Review

Biological Psychiatry: GOS

Mental Health Across the Metabolic Spectrum

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ABSTRACT

Understanding the relationship between metabolism and mental health involves examining how disruptions in one system influence the other. The specific mechanisms by which metabolic processes impact the mind—and how mental well-being, in turn, affects metabolic regulation—are poorly understood. This shortcoming is attributable to the complex and multilayered nature of both the metabolic network and mental processes, as well as the lack of robust quantitative methods to analyze the workings of the mind. Inborn errors of metabolism exemplify this complexity, with over one-fourth being associated with psychiatric manifestations. Despite their high prevalence, psychiatric deficits in individuals with inborn errors of metabolism remain challenging to recognize and manage due to phenotypic variability, limited clinical training in neurometabolism, and gaps in research. To identify intersections between metabolism and mental health, here we assessed the effects of metabolic dysregulation on mental function, focusing on inborn errors of metabolism.

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The relationship between metabolism and mental health is an increasingly active area of research. Recent studies have begun to examine how metabolic dysfunction affects cognitive performance and psychological well-being (1–3). These reports have linked both inherited and acquired metabolic disorders to a range of psychiatric conditions, including intellectual disability, mood disorders, and psychosis (defined here to encompass schizophrenia, delusional disorder, and related conditions as per DSM-5-TR). However, the precise mechanisms by which specific metabolic deficits contribute to distinct psychiatric phenotypes remain largely unknown. This challenge is further complicated by the general underreporting and limited characterization of psychiatric symptoms in individuals with metabolic diseases. Current understanding largely depends on correlating the timing and type of psychiatric symptoms with metabolic disorders and observing improvements after metabolic interventions. Addressing these interactions requires a comprehensive approach that integrates biochemistry, neuroscience, and psychiatry to thoroughly investigate the links between metabolism and mental health.

To fully grasp the spectrum of psychiatric deficits associated with metabolic diseases, especially inborn errors of metabolism (IEMs), it is essential to consider the varied cognitive and behavioral impairments in which these conditions result. IEMs arise from genetic defects that disrupt the transport or enzymatic modification of metabolites, leading to energy deficiencies, impaired biosynthesis, or the buildup of toxic compounds. Such metabolic disruptions are thought to drive the neuropsychiatric symptoms observed in individuals with IEMs (4). Psychiatric manifestations of IEMs have been categorized into 3 groups: acute episodes, chronic symptoms that arise during adolescence or adulthood, and gradual onset of cognitive impairment and behavioral changes (2). However, this classification does not fully capture the contributions of specific metabolic processes to mental health across the lifespan. To address these gaps, this study presents a comprehensive dataset for analyzing psychiatric phenotypes in IEMs, tracking symptom progression, and examining links to neurological deficits, brain imaging findings, and neuropathology. Furthermore, it can be used to analyze responses to psychiatric treatments, including resistance to therapies and adverse effects. Our goal here was to provide a fresh perspective on how metabolic dysfunction impacts mental health and lay the groundwork to identify new disease mechanisms and develop interventions to improve patient outcomes in the future.

METHODS

Search Strategy

We conducted a comprehensive search to identify IEMs linked to psychiatric symptoms using the IEMBase (4). This database provides age-based clinical information classifying metabolic diseases under the International Classification of Inherited Metabolic Disorders without including individual patient data (5). Therefore, our analysis focused on disease-level information. Our search covered a wide range of psychiatric symptoms (Table S1) and was expanded using PubMed, OMIM, and Google Scholar to include IEM-associated psychiatric conditions and treatments not listed in IEMBase. Identified psychiatric symptoms were categorized using DSM-5-TR (Table S2). General terms like “psychiatric disease” or “mental problems” were grouped under “other psychiatric conditions.” IEMs not matching these criteria were excluded from the final list. Given the rarity of multiple concurrent IEMs in patients, each IEM was treated as uniquely associated with its psychiatric manifestations.

Study Selection

The 2 authors independently verified each disease listed in IEMBase by consulting PubMed, OMIM, and Google Scholar. If

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no publications described psychiatric deficits as in IEMBase, the IEM in question was still included as a potential cause of psychiatric involvement because detailed accounts of psychiatric symptoms in these conditions are often lacking in the literature. IEMs with nonspecific terms like "psychiatric deficits" or "mental dysfunction" were also included. Articles, including titles, abstracts, and full-text articles in English, were evaluated based on the preestablished inclusion and exclusion criteria. The authors then discussed findings to finalize the inclusion of each IEM in the dataset.

Database

We categorized IEMs with psychiatric deficits using the International Classification of Inherited Metabolic Disorders database (6) (Tables S3 and S4). Key variables included 1) disease name, 2) signs and symptoms across age groups (neonatal to adulthood), 3) psychiatric deficits, 4) neurological deficits, 5) brain imaging findings, 6) treatments, 7) treatment ineffectiveness, 8) side effects, and 9) PubMed ID references for supporting articles. For clinical and structural variables, we adapted IEMBase notation for frequency of occurrence (+/−: may occur, +: usually present, ++: almost always present, +++: always present) and converted these into numerical values for quantification and visualization (+/− = 0.5, + = 1, ++ = 2, +++ = 3). Missing data were assigned a value of 0.

Data Analysis and Visualization

Statistical analyses were conducted using R (version 4.1.1). Our approach was primarily descriptive and exploratory, designed to identify patterns and associations rather than to establish causal relationships. For 2 numerical variables, we applied an independent Student's *t* test, using the *F* test to determine variance equality. For 3 or more groups, we used a Kruskal-Wallis test with Dunn's post hoc testing for nonnormally distributed variables. The significance level (alpha) was set at .05.

RESULTS

All IEM Groups Are Associated With Psychiatric Manifestations

We identified a total of 1620 IEMs (Figure 1A). We found that the most prevalent category was disorders of complex molecule and organelle metabolism, which accounted for 22.4% of the diseases reviewed. This was followed by disorders of intermediary metabolism of energy (20.9%) and nutrients (13.5%). Other groups included lipid metabolism and transport, metabolism of heterocyclic compounds, cell signaling, cofactor and mineral metabolism, other types of intermediary metabolism, and unclassified disorders (Figure 1A). Following the inclusion criteria specified earlier, we found that 424 IEMs were associated with psychiatric deficits, representing 26.2% of all conditions surveyed (Figure 1B and Table S4). Among these, disorders of complex molecules were the most common, accounting for 32.5%—more than twice the prevalence of the second and third most common IEMs associated with psychiatric deficits. We further categorized these conditions into subgroups following the International Classification of Inherited Metabolic Disorders (Figure 1C). The subgroup most frequently associated with psychiatric deficits was metabolite repair and proofreading disorders, with a relative frequency of 75%, followed by disorders of neurotransmitters and complex molecule degradation. Psychiatric phenotypes categorized using DSM-5-TR showed that neurodevelopmental disorders were the most prevalent psychiatric manifestation in IEMs, accounting for 64.3% of cases—6 times higher than the prevalence of the second most common group, behavioral disorders (Figure 1D). This group was followed by psychosis and depression, while eating and personality disorders were the least reported, at 0.3% and 0.2%, respectively.

Neurodevelopmental Disorders Are the Most Common Psychiatric Conditions

Neurodevelopmental disorders had a prevalence of 40% to 75% within each IEM group (Figure 2A). This frequency was 3 to 7 times higher than that of the second most common psychiatric condition in each IEM group, underscoring the profound impact of metabolic deficits on cognitive development. Due to their widespread prevalence, we further subdivided neurodevelopmental disorders into 3 categories: intellectual disability (covering various intellectual, learning, and speech impairments and developmental delay), autism spectrum disorder, and all forms of attention-deficit /hyperactivity disorder (ADHD). Intellectual disability was the most prevalent, ranging from 54% to 100% (Figure S1), while autism spectrum disorder and ADHD showed prevalence ranges of 10% to 28% and 5% to 16%, respectively. This suggests that metabolic deficits have a stronger influence on cognitive development than on behavioral or social deficits typically associated with autism spectrum disorder or ADHD. In the group of other intermediary metabolic disorders, psychosis was the dominant condition (~60%), although neurodevelopmental disorders remained significant (~40%). Behavioral disorders, neurocognitive deficits, and psychosis were observed across IEM groups with 5% to 15% prevalence.

The timing of psychiatric deficits across age groups followed a bimodal distribution (Figure 2B). In most IEMs, neurodevelopmental and behavioral disorders peaked during infancy and childhood, while depression, anxiety, and neurocognitive problems (such as dementia and delirium) were more common during adolescence and adulthood. Comparing psychiatric deficits across ages in IEM groups revealed differences between neurodevelopmental impairments and later-onset conditions. In complex molecule disorders, neurodevelopmental deficits were more frequent than depression and behavioral issues during infancy and childhood. Energy metabolism disorders showed behavioral and neurodevelopmental deficits in infancy, with neurocognitive conditions predominating in adulthood. In lipid metabolism disorders, neurodevelopmental deficits were more common during childhood, while neurocognitive ones emerged later. Cofactor metabolism disorders exhibited marked differences in infancy, whereas anxiety was the primary psychiatric condition in adulthood for cell signaling abnormalities. In heterocyclic compound disorders, childhood neurodevelopmental and behavioral issues surpassed anxiety. Taken together, these findings suggest that understanding the age of onset of

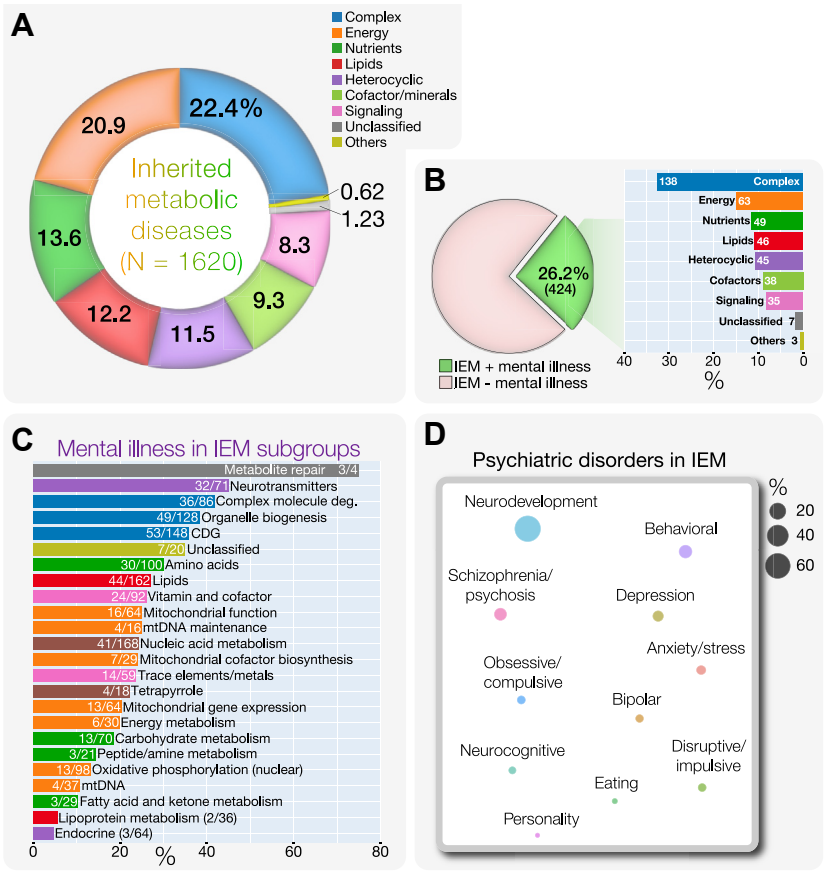

Figure 1. Distribution of psychiatric symptoms across inborn errors of metabolism (IEM) groups. **(A)** Distribution of all IEM groups. **(B)** Fraction of IEMs with psychiatric involvement and group distribution (absolute values are included in each bar). **(C)** Relative frequencies of psychiatric involvement in subgroups of IEM, with the number of IEMs linked to psychiatric conditions within each subgroup shown in each bar. **(D)** Relative frequencies of psychiatric conditions as defined by DSM-5-TR. CDG, congenital disorder of glycosylation; mtDNA, mitochondrial DNA.

psychiatric deficits is crucial for determining the impact of metabolic abnormalities on mental health across the lifespan and for guiding timely interventions.

Most IEMs With Psychiatric Deficits Exhibit Neurological Manifestations

Neurological deficits are estimated to occur in approximately 85% of patients with IEMs (7). In this context, we investigated whether a similar prevalence of neurological problems exists when psychiatric conditions co-occur with IEMs. Our analysis revealed that nearly 97% of IEMs linked to psychiatric conditions also involved neurological deficits (Figure 3A). Seizures were the most frequent neurological manifestation, appearing in 33.6% of conditions (Figure 3B). The group of other neurological disorders—including nonspecific conditions such as encephalopathy, hypotonia, and spasticity—accounted collectively for 27.6%. Cerebellar deficits were identified in 13.5% of IEMs, while movement disorders were present in 11.4%. Headaches were rare, being reported in only 0.33% of conditions.

Neurodevelopmental disorders were the most common psychiatric conditions associated with neurological deficits, accounting for 74.2% of all psychiatric manifestations. Seizures were particularly prominent in this group, with a prevalence of 41.9% (Figure 3C). Behavioral disorders followed at 11%, while conditions like psychosis, depression, anxiety, and obsessive-compulsive disorder were less common. Within the group of seizures, neurodevelopmental disorders accounted for 80.8% of all psychiatric diagnoses, followed by behavioral disorders (10.6%) and psychosis (3.3%). In the group of other neurological deficits, neurodevelopmental disorders were also predominant, being observed in 71.6% of cases, with behavioral disorders at 13.7% and psychosis at 5.5%. Cerebellar deficits were most frequently associated with neurodevelopmental conditions (66%), followed by behavioral disorders, anxiety, depression, and psychosis. Across individual IEM groups, neurodevelopmental disorders were consistently linked to most neurological deficits (Figure 3D). Seizures were the most common neurological manifestation, with a prevalence ranging from 21.1% to 50% across different IEM groups. Notably, in disorders of energy metabolism and heterocyclic compounds, other neurological deficits were more common than seizures, and seizures were absent in unclassified IEMs. The prevalence of seizures varied by psychiatric condition and IEM group, ranging from approximately 15% to 30% in neurodevelopmental disorders to 1% to 4% in psychosis and behavioral conditions.

Unlike most IEM groups, where neurological deficits mainly accompanied neurodevelopmental and behavioral disorders, disorders of complex molecules and cofactor metabolism showed a broader distribution of neurological deficits across

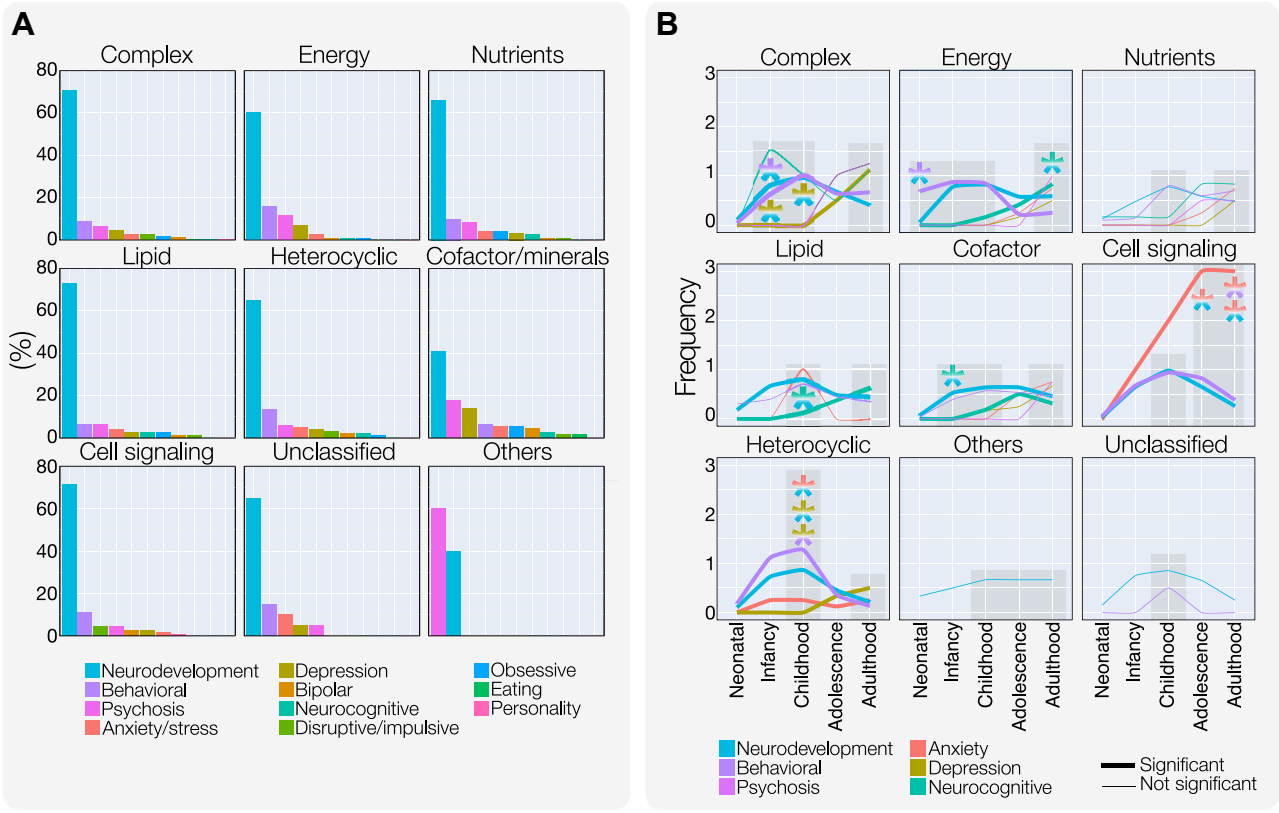

Figure 2. Psychiatric conditions within inborn errors of metabolism (IEM) groups and their frequency distribution across ages. **(A)** Relative frequencies of psychiatric conditions as defined by DSM-5-TR within each IEM group. **(B)** Distribution of the frequency of psychiatric deficits across ages within each IEM group. The data at each time point are expressed as means. Statistical analysis was performed using Kruskal-Wallis tests with Dunn post hoc tests for multiple comparison correction. Most significant differences were observed between neurodevelopmental disorders (light blue) and other psychiatric conditions (indicated by other colors), as shown by the color distribution of the asterisks. $^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$.

various psychiatric conditions. In disorders of complex molecules, sensory deficits were linked to personality and disruptive/impulsive disorders in 0.8% of cases, making it the only IEM group where these psychiatric conditions had an associated neurological deficit. In disorders of cofactor metabolism, eating disorders were uniquely linked to seizures, accounting for 2.5% of cases with a neurologic deficit and being the only example where eating disorders had neurological manifestations. Altogether, these observations prompt several questions: Why are seizures the most common neurological problem associated with psychiatric conditions in IEMs, and why are they less frequent in psychosis, depression, or anxiety than in neurodevelopmental disorders? More studies are needed to understand the role of age in these patterns. Additionally, it is important to investigate whether metabolic pathways involved in disorders of complex molecules and cofactor metabolism play a more central role in both neurological and mental functions than other pathways.

The White Matter Is the Most Involved Brain Region

Consistent with the data described so far, neurodevelopmental disorders were most frequently linked to brain imaging abnormalities (90.1%) (Figure 4A). This was followed by behavioral disorders (75%), eating disorders (66.6%), and psychosis (61.4%). In our literature review to corroborate psychiatric conditions associated with IEMs listed in IEMBase (868 articles) (see Table S4), we found that magnetic resonance imaging (MRI) T1 and T2 sequences were the most used (18.8% and 25.8%), followed by FLAIR and diffusion MRI (7.3% and 2.5%). Notably, 25.3% of articles did not specify MRI sequences, and 34.4% lacked MRI data.

We categorized lesions as developmental (e.g., hypoplasia, dysplasia), degenerative (e.g., neurological decline, atrophy), combined, or classified as "other" for isolated, nonprogressive abnormalities. The degenerative phenotype was the most common (49.3%), followed by combined developmental and degenerative changes (25%) and other imaging phenotypes (11.8%). Purely developmental defects accounted for 7% of the total (Figure 4B). Disorders of complex molecules were most frequently associated with a degenerative phenotype (15.6%) (Figure 4C), followed by disorders involving energy metabolism, heterocyclic compounds, and cofactor metabolism. Neurodevelopmental disorders showed neurodegeneration rates of 50% to 70% across all IEM groups, while behavioral conditions accounted for 20% to 30% (Figure S2). A mixed developmental and degenerative phenotype was mainly observed in disorders of complex molecules, occurring

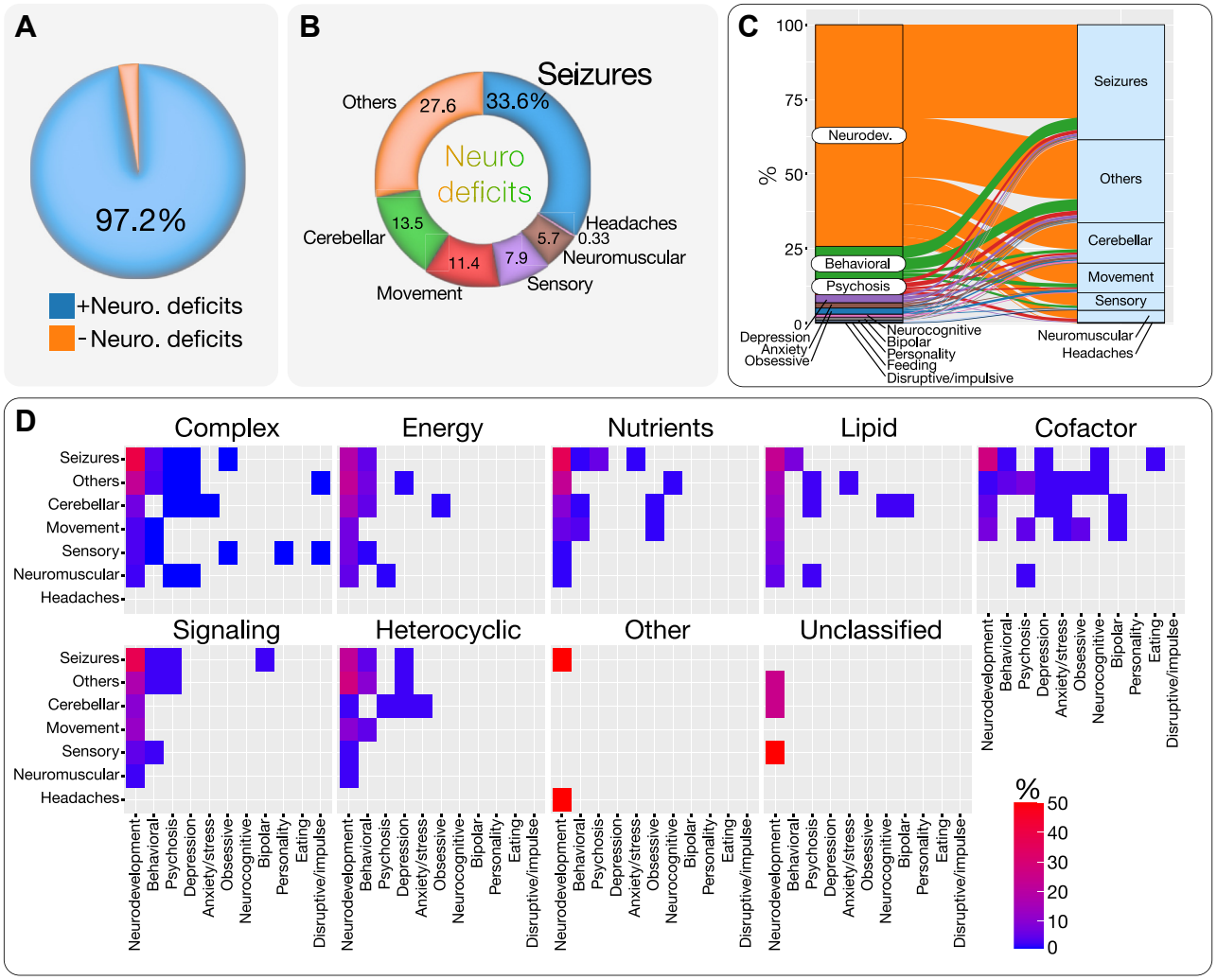

Figure 3. Neurological (neuro.) deficits associated with psychiatric conditions in inborn errors of metabolism (IEMs). **(A)** Relative frequencies of neurological and nonneurological deficits in IEMs with psychiatric manifestations. **(B)** Frequencies in individual groups of neurological disorders. **(C)** Connectome of psychiatric conditions (left) with neurological deficits (right). **(D)** Relative frequencies of coexistence between psychiatric conditions and neurological disorders in each IEM group.

3 times more frequently than the next most common group, energy metabolism disorders (Figure 4C). Among developmental defects, complex molecule disorders were again most prevalent (48.4%), followed by lipid metabolism and cell signaling (Figure S3). The other group showed a more varied distribution, with complex molecule disorders at 22.6%, followed by nutrient metabolism, cell signaling, and cofactor and mineral metabolism.

The white matter was affected in 26.2% of cases, making it the most frequently involved brain structure (Figure 4D), followed by the entire brain (21.5%), cerebellum (15.3%), and corpus callosum (10.2%). Across 5 of the 8 psychiatric categories, white matter was the most affected region, with a prevalence of 17.5% to 27% (Figure 4E). For anxiety and neurocognitive disorders, the entire brain was more commonly involved than the white matter, while eating disorders primarily affected the entire brain and cerebral cortex (50% each) without white matter involvement. Atrophy was the most prevalent lesion, occurring in 80.5% of instances involving the entire brain, 70.1% involving the cerebellum, and 70% involving the cortex (Figure 4F). Nonspecific MRI findings, such as abnormal T1/T2 signals, were most frequent in the white matter (73.6%) and basal ganglia (45.8%). Developmental defects, including hypoplasia, were predominant in the corpus callosum, representing 90.2% of the cases. Overall, these findings underscore the high prevalence of brain structural abnormalities and the importance of imaging in diagnosing psychiatric symptoms related to metabolic diseases.

Neurodegeneration Is More Prevalent in Psychiatric Conditions That Present Later in Life

Figure 5A illustrates the distribution of imaging phenotypes within each psychiatric condition, without considering the

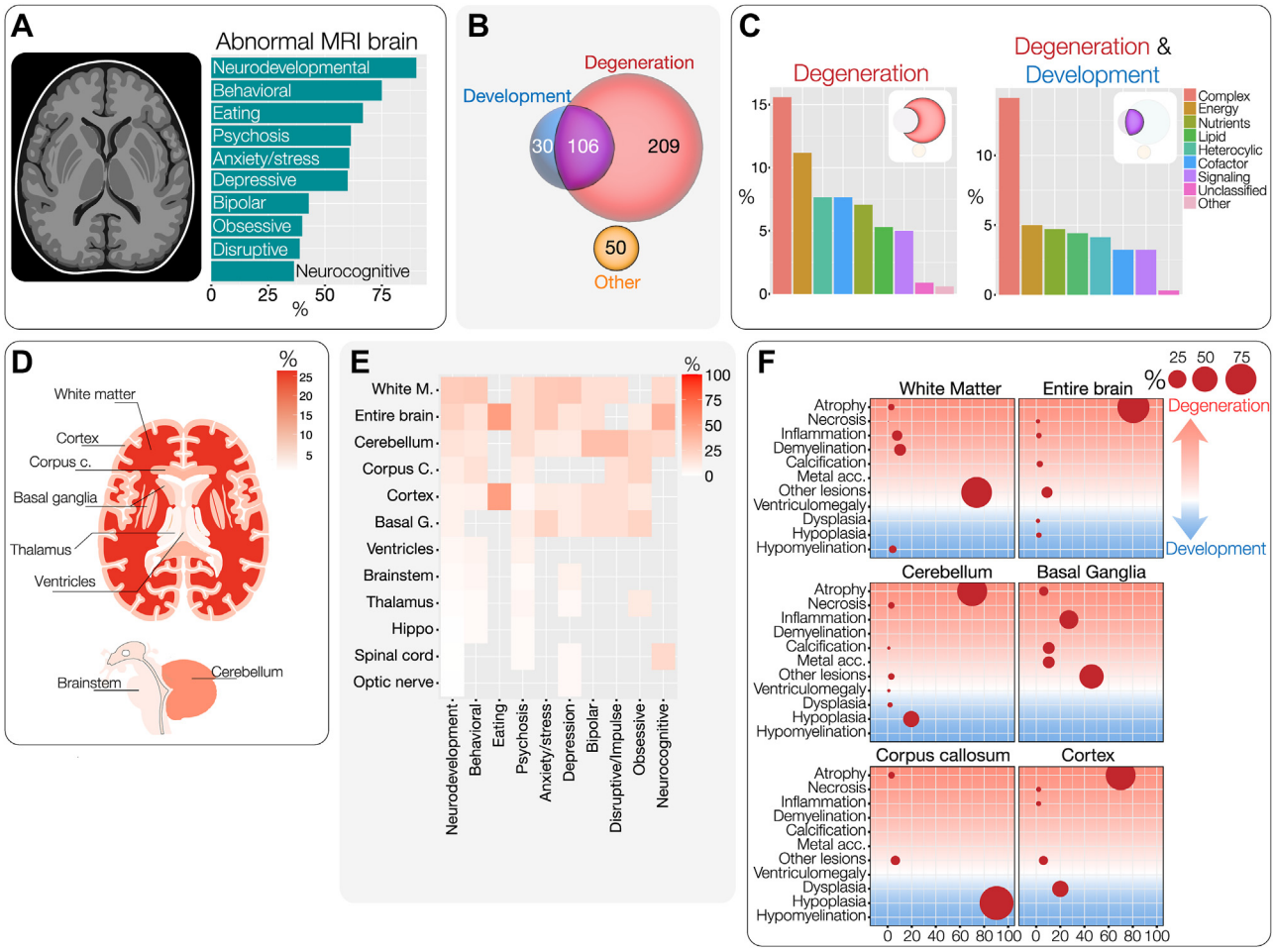

Figure 4. Brain imaging findings in inborn errors of metabolism (IEMs) with psychiatric deficits. **(A)** Relative frequencies of abnormal magnetic resonance imaging (MRI) brain findings in each psychiatric condition. (Image obtained from BioRender [https://www.biorender.com].) **(B)** Grouping imaging findings into degenerative, developmental, both, and other. **(C)** Distribution of IEM groups within degenerative and both degenerative and developmental phenotypes. **(D, E)** Brain regions involved in IEMs with psychiatric conditions. **(F)** Types of lesions within each anatomical region of the brain.

underlying metabolic disease. Psychiatric deficits that primarily appear in early life, such as neurodevelopmental and behavioral disorders (Figure 2B), were more frequently associated with structural developmental changes in the brain, either alone (5%–8%) or combined with degenerative features (33%–35%). In contrast, later-onset conditions like psychosis and depression showed fewer developmental abnormalities, with degenerative findings being more prevalent (73%–88%). By comparison, neurodevelopmental and behavioral disorders had significantly fewer degenerative findings (46%–53%).

Given these data, we further evaluated the timing of presentation of psychiatric conditions based on the imaging phenotype. In degenerative IEMs, particularly those involving disorders of complex molecules, the pattern described earlier in Figure 2B was still evident. Behavioral and neurodevelopmental disorders showed increased severity during childhood (Figure 5B), while conditions such as psychosis, depression, and neurocognitive disorders were more prevalent during adolescence and adulthood. Statistical analysis revealed significant differences in the onset and progression of neurodevelopmental disorders compared with depression and psychosis in infancy and childhood. A similar pattern was noted in energy and nutrient metabolism disorders linked to neurodegeneration, with early-life dominance of neurodevelopmental and behavioral disorders, while psychosis, depression, and neurocognitive conditions became more common in adolescence and adulthood. Developmental brain anomalies were most common in disorders of complex molecules, cell signaling, and heterocyclic compounds (Figure 5C). Neurodevelopmental and behavioral disorders were the only psychiatric deficits in IEMs with age-specific data in IEMBase, peaking in childhood and declining by adulthood in complex and heterocyclic molecule disorders, while behavioral disorders persisted.

When developmental and degenerative conditions coexisted, the severity of psychiatric disorders varied slightly (Figure 5D). The main IEM categories with both defect types included complex molecules, energy metabolism, and heterocyclic compounds. Neurodevelopmental, behavioral, and anxiety disorders linked to heterocyclic compounds and nutrient metabolism appeared early in life, while psychosis became more prominent

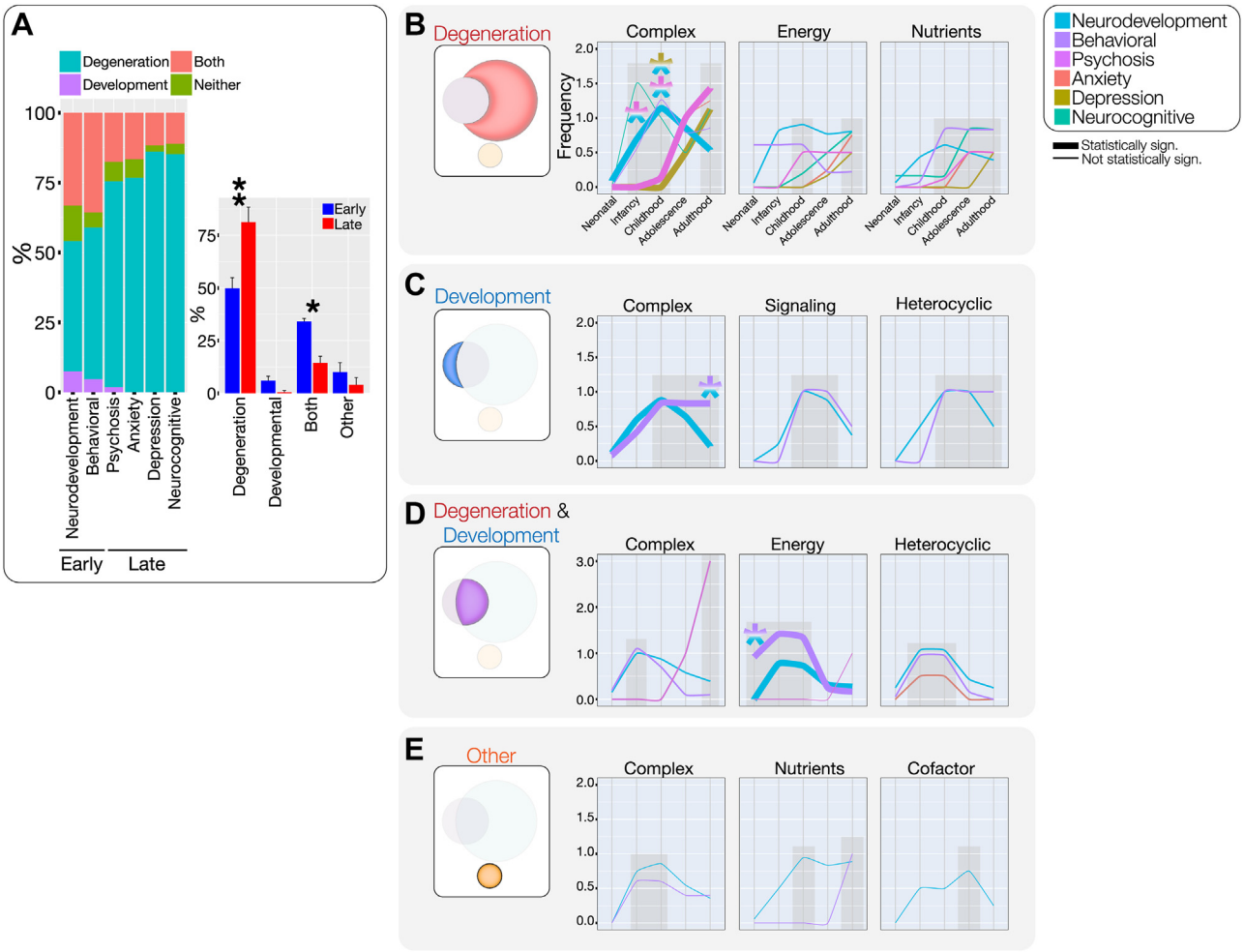

Figure 5. Distribution of imaging phenotypes within psychiatric conditions and inborn errors of metabolism groups. **(A)** Imaging patterns within each psychiatric condition and their frequencies in early and late presentations. Unpaired Student's *t* tests were performed to compare early- and late-presenting conditions within each imaging phenotype. **(B–E)** Frequency distribution of psychiatric conditions with the top 3 most common inborn errors of metabolism groups per imaging phenotype. The data at each time point were expressed as means. Statistical analysis was performed using Kruskal-Wallis tests with Dunn post hoc tests for multiple comparison correction. As in Figure 2, most statistical differences were between neurodevelopmental disorders (light blue) and other psychiatric conditions (indicated by other colors), as shown by the color distribution of the asterisks. $^{*}p < .05$, $^{**}p < .01$. sign., significant.

in adulthood (Figure 5D and Figure S4). For other IEM groups, behavioral and neurodevelopmental disorders were the most reported conditions, peaking in infancy and childhood, while psychosis and depression appeared later (Figure S4). In cases without clear developmental or degenerative imaging features (Figure 5E), neurodevelopmental and behavioral disorders followed an early-life pattern, except for behavioral deficits in nutrient and energy metabolism disorders, which were more common in adulthood (Figure 5E and Figure S4). Despite some exceptions, age-related patterns of psychiatric conditions in IEMs remained consistent across imaging phenotypes.

Metabolic Treatments Are the Most Used in IEMs With Psychiatric Manifestations

The therapeutic landscape for psychiatric manifestations in individuals with IEMs presents unique challenges, given the reported tendency to exhibit side effects or unusual reactions (8). To analyze the treatment strategies, we reviewed the interventions reported in the literature (Table S4) because this information was not available in IEMBase. We found reported treatments for 87 of 424 IEMs with psychiatric manifestations (Figure 6A). Metabolic therapies, the most common approach (29%), included specialized diets, vitamins, and supplements. Among diets, the ketogenic diet was used in conditions such as glucose transporter type 1 deficiency syndrome and pyruvate dehydrogenase deficiency to provide alternative energy sources that circumvent the metabolic defect. Low-protein diets were used to minimize toxic metabolite accumulation in disorders such as phenylketonuria, maple syrup urine disease, and urea cycle disorders. Metabolic treatments were followed by antipsychotics (18.9%), antidepressants (15.5%), and benzodiazepines (6.8%). Notably, we categorized benzodiazepines separately from anxiolytics and sleep medications due to their widespread use for

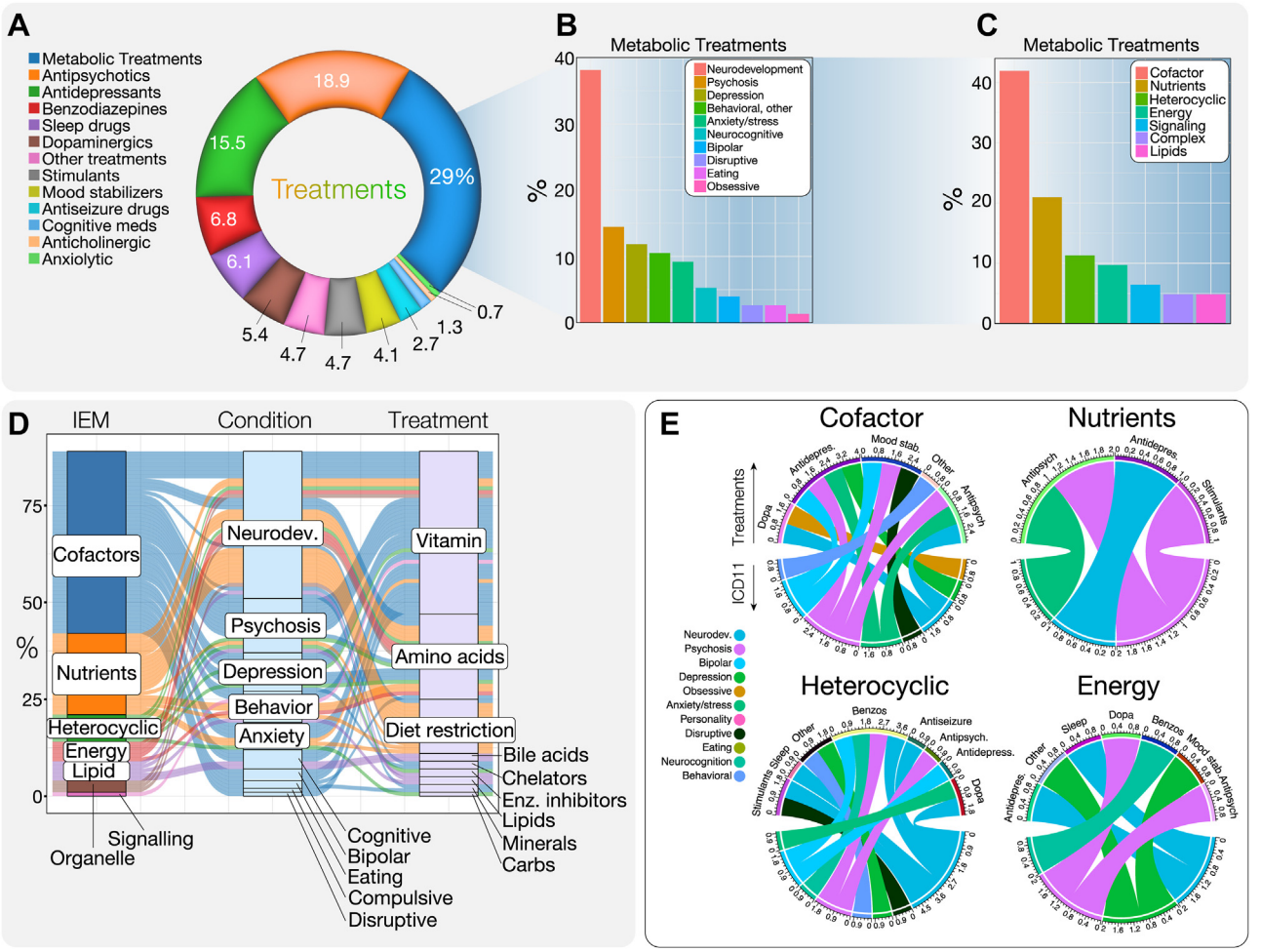

Figure 6. Treatments for psychiatric conditions in inborn errors of metabolism (IEMs). **(A)** Distribution of treatments globally used for psychiatric disorders in IEMs. **(B, C)** Relative frequencies of metabolic therapies within individual psychiatric conditions and IEM groups. **(D)** Connectome of IEM groups, psychiatric conditions, and their respective metabolic treatments based on relative frequencies. **(E)** Use of conventional psychiatric drugs for each psychiatric condition within the top 4 IEM groups treated with metabolic treatments. antidepres, antidepressant; antipsych, antipsychotic; benzos, benzodiazepines; dopa, dopaminergic agents; Enz., enzyme; stab., stabilizer.

various indications beyond anxiety and insomnia, including seizures, agitation, aggressiveness, catatonia, and restlessness.

Metabolic treatments were most often used for neurodevelopmental disorders (38.2%) (Figure 6B). Psychosis, depression, and anxiety followed. Among IEM categories, disorders of cofactor and vitamin metabolism were the most frequently treated, comprising 41.9% of all metabolic treatments administered (Figure 6C). This was followed by disorders of nutrient metabolism, heterocyclic compounds, and energy metabolism. The high prevalence of metabolic interventions is consistent with the nature of these disorders, which often involve deficiencies in synthesizing or processing essential nutrients that can be addressed through supplementation or dietary modifications. Figure 6D shows that disorders of cofactor and vitamin metabolism were managed with vitamins, amino acids, and specialized diets for neurodevelopmental disorders, psychosis, depression, and anxiety. Nutrient and energy metabolism disorders used similar treatments, while lipid metabolism, cell signaling, and complex molecule disorders often required bile acids, enzyme inhibitors, and lipid therapies. Figure 6E lists medications for IEMs managed through metabolic therapies. Cofactor and vitamin disorders used dopaminergic agents, antidepressants, and antipsychotics for neurodevelopmental, mood, and behavioral issues. Nutrient metabolism disorders relied on antipsychotics, antidepressants, and stimulants for psychosis and anxiety. Heterocyclic compound disorders were treated with stimulants and sleep aids, along with benzodiazepines and antiseizure drugs for anxiety and neurodevelopmental deficits. Energy metabolism disorders were treated with antidepressants, sleep aids, dopaminergic agents, and mood stabilizers. For more information on psychiatric treatments across IEMs, see Figure S5.

Psychosis Is Reportedly the Most Difficult to Treat Mental Condition With Medications

Patients with IEMs often show limited or no response to conventional psychiatric drugs, according to our and other

healthcare providers' experiences. However, few studies have explicitly reported pharmacoresistance in patients with IEMs with psychiatric conditions (Table S4). We identified only 18 metabolic diseases in these reports, so the analysis remains descriptive and cannot be reliably generalized to the broader population. Furthermore, comparative analyses of treatment responses between individuals with IEMs and psychiatric diagnoses and those without metabolic diseases could not be conducted. Among the reported cases, disorders of complex molecule metabolism exhibited the highest level of pharmacoresistance, with a prevalence of 38.9% of all IEMs reviewed. This was followed by lipid metabolism disorders (16.7%) and disorders involving cofactors, heterocyclic compounds, cell signaling, and energy metabolism, each of which showed a prevalence of 11.1% (Figure 7A).

Psychiatric conditions in IEMs that showed poor response to standard treatments were led by psychosis, which had a 31% resistance rate (Figure 7B). This was followed by depression (24.1%); bipolar disorder (10.3%); and behavioral syndromes, neurodevelopmental disorders, and anxiety (each at 6.9%). The lowest pharmacoresistance rates were reported for neurocognitive disorders, disruptive behaviors, and catatonia (3.4% each). A closer look at complex molecule disorders indicated that psychosis, depression, and anxiety were particularly resistant to treatment (Figure 7C). These cases often exhibited resistance to antipsychotics, antidepressants, and benzodiazepines. Lipid metabolism disorders were primarily resistant to antipsychotics, benzodiazepines, and mood stabilizers in managing psychosis, depression, and behavioral conditions. Disorders related to cofactors, heterocyclic compounds, and energy metabolism typically showed resistance to antipsychotics when treating psychosis.

Antipsychotics showed the highest failure rate (51.1%) among psychiatric medications for IEMs, followed by antidepressants (23.4%), benzodiazepines (21.3%), and mood stabilizers (4.3%) (Figure 7D). Specific antipsychotics noted for their lack of efficacy were risperidone (8.5%), haloperidol (6.4%), olanzapine (6.4%), clozapine (5.2%), and

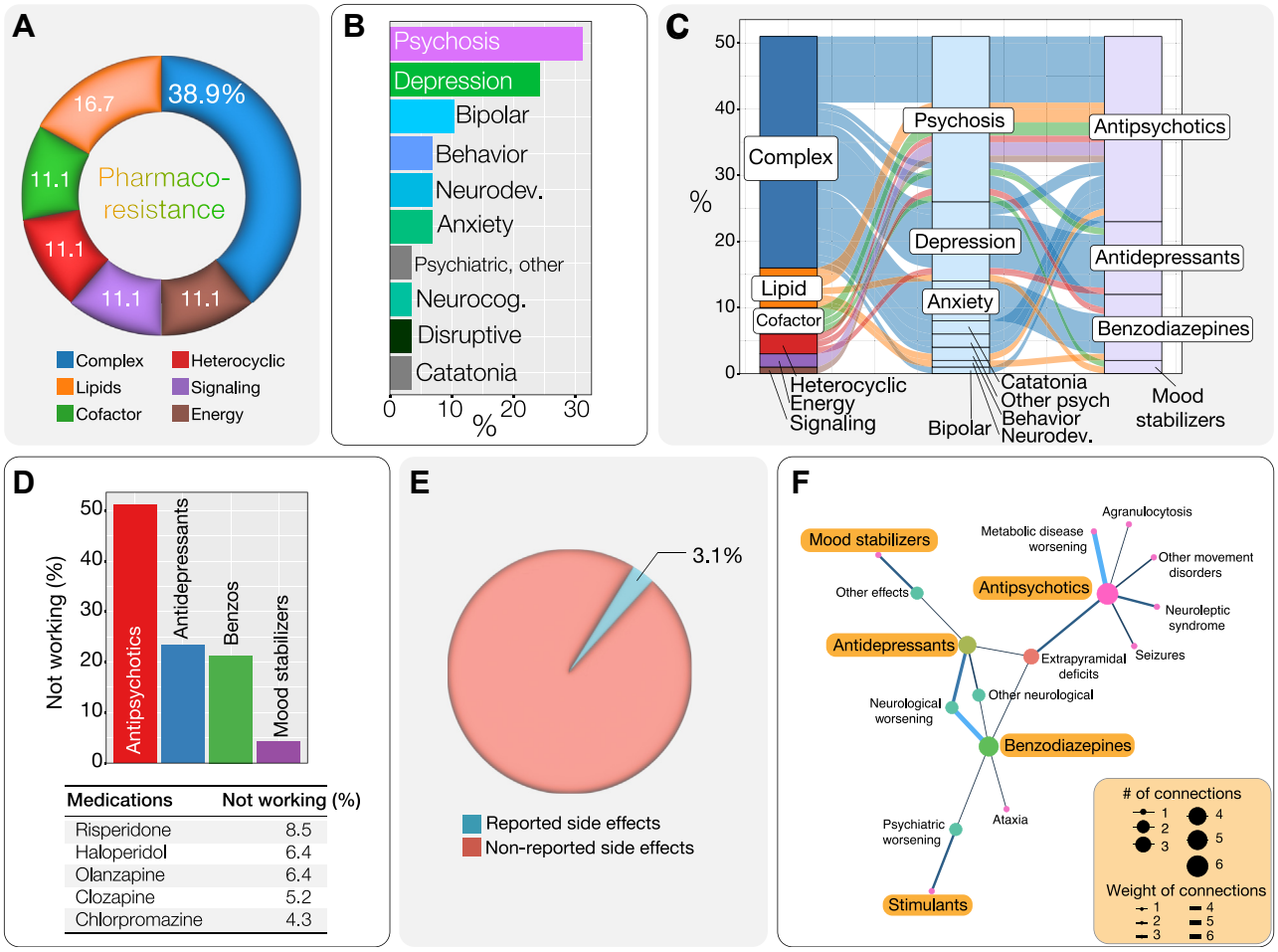

Figure 7. Pharmacoresistance and side-effect profile of psychiatric drugs. **(A)** Distribution of inborn errors of metabolism (IEM) groups based on the percentage of pharmacoresistance reported. **(B)** Frequencies of pharmacoresistance within psychiatric conditions. **(C)** Relative frequencies of pharmacoresistance among IEM groups, psychiatric conditions, and drug groups. **(D)** Relative frequencies of pharmacoresistance across drug groups together with a table detailing the failure rates of antipsychotics. **(E)** Distribution of reported side effects of psychiatric drugs in IEMs with psychiatric manifestations. **(F)** Distribution of side-effect profiles per drug group. benzos, benzodiazepines; neurocog., neurocognitive; neurodev., neurodevelopmental.

chlorpromazine (4.3%). Adverse effects were reported in only 3.1% of IEMs reviewed and were comparable in nature to those seen in patients without metabolic diseases (9) (Figure 7E). Antipsychotics were associated with an exacerbation of the underlying metabolic condition (35.3%) and neuroleptic syndrome (17.6%), as well as breakthrough seizures, movement disorders, and agranulocytosis. Benzodiazepines and antidepressants were linked to a worsening of underlying neurological deficits and, less frequently, to the onset of new extrapyramidal deficits and ataxia. Stimulants, on the other hand, were associated with an exacerbation of psychiatric symptoms (Figure 7F). Together, these findings highlight the need to report both the effectiveness and side effects of psychiatric drugs in individuals with IEMs.

DISCUSSION

More than one-fourth of IEMs are associated with psychiatric manifestations. Despite their high prevalence, recognizing and managing psychiatric deficits in these individuals remains a significant challenge. This complexity arises from the inherent phenotypic variability of metabolic diseases, the lack of formal clinical training in neurometabolism among healthcare providers, and the scarcity of research with limited characterization of psychiatric deficits in these patients. The rarity of IEMs, with some occurring as infrequently as 1 in 100,000 individuals (10), further complicates the recognition and proper management of these patients (1). Our findings highlight that psychiatric symptoms in IEMs often have distinct features, such as co-occurrence with neurological deficits and abnormal brain imaging (Figures 3A and 4A). Other key indicators include a family history of IEMs and symptoms triggered by metabolic stressors like high-protein diets, fever, or fasting (11). Systemic signs, such as cardiomyopathy, liver dysfunction, or renal problems, can also point to an underlying metabolic condition (3).

Our study shows that most psychiatric deficits arise within the context of neurodegeneration. This is followed in frequency by structural neurodevelopmental problems, either in combination with degenerative features or alone, and anatomical defects that do not fall into either category. Overall, structural brain damage occurred in approximately 93% of IEM cases with psychiatric manifestations, supporting the need for brain imaging when a metabolic disease is suspected (Figure 4B). Questions that arise from these findings include how IEMs disrupt the assembly and integrity of the developing and mature brain, what determines the age of onset of brain damage, and how developmental and degenerative features coexist or precede one another. Emerging evidence reveals significant parallels between the cellular and molecular mechanisms involved in both degeneration and developmental defects of the nervous system in IEMs (12). Common neurodevelopmental defects reported in postmortem cases include impaired cell proliferation, migration, neuronal arborization, and synaptic formation (13). These defects can be exacerbated by inflammation, reactive astrocytosis, and protein aggregation, features commonly seen in neurodegeneration (12). In our cohort, the coexistence of both developmental and degenerative defects was most prevalent in disorders of complex molecules and organelle metabolism (Figure 4C). Diseases within this group, such as lysosomal storage disorders or beta-propeller protein-associated neurodegeneration, have been associated with ADHD, autism, or Rett-like syndromes that later progress to neurodegeneration (12). This pattern has also been observed in disorders of energy and nutrient metabolism, which first disrupt brain development and then evolve into neurodegenerative phenotypes (14,15). The variability in symptom progression highlights the need to elucidate the mechanisms that drive brain developmental defects, age-related psychiatric deficits, and transitions from developmental to degenerative presentations. A deeper understanding of these mechanisms and their links to psychiatric manifestations is crucial for designing more effective therapies.

Important variables that could help investigate these mechanisms are the timing of symptom onset and the underlying neuropathology. We found that the pattern of presentation resembled a bimodal distribution, with neurodevelopmental and behavioral disorders peaking in childhood (Figure 5B and Figure S4). In contrast, psychosis, depression, anxiety, and neurocognitive disorders were more prevalent in adolescence and adulthood, consistent with previous studies of patients without metabolic disorders (12,16,17). We found that psychiatric deficits that present early in life were more associated with developmental structural defects of the brain, with or without degenerative features, whereas those that present later tended to manifest neurodegeneration primarily. Although it is likely an important variable, the underlying imaging phenotype and neuropathology does not fully explain the pattern of presentation of psychiatric disorders. For example, metabolic diseases without brain structural changes or presenting isolated, nonprogressive lesions had a similar bimodal distribution of psychiatric deficits across IEMs, with some exceptions. This suggests that while the specific metabolic dysfunction is a relevant contributor to the psychiatric phenotype and its timing of presentation, its impact likely varies depending on the developmental stage and degree of brain maturation. An example of this phenomenon is phenylketonuria, a disorder of phenylalanine metabolism and one of the most common IEMs. Phenylketonuria is a well-documented cause of neurodevelopmental and behavioral disorders, even when treated early (18). Recent studies have shown that prenatal exposure to high phenylalanine levels correlates with an increased probability of hyperactive/impulsive behaviors, while postnatal exposure correlates with an increased prevalence of inattentive behaviors (19–21). As these patients enter adulthood, early treated individuals tend to develop depression, anxiety, phobias, social isolation, and psychosis (18). Late-treated or off-diet adults have an even higher probability of experiencing these mental conditions (18,22). Overall, understanding the lifelong impact of metabolic dysfunction is essential for identifying vulnerabilities and timely interventions to mitigate psychiatric risks.

Diagnosing and managing the underlying IEM is key to effectively treating psychiatric symptoms. In our study, nearly 29% of all reported therapeutic approaches involved metabolic treatments, including specialized diets, vitamins, amino acids, and other supplements (Figure 6). This was particularly evident in disorders of cofactor and vitamin metabolism, which accounted for 41.9% of all IEM groups treated with metabolic interventions. Metabolic treatments reported in the literature often show dramatic improvements in psychiatric manifestations, especially for

disorders of cofactor, energy, or nutrient metabolism (23,24), highlighting the importance of directly addressing the metabolic dysfunction in these cases. We found that the most challenging psychiatric conditions to treat with conventional drugs were psychosis, depression, and bipolar disorder (Figure 7B), primarily in the context of disorders of complex molecules. However, we remain cautious about making broad conclusions due to the limited number of reports in the current literature about treatment effectiveness in this patient population. Side effects of psychiatric drugs were documented in 3.1% of IEMs, mainly associated with antipsychotics, benzodiazepines, and antidepressants (Figure 7F). Therefore, large-scale studies are needed to better understand the impact of metabolic treatments on these conditions and their integration with pharmacological care. Altogether, this review highlights the profound impact of metabolic disorders on mental health and aims to inspire research into the bidirectional relationship between metabolic dysfunction and mental illnesses.

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