Original Article

Large-scale genomic data-mining implicates dysregulated nuclear receptor-mediated signaling in mental illness

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Abstract

Aim: Mental illness comprises a group of heterogeneous conditions attributable to a complex interplay between hereditary and environmental components. Acting at the interface between environmental stimuli and their genomic actions, nuclear receptors

(NRs) appear uniquely suited to facilitate GxE interactions in the context of mental health. Genetic disruptions to the NR transcriptomic complex (NTC) give rise to neuropsychiatric pathologies, and epidemiological risks involving a steroid response are among the most replicated in psychiatry. Importantly, pharmacological targeting of NR-mediated signaling is clinically effective in the treatment of psychiatric disorders. Here we systematically interrogate large-scale deposited data to provide a comprehensive evaluation of the genomic NTC risk burden in mental illness.

Methods: Utilizing data from large, recent genome-, exome-, and methylome-wide association studies on psychiatric disorders, we assess the representation of NTC genes among top associated loci and test the gene set associations for NTC and NR target genes using GWAS summary statistics. Through data mining and transcriptomic profiling of NR-mediated signaling in the diseased and healthy human brain, we categorize psychiatry-relevant NTC gene networks.

Results: We find that NTC genes are significantly overrepresented in genome-, methylome-, and exome-wide associated loci and that the NTC, as well as NR target gene sets, are overall associated with mental illness. Accordingly, we identify transcriptomic NTC signatures in patient brain samples. In line with a key role for orchestrated NR-mediated signaling in the developing brain, particularly NTC co-expression networks with prenatal peak expression are enriched with differentially methylated, sex-biased and psychiatry-associated risk variants.

Conclusion: Here we provide multilevel evidence that support genomic NR-mediated signaling as a common and core molecular mechanism in mental illness, and we highlight specific NR-signaling pathways with putative diagnostic and pharmacological intervention potential in psychiatry.

Keywords: Nuclear receptor, mental disorders, GWA studies

INTRODUCTION

Psychiatric disorders (PDs) comprise a heterogeneous group of conditions collectively characterized by changes in patterns of thoughts, emotions and behaviors. Suggestive of interconnected etiologies, clinical and therapeutic profiles are overlapping and identified risks are typically non-specifically associated with a range of mental disorders [1–5]. Most PDs are highly heritable and thousands of genetic variants are likely to contribute [6–11]. The effect of genetic risk is further conditional on environmental factors, resulting in complex gene-environment interactions (GxE) [12]. Understanding how hereditary risk and environmental exposures collectively shape the developing brain and mind is thus key to comprehend the pathobiology of mental illness and to the implementation of precision medicine in psychiatry.

Acting at the interface between environmental stimuli, endocrine signaling and their genomic actions, a group of ligand-inducible transcription factors, nuclear receptors (NRs), appear uniquely suited to facilitate GxE in the context of mental health [13,14]. NRs function as biological sensors that respond to a variety of xenobiotics, steroids and endogenous lipid-, and cholesterol-derived compounds [15,16]. Epidemiological risk factors involving a steroid or steroid-like response are among the most replicated in psychiatry [17–27] and several NR ligands have been associated with PDs (e.g. retinoic acid [28–30]; vitamin D [17,19]; stress- [31], sex- [32–35], thyroid hormones [36], endocannabinoids [37,38] and polyunsaturated fatty acids (PUFAs) [39,40]). Upon activation, NRs facilitate fine-tuned transcriptional regulation of defined sets of promotor hormone response element (HRE)-containing target genes in a cell-, tissue-, and developmental-specific manner. In this way, NRs play essential roles in the developing and mature central nervous system (CNS) [41,42] and have crucial and diverse functions in many aspects of human metabolism, reproduction, inflammation, and physiology [41]. Consequently, NRs are highly intolerant to loss of function (LoF) mutations [43], and genetic defects in at least 20 of the 48 NRs encoded by the human genome are associated with pathological states– including neurological disorders and mental illness [44,45]. The latter is highlighted

by the severe intellectual disability displayed by autism spectrum disorder (ASD) and epilepsy cases harboring LoF mutations in genes encoding retinoic acid receptor-related orphan receptors (*RORA* [46] and *RORB* [47]). Genetic variation in and around a large fraction of NRs has furthermore been associated with PDs and psychiatry-related traits (see **Supplementary Table 1** for a summary). The transcriptional activity and specificity of NRs is ensured through a dynamic interplay with a comprehensive, but loosely defined, co-regulator complexome, encompassing >500 NR coregulators [48,49] – collectively the NR transcriptome complex (NTC). The specific interactions between individual NRs and their coregulators are in part determined by the biophysical binding to NR interaction domains (NRIDS) on the regulators [50]. NR coregulators often contain multiple NRIDs and display overlap in their specificity and affinity for NRs [50]. In addition, genes may contain several different HREs and NR coregulators may dictate opposite transcriptional outcomes, depending on cellular context [51,52]. The modes by which NR coregulators affect NR action are diverse and include direct recruitment of transcriptional machinery as well as chromatin remodeling, histone modifications and chaperone activity [53,54]. The complexity of NR coregulator interactions is reflected in the palette of pathologies associated with genetic variation to this group of transcriptional regulators [55]. Like it has been reported for NRs, LoF mutations in several NR coregulators lead to intellectual disability and mental health problems [56–61]. Supporting an overall increased genetic risk load in NR transcriptional networks in mental illness, genetic variation in loci harboring NR coregulators has been reported in a range of PDs (see **Supplementary Table 1** for a summary), and increased polygenic burden in retinoid and glucocorticoid biogenesis and signaling pathways has recently been associated with schizophrenia and depression, respectively [18,62]. The importance of NR coregulator-mediated modulation of NR action has further been demonstrated by molecular genetic studies in preclinical models [45], where genetic disruption to NR coregulators generally results in behavioral impairments and neurobiological alterations with translational relevance to PDs [56,63–70]. Collectively, ample evidence implicates dysregulated NR-mediated signaling in the pathoetiology of mental illness, and it is thus conceivable, that genetic vulnerability to NR-mediated signaling, in combination

with their ligand-associated risk factors, collectively shape the risk and clinical manifestation of PDs.

Here, we provide a comprehensive and systematic data-mining effort and functional genomic analysis of the NTC in large-scale genetic and epigenetic data, and present new evidence that supports dysregulated NR-mediated signaling as a common and core molecular pathway in mental illness with significant diagnostic and therapeutic potential in psychiatry.

METHODS

Gene set selection, filtering and overlap analyses

NTC gene set: NTC gene set includes genes encoding NRs and NR coregulators in the human genome. A defined list of NR coregulators was obtained by compiling curated entities from the now deprecated Nuclear Receptor Signaling Atlas (NURSA; http://www.nursa.org), NRID containing NR coregulators with validated biophysical NR interactions from a recent large-scale peptide array-based study [50], and minimal endogenous modules (MEMOs) of NR coregulators identified in a recent comprehensive IP/MS-based study of endogenous human coregulator protein complex networks [49]. The final list consisting of 48 NR encoding genes and 522 NR coregulator-encoding genes can be viewed in **Supplementary Table 2**.

Genome-wide associated gene sets

For the analysis of overlap between NTC gene sets and genes in genome-wide significant (GWS) loci in psychiatric disorders, the following PGC/iPSYCH PD GWASs were assessed: Schizophrenia (SZ) [71], bipolar disorder (BPD) [10], major depressive disorder (MDD) [8], Autism spectrum disorder (ASD) [10], attention deficit/hyperactivity disorder (ADHD) [11] and cross-disorder (CD) [4] which includes SZ, BPD, MDD, ASD, ADHD, anorexia nervosa, obsessive-compulsive disorder, and Tourette syndrome. For the illustration of NTC genes among genes in GWS loci in SZ (**Figure 1**), a smaller PGC GWAS [7] with 108 GWA loci was used with the readability

of the illustration in mind. Additionally, the following non-PD GWAS was assessed: Alzheimer's disease (ALZ) [72]; type 2 diabetes (T2D) [73], heart failure (HF) [74], body mass index (BMI) [75], height [75], and COVID-19 (positive vs population) downloaded from GRASP [76]. **See Supplementary Table 3** for details. PGC genotype data has all been processed using the PGC-developed Ricopili pipeline [77], so in order to obtain comparable locus boundaries and thus GWS gene sets, summary statistics from non-PGC studies were similarly processed using Ricopili with 1000 Genomes Project (Phase 3 v5a) as reference.

Exome-wide associated gene sets

For the analysis of overlap between NTC genes and genes harboring rare coding variants (RCVs), only large whole exome sequencing studies (WESs) with >3000 individuals (patients and healthy controls) identifying genes with RCVs were assessed. This is limited to: SZ [78] and ASD [79]. **See Supplementary Table 4** for details.

Methylome-wide associated gene sets

In order to assess the epigenetic burden on NTC genes in patient blood and the developing fetal brain, we utilized data from large epigenome-wide association studies of common mental disorders. These were: SZ [80–82]; MDD [83]; ADHD [84,85], ASD [86], as well as a methylomic study of fetal brain development [87]. Although varying between studies, p-value cut-offs were comparable. Looking at the top findings reported by the authors in each study, we removed duplicated gene names and findings that did not map to any gene (for an overview, see **Supplementary Table 5**).

All gene sets were filtered based on the following criteria: protein-coding and detected (RPKM≠0) in human brain tissue at any developmental stage as assessed in the BrainSpan database [88]. MHC region was excluded from all data sets. For each phenotype, we determined the fraction of protein-coding, brain-expressed genes that overlapped with our list of NTC encoding genes and compared the fractions across studies. Significance of overlap were determined using one-sided Chi2 tests.

Gene set association analyses

Gene set analysis was performed with MAGMA [89] using default settings, based on summary statistics from selected publicly available GWASs (See **Supplementary Table 3** for details). SNPs outside protein-coding and brain detected (RPKM≠0) genes, as well as SNPs within the MHC region and imputed SNPs with info score < 0.8 were excluded from the analyses.

For the analysis of promotor HRE containing genes, available curated and non-redundant set of transcription factor binding sites (TFBSs) for NR monomers, HOCOMOCOv11_core_HUMAN, were downloaded from the HOCOMOCO collection [90] (http://www.cbrc.kaust.edu.sa/hocomoco11) and genomic positions were identified using the FIMO tool (http://meme-suite.org/tools/fimo) [91]. Subsequently, lists were generated for each NR with genes containing their HRE within their promotor sequences (2000 bp upstream of TSS). Gene annotation files contained every human protein encoding gene detected in brain tissue (www.brainspan.org, RPKM≠0 in any sample). For the assessment of similarities between HRE gene sets, pairwise Jaccard similarity coefficients and significance of overlap were calculated using the GeneOverlap R package (version 1.24.0) [92].

Cortical transcriptomic profiling of NTC and HRE gene sets in patients

We used available analyses of differentially expressed genes (DEGs) in the dorsolateral prefrontal cortex of 258 SZ patients and 271 healthy controls from the CommonMind Consortium (CMC – CommonMind.org Synapse ID: syn5607652) [93].

Enrichment analysis of transcription factor binding sites (TFBSs) was carried out according to Gearing et al [94] using CiiiDER. Briefly, promotor sequences (2000 bp upstream of TSS) were extracted from the Homo sapiens GRCh38.94 genome file. Identification of transcription factor binding sites in these sequences was performed with HOCOMOCOv11_core_HUMAN transcription factor position frequency matrices

(downloaded from the HOCOMOCO collection [90] (http://www.cbrc.kaust.edu.sa/hocomoco11)) and a deficit cut-off of 0.15. CiiiDER enrichment analysis of overrepresented NR TFBSs in DEG query sequences compared to non-DEG query sequences (from 1,000 genes with p~1 and logFC~0) was determined by comparing the number of sequences with predicted TFBSs to the number of those without, using a Fisher's exact test.

Brain transcriptomic profile of the nuclear receptor transcriptome complex

Normalized gene expression values (RPKM) for 16 different brain tissues in the developing and mature brain was downloaded from www.brainspan.org [88]. Developmental stages were defined as: Prenatal (8pcw–24pcw); Early childhood (4mos–4yrs); Puberty (8yrs–19yrs), and Adulthood (21yrs–40yrs) and average RPKM within groups plotted with hierarchical clustering (average correlation with row centering) using ClustVis [95]. Human brain cell type-specific gene expression annotations were obtained from McKenzie et al. [96]. List of genes displaying sex-biased expression in 16 brain tissues across four developmental stages (prenatal, early childhood, puberty and adulthood) were assessed in a publicly available human dataset (www.brainspan.org) [88] and obtained from Shi et al. [97]. The significance of overlap between NTC gene sets and brain sex-biased genes was analyzed using permutation analysis (n=10,000 permutations) based on a list of all protein-coding and brain-expressed genes. In each permutation, a gene set was sampled with the same number of genes as NTC or NTC subset (NR or NR coregulator) gene set. The *p-value* of the significance of the overlap was estimated as the number of permuted gene sets that contained equally many or more genes present in sex-biased gene set as the NTC gene set, divided by the total number of permutations.

RESULTS

Common and rare psychiatry-associated genetic variation is enriched with genes implicated in nuclear receptor-mediated signaling

Whereas genetic variation in NR and NR coregulators, individually, has been

associated with PDs in association and linkage studies, the genetic risk profile of the NR transcriptome complex (NTC) as a whole has not been systematically assessed at a large-scale, whole-genome level. >300 curated NR coregulators have been reported by the Nuclear Receptor Signaling Atlas consortium, but recent efforts have both added to this list and significantly extended the known interactions between NRs and NR coregulators (**Supplementary Table 6**) [49,50]. Hence, we composed a defined list of NTC encoding genes based on curated databases and strictly validated protein-protein interactions (NR gene set – 48 genes / NR coregulator gene set – 522 genes), and mapped the overlay of these lists with genes annotated to genome-wide significantly associated (GWS) loci in PDs [7–11,71]. Consistently, ~15% of loci across diagnostic entities harbored NTC encoding genes, except for ASD, where only three GWS loci have been identified (**Figure 1 and supplementary Table 7**). In addition, >13% of all brain-expressed NTC genes reside in loci associated with either ADHD, BPD, MDD, SZ or CD (**Figure 1** and **Supplementary Table 8)**. Individually, this represents a significant overrepresentation in MDD (Chi2 test (one-tailed), p=0.012) and SZ (Chi2 test (one-tailed), p=0.002). Notably, >20% of NTC genes in GWS loci are associated with two or more PDs (e.g. *EP300* and *ESR2*). A similar overlap was seen for non-psychiatric traits whose biology is closely interlinked with NR-mediated signaling [98–105] (**Supplementary Table 7**).

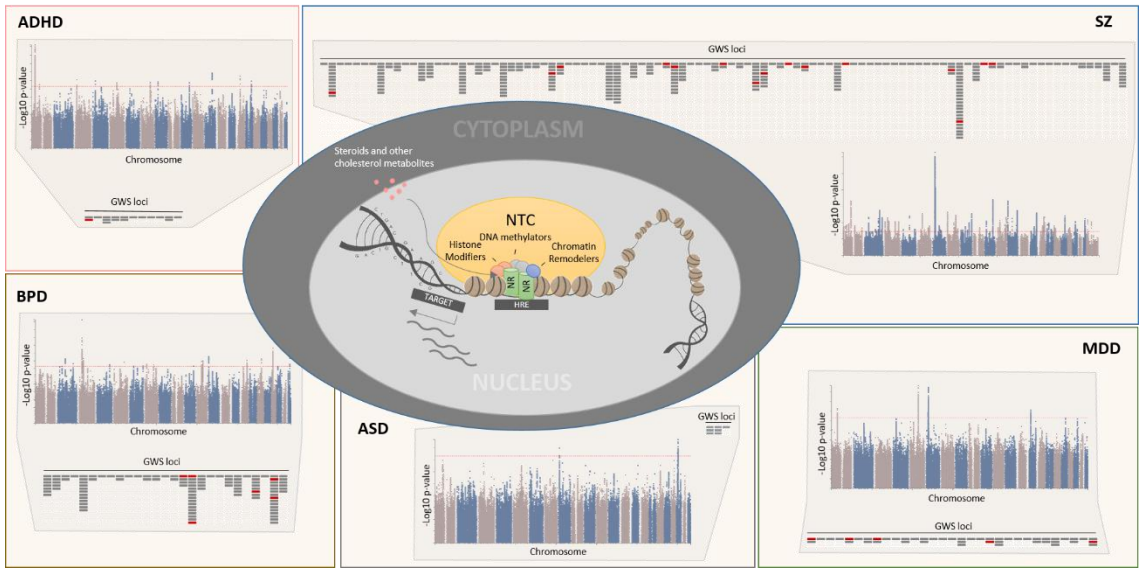

Figure 1 | Genetic support for dysregulated NR-mediated signaling in mental illness. Consistently, ~15% of risk loci in PDs harbor genes encoding NTCs. Manhattan plots show the SNP based association landscape for each of the five psychiatric disorders (attention deficit hyperactivity disorder (ADHD) [11]; schizophrenia (SZ) [7] (for presented analyses, data from a newer, larger GWAS [71] was used); bipolar disorder (BPD); autism spectrum disorder (ASD); and major depressive disorder (MDD)) with red dotted line marking the significance cut-off for genome-wide significant associated signals. Brain-expressed protein-coding genes within each locus are shown as columns of tiles, where NTC encoding genes are highlighted in red.

Genetic variants displaying GWS account for only the most significant, small fraction of the total heritability of PDs. Hence, to further explore the genetic PD burden in the NTC, we employed a gene set analysis approach based on the aggregated association of individual genetic markers within the NTC gene set [89]. Analyses using the most recent, available GWAS summary statistics from each of the five PDs, SZ, BPD, ASD, ADHD and MDD,[7–11,71] as well as the to date, largest cross disorder (CD) GWAS [4], revealed a significant association of the NR gene subset of the NTC to both MDD (p=0.008) and BPD (p=0.005), while the NR coregulator subset and complete NTC gene set showed association to BPD (p=0.003) and SZ (p=0.033) (**Figure 2 and Supplementary Table 9**). While not taking into the account the significant genetic overlap between PDs [5], these associations remained significant for MDD and BPD even after adjusting for multiple testing by applying a conservative Bonferroni correction (**Figure 2**). When we applied the same approach to summary statistics from GWAS on non-psychiatric disorders where NR-mediated signaling has been reported to play a role [98–105], a very significant association was seen for the NR coregulator subset in height and BMI, and a moderate significant association of the NR coregulator subset to heart failure (HF) (**Supplementary Figure 1**; p=0.002). For COVID-19 (positive vs population), in which NR biology play no obvious role, no association was observed (**Supplementary Figure 1**).

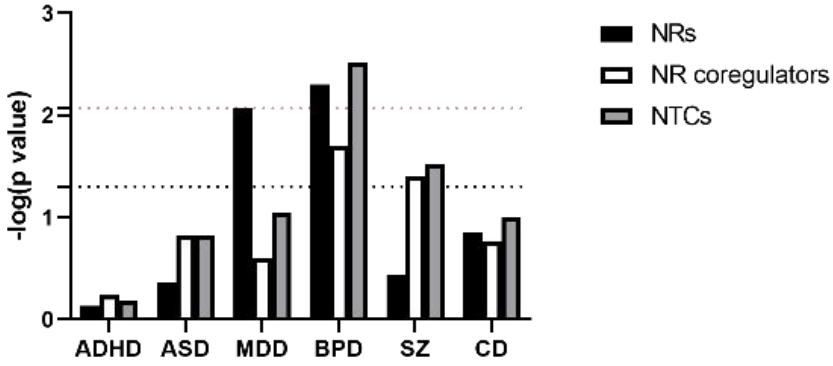

Figure 2 | MAGMA gene set association analysis of the NTC gene set with separate analyses for the NR-, NR coregulator subsets using summary statistics from large, recent GWASs on the psychiatric disorders: attention deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), major depressive disorder (MDD), bipolar disorder (BPD), schizophrenia (SZ) and cross disorder (CD). Black/red dotted lines mark nominal/Bonferroni-adjusted significance cut-off.

Whereas common variants of small effect contribute to all PDs [106], particularly early onset disorders, like ASD, are enriched with rare coding variants (RCVs) [107]. In order to assess the genetic burden of NTC RCVs in PDs, we focused on large (>3000 cases and controls) WES studies, which have been conducted in SZ [78] and ASD [79]. In these studies, PD-associated RCVs were identified in SZ (a single gene) and ASD (102 genes). Strikingly, 19% of genes with ASD-associated RCVs are NTC-encoding genes (**Supplementary Table 8**), representing a significant overrepresentation (Chi2 test (one-tailed), $p<0.0001$). Furthermore, 32% of identified ASD-associated NTC RCV-harboring genes reside in PD GWS loci (e.g. *RORB* and *FOXP1*), thus supporting the pathoetiological relevance of particularly these NTC genes within multi-gene GWS loci.

Patient epigenetic signature and brain transcriptomic profile support the implication of dysregulated nuclear receptor-mediated signaling in mental illness

Complementing genome-wide studies of DNA sequence variation, studies of variation to the epigenome have the potential to reveal biosignatures associated with

disease-causing factors in mental illness [108]. Particularly, methylome-wide association studies (MWASs) have revealed hundreds of DNA methylation changes associated with PDs and psychiatry-related traits [81–85,109–115]. The epigenome is dynamic and changes in response to environmental [116] as well as endogenous factors (e.g. hormonal transitions [117,118] and aging [119]) plays a crucial role in the orchestration of gene transcription in the developing human brain [87]. Clinical MWASs in brain tissues are rare and yet of small sample sizes. Hence, we assess the burden of genes with changes in DNA methylation associated with PDs among the NTC gene set in the to date largest patient blood MWASs. From neonatal samples, data was available for ADHD and ASD, where ~16% of findings with differential methylation were annotated to NTC genes (**Supplementary Table 5 and 9**; Chi2 test (one-tailed), ASD: p=0.001 and ADHD: p=0.050). From adults, samples have been collected and analyzed in ADHD, MDD and SZ cases. Whereas none of the two differentially methylated genes identified in ADHD encode NTC genes, ~7% of differentially methylated genes in MDD belonged to the NTC (**Supplementary Table 5 and 8**; Chi2 test (one-tailed), p=0.024). Similar overlap (~5% and 10%) was seen in two independent studies in SZ cases (**Supplementary Table 5 and 8**; Chi2 test (one-sided), p=0.037 [80] and; p<0.0001 [81]), whereas meta-analyses of SZ MWASs using a more stringent significance cut-off did not find NTC genes among 10 differentially methylated genes [82] (**Supplementary Table 5 and 8**). Notably, several differentially methylated NTC genes harbor ASD RCVs or reside in PD GWS loci (e.g. *GATAD2A*, *RERE*, *CREBPB* and *FOXP1)*, and several NTC genes were differentially methylated in more than one dataset/disorder (*FOXP1*, *EP400*, *TRERF1* and *SKI*) ((**Figure 3** and **Supplementary Table 5 and 8**). Interestingly, data from a large MWAS of epigenetic plasticity during early fetal brain development reveals that >40% of NTC genes undergo dynamic DNA methylation changes during early fetal brain development (**Supplementary Table 5**), thus supporting an important and meticulously orchestrated role for the NTC in transcriptional regulation in the developing human brain. NR-mediated signaling, however, remains important throughout life and altered cerebral expression of NR encoding genes have been reported in adult SZ cases [120]. To explore the transcriptomic signature of NTC genes in

brain tissue from PD cases, we examined data from a comprehensive brain whole-transcriptome study conducted on postmortem dorsolateral prefrontal cortex (DLPFC) samples from 258 SZ patients and 271 healthy controls [93]. While only a minor fraction of NTC genes (*PRKDC*, *PSMD1*, *AKAP13*, *IDE*, *SMAD3*, *HR*, *GADD45A*, *RBFOX2* and *LCORL*) were differentially expressed in SZ cases compared to healthy controls (**Figure 4A**), a quantitative analysis of promotor HREs in differentially expressed genes (DEGs) compared to genes displaying no regulation in cases revealed a nominally significant enrichment of RXRβ (p=0.003), RORγ (p=0.036), PR (p=0.038), and HNF4α (p=0.048) HRE sets in upregulated DEGs, and RORγ (p=0.026), RXRα (p=0.028) and RARγ (p=0.049) HRE sets in downregulated DEGs (**Supplementary Table 10**).

Psychiatric disorder risk enrichment among genes containing NR binding motifs

Both NTC members and NR ligands have been associated with PDs, but the contribution of their respective genomic actions in relation to PD risk is poorly understood. NRs bind to DNA as monomers, homodimers and as heterodimers, most commonly in a bimolecular complex with the retinoid X receptor (RXR) [121]. However, a recent study has demonstrated widespread binding of NRs to half-sites, and that half-site binding can drive transcription [122]. Hence, to assess the aggregated genetic burden in target genes of individual NRs, we used an *in silico* approach to test the gene set association of promotor HRE half-site containing target genes of PD associated NTCs using GWAS summary statistics. First, we assessed the association of HRE genes governed by NRs associated to PDs in GWASs or WESs. Whereas we did not see a significant association of RARE containing genes governed by SZ-associated RARγ, RORE gene set governed by CD associated RORα was significantly associated with ASD (**Figure 3**, **Table** 1 and **Supplementary Table 8**; p=0.022). Next, we profiled the risk landscape of HRE gene sets in general using summary statistics from both PDs and non-PDs. This revealed nominally significant association of: ARE (p=0.046) and FXRE (p=0.049) gene sets with ADHD; PPARE p= (p=0.045), FXRE (p=0.023), RORE (p= 0.022) and NR1D1 targets (p= 0.046) with ASD; DAX1 target genes with SZ (p=0.027);

ERE (p=0.042), GRE (p=0.036), PGRE (p=0.011), RARE (p=0.047) and TRE (p=0.031) with MDD; and ERE (p=0.045), FXRE (p=0.004), and RXRE (p=0.042) with CD (**Figure 3 and Supplementary Table 8**). In addition, a number of HRE gene sets showed association to non-PDs, including FXRE to BMI (p<0.0001) and height (p<0.0001). While the association between FXRE and BMI/height remained significant following a conservative Bonferroni correction for multiple testing, it is important to realize that NRs regulate distinct yet highly overlapping gene programs [122]. In order to assess the overlap of HRE gene sets, we assessed and plotted their pairwise similarities (**Supplementary Figure 3** and **Supplementary Table 11**). Not surprisingly, > 95% of HRE gene sets displayed a significant overlap of genes, with particularly closely related superfamily members displaying the highest degree of overlap in their target gene sets (e.g. GR and AR, ERα and ERβ, HNF4γ, HNF4α, and PXR and CAR), thus arguably reducing the number of effective independent tests performed.

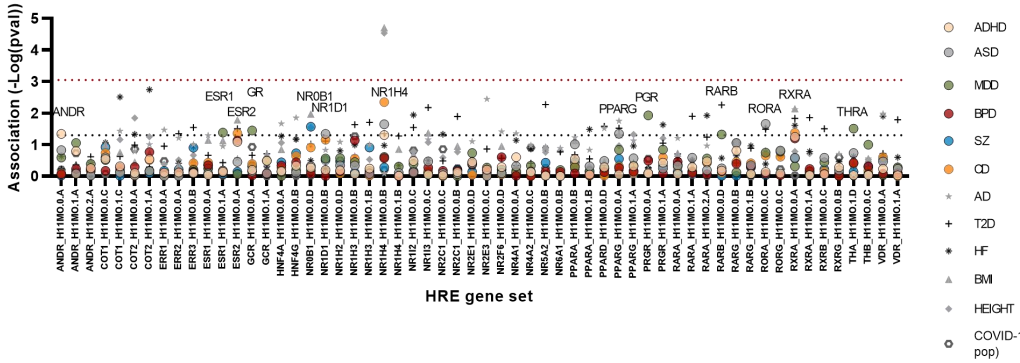

Figure 3 | MAGMA analyses of HRE gene set association using summary statistics from ADHD, ASD, MDD, BPD, SZ and cross disorder (CDG2) GWAS as well as from a range of non-psychiatric disorders (Alzheimer's disease (AD), type 2 diabetes (T2D), body mass index (BMI), heart failure (HF), height and COVID-19. Red dotted line marks Bonferroni-adjusted significance cut-off.

Brain-transcriptomic profile of the nuclear receptor transcriptome complex hints at a neurodevelopmental impact of psychiatry-associated nuclear receptor networks

The transcriptional activity of NRs critically depends on their interactions with NR

coregulators. The biophysical interactions have been established *in vitro* between a range of NRs and NR coregulators [50] (see **Supplementary Table 6** for a list of well-documented interactions), but the biological relevance of these interactions in the brain depends on their co-expression in the same structures and individual brain cells. Hence, we assessed single cell expression characteristics of NTC genes and identified gene sets that are specific to individual brain cell types [96]. 23% of NRs and 13% of NR coregulators are exclusively expressed in specific brain cell types (**Supplementary Figure 4 and Supplementary Table 8**). For the NRs, this includes: *PPARA* and *RORA* (astrocytes); *NGFIB*, *PGR* and *PPARD* (endothelia); *NURR1* and *PPARG* (microglia); *ESR1* and *THRB* (neurons) and *DAX1* (oligodendrocytes).

Next, we clustered NTC genes based on co-expression characteristics in the developing human brain (**Figure 4**). This revealed eight distinct larger co-expression clusters each characterized by peak expression in specific developmental stages or tissues. While the majority of NR encoding genes peak postnatally (**Figure 4 and Supplementary Table 8**; Cluster 1-6), a subset (*NURR1*, *NOR-1*, *NR5A2*, *TR4*, *COUP-TF1*, *COUP-TF2*, *RORB*, *THRA*, *RARA* and *ESR2*) peak at the earliest stage of development (**Figure 4 and Supplementary Table 8**; Cluster 7). Within this group, *COUP-TF1* and *2* are particularly abundantly expressed in the amygdala, while *NOR-1* expression peaks in hippocampus (**Figure 4**). Interestingly, the cluster of NTC genes peaking prenatally hosts the highest density of genes in PD GWS loci and ~80% of RCV harboring NTC genes associated with the early onset PD, ASD. Further interesting, a cluster of 23 NTC genes are predominantly expressed in striatal tissue, with a subset displaying very high expression in prenatal striatal tissue. This striatal-dominant cluster includes the NR encoding genes *RARB*, *RXRG* and *SF1* as well as *FOXP1* identified in both SZ MWAS and ASD WES (**Figure 4** and **Supplementary Table 8**; Cluster 4). A third cluster with peak expression in the cerebellum houses nine NR encoding genes (*ESRRA*, *NR2F6*, *RARG*, *RORC*, *RXRB*, *SHP*, *ESRRG*, *RORA* and *ESRRB*), of which the CD GWS *RORA* along with *ESRRA* and *ESRRG* display particularly high expression in the prenatal cerebellum (**Figure 4** and **Supplementary Table 8**; Cluster 1). A summary of brain

cell-specific, co-expressed NTC genes is presented in **Supplementary Figure 5**.

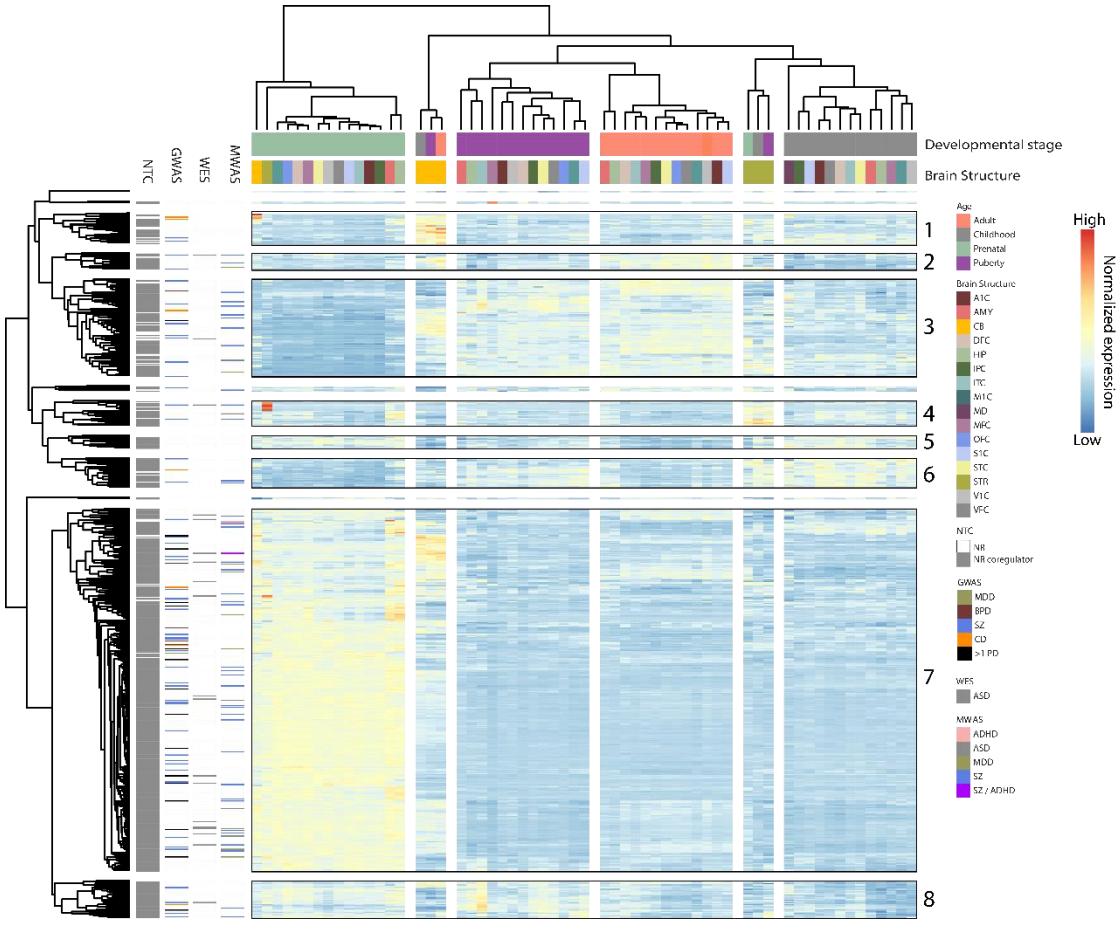

Figure 4 | Expression of NR and NR coregulator encoding genes across 16 brain structures and four developmental stages. Row annotations include: NTC subtype (NR/NR coregulator); genes in GWAS/WES/MWAS loci. Genes fall in eight major clusters defined by most abundant expression in: 1) cerebellum; 2) adults; 3) puberty and adulthood; 4) striatum; 5) prenatally and in childhood; 6) childhood; 7) prenatally; and 8) prenatally and puberty. A1C: Primary auditory cortex; AMY: Amygdala; CBC: Cerebellar cortex; DFC: Dorsolateral prefrontal cortex; HIP: Hippocampus; ITC: Inferolateral temporal cortex; M1C: Primary motor cortex; MD: Mediodorsal nucleus of thalamus; MFC: Anterior cingulate cortex; OFC: Orbital frontal cortex; S1C: Primary somatosensory cortex; STC: Posterior superior temporal cortex; STR: Striatum; V1C: Primary visual cortex; VFC: Ventrolateral prefrontal cortex).

Sex-biased expression of the nuclear receptor transcriptome complex in the developing and mature human brain

Sex differences are common in PDs where symptom profiles and severity differ between men and women [20–25] and, e.g., women are more susceptible to affective disorders than men [24,25]. Brain development follows sex differential trajectories [123] with concordant regional sex-biased expression of comprehensive gene sets. Sex hormones act throughout the brain of both men and women, but subtle differences exist in their genomic and non-genomic actions [124]. Sex-biased expression of the ASD candidate and CD GWS annotated gene, *RORA*, has been suggested as a contributor to the sex-bias in ASD [125]. We speculated that sex-biased expression of NTC genes in general contribute to the sex-biases in mental illness. Hence, we assessed the overlap between the NTC gene sets and reported sex-differentially expressed genes across brain regions at four developmental stages (prenatal, early childhood, puberty and adulthood) [97].

Whereas we did not find significant enrichment of NTC genes overall, we found that sex-biased genes are significantly enriched with NR encoding genes at the prenatal stage, with particular enrichment among sex-biased genes in medial frontal cortex (p=0.006), orbitofrontal cortex (p=0.004) and in the striatum (p=0.010) (**Figure 5 and Supplementary Table 12**). In frontal cortical tissues this includes *RORB*, *NR4A2*, *NR4A3*, and *NR3C2*, the expression of which are all higher in women than in men. In striatal tissue *NURR1*, *NR1D2*, *NR2F6* and *THRB* are all sex-differentially expressed with expression being higher in men – except for *NR2F6* that is female-biased. Several NR coregulators are similarly sex-differentially expressed in these structures in the prenatal stage. At later developmental stages expression of sex-biased NTC genes is consistently higher in women compared to men (**Figure 5**). Interestingly, NTC genes in SZ GWS loci are significantly overrepresented among NTC genes that display male-biased expression in the prenatal striatum (Fisher's exact test; p=0.0193), and NTC genes with ASD-associated RCVs among female-biased genes in the prenatal orbito-, and medial frontal cortex (Fisher's exact test; p=0.003). The density of PD-associated NTC genes were furthermore high in the cluster of genes with female-biased cortical expression in puberty (**Figure 5**). Among genes reported to be

sex-differentially methylated in the earliest stages of fetal brain development, only a minor fraction encodes NTC genes (**Supplementary Table 5**), but particularly SZ MWAS risk genes clustered among genes with female-biased thalamic dominant expression (**Figure 5)**.

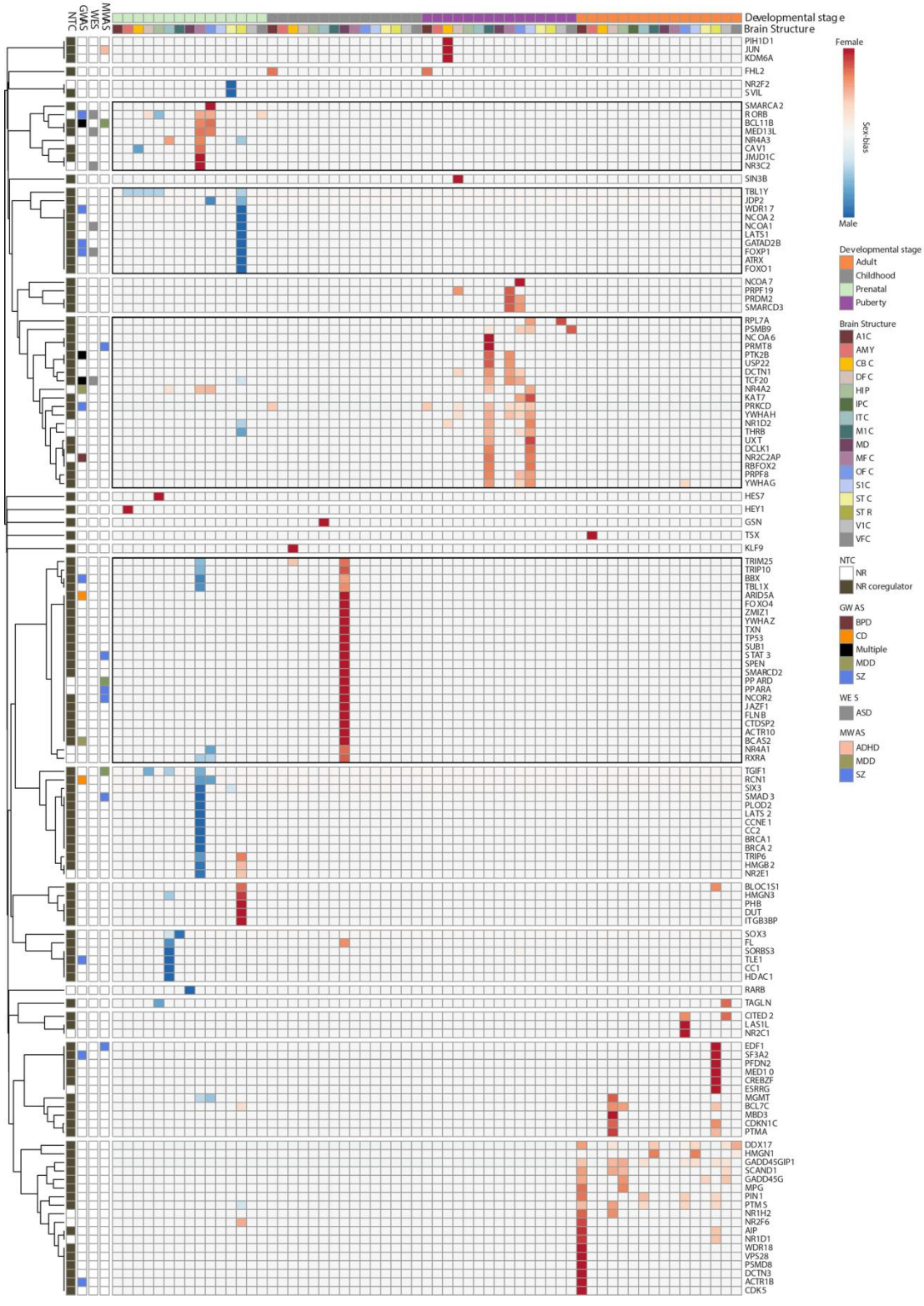

Figure 5 | Sex-biased expression of NTC genes. Mapped are NTC genes that are sex-differentially expressed in the developing human brain as reported in Shi et al [97]. Red indicates higher expression in females while blue indicates higher expression in males. Common and rare variants in NTC genes associated with particularly SZ and ASD are enriched in clusters with female-biased expression in the anterior cingulate cortex (MFC) and orbital frontal cortex (OFC) and male-biased expression in striatum (STR) during prenatal development. SZ MWAS risk genes cluster with genes expressed with female-biased MD (mediodorsal nucleus of thalamus) in childhood.

DISCUSSION

Human brain development is a protracted process that begins in the early prenatal stage, and extends through late adolescence and even adulthood [126]. The process is genetically organized, but shaped and adapted in the context of environmental input. Neither genes nor environmental clues are determinative in terms of outcome, but disruption to either may affect the maturing brain and mind. The CNS and the endocrine systems work in synergy to sense and act upon endogenous and environmental cues. Whereas the CNS response is rapid and mostly transient, the endocrine response maintains homeostasis and long-term control through various molecular mechanisms that include the genomic actions of ligand-activated NRs. In line with the scientific consensus that the origin of psychopathology is neurodevelopmental, the brain is most vulnerable to the effect of steroid imbalances and disrupted NR-mediated signaling at the earliest stages of development [127–130]. Balanced NR-mediated signaling, however, remains important throughout life, and steroid levels exhibit a maximum in young men and women (～20 years)[131], but vary greatly in abundance during periods of hormonal transition (childhood, puberty, post-partum, and menopause), thus overlapping with the vulnerability periods and age of onset of many PDs. Altered steroidogenic activity and imbalances in total circulating cholesterol and other lipid metabolites have furthermore been reported in a range of PDs [132,133]. In addition to endogenous steroids and derivatives of retinoids, fatty acids, cholesterol, lipophilic hormones and vitamins, NRs further act as sensors for a range of xenobiotics, antibiotics and synthetic compounds [16]

514 – with implications for the therapeutic effect of CNS drugs and CNS side effects of
515 non-CNS targeting drugs [134]. NR-mediated signaling thus constitutes a delicate
516 molecular mechanism that is both vulnerable to biological dysregulation and interesting
517 as a pharmacological target in the context of mental health.
518
519 **Genomic vulnerability to dysregulated nuclear receptor-mediated signaling in**
520 **mental illness**
521 We find that the genetic NTC risk burden is high across psychiatric diagnostic entities.
522 Particularly, we find that on average ~15% of SZ, MDD and BPD GWS loci harbor
523 NTC genes, and that the NTC gene set display overall significant association to these
524 disorders. In addition, nearly 20% of ASD-associated RCV-harboring genes are
525 members of the NTC. Although genetic studies have highlighted the implication of
526 individual NR and NR coregulator-encoding genes in mental illness, this is the first
527 study to demonstrate a consistently elevated genetic burden in the NTC in PDs. The
528 biological relevance of this overrepresentation of NTC genes among PD risk genes is
529 further substantiated by the high number of NTC genes that reside in multi-PD and CD
530 GWS loci and the enrichment of NTC genes among differentially methylated genes in
531 PDs. We note that particularly the NR subset of the NTC is associated with affective
532 disorders, whereas the risk burden in NR coregulators is dominant in SZ and ASD.
533 Interestingly, NR-encoding genes generally peak in their expression postnatally,
534 whereas NR coregulators—particularly those associated with ASD and SZ—peak in
535 their expression at the earliest stages of brain development. This may be related to the
536 differences in onset between affective and non-affective PDs. In this regard, it is
537 interesting to note that ASD risk NTC genes cluster among genes that display
538 female-biased expression in the prenatal cortex and male-bias in the prenatal striatum,
539 while non-SZ GWS NTC genes, on the contrary, overlap with genes that are
540 male-biased in the prenatal cortex and female-biased in the postnatal thalamus and
541 cortex. It is thus conceivable that differences in baseline NTC gene expression in males
542 and females impact on their vulnerability to genetic alterations in these gene sets and,
543 consequently, on their sex-biased PD risk profiles.

PD-associated NRs are not restricted to the endocrine receptor subclass of the NR family, but include lipid sensors, and adopted and true orphan receptors, thus potentially broadly bridging the gap between genetic and epidemiological risk. In line with this notion, many PD-associated NR coregulators are ubiquitously expressed in the brain and share a broad range of interactions with PD-associated NRs (**Figure 6** and **Table 1)**. This includes the bromodomain-containing, epigenetic readers, p300, p400, and BRD8. *EP400* is differentially methylated in blood from both ASD and SZ cases, and *BRD8* is positioned in a SZ GWS locus. Besides from its association to SZ, MDD and CD, genetic variation in *EP300* has furthermore been associated with amygdaloid dysfunction in healthy subjects [135]. Altered p300 activity, or the activity of similar broad-action NR coregulators, may thus widely affect NR-mediated signaling and confer vulnerability to a spectrum of epidemiological risk associated with a NR-ligand associated molecular response.

The functional output of signaling through NRs is a change in transcription of gene sets containing promotor HRE sequences. Whereas we do not find a strong transcriptomic NTC signature in postmortem brain samples from adult SZ cases, the enrichment of particular HRE sequences in the promotors of DEGs is in agreement with altered cerebral NR-mediated signaling in SZ. However, it is important to note that many commonly administered drugs in psychiatry and comorbid disorders will affect CNS NR-mediated signaling. Hence, it is not possible to ascribe observed enrichment to disorder biology or treatment.

At the genomic level, we find that some HRE-containing gene sets are associated with individual PDs, whereas others display association to PDs in general. This includes the HRE target genes of gonadosteroid receptors (PGR and ERα), and the retinoic acid receptor (RARβ), which are exclusively associated with MDD, and RORα HRE targets which have no association to PDs besides ASD. On the other hand, the retinoic acid receptor X α (RXRα) target genes appear to be more generally associated with mental illness in line with the role of RXRs heterodimeric complexes [121].

Supporting the biological relevance of the observed associations, subsets of HRE gene sets displayed association to diseases in which NRs are reportedly involved. This includes association of target genes of the NR1I subfamily of NRs (PXR and CAR that are generally implicated with regulation of energy metabolism and insulin sensitivity [136,137]) and the phenotypically interlinked diseases/traits: type 2 diabetes (T2D), heart failure, and body mass index (BMI). PPARs have been associated with T2D [138] and AD [101]. Interestingly, the VDRE gene set was significantly associated with AD and T2D in line with the reported associations between low serum 25-hydroxyvitamin D levels and AD and T2D [139], but not with e.g. ASD and SZ that has been associated with early life vitamin D deficiency [17,19]. RXRE was nominally significantly associated with Alzheimer's disease (AD), where RXR agonist administration leads to significant decrease in brain amyloid burden [140]. On the contrary, no association was observed between HRE gene sets and COVID-19 (positive vs population), where NR biology plays no obvious biological role.

Genetic, epidemiological, empirical and pharmacological evidence highlight distinct psychiatry-relevant nuclear receptor-mediated signaling pathways

Cell type- and tissue-specific co-expression is required for biophysical assemblage and psychiatry-relevant genomic signaling by distinct NTCs. We clustered NTC genes based on their co-expression characteristics in the developing human brain and identified networks of putative cell-specific NTCs with meticulously documented interactions. This revealed NTCs of known biological relevance, as well as novel NTCs

with putative pharmacological potential in psychiatry. Here we highlight selected NTCs whose implication in PDs are supported by multilevel genomic, and known epidemiological, empirical and pharmacological evidence.

Estrogen, androgen and progesterone receptors

Among NRs whose implication in PDs is supported by strong and multilevel evidence are gonadosteroid-binding receptors. Women who are in their peak estrogen-producing years or transitioning to menopause are at an elevated risk of developing affective disorders, as are women who are experiencing hormonal fluctuations, e.g. during menstrual periods and *post partum* [141]. Sex-biases characterize PDs in general, and altered levels of progesterone and androgens have been reported in SZ and estrogens in numerous PDs [142]. In addition, hormone replacement therapy has successfully been used in the treatment of PDs, including MDD, BPD, ASD, ADHD and SZ [35] with positive outcomes of testosterone replacement therapy in MDD [143]. Estrogen replacement therapy has been successful in *postpartum* depression [143], and has demonstrated antimanic effects in women with BPD (Tamoxifen and Raloxifene) [144] and improvement of positive and negative symptoms in SZ patients [35,145]. At the genetic level, the estrogen receptor-encoding gene (*ESR2*) resides in a GWS locus associated with both CD and MDD, and older association studies have repeatedly implicated ESRs with a range of PDs and psychiatry-related traits. Convincingly, the ESRE target gene set of ERβ is similarly associated with CD, thus strongly supporting a pathobiological relevance of imbalanced genomic ERβ signaling in mental illness at a broader level. Interestingly, *ESR2* locates to a different co-expression cluster than the genes encoding the other gonadosteroid-sensing receptors (ERα, AR, PGR). Particularly, the *ESR2* gene cluster peaks prenatally, while the others peak during puberty and adulthood. However, ERα and PGR both display a link to MDD, as their target ESRE and PGRE gene sets are both associated with MDD (**Figure 6**). DEGs identified in SZ postmortem brains are further enriched with PGRE in their promotor sequences. All gonadosteroid receptors share a range of NR coregulators, but both *ESR1* and *PGR* show cell-specific expression (neurons and endothelia, respectively) and have potential receptor-specific

NR coregulators from within their co-expression clusters. For ERα, this includes SZ GWS *PRMT8*, although their biophysical interaction remains to be systematically examined.

Corticosteroid receptors

Exposure to traumatic, maternal and early life stress is a major risk factor in many psychiatric disorders, including SZ, BPD, MDD, and anxiety disorders [26,146,147]. Among the NTC genes that harbor ASD-associated RCVs is *NR3C2* encoding the mineralocorticoid receptor (MR). MR is a high-affinity corticosteroid receptor that acts in synergy with the glucocorticoid receptor (GR) to mediate the molecular stress response. Both GR and MR belong to a gene co-expression cluster with peak expression in puberty and adulthood, but whereas GR is widely expressed in the brain and peak in cerebellar tissue, MR expression peaks in limbic tissues, in accordance with previously published reports [148]. MR plays a well-documented and sex-biased role in stress resilience and depression [149], where a functional MR haplotype protects against depression following early life trauma [150]. Unlike MRE target genes, the GRE gene set showed a significant association to MDD (**Figure 6**). This is in line with a recent study that demonstrated that genetic differences in the immediate transcriptome response to stress predict the risk of several PDs [18].

Retinoid binding nuclear receptors

Retinoids play a crucial role in developmental pathways, but are also essential to a number of postnatal processes, including synaptic plasticity[28]. Retinoid signaling is mediated through binding to RARs and PPARs in heterodimeric partnership with RXR. Low maternal retinol is a risk factor in SZ in adult offspring [29], and membrane levels of several polyunsaturated fatty acids, which signal through the same receptors [151,152], have been associated with psychotic, depressive, and manic symptoms in individuals at ultrahigh risk for psychosis [39]. Accumulating evidence has implicated retinoid signaling in the pathoetiology of particularly SZ (recently reviewed in Reay et al [28]), and PPAR/RXR and RAR/RXR complexes have been proposed as therapeutic strategies in CNS disorders [153]. Among the RXRs, none have been found in PD GWS loci, however, here we report that the RXRE target gene set of RXRα is significantly associated with CD. Whereas RXR-encoding genes are not restricted to specific cell types, their heterodimeric partners, PPARs, are. PPARγ is specific to microglia, PPARα to astrocytes and PPARδ to endothelia among brain cells – and both *PPARA* and *PPARG* are co-expressed with PD-associated coregulators in these specific cells. While none of the three receptors have been associated with PDs in GWASs, *PPARA* and *PPARD* are differentially methylated in blood from, respectively, SZ and MDD patients. In addition, we find that the PPARE target gene set of PPARγ is significantly associated with ASD. It is further noteworthy that both PPARα and γ can bind and respond to cannabinoids [154] – thus providing a potential genetic link to the risks and phenotypes associated with cannabis use in PDs [155].

Among the RAR encoding genes, only *RARG* resides in a PD GWS locus (SZ), whereas we find that the RARE target gene set of RARβ is associated with MDD. *RARB* and *RARG* have different expression profiles, and where *RARG* cluster with genes with peak expression in cerebellum, *RARB* expression peaks in striatal tissue. RARβ and RARγ share a number of NR coregulator interaction partners genetically associated with PDs **(Figure 6)**.

RORs

679 Patients with pathogenic variations in retinoic acid receptor-related orphan receptors
680 (RORs) present with ASD as well as seizures. Both of the RORs (RORα and RORβ)
681 are located in PD GWS loci. The *RORB* gene is associated with SZ and further harbors
682 ASD associated RCVs. *RORB* is specifically expressed in astrocytes and resides in a
683 gene co-expression cluster that peaks during prenatal brain development. Besides
684 *RORB*, none of the NTC genes with prenatal peaks are astrocyte specific, but single cell
685 genomics in ASD cortical tissue have associated altered glial *RORB* expression with
686 ASD [156]. Further supporting the involvement of ROR-mediated signaling in ASD,
687 RORα resides in a CD GWS locus and its RORE-containing target genes are
688 significantly associated with ASD (**Figure 6**). This is in agreement with reported ASD
689 risk genes under RORα transcriptional regulation [157]. Similarly, an association has been
690 found between ASD and the significantly overlapping HRE-containing target genes of
691 NRID1 (Rev-ErbA-Alpha) that reportedly acts as a repressor of RORE gene sets [158].
692 Reduced *RORA* transcript and/or protein levels has been reported in both blood and
693 postmortem brain tissue from ASD cases [159]. RORs are involved in a number of
694 psychiatry-relevant pathways including neurogenesis, stress response, and modulation
695 of circadian rhythms [160]. RORα binds with high affinity to the brain-specific
696 cholesterol-metabolite, 24S-hydroxysterol (cerebrosterol), which has been found
697 differentially abundant in plasma and suggested as a biomarker in ASD [161].
698
699 *Orphan receptors*
700 Located in an MDD GWA locus, *NURR1* is specifically expressed in microglia and
701 co-expressed with the SZ GWS NR coregulators, *CNOT1* and *GMEB1*. However, the
702 biophysical interaction of these coregulators with NURR1 has not been systematically
703 examined. Although classified as an orphan receptor, NURR1 activity can be
704 modulated by several small molecules (incl. docosahexaenoic acid (DHA) and other
705 unsaturated fatty acids) [162], as well as non-steroidal anti-inflammatory drugs [163].
706 NURR1 has been characterized as a neuroprotective and anti-inflammatory
707 transcription factor [164] and suggested as a therapeutic target in Parkinson's disease [165].
708 The monomer NBRE targets of NURR1 are not significantly associated with any PD,

but as NURR1 can bind DNA as a heterodimer with RXRs, it has the potential to modulate CD-associated RXRE target genes.

Little is reported about a role for the DAX1 receptor in mental illness. It is an orphan receptor and it has been reported to act as a repressor of other NRs through heterodimeric interactions with e.g. MR and GR [166,167]. However, in the brain, DAX1 is specifically expressed in oligodendrocytes. We find that the HRE half-site targets of DAX1 display significant association with SZ and interact with several PD-associated NR coregulators (**Figure 6**).

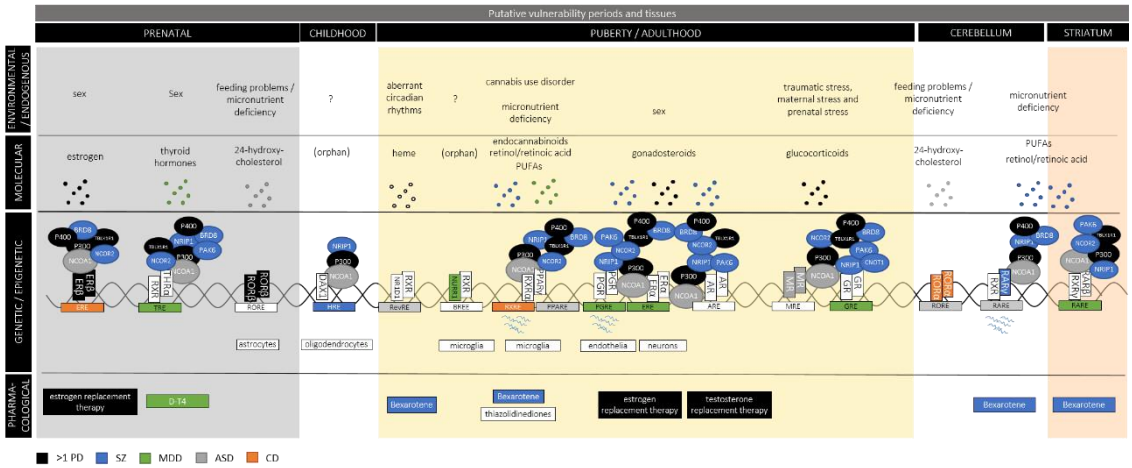

Figure 6 | NR-signaling pathways with high genetic risk burden. Illustrated are individual NRs and their experimentally validated associated NTC, their HRE target genes, resulting transcripts, selected ligands and linked epidemiological risks as well as selected psychiatry-relevant drugs. The illustration is divided into experimental levels (epidemiological, molecular, genetic and pharmacological) as well as the developmental stage/brain structure in which the individual NR-encoding genes peak in expression. Entities associated with SZ are highlighted in blue, MDD in green, ASD in grey, CD in orange and multiple PDs in black.

Therapeutic potential of targeting nuclear receptor biology in psychiatry

The activity of NRs can be pharmacologically modulated by specific ligands, thereby allowing for agonism, partial agonism, and antagonism. This has made them primary

therapeutic targets for decades [168], and approximately 16% of FDA approved drugs target NRs [169]. A wide spectrum of somatic disorders has successfully been targeted by drugs directed at NRs. PPARγ-targeting thiazolidinediones are used in the treatment of diabetes, cardiovascular disease and cancer [170]; selective ER modulators in ER-positive and metastatic breast cancer [171], and RXR/RAR-targeting isotretinoin against acne. Furthermore, the well-known drug Bexarotene, a selective RXR agonist, has been effectively used in the treatment of cutaneous T-cell lymphoma. A range of NR-targeting drugs have also proven efficient in non-psychiatric disorders of the CNS, though most have yet to demonstrate clinical efficacy and sustainability in phase III trials. Whereas NR modulators are increasingly recognized as potentially powerful therapeutics for neurodegenerative CNS diseases [105,172–175], a similar shift in focus remains to be seen for drug discovery programs in PDs. NRs have been suggested as therapeutic targets in PDs [176], and pharmacological targeting of NR mediated signaling has demonstrated clinical efficacy in the treatment of PDs [177], as assessed following administration of thyroid hormones (Liothyronine), progesterone receptor antagonist (Mifepristone), and Bexarotene in affective disorders and SZ, respectively [178,179].

Despite their positive effects, but likely owing to their wide applicability, many drugs targeting NRs are associated with serious adverse effects [170,171], affecting also the CNS—for instance, suicidal behavior following administration of the widely prescribed acne-drug, Accutane (isotretinoin) [180]. Other NR-targeting therapeutic strategies completely fail to demonstrate clinical efficacy, in which cases poor penetration of the blood-brain barrier seems to be the main impediment. Interestingly, a recently developed fatty acid amide hydrolase (FAAH)-targeting prodrug strategy appears to successfully facilitate blood-brain barrier diffusion through masking of small molecule carboxylate-containing NR modulators of therapeutic relevance to CNS disorders including ligands for TR, RXR, PPAR, LXR, ER, RAR [42].

NRs are extensively expressed throughout the brain, in many tissues and cell types, making them particularly difficult to target without side effects. In the wake of this realization, an accumulating interest has risen, that involves the targeting of NR coregulators, which tend to be restricted to certain regions and cell types of the brain.

Though commonly viewed as "undruggable" targets due to their large and flexible structures, potent small-molecule drugs have been developed to overcome this obstacle [181]. Other drugs target NR coregulators in an indirect manner through direct interaction with their NR, modulating the interaction between coregulator and NR, and thus the regulation of target genes [182,183]. We show that both the NR and NR coregulator components of the NTC are overrepresented among PD risk genes, supporting the biological relevance of targeting this group of endogenous coregulators in psychiatry.

Here we provide a resource for targeting psychiatry-relevant NTC networks with narrow cell specificity and defined sets of co-expressed interaction partners, which may significantly constrain the burden of off-target effects, favoring drug precision and safety in NR-based CNS therapeutics.

Perspectives and future research directions

There is an urgent need to identify molecular mechanisms implicated with PDs in order to progress the development of improved diagnostic tools and personalized medicine in psychiatry. Through mining of large-scale genomics data, we uncover an unacknowledged genetic burden in NTC genes and their downstream genomic targets, supporting dysregulated NR-mediated signaling as a common and core molecular pathway in PDs. It is thus conceivable that NRs bridge the gap between genetic and epidemiological risk in mental illness, and that genetic burden on associated molecular pathways may direct the individual's vulnerability to adverse exposures and predict their clinical risk profile. This holds both a potential for drug discovery potential as well as options in terms of molecular diagnostics and patient stratification. NR-mediated signaling has been suggested as a therapeutic target in PDs [176], but due to the complexity of the NR interaction network, it is challenging to target specific functions of the network while avoiding serious adverse effects. The mechanisms by which individual cells modulate tissue-specific psychiatry-relevant NR ligand responsiveness is thus a fundamental issue in targeting NR-mediated signaling in the brain. Here we categorize the genetic and epigenetic NTC risk burden in clusters of cell-specific and co-expressed genes that may provide a useful framework for future

793 CNS NR therapeutic strategies in psychiatry.

794

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Table 1 | Summary of genetic/epigenetic associations of NTC genes to psychiatric disorders

								Interacting NR coregulators				
Family	**Gene name**	**Gene symbol**	**Gene synonym**	**GWAS**	**WES**	**MWAS**	**GWAS catalogue**	**GWAS**	**WES**	**MWAS**	**GWAS catalogue**	**HRE gene set association**
0B	Short heterodimeric partner	NR0B2	SHP					BBX (SZ), BRMS1 (BPD)	SIN3A (ASD)			
0B	Dosage-sensitive sex reversal-adrenal hypoplasia congenital critical region on the X chromosome, Gene 1	NR0B1	DAX1									SZ
1A	Thyroid hormone receptor-α	NR1A1	THRA					EP300 (CD/SZ/MDD), NRIP1 (SZ)	NCOA1 (ASD)	NCOR2 (SZ)	MGMT (Anorexia Nervosa), NCOR2 (Cocaine dependence), TBL1Y (ASD)	MDD
1A	Thyroid hormone receptor-β	NR1A2	THRB				SZ, MDD in trauma-unexposed individuals, General cognitive ability, Intelligence	EP300 (CD/SZ/MDD), NRIP1 (SZ)	NCOA1 (ASD)	NCOR2 (SZ)	MGMT (Anorexia Nervosa), NCOR2 (Cocaine dependence), TBL1Y (ASD)	
1B	Retinoic acid receptor-α	NR1B1	RARA					EP300 (CD/SZ/MDD), NRIP1 (SZ)	NCOA1 (ASD)	NCOR2 (SZ)	MGMT (Anorexia Nervosa), NCOR2 (Cocaine dependence), TBL1Y (ASD)	
1B	Retinoic acid receptor-β	NR1B2	RARB				Oppositional defiant disorder dimensions in ADHD	EP300 (CD/SZ/MDD), NRIP1 (SZ)	NCOA1 (ASD)	NCOR2 (SZ)	NCOR2 (Cocaine dependence), TBL1Y (ASD)	MDD
1B	Retinoic acid receptor-γ	NR1B3	RARG	SZ			BPD or attention deficit hyperactivity disorder, Personality traits in BPD	EP300 (CD/SZ/MDD), NRIP1 (SZ)	NCOA1 (ASD)	NCOR2 (SZ)	MGMT (Anorexia Nervosa), NCOR2 (Cocaine dependence), TBL1Y (ASD)	
1C	Peroxisome	NR1C	PPARA			SZ		EP300	NCOA1	NCO	NCOR2	

	proliferator-activated receptor-α	1					(CD/SZ/MDD), NRIP1 (SZ)	(ASD)	R2 (SZ)	(Cocaine dependence), TBL1Y (ASD)	
1C	Peroxisome proliferator-activated receptor-δ	NR1C2	PPARD		MDD	Response to antipsychotic treatment	EP300 (CD/SZ/MDD), NRIP1 (SZ)	NCOA1 (ASD)	NCOR2 (SZ)		
1C	Peroxisome proliferator-activated receptor-γ	NR1C3	PPARG				EP300 (CD/SZ/MDD), NRIP1 (SZ)	CREBBP (ASD), NCOA1 (ASD)	NCOR2 (SZ)	MGMT (Anorexia Nervosa), NCOR2 (Cocaine dependence), TBL1Y (ASD)	ASD
1D	Reverse-Erb-α	NR1D1									ASD
1F	Retinoic acid receptor-related orphan receptor-α	NR1F1	RORA	CD		General cognitive ability, SZ, Educational attainment (MTAG), Educational attainment (years of education), Depression (quantitative trait), Response to citalopram treatment	EP300 (CD/SZ/MDD)				ASD
1F	Retinoic acid receptor-related orphan receptor-γ	NR1F3	RORC			Insomnia	EP300 (CD/SZ/MDD), NRIP1 (SZ)	NCOA1 (ASD)			
1F	Retinoic acid receptor-related orphan receptor-β	NR1F2	RORB	SZ	ASD	Depressive symptoms (SSRI exposure interaction)					
1H	Liver X receptor-β	NR1H2	LXRB				EP300 (CD/SZ/MDD), NRIP1 (SZ)	NCOA1 (ASD)	NCOR2 (SZ)	MGMT (Anorexia Nervosa)	
1H	Liver X receptor-α	NR1H1	LXRA				EP300 (CD/SZ/MDD), NRIP1 (SZ)	NCOA1 (ASD)			
1H	Farnesoid X receptor-α	NR1H4	FXRA				EP300 (CD/SZ/MDD), PRMT1 (SZ), NRIP1 (SZ)	NCOA1 (ASD)	NCOR2 (SZ)	MGMT (Anorexia Nervosa)	CD, ASD, ADHD
1I	Vitamin D receptor	VDR					EP300 (CD/SZ/MDD), NRIP1 (SZ), NCOA1 (ASD)		NCOR2 (SZ)	MGMT (Anorexia Nervosa)	
1I	Pregnane X	NR1I	PXR				NRIP1 (SZ)	NCOA1		MGMT	

	receptor	2					(ASD)		(Anorexia Nervosa)	
1I	Constitutive androstane receptor	NR1I3	CAR				NCOA1 (ASD)			
2A	Hepatocyte nuclear factor-4-α	HNF4A								
2B	Retinoid X receptor-α	RXRA				EP300 (CD/SZ/MDD), NRIP1 (SZ)	NCOA1 (ASD)	NCOR2 (SZ)	MGMT (Anorexia Nervosa)	CD
2B	Retinoid X receptor-β	RXRB				EP300 (CD/SZ/MDD), NRIP1 (SZ)	NCOA1 (ASD)			
2B	Retinoid X receptor-γ	RXRG					NCOA1 (ASD)			
2C	Testicular orphan nuclear receptor 4	NR2C2	TR4			NR2C2AP (BPD)				
2F	Chicken ovalbumin upstream promoter-transcription factor-α	NR2F1	COUP-TF1			BCL11B (CD/SZ)	NCOA1 (ASD)			
2F	Chicken ovalbumin upstream promoter-transcript	NR2F2	COUP-TF2			BCL11B (CD/SZ)				
2F	V-Erb-A Avian Erythroblastic Leukemia Viral Oncogene Homolog-Like 2	NR2F6					NCOA1 (ASD)			
3A	Estrogen receptor-β	ESR2		CD / MDD	Educational attainment (years of education), Depression, Educational attainment (years of education),	EP300 (CD/SZ/MDD)	NCOA1 (ASD)	NCOR2 (SZ)		CD
3A	Estrogen receptor-α	ESR1			Educational attainment (MTAG), Alcohol dependence, Developmental language disorder, Anxiety ASD spectrum disorder, Attention deficit hyperactivity disorder symptoms (maternal expressed emotions interaction),	EP300 (CD/SZ/MDD), SRA1 (SZ)	NCOA1 (ASD)	NCOR2 (SZ)		MDD
3B	Estrogen-related receptor-β	ESRRB				EP300 (CD/SZ/MDD), NRIP1 (SZ)	NCOA1 (ASD)		MGMT (Anorexia Nervosa)	
3B	Estrogen-related	ESRR			Major	EP300	NCOA1			

	receptor-γ	G			depression and alcohol dependence, Alcohol consumption, Cognitive aspects of educational attainment, Cognitive performance, Cognitive performance (MTAG), General cognitive ability, Intelligence, Intelligence (MTAG), Major Depressive disorder, Adventurousness	(CD/SZ/MDD), TLE1 (SZ), NRIP1 (SZ)	(ASD)			
3B	Estrogen-related receptor-α	ESRRA				NRIP1 (SZ)	NCOA1 (ASD)		MGMT (Anorexia Nervosa), NCOR2 (Cocaine dependence), TBL1Y (ASD)	
3C	Androgen receptor	AR				EP300 (CD/SZ/MDD), KAT5 (SZ), SMARCD1 (SZ), BCL7A (SZ), NRIP1 (SZ)	NCOA1 (ASD), ARID1B (ASD), SMARCC2 (ASD)	NCOR2 (SZ)		
3C	Mineralocorticoid receptor	NR3C2	MR	ASD	SZ, Well-being spectrum (multivariate analysis), Benign childhood epilepsy with centro-temporal spikes	EP300 (CD/SZ/MDD), NRIP1 (SZ)	NCOA1 (ASD)		NCOR2 (Cocaine dependence), TBL1Y (ASD)	
3C	Glucocorticoid receptor	NR3C1	GR		Night sleep phenotypes	EP300 (CD/SZ/MDD), SMARCD1 (SZ), BCL7A (SZ), NRIP1 (SZ)	NCOA1 (ASD), ARID1B (ASD), SMARCC2 (ASD)	NCOR2 (SZ)		MDD
3C	Progesterone receptor	NR3C3	PGR			EP300 (CD/SZ/MDD), SRA1 (SZ), NRIP1 (SZ)	NCOA1 (ASD)	NCOR2 (SZ)	NCOR2 (Cocaine dependence), TBL1Y (ASD),	MDD

								TBL1Y (ASD)
4A	Nerve growth factor 1B	NR4A1	NGFI-B			EP300 (CD/SZ/MDD)	NCOA1 (ASD)	
4A	Neuron-derived orphan receptor-1	NR4A3	NOR-1			EP300 (CD/SZ/MDD)		
4A	Nurr-related factor 1	NR4A2	NURR1	MDD				
5A	Steroidogenic factor-1	NR5A1	SF1				NCOA1 (ASD)	
6A	Liver receptor homolog-1	NR5A2	LRH1		General cognitive ability, Nicotine dependence	EP300 (CD/SZ/MDD)	NCOA1 (ASD)	

DECLARATIONS

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Authors' contributions

JGD, and PQ wrote the manuscript. JGD, AS, JP and PQ performed the experiments. JGD, AS, JP and PQ performed the statistical analyses. PQ conceived the basic idea and initiated the study. JG, ADB and PQ designed and directed the study. All authors have read and approved the final manuscript.

Availability of data and materials

Not applicable.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

REFERENCES

1. Lee SH, Ripke S, Neale BM, et al. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nat Genet*. 2013;45(9):984-994. doi:10.1038/ng.2711
2. Cross-Disorder Group of the Psychiatric Genomics Consortium. Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. *Lancet (London, England)*. 2013;381(9875):1371-1379. doi:10.1016/S0140-6736(12)62129-1
3. Uher R. Gene-environment interactions in severe mental illness. *Front psychiatry*. 2014;5(MAY):48. doi:10.3389/fpsyt.2014.00048
4. Lee PHPH, Anttila V, Won H, et al. Genomic Relationships, Novel Loci, and Pleiotropic Mechanisms across Eight Psychiatric Disorders. *Cell*. 2019;179(7):1469-1482.e11. doi:10.1016/j.cell.2019.11.020
5. Smeland OB, Bahrami S, Frei O, et al. Genome-wide analysis reveals extensive genetic overlap between schizophrenia, bipolar disorder, and intelligence. *Mol Psychiatry*. 2020;25(4):844-853.

854 doi:10.1038/s41380-018-0332-x
855 6. Wray NR, Lee SH, Mehta D, Vinkhuyzen AAE, Dudbridge F, Middeldorp CM. Research Review:
856 Polygenic methods and their application to psychiatric traits. *J Child Psychol Psychiatry*.
857 2014;55(10):1068-1087. doi:10.1111/jcpp.12295
858 7. Ripke S, Neale BM, Corvin A, et al. Biological insights from 108 schizophrenia-associated
859 genetic loci. *Nature*. 2014;511(7510):421-427. doi:10.1038/nature13595
860 8. Wray NR, Ripke S, Mattheisen M, et al. Genome-wide association analyses identify 44 risk
861 variants and refine the genetic architecture of major depression. *Nat Genet*. 2018;50(5):668-681.
862 doi:10.1038/s41588-018-0090-3
863 9. Grove J, Ripke S, Als TDTD, et al. Identification of common genetic risk variants for autism
864 spectrum disorder. *Nat Genet*. 2019;51(3):431-444. doi:10.1038/s41588-019-0344-8
865 10. Stahl EA, Breen G, Forstner AJ, et al. Genome-wide association study identifies 30 loci
866 associated with bipolar disorder. *Nat Genet*. 2019;51(5):793-803.
867 doi:10.1038/s41588-019-0397-8
868 11. Demontis D, Walters RKK, Martin J, et al. Discovery of the first genome-wide significant risk
869 loci for attention deficit/hyperactivity disorder. *Nat Genet*. 2019;51(1):63-75.
870 doi:10.1038/s41588-018-0269-7
871 12. Uher R, Zwicker A. Etiology in psychiatry: embracing the reality of poly-gene-environmental
872 causation of mental illness. *World Psychiatry*. 2017;16(2):121-129. doi:10.1002/wps.20436
873 13. Yamamoto K. Steroid Receptor Regulated Transcription of Specific Genes and Gene Networks.
874 *Annu Rev Genet*. 1985. doi:10.1146/annurev.genet.19.1.209
875 14. Mangelsdorf DJ, Thummel C, Beato M, et al. The nuclear receptor superfamily: The second
876 decade. *Cell*. 1995. doi:10.1016/0092-8674(95)90199-X
877 15. Mohan R, Heyman RA. Orphan nuclear receptor modulators. *Curr Top Med Chem*.
878 2003;3(14):1637-1647. doi:10.2174/1568026033451709
879 16. Sladek FM. What are nuclear receptor ligands? *Mol Cell Endocrinol*. 2011;334(1-2):3-13.
880 doi:10.1016/j.mce.2010.06.018
881 17. Eyles DW, Trzaskowski M, Vinkhuyzen AAE, et al. The association between neonatal vitamin D
882 status and risk of schizophrenia. *Sci Rep*. 2018;8(November):1-8.
883 doi:10.1038/s41598-018-35418-z

884 18. Arloth J, Bogdan R, Weber P, et al. Genetic Differences in the Immediate Transcriptome
885 Response to Stress Predict Risk-Related Brain Function and Psychiatric Disorders. *Neuron*.
886 2015;86(5):1189-1202. doi:10.1016/j.neuron.2015.05.034
887 19. Lee BK, Eyles DW, Magnusson C, et al. Developmental vitamin D and autism spectrum
888 disorders: findings from the Stockholm Youth Cohort. *Mol Psychiatry*. November 2019.
889 doi:10.1038/s41380-019-0578-y
890 20. Zagni E, Simoni L, Colombo D. Sex and Gender Differences in Central Nervous System-Related
891 Disorders. *Neurosci J*. 2016;2016:1-13. doi:10.1155/2016/2827090
892 21. Canuso CM, Pandina G. Gender and schizophrenia. *Psychopharmacol Bull*. 2007;40(4):178-190.
893 22. McLean CP, Asnaani A, Litz BT, Hofmann SG. Gender differences in anxiety disorders:
894 Prevalence, course of illness, comorbidity and burden of illness. *J Psychiatr Res*.
895 2011;45(8):1027-1035. doi:10.1016/j.jpsychires.2011.03.006
896 23. Riecher-Rössler A. Oestrogens, prolactin, hypothalamic-pituitary-gonadal axis, and
897 schizophrenic psychoses. *The Lancet Psychiatry*. 2017;4(1):63-72.
898 doi:10.1016/S2215-0366(16)30379-0
899 24. Diflorio A, Jones I. Is sex important? Gender differences in bipolar disorder. *Int Rev Psychiatry*.
900 2010;22(5):437-452. doi:10.3109/09540261.2010.514601
901 25. Kuehner C. Why is depression more common among women than among men? *The Lancet*
902 *Psychiatry*. 2017;4(2):146-158. doi:10.1016/S2215-0366(16)30263-2
903 26. Heim C, Newport DJ, Mletzko T, Miller AH, Nemeroff CB. The link between childhood trauma
904 and depression: Insights from HPA axis studies in humans. *Psychoneuroendocrinology*.
905 2008;33(6):693-710. doi:10.1016/j.psyneuen.2008.03.008
906 27. Shi L, Lu Z-A, Que J-Y, et al. Prevalence of and Risk Factors Associated With Mental Health
907 Symptoms Among the General Population in China During the Coronavirus Disease 2019
908 Pandemic. *JAMA Netw Open*. 2020;3(7):e2014053. doi:10.1001/jamanetworkopen.2020.14053
909 28. Reay WR, Cairns MJ. The role of the retinoids in schizophrenia: genomic and clinical
910 perspectives. *Mol Psychiatry*. 2020;25(4):706-718. doi:10.1038/s41380-019-0566-2
911 29. Bao Y, Ibram G, Blaner WS, et al. Low maternal retinol as a risk factor for schizophrenia in adult
912 offspring. *Schizophr Res*. 2012;137(1-3):159-165. doi:10.1016/j.schres.2012.02.004
913 30. Lane MA, Bailey SJ. Role of retinoid signalling in the adult brain. *Prog Neurobiol*.

914 2005;75(4):275-293. doi:10.1016/j.pneurobio.2005.03.002
915 31. Chrousos GP. Stress and disorders of the stress system. *Nat Rev Endocrinol*. 2009;5(7):374-381.
916 doi:10.1038/nrendo.2009.106
917 32. Stanikova D, Luck T, Bae YJ, et al. Increased estrogen level can be associated with depression in
918 males. *Psychoneuroendocrinology*. 2018;87:196-203. doi:10.1016/j.psyneuen.2017.10.025
919 33. Huber T., Rollnik J, Wilhelms J, von zur Mühlen A, Emrich H., Schneider U. Estradiol levels in
920 psychotic disorders. *Psychoneuroendocrinology*. 2001;26(1):27-35.
921 doi:10.1016/S0306-4530(00)00034-2
922 34. Brzezinski-Sinai NA, Brzezinski A. Schizophrenia and Sex Hormones: What Is the Link? *Front*
923 *Psychiatry*. 2020;11. doi:10.3389/fpsyt.2020.00693
924 35. Hwang WJ, Lee TY, Kim NS, Kwon JS. The Role of Estrogen Receptors and Their Signaling
925 across Psychiatric Disorders. *Int J Mol Sci*. 2020;22(1):373. doi:10.3390/ijms22010373
926 36. Bernal J. *Thyroid Hormones in Brain Development and Function*.; 2000.
927 http://www.ncbi.nlm.nih.gov/pubmed/25905404.
928 37. O'Sullivan SE. An update on PPAR activation by cannabinoids. *Br J Pharmacol*.
929 2016;173(12):1899-1910. doi:10.1111/bph.13497
930 38. Lev-Ran S, Roerecke M, Le Foll B, George TP, McKenzie K, Rehm J. The association between
931 cannabis use and depression: a systematic review and meta-analysis of longitudinal studies.
932 *Psychol Med*. 2014;44(4):797-810. doi:10.1017/S0033291713001438
933 39. Berger M, Nelson B, Markulev C, et al. Relationship Between Polyunsaturated Fatty Acids and
934 Psychopathology in the NEURAPRO Clinical Trial. *Front Psychiatry*. 2019;10.
935 doi:10.3389/fpsyt.2019.00393
936 40. Amminger GP, McGorry PD. Update on Omega-3 Polyunsaturated Fatty Acids in Early-Stage
937 Psychotic Disorders. *Neuropsychopharmacology*. 2012;37(1):309-310.
938 doi:10.1038/npp.2011.187
939 41. Olivares AM, Moreno-Ramos OA, Haider NB. Role of Nuclear Receptors in Central Nervous
940 System Development and Associated Diseases. *J Exp Neurosci*. 2015;9(Suppl 2):93-121.
941 doi:10.4137/JEN.S25480
942 42. Ferrara SJ, Scanlan TS. A CNS-Targeting Prodrug Strategy for Nuclear Receptor Modulators. *J*
943 *Med Chem*. 2020;63(17):9742-9751. doi:10.1021/acs.jmedchem.0c00868

43. Mackeh R, Marr AK, Dargham SR, Syed N, Fakhro KA, Kino T. Single-Nucleotide Variations of the Human Nuclear Hormone Receptor Genes in 60,000 Individuals. *J Endocr Soc*. 2018;2(1):77-90. doi:10.1210/js.2017-00406

44. Achermann JC, Schwabe J, Fairall L, Chatterjee K. Genetic disorders of nuclear receptors. *J Clin Invest*. 2017;127(4):1181-1192. doi:10.1172/JCI88892

45. Haider N, Olivares A, Moreno O, Haider N. Role of Nuclear Receptors in Central Nervous System Development and Associated Diseases. *J Exp Neurosci*. May 2016:93. doi:10.4137/JEN.S25480

46. Guissart C, Latypova X, Rollier P, et al. Dual Molecular Effects of Dominant RORA Mutations Cause Two Variants of Syndromic Intellectual Disability with Either Autism or Cerebellar Ataxia. *Am J Hum Genet*. 2018;102(5):744-759. doi:10.1016/j.ajhg.2018.02.021

47. Rudolf G, Lesca G, Mehrjouy MM, et al. Loss of function of the retinoid-related nuclear receptor (RORB) gene and epilepsy. *Eur J Hum Genet*. 2016;24(12):1761-1770. doi:10.1038/ejhg.2016.80

48. Millard CJ, Watson PJ, Fairall L, Schwabe JWR. An evolving understanding of nuclear receptor coregulator proteins. *J Mol Endocrinol*. 2013;51(3):T23-36. doi:10.1530/JME-13-0227

49. Malovannaya A, Lanz RB, Jung SY, et al. Analysis of the Human Endogenous Coregulator Complexome. *Cell*. 2011;145(5):787-799. doi:10.1016/j.cell.2011.05.006

50. Broekema MF, Hollman DAA, Koppen A, et al. Profiling of 3696 Nuclear Receptor-Coregulator Interactions: A Resource for Biological and Clinical Discovery. *Endocrinology*. 2018;159(6):2397-2407. doi:10.1210/en.2018-00149

51. Tagami T, Madison LD, Nagaya T, Jameson JL. Nuclear receptor corepressors activate rather than suppress basal transcription of genes that are negatively regulated by thyroid hormone. *Mol Cell Biol*. 1997;17(5):2642-2648. doi:10.1128/mcb.17.5.2642

52. Berghagen H, Ragnhildstveit E, Krogsrud K, Thuestad G, Apriletti J, Saatcioglu F. Corepressor SMRT functions as a coactivator for thyroid hormone receptor T3Ralpha from a negative hormone response element. *J Biol Chem*. 2002;277(51):49517-49522. doi:10.1074/jbc.M209546200

53. Tora L, Gronemeyer H, Turcotte B, Gaub M-P, Chambon P. The N-terminal region of the chicken progesterone receptor specifies target gene activation. *Nature*. 1988;333(6169):185-188.

974 doi:10.1038/333185a0
975 54. Shao D, Lazar MA. Modulating nuclear receptor function: may the phos be with you. *J Clin*
976 *Invest*. 1999;103(12):1617-1618. doi:10.1172/JCI7421
977 55. Lonard DM, Lanz RB, O'Malley BW. Nuclear receptor coregulators and human disease. *Endocr*
978 *Rev*. 2007;28(5):575-587. doi:10.1210/er.2007-0012
979 56. Kong Y, Zhou W, Sun Z. Nuclear receptor corepressors in intellectual disability and autism. *Mol*
980 *Psychiatry*. 2020;25(10):2220-2236. doi:10.1038/s41380-020-0667-y
981 57. Tabet A-C, Leroy C, Dupont C, et al. De novo deletion of TBL1XR1 in a child with non-specific
982 developmental delay supports its implication in intellectual disability. *Am J Med Genet Part A*.
983 2014;164(9):2335-2337. doi:10.1002/ajmg.a.36619
984 58. Vaqueiro AC, de Oliveira CP, Cordoba MS, et al. Expanding the spectrum of TBL1XR1 deletion:
985 Report of a patient with brain and cardiac malformations. *Eur J Med Genet*. 2018;61(1):29-33.
986 doi:10.1016/j.ejmg.2017.10.008
987 59. Sakaguchi Y, Uehara T, Suzuki H, et al. Haploinsufficiency of NCOR1 associated with autism
988 spectrum disorder, scoliosis, and abnormal palatogenesis. *Am J Med Genet Part A*.
989 2018;176(11):2466-2469. doi:10.1002/ajmg.a.40354
990 60. Zhou W, He Y, Rehman AU, et al. Author Correction: Loss of function of NCOR1 and NCOR2
991 impairs memory through a novel GABAergic hypothalamus–CA3 projection. *Nat Neurosci*.
992 2019;22(9):1533-1533. doi:10.1038/s41593-019-0449-5
993 61. Sajan SA, Jhangiani SN, Muzny DM, et al. Enrichment of mutations in chromatin regulators in
994 people with Rett syndrome lacking mutations in MECP2. *Genet Med*. 2017;19(1):13-19.
995 doi:10.1038/gim.2016.42
996 62. Reay WR, Atkins JR, Quidé Y, Carr VJ, Green MJ, Cairns MJ. Polygenic disruption of retinoid
997 signalling in schizophrenia and a severe cognitive deficit subtype. *Mol Psychiatry*.
998 2020;25(4):719-731. doi:10.1038/s41380-018-0305-0
999 63. Viosca J, Lopez-Atalaya JP, Olivares R, Eckner R, Barco A. Syndromic features and mild
1000 cognitive impairment in mice with genetic reduction on p300 activity: Differential contribution
1001 of p300 and CBP to Rubinstein–Taybi syndrome etiology. *Neurobiol Dis*. 2010;37(1):186-194.
1002 doi:10.1016/j.nbd.2009.10.001
1003 64. Qvist P, Christensen JH, Vardya I, et al. The Schizophrenia-Associated BRD1 Gene Regulates

Behavior, Neurotransmission, and Expression of Schizophrenia Risk Enriched Gene Sets in Mice. *Biol Psychiatry*. 2017;82(1):62-76. doi:10.1016/j.biopsych.2016.08.037

65. Rajkumar AP, Qvist P, Donskov JG, et al. Reduced Brd1 expression leads to reversible depression-like behaviors and gene-expression changes in female mice. *Transl Psychiatry*. 2020;10(1):239. doi:10.1038/s41398-020-00914-2

66. Qvist P, Eskildsen SF, Hansen B, et al. Brain volumetric alterations accompanied with loss of striatal medium-sized spiny neurons and cortical parvalbumin expressing interneurons in Brd1 +/− mice. *Sci Rep*. 2018;8(1):1-12. doi:10.1038/s41598-018-34729-5

67. Oliveira AMM, Estévez MA, Hawk JD, Grimes S, Brindle PK, Abel T. Subregion-specific p300 conditional knock-out mice exhibit long-term memory impairments. *Learn Mem*. 2011;18(3):161-169. doi:10.1101/lm.1939811

68. Valor LM, Pulopulos MM, Jimenez-Minchan M, Olivares R, Lutz B, Barco A. Ablation of CBP in forebrain principal neurons causes modest memory and transcriptional defects and a dramatic reduction of histone acetylation but does not affect cell viability. *J Neurosci*. 2011;31(5):1652-1663. doi:10.1523/JNEUROSCI.4737-10.2011

69. Zhang Z, Hofmann C, Casanova E, Schütz G, Lutz B. Generation of a conditional allele of the CBP gene in mouse. *Genesis*. 2004;40(2):82-89. doi:10.1002/gene.20068

70. Morimoto Y, Ono S, Yoshida S, et al. A unique missense variant in the E1A-binding protein P400 gene is implicated in schizophrenia by whole-exome sequencing and mutant mouse models. *Transl Psychiatry*. 2021;11(1):132. doi:10.1038/s41398-021-01258-1

71. Ripke S, Walters JTR, O'Donovan MC. Mapping genomic loci prioritises genes and implicates synaptic biology in schizophrenia. *medRxiv*. 2020. doi:10.1101/2020.09.12.20192922

72. Lambert JC, Ibrahim-Verbaas C a, Harold D, et al. Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. *Nat Genet*. 2013;45(12):1452-1458. doi:10.1038/ng.2802

73. Cai L, Wheeler E, Kerrison ND, et al. Genome-wide association analysis of type 2 diabetes in the EPIC-InterAct study. *Sci Data*. 2020;7(1):393. doi:10.1038/s41597-020-00716-7

74. Shah S, Henry A, Roselli C, et al. Genome-wide association and Mendelian randomisation analysis provide insights into the pathogenesis of heart failure. *Nat Commun*. 2020;11(1):163. doi:10.1038/s41467-019-13690-5

1034 75. Yengo L, Sidorenko J, Kemper KE, et al. Meta-analysis of genome-wide association studies for
1035 height and body mass index in ～700000 individuals of European ancestry. *Hum Mol Genet*.
1036 2018;27(20):3641-3649. doi:10.1093/hmg/ddy271
1037 76. Leslie R, O'Donnell CJ, Johnson AD. GRASP: analysis of genotype-phenotype results from
1038 1390 genome-wide association studies and corresponding open access database. *Bioinformatics*.
1039 2014;30(12):i185-i194. doi:10.1093/bioinformatics/btu273
1040 77. Lam M, Awasthi S, Watson HJ, et al. RICOPILI: Rapid Imputation for COnsortias PIpeLIne.
1041 Schwartz R, ed. *Bioinformatics*. 2020;36(3):930-933. doi:10.1093/bioinformatics/btz633
1042 78. Singh T, Kurki MI, Curtis D, et al. Rare loss-of-function variants in SETD1A are associated with
1043 schizophrenia and developmental disorders. *Nat Neurosci*. 2016;19(4):571-577.
1044 doi:10.1038/nn.4267
1045 79. Satterstrom FK, Kosmicki JA, Wang J, et al. Large-Scale Exome Sequencing Study Implicates
1046 Both Developmental and Functional Changes in the Neurobiology of Autism. *Cell*.
1047 2020;180(3):568-584.e23. doi:10.1016/j.cell.2019.12.036
1048 80. Hannon E, Dempster E, Viana J, et al. An integrated genetic-epigenetic analysis of schizophrenia:
1049 evidence for co-localization of genetic associations and differential DNA methylation. *Genome*
1050 *Biol*. 2016;17(1):176. doi:10.1186/s13059-016-1041-x
1051 81. Aberg KA, McClay JL, Nerella S, et al. Methylome-wide association study of schizophrenia:
1052 identifying blood biomarker signatures of environmental insults. *JAMA psychiatry*.
1053 2014;71(3):255-264. doi:10.1001/jamapsychiatry.2013.3730
1054 82. Chan RF, Shabalin AA, Montano C, et al. Independent Methylome-Wide Association Studies of
1055 Schizophrenia Detect Consistent Case–Control Differences. *Schizophr Bull*. 2019;46(2):319-327.
1056 doi:10.1093/schbul/sbz056
1057 83. Aberg KA, Dean B, Shabalin AA, et al. Methylome-wide association findings for major
1058 depressive disorder overlap in blood and brain and replicate in independent brain samples. *Mol*
1059 *Psychiatry*. 2020;25(6):1344-1354. doi:10.1038/s41380-018-0247-6
1060 84. van Dongen J, Zilhão NR, Sugden K, et al. Epigenome-wide Association Study of
1061 Attention-Deficit/Hyperactivity Disorder Symptoms in Adults. *Biol Psychiatry*.
1062 2019;86(8):599-607. doi:10.1016/j.biopsych.2019.02.016
1063 85. Walton E, Pingault J-B-B, Cecil CAM, et al. Epigenetic profiling of ADHD symptoms

trajectories: a prospective, methylome-wide study. *Mol Psychiatry*. 2017;22(2):250-256. doi:10.1038/mp.2016.85

86. Hannon E, Schendel D, Ladd-Acosta C, et al. Elevated polygenic burden for autism is associated with differential DNA methylation at birth. *Genome Med*. 2018;10(1):1-13. doi:10.1186/s13073-018-0527-4

87. Spiers H, Hannon E, Schalkwyk LC, et al. Methylomic trajectories across human fetal brain development. *Genome Res*. 2015;25(3):338-352. doi:10.1101/gr.180273.114

88. Miller JA, Ding S-L, Sunkin SM, et al. Transcriptional landscape of the prenatal human brain. *Nature*. 2014;508(7495):199-206. doi:10.1038/nature13185

89. de Leeuw C a., Mooij JM, Heskes T, Posthuma D. MAGMA: Generalized Gene-Set Analysis of GWAS Data. *PLOS Comput Biol*. 2015;11(4):e1004219. doi:10.1371/journal.pcbi.1004219

90. Kulakovskiy I V, Vorontsov IE, Yevshin IS, et al. HOCOMOCO: towards a complete collection of transcription factor binding models for human and mouse via large-scale ChIP-Seq analysis. *Nucleic Acids Res*. 2018;46(D1):D252-D259. doi:10.1093/nar/gkx1106

91. Grant CE, Bailey TL, Noble WS. FIMO: scanning for occurrences of a given motif. *Bioinformatics*. 2011;27(7):1017-1018. doi:10.1093/bioinformatics/btr064

92. Shen L, Sinai M. GeneOverlap: Test and visualize gene overlaps. R package version 1.2.0,. http://shenlab-sinai.github.io/shenlab-sinai/. Published 2013.

93. Hoffman GE, Bendl J, Voloudakis G, et al. CommonMind Consortium provides transcriptomic and epigenomic data for Schizophrenia and Bipolar Disorder. *Sci Data*. 2019;6(1):180. doi:10.1038/s41597-019-0183-6

94. Gearing LJ, Cumming HE, Chapman R, et al. CiiiDER: A tool for predicting and analysing transcription factor binding sites. Helmer-Citterich M, ed. *PLoS One*. 2019;14(9):e0215495. doi:10.1371/journal.pone.0215495

95. Metsalu T, Vilo J. ClustVis: a web tool for visualizing clustering of multivariate data using Principal Component Analysis and heatmap. *Nucleic Acids Res*. 2015;43(W1):W566-W570. doi:10.1093/nar/gkv468

96. McKenzie AT, Wang M, Hauberg ME, et al. Brain Cell Type Specific Gene Expression and Co-expression Network Architectures. *Sci Rep*. 2018;8(1):8868. doi:10.1038/s41598-018-27293-5

97. Shi L, Zhang Z, Su B. Sex Biased Gene Expression Profiling of Human Brains at Major Developmental Stages. *Sci Rep*. 2016;6:21181. doi:10.1038/srep21181

98. Buroker NE, Young ME, Wei C, et al. The dominant negative thyroid hormone receptor β-mutant Δ337T alters PPARα signaling in heart. *Am J Physiol Metab*. 2007;292(2):E453-E460. doi:10.1152/ajpendo.00267.2006

99. Swanson HI, Wada T, Xie W, et al. Role of nuclear receptors in lipid dysfunction and obesity-related diseases. *Drug Metab Dispos*. 2013;41(1):1-11. doi:10.1124/dmd.112.048694

100. Liu S, Downes M, Evans RM. Metabolic Regulation by Nuclear Receptors. In: *Innovative Medicine*. Tokyo: Springer Japan; 2015:25-37. doi:10.1007/978-4-431-55651-0_2

101. Moutinho M, Landreth GE. Therapeutic potential of nuclear receptor agonists in Alzheimer's disease. *J Lipid Res*. 2017;58(10):1937-1949. doi:10.1194/jlr.R075556

102. Fitz NF, Nam KN, Koldamova R, Lefterov I. Therapeutic targeting of nuclear receptors, liver X and retinoid X receptors, for Alzheimer's disease. *Br J Pharmacol*. 2019;176(18):3599-3610. doi:10.1111/bph.14668

103. Corredor B, Dattani M, Gertosio C, Bozzola M. Tall Stature: A Challenge for Clinicians. *Curr Pediatr Rev*. 2019;15(1):10-21. doi:10.2174/1573396314666181105092917

104. De Magalhaes Filho CD, Downes M, Evans RM. Farnesoid X Receptor an Emerging Target to Combat Obesity. *Dig Dis*. 2017;35(3):185-190. doi:10.1159/000450909

105. Skerrett R, Malm T, Landreth G. Nuclear receptors in neurodegenerative diseases. *Neurobiol Dis*. 2014;72 Pt A:104-116. doi:10.1016/j.nbd.2014.05.019

106. Rees E, Owen MJ. Translating insights from neuropsychiatric genetics and genomics for precision psychiatry. *Genome Med*. 2020;12(1):43. doi:10.1186/s13073-020-00734-5

107. Owen MJ, O'Donovan MC. Schizophrenia and the neurodevelopmental continuum:evidence from genomics. *World Psychiatry*. 2017;16(3):227-235. doi:10.1002/wps.20440

108. Aberg KA, Xie LY, McClay JL, et al. Testing two models describing how methylome-wide studies in blood are informative for psychiatric conditions. *Epigenomics*. 2013;5(4):367-377. doi:10.2217/epi.13.36

109. Mill J, Tang T, Kaminsky Z, et al. Epigenomic profiling reveals DNA-methylation changes associated with major psychosis. *Am J Hum Genet*. 2008;82(3):696-711. doi:10.1016/j.ajhg.2008.01.008

110. Ladd-Acosta C, Hansen KD, Briem E, Fallin MD, Kaufmann WE, Feinberg AP. Common DNA methylation alterations in multiple brain regions in autism. *Mol Psychiatry*. 2014;19(8):862-871. doi:10.1038/mp.2013.114

111. Starnawska A, Tan Q, McGue M, et al. Epigenome-wide association study of cognitive functioning in middle-aged monozygotic twins. *Front Aging Neurosci*. 2017;9(DEC):1-10. doi:10.3389/fnagi.2017.00413

112. Ianov L, Riva A, Kumar A, et al. DNA Methylation of Synaptic Genes in the Prefrontal Cortex Is Associated with Aging and Age-Related Cognitive Impairment. *Front Aging Neurosci*. 2017;9. doi:10.3389/fnagi.2017.00249

113. Ciernia AV, LaSalle J. The landscape of DNA methylation amid a perfect storm of autism aetiologies. *Nat Rev Neurosci*. 2016;17(7):411-423. doi:10.1038/nrn.2016.41

114. Montano C, Taub MA, Jaffe A, et al. Association of DNA Methylation Differences With Schizophrenia in an Epigenome-Wide Association Study. *JAMA psychiatry*. 2016;73(5):506-514. doi:10.1001/jamapsychiatry.2016.0144

115. Córdova-Palomera A, Fatjó-Vilas M, Gastó C, Navarro V, Krebs M-O, Fañanás L. Genome-wide methylation study on depression: differential methylation and variable methylation in monozygotic twins. *Transl Psychiatry*. 2015;5(4):e557-e557. doi:10.1038/tp.2015.49

116. Palma-Gudiel H, Córdova-Palomera A, Eixarch E, Deuschle M, Fañanás L. Maternal psychosocial stress during pregnancy alters the epigenetic signature of the glucocorticoid receptor gene promoter in their offspring: a meta-analysis. *Epigenetics*. 2015;10(10):893-902. doi:10.1080/15592294.2015.1088630

117. Chen S, Mukherjee N, Janjanam VD, et al. Consistency and Variability of DNA Methylation in Women During Puberty, Young Adulthood, and Pregnancy. *Genet Epigenet*. 2017;9:1179237X1772154. doi:10.1177/1179237X17721540

118. Lomniczi A, Loche A, Castellano JM, et al. Epigenetic control of female puberty. *Nat Neurosci*. 2013;16(3):281-289. doi:10.1038/nn.3319

119. Jung M, Pfeifer GP. Aging and DNA methylation. *BMC Biol*. 2015;13(1):7. doi:10.1186/s12915-015-0118-4

120. Corley SM, Tsai S-Y, Wilkins MR, Shannon Weickert C. Transcriptomic Analysis Shows Decreased Cortical Expression of NR4A1, NR4A2 and RXRB in Schizophrenia and Provides

Evidence for Nuclear Receptor Dysregulation. Hashimoto K, ed. *PLoS One*. 2016;11(12):e0166944. doi:10.1371/journal.pone.0166944

121. le Maire A, Teyssier C, Balaguer P, Bourguet W, Germain P. Regulation of RXR-RAR Heterodimers by RXR- and RAR-Specific Ligands and Their Combinations. *Cells*. 2019;8(11). doi:10.3390/cells8111392

122. Penvose A, Keenan JL, Bray D, Ramlall V, Siggers T. Comprehensive study of nuclear receptor DNA binding provides a revised framework for understanding receptor specificity. *Nat Commun*. 2019;10(1):2514. doi:10.1038/s41467-019-10264-3

123. Lenroot RK, Gogtay N, Greenstein DK, et al. Sexual dimorphism of brain developmental trajectories during childhood and adolescence. *Neuroimage*. 2007;36(4):1065-1073. doi:10.1016/j.neuroimage.2007.03.053

124. Marrocco J, McEwen BS. Sex in the brain: hormones and sex differences. *Dialogues Clin Neurosci*. 2016;18(4):373-383. doi:10.31887/DCNS.2016.18.4/jmarrocco

125. Hu VW, Sarachana T, Sherrard RM, Kocher KM. Investigation of sex differences in the expression of RORA and its transcriptional targets in the brain as a potential contributor to the sex bias in autism. *Mol Autism*. 2015;6(1):7. doi:10.1186/2040-2392-6-7

126. Lenroot RK, Giedd JN. The changing impact of genes and environment on brain development during childhood and adolescence: Initial findings from a neuroimaging study of pediatric twins. *Dev Psychopathol*. 2008;20(4):1161-1175. doi:10.1017/S0954579408000552

127. Ahmed OM, El-Gareib AW, El-bakry AM, Abd El-Tawab SM, Ahmed RG. Thyroid hormones states and brain development interactions. *Int J Dev Neurosci*. 2008;26(2):147-209. doi:10.1016/j.ijdevneu.2007.09.011

128. Maternal Thyroid Deficiency during Pregnancy and Subsequent Neuropsychological Development of the Child. *N Engl J Med*. 1999;341(26):2015-2017. doi:10.1056/NEJM199912233412613

129. Zoeller RT, Rovet J. Timing of Thyroid Hormone Action in the Developing Brain: Clinical Observations and Experimental Findings. *J Neuroendocrinol*. 2004;16(10):809-818. doi:10.1111/j.1365-2826.2004.01243.x

130. Pertile RAN, Cui X, Eyles DW. Vitamin D signaling and the differentiation of developing dopamine systems. *Neuroscience*. 2016;333:193-203. doi:10.1016/j.neuroscience.2016.07.020

131. Labrie F, Bélanger A, Cusan L, Gomez J-L, Candas B. Marked Decline in Serum Concentrations of Adrenal C19 Sex Steroid Precursors and Conjugated Androgen Metabolites During Aging. *J Clin Endocrinol Metab*. 1997;82(8):2396-2402. doi:10.1210/jcem.82.8.4160

132. Baron-Cohen S, Auyeung B, Nørgaard-Pedersen B, et al. Elevated fetal steroidogenic activity in autism. *Mol Psychiatry*. 2015;20(3):369-376. doi:10.1038/mp.2014.48

133. Holsboer F. The Corticosteroid Receptor Hypothesis of Depression. *Neuropsychopharmacology*. 2000;23(5):477-501. doi:10.1016/S0893-133X(00)00159-7

134. Xu D, Huang S, Wang H, Xie W. Regulation of brain drug metabolizing enzymes and transporters by nuclear receptors. *Drug Metab Rev*. 2018;50(4):407-414. doi:10.1080/03602532.2018.1554673

135. Erk S, Mohnke S, Ripke S, et al. Functional neuroimaging effects of recently discovered genetic risk loci for schizophrenia and polygenic risk profile in five RDoC subdomains. *Transl Psychiatry*. 2017;7(1):e997-e997. doi:10.1038/tp.2016.272

136. Hukkanen J, Hakkola J, Rysä J. Pregnane X receptor (PXR) – a contributor to the diabetes epidemic? *Drug Metabol Drug Interact*. 2014;29(1). doi:10.1515/dmdi-2013-0036

137. Gao J, He J, Zhai Y, Wada T, Xie W. The Constitutive Androstane Receptor Is an Anti-obesity Nuclear Receptor That Improves Insulin Sensitivity. *J Biol Chem*. 2009;284(38):25984-25992. doi:10.1074/jbc.M109.016808

138. Cipolletta D, Feuerer M, Li A, et al. PPAR-γ is a major driver of the accumulation and phenotype of adipose tissue Treg cells. *Nature*. 2012;486(7404):549-553. doi:10.1038/nature11132

139. Dalgard C, Petersen MS, Weihe P, Grandjean P. Vitamin D Status in Relation to Glucose Metabolism and Type 2 Diabetes in Septuagenarians. *Diabetes Care*. 2011;34(6):1284-1288. doi:10.2337/dc10-2084

140. Cummings JL, Zhong K, Kinney JW, et al. Double-blind, placebo-controlled, proof-of-concept trial of bexarotene in moderate Alzheimer's disease. *Alzheimers Res Ther*. 2016;8(1):4. doi:10.1186/s13195-016-0173-2

141. Gordon JL, Peltier A, Grummisch JA, Sykes Tottenham L. Estradiol Fluctuation, Sensitivity to Stress, and Depressive Symptoms in the Menopause Transition: A Pilot Study. *Front Psychol*. 2019;10. doi:10.3389/fpsyg.2019.01319

142. Thomas N, Gurvich C, Hudaib A-R, Gavrilidis E, Kulkarni J. Dissecting the syndrome of

schizophrenia: Associations between symptomatology and hormone levels in women with schizophrenia. *Psychiatry Res*. 2019;280:112510. doi:10.1016/j.psychres.2019.112510

143. Dwyer JB, Aftab A, Radhakrishnan R, et al. Hormonal Treatments for Major Depressive Disorder: State of the Art. *Am J Psychiatry*. 2020;177(8):686-705. doi:10.1176/appi.ajp.2020.19080848

144. Meinhard N, Kessing LV, Vinberg M. The role of estrogen in bipolar disorder, a review. *Nord J Psychiatry*. 2014. doi:10.3109/08039488.2013.775341

145. De Boer J, Prikken M, Lei WU, Begemann M, Sommer I. The effect of raloxifene augmentation in men and women with a schizophrenia spectrum disorder: A systematic review and meta-analysis. *npj Schizophr*. 2018. doi:10.1038/s41537-017-0043-3

146. Popovic D, Schmitt A, Kaurani L, et al. Childhood Trauma in Schizophrenia: Current Findings and Research Perspectives. *Front Neurosci*. 2019;13:274. doi:10.3389/fnins.2019.00274

147. Aas M, Henry C, Andreassen OA, Bellivier F, Melle I, Etain B. The role of childhood trauma in bipolar disorders. *Int J bipolar Disord*. 2016;4(1):2. doi:10.1186/s40345-015-0042-0

148. ter Heegde F, De Rijk RH, Vinkers CH. The brain mineralocorticoid receptor and stress resilience. *Psychoneuroendocrinology*. 2015;52:92-110. doi:10.1016/j.psyneuen.2014.10.022

149. Endedijk HM, Nelemans SA, Schür RR, et al. The Role of Stress and Mineralocorticoid Receptor Haplotypes in the Development of Symptoms of Depression and Anxiety During Adolescence. *Front Psychiatry*. 2020;11. doi:10.3389/fpsyt.2020.00367

150. Vinkers CH, Joëls M, Milaneschi Y, et al. Mineralocorticoid receptor haplotypes sex-dependently moderate depression susceptibility following childhood maltreatment. *Psychoneuroendocrinology*. 2015;54:90-102. doi:10.1016/j.psyneuen.2015.01.018

151. Bordoni A, Di Nunzio M, Danesi F, Biagi PL. Polyunsaturated fatty acids: From diet to binding to ppars and other nuclear receptors. *Genes Nutr*. 2006;1(2):95-106. doi:10.1007/BF02829951

152. Lengqvist J, Mata de Urquiza A, Bergman A-C, et al. Polyunsaturated Fatty Acids Including Docosahexaenoic and Arachidonic Acid Bind to the Retinoid X Receptor α Ligand-binding Domain. *Mol Cell Proteomics*. 2004;3(7):692-703. doi:10.1074/mcp.M400003-MCP200

153. van Neerven S, Kampmann E, Mey J. RAR/RXR and PPAR/RXR signaling in neurological and psychiatric diseases. *Prog Neurobiol*. 2008;85(4):433-451. doi:10.1016/j.pneurobio.2008.04.006

154. O'Sullivan SE. Cannabinoids go nuclear: evidence for activation of peroxisome

proliferator-activated receptors. *Br J Pharmacol*. 2007;152(5):576-582. doi:10.1038/sj.bjp.0707423

155. Leweke FM, Koethe D. Cannabis and psychiatric disorders: it is not only addiction. *Addict Biol*. 2008;13(2):264-275. doi:10.1111/j.1369-1600.2008.00106.x

156. Velmeshev D, Schirmer L, Jung D, et al. Single-cell genomics identifies cell type–specific molecular changes in autism. *Science (80-)*. 2019;364(6441):685-689. doi:10.1126/science.aav8130

157. Sarachana T, Hu VW. Genome-wide identification of transcriptional targets of RORA reveals direct regulation of multiple genes associated with autism spectrum disorder. *Mol Autism*. 2013;4(1):14. doi:10.1186/2040-2392-4-14

158. Kojetin DJ, Burris TP. REV-ERB and ROR nuclear receptors as drug targets. *Nat Rev Drug Discov*. 2014;13(3):197-216. doi:10.1038/nrd4100

159. Nguyen A, Rauch TA, Pfeifer GP, Hu VW. Global methylation profiling of lymphoblastoid cell lines reveals epigenetic contributions to autism spectrum disorders and a novel autism candidate gene, RORA , whose protein product is reduced in autistic brain. *FASEB J*. 2010;24(8):3036-3051. doi:10.1096/fj.10-154484

160. Jetten AM. Retinoid-Related Orphan Receptors (RORs): Critical Roles in Development, Immunity, Circadian Rhythm, and Cellular Metabolism. *Nucl Recept Signal*. 2009;7(1):nrs.07003. doi:10.1621/nrs.07003

161. Grayaa S, Zerbinati C, Messedi M, et al. Plasma oxysterol profiling in children reveals 24-hydroxycholesterol as a potential marker for Autism Spectrum Disorders. *Biochimie*. 2018;153:80-85. doi:10.1016/j.biochi.2018.04.026

162. de Vera IMS, Giri PK, Munoz-Tello P, et al. Identification of a Binding Site for Unsaturated Fatty Acids in the Orphan Nuclear Receptor Nurr1. *ACS Chem Biol*. 2016;11(7):1795-1799. doi:10.1021/acschembio.6b00037

163. Willems S, Kilu W, Ni X, et al. The orphan nuclear receptor Nurr1 is responsive to non-steroidal anti-inflammatory drugs. *Commun Chem*. 2020;3(1):85. doi:10.1038/s42004-020-0331-0

164. Pan T, Zhu W, Zhao H, et al. Nurr1 deficiency predisposes to lactacystin-induced dopaminergic neuron injury in vitro and in vivo. *Brain Res*. 2008;1222:222-229. doi:10.1016/j.brainres.2008.05.022

165. Decressac M, Volakakis N, Björklund A, Perlmann T. NURR1 in Parkinson disease—from pathogenesis to therapeutic potential. *Nat Rev Neurol*. 2013;9(11):629-636. doi:10.1038/nrneurol.2013.209

166. Zhou J, Oakley RH, Cidlowski JA. DAX-1 (Dosage-Sensitive Sex Reversal-Adrenal Hypoplasia Congenita Critical Region on the X-Chromosome, Gene 1) Selectively Inhibits Transactivation But Not Transrepression Mediated by the Glucocorticoid Receptor in a LXXLL-Dependent Manner. *Mol Endocrinol*. 2008;22(7):1521-1534. doi:10.1210/me.2007-0273

167. Obradović D, Tirard M, Némethy Z, Hirsch O, Gronemeyer H, Almeida OFX. DAXX, FLASH, and FAF-1 Modulate Mineralocorticoid and Glucocorticoid Receptor-Mediated Transcription in Hippocampal Cells—Toward a Basis for the Opposite Actions Elicited by Two Nuclear Receptors? *Mol Pharmacol*. 2004;65(3):761-769. doi:10.1124/mol.65.3.761

168. Zhao L, Zhou S, Gustafsson JÅ. Nuclear Receptors: Recent Drug Discovery for Cancer Therapies. *Endocr Rev*. 2019. doi:10.1210/er.2018-00222

169. Santos R, Ursu O, Gaulton A, et al. A comprehensive map of molecular drug targets. *Nat Rev Drug Discov*. 2016. doi:10.1038/nrd.2016.230

170. Marciano DP, Chang MR, Corzo CA, et al. The therapeutic potential of nuclear receptor modulators for treatment of metabolic disorders: PPARγ, RORs, and Rev-erbs. *Cell Metab*. 2014;19(2):193-208. doi:10.1016/j.cmet.2013.12.009

171. McKenna NJ. Research resources for nuclear receptor signaling pathways. *Mol Pharmacol*. 2016;90(2):153-159. doi:10.1124/mol.116.103713

172. Corona JC, Duchen MR. PPARγ as a therapeutic target to rescue mitochondrial function in neurological disease. *Free Radic Biol Med*. 2016;100:153-163. doi:10.1016/j.freeradbiomed.2016.06.023

173. Moutinho M, Codocedo JF, Puntambekar SS, Landreth GE. Nuclear Receptors as Therapeutic Targets for Neurodegenerative Diseases: Lost in Translation. *Annu Rev Pharmacol Toxicol*. 2019;59:237-261. doi:10.1146/annurev-pharmtox-010818-021807

174. Kim C-H, Han B-S, Moon J, et al. Nuclear receptor Nurr1 agonists enhance its dual functions and improve behavioral deficits in an animal model of Parkinson's disease. *Proc Natl Acad Sci*. 2015;112(28):8756-8761. doi:10.1073/pnas.1509742112

175. Tong M, Dominguez C. Targeting Alzheimer's Disease Neuro-Metabolic Dysfunction with a

Small Molecule Nuclear Receptor Agonist (T3D-959) Reverses Dise ase Pathologies. *J Alzheimer's Dis Park*. 2016;6(3). doi:10.4172/2161-0460.1000238

176. Sharma RP. Schizophrenia, epigenetics and ligand-activated nuclear receptors: a framework for chromatin therapeutics. *Schizophr Res*. 2005;72(2-3):79-90. doi:10.1016/j.schres.2004.03.001

177. Carta MG, Paribello P, Preti A. How promising is neuroactive steroid drug discovery? *Expert Opin Drug Discov*. 2018;13(11):993-995. doi:10.1080/17460441.2018.1518974

178. Lerner V, Miodownik C, Gibel A, et al. The Retinoid X Receptor Agonist Bexarotene Relieves Positive Symptoms of Schizophrenia. *J Clin Psychiatry*. 2013;74(12):1224-1232. doi:10.4088/JCP.12m08160

179. Touma KTB, Zoucha AM, Scarff JR. Liothyronine for Depression: A Review and Guidance for Safety Monitoring. *Innov Clin Neurosci*. 14(3-4):24-29. http://www.ncbi.nlm.nih.gov/pubmed/28584694.

180. Layton A. The use of isotretinoin in acne. *Dermatoendocrinol*. 2009;1(3):162-169. doi:10.4161/derm.1.3.9364

181. Song X, Chen J, Zhao M, et al. Development of potent small-molecule inhibitors to drug the undruggable steroid receptor coactivator-3. *Proc Natl Acad Sci U S A*. 2016. doi:10.1073/pnas.1604274113

182. Raj G V., Sareddy GR, Ma S, et al. Estrogen receptor coregulator binding modulators (ERXs) effectively target estrogen receptor positive human breast cancers. *Elife*. 2017. doi:10.7554/eLife.26857

183. Wang L, Cheng CM, Qin J, et al. Small-molecule inhibitor targeting orphan nuclear receptor COUP-TFII for prostate cancer treatment. *Sci Adv*. 2020;6(18):1-12. doi:10.1126/sciadv.aaz8031