The shared genetic architecture of schizophrenia, bipolar disorder and lifespan

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Abstract

Psychiatric disorders such as Schizophrenia (SCZ) and Bipolar Disorder (BD) represent an evolutionary paradox, as they exhibit strong negative effects on fitness, such as decreased fecundity and early mortality, yet they persist at a worldwide prevalence of approximately 1%. Molecular mechanisms affecting lifespan, which may be widely common among complex diseases with fitness effects, can be studied by the integrated analysis of data from genome-wide association studies (GWAS) of human longevity together with any disease of interest. Here, we report the first of such studies, focusing on the genetic overlap -pleiotropy- between two psychiatric disorders with shortened lifespan, SCZ and BD, and human parental lifespan (PLS) as a surrogate of life expectancy. Our results are twofold: first, we demonstrate extensive polygenic overlap between SCZ and PLS and to a lesser extend between BD and PLS. Second, we identified novel loci shared between PLS and SCZ (n=39), and BD (n=8). Whereas most of the identified SCZ (66%) and BD (62%) pleiotropic risk alleles were associated with reduced lifespan, we also detected some antagonistic protective alleles associated to shorter lifespans. In fact, top-associated SNPs with SCZ seems to explain longevity variance explained (LVE) better than many other life-threatening diseases, including Type 2 diabetes and most cancers, probably due to a high overlap with smoking-related pathways. Overall, our study provides evidence of a genetic burden driven through premature mortality among people with SCZ, which can have profound implications for understanding, and potentially treating, the mortality gap associated with this psychiatric disorder.

Introduction

Schizophrenia (SCZ) and Bipolar Disorder (BD) are mental disorders that greatly impact the quality of life of affected individuals and rank globally among the leading causes of human disability and cost to health systems (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017). Large genome-wide association studies (GWAS) show that SCZ and BD are highly polygenic diseases with many known associated genetic variants with small effects (Pardiñas et al., 2018; Prata et al., 2019; Stahl et al., 2019), jointly explaining between one half to one third of the genetic risk of each disease (Sullivan, 2005; Wray and Gottesman, 2012). Recently, large amounts of data have accumulated suggesting a genetic overlap between SCZ, BD and many brain disorders, as well as other medical conditions and personality traits (Ole A Andreassen et al., 2013; Ole A. Andreassen et al., 2013; Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019; Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Smeland et al., 2019, 2017; Zuber et al., 2018), which would be consistent with the hypothesis that psychiatric disorders may arise from complex trade-offs with other traits and diseases and may be considered as byproducts of other adaptive functions.

People affected by SCZ and BD often die at a considerably younger age than the rest of the population (Olfson et al., 2015; Roshanaei-Moghaddam and Katon, 2009; Walker et al., 2015) and suffer from increased morbidity rates (Vancampfort et al., 2017). While the decline in mortality rates in developed countries has extended average lifespans by nearly a decade, such improvements have not been observed in psychiatric patients (Lee et al., 2017; Lomholt et al., 2019; Oakley et al., 2018; Staudt Hansen et al., 2019). In SCZ, metabolic alterations induced by the use of antipsychotic drugs may contribute to premature mortality by increasing the risk of diabetes and cardiovascular disease (Hjorthøj et al., 2017; Laursen et al., 2014, 2012). However, both high doses and a lack of antipsychotic use are associated with a higher risk of death, indicating that factors other than antipsychotic treatment influence mortality (Torniainen et al., 2015). Intrinsic factors associated with SCZ and BD also contribute to increased mortality, including an increased risks of suicide and accidents, poor health care and poor health habits including smoking (Olfson et al., 2015). Besides the potential contribution of all these factors to mortality, intrinsic accelerated biological aging may also play a role in the premature mortality and the increased morbidity observed (Nguyen et al., 2018; Rizzo et al., 2014; Saha et al., 2007), which points toward the downstream expression of molecular mechanisms that may be shared between mortality and these psychiatric disorders (Kirkpatrick et al., 2008; Kirkpatrick and Kennedy, 2017). In this regard,

recent GWAS on parental lifespan and offspring genotypes offer the prospect of illuminating biological systems involved in lifespan and enable the discovery of genetic variants affecting all-cause mortality (Timmers et al., 2019).

How common risk alleles persist in the population, given the early mortality and decreased fecundity associated with psychiatric disorders (Power et al., 2013), has been long debated (Crespi et al., 2007; Shaner et al., 2004; Srinivasan et al., 2016). To date, studies evaluating the evolutionary footprint on the disease risk alleles, mainly conducted on SCZ, support the action of background selection contributing to the persistence of common risk alleles in the population, as a consequence of purifying selection in regions of low recombination (Pardiñas et al., 2018). On the other hand, some limited empirical evidence suggests that standing genetic variation for longevity is enriched with mutations with pleiotropic effects (Maklakov et al., 2015; Rodríguez et al., 2017). This would fit the well-known antagonistic pleiotropy (AP) theory of aging, according to which genetic variants with beneficial effects early in life can be selected for despite their negative effects late in life (Williams, 1957), a prediction that, in general terms, matches recent observations on alleles that either protect from or increase the risk of human disease (Rodríguez et al., 2019, 2017). The study of how psychiatric disorders would fit in such scenario can benefit from the tests based on DNA sequence polymorphism that have been developed to detect past selective events in humans (Huber et al., 2016; Sabeti et al., 2007; Voight et al., 2006) and which, surprisingly, have been only partially applied to the understanding of psychiatric disorders (Crespi et al., 2007; Pardiñas et al., 2018).

Given the public health significance of psychiatric disorders and the treatment implications of any etiological findings, it is essential to determine the nature of genetic pleiotropy between psychiatric disorders and mortality, if it does exist at all; and to identify the specific genes and pathways driving these potential trade-offs. Here, we used genetic epidemiology and genome enrichment analysis to perform a detailed study on the polygenic overlap between SCZ, BD, and parental lifespan (PLS), identifying both, novel candidate loci associated to the diseases and specific loci potentially explaining shared positive and negative comorbidities between these phenotypes. We show for the first time that single nucleotide polymorphisms (SNPs) increasing the risk for SCZ and BD are, at large, associated with a greater risk of living shorter lives, confirming clinical observations. Still, we detect some remarkable exceptions, unveiling the existence of variants with pleiotropic effects consistent with the AP theory of aging, since they seem to protect from these diseases at the cost of

shorter lives. Altogether, our approach provides early insights to elucidate the shared pathophysiology between psychiatric disorders and lifespan.

Methods and Materials

Genome-wide association study (GWAS) samples

GWAS summary statistics on SCZ were obtained from Pardiñas et al. 2018, which comprised association analyses of a total of 40,675 patients with SCZ and 64,643 controls from European ancestry (Pardiñas et al., 2018). The summary statistics on BD were obtained from the Psychiatric Genomic Consortium (PGC, https://www.med.unc.edu/pgc/) and included 20,352 patients with BD and 31,358 controls, all from European descent (Stahl et al., 2019). We also obtained GWAS data on ~1 million PLS from ~450,000 European individuals from the UK Biobank (Timmers et al., 2019).

Preprocessing

All GWAS summary statistics were referenced to a set of 9,546,816 single nucleotide polymorphisms (SNPs) generated from the 1,000 Genomes Project (1KGP, http://www.internationalgenome.org/). SNPs that were non-biallelic, without rsIDs, duplicated, or with strand-ambiguous alleles were removed. SNPs with INFO scores < 0.9 in the summary statistics files, those mapping to the extended major histocompatibility complex (MHC, genomic position in hg 19; chr6: 25,119,106 – 33,854,733) and the 8p23.1 region (chr8: 7,200,000 – 12,500,000), which are prone to rearrangements (Smeland et al., 2019), SNPs located on chromosomes X, Y and mitochondria, and SNPs with sample sizes 5 standard deviations away from the mean were also filtered out. Finally, a common set of 3,206,698 SNPs were kept in all datasets. All ORs and Betas from the summary statistics were transformed to *z*-scores. We evaluated the directional effects of the loci shared between psychiatric disorders and PLS by comparing their z-scores. GWAS data was obtained from common data sources, resulting in overlapping control individuals between BD and SCZ. Thus, all p-values were adjusted for standard genomic control (GC) and Z-scores were adjusted for sample overlap between GWAS, using intergenic SNPs as implemented in the *pleioFDR* script (Lin and Sullivan, 2009; Schork et al., 2013), adjusting the joint distribution of two GWAS and allowing for the use of the corrected summary statistics in downstream analysis.

The European populations from the 1KGP were used as the reference panel for the computation of the linkage disequilibrium (LD) structure between SNPs. Independent genomic loci were identified as described in Smeland et al. (Smeland et al., 2019). To define distinct genomic loci, we merged any physically overlapping lead SNPs (LD

blocks <250 kb apart), and the borders were defined by identifying all SNPs in LD ($r^2 \geqq 0.1$) with one of the independent significant SNPs in the locus. The region containing all these candidate SNPs was defined as a single independent genomic locus and the most significant SNP within the region was selected as the lead SNP.

Shared genetic architecture

A frequent method for visualization of the enrichment of statistical association relative to the null hypothesis is through conditional or stratified Q-Q plots. When investigating polygenic shared architecture between two traits, the p-values of the primary trait are plotted conditioning on different strengths of association with a secondary trait (e.g., P < 1e-01, 1e-02 or 1e-03). Thus, the visualization of a leftward deflection in the primary trait of interest is an indicator of a shared polygenic architecture between the two traits (Zuber et al., 2018). To test for differential fold enrichment of each the three Q-Q plot strata represented in the Q-Q plots we used LD score regression (LDSC) with the total LD score as covariate (Finucane et al., 2015). Multiple-testing correction was performed for all the traits and for the three strata using the Benjamin-Hochberg (BH) procedure. LDSC was also used to compute genome-wide pairwise genetic correlations (r) across the studied traits (Bulik-Sullivan et al., 2015).

Conditional Q-Q plots suffer from arbitrary thresholds and do not identify the specific pleiotropic regions of the genome. We employed the conjunctional FDR (conjFDR) to detect SNPs associated jointly with both traits at the same time. conjFDR weights both traits equally and is a suitable technique to discover novel associations that are otherwise not detected (Andreassen et al., 2014; Ole A. Andreassen et al., 2013). We used pleioFDR (https://github.com/precimed/pleiofdr) to identify genetic loci jointly associated with two phenotypes, setting a conjFDR level of 0.05 for each phenotypic pairwise comparison. For the identification of novel loci associated to each disease, we downloaded the GWAS Catalog database (v1.0) and searched for associations containing either the words “schizophrenia” or “bipolar disorder” and kept any significant (P<1e-05) association within the boundaries of each defined loci. When no associations were previously reported, the locus was defined as novel.

Pleiotropy and Evolutionary Analysis

In genetics, the term “pleiotropy” refers to one genetic variant influencing multiple phenotypes (Paaby and Rockman, 2013). In the context of the AP evolutionary theory of aging and the present work, pleiotropic effects can be divided into agonistic and antagonistic with relation to their effects on the diseases under study and lifespan. For

each SNP, the same allele may increase susceptibility to the disease and decrease lifespan (referred to as agonistic pleiotropy) or decrease the susceptibility to the disease while shortening lifespan (antagonistic pleiotropy). Since SNPs are binary in nature (one allele mirroring the effect of the other) and because we always referred to the derived allele, we included in the antagonistic category not only those SNPs having a derived allele that decreased the susceptibility to disease and decreased lifespan but also those ancestral alleles reported increase disease susceptibility while lengthening lifespan.

We also used the ρ-HESS software to estimate genetic correlations based on smaller LD-based segments of the genome (Shi et al., 2017). For all ρ-HESS analyses, we used the 1000 Genomes Project Phase 3 European reference panel and reported the number of genomic regions displaying significant local genetic correlations after correction for the total number of partitions (1655, after MHC removal). We assumed no sample overlap between the two psychiatric disorders and PLS. To further investigate the causal effect of SCZ on PLS we performed two-sample Mendelian Randomization (MR) using SCZ GWAS (Pardiñas et al., 2018) as exposure and PLS GWAS (Timmers et al., 2019) as outcome. Effect estimates and standard errors were extracted for each variant from the GWAS summary statistics and used to estimate inverse variance weighted (IVW) effect estimates (Hemani et al., 2018). Heterogeneity in the IVW estimates was tested using the Cochran's Q test. For the analyses we used the *TwoSampleMR* R package (https://github.com/MRCIEU/TwoSampleMR).

We evaluated whether molecular signatures of natural selection were different between the loci showing agonistic and antagonistic effects in SCZ and PLS. For each identified SNP, standard precomputed statistics for recent positive selection (XP-EHH, iHS) and local genetic adaptation (F_{ST}) were obtained from the 1,000 Genomes Selection Browser (http://hsb.upf.edu/hsb_data). The XP-EHH and iHS tests search for long range haplotypes with relatively high frequencies, a signature that is not expected under neutrality, but easily observed during and after a recent classical selective sweep. The XP-EHH statistic explores the integrated extended haplotype homozygosity profiles between two populations at the same SNP and is expected to be especially informative when alleles under selection are close to fixation in one of the populations (Sabeti et al., 2007). Absolute values of iHS can be used to evaluate the strength of ongoing positive selection signals at a particular locus in a given population (Voight et al., 2006). Whereas the signal of the XP-EHH statistic indicates whether selection have occurred on the tested or reference population, the signal of the iHS indicates in which particular allelic background selection is occurring. As for the F_{ST}

fixation index (Weir and Cockerham, 1984), it is a measure of population differentiation that allows detecting extremely differentiated adaptive variants resulting from geographically restricted selective pressures when comparing populations living in contrasting environments. Both XP-EHH and F_{ST} were obtained for the CEU population using the Yoruban population as reference. We also investigated the strength of background (purifying) selection through the B-statistic score, which was obtained for each SNP by linear interpolation when the corresponding genomic position did not exist in the original data from Huber et al. 2016. Finally, data on allele frequency and the derived alleles were obtained from Ensembl (www.ensembl.org).

Impact of loci on lifespan: variance explained

We calculated the lifespan variance explained (LVE) for each SNP as $2pqa^2$, where p and q are the frequencies of the reference alleles in the PLS GWAS (Timmers et al., 2019), and a is the SNP effect size in years of life. Then, lead SNPs at conjFDR<0.05 for SCZ and PLS, as well as independent genome-wide significant SNPs associated to SCZ and BD (Pardiñas et al., 2018; Stahl et al., 2019) from latest GWAS were ordered by LVE and total LVE was calculated by summing SNPs with significant effects on lifespan. Significance was determined by setting an FDR threshold of 0.1. To test the effect direction on pleiotropic variants, the risk allele and the direction of the effects (z-scores) were kept for each SNP. Disease-protective alleles were signed negatively when decreasing lifespan and positively when increasing lifespan, and vice versa for the alternative alleles. To compare with our results, we retrieved LVE for genome-wide significant disease SNPs from Timmers et al. 2019.

Functional analysis

All cross-phenotype-associated SNPs at conjFDR<0.05 were functionally annotated and mapped to closest genes with ANNOVAR using the default parameters in FUMA (Watanabe et al., 2017). Then, to explore the biological mechanisms underlying cross-phenotype-associated genetic loci, enrichment analysis was performed with *GENE2FUNC* from FUMA. FDR was controlled using the Benjamini-Hochberg (BH) procedure. In all cases, the complete set of protein-coding genes was used as the background.

Results

Shared genetic architecture between SCZ, BD and PLS.

Consistent with previous studies, SCZ and BD present a highly significant positive genetic correlation (r=0.67, P=4.87e-178, Cross-Disorder Group of the Psychiatric Genomics Consortium et al., 2019). In contrast, PLS was negatively associated with SCZ (r= -0.1, p= 0.0013), and no relationship was observed between PLS and BD (r= -0.06, P=0.06). Again consistently with previous findings (Ole A. Andreassen et al., 2013), both conditioning on BD and SCZ resulted in a strong deflection to the left when conditioning on the primary trait. Most of the 373 associated loci at conjFDR < 0.05 (98.4%) harbor alleles that increase the risk for both SCZ and BD. Only 6 loci (1.6%) present alleles with opposing effects on SCZ and BD (Supplementary Figure 1 and Supplementary Table 1).

Conditioning SCZ on PLS, Q-Q plots showed a stronger leftward deflection from the line of no association (blue line), with increasingly stronger association with PLS (Figure 1A). By contrast, BD showed weaker enrichment conditioning on PLS (Figure 1B). The reverse conditional Q-Q plots, fixing PLS as the main trait of interest and conditioning on either SCZ or BD as secondary traits, provide corresponding results (Supplementary Figure 2). We did not find substantial changes in the enrichment pattern when including all SNPs mapping onto the MHC and 8p23.1 regions (Supplementary Figure 3). Testing the statistical significance of enrichment with the Q-Q plot strata of psychiatric disorders as the primary trait, SCZ and BD, and PLS as the secondary trait, we detected an enrichment for SCZ given PLS (P=8.53e-13 and P=3.8e-04 conditioning on PLS p-value <1e-01 and <1e-02) and for BD given PLS (P=1.66e-07 and P=3.65e-03 conditioning on PLS p-value <1e-01 and 1e-02, Supplementary Table 2).

A total of 39 near-independent genomic loci ($r^2 < 0.1$) were jointly associated with SCZ and PLS at conjFDR < 0.05 (Figure 2A). It is worth mentioning that 29 of these loci were not identified in the original SCZ GWAS (Pardiñas et al., 2018), while, according to the GWAS Catalog (MacArthur et al., 2017), 12 of these 29 loci were previously reported at P<1e-05 in other SCZ studies, yielding a total of 17 novel SCZ risk loci (Table 1).

The observation of extensive pleiotropy naturally leads to the exploration of functional enrichment among the shared SNPs to better understand the underlying biology. The loci with conjFDR value <0.05 shared between SCZ and PLS (769 SNPs, Supplementary Table 3) were enriched in Acetylcholine Gated Channel complex (FDR=0.0002), Acetylcholine Receptor Activity (FDR=0.0004), and Permeable Nicotinic Acethylcholine Receptors (FDR=1.74e-05) among others (Supplementary Table 4). An

even higher enrichment pattern was found when only accounting for agonistic loci, while antagonistic loci showed enrichment in different pathways, such as Inositol 1,4,5 trisphosphate binding (P=0.08, Supplementary Tables 5-6). The discovered smoking-related pathways in our study were not amongst the most relevant in SCZ when evaluating GWAS associations (Pardiñas et al., 2018) with FUMA, but where present in PLS (Timmers et al., 2019).

Findings for BD were scarcer, with only 8 loci shared between BD and PLS at a conjFDR<0.05 (Table 1 and Figure 2B), 7 of which were not identified in the original BD GWAS (Stahl et al., 2019). Among these 7 loci, one was previously associated with BD according to the GWAS Catalog, yielding a total of 6 novel risk loci for BD. Just as in SCZ, the inclusion of the MHC and 8p23.1 regions did not result in differences in the enrichment pattern (Supplementary Figure 3). Although, we did not observe the same degree of overlap between PLS and BD, we also carried out enrichment analysis for all SNPs with a conjFDR<0.05 (Supplementary Table 7) shared between BD and PLS (n=113), but no functional enrichment was obtained.

Only two loci, corresponding to *SYNE1* and *HSPA9*, were significant in both conjunctional analyses (SCZ or BD and PLS) and in the two instances, the alleles that increased the risk for both disorders, also decreased lifespan. Finally, using data from the GWAS catalog (MacArthur et al., 2017) we identified many SNPs (among all conjFDR<0.05) as pleiotropic with other traits/diseases such as lung cancer, smoking initiation, Parkinson's Disease, and many cognitive abilities (Supplementary Table 8).

To further explore the landscape of pleiotropic effects, we examined lead SNPs from all independent loci at conjFDR<0.05 and their effects (z-scores) in SCZ, BD and PLS. As denoted by the sign of the effect sizes, among the 39 loci identified in the conjunction approach, 26 (66.7%) showed agonistic evolutionary effects in SCZ and PLS with the alleles that increased the risk for developing the disease also shortening lifespan. The remaining pleiotropic variants (n=13, 33.3%) showed antagonistic effects, with opposite evolutionary effect directions. That is, alleles protecting from the disease also shorten lifespan (which means that the alternative alleles increase disease risk, while associating with longer lifespans), that were compatible with the AP theory of aging (Figure 3A). Finally, among the 8 loci shared between BD and PLS, we found 3 (37.5%) with evolutionary antagonistic effects compatible with AP, while the rest increased the risk of BD and shortened lifespan (Figure 3B). Thus, the proportion of antagonistic variants in SCZ and BD with PLS was similar. Furthermore, the agonistic/antagonistic pattern was consistently observed for the SCZ and BD GWAS

genome-wide variants at different thresholds of association with PLS (Supplementary Figure 4).

SNPs assigned to the antagonistic category presented differential molecular evolutionary signatures compared to the agonistic pleiotropic variants. First, agonistic loci in SCZ and PLS showed lower minor allele frequencies (MAF; Mann-Whitney (M-W) test, P=0.04), lower derived allele frequencies (DAF; one-sided M-W test, P=0.04), lower iHS (P=0.02), and lower absolute value of XP-EHH (P=0.004); which are all consistent with agonistic loci not presenting trade-offs with traits that would increase fitness. Although not significant, SNPs with antagonistic effects (n=13) were found in regions with weaker background selection, as measured with the B-statistic (M-W test, P=0.06). Population differentiation, measured by F_{ST}, did not show significant differences (M-W test, P=0.13) between either group of SNPs (Figure 4).

Additionally, among the loci jointly associated with both psychiatric disorders and PLS, 3 regions were found to be genetically correlated (P<0.05/1655) between SCZ and PLS using ρ-HESS (Shi et al., 2017), and no regions between BD and PLS (Supplementary Table 9). We also aimed to find evidence for putative causal relationships between SCZ and PLS using ρ-HESS and found not clear direction consistent with a putative causal relationship between both traits (Supplementary Figure 5).

To further knowledge on the nature of pleiotropic relationships conducted an exploratory MR study of the causal effect of SCZ on PLS indicating no evidence of causality. The random effects of the inverse-variance weighted (IVW) estimate indicated that the Odds Ratio (OR) for PLS was 0.98 (95% CI of 0.96-1.00) per standard deviation increase in SCZ (P=0.15). In addition, there was strong evidence for heterogeneity amongst SNPs (Cochran's Q value= 221, p=7.55e-17), indicating alternative pathways from some of the SNPs to the outcome, known as horizontal pleiotropy (Smith and Hemani, 2014), that is, true direct pleiotropic effects (Supplementary Table 10).

To study the relative contributions of the discovered variants to PLS variance, we calculated the LVE of each locus. Altogether, the cumulative LVE sum of the 39 lead SNPs jointly associated with SCZ and PLS, and BD and PLS were 0.52 years^2 and 0.09 years^2, respectively. Collectively, all SCZ and PLS antagonistic SNPs (n=13) explained 0.17 years^2, while the agonistic SNPs (n=26) explained 0.35 years^2 (Supplementary Figure 6). To contextualize these results, we compared the impact of risk alleles for SCZ and BD on lifespan with the life-shortening impact of alleles

associated to other severe, life-threatening diseases. We evaluated the LVE explained by the genome-wide significant associated loci to SCZ (our filtered dataset contained 110 out of the 145 associated variants in the original GWAS) and BD (which contained 18 out of 30 associated variants), which explained up to 0.14 years^2 and 0 years^2, respectively. Indeed, for top SNPs associated with SCZ we observed more variation in lifespan than what is explained by genome-wide significant SNPs of Type 2 diabetes (0.04 years^2) and all cancers, excluding lung cancer (0.12 years^2); and slightly less LVE than smoking/lung cancer SNPs (0.15 years^2, data obtained from Timmers et al., 2019).

Discussion

Despite a growing body of empirical research on psychiatric disorders and the accompanied improvements in treatments, the mortality gap between people with SCZ or BD and the general population has widened (Hjorthøj et al., 2017; Lee et al., 2017; Saha et al., 2007). Recent findings suggest that this is not entirely due to disease-associated causes, such as for instance suicide and medication, and that patients with SCZ and BD show evidence of accelerated aging (Kirkpatrick et al., 2008; Kirkpatrick and Kennedy, 2017). Numerous physiological changes associated with normal aging occur earlier in people with SCZ, including the premature onset of other medical illnesses, shortened telomeres, increased inflammation and oxidative stress (Kirkpatrick and Kennedy, 2017). In the current study, we analyzed large GWAS datasets (Pardiñas et al., 2018; Stahl et al., 2019; Timmers et al., 2019) to dissect the genetic overlap between SCZ, BD, and PLS. Our analysis showed that large fractions of the genomic architectures underlying SCZ and BD also influence lifespan, especially in the case of SCZ.

Beyond the overall evidence of shared genetic architecture, we identified 39 genomic loci jointly associated with SCZ and PLS and 8 loci jointly associated with BD and PLS. Among the shared loci, 17 are novel SCZ risk loci and six are novel BD risk loci, demonstrating the improved power gained by combining GWAS in a conjFDR approach for SNP discovery (Ole A. Andreassen et al., 2013). Furthermore, we used the ρ-HESS method and identified genetic local correlations of 3 regions of the genome between SCZ and PLS. However, the SNPs associated with lifespan for both diseases did not fully overlap, in fact, only 2 loci were shared (corresponding to *HSPA9* and *SYNE1* genes), which was in contrast to their otherwise high degree of genetic overlap (Bipolar Disorder and Schizophrenia Working Group of the Psychiatric Genomics

Consortium, 2018). These divergent results highlight the unique genetic relationships between lifespan, SCZ and BD.

As we have done here for the first time, uncovering shared mechanistic pathways is fundamental to understanding the relationship between mental disorders and lifespan (Kirkpatrick and Kennedy, 2017). The enrichment analysis of all SNPs having a conjFDR value < 0.05 in the loci shared between SCZ and PLS (n=769) implicated biological pathways associated with acetylcholine binding and nicotinic pathways. Interestingly, SCZ and lung cancer were previously found to be pleiotropic (Farré et al., 2019) as exemplified by the locus on chromosome 15 including the *CHRNA3* gene, that was strongly associated with lung cancer and SCZ (Zuber et al., 2018). Indeed, SCZ patients had a higher prevalence of a smoking history than the general population, which in turn is strongly associated with mortality (de Leon and Diaz, 2005). Remarkably, these enrichments were driven by the agonistic loci, while antagonistic loci showed enrichment in pathways related to inositol binding, although not significant after FDR correction. On the other hand, we were unable to identify any significant pathways for SNPs jointly associated with BD and PLS, probably because of the little statistical power afforded by the small number of loci identified (n=8). Interestingly, in SCZ, our preliminary MR and ρ-HESS analyses to estimate the causal influence of one trait upon the other suggests that there is not causality between both traits, indicating that variants may have independent effects on SCZ and PLS. However, it is likely that disease risk-alleles may impact on lifespan through pleiotropic relationships increasing or reducing the risk of secondary comorbid conditions (p.e. smoking) with a final impact on lifespan.

To date, inconsistent results have also been proposed to explain the high frequency of risk alleles for psychiatric disorders (Crespi et al., 2007; Pardiñas et al., 2018; Power et al., 2013; Shaner et al., 2004; Srinivasan et al., 2016). One of the proposed hypotheses is that causal genetic variants may not be completely deleterious and may also confer some benefits that maintain these variants at relatively high frequencies (Crespi et al., 2007). For instance, increased load of risk alleles may, in the absence of the disorder itself, confer reproductive advantages, thus offsetting the effects of negative selection. However, previous research suggested no strong evidence for this hypothesis (Escott-Price et al., 2019; Mullins et al., 2017). In contrast, while most identified SCZ (~66%) and BD risk alleles (~62%) were associated with reduced lifespan in our analyses, consistent with the observed premature mortality in these individuals, a substantial fraction of disease risk alleles (~35%) were associated with longer lifespan, providing some evidence for the existence of the AP theory of aging.

Among the genes fitting the antagonistic pleiotropy paradigm in our study, some genes (*SDCCAG8, PLCL1, ERBB4 and UFM1*) have been previously suggested to undergo positive selection in humans (Abdellaoui et al., 2013; Barreiro and Quintana-Murci, 2010; Pickrell et al., 2009; Schlebusch et al., 2012; Williamson et al., 2007). Although our analysis focused on sub-GWAS associations we also demonstrated that the same pattern of agonist and antagonist pleiotropy with lifespan is observed in significant GWAS SCZ and BD hits, providing stronger evidence for the pattern here uncovered in both disorders.

In this context, risk alleles for these diseases can be divided in, at least, two different categories: risk alleles with agonistic negative effects on other traits; and risk alleles with antagonistic (beneficial) effects on other traits. Thus, alleles with negative fitness consequences early in life that are partially offset by positive fitness consequences on other traits (reducing all-cause mortality and affecting longevity), may help explaining the persistence of these susceptibility alleles in the population. This mixture of directional effects is both, fitting to the absence or near absence of genetic correlations between the traits, and consistent with the idea that antagonistic pleiotropy may be more widespread than typically considered (Rodríguez et al., 2019, 2017).

It has also been recently proposed that risk variants for SCZ are enriched in regions of strong background selection (Pardiñas et al., 2018). However, these two classes of variants (agonistic and antagonistic with lifespan) may not undergo the same adaptive pressures and may be detectable using evolutionary tests. We found that SNPs with antagonistic effects tend to be in regions with patterns of variation more closely resembling those expected under positive selection than the SNPs with agonistic effects. Moreover, they also tend to be in regions with weaker background selection relative to SNPs with agonistic effects. Although these results are not conclusive, given the small number of variants used, they suggest that SCZ risk variants compatible with the AP theory of aging can reach higher frequencies, perhaps reflecting the antagonistic compensatory effects between disease risk and lifespan. Also, it suggests that extending such analyses to the study of other diseases will help on understanding its evolutionary and genetic trade-offs.

Finally, the LVE by all significant loci (conjFDR < 0.05) in SCZ and PLS was 0.52 years^2 (0.4% of the total LVE) but was much more modest in BD (0.09 years^2). Surprisingly, in SCZ these SNPs show greater variance than the largest LVE SNPs for known life-shortening diseases (Timmers et al., 2019). Together, loci explaining the most lifespan variance are agonistic (loci containing disease-risk alleles decreasing

lifespan and their reverse, disease-protective alleles that increase lifespan), with a cumulative contribution to variance of 0.35 years^2. This is consistent with the premature mortality observed in SCZ patients (Olfson et al., 2015; Roshanaei-Moghaddam and Katon, 2009; Walker et al., 2015). Thus, reflecting that in addition to suicide, medication and other intrinsic factors, underlying genetic factors such as the smoking-related pathways can be added as one of the factors determining shorter lifespan in SCZ patients. Also, the genome-wide significant SNPs associated with SCZ, coming from the latest GWAS, explained 0.14 years^2 (0.11% of total LVE), more than SNPs associated to Type 2 Diabetes (0.04 years^2) and cancers (other than smoking cancer, 0.11 years^2).

Some limitations need to be mentioned. Given the very low heritability explained by the PLS GWAS, in accordance with low lifespan heritability estimates of 0.07-0.12 (Graham Ruby et al., 2018; Kaplanis et al., 2018) and the indirect use of parent genotypes, our study can capture only tiny amounts of parental longevity variation. Similarly, the effects on lifespan of the reported variants derive, in any case, from variants that explain only a small portion of the variance in each disorder. At the same time, the GWAS power for BD (n = 51,710) is below that of SCZ (n = 105,318), which limits the validity of comparing the present findings for the two disorders. Still, our study provides strong evidence of shared genetic architecture between both disorders and lifespan. Also, the PLS GWAS excluded individuals whose parents died before the age of 40 (Timmers et al., 2019), which involves a lack of young onset disease alleles that may bias the results. Finally, as in all GWAS results, an SNP represents through LD a region containing several possible causal variants, even if both, trans-ethnic studies (Marigorta and Navarro, 2013) and Massively Parallel Reporter Assays (van Arensbergen et al., 2019) suggest that SNPs usually tag a single causal variant. Further research is therefore needed to determine the true underlying causal variants between the detected associations.

In conclusion, our study demonstrates, for the first time, overlapping genetic architecture between PLS and the psychiatric disorders SCZ and BD, providing a molecular framework for the accelerated aging hypothesis leading to the observed premature mortality (Kirkpatrick et al., 2008; Kirkpatrick and Kennedy, 2017). We detect novel associations for both, SCZ and BD, and pinpoint genetic variants consistent with the AP theory of aging bearing molecular signatures suggestive of the action of natural selection. Our findings suggest that the genetic relationships between SCZ, BD, and lifespan are more complex than what is expressed by their overall genetic correlations, arising from a combination of agonistic and antagonistic effects,

which may help explaining the increased mortality observed in these groups of patients and, at the same time, the persistence of some risk variants in the population.

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Conflict of interest

The authors declare that no competing interests exist.

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Table legend

Table 1. List of loci jointly associated with SCZ and PLS; and BD and PLS.

Figure legends

Figure 1. Conditional Q-Q plots of nominal versus empirical (-log10) p-values (corrected for inflation) between SCZ (left, A) and BD (right, B), as a function of significance with PLS, at the level of $p<10^{-1}$ (red line), $p<10^{-2}$ (yellow line), and $p<10^{-3}$ (purple line), respectively. The blue line indicates the standard enrichment of the main trait of interest (SCZ and BD) including all SNPs, irrespective of their association with the secondary trait (i.e., PLS). The gray dashed line indicates the null distribution of p-values.

Figure 2. Manhattan plot for independent ($r2 < 0.1$) loci associated with both A) SCZ, and B) BD and PLS, as defined by conjunction false discovery rates (conjFDR) after excluding single nucleotide polymorphisms in the MHC and 8p23.1 regions. Gene labels are annotated as the nearby genes to the independent lead SNPs by FUMA. The dashed black line represents the conjFDR threshold of 0.05.

Figure 3. Pleiotropic plot. For those lead SNPs that were conjFDR<0.05 (n=39 for SCZ and n=8 for BD), the conjFDR values and the direction of the effects (z-scores) of the derived alleles are plotted for PLS (x-axis) against A) SCZ or B) BD (y-axis). Gene labels are annotated as the nearby genes to the independent lead SNPs by FUMA. Graph regions whose effects are consistent with the AP theory of aging are shadowed in yellow.

Figure 4. Boxplots of minor allele frequencies (MAF), iHS statistic, XP-EHH statistic, derived allele frequencies (DAF), FST statistic, and B-statistic measure of background selection, between the lead SNPs showing agonistic (n=26) and antagonistic effects (n=13) from SCZ and PLS (conjFDR<0.05). P-values from the corresponding Mann-Whitney test are shown in the corner of each plot.