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COMPREHENSIVE INVITED REVIEW

Mitochondria, Metabolism, and Redox Mechanisms in Psychiatric Disorders

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Abstract

Significance: Our current knowledge of the pathophysiology and molecular mechanisms causing psychiatric disorders is modest, but genetic susceptibility and environmental factors are central to the etiology of these conditions. Autism, schizophrenia, bipolar disorder and major depressive disorder show genetic gene risk overlap and share symptoms and metabolic comorbidities. The identification of such common features may provide insights into the development of these disorders.
Recent Advances: Multiple pieces of evidence suggest that brain energy metabolism, mitochondrial functions and redox balance are impaired to various degrees in psychiatric disorders. Since mitochondrial metabolism and redox signaling can integrate genetic and environmental environmental factors affecting the brain, it is possible that they are implicated in the etiology and progression of psychiatric disorders.
Critical Issue: Evidence for direct links between cellular mitochondrial dysfunction and disease features are missing.
Future Directions: A better understanding of the mitochondrial biology and its intracellular connections to the nuclear genome, the endoplasmic reticulum and signaling pathways, as well as its role in intercellular communication in the organism, is still needed. This review focuses on the findings that implicate mitochondrial dysfunction, the resultant metabolic changes and oxidative stress as important etiological factors in the context of psychiatric disorders. We also propose a model where specific pathophysiologies of psychiatric disorders depend on circuit-specific impairments of mitochondrial dysfunction and redox signaling at specific developmental stages. *Antioxid. Redox Signal.* 31, 275–317.

Keywords: psychiatric disorders, mitochondria, redox signaling, oxidative stress, metabolism, circadian rhythm

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I. Introduction

Psychiatric disorders are conditions that affect the thoughts, emotions, and behaviors of an individual, causing difficulties in daily life activities, work accomplishments, and social interactions. These conditions are considered the result of a complex interplay between genetic and environmental factors (Fig. 1). Although these disorders affect a significant proportion of the world's population (19, 119, 244, 376), clinical care remains difficult in terms of diagnosis and treatment. For the past 40 years, psychiatric disorder classification in distinct entities has been applied to clinical practice and in genetics and brain imaging research studies (10). Currently, treatment strategy is guided by sets of symptoms along with the clinical course manifested by the patient. However, symptoms are common to different conditions or they do not fit neatly into categories in some patients or symptoms may progress in time, causing different diagnoses to be given to the same patient. Adding to these challenges is the extremely slow progress in the development of new treatments as compared with other medical fields.

Some research is moving away from the categories approach to psychiatric illness and converging toward more fundamental mechanisms of brain development and neuronal connectivity. In 2010, Craddock and Owen proposed a linear succession of five clinical syndromes (mental retardation/intellectual disability, autism spectrum disorder [ASD], schizophrenia [SZ], schizoaffective disorder, and bipolar/unipolar mood disorder) based on opposing gradients of neurodevelopment and affective pathology (83). This model postulates stochastic combinations of genetic variations and environmental elements influencing cellular functions and possibly determining abnormal neuronal development and biology, resulting in clinical symptoms.

The genetics of these disorders is complex. Current hypothesis suggests that an unknown number of genetic risk variants with small-size effects distributed in networks coding for functional pathways may be at the origin of psychiatric disorders (84, 95, 135, 444). Several studies showed evidence of susceptibility loci or copy number variants (CNVs) that are common across mental disorders and evidence of specificity of susceptibility genes (51, 85, 261). Recently, Gandal *et al.* analyzed the published gene-expression data from cerebral cortex across five psychiatric disorders (ASD, SZ, bipolar disorder [BD], major depressive disorder [MDD], and alcoholism) and showed the existence of disorder-specific modules of gene coexpression and common genetic factors that trigger a considerable proportion of the gene-expression overlap between the disorders (140). In addition, the data suggest that these genetic effects are mainly indirect through signaling cascades involved in development and cellular communication. The results from this study remarkably uncovered how individual and shared genetic effects and environmental factors might lead to a range of symptoms. Interestingly, the observed gradient of synaptic gene down-regulation is compatible with the disorder spectrum proposed by Craddock and Owen (83, 140).

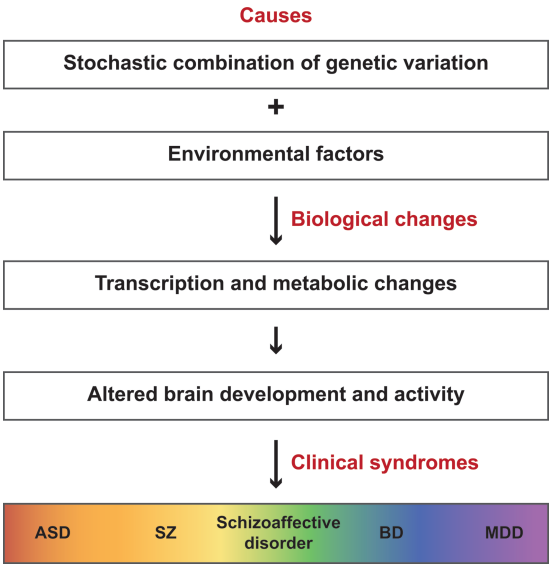

FIG. 1. The dimensional model proposes that psychiatric disorders are a spectrum of clinical syndromes with overlapping causes, biological dysfunctions, and symptoms. Stochastic arrangement of genetic *de novo* mutations or common variations is challenged by environmental factors and may cause transcription and metabolic changes. If these changes affect brain development, circuitry, and function, they lead to psychiatric symptoms. The spectrum of clinical syndromes is illustrated by a light spectrum. ASD, autism spectrum disorder; BD, bipolar disorder; MDD, major depressive disorder; SZ, schizophrenia. Color images available online.

Mitochondria are sophisticated organelles that respond to internal and external cues by controlling central functions in the cell, such as energy metabolism, redox status, retrograde signaling, calcium (Ca^{2+}) homeostasis, and apoptosis. Multiple pieces of evidence suggest that brain energy metabolism, mitochondrial functions, and redox balance are impaired to various degrees in psychiatric disorders. Since mitochondrial metabolism and redox signaling can integrate genetic and environmental factors affecting the brain, it is possible that these downstream mechanisms may act as key regulators in the plethora of symptom gradients observed in psychiatric conditions (Fig. 2). At the clinical level, psychiatric disorders share common physical comorbidities that are associated with alterations in circadian rhythm (such as sleep, feeding, and activity/rest phases) and metabolism (such as diabetes and obesity) (23, 289, 323), both of which are closely regulated by mitochondria and redox balance. For instance, Karatsoreos *et al.* showed that shifting mice to a 20-h light/dark cycle resulted in weight gain, hormone changes, reduction in the complexity of the neuronal network in the prelimbic prefrontal cortex, and behavioral modifications (211). At the cellular level, mitochondrial oxidative phosphorylation (94, 339, 391), redox changes (226), and antioxidant defense (470) are not only regulated in a circadian manner but also signal back to the core clock.

Here, we provide a comprehensive review exploring the multifaceted mitochondrial roles and interactions with other organelles and redox mechanisms in the context of normal brain function and associated with the major psychiatric conditions, ASD, SZ, BD, and MDD. It is our aim to provide an update on current knowledge and controversies and to highlight the research relevant to the context of psychiatric disorders.

II. Clinical Features and Metabolic Endophenotypes of Psychiatric Disorders

A. Autism spectrum disorder

The global prevalence of autism and other pervasive developmental disorders is estimated to be around 62 in 10,000 children (119), although there is still lack of evidence from the majority of the world's population. An ASD diagnosis is defined by deficits in communication and social interactions accompanied by restrictive and repetitive behaviors (11). Though the rate of diagnosis has increased over the past two decades, current diagnostic methods depend on the appearance of behavioral abnormalities (131). There are some cases of ASD accompanied by syndromes of known molecular etiology, such as the fragile X syndrome, that are called syndromic ASD (490). However, these syndromes can only be

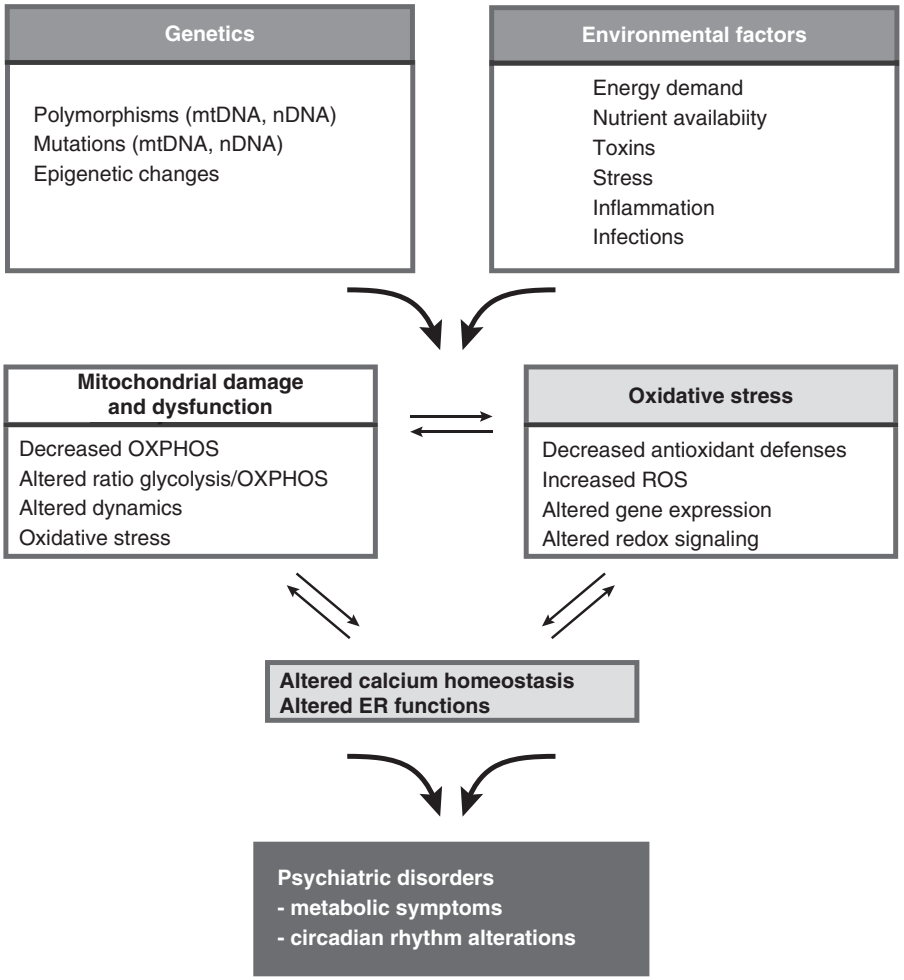

FIG. 2. Proposal for bioenergetics, redox and metabolism alterations in psychiatric disorders. How the tight connection between mitochondrial and ER functions and redox regulation are affected in psychiatric disorders is discussed in the text. ER, endoplasmic reticulum; mtDNA, mitochondrial DNA; nDNA, nuclear DNA; OXPHOS, oxidative phosphorylation; ROS, reactive oxygen species.

recognized through genome-wide testing that is not hypothesis driven (*e.g.*, microarray or whole-exome sequencing) (127).

Although a clinical genome-wide association study (GWAS) using ASD cohorts has generally not yielded consistent results (415), considerable progress has been made by genetically analyzing ASD families. Whole-exome sequencing and CNV analysis have uncovered rare *de novo* mutations in patients with ASD (147, 394). These mutations are extremely heterogeneous, and none account for more than 1% of ASD cases (102). In parallel, recent advances in the field of systems biology have caused a paradigm shift in the biomedical sciences, from single-gene causation models to pathway-perturbation models (95). Gene-network analysis of high-confidence risk variants in ASD families has implicated molecular processes that are important for human fetal cortical development (335, 472). However, many of these identified gene networks are involved at multiple stages of development and in a variety of neuronal cell types (such as neural stem cells and immature neurons).

Many different interventions and treatments have been proposed and implemented for ASD. Unfortunately, most of these treatments have not been adequately evaluated, making an evidence-based approach to ASD treatment difficult. Early psychosocial interventions are the most frequently evaluated for preschool children with ASD (160, 214, 344, 363, 432). Pharmacological interventions, such as risperidone and aripiprazole, are used mostly for patients with moderate to severe behavioral symptoms (99, 185, 386). There is very little evidence for interventions aimed at the core symptom of ASD, such as restricted and repetitive behavior, including antipsychotic medication (92, 344, 386).

B. Schizophrenia

SZ is a devastating psychiatric disorder affecting $\sim$70 million people worldwide (about 1% of the global population) (376). People with the disorder demonstrate a range of symptoms, including positive symptoms, such as delusions and hallucinations, and negative symptoms, such as withdrawal from surroundings, avolition, and flattened affect. SZ individuals often also show cognitive impairments, namely difficulty with speech, concentration, and thought organization. The accumulation of symptoms represents a heavy burden for individuals with SZ and they are at higher risk for suicide, substance abuse, and homelessness (376). Most cases of SZ are diagnosed in adolescence or young adulthood, and there is a strong neurodevelopmental component to SZ risk. Brain imaging showed that SZ patients have smaller brains and myelination defects (272).

Although evidence has established a genetic basis for SZ for some time, with family and twin studies consistently demonstrating high heritability (70, 184, 428), only recently have specific genetic risk factors been conclusively identified. The identified genetic risk for SZ includes rare CNVs and common variants, reflecting a cumulative risk of more than 100 variants altogether (390). The current picture emerging in the field indicates that there is not a one-to-one Mendelian mapping between these SZ risk alleles and diagnosis but instead a number of genetic variants with small effects, resembling a classic polygenic model (135, 444).

Antipsychotic medications in addition to cognitive and behavioral therapies can help alleviate SZ symptoms; however, it is estimated that 20%–60% of patients remain resistant to known treatments (295, 307).

C. Mood disorders: BD and MDD

Among the many mood disorders that exist, the most prevalent are BD and MDD. BD affects 1% (244) and MDD affects 11%–15% (48) of the population. BD is a debilitating condition comprising cyclic shifts in mood and energy levels, resulting in a disruption in the ability to carry out daily tasks. Mood states range from elated and high-energy states, known as manic episodes, to sad and low-energy periods, known as depressive episodes. Manic episodes consist of symptoms such as inflated self-esteem, decreased need for sleep, fleeting ideas, and increased goal-directed activities. High-energy episodes that are relatively mild in severity, lasting more than 4 days, are referred to as hypomanic episodes (11). In addition, a substantial proportion of subjects with BD tends to experience mixed episodes of both depressive and manic/hypomanic symptoms.

MDD is diagnosed by the presence of at least five symptoms, including depressed or sad mood; diminished interest in pleasure or anhedonia; significant weight loss or weight gain; insomnia or hypersomnia; fatigue; excessive feelings of worthlessness or guilt; diminished ability to think or concentrate; and psychomotor agitation and recurrent thoughts of death or suicidal ideas, for at least 2 weeks (11). Twin studies estimate nearly 90% heritability for BD (244) and 40% heritability for MDD (429). Theoretically, susceptibility alleles may have large- or small-effect sizes and their frequencies are either common or rare and, apart from single-nucleotide variations in nuclear DNA, other mechanisms probably contribute to inherited risk for disease, including mitochondrial DNA (mtDNA) variation and epigenetic modifications (84).

Different types of psychosocial and pharmacological treatment options are available for controlling and preventing the symptoms of BD and MDD. Medications for BD usually fall into one of three categories: classic mood stabilizers, antipsychotics, and antidepressants. Treatment often involves a combination of psychotherapy and mood-stabilizing agents and/or atypical antipsychotics. Lithium (Li) is the most commonly prescribed mood stabilizer and has proven to be highly effective in reducing mania with milder effects on depressive symptoms (144). For Li, among other targets, Wnt signaling has been implicated in the therapeutic mechanism (146, 175, 454). Valproic acid (VPA) and carbamazepine, both antiepileptic drugs, are used to treat the manic or mixed phases of BD (144). Alternative or augmented treatments to Li include antipsychotics such as haloperidol, quetiapine, aripiprazole, olanzapine, and risperidone or antidepressants (144). For MDD, antidepressants are used in combination with various psychosocial therapies. There are numerous classes of antidepressants, including selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors, monoamine inhibitors, and tricyclic antidepressants. SSRIs remain the most prescribed class of antidepressants and are a primary treatment modality for depression (263).

D. Circadian rhythm and metabolism

An individual can tune in and adapt to the external environment only by the synchronization of internal rhythms to external ones. Circadian rhythms play a role in governing many biological functions across multiple organs, including the brain

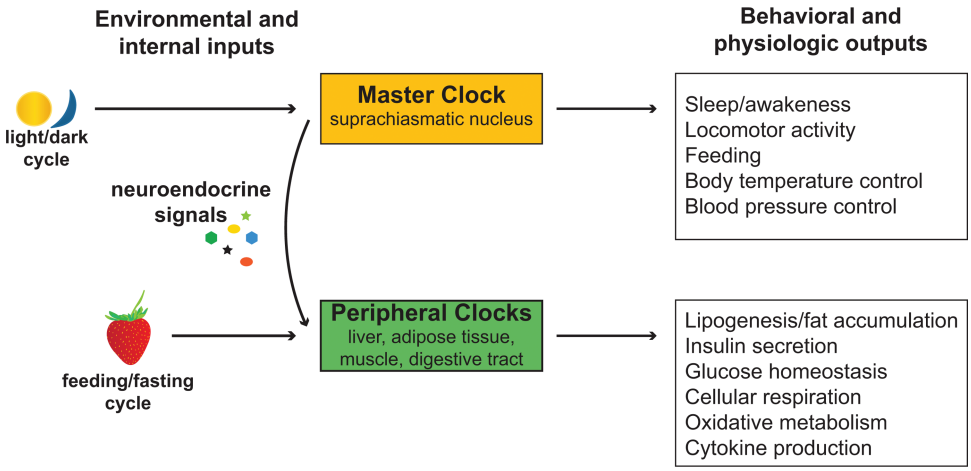

FIG. 3. Master SCN and peripheral clocks. Circadian rhythm in mammals is primarily regulated by the master clock of the SCN in response to an environmental signal, light. Peripheral clocks are synchronized in response to nutrients and to neuroendocrine cues from the SCN. Outputs of SCN and peripheral clocks impact behavior and physiology such as feeding, sleep, hormone secretion, and metabolic homeostasis. Although they are not depicted and not well known, the hormones and products of metabolism may modulate the rhythm of SCN neurons. SCN, suprachiasmatic nucleus. Color images are available online.

(209). The suprachiasmatic nucleus (SCN) of the hypothalamus generates and synchronizes biological rhythms (such as endocrine and neuronal) and metabolic signals in response to light stimuli (418) (Fig. 3). The circadian signals, in turn, entrain the peripheral clocks (296) that are found in virtually every cell and organ and thus in different cerebral structures, including those involved in neuropsychiatric disorders.

Molecular oscillations result from a negative feedback between *CLOCK* (clock circadian regulator; or the related neuronal Per-Arnt-Sim domain-containing protein 2, *NPAS2*), *BMAL1/ARNTL* (aryl hydrocarbon receptor nuclear translocator like), period (*PER1–3*), and cryptochrome (*CRY1–2*) genes. The transcription factors CLOCK and BMAL1 heterodimerize and activate transcription of period and cryptochrome genes. PER and CRY proteins also form heterodimers and are inhibitors of CLOCK and BMAL1 function. Another set of core clock genes are nuclear receptors' family members REV-ERB (or the nuclear receptor subfamily 1 group D, *NR1D1–2*) and ROR (or retinoic acid receptor-related orphan receptors *RORA-C*). *REV-ERBα/NR1D1* transcription is activated by BMAL1/CLOCK heterodimers and repressed by CRY/PER heterodimers, resulting in circadian oscillations of REV-ERBα. In turn, REV-ERBα represses *BMAL1* transcription. *REV-ERBβ/NR1D2* expression also oscillates in a circadian fashion and can repress *BMAL1* transcription (165). RORA competes with REV-ERBα for binding of their shared DNA-binding elements to the RORE response element in the *BMAL1* promoter, leading to *BMAL1* expression being repressed by REV-ERBα and activated by RORA. The oscillating expression of *RORA* and *REV-ERBα* in the SCN leads to the circadian pattern of *BMAL1* expression (4, 385). This REV-ERBα/RORA feedback loop interconnects the positive and negative limbs of the core circadian clock (Fig. 4).

Although the brain's master clock SCN is entrained by daily light-dark cycles, the dominant timing cue for peripheral clocks appears to be feeding time or availability of food (Fig. 3). Disruption of clock function in the liver and pancreas leads to impaired glucose homeostasis (246, 282, 381). Adipocytes rhythmically release leptin, a neuroactive peptide that regulates satiety through its actions centrally in the arcuate nucleus of the hypothalamus (223). When leptin rhythms are disrupted in mutant mice lacking PER1 and PER2 or both CRY1 and CRY2, the animals show either extreme weight gain or weight loss. These changes are mediated by rhythmic behavior and feeding (223), highlighting the role of the circadian system as a co-ordinator of physiology across peripheral organs and the central nervous system.

The clock modulates metabolism, but the metabolic status of the cell also influences the clock machinery. Although not all peripheral tissues are entrained by feeding, there is clear evidence that circadian clocks in the liver, adipose tissue, muscle, and kidney are responsive to acute changes in nutrients and/or downstream signaling pathways involved in energy supply (115). Restricted feeding can partially rescue hepatic rhythmicity in *CRY1–2* double knockout mice (460) and kidney and liver rhythmicity in the forebrain/SCN-specific *BMAL1* knockout mice (198). Mice models of obesity and diabetes have disrupted circadian expression of CLOCK and its target genes, in addition to alterations in locomotor activity, feeding pattern, and sleep regulation (202, 237).

Transcription studies have shown that many genes involved in biosynthetic and metabolic processes are rhythmic, with their expression changing throughout the circadian cycle (5, 232, 320, 333, 501). Interestingly, several of these genes encode rate-limiting enzymes in essential metabolic pathways (159, 333). Human plasma samples collected for 48 h revealed that a majority of metabolites (109 out of 171 metabolites) oscillate during a complete 24-h wake/sleep cycle (91). Thus, for humans, most circulating metabolites display rhythmic diurnal oscillation under normal physiological conditions. This rhythmicity likely helps to coherently communicate time of day to tissues throughout the body, maintains tissue-specific synchronization of peripheral clocks, and promotes efficient temporal gating of circadian metabolic pathways (115). In particular, the nicotinamide adenine dinucleotide (NAD^+) biosynthesis cycle

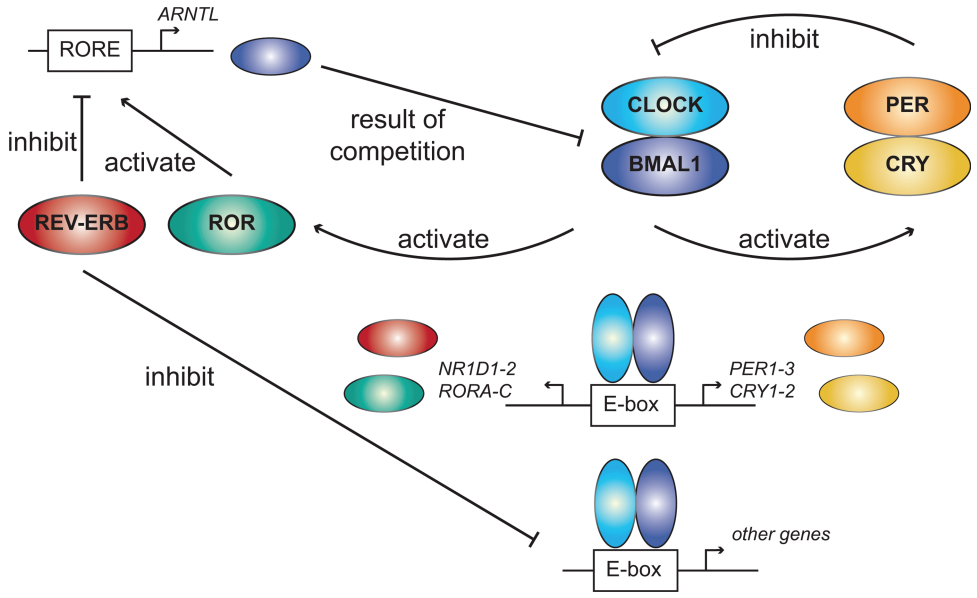

FIG. 4. Circadian core clock gene regulation. Core components of the circadian clock showing a principal transcription/translation feedback loop composed of CLOCK, BMAL1/ARNTL, PER1–3, and CRY1–2. An intertwined regulatory loop regulates the expression of *BMAL1* by competition between NR1D1–2 (inhibitors) and RORA-C (activators) for binding to the ROR enhancer elements (RORE) in the promoter. BMAL1/ARNTL, aryl hydrocarbon receptor nuclear translocator like; CLOCK, clock circadian regulator; CRY, cryptochrome; NR1D, nuclear receptor subfamily 1 group D; PER, period; ROR, retinoic acid receptor-related orphan receptors. Color images are available online.

provides a feedback that participates in the transcriptional regulation of the core clock (27). CLOCK/BMAL1 also regulates the expression of *NAMPT* that encodes nicotinamide phosphoribosyltransferase, the rate-limiting enzyme of the NAD^+ salvage pathway (325, 357). Therefore, NAD^+ levels oscillate and drive the activity of sirtuin SIRT1, which is an NAD^+-dependent histone deacetylase that inhibits CLOCK/BMAL1 (20, 324). SIRT1 also interacts with PGC-1α (peroxisome proliferator-activated receptor γ coactivator 1α) to enhance the gluconeogenic pathway (369), promoting fat mobilization in starved mice, and triggers lipolysis in differentiated adipose cells (343).

Circadian rhythm and molecular clock mechanism dysregulation are observed across psychiatric diagnoses (247). Single-nucleotide polymorphisms (SNPs) in core circadian clock genes have been associated with ASD (326, 485), SZ (434), BD (327, 397, 412), and MDD (189, 239, 398). There is still a debate as to whether the symptoms of circadian disruption are a byproduct of these disorders or a major contributing factor (210). Impaired circadian rhythms may lead to anxiety and difficulties in adapting to changes in psychiatric disorders such as ASD, SZ, and mood disorders.

ASD is often associated with sleep disorders (9, 365) and low levels of melatonin (294, 445, 446), which led to the theory that circadian rhythms could be involved in ASD etiology (456, 473). Moreover, ASD was found to be associated with circadian rhythm disruption at critical brain developmental periods (145). *CLOCK* and *BMAL1* drive daily patterns of a number of clock-controlled genes, many of which code for synapse molecules associated with ASD susceptibility (145). Conversely, circadian-relevant genes were reported to be highly polymorphic in 28 ASD patients (485). Another screening for circadian-relevant genes in 110 high-functioning autistic patients detected significant allelic association for *PER1* and *NPAS2*, although these associations were not significant after correction for multiple testing (326).

There are numerous studies linking circadian disruption and SZ (352, 476, 482). In a study of 34 patients and the same number of healthy controls, reduced sleep efficiency, longer sleep latencies, and increased number of nighttime awakenings were observed for SZ, along with the loss of the negative correlations of saliva melatonin levels with sleep latency and total sleep time and positive correlations with sleep efficiency (1). Moreover, sleep onset and sleep maintenance insomnia are independent of the course and pharmacological status of the patient (313). In a GWAS analysis of a United Kingdom biobank, a genetic correlation between longer sleep duration and SZ risk was observed (249). In addition, an SNP analysis showed a *CLOCK* gene T3111C polymorphism in 145 Japanese schizophrenic patients compared with controls (434), but the same polymorphism was not observed in patients with BD or MDD in another study of the Japanese population (230). CNVs in the vasoactive intenstinal polypeptide receptor, *VIPR1*, gene encoding for the receptor for vasoactive intestinal polypeptide that is also found in the SCN are associated with increased risk of developing SZ (453). Recently, a loss of rhythmic expression of *CRY1* and *PER2* genes was observed in primary fibroblasts from 11 SZ patients with poor sleep, compared with controls (205). Animal models also link circadian rhythm and SZ. The ''blind drunk'' mouse line carries a mutation in the gene *SNAP25* (synaptosomal associated protein 25) that leads to disruption of exocytosis. These mice show SZ-like endophenotypes (201) and phase-advance rest-activity cycles while also showing a fragmentation of their circadian rhythm (331).

Existing hypotheses about the biological mechanisms underlying dysregulation of circadian rhythms in BD include changes in melatonin levels, in expression of melatonin

receptors in the central nervous system, and in daily cortisol profiles (480). During mania, sleep patterns are significantly disrupted (368). Genetic evidence links circadian rhythm dysregulation with BD. *CRY2* has been associated with rapid cycling in BD (406), and two polymorphisms on the *CLOCK* and TIMELESS (timeless circadian clock) genes have been linked to Li responsiveness (378). In addition, *PER2*, *CRY1*, and *REV-ERB*α expression increased individual responsiveness to the therapeutic effects of Li (392). Several key clock genes affect behavior in mice (288, 289) and mutations in the *CLOCK* gene can lead to mania-like behaviors in mice (316, 377). In addition, Li was shown to lengthen the circadian clock in hamsters (197).

Increased sleep latency, poor sleep quality, and reduced latency to first rapid eye movement sleep are well documented in MDD (443). The circadian patterns of gene expression in the postmortem human brain were disrupted in 34 patients with MDD. Cyclic patterns were much weaker in the brains of patients with MDD due to shifted peak timing and potentially disrupted phase relationships between individual circadian genes (258). In SNP studies, winter depression was associated with the *PER2*, *CRY2*, *BMALl*, and *NPAS2* genes (251, 338). In addition, *CRY1* was found to be associated with MDD in 105 Chinese patients (189) and *CRY2* was found to be associated with MDD in 383 Finnish patients (239). A study investigating 8 clock genes in 592 MDD patients showed that *CLOCK* and *PER3* influenced the risk of depression in a sex-dependent manner (398). Interestingly, agomelatine is used to treat depression and is a melatonin receptor agonist with serotonergic activity (93). In animal models, agomelatine can re-synchronize the circadian rhythm (278, 314). In humans, agomelatine can increase the amplitude of circadian rhythms in the rest-activity cycle, including sleep, which was accompanied by an improvement of depressive symptoms (215).

Recently, it was shown that the transcriptional coactivator PGC-1α, which is the master regulator of mitochondrial biogenesis and energy metabolism, is an essential component of the circadian clock in the liver and muscle (264). The fact that a regulation loop exists between clock machinery and metabolism is interesting because somnolence and appetite increase are the most frequent adverse effects that precede the actual clinical benefits of antipsychotics (267). Studies show that the various areas of neurotransmission altered by antipsychotics may affect energy and glucose regulation (170). More intriguing is the observation that second-generation antipsychotics (SGAs) with the most intense metabolic effect and somnolence may be the most effective agents in the most severe forms of SZ and BD (109). It is possible that the interplay of circadian rhythm and metabolism contributes to these effects.

Even though SCN generates and synchronizes biological rhythms, optimizing the biological and physiological functions of multiple organs, the SCN itself is resistant to most rhythmic signals that it synchronizes. Evidence such as the arthropathy developed by *BMAL1* null mice suggests that disruption of the circadian system can cause pathological conditions through disturbances in peripheral clock regulation rather than in the SCN (50). Hence, it has been postulated that the links between deregulation of circadian rhythms and psychiatric disorders may be due to problems within the peripheral clocks in the brain (297). Indeed, glucocorticoid ultradian rhythmicity directly induced cyclical gene pulsing of *PER1* expression in the rat hippocampus (80), and clamping the diurnal variation of corticosterone suppressed the daily rhythm of *PER1* expression in the dentate gyrus but not in the SCN (151). We can assume that disruption of peripheral brain clocks likely affects the expression of many downstream genes, causing some of the symptoms observed in psychiatric patients. Importantly, this deregulation occurs at both the systemic and cellular levels. Recent evidence suggests that disruption of the circadian clock may contribute to individual vulnerability to psychiatric disorders by altering the structure and function of neural circuits (150, 211). A study using the Syrian hamster as an animal model for jet lag has demonstrated that jet lag can cause deficits in neurogenesis, learning, and memory that persist even after cessation of the experimental jet lag condition (150). Disrupting the circadian clock in mouse models has been shown to cause morphological changes in neurons in the medial prefrontal cortex, with simultaneous behavioral and cognitive changes (211). Moreover, the disruption of the molecular clock delayed the onset of critical period plasticity, which was restored by pharmacological enhancement of γ-aminobutyric acid (GABA)ergic transmission (235). These findings suggest that clock genes control critical periods of postnatal cortex development in parvalbumin interneurons that are known to play a pivotal role in critical period plasticity (181).

Advances in the understanding of the link between circadian rhythm and psychiatric disorders will increase awareness that synchronization of internal rhythms may alleviate some of the symptoms associated with psychiatric disorders, which holds positive implications for understanding the ultimate disease etiology and development of therapeutic agents.

III. Cellular Energy Metabolism and Brain Activity in Psychiatric Disorders

The brain energy requirement at resting state is immense, corresponding to more than 20% of the body's consumption, and the majority of it is used for neuronal computation and information processing (121, 255). Howarth *et al.* calculated that, in the cerebral cortex, this signaling energy is spent mainly on postsynaptic glutamate receptors, action potentials, and resetting the ion gradients to maintain resting potentials; presynaptic transmitter release and transmitter recycling consume only 9% (188). A considerable amount of the energy consumed in the brain is for nonsignaling or housekeeping functions in neurons and glial cells such as cytoskeleton dynamics, neurotransmitter synthesis and recycling, and lipid turnover and proton leak across the inner mitochondrial membrane (IMM) (121, 401). For a comprehensive investigation of brain bioenergetics, different levels of complexity have to be considered and data obtained must be integrated from the whole brain, specific cell types, and intracellular organelles. For brain studies, magnetic resonance spectroscopy (MRS), functional magnetic resonance imaging (fMRI), and positron emission tomography (PET) techniques allow for *in vivo* visualization of metabolic fluxes and energy supply to different areas of the brain in relation to neuronal activity (276). It is now possible to translate the data obtained *in vivo* from human brain imaging to the cellular level. A major technological innovation of the past decade was somatic cell reprogramming into induced pluripotent

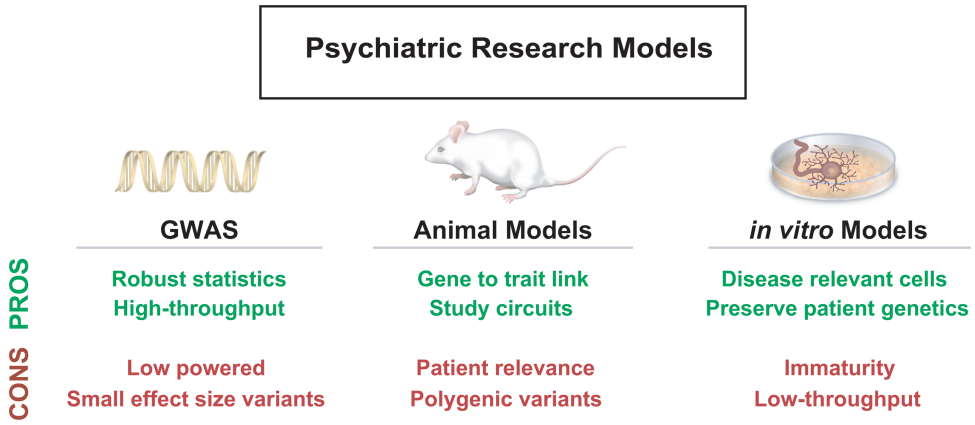

FIG. 5. Comparison of different models for the study of psychiatric disorders. Diverse tools and research models are necessary to enlighten the etiological mechanisms underlying psychiatric disorders. GWAS as well as, studies involving animals or cells in a dish have unique advantages and disadvantages but complement each other. GWAS, genome-wide association studies. Color images are available online.

stem cells (iPSCs) and the elaboration of numerous protocols for their conversion into neurons, astrocytes, oligodendrocytes, and microglia (46, 64, 110, 315, 384, 433) (Fig. 5). This methodology represents a significant advance by allowing modeling of neurodegenerative and neuropsychiatric disorders (46, 82). Recently, the study of primary human neurons and glial cells has also become possible through the development of protocols for the isolation of individual cell types and culture of live cells from the brain (494).

A. Oxidative phosphorylation and glycolysis in brain cells

One of the principal functions of mitochondria is to generate chemical energy for the cell. The four respiratory chain complexes (CI–CIV) and adenosine triphosphate (ATP) synthase carry out oxidative phosphorylation by using electron donors generated in the mitochondrial matrix by the tricarboxylic acid (TCA) cycle and fatty acid β-oxidation or by cytosolic glycolysis. Electron transfer across the respiratory chain is coupled with proton translocation to the intermembrane space by complexes I, III, and IV, providing the proton-motive force across the inner membrane that is used by ATP synthase to synthesize ATP (Fig. 6). Blue-native gel electrophoresis experiments showed that, in mammalian cells, the respiratory complexes are organized into supercomplexes with different conformations (CI/CIII/CIV also named respirasome, CI/CIII, and CIII/CIV) (161, 250, 388). The functional significance of mitochondrial supercomplexes is still unresolved (24, 305). However, it is recognized that assembly of the supercomplexes is dynamic, co-ordinates the electron flux from different substrates (250), and reduces reactive oxygen species (ROS) production at complex I (280) (Fig. 6). Lopez-Fabuel *et al.* reported that distinctive assembly of complex I into supercomplexes in neurons and astrocytes is regulated by the expression of the NDUFS1 (NADH:ubiquinone oxidoreductase core subunit S1) subunit and correlates with the bioenergetics differences between these cell types (268). Neurons, which depend on oxidative phosphorylation unlike astrocytes, showed a larger proportion of complex I in supercomplexes, an increased amount of NDUFS1, and lower ROS generation than astrocytes. Interestingly, overexpression of NDUFS1 in astrocytes promoted complex I assembly in supercomplexes and reduced ROS production; the opposite was observed by knocking down NDUFS1 in the neurons. Other studies showed that mtDNA variants could affect respiratory complex assembly. The mitochondrial disorder Leber's hereditary optic neuropathy is caused by three-point mutations in two subunits of complex I (*MT-ND1* and *MT-ND4*) that cause defective complex I assembly and stability (342). These data emphasize the importance of supercomplexes assembly in the cells' energy metabolism, and it is attractive to think that some of the mtDNA polymorphisms and mutations found in patients suffering from mental disease could affect this process.

Another essential factor is the maintenance of a correct balance in phospholipid types at the vicinity of the supercomplexes. Cardiolipin is a phospholipid present in the IMM that is necessary for supercomplex assembly and stabilization. The reverse occurs for another phospholipid: Phosphatidylethanolamine destabilizes supercomplex assembly (305). Notably, brain phospholipidome is disturbed in the mouse model of depression induced by chronic unpredictable stress, presenting reduced cardiolipin and increased phosphatidylethanolamine and markers of oxidative stress (124). Two studies suggest that phospholipid metabolism may be altered in BD patients. A decreased ratio of phosphomonoesters to phosphodiesters was found in patients with bipolar depression (399), and the gene SEC14 and spectrin domain containing 1, *SESTD1*, that encodes a protein that binds phospholipids was identified by GWAS in BD patients who were responsive to lithium (410).

The oxidative phosphorylation machinery is positioned at the inner membrane cristae, which provide a suitable environment for electron transfer and proton translocation (Fig. 7). The cristae are formed by invagination of the inner membrane toward the matrix and separated from the rest of the membrane by the cristae junctions. The processes of formation and structuring that determine the cristae shape are not completely known but are associated with mitochondrial fusion and with the increased insertion of phospholipids and protein complexes when mitochondrial biogenesis is stimulated

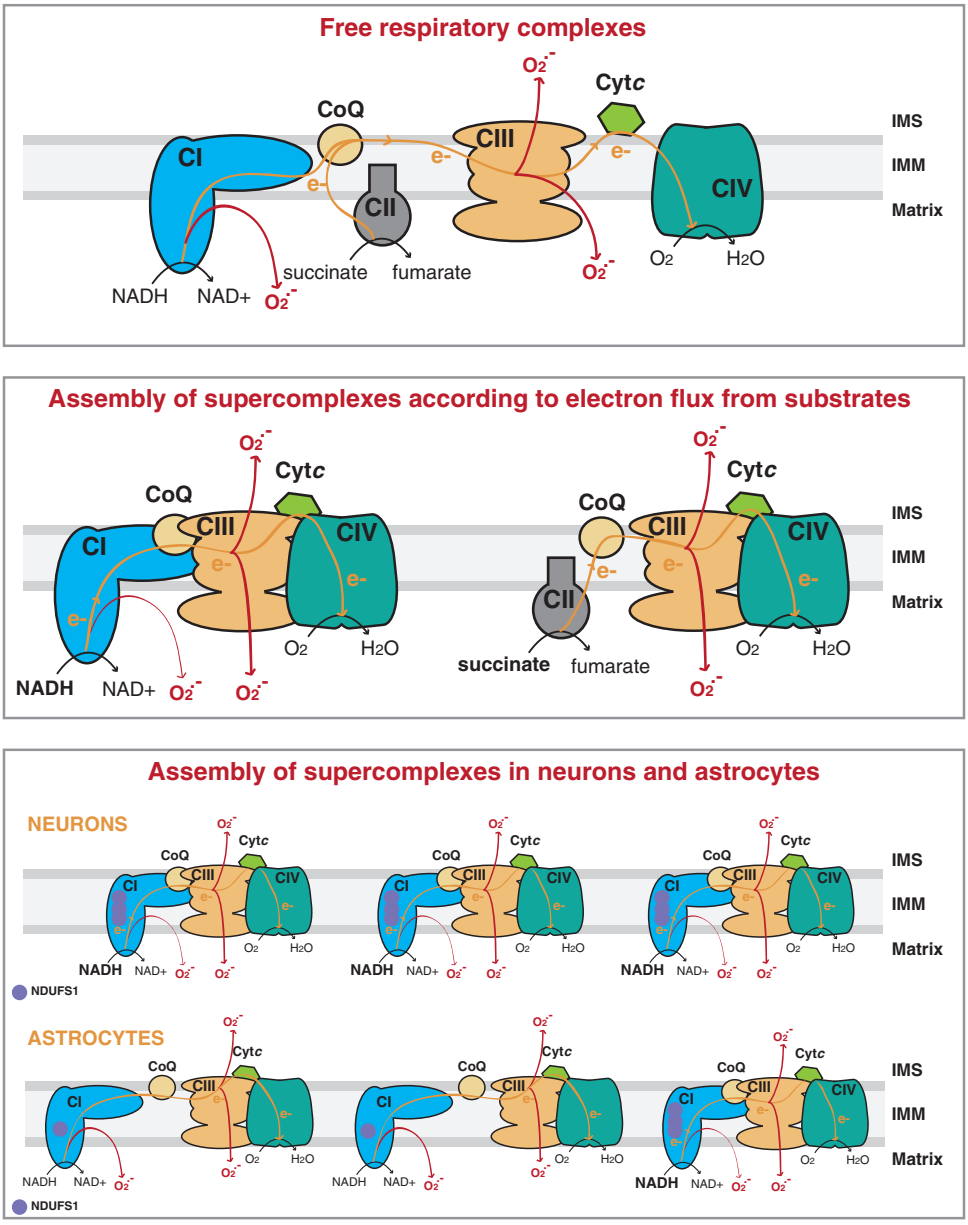

FIG. 6. Assembly of respiratory complexes into supercomplexes. Assembly of supercomplexes (CI/CIII/CIV, CI/CIV, and CIII/CIV) is dynamic and coordinates the flux of electrons from different substrates and reduces $O_2^{\bullet-}$ production at CI. In neurons, the high expression of NDUFS1 promotes CI assembly into supercomplexes and reduced superoxide production. In astrocytes, NDUFS1 expression is lower with a higher proportion of free CI and superoxide production. CI, complex I (NADPH:ubiquinone oxidoreductase); CII, complex II (succinate:uniquinone oxidoreductase; CIII, complex III (ubiquinol-cytochrome *c* oxidoreductase); CIV, complex IV (cytochrome *c* oxidase); IMM, inner mitochondrial membrane; IMS, intermembrane space; NDUFS1, NADH:ubiquinone oxidoreductase core subunit S1; $O_2^{\bullet-}$, superoxide. Color images are available online.

(176, 293, 499). Cogliati *et al.* showed that cristae shape determines respiratory supercomplex assembly and mitochondrial respiration efficiency *in vitro* and, in mouse models of OPA1 (mitochondrial dynamin-like GTPase or optic atrophy protein 1), conditional acute deletion or overexpression (76). OPA1 is required for mitochondrial fusion, regulation of apoptosis, and respiration. The increase in the amount of proteins and dimerization of ATP synthase provide the initial bending of the inner membrane and cristae formation (414, 423). The mitochondrial contact site and cristae organizing system (MICOS) is anchored at the cristae junctions, where it stabilizes the membrane bending and cristae morphology (240, 356). MICOS defines the boundaries of the two compartments of the inner membrane, the cristae and the inner boundary membrane, which is in close proximity to the outer membrane and contains the transport machineries (Fig. 7). Mitofilin/MIC60 and MIC10 are the core subunits of the two dynamic supercomplexes composing MICOS, in addition to at least six other proteins (356). Knocking down MIC60, MIC10, and MIC19 by short-hairpin-mediated RNA interference (shRNA) in mouse embryonic fibroblasts resulted in loss of most of the cristae junctions, demonstrating the critical role of MICOS in cristae organization (257). DISC1 (disrupted in schizophrenia 1), which is a genetic risk factor for multiple psychiatric disorders, interacts with MIC60 and is a component of MICOS (337, 346). DISC1 deficiency induced in a stable human neuroblastoma cell line by expression of shRNA caused mitochondrial fragmentation, partial disassembly of the MICOS complex, reduction of mtDNA content, and impaired assembly and activity of respiratory complexes (346).

Energy can also be generated in the cytoplasm by glycolysis (Fig. 8). Under aerobiosis, the glycolysis end product is pyruvate, which is transported to the mitochondria to fuel the TCA cycle and oxidative phosphorylation. Under anaerobiosis or hypoxia, glycolysis converts pyruvate into lactate.

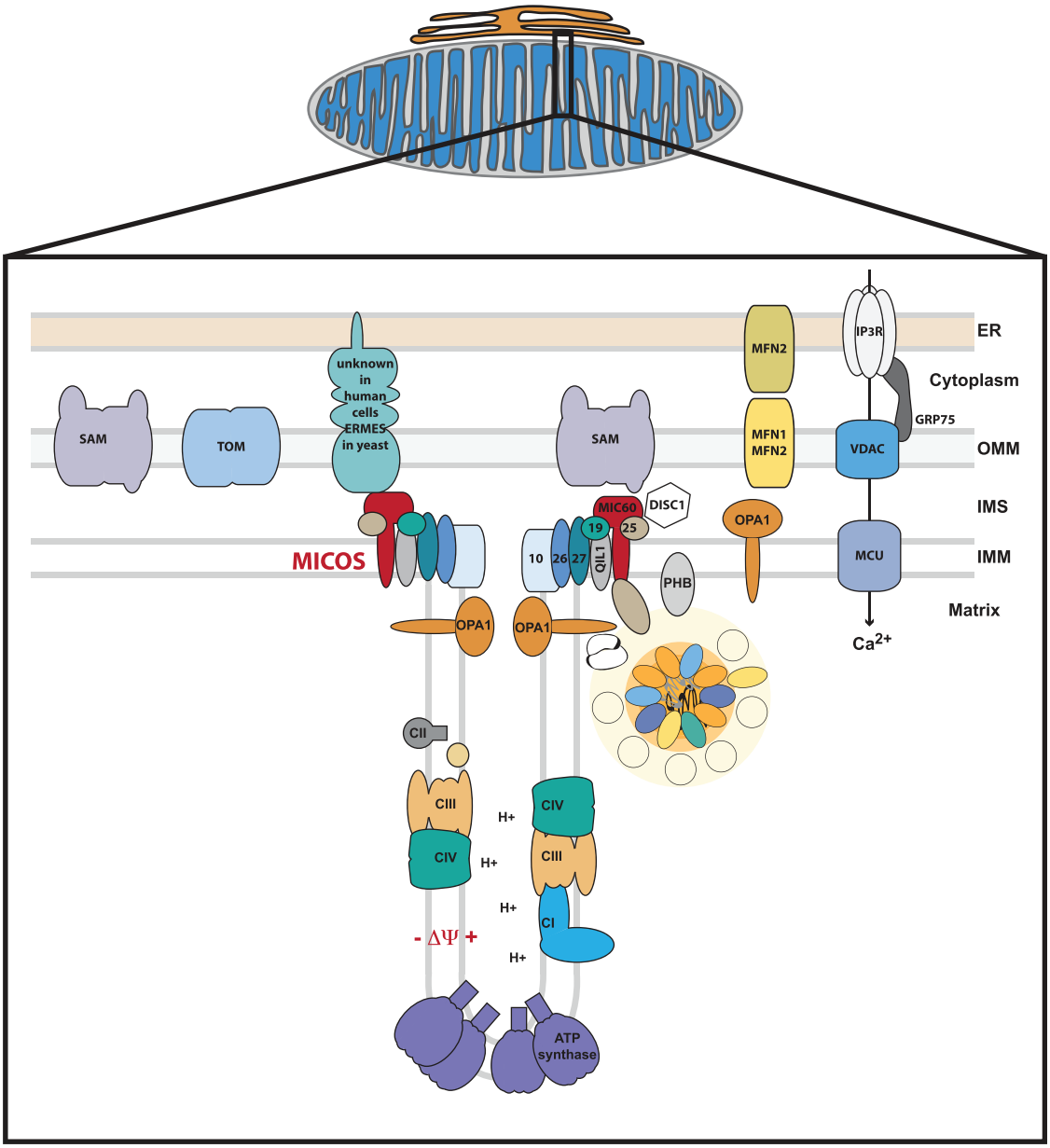

FIG. 7. Organization of mitochondrial and ER membranes. The oxidative phosphorylation machinery is located at the inner membrane cristae. The MICOS complexes (MIC60, MIC10, MIC19, MIC25, MIC26, MIC27, QIL1, and DISC1) define the boundaries of the cristae. In yeast, MICOS interacts with the ERMES complex, providing a communication platform between the IMM and OMM and the ER membrane; a mammalian equivalent has not been identified yet. OPA1 is also required to shape the cristae at the inner membrane. OPA1 and mitofusins MFN1–2 are implicated in mitochondrial fusion and are present in the three membranes. The TOM complex is a multiunit translocase that mediates import of precursor proteins into the mitochondrial internal compartments. The SAM is necessary for the integration of proteins in the OMM. Direct Ca^{2+} transfer between the ER lumen and the mitochondria occurs *via* the complex IP_3R/GRP75/VDAC and the MCU. Ca^{2+}, calcium; DISC1, disrupted in schizophrenia 1; ERMES, ER-mitochondria encounter structure; GRP75, heat shock protein family A (Hsp70) member 9; IP_3R, inositol 1,4,5-trisphosphate receptor; MCU, mitochondrial calcium uniporter; MFN, mitofusin; MICOS, mitochondrial contact site and cristae organizing system; OMM, outer mitochondrial membrane; OPA1, mitochondrial dynamin-like GTPase or optic atrophy protein 1; PHB, prohibitin; SAM, sorting and assembly complex; TOM, translocase complex; VDAC, voltage-dependent anion channel. Color images are available online.

A metabolic switch to aerobic glycolysis (also named the Warburg effect) occurs in certain cell types, such as cancer cells, stem cells, and astrocytes, when glucose is converted to lactate in the presence of oxygen (340, 442, 461). *In vitro* studies showed that embryonic stem cells, iPSCs, and neural progenitors have a metabolic preference for glycolysis; therefore, glucose metabolism reprogramming is crucial in neuronal differentiation (2, 442, 492, 497, 498). Several factors and pathways have been identified during this process: the PI3K-AKT-mTOR (phosphoinositide-3-kinase–protein kinase B–mammalian target of rapamycin) pathway, the nuclear coactivator PGC-1α, and the mitochondrial

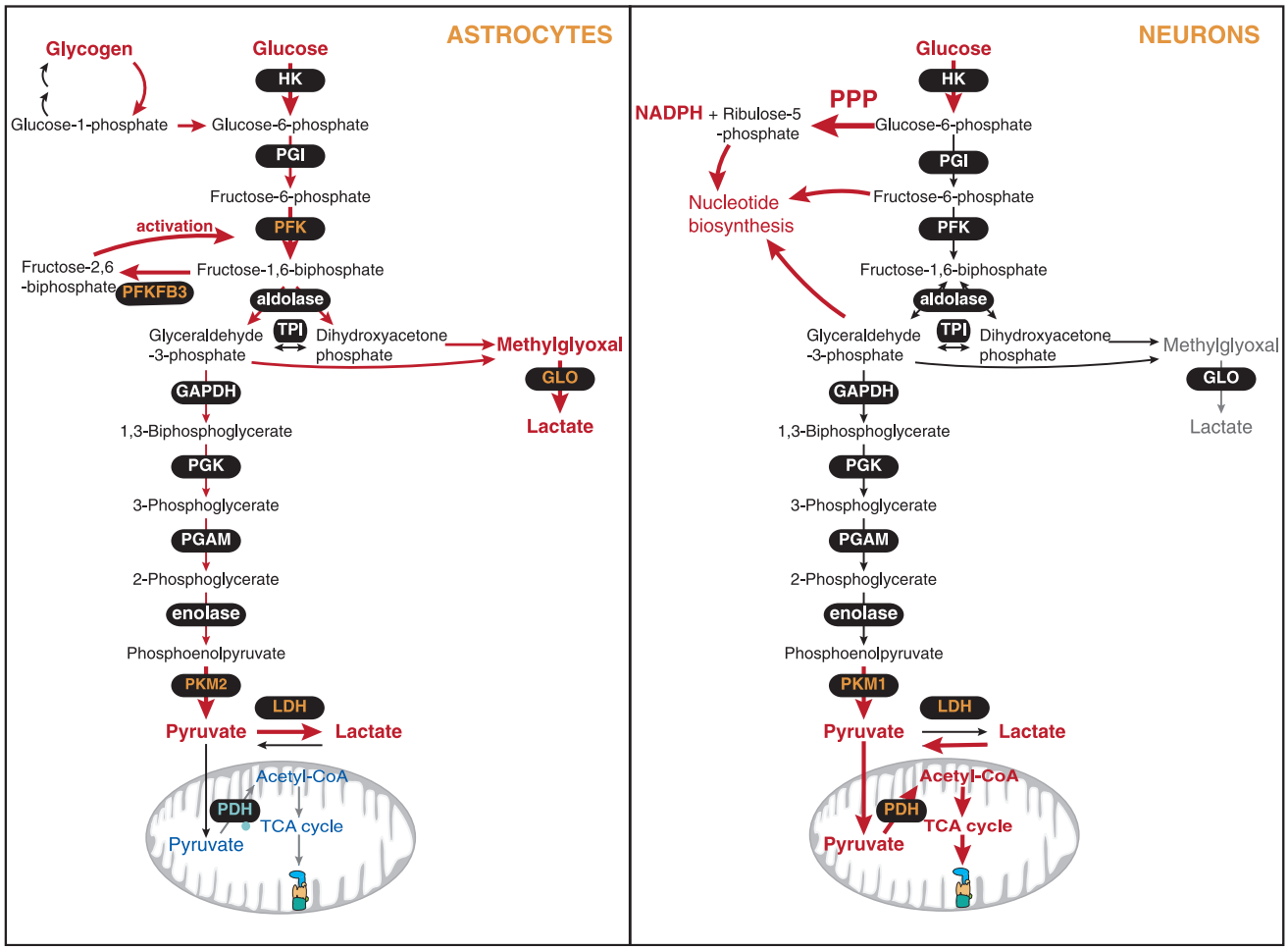

FIG. 8. Energy metabolism differences between astrocytes and neurons. Preferential channeling of glucose toward glycolysis in astrocytes and toward PPP in neurons is the result of multiple regulatory steps. The enzyme PFKFB3 is fully active in astrocytes and constantly degraded in neurons. This enzyme generates fructose-2,6-bisphosphate, which is a strong activator of PFK. Astrocytes express the pyruvate kinase PKM2, which upregulates the glycolytic flow toward pyruvate; in contrast, neurons express PKM1, which shunts glycolytic intermediates to other pathways, including nucleotide biosynthesis. Astrocytes express pyruvate dehydrogenase kinase PDK4, which phosphorylates PDH, causing inhibition of activity. The LDH isoforms are also differentially expressed in astrocytes and neurons and influence the direction of the reaction. Glucose is preferentially metabolized in neurons by the PPP, which generates reducing equivalents in the form of NADPH, which are essential for reduction of GSSG and cellular antioxidant defense. Glycolysis generates MG, which is detoxified by the GLO system that is highly expressed in astrocytes. Glycogen is a glucose storage molecule in astrocytes. GAPDH, glyceraldehyde 3-phosphate dehydrogenase; GLO, glyoxalase; GSSG, oxidized glutathione; HK, hexokinase; LDH, lactate dehydrogenase; MG, methylglyoxal; NADPH, nicotinamide adenine dinucleotide phosphate; PDH, pyruvate dehydrogenase complex; PFK, phosphofructokinase; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3; PGAM, phosphoglycerate mutase; PGI, glucose-6-phosphate isomerase; PGK, phosphoglycerate kinase; PKM, pyruvate kinase; PPP, pentose phosphate pathway; TCA, tricarboxylic acid; TPI, triosephosphate isomerase. Color images are available online.

transcription factor A (TFAM) (2, 497). Mitochondrial biogenesis and the proportion of elongated mitochondria are increased in co-ordination with the induction of oxidative phosphorylation, but a transient oxidative stress is also detected in the early phases of differentiation (2, 448, 463, 484). In agreement with these observations, the induction of antioxidant defenses is necessary for accurate neuronal differentiation (2, 495). Cultures of primary neurons from Nrf2-null mice present a delay in neurite outgrowth (495). The transcription factor Nrf2 (nuclear factor, erythroid 2 like 2 also named NFE2L2) is a master regulator of the cellular antioxidant response. Further, several reports suggest that the transient higher ROS levels may act as an intracellular signal of neuronal differentiation (2, 30, 430). The biological function of neurons, which is to signal transmission, is a tributary of a sophisticated biochemical metabolism. Appropriately, major regulators of neuronal differentiation and brain development are also implicated in signaling metabolic changes, such as the PI3K-AKT-mTOR pathway (464), or are redox sensitive, such as the Wnt-β-catenin pathway (137). Notably, these signaling pathways are implicated in the pathogenesis of BD, MDD, SZ, and ASD. However, although not yet proven, it is strongly supposed that in a patient's brain the differentiating neurons have metabolic and/or redox alterations that could contribute to the neurodevelopmental defects observed in psychiatric conditions.

Astrocytes have functional mitochondria that are proficient in oxidative phosphorylation (268). The preferential energy metabolism toward glycolysis in astrocytes and toward oxidative phosphorylation in neurons is the result of several metabolic tunings and not the blockade of entire pathways (Figs. 6 and 8). One of these is the differential expression of NDUFS1 subunit previously mentioned (268). Neurons and astrocytes differentially express pyruvate kinase (PKM) isoforms generated by alternative splicing that catalyze the last glycolysis step and pyruvate synthesis (493). Neurons express PKM1, whereas astrocytes express PKM2, which contains an inducible nuclear translocation signal that allows the cell to upregulate the glycolytic flux in response to increased energy demand. The entry of pyruvate into the TCA cycle is determined by the pyruvate dehydrogenase complex (PDH) activity, which is inhibited when the complex is phosphorylated. The level of PDH phosphorylation in astrocytes is higher and correlated to a lower PDH activity compared with neurons (171, 195), which favors pyruvate deviation to lactate production in astrocytes. Further, Herrero-Mendez *et al.* showed that the glycolysis regulator enzyme 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3) is fully active in astrocytes and constantly degraded in neurons (182). Interestingly, they also showed that activation of glycolysis in neurons by upregulation of PFKFB3 reduced the amount of glucose metabolized by the pentose phosphate pathway (PPP), causing oxidative stress and cell death by apoptosis. The PPP generates reducing equivalents in the form of NADPH (nicotinamide adenine dinucleotide phosphate), which are essential for a reduction of oxidized glutathione (GSSG) and cellular antioxidant defense.

Although neuron bioenergetics relies on oxidative phosphorylation, glycolysis is preferred in specific contexts, generally in response to a sudden increase in ATP demand. Cytosolic Ca^{2+} clearance after neuronal stimulation is critical for survival and is performed by ATP-dependent mechanisms. In acute slices, the fast clearance of Ca^{2+} in cerebellar granule and purkinje cells is mainly executed by a plasma membrane Ca^{2+}-ATPase pump that is fueled by glycolysis (196). Also, the fast axonal transport of vesicles requires a continuous energy supply over long distance; this demand is met by the presence of glyceraldehyde 3-phosphate dehydrogenase (GAPDH) at the vesicular membrane and glycolysis (491). Glycolysis is also necessary for synaptic vesicle recycling at nerve terminals (358). Recently, Díaz-García *et al.* used metabolic biosensors and reported that, in acute hippocampal slices and in the brain of awake mice, neuronal stimulation induces a transient increase in glycolysis (105).

B. Glucose metabolism and glutamatergic neurotransmission

Brain glucose metabolism is remarkable in terms of metabolic specialization and co-ordination among the different cell types. Neuronal energy demands are dynamic and can change very rapidly depending on the activation state. Functional hyperemia is the physiological response that regulates the blood flow, ensuring that the neuronal energy requirements are met despite the variations in activity. This is achieved by the neurovascular coupling or signaling from neurons to the vasculature, mostly through mediation of astrocytes, which are localized between the vasculature and the neurons (328). Astrocytes have end-foot processes that cover a significant area of the capillaries and fine processes that ensheathe the synapses. The excitatory synaptic release of glutamate causes oscillation in the intracellular Ca^{2+} concentration in astrocytes that trigger the release of vasoactive compounds (500). Mishra *et al.* showed that, in adult rats, different signaling cascades control blood flow at the level of arterioles and capillaries (310). Arterioles dilation depends on NMDAR (*N*-methyl-D-aspartate receptor or glutamate receptor) activation and Ca^{2+}-dependent nitric oxide (NO) generation by interneurons. The astrocyte Ca^{2+} transients evoked by postsynaptic ATP release and activation of purinergic receptor P2X1 result in an enzymatic cascade that leads to the release of prostaglandin E2 that relaxes pericytes, which dilates the capillaries and increases the supply of glucose and oxygen.

In 1994, Pellerin and Magistretti observed that glutamate uptake by astrocytes stimulates glycolysis and they proposed the astrocyte-neuron lactate shuttle (ANLS) model to describe the connection between glutamatergic neurotransmission and glucose utilization in the cortex (340). The ANLS model predicts that astrocytes respond to a rise in neuronal activity by increasing glucose uptake at end-feet that contact the vasculature and by increasing glycolysis and lactate release to the extracellular space that is used as a respiratory substrate to sustain neuronal activity. This model provides the foundation of our understanding of neuroenergetics by integrating multiple metabolic and signaling pathways between neurons and other cell types (284, 341). However, more recent evidence, especially that obtained from *in vivo* studies, challenges the ANLS model, as recently reviewed (284, 436).

In opposition to direct glucose uptake by astrocytes from the blood vessels predicted by the ANLS model, glucose diffuses across the endothelial membrane from the blood flow into the extracellular fluid and is transported into the different cell types, including neurons (271, 300). The facilitated glucose transporter 1 (GLUT1) mediates glucose diffusion from endothelial cells and into astrocytes and oligodendrocytes (300, 379). Neurons express a high-affinity glucose transporter 3 (GLUT3), which ensures provision under low glucose levels, and GLUT4, which is necessary for presynaptic function (21, 403). Data obtained over the years, and more recently using quantitative fMRI, showed that the rate of neuronal glucose oxidation is proportional to the glutamatergic neurotransmission (191). However, Lundgaard *et al.*, using a fluorescent glucose analog and two-photon microscopy, showed that stimulation causes higher glucose uptake in neurons than in astrocytes in the brain of awake mice, suggesting that on activation neuronal glycolysis is increased (271). Another *in vivo* study also reported a transient increase in glycolysis in neurons upon activation, leading the authors to propose that glycolysis provides a prompt response to a rise in energy demand that is followed by enduring oxidative phosphorylation (105). At the same time, the astrocyte support of neuronal oxidative phosphorylation was confirmed *in vivo*. Mächler *et al.* showed evidence of a lactate gradient from astrocytes to neurons by using a biosensor for lactate and two-photon microscopy (274). In addition, synaptic activity induces changes in astrocyte gene expression of components of metabolic pathways that include an increase in glucose metabolism and lactate export (177). Interestingly, there is *in vivo* evidence that oligodendrocyte NMDAR

stimulation results in increased lactate export that supports axonal energy metabolism (379). Therefore, to explain brain bioenergetics, a more complex version of the ANLS model is needed that incorporates neuronal rest/activity states, a temporal component, and other cells types (such as oligodendrocytes).

C. Bioenergetics and neurotransmission in psychiatric disorders

There is no direct link between mitochondria and autism, but the existing neuroimaging, *in vitro* and postmortem data are consistent with mitochondrial dysfunction in ASD and were recently reviewed (71, 186). The prevalence of mitochondrial disease in ASD children (below 20 years old) is 5%–7%, which is 500-fold higher than in the general population (330, 375). However, only 23% of the autistic children with diagnosed mitochondrial disease have mutations in mtDNA, suggesting that for the majority of patients mitochondrial dysfunction is secondary to ASD (375). Accordingly, the ASD children with mitochondrial disease may have a phenotypic presentation indistinguishable from idiopathic ASD or may present uncommon symptoms (375, 468).

In 1985, Coleman and Blass described four autistic patients with lactic acidosis and proposed the existence of a subgroup of patients with deficiencies in carbohydrate metabolism (79). Other evocative studies followed, but in 1993 an *in vivo* pilot study using ^{31}P-MRS showed evidence of alterations in brain energy and phospholipid metabolism in patients' prefrontal cortex (309). Notably, this study showed that the decrease in phosphocreatine levels was correlated with the neuropsychological and language deficits. However, later studies using ^{1}H-MRS showed variability in metabolites and neurotransmitters across brain regions and patients' age. The results reported by these studies and their limitations, regarding principally the ^{1}H-MRS methodology and the patient spectrum heterogeneity, were accurately reviewed recently (130). A decrease in *N*-acetyl-aspartate and creatine is reproducibly and significantly observed in multiple regions of the brain of ASD children but not in adults; adult reports are scarce and inconclusive (130, 194).

A systematic review and meta-analysis of five studies revealed that the levels of lactate were significantly higher in ASD children compared with controls (375). Also indicative of decreased mitochondrial function, Essa *et al.* found a peripheral reduction in ATP and NAD^+/NADH levels and an increase in oxidative stress markers in autistic children (123). The activity of respiratory chain complexes (I, III, and IV) in muscle biopsies was lower than normal in autistic patients with evocative symptoms or those diagnosed with mitochondrial disease (164, 468) and in idiopathic patients (153). A decrease in the oxidative phosphorylation capability was also observed in the ASD brain. The activities of complex I, ATP synthase and PDH were significantly reduced in 14 young autistic patients (mean, 10 years old) compared with age-matched controls in postmortem prefrontal cortex samples (163). Further, Tang *et al.* reported reduced activity of complexes I and IV in postmortem samples of Broadman area 21 (BA21) temporal lobe of young autistic children compared with controls (438). Although the measures of enzymatic activities in postmortem samples are questionable, the authors also analyzed the samples by Western blot and showed that the protein levels of complexes I, III, IV, and ATP synthase were decreased compared with controls in young children (<10 years) (438). However, for older ASD patients (more than 45 years), only complex III protein expression was lower in postmortem BA21 temporal lobe (438). Chauhan *et al.* also found a decrease in protein expression of complexes II, III, and ATP synthase in temporal cortex, of complex I in frontal cortex, and of complex III and ATP synthase in cerebellum of postmortem brains of young (4–10 years) autistic children compared with controls (68). In agreement with these data, a decrease in transcription of genes related to mitochondrial oxidative phosphorylation (complexes I, III and ATP synthase) was observed in the BA19 occipital cortex of nine autistic patients (<60 years old) compared with age-matched controls (152).

Given that only a small number of studies included adult individuals, it is difficult to draw conclusions. However, the available data suggest that major deficiencies in mitochondrial energy metabolism occur early in life, are attenuated with aging, and are close to normal in adults (68, 130, 438). If this finding is confirmed in future studies, it indicates that decreased oxidative phosphorylation contributes to the etiology and heterogeneity of the disorder. In addition, it implies that brain adaptation to ASD and mitochondrial dysfunction during development favored neuronal energetics over neurotransmission and connectivity. The balance of neural excitation/inhibition (E/I) is established during development and is mediated by the relative contributions of excitatory and inhibitory synaptic inputs to a cortical neuron or a network (100). Increased excitatory activity caused by glutamate receptor activation or reduced GABAergic signaling result in excitotoxicity and neuronal degeneration and seizures that are common in autistic patients (45). Increased inhibitory activity disturbs synaptic plasticity and the processes of learning and memory. Alterations in the E/I balance have been suggested to be fundamental for ASD behavioral and cognitive phenotypes and were critically reviewed recently (106). However, the imbalance direction varies according to the cohorts studied; most studies suggest that excitation is increased relative to inhibition in ASD, but increased inhibition was also observed (106).

Evidence also suggests that alterations in excitatory and inhibitory synapses contribute to the positive, negative, and cognitive symptoms in SZ (306, 408). A prominent hypothesis presents NMDAR hypofunction in the limbic system during development as a major player in the emergence of the disorder (408). A significant increase in glutamate levels was observed by using MRS in several regions of the brain of SZ patients (113, 301). However, a meta-analysis of 59 studies found no association between glutamate levels and age of patients, symptom severity, or antipsychotic dose (301). Interestingly, McCullumsmith *et al.* showed that gene expression of the major glutamate transporter in astrocytes (sodium-dependent glutamate/aspartate transporter 2, *EAAT2*) is decreased in the mediodorsal nucleus of the thalamus of SZ patients, which suggests that the capacity of astrocytes to remove the glutamate from the synaptic clef and convert it to the nontoxic glutamine may be compromised (290).

Likewise, alterations in glutamatergic neurotransmission are taken into consideration in the etiology of mechanisms and therapeutic opportunities for mood disorders (90, 321). The first report of the antidepressant effect of ketamine, a noncompetitive antagonist at NMDR, in a clinical trial (34)

stimulated the fundamental research and investigation of the therapeutic potential of this pathway for drug development. Despite this upsurge of interest, only a small number of reports with unconvincing results are available regarding the state of glutamatergic transmission in the brain of MDD patients (321). Nonetheless, imaging using ^{1}H-MRS detected a reduction in glutamate levels in the prefrontal cortex and anterior cingulate cortex in MDD patients (22, 179, 400). In contrast, an increase in glutamate levels was consistently observed *in vivo* in the brain frontal areas in nonmedicated BD patients compared with controls (88, 304, 409). This increase was independent of the mood phase, but conflicting results were obtained in patients treated with Li and VPA (133, 409, 424). Proteomics and transcription studies using postmortem brain tissue from BD patients substantiated the MRS findings (116, 156, 178, 359).

Studies using *in vivo* imaging, postmortem brains, or other models showed impaired oxidative phosphorylation and increased glycolysis in SZ and BD patients, which were recently reviewed (229, 427). A recent metabolome analysis showed an increase in isocitrate in cerebrospinal fluid of BD patients, suggesting impaired activity of the TCA cycle enzyme, isocitrate dehydrogenase (489). Fewer studies were reported for depression but also point to alterations in bioenergetics in patients (233). A review of PET studies revealed that MDD patients have reduced blood flow and glucose metabolism in the prefrontal cortex, anterior cingulate cortex, and caudate nucleus (459). Interestingly, some reports suggest that antipsychotic medication causes a decrease in the activity of respiratory complexes that could be related to the high prevalence of metabolic syndromes in patients under SGA treatment (31, 371, 387).

Mertens *et al.* showed that dentate gyrus granule neurons derived from iPSCs of BD patients have mitochondrial abnormalities compared with neurons differentiated from controls (302). This study also revealed that patient-derived neurons displayed hyperactivity that was normalized with Li treatment, but only in cells from patients who have a clinical history of therapeutic Li response. These results were reproduced recently by using a different patient cohort, demonstrating that the hyperactivity phenotype of patient neurons is robust and can be used to predict Li responsiveness (419).

Even though some findings are inconsistent, the largest proportion of data reported converge to support the hypothesis that mitochondrial dysfunction, with a reduction in oxidative phosphorylation and an increase in glycolysis, participates in the pathophysiology of ASD, SZ, BD, and MDD. Alterations in glutamatergic neurotransmission are also present in patients suffering from these disorders. These cellular functions are intrinsically dependent on one another; it would be interesting in the future to explore which is at the source of the phenotypes, glutamatergic transmission, or mitochondrial dysfunction.

IV. Mitochondrial Dysfunction in Psychiatric Disorders

Alterations in the mitochondrial genome have been described in patients suffering from mental illness, which may be significant to the pathophysiology of psychiatric disorders (18). Another indication of the repercussions of mtDNA changes is the observation that patients suffering from mitochondrial diseases often present comorbidity of psychiatric symptoms, such as mood disorder, cognitive impairment, psychosis, and anxiety (17, 125). Patients with MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes), which is caused by mutations in several mitochondrial genes, occasionally present SZ-like symptoms (216, 318).

The human mitochondrial genome is a circular double 16.6 kb DNA molecule composed of 37 genes and a variable noncoding sequence of $\approx$1.1 kb named displacement-loop (D-loop), which contains the initiation sites for replication and transcription (12) (Fig. 9). Retrograde signaling is an essential mitochondrial function necessary for communication of mitochondria not only with the rest of the cells but also with cells in distant organs. The mtDNA encodes mitochondria-derived peptides, such as humanin and MOTS-c (mitochondria open reading frame of the 12S rRNA-c), which act as systemic signals that protect neurons from insult or mediate insulin and metabolic homeostasis (166, 252). The mtDNA is maternally inherited and, although initial studies suggested maternal transmission in SZ and BD, these findings were not subsequently confirmed (248, 292, 317, 347, 477).

A. Alterations in nucleoid organization and replication

Each mitochondrion contains multiple copies of its genome tightly packaged with proteins into nucleoids (Fig. 10). The nucleoid proteins associated with the mtDNA were not conserved during evolution, and the ones found in human mitochondria are different from those found in yeast or other organisms (241). As the nucleoids are heritable units of mitochondria (199), accurate replication and maintenance of mtDNA, segregation and degradation of mutated DNA molecules and transmission to the progeny are controlled by nuclear genes and coupled to mitochondrial dynamics and cellular metabolism. The nucleoids are small spherical structures of $\approx$100 nm that are associated with the inner membrane and distributed regularly in the mitochondrial network (7, 74, 141, 350). The number of mtDNA copies per nucleoid in mammalian cells is not fully elucidated. Most of the studies report 3–10 copies of mtDNA per nucleoid in human cells (7, 74, 193, 241), but data obtained using super-resolution microscopy showed that in fibroblasts each nucleoid carries a mean of 1.4 mtDNA molecules (242). The organization of the nucleoids is multi-layered, with an inner core composed of mtDNA and DNA-packaging proteins, also necessary for transcription and replication, and an adaptable outer layer with temporary recruited proteins that perform specific functions (40).

In human cells, the TFAM is the architectural protein that packages and organizes the mtDNA inside the nucleoid, at an average of 1 TFAM per 10 nucleotides (6). Other major proteins required for replication present in the inner core are the DNA helicase Twinkle, the mitochondrial single-stranded DNA binding protein mtSSB, and the mitochondrial DNA polymerase γ (POLG) (141). The Lon peptidase 1 (LONP1) is also present in the inner core and degrades phosphorylated TFAM, participating in the fine regulation of mtDNA packaging and content (269).

Changes in the regulatory pathways and metabolism in a patient's cells may lead to alterations in the expression of the proteins required for replication and stability of mtDNA. For instance, TFAM is phosphorylated by the protein kinase A (PKA) targeting the transcription factor for proteolysis by

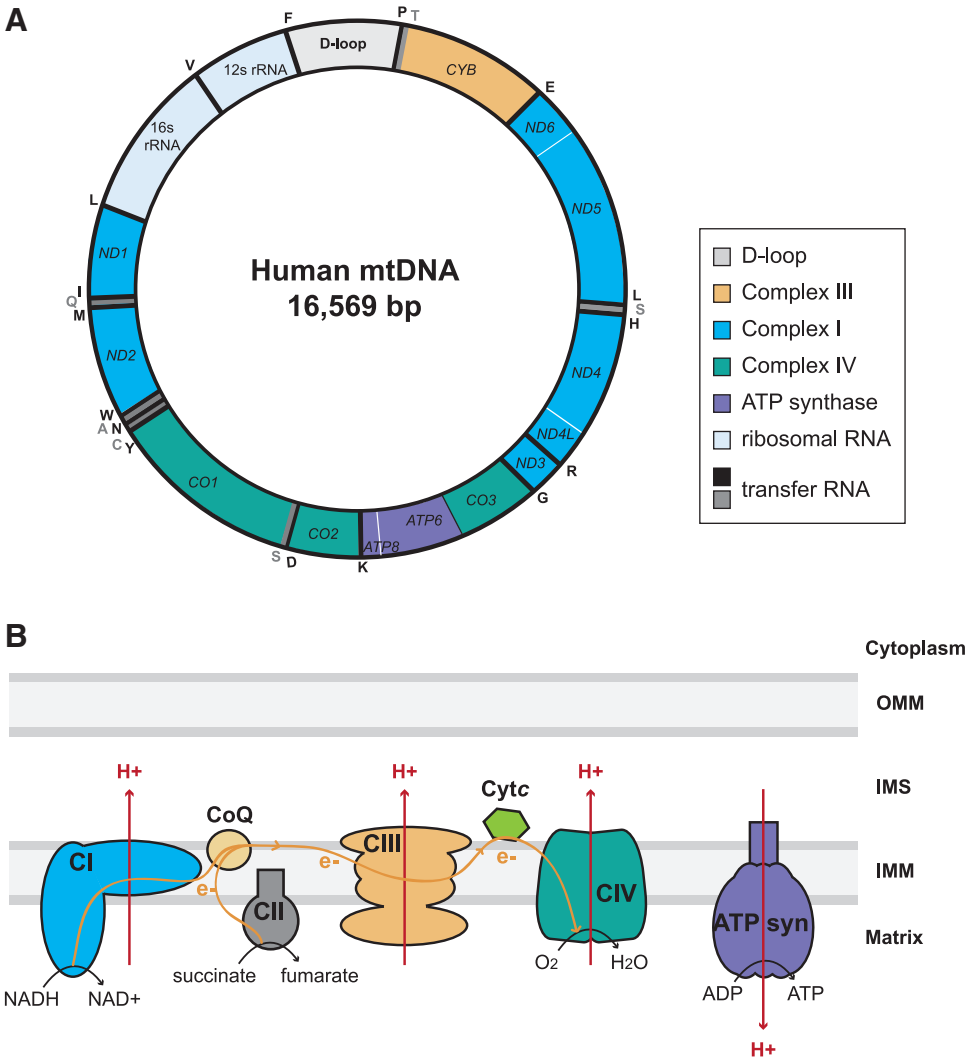

FIG. 9. Human mitochondrial genome and the respiratory chain. (A) Gene distribution in the genome and functional categories. Genes MT-ND1, MT-ND2, MT-ND3, MT-ND4, MT-ND4L, MT-ND5, and MT-ND6 encode subunits of NADH:ubiquinone oxidoreductase (CI); MT-CYB encode a subunit of ubiquinol-cytochrome *c* oxidoreductase (CIII); MT-CO1, MT-CO2, and MT-CO3 encode subunits of cytochrome *c* oxidase (CIV); MT-ATP6 and MT-ATP8 encode subunits of ATP synthase. The other genes encode ribosomal RNAs or transfer RNAs. For further information, the complete list of mtDNA mutations and polymorphisms is available on the website mitomap.org **(B)** Schematic representation of the mitochondrial respiratory chain. The reduced cofactors NADH and $FADH_2$ donate electrons to complex I and complex II, respectively, which are transferred to electron (e^-) carriers, CoQ and Cyt*c*, and to complexes III and IV. Electrons from complex IV are accepted by oxygen with formation of water. The electron transfer is coupled to proton pumping from the matrix to the IMS through complexes I, III, and IV, generating an electrochemical gradient that is used to synthesize ATP by ATP synthase. ATP, adenosine triphosphate; CoQ, coenzyme Q; Cyt*c*, cytochrome *c*; D-loop, mtDNA displacement loop. Color images are available online.

LONP1 (269). PKA levels are increased in the platelets of BD patients, which may cause increased phosphorylation and degradation of TFAM (439). An interesting study showed that VPA increased the mtDNA copy number, the expression of POLG, and the gene expression of the master mitochondrial biogenesis *PGC-1α* in fibroblasts from five patients carrying pathogenic mutations in *POLG* gene (405). Recent data showed the presence of deleterious *POLG* variants in Japanese subjects with BD (212). Also, the protein levels of POLG, TFAM, OPA1, and mitofusin (MFN)2 are decreased in postmortem samples of the temporal lobe of ASD patients compared with controls (438). More studies are needed to evaluate the contribution of changes in the nuclear genes that affect mtDNA stability to the pathogenesis of psychiatric disorders; however, it is likely that mutations in these genes may modulate the severity of the mitochondrial features and the patients' symptoms.

The number of mtDNA copies is correlated to the expression of bioenergetics and metabolism genes (87, 364) and to increased oxidative stress (265). Likewise, it also varies between cell types and tissues; whole-exome sequencing has shown that the muscle and brain have more mtDNA copies than less energy-demanding organs, such as the lungs (87). Methylation of the *POLG* gene was also shown to be implicated

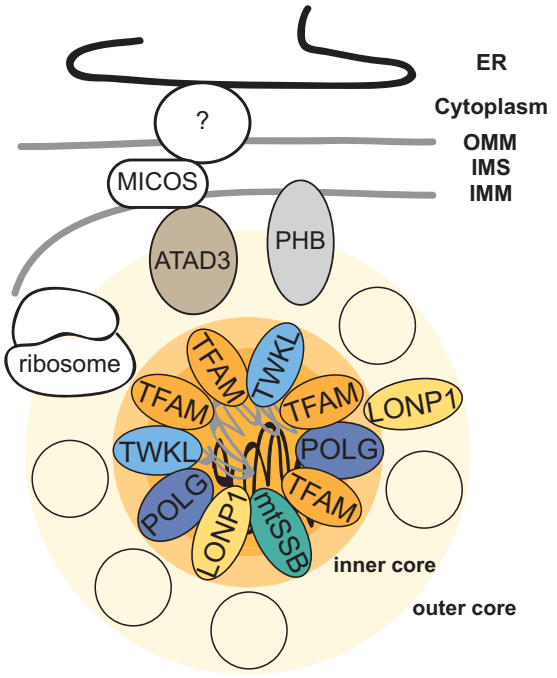

FIG. 10. Mitochondrial nucleoid organization and membrane contacts. Schematic representation of the nucleoid and interactions with the mitochondrial and ER membranes in human cells. The inner core of the nucleoid is composed of mtDNA and proteins that are necessary for packaging, transcription, and replication (TFAM, TWKL, mtSSB, and POLG). The outer layer is composed of proteins recruited temporarily to perform specific functions, of ribosomes and proteins required for RNA processing and translation, and of proteins that contact the IMM (prohibitin and ATAD3). The peptidase LONP1 is present in the inner and outer cores. It is possible that the nucleoid contacts the mitochondrial and ER membranes through ATAD3, MICOS, and an unidentified complex. ATAD3, ATPase family, AAA domain-containing protein 3; LONP1, Lon peptidase 1; mtSSB, single-stranded DNA binding protein; POLG, DNA polymerase γ; TFAM, mitochondrial transcription factor A. Color images are available online.

as it varies in cells with different metabolic activity and from different tissues (221, 254). In healthy subjects, an increase in mtDNA copy number is positively correlated with telomere length (450). Numerous studies showed that telomere shortening is a natural result of aging that can be modulated by recombination, genetic factors, and psychosocial and oxidative stresses (122, 351). A direct link between telomere dysfunction and the reduction of mitochondrial mass and energy production has been reported (383). Therefore, it is not surprising that the number of mtDNA copies tends to decrease in pathological conditions that involve mitochondrial dysfunction (81).

For psychiatric disorders, reports investigating mtDNA copy numbers and telomeres showed diverse and sometimes conflicting results. Tyrka *et al.* observed significantly higher mtDNA copy numbers and shorter telomeres in leukocytes from individuals with depressive and anxiety disorders (451). A large study conducted on 210 young subjects with MDD and 217 healthy controls revealed no significant differences between patients and controls in terms of leukocyte mtDNA copy numbers (180). The opposite was observed in studies of older cohorts; the mtDNA copy number of the MDD group was significantly lower than that of the controls (65, 228). Similarly, no change in mtDNA copy number was observed in leukocytes from young, unmedicated patients having short illness duration BD (96). However, a significant decrease in leukocyte mtDNA copy number was observed in older euthymic patients with BD when compared with controls (66). Since no biochemical data were included in these studies, it is not possible to make inferences about the mitochondrial bioenergetics, but it is conceivable that MDD and BD duration and the age of the subjects have an impact on the mtDNA copy number. Vawter *et al.* analyzed the mtDNA copy number in dorsolateral prefrontal cortex in postmortem brains from patients with MDD and BD and only found decreased mtDNA copy numbers in patients with BD compared with controls after controlling for the effects of agonal duration and pH (455). Other studies failed to show differences in samples from the frontal cortex of BD and SZ subjects compared with controls (207, 380). Unfortunately, there are no reports on the effect of drug treatments on the mtDNA copy number for MDD or BD. Studies showed a tendency for decreased telomeres in MDD (187, 458) and BD (349). Li *et al.* measured significantly lower mtDNA copy number and identical telomere length in 134 first-episode, antipsychotic-naive SZ patients compared with 144 healthy controls (259). Of these, 89 patients followed an 8-week risperidone treatment and, surprisingly, the findings suggest that the telomere length and mtDNA copy number can be used as predictors of antipsychotics response in SZ patients. In summary, available data suggest a decrease in mtDNA copy number with illness progression for SZ, BD, and MDD, which is in agreement with a reduction in the expression of mitochondrial genes and a decrease in energy metabolism. Regarding ASD, the telomeres were also shorter in leukocytes from adults with the condition from childhood (260). Conversely, different studies showed an increased number of mtDNA copies in peripheral blood samples from children with ASD when compared with nonaffected siblings or controls (69, 153, 487) A significant increase in mtDNA copies was also found in the prefrontal cortex of children with ASD (163). Giulivi *et al.* also reported decreased oxidative phosphorylation and increased generation of hydrogen peroxide (H_2O_2), in addition to an increase in mtDNA copy number and deletions, in lymphocytes from ASD children (153). The increased replication of mtDNA may be a compensatory mechanism for the increased oxidative stress and mutation of the mitochondrial genome in young children. It is possible that, similar to what is observed for the other psychiatric disorders, the mtDNA copy number decreases with age in ASD.

B. mtDNA polymorphisms and mutations

There is considerable mtDNA diversity between human populations and among individuals that results from the accumulation of substitutions during evolution (462). The mitochondrial oxidative phosphorylation activity can change depending on the mtDNA variants. The 7028C>T polymorphism in the *MT-CO2* gene causes a reduction in complex IV (cytochrome *c* oxidase, CIV) activity and protein amount in cybrids (155). Kazuno *et al.* showed alterations in mitochondrial pH and Ca^{2+} in cybrids containing the 10398A>G

and 8701A>G polymorphisms by whole mtDNA sequencing (220). Interestingly, the 10398A>G polymorphism in *MT-ND3* gene was also associated with susceptibility to BD in the Japanese population (218) and to Li response (466). In 2000, Kato *et al.* reported a nominal association of 5178C genotype (in *MT-ND2* gene encoding a subunit of complex I, NADH:ubiquinone oxidoreductase, CI) with BD (217). A comparison of the brain intracellular pH by ^{31}P-MRS in bipolar patients showed that the pH was significantly lower in the 5178C group, suggesting that this polymorphism may modulate vulnerability in the patients by altering mitochondrial respiration. Another polymorphism, 3644T>C in *MT-ND1* gene, was identified in six BD patients with comorbid symptoms suggestive of mitochondrial disorders and affecting CI activity and mitochondrial membrane potential in cybrids (319). The variant 12027T>C in the gene *MT-ND4* encoding another subunit of CI was associated with SZ and superoxide ($O_2^{\bullet-}$) production in the brain (281).

A few other mtDNA variants were reported for BD, MDD, and SZ in genetic studies without any correlation to the potential biochemical changes and mitochondrial function (18, 355, 395, 452, 457). In addition, many studies failed to show any correlation between mtDNA variation and mental disorders (18, 169). Therefore, current information is insufficient to implicate specific mtDNA haplogroups in the risk of developing any psychiatric disorder (36, 222, 291, 370, 395, 452).

The most common mutations observed in individuals with conditions caused by mtDNA defects are point mutations (single base substitution, deletion, or insertion) and large deletions (422, 440). Mutations in mtDNA may be maternally inherited or somatic, accumulating with age in the normal brain and other organs (60, 393, 440). An increased mutation rate may also be caused by inherited nuclear gene mutations that impact mtDNA replication, transcription, and maintenance of copy number (440). Interesting studies in transgenic mice expressing a proofreading-deficient POLG specifically in neurons suggested that increased somatic mtDNA mutation affected mood, since the mice presented spontaneous and recurrent episodes of depression (213). A comprehensive anatomical search showed that the mtDNA mutations accumulated at high level in the paraventricular thalamic nucleus (PVT) in these mice. Further, inhibition of neural transmission in PVT neurons caused depression-like episodes, suggesting that mitochondrial dysfunction in this specific neuronal population affects mood. Indeed, postmortem brains of patients with mitochondrial disorder and comorbid mood symptoms also revealed accumulation of *MT-CO1*-negative cells in the paraventricular thalamus (222). In another study of brain-specific conditional knockout of *SLC25A4* or *ANT1*, a causal gene of mitochondrial disease linked with BD that encodes an ADP, ATP carrier, the MT-CO1-negative cells were preferentially observed in dorsal raphe serotonergic neurons, which could explain the diminished delay discounting behavioral phenotype of these mice (219). Although mtDNA mutations have been reported in psychiatric disorders over the past 25 years in studies using different technologies (18, 103, 157, 348, 395), the information gathered did not clearly indicate that mtDNA mutations participate in the etiology of these conditions. However, it is possible that an accumulation of deleterious mutations may occur in a specific neural circuit.

C. Mitochondrial dynamics and interaction with the endoplasmic reticulum

Mitochondria are dynamic and motile organelles existing in the form of reticular networks or small structures with variable sizes. Optimal morphology, mass, and distribution are necessary to provide energy, buffering Ca^{2+} waves, and retrograde signaling, among other functions in the cell, and are the result of tightly regulated biogenesis, degradation, fusion, and fission (132, 345) (Fig. 11). These processes are regulated by internal and external cues, such as energy demand, nutrient availability, stress, and apoptosis (262, 426). Balanced fusion and fission events are thus essential for mitochondrial homeostasis and cell survival; excess increases in fusion or fission are deleterious and lead to ATP decrease and apoptosis (132, 345). Mitochondria are interconnected or aggregated in small regions of the cell when the equilibrium is directed toward fusion. In contrast, when the equilibrium is directed toward fission, mitochondria are fragmented, respiration-incompetent and tend to lose mtDNA. Recently, Schmitt *et al.* used a combination of *in vitro* and *in vivo* models and showed that a circadian clock controls mitochondrial dynamics and metabolic flux *via* DRP1 (dynamin 1 like) phosphorylation (391). DRP1 is central in mitochondrial fission. Even more interesting, cyclic DRP1 phosphorylation is necessary for feedback regulation of the core clock, suggesting that changes in mitochondrial dynamics may have repercussions in the regulation of circadian rhythm. Considering the interconnection between mitochondrial bioenergetics, oxidative stress, mitochondrial dynamics, and circadian regulation, it is not surprising that abnormalities in the structure or number and/or changes in the expression of proteins implicated in mitochondrial dynamics have been described in ASD, SZ, and BD (63, 129, 367, 387, 438).

The sites of contact between the mitochondrion and the endoplasmic reticulum (ER) are important for mtDNA replication, for maintenance of lipid and Ca^{2+} homeostasis, in the initiation of autophagy and mitochondrial division, and in sensing metabolic shifts (256, 303, 354, 449) (Fig. 7). Mitochondria actively participate in the intracellular regulation of Ca^{2+} signaling by buffering the Ca^{2+} waves released by the ER or from the plasma membrane. In general, intensification in energy demand is correlated with an increase in Ca^{2+}, but alterations in the mitochondrial oxidative phosphorylation capacity are often associated with poor handling of Ca^{2+} fluxes (37). Two regulators of Ca^{2+} transfer at the ER-mitochondria contact sites described recently are the ROS molecule, hydrogen peroxyde, and DISC1 (42, 336). Even though the gene *CACNA1C* (calcium voltage-gates channel subunit α-1C) encoding a Ca^{2+} channel is commonly found to be associated with ASD, SZ, BD, and MDD, very few studies have addressed this question (35, 85). Mitochondria are subjected to multiple pathways of quality control to ensure that damaged or unnecessary organelles are eliminated. This can be achieved by different mechanisms, including mitochondria-derived vesicles that transport damaged material for degradation by the lysosomes and a selective form of autophagy called mitophagy that eliminates whole mitochondria (345, 488). Autophagy is a cellular response to nutrient starvation regulated by activation of autophagy-related genes by the PI3K pathway and the repression of the mTOR kinase (234). Recent findings suggest that autophagy is impaired in ASD, SZ, and MDD (203, 227, 299, 437).

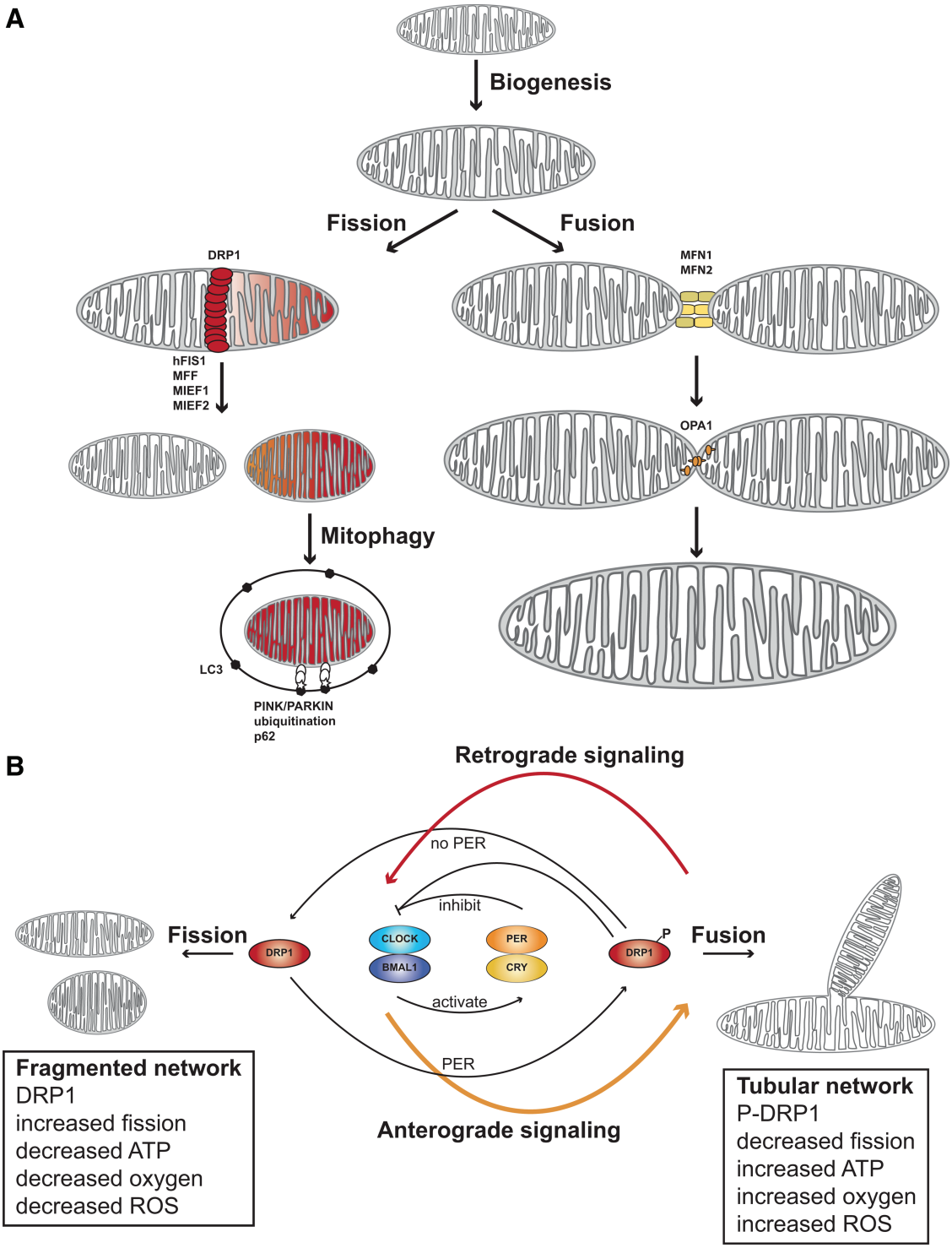

FIG. 11. Mitochondrial dynamics and regulation by the core circadian clock. (A) Schematic representation of mitochondrial biogenesis, fusion, fission, and mitophagy. Mitochondrial mass is regulated by biogenesis and mitophagy, among other degradation processes. Fusion and fission processes are necessary for mtDNA replication and maintenance and optimal functioning of oxidative phosphorylation. Mitofusins MFN1–2 and OPA1 are localized in the outer and inner membrane, respectively, and are responsible for successive fusion of these membranes. Active nonphosphorylated DRP1 oligomerizes and causes constriction of outer membrane and mitochondrial fission with the participation of other proteins (hFIS1, MFF, MIEF1–2). Mitochondrial dysfunction (*e.g.*, depolarization of the internal membrane) induces fission, and defective mitochondria are targeted for mitophagy by PINK and PARKIN. **(B)** The circadian clock controls the rhythmic mitochondrial dynamics and metabolic fluxes by DRP1 phosphorylation at amino acid S637. The DRP1 phosphorylation cycles also regulate the core clock. Circadian rhythm, metabolism, and mitochondrial dynamics are connected and regulated by anterograde and retrograde signaling. DRP1, dynamin 1 like. Color images are available online.

V. Oxidative Stress and Antioxidant Defense in Psychiatric Disorders

The brain is particularly susceptible to oxidative damage caused by what Halliwell meticulously described in 13 ''problems'' (172). Cobley *et al.* revisited these recently (75). Major reasons are that brain function is dependent on redox signaling for synaptic plasticity and memory (231, 417), action potentials cause Ca^{2+} fluxes that are redox regulated and latent oxidative stress inducers (42, 183), and neurotransmitter metabolism and auto-oxidation generate ROS (75, 172). A possible role for oxidative stress in the pathophysiology of psychiatric disorders has been sought for more than 30 years with occasionally conflicting results (78, 118, 361). Although we are far from having validated oxidative stress biomarkers that could be used in the clinic for diagnostics and prognostics, the accumulated research data point to the involvement of oxidative stress in the pathophysiology of psychiatric disorders.

A. Redox mechanisms and signaling in the brain

Aerobic life and energy metabolism are indissociable from the production of oxidant molecules. However, ROS are not only an undesirable consequence of metabolic activity, produced as a side product of mitochondrial respiratory complexes, dehydrogenases, and oxidases; some of these molecules have important signaling functions (2, 42, 43, 75). Cellular oxidative stress state occurs when an imbalance between ROS generation and antioxidant defenses cause irreparable oxidative damage. It was shown 20 years ago that treatment of bacteria and yeast cultures with low concentrations of H_2O_2 induced an adaptive response to oxidative stress, making cells more resistant to subsequent insults (62). More recently, Calabrese *et al.* proposed the concept of hormetic dose response or hormesis (a term coined in 1943 by Southam and Ehrlich) as a primary reponse of biological systems to stress conferring resistance and promoting health and its implication in neurodegenerative and psychiatric disorders (54, 57, 58). At low concentrations, in physiological conditions, ROS and reactive nitrogen species (RNS) reversibly modify proteins in thiol groups, acting as redox switches regulating the activity of transcription factors and signaling pathways, such as Nrf2 and heat shock factor 1 (3, 311, 366). More generally, the hormetic adaptive response to different stresses is mediated by the vitagene network, which encodes among others heat shock proteins, heme oxygenase 1, the thioredoxin system, and sirtuins (55, 59, 360). Interestingly, the neuroprotective effect of dietary antioxidant molecules such as resveratrol, sulforaphane, or carnosine, is also mediated by the activation of hormetic mechanisms (56). Evidence accumulates on the beneficial effects of low doses of oxidants in health, providing new therapeutic targets (55, 366).

NADPH oxidases (NOXs) are a significant source of ROS in the brain. These enzymes regulate activation of microglia and inflammatory response, and neuronal development (411). NOXs are membrane enzymes that produce bursts of ROS in the extracellular space or the lumen of organelles in a regulated manner (411). NOX2 (also known as $gp91^{phox}$ because it is expressed in phagocytic cells) is the best studied and generates superoxide from NADPH by electron transfer to oxygen at the plasma membrane. NOX2 interacts with the transmembrane $p22^{phox}$ protein forming an inactive complex, which is activated by multiple regulatory cytosolic proteins (411). ROS generated by NOXs contribute to distinct phases of neuronal differentiation and function: neurogenesis, axonal outgrowth and guidance, NMDAR-mediated plasticity, long-term potentiation, and memory (43). Therefore, strict regulation of NOX enzymes is essential for normal brain development and function and changes were detected in psychiatric disorders (192, 389, 396, 465).

B. Antioxidant response in brain cells

$O_2^{\bullet-}$ is converted enzymatically into the membrane-permeant H_2O_2 by superoxide dismutase (SOD) (Fig. 12). Excess superoxide causes an increase in the intracellular free iron pool by releasing iron from iron-sulfur clusters. This is dangerous because it favors the Fenton reaction, leading to the generation of hydroxyl radical ($HO^{\bullet}$), which is extremely reactive and can damage any biological macromolecule. Excess $O_2^{\bullet-}$ can also react with NO to generate the deleterious peroxynitrite ($ONOO^-$). Although highly toxic, the only cellular protection against $HO^{\bullet}$ and $ONOO^-$ is the removal of $O_2^{\bullet-}$ by SODs. Detoxification of H_2O_2 relies on the action of multiple scavenging enzymes, such as catalases, glutathione peroxidases (GPXs), and peroxiredoxins (475). Peroxides (mostly formed from oxidized lipids and proteins) are reduced by GPXs using reducing equivalents from reduced glutathione (GSH), which is simultaneously oxidized to GSSG. GSH is regenerated from GSSG by glutathione reductase by using NADPH as the electron donor. The cellular thiol redox status is maintained by the glutathione/glutaredoxin (GRX) and thioredoxin/thioredoxin reductase systems, which reduce the oxidized sulfydryl groups of proteins (33). The damaged bases are removed from the DNA by the base excision repair pathway to maintain DNA integrity (469). The master regulator of phase II antioxidant response is Nrf2, which activates genes containing the antioxidant response element in the promoter (Fig. 13). In oxidative stress conditions, the Nrf2-mediated transcription program induces adaptive metabolic changes that are necessary for survival, including increases in the expression of detoxifying mechanisms and repair systems (208). In normal conditions, Nrf2 is a cytoplasmic protein associated with KEAP1 (Kelch-like ECH-associated protein 1), which is an adaptor subunit of Cullin 3-based E3 ubiquitin ligase, which efficiently promotes Nrf2 ubiquitination and degradation by the proteasome (431). Under oxidative stress conditions, KEAP1 is modified, releasing Nrf2 that is phosphorylated at Ser40 by protein kinase C (PKC) and translocated to the nucleus (190). PI3K is also implicated in the nuclear translocation of Nrf2 by controlling actin reorganization and cytosolic Ca^{2+} rise (208).

Methylglyoxal (MG) is predominantly formed by glycolysis by fragmentation of glyceraldehyde-3-phosphate and dihydroxyacetone phosphate (8). It is a cell-permeant, highly reactive dicarbonyl compound that generates advanced glycation end products (AGEs) from proteins, lipids, and nucleic acids. The formation of AGEs constitutes a biochemical complication of diabetes causing vascular inflammation and is also implicated in aging, neurodegenerative disorders, and possibly autism (101, 277, 285). MG is mostly detoxified by the glyoxalase system (Fig. 8). The product of the spontaneous reaction between MG and GSH is detoxified by the

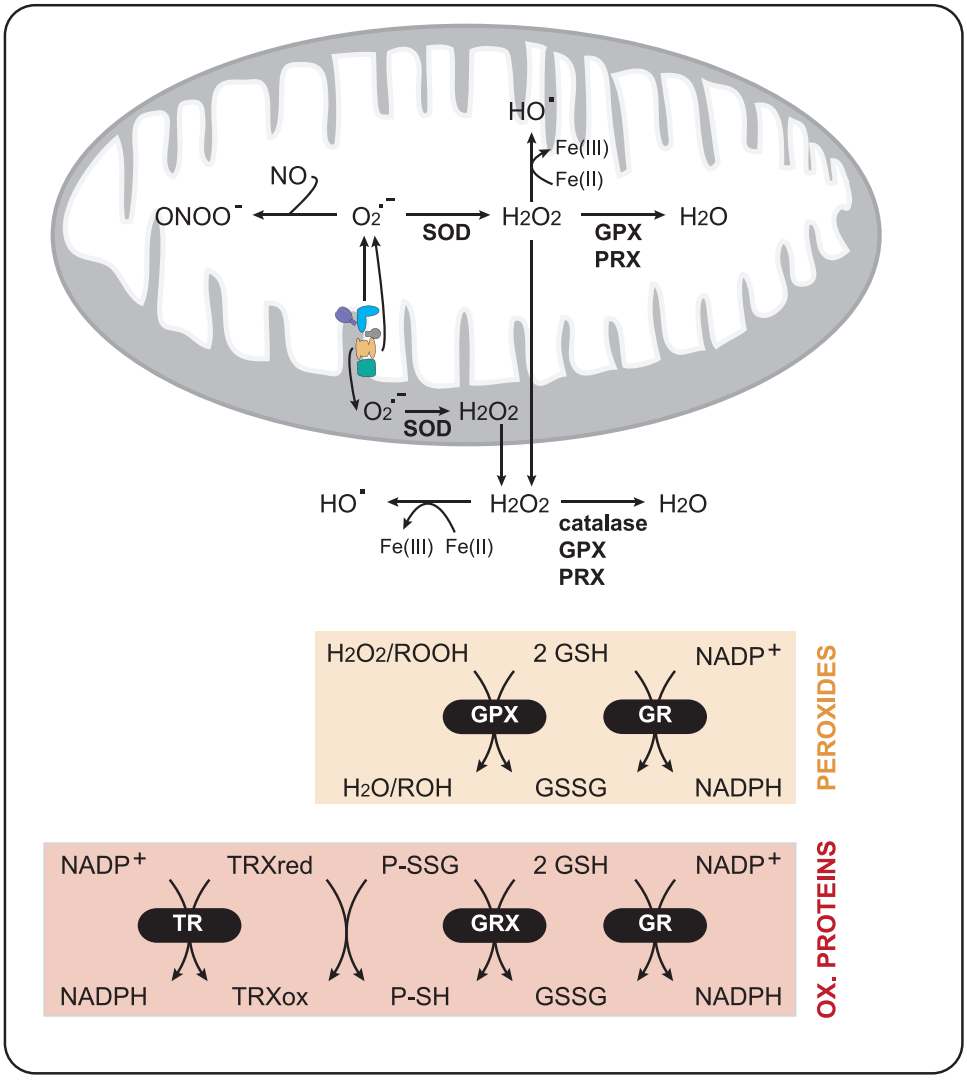

FIG. 12. ROS generation and cellular antioxidant defense enzymes. Superoxide ($O_2^{\bullet -}$) is produced by complexes I and III of the electron transport chain and converted into H_2O_2 by SODs or into $ONOO^-$ by reacting with NO. H_2O_2 can react with ferrous iron to produce the $HO^{\bullet}$. H_2O_2 and other peroxides are detoxified by GPXs, which oxidizes glutathione. H_2O_2 is also scavenged by catalases and PRX. Peroxiredoxins can also scavenge $ONOO^-$. GSSG is reduced to GSH by GR using electrons from NADPH. The cellular thiol redox status is maintained by the TRX/TR and glutathione/glutaredoxin systems by reducing the oxidized sulfydryl groups of proteins. GPXs, glutathione peroxidases; GR, glutathione reductase; GSH, reduced glutathione; $HO^{\bullet}$, hydroxyl radical; H_2O_2, hydrogen peroxide; NO, nitric oxide; $ONOO^-$, peroxynitrite; PRX, peroxiredoxins; SODs, superoxide dismutases; TR, thioredoxin reductase; TRX, thioredoxin. Color images are available online.

glyoxalase 1 (GLO1) generating S-D-lactoylglutathione, which is converted into D-lactate by the glyoxalase 2 (GLO2) regenerating GSH (8). The two reactions are important: GLO1 rapidly transforms MG into the nontoxic S-D-lactoylglutathione, and GLO2 regenerates reduced GSH that is necessary for antioxidant protection. Bélanger *et al.* reported that, in mouse primary cortical cultures, enzymatic activity of glyoxalases is significantly higher in astrocytes compared with neurons, 9.9-fold for GLO1 and 2.5-fold for GLO2 (29). GLO1 enrichment in astrocytes was also confirmed *in vivo* and is consistent with a lower accumulation of AGEs in astrocytes compared with neurons, despite their higher glycolysis rate (29). Neurons are highly sensitive to MG toxicity, which is associated with AGE accumulation and oxidative stress (29, 104). Interestingly, astrocytes protect neurons against MG toxicity in co-cultures (29). Therefore, these differences show that the antioxidant defenses are adapted to the type of metabolism of brain cells.

In a counterintuitive manner considering the high oxidative metabolism and signal transmission, neuronal antioxidant defenses are apparently frail (41, 111). The GSH and NADPH levels are lower in neurons than in astrocytes (29, 111). In agreement with these data, Jimenez-Blasco *et al.* showed that Nrf2 is highly unstable and continuously degraded in neurons but remarkably stable in astrocytes in rat primary cortical cultures (204). It is possible that other antioxidant defense mechanisms operate in neurons. The synaptic activity at NMDAR is coupled with transcriptional increase in glutathione and thioredoxin-peroxiredoxin antioxidant systems in neurons (28, 334) (Fig. 14). In astrocytes, NMDAR-mediated transduction pathway leads to Nrf2-dependent increase in GSH synthesis through a complex mechanism not involving KEAP1/CUL3. Stimulation of glutamate receptors results in Ca^{2+} release from the ER and activation of PKCδ that phosphorylates and activates the p35/cyclin-dependent kinase 5 (CDK5) complex, which, in turn, phosphorylates Nrf2 that is sufficient for nucleus translocation and transcriptional activation of antioxidant genes (204). In these conditions, astrocytes secrete precursors that are used by the neurons for *de novo* GSH biosynthesis (astrocyte-neuronal glutathione shuttle) (41, 112, 204). These results show that the coupling of glutamatergic neurotransmission and metabolic adaptation in astrocytes ensures redox protection of active neurons. However, the adverse consequences of this coupling are that low NMDAR activity leads to deficits in glutathione systems and neuronal death (28).

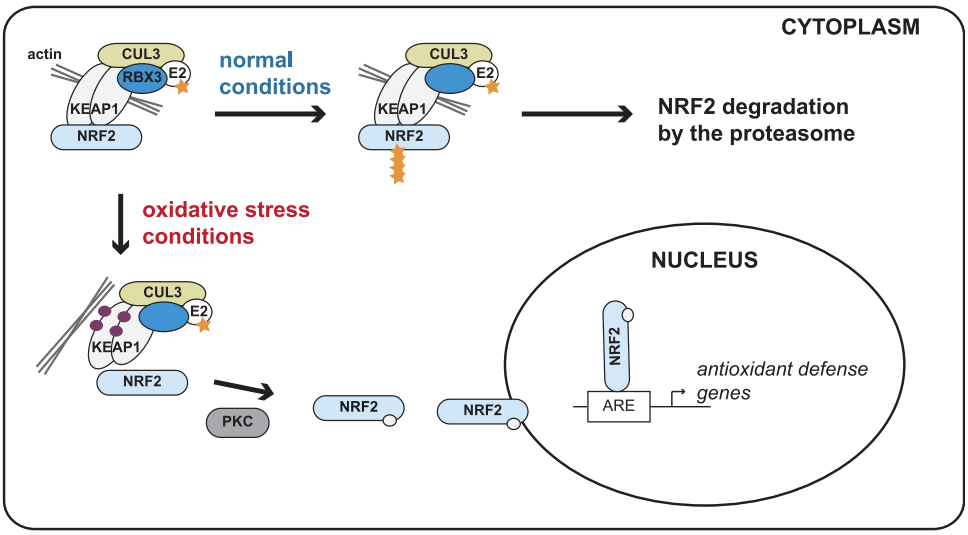

FIG. 13. Nrf2 regulation in normal and oxidative stress conditions. In normal conditions, Nrf2 is a cytoplasmic protein associated with KEAP1 and CUL3-based E3 ubiquitin ligase, which efficiently promotes Nrf2 ubiquitination and degradation by the proteasome. Under oxidative stress conditions, KEAP1 cysteines are oxidized and Nrf2 is released, phosphorylated by PKC, and translocated to the nucleus. KEAP1, Kelch-like ECH-associated protein 1; Nrf2, nuclear factor, erythroid 2 like 2; PKC, protein kinase C. Color images are available online.

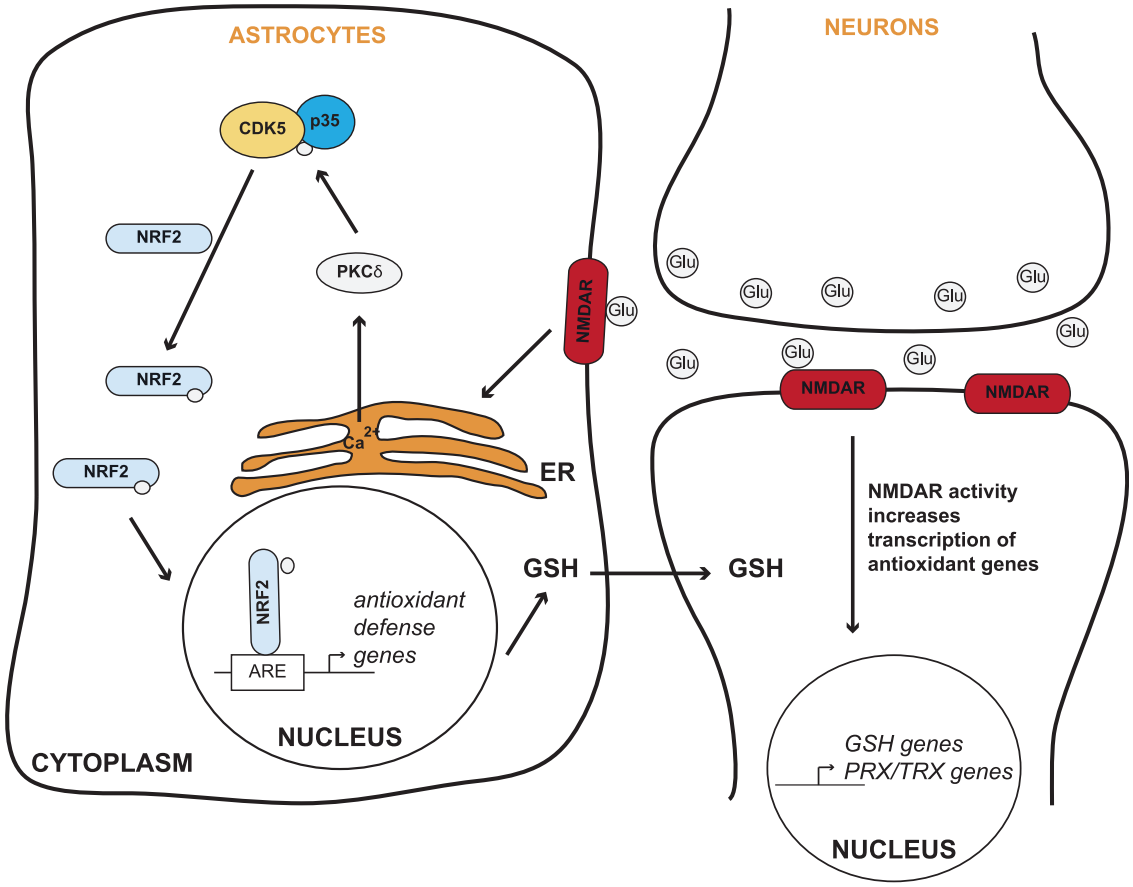

FIG. 14. Glutamatergic transmission regulates antioxidant defense in astrocytes and neurons. In neurons, synaptic activity at NMDAR is coupled with a transcriptional increase in glutathione and thioredoxin-peroxiredoxin antioxidant systems independently of Nrf2. In astrocytes, stimulation of glutamate receptors (NMDAR) results in Ca^{2+} release from the ER and activation of PKCδ that phosphorylates and activates the p35/CDK5 complex, which, in turn, phosphorylates Nrf2, which is sufficient for nucleus translocation and transcriptional activation of antioxidant genes. Astrocytes secrete precursors and GSH that are used by the neurons. CDK5, cyclin dependent kinase 5; NMDAR, *N*-methyl-D-aspartate receptor or glutamate receptor. Color images are available online.

The opposite was also observed; chemical-induced reduction of GSH synthesis causes NMDR hypofunction in rat CA1 pyramidal neurons (421). In addition, glutathione modulates the redox-sensitive sites in NMDAR (425). These observations suggest that, in normal homeostatic conditions, a virtuous cycle ensures synaptic activity and antioxidant protection. Dysfunctions in either of these functions have negative effects and are implicated in several neurodevelopmental disorders, particularly in schizophrenia but also in autism and mood disorders (149, 174, 253).

C. Oxidative stress and antioxidants in psychiatric disorders

Oxidative stress can be identified in patients by biochemical indicators of the extent of damage (89, 134, 283) or by glutathione brain imaging (353). ROS/RNS direct detection is usually not used in biomedical research (107). The biomarkers of oxidative stress generally used are the products of oxidation of proteins, amino acids, lipids or nucleic acids, and antioxidant defense enzymatic activities. The analysis of the published data, including meta-analyses, of biomarkers in peripheral tissues of patients with psychiatric disorders is frequently inconclusive regarding the oxidative stress status of these patients. This is related to drawbacks in the choice of biomarkers and in the detection methods (89, 134, 283). Biomarker detection is problematic; some methods are not specific, and others that are specific are too complex to use for clinical diagnostic. Efforts are being made to select biomarkers that can be measured easily and specifically and are good indicators of oxidative stress (89, 118). The measurement of brain glutathione *in vivo* using ^{1}H-MRS may also vary depending on the method used (353). Adding to these difficulties, other parameters, such as the length of disease and drug treatments, can add intricacy to the evaluation. Another important concern is that the activation of antioxidant protection in brain cells is different from other tissues and the correlation between peripheral and brain oxidative status is poorly known in health and disease conditions. However, this information is crucial for the selection of peripheral oxidative stress biomarkers that are predictors of disease. Regardless of all these obstacles, the combination of evidence obtained from peripheral tissues and central nervous system indicates the involvement of oxidative stress in autism, SZ, BD, and MDD (136, 143, 162, 353, 407, 413). Oxidative and antioxidant defense biomarkers were also reported in multiple animal models for these disorders and were reviewed recently by Smaga *et al.* (407). Hopefully, future studies using iPSC-derived cell models will also improve our understanding of the underlying mechanisms of ROS/RNS generation and detoxification in the pathophysiology of psychiatric disorders.

1. Autism spectrum disorder. A recent proposal to integrate the risk factors of ASD considers that genetic susceptibility and environmental factors may be linked by oxidative stress (279, 298). Multiple studies have shown the presence of molecules indicative of oxidation in blood samples of autistic patients (73, 117, 123, 162, 200, 225). In 2012, Frustaci *et al.* did a meta-analysis of 39 original reports that compared antioxidant biomarkers and confirmed a significantly lower level of GSH and GPX activity and higher level of GSSG in the plasma of fasting autistic children than in controls (136). The plasma decrease in GSH in autistic children was replicated in recent studies and is one of the most reproducible oxidative stress measures (332, 373).

Two studies reported the postmortem glutathione redox status in various regions of the brain of autistic patients compared with age-matched controls (67, 374). Chauhan *et al.* showed a reduction in glutathione antioxidant capacity, specifically in patients' temporal cortex and cerebellum, as evidenced by the increase in GSSG and the decrease in GSH, GSH/GSSG, and total glutathione (67). No difference was observed between autistic children and controls in the frontal, parietal, and occipital cortex regions (67). Interestingly, lipid peroxidation was detected in the same brain regions (68) and the activities of GPX and glutathione-*S*-transferase (GST) antioxidant enzymes were decreased in the cerebellum (162). In agreement with these data, Rose *et al.* also observed the increase in GSSG and the decrease in GSH and GSH/GSSG levels in young and adults with ASD (374). In addition, their results showed evidence of protein and DNA damage and chronic inflammation in those same regions of the brain using the biomarkers 3-nitrotyrosine, 8-oxo-deoxyguanine, and 3-chlorotyrosine, respectively. No alteration of glutathione metabolism was detected *in vivo* in the brain of adult patients using ^{1}H-MRS, but the imaged areas (basal ganglia, dorsomedial prefrontal cortex, dorsolateral prefrontal cortex, and dorsal anterior cingulate cortex) were not exactly the same as those analyzed earlier in postmortem samples (114, 120). The identification of genetic variation in several genes necessary for glutathione synthesis (glutamate-cysteine ligase [GCL] and cystathione gamma-lyase) and antioxidant glutathione-dependent pathways (GPX, GST, and GRX) that confer susceptibility to ASD supports the hypothesis that glutathione metabolism is disturbed in this disorder (44, 200, 308, 471, 479).

The rs2736654 SNP (C>A) in the *GLO1* gene that causes an Ala111Glu change in the enzyme was identified in 2004 as a risk factor for ASD (206). Barua *et al.* found that Glu-Glo1 enzyme activity is lower than the Ala-isoform and leads to accumulation of MG in lymphoblastoid cells (26). The association between *GLO1* variants was observed in a few of the following studies, but not all (138, 238, 362, 481). Since glutathione metabolism and *GLO1* are among the susceptibility genes for ASD, Maher proposed that this genetic vulnerability that affects redox status coupled with toxic diet-derived MG and AGEs may provide a link between oxidative stress, inflammation, and mitochondrial dysfunction and be the source of the neurodevelopmental and neuropathological changes in autistic brain (277).

The accumulated evidence pointing to oxidative stress as an important factor in the etiology of ASD raised the question of the potential therapeutic benefits of antioxidants. *N*-acetylcysteine (NAC) was tested in a pilot double-blind, randomized, placebo-controlled study and showed a reduction in irritability (173); however, these results were not replicated in recent clinical trials (98, 474). Nevertheless, another clinical trial showed that the association of NAC with risperidone was more efficient than risperidone alone in decreasing irritability in children and adolescents (148). A 3-month treatment with coenzyme Q_{10}, which is a component of the electron transport chain with antioxidant properties, improved behavior in ASD children (167). Other interesting

natural molecules tested in clinical trials with beneficial results in behavior and social interaction were sulforaphane and luteolin (404, 435), although the effect of these molecules may be more related to an adaptive response to stress than to antioxidant properties (55, 56). These studies showed that all these drugs are well tolerated and have no major adverse effects, suggesting that their use as supportive therapies may magnify the beneficial results of primary treatments.

2. Schizophrenia. Oxidative stress and inflammation are proposed to be at the center of SZ etiology, integrating genetic and environmental factors (such as prenatal infections, hypoxia at birth, and malnutrition) early in neurodevelopment and contributing to NMDAR hypofunction and onset of psychosis (25, 272, 306, 420). In 2013, a meta-analysis of 44 studies of oxidative stress markers in serum, plasma, and erythrocytes in patients with SZ or related psychotic disorders showed that the changes in specific parameters were largely correlated with the clinical status (128). Therefore, the authors described their findings as state markers, if symptom dependent, or as trait markers, if symptom independent. The levels obtained in cross-sectional studies support total antioxidant status, catalase, and plasma nitrite as state markers and red blood cells SOD as a trait marker for SZ (128). A recent review extensively lists the 100 studies that identified an association between oxidative stress and SZ (236). Glutathione levels were consistently decreased in peripheral samples, in cerebrospinal fluid, and in postmortem caudate nucleus and prefrontal cortex from drug-naive or treated patients compared with controls (108, 143, 236, 483, 486). *In vivo* measurements of brain GSH using ^{1}H-MRS gave mixed results, possibly related to the heterogeneity of symptoms and medications of the patients involved in these analyses (108, 287, 441, 478). Nonetheless, Matsuzawa *et al.* found a significant negative correlation between GSH levels in the posterior medial prefrontal cortex and the severity of negative symptoms in patients (287). The search for polymorphisms and CNVs in glutathione-antioxidant defense genes in worldwide populations also gave inconsistent results (72, 158, 286, 447). However, it was shown that specific trinucleotide polymorphisms in the *GCLC* gene, encoding the catalytic subunit of GCL, are more frequent in SZ patients and cause lower GCL expression and activity and a decrease in the total glutathione content (168). Interestingly, the GCL activity in patients' fibroblasts increases to lower levels than those observed in control cells after treatment with the oxidant tert-butylhydroquinone (168), suggesting that impaired glutathione synthesis may disturb the patient's cells redox status and be a risk factor for SZ (168, 447).

Deficits in fast-spiking parvalbumin-positive interneurons (PVIs) and impaired myelination are two pathological features of SZ that are believed to contribute to altered brain connectivity and psychotic symptoms (25, 174, 272, 420). A recent mechanistic hypothesis proposes that early-life NMDAR hypofunction, redox imbalance, and neuroinflammation converge to cause impaired development of oligodendrocytes and PVIs and dysfunction of the associated networks (25, 272, 420). Monin *et al.* demonstrated that glutathione is necessary for normal myelination and white matter maturation in the human and mouse prefrontal cortex (312). The GABAergic PVIs are crucial for the synchronization of pyramidal neurons firing during sensory and cognitive tasks. Animal studies using different models (such as genetic deficit of GSH synthesis or knockdown of the mitochondrial biogenesis regulator PGC-1α) showed that PVIs are particularly vulnerable to oxidative stress during the early phases of development that lead to long-term impairments in the prefrontal cortex (53, 61, 270). Cabungcal *et al.* showed that in a developmental SZ rodent model (neonatal ventral hippocampal lesions) antioxidant treatment with NAC of young and adolescent animals prevented the prefrontal cortex reduction in PVIs and the electrophysiological and behavior deficits (52). It was shown *in vitro* that the antipsychotic drugs clozapine and olanzapine have good antioxidant properties and ziprosidone, risperidone, quetapine, and haloperidol have reduced or no antioxidant activity (47, 382). However, there are no reports on the redox status of SZ patients treated specifically with clozapine or olanzapine.

The authors of a recent review of 22 randomized controlled trials on the effect of antioxidant add-on to antipsychotic therapy in adult SZ patients concluded that the results obtained were limited and that there was a need for larger trials and longer follow-up periods for evaluation of improvement of acute psychotic episodes and core symptoms and prevention of relapse (275). Nonetheless, from all the molecules tested (*Ginkgo biloba* extract, NAC, allopurinol, dehydroepiandrosterone, ascorbic acid, α-tocopherol, and selegiline), *G. biloba* extract and NAC gave promising results. Another review study of 29 clinical trials that tested NAC, several fatty acids, α-lipoic acid, ascorbic acid, α-tocopherol, and aspirin also revealed the promising effects of NAC (236). Unfortunately, according to the preclinical data obtained with animal models, the most beneficial temporal window for antioxidant treatment would be before psychotic symptoms appear, meaning before diagnosis.

3. Mood disorders. Oxidative stress and inflammation markers were reported for mood disorders in depression and manic phases in multiple studies and meta-analyses. A significant increase in lipid peroxidation, NO levels, and DNA/RNA damage was found in BD patients compared with controls, irrespective of disease phase and treatments, in 2 meta-analyses of 13 and 29 studies using peripheral and postmortem brain samples (15, 49). Other meta-analyses also identified lipid peroxidation and DNA damage increases in patients with depression (depressive symptoms, BD, and MDD) compared with controls (39, 266). Sowa-Kućma *et al.* compared seven immune and oxidative biomarkers in BD and MDD patients (in acute depressive or euthymic phase) and found no difference between the two pathologies (413). In addition, they showed that lipid peroxidation was significantly associated with immune activation and that it was a good predictor of mood disorders, atypical depression, melancholia, and suicidal thoughts (413). By contrast, another study showed a positive correlation between lipid peroxidation and anxiety, but not depression, in medication-free MDD patients (416). The SOD activity increased in medicated manic and depressed patients compared with euthymic patients and controls, suggesting that antioxidant defense may oscillate depending on the BD phase and independently of medication (13, 243).

Unlike ASD and SZ, where low glutathione levels are the most significant oxidative stress biomarkers, in BD and MDD only a few studies measured the glutathione redox status.

Total and GSH concentration was decreased and GSSG was increased in the plasma of medicated BD patients compared with healthy controls (372). A decrease in total plasma glutathione was also detected in the plasma of BD patients who had experienced at least one psychotic episode compared with healthy controls (329). In agreement with these observations, Gawryluk *et al.* found low levels of GSH and GSSG in postmortem samples of prefrontal cortex of BD patients compared with controls (143). In addition, the authors did not observe any change in the enzymes GCL, glutathione reductase, GPX, and GST of the glutathione-dependent antioxidant pathway (142, 143). *In vivo* ^{1}H-MRS studies were performed in young BD patients and revealed no change in GSH in several cortical regions relative to healthy controls (154, 245). However, low levels of GSH were detected by using ^{1}H-MRS in MDD patients compared with controls (402). Data are largely missing on oxidative stress evolution during progression of BD and MDD, but they seem to be reliably detected at later stages (14, 97, 154, 402). This finding distinguishes ASD and SZ from BD and MDD; for the former, oxidative stress is an important factor in the etiology of the disorders whereas for the latter it seems to be a secondary factor in the pathology.

Mood stabilizers and SSRIs have antioxidant properties. Several studies showed a decrease in redox biomarkers in cellular and animal models and in BD patients treated with Li and VPA (16, 32, 86, 273). However, the results reported for SSRIs effect in MDD patients are variable; some studies found antioxidant qualities (38, 224) and others not (139). A meta-analysis of five double-blind, randomized, placebo-controlled trials using NAC for depressive patients with diverse conditions concluded that there was an improvement in the symptoms (126). Another recent meta-analysis of randomized controlled trials assessed the efficacy and safety of adjunctive NAC, showing its usefulness in SZ but not in BD and MDD (496). Although the data obtained with classical antioxidant molecules are mainly unsatisfactory, recent studies showed that ketamine and minocycline, which interfere with glutamatergic neurotransmission, are promising drugs for treatment of depression (77). Interestingly, it has recently been shown that ketamine used in treatment-resistant depression affects energy metabolism and antioxidant capacity in the hippocampus of treated mice (467). Minocycline is an antibiotic that crosses the blood–brain barrier and has antioxidant and anti-inflammatory properties. The recent results of a pilot study suggest that minocycline treatment increases GSH levels in the brain of BD patients, reduces depression symptoms, and is well tolerated (322).

VI. Toward a Specific Pathophysiology for Individual Psychiatric Disorder

Mitochondrial dysfunction and impaired redox signaling are not specific to mental disorders but are also implicated in multiple disorders, such as diabetes mellitus and Parkinson's disease. In the case of these diseases, pancreatic β cells or dopaminergic neurons are affected. Thus, mitochondrial and redox impairment are not at all specific to any disease, but the affected cells are specific to each disorder. As mentioned earlier, alterations in mitochondrial bioenergetics and redox signaling are common features of the four psychiatric disorders, ASD, SZ, BD, and MDD. Although recent genetic, neuroimaging, and iPSC studies pointed out that these disorders share some common biological background, these disorders have been well characterized and have clinically distinctive features.

Why do these common cellular deficiencies in mitochondrial metabolism and redox regulation cause distinctive clinical features? We propose that: the timing of its role in the pathophysiology (such as early in life in ASD or aging in BD), the affected cell types (such as parvalbumin neurons in SZ), and the affected brain area (such as PVT or dorsal raphe in BD or MDD) by these deficiencies may be specific and contributing to each psychiatric disorder. The next step of research in this field would be the identification of the affected brain regions and cell types, and the timing of the mitochondrial and redox dysfunction in each of the psychiatric disorders.

VII. Concluding Remarks

The studies reviewed here aimed at describing recent views about the regulation pathways and mechanisms of mitochondrial bioenergetics in brain cells and at shedding light on the role of mitochondrial dysfunction and redox alterations in the pathophysiology of psychiatric disorders. From the data presented, it is clear that these dysfunctions are present in the patients and also suggest that they play a more prominent role in the development and progression of ASD and SZ than of BD and MDD.

The heterogeneity and spectral nature of psychiatric disorders lead frequently to results that lack specificity to make statistically significant conclusions with the risk of missing relevant features. The search for common biological defects may be a way to circumvent this obstacle and give momentum to research in the field to achieve better knowledge, better models, and better therapies for psychiatric disorders.

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Abbreviations Used

AGE = advanced glycation end-product
AKT = protein kinase B
ANLS = astrocyte-neuron lactate shuttle
ASD = autism spectrum disorder
ATP = adenosine triphosphate
BA = Broadman area
BD = bipolar disorder
BMAL1/ARNTL = aryl hydrocarbon receptor nuclear translocator like
Ca^{2+} = calcium
CDK5 = cyclin-dependent kinase 5
CI = NADH:ubiquinone oxidoreductase
CII = succinate:ubiquinone oxidoreductase
CIII = ubiquinol-cytochrome *c* oxidoreductase
CIV = cytochrome *c* oxidase
CLOCK = clock circadian regulator
CNV = copy number variant
CRY = cryptochrome
D-loop = mtDNA displacement loop
DISC1 = disrupted in schizophrenia 1
DRP1 = dynamin 1 like
E/I = excitation/inhibition
ER = endoplasmic reticulum
fMRI = functional magnetic resonance imaging
GABA = γ-aminobutyric acid
GAPDH = glyceraldehyde 3-phosphate dehydrogenase
GCL = glutamate-cysteine ligase
GLO = glyoxalase
GLUT = facilitated glucose transporter
GPX = glutathione peroxidase
GRX = glutaredoxin
GSH = reduced glutathione
GSSG = oxidized glutathione
GST = glutathione-*S*-transferase
GWAS = genome-wide association study
$HO^{\bullet}$ = hydroxyl radical
H_2O_2 = hydrogen peroxide
Hsf1 = heat shock factor 1
IMM = inner mitochondrial membrane
iPSC = induced pluripotent stem cell
KEAP1 = Kelch-like ECH-associated protein 1
Li = lithium
LONP1 = Lon peptidase 1
MDD = major depressive disorder
MFN = mitofusin
MG = methylglyoxal
MICOS = mitochondrial contact site and cristae organizing system
MRS = magnetic resonance spectroscopy
mtDNA = mitochondrial DNA
mTOR = mammalian target of rapamycin
mtSSB = single-stranded DNA binding protein
NAC = *N*-acetylcysteine
NAD^+ = nicotinamide adenine dinucleotide
NADPH = nicotinamide adenine dinucleotide phosphate
NDUFS1 = NADH:ubiquinone oxidoreductase core subunit S1
NMDAR = *N*-methyl-D-aspartate receptor or glutamate receptor
NO = nitric oxide
NOX = NADPH oxidase
NPAS2 = Per-Arnt-Sim domain-containing protein 2
NR1D = nuclear receptor subfamily 1 group D
Nrf2 = nuclear factor, erythroid 2 like 2
$O_2^{\bullet-}$ = superoxide
OMM = outer mitochondrial membrane
$ONOO^-$ = peroxynitrite
OPA1 = mitochondrial dynamin-like GTPase or optic atrophy protein 1
PDH = pyruvate dehydrogenase complex
PER = period

Abbreviations Used (Cont.)

PET = positron emission tomography
PI3K = phosphoinositide-3-kinase
PFKFB3 = 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase
PGC-1α = peroxisome proliferator-activated receptor γ coactivator 1α
PKA/C = protein kinases A/C
PKM = pyruvate kinase
POLG = DNA polymerase γ
PPP = pentose phosphate pathway
PVI = parvalbumin-positive interneuron
PVT = paraventricular thalamic nucleus
RNS = reactive nitrogen species
ROR = retinoic acid receptor-related orphan receptors
ROS = reactive oxygen species
SCN = suprachiasmatic nucleus
SGAs = second-generation antipsychotics
shRNA = short-hairpin mediated RNA interference
SIRT = sirtuin
SNP = single-nucleotide polymorphism
SOD = superoxide dismutase
SSRI = selective serotonin reuptake inhibitor
SZ = schizophrenia
TCA = tricarboxylic acid
TFAM = mitochondrial transcription factor A
VPA = valproic acid