Spatial and functional profiles distinguish target sets of Parkinson's disease and antipsychotic drugs with different clinical effects.

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Spatial and functional profiles distinguish target sets of Parkinson's disease and antipsychotic drugs with different clinical effects

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Several studies have examined the genetic factors shared between Parkinson's disease (PD) and schizophrenia (SZ), but the biological themes underlying their clinical relationships remain less explored. We employed systematic transcriptomic and network analyses to examine the genes targeted by two sets of antipsychotic drugs (APDs) – first-generation APDs inducing Parkinsonism and second-generation APDs typically effective against psychotic symptoms in PD – and two sets of PD drugs, one at risk of psychosis and the other with a lower risk of psychosis. Although global brain expression patterns did not effectively differentiate between the targets of the two sets of APDs, they did differentiate the targets of the two PD drug sets. However, both APD and PD target sets showed differences in mean expression levels in specific brain regions. Moreover, they showed significant enrichment for genes highly expressed in distinct adult and prenatal brain structures relative to the overall distribution of such genes among all brain-expressed genes. Specific neurotransmitter systems, either individually or in combinations, appeared to underlie the clinically informed drug categories, indicating their differential roles in inducing or not inducing PD and psychosis. Additionally, the target sets formed distinct network modules representing different biological mechanisms and exhibited differential proximity to putative PD and SZ risk genes in the human interactome. In summary, our study identified specific spatial and functional features that distinguish the target sets of PD and antipsychotic drugs with different clinical effects.

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INTRODUCTION

The clinical relationship between Parkinson's disease (PD) and schizophrenia (SZ) is complex. Drugs used for treating PD increase the risk of patients developing psychotic symptoms [1–3], while those used for treating SZ induce various motor symptoms, including Parkinsonism, dystonia, and dyskinesia [4]. Drug-induced Parkinsonism is the second most common cause of Parkinsonian symptoms in patients, after PD [4, 5]. It is frequently misdiagnosed as PD, often leading to the use of anti-PD drugs instead of discontinuation of the antipsychotic drugs (APDs) responsible for the condition. Although withdrawal of APDs usually helps manage the symptoms, 10–50% of patients may experience persistent symptoms due to APD-induced damage of the dopamine receptors or symptom exacerbation from underlying preclinical factors predisposing to PD [4]. First-generation antipsychotic drugs (FGAs), including sertindole, loxapine, perphenazine, prochlorperazine, chlorpromazine, haloperidol, and sulpiride, with high dopamine D_2 receptor affinity, tend to induce Parkinsonism [6]. Second-generation antipsychotic drugs (SGAs), such as aripiprazole, ziprasidone, quetiapine, and clozapine, which block both serotonin 5-HT_{2A} receptor and D_2 receptor and exhibit different drug-D_2 receptor disassociation profiles compared to FGAs, also induce Parkinsonism, albeit with prolonged use [4, 7, 8]. Of these, clozapine demonstrates the lowest propensity to induce Parkinsonism and is often used to manage psychotic symptoms in PD patients [9]. Anti-PD drugs, such as levodopa and selegiline, induce visual hallucinations and paranoid delusions in 20–30% of PD patients [10], depending on multiple factors such as age, disease severity, comorbidities and schizotypy in individuals [11–13]. The symptoms often subside upon withdrawal of these drugs, albeit aggravating Parkinsonism.

While PD and SZ have distinct mechanisms as disorders, their overlap increases with drug administration. Despite some insightful case studies on PD-SZ comorbidity management [3, 14–16], the broader biological themes underlying the clinical relationships of the two disorders remain less explored. The effects of APDs and PD drugs on PD and SZ symptoms are likely influenced by complex factors, including regional drug action [17–21], impact on multiple neurotransmitter systems and other biological mechanisms [22–25], and drug target interactions with PD and SZ genetic risk factors [26, 27]. In this study, we systematically analysed the targets of APD and PD drugs to elucidate patterns in their transcriptomic and interactomic (i.e., the protein-protein interaction network) landscapes that can explain their distinct effects on PD and SZ symptoms, respectively. Specifically, we examined whether brain expression trends help distinguish the targets of drugs with and without side effects. We also examined whether these targets participate in distinct biological mechanisms and

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show specific associations with genes harbouring PD- and SZ-associated variations in the interactome, based on the tendency of the drugs to induce or not induce side effects.

RESULTS

Compilation of antipsychotic and PD drug targets

To examine APD and PD drug targets, we adopted a systematic approach involving transcriptomic and network analyses (Fig. 1). We collected PD and antipsychotic drugs from the Drug Bank database [28] and categorised them based on their clinical activity in SZ and PD respectively, using the TWOSIDES database [29], a compendium of drugs and their contraindications. The drugs were grouped into four categories: (i) seven FGAs known to induce Parkinsonism: sertindole, loxapine, perphenazine, prochlorperazine, chlorpromazine, haloperidol, and sulpiride, (ii) six SGAs used for managing psychotic symptoms in PD: olanzapine, risperidone, clozapine, ziprasidone, aripiprazole, and quetiapine, (iii) five PD drugs that are at risk of inducing psychosis: levodopa, ropinirole, biperiden, selegiline and entacapone, and (iv) seventeen PD drugs that are at lower risk of inducing psychosis: amantadine, benserazide, bornaprine, bromocriptine, carbidopa, droxidopa, istradefylline, melevodopa, opicapone, pergolide, piribedil, pramipexole, profenamine, rasagiline, rotigotine, safinamide, and tolcapone (see **Methods**). A detailed explanation of the drug categorisation can be found in Supplementary Methods. To identify the proteins targeted by these drugs, we used the drug-gene interaction database (DGIdb) [30]. The numbers of proteins targeted by each drug category were as follows: (i) 90, (ii) 133, (iii) 33, and (iv) 52 proteins (Supplementary Data File 1).

To study the shared and distinct effects of APDs on Parkinsonian symptoms, we compiled three drug target sets (Supplementary Fig. 1a), namely, that of targets (1) common to both FGAs and SGAs, (2) exclusive to FGAs, and (3) exclusive to SGAs. Similarly, to examine the PD drugs differing in their tendency to induce psychotic symptoms, we assembled three drug target sets (Supplementary Fig. 1b), namely, that of targets (1) shared among the PD drugs, irrespective of their risk of inducing psychosis, (2) unique to PD drugs at risk of psychosis, and (3) unique to PD drugs at lower risk of psychosis.

Trends in antipsychotic and PD drug target expression distributions in the brain

Our primary objective was to use principal component analysis (PCA) to determine whether distinct brain regions help distinguish targets of drugs that induce side effects, from targets of drugs that do not. We aimed to predict with confidence that genes targeted by drugs inducing or not inducing side effects tend to cluster within distinct areas on the principal component (PC) plot, exhibiting specific characteristics (e.g., gene expression variations, regional specificities, etc.). We compiled the spatial expression profiles of the genes encoding the drug targets from the normalised adult brain microarray dataset of Allen Brain Atlas (see **Methods**) [31]. PCA was performed using the ClustVis toolkit [32]. The input matrices contained the $\log_2$-transformed average probe intensities of antipsychotic and PD drug target genes, categorised as shared or unique targets, across the 13 regions in the dataset. Note that unless stated otherwise, normalised transcriptomic data is used for analysis.

In PCA of APD targets, PC1 and PC2 captured 94.5% and 2.7% of the expression variance, respectively. Figure 2a shows the component scores of specific categories of APD targets, calculated as linear combinations of the original variables (i.e., average gene expression in 13 major brain areas) and their corresponding loading strengths. Three prediction ellipses effectively enclosed the three drug target groups (shared FGA/SGA targets, unique FGA targets and unique SGA targets) with a high predictive accuracy of 95%, indicating that a new observation from the same category is highly likely to fall within the ellipse (Fig. 2a). However, the three groups of genes clustered together, with overlapping prediction ellipses, indicating similar expression patterns. To identify regional contributions to the grouping patterns shown in Fig. 2a, we evaluated regional loading strengths [33] on PC1 (the axis that captures the maximum variance in the expression data). As shown in Fig. 2b, all 13 brain regions played comparable roles in producing the scatter along PC1, likely suggesting widespread effects of the drugs in the brain. Nevertheless, the size of the ellipses indicated differences in expression variability among the three groups (Fig. 2a). The shared targets exhibited higher variability compared to the unique targets of SGAs and FGAs.

In the case of PD drug targets, PC1 and PC2 respectively accounted for 92.5% and 3.5% of the variance (Fig. 2c). The shared targets of PD drugs, regardless of their risk of inducing psychosis, and the unique targets of PD drugs at risk of psychosis exhibited overlapping expression patterns of reduced variability. On the other hand, the targets of PD drugs with lower risk of psychosis showed high expression variability. The corresponding ellipse encompassed the ellipses of the former two groups. All the 13 brain areas contributed equally to the scatter plot (Fig. 2d).

Altogether, while global expression patterns did not differentiate between the target sets of FGAs and SGAs with varied Parkinsonism outcomes, a notable difference in global expression variability emerged between PD drugs at risk of psychosis and at lower risk of inducing psychosis.

Next, we assessed whether genes in Fig. 2a and c were primarily influenced by drugs with specific mechanisms of action (Supplementary Note 1, Supplementary Data Files 2–3 and Supplementary Figs. 2–7). Dopaminergic system-targeting drugs influenced shared APD and unique FGA targets, while drugs acting on multiple systems, including adrenergic, dopaminergic, histamine, serotonergic, and gamma-aminobutyric acid (GABA) systems, influenced unique SGA targets. Dopamine precursors and decarboxylase inhibitors predominantly influenced shared targets of PD drugs and PD drugs at risk of psychosis, whereas drugs acting on adrenergic, dopaminergic, and serotonergic systems, as agonists or antagonists, and monoamine oxidase inhibitors influenced targets of PD drugs at lower risk of psychosis.

Regional specificities of antipsychotic and PD drug targets

From PCA, brain areas appeared to contribute equally to the expression distributions of drug targets. However, we investigated the region-wise normalised gene expression distributions in greater detail. Specifically, we examined whether regional statistically significant differences existed among the drug target categories. Unique targets of FGAs exhibited higher expression than the unique targets of SGAs across all 13 brain areas (Fig. 3a–m), with the most significant differences observed in the midbrain (Wilcoxon rank-sum test: p-value = 0.018), diencephalon (p-value = 0.019), and pons (p-value = 0.019). This suggested that the tendency of FGAs to induce Parkinsonism could be attributed to their strong influence on PD-related regions such as the midbrain. The mean expression levels of the unique targets of PD drugs at risk of psychosis were found to be higher than those of the unique targets of PD drugs at lower risk of inducing psychosis across ten brain areas (Fig. 3n–z). This difference was highly statistically significant in the white matter (Wilcoxon test: p-value = 1.3E-03) – including at the level of its subdivisions, namely, the cingulum bundle (p-value = 2.3E-03) and the corpus callosum (p-value = 1.8E-03) (Supplementary Fig. 8) – and the cerebellum (p-value = 0.018), medulla oblongata (p-value = 0.031), and pons (p-value = 0.034). PD drug action in these regions could be responsible for the induction or aggravation of psychotic symptoms.

Shifting our focus away from global distribution patterns and regional mean expression levels, we now examined whether

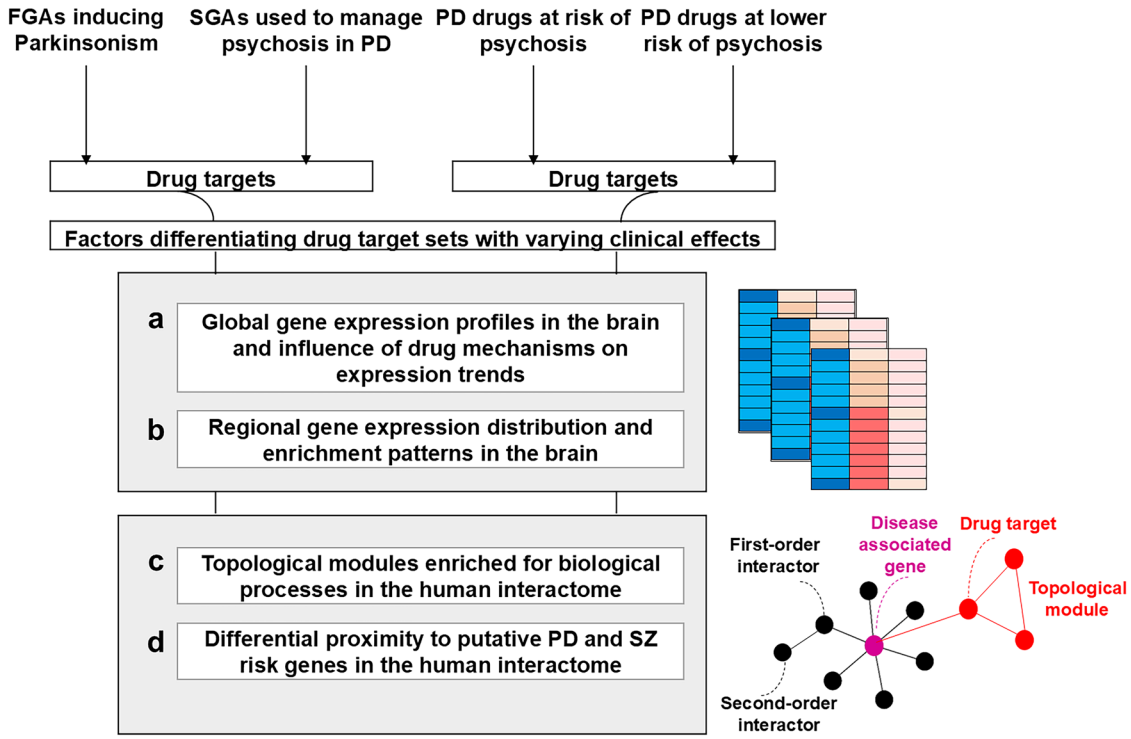

Fig. 1 Flow chart depicting the concepts examined in the study. Antipsychotic drugs exhibiting two distinct clinical effects were collected, specifically, first-generation antipsychotics (FGAs) causing Parkinsonism and second-generation antipsychotics (SGAs) used to manage psychotic symptoms in Parkinson's disease (PD). Similarly, PD drugs with two effects were compiled, those at risk of inducing psychosis and those at lower risk of psychosis. The genes targeted by these four drug categories were identified. Subsequently, we investigated four factors (**a**–**d**) that could potentially help differentiate the target sets of PD and antipsychotic drugs with varying clinical effects: **a** The global expression trends of the drug targets in the brain and the impact of the different neurotransmitter systems that the drugs regulate on these trends; **b** The regional variations in the expression levels of drug targets and their numerical overrepresentation among genes highly expressed in specific brain regions; **c** The topological modules formed by the drug targets in the human interactome and their enrichment for specific biological processes; **d** The proximity of the drug targets to genes associated with PD and SZ, as well as their first-order and second-order interactors.

genes highly expressed in specific brain regions were more prevalent (i.e., numerically overrepresented) among the targets of a specific drug category (compared to all brain-expressed genes).

For the analysis, we compiled gene lists from four normalised transcriptomic datasets (Supplementary Methods): (i) RNA-sequencing data covering 26 brain regions during development [34], (ii) prenatal microarray data of 516 prenatal structures [31], (iii) adult microarray data encompassing 232 brain structures [31], all sourced from Allen Brain Atlas, and (iv) the RNA-sequencing data of 13 adult brain regions from GTEx [35].

To identify the regions associated with the six drug target sets, we used hypergeometric tests to examine the distribution of genes highly expressed in specific regions within these sets. A p-value < 0.05, obtained after correction for multiple hypotheses using the Benjamini-Hochberg (BH) method was considered statistically significant. The shared targets of FGAs, SGAs and PD drugs (irrespective of whether they induce psychosis or not) were enriched for expression in the caudate nucleus and putamen (Fig. 4a, d). This can be attributed to the predominant action of these drugs on dopamine pathways and the high density of dopamine receptors in these brain structures [36]. Additionally, the shared targets of FGAs and SGAs showed enrichment in the prenatal amygdalostriatal transition area (Fig. 4a). The unique targets of FGAs were enriched in the amygdala, hippocampus, and anterior cingulate cortex (Fig. 4b). On the other hand, the unique targets of SGAs were enriched in the prenatal reticular and centromedian nuclei of the thalamus and the adult pontine central grey, suggesting the involvement of the serotonergic pathway (Fig. 4c). Finally, the unique targets of PD drugs at lower risk for psychosis showed expression in the adult hypothalamus and the prenatal periventricular nucleus (Fig. 4e). To delineate the implications of drug target enrichment in foetal structures, we identified the specific targets responsible for these enrichments and their involvement in biological processes (Supplementary Note 2).

Overall, regional variations in mean expression levels and numerical enrichment for region-specific genes help distinguish the target sets of drugs with different clinical effects.

Network modules of antipsychotic and PD drug targets in the human interactome

Interestingly, we noted a higher-than-expected number of functional associations, including protein-protein interactions (PPIs), among the APD targets and the PD drug targets, separately (Supplementary Note 3). This prompted us to examine the higher-order relationships of these target sets in the protein interactome [37–39]. For this, we generated the networks of the drug targets shared between or exclusive to FGAs and SGAs (Fig. 5a–c) and the networks of the targets shared between or exclusive to PD drugs at risk or lower risk of inducing psychosis (Fig. 5d–f) using the STRING database [40]. We then identified topological modules within these networks using the Markov Clustering (MCL) algorithm. Enriched Gene Ontology biological processes in these modules were determined using hypergeometric tests (p-value < 0.05 after correction for multiple hypotheses). We hypothesized that the modules and the associated biological processes likely influenced the clinical effects of the drugs.

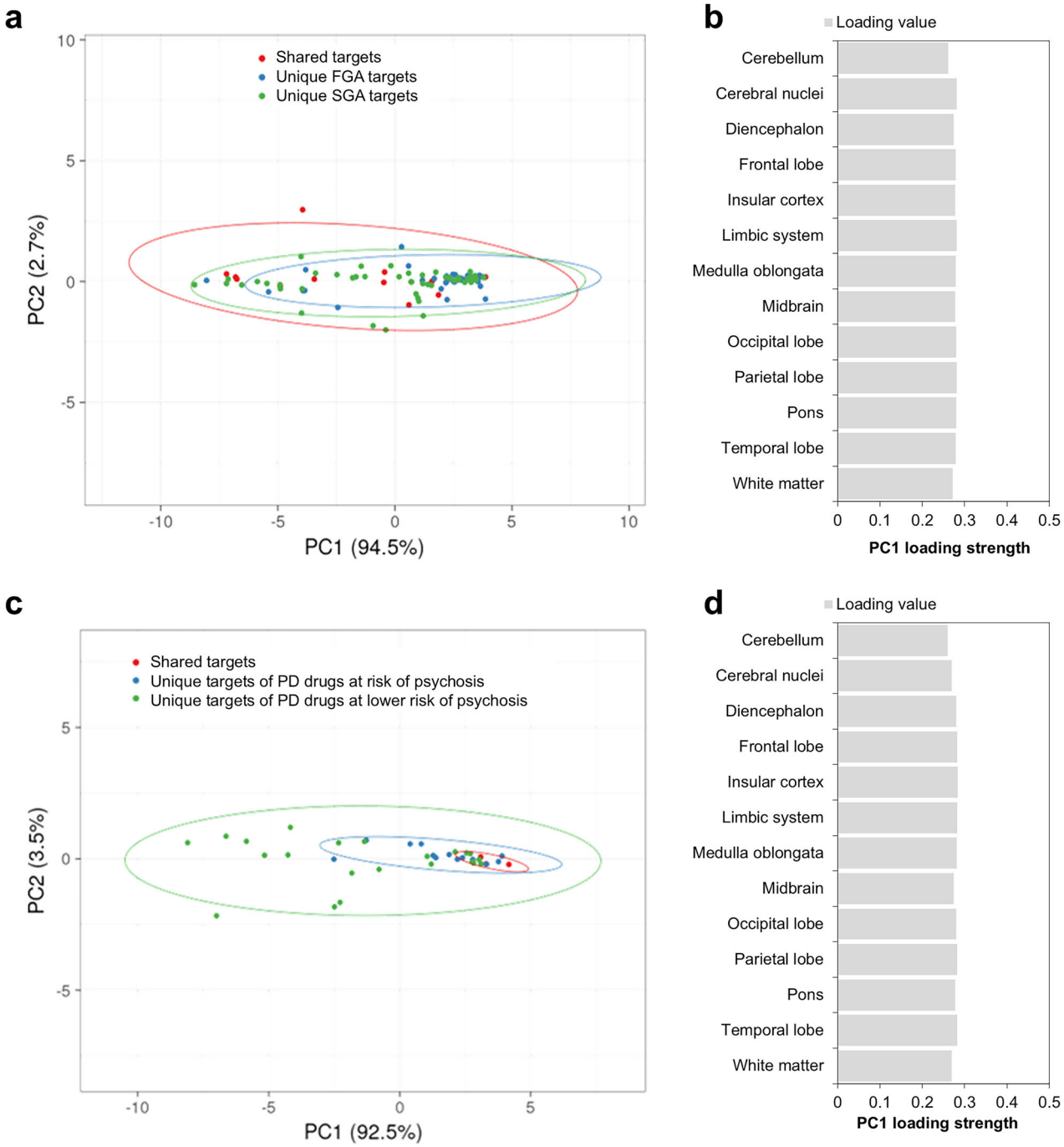

Fig. 2 Principal component analysis of the drug targets revealed their clustering into overlapping ellipses, albeit of differing expression variability in the brain. PCA was performed with the $\log_2$-transformed probe intensities of the drug targets in 13 major brain areas in the microarray dataset of Allen Brain Atlas. A data matrix with brain regions (rows) and the drug targets (columns) was constructed out of these log-transformed values. Unit variance scaling was applied across this matrix for normalisation. Singular value decomposition with imputation was used to extract the principal components (PCs). In **a**, the component scores ($n = 93$) corresponding to PC1 and PC2 explaining 94.5% and 2.7% of the total variance have been plotted along X and Y axes respectively. The three prediction ellipses correspond to the shared targets of FGAs and SGAs (red), the unique targets of FGAs (blue), and the unique targets of SGAs (green). The probability of a new data point from the same group falling within these ellipses is 0.95. In **b**, the loading strengths of the 13 dimensions, i.e., the brain regions, contributing to PC1, have been shown. In **c**, the component scores ($n = 38$) corresponding to PC1 and PC2 explaining 92.5% and 3.5% of the total variance have been plotted along X and Y axes respectively. The three prediction ellipses correspond to the shared targets of the PD drugs irrespective of whether they induce psychosis or not (red), the unique targets of PD drugs at risk of psychosis (blue), and the unique targets of PD drugs at lower risk of psychosis (green). In **d**, the loading strengths of the brain regions contributing to PC1 have been shown.

From the network of drug targets shared between FGAs and SGAs, we identified five modules enriched for dopaminergic, serotonergic and adrenergic signalling, dopamine and serotonin clearance, and FYN proto-oncogene activation downstream of neurotrophic receptor tyrosine kinase 2 (Fig. 5a). These processes likely contribute to the common pharmacological effects observed in both FGAs and SGAs. From the network of exclusive FGA targets, we found two modules enriched in adrenergic and

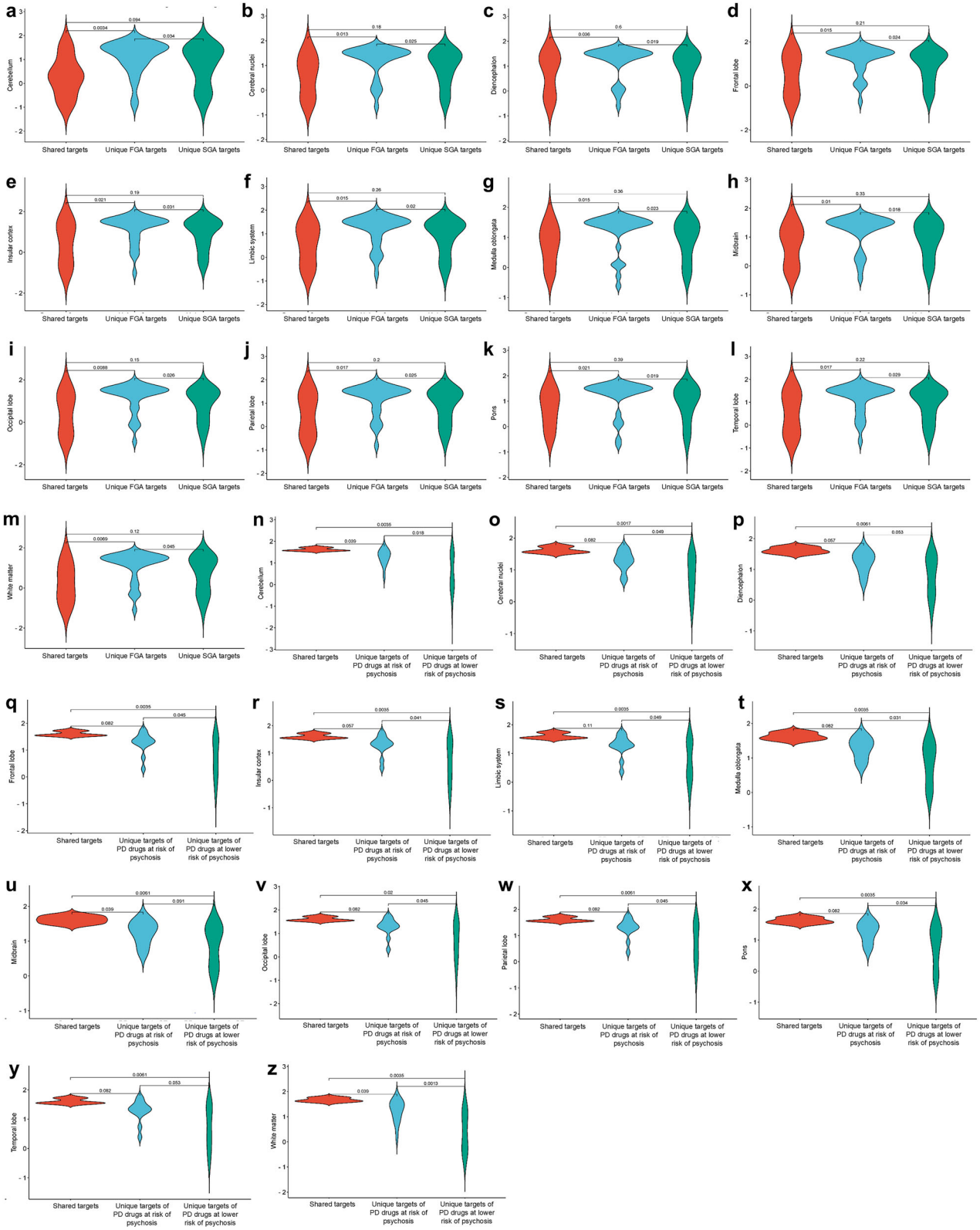

Fig. 3 The targets of FGAs and SGAs and PD drugs at risk (or not) of inducing psychosis exhibit differences in region-wise gene expression distributions. The varying average probe intensity distributions of the shared targets of FGAs and SGAs (red), the unique targets of FGAs (blue), and the unique targets of SGAs (green) in 13 major brain areas (see Y axes) have been shown using the violin plots in **a**–**m**. The varying average probe intensity distributions of the shared targets of PD drugs irrespective of whether they induce psychosis or not (red), the unique targets of PD drugs at risk of psychosis (blue), and the unique targets of PD drugs at lower risk of psychosis (green) in 13 major brain areas (see Y axes) have been shown using the violin plots in **n**–**z**. In **a**–**z**, the *p*-values denoting the statistical differences between pairs of drug target categories were computed using the Wilcoxon rank sum test and adjusted for multiple hypotheses using the Benjamini-Hochberg method.

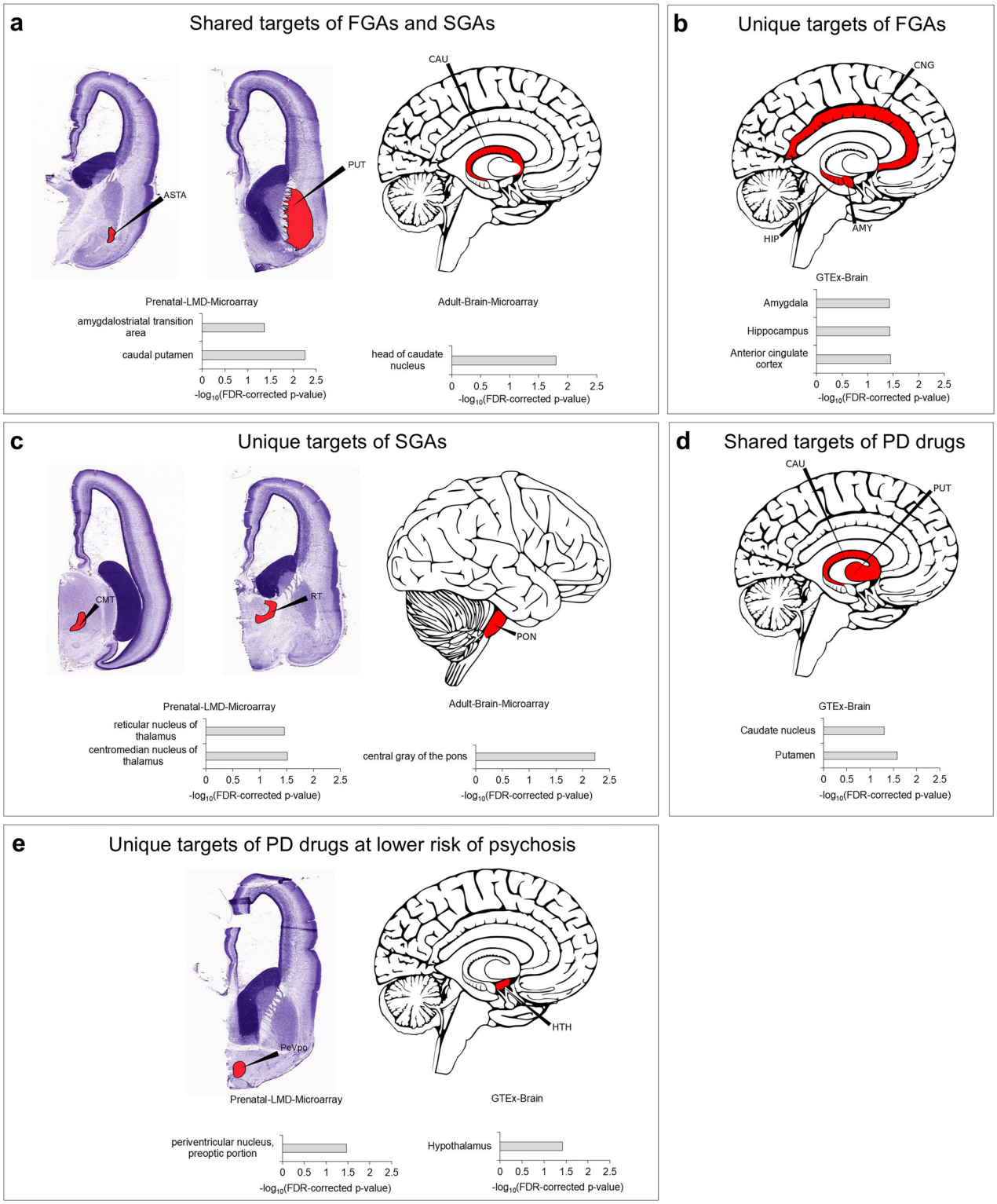

Fig. 4 Antipsychotic and PD drug targets showed differential enrichment patterns in specific brain regions. The enrichment of the drug targets for genes showing high expression in specific regions extracted during prenatal stages (LMD microarray dataset), from adults (Allen Brain Atlas microarray and GTEx RNA-sequencing datasets), and during prenatal and adult stages (Allen Brain Atlas developmental transcriptome RNA-sequencing dataset), was examined. **a–c** show the specific areas in which the shared and unique targets of SGAs and FGAs are highly expressed, with the adult areas marked in brain maps and the prenatal areas highlighted against the background of Nissl-stained brain sections (Interactive Atlas Viewer, Allen Brain Atlas). **d** and **e** show the specific areas in which the shared targets of PD drugs and the unique targets of PD drugs at lower risk of psychosis are highly expressed. The accompanying bar graphs show the $-\log_{10}(p\text{-value})$ of enrichment after correction for multiple hypotheses using the Benjamini-Hochberg method. Note that the specific regions that showed enrichment at p-value < 0.05 after correction (i.e., $-\log_{10}(p\text{-value}) > 1.30103$) are shown in the brain maps and Nissl-stained brain sections.

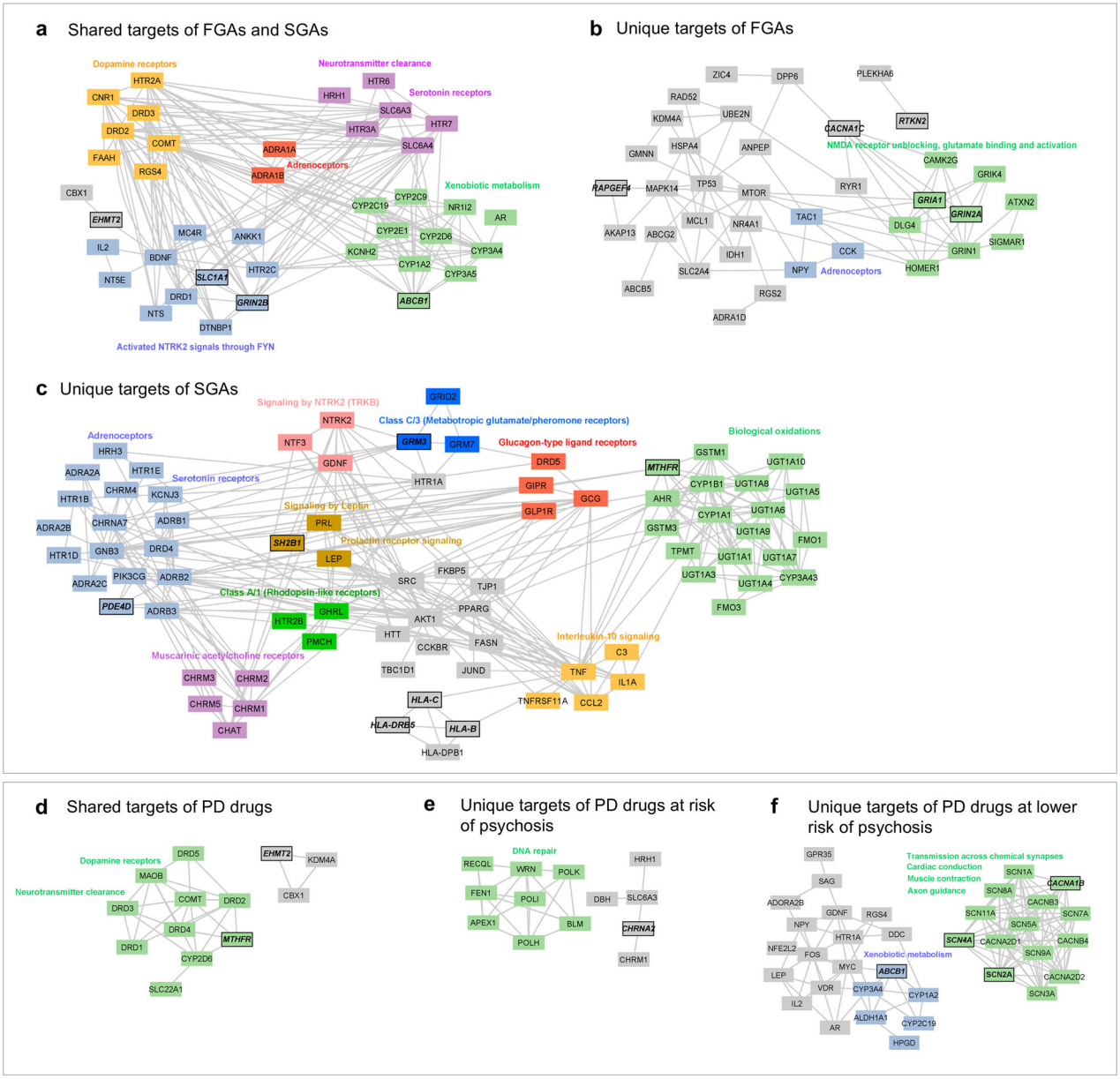

Fig. 5 FGA and SGA targets and targets of PD drugs at risk of psychosis and at lower risk of psychosis are involved in different network modules in the human interactome. The networks of the proteins targeted by **a** shared targets of FGAs and SGAs, **b** unique targets of FGAs, **c** unique targets of SGAs, **d** shared targets of PD drugs, **e** unique targets of PD drugs at risk of psychosis and **f** unique targets of PD drugs at lower risk of psychosis, were constructed using the STRING database. Network nodes represent proteins and edges represent protein-protein associations retrieved from the STRING database. The topological modules in these networks were identified using the MCL algorithm. The nodes in the topological modules enriched for specific biological processes have been denoted using separate colours. In **a**–**c**, genes shown in bold italics are unique SZ-associated genes (that are not associated with PD) found in the network. In **d**–**f**, genes shown in bold are unique PD-associated genes (that are not associated with SZ) and those shown in bold italics are unique SZ-associated genes (that are not associated with PD) found in the network.

glutamatergic signalling pathways (Fig. 5b). Compared to FGAs, the network of exclusive SGA targets revealed drug action in a broader range of neurotransmitter pathways through nine modules (Fig. 5c), including adrenergic, serotonin, muscarinic cholinergic receptor and neurotrophic receptor tyrosine kinase 2 signalling, as well as interleukin and leptin signalling. They likely account for the beneficial effects of SGAs in PD, such as managing comorbid psychosis without exacerbating Parkinsonism. We additionally explored whether the wide-ranging effects of the unique SGA targets could be attributed to single drugs, like clozapine [41], known to interact with multiple receptors (Supplementary Note 4 and Supplementary Fig. 9).

A topological module enriched for dopaminergic signalling and neurotransmitter clearance was identified from the target network of PD drugs, regardless of whether they induce psychosis or not (Fig. 5d), suggesting the involvement of these pathways in the common pharmacological effects of PD drugs. The network of drug targets exclusive to PD drugs at risk of psychosis revealed a module enriched for DNA repair processes (Fig. 5e), suggesting the involvement of these processes in the unique side effects produced by this category of PD drugs. In the network of drug targets exclusive to PD drugs at lower risk for psychosis, a topological module enriched for neurotransmission, cardiac conduction, muscle contraction, and axon guidance was detected

(Fig. 5f), indicating the role of these processes in governing the beneficial effects of this category of PD drugs.

The results indicated that drug target sets formed distinct modules with specific biological functions in the human interactome. These functions likely influenced the clinical effects of the drugs.

Relationship of antipsychotic drug targets to putative PD and SZ risk genes in the human interactome

We examined the enrichment of the FGA and SGA targets among genes exclusively associated with SZ, exclusively associated with PD, and shared between PD and SZ, and their immediate interactors (i.e., first-order interactors) and their interactors two steps removed (i.e., second-order interactors) in the neighbourhood network. For this, 795 genes harboring SZ-associated variations, 137 genes with PD-associated variations and 18 with variations linked to both disorders, were collected from the DisGeNET database [42]. Each of these genes had a stringent disease association score cutoff of 0.7 or higher (Supplementary Data File 4). PPI data was collected from BioGRID [43] and HPRD [44] (see **Methods**).

Fig. 6a, b shows that FGA targets were exclusively enriched among the first-order interactors of unique PD genes. These first-order interactors were particularly enriched for monoamine transport-related genes (BH-corrected p-value = 2.07E-05; *SLC6A4*, *DRD2*, *DTNBP1*, and *TOR1A*). On the other hand, Fig. 6c, d shows that SGA targets were enriched for the unique SZ genes themselves, rather than their interactors. Fourteen SZ genes were responsible for this enrichment, namely, *ABCB1*, *EHMT2*, *GRIN2B*, *GRM3*, *HLA-B*, *HLA-C*, *HLA-DRB3*, *HLA-DRB5*, *ITIH3*, *MSANTD1*, *MTHFR*, *PDE4D*, *SH2B1* and *SLC1A1*. Statistically significant enrichment for interferon signalling was detected from these genes (BH-corrected p-value = 6.29E-03; *HLA-B*, *HLA-C*, *HLA-DRB3*, and *HLA-DRB5*). This enrichment remains significant even after applying a more conservative FDR-correction test [45] (p-value = 6.14E-03). No significant signals were observed for PD drug targets. Altogether, this suggested that the tendency for FGA targets to directly interact with PD-associated genes and SGA targets to be SZ-associated genes likely contributed to their distinct clinical effects.

DISCUSSION

In this study, we employed systematic transcriptomic and network analyses to examine the targets of APD and PD drugs associated with different clinical effects on Parkinsonism and psychotic symptoms.

Insights from drug target expression patterns

The similar global expression patterns of FGA and SGA targets (Fig. 2a), both shared and unique, likely resulted from the primary actions of the drugs on the dopaminergic system (Supplementary Figs. 2-4). While unique SGA targets were also influenced by the combined effects of the drugs on other systems like cholinergic, adrenergic, GABA, and histamine, these effects usually occurred in conjunction with the dopaminergic system, often alongside the serotonergic system (Supplementary Fig. 4). Although serotonergic and dopaminergic systems are regulated by distinct components [46], when pharmacologically modulated, their responses become interconnected in the synthesis, degradation, and activation pathways [47, 48]. This may explain why instances where these drugs act on the serotonergic system alone or on other systems in combination with the serotonergic system but without the dopaminergic system do not produce noticeable differences in the global expression profiles (Fig. 2a).

On the other hand, there are clearer distinctions between the targets of PD drugs that are at risk of psychosis and that are not, both shared and unique (Fig. 2c). Specifically, the targets of PD drugs at lower risk of psychosis show the highest variability in gene expression. This variability is likely influenced by drug action on adrenergic, dopaminergic, and serotonergic systems, in multiple directions, including both agonistic and antagonistic effects, as well as on intermediate players in the dopamine enzymatic cycle, such as monoamine oxidase (Supplementary Fig. 7). In contrast, the unique targets of PD drugs at risk of psychosis are likely influenced by drug action specifically on dopaminergic activation (Supplementary Fig. 6). This is also the case for the shared targets of PD drugs, albeit in conjunction with actions on decarboxylase within the dopamine enzymatic cycle (Supplementary Fig. 5). Action on individual components of the dopaminergic system likely influenced the confinement of the prediction ellipses of the two drug target sets within the ellipse enclosing the targets of PD drugs at lower risk of psychosis (Fig. 2c).

Global trends suggested widespread effects of APDs (Fig. 2b) and PD drugs (Fig. 2d). Nevertheless, regional gene expression variations (Fig. 3) and numerical enrichments (Fig. 4) suggested the influence of local drug actions on the development of Parkinsonism with APDs and psychotic symptoms with PD drugs. Notably, unique FGA targets exhibited higher mean expression levels than SGAs in 13 brain areas, with the most significant differences observed in the midbrain, a region central to PD pathology. Specifically, prolonged use of drugs such as haloperidol can induce a hypodopaminergic state in the nigrostriatal pathway due to excessive depolarisation and subsequent inactivation of dopaminergic neuron spike generation. This, in turn, could precipitate Parkinsonian symptoms [49, 50]. The targets of PD drugs at risk of psychosis showed higher expression than those at lower risk in the cingulum bundle, suggesting its potential role in precipitating SZ symptoms. The cingulum bundle connects the neocortex and the limbic system. Abnormalities in this white matter tract have been noted in SZ patients [51–53], possibly signifying reduced interaction across emotional and cognitive domains. Quetiapine promotes the differentiation of neural progenitor cells into oligodendrocytes and facilitates myelination in rat embryonic cultures [54]. With chronic use, quetiapine improves the working memory deficits arising from cortical demyelination in both rats and mice [54, 55]. Although such studies allude to the beneficial effects of SGAs, conflicting reports also exist [56]. Nevertheless, the enrichment of targets of PD drugs – specifically of those at risk of inducing psychosis – in the cingulum bundle, which is potentially relevant to SZ aetiology, warrants further experimental investigation. Lastly, the enrichment of specific categories of drug targets in foetal structures raises complex possibilities (Supplementary Discussion).

Insights from the networks of drug targets

Network analyses revealed functional modules collectively targeted by the drug categories, providing insights into their implications for clinical effects. The identification of network modules of unique SGA targets related to multiple neurotransmitter systems aligns with non-dopaminergic theories of SZ. These theories view SZ as a multifactorial disorder, with changes in serotonergic, glutamatergic, cholinergic, and neurotrophin signalling pathways, in addition to abnormalities in the dopaminergic system, contributing to the disease symptoms [57–59]. Hence, in complex cases where psychosis is comorbid with PD, and an imminent risk exists of APDs worsening Parkinsonism, exploring alternative neurotransmitter systems for therapeutic relief may be necessary. Additionally, modules of unique SGA targets related to interferon and interleukin signalling suggest that the broad-spectrum effects of APDs may operate at the interface of neurotransmitter pathways and the neuroimmune axis, an area that is being actively researched.

The oxidation of dopamine by monoamine oxidase A leads to H_2O_2 and free radical generation, potentially leading to DNA damage and influencing the development of PD. Although there is limited literature on this topic, a study has shown that the DNA

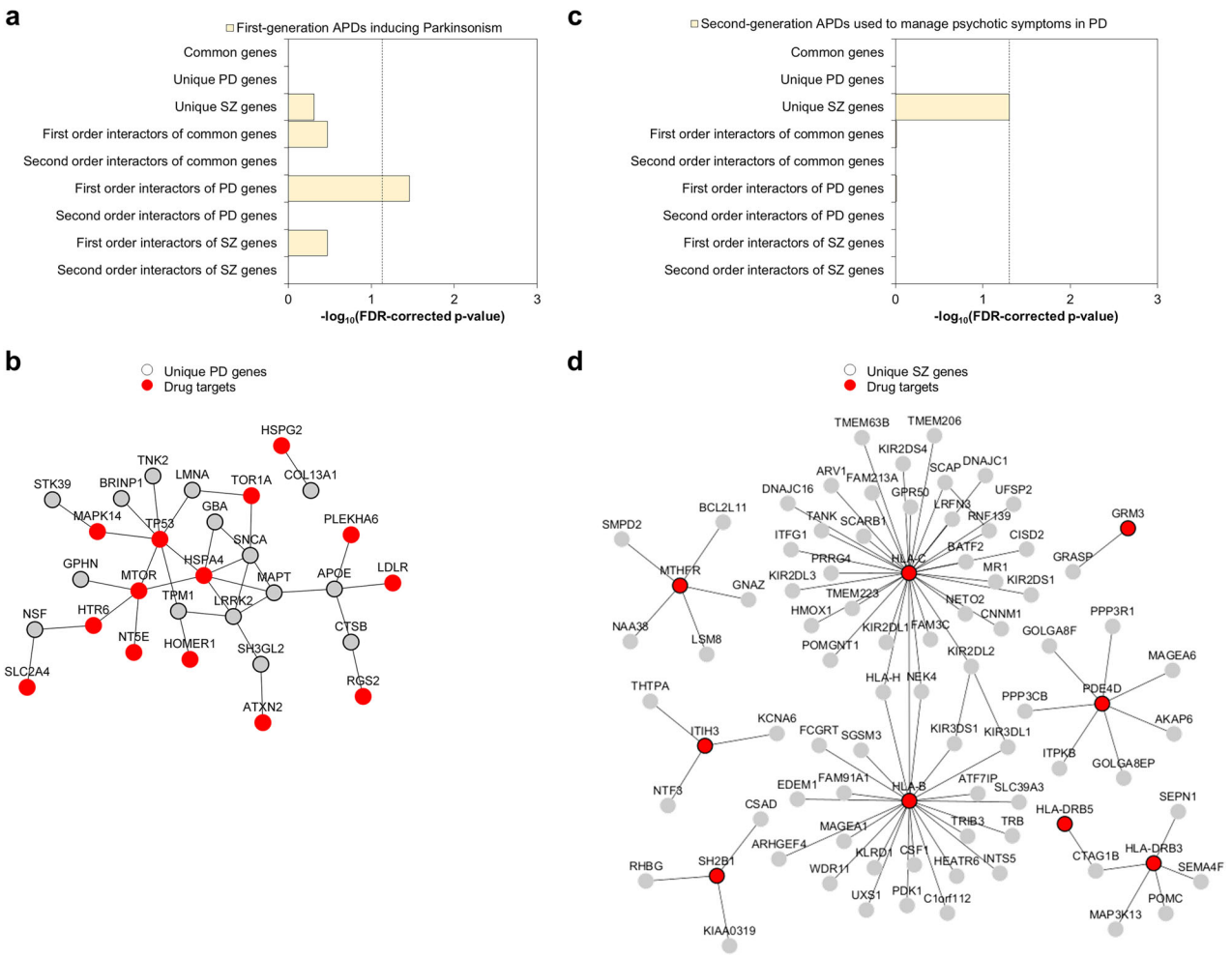

Fig. 6 The different effects of FGAs and SGAs could be attributed to their associations with PD and SZ-associated genes. The network proximity of FGA and SGA drug targets to genes associated exclusively with PD or SZ, as well as genes shared between the two disorders, were examined. Specifically, the enrichment of FGA and SGA targets among the following sets were assessed: unique PD genes, first-order interactors of unique PD genes in the interactome (i.e., their direct interactors), and second-order interactors of unique PD genes (i.e., genes interconnected to unique PD genes via an intermediate interactor, separated by two steps/interactions). Similar sets were assembled for unique SZ genes and shared PD/SZ genes. **a** and **b** show the exclusive enrichment of FGA targets for the first-order interactors of unique PD genes (direct interactors). **c** and **d** show the exclusive enrichment of SGA targets for the unique SZ genes themselves rather than their interactors. The bar graphs in **a** and **c** show the $-\log_{10}(p\text{-value})$ of enrichment after correction for multiple hypotheses using the Benjamini-Hochberg method. The network nodes in **b** and **d** represent proteins and edges represent protein-protein interactions.

damage observed in the peripheral blood cells of PD patients progressively decrease after the intake of the dopamine precursor levodopa [60]. Elevated levels of levodopa may also disrupt a cycle in which dopamine turnover increases and free radicals are generated as a compensatory response to dopaminergic neuron loss. However, the identification of a DNA repair module formed by eight unique targets of PD drugs at risk of psychosis suggests a more direct involvement of this drug category in countering DNA damage. Of these, both levodopa and entacapone target DNA polymerases, while levodopa additionally targets helicases and endonucleases.

Antipsychotic drugs often trigger Parkinsonian symptoms due to altered sensitivity in signalling pathways [4]. We found that the targets of FGAs are immediate interactors of genes harbouring PD-associated variations in the human interactome. Therefore, PD-associated variations and their effects in the surrounding PPI network [61] may influence patient sensitivity to FGAs that target genes within this network.

Our study has several limitations. First, to the best of our knowledge, no single study has recorded, at the same time, the side effects of PD and antipsychotic drugs, such as the frequency of psychotic symptoms in response to levodopa treatment. Additionally, we are not aware of studies that have tried to integrate the interaction between gene expression data, and the side effects of PD and antipsychotic drugs. Therefore, at this point, it may be difficult to comprehensively verify the validity of our findings in a clinical setting. However, our observations provide a window of opportunity, for a more careful look at the clinical setting, and a potential for designing hypothesis-driven studies in the future. Additionally, the predictive value of the spatial and functional correlates can be assessed using new drugs in clinical development or entering the market.

Second, SGAs as a group have shown greater therapeutic success in treating psychosis in other disorders, primarily due to their lower risk of inducing motor abnormalities such as dystonia, tardive dyskinesia, Parkinsonism, akathisia, and shuffling gait [62–66]. Several factors contribute to this, namely, their weak D_2 receptor antagonism, activity on receptors other than dopamine receptors, faster dissociation kinetics from D_2 receptors, and optimal levels of D_2 receptor occupancy [62]. However, the different SGAs themselves vary in their tendency to induce extrapyramidal symptoms, with clozapine showing no such

tendency and high doses of risperidone inducing Parkinsonism [62]. While the current study does not explore these nuances, it tries to identify the processes by which SGAs are more effective in the management of SZ, and are also useful in reducing psychotic symptoms in those with PD (when exposed to dopamine agonists), as compared to FGAs.

Lastly, the network-based results should be updated as the human interactome and the PD-SZ genetic architecture expand.

CONCLUSIONS

This analysis seeks to understand the properties of PD and antipsychotic drug targets that likely explain the different clinical effects of these drugs. Several new insights into their mechanisms were gained. PD drugs that do not cause psychotic symptoms are associated with widespread and variable changes in gene expression. This suggests that the effectiveness and side-effect profile of PD drugs may be linked to their ability to broadly modulate gene expression, a finding that can help develop drugs that manage PD symptoms without causing psychosis. Unique targets of FGAs (linked to Parkinsonism) had higher mean expression levels than SGA targets in the midbrain. Similarly, targets of PD drugs at the risk of causing psychosis had higher expression in white matter compared to those without such risk. Both findings highlight the connections between side-effect profiles and disease-associated regional specificities. Multiple neurotransmitter (e.g., adrenergic, serotonin, and cholinergic) and immune (e.g., interleukin) signalling modules, suggesting non-dopaminergic and neuroimmune involvement, were identified among unique SGA targets. This indicates that SGAs may work through complex mechanisms involving both neural and immune components, broadening the understanding of how SGAs function and opening new avenues for developing treatments that target these pathways. FGA targets directly interacted with putative risk genes for PD, while many SGA targets overlapped with putative risk genes for SZ. Further dissection of the interaction between genetic risks and side-effects may help develop better targeted therapies. In summary, we identified spatial and functional correlates of varying clinical effects in PD and antipsychotic drugs, including distinct global and regional expression patterns, topological modules, and differential network proximity to PD- and SZ-associated genes in the human interactome.

METHODS

Analysis of global drug target expression profiles

The Drug Bank database [28] (version 5.1.8) was used to compile the PD and antipsychotic drug lists. We then used the TWOSIDES database [29] (version 0.1) – a publicly available database of drugs and associated adverse events – to categorise these drugs with respect to their effects on the disease pairs (Supplementary Methods). We examined the spatial expression patterns of the targets of drugs belonging to the four categories using the adult microarray data available in the Allen Brain Atlas (Supplementary Methods) [31]. Normalized expression values (probe intensities) were available for 93 of the 182 APD target genes and 38 of the 70 PD drug target genes. We computed the average expression of each target across samples in the 13 major areas, obtaining gene expression summary measures. PCA, implemented using Clustvis [32], transformed the original log-transformed probe intensities into uncorrelated variables (Supplementary Methods). To examine the influence of specific drug mechanisms on the PC plots, we used Drug Bank data (Supplementary Methods).

Analysis of regional drug target expression profiles

To examine the regional gene expression distributions of the three drug target categories linked to APDs and PD drugs, we applied the Wilcoxon rank sum test, comparing their average probe intensities across 13 brain regions in the Allen Brain Atlas [31]. Next, we examined the numerical overrepresentation of drug targets with high expression in specific brain regions using four independent transcriptomic datasets (Supplementary Methods). The gene matrix transpose files compiled from the datasets served as inputs for a gene over-representation analysis based on hypergeometric distribution (Supplementary Methods). The p-values derived from this analysis were corrected for multiple hypothesis using the BH method.

Network analysis of drug targets

We used the STRING database [40] to examine the interconnectivity of APD and PD drug targets (Supplementary Methods). Subsequently, we constructed and extracted topological modules from three distinct networks of APD targets and three networks of PD drug targets (Supplementary Methods). Cytoscape was used to visualize the networks [67].

The enrichment of topological modules for genes associated with specific biological processes (Gene Ontology [68]) was computed using WebGestalt [69]. Statistical significance was determined through hypergeometric tests, corrected using the BH method, with a BH-corrected p-value < 0.05 considered significant. We compiled genes harboring variations associated with PD, SZ, or both from the DisGeNET database [42] (version 7) and identified their first-order and second-order interactors from PPI repositories BioGRID [43] (version 4.3.194) and HPRD [44] (version 9) using BisoGenet (Supplementary Methods) [70]. Drug target enrichment for various disease gene sets and interactome subsets was calculated using hypergeometric tests with BH correction.

DATA AVAILABILITY

The lists of proteins targeted by the four categories of PD and antipsychotic drugs and the genes associated with PD and SZ compiled from the DisGeNET database have been made available as Supplementary Data Files 1, 4, respectively.

REFERENCES

1. Zahodne LB, Fernandez HH. Pathophysiology and treatment of psychosis in Parkinson's disease. Drugs Aging. 2008;25:665–82.
2. Stoner SC, Dahmen MM, Makos M, Lea JW, Carver LJ, Rasu RS. An exploratory retrospective evaluation of ropinirole-associated psychotic symptoms in an outpatient population treated for restless legs syndrome or Parkinson's disease. Ann Pharmacother. 2009;43:1426–32.
3. Sakhardande KA, Reddi VSK, Mishra S, Navin K, Ramu A, Arunachal G, et al. Homozygous PLA2G6 (PARK 14) gene mutation associated neuropsychiatric phenotypes from southern India. Parkinsonism Relat Disord. 2021;90:49–51.
4. Shin H-W, Chung SJ. Drug-induced parkinsonism. J Clin Neurol. 2012;8:15–21.
5. Benito-León J, Bermejo-Pareja F, Rodríguez J, Molina JA, Gabriel R, Morales JM, Group NDiCSS. Prevalence of PD and other types of parkinsonism in three elderly populations of central Spain. Mov Disord. 2003;18:267–74.
6. Janno S, Holi M, Tuisku K, Wahlbeck K. Prevalence of neuroleptic-induced movement disorders in chronic schizophrenia inpatients. Am J Psychiatry. 2004;161:160–3.
7. Kuroki T, Nagao N, Nakahara T. Neuropharmacology of second-generation antipsychotic drugs: a validity of the serotonin–dopamine hypothesis. Prog Brain Res. 2008;172:199–212.
8. Stahl SM. "Hit-and-Run" actions at dopamine receptors, part 2: illustrating fast dissociation from dopamine receptors that typifies atypical antipsychotics. J Clin Psychiatry. 2001;62:747–8.
9. Group PS. Low-dose clozapine for the treatment of drug-induced psychosis in Parkinson's disease. N Engl J Med. 1999;340:757–63.
10. Kuzuhara S. Drug-induced psychotic symptoms in Parkinson's disease. Problems, management and dilemma. J Neurol. 2001;248:28–31.
11. Fénelon G, Mahieux F, Huon R, Ziégler M. Hallucinations in Parkinson's disease: prevalence, phenomenology and risk factors. Brain. 2000;123:733–45.
12. Oehrn CR, Schönenkorb J, Timmermann L, Nenadić I, Weber I, Grant P. Schizotypy in Parkinson's disease predicts dopamine-associated psychosis. Sci Rep. 2021;11:759.
13. Mohr C, Ettinger U. An overview of the association between schizotypy and dopamine. Front Psychiatry. 2014;5:184.
14. Grover S, Sahoo S, Goyal MK. Schizophrenia with comorbid idiopathic Parkinson's disease: a difficult clinical management scenario. Indian J Psychol Med. 2017;39:823–7.
15. Sharma S, Aggarwal N. Idiopathic Parkinson's disease and schizophrenia: dilemma in diagnosis and treatment of a case. Iran J Psychiatry. 2019;14:179.

16. Oh J, Shen G, Nan G, Kim J-M, Jung K-Y, Jeon B. Comorbid schizophrenia and Parkinson's disease: a case series and brief review. Neurol Asia. 2017;22:139–42.
17. Pilowsky L. Probing targets for antipsychotic drug action with PET and SPET receptor imaging. Nucl Med Commun. 2001;22:829–33.
18. Xiberas X, Martinot J, Mallet L, Artiges E, Loc'h C, Maziere B, et al. Extrastriatal and striatal D2 dopamine receptor blockade with haloperidol or new antipsychotic drugs in patients with schizophrenia. Br J Psychiatry. 2001;179:503–8.
19. Xiberas X, Martinot J-L, Mallet L, Artiges E, Canal M, Loc'h C, et al. In vivo extrastriatal and striatal D2 dopamine receptor blockade by amisulpride in schizophrenia. J Clin Psychopharmacol. 2001;21:207–14.
20. Ng B, Varoquaux G, Poline JB, Thirion B, Greicius MD, Poston KL. Distinct alterations in Parkinson's medication-state and disease-state connectivity. Neuroimage Clin. 2017;16:575–85.
21. Yang C, Zhang T, Wang W, Xiang Y, Huang Q, Xie C, et al. Brain-region specific metabolic abnormalities in Parkinson's disease and levodopa-induced dyskinesia. Front Aging Neurosci. 2020;12:75.
22. Kusumi I, Boku S, Takahashi Y. Psychopharmacology of atypical antipsychotic drugs: From the receptor binding profile to neuroprotection and neurogenesis. Psychiatry Clin Neurosci. 2015;69:243–58.
23. Subbanna M, Shivakumar V, Venugopal D, Narayanaswamy JC, Berk M, Varambally S, et al. Impact of antipsychotic medication on IL-6/stat3 signaling axis in peripheral blood mononuclear cells of drug-naive schizophrenia patients. Psychiatry Clin Neurosci. 2020;74:64–69.
24. Leboyer M, Godin O, Terro E, Boukouaci W, Lu C-l, Andre M, et al. Immune signatures of treatment-resistant schizophrenia: a fondamental academic centers of expertise for schizophrenia (FACE-SZ) study. Schizophr Bull Open. 2021;2:sgab012.
25. Akkouh IA, Hribkova H, Grabiec M, Budinska E, Szabo A, Kasparek T, et al. Derivation and molecular characterization of a morphological subpopulation of human ipsc astrocytes reveal a potential role in schizophrenia and clozapine response. Schizophr Bull. 2022;48:190–8.
26. Barrio-Hernandez I, Beltrao P. Network analysis of genome-wide association studies for drug target prioritisation. Curr Opin Chem Biol. 2022;71:102206.
27. Sadler MC, Auwerx C, Deelen P, Kutalik Z. Multi-layered genetic approaches to identify approved drug targets. Cell Genom. 2023;3:100341.
28. Wishart DS, Knox C, Guo AC, Cheng D, Shrivastava S, Tzur D, et al. DrugBank: a knowledgebase for drugs, drug actions and drug targets. Nucleic Acids Res. 2008;36:D901–D906.
29. Tatonetti NP, Patrick PY, Daneshjou R, Altman RB. Data-driven prediction of drug effects and interactions. Sci Transl Med. 2012;4:125ra131.
30. Griffith M, Griffith OL, Coffman AC, Weible JV, McMichael JF, Spies NC, et al. DGIdb: mining the druggable genome. Nat Methods. 2013;10:1209–10.
31. Hawrylycz MJ, Lein ES, Guillozet-Bongaarts AL, Shen EH, Ng L, Miller JA, et al. An anatomically comprehensive atlas of the adult human brain transcriptome. Nature. 2012;489:391.
32. 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:W566–70.
33. Holland SM. Principal components analysis (PCA). Athens, GA: Department of Geology, University of Georgia; 2008. p. 30602–2501.
34. Sunkin SM, Ng L, Lau C, Dolbeare T, Gilbert TL, Thompson CL, et al. Allen brain atlas: an integrated spatio-temporal portal for exploring the central nervous system. Nucleic Acids Res. 2012;41:D996–1008.
35. Consortium G. The genotype-tissue expression (GTEx) pilot analysis: multitissue gene regulation in humans. Science. 2015;348:648–60.
36. Palacios JM, Camps M, Cortes R, Probst A. Mapping dopamine receptors in the human brain. J Neural Transm Suppl. 1988;27:227–35.
37. Ganapathiraju MK, Thahir M, Handen A, Sarkar SN, Sweet RA, Nimgaonkar VL, et al. Schizophrenia interactome with 504 novel protein–protein interactions. NPJ Schizophr. 2016;2:1–10.
38. Lim J, Hao T, Shaw C, Patel AJ, Szabó G, Rual J-F, et al. A protein–protein interaction network for human inherited ataxias and disorders of Purkinje cell degeneration. Cell. 2006;125:801–14.
39. Sakai Y, Shaw CA, Dawson BC, Dugas DV, Al-Mohtaseb Z, Hill DE, et al. Protein interactome reveals converging molecular pathways among autism disorders. Sci Transl Med. 2011;3:86ra49.
40. Szklarczyk D, Gable AL, Nastou KC, Lyon D, Kirsch R, Pyysalo S, et al. The STRING database in 2021: customizable protein–protein networks, and functional characterization of user-uploaded gene/measurement sets. Nucleic Acids Res. 2021;49:D605–12.
41. Khokhar JY, Henricks AM, Sullivan ED, Green AI. Unique effects of clozapine: a pharmacological perspective. Adv Pharmacol. 2018;82:137–62.
42. Piñero J, Bravo À, Queralt-Rosinach N, Gutiérrez-Sacristán A, Deu-Pons J, Centeno E et al. DisGeNET: a comprehensive platform integrating information on human disease-associated genes and variants. Nucleic acids research 2016;45:gkw943.
43. Stark C, Breitkreutz B-J, Reguly T, Boucher L, Breitkreutz A, Tyers M. BioGRID: a general repository for interaction datasets. Nucleic Acids Res. 2006;34:D535–D539.
44. Keshava Prasad T, Goel R, Kandasamy K, Keerthikumar S, Kumar S, Mathivanan S, et al. Human protein reference database—2009 update. Nucleic Acids Res. 2009;37:D767–D772.
45. Raudvere U, Kolberg L, Kuzmin I, Arak T, Adler P, Peterson H, et al. g: Profiler: a web server for functional enrichment analysis and conversions of gene lists (2019 update). Nucleic Acids Res. 2019;47:W191–W198.
46. Hashemi P, Dankoski EC, Lama R, Wood KM, Takmakov P, Wightman RM. Brain dopamine and serotonin differ in regulation and its consequences. Proc Natl Acad Sci USA. 2012;109:11510–5.
47. Kapur S, Remington G. Serotonin-dopamine interaction and its relevance to schizophrenia. Am J Psychiatry. 1996;153:466–76.
48. Szlachta M, Kuśmider M, Pabian P, Solich J, Kolasa M, Żurawek D, et al. Repeated clozapine increases the level of serotonin 5-HT1AR heterodimerization with 5-HT2A or dopamine D2 receptors in the mouse cortex. Front Mol Neurosci. 2018;11:40.
49. Chiodo LA, Bunney BS. Typical and atypical neuroleptics: differential effects of chronic administration on the activity of A9 and A10 midbrain dopaminergic neurons. J Neurosci. 1983;3:1607–19.
50. Valenti O, Cifelli P, Gill KM, Grace AA. Antipsychotic drugs rapidly induce dopamine neuron depolarization block in a developmental rat model of schizophrenia. J Neurosci. 2011;31:12330–8.
51. Tang J, Liao Y, Zhou B, Tan C, Liu T, Hao W, et al. Abnormal anterior cingulum integrity in first episode, early-onset schizophrenia: a diffusion tensor imaging study. Brain Res. 2010;1343:199–205.
52. Whitford TJ, Lee SW, Oh JS, de Luis-Garcia R, Savadjiev P, Alvarado JL, et al. Localized abnormalities in the cingulum bundle in patients with schizophrenia: a diffusion tensor tractography study. Neuroimage Clin. 2014;5:93–99.
53. Chawla N, Deep R, Khandelwal SK, Garg A. Cingulum bundle integrity in schizophrenia with auditory verbal hallucinations: a diffusion tensor imaging tractographic study. Indian J Med Res. 2022;156:535.
54. Xiao L, Xu H, Zhang Y, Wei Z, He J, Jiang W, et al. Quetiapine facilitates oligodendrocyte development and prevents mice from myelin breakdown and behavioral changes. Mol Psychiatry. 2008;13:697–708.
55. Zhang Y, Zhang H, Wang L, Jiang W, Xu H, Xiao L, et al. Quetiapine enhances oligodendrocyte regeneration and myelin repair after cuprizone-induced demyelination. Schizophr Res. 2012;138:8–17.
56. Konopaske GT, Dorph-Petersen K-A, Sweet RA, Pierri JN, Zhang W, Sampson AR, et al. Effect of chronic antipsychotic exposure on astrocyte and oligodendrocyte numbers in macaque monkeys. Biol Psychiatry. 2008;63:759–65.
57. Yang AC, Tsai S-J. New targets for schizophrenia treatment beyond the dopamine hypothesis. Int J Mol Sci. 2017;18:1689.
58. Berman JA, Talmage DA, Role LW. Cholinergic circuits and signaling in the pathophysiology of schizophrenia. Int Rev Neurobiol. 2007;78:193–223.
59. Nieto R, Kukuljan M, Silva H. BDNF and schizophrenia: from neurodevelopment to neuronal plasticity, learning, and memory. Front Psychiatry. 2013;4:45.
60. Cornetta T, Palma S, Aprile I, Padua L, Tonali P, Testa A, et al. Levodopa therapy reduces DNA damage in peripheral blood cells of patients with Parkinson's disease. Cell Biol Toxicol. 2009;25:321–30.
61. Barabási A-L, Gulbahce N, Loscalzo J. Network medicine: a network-based approach to human disease. Nat Rev Genet. 2011;12:56–68.
62. Aringhieri S, Carli M, Kolachalam S, Verdesca V, Cini E, Rossi M, et al. Molecular targets of atypical antipsychotics: From mechanism of action to clinical differences. Pharmacol Ther. 2018;192:20–41.
63. Correll CU, Leucht S, Kane JM. Lower risk for tardive dyskinesia associated with second-generation antipsychotics: a systematic review of 1-year studies. Am J Psychiatry. 2004;161:414–25.
64. Geddes J, Freemantle N, Harrison P, Bebbington P. Atypical antipsychotics in the treatment of schizophrenia: systematic overview and meta-regression analysis. BMJ. 2000;321:1371–6.
65. Bagnall A-M, Jones L, Ginnelly L, Lewis R, Glanville J, Gilbody S, et al. A systematic review of atypical antipsychotic drugs in schizophrenia. Health Technol Assess (Rockv). 2003;7:1–193.
66. Chouinard G. New nomenclature for drug-induced movement disorders including tardive dyskinesia. J Clin Psychiatry. 2004;65:9–15.
67. Shannon P, Markiel A, Ozier O, Baliga NS, Wang JT, Ramage D, et al. Cytoscape: a software environment for integrated models of biomolecular interaction networks. Genome Res. 2003;13:2498–504.
68. Gene Ontology Consortium. The gene ontology (GO) database and informatics resource. Nucleic Acids Res. 2004;32:D258–61.
69. Liao Y, Wang J, Jaehnig EJ, Shi Z, Zhang B. WebGestalt 2019: gene set analysis toolkit with revamped UIs and APIs. Nucleic Acids Res. 2019;47:W199–205.

70. Martin A, Ochagavia ME, Rabasa LC, Miranda J, Fernandez-de-Cossio J, Bringas R. BisoGenet: a new tool for gene network building, visualization and analysis. BMC Bioinformatics. 2010;11:1–9.

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AUTHOR CONTRIBUTIONS

Kalyani B Karunakaran – Conceptualisation, Methodology, Data Curation, Formal Analysis, Visualisation, Writing - Original Draft, Writing - Review & Editing. Sanjeev Jain – Conceptualisation, Methodology, Supervision, Writing - Review & Editing. Darius Widera – Conceptualisation, Methodology, Supervision, Writing - Review & Editing. Graeme S Cottrell – Conceptualisation, Methodology, Supervision, Project Administration, Writing - Review & Editing.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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