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## Original article

## Genetic studies of psychosocial disability establish correlations and causal relationships with neuropsychiatric disorders

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## ABSTRACT

Psychosis is a clinically heterogenous disorder associated with significant difficulties with social and occupational function (psychosocial disability; PD). While environmental and cognitive factors are identified predictors of PD, the genetic contribution remains unclear. Here, we investigated the hypothesis that objective social participation (SP) and occupational engagement are genetically influenced.

We performed mixed-linear-model genome-wide association studies of these phenotypes in the UK Biobank ( $N \sim 404,500$ ) and a series of post-hoc analyses including Mendelian randomization (MR) to interpret findings. SP was defined as the frequency of social visits and leisure activities based on response to questionnaires. Occupational engagement was represented by two variables: occupational function (OF) and the established Not in Education, Employment, and Training (NEET) measure, both derived from employment status responses. We identified 17 independent loci for SP, with a SNP-based heritability of 4.1%. A list of contributory genes included *TNRC6B*, *STAU1*, *CDH7*, *GBE1*, *DDX27*, and several known schizophrenia risk genes including *CSE1L*, *ZNF536* and *TCF4*. The regulation of synaptic signalling was implicated in the biology of SP by gene-set analysis. SNP-based heritabilities for OF and NEET were 1.8% and 1.3% respectively and *DRD2* was associated with both phenotypes by gene-based analysis. Reduced SP and occupational engagement demonstrated genetic correlations with an increased risk for neuropsychiatric disorders, socioeconomic deprivation, lower cognitive ability, loneliness, neuroticism and chronic pain. MR indicated that attention-deficit hyperactivity disorder and schizophrenia were likely causal for reduced occupational engagement.

PD has a genetic component with shared genetic links and relationships with neuropsychiatric disorders and related traits.

## 1. Introduction

Psychosocial disability (PD) refers to the social and occupational challenges associated with mental ill-health (Griffiths et al., 2019). These challenges are considered distinct from psychiatric disability, which encapsulates clinical impairment. Although a common impairment in neuropsychiatric disorders (Judd et al., 2000; Siskind et al., 2012), there is little consensus on how to define social and occupational function in the literature (Cowman et al., 2024). Here, we define social

participation (SP) as the degree to which an individual actively participates in social activities and/or interactions, and occupational engagement as the extent to which an individual actively engages occupationally/vocationally. We aimed to objectively capture how well a person actively functions in society rather than how a person subjectively views their function.

PD is widely reported in psychosis and related disorders including schizophrenia (SCZ) and bipolar disorder (BD) (Häfner and an der Heiden, 1999; Siskind et al., 2012). Although psychosis is generally

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characterised by positive, negative, and cognitive symptoms, deficits in social and occupational function are also key features. Psychosis is a leading cause of burden in terms of years lived with disability worldwide (GBD Mental Disorders Collaborators, 2022) and has a lifetime prevalence of ~3% (Perälä et al., 2007). Often present prior to symptom onset, psychosocial difficulties have been linked to both development (Devoe et al., 2019; Velthorst et al., 2010) and trajectory (Austin et al., 2015; Cowman et al., 2025) of psychosis, making social and occupational function potentially valuable early intervention targets.

Community detachment, education and hobby avoidance, and impairment in work-related activities are common psychosocial challenges in psychosis (Penn et al., 2005). Even during periods of clinical remission, up to 50% of individuals with psychosis fail to regain full psychosocial functioning (Chang et al., 2018; Tohen et al., 2003). This reflects the fact that current pharmacological interventions have scant effects on social and occupational deficits. Factors such as cognitive performance (Cowman et al., 2021; Santesteban-Echarri et al., 2017), adverse life events (Turner et al., 2020), duration of untreated psychosis (Fraguas et al., 2014), and sociodemographic factors significantly contribute to PD in psychosis. However, functional deficits remain understudied and the biological underpinnings of SP and occupational engagement remain unclear. Understanding the genetic determinants of SP and occupational engagement is a fundamental step in the prediction of functional outcomes and in overcoming the persistent problem of poor functional recovery in psychosis.

Several genome-wide association studies (GWAS) have explored the genetics of social phenotypes including social interaction (Day et al., 2018), loneliness (Day et al., 2018; Watanabe et al., 2019), sociability (Bralten et al., 2021), and social-isolation (Socrates et al., 2024). In the largest GWAS to date, 17 independent genomic regions were linked to social-isolation (Socrates et al., 2024), implicating *ARFGEF2*, *ZNF536*, *CSE1L*, and *DIAPH3*, genes associated with social deficit disorders including SCZ (Ruderfer et al., 2018) and attention deficit hyperactivity disorder (ADHD) (Demontis et al., 2019; Middeldorp et al., 2016). Despite other studies also linking social phenotypes to genes implicated in these disorders (Bralten et al., 2021; Day et al., 2018), there is little homogeneity in results. In the UKB, GWASs for specific domains of social functioning have been performed. For frequency of friend/family visits, lead SNPs near genes associated with social functioning phenotypes were identified (Bralten et al., 2021; Socrates et al., 2024) as well as several novel genes. GWASs were also carried out for leisure activity type (e.g. Sports Club/Gym), however, results had little concordance with previous research. Research to date has been largely unsuccessful in identifying robust genetic variants associated with social functioning, likely due to the varying interpretations of social function.

GWASs of occupational function (OF) are limited. Research focuses on socioeconomic status (SES) to investigate the genetic determinants of OF and proxy phenotypes such as educational attainment (Lee et al., 2018; Okbay et al., 2016) and income (Hill et al., 2019, 2016) neglecting occupational status. Twin studies show that heritability of occupational status (35-45%) (Van Hootegem et al., 2024) is comparable to that of educational attainment (~40%) and income (~40%) (Van Hootegem et al., 2024). To date, just two GWASs of occupational status have been conducted. The first carried out individual GWASs for each current employment type in the UKB (Watanabe et al., 2019) (e.g. employed/unemployed/retired), identifying eight lead-SNPs. The most recent study identified 106 variants (Akimova et al., 2024). Further analyses revealed a strong genetic correlation between occupational status, educational attainment, and income despite evidence that occupational status may be somewhat empirically distinct.

In the present study, we conducted GWASs of SP OF and NEET in >404,000 participants from the UKB using a mixed linear methods approach (Jiang et al., 2019). We performed SNP-based heritability and explored genetic correlations with ~1,500 traits and psychiatric disorders. We integrated multiple functional genomics datasets, performed gene prioritisation and transcriptome-wide association analysis to

identify susceptibility genes. Finally, we implemented Mendelian randomization, investigating the casual relationships between our phenotypes and associated traits and disorders.

## 2. Methods

### 2.1. Study design and population

This was a large-scale, cross-sectional analysis of UKB participants. The UKB is a biomedical database containing extensive genetic and phenotypic data for 502,292 individuals aged 37-73 years from across the United Kingdom. Participants were recruited from 23 assessment centers during the period of 2006-2010, capturing rural and urban demographics with heterogeneous ethnic and socioeconomic backgrounds. The average age at recruitment was 56.5 years with female sex more common (54%). This research was conducted under the UKB application number 98153 and follows UKB Ethics and Governance Framework.

### 2.2. Phenotypes

SP was constructed by creating a composite score from two UKB database questions; (1) number of leisure/social activities attended weekly, and (2) frequency of friend/family visits. Possible scoring ranged from 0 to 10. Occupational engagement was represented by two individual variables: OF and Not in Education, Employment, and Training (NEET) status, a pre-established variable from youth mental health research (Social Exclusion Unit, 1999). Both variables were derived from the UKB database question on current employment status. Scoring ranged from -2 to 4 for OF, while NEET status was binary (0=non-NEET, 1=NEET; see Supplementary Information).

### 2.3. Phenotypic data on disorders of interest

Individuals with SCZ, BD, major depressive disorder (MDD), and ADHD were grouped by UKB ICD-10 diagnosis codes. The unaffected group was created by removing all individuals with any of the above ICD-10 diagnoses. R software (v4.3.1) (R Core Team, 2023) was used to calculate mean scores and distributions and perform general linear models to compare neuropsychiatric and the unaffected groups (see Supplementary Information).

### 2.4. Genetic data

The genotype dataset made available by the UKB in the December 2023 release was used. Genetic data was genotyped using the Applied Biosystems UK Biobank Axiom Array (The UK Biobank, 2014) or the Applied Biosystems UK BiLEVE Axiom Array (Wain et al., 2015). Genotypes were imputed as described previously (Bycroft et al., 2018). Quality control (QC) measures were applied to the imputed data, filtering variants with a minor allele frequency >0.0001 and an imputation quality information score >0.9 ( $n$  variants=15,857,586), along with others.

### 2.5. Statistical analyses

GWASs of SP, OF, and NEET status were performed with fastGWA (Jiang et al., 2019) using genome-wide complex trait analysis (GCTA) software (v1.94.1). FastGWA maximizes power through a genetic relationship matrix that allows the inclusion of related individuals within analyses. GWASs were performed adjusting for age, sex, array, Townsend Deprivation Index (TDI) scores, assessment center and the first 20 principal components. Analyses were restricted to participants of White-British ancestry.

## 2.6. SNP-based heritability

LD score regression (LDSC) (v1.0.1) was applied to estimate the SNP-based heritability from GWAS summary statistics (Bulik-Sullivan et al., 2015). Pre-computed LD scores from the 1000 Genomes Project (1KGP) European samples were used to carry out the analysis (<https://github.com/bulik/ldsc>).

## 2.7. Statistical fine-mapping

To narrow the credible window of the risk loci and identify potentially causal variants associated with SP and OF, sum of single effects (SuSiE) (Zou et al., 2022) was used with the 1KGP European reference panel (Phase 3) (The 1000 Genomes Project Consortium et al., 2015). Credible sets were identified using the susieR package (v0.12.35) (Wang et al., 2020).

## 2.8. Functional annotation

FUMA online pipeline (v1.5.2) (Watanabe et al., 2017) was used to map and annotate fastGWA outputs. Annotation was performed for all nominally significant SNPs and any variant in LD ( $r^2 \geq 0.6$ ). ANNOVAR was used to identify genic positions of SNPs, while Combined Annotation Dependent Depletion (CADD) scores were generated to determine variant pathogenicity (CADD score  $> 12.37$  = potentially pathogenic).

## 2.9. Gene-based analysis

Gene-based analysis was carried out using Multi-marker Analysis of GenoMic Annotation (MAGMA) (v1.6.) within the Functional Mapping and Annotation (FUMA) online tool (v1.5.2) (Watanabe et al., 2017). Gene-set analyses were implemented using 10,678 gene sets from MsigDB (v6.2) (curated gene-sets: 4,761; GO terms: 5,917). A Bonferroni correction threshold of  $P < 2.63e-6$  was applied (0.05/19036 protein coding genes).

## 2.10. Gene-mapping

Genome-wide significant loci were mapped to genes using positional, eQTL, and 3D chromatin interaction mapping strategies using FUMA (v1.5.2) (Watanabe et al., 2017).

## 2.11. Gene prioritization

To annotate potentially functional genes associated with the phenotype-specific variants, Polygenic Priority Score (PoPS) was performed using 57,543 gene-based features from 77 gene expression datasets (Weeks et al., 2023) (see Supplementary Information).

## 2.12. Transcriptome-wide association study

A transcriptome-wide association study (TWAS) analysis was conducted using precomputed gene expression weights from 1,321 PsychENCODE postmortem brain samples (Gandal et al., 2018). FUSION software (Gusev et al., 2016) was used to examine whether SNPs influencing gene expression (12,041 genes) were associated with SP and OF ( $P_{\text{bon}} < 4.19e-06$ ). TWAS fine-mapping was performed using FOCUS (v0.09) (Mancuso et al., 2019) in regions including a TWAS significant gene.

## 2.13. Genetic correlation analyses

Bivariate genetic correlations were calculated between our UKB phenotypes and summary statistics from the Psychiatric Genomics Consortium using LDSC (v1.0.1). A batch genetic correlation was also performed with all 1,583 publicly available phenotypes in the Complex

Traits Genetics Virtual Lab (CTG-VL) (Cuéllar-Partida et al., 2019).

## 2.14. Mendelian randomization

Mendelian randomization (MR) was conducted using the TwoSampleMR R package (v0.6.8) (Hemani et al., 2018). Instrumental variables were genome-wide significant (GWS) SNPs reported in GWAS of European ancestry samples only and minus UKB samples. The MR-Egger method was used for analyses to account for potential horizontal pleiotropy.

Further detail on all materials and methods is supplied in Supplementary Information.

## 3. Results

### 3.1. UKB SP and OF and NEET demographics

Of the 487,409 UK Biobank participants with genotype data, 404,403 (54.2% female, mean age 56.9 years,  $sd=7.99$ ) were available for GWAS analysis of SP after filtering and QC was performed. The SP scores ranged from 0-7, with a population mean of 4.28. For OF and NEET status variables, 404,569 (54.2% female, mean age 56.9 years,  $sd=8.00$ ) and 404,469 individuals (54.2% female, mean age 56.9 years,  $sd=8.00$ ), respectively, were included in the final GWAS analyses. Scoring for OF ranged from -2-4, with 59.1% attaining a score of 1 (mean score 0.61). NEET status was scored simply as 0 or 1, of which 42.9% reported being of NEET status (1).

### 3.2. Diagnostic comparison of mean phenotypic scores

The mean SP scores were significantly lower for participants with SCZ (mean score=4.08,  $P=6.95e-4$ ) and MDD (mean score=4.22,  $P=4.16e-18$ ) compared to the unaffected group (mean score=4.28; S1 Figure A; S1 Table). Mean OF scores across all psychiatric disorders were significantly lower (SCZ mean score=0.001,  $P=3.38e-57$ ; BPD mean score=0.15,  $P=3.53e-33$ ; MDD mean score=0.36,  $P=1.41e-151$ ) compared to the unaffected group (mean score=0.63; S1 Figure B). The proportion of NEET status assignment in all psychiatric groups also significantly differed from the unaffected group (SCZ  $P=9.65e-259$ ; BPD  $P=1.01e-156$ ; MDD  $P=0$ ; S1 Figure C; S1 Table).

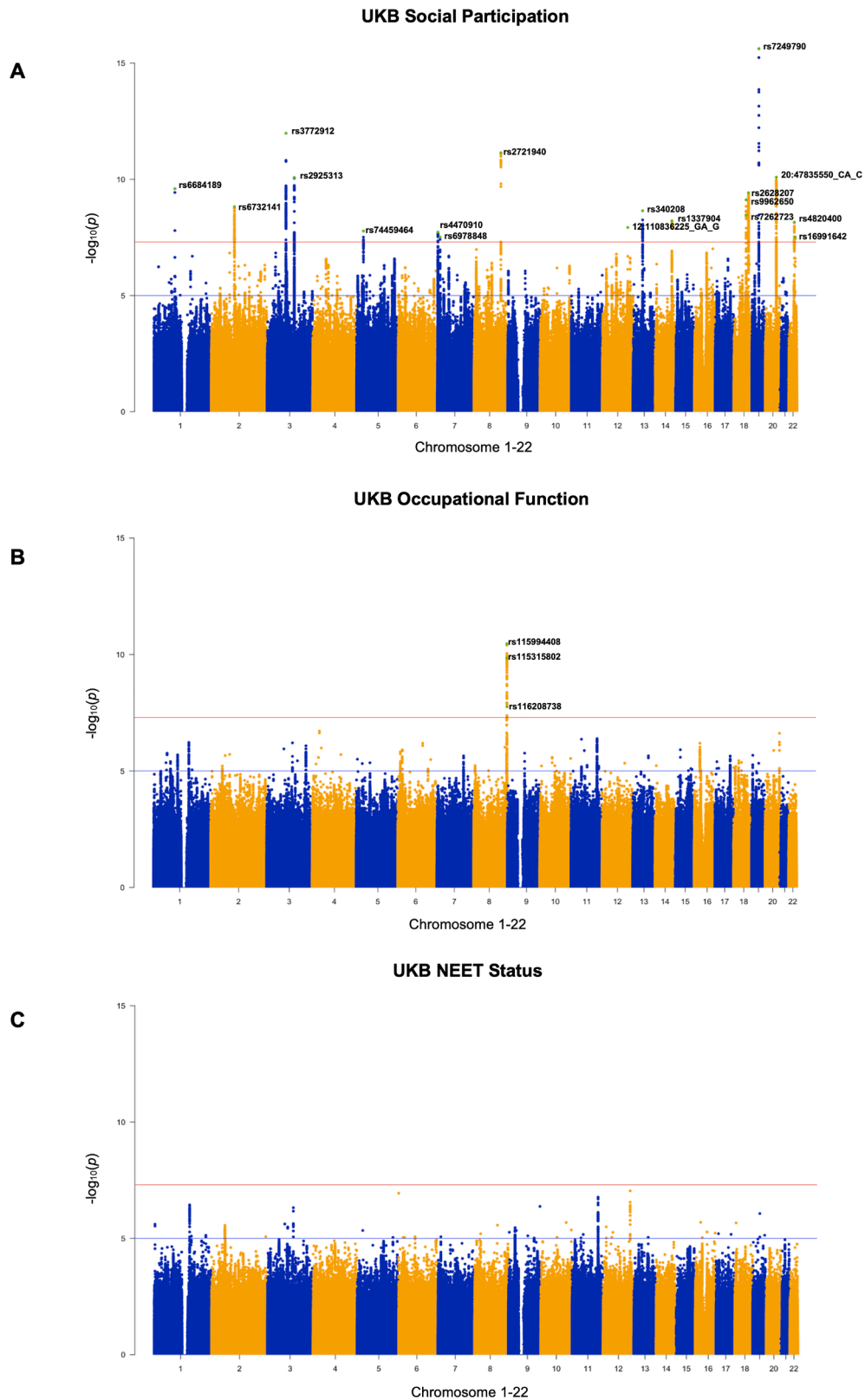
### 3.3. GWAS results

In total, 839 SNPs surpassed the GWS threshold for SP ( $P < 5e-8$ ; Manhattan plot in Fig. 1 A, Q-Q plot in S2 Figure A, S2 Table), with 18 lead-SNPs present at 17 independent genomic risk loci (Table 1). LDSC-based SNP-heritability ( $h^2_{\text{SNP}}$ ) for SP was 4.1% (S.E.=0.002). For OF, 65 SNPs surpassed the GWS threshold (S3 Table), with three lead-SNPs identified at a single independent locus (chr 8:143,311,088-145,746,556; Fig. 1 B, S2 Figure B, S4 Table). There were no GWS SNPs identified for NEET status (Fig. 1 C, S2 Figure C). The  $h^2_{\text{SNP}}$  for OF was 1.8% (S.E.=0.002) and for NEET status was 1.3% (S.E.=0.002).

We performed sex-specific analysis to investigate gender-based effects but no evidence of a sex-specific effect was found. We also performed a GWAS of the unaffected group excluding individuals with SCZ, BPD and MDD. The data indicated that inclusion of individuals with a diagnosis of a psychiatric disorder was not a major driver of the genetic associations detected for SP or OF (see Supplementary Information).

### 3.4. Statistical fine-mapping

Using the Bayesian fine-mapping approach, SuSiE, we identified fifteen 95% credible sets of potentially causal variants for 13 genomic loci associated with SP (S5 Table). Three credible causal variants with a PIP score  $> 0.5$  were identified, each representing an independent association signal at a different genomic risk locus. All three were



**Fig. 1.** Manhattan plots of the observed  $-\log_{10} P$ -values (y-axis) and the distribution of SNPs across chromosomes (x-axis) associated with the derived SP (A) ( $n=404,403$ ), OF (B) ( $n=404,569$ ) and NEET status (C) ( $n=404,469$ ) phenotypes in the UK Biobank cohort. The red line indicates the GWS threshold ( $P<5e-08$ ). Green dots and rsIDs denote the lead variants identified.

**Table 1**  
Location and significance values of the lead-SNPs at the GWS loci for SP.

SNP	CHR	POS	A1	A2	BETA	P	LOCUS	START <sup>a</sup>	END <sup>a</sup>	GENES <sup>b</sup>
rs6684189	1	91093014	T	C	-0.0209775	2.5464E-10	1	91088884	91097495	U3
rs6732141	2	100743492	C	G	0.0193749	1.51525E-09	2	100602518	100835734	AFF3
rs3772912	3	81698481	G	A	0.0237002	1.03979E-12	3	81499039	81986136	GBE1
rs2925313	3	117675543	T	G	0.0212319	8.3773E-11	4	117493729	117821879	LSAMP
rs74459464	5	29683773	C	A	-0.0495244	1.68067E-08	5	29596216	29713841	UBL5P1
rs4470910	7	2071723	T	C	0.0234068	1.88236E-08	6	1899447	2110850	MAD1L1, AC069288.1, AC110781.3
rs6978848	7	11247142	A	G	0.0179937	3.04755E-08	7	11244621	11253967	AC004538.3
rs2721940	8	116636281	C	A	-0.0224124	7.17991E-12	8	116563879	116645056	TRPS1
12:110836225_GA_G	12	110836225	G	GA	0.019815	1.18418E-08	9	110549533	111116655	ANAPC7, IFT81, VPS29, ARPC3, GPN3, RAD9B, PPTC7, TCTN1, HCVN1, ATP2A2, FAM216A
rs340208	13	60478605	T	A	0.0207035	2.267E-09	10	60367014	60785511	DIAPH3
rs13379045	14	91528977	C	A	0.0200233	6.10752E-09	11	91445077	91555547	RPS6KA5, DGLUCY
rs72627231	18	53195964	T	C	-0.021038	7.66951E-10	12	53195249	53621933	TCF4
rs9962650	18	53574043	G	C	0.0191538	3.44831E-09	12	53195249	53621933	RP11214L13.1
rs2628207	18	63546386	T	C	0.0219922	3.78661E-10	13	63407300	63616633	CDH7
rs7249790	19	30937444	G	C	0.0268073	2.39784E-16	14	30905494	30970357	ZNF536
20:47835550_CA_C	20	47835550	C	CA	0.0219482	8.13538E-11	15	47508077	47935069	DDX27, ARFGF2, CSE1L, STAU1, ZNFX1, KCNB1
rs4820400	22	40548084	T	G	0.0188991	7.02231E-09	16	40544337	40720963	TNRC6B
rs16991642	22	44595839	C	T	-0.0191154	3.0962E-08	17	44582264	44607514	PARVG

<sup>a</sup> START and END define the locus within which the lead SNPs are located.

<sup>b</sup> GENES includes those mapped to locus co-ordinates. Where no gene mapped to locus co-ordinates, the nearest gene according to ANNOVAR annotations (Ensembl gene build 85) was included. Genes mapped to the associated SNPs by gene prioritisation strategies are also included.

previously defined as the lead variant at all three genomic regions (rs3772912 (chr 3, intron of *GBE1*), PIP=0.76; rs7249790 (chr 19, intron of *ZNF536*), PIP=0.70; rs6684189 (chr 1, upstream of *U3*), PIP=0.70). No 95% credible sets of potentially causal variants were identified for the OF locus.

### 3.5. Functional annotation

CADD scores >12.37 were observed for 77 SP-associated SNPs (3.7%; S6 Table) across 15 of the significant genomic risk loci. Four of the six SNPs with the highest CADD scores (>20) were missense variants (rs1130146 and rs11553387 in *DDX27*, rs2229519 in *GBE1* and rs2291343 in *CDH7*). Nineteen SNPs (3.4%) exceeded the CADD score threshold for OF (S7 Table) at the single significant genomic locus and included rs114379623 (a missense variant in *TOP1MT*) and rs115510595 (a 3' UTR variant in *ZNF696*).

### 3.6. Gene-based analysis

MAGMA gene-based analyses identified 17 genes ( $P < 2.63e-6$ ) for the SP phenotype (S8 Table) and the top genes included *CDH7* ( $P = 5.57e-12$ ), *GBE1* ( $P = 5.90e-11$ ) and *ZNF536* ( $P = 1.20e-10$ ). For OF, three genes including *DRD2* ( $P = 4.47e-08$ ), *TNRC6A* ( $P = 1.75e-06$ ) and *TTC12* ( $P = 2.03e-06$ ) surpassed the significance threshold (S9 Table), while *DRD2* ( $P = 2.77e-07$ ) and *GRIN2B* ( $P = 2.04e-06$ ) were the genes identified for NEET status (S10 Table).

### 3.7. Gene-set and tissue analysis

Investigating biological functions, gene-set analysis showed that the gene-set responsible for the regulation of synaptic structure/activity was significantly enriched for genes associated with the SP phenotype ( $P_{\text{bon}} = 0.03$ ).

Based on 53 tissue types from GTEx v8, the MAGMA analysis revealed that SP-associated genes were most significantly enriched across 11 brain regions including the cerebellum, cortex, hippocampus, basal ganglia, hypothalamus, and amygdala (S3 Figure). These genes were generally implicated in brain and pituitary tissues (S4 Figure).

No gene-set or specific tissue-type were significantly enriched for genes associated with the occupational variables (S5-S8 Figure).

### 3.8. Gene mapping

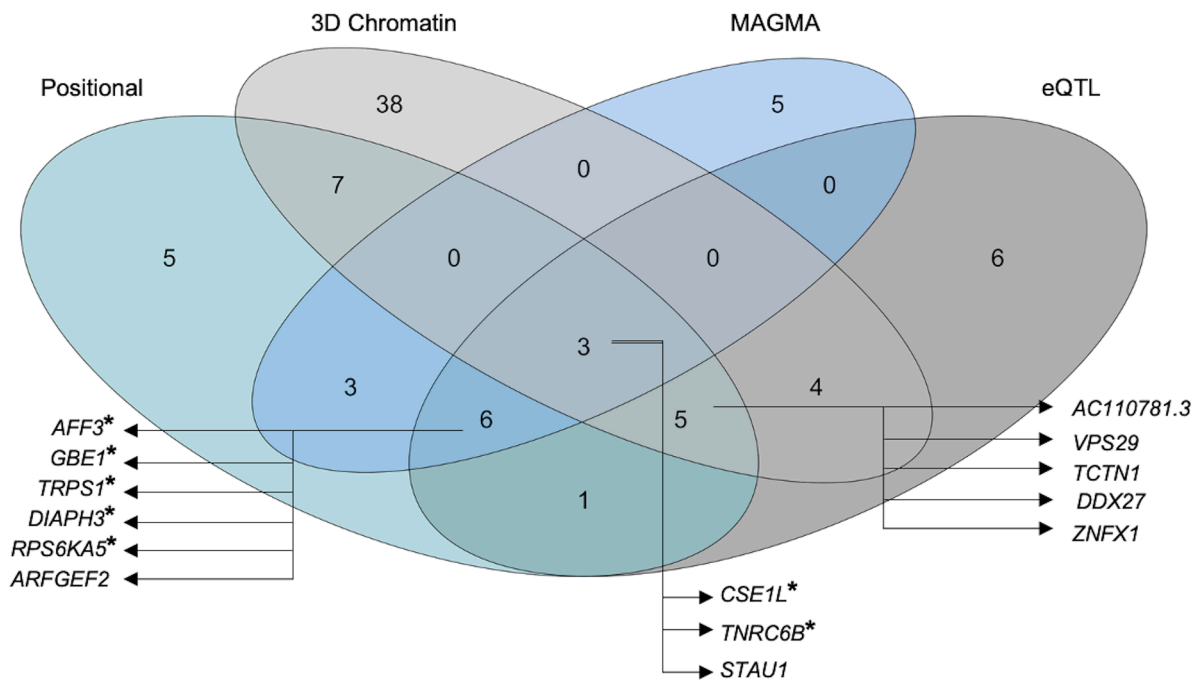
Seventy-eight unique genes were implicated for SP. Of the 17 genes identified by the earlier gene-based MAGMA analysis, 12 overlapped with those identified by the gene-mapping approaches. In total, three genes were observed across all four approaches: *CSE1L*, *STAU1*, and *TNRC6B* (Fig. 2 A; S11 Table).

Seventy-seven individual genes were positionally mapped for OF. Across approaches, 65 genes were identified by at least two approaches and six genes were implicated by all strategies (*C8orf31*, *GPA11*, *RHPN1*, *SHARPIN*, *TSNARE1*, and *VPS28*), although none of these genes overlapped with those identified by the MAGMA analysis (Fig. 2 B; S12 Table).

All 30 genes implicated in NEET status were positional as the absence

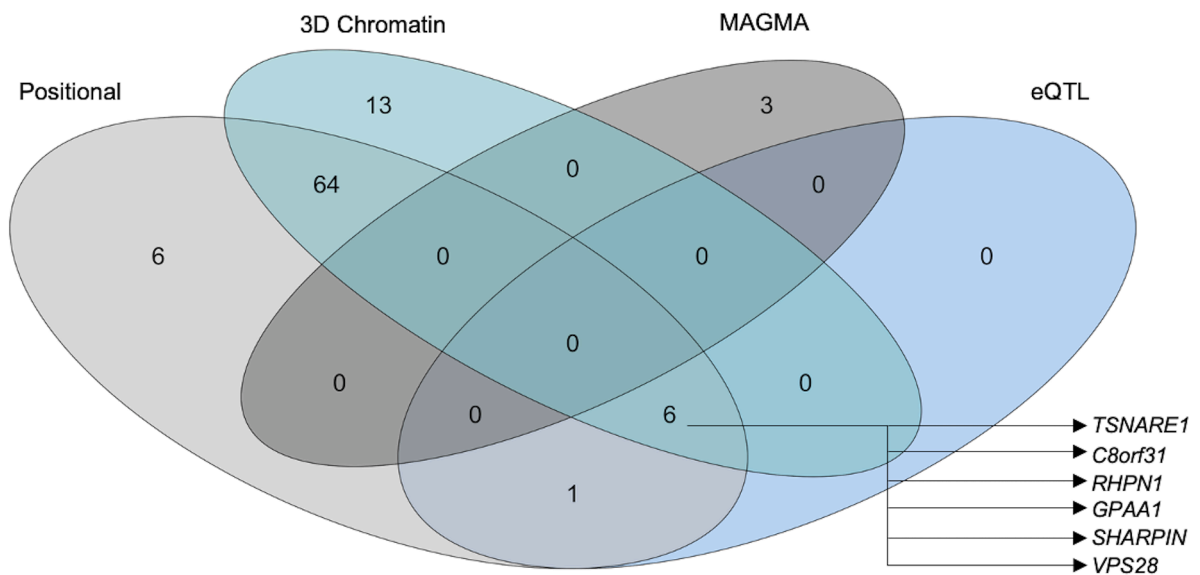
**Gene-mapping Overlap – Social Participation**

**A**



**Gene-mapping Overlap – Occupational Function**

**B**



**Fig. 2.** Venn diagram visualising the number of genes mapped to the SP (A) and OF (B) phenotypes by each approach and the number of overlapping genes between outputs. Asterix (\*) denotes the genes also prioritized by PoPS.

of genome-wide significant symptoms prevented further analysis. This included both genes identified by MAGMA analysis, *DRD2* and *GRIN2B* (S13 Table).

**3.9. Gene prioritization**

We computed PoPS scores for all protein coding genes within 500-kb of the 869 and 65 GWS associations for SP and OF, respectively. In total, 16 genes were prioritised for SP (S14 Table) and two genes for OF. The highest scoring genes for SP according to PoPS were *CDH7*, *GBE1*, and

ZNF536, the same top three genes implicated by the MAGMA analysis. Of the 16 genes prioritized for SP, two genes, *TNRC6B* and *CSEIL*, were previously implicated across all three gene-mapping approaches (S15 Table). For OF, both prioritized genes, *LY6H* and *PARP10*, were previously mapped in two approaches, positional and 3D chromatin interaction.

### 3.10. Transcriptome-wide association analysis

TWASs were performed for SP and OF using FUSION and eQTL gene expression data from the PsychENCODE Consortium (Gandal et al., 2018). Of the 11,934 genes analysed, the expression of six genes encompassing four independent genomic risk loci were significantly associated with SP ( $P\text{-Bon} < 4.19\text{e-}06$ ; S9 Figure A; S16 Table). Among the significant genes were *TRSP1* ( $P=2.08\text{e-}12$ ), *CSEIL* ( $P=3.95\text{e-}09$ ), and *STAU1* ( $P=7.22\text{e-}07$ ), all of which were previously mapped to SP. No genes were identified for OF (S9 Figure B). Within the 90%-credible set, FOCUS fine-mapping prioritized five genes across five distinct genomic loci ( $\text{PIP} > 0.8$ ). This included *TRPS1*, *CSEIL*, *UR11*, *AFF3*, and *GBE1* (S17 Table).

### 3.11. Genetic correlations

LDSC analysis identified significant genetic correlations between lower SP and greater risk of ADHD, ASD, SCZ, and MDD but not BD. Greater risk of ADHD, BD, MDD, and SCZ was significantly genetically correlated with both lower OF and being NEET (Fig. 3).

The batch genetic correlation revealed that SP, OF, and NEET status showed significant genetic correlations with 39, 365, and 291 traits respectively from across 1,583 published GWASs (S18-20 Table). Lower SP was genetically correlated with greater loneliness and socioeconomic deprivation and lower educational attainment (Fig. 3). Lower OF was genetically correlated with greater loneliness, and socioeconomic deprivation (TDI), while higher OF was genetically correlated with greater educational attainment, higher cognitive performance, and higher fluid intelligence (Fig. 3). NEET status was genetically correlated with lower educational attainment, fluid intelligence, cognitive performance and higher scores for neuroticism (Fig. 3). In terms of physical health factors, lower OF and a NEET status were genetically correlated with Body Mass Index (BMI), Chronic Obstructive Pulmonary Disease (COPD) and heart failure (Fig. 3), as well as several other related phenotypes (See S19 & S20 Table). Most interestingly, greater chronic pain was genetically correlated with lower scores for all three phenotypes.

### 3.12. Mendelian randomization

MR was performed to investigate the causal relationships between SP and psychiatric disorders (SCZ, BD, MDD, ADHD, and ASD) and EA. SP

did have a nominally significant causal effect on MDD while both BD and ADHD had nominally significant causal effects on SP. For the occupational engagement phenotypes, ADHD had a significant causal effect on OF ( $P=0.00037$ ) and SCZ had a significant causal effect on NEET ( $P=0.00034$ ; Fig. 4; S21 Table) with both results surviving multiple test correction. This indicates vertical pleiotropy between these two disorders and our UKB occupational engagement phenotypes.

## 4. Discussion

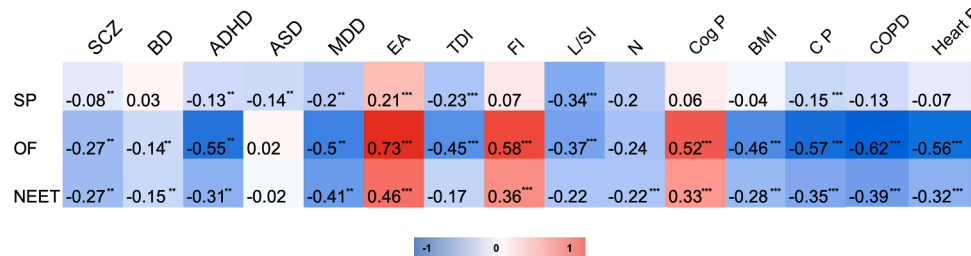
To our knowledge, this is the first study to investigate the genetics of objective social functioning using UKB data. Here, we define objective functioning as a measure of active participation and engagement, capturing how well an individual outwardly functions despite subjective emotional influence. Although active functioning has been previously incorporated into social phenotypes (Day et al., 2018), our aim was to solely capture outward functioning. We also investigated the genetics of occupational engagement, that is, the extent to which an individual actively engages occupationally/vocationally. A summary of results is provided in Table 2.

We observed that mean SP scores were significantly lower for participants with SCZ and MDD in the UKB. Mean OF scores were significantly lower and the proportion of individuals that were NEET was significantly higher across all psychiatric disorders tested. This indicated that our phenotypes indexing psychosocial disability were relevant to psychotic and other psychiatric disorders. By performing GWASs of these phenotypes excluding individuals with psychiatric disorders for comparison with our overall GWASs, we demonstrated that inclusion of these individuals is not responsible for the genetic associations detected. We detected no major sex-specific effects in our association analysis.

Educational Attainment; BD: Bipolar Disorder; BMI: Body Mass Index; COPD: Chronic Obstructive Pulmonary Disease.

### 4.1. Genetics of SP

We interpreted the GWAS results using a series of gene mapping approaches in combination with the MAGMA gene-based association test, gene prioritization (Weeks et al., 2023) and TWAS. *CSEIL* was identified by all methods. It plays a role in cell proliferation and apoptosis (Ruderfer et al., 2018) and has been repeatedly linked to SCZ (Ripke et al., 2014). The *STAU1* gene, identified by all methods except gene prioritization, maps to the same locus as *CSEIL*. This is a multi-functional double-stranded RNA-binding protein involved in neuronal differentiation. *TNRC6B* was also consistently associated with SP. It is involved in translational inhibition (Baillat and Shiekhhattar, 2009), which has been repeatedly linked to intellectual disability, social deficit disorders, and subsequent behavioural abnormalities (Granadillo et al., 2020).



**Fig. 3.** Heatmap of the genetic correlation results from LD score regression and batch genetic correlation for SP, OF, and NEET status with relevant traits of interest. Asterisk indicates a significant genetic correlation (LDSC multiple testing threshold  $P < 0.01$  (\*\*); Batch correlation multiple testing threshold  $P < 1.39\text{e-}5$  (\*\*\*)). Colour legend depicts strength of the positive/negative correlations. EA: Educational Attainment; TDI: Townsend Deprivation Index; FI: Fluid Intelligence; L/SI: Loneliness/Social isolation; Neuro: Neuroticism; Cog Per: Cognitive Performance; BMI: Body Mass Index; C. P: Chronic Pain; COPD: Chronic Obstructive Pulmonary Disease; Heart F: Heart Failure. Note: To aid interpretation, NEET status values have been reversed. Note: Traits reported on were selected for one of two reasons; a previously established genetic relationship with social and occupational variables/ a recurrent relationship with the derived SP and OE variables across the batch correlation (BMI, Chronic Pain, COPD and Heart Failure).

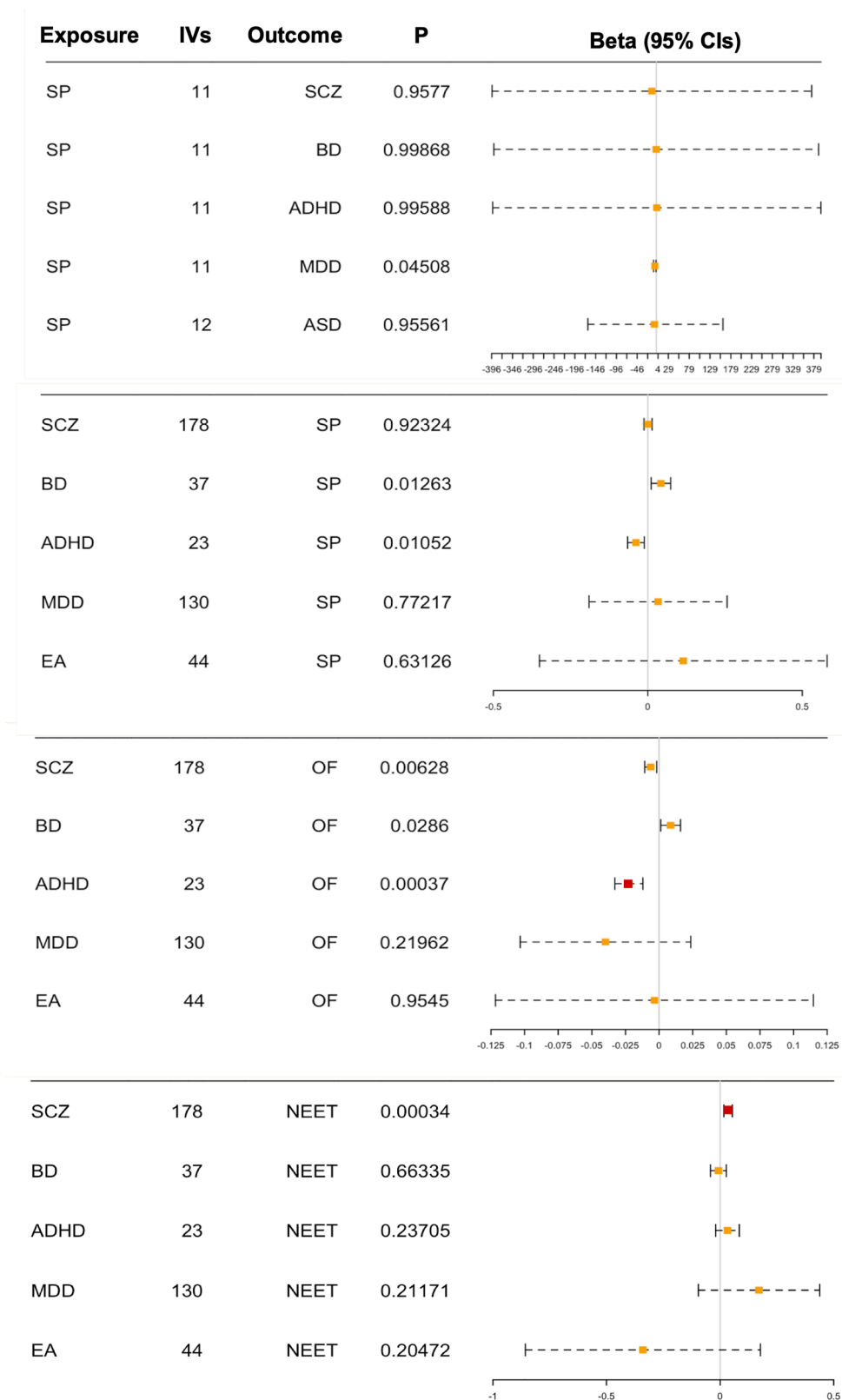


Fig. 4. MR forest plot of exposure (SP, SCZ, BD, ADHD, MDD, EA) versus outcomes (SCZ, BD, ADHD, MDD, ASD, SP, OF, NEET status). Plot shows the 95% confidence intervals (CIs) of the effect estimates ( $\beta$ ). Each line represents the CI and red dots identify associations that reach the  $P_{bon}$  threshold.

The strongest association signal for SP was at *ZNF536* where the lead SNP was identified as a credible causal variant. A transcriptional repressor gene involved in regulating neuronal differentiation (Qin et al., 2009), *ZNF536* was previously implicated in a GWAS of

social-isolation (Socrates et al., 2024). There is also evidence that *ZNF536* increases risk for SCZ and ASD (Kim et al., 2024).

The second strongest association was at *GBE1* where the associated haplotype contains a missense variant in exon 5 of the gene. *GBE1*,

**Table 2**  
Summary of findings from the GWASs and post-hoc analyses for the UKB derived phenotypes.

PHENO	N	GWAS LOCI	$h^2$ SNP	SuSiE	FUNCTIONAL ANNOT <sup>a</sup>	MAGMA	GENE-SET TISSUE ANALYSIS	GENE MAPPING <sup>b</sup>	PoPS	TWAS & FOCUS	GENETIC CORR. <sup>c</sup>	MR
Social Participation (SP)	404,403	17 (18 Lead SNPs)	4.1%	3 SNPs: rs3772912, rs7249790, rs6684189	77 SNPs	<i>CDH7, GBE1, ZNF536, CSE1L, STAU1, LSAMP, TNRC6B, ARFGEF2, RPS6KA5, AFF3, DCC, DIAPH3, ST6GALNA, C3, SUN2, SEMA6D, APBA2, TRPS1</i>	<u>Gene-set:</u> <i>synaptic structure/activity regulation</i> <u>Tissue:</u> brain and pituitary	78 Genes (mapped across all approaches; <i>CSE1L, STAU1, TNRC6B</i> )	16 Genes; <i>CDH7, GBE1, ZNF536, LSAMP, AFF3, RPS6KA5, TCF4, TNRC6B, TRPS1, DIAPH3, CSE1L, THSD7A, MAD1L1, PPP1CC, PARVG, BARHL2</i>	<u>TWAS:</u> 6 Genes; <i>TRPS1, CSE1L, DDX27, TCTN1, STAU1, DGKG</i> <u>FOCUS:</u> 5 Genes; <i>TRPS1, CSE1L, UR1L, AFF3, GBE1</i>	<u>Lower SP:</u> Increased risk for ADHD, ASD, SCZ & MDD. Greater loneliness, socio-economic deprivation & chronic pain. <u>Higher SP:</u> Greater EA.	<u>SP:</u> nominally significant causal effect on MDD ( $P=0.045$ ) <u>BD &amp; ADHD:</u> nominally significant causal effects on SP ( $P=0.013$ ; $P=0.011$ )
Occupational Function (OF)	404,569	1 (3 Lead SNPs)	1.8%	0 SNPs	19 SNPs	<i>DRD2, TTC12, TNRC6A</i>	None	90 Genes (6 mapped across all approaches; <i>C8orf31, GPAA1, RHPN1, SHARPIN, TSNARE1, VPS28</i> )	2 Genes; <i>LY6H, PARP10</i>	0 Genes	<u>Lower OF:</u> Increased risk for ADHD, BD, MDD, & SCZ. Greater loneliness, socioeconomic deprivation & lower EA. Increased chronic pain & elevated BMI. Greater risk for COPD, heart failure and other cardiovascular & respiratory issues. <u>Higher OF:</u> Greater EA, cognitive performance & fluid intelligence.	<u>ADHD:</u> significant causal effect on OF ( $P=0.0004$ )
NEET Status	404,469	0	1.2%	N/A	N/A	<i>DRD2, GRIN2B</i>	N/A	30 Genes (positional only; included both MAGMA genes)	N/A	N/A	<u>NEET Status:</u> Increased risk for ADHD, BD, MDD, & SCZ. Reduced EA, fluid intelligence, & cognitive performance and increased neuroticism. Increased chronic pain & BMI. Greater risk for COPD, heart failure and other cardiovascular & respiratory issues.	<u>SCZ:</u> significant causal effect on NEET ( $P=0.0003$ )

<sup>a</sup> Functional Annotations; SNPs with CADD scores >12.37

<sup>b</sup> Gene mapping approaches include positional, 3D Chromatin, eQTL

<sup>c</sup> Genetic Correlations; ADHD: Attention Deficit Hyperactivity Disorder; ASD: Autism Spectrum Disorder; SCZ: Schizophrenia; MDD: Major Depressive Disorder; EA:

involved in glycogen production, was previously implicated in a GWAS of sociability (Bralten et al., 2021). The lead variant at *GBE1* has also been implicated in neuroticism (Kichaev et al., 2019), a trait often accompanied by social unease (Connor-Smith and Flachsbart, 2007). The associated haplotype at two additional genes contained also a missense variant; *CDH7* and *DDX27*. *CDH7*, the gene with the highest prioritization score has been previously linked to neuroticism (Hindley et al., 2023), and cognitive function (Lee et al., 2018), while *DDX27* maps to the same locus as *CSE1L* and *STAU1*.

There was evidence to suggest that pathways involved in the regulation of synaptic signalling may play a role in the biology of SP. Enrichment of genes in synaptic pathways has been shown in multiple psychotic disorders, including SCZ (Ruderfer et al., 2018) and BD (Mullins et al., 2021). Further probing into the relationship between SP-associated genes and neuropsychiatric disorders revealed a link between SCZ and *TCF4* (Trubetskoy et al., 2022). Our lead SP variant at *TCF4* (rs72627231) surpassed GWS in the most recent SCZ GWAS (Trubetskoy et al., 2022) and is in high LD ( $r^2=0.52$ ) with one of the lead SCZ variants at that same locus, suggesting independent association of the same variant at *TCF4* with both phenotypes.

#### 4.2. Genetics of OF and NEET

The current work is among the few studies that have investigated the genetic basis of occupational engagement, as defined by occupational status. Our only GWS locus for OF contained three lead SNPs, each of which had a low minor allele frequency. Gene mapping approaches proposed six genes in the region (*C8orf31*, *GPA1*, *RHPN1*, *SHARPIN*, *TSNARE1*, and *VPS28*) and gene prioritization proposed another two (*LY6H* and *PARP10*). Functional annotation indicated that one of the associated haplotypes included a missense variant in *TOP1MT*. It is thus a difficult region to tease apart. *TSNARE1*, strongly associated with SCZ (Wang et al., 2018), belongs to a group of proteins believed to increase SCZ risk via synaptic dysfunction (Chen et al., 2021). *LY6H* is putatively involved in neurodegeneration in Alzheimer's disease (Wu et al., 2021) while *PARP10* plays a undefined role in the pathogenesis of ASD (Dong et al., 2018).

The MAGMA gene-based association test identified three GWS genes for OF, not located at the single GWS significant locus for OF. These genes are *DRD2* and *TTC12* on chromosome 11, and *TNRC6A* on chromosome 16. Here, individual SNPs approached GWS levels such that in combination within the gene-based test, they produced a GWS result at the gene level. It was similar for NEET where there were no GWS SNPs but GWS genes, *DRD2* and *GRIN2B*. *DRD2* encodes the dopamine D2 receptor, a target of most effective antipsychotic drugs, and is associated with SCZ (Trubetskoy et al., 2022). The most associated SNPs for OF (rs7125588) and NEET (rs4309187) are not in LD with each other, but each is in high LD with one of the two independent lead SNPs for SCZ. This suggests independent association of variants at *DRD2* with OF and SCZ and with NEET and SCZ. Like *DRD2*, SNPs at *GRIN2B* are associated with SCZ (Trubetskoy et al., 2022). However, in contrast to *DRD2*, the most associated SNP for NEET (rs10492134) at *GRIN2B* was not in LD with the lead associated SNP for SCZ (rs61920311).

#### 4.3. Correlations and causal relationships

Genetic correlations showed evidence of a shared genetic aetiology between our phenotypes and major psychiatric disorders, personality traits, cognitive phenotypes, educational attainment, social measures, and several physical health outcomes i.e., chronic pain, weight, and cardiovascular and respiratory abnormalities. These results suggest that SP, OF, and NEET cut across both mental and physical health. We showed a negative correlation between SP and neuroticism, lending support to the previously established link between social impairment and anxiety (Bralten et al., 2021) and the idea that there may be common genetic factors driving reduced social functioning and increased

neuroticism (Socrates et al., 2024).

Despite SNP-based heritability estimates being low at 1-4% for SP, OF and NEET, the MR analysis revealed evidence of causality of psychiatric disorders on these phenotypes; ADHD being causal for lower OF and SCZ being causal for an increased likelihood of having NEET status. This provides evidence that greater occupational functioning may be a consequence of genetic liability to SCZ. In reverse, there was some evidence that reduced SP may be causal for MDD. Further evidence for this causal link is required but if established, it supports targeting SP by intervention to reduce the burden of MDD in the population.

#### 4.4. Strengths and limitations

A major strength of the study is the large sample size made possible by using fastGWA (Jiang et al., 2019) to maximize sample size by retaining related individuals. Another strength is that we used active functioning measures to avoid the influence of subjective feelings. This also proved to be one of the main limitations, in that trying to measure active functioning limited suitable UKB social and occupational variables. We did attempt to create a latent variable for SP using available UKB social variables, but no one set of variables could be adequately collapsed into a single construct. As a result, we used a composite score to measure SP. While several factors were adjusted for in this study, we did not covary for cognitive performance or educational attainment. Although potential confounders, participant data for cognitive performance and educational attainment (Okbay et al., 2022) were only available for less than half of our sample from the UKB, which would have impacted the power of the study. We did perform an analysis using an older method for calculating educational attainment (Lee et al., 2018; Okbay et al., 2016) as a covariable where data was available for nearly our entire sample. This produced comparable results to those from the original GWASs (beta values correlated at  $>0.97$ ) leading us to conclude that educational level did not confound our results. Another limitation is that participants in this sample were of white British ancestry, meaning our results are not generalizable to other ancestral groups. Further, all data utilized within the current study was cross-sectional and from a single data collection timepoint. Future research should aim to incorporate longitudinal measures to study the underlying genetics of active social and occupational functioning.

#### 4.5. Conclusion

We have demonstrated a significant genetic component to PD. Using a combination of gene mapping, prioritization and association tests, we have established a list of genes influencing the SP and OF phenotypes including some also associated with SCZ. The low heritabilities detected may indicate that other genetic factors not yet identified are at play here. This may alternatively indicate that environmental factors account for much of the individual variation in psychosocial functioning. Despite this, there is evidence of a shared aetiology between PD and neuropsychiatric disorders and other psychological and health-related phenotypes. In addition, there is evidence for small but significant causal relationships between neuropsychiatric disorders and occupational engagement that require further exploration.

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#### CRediT authorship contribution statement

**Evie Doherty:** Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Aodán Laighneach:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation. **Mia Casburn:** Writing – review & editing, Methodology, Investigation,

Formal analysis, Data curation. **Fergus Quilligan:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation. **Gary Donohoe:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Conceptualization. **Dara M. Cannon:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Conceptualization. **Derek W. Morris:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Conceptualization.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.psychres.2026.116963](https://doi.org/10.1016/j.psychres.2026.116963).

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