Πανεπιστήμιο Ιωαννίνων
Σχολή Επιστημών Υγείας
Ιατρικό Τμήμα

Μεταπτυχιακό Πρόγραμμα «Βασικές Βιοϊατρικές Επιστήμες (ΒΒΕ)»

Μεταπτυχιακό Δίπλωμα Ειδίκευσης (ΜΔΕ)

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Η έγκριση της

Μεταπτυχιακού Διπλώματος Ειδίκευσης από το Τμήμα Ιατρικής του Πανεπιστημίου Ιωαννίνων δεν υποδηλώνει αποδοχή των γνωμών του συγγραφέα Ν. 5343/32, άρθρο 202, παράγραφος 2 (νομική κατοχύρωση του Ιατρικού Τμήματος)

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Abbreviations

ACC	Anterior cingulate cortex
ATP	Adenosine triphosphate
Bad	BCL2 associated agonist of cell death
Bak	Bcl-2 homologous antagonist/killer
Bax	BCL2 associated X, apoptosis regulator
Bcl-2	B-cell lymphoma 2
Bcl-xL	B-cell lymphoma-extra large
BLA	Basolateral amygdala
Bnip3	BCL2 interacting protein 3
BNST	Bed nucleus of the stria terminals
CAPS	Clinician administered PTSD scale
CMS	Chronic mild stress
CSDS	Chronic social defeat stress
DISC1	Disrupted in schizophrenia 1
DNA	Deoxyribonucleic acid
Drp1	Dynamin-related protein 1
ER	Endoplasmic reticulum
ETC	Electron transport chain
Fis1	Mitochondrial fission 1
GTP	Guanosine triphosphate
IMM	Inner mitochondrial membrane
KO	Knock out
LC3	Microtubule-associated protein 1A/1B-light chain 3
LH	Learned helplessness
l-OPA1	long-OPA1
Mff	Mitochondrial fission factor
Mfn1	Mitofusin 1
Mfn2	Mitofusin 2
MiD49	Mitochondrial dynamics protein 49
MiD51	Mitochondrial dynamics protein 51
Miro1	Mitochondrial rho GTPase 1
mPTP	Mitochondrial permeability transition pore
mtDNA	Mitochondrial DNA
mtDNAcn	Mitochondrial DNA copy number
MTPF1	Mitochondrial fission process protein 1
NAc	Nucleus accumbens
NRF1	Nuclear respiratory factor 1
NRF2	Nuclear respiratory factor 2
OMA1	Metalloendopeptidase OMA1, mitochondrial
OMM	Outer mitochondrial membrane
OPA1	Optic atrophy 1
OXPHOS	Oxidative phosphorylation
p62/SQSTM1	Sequestosome-1

PARL	Presenilin-associated rhomboid-like protease
PBMCs	Peripheral blood mononuclear cells
PFC	Prefrontal cortex
PGC-1a	Peroxisome proliferator-activated receptor-gamma coactivator
Pink1	PTEN induced kinase 1
PTSD	Post-traumatic stress disorder
ROS	Reactive oxygen species
rRNA	Ribosomal RNA
s-OPA1	Short-OPA1
TFAM	Transcription factor A, mitochondrial
TOM	Translocase of the outer mitochondrial membrane
tRNA	Transfer-RNA
TSPO	Translocator protein
VDAC1	Voltage dependent anion channel 1
WHO	World health organization
YME1L	ATP-dependent zinc metalloprotease YME1L

**In this thesis, gene names are written with capital letters while protein names are written with small letters with the first one capital (*e.g. MFN2 gene, Mfn2 protein)

Chapter I

Psychiatric Disorders & Mitochondria

Psychiatric Disorders

Psychiatric disorders affect millions of people worldwide influencing their emotions, behavior, mood and their quality of life (Ferrari, 2022). Therefore, exploring causal factors for psychiatric disorders is pivotal for global health. Despite the advanced knowledge, tools and strategies for therapy that have been developed for psychiatric disorders, mental health parameters deteriorate from year to year. This is indicated by a recent epidemiologic study of Ferrari et al. who showed a 48.1% increase of mental disorders cases between 1990 and 2019 globally (Ferrari, 2022).

Genetic and environmental factors affect the occurrence of psychiatric disorders (Assary et al., 2018). In particular, many susceptibility genes with small effects have been found to confer risk for psychiatric disorders, yet the interaction among these genes as well as gene-environment interactions are not fully elucidated ("Genetics of Psychiatric Disorders," 2005). From pertinent environmental factors, stress exposure is the most studied parameter contributing to psychopathology (Davis et al., 2017). The modern, high demanding and stressful lifestyle adds a greater risk to the occurrence of mental disorders. Numerous animal models of stress-induced, psychiatric-related phenotypes have been developed and studied to investigate the molecular mechanisms of psychopathology (Wegener & Neigh, 2021). However, their molecular underpinnings are widely unexplored. Moreover, there is an emerging need for new therapeutic treatments to increase the life quality of people suffering from such disorders. One such promising yet widely unexplored target is the mitochondrion.

Mitochondria

Mitochondria are subcellular double membrane organelles that carry a varying number of copies of their own circular double-stranded mitochondrial DNA (mtDNA) (***Figure 1***). In humans, mtDNA is a circular, double-stranded DNA with 37 genes encoding (Taanman, 1999):

- 13 protein subunits of respiratory chain complexes I, III, IV and V
- 22 mitochondrial tRNAs
- 12S and 16S rRNA

Mitochondrial proteins are predominantly encoded by the nuclear genome and then delivered to the mitochondrion (Javadov et al., 2020).

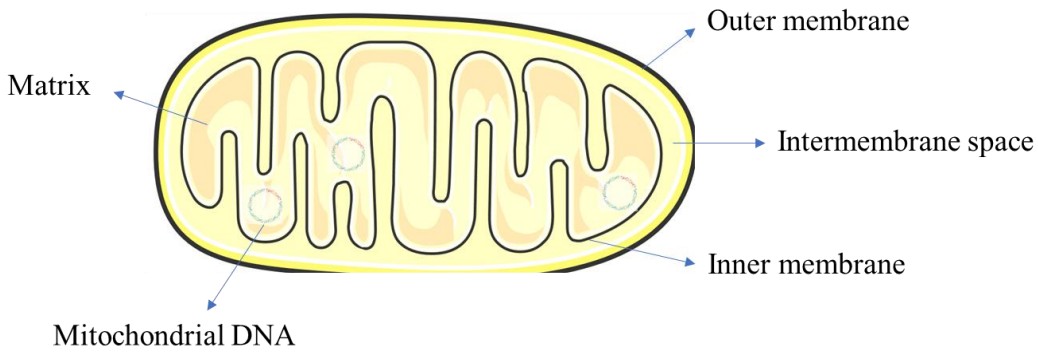

***Figure 1*: The mitochondrial structure**. *Schematic representation of a mitochondrion including: the inner membrane, the outer membrane, the intermembrane space and the matrix. The copies of mtDNA are located in the matrix. (Figure was generated using bioicons)*

Mitochondria perform a plethora of functions in the cell as they orchestrate cell metabolism, redox status and calcium buffering (Spinelli & Haigis, 2018). In the core of mitochondrial functions is the energy production, as mitochondria are typically referred as the "powerhouses of the cell". Energy production depends on the process of oxidative phosphorylation (OXPHOS) that is closely related with the electron transport chain (ETC) and the citric acid cycle (also known as Krebs cycle). Notably, OXPHOS produces reactive oxygen species (ROS) as by-products that are mainly responsible for oxidative stress. Increased oxidative stress results in oxidation and damage of lipids, proteins and DNA that in turn affects cell viability. Moreover,

mitochondria respond to the energy and metabolic demands of the cell by changes in their number, shape/size and distribution via mitochondrial dynamics processes that are discussed in detail below (see Chapter II).

The brain has high energy requirements and thus it is highly dependent on mitochondrial energy production (Rango & Bresolin, 2018). Therefore, the role of mitochondria in psychiatric disorders is an emerging issue under investigation (Giménez-Palomo et al., 2021). An introduction on the global prevalence and the basic knowledge on psychiatric disorders as well as the current view on mitochondrial contribution to the etiology of each of these disorders are discussed below. In particular for this thesis, considered psychiatric disorders include bipolar disorder, schizophrenia, anxiety disorders, depression and post-traumatic stress disorder.

Bipolar Disorder

Forty-five million individuals suffer from bipolar disorder worldwide (James et al., 2018). Bipolar disorder is formerly known as manic depression and bipolar disorder patients suffer from mood disturbance episodes characterized by periods of depression and periods of high mood (mania) (Anderson et al., 2012). Mood stabilizers, like lithium, are typically used to control the symptomatology of bipolar disorder and several pieces of evidence reviewed by Pereira et al. support that these medicines also affect (directly or indirectly) mitochondrial function (Pereira et al., 2018).

Mitochondrial alterations as well as upstream pathways that could impair mitochondrial function in bipolar disorder have already been reviewed (Clay et al., 2011; Machado et al., 2016). Importantly, there is an established link between bipolar disorder and aberrations in mitochondrial energy production via OXPHOS (Morris et al., 2017). It is reported that mitochondrial energy production is increased in mania phases and decreased in depression phases of patients suffering from bipolar disorder (Morris et al., 2017). Additionally, gene expression for subunits of the ETC appears to be reduced in the frontal cortex of individuals with bipolar disorder (Sun et al., 2006). Moreover, oxidative stress markers are increased in peripheral cells of individuals suffering from bipolar disorder compared to controls (Andreazza et al., 2008). Overall, dysregulated mitochondrial bioenergetics is a strong underlying molecular mechanism that plays a crucial role in the pathobiology of bipolar disorder.

Schizophrenia

According to the World Health Organization (WHO), 24 million individuals suffer from schizophrenia worldwide (World Health Organization, 2022). Patients with schizophrenia suffer from impaired reality perception and additional changes in behavior, such as delusions, hallucinations and negative emotions with high lifetime risk for suicide (Sher & Kahn, 2019). Moreover, current schizophrenia treatments are characterized by severe side effects and low efficiency (Patel et al., 2014).

The neurobiological basis of schizophrenia is closely related to mitochondrial deficits and several studies have already discussed this by reviewing a number of clinical and preclinical data (Flippo & Strack, 2017; Park & Park, 2012; Prabakaran et al., 2004; Roberts, 2017). Differential expression of mitochondria-related genes was reported in both prefrontal cortex (PFC) and hippocampus of patients suffering from schizophrenia compared to controls (Altar et al., 2005; Karry et al., 2004; Prabakaran et al., 2004). Interestingly, two schizophrenia candidate genes, Disrupted In Schizophrenia 1 (DISC1) and G72, are involved in mitochondrial functions that further support the implication of mitochondria in schizophrenia (Flippo & Strack, 2017). Filiou et al have found that G72/G30 transgenic mice, a mouse model of schizophrenia-like symptoms, show altered protein levels of mitochondrial and oxidative stress- related readouts compared to wild type mice (Filiou et al., 2012).

Anxiety Disorders

Anxiety disorders include a wide range of conditions such as generalized anxiety disorder, panic disorder, social anxiety disorder and phobias (National Institute of Mental Health, 2022). Individuals suffering from anxiety disorders present type-specific emotional and behavioral symptoms (Craske et al., 2011). Notably, every individual with an anxiety disorder struggles with persistent worry or fear. According to WHO, 264 million people globally suffer from anxiety disorders, with females being more vulnerable than males (World Health Organization, 2017). Current therapies for anxiety disorders are ineffective with low rates of treatment responders and severe side effects (Bystritsky, 2006; Garakani et al., 2020). Thus, the high prevalence of anxiety disorders requires the design of sufficient and personalized treatments.

Mitochondria have gained the attention in the neurobiological basis of anxiety during the last decade and the interplay of mitochondria and anxiety has been recently reviewed by Filiou and Sandi highlighting the significance of targeting mitochondria to relieve anxiety symptoms (Filiou & Sandi, 2019). Clinical and mostly several pre-clinical studies support the notion that mitochondrial dysfunction is a pathological factor for anxiety disorders. In a human cohort with panic disorder, altered expression of OXPHOS genes was observed in blood samples (Misiewicz et al., 2019). Mice of high anxiety related behavior show changes in the levels of protein and metabolites implicated in mitochondrial metabolism, import and OXPHOS (Filiou et al., 2011, 2014; Y. Zhang et al., 2011). Moreover, it has been shown that mitochondrial function in the nucleus accumbens of high anxiety-related behavior rats is implicated in the social ranking (Hollis et al., 2015). Therefore, these data pinpoint the modulatory role of mitochondrial pathways in anxiety.

Depression

Depression is a leading cause of disability and a major mental health problem that according to the WHO affects 5% of adults globally (World Health Organization, 2021). Individuals with depression experience severe negative emotional symptoms that disable them from feeling pleasure. Depression is also a major risk factor for suicide (Bachmann, 2018). Moreover, depression is highly comorbid with other psychiatric diseases and the available medication is very slow, as antidepressants take a long time to exert their therapeutic effects (J. Kim & Schwartz, 2020; Steffen et al., 2020).

Investigation of the mitochondria-related pathobiological basis and treatment strategies of depression is well-documented in several reviews (Allen et al., 2018; Bansal & Kuhad, 2016; Karabatsiakis & Schönfeldt-Lecuona, 2020; Rappeneau et al., 2020). Clinical studies support oxidative damage as a key feature of depression as many markers of oxidative stress appear to be differentially expressed in individuals suffering from depression (Rappeneau et al., 2020).

Post-traumatic stress disorder (PTSD)

According to the American Psychiatric Association (American Psychiatric Association, 2020), 3,5% of adults in the USA are affected by Post-Traumatic Stress Disorder (PTSD) every year. PTSD can be caused by exposure of an individual to a serious traumatic or threatening event with the individual struggling with emotional thoughts and flashbacks long after the end of the event. Moreover, symptomatology of PTSD can include negative mood and emotions, avoidance of situations or places or people who remind them the traumatic event as well as Intrusive memories over the traumatic experience (Bisson et al., 2015). Current treatment strategies to control the symptomatology of PTSD include psychological therapies or medicines and psychological therapies appear to be more effective than.

Studies in humans and rodents support a role of mitochondria in PTSD. Postmortem prefrontal cortex of individuals with PTSD show differential expression of genes related to mitochondrial dysfunction and OXPHOS compared to controls (Su et al., 2008). Moreover, mitochondria-related gene expression profiles are different in the amygdala of a rat model of PTSD compared to controls (H. Li et al., 2014).

Overall, recent literature indicates that mitochondrial functions and especially OXPHOS are implicated in the neurobiology of psychiatric disorders. However, the role of mitochondrial dynamics in the context of psychopathology remains elusive. To address this question, the molecular machinery of mitochondrial dynamics is discussed below (see Chapter II). In particular, in the next chapter we will summarize the molecular pathways involved in each of the mitochondrial dynamics processes, such as mitochondrial biogenesis, fission, fusion and mitophagy.

Chapter II

Mitochondrial Dynamics

The first observation on dynamic changes of the mitochondrial network was reported in the early 20th century by Margaret Reed Lewis and Warren Lewis who detected changes of mitochondrial shape and branching in tissue cultures of living cells, by the use of microscopy (Lewis & Lewis, 1915). Later on, a great deal of effort was made to understand the machinery involved in the processes of mitochondrial fission/fusion and how these dynamic changes shape mitochondrial function. Many years later, Chen et al discovered that two GTPase, Mitofusin 1 (Mfn1) and Mitofusin 2 (Mfn2), facilitate mitochondrial fusion in mammalian cells (Chen et al., 2003). Sidney Scott and Daniel Klionsky introduced the term “mitophagy” for the autophagic elimination of mitochondria in 1998 (Scott & Klionsky, 1998). The recruitment of the E3 ligase Parkin in damaged mitochondria to mediate mitophagy, in 2008, was a hallmark in the history of mitophagy research (Narendra et al., 2008).

Below, the processes of mitochondrial biogenesis, fission, fusion and mitophagy, as well as the molecular players involved in each category are summarized.

Mitochondrial biogenesis

Mitochondrial biogenesis is the process that leads to the generation of new mitochondria and aims to increase metabolic capacity of the cell. Mitochondrial biogenesis is achieved by self-replication of pre-existing mitochondria and not a *de novo* synthesis of new mitochondria. It is supported that this mechanism is closely related to the ancestry of mitochondria. According to the widely supported endosymbiosis hypothesis mitochondria originate from endosymbiosis of anaerobic prokaryotic organisms with eukaryotic cells. Therefore, mitochondrial biogenesis involves both nuclear and mitochondrial encoded genes. A well-known trigger for the induction of mitochondrial biogenesis in muscle is intense exercise (Jornayvaz & Shulman, 2010). In neurons, mitochondrial biogenesis is of major importance, as impaired biogenesis is implicated in neurodegeneration (Li et al., 2017). Whether mitochondrial biogenesis is only performed in the cell soma or also in the periphery of neurons, is under investigation and recent advances on this topic are reviewed elsewhere (Cardanho-Ramos & Morais, 2021).

The epicenter of the molecular machinery of mitochondrial biogenesis is the peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1a) protein (Gureev et al., 2019) (***Figure 2***). Upstream activators of PGC-1a are proposed to be the levels of ATP (Jäer et al., 2007; Ojuka et al., 2003). Mitochondrial biogenesis requires the expression of both nuclear DNA and mtDNA encoded genes (Hock & Kralli, 2009). Thus, PGC-1a activates the transcription factors known as nuclear respiratory factors 1 and 2 (NRF1 and NRF2). These factors increase the expression of nuclear-encoded mitochondrial genes. In turn, they activate, the mitochondrial transcription factor A (TFAM) that holds a major role in transcription and replication of mtDNA. Therefore, the expression of mitochondria-related genes encoded by both nuclear DNA and mtDNA is induced via PGC-1a. Moreover, knock out (KO) of the PGC-1a induces a significant decrease of mitochondria in neuronal dendrites and synapse number (Cheng et al., 2012).

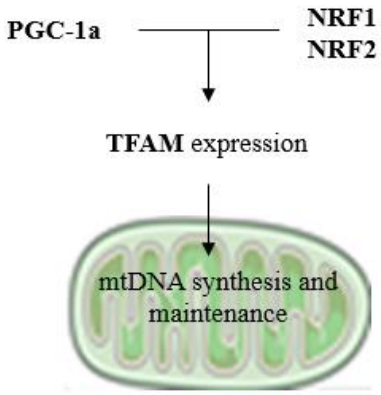

Figure 2: *Mitochondrial Biogenesis. PGC-1a together with NRF1 and NRF2 induce the expression of TFAM, which regulates on mtDNA synthesis and maintenance. (Figure was generated using bioicons)*

Mitochondrial Fission

Mitochondrial fission is the process by which a mitochondrion is divided into two daughter mitochondria, by scission. Mitochondrial fission is performed either when there is a need for more mitochondria or when there is need for elimination of damaged/ dysfunctional mitochondria, thus facilitating mitochondrial quality control, by leading towards mitophagy (Kleele et al., 2021; Youle & van der Bliek, 2012). A critical point to identify whether fission is related with mitochondrial biogenesis or mitophagy is the position of fission sites and, in particular, whether scission will occur in the midzone or in the periphery of the mitochondrion. Peripheral or midzone fission is achieved by the outer mitochondrial membrane (OMM)-bounded adaptors mitochondrial fission 1 (Fis1) or mitochondrial fission factor (Mff) proteins, respectively. This defines whether the process of mitochondrial fission will produce two healthy/functional mitochondria or one functional and one defective mitochondrion that would be eliminated by the process of mitophagy, respectively (Kleele et al., 2021).

Increased levels of mitochondrial fission are implicated in the pathobiology of Huntington's disease and modulation of fission is a suggested therapeutic strategy for this disorder (Reddy, 2014). Furthermore, accumulating data from the literature support that dynamin-related protein 1 (Drp1), a GTPase and key modulator of fission, plays a role in the normal neuronal development (Flippo & Strack, 2017; Wakabayashi et al., 2009).

The fission machinery and the processes of OMM and inner mitochondrial membrane (IMM) fission are summarized below (***Figure 3***):

1. *Determination of mitochondrial fission sites by the endoplasmic reticulum (ER)-mitochondria contact sites*

   Mitochondria-ER contact sites are crucial in the initiation of mitochondrial fission (Friedman et al., 2011). These sites mark the region where mitochondrial scission will occur via constriction mediated by the cytoskeleton and actin remodeling proteins that harbor on the OMM and ER.

2. *Recruitment of cytosolic protein Drp1 on the OMM*

   The key step for mitochondrial fission is the recruitment of the Drp1 from the cytosol on ER-mitochondria contact sites (Otera et al., 2013). For this, Drp1 binds to OMM proteins and not directly to the phospholipids of the OMM (Gandre-Babbe & van der Bliek, 2008). Such OMM proteins are Mff, mitochondrial dynamics proteins 49 and 51 (MiD49 and MiD51). On these sites, Drp1 accumulates, forms ring-like structures and GTP hydrolysis drives conformational changes of the ring-like structures to facilitate fission. Fis1 acts as an adaptor of Drp1. However, in mammals Fis1 has been suggested to have a role in mitophagy after fission on the peripheral mitochondrial zone (Z. Zhang et al., 2019) and to inhibit fusion (Yu et al., 2019).

3. *Mitochondrial fission process protein 1 (MTPF1) and replicating mtDNA have a potential role on the IMM fission*

   Less is known about fission of the IMM. It is proposed that fission sites of the IMM are marked by the replicating mtDNA (Yan et al., 2019). An IMM protein known as mitochondrial fission process protein 1 (MTPF1) is supported to have a role in IMM fission but its complete function during fission is not clear yet (Tondera et al., 2005)

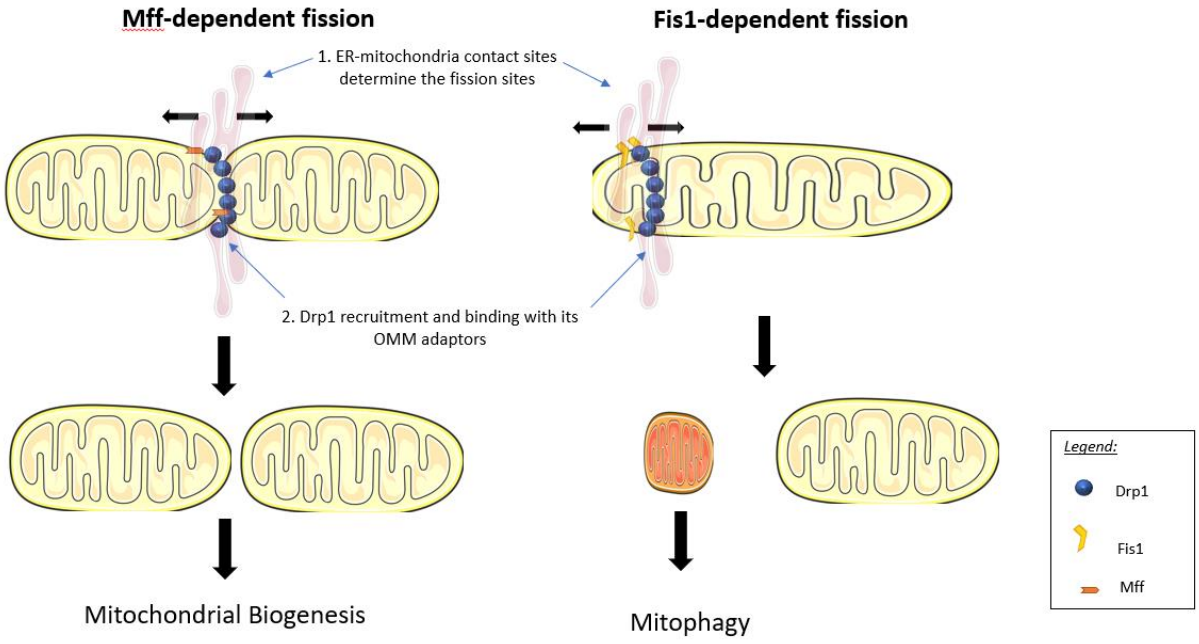

Figure 3: *Mitochondrial Fission. Midzone fission is mediated by Mff and produces two healthy daughter mitochondria (left panel). Peripheral fission is mediated by Fis1 and produces one healthy and one dysfunctional mitochondrion that would be eliminated via mitophagy (right panel). ER-mitochondria contact sites, as well as Drp1 recruitment are essential for both midzone and peripheral fission. (Figure was generated using bioicons)*

Mitochondrial Fusion

Key proteins of mitochondrial fusion are the dynamin related GTPases: Mfn1, Mfn2 and the optic atrophy 1 (Opa1) (Song et al., 2009; Tilokani et al., 2018). Both Mfn1 and Mfn2 are located in the OMM. Opa1 resides in the IMM. Mitochondrial fusion is a quality control mechanism which is involved in fixing damaged mitochondria. During mitochondrial fusion, a damaged/dysfunctional mitochondrion is fused with a functional mitochondrion in order to elevate energy production (in the form of ATP) to respond to cellular metabolic demands (Youle & van der Bliek, 2012).

Mfn2 plays a protective role against neurodegeneration in hippocampal and cortical neurons (Han et al., 2020) as well as in Purkinje neurons of the cerebellum (Chen et al., 2007). Moreover, Mfn2 knock out mice display impaired mitochondrial transport in the axons of

dopaminergic neurons that project to the striatum and in turn abnormal axonal development (Lee et al., 2012). Opa1 has a role in neurodegenerative and neurodevelopmental events; a wide variety of mutations in the Opa1 gene lead to the neuropathy named Autosomal Dominant Optic Atrophy (Alexander et al., 2000; Weisschuh et al., 2021) and in rat primary cortical neurons Opa1 deficiency results in perturbations in mitochondrial function, distribution, synaptic maturation and dendritic outgrowth (Bertholet et al., 2013).

The two major steps for mitochondrial fusion include (***Figure 4***):

A. *Fusion of the OMMs of the two for "fusion-candidate" mitochondria is mediated by Mfn1 and Mfn2*

   Mfn1 and Mfn2 that are located on the OMM, interact as homo- or hetero-complexes in order to mediate the fusion of the OMM (Chen et al., 2003). Interaction between mitofusins increases the contact area of the fusion-candidate mitochondria and GTP hydrolysis drives conformational changes of mitofusins to promote the fusion of the OMM (Chen et al., 2003).

   Despite the fact that both Mfn1 and Mfn2 display crucial roles in mitochondrial fusion, it has been reported that Mfn2 has a wider repertoire of functions. Mfn2 plays additional roles in ER-mitochondria tethering (Han et al., 2021), cell metabolism (Emery & Ortiz, 2021), mitophagy and apoptosis (Joaquim & Escobar-Henriques, 2020). Therefore, function and dysfunction of mitofusins is a current topic under investigation in order to disentangle disease-pertinent molecular mechanisms (Dorn, 2020).

B. *Fusion of the IMMs is mediated by Opa1*

   Opa1 is a dynamin-related GTPase located in the OMM. Thus, GTP hydrolysis promotes conformational changes of Opa1 to mediate fusion of the IMM. Opa1 can undergo post-transcriptional and post-translational modification that define its maturation and activities. The uncleaved form of Opa1 protein is called long-Opa1 (l-Opa1). In yeast and mammalian cells, cleavage of the N-terminal of Opa1 by the metallopeptidases Oma1 and Yme1l, produce the cleaved form called short-Opa1 (s-Opa1). It has been proposed that l-Opa1 is implicated in the fusion of IMM while the s-Opa1 is fission-related, however the balanced levels of both forms possess a functional role during fusion and mitodynamics (Ge et al.,

2020; Sabouny & Shutt, 2020). The function of Opa1 depends on Mfn1 and not Mfn2 (Cipolat et al., 2004); Overexpression of Opa1 in mouse embryonic fibroblasts can induce fusion in double KO Mfn2 cells but not in double KO Mfn1 cells.

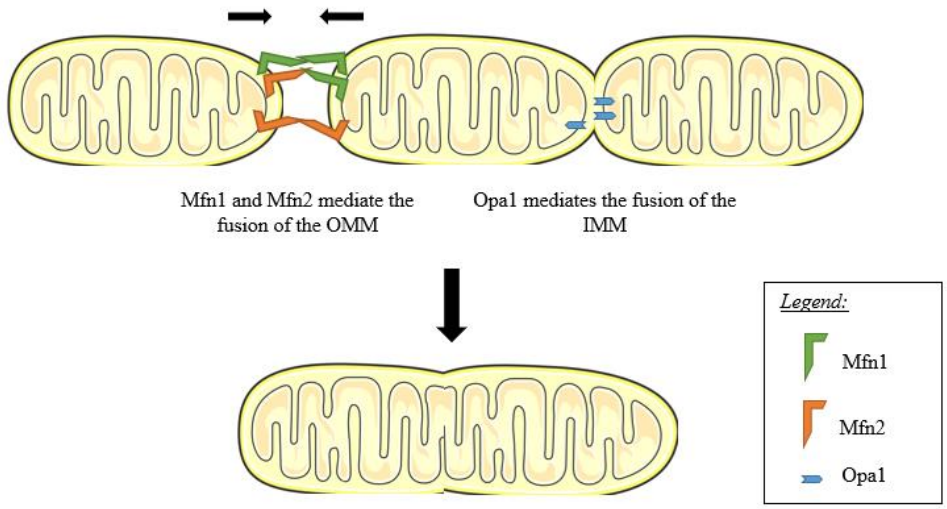

Figure 4: ***Mitochondrial Fusion****. Mitochondria that are to be fused, come in a close proximity and the OMM-bounded Mfn1 and Mfn2 interact as homo- or hetero-dimers to facilitate the fusion of the OMM. Fusion of the IMM is mediated by Opa1. (Figure was generated using bioicons)*

Mitophagy

Mitophagy is a mitochondrial quality control mechanism and mitochondrial removal is operated by selective autophagic death (Ng et al., 2021). Mitophagy facilitates the elimination of dysfunctional and or damaged mitochondria in order to avoid bioenergetic aberration and cell death. In neurons, impaired mitophagy is implicated in neurodegeneration as several studies support impaired mitophagy as a causal pathobiological factor in neurodegenerative disorders. For instance, mutations in Pink1 or Parkin are associated with Parkinson's Disease (Cookson, 2012; Ishihara-Paul et al., 2008). In their review, Swerdlow and Wilkins discuss the role of mitophagy in neurodegenerative diseases and mitophagy-targeted therapy (Swerdlow & Wilkins, 2020).

Several pathways for mitophagy have been proposed (Onishi et al., 2021). The best-studied is the ubiquitin-dependent Pink1/Parkin mitophagy pathway. Each step in this process is discussed below (***Figure 5***).

1. *Mitochondrial depolarization*

   Loss of mitochondrial polarity of defective mitochondria

2. *Pink1 self-activation*

   Pink1 is a nuclear-encoded mitochondrial serine/threonine kinase. In healthy mitochondria, Pink1 protein levels are strictly regulated via degradation; Pink1 is imported to the mitochondrion via the translocase of the outer mitochondrial membrane (TOM) complex. In the IMM, presenilin-associated rhomboid-like protease (PARL) mediates the degradation of Pink1 in order to keep its levels low (Jin et al., 2010).

   Under mitochondrial depolarization, the import of Pink1 in the mitochondrion is arrested. Pink1 accumulates on the OMM, forms a complex with TOM and as a dimer self-phosphorylates and in turn activates (Lazarou et al., 2012; Rasool et al., 2022)

3. *Pink1-mediated activation of Parkin*

   Parkin is an E3 ubiquitin ligase with cytosolic distribution in a self-inhibited form. When Pink1 is activated, it facilitates the activation of Parkin *via* phosphorylating its ubiquitin-like domain (Caulfield et al., 2014). Another proposed mechanism supports that Pink1 before its degradation interacts with Parkin in the cytosol leading to Parkin's inhibition (Fedorowicz et al., 2014)

4. *Ubiquitinoylation of OMM proteins via Parkin*

   The active form of Parkin is recruited to the target mitochondrion and ubiquitinylates many proteins of the OMM including Mfn1, Mfn2, mitochondrial Rho GTPase 1 (Miro1) and voltage dependent anion channel 1 (VDAC1) (Scarffe et al., 2014). This serves as a signal for autophagic death of the ubiquitin-coated mitochondrion.

5. *Phosphorylation of Parkin's substrates by Pink1*

   Pink1 on its turn phosphorylates the ubiquitins on the OMM proteins, resulting in a positive feedback loop (Scarffe et al., 2014).

6. *Autophagosome biogenesis and selective engulfment of the targeted mitochondrion*

   Autophagosomes are membrane-based organelles that mediate autophagy. A highly coordinated repertoire of proteins is involved in the formation of autophagosome (Nakatogawa, 2020), with microtubule-associated protein 1A/1B-light chain 3 (LC3) that holding a key role and being a common marker in the biogenesis of the autophagosome (Nakatogawa, 2020; Tanida et al., 2008) Autophagy adaptors act as platforms for the binding of phagophore on the surface of the targeted for autophagy mitochondrion (Heo et al., 2015). These adaptors are recruited in a Pink1/Parkin-related manner and they contain two domains: (i) the ubiquitin-associated domain that binds to the ubiquitin chains of the OMM proteins, (ii) the LC3-interacting domain that binds to the LC3 of the autophagosome. The formed structure that consists of an engulfed damaged mitochondrion by autophagosome is commonly referred as “mitophagosome” in the literature.

7. *Formation of autophagolysosome*

   Finally, the autophagosome that engulfed the damaged mitochondrion is fused with lysosomes. In mammals this is mediated by the interaction of protein that localize on the surface of autophagosome and lysosomes respectively (Nguyen et al., 2016).

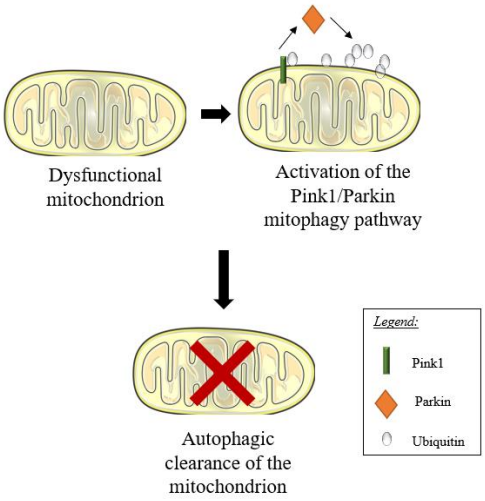

Figure 5: ***Mitophagy****. In dysfunctional mitochondria, Pink1 import into the mitochondrion is arrested. Thus, Parkin is activated and ubiquitinylates OMM-bounded proteins that act as the signal for the selective autophagic death of the mitochondrion. (Figure was generated using bioicons)*

Overall, as mitochondria are in charge of the energy production and numerous fundamental cell functions, a healthy mitochondrial population should be strictly controlled. This is achieved by the highly coordinated processes of mitochondrial dynamics, which are discussed above.

The evolving literature and emerging interest on impaired mitochondrial turnover and dynamics in disease, brings to the light the need to unravel the implicated molecular mechanisms and address how dysfunction or alterations in these processes may contribute to disease pathobiology (El-Hattab et al., 2018; Yapa et al., 2021). In particular, the role of mitochondrial dynamics has already been discussed in neurogenesis (Belenguer et al., 2019), neurodegeneration (Yang et al., 2021) and neuroinflammation (de Oliveira et al., 2021). In psychiatry though, additional efforts are needed to elucidate the contribution of mitochondrial dynamics in the underlying pathobiology and, therefore, to reveal new candidate biomarkers for diagnosis and therapeutic management of psychiatric disorders. The current clinical and preclinical literature on whether and how mitochondrial dynamics are impaired in psychiatric disorders is summarized below.

Chapter III

Exploring mitochondrial dynamics in neuropsychiatric disorders

The psychiatric disorders that are discussed in this review are bipolar disorder, schizophrenia, anxiety disorders, depression and PTSD. In our analysis we considered published papers both on patient cohorts and animal-models, measuring mitochondrial dynamics-related parameters including:

(i) protein or mRNA levels of genes related to mitochondrial dynamics,

(ii) mitochondrial morphology, number or distribution,

(iii) mtDNA copy number

in the brain or in peripheral material of individuals suffering from psychiatric disorders or animal models of the aforementioned disorders vs. controls. In vitro studies, as well as drug-studies investigating medication effects on mitochondrial dynamics were excluded**.**

Bipolar Disorder

Brain tissue

Investigation of mitochondrial morphology revealed differences in the brain of patients suffering from bipolar disorder vs. controls (Cataldo et al., 2010). Postmortem PFC neurons from the bipolar disorder group showed an increased number of mitochondria of smaller size, but no cellular distribution differences, compared to the control group (Cataldo et al., 2010). Furthermore, the authors suggested that overcoming the pitfalls of this study, including PFC-specific analysis, unrecorded medication history and the small number of participants, would contribute towards a better characterization of mitochondrial network changes in the brain of bipolar disorder patients (Cataldo et al., 2010).

Considering that mitochondrial dynamics regulate the shape and morphology of the mitochondrion (Yu et al., 2020), a later study investigated the levels of mitochondrial dynamics-related proteins, in post-mortem brains of bipolar disorder patients vs. controls (Rosenfeld et al., 2011). In particular, the authors found no differences in the protein levels of PFC specimens for the fusion and fission-related proteins tested, including Opa1, Mfn1 and Drp1, between the two groups (Rosenfeld et al., 2011).

It is suggested that oxidative damage leads to the activation of apoptosis which can result in the morphological abnormalities that shape bipolar disorder brain pathobiology (Gigante et al., 2011). Notably, there is an interplay between apoptotic processes related to mitochondria and bipolar disorder (Kim et al 2010); Postmortem PFC analysis of bipolar disorder patients showed reduced levels of the anti-apoptotic Bcl-2 expression, while the expression of the apoptosis-related Bax, Bad, caspase-3 and caspase-9 were increased, in both protein and mRNA levels compared to the control group (Kim et al. 2010).

Table 1: Included studies on postmortem human brain and mitochondrial dynamics in bipolar disorder.

Sex	**Brain region**	**Mitochondrial dynamics**						**Citation**
		Biogenesis	**Fission**	**Fusion**	**Mitophagy**	**Morphology/ Distribution**	**mtDNAcn**	
m/f	PFC					↑ number of small mt ─mt distribution		(Cataldo et al., 2010)
m/f	PFC		─Drp1●	─Opa1● ─Mfn1●				(Rosenfeld et al., 2011)

(●protein levels, m:male, f:female, PFC: prefrontal cortex, mt: mitochondria, mtDNAcn: mitochondrial DNA copy number, ↑: elevated in the psychiatric disorder group vs. the control group, ↓: reduced in the psychiatric disorder group vs. the control group, ─ :no differences between the psychiatric disorder group vs. the control group)

Peripheral material

Studies on mitochondrial morphology and distribution from lymphoblasts of individuals suffering from bipolar disorder, have generated conflicting results (Cataldo et al. 2010; Rosenfeld et al. 2011). Fibroblasts and lymphoblastoids from bipolar disorder patients show an increased number of ring- and cup-shaped mitochondria and higher mitochondrial density closer to the nuclear envelope -which gradually decreased moving from the nucleus toward the cell periphery- than that of the control group (Cataldo et al., 2010). Thus, the authors suggest that the observed atypically shaped and distributed mitochondria in peripheral cells of individuals with bipolar disorder can be indicative of increased oxidative stress or a transient remodeling of their structure, in order to respond to the energy demands of the cell (Cataldo et al., 2010; Liu & Hajnóczky, 2011). However, another study published a year later (Rosenfeld et al., 2011), did not confirm these results in lymphoblastoids of another bipolar disorder cohort, as no differences in the structure and connectivity were observed in the bipolar disorder cohort compared to controls. Remarkably, Rosenfeld et al, suggested that the discrepancy between their results with those of Cataldo et al., could lie to differences in the imaging analysis process (Rosenfeld et al., 2011).

Peripheral blood mononuclear cells (PBMCs) from individuals suffering from bipolar disorder showed differences in mRNA and protein levels of genes related to apoptosis and mitochondrial dynamics compared to controls (Scaini et al. 2017). Samples from individuals suffering from bipolar disorder showed lower protein levels of anti-apoptotic factors (Bcl-xL, Bcl-xL/Bak dimer and surviving), yet higher levels of the active form of the pro-apoptotic protein, caspase-3, compared to the control group. Intriguingly, protein and mRNA levels of key players of mitochondrial fusion, such as Mfn2 and Opa1, were increased, while the levels of the fission regulator Fis1, were significantly decreased in the bipolar disorder compared to the control group. Notably, the levels of Opa1 and Fis1 negatively correlated with the protein levels of caspase-3 and Bcl-xL, respectively. Furthermore, the levels of fusion-related protein, Mfn2, positively correlated with the levels of anti-apoptotic dimer Bcl-xL/Bak (Scaini et al. 2017). Insufficient expression of fusion-related proteins can result in the activation of apoptotic pathways (Olichon et al., 2003) and excessive fission induces mitochondrial fragmentation (Westermann, 2010). Therefore, Scaini et al, suggest that the imbalance of mitochondrial dynamics towards fission and the observed enhanced protein levels of pro-apoptotic proteins, point towards mitochondrial dysfunction as a

mechanism implicated in bipolar disorder pathobiology (Scaini et al. 2017). Overall, the authors report mitochondrial fragmentation and activation of apoptosis in bipolar disorder (Scaini et al. 2017).

The involvement of fission/fusion imbalance towards fission and apoptotic pathways in the pathomechanisms of bipolar disorder gives rise to the question: *Is mitophagy affected in bipolar disorder*? Damaged mitochondria are depolarized and eliminated through mitophagy mediated by the Pink1-Parkin pathway (Kornmann, 2014). PBMCs from patients suffering from bipolar disorder exhibited alterations in the expression of mitophagy-related proteins, both in mRNA and protein levels, compared to controls (Scaini et al. 2019). The mRNA and protein levels of the mitophagy-related Parkin and the autophagy-related p62/SQSTM1 and LC3 were decreased in the PBMCs of bipolar disorder patients compared to the control group. Yet, mRNA levels of mitophagy (Pink1) and autophagy (Beclin-1 and Bnip3) players did not differ significantly between the two groups. Moreover, the mRNA and protein levels of TSPO and VDAC, two components of the mitochondrial permeability transition pore (mPTP), were found to be significantly higher in bipolar disorder than in the control group and their expression levels negatively correlated with those of Parkin and p62/SQSTM1 proteins. This negative correlation can be justified considering that TSPO and VDAC induce ROS-dependent inhibition of mitophagy (Scaini et al. 2019).

Emerging evidence supports the significance of evaluating mtDNA copy number (mtDNAcn) in pathology (Filograna et al., 2021). Several studies have studied the association of bipolar disorder with changes in the mtDNAcn (Chang et al., 2014; de Sousa et al., 2014; Fries et al., 2017); However, these studies generated diverging results. The first study reported significantly decreased mtDNAcn in the leukocytes of individuals with bipolar disorder compared with those of the control group (Chang et al., 2014). The second study of de Sousa et al., investigated leucocyte mtDNAcn in a cohort of individuals suffering from bipolar disorder before (basal) and after lithium administration, compared to those of a control, age-matched group (de Sousa et al., 2014). The authors found no differences on the basal mtDNAcn between the bipolar disorder and the control group (de Sousa et al., 2014). In the third study, mtDNAcn from peripheral blood though, was significantly increased in the bipolar disorder group compared to the control group (Fries et al., 2017). However, in this study the authors did not include information on the

psychotropic medication received by the bipolar disorder group, a factor that may affect their results (Fries et al., 2017).

A meta-analysis of studies of mtDNAcn estimation in peripheral cells of bipolar disorder patients did not demonstrate significant association between mtDNAcn and bipolar disorder (Yamaki et al. 2018). Inclusion criteria for the meta-analysis were: (1) studies measuring mtDNAcn in peripheral cells of a bipolar disorder cohort and (2) comparing mtDNAcn of the bipolar disorder cohort with those of the control group. The authors found a significant ethnicity-related negative association between mtDNAcn and bipolar disorder: A sub-cohort meta-analysis of studies only in bipolar disorder patients of Asian descent reported significantly lower mtDNAcn in their peripheral cells compared to the peripheral cells of control individuals. Thus, the authors suggest that ethnicity may be another risk factor that should also be taken into consideration in the investigation of mitochondrial mechanisms involved in bipolar disorder (Yamaki et al. 2018). Moreover, it has been shown that the mood states of individuals suffering from bipolar disorder (euthymic, depressive, manic) may influence the mtDNAcn in leukocytes (Wang et al., 2018). Another study that investigated mtDNAcn in PBMCs of patients with bipolar disorder vs. controls was that of Scaini et al. (Scaini et al. 2017). Despite the fact that bipolar disorder patients showed altered expression of mitodynamics and apoptosis players (as discussed above), there was no significant differences on the mtDNAcn in the bipolar disorder group compared to the control group (Scaini et al. 2017).

Table 2: Included studies on human peripheral material and mitochondrial dynamics in bipolar disorder.

Sex	**Cell type**	**Mitochondrial dynamics**						**Citation**
		Biogenesis	**Fission**	**Fusion**	**Mitophagy**	**Morphology/ Distribution**	**mtDNAcn**	
m/f	Skin Fibroblasts and Lymphoblastoids					↑ number of ring- and cup-shaped mt ↑ mt density closer to the nucleus		(Cataldo et al., 2010)
m/f	Lymphoblastoids					─morphology and distribution		(Rosenfeld et al., 2011)
m/f	PBMCs		↑ Fis1 ◊●	↓Mfn2 ◊● ↓Opa1 ◊●			─mtDNAcn	(Scaini et al. 2017)
m/f	PBMCs				↓Parkin◊● ─Pink1◊ ↓p62/SQSTM1◊● ↓LC3◊● ─Beclin1◊ ─Bnip3◊ ↑ TSPO◊● ↑ VDAC◊●			(Scaini et al. 2019)
m/f	PBMCs						─mtDNAcn	(Yamaki et al., 2018)

Sex	Cell type	Mitochondrial dynamics						Citation
		Biogenesis	Fission	Fusion	Mitophagy	Morphology/ Distribution	mtDNAcn	
m/f	Leukocytes						─mtDNAcn	(de Sousa et al., 2014)
m/f	Leukocytes						↓mtDNAcn	(Chang et al., 2014)
m/f	Peripheral blood						↑mtDNAcn	(Fries et al. 2017)
m/f	Peripheral blood						↑↓mtDNAcn (based on the mood state)	(Wang et al., 2018)

(●protein levels, ◊mRNA levels, m:male, f:female, PBMCs: peripheral blood mononuclear cells, , mt: mitochondria, mtDNAcn: mitochondrial DNA copy number, ↑: elevated in the psychiatric disorder group vs. the control group, ↓: reduced in the psychiatric disorder group vs. the control group, ─ :no differences between the psychiatric disorder group vs. the control group)

Schizophrenia

Brain tissue

Oligodendrocyte pathology has been highlighted in relation to the etiology of schizophrenia (Cassoli et al., 2015). Oligodendrocytes from PFC white matter revealed differences in mitochondria-related parameters (number and volume fraction) between patients suffering from schizophrenia and controls. In particular, mitochondrial number and density in oligodendrocytes adjacent to microglia derived from patients suffering from schizophrenia and facing mostly positive symptoms was reduced compared to controls (Uranova et al., 2018). On the other hand, no significant differences were found in mitochondrial numbers in oligodendrocytes adjacent to myelin between any of the schizophrenia subgroups according to the symptomatology (mainly positive or negative symptoms) and the control group. However, volume fraction of mitochondria from oligodendrocytes adjacent to myelin was significantly reduced in subgroups of schizophrenia patients with positive or negative symptoms compared to the control group. Notably, there was a significant effect of schizophrenia age of onset on mitochondrial number and density only for oligodendrocytes adjacent to microglia compared to controls. Subgroup analysis based on age of schizophrenia onset revealed reduced mitochondrial number and density only in participants with a < 21years old during schizophrenia onset compared to age-matched controls (Uranova et al., 2018). In their review, Bernstein et al. highlight that increased mitophagy is implicated in oligodendrocyte pathology in schizophrenia progression (Bernstein et al., 2020).

Mitochondrial density shows alterations in the neurons of putamen and caudate nucleus of patients suffering from schizophrenia compared to controls and antipsychotic use appear to have an effect on these changes (Somerville et al. 2011). Subgroup analysis of the full schizophrenia cohort, according to the type of antipsychotic medication (atypical, typical or no use), revealed differences in mitochondrial density: dendrites in the caudate nucleus show increased mitochondrial density on typical antipsychotics users group and on no-antipsychotics users compared to controls (Somerville et al. 2011). Opposingly, mitochondrial number per synapse in the putamen appears to be significantly reduced both in schizophrenia full cohort and subgroups of individuals based on the type of antipsychotic treatment (atypical and typical users) (Somerville et al. 2011). Yet, significantly decreased mitochondrial number per synapse was only observed in the full schizophrenia cohort compared to controls in the caudate nucleus (Somerville et al. 2011).

Remarkably, the overall mitochondrial number in the caudate nucleus and putamen did not significantly differ between the schizophrenia and the control groups. Therefore, Somerville et al. suggest that differences on the mitochondrial number on synapses and dendrites reflect perturbations of the mitochondrial transport system, which in turn affects the distribution of existing mitochondria (Somerville et al. 2011).

In the anterior cingulate cortex (ACC), mitochondrial number and density, as measured by electron microscopy, differ in individuals with schizophrenia compared to controls (Roberts et al., 2015). In the neuropil, mitochondrial size and number did not show alterations between the two groups. However, in specific types of axon terminals of ACC layers 5 and 6 -and not in the whole neuropil- mitochondrial density was significantly lower in schizophrenia individuals compared to controls. Mitochondrial number was also decreased in the neuronal somata in layers 5 and 6 of schizophrenia group compared to the control group (Roberts et al., 2015). Mitochondrial size showed no significant differences in the neuropil and neuronal somata in the ACC (layers 3,5 and 6 separately and combined analysis) of individuals suffering from schizophrenia compared to controls (Roberts et al., 2015). Overall, the authors suggest that interpretation of their results is difficult due to small size of the study cohort, but overall, the data of this study suggest a significantly decreased mitochondrial number in neuronal somata and axon terminals of schizophrenia ACC compared to controls (Roberts et al., 2015).

Investigation of the levels of mitochondrial dynamics-related proteins revealed an imbalance between fission and fusion (Rosenfeld et al., 2011). Protein levels of the fusion-related protein Opa1 were significantly decreased in the PFC of patients suffering from schizophrenia compared to controls (Rosenfeld et al., 2011). Intriguingly, the authors did not find changes in the protein levels of Mfn1, another fusion-related protein tested in this cohort. Moreover, the protein levels of the crucial mediator of fission, Drp1, did not significantly differ between patients suffering from schizophrenia and the control group (Rosenfeld et al., 2011).

Another study analyzed the protein levels of Mfn2, in the ACC, which is one of most implicated brain regions in schizophrenia (Nelson et al. 2015; Barksdale et al. 2014). Mfn2 protein levels were not significantly different between the schizophrenia and the control group (Barksdale et al. 2014). Further subgroup analysis of the schizophrenia cohort according to antipsychotic medicine type (atypical and typical) and medication response (responders, non-responders) did not

show significant changes in Mfn2 protein levels between these schizophrenia subgroups and controls (Barksdale et al. 2014). However, the effect of sex was not investigated in this study (Barksdale et al. 2014). Additionally, a significant positive correlation was observed between Mfn2 with both calcineurin and synaptophysin (Barksdale et al. 2014). Synaptophysin and calcineurin have crucial regulatory and active roles respectively, during endocytosis of synaptic vehicles (Daly et al. 2000; Wu et al. 2014).

Table 3: Included studies on human brain tissue and mitochondrial dynamics in schizophrenia

Sex	**Brain region**	**Mitochondrial dynamics**						**Citation**
		Biogenesis	**Fission**	**Fusion**	**Mitophagy**	**Morphology/ Distribution**	**mtDNAcn**	
m/f	PFC					↓volume density ↓number of mt		(Uranova et al., 2018)
m/f	ACC					↓volume density ↓ number of mt -Size of mt		(Roberts et al., 2015)
m/f	Caudate nucleus Putamen					↑ number of mt (dendrites) ↓ number of mt (synapses) ─overall mt number in caudate and putamen		(Somerville et al. 2011)
m/f	ACC			─Mfn2●				(Barksdale et al. 2014)
m/f	PFC		─Drp1●	↓OPA1●				(Rosenfeld et al., 2011)

(●protein levels, m:male, f:female, PFC: prefrontal cortex, ACC: anterior cingulate cortex, mt: mitochondria, mtDNAcn: mitochondrial DNA copy number, ↑: elevated in the psychiatric disorder group vs. the control group, ↓: reduced in the psychiatric disorder group vs. the control group, ─ :no differences between the psychiatric disorder group vs. the control group)

Peripheral material

There is evidence for alterations of mitochondrial dynamics in the periphery in schizophrenia (Rosenfeld et al., 2011). Mitochondria of schizophrenia patients show abnormalities in their mitochondrial network indicative of mitochondrial fragmentation; schizophrenia-derived lymphoblastoids show an increased number of filamentous shaped mitochondria with unequal cellular distribution compared to those of the control group (Rosenfeld et al., 2011).

The observed mitochondrial network abnormalities were accompanied by reduced levels of the fusion-related protein Opa1 in lymphoblastoids of patients suffering from schizophrenia compared to control individuals (Rosenfeld et al., 2011). However, no differences were detected in the levels of another fusion-related protein Mfn1 and the fission-related Drp1 and Fis1 between the two groups (Rosenfeld et al., 2011). Altogether, these results indicate an imbalance between the processes of fission and fusion in lymphoblastoids of patients suffering from schizophrenia compared to controls (Rosenfeld et al., 2011). Rosenfeld et al, suggest that the non-analogous reduction of the protein levels of the mitochondrial fusion related proteins - Opa1 and Mfn1- in lymphoblastoids explains the observed partially fragmented mitochondrial network in the lymphoblastoids of the schizophrenia group.

Recently, it has been found that leukocytes from schizophrenia patients show significantly reduced mtDNAcn compared to controls (Shivakumar et al. 2020). The schizophrenia cohort consisted of schizophrenia patients who do not receive antipsychotic treatment. The authors support that the strength of their study was that recruited schizophrenia patients were not under any antipsychotic treatment (Shivakumar et al. 2020) as it is proposed that the use of antipsychotics negatively correlates with mtDNAcn in leukocytes of patients with other major psychiatric disorders (Chang et al. 2015). Notably, the differences between schizophrenia and control group remained after adjustment for age and sex (Shivakumar et al. 2020). Moreover, no significant correlation was detected between mtDNAcn and positive or negative schizophrenia symptoms. The authors support that the reduction on mtDNAcn could be used as a proxy marker for mitochondrial function in schizophrenia antipsychotic-free patients (Shivakumar et al. 2020).

Table 4: Included studies on human peripheral material and mitochondrial dynamics in schizophrenia

Sex	Cell type	Mitochondrial dynamics						Citation
		Biogenesis	**Fission**	**Fusion**	**Mitophagy**	**Morphology/ Distribution**	**mtDNAcn**	
m/f	Lymphoblastoids		─Drp1● ─Fis1●	↓OPA1● ─Mfn1●		↑filamentous shaped mt Unequal cytosolic distribution of mt		(Rosenfeld et al. 2011)
m/f	Leukocytes						↓mtDNA cn	(Shivakumar et al., 2020)

(●protein levels, m:male, f:female, mt: mitochondria, mtDNAcn: mitochondrial DNA copy number, ↑: elevated in the psychiatric disorder group vs. the control group, ↓: reduced in the psychiatric disorder group vs. the control group, ─ :no differences between the psychiatric disorder group vs. the control group)

Anxiety Disorders

Brain tissue

Chronic stress is a well-known risk factor for anxiety disorders (Khan & Khan, 2017). Despite the fact that social defeat stress is typically used as a behavioral paradigm for modeling depression-like behaviors (Hollis & Kabbaj, 2014), Misiewicz et al. used chronic social defeat stress (CSDS) to disentangle anxiety-related molecular mechanisms. The authors subjected two male mouse strains (C57BL/6NCrl (B6) and DBA/2NCrl (D2)) that differ in their susceptibility and resilience to stress (Pleil et al., 2012) to CSDS. Then, CSDS mice were assessed in the social avoidance test and in turn, according to the social interaction ratio, each strain was divided in two groups: stress-susceptible and stress-resilient (Misiewicz et al., 2019). Remarkably, the authors found that mitochondrial pathways are implicated in anxiety-related behavior in a key brain area of stress associated anxiety behavior: the bed nucleus of the stria terminals (BNST) (Misiewicz et al. 2019; Avery et al. 2015). It is noteworthy that the morphology and the number of mitochondria in the BNST were associated with stress-susceptibility; the BNST of B6 stress-susceptible mice showed increased mitochondrial number and mitochondria of smaller size compared to B6 control and stress-resilient mice. Moreover, D2 stress-susceptible mice had slightly elongated mitochondria compared to D2 stress-resilient mice (Misiewicz et al., 2019). Thus, the morphological and numerical changes in mitochondria reflecting perturbations in mitochondrial dynamics may constitute a mechanism associated with high anxiety and/or stress-resilience.

The interplay between anxiety and mitochondrial dynamics has been also discussed in a recent study which investigated the role of mitophagy in basolateral amygdala (BLA) upon CSDS (Duan et al., 2021). A 30-day and a 10-day CSDS paradigm were applied in C57BL/6 mice. Again, defeated mice were divided in two groups (stress-resilient and stress-susceptible) based on their social interaction score (Duan et al., 2021). Notably, both stress-resilient and stress-susceptible mice showed increased anxiety-related behavior after 10-days and 30-days of CSDS, compared to unstressed controls. However, depression-related behavior was induced only after 30-days CSDS and was observed only in the stress-susceptible vs. unstressed control group comparison. Intriguingly, mitochondrial size and mass in BLA of CSDS mice was altered according to the duration of CSDS protocol; The 30-day CSDS protocol induced a reduction in mitochondrial size

and total mass of both stress-resilient and stress-susceptible defeated mice vs. unstressed controls, while the 10-day CSDS protocol had no effect (Duan et al., 2021).

According to the authors, the mitochondrial loss in BLA, that was induced by 30-days CSDS, indicates unbalanced mitochondrial biogenesis and mitophagy (Duan et al., 2021). Mice which underwent 30-days CSDS showed increased mitochondrial replication and mutagenesis but decreased mtDNAcn in BLA compared to unstressed controls. Moreover, the protein and mRNA levels of the mitochondrial biogenesis-related transcription factors PGC-1a and TFAM did not differ in the BLA between 30-days CSDS mice and unstressed controls. Intriguingly, the 30-days CSDS group showed elevated mitophagy in BLA compared to the unstressed control group. Electron microscopy revealed more mitophagosome-like structures and reduced mitochondrial number in the BLA of the 30-days CSDS group than in the unstressed controls. Additionally, microscopy-based and molecular data showed that autophagy was not affected by 30-days CSDS, as autophagosome-like structures and protein levels of the autophagy markers LC3 and p62 did not differ between the 30-days CSDS and the unstressed control group. 10-days CSDS mice showed no alterations in mitophagy-related readouts compared to unstressed controls.

Then, it was tested whether the well-established Pink1-Parkin mitophagy pathway is implicated. To do so, double KO mice for either Pink1 or Parkin (Pink1-/- mice and Parkin-/- mice, respectively) were exposed in 30-days CSDS (Duan et al., 2021). Protein levels of Parkin and Pink1 were increased in the BLA of Pink1-/- and Parkin-/- 30-days CSDS mice, respectively, compared to unstressed controls. Moreover, unlike 30-days CSDS wild type mice, 30-days CSDS KO mice did not differ in mitophagy-related parameters tested compared to KO unstressed controls. Therefore, the authors suggested that the CSDS-induced elimination of damaged mitochondria was mediated by the Pink1-Parkin mitophagy pathway (Duan et al., 2021). Furthermore, both Pink1 and Parkin KO CSDS mice show no changes in their anxiety-related behavior compared to KO unstressed controls. Thus, the authors indicate that Pink1 and Parkin are implicated in elevated anxiety-related behavior induced by CSDS (Duan et al., 2021).

In addition, the authors explored whether the mitochondrial deficiency provokes increased anxiety-related behavior. Surprisingly, induction of mitochondrial loss in BLA (by injection with mtKillerRed, a fluorescent protein with mitochondrial localization that upon photostimulation produces ROS and induces mitochondrial damage, but not cell death) increased anxiety-related

behavior as well as mitophagosome-like structures and reduced the number of mitochondria in the BLA of mitochondria deficiency-induced mice compared to control mice (Duan et al., 2021).

Another recent study in male rats of high and low anxiety-related behavior investigated potential links between mitochondrial dynamics and anxiety, in the nucleus accumbens (NAc) (Gebara et al., 2021). Although the total mitochondrial number did not differ between the high and the low anxiety-related behavior group, high anxiety-related behavior rats showed larger mitochondria tissue coverage and atypical morphology, suggestive of mild mitochondrial swelling, compared to the low anxiety-related behavior group. Additionally, high anxiety-related behavior rats presented a reduced percentage of contact sites between ER and mitochondria compared to the low anxiety-related behavior group (Gebara et al., 2021). ER-mitochondria interactions are involved in mitochondrial dynamics via Mfn2 (de Brito & Scorrano, 2008). Interestingly, in NAc tissue from the high anxiety-related behavior group of rats, lower protein and mRNA levels of Mfn2 were observed than in rats with low anxiety-related behavior (Gebara et al., 2021). However, the authors found no differences in the levels of other mitochondrial fusion-machinery proteins, such as Mfn1 and Opa1. The observed changes in the levels of Mfn2 were region-specific, as there were no significant changes in other brain regions analyzed (i.e., cortex, central and BLA). Moreover, outbred high anxiety-related behavior rats showed increased immobility time in the forced swim test and thus increased depression-related behavior compared to low anxiety-related behavior group (Gebara et al., 2021). The observed differences in high anxiety-related behavior group were reversed by Mfn2 overexpression, as high anxiety behavior rats, overexpressing Mfn2, showed mitochondrial and the aforementioned behavioral characteristics towards the profile of the low anxiety-related behavior group. Overall, these data suggest a prominent role of Mfn2 in the crosstalk of anxiety manifestation and mitochondrial dysfunction (Gebara et al., 2021).

Alterations in mitochondrial fusion are indicated in the cingulate cortex of a relevant mouse model of trait anxiety; proteomic analysis of cingulate cortex synaptosomes derived from high anxiety-related behavior (HAB) mice showed higher OPA1 protein levels than in low anxiety-related behavior (LAB) mice (Filiou et al., 2011).

Table 5: Included studies on brain tissue and mitochondrial dynamics in anxiety disorders

Sex	Brain region	Mitochondrial dynamics						Citation
		Biogenesis	**Fission**	**Fusion**	**Mitophagy**	**Morphology/ Distribution**	**mtDNAcn**	
m	BNST (Mouse)					Changes on number and morphology of mt related to stress-susceptibility or stress-resiliance		(Misiewicz et al., 2019)
m	BLA (Mouse)	─PGC-1a◊ ─TFAM◊ ↑mtDNA replication			↑mitophagosome-like structures	↓mt size ↓total mt mass	↓mtDNAcn	(Duan et al., 2021)
m	NAc (Rat)			↓ Mfn2◊● ─Mfn1◊● ─Opa1◊●		─total number of mt ↑mt tissue coverage ↑mt swelling ↑ER-mt contact sites		(Gebara et al., 2021)
m	Cingulate cortex (Mouse)			↑ Opa1●				(Filiou et al., 2011)

●*protein levels*, ◊*mRNA levels*, *m:male, BNST: bed nucleus of the stria terminals, NAc: Nucleus accumbens, BLA: basolateral amygdala, mt: mitochondria, mtDNAcn: mitochondrial DNA copy number, ↑: elevated in the psychiatric disorder group vs. the control group, ↓: reduced in the psychiatric disorder group vs. the control group, ─ :no differences between the psychiatric disorder group vs. the control group)*

Peripheral material

Evidence for mitochondrial dynamics alterations in anxiety-related behavior in peripheral cells is limited. In human-oriented studies this could be attributed to the heterogeneity of anxiety disorder classification in human cohorts in clinical studies.

Depression

Brain tissue

Deficits on brain mitochondrial dynamics in depression rise up mainly from rodent studies using stress-induced depression models. Chronic mild stress (CMS) is a paradigm developed in the late 20th century that is used to model depression-like behaviors (Willner, 2017). It has been reported that mice subjected to CMS show increased depression-like behavior and decreased mitochondrial respiration rate as well as loss of mitochondrial membrane potential in cortex, hippocampus and hypothalamus compared to controls (Gong et al., 2011). Moreover, mitochondrial morphology was impaired in these brain regions of the CMS group vs. the control group as mitochondria appeared to be swollen with cracked membranes and abnormal cristae morphology (Gong et al., 2011).

The protein TSPO is located on the OMM and has been shown to have a regulatory role in anxiety and depression-related behaviors (Barron et al., 2021). Moreover, in vitro studies indicate that TSPO, via its interaction with VDAC1, mediate the inhibition of mitophagy downstream of the Pink1/Parkin pathway (Gatliff et al., 2014). Considering the growing interest on the role of mitophagy in the pathobiology of depression (Tripathi et al., 2021), in vivo human brain studies will provide evidence on the underlying molecular mechanisms in depression.

The learned helplessness (LH) paradigm is usually applied to model depression-related behavior in animal studies (Anisman & Merali, 2001; Vollmayr & Gass, 2013). Li et al. used this paradigm in male mice and investigated changes related to the TSPO-mediated mitophagy pathway (Li et al., 2016). Behavioral changes were assessed by forced-swim test, shuttle box test and novelty suppressed feeding test. Behavioral analysis revealed that the LH group showed increased anxiety-like and depression-related behavior compared to controls. Moreover, reduced protein levels of the mitophagy regulators TSPO and VDAC1 and the mitophagy players Pink1 and Beclin1 were reported in the mesencephalon of LH compared to control mice. However, the protein levels of Parkin were higher in the LH group than in the control group and it is proposed that this increase may be related to the recruitment of Parkin for mitophagy induction (Li et al., 2016). Additionally, the LH group showed a trend towards decreased protein expression ratio of Bcl-2/Bax compared to controls, and according to the authors, this reduction may point toward increased neuronal apoptosis (Li et al., 2016).

The CSDS paradigm was used by Guo et al. in order to investigate mitophagy in a mouse model of depression-related behavior (Guo et al., 2022). This study was focused on male C57BL/6 mice. Mitochondrial integrity in hippocampal neurons was reduced in CSDS group compared to controls as revealed by transmission electron microscopy. Moreover, the protein levels of the mitophagy-related Pink1, Parkin and autophagy-related Beclin1, ATG5, LC3, p62 and LAMP2 were significantly higher in the hippocampal brain lysates of the CSDS group than in controls (Guo et al., 2022). Overall, the results indicated increased mitophagy and autophagy in hippocampal neurons of CSDS mice compared to controls (Guo et al., 2022);

It has been shown that prenatal stress in rats induces increased depression-related behavior and decreased expression of PGC-1a in the adult male offsprings compared to those of the prenatally unstressed group (Głombik et al., 2015). Notably, both the mRNA and protein levels of PGC-1a were significantly reduced in the PFC and hippocampus of prenatally stressed offspring compared to the unstressed group (Głombik et al., 2015).

Table 6: Included studies on brain tissue and mitochondrial dynamics in depression

Sex	Brain region	Mitochondrial dynamics						Citation
		Biogenesis	**Fission**	**Fusion**	**Mitophagy**	**Morphology/ Distribution**	**mtDNAcn**	
m	Cortex HIP HYP (Mouse)					Swollen mt with disrupted matrix		(Gong et al., 2011)
m	Mesencephalon (Mouse)				↓Pink1● ↑Parkin● ↓Beclin● ↓TSPO● ↓VDAC●			(Li et al., 2016)
m	HIP (Mouse)				↑Pink1● ↑Parkin● ↑Beclin1● ↑ATG5● ↑LC3● ↑p62● ↑LAMP2●			(Guo et al., 2022)
m	PFC HIP (Rat)	↓PGC-1a◊●						(Głombik et al., 2015)

(●protein levels, ◊mRNA levels, m:male, PFC: prefrontal cortex, HIP: Hippocampus, HYP: Hypothalamus, mt: mitochondria, mtDNAcn: mitochondrial DNA copy number, ↑: elevated in the psychiatric disorder group vs. the control group, ↓: reduced in the psychiatric disorder group vs. the control group, ─ :no differences between the psychiatric disorder group vs. the control group)

Peripheral material

It has been recently found that PBMCs from patients with depression show altered protein expression related to fission/fusion, mitophagy and apoptosis compared to controls (Scaini et al. 2021b). The authors report increased levels of fission- (Fis1), fusion- (Opa1, Mfn2), mitophagy/autophagy- (Pink1, p62/SQSTM1, LC3) and apoptosis- (caspase 3) related proteins in patients suffering from depression compared to control individuals. However, the protein levels of Parkin were significantly lower in depressed patients compared to the control group. Along these lines, the authors suggest that their results offer insights on the role of impaired mitophagy in depression (Scaini et al. 2021b).

Only few studies highlight an impaired mitochondrial biogenesis in patients with depression (Alcocer-Gómez et al. 2016; Ryan et al. 2019). In particular, patients of both sexes who suffer from depression showed significantly lower mRNA levels of PGC-1a than controls, in whole blood (Ryan et al. 2019). However, participants of the depression group were not drug-naïve. Thus, the authors support the need for future studies in order to verify that the reduction of PGC-1a mRNA levels is depression-related and not an artifact of antidepressant medication (Ryan et al. 2019). Moreover, PBMCs from female patients suffering from depression show reduced mRNA levels of the mitochondrial biogenesis-related genes PGC-1a, TFAM and NRF1 (Alcocer-Gómez et al., 2016). In this study, the participants with depression were recruited prior to antidepressant medication prescription (Alcocer-Gómez et al., 2016). Chung et al. investigated the relative methylation ratio in PGC-1a promoter region of patients suffering from depression vs. controls. Intriguingly, leukocytes from patients with depression showed significantly reduced methylation ratio in the PGC-1a promoter compared to the control group (Chung et al., 2019).

Several clinical studies produce inconclusive results for mtDNAcn in peripheral cells of patients with depression. Leukocytes from patients suffering from depression show lower mtDNAcn than the control group (Chang et al., 2015). Additionally, antipsychotic use showed a significant negative association with mtDNAcn in patients with depression (Chang et al., 2015). However, other studies show increased mtDNAcn in depressed patients compared to the control group (Chung et al., 2019). Moreover, mtDNAcn showed a significant negative correlation with the age of patients with depression (Chung et al., 2019). Such discrepancies could be explained due to co-founding factors such as the blood cell type, which was analyzed, age, ethnicity,

antidepressant medication, family history and other demographic characteristics of the cohorts under investigation. It is also noteworthy that geriatric depression has been associated with reduced mtDNAcn, also (Kim et al. 2011). It has been shown that leukocytes from women with age older than 60 years old, display reduced mtDNAcn compared to the control group (Kim et al. 2011).

Table 7: Included studies on human peripheral cells and mitochondrial dynamics in depression

Sex	**Cell type**	**Mitochondrial dynamics**						**Citation**
		Biogenesis	**Fission**	**Fusion**	**Mitophagy**	**Morphology/ Distribution**	**mtDNAcn**	
m/f	PBMCs		↑Fis1●	↑Opa1● ↑Mfn2●	↑Pink1● ↓ Parkin● ↑p62/SQSTM1● ↑LC3●			(Scaini et al. 2021b)
f	PBMCs	↓ TFAM◊ ↓PGC-1a◊ ↓NRF1◊						(Alcocer-Gómez et al., 2016)
m/f	Whole blood	↓ PGC-1a◊						(Ryan et al. 2019)
m/f	Leukocytes						↓mtDNAcn	(Chang et al., 2015)
m/f	Leukocytes	↓ ratio of methylated to unmethylated promoter of PGC-1a					↑mtDNAcn	(Chung et al., 2019)
f	Leukocytes						↓mtDNAcn (old women with depression)	(Kim et al., 2011)

(●protein levels, ◊mRNA levels, m:male, f:female, PBMCs: peripheral blood mononuclear cells, mtDNAcn: mitochondrial DNA copy number, ↑: elevated in the psychiatric disorder group vs. the control group, ↓: reduced in the psychiatric disorder group vs. the control group, ─ :no differences between the psychiatric disorder group vs. the control group)

Post-Traumatic Stress Disorder

Brain tissue

Studies focusing on brain-specific alterations in mitochondrial dynamics and PTSD are limited. Thus, considering that peripheral cells of PTSD patients show alterations in the mtDNAcn (discussed below), investigation of mitochondrial dynamics in the brain would provide insights on the role of mitophagy in PTSD.

Peripheral material

Due to the high prevalence of PTSD in veterans, this group is commonly used as a human-based model for the research on PTSD-related pathology (Lawson, 2014). Evaluation of mtDNAcn in granulocytes of male veterans with current combat-related PTSD (PTSD group) revealed differences compared to veterans without PTSD (control group); The PTSD group showed decreased mtDNAcn compared to controls (Bersani et al., 2016). Notably, in the PTSD cohort individuals suffering from PTSD that showed concurrent depression were included and many of them were under antidepressant treatment (Bersani et al., 2016). mtDNAcn did not show differences between PTDS+depression vs. PTDS-depression and PTSD+antidepressants vs. PTSD-antidepressants (Bersani et al., 2016).

To investigate the association between symptom severity of individuals suffering from PTSD and mtDNAcn, the PTSD group was divided in three subgroups according to the Clinician-Administered PTSD Scale (CAPS) current scale scores: mild, moderate and severe PTSD (Bersani et al., 2016). The moderate PTSD subgroup had higher mtDNAcn than the mild and the severe PTSD subgroups. No differences were observed between the moderate and the control group (Bersani et al., 2016). Overall, the authors indicate a reduction of mtDNAcn in male veterans suffering from PTSD compared to controls and propose the need for further studies on women-oriented PTSD cohorts.

Table 8: Included studies on human peripheral cells and mitochondrial dynamics in PTSD

Sex	**Cell type**	**Mitochondrial dynamics**						**Citation**
		Biogenesis	**Fission**	**Fusion**	**Mitophagy**	**Morphology/ Distribution**	**mtDNAcn**	
m	Granulocytes						↓mtDNAcn	(Bersani et al., 2016)

(m:male, mtDNAcn: mitochondrial DNA copy number, ↑: elevated in the psychiatric disorder group vs. the control group, ↓: reduced in the psychiatric disorder group vs. the control group, ー:no differences between the psychiatric disorder group vs. the control group)

Chapter IV

Discussion

Psychiatric disorders affect the life quality of millions of people worldwide (Ferrari, 2022). It is anticipated that the cost of poor mental health in the global economy would rise up to 6 trillion dollars/year by 2030 (The Lancet Global Health, 2020). Unfortunately, current therapies are largely ineffective as a significant percentage of patients suffering from psychiatric disorders do not respond to the available treatments (Howes et al., 2021). Therefore, there is an eminent need to devise new strategies for therapy in order to improve psychiatric health management. Mitochondria are emerging therapeutic targets in psychiatric disorders (Giménez-Palomo et al., 2021). Mitochondria-targeted therapeutic strategies have been implemented in rodents to alleviate symptoms of depression (Głombik et al., 2021), anxiety (Filiou & Sandi, 2019; Nussbaumer et al., 2016) and bipolar disorder (Pereira et al., 2018). The mitochondrial pool in cell populations is tremendously versatile, as mitochondrial dynamics (e.g biogenesis, fission, fusion and mitophagy) alters mitochondrial numbers to respond to the constantly changing energetic needs. Deficits in mitochondrial dynamics have already been discussed in neurodegenerative disorders (Burté et al., 2014; Uittenbogaard & Chiaramello, 2014; Yapa et al., 2021). Thus, investigating the role of mitochondrial fission, fusion and mitophagy in psychobiology is an emerging field of study in psychiatry.

To the best of our knowledge, there are no reviews to date addressing existing data on perturbations of mitochondrial dynamics in psychiatric disorders. Here, we discuss the available clinical and preclinical literature on mitochondrial dynamics-related changes in major psychiatric disorders -including bipolar disorder, schizophrenia, anxiety disorders, depression and PTSD. To investigate brain-specific and periphery-specific alterations in mitochondrial dynamics, we have categorized these studies according to the biological material used in each disorder (brain tissue and peripheral material).

Evidence of impaired mitochondrial structure in psychiatric disorders

Variations in mitochondrial structure, number and/or distribution were observed in all psychiatric disorders discussed, except for PTSD (perhaps due to the limited available literature on this disorder) (addressed in chapter III). Upon mitochondrial fission and fusion, mitochondrial ultrastructure is changed. Mitochondrial morphology is associated with mitochondrial function (Glancy et al., 2020). For instance, via the process of mitochondrial fusion elongated mitochondria are produced that are supported to maintain mitochondrial function through spreading of metabolites and enzymes in both of the fused mitochondrial compartments (Westermann, 2012). Additionally, cristae shape is associated with OXPHOS system efficiency and mitochondrial energy production (Afzal et al., 2021; Cogliati et al., 2013). Morphological differences of mitochondria were found in human brain and peripheral cells of bipolar disorder patients (Cataldo et al., 2010), in peripheral cells of schizophrenia patients (Rosenfeld et al., 2011) and in several brain regions of rodent models of anxiety-related (Duan et al., 2021; Gebara et al., 2021; Misiewicz et al., 2019) and depression-like (Gong et al., 2011) phenotypes.

Based on the findings of Cataldo et al. reporting that fibroblasts and lymphoblasts of bipolar disorder patients have increased numbers of ring-shaped mitochondria compared to controls (Cataldo et al., 2010), we hypothesize that this could be the result of mitochondrial depolarization (Miyazono et al., 2018), a triggering event for the initiation of the Pink1/Parkin mitophagy pathway. In addition, Cataldo et al. observed that the mitochondrial density was elevated in the perinuclear region in peripheral material of bipolar disorder patients than controls (Cataldo et al., 2010). Therefore, we suggest that elevated mitophagy may contribute to the pathobiology of bipolar disorder as mitochondrial gathering in the perinuclear area is mediated by p62/SQSTM1 and Parkin (Okatsu et al., 2010). Yet, this needs further investigation in order to estimate the levels of mitophagy and mitophagy-related molecular players in fibroblasts and lymphoblastoids of bipolar disorder patients as well as in other cell types in the periphery and the brain.

An imbalance between mitochondrial fission and fusion could be involved in schizophrenia, as lymphoblastoids derived from schizophrenia patients showed elevated filamentous mitochondrial network compared to controls (Rosenfeld et al., 2011). Moreover, it is proposed that the mitochondrial transport system is impaired in the neurons of caudate nucleus

and putamen of patients suffering from schizophrenia (Somerville et al., 2011). An interesting mitochondrial dynamics candidate that plays a role in mitochondrial trafficking is Mfn2 (Misko et al., 2010). Therefore, investigating the role of Mfn2 in brain neurons would shed light on the mitochondrial dynamics-related mechanisms which may be implicated in the pathogenesis of schizophrenia.

An increase in mitophagy-related parameters, including an increased number of mitophagosome-like structures and decreased mitochondrial size and mass were observed in the BLA of a mouse model of CSDS-induced anxiety-related behavior compared to unstressed control mice (Duan et al., 2021). When mitochondrial damage exceeds the capacity of mitophagy to maintain a healthy mitochondrial population, mitochondria-related apoptosis is activated (Wanderoy et al., 2020). Mitochondria during apoptosis get swollen. This feature was observed in the brain of rats with high anxiety-related behavior, where Gebara et al. found increased mitochondrial swelling in the NAc of the high anxiety-related behavior group compared to the low anxiety-related behavior group (Gebara et al., 2021). In the same study, ER-mitochondria contact sites were increased in the high anxiety-related behavior group compared to the the low anxiety group (Gebara et al., 2021) and these contact sites are of major importance for mitochondrial function, fission and apoptosis (Rowland & Voeltz, 2012).

Mitochondria-related apoptosis could be a potential contributor in stress-related disorders. An indication for this is the observation of Gong et al. of swollen mitochondria with abnormal structure in brain regions associated with modulation of stress responses in chronically mildly stressed mice compared to controls (Gong et al., 2011). Along these lines, an imbalanced mitochondrial turnover system is also highlighted by differences in the mitochondrial morphology and structure. Therefore, future research on the molecular players involved in deficits in the dynamically orchestrated maintenance of functional mitochondrial populations is important in order to disentangle the molecular basis of psychiatric disorders.

Evidence of altered mRNA or protein levels of mitochondrial dynamics-related genes in psychiatric disorders

The fusion-related Opa1 is expressed in several human brain regions and cell types (Bette et al., 2005) and a wide variety of mutations in the Opa1 gene lead to a neuropathy termed Autosomal Dominant Optic Atrophy (Alexander et al., 2000; Weisschuh et al., 2021). The protein levels of Opa1 were significantly decreased in brain tissue and peripheral cells of individuals suffering from schizophrenia vs. controls (Rosenfeld et al., 2011). Notably, a reduction in protein and mRNA levels of Opa1 was observed by Scaini et al in peripheral material of bipolar disorder patients compared to the control group (Scaini et al., 2017). On the other hand, the protein levels of Opa1 were significantly increased in PBMCs derived from individuals suffering from depression (Scaini et al., 2021) compared to controls as well as in the cingulate cortex of a mouse model of high anxiety (Filiou et al., 2011) vs. the low anxiety group. This observation indicates that Opa1 is an emerging candidate molecular player implicated in psychopathology.

According to the literature discussed in our review, an imbalance in the mitochondrial turnover is observed in depression. Expression of the major player of mitochondrial biogenesis PGC-1a was decreased both in mRNA and/or protein levels in depression; This effect was observed in the hippocampus and PFC of a rat model of depression (Głombik et al., 2015) as well as in peripheral cells of individuals suffering from depression compared to controls (Alcocer-Gómez et al., 2016; Ryan et al., 2019). Opposingly, the protein levels of the mitophagy players Pink1 and Parkin in the hippocampus (Guo et al., 2022) and only Parkin levels in the mesencephalon (Li et al., 2016) of rodent models of depression were significantly increased as well as in peripheral cells of individuals suffering from depression (Scaini et al., 2021) compared to controls.

Mfn2 is a multifunctional protein involved in multiple pathways in addition to regulating mitochondrial fusion; It has been shown that the wide repertoire of Mfn2 functions includes ER-mitochondria tethering (Han et al., 2021), cell metabolism (Emery & Ortiz, 2021), mitophagy and apoptosis (Joaquim & Escobar-Henriques, 2020). Therefore, function and dysfunction of mitofusins is a current topic under investigation to disentangle the molecular mechanisms that could lead to disease (Dorn, 2020). Interestingly, both Mfn2 protein and mRNA levels were significantly decreased in the NAc of a rat model of anxiety (Gebara et al., 2021) and in peripheral

cells of bipolar disorder patients compared to controls (Scaini et al., 2017). However, in human-derived PBMCs, Mfn2 protein levels were significantly higher in the depression compared to the control group.

Evidence on mtDNAcn and psychiatric disorders

The evaluation of mtDNAcn is commonly used in the literature to estimate the levels of mitochondrial numbers and biogenesis. It should be noted that mtDNAcn as a marker of mitochondrial abundance is not particularly accurate as mitochondrial populations are highly heterogeneous in each cell-type and additionally the copies of mtDNA per mitochondrion and the number of mitochondria per cell vary (Filiou & Sandi, 2019). Nevertheless, we included here studies measuring mtDNAcn mostly in peripheral material of patients suffering from psychiatric disorders in order to evaluate unbalanced mitochondrial dynamics in the periphery. In these studies, we did not identify consistent results on the directionality of the change of mtDNAcn in psychiatric disorders vs. control groups. Therefore, combining data pointing towards altered mtDNAcn along with data from microscopy techniques could provide a more accurate reflection of mitochondrial numbers.

Sex-dependent effects have only recently been addressed in detail in psychiatric research (Shobeiri et al., 2022). For instance, mood disorders affect more women than men worldwide. However, the available studies on anxiety disorders and mitochondrial dynamics are predominantly focused on male populations. To the best of our knowledge, only two studies were found to investigate mitochondrial biogenesis-related parameters on human female populations suffering from depression. Kim et al. found significantly reduced mtDNAcn in the leukocytes of old women with depression than in the control group (Kim et al., 2011). Moreover, PBMCs from female patients suffering from depression show reduced mRNA levels of the mitochondrial biogenesis-related genes PGC-1a, TFAM and NRF1 (Alcocer-Gómez et al., 2016).

Limitations

Since the field of mitochondrial dynamics alterations in psychiatry is still in its infancy, several limitations should be taken into consideration in the interpretation of the findings of the included studies discussed here.

- Mitochondrial heterogeneity, i.e. varying mtDNA numbers within each mitochondrion, mitochondrial numbers within cell type and tissue, as well as heteroplasmy constitute a challenge in mitochondrial biology. For instance, altered expression of genes related to mitochondrial dynamics in human cohorts were mainly focused on peripheral material and not specifically in the affected brain regions of each psychiatric disorder patient group that would help to detect the contribution of defective mitochondrial turnover system in psychopathology.
- The low number of participants in the clinical cohorts reduces the chance of reaching statistical significance levels. Also, the material analyzed is heterogeneous, including demographic characteristics of patient cohorts used for clinical studies and different strains of animal models studied.
- As psychiatric medication is shown to affect mitochondrial pathways (Chan et al., 2020), another source of bias could be that clinical studies discussed in this review did not consider potential drug effects on mitochondrial dynamics. Therefore, it is inconclusive to identify whether the mitochondrial dynamics-related changes are a causal factor involved in the etiology of psychiatric disorders or a consequence of the medication.
- The stochastic examination of selected mitochondrial dynamics- related molecular players in each study and not an extensive, high-throughput analysis of the entire molecular pathway of each process and its regulatory systems can not fully elucidate changes in each mitochondrial dynamics process.
- Depression and anxiety disorders are more common in female compared to male human populations. However, included rodent studies were examining mitochondrial dynamics changes mainly in male mouse models of these disorders.

Conclusion and future perspectives

The high prevalence and the effects of psychiatric disorders in the economy and global health worldwide require intense research efforts to understand the biological basis of psychopathology and identify novel targets for effective therapy. An emerging and promising target is mitochondrial function, as there is accumulating evidence for the implication of mitochondrial in psychiatry (Allen et al., 2018; Filiou & Sandi, 2019; Pereira et al., 2018). Interestingly, it has been shown that targeting mitochondria to alleviate anxiety symptoms is a promising therapeutic approach for mood disorders, as selective pharmacological targeting of mitochondria exerts anxiolytic effects in high anxiety mice (Nussbaumer et al., 2016). The effects of psychiatric medication on mitochondrial function are also observed in bipolar disorder. In particular, Kuperberg et al in their review summarize data on the role of mitochondria in bipolar disorder, the significance of targeting mitochondria for bipolar disorder therapy and discuss the effects of current available medication for bipolar disorder on mitochondria (Kuperberg et al., 2021). For instance, lithium is a typically used drug in the manic phases of bipolar disorder patients that has effects on mitochondrial function (Lundberg et al., 2020).

Mitochondrial dynamics is an emerging target for anti-psychiatric interventions, as several lines support impaired biogenesis, fission/fusion and mitophagy in patients and rodent models of psychiatric disorders (Guo et al., 2022; Duan et al., 2021; Rosenfeld et al., 2011). In particular, focusing on the molecular players implicated in the balance of mitochondrial biogenesis and mitophagy could be a potential target for the therapy of depression. Elucidating the role of each mediator in mitochondrial dynamics, the effects of the respective changes in the implicated machineries and the interplay between the molecular players of the mitochondrial dynamics processes will allow putting together the missing pieces to unravel the role of mitochondrial dynamics in disease and to develop novel candidate therapeutic targets. Future clinical studies that would examine the expression of mitochondrial dynamics-related proteins in affected brain regions of drug-naïve psychiatric disorder patients would be helpful to elucidate the contribution of defective mitochondrial turnover mechanisms in psychopathology. Overall, several data support that mitochondrial dynamics is a potential target to alleviate psychiatric symptoms and improve life quality globally.

Abstract

Psychiatric disorders affect millions of people worldwide and are among the leading causes of global disease burden. As current treatments are largely ineffective with low response rates and severe side-effects, understanding the underlying molecular mechanisms involved in psychiatric disorders will provide novel therapeutic targets to improve psychiatric health management.

Mitochondria are emerging pathobiology hubs and promising targets for therapeutic approaches in psychiatry. Although the modulatory role of mitochondrial pathways in neuropsychiatric phenotypes has received increasing attention, little is known about how alterations in the morphology, shape, number and distribution of mitochondrial populations can contribute to psychopathology. Deficits in the processes regulating these events, collectively known as mitochondrial dynamics (i.e. mitochondrial biogenesis, fission, fusion and mitophagy) have only recently been discussed in the context of psychobiology.

Here, we summarize the existing data on changes in mitochondrial dynamics in major psychiatric disorders – including bipolar disorder, schizophrenia, anxiety disorders, depression and post-traumatic stress disorder (PTSD) – by addressing mitochondrial dynamics-related readouts in disease vs. control groups. Moreover, we also discuss brain-specific and periphery-specific alterations of mitochondrial dynamics as a common mechanism contributing to psychopathology.

Critically reviewing current literature on which molecular players of mitochondrial dynamics machines are affected in psychiatric disorders will pave the way towards understanding the molecular mechanisms of psychiatric disorders and devising novel, personalized therapy approaches to alleviate disease symptomatology in patients suffering from psychiatric disorders.

Περίληψη

Εκατομμύρια άνθρωποι υποφέρουν από ψυχιατρικές διαταραχές, οι οποίες αποτελούν ένα από τα σημαντικότερα προβλήματα υγείας παγκοσμίως. Δεδομένου ότι οι υπάρχουσες θεραπείες είναι σε μεγάλο ποσοστό μη αποτελεσματικές, με χαμηλό ποσοστό ατόμων να ανταποκρίνεται σε αυτές και σοβαρές παρενέργειες, η κατανόηση των μοριακών μηχανισμών που εμπλέκονται στις ψυχιατρικές διαταραχές θα προσφέρει νέους θεραπευτικούς στόχους για την επιτυχή αντιμετώπισή τους.

Τα μιτοχόνδρια αναδεικνύονται ως κομβικά σημεία παθοβιολογίας και πολλά υποσχόμενοι στόχοι για θεραπευτικές προσεγγίσεις στην ψυχιατρική. Παρόλο που ο ρυθμιστικός ρόλος μονοπατιών που σχετίζονται με τα μιτοχόνδρια στην ψυχιατρική έχει λάβει μεγάλο ενδιαφέρον, γνωρίζουμε λίγα πράγματα για το πώς αλλαγές στη δυναμική των μιτοχονδριακών πληθυσμών μπορεί να συμβάλει στην ψυχοπαθολογία. Διαταραχές στις διεργασίες της μιτοχονδριακή βιογένεσης, σύντηξης, σχάσης και μιτοφαγίας, οι οποίες είναι γνωστές ως σύνολο ως «μιτοχονδριακή δυναμική» έχει ξεκινήσει να μελετάται πρόσφατα στην νευροψυχιατρική.

Στην παρούσα μελέτη συνοψίζουμε τα υπάρχοντα δεδομένα που αφορούν αλλαγές στην μιτοχονδριακή δυναμική σε ψυχιατρικές διαταραχές – όπως η διπολική διαταραχή, η σχιζοφρένεια, οι αγχώδεις διαταραχές, η κατάθλιψη και το μετά-τραυματικού στρες – διερευνώντας παραμέτρους που σχετίζονται με την μιτοχονδριακή δυναμική μεταξύ ομάδων ασθενών και ομάδων μαρτύρων. Επιπρόσθετα, μελετάμε τις αλλαγές της μιτοχονδριακής δυναμικής είτε σε εγκεφαλικές περιοχές ή σε περιφερικό υλικό ως έναν μηχανισμό που συμβάλει στην ψυχοπαθολογία.

Η ενδελεχής επισκόπηση της υπάρχουσας βιβλιογραφίας στο ποιοι και πώς μοριακοί τελεστές που σχετίζονται με την μιτοχονδριακή δυναμική επηρεάζονται στις ψυχιατρικές διαταραχές θα μας οδηγήσει στην κατανόηση των εμπλεκόμενων μοριακών παθοφυσιοφυσιολογικών μηχανισμών καθώς και στο σχεδιασμό νέων εξατομικευμένων θεραπευτικών προσεγγίσεων για ασθενείς που υποφέρουν από ψυχιατρικές διαταραχές.

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