Efficacy difference of antipsychotics in Alzheimer's disease and schizophrenia: explained with network efficiency and pathway analysis methods

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Abstract

Approximately 50% of Alzheimer's disease (AD) patients will develop psychotic symptoms and these patients will experience severe rapid cognitive decline compared with those without psychosis (AD-P). Currently, no medication has been approved by the Food and Drug Administration for AD with psychosis (AD+P) specifically, although atypical antipsychotics are widely used in clinical practice. These drugs have demonstrated modest efficacy in managing psychosis in individuals with AD, with an increased frequency of adverse events, including excess mortality. We compared the differences between the genetic variations/genes associated with AD+P and schizophrenia from existing Genome-Wide Association Study and differentially expressed genes (DEGs). We also constructed disease-specific protein–protein interaction networks for AD+P and schizophrenia. Network efficiency was then calculated to characterize the topological structures of these two networks. The efficiency of antipsychotics in these two networks was calculated. A weight adjustment based on binding affinity to drug targets was later applied to refine our results, and 2013 and 2123 genes were identified as related to AD+P and schizophrenia, respectively, with only 115 genes shared. Antipsychotics showed a significantly lower efficiency in the AD+P network than in the schizophrenia network (P < 0.001) indicating that antipsychotics may have less impact in AD+P than in schizophrenia. AD+P may be caused by mechanisms distinct from those in schizophrenia which result in a decreased efficacy of antipsychotics in AD+P. In addition, the network analysis methods provided quantitative explanations of the lower efficacy of antipsychotics in AD+P.

Keywords: Psychosis in Alzheimer's disease, Antipsychotics, Network analysis, Systems pharmacology

Introduction

Alzheimer's Disease (AD) is a chronic neurodegenerative disease commonly seen in aging population. AD is also responsible for a significant decrease in the quality of life [1]. The estimated annual cost of AD is $604 billion worldwide and will triple by the year 2050 [2].

Psychosis is defined by the occurrence of delusions and/or hallucinations. It is observed as a common complication of AD. Approximately 50% of patients are likely to develop psychotic symptoms after onset of AD (AD with psychosis, or AD+P). AD+P patients have more severe cognitive impairments and a more rapid cognitive decline than AD patients without psychosis (AD-P)

[3]. AD+P is also associated with higher rates of co-occurring agitation, aggression, depression, mortality, functional impairment and increased caregiver burden compared with AD-P [3].

Currently, there are no medications approved by the Food and Drug Administration (FDA) for AD+P specifically. Second-generation antipsychotics (SGAs), such as Aripiprazole, Olanzapine, Quetiapine and Risperidone, which were developed for the treatment of schizophrenia (SCZ), have been widely used and recommended by geriatric experts in the management of psychosis in AD [4–6]. Use of SGAs to treat AD+P is greatly limited by their increased rates of adverse events [7, 8], prompting the FDA to issue a 'black-box' warning in 2005 to highlight the increased

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mortality for patients with dementia who are treated with SGAs [9]. Additionally, antipsychotics have demonstrated modest efficacy in treating psychosis, aggression and agitation in individuals with dementia [10–12]. Therefore, safer and more efficacious medications for AD+P are needed for managing psychotic symptoms in AD.

Psychotic symptoms exist in many neurodegenerative disorders (e.g., Lewy body dementia), as well as other psychiatric disorders (bipolar with psychosis). However, the prototypic psychotic disorder is schizophrenia, and the efficacy of most antipsychotic medications for treating psychosis was established in treating this disorder. Therefore, we are currently using medications indicated for schizophrenia to treat AD+P [4–6].

Network biology has been widely used in studying the interactions among genes, proteins and molecules. With the significant increase in available data, network models can be built to describe and simulate human interactome networks to provide a lot of information and greatly aid drug discovery and development. As a matter of fact, network analysis method has been put into practice in multiple studies and publications [13–17]. In addition, network efficiency is a computable quantity that can describe the interactions between distant elements within complex networks [18]. It measures how efficiently a node can exchange information with other parts of the network [19], which has been widely used in current drug discovery process [20]. The two major assumptions of the use of network efficiency as a measure for drug efficiency are: (i) a mechanism targeted by a drug can be represented as a network and (ii) all elements of this network must interact for appropriate functioning of the targeted mechanism [18]. In our study, we fulfilled these two assumptions by combining the genes associated with AD+P and drug targets with pharmaceutical actions and connecting them with latest protein–protein interaction data. Therefore, we believe that the network efficiency in our study can be considered as strong predictors for drug efficacy in real world.

In a recent study, Dr Robert Sweet and his group conducted a genome-wide association study (GWAS) to identify risk loci for AD+P compared with AD-P patients [21]. In this paper, the researchers compared the genetic correlations of AD + P with select phenotypes AD, amyotrophic lateral sclerosis, Parkinson's disease, intelligence, schizophrenia, depressive symptoms and bipolar disorder. AD+P showed significantly genetically correlation with depressive symptoms, and in contrast, AD + P was not significantly genetically correlated with AD and schizophrenia.

Studies of familial aggregation of AD+P have established that the risk for AD+P is, in part, genetically mediated [22]. However, despite some symptomatic overlap, AD+P is not genetically correlated with schizophrenia risk [21, 23]. Therefore, identifying the similarities and differences between their associated genetic mechanisms may provide a mechanism for understanding the reduced benefit of antipsychotics in AD+P. In this study, we applied network analytic approaches incorporating transcriptomic and genomic data from AD+P and schizophrenia subjects to accomplish this goal.

Material and methods
Dataset collection

Thanks to the great improvement of gene sequencing technologies, we now have access to a batch of high-quality, large-scale genetic studies about schizophrenia (e.g. biological insights from 108 schizophrenia-associated genetic loci by Ripke S.) [24] that can provide reliable genetic insights for schizophrenia. Differentially expressed genes (DEGs) and GWAS data for AD+P were used to construct the protein–protein interaction (PPI) networks [21]. GWAS data for schizophrenia was collected from GWAS Catalog (https://www.ebi.ac.uk/GWAS/home), and DEGs were collected from the CommondMind Consortium [25] and the psychENCODE cohorts [26]. Genes from GWAS and DEGs are pooled together to create an inclusive gene set that will represent the genetic characteristics of the disease as accurate as possible and these genes were used to construct the networks, respectively. These gene names were then converted to protein names by batch search function in the UniProt database [27].

Information about antipsychotics and their targets was extracted from DrugBank (Supplementary ST1) (https://www. drugbank.ca/) [28]. The pharmacological action label of a drug provides information about whether binding to a target contributes to the pharmacological effects. For example, Olanzapine can bind to multiple neuronal receptors, including the dopamine receptors D1, D2, D3 and D4, the serotonin receptors 5HT2A, 5HT2C, 5HT3 and 5HT6, the alpha-1 adrenergic receptor, the histamine receptor H1 and multiple muscarinic receptors. However, Olanzapine's antagonistic effect toward the DRD2 receptor in the mesolimbic pathway and serotonin receptor 5HT2A in the frontal cortex are considered key in achieving its pharmacological effects [29]. Thus, DRD2 receptor and 5HT2A are labeled with known pharmacological action while other receptors are labeled as unknown pharmacological action. Genes extracted from the databases were first examined if they have corresponding coded proteins for PPI data extraction. We constructed the networks with all the drug targets (known and unknown pharmacological actions) and only targets with known drug targets. We found that the networks showed similar characteristics in network structures and metrics (Supplementary ST2). We also conducted network efficiency analysis with the networks built with all drug targets and the results showed similar patterns and trends (Supplementary ST3 and ST4). Therefore, only targets with known pharmacological actions were included in the following study. For further network analysis, the largest connected network was defined as the main network which included the majority of disease proteins and drug targets. Proteins that are not connected with the main network were removed from the network. Antipsychotics are evaluated as two sub-groups: first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs). FGAs are D2 antagonists and SGAs are 5HT2A/D2 antagonists [30].

PPI data were collected from STRING (https://string-db.org/) [31]. The PPI networks were constructed and analyzed with python package networkx (https://networkx.github.io/) [32]. The interaction network was shown in the molecular action view with a medium confidence level (>0.4) which is commonly used in other literature [33]. AD+P-related proteins and schizophrenia-related proteins were joined with targets of antipsychotics to construct two disease-targets networks, i.e. AD+P-targets PPI network (AD + P network) and schizophrenia-targets PPI network (SCZ network). Lists of removed genes from the AD+P network and the SCZ network can be found in supplementary materials (Supplementary ST5). We also included the proteins which served to bridge between disease module proteins and target module proteins in our disease-targets networks, even if these bridging proteins were not included in the disease or target protein sets originally. Networks were constructed based on GWAS and DEGs data separately and combined to test which method can best reflect the associations among drug targets and diseases (Supplementary ST6 and ST7).

In addition, pathway enrichment analysis was conducted through the ingenuity pathway analysis (IPA, QIAGEN Inc., https://www.qiagenbioinformatics.com/products/ingenuitypathway-analysis).

Network analysis

Network analysis approaches are incorporated to explain the modest efficacy of antipsychotics in AD+P. We hypothesized that the structure differences between protein–protein interaction (PPI) networks of AD+P and schizophrenia might result in different signaling transduction initiated by the antipsychotics and thus affect the drug efficacy. Network approaches have been used in predicting and identifying the disease genes in multiple studies and some of the results have been verified [34, 35]. While the drug actions depend on the complex signaling transduction networks of cells or the complicated profile of drug potency and selectivity, the effect of a drug can be evaluated by the impact of the drug's targets toward a PPI network representing a disease [36]. Therefore, we built two PPI networks for AD+P and schizophrenia, respectively, with targets of antipsychotics added to evaluate the effects of antipsychotics in these two diseases in a quantitative manner.

The efficiency of nodes in the network was calculated based on the built-in algorithm of networkx [19, 32]. Efficiency is a measurement of how efficiently a node can exchange information with other parts of the network [19], which has been widely used in neurological research. We calculated several graph-based metrics to characterize their topological organization at different levels, including global small-world network efficiency (global efficiency, local efficiency) and nodal efficiency. The definition and calculation methods are briefly introduced below in the context of an undirected network G with N nodes and K edges.

Small-world efficiency

Efficiency is a biologically relevant metric to describe biological signaling networks from the perspective of parallel information propagation and exchange [37]. It can be calculated at both global and local levels. Mathematically, global efficiency is defined as

$$E_{glob}(G) = \frac{1}{N(N-1)} \sum_{i \neq j \in G} \frac{1}{d_{ij}}, \qquad (1)$$

where N is the total node number of the connected network G, d_{ij} is the shortest path length from node i to node j in the network. Global efficiency mainly measures the ability of parallel information transmission over the network [19].

The local efficiency of G is defined as

$$E_{loc}(G) = \frac{1}{N} \sum_{i \in G} E_{glob}(G_i), \qquad (2)$$

where N is the total node number of the connected network G, $E_{glob}(G_i)$ is the global efficiency of G_i, the subgraph contained all the neighbors of node i (i.e. nodes linked directly to node i). The result of local efficiency measures the fault tolerance of the network, indicating the capability of information exchange for each subgraph when the index node is eliminated [19].

A small-world network is a type of mathematical graph in which most nodes are not neighbors of one another, but the neighbors of any given node are likely to be neighbors of each other and most nodes can be reached from every other node by a small number of hops or steps [38]. Small-world coefficient (sigma) is proposed to be used to accurately distinguish small-world network (sigma >1) [39–41]. The calculation of sigma is defined as follows [42]:

$$C = \frac{1}{N} \sum_{i \in G} Ci \qquad (3)$$

$$\sigma = \frac{C}{Cr} / \frac{L}{Lr}, \qquad (4)$$

where N is the total node number of the connected network G, C and L are, respectively, the average clustering coefficient and average shortest path length of G, and Cr and Lr are, respectively, the average clustering coefficient and average shortest path length of an equivalent random graph.

Nodal efficiency

To measure the efficiency of a certain node, two major factors should be taken into consideration: (i) the number of nodes that can be connected to this node through edges in the network (N); (ii) the path lengths between other connected nodes and the node of interest (d_{ij}). Therefore, nodal efficiency of a node (i) is calculated as follows:

$$E(i) = \frac{1}{N-1} \sum_{i \neq j \in G} \frac{1}{d_{ij}}, \qquad (5)$$

where N is the total node number of the connected network G, d_{ij} is the shortest path length from node i to node j in the network. Nodal efficiency measures the ability of information propagation between a node and the remaining nodes in the network. A node with high nodal efficiency indicates high capability of information transmission with other nodes and can therefore be categorized as a hub.

Method validation

Before we apply network analysis methods to antipsychotics in AD+P and SCZ networks, we want to validate its ability to detect the efficiency differences of drugs in diseases. To accomplish that, we use FGAs, SGAs and benzodiazepines as examples to test their efficacy differences in schizophrenia. Abundant studies have shown that in schizophrenia, SGAs have slightly higher efficacy than FGAs [43], and both FGAs and SGAs are significantly more efficacious than benzodiazepines [44]. Therefore, SGAs and FGAs will serve as positive examples and benzodiazepines will serve as negative examples.

We use these three categories of medications to evaluate six network metrics: Degree centrality [45], Closeness centrality [45], Betweenness centrality [45], Clustering coefficient [46] and Integrated Value of Influence (IVI) [47]. Networks were processed and analyzed with python package networkx [32].

Statistical analysis

Nodal efficiency values are calculated as described above for antipsychotics' targets in AD+P network and SCZ network, respectively. Therefore, the efficiency of targets in two networks can be compared in pairs to evaluate the difference of drug effects in two diseases. After testing, the distribution of efficiency values does not follow normal distribution, as such Wilcoxon signed-rank test [48] is used to determine whether two dependent samples were selected from populations having the same distribution.
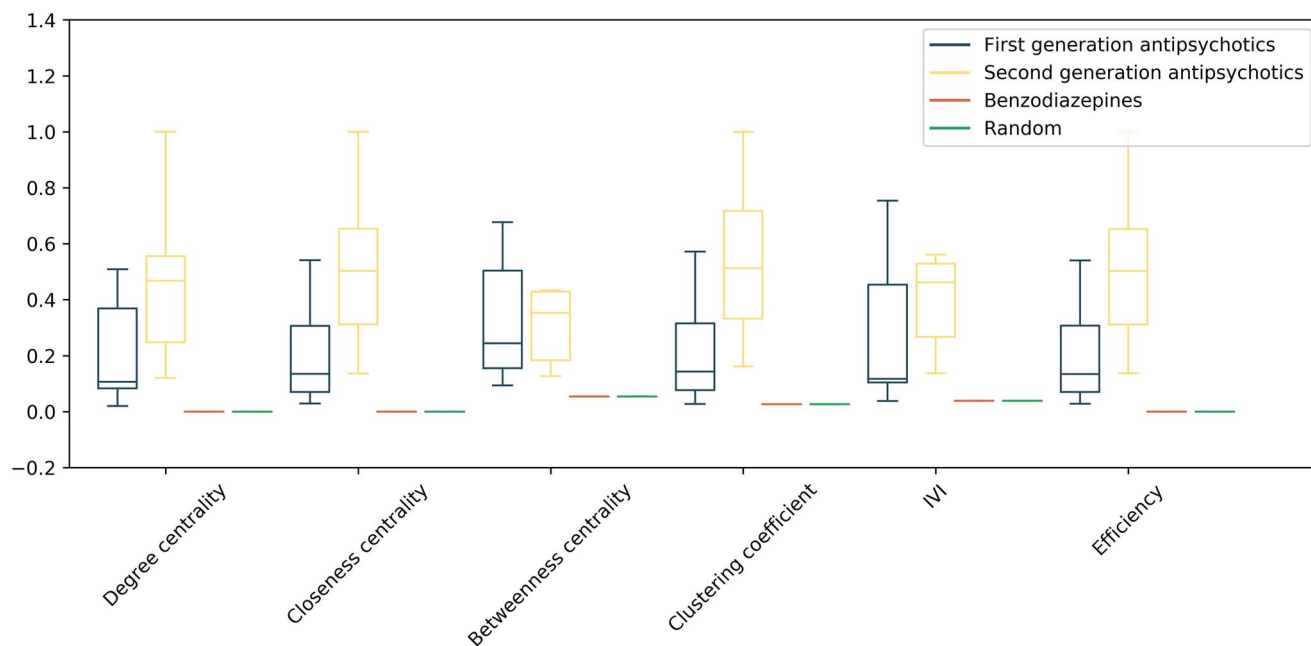
Figure 1. The distribution of network metrics values among three categories of medications in three networks with random network.

Binding affinity-based weight calculation

Binding affinity values, including Ki, EC50, IC50 and AC50, for drugs against their targets were extracted from ChEMBL (https://www.ebi.ac.uk/chembl/) [49] with provided web service (Supplementary ST8 and ST9). Those values were used as the measurement for the strength of drug-target interactions.

To align the effect of different binding affinity measurements, a relative strength (RS) for each target is calculated for different measurements as follows:

$$RS = Binding_{reference}/Binding_{drug-target}, \qquad (6)$$

where $Binding_{reference}$ is the minimum binding value achieved by any antipsychotics with a certain target and $Binding_{drug-target}$ is the binding value for a certain antipsychotics and target pair.

Standard protocol approvals, registrations and patient consents

The genetic data used in this study is contributed by Dr Robert Sweet's lab [21] and the collection of clinical data and genetic samples was approved by each source programs' local Institutional Review Board or Medical Ethics Committee, as appropriate.

Results
Network analysis method validation

To validate the network analysis methods, an SCZ network with FGAs' targets and an SCZ network with SGAs' targets were constructed. In addition, to account for psychoactive effects not specifically targeting psychosis, an SCZ network with benzodiazepines' targets was constructed. To present a baseline for the network metrics, we constructed a random network with same node number with the largest networks among the three networks (1462 nodes). The network metrics for drug targets in these three networks were calculated by implemented methods in networkx [21]. The efficiency value of each medication was considered equal to the sum of all its targets' efficiency values. Kruskal–Wallis H-test was performed to test if there

Table 1. Results of statistical tests for six network metrics

Network metrics	H	P value
Degree centrality	51.5	1.36×10^{-09}
Closeness centrality	55.1	2.90×10^{-10}
Betweenness centrality	49.3	1.38×10^{-09}
Clustering coefficient	50.4	2.37×10^{-09}
IVI	45.6	3.64×10^{-08}
Efficiency	55.1	2.90×10^{-10}

H: Test statistic for Kruskal–Wallis H-test [50].

are statistical differences among the three categories in three networks because the distributions of calculated metrics do not follow normal distribution [50]. As shown in Table 1, all metrics showed significance among the three groups and the distributions are shown in the box plot (Figure).

As shown in the box plot (Figure), FGAs and SGAs showed comparable values in three networks while SGAs are slightly higher than FGAs. On the other hand, benzodiazepine's network metrics values are close to 0 indicating they may not possess any potential beneficial effect against schizophrenia, in accordance with the conclusion drawn by extensive evidence-based research [44]. The random network showed close to 0 topological features compared with FGAs and SGAs while benzodiazepines showed similar metrics with random networks.

Based on the results discussed above, the network analysis method is not only capable of distinguishing effective and non-effective treatments (antipsychotics and benzodiazepines) but is also able to differentiate the minor difference between sub-class of medications (FGAs and SGAs).

Overview of genetic variations associated with AD+P and schizophrenia

From the sources mentioned above, 975 genome-wide associated variations and 1077 DEGs were identified for AD+P relative to AD-P, and 1668 genome-wide associated variations and 464 DEGs were identified for schizophrenia based on their significance. In total, 1607 and 2123 unique genes were identified as associated
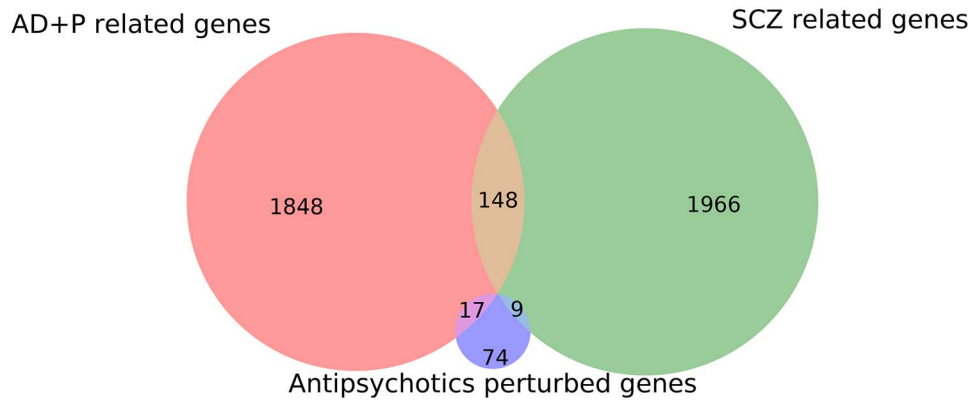
Figure 2. The Venn diagram of AD+P and schizophrenia-related genes and antipsychotics' targets genes.
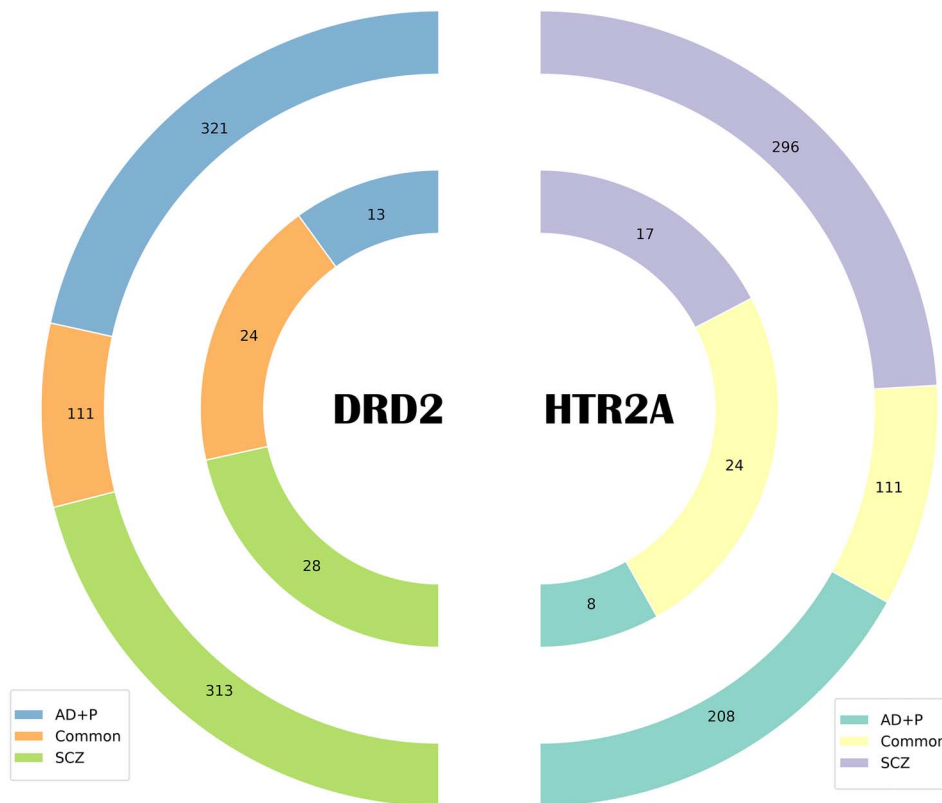

Figure 3. DRD2 and HTR2A share some common target genes but there is a significant portion of their downstream genes that do not overlap with each other. Taken together, the pathways represented by these different genes can be the keys to answer why SGAs are less efficient in AD+P than in schizophrenia. Comparison of first and second neighbors of DRD2 and HTR2A in AD+P network and SCZ network.

with AD+P and schizophrenia, respectively. Meanwhile, 75 targets were collected from DrugBank for 21 antipsychotics that are commonly used in clinical settings, including 10 FGAs and 11 SGAs (full list of drugs and targets in Supplementary ST1).

Consistent with prior observations that AD+P and schizophrenia have limited shared genetic risk, only 148 genes overlapped between these disorders. Antipsychotics' pharmacological targets are also jointly presented in Figure 2, 17 antipsychotics target genes overlap with AD+P and 9 overlap with schizophrenia.

Parameter descriptions of AD+P network and SCZ network

Target-disease networks for AD+P and schizophrenia are constructed based on the previously identified genes and target

proteins for antipsychotics. Only genes having interactions with other genes within the network are included. The basic information for the two networks can be found in Table 2. Both networks are confirmed as small-world networks, with small-world coefficient (sigma) > 1 as we described in section Small-world efficiency. The AD+P network showed higher global and local efficiency reflecting its larger network size.

Decreased drug efficacy in AD+P compared to schizophrenia
Decreased efficacy for major antipsychotics' targets in AD+P compared with schizophrenia

Nodal efficiency values were calculated for antipsychotics' targets to evaluate for differences between AD+P and schizophrenia.

Table 2. General network parameters for AD+P and SCZ networks

	Node number	Global efficiency	Local efficiency	Small-world coefficient (sigma)
AD+P network	1512	0.289	0.262	5.825
SCZ network	1249	0.297	0.270	7.518

SCZ network: protein–protein interaction network with schizophrenia-related genes and targets of antipsychotics. [a] AD + P network: protein–protein interaction network with AD+P-related genes and targets of antipsychotics.

Table 3. Efficiency of major targets of antipsychotics in AD+P network and SCZ network

Targets	Efficiency in AD+P network	Efficiency in SCZ network
DRD2	0.363	0.381
HTR2A	0.337	0.371
DRD1	0.332	0.347
ADRA1A	0.29	0.319
DRD3	0.315	0.33
HRH1	0.309	0.311
HTR1A	0.304	0.355
DRD4	0.307	0.337
Paired Wilcoxon Test	$W = 36, P = 0.0039$	

[a]DRD2: Dopamine Receptor D2; DRD3: Dopamine Receptor D3; DRD4: Dopamine Receptor D4; HTR1A: 5-Hydroxytryptamine Receptor 1A; HTR2A: 5-Hydroxytryptamine Receptor 2A; ADRA1A: Adrenoceptor Alpha 1A; HRH1: Histamine Receptor H1; AD+P network: protein–protein interaction network with AD+P-related genes and targets of antipsychotics; SCZ network: protein–protein interaction network with schizophrenia-related genes and targets of antipsychotics

Efficiency values for the major targets of antipsychotics are shown in Table 3. Antipsychotic targets in the AD+P network showed a significantly lower efficiency than those in the SCZ network ($P = 0.0039$).

The results in Table 3 indicate that these targets have less impact in AD+P compared with schizophrenia when perturbed with the same strength and can be interpreted as the antipsychotics targeting these proteins may therefore be less efficacious in AD+P than in schizophrenia.

Decreased efficiency for antipsychotics in AD+P compared with schizophrenia

To acquire a more direct measure, efficiencies of antipsychotics were calculated in the networks. The efficiency value of each antipsychotic was considered equal to the sum of all its targets' efficiency. FGAs and SGAs were calculated separately in two sets of networks. As Table 4 showed, all SGAs have lower efficiency values in the AD+P network compared with the SCZ network ($P < 0.001$). This might indicate that these SGAs would have lower activity in AD+P than in schizophrenia.

As for FGAs, their efficiency values were also calculated in AD+P network and SCZ network. Like SGAs, FGAs showed significantly lower values in AD+P than in schizophrenia (Table 5) ($P < 0.001$). In addition, some FGAs, like Chlorpromazine and Thioridazine, showed higher or comparable efficiency values with the top SGAs. These results can be interpreted in two ways: (i) the results are biased by the amount of study because more studies are done on FGAs so they have more known targets included in the database; (ii) since the network analysis method can only evaluate drug efficiency, it is possible that Chlorpromazine may have comparable or better efficacy than some SGAs. As a matter of effect, Chlorpromazine is reliable for its efficacy and one of the most tested FGAs. It has been used as a 'gold standard' to

Table 4. Network efficiency of second-generation antipsychotics calculated from AD+P network and SCZ network

Drugs	Efficiency in AD+P network	Efficiency in SCZ network
Paliperidone	1.694	1.831
Brexpiprazole	1.643	1.799
Sertindole	1.337	1.45
Aripiprazole	0.726	0.779
Clozapine	0.726	0.779
Iloperidone	0.726	0.779
Olanzapine	0.726	0.779
Quetiapine	0.726	0.779
Risperidone	0.726	0.779
Ziprasidone	0.726	0.779
Lurasidone	0.352	0.386
Pimavanserin	0.352	0.386
Paired Wilcoxon Test	$W = 78, P < 0.001$	

[a] AD+P network: protein–protein interaction network with AD+P-related genes and targets of antipsychotics; SCZ network: protein–protein interaction network with schizophrenia-related genes and targets of antipsychotics.

Table 5. Efficiency of first-generation antipsychotics in AD+P network and SCZ network

Drugs	Efficiency in AD+P network	Efficiency in SCZ network
Chlorpromazine	2.311	2.489
Thioridazine	1.675	1.798
Thiothixene	1.068	1.138
Trifluoperazine	0.961	1.037
Loxapine	0.726	0.779
Mesoridazine	0.726	0.779
Fluphenazine	0.716	0.752
Perphenazine	0.716	0.752
Haloperidol	0.699	0.755
Molindone	0.374	0.393
Paired Wilcoxon Test	$W = 55, P < 0.001$	

[a] AD+P network: protein–protein interaction network with AD+P-related genes and targets of antipsychotics; SCZ network: protein–protein interaction network with schizophrenia-related genes and targets of antipsychotics.

compare the efficacy of older and newer antipsychotic drugs. According to randomized controlled trials (RCTs) that compared chlorpromazine with any other atypical antipsychotic drugs for schizophrenia, it showed comparable efficiency with olanzapine, risperidone and quetiapine [51]. Therefore, it is reasonable that Chlorpromazine showed comparable efficiency values with the SGAs.

Weighted efficiency based on binding affinity values for antipsychotics in AD+P and schizophrenia

In the above sections, the efficiency values for antipsychotics were calculated as a simple sum of efficiency values from all its targets. A simple sum method is accurate under the assumption that all

Table 6. Weighted efficiency of selected antipsychotics in AD+P network and SCZ network

Drugs	Weighted efficiency in AD+P network	Weighted efficiency in SCZ network
Sertindole	8.535	9.357
Fluphenazine	4.016	4.206
Ziprasidone	3.619	3.964
Risperidone	0.967	1.058
Lurasidone	0.799	0.877
Loxapine	0.681	0.746
Clozapine	0.194	0.212
Olanzapine	0.177	0.193
Pimavanserin	0.092	0.101
Aripiprazole	0.025	0.026
Haloperidol	0.014	0.014
Quetiapine	0.008	0.009
Paired Wilcoxon Test	$W = 66, P = 0.0016$	

[a] AD+P network: protein–protein interaction network with AD+P-related genes and targets of antipsychotics; SCZ network: protein–protein interaction network with schizophrenia-related genes and targets of antipsychotics.

antipsychotics can impact their targets at the same strength. To acquire a more accurate result, binding affinity-weighted efficiency values were calculated for 12 antipsychotics for which data was available and 21 drug-target pairs were included. All the targets included in this section have been validated for pharmacological effects. Weights and weighted efficiencies were calculated as

$$W_{drug-target} = 10 \times RS \tag{7}$$

$$E_{weighted}(i) = W_{drug-target} * E(i), \tag{8}$$

where $W_{drug-target}$ is the weight for a drug-target pair, and S is the relative strength of the binding affinity between drug and target. Therefore, weighted efficiency for an antipsychotic can be calculated by the sum of all $E_{weighted}$ from its targets. As we can be seen in Table 6, the values of weighted efficiency for antipsychotics are significantly lower in AD+P network ($P = 0.0016$) than in the SCZ network.

Different pathways involved in AD+P and schizophrenia networks

To get a more detailed look at how AD+P network and SCZ network react toward antipsychotics, several of the commonly used SGAs (Aripiprazole, Olanzapine, Quetiapine and Risperidone) were selected as examples to explore the pathways that are affected when administered. All SGAs share DRD2 and HTR2A as major targets. The signaling pathways represented by first and second neighbors of these two targets are of great value since information flow attenuates quickly in networks [52].

Furthermore, pathway enrichment analysis was conducted for the genes that are exclusively affected in the AD+P network by DRD2 and HTR2A (489 genes for DRD2, 233 for HTR2A). The ten most significant pathways are shown in Table 7. The pathways identified in Table 7 are more specific for the AD+P network compared with the SCZ network.

From the pathways identified in Table 7, we can see a strong association with inflammation reactions in human tissue and can also see an association with autophagy and apoptosis. In addition, RNA synthesis and cell cycle-related pathways are highlighted in our results. Since HTR2A and DRD2 are the most targeted drug targets for antipsychotics and are involved in multiple biological processes that play important roles in human neurological

activities, the difference of their downstream effect can tell us a lot about how they respond differently to the medications. Just like we showed in Table 7, the results of the pathway analysis suggest a tighter bound between AD+P and neuroinflammation. As a matter of fact, AD+P was identified to be more correlated with depressive symptoms rather than schizophrenia suggestive of a possibility of different mechanisms behind the psychotic symptoms in AD+P and schizophrenia. In comparison with the functional annotation studies conducted with the DEGs by Dr Sweet's lab, our results showed a stronger presence of neuroinflammation which may provide insights for novel drug development.

Discussion and conclusion

In this study, we elucidated the underlying sources of efficacy differences of antipsychotics in AD+P and schizophrenia by using network efficiency and pathway analysis on combined disease-target networks. The major targets of antipsychotics are found to have lower efficiency in the AD+P network than in the SCZ network, indicative of antipsychotic's interaction with these targets may modulate AD+P less efficiently. Finally, we identified novel comprehensive pathways that are engaged by antipsychotics in AD+P, but not in schizophrenia, and which may contribute to the limited efficacy or enhanced toxicity of these medications in AD+P.

Multiple meta-analysis studies have reported modest efficacy of antipsychotics in treating AD+P [4, 53]. In those studies, Aripiprazole, Olanzapine, Quetiapine and Risperidone were most extensively studied. Though no significant effect was reported across trials and measurements, individual agents showed some efficacy on specific outcome measures. In our results, Aripiprazole, Olanzapine, Quetiapine and Risperidone are ranked 4th, 7th, 8th and 9th in Table 4 as the leading part in SGAs, but changed to 10th, 8th, 12th and 4th when they were weighted in Table 6. The ranks of these four SGAs concur well with other evidence of efficacy where Risperidone > Aripiprazole > Olanzapine > Quetiapine was suggested [54]. Risperidone, as the only antipsychotic licensed for the treatment of aggression (in Europe but not in the USA), has been reported by multiple studies including clinical trials as having beneficial effects against AD+P [54, 55].

While not many antipsychotics have been tested against AD+P, the results of this study can help nominate and repurpose antipsychotics that may possess higher efficacy in treating AD+P. Three antipsychotics, Sertindole, Fluphenazine and Ziprasidone, showed higher weighted efficacy than Risperidone which is the most effective and commonly used SGA in the clinic. Fluphenazine is an FGA, and is uncommonly used in AD+P due to extrapyramidal side effects, and thus we can rule it out from the list [56]. Sertindole and Ziprasidone provide better efficacy and safety profiles in treating psychosis [57, 58]. Previous studies also showed that Sertindole has better performance than other SGAs on cognitive functions such as processing speed and executive function while Ziprasidone has better performance on composite score, executive function and processing speed, working memory and memory and verbal learning [59]. The benefits of Sertindole and Ziprasidone can be supported by their higher affinity for 5HT6, 5HT2C and 5HT3 receptors [60, 61]. Therefore, we believe that Sertindole and Ziprasidone are promising candidates with improved efficacy in treating AD+P among SGAs.

The results of pathway enrichment analysis showed that when similar perturbation is applied to major antipsychotics' targets, such as DRD2 and HTR2A, AD+P patients will have different reactions compared to schizophrenia patients because the pathways influenced by the perturbation are different under the two disease

Table 7. Overrepresented specific pathways of AD+P

Targets	Pathways	P-value *	Overlaps with dataset	Genes overlapped with datasets
DRD2	Cell Cycle: G2/M DNA Damage Checkpoint Regulation	5.62E−09	0.22	ATR,BORA,BTRC,CDK1,PPM1D,PRKDC,RPS6KA1,WEE1, YWHAB,YWHAH,YWHAZ
	tRNA Charging	1.48E−05	0.179	AARS2,DARS1,EPRS1,GARS1,LARS2,RARS2,SARS1
	Role of PKR in Interferon Induction and Antiviral Response	3.16E−05	0.0882	ATF3,CASP8,HSP90AB1,IFIH1,IFNGR1,IRF1,JAK1,MAPK3, MARCO,NLRP3,STAT1,TRAF6
	Cyclins and Cell Cycle Regulation	6.76E−05	0.107	ATR,BTRC,CDK1,HDAC4,PPP2CA,RB1,RBL2,TGFB3,WEE1
	Systemic Lupus Erythematosus In B Cell Signaling Pathway	8.71E−05	0.0614	BCL2L1,CALML5,CD40,CTNNB1,IFIH1,IFNGR1,JAK1,LYN, MAPK3,PIK3CB,PIK3R5,PTPN11,RASGRP3,SHE,STAT1,TGFB3, TRAF6
	IL-22 Signaling	1.23E−04	0.208	IL10RB,IL22RA2,JAK1,MAPK3,STAT1
	Urate Biosynthesis/Inosine 5′-phosphate Degradation	1.62E−04	0.286	IMPDH1,IMPDH2,NT5C,NT5C1A
	EIF2 Signaling	2.88E−04	0.0628	ACTA2,ATF3,IGF1R,MAPK3,PIK3CB,PIK3R5,PPP1CB,RPL13A, RPL21,RPL32,RPL6,RPS14,RPS6,RPS8
	Phosphatidylcholine Biosynthesis I	3.02E−04	0.429	CHKA,PCYT1A,PCYT1B
	Wnt/β-Catenin Signaling	3.09E−04	0.0694	BMPR2,BTRC,CDH2,CSNK1A1,CTNNB1,PIN1,PPP2CA,SOX2, SOX9,TGFB3,TLE1,WNT8B
HTR2A	IL-22 Signaling	3.55E−06	0.208	IL10RB,IL22RA2,JAK1,MAPK3,STAT1
	Systemic Lupus Erythematosus In B Cell Signaling Pathway	2.51E−05	0.0433	CALML5,CD40,CTNNB1,FGR,IFNGR1,JAK1,LYN,MAPK3, PIK3CB,PIK3R5,PTPN11,STAT1
	Phosphatidylcholine Biosynthesis I	3.39E−05	0.429	CHKA,PCYT1A,PCYT1B
	Rac Signaling	7.76E−05	0.058	IQGAP1,ITGAL,MAPK3,PIK3CB,PIK3R5,PIP4K2A,PIP4K2C, PTK2B
	Role of JAK family kinases in IL-6-type Cytokine Signaling	1.05E−04	0.16	JAK1,MAPK3,PTPN11,STAT1
	JAK/Stat Signaling	1.78E−04	0.0732	JAK1,MAPK3,PIK3CB,PIK3R5,PTPN11,STAT1
	RhoA Signaling	2.57E−04	0.0565	ARHGEF1,GNA12,IGF1R,PIP4K2A,PIP4K2C,PPP1CB,PTK2B
	RhoGDI Signaling	3.31E−04	0.0419	ARHGEF1,GNA11,GNA12,GNB4,GRIP1,ITGAL,PIP4K2A, PIP4K2C,RHOU
	Interferon Signaling	4.47E−04	0.111	IFNGR1,IRF1,JAK1,STAT1
	Trans, trans-farnesyl Diphosphate Biosynthesis	9.77E−04	0.4	FDPS,IDI1

[a]P-value calculated by the right-tailed Fisher's Exact Test; AD+P: Alzheimer's disease with psychosis.

conditions. The identified overrepresented pathways shown in Table 7 indicate a special role of neuroinflammation and RNA synthesis in AD+P compared with schizophrenia. Furthermore, many studies have reported the role of neuroinflammation in the pathogenesis of AD [23, 62] and schizophrenia [63]. The results of our study showed that though inflammation processes are involved in both conditions, different responses can be activated in AD+P and schizophrenia patients and can be used to explain the causal relationship between activated systemic inflammation and the development of neuropsychiatric symptoms in AD [62]. The accordance between the existing reports and results of our pathway enrichment analysis provides additional support for the rationale of our results. The different pathways affected in AD+P and schizophrenia may also have a peripheral effect that can increase the risks of adverse events for antipsychotics in AD+P patients. Infection, for example, is a common adverse event reported by multiple studies [64, 65] and can be associated with the interruption of immune systems caused by these antipsychotics [66, 67].

The size difference between the AD+P and SCZ networks may raise bias. To minimize the possible bias, multiple approaches were considered, including filtering nodes and edges with certain threshold to fix the size or density of networks. However, these approaches may introduce new bias to this study by enforcing noise in a smaller network and ignore significant connections in a larger network. Furthermore, since these two networks are categorized as small-world networks, their connectivity parameters

are not sensitive to changes in network size by definition [38]. Additionally, a study indicated that the average path length and the cluster coefficient in a small-world network are not sensitive to change of node number or to average degree [68]. Since our efficiencies are calculated based on the path lengths in different networks, we believe it is safe to say the bias caused by network size in our measurement is minimized and acceptable.

Collectively, the result of this study not only provides a possible explanation for antipsychotics' modest efficacy in AD+P but can also help nominate antipsychotics that may possess higher efficacy in treating AD+P which should be tested and validated in further studies, especially for Sertindole and Ziprasidone. In addition, the methodology we used in this study showed great accordance with other reported pieces of evidence by incorporating bioactivity data with network analysis approaches. This methodology can be applied to provide support and guidance in drug repurposing or treatment optimization studies for building personalized therapies for these patients.

Key Points

- Recent breakthroughs in AD+P genetics studies (GWAS and DEGs) provided unprecedented opportunities in mechanism studies and treatment screenings for AD+P.
- By combining network analysis and systems pharmacology approaches, we were able to quantitatively evaluate

the differences for antipsychotics' efficacy in AD+P and schizophrenia.

- We found that antipsychotics' targets are less connected to the proteins that are involved in AD+P compared to schizophrenia, which is accordant to the reported decrease in efficacy of antipsychotics in AD+P.
- By incorporating binding affinity data into the network analysis, we got the consistent conclusions on the decreased efficiency of antipsychotics in AD+P.

Data availability

Data sources used in this study are described in the Methods and Materials sections. Genes that are associated with AD+P and schizophrenia were collected and combined from multiple sources, and we are happy to provide the formatted data upon request. The drugs and their targets along with binding affinity data are included in the supplementary materials.

Supplementary Data

Supplementary data are available online at https://academic.oup.com/bib.

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