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Central insulin dysregulation in antipsychotic-naïve first-episode psychosis: *In silico* exploration of gene expression signatures

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ABSTRACT

Antipsychotic drug (AP)-naïve first-episode psychosis (FEP) patients display premorbid cognitive dysfunctions and dysglycemia. Brain insulin resistance may link metabolic and cognitive disorders in humans. This suggests that central insulin dysregulation represents a component of the pathophysiology of psychosis spectrum disorders (PSDs). Nonetheless, the links between central insulin dysregulation, dysglycemia, and cognitive deficits in PSDs are poorly understood. We investigated whether AP-naïve FEP patients share overlapping brain gene expression signatures with central insulin perturbation (CIP) in rodent models. We systematically compiled and meta-analyzed peripheral transcriptomic datasets of AP-naïve FEP patients along with hypothalamic and hippocampal datasets of CIP rodent models to identify common transcriptomic signatures. The common signatures were used for pathway analysis and to identify potential drug treatments with discordant (reverse) signatures. AP-naïve FEP and CIP (hypothalamus and hippocampus) shared 111 and 346 common signatures respectively, which were associated with pathways related to inflammation, endoplasmic reticulum stress, and neuroplasticity. Twenty-two potential drug treatments were identified, including antidiabetic agents. The pathobiology of PSDs may include central insulin dysregulation, which contribute to dysglycemia and cognitive dysfunction independently of AP treatment. The identified treatments may be tested in early psychosis patients to determine if dysglycemia and cognitive deficits can be mitigated.

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1. Introduction

Individuals with psychosis spectrum disorders (PSDs) including schizophrenia face a 20–25-year reduction in life expectancy which has been strongly associated with increased risk of cardiovascular disease (Olfson et al., 2015; Vermeulen et al., 2017). A significant contributor to the increased cardiovascular risk in PSDs is the high rate of metabolic comorbidities among these patients (Mamakou et al., 2018; Mitchell et al., 2013). Multiple exogenous factors confer the metabolic risk in PSDs, including antipsychotic (AP) medications, the cornerstone treatment for PSDs (Mitchell et al., 2013). However, it is increasingly established that metabolic abnormalities, particularly dysglycemia, precede initiation of AP treatment and present early in the illness course of PSDs. Notably, individuals at high-risk or experiencing their first-episode of psychosis (FEP) present with markers of dysregulated glucose metabolism (Chen et al., 2016; Chouinard et al., 2019; Perry et al., 2016; Ryan et al., 2003; Van Nimwegen et al., 2008). Additionally, schizophrenia patients face a three-fold increase in risk for type 2 diabetes (T2D), even before being exposed to APs (Rajkumar et al., 2017). This suggests that dysglycemia may be an intrinsic feature of PSDs, where the pathobiology of PSDs drive dysregulations that contribute to psychopathology and premorbid dysglycemia independent of the effects of lifestyle and AP exposure.

While the exact pathophysiological mechanisms underlying dysglycemia intrinsic to PSDs remain understudied, impaired central insulin action has been suggested to play a role (Agarwal et al., 2020a). Specifically, insulin signalling in the hypothalamus represents an important regulator of whole-body glucose homeostasis. In humans, administering intranasal insulin, which acts on the central nervous system (CNS), decreases hepatic glucose production (Dash et al., 2015). Conversely, preclinical perturbations that disrupt central insulin signalling produces hyperglycemia, and preclinical manipulations of central insulin signalling result in metabolic phenotypes that overlap with those observed in AP-naïve FEP patients (Koch et al., 2008). Indeed, AP-naïve FEP patients demonstrate hepatic insulin resistance and increased hepatic glucose production that is not attributable to other factors known to associate with hepatic insulin resistance (*e.g.*, intra-abdominal fat mass) (Van Nimwegen et al., 2008). Thus, it may be postulated that abnormalities in central insulin signalling produce hepatic insulin resistance intrinsic to PSDs (Agarwal et al., 2020a).

Further, PSDs are associated with premorbid cognitive dysfunction in addition to dysglycemia (Mohn-Haugen et al., 2022). Interestingly, this may also be explained by central insulin dysregulations where by central insulin has an established role in regulating cognition (Agarwal et al., 2020a). In addition, individuals with schizophrenia and comorbid type 2 diabetes demonstrate worse cognitive impairments than normo-glycemic individuals with schizophrenia (Bora et al., 2017; MacKenzie et al., 2018). Moreover, rodents with insulin resistance in the hippocampus demonstrate worsened cognition (Grillo et al., 2015; McNay et al., 2010). In FEP patients, cognitive dysfunction primarily arises from the connectivity between the hippocampus and dorsolateral prefrontal cortex (DLPFC). In turn, administering intranasal insulin enhances the hippocampus-DLPFC network (Kullmann et al., 2017). Taken together, central insulin dysregulation may represent a common mechanism linking premorbid cognitive and metabolic dysfunctions in PSDs (Agarwal et al., 2020a), and further exploring this hypothesis may help inform novel treatment options for both the metabolic and cognitive aspects of PSDs.

Here, we aimed to examine whether central insulin dysregulation characterizes PSDs at the gene expression level. Specifically, we investigated whether AP-naïve FEP patients share overlapping brain gene expression patterns with central insulin perturbation (CIP) in rodent models by meta-analyzing published transcriptomic datasets. We reasoned that examining AP-naïve FEP patients would better parse out gene expression changes directly associated with PSDs, independent of confounding extrinsic factors such as AP use. Hence, overlapping gene expression patterns that are shared between AP-naïve FEP and CIP rodent models may represent a common mechanism between PSDs and central insulin dysregulation. Because postmortem brain transcriptomics are generally unavailable in young AP-naïve FEP patients, we instead used peripheral tissue transcriptomics for our investigations given significant transcriptomic overlaps in peripheral blood and brain (Hess et al., 2016; Sullivan et al., 2006). Additionally, transcriptomic data repositories were probed for hippocampal and hypothalamic transcriptomics of CIP rodent models, considering the role of these respective brain regions in metabolism and cognition. The overlapping gene expression signatures between AP-naïve FEP and CIP rodent models were analyzed to identify associated biological pathways and candidate pharmacological treatments for intrinsic dysglycemia and cognitive dysfunction in PSDs. Taken together, our analyses revealed that PSDs may share overlapping gene expression changes to those of central insulin dysregulation. These alterations may be mediated by endoplasmic reticulum (ER) stress, inflammation, and neuroplasticity processes. Further, several potential drug treatments were identified, which could hold important implications for dually mitigating dysglycemia and cognitive deficits intrinsic to PSDs.

2. Methods

The workflow consisted of the following: 1) systematic search and selection of datasets; 2) differential expression analysis; 3) meta-analysis; 4) pathway enrichment analysis; and 5) iLINCS connectivity analysis to identify candidate drug treatments (Fig. 1).

2.1. Antipsychotic-naïve first-episode psychosis database

Transcriptomic datasets examining peripheral tissue of AP-naïve FEP patients were identified through a systematic search. Ovid PsychINFO, EMBASE, MEDLINE, and Gene Expression Omnibus (GEO; https://www.ncbi.nlm.nih.gov/gds) were searched for studies published before March 2021 (*PROSPERO* ID: 185,602). The search string combined keywords and MeSH terms comprising three conceptual groups: antipsychotic-naïve, psychosis, and transcriptomics (Table S1). Covidence (https://www.covidence.org/) was used for study de-duplication and selection. Two reviewers (JL and MP) independently screened the studies based on title and abstract, then full-text according to prespecified eligibility criteria. Inclusion criteria were: 1) absence of prior AP exposure; 2) clinically confirmed FEP; 3) adult age (18–65); and 4) use of transcriptomics approaches in the respective studies. Exclusion criteria included: 1) lack of an unaffected comparison group; 2) study examined too few genes (inferred from the range of p-values of the reported genes); or 3) co-morbidities or medications deemed as potential confounders on metabolism. Discussions regarding study inclusion and exclusion were resolved between the two reviewers and involved a third reviewer (MKH), when necessary.

From the included studies, we extracted differential gene expression data, comprising the gene symbol, log fold-change, and p-value. Where available, full differential expression analysis results were extracted. Otherwise, partial results were extracted (i.e., studies that reported significant genes only). While using raw data would be ideal to ensure consistent processing and analysis of transcriptomic data across studies, only one of the five included studies provided raw gene expression data. Attempts were made to contact authors of unpublished studies (e.g., conference abstracts).

2.2. Central insulin perturbation database

To curate a database of hypothalamic and hippocampal transcriptomic changes that result from impaired central insulin action, we searched GEO with the following well established perturbations that impair central insulin signalling: high-fat diet (Ono et al., 2008), insulin receptor knockout and knockdown (Obici et al., 2002a, 2002b),

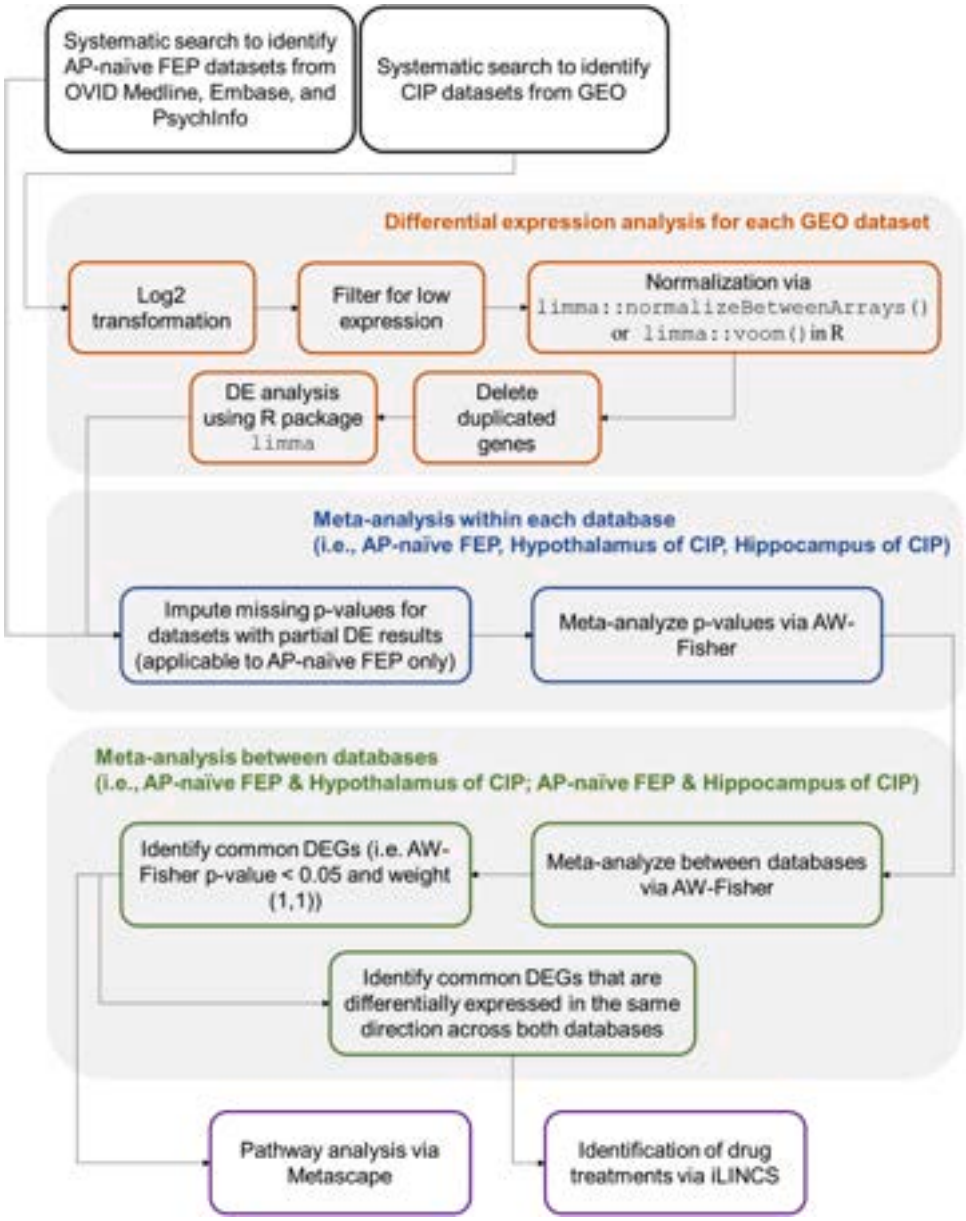

Fig. 1. Study workflow. AP-naïve FEP=antipsychotic-naïve first-episode psychosis, GEO=Gene Expression Omnibus, DEG=differentially expressed gene, iLINCS=Library of Integrated Network-Based Cellular Signatures.

phosphoinositide 3-kinase (PI3K) inhibition (Obici et al., 2002a), AMP-activated protein kinase (AMPK) agonism (Perrin et al., 2004), mitogen-activated protein kinase (MEK) inhibition (Filippi et al., 2012), Cannabinoid Receptor Type 1 (CB_1R) agonism (O'Hare et al., 2011), nitric oxide synthase (NOS) inhibition (Shankar et al., 1998), resistin treatment (Muse et al., 2007; Singhal et al., 2007), and neuropeptide Y (NPY) treatment (Marks and Waite, 1997; Van Den Hoek et al., 2008, 2004). The bolded terms for each perturbation in Table S3 were searched with and without abbreviations in the following manner: (bolded term, e.g. *NPY* OR *neuropeptide Y*) AND (*hypothalamus* OR *hypothalamic* OR *hippocampus* OR *hippocampal*). The search was conducted in July 2019 and updated in March 2021. Each dataset was screened independently by two reviewers (JL, WBM, RA). Inclusion criteria were: 1) transcriptomic changes that result from the specified molecular perturbations, and 2) transcriptomic analysis of hypothalamic or hippocampal tissue. Exclusion criteria were: 1) brain tissues derived from metastases or tumors; 2) lack of an appropriate control group; or 3) application of multiple perturbations (in addition to the specified central insulin perturbations). Raw data for the included studies were extracted.

2.3. *Differential expression analysis*

Differential expression analysis was conducted on the CIP rodent model datasets using a pipeline consisting of log2 transformation, filtering to remove genes with low expression, quantile normalization in R, and differential expression analysis. Log2 transformation was applied to datasets that met one of the two following conditions: 1) the 99th quantile is greater than 100, or 2) the range of the data is greater than 50 and the first quartile is greater than 0. The data were then filtered for low expression. For sequencing data, genes whose count per million (CPM) was less than 1 in more than half of the samples were filtered. For microarray data, genes that have negative values before any transformation in more than half of the samples were filtered. Genes that were present in the AP-naïve FEP results were kept from filtering. Then, quantile normalization in R was performed as needed. For genes with duplicate records, the record with the greatest variance was retained.

Subsequently, we identified differentially expressed genes (DEGs) for each study through the limma package in R (Ritchie et al., 2015). For studies with multiple contrasts, contrasts with completely different samples were treated as different studies, and two-group DE analysis was conducted on each contrast separately. On the other hand, studies with multiple contrasts that shared the same control group were fitted into the full model and tested for the global null, whether there is at least one contrast that shows a significant difference between the control and the treatment groups.

2.4. Meta-analysis

Meta-analysis was first performed among studies within each database (AP-naïve FEP, hypothalamus of CIP rodent models, and hippocampus of CIP rodent models). The AP-naïve FEP datasets were meta-analyzed using the truncated p-values combination method (Tang et al., 2014), where the missing p-values for partial differential expression datasets were imputed using mean imputation, followed by combination of p-values for all studies using adaptively weighted Fisher's method (AW-Fisher) (Huo et al., 2020). Because the CIP datasets were comprised of full differential expression data only, AW-Fisher was applied directly on the differential expression results to combine the p-values. The resulting meta-analyzed data from each database were then meta-analyzed with each other using AW-Fisher to identify common DEGs between: 1) AP-naïve FEP and the hypothalamus of CIP rodent models, and 2) AP-naïve FEP and the hippocampus of CIP rodent models. Common DEGs were defined as genes with AW-Fisher p-value $<$ 0.05 and weight (1,1). Additionally, a weighted average of log fold-changes were calculated for each gene across studies that reported log fold-changes, where the weight was determined by the inverse p-value of each gene within each study.

2.5. Scripts

All scripts used in the analysis are deposited in GitHub (https://github.com/XiangningXue/FEP_MetaAnalysis)

2.6. Pathway enrichment analysis by metascape

Metascape is an annotation and analysis tool for gene expression data (Zhou et al., 2019). To conduct pathway analysis, we inputted the gene symbol and p-values of the common DEGs. The full list of genes that overlapped across studies was inputted as background genes. The following parameters were applied: minimum overlap of 3 and minimum enrichment of 1. The following pathway databases were applied: GO Biological Processes, Reactome Gene Sets, and KEGG Pathway. Pathways with $\leq$ 5 gene members were excluded to avoid challenges with interpreting small pathways.

2.7. Identification of drug treatments via iLINCS

iLINCS (www.ilincs.org/ilincs/) (Pilarczyk et al., 2022) was used to identify chemical perturbagens that have gene expression patterns discordant to the common DEGs. We reasoned that pharmacological agents with discordant gene expression patterns may be able to correct the DEGs shared between AP-naïve FEP and early dysglycemia, and in effect, treat intrinsic dysglycemia in PSDs. This was done through the connectivity analysis feature on iLINCS and selecting the Connectivity Map signature library that contains transcriptomic profiles of various pharmacological agents. The "concordance score" of the connectivity analysis relies on the direction of dysregulation of each gene signature. As such, we first selected overlapping DEGs that were dysregulated in the same direction (upregulated or downregulated in both AP-naïve FEP and CIP) based on the sign of the average log-fold change. The list of upregulated and downregulated genes was inputted into iLINCS. Drugs that are highly discordant to the inputted signatures based on a previously used concordance score of ≤ -0.321 (O'Donovan et al., 2021) were identified as potential treatments.

3. Results

3.1. Systematic search results

The AP-naïve FEP search identified 712 records, of which 5 were included (Fig. 2) (Gassó et al., 2017; Kumarasinghe et al., 2013; Leirer et al., 2019; Sainz et al., 2013; Xavier et al., 2020). One study examined transcriptomics in two different tissue types (Gassó et al., 2017), which were each treated as individual studies in subsequent analyses. Thus, a total of 6 datasets were retrieved. The AP-naïve FEP studies applied transcriptomics to whole blood ($N = 3$), peripheral blood mononuclear cells ($N = 1$), fibroblasts ($N = 1$), and lymphoblastoid tissue ($N = 1$). Complete differential expression data were available for 3 datasets, while partial differential expression data were available for the remaining 3 datasets. Full study characteristics are detailed in Table S3.

For CIP rodent model studies, of the 138 studies initially identified, 15 studies were included that examined the hypothalamus ($N = 7$; GSE127056 (Vagena and Baillie, 2019), GSE113943 (Williams et al., 2018), GSE104338 (Mutch, 2018), GSE73436 (Lam, 2016), GSE104709 (Perron et al., 2018), GSE167264 (Roh, 2021), GSE157077 (Samad et al., 2020)) and hippocampus ($N = 8$; GSE63174 (Sharma et al., 2014), GSE57823 (Bilkei-Gorzo et al., 2017), GSE64607 (Guerrieri and van Praag, 2015), GSE88723 (Hermey and Blüthgen, 2017), GSE116813 (Pevsner, 2018), GSE50873 (Kobilo et al., 2014), GSE167264 (Roh, 2021), GSE154434 (Liu and Jin, 2021)) (Fig. 3). The hypothalamic studies employed high-fat diet ($N = 6$) and AMPK knock-in ($N = 1$) as central insulin perturbations. The hippocampal studies applied high-fat diet ($N = 3$), CB1R agonist ($N = 2$), AMPK activation ($N = 2$), and MEK inhibitor ($N = 1$) as central insulin perturbations. Full study characteristics are presented in Table S4.

3.2. Common differentially expressed genes

Impaired central insulin action in PSDs was supported by findings of overlapping gene expression patterns across AP-naïve FEP and CIP rodent models. We conducted meta-analyses which identified AP-naïve FEP and the hypothalamus of CIP rodent models to share 111 common DEGs. Of these common DEGs, 27 were upregulated and 23 were downregulated. AP-naïve FEP and the hippocampus of CIP rodent models were found to have 346 common DEGs, of which 77 were upregulated and 88 were downregulated (Table S5).

3.3. Pathway enrichment analysis

The overlapping gene expression patterns between AP-naïve FEP and CIP rodent models were subject to pathway enrichment analysis in order to explore associated pathways. Table 1 presents the top 15 biological processes associated with the overlapping gene expression signatures of AP-naïve FEP human subjects and the hypothalamus of CIP rodent models. The top 15 processes were primarily related to inflammation, including inflammatory response, antimicrobial humoral response, chemokine production, inhibitors of nuclear factor kappa-B kinase subunit β (IKKβ)/nuclear factor kappa B (NF-κB) signaling, B-cell activation, positive regulation of interleukin (IL)−10 production, IL-4 and IL-13 signaling, extracellular signal-regulated kinase (ERK)1/ERK2 cascade, and nerve growth factor (NGF)-stimulated transcription. The full list of pathways is presented in Table S6A.

The top 15 pathways associated with the overlap between AP-naïve FEP and the hippocampus of CIP rodent models were primarily related to ER stress (positive regulation of proteolysis, glycosylation, and positive regulation of toll-like receptor signaling), and inflammation (myeloid leukocyte activation and toll-like receptor signaling). Additionally, processes related to neuroplasticity were identified including

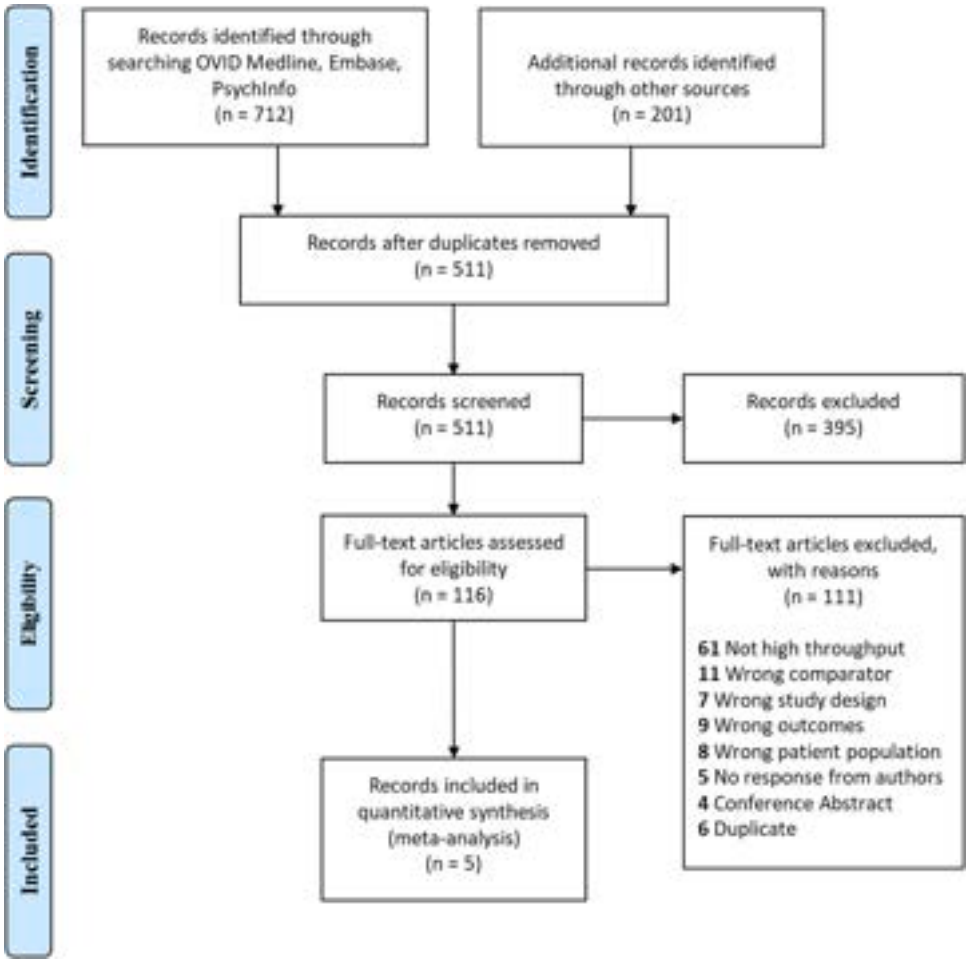

Fig. 2. PRISMA Flowchart of Antipsychotic-Naïve First-Episode Psychosis (AP-naïve FEP).

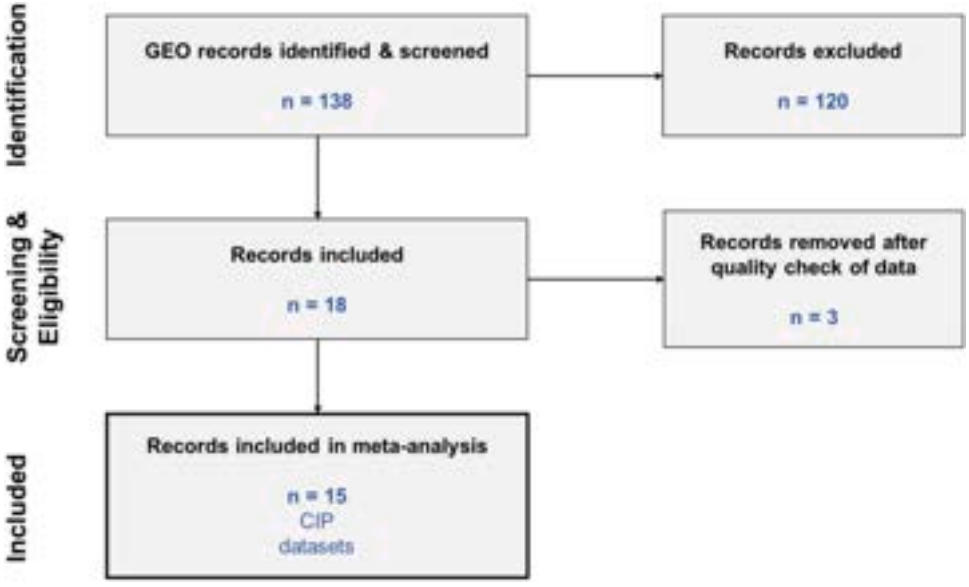

Fig. 3. Flowchart of Included and Central Insulin Perturbation (CIP) studies.

negative regulation of cell secretion, protein localization to membrane, RAB geranylgeranylation, neuronal apoptosis, and the vascular endothelial growth factor (VEGF) receptor signaling pathway (Table 1). The full list of pathways is presented in Table S6B.

3.4. iLINCS identification of drug treatments

We inputted the commonly upregulated and downregulated genes that AP-naïve FEP shared with each of the hypothalamus and

Table 1
Top 15 Functional Clusters Enriched in the Common Signatures Between Antipsychotic-Naïve First-Episode Psychosis and Central Insulin Perturbation datasets.

Pathway name	# Genes found	-Log(P-value)	Gene Members
AP-naïve FEP & Hypothalamus of CIP			
Inflammatory response	21/147	5.586	BCL6,C5AR1,CASP1,CD6, CYBB,F2R,FOS,FPR1, NOTCH1,PPBP,PRCP, S100A8,S100A9,STAT3, TIMP1,TNFRSF1A,LY86, LY96,PLD3,PYCARD, AKNA
Antimicrobial humoral response	6/14	4.656	BCL3,LCN2,PPBP,S100A8, S100A9,OCIAD2
Peptide ligand-binding receptors	5/16	3.198	C5AR1,F2R,FPR1,PPBP, HEBP1
Neural precursor cell proliferation	5/18	2.939	C5AR1,ID2,NOTCH1, LEF1,AKNA
Chemokine production	5/19	2.823	CD74,EIF2AK2,S100A8, S100A9,PYCARD
I-kappaB kinase/NF-kappaB signaling	11/83	2.821	BCL3,CASP1,CD74,F2R, LGALS1,S100A4,TFRC, TNFRSF1A,LY96, PYCARD,CXXC5
B cell activation	10/72	2.761	BCL3,BCL6,CD27,CD74, CD79A,LGALS1,LYL1, TFRC,LEF1,DOCK11
Positive regulation of interleukin-10 production	3/6	2.726	BCL3,STAT3,PYCARD
Interleukin-4 and Interleukin-13 signaling	6/34	2.344	BCL6,F13A1,FOS,LCN2, STAT3,TIMP1
Energy homeostasis	3/8	2.309	PRCP,STAT3,PASK
Interleukin-10 signaling	4/17	2.149	FPR1,STAT3,TIMP1, TNFRSF1A
NGF-stimulated transcription	3/9	2.149	FOS,ID2,LYL1
Positive regulation of ERK1 and ERK2 cascade	5/31	1.856	C5AR1,CD74,F2R, NOTCH1,PYCARD
Peptide secretion	6/44	1.791	ABCA1,CD74,F2R,ACSL4, S100A8,PASK
Cell activation involved in immune response	19/245	1.715	BCL3,BCL6,C5AR1,CD74, CYBB,FPR1,LCN2, LGALS1,PPBP,PRCP, S100A8,S100A9,STAT3, TFRC,CD93,BRI3, PYCARD,LEF1,DOCK11
AP-naïve FEP & Hippocampus of CIP			
Defense response to bacterium	11/22	3.176	CEBPB,CYBA,GRN, PRKCD,RPL30,RPL39, TNFRSF1A,PGLYRP1, SYT11,TBK1,OCIAD2
Negative regulation of secretion by cell	8/15	2.651	F2R,NOTCH1,TNFRSF1A, TNFRSF1B,UCP2,ERP29, SYT11,MIDN
Antimicrobial humoral response	5/7	2.521	HMGN2,RPL30,RPL39, PGLYRP1,OCIAD2
Negative regulation of kinase activity	18/54	2.283	CEBPA,DUSP1,DUSP6, GBA,GPS1,HSPB1,NCK1, PDPK1,PPP2R1A,PRKCD, YWHAG,GMFG,TRIB1, PRDX3,FBXO7,TESC, GGNBP2,MIDN
Positive regulation of cellular amide metabolic process	13/35	2.212	DDX3X,EEF2,IFNGR1, NCK1,PRKCD,RPL30, TNFRSF1A,VIM,NSMAF, USP16,MRPS27,PABPC1, POLDIP3
Nuclear-transcribed mRNA catabolic process, nonsense-mediated decay	16/47	2.18	ETF1,GSPT1,EXOSC10, PPP2R1A,RPL12,RPL24, RPL30,RPL39,RPS2, RPS10,RPS11,RPS15A, RPS20,RPS25,UPF2, PABPC1
Positive regulation of toll-like receptor signaling pathway	5/8	2.165	CYBA,DDX3X,PJA2, RTN4,SLC15A4
Negative regulation of neuron apoptotic process	9/21	2.119	ADAM8,CEBPB,F2R,FYN, GBA,GRN,PDPK1,RASA1, OXR1
Myeloid leukocyte activation	45/179	2.003	ADAM8,ALDOA,ANPEP, RHOG,CD47,CEBPA, CTSB,CTSD,CTSZ,CYBA, DDX3X,EEF2,GRN, IFNGR1,ILF2,IMPDH1, ITGAM,LAMP2,LTA4H, LTBR,PDPK1,PRKCD, S100A11,SLC2A3, STXBP2,TIMP2, TNFRSF1B,CST7,CPNE3, PGLYRP1,GMFG,PJA2, CCT8,IQGAP2,TMC6, SYT11,BRI3,GCA,RAP2C, TMBIM1,TXNDC5,LRG1, SLC15A4,RAB37, TBC1D10C
Positive regulation of osteoblast differentiation	4/6	1.919	CEBPA,CEBPB,CLIC1, PDLIM7
RAB geranylgeranylation	7/16	1.792	RAB5A,PTP4A2,RAB32, RAB21,RAB8B,RAB40C, RAB37
Positive regulation of proteolysis	22/78	1.732	ADAM8,ATP2A3,CEBPA, CSNK1D,CTSD,DDX3X, ENO1,F2R,FYN,GBA,GRN, MBP,NRDC,TNFRSF1B, USP5,OGT,FADD,RBX1, PSME3,TRIB1,ARIH2, UBQLN1
Vascular endothelial growth factor receptor signaling pathway	10/28	1.676	CYBA,FYN,HSPB1,ITGA5, NCK1,PRKCB,PXN, MAPKAPK3,MAPKAPK2, PRKD2
Protein localization to membrane	34/138	1.494	RHOG,AP2M1,FYN, ITGAM,PDPK1,RPL12, RPL24,RPL30,RPL39, RPS2,RPS10,RPS11, RPS15A,RPS20,RPS25, SSR1,SSR2,TNFRSF1A, YWHAG,SLMAP,NUMB, VAMP5,EHD1,SEC61B, RAB32,CLSTN1,TSPAN17, SH3GLB1,ASB3,RAB8B, TESC,RAB40C,TMBIM1, PLEKHF1
Glycosylation	9/26	1.462	GBA,PLOD1,OGT,PLOD3, GBGT1,ALG5,SLC35C2, UBE2J1,KRTCAP2

AP-naïve FEP=antipsychotic-naïve first-episode psychosis, CIP=central insulin perturbation.

hippocampus of CIP rodent models into iLINCS to identify FDA-approved drugs with discordant gene signatures (Table 2). Of note, several antidiabetic agents were identified to reverse overlapping signatures between FEP and CIP (hypothalamic and/or hippocampal), including metformin, chlorpropamide, troglitazone, and rosiglitazone, which is consistent with central insulin's role in regulating glucose homeostasis. Of these drugs, the antidiabetic agent chlorpropamide, a sulfonylurea, was identified to have gene expression signatures discordant to both the hypothalamic and hippocampal CIP overlap with AP-naïve FEP. These agents may mitigate the overlapping gene expression changes of AP-naïve FEP and CIP, supporting the presence of shared mechanistic pathways between dysglycemia and PSDs.

4. Discussion

Increasing evidence suggest that central insulin dysregulation could be involved in the early pathophysiology of PSDs (Agarwal et al., 2020a). Additionally, considering the role of CNS insulin in cognition

Table 2
FDA-Approved Drugs Identified by iLINCS (Library of Integrated Network-Based Cellular Signatures) that are Discordant with Common Signatures of Antipsychotic-Naïve First-Episode Psychosis and Central Insulin Perturbation Rodent Models. The Canonical Mechanism of Action was Referenced from DrugBank (https://go.drugbank.com/) and the Classification from Anatomical Therapeutic Chemical (https://www.whocc.no/atc_ddd_index/).

Perturbagen	Anatomical Therapeutic Chemical First Level Classification	Canonical Mechanism of Action (DrugBank)
AP-naïve FEP & Hypothalamus of CIP		
Daunorubicin	Antineoplastic and immunomodulating agents	DNA topoisomerase inhibitor
Chlorpropamide	Alimentary tract and metabolism	ATP-binding cassette sub-family C member 8 inhibitor
Irinotecan	Antineoplastic and immunomodulating agents	DNA topoisomerase inhibitor
Mestranol	Not available	Estrogen receptor agonist
Tamoxifen	Antineoplastic and immunomodulating agents; anti-estrogen	Estrogen receptor competitive inhibitor; Protein Kinase C inhibitor; sex hormone-binding globulin inducer
Mitoxantrone	Antineoplastic and immunomodulators	DNA topoisomerase 2-alpha inhibitor
Cycloserine	Antiinfectives for systemic use	D-alanine synthetase inhibitor, Alanine racemase inhibitor
Metformin	Alimentary tract and metabolism; antidiabetic; biguanide	Inhibits mitohcondrial complex 1 in the liver
Dipyridamole	Blood and Blood Forming Organs	Stimulates prostacyclin release and likely inhibits adenosine deaminase and phosphodiesterase-> degrade cAMP
Fulvestrant	Antineoplastic and immunomodulating agents; anti-estrogen	Estrogen receptor alpha antagonist
Alprostadil	Cardiovascular system	Prostaglandin E2 receptor EP2,1 subtypes agonist
Colchicine	Musculo-skeletal system	Tubulin beta chain inhibitor/ binder
Simvastatin	Cardiovascular system; lipid modifying agents	HMG-CoA reductase inhibitor
Doxorubicin	Antineoplastic and immunomodulators	DNA topoisomerase 2-alpha inhibitor
Clobetasol	Dermatologicals	Bind to glucocorticoid receptor
AP-naïve FEP & Hippocampus of CIP		
Medrysone	Sensory organs	Not fully elucidated;
Chlorpropamide	Alimentary tract and metabolism	ATP-binding cassette sub-family C member 8 inhibitor
Troglitazone	Alimentary tract and metabolism	Peroxisome proliferator-activated receptor (PPARγ) agonist
Rosiglitazone	Alimentary tract and metabolism	Peroxisome proliferator-activated receptor (PPARγ) agonist
Promazine	Nervous system	Dopamine D2 receptor antagonist and sertonin type 2 receptors
Saquinavir	Anti-infectives for systemic use	HIV-1 protease inhibitor
Valproic acid	Nervous system	Not fully elucidated; inhibit succinic semialdehyde dehydrogenase; impacts ERK pathway; indirectly inhibits myoinositol-1-phosphate synthetase; direct inhibitor of histone deacetylase
Ethotoin	Nervous system	Sodium Channel inhibitor

AP-naïve FEP=antipsychotic-naïve first-episode psychosis, CIP=central insulin perturbation.

and regulation of glucose homeostasis, disruptions in brain insulin action may represent a shared mechanism explaining the association between dysglycemia and cognitive impairments in PSDs (Agarwal et al., 2020a). This raises the question of whether the pathology of PSDs is characterized by central insulin dysregulation at the gene expression level. To investigate this, we examined whether AP-naïve FEP patients present with an overlap in DEGs as compared to the hippocampus and hypothalamus of CIP rodent models. In support of central insulin dysregulation underlying metabolic and cognitive dysregulation in PSDs, we found that AP-naïve FEP transcriptome signatures share 111 and 346 common DEGs with transcriptome signatures from rodent models of perturbations in central insulin action on hypothalamic and hippocampal tissues, respectively. Additionally, our pathway analyses examining overlapping gene signatures of AP-naïve FEP and CIP rodent models point to several mechanisms that may mediate the interplay between central insulin, dysglycemia, and cognitive dysfunction in PSDs (Fig. 4).

4.1. Overlapping hypothalamic gene signatures

The common gene expression signatures between AP-naïve FEP and hypothalamic insulin signalling disruptions suggest inflammation as a common mediator of central insulin and intrinsic dysglycemia in PSDs. Notably, we observed shared involvement of IKKβ/NF-κB signaling, and pathways related to cytokines, chemokines, NGF and ERK1/2 action, all of which have been linked to inflammation (Benomar and Taouis, 2019; Fodelianaki et al., 2019). This is consistent with the growing evidence supporting inflammation as an intrinsic feature of PSDs (Khandaker et al., 2015; Prestwood et al., 2021) and an established disruptor of hypothalamic insulin signaling. Indeed, altered hypothalamic insulin signaling leads to whole body insulin resistance and dysregulation of hepatic glucose production (Belsham and Dalvi, 2021; Benomar and Taouis, 2019; Jais and Brüning, 2017; Lewis et al., 2021). Specifically, NF-κB is a transcription factor that increases the expression of proinflammatory cytokines, including IL-6 and IL-1β, which subsequently disrupt hypothalamic insulin signaling (Benomar and Taouis, 2019). IKKβ/NF-κB signaling also interferes with hypothalamic insulin signaling by upregulating suppressors of cytokine signaling 3 (SOCS3); SOCS3 impairs insulin-dependent phosphorylation of the insulin receptor and targets the insulin receptor substrate (IRS)1/2 for proteasomal degradation, both of which are required for insulin signaling transduction (Benzler et al., 2015; Howard and Flier, 2006; Zhang et al., 2008). Similarly, ERK1/2 activation promotes production of proinflammatory cytokines, including IL-6, and IL-1β (Benomar and Taouis, 2019). On the other hand, NGF suppresses IL-6 and IL-1β action (Fodelianaki et al., 2019), suggesting that reduced NGF action may potentiate hypothalamic inflammation and further disrupt insulin signaling. Regarding chemokines, CCL5 has been implicated in hypothalamic regulation of glucose tolerance (Chou et al., 2016; Morari et al., 2014). CCL2, which has been linked to type 2 diabetes (Panee, 2012), is upregulated in the hypothalamus of rodents fed a high-fat diet, a known central insulin perturbation (Morari et al., 2014). In line with this, FEP patients demonstrate increased levels of NF-κB activation (Song et al., 2009), IL-6 and IL-1β (Gallego et al., 2018; Goldsmith et al., 2016; Orlovska-Waast et al., 2019; Pillinger et al., 2019; Prestwood et al., 2021; Upthegrove et al., 2014), and CCL2 (Frydecka et al., 2018), while NGF is reduced (Kale et al., 2009). Thus, hypothalamic inflammation may induce central insulin resistance, contributing to intrinsic glucose dysregulation in PSDs.

4.2. Overlapping hippocampal gene signatures

Consistent with the suggested role of hippocampal insulin in cognition (Agarwal et al., 2020a), the overlap between AP-naïve FEP and the hippocampus of CIP rodent models was associated with processes suggestive of neuroplasticity: neuronal apoptosis, regulation of cell secretion, and protein localization to membranes, specifically Rab geranylgeranylation, which regulates neuronal receptor trafficking (Hausser and Schlett, 2019). Our pathway analyses suggest three potential mediators between cognition and central insulin action:

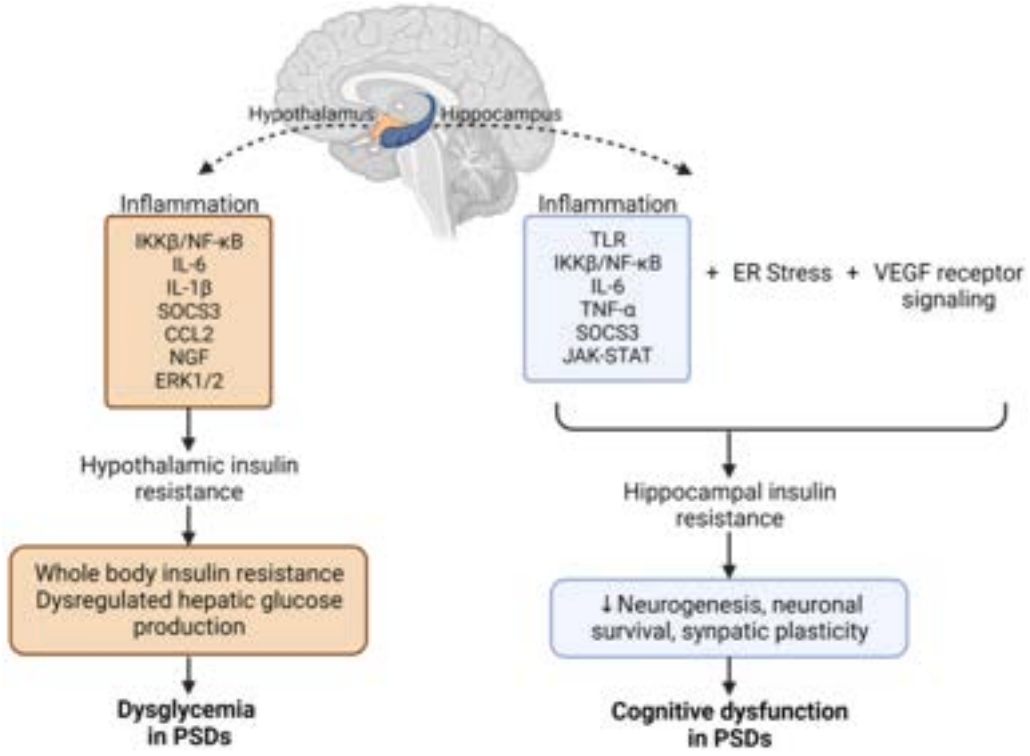

Fig. 4. Summary of Potential Mechanisms Responsible For Putative Link Between Central Insulin Dysregulation and Psychosis Spectrum Disorders.

inflammation (myeloid leukocyte activation and toll-like receptor signaling), ER stress (positive regulation of proteolysis, glycosylation, and toll-like receptor signaling), and VEGF receptor signaling. Microglia, the resident myeloid cells of the brain, produce proinflammatory cytokines such as TNF-α and IL-6, which inhibit IRS signalling and insulin's ability to promote neurogenesis, synaptic plasticity, and neuronal survival (Biessels and Reagan, 2015; Spinelli et al., 2019). IL-6 modulates hippocampal synaptic plasticity through Janus kinase-signal transducer and activator of transcription protein (JAK-STAT) signalling (Nicolas et al., 2013). While not present in the top 15 pathways, TNF-α production and JAK-STAT signaling were significantly enriched in the AP-naïve FEP and the hippocampus of CIP rodent models overlap analyses ($p<0.05$; Table S9), supporting the potential relevance of these cytokines in central insulin action and cognitive deficits. Toll-like receptor signalling and ensuing activation of IKKβ/NF-κB signaling would also be expected to induce insulin resistance through IRS inhibition and upregulation of cytokine production (Kuga et al., 2017; Rolls et al., 2007), thereby impacting hippocampal apoptosis and neurogenesis (Rolls et al., 2007). Moreover, ER stress may also participate in the interplay between inflammation and central insulin dysregulation in PSDs. To this point, chronic ER stress has been postulated to contribute to the pathology of PSDs (Kim et al., 2021, 2018; Muneer and Shamsher Khan, 2019; Patel et al., 2017). Perturbed central insulin signaling in rodents via high-fat diet is linked to hippocampal ER stress, elevated IL-6 and TNF-α activation, reduced hippocampal insulin signalling, increased neuronal apoptosis, and cognitive impairments (Sims-Robinson et al., 2016; Wang et al., 2016). Increased VEGF levels have also been associated with cognitive impairments in mice and humans fed a high-fat diet (Jais et al., 2016; Schüler et al., 2018). While the exact mechanisms are unclear, these may relate to the role of VEGF in glucose transport and uptake into the brain and subsequent fuel utilization by neurons (Jais et al., 2016; Schüler et al., 2018). In addition, certain member proteins of the VEGF family have been associated with hyperglycemia. For example, VEGF-A has been shown to mitigate insulin resistance by promoting angiogenesis and reducing inflammation. On the other hand, inhibiting VEGF-C and VEGF-D improves insulin sensitivity and reduces tissue inflammation in rodents (Karaman et al., 2015; Zafar et al., 2018). Although the cited studies did not directly investigate VEGF signaling in the brain in relation to central insulin dysregulation, VEGF in the CNS is known to crosstalk with canonical insulin signaling pathways, which are linked to regulation of glucose homeostasis and neuroprotection (Jais et al., 2016; Matsuzaki et al., 2001; Simons et al., 2016). Taken together, interactions between inflammation, ER stress, and central insulin dysregulation in the hippocampus may underlie intrinsic cognitive dysfunctions in PSDs.

4.3. *Novel potential treatments for dysglycemia and cognitive dysfunction*

Since the identified pharmacological agents have gene expression patterns discordant to the common gene expression signatures of AP-naïve FEP and CIP rodent models, these drugs may correct the common gene expression changes and, in effect, treat dysglycemia and premorbid cognitive dysfunction in PSDs. Notably, several antidiabetic agents were identified, encompassing biguanides (i.e., metformin), sulfonylureas (i.e., chlorpropamide), and thiazolidinediones (i.e., troglitazone, and rosiglitazone). This is consistent with central insulin's role in regulating whole body glucose homeostasis and provides further support for the interplay between central insulin and dysglycemia in PSDs. Of these drugs, the antidiabetic agent chlorpropamide was identified as a potential treatment for both the AP-naïve FEP gene expression patterns that overlap with the hypothalamus and hippocampus of CIP rodent models. We posit that chlorpropamide's well-established actions on K_{ATP} channels in the periphery in pancreas may also underpin its potential therapeutic actions in PSDs given the importance of these channels in brain regions like the hippocampus to modulate cognition and memory, and in the hypothalamus to modulate hepatic glucose production (Betourne et al., 2009; Kowalchuk et al., 2021).

In terms of potential clinical use, chlorpropamide, an older sulfonylurea, has been discontinued or withdrawn from the market. While other sulfonylureas are available, they are no longer first line agents for

dysglycemia due to safety risks. Rosiglitazone, a thiazolidinedione, retains FDA approval for management of type 2 diabetes. This class of drugs is known to target the peroxisome proliferator-activated receptor (PPAR) and act as insulin sensitizers. Interestingly, pioglitazone, another FDA approved thiazolidinedione, has been shown to improve working memory in a GluN1 knockdown mouse model of schizophrenia (Sullivan et al., 2019). Additionally, among two randomized controlled trials (RCTs) testing pioglitazone in schizophrenia patients (Iranpour et al., 2016; Smith et al., 2013), improvements in PANSS negative scores were observed in one study (Iranpour et al., 2016). These points altogether support PPAR-agonists as promising therapeutic targets. However, associated risks of congestive heart failure and other adverse effects limit the use of thiazolidinediones to second- or third-line therapies for type 2 diabetes and has resulted in withdrawal of their use in certain world markets.

On the other hand, metformin remains the first-line pharmacological treatment for type 2 diabetes and is also now recommended off-label to mitigate or prevent AP-induced weight gain (Flory and Lipska, 2019; Wharton et al., 2020). Several RCTs have demonstrated beneficial effects of early metformin treatment in FEP patients in attenuating AP-induced dysglycemia (Agarwal et al., 2021; Wu et al., 2012, 2008a, 2008b). Our analyses suggest that early metformin treatment could additionally target both intrinsic and AP-related causes of metabolic dysfunction in PSDs. Mechanistically, metformin exerts its antidiabetic effects primarily through liver AMPK activation and suppressing hepatic glucose production. Interestingly, metformin has been suggested to improve brain insulin action through both AMPK and non-AMPK-dependent mechanisms (Ruegsegger et al., 2019). Further, metformin has been shown to improve cognition in insulin-resistant rats (Pintana et al., 2012), although the effect of metformin on cognitive performance across different models of disease remains controversial (Agarwal et al., 2020b). To our knowledge, a single study by our group explored metformin on cognitive performance in adults with schizophrenia, failing to find an effect (Agarwal et al., 2021). However, it was likely underpowered to detect effects on cognition and examined a cohort with established overt dysglycemia (i.e., prediabetes or type 2 diabetes) related, in part, to extrinsic illness related factors such as antipsychotic drugs and lifestyle. That said, it remains to be determined in well designed and adequately powered studies whether metformin and other identified classes of drugs (or their molecular targets) may represent pharmacological treatments that can mitigate both intrinsic dysglycemia and cognitive deficits in early PSDs in part through suggested effects on central insulin action.

4.4. Limitations

Although our findings build on growing literature supporting intrinsic metabolic dysfunction in PSDs, some limitations should be noted. The heterogeneity among datasets due to differing types of central insulin perturbations, transcriptomic platforms, and species analyzed (i.e., rat, mouse, humans) may have confounded the findings. Additionally, most hypothalamic CIP studies employed high-fat diet as the perturbation, indicating that the pathways and transcriptomic signatures may include disruptions attributable to increases in adiposity. That said, emerging literature supports that, in addition to dysglycemia, patients with PSDs pre-AP exposure have increased adiposity (Smith et al., 2021). Further, because most FEP studies used blood-derived tissue, we observed processes occurring in the blood (e.g., heme metabolic process) that may be less specific or informative to brain mechanisms. Regardless, the general unavailability of post-mortem brains of young AP-naïve FEP patients along with the significant transcriptomic overlap between blood and brain (Hess et al., 2016; Sullivan et al., 2006) supports our use of peripheral tissue as a viable alternative. Furthermore, the pathway and iLINCS analyses rely on existing datasets that tend to be biased towards biological processes and drugs that are well-studied. For instance, our iLINCS analysis was characterized by multiple hits for anticancer drugs, which may in part be attributable to the relatively well-studied nature of cancer. Moreover, the drug datasets that iLINCS utilizes contains few neurons or blood-derived tissue. Nonetheless, our iLINCS analyses were also characterized by several antidiabetic agents, which would be expected to correct dysglycemia in PSDs and hence provides support for the clinical validity of our results.

5. Conclusion

Collectively, our findings support growing evidence of intrinsic links between the pathology of PSDs and central insulin dysregulation at a gene expression level. From a mechanistic standpoint, hypothalamic and hippocampal insulin resistance may overlap with PSDs via pathways of inflammation, ER stress, and neuroplasticity. We also identified several diabetes drugs that may be repurposed as potential drug treatments for PSDs through their abilities to mitigate PSD-related central insulin dysregulations. Such treatments may not only improve dysglycemia but also improve cognitive deficits intrinsic to PSDs, providing a novel therapeutic strategy in ameliorating several PSD symptom domains.

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Author contributions

JL, WBM, GT, RM, ZF, RWL, and MKH were involved in study design and conception. JL, WBM, EA, RA, and MP were involved in the systematic search and article screening. JL and XX were involved in data extraction, analysis, and drafted the first version of the manuscript. All authors contributed to writing and editing the final manuscript.

Data availability statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study. Fig. 4 was created using BioRender (BioRender.com).

Declaration of Competing Interest

MKH has received consultant fees from Alkermes.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2023.115636.

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