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Schizophrenia, a disease of impaired dynamic metabolic flexibility: A new mechanistic framework

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ABSTRACT

Schizophrenia is a chronic, neurodevelopmental disorder with unknown aetiology and pathophysiology that emphasises the role of neurotransmitter imbalance and abnormalities in synaptic plasticity. The currently used pharmacological approach, the antipsychotic drugs, which have limited efficacy and an array of side-effects, have been developed based on the neurotransmitter hypothesis. Recent research has uncovered systemic and brain abnormalities in glucose and energy metabolism, focusing on altered glycolysis and mitochondrial oxidative phosphorylation. These findings call for a re-conceptualisation of schizophrenia pathophysiology as a progressing bioenergetics failure. In this review, we provide an overview of the fundamentals of brain bioenergetics and the changes identified in schizophrenia. We then propose a new explanatory framework positing that schizophrenia is a disease of impaired *dynamic metabolic flexibility*, which also reconciles findings of abnormal glucose and energy metabolism in the periphery and in the brain along the course of the disease. This evidence-based framework and testable hypothesis has the potential to transform the way we conceptualise this debilitating condition and to develop novel treatment approaches.

1. Introduction

The aetiology and pathophysiology of schizophrenia have remained largely unknown. It is presently conceptualized as a neurodevelopmental disorder, instigated by a complex interaction of a large number of susceptibility genes and environmental factors, such as maternal infection and malnutrition, early trauma and heavy psychoactive drug use during adolescence (Jauhar et al., 2022)

Mounting evidence from a variety of transcriptomic, proteomic, metabolomics and brain imaging studies points toward the possibility that schizophrenia is a systemic disorder and involves abnormal glucose and energy metabolism both in the periphery and in brain (Pillinger et al. 2018; Herberth et al. 2011; Tomasik et al. 2019; Sullivan et al. 2018b; Nascimento and Martins-de-Souza 2015; Zuccoli et al. 2017; Ben-Shachar 2017; Holper et al. 2019; Henkel et al. 2022; Townsend et al. 2022; Stein et al. 2023). Glucose has a major, sometimes exclusive, role as an energy substrate to fuel synaptic activity and support biogenesis to sculpt the brain during development and experience-dependent neuroplasticity. In addition, glucose metabolites are involved in the production of a variety of macromolecules including proteins, lipids, carbohydrates, nucleotides and major neurotransmitters, such as glutamate, GABA and acetylcholine, as well as in the regulation of redox processes in the neurons (Dienel 2019a). Therefore, abnormal glucose and energy metabolism can have profound influence on many aspects of brain development and function. It follows that the brain must have an efficient, highly adaptable mechanism to maintain normal glucose metabolism to avoid deleterious malfunctioning.

The ability to successfully adapt metabolism to supply and demand is known as *metabolic flexibility*, a term traditionally used in the context of fuel selection during transition from fasting to fed states, or to explain insulin resistance (Goodpaster and Sparks 2017). We adopt this concept and extend it to *dynamic* metabolic flexibility to describe how neurons, together with astrocytes and oligodendrocytes, in response to constant changing requirements *over time* during development, activation and inhibition, select the most efficient metabolic pathways to support optimal functioning. In this review, we propose that a genetically- and/or environmentally - induced bioenergetic imbalance between glycolytic and oxidative energy production and a diminishing dynamic metabolic flexibility within and between neurons and glia cells, contribute to the pathophysiology of schizophrenia. We provide an

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overview of glucose metabolism, with special emphasis on aerobic glycolysis (AG) and its link to mitochondrial oxidative phosphorylation (OXPHOS) in the healthy brain and in the brain of schizophrenia patients. We review evidence for bioenergetic abnormalities identified systemically and in brain, both *in-vivo* and in post-mortem specimens, in an endeavour to reconcile contradicting results and to formulate a theoretical framework for future research and novel approaches to treat schizophrenia. This review explicitly goes beyond recent papers focusing exclusively on central bioenergetics in schizophrenia (Henkel et al. 2022; Stein et al. 2023; Pruett and Meador-Woodruff 2020) by integrating central findings with the widely demonstrated peripheral energy metabolism abnormalities within a unified explanatory framework.

2. Glucose in the shaping and maintenance of the brain

The adult human brain, although constituting just 2–3% of total body weight, is responsible for the consumptions of a nearly 20% of the body's basal metabolic rate (Harris et al. 2012). The developing human brain is even more bio-energetically expensive utilising more than 40% of the body's basal metabolism (Goyal and Raichle 2018). The total daily glucose utilization by the brain peaks at age 4–5 years, and corresponds to 66% of the body's resting metabolic rate (Kuzawa et al. 2014), (Chugani et al. 1987). During adolescence the high glucose metabolism supports growth, synaptic proliferation, and remodelling (Goyal and Raichle 2018), as well as synthesis, release and recycling of neurotransmitters, all energetically expensive (Harris et al. 2012).

Glucose is the main energy substrate in the brain (Dienel 2019a). The high-energy molecule, adenosine triphosphate (ATP), is produced from glucose through glycolysis, the non-oxidative breakdown of glucose to pyruvate and lactate in the cytoplasm, and through the tricarboxylic acid (TCA) cycle and oxidative phosphorylation (OXPHOS) in the mitochondria (Dienel 2019a). Glucose is not only the major source for ATP but is also used for the biosynthesis of ribose to form ribonucleic acids, fatty acids and cholesterol. In addition, glucose through the pentose-phosphate pathway (PPP) is involved in the protection against

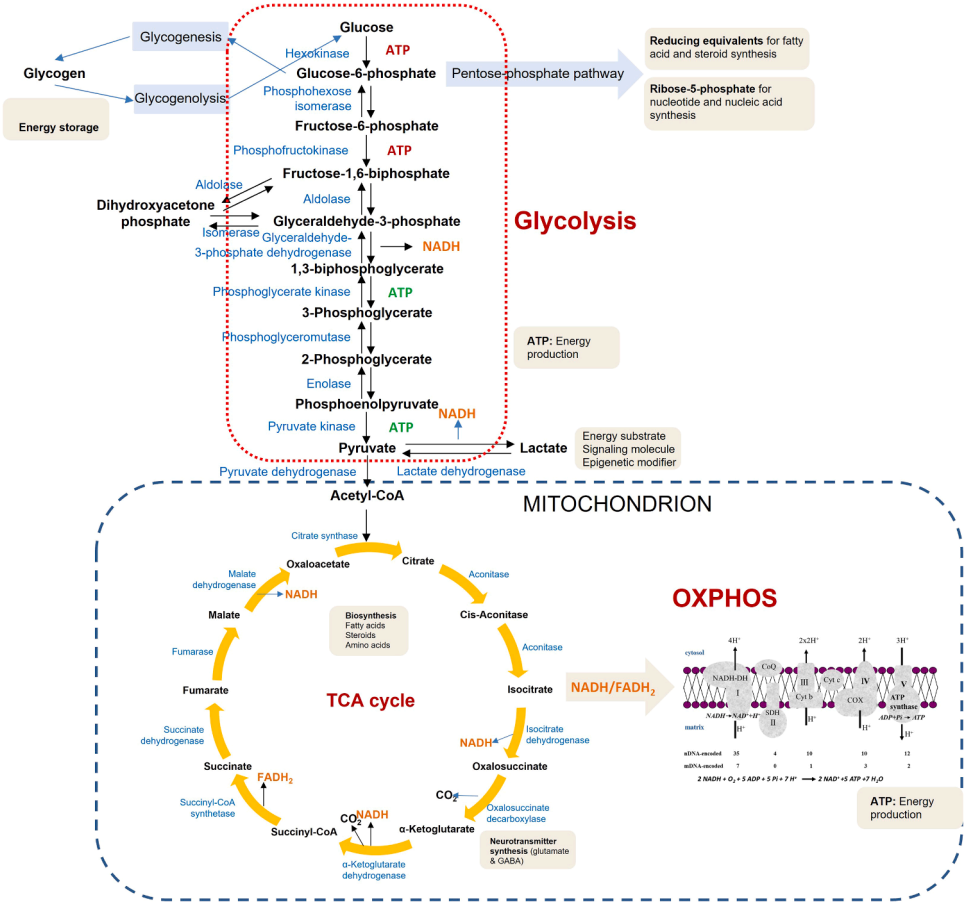

Fig. 1. *The metabolism of glucose through glycolysis, the TCA cycle and the oxidative phosphorylation (OXPHOS).*
Glucose is transported from the blood into brain cells via glucose transporters and irreversibly phosphorylated by hexokinase to produce glucose-6-phosphate (G6-P) that is trapped intracellularly. G6-P can continue down the glycolytic pathway, enter the pentose-phosphate pathways (PPP), serving as a precursor for NADPH, pentoses and ribose-5-phosphate, or be stored as glycogen. Its glycolytic downstream metabolites, fructose-6-phosphate (F6-P) and 3-phosphoglycerate (3PG) are precursors for a number of amino acids, and neurotransmitter/modulators. After further metabolised by a cascade of enzymatic steps, the end-product of glycolysis is pyruvate, which can be oxidized to acetyl-coenzyme A (CoA) by the pyruvate dehydrogenase complex (PDH), reduced to lactate, transaminated to alanine or carboxylated to oxaloacetate (OAA). Acetyl-CoA enters the tricarboxylic acid (TCA) cycle, in which two carbons enter the cycle by condensation of acetyl-CoA with OAA, and two carbons leave the cycle as CO2 to regenerate OAA. During this cycling four molecules of reducing agents (three NADH and one FADH2) are produced, which are oxidized via the oxidative phosphorylation (OXPHOS) system. Electrons are transferred from the reduced electron carriers NADH and FADH2 through the respiratory components to molecular oxygen. During the electron flow protons (H^+) are pumped from the matrix to the intermembrane space through complex I, III and IV, forming an electrochemical gradient, which is used by complex V to produce ATP. The net ATP yield from glycolysis is two ATP, whereas OXPHOS produces ~32 ATP molecules. *Abbreviations:* NADH-DH - NADH-ubiquinone oxidoreductase (complex I); CoQ - coenzyme Q; SDH - succinate ubiquinone oxidoreductase (complex II); Cyt b - ubiquinonferricytochrome c oxidoreductase (complex III); Cyt c - cytochrome c; COX - cytochrome c oxidase (complex IV); ATP synthase or ATPase (complex V).

oxidative stress, and through the TCA cycle in the production of amino acids such as glutamate and subsequently GABA (Dienel 2019a) (Fig. 1). Therefore, deficits in glucose and energy supply can lead to impaired dynamic regulation of key brain molecular circuits ultimately resulting in abnormal brain function and behaviour (Kann et al. 2014).

2.1. The metabolic fate of glucose in brain: an intimate relationship between neurons and glia

Neurons utilize most of the ATP produced from glucose metabolism compared to other cell types in the brain. In the brain, neuronal ATP is generated by a close, symbiotic relationship with astrocyte. Although the exact details of this intricate relationship have not been fully understood, there is evidence that through their end-feet, covering 99.7% of brain capillary (Mathiisen et al. 2010), astrocytes take up glucose and metabolize it to lactate through glycolysis. Lactate is then secreted and taken up by neurons, converted by lactate dehydrogenase (LDH) to pyruvate, which is further metabolised through the TCA and the OXPHOS (Magistretti and Pellerin 1999; Wyss et al. 2011). This astrocyte-neuron lactate shuttle (ANLS) hypothesis (Magistretti 2006; Wyss et al. 2011; Herrero-Mendez et al. 2009; Bolanos et al. 2010) claims that upon increased activity, neurons, which are unable to upregulate glycolysis on demand, rely on astrocytes lactate as an energy substrate (Magistretti and Allaman 2015). Recent research demonstrated that neurons are also capable of increasing glycolysis upon increased activity (Dienel 2019b; Yellen 2018) (Rangaraju et al. 2014) and do not necessarily have to rely on astrocytic lactate to produce extra ATP (Yellen 2018; Dienel 2019b; Bas-Orth et al. 2017). Others have shown that oligodendrocytes also produce lactate, which is efficiently taken up by myelinated axons for ATP production (Fünfschilling et al. 2012; Simons and Nave 2016).

2.2. Aerobic glycolysis (AG) and OXPHOS in brain

Most of the glucose in neurons is completely oxidized through OXPHOS in order to supply their large ATP requirement (Harris et al. 2012; Hall et al. 2012). However, approximately 10% to 12% of the total glucose consumed by a normal adult brain is metabolized by AG. The shift of glucose consumption toward AG and activation of the PPP is a well-described phenomenon in cancer cells and is termed 'Warburg effect' (Lunt and Vander Heiden 2011; Vaishnavi et al. 2010; Upadhyay et al. 2013). In essence, during AG glucose is metabolized to pyruvate, which is converted by LDH to lactate that is removed to the extracellular space through monocarboxylate transporters (MCTs). Although the ATP yield of AG is only ~6.25% of complete glucose oxidation, the rate of ATP production through AG is about twice as high as through OXPHOS (Pfeiffer et al. 2001).

An additional phenomenon in cancer bioenergetics is the 'Reverse Warburg Effect', occurring when glycolysis in the cancer-associated stroma metabolically supports the *adjacent* cancer cells, by transferring lactate and pyruvate through MCT (Wilde et al. 2017; Pavlides et al. 2009). This phenomenon shows close parallels with astrocytes/oligodendrocytes-neurons relationship described above (Bas-Orth et al. 2017). Regardless of whether Warburg effects occur in neurons or glial cells or both, it was shown to be functionally important in different forms of activity-dependent plasticity, such as long-term

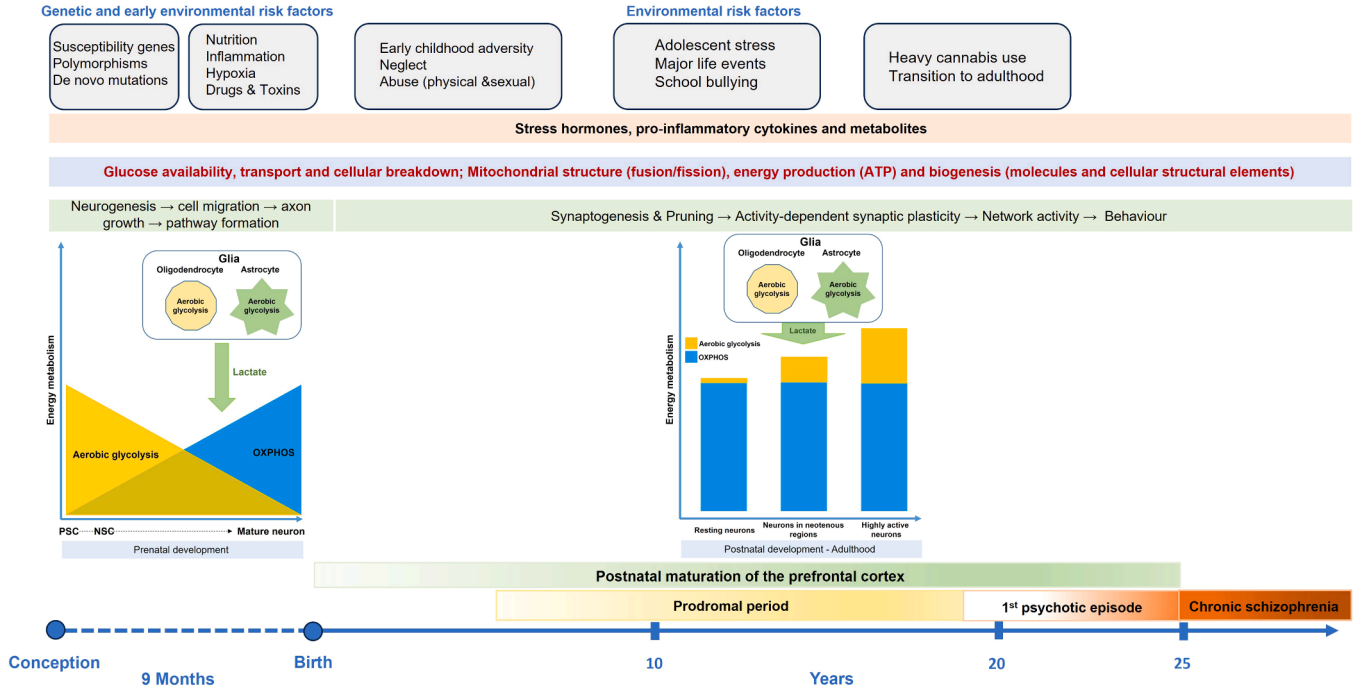

Fig. 2. *Schizophrenia risk factors and the dynamic metabolic flexibility during development, adulthood and in response to activation*
During early embryonic development pluripotent stem cells (PSC) rely mostly (70–90%) on glycolytic process to metabolise glucose for ATP production and for biosynthesis to support the rapid generation of new cells. As the PSC differentiate into neuronal precursor cells (NPC) there is a proportionally higher reliance on glycolytic processes than on OXPHOS. Glucose metabolism is then switching almost exclusively to OXPHOS as precursor cells mature into neurons. At this stage neuronal OXPHOS is supported by glial (astrocytic and oligodendrocytic) lactate, taken up by neurons to be converted to pyruvate and processed through the TCA cycle. The energy requirement increases rapidly in mature neurons during activation when excess ATP is indispensable to maintain synaptic excitation. Neurons can then take advantage of their own aerobic glycolytic (AG) capacity to generate this excess ATP very rapidly. In addition, the astrocyte-neuron lactate shuttle (ANLS) provides lactate as energy substrate to neurons in response to the glutamatergic signal from firing excitatory neurons. These fundamental bioenergetic switches are susceptible to schizophrenia risk factors, such as risk genes, prenatal malnutrition and infection/immune activation, adverse childhood experience, stress, trauma and heavy cannabis use during childhood and adolescence. The biological processes driven by these risk factors, including the activation of stress hormones, cytokines and metabolites, in turn, impact glucose availability, transport and breakdown as well as mitochondrial bioenergetic and synthetic processes to dysregulate neurodevelopment and adult synaptic plasticity.

memory (Harris et al. 2019).

During early developmental stages AG is at its highest level (Fig. 2), and at its peak accounts for nearly 30% of the glucose utilization (Goyal and Raichle 2018). Essentially, glucose metabolism through AG supports the intensive cell division through the biosynthesis of proteins, lipids, complex carbohydrates and ribonucleic acid (Goyal and Raichle 2018). In the mature brain, the highest AG rate is observed in the default mode network (DMN) (Raichle et al. 2001) and in regions with increased expression of genes related to synapse formation and growth, such as the frontal cortex.

In summary, we argue that AG in the brain subserves both structural and functional plasticity specifically at high-energy demands providing rapid energy substrates and molecular building blocks, whereas OXPHOS mainly supports functional synaptic plasticity during development and in the mature brain.

The OXPHOS activity and glycolysis are interconnected and impairment in one system affects the other and vice versa. Four enzyme complexes (CoI-IV) arranged in a specific orientation in the inner mitochondrial membrane, and two electron-carriers ubiquinone and cytochrome-c form the electron transport chain (ETC) (Fig. 1). ETC together with the fifth complex, ATP synthase (CoV), form the OXPHOS system. Mitochondrial dysfunction in general, and that of OXPHOS in particular, has been linked to a wide range of damaging processes including ROS production and apoptosis leading to cell death or milder defects resulting in cellular malfunction, synapse damage and axon degradation (Ricci et al. 2004; Li et al. 2004; Cobley 2018; Smith and Gallo 2018). In addition, presynaptic action potentials, neurotransmitter release, postsynaptic currents, and postsynaptic action potentials, all highly depend on O_2 and ATP, indicating that the OXPHOS is a key player in information processing in the brain (Hall et al. 2012).

3. Bioenergetic deficits in schizophrenia

Numerous studies have reported alterations in energy metabolism, glycolysis and the OXPHOS pathways, in the brain and periphery in schizophrenia (Prabakaran et al. 2004; Herberth et al. 2011; Holmes et al. 2006; Martins-de-Souza et al. 2012; Chouinard et al. 2018; Chouinard et al. 2017; Du et al. 2014; Sullivan et al. 2018a; Sullivan et al. 2018b; English et al. 2011). These changes were demonstrated *in-vitro* and *in-vivo* using imaging and molecular means. Since recent papers have reviewed these findings extensively (Henkel et al. 2022; Stein et al. 2023; Zhang et al. 2024; Liu et al. 2024; Pruett and Meador-Woodruff 2020), here we provide a shot summary with special emphasis on aspects relevant to the impaired dynamic metabolic flexibility framework. While we value the contribution of the relevant preclinical research we placed the main emphasis on reviewing data from patients with schizophrenia for more clarity with regards to the interpretability of animal models in the human context. However, the preclinical literature on genetic, neurodevelopmental, stress-based and pharmacological animal models, seems to be unequivocal in showing widespread abnormalities in virtually all aspects of brain energy metabolism, including insulin resistance (Ernst et al. 2012) and elevated brain lactate (Hagihara et al. 2023), most are in line with the human findings (Hagihara et al. 2023; Kolar et al. 2021) (Fig. 3). More recently, progressive metabolic dysregulation of glycolytic and Krebs cycle enzymes was identified following repeated inhibition of NMDA receptors activity in a region-specific manner (Kolar et al. 2022). In addition, it was found that the haploinsufficiency of mitochondria-associated genes within the Ch22q11.2 region is mainly associated with increased oxidative stress, altered energy metabolism, and calcium homeostasis in animal models. Studies on IPSCs from Ch22q11.2 deletion syndrome (DS) carriers corroborate findings of deficits in the brain energy metabolism, implying a causal role between impaired mitochondrial function and the development of schizophrenia in 22q11.2DS (Kolar et al. 2023). These results from preclinical studies do not only support the data obtained from patients with schizophrenia but they also highlight the utility of these models to reconcile contradicting human findings and better understand underlying mechanisms.

3.1. Altered AG and lactate production in schizophrenia

Earlier linkage analysis in schizophrenia identified three genes

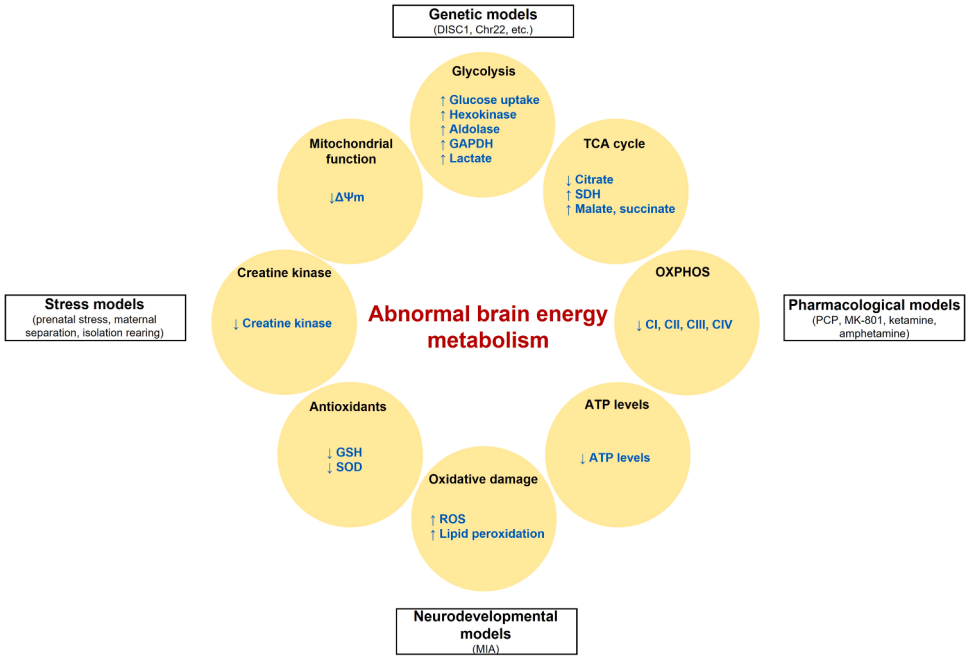

Fig. 3. *A summary overview of brain energy metabolism abnormalities in animal models for schizophrenia (adapted from data reported by (Kolar et al. 2021))*
Results from a variety of schizophrenia-relevant animal models indicate widespread abnormalities in brain energy metabolism affecting glycolysis, the TCA cycle, OXPHOS and other mitochondrial functions, which are mostly in line with the respective human findings. For further details see (Sarnyai et al. 2011; Sarnyai et al. 2015; Hagihara et al. 2023; Kolar et al. 2021; Kolar et al. 2022; Kolar et al. 2023; Cox et al. 2016).

involved in glycolysis and two variants in its regulation (6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 2 (Pfkfb2; 1q32.2), hexokinase 3 (HK3; 5q35.3) and pyruvate kinase 3 (PK3; 15q23) and phosphoenolpyruvate carboxykinase 1 (PCK1) and fructose-1,6-biphosphatase (FBP1), respectively) (Stone et al. 2004; Tanner et al. 2018; Olsen et al. 2008), suggesting abnormal aerobic glucose metabolism as an inherent part of the disease pathophysiology.

Elevated blood glucose levels and insulin resistance have been repeatedly shown in first-episode, drug-naïve patients with schizophrenia (Pillinger et al. 2017; Steiner et al. 2017; Steiner et al. 2018; Greenhalgh et al. 2017; Perry et al. 2016), providing ample substrate for glycolysis. A recent in-silico exploration of gene expression signatures in antipsychotic-naïve first episode psychosis has revealed glucose dysregulation overlapping with that of non-psychiatric subjects exhibiting early dysglycemia (Lee et al. 2024). Metabolomic profiling of unmedicated patients also revealed increased serum glucose and lactate level (Xuan et al. 2011; Herberth et al. 2011).

An accepted indicator of AG and of its preference over OXPHOS is elevated levels of lactate (Schurr 2014). Evidence for abnormal glycolysis and lactate in schizophrenia stems from studies of the systemic circulation, cerebrospinal fluid (CSF) and functional brain imaging or *post-mortem* specimens. A very recent, thorough systematic review and meta-analysis of blood and brain lactate levels in schizophrenia unequivocally shows elevated brain lactate levels, both in vivo and post-mortem, independent of the method used for lactate measurement (Liu et al. 2024). Although, 5 out of 7 studies showed increased blood lactate levels, the meta-analysis of all 7 studies established no statistically significant difference in blood lactate levels in schizophrenia patients, compared to the control group (Liu et al. 2024). However, the outcomes of the sensitivity analysis suggested that the results of this meta-analysis would be affected by the exclusion of one study in which results might be due to the administration of herbal supplements (Liu et al. 2024; Huang et al. 2021).

In summary, analyses of peripheral blood provide strong, converging evidence for hyperglycaemia and overactive glycolysis in un-medicated, first-episode patients with schizophrenia along with elevated lactate levels in the brain and the periphery.

3.2. Functional brain imaging studies

Abnormal brain glucose metabolism in schizophrenia has long been suggested based on decreased cerebral glucose utilization, assessed by brain imaging (Buchsbaum and Hazlett 1998; Siegel et al. 1995; Siegel et al. 1993; Hazlett et al. 1998; Hazlett et al. 2004; al-Mousawi et al. 1996). A more complex picture emerged by a large meta-analysis of functional brain imaging studies showing reduced activation in the left dorsolateral PFC, rostral/dorsal anterior cingulate cortex, left thalamus, and inferior/posterior cortical areas, while an increased activation in several midline cortical areas in patients (Minzenberg et al. 2009). A recent systematic review and meta-analysis of ^{18}FDG-PET studies in schizophrenia revealed decreased frontal cortical glucose utilisation, which was more pronounced in chronic than in first-episode cases and more pronounced in medicated than in un-medicated patients (Townsend et al. 2022). Using a more direct imaging approach Du et al. (Du et al. 2014) provided compelling evidence for abnormal bioenergetics, suggestive of a shift towards AG not only in chronic schizophrenia (Du et al. 2014) but also in first-episode psychosis (FEP) (Yuksel et al. 2021), as demonstrated by reduced forward rate constant (k[f]) of creatine kinase, reduction in phosphocreatine/adenosine triphosphate ratio and in NAD^+/NADH ratio in FEP patients (Chouinard et al. 2017). In chronic schizophrenia, an NMR spectroscopy study showed decreased ATP concentration in temporal cortical areas, but an increase in the basal ganglia, indicating abnormalities in the OXPHOS (Fujimoto et al. 1992). Moreover, a reduction in metabolic rate during verbal working memory tasks was observed in the posterior cingulate cortex (Haznedar et al. 2004). Interestingly, some of these energy metabolism abnormalities are shared with patient's unaffected siblings, similar to the findings of systemic glucose metabolism abnormalities (Chouinard et al. 2018; Chouinard et al. 2017), emphasizing a possible genetic/heritable or epigenetic contribution in the underlying biology.

3.3. Post-mortem brain studies

Post-mortem studies support AG hypoactivity in chronic patients. Recent laser capturing studies of dorsolateral prefrontal cortex (DLPFC) specimens of schizophrenia patients showed decreased mRNA expression and activity of two glycolytic enzymes (hexokinase 1-HXK1 and PFK1) and two glucose transporters (GLUT1 and GLUT3), while lactate/pyruvate transporter MCT1 expression was increased, potentially providing excess entry for astrocyte-derived lactate. (Sullivan et al. 2018a). Changes in glycolytic enzyme expression were identified in neurons but not in astrocytes, suggesting the lack of compensatory up-regulation by astrocytes (Sullivan et al. 2018a). In an independent follow-up study, the decreased PFK expression was replicated and a decreased expression of glucose phosphate isomerase (GPI) transcript in DLPFC pyramidal neurons was identified (Sullivan et al. 2019b). Transcriptomic and proteomic studies of the DLPFC striatum and the posterior cingulate cortex specimens from patients revealed a decrease in transcripts and proteins of various major glycolytic enzymes (Nascimento and Martins-de-Souza 2015; Zuccoli et al. 2017; Prabakaran et al. 2004; Altar et al. 2005; Dean et al. 2016; Reis-de-Oliveira et al. 2020). Altered expression and activities of the TCA cycle enzymes have also been demonstrated using post-mortem DLPFC samples from schizophrenia patients (Bubber et al. 2011; Middleton et al. 2002; Reis-de-Oliveira et al. 2020). Mostly, enzymes of the first half of the TCA cycle were lower, whereas enzymes comprising the second half of the TCA were higher than controls, possibly reflecting a compensatory response to reduced activities of enzymes in the first half (Bubber et al. 2011). However, changes in bioenergetics are not always uniform across the entire human brain and different structures/networks show unique alterations. In fact, a recent cell type-specific molecular profiling of the subgenual anterior cingulate cortex, a region implicated in mood and cognitive control, revealed significantly increased expression of genes involved in bioenergetic processes in the layer5/6 excitatory pyramidal (PYR) neurons, whereas decreased expression of bioenergetics-related transcripts in vasoactive intestinal peptide- (VIP), somatostatin- (SST), and parvalbumin- (PVALB) expressing inhibitory interneurons (Arbabi et al. 2024) (Fig. 4).

In summary, if we consider all reported brain glycolytic changes a consistent picture emerges of a hyperactive AG during the early/acute stage of psychosis, in good correspondence with results from animal models (Fig. 3), while hypoactive brain AG in the DLPFC in chronic schizophrenia. The regional differences in bioenergetic impairments may contribute the altered network activity and the emergence of the symptoms in psychosis.

3.4. Impaired oxidative phosphorylation

Numerous studies have demonstrated dysfunctional mitochondria in schizophrenia [(For reviews see (Ben-Shachar 2017; Cuperfain et al. 2018; Flippo and Strack 2017; Roberts 2017)]. Brain imaging revealed abnormal production rates of high-energy phosphates and reduced NAD^+/NADH ratio, pointing at a decreased activity of the OXPHOS (Du et al. 2014; Fujimoto et al. 1992; Volz et al. 2000; Ongur et al. 2009; Pettegrew et al. 1991). Concomitantly, abnormal OXPHOS complexes enzymatic activity and their subunits' levels (primarily CoI and CoIV) were reported in both brain and peripheral cells of patients (Holper et al. 2019; Rajasekaran et al. 2015; Cavelier et al. 1995; Prince et al. 1999; Maurer et al. 2001; Akarsu et al. 2014; Ben-Shachar et al. 1999). The transcriptome, proteome and metabolome of different brain areas and somatic cells show robust alterations in mitochondria-related transcripts, proteins and metabolites in schizophrenia, including those of the

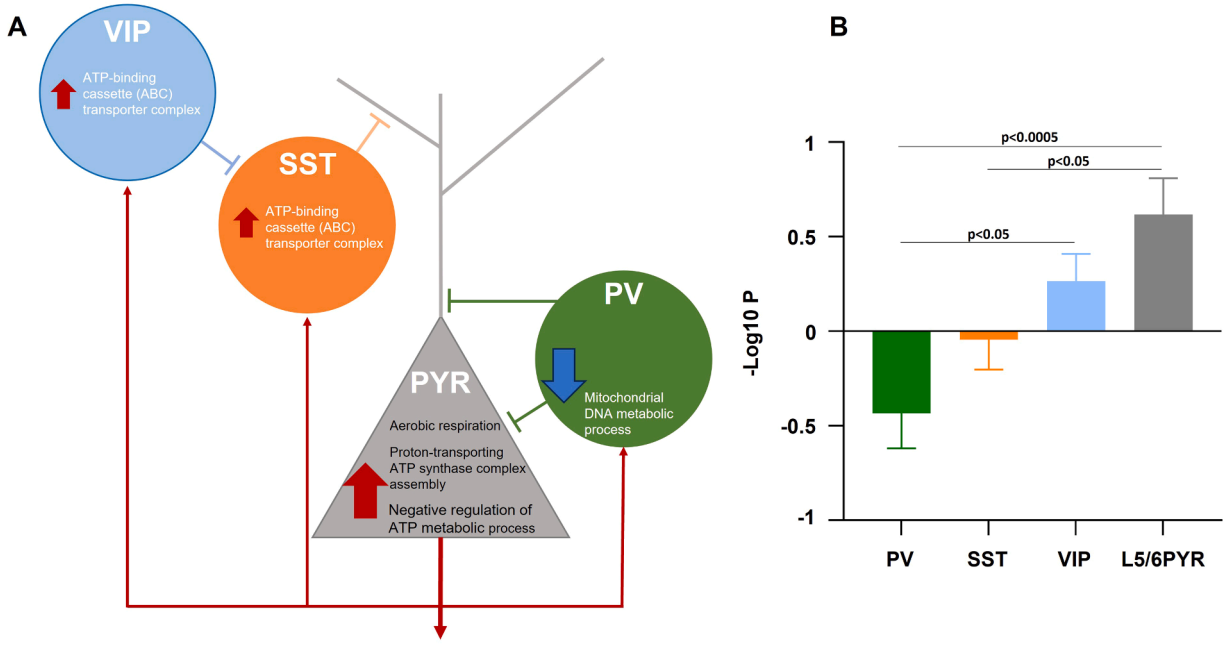

Fig. 4. *Differential bioenergetic pathway activity in the subgenual anterior cingulate cortex (sgACC) in schizophrenia (data derived from (Arbabi et al. 2024))*
A recent transcriptomic study (Arbabi et al. 2024) identified cell type-specific transcriptional alterations in neuronal subpopulations that make up cortical microcircuits: excitatory pyramidal (PYR) neurons and vasoactive intestinal peptide- (VIP), somatostatin- (SST), and parvalbumin- (PV) expressing inhibitory interneurons by using laser capture microdissection followed by RNA sequencing. The cell type-specific molecular profiling of sgACC, a region implicated in mood and cognitive control, revealed hundreds of differentially expressed genes and biological pathways. They characterized the biological effects of transcriptomic dysregulation in neuronal subtypes using differential pathway activity analysis and identified "bioenergetics" as one of the main broad biological terms and within it 18 "bioenergetics"-relevant GO biological process. A: The significantly "bioenergetic" biological processes are summarized for each cell type. B: We analysed the -Log10 P values for the 18 "bioenergetics"-relevant GO biological process using data made available in the supplementary materials and identified an overall significant difference between cell types (ANOVA F[3, 68]=6.856; $p = 0.0004$) with an overall up-regulation of "bioenergetics"-relevant GO biological process in the Layer 5/6 pyramidal neurons (L5/6PYR) compared to PV ($p < 0.0005$) and SST ($p < 0.05$) interneurons, and in a lesser extent in VIP interneurons compared to PV interneurons ($p < 0.05$). These results suggest that the widespread down-regulation of "bioenergetics"-relevant GO biological processes may render the PV interneurons unable to properly exert an inhibitory control over the L5/6PYR, which may contribute in the overall upregulation of "bioenergetics"-relevant GO biological processes in the excitatory pyramidal neurons in the sgACC in schizophrenia.

OXPHOS (Sethi and Brietzke 2015; Hjelm et al. 2015; Park and Park 2012; Brennand et al. 2015; Jiang et al. 2019; Reis-de-Oliveira et al. 2020). Among the most robustly changed proteins are the labile subunits of CoI including NDUFV1 and NDUFV2, the substrate site bearing subunit and the excessive electrons acceptor antioxidant subunit, respectively (Lazarou et al. 2007; Dieteren et al. 2012). A recent multivariate meta-analyses of mitochondrial Co-I and IV activities and subunits' expression in peripheral tissue and different brain areas of patients with mental disorders, substantiates the dysregulation of CoI and less so of CoIV, in schizophrenia (Holper et al. 2019; Dror et al. 2002; Ben--Shachar and Karry 2008). There are replicated associations between variant genes for CoI subunits and risk of schizophrenia. There are also replicated post-mortem findings of reduced number of mitochondria and abnormal mitochondrial morphology, reduced CoI subunit expression and reduced CoI activity in people with schizophrenia who were taking antipsychotics, compared to controls (Whitehurst and Howes 2022).

Although genome-wide association studies in schizophrenia have failed to consistently replicate genetic risk factors among the OXPHOS genes (Biological insights from 108 schizophrenia-associated genetic loci 2014; Avramopoulos 2018; Need et al. 2009), a growing number of studies report mitochondria-related susceptibility loci and associated risk genes. Among >300 putative schizophrenia risk genes, there was significant enrichment of mitochondrial genes, supporting the potential role of mitochondria and OXPHOS abnormality in schizophrenia pathogenesis (Hjelm et al. 2015). One of CoI subunit, NDUFV2, which in our hands shows the most robust and consistent alteration in schizophrenia, has been reported a high probability risk gene for the disease (Ayalew et al. 2012; Washizuka et al. 2006; Xu et al. 2008). mtDNA SNPs as risk factors (Verge et al. 2011), possibly due to somatic rather than inherited mutations, were also reported, specifically SNPs in mtDNA encoded CoI subunits ND1, ND4 and ND5 (Marchbanks et al. 2003; Martorell et al. 2006). The role of mitochondria-related genes is further substantiated by the observation that many patients with congenital mitochondrial diseases suffer from psychotic-like symptoms, in particular those with a variety of mutations in CoI genes (Verge et al. 2011; Fattal et al. 2006). In line with the latter are the data suggesting that CoI plays a major role in controlling oxygen consumption and neuronal bioenergetics (Telford et al. 2009).

ATP synthase, or Complex V, is a mitochondrial enzyme-complex localized in the inner mitochondrial membrane, which catalyzes the synthesis of ATP from ADP and phosphate, with the proton gradient across the membrane being its driving force. Recent meta-analysis of the expression of 16 ATP synthase encoding genes in brain samples of individuals with schizophrenia vs. healthy controls showed significant down-regulation of two ATP synthase encoding genes detected in schizophrenia, ATP5A1 and ATP5H, and a trend towards down-regulation of five further ATP synthase genes (Katz Shroitman et al. 2023). Importantly, this analysis found no significant correlation between antipsychotic treatment and either of the genes' expression levels, indicating that the down-regulation may be an inherent feature associated to schizophrenia rather than a function of the treatment (Katz Shroitman et al. 2023).

Two recent post-mortem analyses further support impaired mitochondrial function in schizophrenia. Transcriptomic profiling for a gene set indexing mitochondrial functional pathways in the DLPFC grey matter and in layer 3 and layer 5 pyramidal neurons identified that 41%

of mitochondrial-related genes were differentially expressed in schizophrenia, 83% of them down-regulated, in a manner not attributable to antipsychotic medications (Glausier et al. 2020). More recently, single-nucleus RNA sequencing of over 200,000 neurons from the DLPFC of patients with schizophrenia and matched controls found down-regulation in the expression of energy metabolism-related genes (OXPHOS- and ATP-synthase-related genes) in the upper-layer GABA-ergic inhibitory interneurons (Batiuk et al. 2022).

Mitochondrial deficits were associated with defective neuronal differentiation and dendritic arborisation (Ni et al. 2019; Shao et al. 2019). In addition, it has been recently demonstrated that midbrain dopaminergic, excitatory glutamatergic and cortical inhibitory GABA-ergic neurons derived from schizophrenia-iPSCs (SZ-iPSCs) show impaired differentiation into mature neurons associated with abnormal expression of mitochondrial genes including those of the OXPHOS as well as compromised mitochondrial function (Robicsek et al. 2013; Ni et al. 2019; Ben-Shachar 2017; Ben-Shachar and Ene 2018; Ben-Shachar and Karry 2008; Bergman and Ben-Shachar 2016; Robicsek et al. 2018). (Ni et al. 2019). Interestingly, genetic disruption of mitochondrial ATP production in murine parvalbumin-positive GABA-ergic interneurons revealed abnormal gamma oscillation along with impaired sensorimotor gating and sociability, cardinal behavioural endophenotypes of schizophrenia (Inan et al. 2016). On the other hand, transplantation of isolated active healthy mitochondria restored mitochondrial abnormalities as well as the differentiation efficiency of SZ-iPSCs (Robicsek et al. 2018). In an animal model of the disorder intra-prefrontal cortex injection of healthy mitochondria restored both mitochondrial function and core schizophrenia-related behavioural responses (Robicsek et al. 2018). Collectively, these data suggest a causal link between mitochondria, neuronal differentiation and function and individual behavioural responses.

Consolidating the AG and OXPHOS findings over the course of the disease we can see that multiple mitochondrial abnormalities in OXPHOS and insufficient ATP production are present from the early stage of the disease (Ni and Chung 2020), as demonstrated by imaging findings of decreased OXPHOS activity and the compensatory shift toward glycolysis, reflected by excessive lactate production and decreased pH (Rowland et al. 2016; Ben-Shachar and Laifenfeld 2004). However, over time, the glycolysis pathway may become exhausted in neurons, which will further exacerbate the neuronal ATP deficits, resulting in a continued lactate over-production, likely by glial cells, to provide alternative bioenergetic substrates.

Beyond being an effective energy substrate to maintain neuronal function, lactate plays an additional role in the brain modulating neuronal excitability and neuronal plasticity and in supporting memory (Magistretti and Allaman 2018). In schizophrenia, due to the impaired neuronal OXPHOS, the bioenergetic potentials of lactate cannot be fully utilized. Therefore, in a bio-energetically compromised brain, lactate's inhibitory effect on excitatory, but not fast spiking GABA-ergic inhibitory, neurons (Clasadonte et al. 2017; Nagase et al. 2014; Bozzo et al. 2013; de Castro Abrantes et al. 2019; Sada et al. 2015), will dominate and alter excitatory/inhibitory balance, which may result in abnormal network activity and can give rise to changes in behaviour and cognition typical of schizophrenia. Indeed, in schizophrenia, elevated brain lactate levels, measured by magnetic resonance imaging, were associated with schizophrenia-typical cognitive dysfunctions (Rowland et al. 2016). A recently uncovered additional function of lactate is modification of histones by lysine lactylation, resulting in changes of expression of homeostatic genes that have been shown to play a role in pro-inflammatory processes (Zhang et al. 2019) that are of relevance to schizophrenia pathophysiology. Therefore, increased lactate levels derived from the systemic circulation and from brain astrocytes and oligodendrocytes, as a part of a compensatory attempt in response to impaired mitochondrial ATP production, will likely enhance the deleterious effects of altered AG and OXPHOS, impinging on brain function over time.

4. Dynamic metabolic flexibility in the brain in health and in schizophrenia: towards an evidence-based theoretical framework

Recent research in brain bioenergetics has highlighted that regional rates of energy use might be mostly *constrained by supply*, rather than driven by demand, given the properties of the brain capillary network, the highly stable rate of oxygen delivery to the whole brain under physiological conditions, and homeostatic constraints (Herculano-Houzel and Rothman 2022). The near-capacity brain energy budget makes the brain susceptible to loss of ability to maintain metabolic homeostasis of fuels (glucose and ketones), waste products (protons and lactate), ions (primarily K^+), neurotransmitters (glutamate and GABA), and energy metabolism intermediates during vulnerable periods. The structural development, maturation, adaptive neuroplasticity, and optimal functioning of the brain depend on successfully meeting the rapidly changing energy requirements driven by developmental needs and synaptic activity. The dynamic metabolic flexibility allows the brain to optimally utilise limited energy resources by effectively switching between glycolytic and OXPHOS-driven ATP production through utilising a genetic program for metabolic remodelling and taking advantage of the mutual metabolic interactions between neurons and glia cells. A damage to the integrity of this dynamic metabolic flexibility will hamper, depending on the timing of the event, normal early brain development, circuit development and maturation during adolescence and synaptic activity. Schizophrenia has been conceptualised as a neurodevelopmental disorder (Marenco and Weinberger 2000), with excess vulnerability during fetal development, childhood and adolescence/early adulthood. In the following section we review the evidence on how major schizophrenia risk factors interfere with elements of the dynamic metabolic flexibility, AG and OXPHOS, across development (Fig. 2).

4.1. Prenatal development: genetic and environmental risk

A convergent body of epidemiological, preclinical, and prospective observational research supports the embryonic/fetal period of brain development as being particularly susceptible to disorganizing influences of disrupted energy metabolism. During prenatal development, from conception, both genetic end environmental factors can influence brain bioenergetics.

4.1.1. Susceptibility genes

Although, schizophrenia is a highly polygenic condition with the majority of the currently explained heritability coming from common alleles of small effect but with additional contributions from rare copy number and coding variants (Owen et al. 2023), a number of identified risk genes may have an effect on brain energy metabolism. Here we highlight three very diverse genes, DISC1, C4 complement component gene, and the gene encoding histone methyl transferase SETD1A, to illustrate the links between genetic factors, brain bioenergetics, and abnormal neurodevelopment that may underlie schizophrenia. Disrupted-in-Schizophrenia-1 (DISC1) function has been associated with the structural and functional integrity of the mitochondria (Atkin et al. 2011; Norkett et al. 2016; Park et al. 2016; Park et al. 2010; Pinero-Martos et al. 2016). DISC1 depleted cells have decreased mitochondrial DNA (mtDNA) content and steady state levels of OXPHOS subunits. Therefore, OXPHOS complexes are partially disassembled, which results in severe bioenergetic defects, evidenced by impaired oxygen consumption, ATP synthesis and mitochondrial membrane potential (Pinero-Martos et al. 2016). Furthermore, a reduction in DISC1 function induced mitochondrial dysfunction, evidenced by decreased mitochondrial NADH dehydrogenase activities, reduced cellular ATP contents, and perturbed mitochondrial Ca^{2+} dynamics (Park et al. 2010). Functionally, genetic inhibition of DISC1 signalling by knockdown of mouse endogenous DISC1 (DISC1-KD) and expression of a dominant-negative,

C-terminus truncated human DISC1 (DN-DISC1), decreased mRNA and protein levels of glucose transporter 4 and glucose uptake by primary astrocytes. Decreased astrocytic glucose uptake was associated with reduced OXPHOS and glycolysis as well as diminished lactate production *in-vitro* and *in-vivo* (Jouroukhin et al. 2018). From a neurodevelopmental point of view, a single point mutation on the DISC1 gene caused striking tangential interneuron migration deficits in the embryonic brain and selective alterations of calbindin- and parvalbumin-expressing interneurons in the cortex and hippocampus, decreased GAD67/PV co-localization and mis-positioned interneurons across the neocortex when compared to wild-type littermates (Lee et al. 2013). This is of particular significance as such findings in interneuron migration, positioning and morphology have been identified in post-mortem cortical tissue from people with schizophrenia (Benes and Berretta 2001; Yang et al. 2022).

The complement system, particularly the component C4, involved in microglial functions such as synapse formation and synaptic pruning, has been identified as a major risk gene for schizophrenia (Woo et al. 2020; Sekar et al. 2016). The complement system and its C4 component influence mitochondrial function and regulates cell metabolism (Hess and Kemper 2016), through which it can influence brain development both pre- and post-natally. The overexpressing C4A in mice reduced cortical synapse density, increased microglial engulfment of synapses, and altered mouse behaviour (Yilmaz et al. 2021).

Loss of function mutations affecting the histone methyl transferase SETD1A have been implicated in the aetiology of schizophrenia (Singh et al. 2016). Disruption of SETD1A in human induced pluripotent stem cell (hiPSC)-derived neurons resulted in a significant reduction in several glycolytic enzymes including hexokinase-2, pyruvate kinase, and lactate dehydrogenase-A, as well as in reduced lactate level, lower basal glycolysis rate; and lower spare and maximal mitochondrial OXPHOS capacity, suggesting that whilst SETD1A haploinsufficient neurons are metabolically normal under non-challenged conditions, they might be more susceptible to metabolic stress, such as low glucose supply or increased ATP demand (Chong et al. 2022). In parallel to the bioenergetic impairments the same neurons also showed reduced neurite outgrowth and spontaneous activity, two phenotypes commonly associated with schizophrenia (Chong et al. 2022). These results suggest that metabolic dysfunction contributes to neuronal phenotypes caused by SETD1A haploinsufficiency. Gene expression changes show significant enrichment for mitochondria-related genes in the brain of in Setd1a± mice (Bosworth et al. 2024).

Collectively, these results suggest that underlying genetic susceptibility, the presence of risk genes, may interfere with glucose metabolism and OXPHOS in neurons and astrocytes as well as with their mutual bioenergetic interactions in the prenatal brain, giving rise to a pathological developmental trajectory and symptom development in early adulthood.

4.1.2. Malnutrition and immune activation

The major environmental risk factors for schizophrenia include malnutrition and prenatal (maternal) inflammation (Ortiz-Valladares et al. 2024; Brown and Meyer 2018). Metabolomic profiling of the prefrontal cortex from rats exposed to prenatal protein malnutrition revealed differential expression of key metabolic pathways related to energy metabolism and glutamate metabolism, including increasing concentration of glucose-6-phosphate and lactate, reflecting increased glycolytic flux in astrocytes, which may produce a corresponding decrease in the activity of PPP, resulting in the loss of the antioxidant NADPH. Furthermore, reduced oxaloacetate and α-ketoglutarate were also identified, which indicates an impaired activity of the TCA cycle and consequently ATP production (Xu et al. 2019). Maternal protein malnutrition in rats resulted in long-lasting mitochondrial abnormalities shown by decreased OXPHOS markers and oxidative stress in the prefrontal cortex of the adult offspring (de Sousa Fernandes et al. 2024). These functional abnormalities in glucose metabolism and mitochondrial activity may contribute to disrupted neurodevelopment (Rushmore et al. 2022). A recent study identified reduction in neuron numbers in specific parahippocampal subregions: the medial entorhinal cortex and pre-subiculum as a result of prenatal protein malnutrition (Amaral et al. 2024). Similarly, very significant decrease in mPFC volume and average neuronal size was observed in prenatally malnourished rats (Cruz-Rizzolo et al. 2017). Prenatal undernutrition may also disrupt myelin formation, rendering individuals more susceptible to the later development of schizophrenia (Ortiz-Valladares et al. 2024).

Maternal viral and bacterial infection, and resulting immune activation, has been identified as an important risk factor for schizophrenia (Brown and Meyer 2018; Estes and McAllister 2016). Inflammatory molecules as primary mediators play a key role for both healthy and abnormal brain development in-utero, at which time the developing embryo responds to 'suboptimal' conditions by producing structural and functional changes in cells, tissues and systems that modulate susceptibility for schizophrenia (Knuesel et al. 2014). Mitochondria, which are sensitive to immune alterations, are fundamentally important to many of these processes, and thus may mediate some of the inflammatory-related influences on brain development (Gyllenhammer et al. 2022). Specifically, both mitochondrial biogenesis and bioenergetics regulate fate decisions of NPCs to either proliferation or differentiation. Differentiated NSCs are characterized by low mitochondrial and mtDNA content, and the switch from AG to mitochondrial OXPHOS controls the shift from NSC proliferation to NSC differentiation into NPCs and subsequent cell types (Folmes and Terzic 2014; O'Brien et al. 2015). Furthermore, neuronal migration, a highly energetic process, is also critically dependent on mitochondrial dynamics and bioenergetics as shown by altered interneuron migration induced by the genetic disruption of OXPHOS in mice, suggesting that interneuron polarity during migration is particularly sensitive to disruptions in mitochondrial bioenergetics, and that OXPHOS is required for normal migration of interneurons from the basal forebrain to the neocortex (Lin-Hendel et al. 2016). This is particularly relevant as it have been shown that embryonic and perinatal neurodevelopmental insults in neuronal migrations cause neuronal functional and behavioural deficits in affected adult animals, which are similar to those of people with schizophrenia (Muraki and Tanigaki 2015; Toudji et al. 2023).

Maternal immune activation (MIA) affects the brain's ability of handling glucose at the functional level in the adult offspring. For example, [18F]-FDG PET demonstrated that MIA offspring displayed higher brain glucose consumption in the whole brain after weaning (Guerrin et al. 2022). Similar brain imaging approach has shown that animals exposed to MIA had lower glucose uptake in the ventral hippocampus and PFC already prior to the emergence of the behavioural symptoms, and a higher metabolism in the amygdala and nucleus accumbens (Hadar et al. 2015). Intriguingly, a decrease in brain volume, which could be related to the impaired brain bioenergetic processes, was observed in one-year-old animals exposed to MIA in-utero compared with control groups (da Silveira et al. 2017).

In summary, diverse variety of insults during prenatal development, driven by genetic and/or environmental factors, can result in interlinked abnormalities of brain bioenergetic process, such as glycolysis and OXPHOS, neurodevelopment and adult psychopathology.

4.2. Childhood and young adulthood: stress and drugs

Early life stress and trauma have been consistently identified through extensive meta-analyses and umbrella reviews as major risk factors in schizophrenia (Bailey et al. 2018; van Winkel et al. 2008; Hailes et al. 2019; Varese et al. 2012). In addition, excessive substance use during late adolescence and early adulthood emerges as a significant risk factor (Matheson et al. 2023). In the following section we will identify biological links between stress/trauma and cannabis use and glycolytic and mitochondrial energy generating processes in the brain that can

contribute to the impaired dynamic metabolic flexibility we propose to contribute to the development of schizophrenia.

4.2.1. Stress and trauma: the role of cortisol

Although different stressors and traumatic experience activate a variety of molecular pathways both systemically and in the brain, the mechanisms involved in stress neurobiology include the activation of the autonomic nervous system, the hypothalamic-pituitary-adrenal (HPA) axis resulting in the elevation of the main stress-responsive glucocorticoid hormone, cortisol and the release of pro-inflammatory cytokines, such as IL-6, TNF-alpha and interferons (McEwen 1998). Here we advocate for the hormonal stress mediator cortisol as it has a direct and functionally significant effects on brain energy metabolism.

Importantly, the relationship between stress and mitochondria is dynamic and bidirectional. Mitochondrial defect produces a unique stress-response signature. The mutation or deletion of mitochondrial genes resulting in impaired mitochondrial respiratory chain function, energy exchange, and mitochondrial redox balance generated excessive corticosterone increase, in mice (Picard et al. 2015). On the other hand, cortisol is intimately involved in regulating energy metabolism in the body and in the brain (Jaszczyk and Juszczak 2021). Acute glucocorticoid administration increases the expression of pyruvate dehydrogenase kinase (Connaughton et al. 2010), a key enzyme to inhibit the conversion of pyruvate to acetyl-CoA and thereby blocking glucose oxidation but increasing the pyruvate-to-lactate conversion, likely shifting the metabolism towards AG. Chronic exposure to corticosterone resulted an overexpression of the neuronal glucose transporter GLUT3, supplying more energy to neurons subjected to chronic stress (Herbet et al. 2022). Furthermore, the altered expression of the *Ldha* and *Ldhb* genes indicate the brain's attempts to produce and use lactate to optimize energy production under stress. However, the decrease in the expression of the *Gapdh* gene may indicate a redirection of energy metabolism from AG to the pentose–phosphate pathway (Herbet et al. 2022). Further links between stress, cortisol and brain bioenergetics are highlighted by the fact that mitochondria mediate the stress response partially by sensing the levels of glucocorticoids (Herbet et al. 2022). Glucocorticoids, through their genomic effects, induce profound changes in mitochondrial physiology. They bind to mitochondrial glucocorticoid-response elements (GREs) localized within the genes encode the catalytic subunits of cytochrome c, the terminal oxidase of the mitochondrial electron transport chain (Demonacos et al. 1996). In the short term, glucocorticoids produce adaptive changes, including increase mitochondrial biogenesis and ATP production, but long-term stress or cortisol exposure produces maladaptive, deleterious effects, such as decreased mitochondrial biogenesis and ATP production, as well as increased production of reactive oxygen species, disturbances in OXPHOS, mitochondrial fusion/fission dysregulation and increased apoptosis (Głombik et al. 2021). At a functional level, early environmental influences, such as early handling in mice, have profound effects on the bioenergetic processes of the brain, including increased expression of glycolytic enzymes without impacting OXPHOS, and a positive and negative correlation between anxiolytic-like behavior and the expression of the Krebs cycle enzymes isocitrate-dehydrogenase and citric synthase, respectively (Thomou et al. 2024). The impact of the psychosocial experience on mitochondrial activity has been recently demonstrated in humans (Trumpff et al. 2024). By combining longitudinal antemortem assessments of psychosocial factors with postmortem brain (dorsolateral prefrontal cortex) proteomics in older adults, it was found that higher well-being is linked to greater abundance of the mitochondrial OXPHOS machinery, whereas higher negative mood is linked to lower OXPHOS protein content. Psychosocial factors explained a quarter of the variance in the abundance of OXPHOS Complex I, the primary biochemical entry point that energizes brain mitochondria. A strong cell-type-specific association for positive psychosocial experiences and mitochondria was found in glia but opposite associations in neurons (Trumpff et al. 2024). Collectively, these results suggest that stress, at least in part through circulating cortisol, is capable of influencing different aspects of brain energy metabolism, including glycolysis and mitochondrial OXPHOS, according to energetic needs through life.

4.2.2. Adolescent cannabis use

A major review of 26 systematic reviews and meta-analysis of the published literature (Hasan et al. 2020) and a recent consensus paper (D'Souza et al. 2022) have concluded that exposure to cannabis increases the risk for psychoses ranging from transient psychotic states to chronic recurrent psychosis. The greater the dose, and the earlier the age of exposure, the greater the risk. For some psychosis outcomes, the evidence supports potential causality. CB1 cannabinoid receptors are ideally located on the mitochondrial membrane in striato-nigral neurons to affects bioenergetic processes and behaviour (Soria-Gomez et al. 2021). In these neurons cannabinoid stimulation of CB1 receptors resulted in a decreased mitochondrial respiration, which mediated the cataleptic effects of the cannabinoids (Soria-Gomez et al. 2021). Stimulation of astrocytic mitochondrial CB1 receptors impairs glucose metabolism and lactate production in the brain through a reduction of the complex I subunit NDUFS4 and resulting excess production of reactive oxygen species (Jimenez-Blasco et al. 2020). Chronic administration of delta9-tetrahydrocannabinol (THC) to juvenile mice in doses that are relevant to human recreational use, resulted in a widespread upregulation of most of the essential building blocks of the brain mitochondrial complexes I-V, along with the disruption of the integrity of the mitochondrial membrane (Beiersdorf et al. 2020). Thus, it is likely that the exposure of the juvenile brain to repeated doses of THC during a critical period of development imposes lifelong alterations to cellular bioenergetics, which may serve as a mechanism to mediate the increased risk of developing schizophrenia following heavy adolescence cannabis use.

In summary, the different schizophrenia risk factors across development, such as genetic and environmental risks, can plausibly interfere with energy metabolism processes in the brain, both with AG and mitochondrial OXPHOS. It is not known at present if such effects are more prominent in neurons or in glia. However, a recent, detailed morphological analysis of cell-specific expression of key mitochondrial enzymes showed very low expression levels of OXPHOS-related genes in astrocytes of the human neocortex and hippocampus (Dobolyi et al. 2024), suggesting that most of the OXPHOS targeting occurs in neurons, while the impact on AG can take place in both neurons and glia.

4.3. The breakdown of the dynamic metabolic flexibility

The impaired dynamic metabolic flexibility hypothesis posits that the critical points of metabolic flexibility are adversely affected by schizophrenia risk factors resulting in the inability to meet the actual energy requirements and to support synaptic activity and other neuronal functions. In this section, we will review how such endangerment of the effective switching between metabolic programs within neurons and glia contribute to their malfunction (Fig. 5).

4.3.1. Early neurodevelopmental metabolic switching

During early embryonic development pluripotent stem cells (PSC) rely mostly (70–90%) on glycolytic process for ATP production and biosynthesis supporting the rapid generation of new cells (Lees et al. 2015). It has been shown that as PSC differentiate into neuronal stem cells (NSC) there is a proportionally higher reliance on glycolytic processes than on OXPHOS (Lees et al. 2018). This is likely to be driven by two main factors. On one hand, lower reliance on OXPHOS avoids damage from reactive oxygen species (ROS) generated in the electron transport chain (Khacho et al. 2016). On the other hand, active AG enables NSCs to use TCA cycle intermediates for anabolic purposes such as amino acid and nucleotide biosynthesis, critical during this early stage of development. As NSC differentiate into neurons, glucose metabolism switches almost exclusively to OXPHOS, which seems to be required for

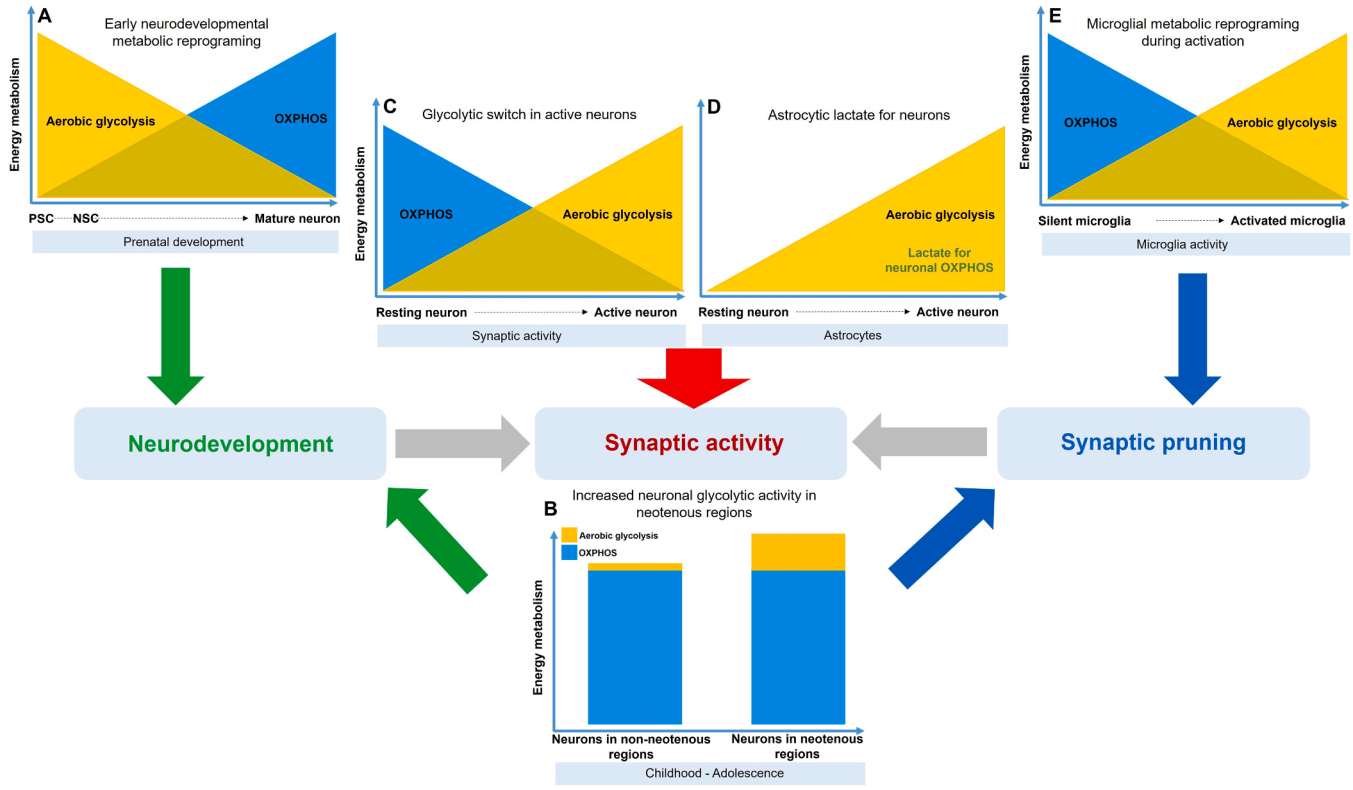

Fig. 5. *Key bioenergetic switching points in the brain during development, maturation and heightened activity*
A: During prenatal development the pluripotent stem cells (PSC) and neuronal stem cells (NSC) largely rely on AG to produce ATP and cellular building blocks. NSCs then switch to OXPHOS for ATP production while they are differentiating into mature neurons. B: In neotenous brain regions, where the transcriptional pattern retains early developmental characteristics, such as the prefrontal cortex higher AG persists during childhood and adolescence to support further post-natal neural development, synaptogenesis and synaptic plasticity. C: Neurons are capable to increase their AG during activation to assure timely and site-specific production of ATP to support heightened synaptic activity. D: Astrocytes provide actively firing glutamatergic, excitatory, neurons with excess ATP through the production of lactate by their increased AG taking advantage of their end feet strategically localised around brain capillaries. E: Microglia switch their metabolism from OXPHOS to AG during activation by immune signals. Activated microglia then contribute to synaptic pruning during adolescence and early adulthood to form mature prefrontal cortical networks.

neuronal differentiation (Zheng et al. 2016). At this stage neuronal OXPHOS is likely supported by astrocytic and oligodendrocytic lactate (Pellerin and Magistretti 2011). Such dynamic metabolic flexibility of glycolysis and mitochondrial functions, the TCA cycle and OXPHOS, contributes to the balance between cell division and differentiation (Rumpf et al. 2023). Well-characterised schizophrenia risk factors, including susceptibility genes and their downstream pathways, prenatal protein malnutrition and maternal immune activation due to viral or bacterial infections, may influence the molecular machinery that underlies switching from AG to OXPHOS in NSC, leading to abnormalities in neurogenesis, cell differentiation, migration, positioning, and pathway formation. This can give rise to an abnormal neurodevelopmental trajectory, resulting in a heightened risk state to develop psychosis in late adolescence/early adulthood.

4.3.2. *Maintained neuronal AG in neotenous brain regions*

In young adults, a portion of resting glucose consumption exceeds that predicted by oxygen consumption rates (Blazey et al. 2018) (Fig. 2). Though the role(s) of this excess glucose utilization, which reflects AG, remain uncertain, some studies suggest that AG in the brain may support neurite outgrowth (Segarra-Mondejar et al. 2018), myelination (Fünfschilling et al. 2012), learning (Harris et al. 2019), reducing oxidative stress (Butterfield and Halliwell 2019), rapid and anticipatory neuronal activity (Diaz-Garcia et al. 2017; Miller et al. 2023; Li et al. 2023), and microglial activity (Baik et al. 2019; Holland et al. 2018). AG in the young adult occurs in regions that are transcriptionally neotenous (resemble the expression pattern of early development) and evolutionarily expanded, such as the prefrontal cortex, in humans (Goyal and Raichle 2018; Goyal et al. 2014). It is important to highlight that the human prefrontal cortex does not finish maturing well into the mid-twenties, which means that such maturation processes require biomolecules such as lipids and proteins, that are synthesised in part from molecules derived from the PPP arm of glycolysis. Therefore, one would expect structural and functional consequences of AG impairments contributed by psychosis risk factors such as adversity, stress and cannabis use during adolescence.

4.3.3. *Microglial metabolic reprograming*

The period from adolescence to young adulthood is critical for the mature formation of synapses and network connectivity in the prefrontal cortex. It was hypothesised that schizophrenia results “from a defect of synaptic elimination programmed to occur during adolescence” (Feinberg 1982; Germann et al. 2021). This is driven, in part, by a coordinated elimination or engulfment and pruning of certain synapses by activated microglia and the astrocytes (Huttenlocher 1979; Mordelt and de Witte 2023; Park and Chung 2023; Mallya et al. 2019). Microglia activation, a pro-inflammatory process, is accompanied by a metabolic shift from OXPHOS to AG (Camacho-Morales 2022; Holland et al. 2018; Lauro and Limatola 2020). This microglial metabolic flexibility can be adversely influenced by a number of schizophrenia risk factors, such as susceptibility genes, maternal immune activation, exposure to stress, and drugs of abuse, which will probably cause abnormal synaptic pruning and neural connectivity. In turn, the functional integrity of the prefrontal cortex will be damaged and unable to execute attentional and

cognitive tasks and to control behaviour (Friedman and Robbins 2022).

4.3.4. Meeting demands of high synaptic activity: lactate from astrocytes and glycolytic switch in neurons

It is generally proposed that under basal conditions, neurons produce ATP through mitochondrial OXPHOS, taking advantage of the conversion of astrocytic lactate to pyruvate (Magistretti 2006; Magistretti and Pellerin 1999). This view may need to be refined, as the neuronal soma, but not terminals, seems to rely on AG to metabolise glucose even under resting conditions (Wei et al. 2023). However, the potential risk of neurons relying on AG has recently been highlighted by genetically transforming neurons into an AG phenotype, which resulted in mitochondrial Complex-I disassembly, bioenergetic deficiency, and redox stress, along with cognitive deficits (Jimenez-Blasco et al. 2024). Furthermore, aging-related synapse loss and cognitive impairment were associated with neuronal AG and were normalised by the genetic inhibition of the neuronal glycolytic flux in mice (Zhou et al. 2024). Under high energy requirement (e.g. responding to stimuli, performing a task, learning & memory), neurons continue to use astrocytic lactate, which may become more readily available due to the metabolism of neuronal excitation derived glutamate by astrocytes (Magistretti and Allaman 2018). In addition, neurons may also increase their glycolytic activity by

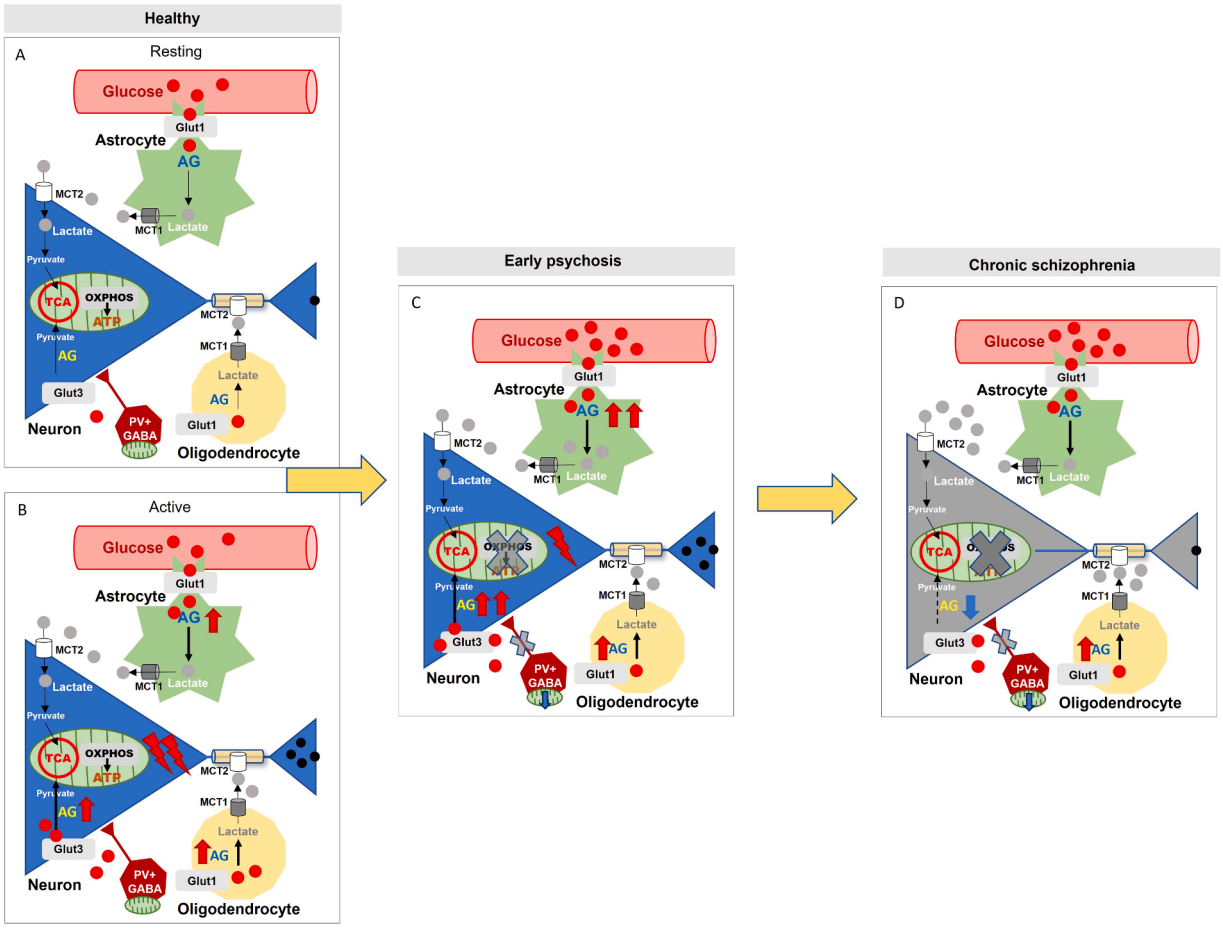

Fig. 6. *Schematic representation of the proposed impaired metabolic flexibility in schizophrenia*
In the healthy brain, under resting conditions (A) the neuronal ATP requirement is mainly met by neuronal OXPHOS utilising glucose-derived lactate that is produced by the astrocyte (and perhaps in lesser extent by oligodendrocytes) and transported through monocarboxylic acid transporters (MCT1 and MCT2). During activation (B), in order to maintain the increased demand for ATP provision due to the heightened excitatory neurotransmission astrocytes increase their glycolytic activity in response to the glutamate stimulus to supply lactate to neurons as energy substrate to fuel neuronal OXPHOS. At the same time, neurons turn on their own aerobic glycolysis (AG) to produce extra ATP rapidly and locally in the synapse where excitatory neurotransmission takes place. Such concerted effort by the glia cells and neurons supports the heightened bioenergetic needs during excitatory activity by producing more ATP molecules faster. During the early stage of the schizophrenia (C) mitochondrial dysfunction, potentially caused by a multitude of factors (susceptibility genes; early environmental effects, such as immune activation due to viral infections or prenatal stress; later environmental factors such as heavy cannabis use and chronic, toxic stress and trauma) is already present, resulting in an impaired bioenergetic state. This may underlie impaired synaptic transmission, neuronal communication and altered functional connectivity, resulting in hallucinations and delusions at the early stage of the disease. As compensatory attempt systemic glucose levels rise, resulting in the well-replicated phenomenon of hyperglycaemia, astrocytes take up more glucose and up-regulate their AG to provide excess lactate to neurons, which cannot be properly utilised due to the underlying mitochondrial OXPHOS deficit. Neurons may benefit from a 'glycolytic shift' to attempt to compensate for the loss of OXPHOS-derived ATP. The increased neuronal AG produces some but sub-optimal amount of ATP, which may not be sufficient to properly maintain synaptic communication. The persistent mitochondrial OXPHOS deficit drives the futile glycolytic compensatory attempts in chronic schizophrenia (D) eventually resulting the downregulation of glycolytic gene/protein expression and enzyme activity in neurons, gradually depriving them from the benefit of AG-derived ATP. Systemically, however, there is a chronic hyperglycaemia, which eventually contributes to insulin resistance and associated systemic metabolic consequences. Excess astrocytic lactate provision through glycolysis is still maintained, brain lactate levels and the MCTs are upregulated in neurons. Neurons may not be able to energetically benefit from the elevated lactate levels due to the mitochondrial OXPHOS impairment. Therefore, lactate is likely to be utilised as an inhibitory neurotransmitter exerting effect on excitatory, but not fast spiking GABA-ergic inhibitory, neurons. Such inhibition will dominate and alter excitatory/inhibitory balance, which may result in abnormal network activity and can give rise to changes in behaviour and cognition typical of chronic schizophrenia.

switching to AG (Diaz-Garcia et al. 2017; Miller et al. 2023; Yellen 2018; Dienel 2019a; Bas-Orth et al. 2017). The fact that neurons have to rely on AG-driven ATP production during increased synaptic activity and that excessive AG has detrimental effects on neuronal energy metabolism and overall function indicates that these metabolism switches have to be tightly regulated within neurons and across neurons and astrocytes. As described in Section 4, genetic and environmental risk factors have demonstrated widespread detrimental effects on both glycolysis and OXPHOS in neurons. Thus, they can influence the genetic program that underlies the neuronal glycolytic switch during activation, resulting in either insufficient ATP provision in the synapse or a glycolytic endangerment of the active neuron.

4.3.5. Impaired dynamic metabolic flexibility over the course of schizophrenia: reconciling central and peripheral energy metabolism abnormalities

Based on the impaired dynamic metabolic flexibility driven by multiple factors across development here we provide a comprehensive explanatory framework and a working hypothesis to reconcile the diverse and, on occasions, seemingly contradictory findings to outline the potential chain of events of impaired energy metabolism flexibility in schizophrenia (Fig. 6).

By definition, all post-mortem data reflect the disease chronic state, while functional brain imaging and studies of peripheral samples tend to focus on first-episode/early stage to avoid the well-known confounding effects of antipsychotics (Ballon et al. 2014; Newcomer 2005). When looking at the bioenergetic changes from this point of view it transpires that during first-episode/early stage there are already signs of mitochondrial OXPHOS malfunction (Townsend et al. 2022) and a glycolytic shift (Du et al. 2014) associated with elevated lactate levels and decreased pH in brain (Rowland et al. 2016) and periphery (Henkel et al. 2022). On the other hand, brain post-mortem analysis from chronic patients, overwhelmingly supports deficits both in glycolysis and OXPHOS, as shown by decreased glycolytic and mitochondrial enzymes. These changes, however, seem to occur on the background of elevated brain, CSF and serum lactate levels.

Mitochondrial abnormalities, especially in the CoI of the ETC, emerge as primary deficits in schizophrenia (Ben-Shachar 2016; Whitehurst and Howes 2022; Katz Shroitman et al. 2023). The most immediate consequence of that is a compensatory attempt by upregulating ATP-synthesis mechanisms not reliant on mitochondrial OXPHOS, such as neuronal AG. In fact, it has been shown in different cell systems that CoI dysfunction and assembly deficits result in a 'glycolytic shift' leading to the activation of AG (Rafikov et al. 2015; Desquiret-Dumas et al. 2019). It is possible that similar mechanisms operate in schizophrenia. We propose that in early stage of the disorder neurons respond to impaired ATP supply with up-regulating neuronal AG in a manner analogous to the "Warburg effect" (Bas-Orth et al. 2017; Diaz-Garcia et al. 2017) Concomitantly, an increase in neuronal glutamate release occurs, which activates the astrocyte/oligodendrocytes-neurone lactate shuttle. Released lactate is then taken-up by neurons and through conversion to pyruvate, fuels mitochondrial TCA cycle and OXPHOS (Magistretti 2006; Magistretti and Allaman 2015; Wyss et al. 2011) analogous to the "reverse Warburg effect" (Micu et al. 2018; Barros 2013). Overall, the compensatory increase in neuronal glycolysis is in line with the "glycolytic shift" identified by brain imaging in the frontal cortex as the disease develops (Du et al. 2014; Chouinard et al. 2017).

During the course of schizophrenia it is likely that the genetically and/or environmentally contributed mitochondrial impairments (Gonçalves et al. 2015) persist, and perhaps even worsen as shown by the decreased expression of subunits comprising Complexes I, IV, and V both in layer 3 pyramidal neurons and PV+ inhibitory interneurons (Glausier 2018). Therefore, over time the continuous compensatory attempts will result in a gradual exhaustion of the AG as reflected by the decreased expression of glycolytic genes (HXK1, PFK1, glucose transporter 1 [GLUT1], and GLUT3 mRNA) in pyramidal neurons (Sullivan et al. 2018a). Impaired AG and consequently deprived PPP glucose-driven biosynthetic processes will result in a negative impact on neuron activation and synaptic plasticity, respectively. In astrocytes glycolytic enzymes remain unchanged (Sullivan et al. 2018a), suggesting the astrocytic lactate production through AG is maintained. However, this lactate cannot be sufficiently used for neuronal ATP production due to the persistent OXPHOS deficit and is accumulated (Sullivan et al. 2019a). Consequently, in a bio-energetically compromised brain, lactate's inhibitory effect on excitatory, but not fast spiking GABA-ergic inhibitory neurons (Clasadonte et al. 2017; Nagase et al. 2014; Bozzo et al. 2013; de Castro Abrantes et al. 2019; Sada et al. 2015), will dominate and alter excitatory/inhibitory balance, which may result in abnormal network activity. These deleterious changes in cellular bioenergetics may disproportionally impact brain networks that would otherwise rely heavily on AG for their normal functioning, such as the default-mode network (DMN) and areas of the dorsolateral prefrontal cortex (Vaishnavi et al. 2010) that have been implicated in schizophrenia (Fair et al. 2008; Buckner and DiNicola 2019). The impairments in DMN activity (Broyd et al. 2009; Kottaram et al. 2019; Hu et al. 2017; Lavigne et al. 2019) and resting state functional connectivity (Bassett et al. 2012) may contribute to abnormal self-referential or introspective mental processes, which depend on these networks. (Fair et al. 2008; Buckner and DiNicola 2019).

The metabolic processes in the brain and in the periphery are intimately linked, thus, systemic alterations in glucose metabolism even in un-medicated, first-episode individuals (Pillinger et al. 2017; Pillinger et al. 2018; Steiner et al. 2017; Steiner et al. 2018; Perry et al. 2016), need to be reconciled with the changes taking place in the brain. Despite its high energy demand, the brain has a low storage capacity, with low levels of glycogen or lipids to metabolise into ATP (Dienel 2019a), which turns maintenance of a steady supply of glucose crucial for a normal brain function (Peters et al. 2004). The "selfish brain" theory formulated by Peters (Peters et al. 2004; Peters et al. 2022), that describes the characteristic of the human brain to cover its own comparably high energy requirements with the utmost priorities when regulating energy fluxes in the organism, helps explaining the co-occurring changes in glucose and energy metabolism in the brain and the periphery in schizophrenia.

The brain senses ATP concentration through ATP-sensitive potassium channels (K_{ATP} channels), which close and depolarise or open and hyperpolarise the neuron in response to increasing or decreasing ATP concentration, respectively. It is proposed that at low brain ATP concentrations the glutamatergic neurons are dominantly active, while at high ATP concentrations the activity of the GABAergic population predominates (Song and Ashcroft 2001; Karschin et al. 1997; Lee et al. 1996; Peters 2011). Low ATP in brain influences systemic glucose concentration by activating the limbic-sympatho-adrenal system to release noradrenaline from sympathetic terminals and adrenaline from the adrenal medulla, which in turn inhibit insulin release and prevents glucose uptake into peripheral tissue. (During et al. 1995; Dunning et al. 1988; Baron et al. 1987; Deibert and DeFronzo 1980; Lembo et al. 1994). Elevated levels of adrenalin and noradrenaline metabolites, together with insulin resistance, were found in first-episode, antipsychotic-naïve schizophrenia (Steiner et al. 2017; Berger et al. 2018). An alternative mechanism has emerged with the recent discovery of the brain's direct control of peripheral glucose and energy metabolism by showing that clusters of hippocampal sharp wave-ripples reliably predicted a decrease in peripheral glucose concentrations (Tingley et al. 2021). We, therefore, suggest that the primary brain energy deficit, a core pathology of schizophrenia, drives the systemic glucose metabolism abnormalities observed in the disease in an attempt to assure adequate glucose provision to the brain.

5. Testing the hypothesis

It has been extensively demonstrated that there are widespread

abnormalities in bioenergetic pathways in the brain of people with schizophrenia, both in vivo and post-mortem, as well as in a variety of relevant animal models. However, at this stage it is not clear whether these abnormalities are linked to the disease pathophysiology and if they are, in what way. This in itself is not surprising as the physiology of a complex dynamic system such as the brain includes many nonlinear (Goyal et al. 2020) and counterintuitive processes (Sturm et al. 2023). We, however, believe that the impaired dynamic metabolic flexibility hypothesis we put forward is testable and the key questions above can be answered to some satisfaction. Furthermore, refined cell-type specific post-mortem studies will provide further evidence with regards to the involvement of neurons versus astrocytes but will not inform us about causality. Longitudinal follow-up studies with ultra-high risk youth to measure brain bioenergetic changes, such as in (Du et al. 2014; Stein et al. 2023; Yuksel et al. 2021) will help to establish the temporal relationship between the appearance of the bioenergetic changes and the symptoms over time. In order to establish causality, the bioenergetic abnormalities should precede the emergence of symptoms. This approach will be able to address the "dynamic" aspects of the metabolic flexibility. Further evidence for the causal role of the bioenergetic abnormalities could emerge from the therapeutic benefit of interventions that primarily target energy metabolism-related processes (Longhitano et al. 2024). However, it is unlikely that clear mechanistic insight to and support for a causative relationship can be gained from studies in humans. Using animal models would open up a number of avenues to test our hypothesis, albeit largely without the benefit of a longitudinal design. For example, we can genetically reprogram bioenergetic processes specifically in either neurons or astrocytes, switching on and off AG, at different developmental milestones, such as during prenatal development by *in-utero* gene transfer, at weaning or in adulthood. Detailed analysis of the transcriptome and the metabolome in a cell-type specific manner in such animals, along with a schizophrenia-related behavioural phenotyping, will allow investigators to causally link induced metabolic reprogramming (impaired dynamic metabolic flexibility) with bioenergetics and behaviour. In such models the use of stable isotope labelled energy substrates (glucose, pyruvate, lactate), with appropriate spectroscopy approaches, will make possible to map out the entire intermediary metabolism in cell-type specific manner. Ultimately, experimental therapeutic approaches, such as mitochondrial transfer (Ben-Shachar and Ene 2018; Robicsek et al. 2018; Ene et al. 2023; Tripathi and Ben-Shachar 2024) or targeted over-expression/inhibition of key glucose metabolic genes (Wei et al. 2023; Jimenez-Blasco et al. 2024) will help to obtain key results to support, or disprove, the dynamic metabolic flexibility hypothesis.

6. Conclusion and clinical implications

The proposed new mechanistic framework that posits schizophrenia as a disease of *impaired dynamic metabolic flexibility* has the potential to transform the way we conceptualise the disease. More importantly, our working hypothesis, summarized in Fig. 6, calls for new therapeutic interventions that aim to provide adequate ATP supply during the early course of the disease, support brain bioenergetics needs and prevent the negative consequences of the failed compensatory attempts. A variety of metabolic approaches for influencing overall energy metabolism, targeting mitochondrial integrity and function, such as ketogenic diet and exogenous ketones (Sarnyai and Palmer 2020), as well as specifically targeting identified metabolic pathways in the brain such as insulin signalling (Henkel et al. 2022), PPAR-alpha (Scheggi et al. 2022; Wada et al. 2020) or sirtuin (Leite et al. 2022) signalling can be considered. As it is beyond the scope of this review, we refer the readers to several review papers on such metabolic therapeutic strategies (Henkel et al. 2022; Sarnyai and Palmer 2020; Ben-Shachar and Ene 2018).

By proposing this new theoretical framework, we suggest that at least a subgroup of individuals, rather than everyone within the diagnostic category, may show brain energy metabolism abnormalities related to the core pathophysiology. The encouraging results from pilot studies using ketogenic metabolic therapy seem to support this notion (Sethi et al. 2024). Due to the intimate connectedness of central and peripheral energy metabolism it is likely that interventions that address peripheral/systemic metabolism, exercise, intermittent fasting, therapeutic dietary interventions, as well weight loss medication, may prove to be helpful. In fact, the combination of such interventions with traditional antipsychotic administration may help to mitigate the unwanted metabolic side effects of atypical antipsychotics.

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CRediT authorship contribution statement

Zoltán Sarnyai: Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Dorit Ben-Shachar:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization.

Declaration of competing interest

The authors, ZS and DBS, declare no conflict of interest.

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