M, Schmid W, Spiegel R (1996): Psychiatric symptoms and CAG expansion in Huntington's disease. *Am J Med Genet*. 67: 53–57.

44. Zappacosta B, Monza D, Meoni C, Austoni L, Soliveri P, Gellera C, *et al.* (1996): Psychiatric symptoms do not correlate with cognitive decline, motor symptoms, or CAG repeat length in Huntington's disease. *Arch Neurol*. 53: 493–497.

45. Berrios GE, Wagle AC, Markova IS, Wagle SA, Ho LW, Rubinsztein DC, *et al.* (2001): Psychiatric symptoms and CAG repeats in neurologically asymptomatic Huntington's disease gene carriers. *Psychiatry Res*. 102: 217–225.

46. Gardiner SL, van Belzen MJ, Boogaard MW, van Roon-Mom WMC, Rozing MP, van Hemert AM, *et al.* (2017): Huntingtin gene repeat size variations affect risk of lifetime depression. *Transl Psychiatry*. 7: 1277.

47. Fu H, Hardy J, Duff KE (2018): Selective vulnerability in neurodegenerative diseases. *Nat Neurosci*. 21: 1350–1358.

Tables

Table 1

Sample sizes of GWAS used as training sets for polygenic risk scores.

DISORDER	NUMBER OF CASES	NUMBER OF CONTROLS
Major depressive disorder (MDD)	170,756	329,443
Bipolar disorder (BPD)	20,352	31,358
Schizophrenia (SCZ)	36,989	113,075
Attention deficit hyperactivity disorder (ADHD)	20,183	35,191
Autism spectrum disorder (ASD)	18,382	27,969
Obsessive-compulsive disorder (OCD)	2,688	7,037
Alzheimer's Disease (AD)	17,008	37,154
Parkinson's Disease (PD)	26,421	442,271
Intelligence	269,867 individuals	

Table 2: HD symptom counts and sex differences in the 5854 individuals with at least one recorded HD symptom diagnosis (positive or negative).

Symptom	Freq (%)	Male		Female		OR(F/M)	P(F/M)
		+	-	+	-		
Depression	66.0	1639	1120	2116	816	1.75 (1.57,1.96)	<2e-16
Irritability	60.3	1757	1005	1675	1252	0.77 (0.69,0.85)	8.76e-7
Psychosis	10.8	299	2396	301	2562	0.94 (0.79,1.12)	0.485
Violent/aggressive behaviour (VAB)	31.2	965	1794	802	2107	0.71 (0.63,0.79)	1.90e-9
Apathy	53.8	1484	1291	1581	1344	1.02 (0.92,1.14)	0.664
Perseverative/obsessive Behaviour (POB)	37.5	1048	1713	1076	1833	0.96 (0.86,1.07)	0.451
Cognitive impairment	57.5	1583	1214	1726	1235	1.07 (0.97,1.19)	0.194

Freq(%) is the frequency of the symptom among individuals in the sample for whom a diagnosis of that symptom was recorded. +/- refer to the number of individuals of each sex with/without the symptom.

Table 3:

Effect of sex, CAG, age at motor onset, disease duration and sample collection (ENROLL vs REGISTRY) on HD symptom frequency

HD Symptom	Sex (F/M)		CAG		AMO		Duration		ENR vs REG		AUC
	OR	p	OR	P	OR	p	OR	P	OR	P	
depression	**1.77**	**8.44e-23**	**0.95**	**7.64e-5**	**0.98**	**6.35e-6**	1.01	0.0572	1.09	0.198	0.592
irritability	**0.77**	**2.36e-6**	**0.94**	**1.06e-5**	**0.98**	**3.85e-9**	**1.02**	**0.000452**	1.06	0.361	0.570
psychosis	0.96	0.684	1.02	0.313	1.01	0.334	**1.06**	**2.77e-14**	0.88	0.242	0.599
VAB	**0.70**	**1.04e-9**	1.00	0.863	**0.99**	**7.95e-5**	**1.04**	**1.32e-12**	0.97	0.630	0.601
apathy	1.04	0.482	1.02	0.156	1.00	0.900	**1.04**	**9.84e-15**	1.06	0.411	0.572
POB	0.99	0.865	1.02	0.0603	1.00	0.322	**1.05**	**1.28e-19**	**1.52**	**5.72e-10**	0.586
Cognitive impairment	1.10	0.0814	**1.05**	**8.75e-5**	1.01	0.112	**1.10**	**2.08e-54**	0.96	0.540	0.638

AUC represents the area under the curve, and is a measure of the ability of the covariates to jointly predict symptom presence. VAB = violent/aggressive behaviour. POB= perseverative/obsessive behaviour. Analysis applied to 5854 individuals with at least one recorded symptom endorsement (not necessarily positive). All variables fitted simultaneously. Significant associations shown in **bold**

Table 4 HD symptom-polygenic risk score associations reaching nominal significance

SYMPTOM	Risk score	PRS CUT-OFF	OR	R^2 (%)	AUC	P VALUE
Depression	**MDD**	**0.01**	**1.17**	**0.78**	**0.547**	**9.01 x 10^{-8}**
	Schizophrenia	*0.05*	*1.12*	*0.37*	*0.528*	*2.47 x 10^{-4}*
	BPD	*0.01*	*1.11*	*0.36*	*0.532*	*3.06 x 10^{-4}*
	Intelligence	0.001	0.93	0.18	0.519	9.51 x 10^{-3}
Irritability	**Schizophrenia**	**0.05**	**1.17**	**0.76**	**0.542**	**1.03 x 10^{-7}**
	MDD	**0.001**	**1.12**	**0.45**	**0.535**	**4.42 x 10^{-5}**
	Intelligence	*1*	*0.90*	*0.37*	*0.531*	*1.99 x 10^{-4}*
Psychosis	**Schizophrenia**	**0.001**	**1.20**	**0.64**	**0.548**	**5.98 x 10^{-5}**
	MDD	0.05	1.14	0.34	0.537	3.40 x 10^{-3}
	Alzheimer's	0.001	1.10	0.19	0.529	0.0265
	Intelligence	0.0001	0.90	0.24	0.534	0.0147
VAB	**Intelligence**	**0.01**	**0.89**	**0.50**	**0.537**	**2.44 x 10^{-5}**
	Schizophrenia	**0.05**	**1.13**	**0.46**	**0.532**	**5.46 x 10^{-5}**
	MDD	**0.001**	**1.13**	**0.44**	**0.536**	**8.45 x 10^{-5}**
	BPD	*0.001*	*1.11*	*0.34*	*0.527*	*5.35 x 10^{-4}*
	ADHD	0.05	1.09	0.22	0.523	5.26 x 10^{-3}
	ASD	0.01	1.06	0.11	0.517	0.0451
POB	*Schizophrenia*	*0.01*	*1.12*	*0.39*	*0.531*	*1.47 x 10^{-4}*
	BPD	0.5	1.08	0.18	0.521	9.25 x 10^{-3}
	Intelligence	0.01	0.93	0.18	0.521	0.0103
	MDD	0.5	1.07	0.15	0.519	0.0188
	OCD	0.001	1.07	0.15	0.521	0.0190
Apathy	**Intelligence**	**1**	**0.90**	**0.41**	**0.534**	**9.27 x 10^{-5}**
	MDD	0.05	1.08	0.18	0.521	9.17 x 10^{-3}
	BPD	0.001	1.07	0.14	0.519	0.0222
	Schizophrenia	0.0001	1.07	0.13	0.518	0.0254
	ASD	0.001	1.06	0.10	0.516	0.0499
Cognitive impairment	**Intelligence**	**0.01**	**0.89**	**0.45**	**0.535**	**3.90 x 10^{-5}**
	Parkinson's	0.0001	1.09	0.26	0.524	1.67 x 10^{-3}
	MDD	0.5	1.09	0.23	0.524	3.51 x 10^{-3}

VAB= violent/aggressive behaviour, POB=perserverative/obsessive behaviour. MDD= major depressive disorder. BPD= bipolar disorder. ASD= autism spectrum disorder. ADHD = attention deficit hyperactivity disorder. R^2= Nagelkerke R^2. OR= Odds ratio for presence of symptom associated with 1 s.d. increase in PRS.

Results in *italics* satisfy the Bonferroni corrected p-value cut-off 7.94 x 10^{-4} (corrected for 63 possible PRS-phenotype comparisons), and results in **bold** satisfy the Bonferroni corrected p-value cut of 1.32 x 10^{-4} (corrected for the 63 PRS-symptom comparisons and 6 PRS cut-offs). Primary symptom-PRS hypotheses (see text) are underlined.

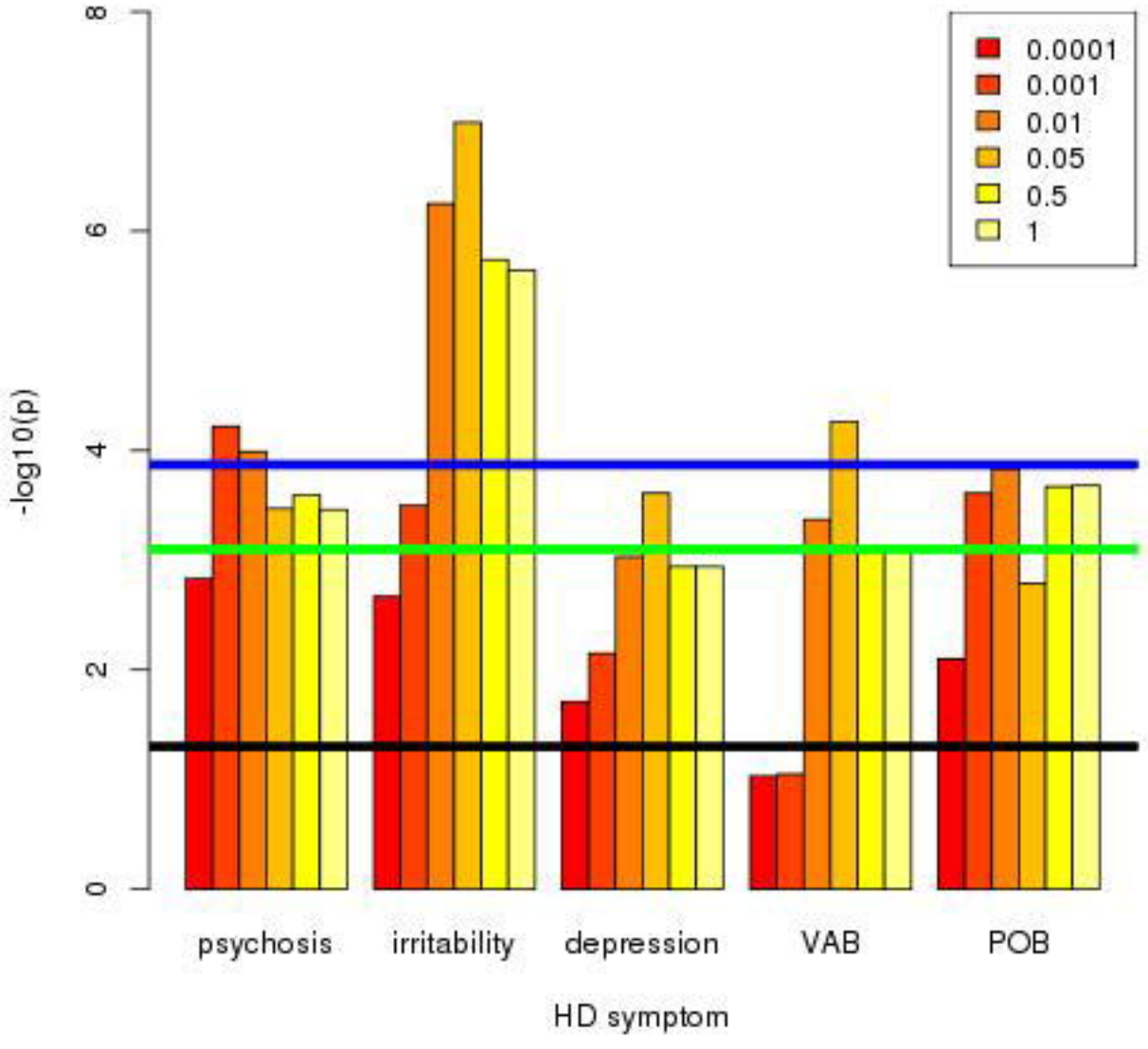
Figure Legends

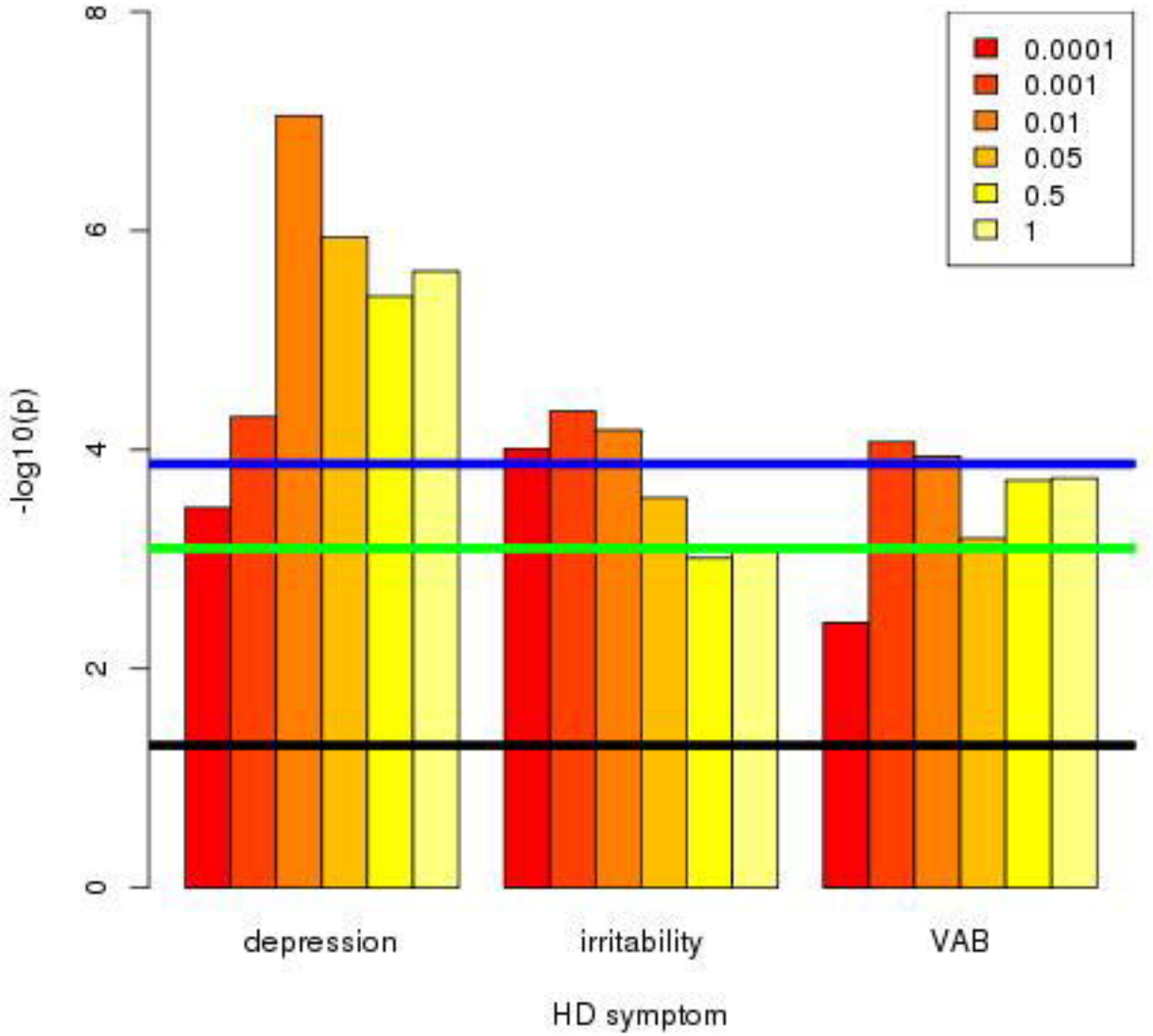
Figure 1. Association of increased schizophrenia PRS with increased HD symptom frequency. Numbers in the box correspond to the p-value thresholds used to derive the PRS. Black line corresponds to nominally significant association (p=0.05). Green line indicates associations significant after Bonferroni correction for 63 PRS-symptom comparisons (9 PRS x 7 symptoms). Blue line indicates associations significant after Bonferroni correction for 63 PRS-symptom comparisons and 6 PRS cutoffs. Note: Only symptoms with at least one p-value reaching the green line are shown.

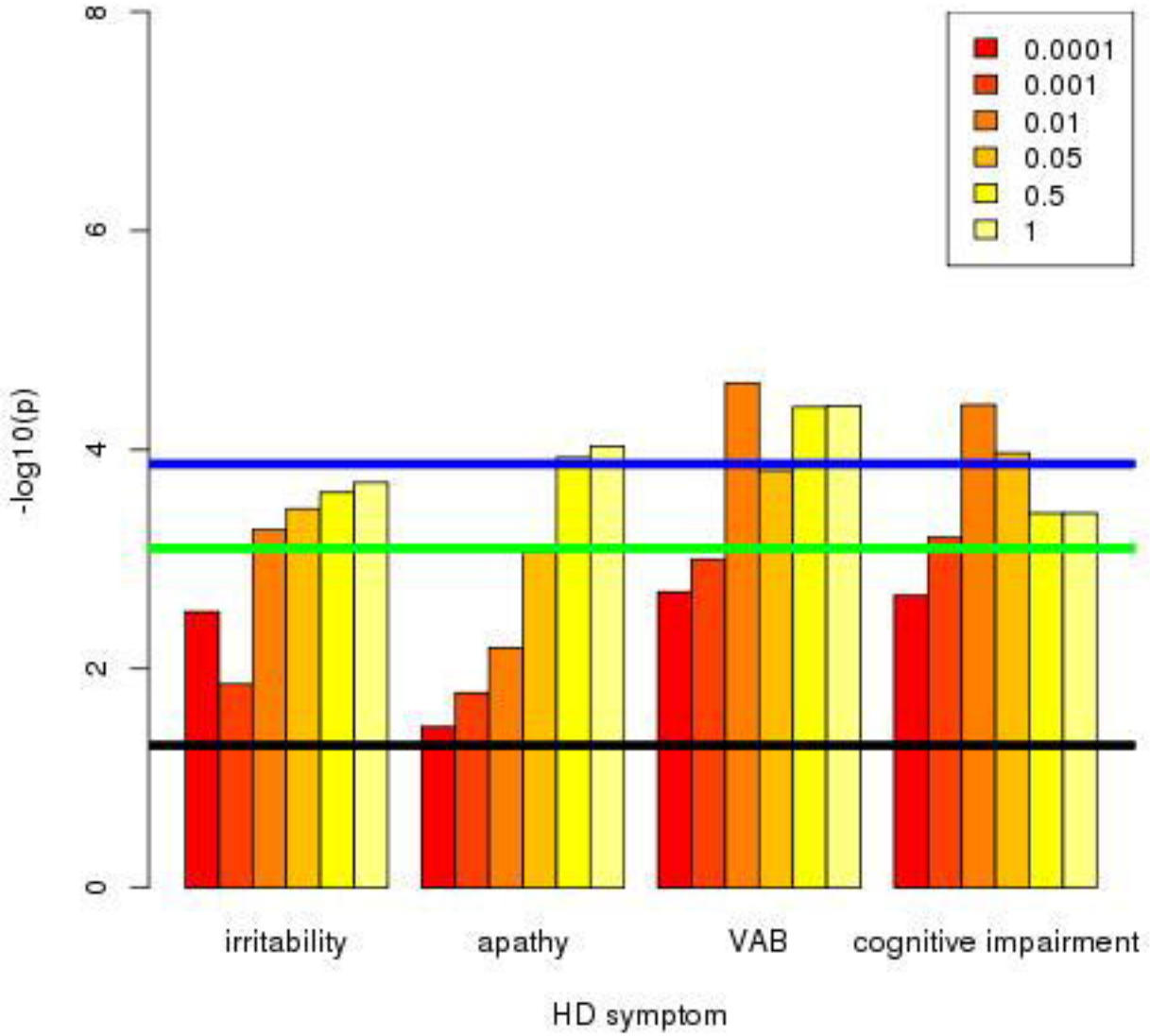
Figure 2. Association of increased major depression PRS with increased HD symptom frequency. Numbers in the box correspond to the p-value thresholds used to derive the PRS. Black line corresponds to nominally significant association (p=0.05). Green line indicates associations significant after Bonferroni correction for 63 PRS-symptom comparisons (9 PRS x 7 symptoms). Blue line indicates associations significant after Bonferroni correction for 63 PRS-symptom comparisons and 6 PRS cutoffs. Note: Only symptoms with at least one p-value reaching the green line are shown.

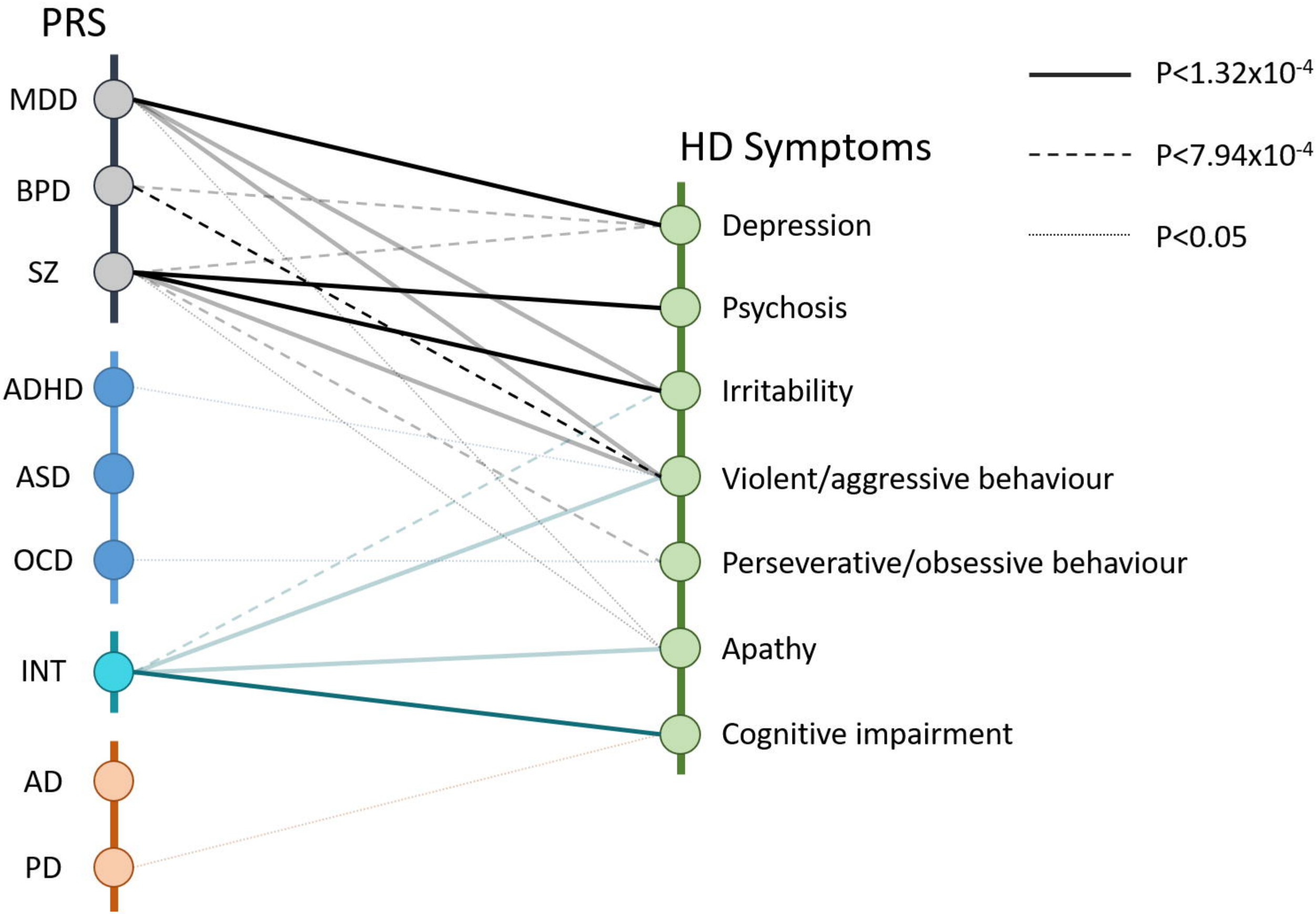
Figure 3. Association of decreased intelligence PRS with increased HD symptom frequency. Numbers in the box correspond to the p-value thresholds used to derive the PRS. Black line corresponds to nominally significant association (p=0.05). Green line indicates associations significant after Bonferroni correction for 63 PRS-symptom comparisons (9 PRS x 7 symptoms). Blue line indicates associations significant after Bonferroni correction for 63 PRS-symptom comparisons and 6 PRS cutoffs. Note: Only symptoms with at least one p-value reaching the green line are shown.

Figure 4. Pattern of association between HD symptoms and PRS from psychiatric, neurodegenerative and cognitive disorders. PRS grouped into psychiatric (black), neurodevelopmental (blue), neurodegenerative (orange) and cognitive (cyan) disorders. Solid lines show associations significant after correcting for 63 PRS-symptom combinations (9 PRS x 7 symptoms) and 6 PRS cutoffs ($p<1.32x10^{-4}$). Dashed lines show associations significant after correcting for 63 PRS-symptom combinations ($p<7.94x10^{-4}$). Dotted lines show nominally significant associations ($p<0.05$) in PRS-symptom combinations that were part of the primary analysis. Bold lines show PRS – symptom associations that are significant after correcting for other PRS and symptoms (Supplementary Table 12)


0.0001
0.001
0.01
0.05
0.5
1
-log10(p)
0
2
4
6
8
psychosis
irritability
depression
VAB
POB
HD symptom


0.0001
0.001
0.01
0.05
0.5
1
-log10(p)
0
2
4
6
8
depression
irritability
VAB
HD symptom


0.0001
0.001
0.01
0.05
0.5
1
-log10(p)
0
2
4
6
8
irritability
apathy
VAB
cognitive impairment
HD symptom


PRS
MDD
BPD
SZ
ADHD
ASD
OCD
INT
AD
PD
HD Symptoms
Depression
Psychosis
Irritability
Violent/aggressive behaviour
Perseverative/obsessive behaviour
Apathy
Cognitive impairment
P<1.32x10-4
P<7.94x10-4
P<0.05