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Genome-wide analyses of empathy and systemizing: heritability and correlates with sex, education, and psychiatric risk

Varun Warrier[1,8], Roberto Toro[2,3,4], Bhismadev Chakrabarti[1, 5], Nadia Litterman[6], David A. Hinds[6,] Thomas Bourgeron[2,3,4*], and Simon Baron-Cohen[1,7,8*]

[1]Autism Research Centre, Department of Psychiatry, University of Cambridge, Cambridgeshire, United Kingdom

[2]Institut Pasteur, Human Genetics and Cognitive Functions Unit, Paris, France

[3]CNRS UMR 3571: Genes, Synapses and Cognition, Institut Pasteur, Paris, France

[4]Université Paris Diderot, Sorbonne Paris Cité, Human Genetics and Cognitive Functions, Paris, France

[5] Centre for Integrative Neuroscience and Neurodynamics, School of Psychology and Clinical Language Sciences, University of Reading, Reading, United Kingdom

[6] 23andMe Inc., Mountain View, California 94043, USA

[7] CLASS Clinic, Cambridgeshire and Peterborough NHS Foundation Trust (CPFT), Cambridgeshire, United Kingdom

[8] **Corresponding authors**: Varun Warrier (vw260@medschl.cam.ac.uk) and Simon Baron-Cohen (sb205@cam.ac.uk). Autism Research Centre, Douglas House, 18B Trumpington Road, Cambridge, CB2 8AH, United Kingdom. Telephone: 0044 (0) 1223 746057. * Joint senior authors.

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Empathy is the drive to identify the mental states of others and respond to these with an appropriate emotion. Systemizing is the drive to analyse or build lawful systems. Difficulties in empathy have been identified in different psychiatric conditions including autism and schizophrenia. In this study, we conducted genome-wide association studies of empathy and systemizing using the Empathy Quotient (EQ) (n = 46,861) and the Systemizing Quotient-Revised (SQ-R) (n = 51,564) in participants from 23andMe, Inc. We confirmed significant sex-differences in performance on both tasks, with a male advantage on the SQ-R and female advantage on the EQ. We found highly significant heritability explained by single nucleotide polymorphisms (SNPs) for both the traits (EQ: 0.11±0.014; P= $1.7x10^{-14}$ and SQ-R: 0.12 ±0.012; P=$1.2x10^{-20}$) and these were similar for males and females. However, genes with higher expression in the male brain appear to contribute to the male advantage for the SQ-R. Finally, we identified significant genetic correlations between high score for empathy and risk for schizophrenia (P= $2.5x10^{-5}$), and correlations between high score for systemizing and higher educational attainment (P= $5x10^{-4}$). These results shed light on the genetic contribution to individual differences in empathy and systemizing, two major cognitive functions of the human brain.

Empathy is the ability to identify other people's thoughts, intentions, desires, and feelings, and to respond to other's mental states with an appropriate emotion[1]. It plays an important role in social interaction and is a key component of both prosocial behaviour and social cognition. Differences in empathy have been observed in several psychiatric conditions, including autism[1], bipolar disorder[2], schizophrenia[3–5], and depression[2,6,7]. Difficulties in empathy contribute to impaired interpersonal functioning[8] and some psychotherapeutic interventions target empathy[8]. Systemizing is the drive to identify patterns to understand and build rule-based systems[9]. Elevated systemizing has been identified in autism[9,10]. Higher systemizing has also been found in schizotypy[11] and anorexia nervosa[12], suggesting that a strong interest in rule-based systems may be a characteristic of several psychiatric conditions. Both empathy and systemizing show marked sex differences, in opposite directions: there is a male advantage in systemizing[10] and a female advantage in empathy[1]. These sex differences are thought to contribute to the high proportion of males diagnosed with autism, although this could also reflect diagnostic practice[13]. The sex difference in empathy and systemizing may also relate to the higher proportion of males in Science, technology, engineering and mathematics[14]. Both traits are related to prenatal testosterone[15,16], which itself is produced in higher levels in males. However, we know little about the genetic architecture of these traits, the mechanisms underlying the sex differences, and the shared architecture with psychiatric conditions.

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To understand the genetic architecture of empathy and systemizing, we collaborated with 23andMe to conduct a Genome Wide Association Study (GWAS) of empathy (n = 46,861) and systemizing (n = 51,564). We employed two widely used self-report measures to quantify the traits: the Empathy Quotient (EQ) for empathy[1] and the revised Systemizing Quotient (SQ-R) for systemizing[10]. The mean score for all participants was 46.4±13.7 on the EQ, and 71±21 on the SQ-R. Males scored higher than females on the SQ-R (76.5±20 in males; 65.4±20.6 in females), and vice-versa on the EQ (41.9±13.5 in males, 50.4±12.6) (Figure 1a and b). For each trait, we conducted three GWAS analyses: a male-only analysis, a female-only analysis, and a non-stratified analysis (Online Methods). Subsequently, we corrected for the three different tests for each trait and used a conservative threshold of $P = 1.66x10^{-8}$. We did not identify any genome wide significant SNPs (Supplementary Figures 1 - 12 and Supplementary Table 1). Gene based analysis identified one significant putative gene, CMT1A Duplicated Region Transcript 4 (*CDRT4),* with q-value < 0.01 for empathy (Supplementary Tables 2 and 3). We identified enrichment in four functional categories for the SQ-R. These are evolutionarily conserved genetic regions in mammals (P=0.0005), fetal open chromatin sites (P= 0.002), histone acetylation sites (P= 0.002), and transcription start sites (P=0.002) (Supplementary Tables 4 and 5).

We used LDSC[17] to calculate the heritability explained by all the SNPs tested (Online Methods). The heritability was 0.11±0.014 for the EQ ($P= 1.7x10^{-14}$), and 0.12±0.012 for the SQ-R ($P=1.2x10^{-20}$; Figure 1*c* and *d* and Supplementary Table 6). To our knowledge, there is no study examining heritability of the SQ-R in twins. One study, investigating the heritability of the reduced EQ (18 items) in 250 twin pairs, identified a heritability of 0.32[18]. The literature on the heritability of empathy and prosociality is inconsistent, with heritability estimates ranging from 0.69 [19] to 0.20[20], though a meta-analysis of different studies has identified a heritability estimate of 0.35 (95% CI – 0.21 – 0.41)[21]. Our analysis therefore suggests that a third of the heritability can be attributed to common genetic variants.

(insert Figure 1 here)

Sex differences in empathy and systemizing[10,13] may reflect genetic as well as non-genetic factors (such as prenatal steroid hormones)[22]. In our dataset, there was significant female advantage on the EQ (P<0.001; Cohen's d = 0.65), and a significant male advantage on the SQ-R (P<0.001; Cohen's d = 0.54) (Figure 1a and b). To investigate the biological basis for the sex-difference observed in the traits, we investigated the heritability of the sex-stratified

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GWAS analyses for both the traits. Our analyses revealed no significance difference between the heritability in the males-only and the females-only datasets for the two traits (P = 0.48 for male-female difference in EQ, and 0.34 for male-female difference in SQ-R) (Figure 1c and d; Supplementary Table 6). Additionally, there was a high genetic-correlation between the males-only and females-only GWAS for both the traits (EQ correlation = 0.82 ± 0.16; P = 2.34×10^{-7}; SQ-R correlation = 1 ± 0.17; P = 3.91×10^{-10}), indicating a high degree of similarity in the genetic architecture of the traits in males and females. This was surprising in light of the significant difference in scores between males and females on the self–report measures.

While there was a significant correlation between the sexes across the genome, the top genes that contribute to these traits may be different between the sexes. Further, these genes may exhibit sex-differential tissue-specific expression patterns. To investigate the contribution of genes, we used MetaXcan[23] to identify nominally significant genes ($P < 0.05$) for the traits in the cortex in the sex-stratified analysis and checked for overlap in the genes identified between the sexes (Online Methods; Supplementary Tables 7 - 10). There was a non-significant underlap between the sets of nominally significant genes in males and females, suggesting that different sets of genes contribute to the traits in males and females (hypergeometric tests; EQ: P = 0.6, 0.7-fold underlap; SQ-R: P = 0.16, 0.7-fold underlap). We next investigated if there is a sex-differential expression of the top genes ($P < 0.05$) in the adult cortex. We hypothesized that some of the phenotypic sex-difference can be explained by sex difference in gene expression in the brain. We used previously identified genes that have sex-differential expression in the adult human cortex using the BrainSpan dataset[24] and identified genes that are more highly expressed in males than females (male-expression genes) and vice-versa (female-expression genes). We compared the two lists with the list of top genes in the sex-stratified analyses for the two traits. We found a significant enrichment for male-expression genes in the males-only dataset for systemizing (hypergeometric test; 1.2-fold enrichment, P = 0.002). We confirmed this observation in an independent dataset of sex-differentially expressed genes in the adult cortex[24] (hypergeometric test; 1.1-fold enrichment, P = 0.024). These results suggest a two-step mechanism for some of the observed sex-difference in SQ-R scores. First, the top genes that contribute to systemizing are different in males and females. Second, the genes that contribute to systemizing in males also have increased expression in males. Genes may exhibit sex-differential expression if they are regulatory targets for steroid hormones or genes on the sex chromosomes. Fetal testosterone is a significant predictor of systemizing[16], yet the mechanisms by which this works is not fully established. While systemizing can be

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largely thought of a pan-cortical process, empathy is known to utilize several sub-cortical and specific cortical regions of the brain[25]. Our analysis is not sensitive enough to identify sex-differential gene expression specific to these regions. Examining sex-differential expression in specific brain regions involved empathy may help explain the female-advantage in empathy.

To investigate how the two traits correlate with psychiatric conditions and IQ, we performed genetic correlation (Online Methods) between the non-stratified GWAS for the two traits and five psychiatric conditions (autism, anorexia nervosa, bipolar disorder, depression and schizophrenia), as well as number of college years (a proxy measure of IQ) (Supplementary Table 13). Individuals with autism, on average, score lower than typical controls on the EQ[1], and score higher than typical controls on the SQ-R[10]. Our genetic correlation analyses mirrored these results. The EQ was negatively, albeit non-significantly, correlated with autism and the SQ-R was positively correlated with autism (nominal significance) (Figure 2). Two such correlations were significant after correcting for multiple comparisons: the EQ-schizophrenia and the SQ-R-college years correlations (Figure 2; Supplementary Table 14). We confirmed the EQ-schizophrenia correlation, using the second PGC schizophrenia dataset (schizophrenia-2), which has a larger sample (79,845 cases and controls compared to 17,115 cases and controls), but is not independent of the first PGC SCZ dataset (rg = 0.1772; se = 0.042; P = 2.49×10^{-5}).

(insert Figure 2 here)

In conclusion, the current study provides insights into the genetic architectures of both empathy and systemizing. We show that up to a third of the heritability of empathy is explained by common SNPs. Similarly, we show that a modest but significant percentage of the variance in systemizing can be attributed to common SNPs. While there is a very significant difference in scores on the two questionnaires between males and females, heritability is similar, with a high genetic correlation between the sexes. However, our research suggests that gender differences in gene expression contribute to higher systemizing in males. This global view of the genomic architecture of empathy and systemizing should not only allow us to better understand psychiatric conditions, but also to improve our knowledge of the biological bases of brain diversity and evolution in humans.

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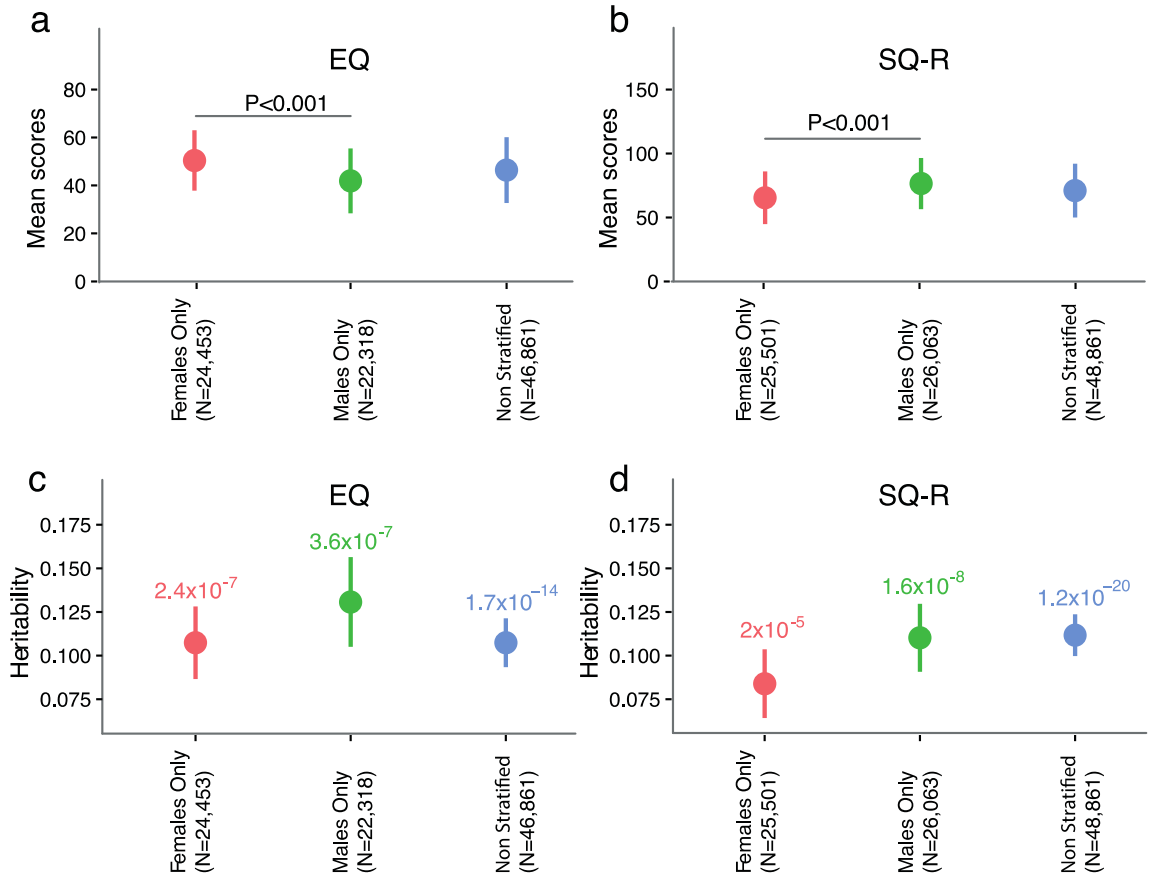

Figure 1: **Mean scores and heritability estimates for SQ-R and EQ**. Mean scores and standard deviations for scores on the EQ (a) and the SQ-R (b). The effect sizes of the difference between males and females on the EQ scores and the SQ-R scores were Cohen's d= 0.65 and Cohen's d = 0.54, respectively. Mean estimates and standard errors for heritability for scores on the EQ (c) and the SQ-R (d). Numbers on top of the graphs represent P-values for each heritability estimate.

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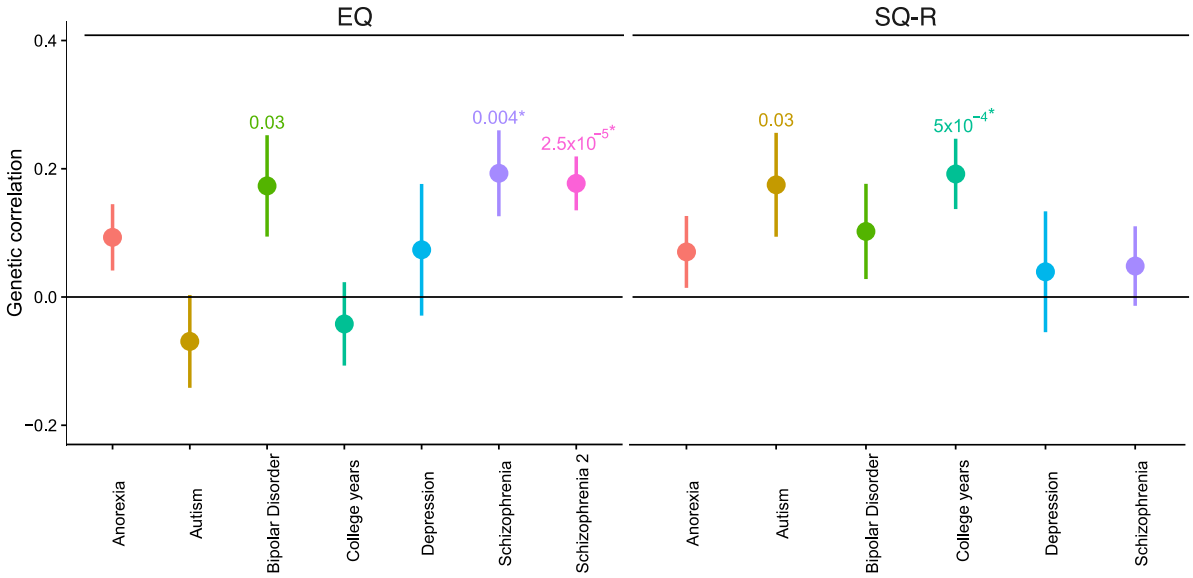

Figure 2: Genetic correlations between SQ-R and EQ and other conditions. *Mean and standard errors shown for genetic correlations between empathy, systemizing and other conditions. P-values are provided for nominally significant correlations. * represents a significant correlation after FDR correction. The sample sizes for the traits are: anorexia (n=17767), autism (n=10263), bipolar disorders (n=11810), college year (n=95427), depression (n=16610), schizophrenia (n=17115), schizophrenia 2 (n=79845).*