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Investigating markers of accelerated aging in patients with Treatment Resistant Depression

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Ph.D. Student: Anna Meloni

Supervisor Prof. Alessio Squassina

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To the present love of those who are not here anymore

To effort and awareness

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Abstract

Mood disorders affect 5.4% of the general population, exert a substantial socioeconomic burden and significantly impact the patients' quality of life. Mood disorders are associated with a reduced life expectancy compared to the general population (up to 20 years), and this is largely accounted for by a higher incidence of age-related disorders, in particular metabolic and cardiovascular illnesses, and suicide. This evidence supported the hypothesis that accelerated biological aging might be a feature of mood disorders, but findings have been so far controversial, and less is known about the role and clinical utility of aging markers in the management of treatment response.

Pharmacological treatments represent the main approach in mood disorders, but treatment resistance concerns 10–30% of patients with major depressive disorder (MDD) and 75% of cases of unresolved morbidity of bipolar disorder (BD) and, as such, the dentification of reliable response biomarkers represent an unmet need.

One of the most studied and effective approaches to manage TRD patients is the electroconvulsive therapy (ECT), but its use is hampered by its invasive nature and side effects. Moreover, the underlying biology of its mechanism of action has yet to be understood.

The general aim of this thesis was to explore markers of accelerated aging, namely leucocyte telomere length (LTL) and mitochondrial DNA copy numbers (mtDNAcn), in patients with TRD and in response to ECT.

To achieve this aim, we performed two studies.

The first study involved a sample of 148 patients with TRD (125 with MDD, and 23 with BD) treated with ECT, where we aimed at: a) exploring if LTL was a marker of TRD by comparing patients with TRD with non-psychiatric controls (NPC); b) investigating if baseline LTL (before ECT treatment) could predict response to ECT; c) exploring the role of genetic variance in this association by leveraging genome wide genotyping data from a sub-group of 107 TRD patients. Findings from this study showed that LTL was negatively correlated with age (Spearman's correlation coefficient = -0.25, $p < 0.0001$) and significantly shorter in treatment-resistant patients with either MDD (Quade's $F = 35.18$, $p < 0.0001$) or BD (Quade's $F = 20.84$, $p < 0.0001$) compared to controls. Conversely, baseline LTL was not

associated with response to ECT or remission. Moreover, we did not detect any significant overlap between genetic variants or genes associated with LTL and response to ECT.

The second study was performed on a sub-sample of 31 TRD patients from the previous study who had been treated with ECT and followed prospectively for one month after the end of the ECT session. Blood samples were collected at two different timepoints, before ECT and one month after the end of ECT session. Here we extended the exploration of the hypothesis of an involvement of accelerated cellular aging by also testing mtDNAcn. The study also included a sample of 65 NPCs. The longitudinal nature of the study allowed us to explore if the changes in depression severity observed after ECT were correlated with changes in LTL and mtDNAcn. We showed that TRD patients had significantly shorter LTL and higher mtDNAcn compared to NPCs (LTL: $t=-2.94$, $p=0.002$; mtDNAcn: $t= 7.36$, $p<0.001$). In the TRD sample, LTL was inversely correlated with Montgomery-Asberg Depression Rating Scale (MADRS) scores at baseline (which measure severity of depressive symptoms). Difference in MADRS scores between baseline and T2 (which measure symptoms improvement) was significantly inversely correlated with difference in LTL (partial correlation controlled for age, $r=-0.40$; $p=0.036$), suggesting that patients with worse improvement in symptoms also show larger shortening in LTL. Changes in mtDNAcn were not associated with response to ECT as a dichotomous trait and were not correlated with LTL.

In conclusion, results from these studies suggest premature cell senescence in patients with severe depression, and that LTL and mtDNAcn may constitute disease biomarker for TRD, confirming the involvement of aging and oxidative factors in depression. mtDNAcn did not show any evidence supporting its utility as predictive biomarkers of response to ECT but the symptoms improvement observed after ECT might be correlated with telomere shortening, suggesting a potential implication of telomere dynamics. Nevertheless, our limited understanding of the biological significance of mtDNAcn and the limited sample size of our studies require further investigation to better delineate the involvement of aging markers in MDD and response to ECT.

1. Introduction

1.1 Burden of disease and definition

Major Depressive Disorder is a psychiatric disorder that affects approximately 280 million people in the world, 3.8% of the population, including 5% of adults (4% among men and 6% among women), and 5.7% of adults older than 60 years *(Institute of Health Metrics and Evaluation. GHDx)* and has a great impact the quality of life of patients and their families. This disorder is equally common in high- and low-income countries *(Kessler et al 2013).*

The socio-economic burden of depression is substantial, representing the leading cause of non-fatal health loss globally (7.5% of all Years Lived with Disability). Furthermore, MDD is one of the major contributors to suicide, a phenomenon that accounts for 1.5% of all deaths worldwide and that constitute one of the top 20 cause of death in 2015, and the second leading cause among 15-29 years old. *(WHO, 2017.)* Between 2010 and 2020, the economic burden of adults with MDD increased by 37.9%, reaching 326.2 billion (year 2020 values) *(Greenberg et al., 2021).*

In the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-V), the diagnostic criteria for MDD include the presence of 5 or more symptoms (at least one of which being either depressed mood or loss of interest/pleasure) among the following: depressed mood, loss of interest/pleasure, weight loss without dieting or gain of >5% of body weight in a month, insomnia od hypersomnia, psychomotor agitation or retardation, fatigue, feeling worthless or excessive/inappropriate guilt, decreased concentration, thoughts of death/suicide) for at least two weeks continuously, representing a change from previous functioning. These symptoms do not have to be caused by physiological effects of a substance or another medical condition, do not have to be attributable to diagnosis of other psychiatric disorders (schizoaffective disorder, schizophrenia, etc.) and the patient does not have an history of manic or hypomanic episode (*American Psychiatric Association. DSM-5, 2013).*

DSM-5 assumes that depression is a single category and that clinical presentations only vary according to severity, even if it allows for modifiers (melancholia and psychosis). This makes MDD an overly broad and heterogeneous diagnosis *(Paris; 2014)*. Different cluster of symptoms can in fact represent subtypes of this disorder. To date patients manifesting one of the two core symptoms (lack

of positive emotions or appearance of negative emotions) or with opposite symptoms (insomnia or hypersomnia / psychomotor agitation or retardation etc.) will receive the same diagnosis of MDD.

1.2 Genetic and biological characteristics

1.2.1 Genetic

A U.S. family-based study estimates the heritability of depression at 52% *(Wang et al., 2017),* for the general population the estimates are in the range of 35-45% *(Kendler et al., 2006)* and of 25% after considering contextual effects such as shared environment *(Munoz et al., 2016).* These studies provide profound evidence for genetic basis of MDD. Heritability is significantly higher in females than in males and most, but not all, genetic risk is shared across sexes *(Kamran et al., 2022)*. MDD has a highly polygenic form of inheritance, with multiple loci of small effect size interacting with each other and with environmental triggers. In psychiatry, the findings of genome wide association study (GWAS) for MDD and associated traits have proven to be more productive than earlier linkage studies and candidate gene association studies (*McIntosh et al., 2019).*

Hundreds of loci have now been reported in different large-sample GWAS that are significantly and strongly associated with MDD and associated traits *(Kendall et al., 2021) (Levey et al., 2021).* The most recent and large GWAS of depression included >1.3 million of participants and identified 243 genetic risk loci associated with MDD *(Als et al., 2023.).* Key genes are linked to synaptic function. In Table 1 genes of particular interest and the respective most impacted tissues are reported *(Fries et al, 2023).*

Table 1. Key genes linked to major depressive disorder.

Gene	**Known function and role**	**Representative impacted tissue**
NEGR1	Brain volume (hippocampus); social behavior and non-social interest; depressive- and anxiety-like behavior	Hypothalamus
DRD2	Reward; depressive-like behavior	Nucleus accumbens
CELF4	Sodium channel function; developmental disorders	Caudate
CCDC71	Cellular lipid metabolism and regulation of fat cell differentiation (predicted)	Amigdala
FADS1	Fatty acid regulation	Cerebellum

SPPL3	Cellular glycosylation processes	Prefrontal cortex (BA9)
TRAF3	Control of type-1 interferon response	Hypothalamus
LAMB2	Cellular adhesion; embryonic development	Blood

Combined with environmental stressors, the genetic variants may induce alterations of small effect at the cellular and physiological level and may ultimately increase the individual's vulnerability to future stressful events. Epigenetic regulation of gene activity has been recognized as a key mechanism conveying the lasting molecular impact of these stressors.

GWAS revealed also the polygenic and pleiotropic nature of psychiatric disorders, as many casual variants are shared between these disorders *(Watanabe et al, 2019).* MDD resulted genetically correlated with BD *(Coleman et al, 2020)*, anxiety and stress related disorders (with NUP210L as a potential mediator of the genetic correlation between these disorders) *(Mei et al., 2022),* late-onset Alzheimer's disease *(Lutz et al., 2020),* attention deficit hyperactivity disorder in childhood or adolescence *(Powell et al., 2021)* and insomnia *(Baranova et al., 2021).*

1.2.2 Molecular pathways and systems

There are different pathways potentially involved in the pathophysiology of MDD, following is a summary of the most studied ones.

Monoamine theory

One of the first theories about the pathophysiology of MDD is the "monoamine theory" that suggests the involvement of a deficiency in monoamines in the brain (serotonin 5-HT, noradrenaline NA) *(Hamon and Blier, 2013).* This hypothesis was supported by the fact that drugs that potentiate 5-HT and NA activity, like monoamine oxidase inhibitors and tricyclic antidepressants, could improve the symptomatology *(Krishnan and Nestler, 2008).* Many studies confirmed this theory but almost one third of the patients treated with drugs that exclusively act on the monoamine pathway do not respond to treatment. Furthermore, it has been shown that, by restricting 5-HT precursor tryptophan, not all patients show depressive episodes *(Kaltenboeck and Harmer, 2018).* The fact that monoamine deficiency may not be crucial in all the patients, point out to the relevance of other pathways and neurotransmitters in the pathophysiology of MDD.

Glutamate pathway

The glutamate system has been associated with depression, in fact many studies detected increased levels of this neurotransmitter in peripheral blood, cerebrospinal fluid, and brain of patients affected by MDD *(Sanacora et al., 2011*). Other studies report decreased glutamate levels in some brain regions, as supported by postmortem findings of reduced number of this kind of synapses *(Duman et al., 2019).* The blockage of N-methyl-D-aspartate receptors (NMDARs) has antidepressant effect while antidepressants reduce glutamate secretion and NMDARs *(Musazzi et al., 2013).* Furthermore, NMDAR antagonists have a strong and rapid antidepressant effect both on animal models and on the main symptoms of MDD patients *(Kadriu et al., 2019).* Preclinical studies show that a-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor (AMPAR) antagonists might reduce the depressive behavior increasing the levels of glutamate receptors 1 and 2 in mouse hippocampus *(Gould et al., 2008).*

GABA

Different studies show that patients with depression have neurotransmission or functional defects of GABA *(Ghosal et al., 2017) (Fee et al., 2017).* Patients with depressive symptoms but not patients in remission seem to show lower brain GABA levels compared to healthy controls *(Schur et al., 2016).* These results are confirmed from different postmortem studies in the prefrontal cortex of MDD patients *(Guilloux et al., 2012) (Karolewicz et al, 2010*). Mouse studies confirmed that a change in GABA levels may induce depressive-like symptoms *(Kolata et al., 2018).* A functional imbalance of GABA and glutamate systems might contribute to the pathophysiology of MDD, and the activation of GABA system could exert antidepressant effects *(Chen et al., 2019).*

Neurotrophins

The neurotrophic hypothesis of depression suggests that decreased levels of neurotrophins cause neuronal atrophy, neurogenesis reduction, glia cells support destruction, and that these effects are attenuated or reversed by antidepressants *(Duman and Li, 2012*). In particular, brain-derived neurotrophic factor (BDNF) resulted reduced by stress in animal studies, while antidepressants were able to counteract this effect *(Li et al., 2018*). Similar evidence was found in humans: BDNF has been reported to be reduced in the peripheral blood of MDD patients and some studies reported an increase of its levels in response to antidepressants and electroconvulsive therapy (ECT) *(Chiou and Huang, 2017) (Youssef et al., 2018) (Kishi et al., 2017).* In accordance with the hypothesis that BDNF

is an important synaptic regulator, Kojima and colleagues found that levels of BDNF pro-peptide were lower in patients with MDD than in controls and that this promoted long-term depression in the hippocampus *(Kojima et al., 2019).*

Stress response / HPA axis

Stress is a proven contributing factor for depression and causes a dysfunction of the HPA axis by promoting the secretion of hormones, including cortisol. 40-60% of MDD patients present an imbalance in the HPA axis, including elevated cortisol levels *(Holsboer and Ising, 2010) (Keller et al., 2017*). The increased cortisol levels are related to the severity of depression *(Nandam et al., 2019).* Depression and cognitive impairments are associated with stress-induced HPA axis dysfunction *(Keller et al., 2017*). Normally, stress promotes the secretion of glucocorticoids that activate glucocorticoid receptors (GRs), and through a negative feedback mechanism this leads to the termination of the stress response. In psychiatric disorders and in MDD in particular, this mechanism might be altered, with an insufficient inhibition of the regulatory feedback *(Keller et al., 2017) (Gomez et al., 2006)*. Membrane and nuclear receptors of glucocorticoids mediate important and different effects in several organs, including brain *(Koning et al., 2019) (Gray et al., 2017).* To date, there are no evidence of an antidepressant effects of treatments that regulate the HPA axis, but MDD patients exhibiting dysfunction of the HPA axis seem to show a worse prognosis *(Mickey et al., 2018) (Stetler and Miller, 2011) (Aubry, 2013).*

Inflammation

The cytokine theory of MDD assume that MDD and a dysregulation of the inflammatory response are deeply associated *(Pariante, 2017).* It has been shown that a sustained immune response may be linked to depression. In particular, specific proinflammatory cytokines and their receptors (such as IL-6, IL 1, TNFα, IL-1β, IL-2, IL-2 receptor, IL-4, IL-10, the IL-1 receptor antagonist, TGFβ, C-reactive protein (CRP)) are involved and for some of them, their levels correlate with symptom severity *(Beurel et al., 2020) (Haapakoski et al., 2015) (Lamers et al., 2020).* CRP has also been associated with treatment response *(Chamberlain et al., 2019*). In response to high levels of damage-associated molecular patterns (DAMPs) and other stress molecules, the inflammasome pathway can be activated *(Alcocer-Gómez et al., 2014) (Miller and Raison, 2016).* The interaction between the peripheral and the central immune system is complex and a peripheric inflammation can spread and cause neuroinflammation in multiple ways *(Miller and Raison, 2016) (Li et al., 2017).* In general,

patients with MDD show increased levels of proinflammatory cytokines and their receptors, chemokines, and soluble adhesion molecules both in peripheral blood and cerebrospinal fluid. Markers of peripheral immune-inflammatory response can be also used as markers of antidepressant therapy response *(Mao et al., 2018) (Haroon et al., 2018).*

Several studies proved that antidepressants significantly reduced peripheral levels of inflammatory cytokines, while untreated patients or non-responders had higher levels *(Kohler et al., 2018) (Syed et al., 2018).*

Additional evidence that inflammation plays a significant role in the pathophysiology of MDD has been provided by recent studies showing that an excessive production of proinflammatory factors and cytokines in the central nervous system (CNS) from the microglia may cause depression-like behavior. An imbalance of the two types of microglia (the one that produces pro-inflammatory cytokines and the one that produces anti-inflammatory cytokines) may contribute to the pathophysiology of depression. *(Innes et al., 2019) (Sochocka et al., 2017) (Zhang et al., 2018)*

Mitochondria dysfunction

Different studies enlightened an association between MDD and altered mitochondrial structure and functions, disrupted mitochondrial dynamics and rare mitochondrial disorders *(Scaini et al., 2022) (Klinedinst et al., 2015) (Kuffner et al., 2020).* Mitochondrial disruption causes higher levels of free radicals and in general oxidative stress, factors that have also been associated with MDD, while the antioxidant capacity is decreased *(Somani et al., 2022).* Oxidative stress may play a role in the alteration of brain structures in MDD and increased oxidative stress can also enhance mitochondrial dysfunction, contributing to inflammatory response *(Bhatt et al., 2020).* Preclinical and clinical studies suggest that mitochondria and oxidative stress play an important role in MDD, highlighting the importance of studying the antidepressant effect of drugs targeting these systems *(Riveros et al., 2022) (Jiménez-Fernández et al., 2015).* Mitochondria involvement in MDD and cellular aging will be further discussed in Section 2.1.

Microbiome-Gut-Brain Axis

Metabolites produced by the interaction of the host metabolism and gut microbes have an impact on physiological processes. Some metabolites can also cross the blood brain barrier, reach the brain, and influence different pathways, while others can trigger peripheral effects with repercussions on the brain (like changing in hormones and cytokine profile) *(Rea et al., 2020) (Cryan et al., 2019)*

(Foster et al., 2013). The gut microbiome differs in MDD patients, and there is a proven correlation between depression and gastrointestinal diseases *(Marin et al., 2017) (Zheng et al., 2016) (McGuinness et al., 2022)*. Among the possible mechanism involved, the hypothesis is that gut microbiota affects the levels of different neurotransmitters both in the gut and in the brain (serotonin, dopamine, noradrenaline, glutamate, and GABA), and is able to impair the gut barrier and promote inflammation *(Diviccaro et al., 2019) (Kiecolt-Glaser et al., 2018).* Preclinical studies show that stress can lead to depressive-like behavior and changes in intestinal microflora composition, while different clinical trials have shown that some probiotic can attenuate depressive-like behavior with antidepressants effect *(O'Mahony et al., 2009) (Hao et al., 2019) (Messaoudi et al., 2011) (Rudzki et al., 2019).* Different studies focused on tryptophan's metabolism through the kynurenine pathway, that can product neurotoxic or neuroprotective metabolites. This pathway is involved in different mechanisms implicated in depression (immune cell activity, stress, oxidative stress, mitochondrial function, BDNF signaling) *(Cervenka et al., 2017) (Chen et al., 2021) (Roth et al., 2021) (Fries et al., 2023).*

1.3 Pharmacological treatments for the management of MDD

The management of MDD consist in managing the acute phase but also maintaining the remission phase and prevent relapse. Different approaches are used to reach this goal, the most important is the pharmacotherapy. Psychotherapy and somatic treatments are other strategies that will be further discussed in Section 1.5.

The ultimate goal of pharmacological treatments is to find a medication that can exert quick effectiveness but with the fewest side effects possible. The main classes of antidepressants are presented in an overview.

- **Monoamine oxidase inhibitors (MAOi)**

  MAOis (ex: Isocarboxazid, Phenelzine, Tranylcypromine, Selegiline) are responsible for blocking the monoamine oxidase enzyme and consequently increase levels of different neurotransmitters (norepinephrine, serotonin, dopamine and tyramine) by blocking the enzyme that is principally responsible for their degradation *(Baker et al., 1992).* There are two types of MAO enzymes, A and B (present in the brain, liver, and platelets), that have different substrates and can be inhibited, selectively or not, by different drugs *(Müller et al., 2017).* Due to the inhibition of monoamine oxidase, these drugs have several side effects such as

hepatotoxicity and hypertensive crises that can lead to intracranial hemorrhages. To date, MAOis are less commonly used. They have similar efficacy compared to tricyclic antidepressants (TCAs) but considering the restrictions (drug interaction, dietary restriction, severe side effects), they are prescribed only in patients that do not respond to all the other classes of antidepressants (*López-Muñoz et al., 2007).*

Their use seems indicated in depression with atypical features (reactive moods, reverse neuro-vegetative symptoms, sensitivity to rejection) *(Henkel et al., 2005*). These drugs are also a potential therapeutic option when the ECT is contraindicated *(Culpepper and Kovalick, 2008).*

- **TCAs**

  TCAs (ex: Imipramine, Amitriptyline, Doxepin, Desipramine, Nortriptyline) inhibit the reuptake of neurotransmitters like serotonin and norepinephrine, increasing their levels in the synapsis cleft *(Hillhouse and Porter, 2015).*

  TCAs show affinity for several types of receptors, and this can cause different side effects: due to the inhibition of cholinergic receptors their use can cause blurred vision, constipation, xerostomia, confusion, urinary retention, tachycardia etc.; due to the alpha-1 adrenergic receptor inhibition they can induce orthostatic hypotension, while due to the blockage of histamine 1 receptor they can cause sedation, increased appetite, weight gain and confusion *(Güloglu et al., 2011) (Trindade et al., 1998) (David and Gourion, 2016).*

  TCAs to date are mainly used when first-line therapies failed and in patients with severe MDD symptoms that required hospitalization *(Anderson, 1998) (Cleare et al., 2015).*

- **Selective Serotonin Reuptake Inhibitors (SSRIs)**

  These drugs selectively inhibit the serotonin reuptake, enhancing its level in the synapsis. SSRIs (ex: Fluoxetine, Paroxetine, Sertraline, Citalopram, Escitalopram) are considered the front-line treatment for MDD both for adults and children *(Garnock-Jones and McCormac, 2010) (Emslie et al., 2005).* SSRIs are also used for the maintenance of remission phase and to prevent relapse *(Kaymaz et al., 2008) (Garnock-Jones and McCormac, 2010).* These drugs have a good tolerability even if some studies show different tolerance rates and side effects mostly sexual and digestive (such as nausea and loss of appetite*) (Amick et al., 2015) (Magni*

et al., 2013). As regards to efficacy, SSRIs result comparable to TCAs but with less severe side effects *(MacGillivray et al., 2003*). Different studies did not highlight significative differences in the efficacy of individual SSRIs (*Montgomery, 2001) (Bauer et al., 2007).*

Importantly, they present a delayed onset of efficacy (2 to 4 weeks), and this can affect the compliance of this class of drugs but also many of the others *(Gelenberg and Chesen, 2000).*

- **Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs)**

  SNRIs (ex: Venlafaxine, Desvenlafaxine, Duloxetine, Levomilnacipran) inhibit the presynaptic neuronal uptake of serotonin and norepinephrine and prolong the effects of the monoamines in the synaptic cleft in the CNS, leading to increased postsynaptic receptor activation and neuronal activities. These drugs are a versatile class of medication with several clinical applications *(Shelton, 2019)*. SNRIs are usually prescribed to patients who do not respond to SSRIs *(Montgomery, 1998)*. Their efficacy results comparable to SSRIs and TCAs *(Thase et al., 2007) (Bauer et al., 2009).*

  The non selectivity of these drugs makes them similar to TCAs, but with less side effects, that include anxiety, insomnia, and restlessness, possible sexual dysfunction and headaches. Compared to SSRIs they can provoke also dry mouth and in rare cases increased blood pressure *(Stewart et al., 1993).*

- **Other antidepressants**

  Mirtazapine: this drug inhibits norepinephrine alpha-2 auto-receptors, allowing more norepinephrine to be released from nerve terminals, and blocks 5-HT2A/2C receptors, thus allowing more serotonin, dopamine, and norepinephrine modulation in the cortex. This drug has different side effects compared to other antidepressants: daytime sedation rates are high, weight gain, although it is associated with a low rate of sexual dysfunction *(Stewart et al., 1993).* Different studies highlighted faster onset of efficacy but not significative differences of effectiveness between this drug and SSRIs *(Quitkin et al., 2001) (Thase et al., 2004).*

  Trazodone: the mechanism of action is still not completely understood; it has both agonist and antagonist properties on serotonin reuptake pumps and 5-HT2A/2C receptors *(Pazzagli et al., 1999) (Haria et al., 1994),* increasing serotonin levels in the CNS. It also blocks the histamine H1 and alpha-1-adrenergic receptors. Trazodone has better tolerance than second-

generation antidepressant and avoids the issue of sexual dysfunction, insomnia, and anxiety that are commonly present with SSRIs and SNRIs therapy *(Fagiolini et al., 2012).* This drug can induce sedation, and this is the side effect that most limits its use. It is mostly prescribed in patients with MDD and anxiety disorder and insomnia *(Golden et al., 2009)*.

Bupropion: it has a dual mechanism, is a norepinephrine–dopamine reuptake inhibitor (NDRI), raising dopamine and norepinephrine levels *(Papakostas et al., 2008).* It is considered comparable to SSRIs in MDD patients with low or moderate anxiety *(Li et al., 2005) (Schwartz and Rashid, 2007)*. Usually, it is prescribed in a combined polytherapy, often added to an initially prescribed SSRI *(Stewart et al., 1993) (Schwartz and Rashid, 2007)*. Bupropion can improve symptoms of fatigue and sleepiness *(Papakostas et al., 2008).* It does not cause sexual dysfunction or weight gain. On the contrary, it may cause weight loss and it is in fact contraindicated in patients with eating disorders.

Vilazodone: this drug both exerts serotonin reuptake inhibition and interacts with serotonin receptors exerting a pro-serotoninergic effect. *(Schwartz and Stahl, 2011)*. In particular it is a strong, pre- and post-synaptic, 5HT1A receptor partial agonist. Vilazodone has lower risk of weight gain and sexual dysfunction compared to other drugs.

Vortioxetine: besides the inhibition of the serotonin reuptake, it has mixed agonist and antagonist effect on different serotonin receptors *(Schatzberg and DeBattista, 2015)*. A meta-analysis ranked vortioxetine above escitalopram, trazodone and sertraline for efficacy and tolerability *(Llorca et al., 2014)*. The possibility of sexual dysfunction, weight gain and sedation are lower compared to other drugs *(Schatzberg and DeBattista, 2015)*. Furthermore, vortioxetine seems to improve cognitive function in adults with recurrent MDD *(McIntyre et al., 2004).*

Ketamine and related molecules: this drug exerts a glutamate modulation through effects at the N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, as well as downstream activation of brain-derived neurotrophic factor (BDNF) and mechanistic target of rapamycin (mTOR) signaling pathways to potentiate synaptic plasticity *(Matveychuk et al., 2020).* It is a fast-acting antidepressant, very useful in

cases of unipolar and bipolar resistant depression and acute suicidal ideation *(Bobo et al., 2016) (Martin, 1989).* This drug can induce common side effects (dizziness, cognitive dysfunction, psychosis, urological dysfunction, nausea, vomiting, cardiovascular symptoms) and prolonged exposure can induce neurotoxicity and drug dependence, other than addiction and drug abuse. For all these reasons it is not recommended in daily clinical practice *(Liu et al., 2016) (Thase et al., 2007) (Caddy et al., 2014) (Sanacora et al., 2017).* More recently, intranasal formulation of esketamine, ketamine entantiomer, has been approved by the FDA for treatment resistant depression and exerts good effects in combination with oral antidepressants *(Daly et al., 2018).*

1.4 Treatment-Resistant Depression

As already mentioned above, pharmacological intervention is the first choice for the management of both unipolar and bipolar depression. It was already highlighted that MDD is a heterogeneous disorder and a significant percentage of people affected are resistant to conventional treatments *(McLachlan, 2018).* It is accepted that even if antidepressants medication can be effective to treat MDD, 1 out of 3 patients fails to achieve remission *(Kennedy and Giacobbe, 2007).* The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, pointed out that the cumulative remission rate after four trials of antidepressant treatment in 14 months, was 67% *(Rush et al., 2006).* The treatment of bipolar depression is complex because there are few drugs with proven efficacy and the use of antidepressants is controversial *(Geddes and Miklowitz, 2013) (Pacchiarotti et al, 2013)*, due to the risk for manic switch *(Vazquez et al., 2011)* and the higher risk of suicidal ideation *(Fergusson et al., 2005) (McElroy et al., 2006)*. However, for both unipolar and bipolar depression, antidepressant treatment in monotherapy or in combination with other psychotropic medications are the first choice, even if only 40 to 60% of treated patients show a significant improvement of symptoms *(InformedHealth.org; acc. Sept. 2021) (Rush et al., 2006)*. TRD in fact concerns 10-30% of patients with MDD *(Rush et al., 2006) (Al-Harbi et al., 2012) (Khan and Brown, 2015)* and 75% of unresolved morbidity of bipolar disorder (BD) *(Tondo et al., 2014).*

TRD is a complex phenomenon, and it is a challenge condition for psychiatrists and primary care clinicians *(Rush et al., 2006).*

The definition of TRD adopted by the Food and Drug Administration (FDA) and the European Medicine Agency (EMA) is failure to respond to two or more antidepressant treatments of adequate dose and duration, despite treatment adherence *(McIntyre et al., 2023)*. Other definitions of TRD have been proposed and several staging models have been developed to classify levels of TRD. Among the most used, the Thase and Rush staging model defines a continuum of failed antidepressant trials *(McIntyre et al., 2023)*. In particular, Stage III of Thase and Rush Staging Method defines TRD as a failure to respond to two or more adequate trials of two or more different classes of antidepressants and to an adequate trial of a TCA drug *(Thase and Rush, 1997).*

Among MDD patients, TRD is associated with the highest direct and indirect medical costs. In fact, people with TRD are twice as likely to be hospitalized and the costs of the hospitalizations are six times higher compared to the average cost of the management of patients with MDD not resistant to treatments *(Crown et al., 2002) (Gibson et al., 2010 (Ivanova et al., 2010).* The higher costs attributable to TRD are caused by an increase of both direct and indirect costs. Direct costs consist of increased need to use healthcare and higher intensity treatments *(Jensen et al., 2022) (McIntyre et al. 2019)*, while indirect costs are consequence of a grater impairment of the psychosocial function of patients with TRD (increased need of disability benefits, workplace disability and absenteeism, negative impact on carers) *(McIntyre et al. 2019) (McIntyre et al. 2014) (Heerlein et al., 2022) (Rathod et al., 2022) (Lynch et al., 2022) (Chan et al., 2022) (Deene et al., 2022).*

Moreover, both current suicidality and lifetime suicide attempts were significantly more common in TRD patients than in non-TRD patients *(Corral et al., 2022)*.

Many studies tried to evaluate factors associated with reduced response to antidepressants, but only fewer examinate factors associated specifically with TRD. In a very recent review, McIntyre and colleagues tried to separate these aspects and to individuate factors associated with TRD *(McIntyre et al. 2023)*:

-Sociodemographic factors

- Age: older people more likely fail multiple trials with monoamine-based antidepressants and this might be evidence that this subpopulation is more prone to develop TRD. Nevertheless, manual-based psychotherapeutic treatments, ECT and repetitive Transcranial Magnetic Stimulation (rTMS) do not seem to be less efficient in patients with depression *(Cuijpers et al., 2020) (Dominiak et al., 2021) (Kaster et al., 2018).*

- Sex: since females affected by depression are more than males and assume antidepressant more frequently *(Kuehner et al., 2017)*, we should expect similar ratio in TRD, but if the relative risk to develop TRD in female is higher has not be proven *(Lähteenvuo et al., 2022)*.

- Socioeconomic position: the STAR*D trial point out that persons with low income and dependence on the public health system, more likely met level 2 criteria (inadequate response to two sequential antidepressants regimen) *(Trivedi et al., 2006)*. Furthermore, people unemployed or with lower educational level, more often are resistant to different antidepressant trials *(isHak et al., 2017)*.

There are not enough investigations to assess if there are any differences among ethnic groups, or based on sexual orientation or gender identity, marital status, in the occurrence of TRD.

-Adverse experience and trauma

Different studies highlighted the association between history of childhood emotional abuse and recurrent and persistent depression as well as treatment resistance to antidepressants *(Teicher et al., 2022) (Wang et al., 2022) (Yang et al., 2021) (Menke et al., 2021) (Williams et al., 2016)*.
A recent study reported that only 15.9% of MDD patients with a history of childhood trauma treated with escitalopram, sertraline or venlafaxine achieve remission after 8 weeks of treatment compared with 84.1% of MDD patients without history of trauma *(McAllister-Williams, 2022)*. Interestingly, it seems that vortioxetine and ketamine response is not reduced in patients with trauma *(Christensen et al., 2020) (O'Brien et al., 2019)*. Yrondi and colleagues showed that life stress in general is directly related to a poorer response to common antidepressants, greater severity of symptoms, greater occurrence of suicidal behaviour and comorbidities, and all these factors relate with a poorer response to medication and possibly with TRD *(Yrondi et al., 2021).*

-Clinical factors

Grater baseline severity of symptoms, illness duration *(Scott et al., 1992)* and psychotic symptoms *(McIntyre et al., 2020)* have been considered highly replicable risk factors for TRD.

Mixed features, present in around 25% of MDD patients, are associated with lower antidepressant response but it remains to be determined if they represent a risk factor specifically for TRD *(McIntyre et al., 2017)*. Anhedonia, core symptom of MDD, might be considered a risk factor for treatment resistance to SSRIs *(Cao et al., 2019) (Goodwin et al., 2017)*.

Cognitive deficits in patients with MDD are associated with lower response to antidepressants and might be considered risk factors for TRD *(McIntyre et al., 2013) (Millan et al., 2012) (Rosenblat et al., 2015)*.

TRD patients often report anxiety symptoms, and the STAR*D trial indicate that MDD patients with anxiety have attenuated response to antidepressants and are more likely to develop TRD *(Fava et al., 2008)*. These results are confirmed by the Group for the Study of Resistant Depression (GSRD), a multinational European research consortium that reported that anxiety disorder is over-represented in persons with TRD *(Kautzky et al., 2019)*.

Psychiatric and physical comorbidities present with higher rate among TRD patients *(McIntyre et al., 2012)*. Furthermore, TRD is also considered a risk factor for physical comorbidities such as cardiovascular disease, type 2 diabetes mellitus, metabolic syndrome and vice versa *(Cao et al. 2022) (Grigolon et al., 2021) (Rashidian et al., 2023) (Toups et al., 2013) (Beran et al., 2022) (McIntyre et al., 2007).*

Although genetic biomarkers to identify patients with TRD are not available yet, some genes have been replicated by early candidate-gene studies, such as: GRIK4, BDNF, SLC6A and KCNK2. However, these results often lack confirmatory evidence in larger cohorts. While pathways including genes involved in actin cytoskeleton, neural plasticity and neurogenesis may be associated with TRD, GWAS studies failed to identify genome-wide association at variant levels *(Fabbri et al., 2019).*

Recently it has been hypothesized that treatment resistance might be characterized by specific biological characteristics *(Klok et al., 2019)* and in support of this hypothesis different studies aimed at identifying candidate biomarkers specifically associated with this condition. Many studies reported elevated serum levels of pro-inflammatory cytokines such as CRP, IL-6, and TNF-alpha (*Strawbridge et al., 2015) (Chamberlain et al., 2019)* in TRD patients. Also, neutrophil-lymphocyte ratio (NLR), a marker of systemic inflammation, seems to be inversely associated with response to antidepressants *(Llorca-Bofí et al., 2021)*, and resulted lower in patients with TRD compared to non-TRD *(Buoli et al., 2022)*. While some products of oxidative damage have been reported to be increased, antioxidant agents (such as albumin, high density lipoprotein cholesterol, uric acid) have been shown to be

decreased in depressed patients compared to controls *(Liu et al., 2015)*. Bilirubin, an endogenous antioxidant might be influenced by oxidative stress and total serum bilirubin levels are reported lower in different psychiatric disorders, including MDD *(Dipnall et al., 2016) (Jayanti et al., 2020)*. Furthermore, lower bilirubin levels measured in serum are found in patients with TRD compared to non-TRD ones *(Buoli et al., 2022).*

1.4.1 Management of TRD

Therapeutic options for the TRD management include augmentation of traditional pharmacological treatments, optimization of the antidepressant pharmacotherapy, novel therapeutic drugs either approved or investigational (such as ketamine, psilocybin, anti-inflammatories), second-generation antipsychotics, psychotherapy, the brain stimulation with repetitive Transcranial Magnetic Stimulation (rTMS), magnetic seizure therapy (MST), deep brain stimulation (DBS), vagus nerve stimulation (VNS) and most of all ECT described in Section 1.5.2 *(Voineskos et al., 2020) (McIntyre et al., 2023).*

The extension of the antidepressant trial in patients with TRD does not guarantee treatment success, but different studies evidenced that a proportion of patients that did not respond to 4-week trials, responded after 5-8 weeks (20%) or after 9-12 weeks (10%) *(Henssler et al., 2018)*. Of course, the treatment extension is not well accepted among patients that prefer the rapidity of antidepressants effects *(Rosenblat et al., 2019)*.

Another strategy is switching antidepressants, even if meta-analytic data are in conflict about the efficacy for TRD *(Brignone et al., 2016) (Bschor et al., 2018)*. In some cases of TRD it can be useful to switch class of antidepressant with a different mechanism of action, for example Fagiolini and colleagues reported the effectiveness of vortioxetine, mixed agonist and antagonist in different serotonin receptors, in patients non-responders to SSRI *(Papakostas et al., 2007) (Fagiolini et al., 2021)*.

Commonly, patients with TRD are treated with a combination of antidepressants. The actual efficacy of polypharmacy has still to be fully investigated, even though different studies suggest this is successful *(Grover et al., 2022) (Strawbridge et al., 2019) (Scott et al., 2023) (Henssler et al., 2022)*.

Ketamine and esketamine (intravenous and intranasal) improve symptoms of TRD and more in general medications that affect glutamatergic pathway seem to be superior to antipsychotics in

adults with TRD *(Zheng et al., 2022) (Nogo et al., 2022) (Zheng et al., 2021) (Wilkowska et al., 2021)*. Despite the proven efficacy of these drug, there are safety concerns for long-term treatment, such as the chance of severe side effects, abuse, and withdrawal *(Schatzberg, 2019)*. These risks might be mitigated by administering these drugs under medical supervision as the best practice recommends *(McIntyre et al., 2021)*.

Another pharmacological strategy for the management of TRD is the prescription of second-generation antipsychotics, but to date the only one evaluated for TRD is the combination of olanzapine and fluoxetine *(Corya et al., 2005) (Corya et al., 2006) (Thase et al., 2007)*.

There are others second generation antipsychotics, such as aripiprazole, cariprazine, quetiapine and risperidone, that have been evaluated for MDD patients who present a partial response to at least one antidepressant *(Strawbridge et al., 2019) (Vázquez et al., 2021) (Berman et al., 2007) (McIntyre et al., 2007) (Fava et al., 2018) (Mahmoud et al., 2007)*.

In small open label or pilot investigations of patients with TRD the utility of psylocibin has been also evaluated. Psylocibin is a psychedelic compound that after metabolization become a partial serotonin receptor agonist. Carhart-Harris and colleagues, in a study of 12 patients, found that this compound have a response rate of 58% up to three months after two doses, even if the psychedelic effects last for approximately six hours and patients experienced transient anxiety and mild tachycardia *(Carhart-Harris et al., 2016).*

It has been proven that patients with TRD, as well as patients with MDD, have increased level of inflammatory cytokines and in particular of C-reactive protein *(Cattaneo et al., 2016) (Strawbridge et al., 2015)*. Since inflammation might play a role in treatment resistance, the use of anti-inflammatory drugs has been investigated. Cyclooxygenase-2 inhibitors (COX-2 inhibitors) have been evaluated in combination with traditional antidepressants *(Na et al., 2014) (Faridhosseini et al., 2014)*, since patients with TRD showed elevated levels of prostaglandin *(Lieb et al., 1983).*

Infliximab, tumor necrosis factor antagonist, has been found to improve depressive symptoms in patients with TRD and elevated levels of CRP compared to TRD patients without elevated inflammatory markers *(Raison et al., 2013)*. Together these findings suggest that anti-inflammatory treatments might contribute to the management of TRD.

Other strategies for the management of TRD are psychotherapy interventions and neurostimulation, which will be further discussed in Section 1.5.

A recent review from Gkesoglou and colleagues evidenced that there are no specific baseline peripheral biomarkers that can be used in the clinical practice to predict the response to different pharmacological and non-pharmacological treatments in TRD patients *(Gkesoglou et al., 2022)*, but especially for invasive treatments such as the electroconvulsive therapy many studies are investigating different biomarkers of response as reported in Section 1.5.2.

1.5 Other strategies for the management of MDD and TRD

1.5.1 Psychotherapy

Psychotherapeutic interventions are extensively used to treat and prevent many psychiatric disorders, such as depression, anxiety, psychosocial difficulties, interpersonal problems. The therapeutic alliance is strengthened by psychotherapy for patients with MDD, it aids the patients to monitor their mood, improve their functioning, better comprehend their symptoms, and master the practical tools they need to cope with stressful events *(Malhi et al., 2015)*. There are multiple psychotherapy approaches and the one chosen usually mainly depends on patient's preference and the clinician availability *(Bennabi et al., 2019).*

Among the most used therapeutic approaches for MDD, cognitive-behavioral therapy (CBT) and interpersonal therapy (IPT) are particularly recommended.

Depression-focused psychotherapy is often considered the initial treatment for mild and moderate cases of MDD. After the remission, psychotherapy is proposed to prevent relapses and maintain remission *(Montgomery, 1989) (Malhi et al., 2015) (Qaseem Aet al., 2016).*

A specific therapeutic support is recommended for patients with chronic depression that present high rates of psychiatric comorbidities, early traumas, and attachment deficits *(Karrouri et al., 2021).*

In Table 2 the most indicated psychotherapeutic approaches and the indication are reported *(Karrouri et al., 2021).*

Table 2. Overview of psychotherapy in different clinical situations of depression

Clinical Situations	Type of psychotherapy	Indication
Mild to moderate MDD	CBT, IPT	Recommended initial treatment
	ST, PEI	Less evidence
Severe MDD	ST, PEI	Add on therapy to pharmacological treatment
After remission	CBT, PEI, MBCT Effective psychotherapy used during episode	Maintenance and prevention
Chronic depression	SIPS, CBASP Specific approach adapted to the patient's preferences	Recommended for comorbidity with personality disorders, early trauma and attachment deficits

Abbreviations: MDD: Major depressive disorder; CBT: Cognitive-behavioral therapy; IPT: Interpersonal therapy; ST: Supportive therapy; PEI: Psycho educational intervention; MBCT: Mindfulness based cognitive therapy; SIPS: Specific and intensive psychotherapeutic support; CBASP: Cognitive Behavioral Analysis System of Psychotherapy.

Cuijpers and colleagues in a meta-analysis highlighted that the effect sizes of studies of psychotherapy in children and even more in adolescents, are significantly smaller than those in adults. Interestingly they found that the effect sizes of psychotherapies were larger in young adults (18-25y), compared to middle-aged adults (24-55 y) while no meaningful differences were observed between middle-aged adults, older adults, and older old adults *(Cuijpers et al., 2020).*

Although psychotherapy is effective in treating MDD, the mechanisms that consent the remission of depressive symptoms are not completely understood *(Chen et al., 2019*). In fact, psychotherapy is mostly aimed at treating the behavioral factors of MDD, such as dealing with stressful life events, lack of exercise, poor coping strategies, and sociocultural factors *(Neitzke, 2016) (Woodend et al., 2015)* and it does not focus on treating biological factors associated with MDD, this is the reason why often a combined treatment strategy is needed for the management of these patients *(Boschloo et al., 2019)*.

In particular for TRD, there are evidence of the effectiveness of psychotherapy interventions *(Markowitz et al., 2022) (Fonagy et al., 2015) (Hauksson et al., 2017)*. Furthermore, in the TRD population there is a high rate of patients with persistent depression of course, and history of trauma that seems to effectively respond to psychological interventions *(Kraus et al., 2022) (Yrondi et al., 2020).*

1.5.2 Somatic treatments

Based on the lack of efficacy of available medications for a significative percentage of patients with MDD, non-pharmacological somatic treatments, and emerging new tools for neuromodulation, are a treatment option for specific groups of patients. *(Rush et al., 2006)*

Here a quick overview of the most used somatic treatments, with a focus on ECT.

- Repetitive transcranial magnetic stimulation (rTMS)

  rTMS is based on a device that generates a pulsating electric current that, by passing through a coil, creates an alternating magnetic field that depolarizes the underlying brain tissues *(Wagner et al., 2007).* It is a biological stimulation that affects brain metabolism and neuronal electrical activity, and it has extensively been studied in MDD *(De Risio et al., 2020).* It has been shown that rTMS can improve depressive symptoms compared to other fictitious stimulations *(Martinotti et al., 2019).*

  According to the World Federation of Societies of Biological Psychiatry's guidelines there are enough evidence of acute efficacy for TMS in depression in medication-free unipolar depressed patients (*Schlaepfer et al., 2010).*

  Combined treatment with rTMS and antidepressants are more efficient than placebo condition with mild side effects. In general, results on rTMS are encouraging but inconsistent, probably due to differences in treatment frequencies, parameters, and stimulation sites *(Brunoni et al., 2012).*

  Recent studies consistently report the efficacy of rTMS for TRD *(Adu et al., 2022)*, even if this efficacy seems to be attenuated by greater severity at baseline and higher number of antidepressant trials failed *(Kar, 2019) (Fitzgerald et al., 2016)*. Nevertheless, many studies point out that ECT might be more effective than the conventional rTMS in the acute and recurrence prevention treatment of TRD *(Zhao et al., 2018) (Health Quality Ontario, 2016)*. Novel forms of rTMS have been validated and proven to be effective for TRD patients: intermittent theta burst stimulation (iTBS) *(Hsu et al., 2019) (Blumberger et al., 2018)*, accelerated high-dose iTBS protocol with magnetic resonance imaging (MRI)-guided functional connectivity targeting also called Stanford Neuromodulation Therapy that have been recently approved by the FDA for TRD *(Cole et al., 2022).*

- Transcranial Direct Current Stimulation (tDCS)

  tDCS consists of a unidirectional constant flux of low-intensity current (1-2 mA) from a sponge electrode (soaked with saline solution) to the other. The effect of this procedure depends on modifications of NMDA-receptor efficacy *(Nitsche et al., 2003) (Nitsche et al., 2004).* It has been shown that tDCS can modulate prefrontal cortex excitability and, because of this effect, can be used as a possible tool for the treatment of depression. The antidepressant effect may also involve long-term neuroplastic changes that continue to occur even after the treatment, a factor that would explain the delayed efficacy.

  tDCS can be used in monotherapy or as a complementary intervention to reduce depressive symptoms in unipolar or bipolar depression patients *(Stagg et al., 2018).* While this treatment resulted to be effective in different studies *(Fregni et al., 2006) (Boggio et al., 2008),* its effects seem to be lower than that of antidepressants and rTMS (*Mutz et al., 2019) (Moffa et al., 2020).*

  The use of this tool has some advantages: it is inexpensive, easy to use, relatively safe (some case reports of skin lesions or burns) *(Palm et al., 2008)* and tolerable, in fact only few side effects are reported (slight tingling under the electrodes, headache, fatigue, and nausea) (*Bikson et al., 2018).* tDCS is associated with heterogenic outcomes in TRD patients *(Ramasubramanian et al., 2022)*

- Vagus Nerve Stimulation (VNS)

  VNS is a surgical option based on the implantation of a pacemaker under the collarbone connected to an electrode surrounding the left vagus nerve that exerts numerous actions such as the enhancement of cortical inhibition and the influence on hippocampal plasticity *(Zuo et al., 2007).* From 2005 is approved by the FDA for patients with chronic or recurrent depression who failed to respond to at least four antidepressant trials; but it is not used very often *(Shah et al., 2014) (Kraus et al., 2022) (Sackeim et al., 2020).*

  Different studies demonstrated the efficacy of VNS in resistant depression *(Cristancho et al., 2011) (Schlaepfer et al., 2018).*

- Deep Brain Stimulation (DBS)

  DBS involves a neurosurgical procedure to stereotactically implant electrodes into a specific brain region; these electrodes are connected to a subcutaneous implantable pulse generator that controls stimulation and provides the power source for the DBS system. Typically, continuous electrical stimulation is provided. DBS is a relatively well-tolerated therapy *(Delaloye and Holtzheimer, 2014).* The target for DBS electrode placement can vary significantly based on the disorder being treated and the neuroanatomical models of the disorder, good efficacy in treatment of Parkinson's disease, essential tremor, dystonia and in several neuropsychiatric disorders *(Johnson et al., 2008) (Nuttin et al., 1999) (Vandewalle et al., 1999) (Laxton and Lozano 2012).* According to literature, DBS of the subgenual cingulate white matter elicited a clinical response in 60% of resistant depression patients after six months and clinical remission in 35% of patients *(Mayberg et al., 2005).* Targeting other brain regions like nucleus accumbens gained interest more recently *(Kosel et al., 2003).* DBS is a relatively well-tolerated therapy, the most common adverse events being associated with the neurosurgical procedure: infection, hemorrhage, perioperative headache, seizure, and lead fracture *(Appleby et al., 2007).* Specific side effects can be associated with acute and chronic stimulation. Different studies did not document the efficacy of DBS compared to sham treatment, for TRD *(Hitti et al., 2021) (Zhou et al., 2018).*

- Magnetic seizure therapy (MST)

  MST is based on the application of a magnetic stimulation of the brain in the patients under anesthesia to induct therapeutic seizures. It exerts a more focal induction, thanks to the enhanced precision in targeting, avoiding possible side effects (*Lisanby et al., 2001)*. MST requires muscle relaxation and general anesthesia, with lower dosages of anesthetic compared to ECT *(White et al., 2006).*

  Evidence supporting its effectiveness on depressive symptoms continues to grow, and it appears to induce fewer neurocognitive effects than ECT *(Kallioniemi et al., 2019) (Bottai, 2008) (McClintock et al., 2011).*

  Although a recent review did not find any different outcome between MST and the electroconvulsive therapy *(Jiang et al., 2021)*, the efficacy of MST for TRD is supported by different studies suggesting the continuation of effect also after the end of the treatment *(Daskalakis et al., 2021) (Tang et al., 2021)*.

- Phototherapy or luxtherapy

  This therapy is based on the fact that intense light exposure was associated with reduced depressed symptoms *(Sack et al., 1990).* Phototherapy resulted effective both for seasonal and non-seasonal depression and has also benefits on sleep deprivation and drug treatments *(Merkl et al., 2009) (Eniola et al., 2016).*

- Electroconvulsive Therapy (ECT)

  ECT is based on the application of electrodes placed on the scalp of patients (under anesthesia and muscle paralysis) and the application of electricity to the brain that generates generalized tonic-clonic seizures *(APA, 2001)*. Seizures induced by this procedure affect brain chemistry, neural activity and connectivity with several clinical effects that have been shown to be helpful for different conditions like psychosis, catatonia, repetitive injurious behavior in autism, status epilepticus and depression *(Lisanby, 2007).*

  The technical parameters, such as temporal waveform, electrode placement, pulse shape and width, train frequency, duration, and directionality, play a crucial role on ECT efficacy and side effects *(Peterchev et al., 2010).* This procedure results safe, with risks linked to surgical procedures under general anesthesia *(Blumberger et al., 2017) (Tørring et al., 2017)*. Mortality rate is estimated at 2.1 per 100,000 treatments *(Tørring et al., 2017)* and it has been shown that ECT reduces all-cause mortality rates decreasing deaths for suicide *(Kaster et al., 2021) (Watts et al., 2021)*. Furthermore, different studies support the safe administration for different patients including pregnant *(Ward et al., 2018)*, adolescents *(Døssing et al., 2021.)* and geriatric patients *(Geduldig and Kellner, 2016.).* In patients receiving maintenance sessions, ECT can also reduce hospital length of stay and number of hospitalizations *(McCall et al., 2018).* Side effects of this procedure can be adverse cognitive events that can normalize in 2 weeks after ECT course *(Semkovska et al., 2020),* including postictal confusion and memory difficulties *(Hammershøj et al., 2022) (Andrade et al., 2016).* Different studies report memory loss extended for years after treatment, but this remains a contested issue *(Squire and Slater, 1983) (Donahue, 2000).*

  ECT is mainly considered the last option for treating depression and in particular treatment-resistant depression *(Karabatsiakis, and Schönfeldt-Lecuona, 2020)*. This is mostly due to the stigma still surrounding ECT, linked to early ECT techniques when it was performed without

enough knowledge on efficacy, safety, patients' choice and without the use of anesthesia and muscle relaxants *(Mathew et al., 2019 (Hermida et al., 2018).*

Even though it is often accompanied by cognitive side effects *(Semkovska et al., 2010),* ECT result highly efficacious for MDD and several other psychiatric disorders. Several studies report higher overall effect size compared to rTMS *(Micallef-Trigona, 2014.) (Berlim et al., 2013),* pharmacotherapies (*Kho et al., 2003) (The UK ECT Review Group, 2003)* including ketamine *(Rhee et al., 2022).* It is a well-established strategy for the management of TRD, with a remission rate of 48% in non-psychotic depression and this remission rate might be even higher for psychotic depression *(Zandi et al., 2022)*. Modifications of different parameters consented to improve the tolerability profile of this treatment maintaining the same efficacy for TRD *(Sackeim et al., 2008)*. Gazdag and Ungvari evidenced that ECT might be more effective in TRD patients when combined with antidepressants rather than alone *(Gazdag and Ungvari, 2019)*. Furthermore, it is recommended by the America Psychiatric Association for the management of both unipolar and bipolar depression *(American Psychiatric Association, 1990).*

The exact mechanisms of ECT that lead to antidepressant effect are still not completely understood, they involve effects on different brain structures and functions through several neurotransmitter systems, inflammatory processes, and neurogenesis *(Maffioletti et al., 2021).* Recently, Deng and colleagues reviewed different theories of mechanism of action of ECT, that will not be analysed in this work *(Deng et al., 2023).*

For the purpose of this work, I will now focus on biomarkers of efficacy and response to ECT *(Maffioletti et al., 2021).*

- <u>Neurotrophins</u>

  The neurotrophic effects of electroconvulsive shock (ECS), an accepted experimental analogue of ECT used in animal studies, and ECT, seem to be linked to the increase of the cerebral concentration of two neurotrophins: BDNF and VEGF (vascular endothelial growth factor) *(Polyakovaet al., 2015) (Altar et al., 2004).* Investigations in humans highlighted the augmentation of hippocampal volume after ECT and the analysis of peripheral tissues of MDD patients after ECT showed an increase in plasma levels of BDNF that could be linked to

changes in the brain. *(Nordanskog et al., 2010).* Studies on patients with MDD confirmed precedent animal studies: after ECT patients showed increased peripheral (plasma and serum) BDNF levels, in accordance with the thesis that this neurotrophin is a mediator of the ECT effects *(Rocha et al., 2016) (Bocchio-Chiavetto et al., 2016).* Some studies investigated whether BDNF could be used as predictor of response if measured before the treatment or in early phases, but three studies reported negative results regard the predictive power of peripheral baseline levels of BDNF **(***Maffioletti, et al., 2019) (Ryan et al., 2018) (Fernandes et al., 2009).*

VEGF resulted enhanced after ECT in TRD patients and lower VEGF serum levels at baseline seem to predict a lack of response to ECT, indicating that this neurotrophin could represent a predictive biomarker of response. *(Minelli et al., 2011) (Maffioletti et al., 2020) (Minelli et al., 2014).* Another neurotrophic factor is GDNF (glial cell-line-derived neurotrophic factor) that resulted increased after ECT in TRD patients, in particular in responders but not in non-responders *(Zhang et al., 2009).*

- <u>Inflammatory and Immune system</u>

  Inflammatory and immune system dysfunction, such increase in pro inflammatory cytokines, have been observed in patients with psychiatric disorders and MDD, and in particular with TRD, for which ECT is one of the most effective treatments. Higher baseline inflammation is linked to a decreased response to antidepressant drugs *(Stippl et al., 2020).* ECT treatment seems to induce an inflammatory-immune response in the short term, with increased inflammatory mediators such as IL-1beta, IL-6 and cortisol, but repeated treatment induce long-term down regulation of these systems (*Yrondi, et al., 2018).* Furthermore, ECT gradually reduces TNF-alpha levels *(Hestad et al., 2003).* After ECT, other mediators have been reported to be increased: neopterin (a protein produced by human monocytes and macrophages after immune activation) and kynurenic acid (produced in the kynurenine pathway that is more active during immune response) *(Lopresti et al., 2014) (Guloksuz et al., 2015).* There are also studies that evidenced higher baseline levels of IL-6 in patients that benefit the most from the treatment, and elevated CRP levels in patients with higher remission rates *(Kruse et al., 2018) (Carlier et al., 2019).* These latter results are in contrast with other evidence that indicate that inflammation contributes to poor treatment response, and therefore further studies are needed.

- Monoaminergic System

  ECT induces an activation of the mesocorticolimbic dopamine system through the regulation of different mechanisms: release of dopamine, the serotoninergic receptors, dopaminergic neurotransmission. These effects are supported by the observation of an improvement of typical dopaminergic functions (motivation, concentration and attention) after ECT treatment *(Nikisch and Mathé, 2008) (Tsen et al., 2013) (Baldinger et al., 2014).* It has also been shown that responders to ECT had higher baseline homovanillic acid (HVA) levels (a monoamine metabolite) compared to non-responders. Furthermore, HVA resulted increased also in cerebrospinal fluid but decreased in plasma of depressed patients after ECT *(Nikisch and Mathé, 2008) (Okamoto et al., 2008).*

- Glutamatergic System

  TRD patients that respond to ECT resulted having increased N-acetylaspartate (an amino acid related to neuron functionality) and glutamine/glutamate levels *(Michael et al., 2003) (Pfleiderer et al., 2003).* Moreover, ECT seems to normalize the reduction of glutamate levels in the anterior cingulate cortex in patients with MDD *(Zhang et al., 2013).*

- Endocrine System

  ECT enhances short-term effects on the release of hormones involved in the hypothalamic-pituitary-adrenal axis, such as adrenocorticotropin (ACTH), prolactin and vasopressin, and the increase is normalized 1 hour post treatment *(Florkowski et al., 1996).* Some studies highlighted a restored neuroendocrine activity, as well as a reduced cortisol response to dexamethasone (in the dexamethasone challenge test) after ECT *(Fosse and Read, 2013) (Vukadin et al., 2011*). This could mediate a restoration of vegetative functions (sleep, appetite, sexuality etc) and the remission of the depressed mood *(Haskett, 2014).*

- Oxidative stress system and mitochondrial biogenesis

  Oxidant status values resulted reduced while antioxidant status was significatively increased after ECT, suggesting that this treatment should not produce an oxidative stress on patients *(Senyurt et al., 2017)*. Studies that evaluate the effects of ECT on serum markers of oxidative stress report a decreased Superoxide dismutase (SOD) activity supporting a decreased oxidative stress after the treatment *(Virit et al., 2011).*

To date the role of mtDNA in response to pharmacological interventions to treat MDD has been poorly investigated, only one study published highlighted higher circulating cell-free mtDNAcn in non-responders to antidepressants compared to responders *(Lindqvist et al., 2018).*

Few studies evaluated mtDNAcn in patients treated with ECT. Ryan and colleagues found that mtDNAcn resulted higher in depressed patients compared to controls, but this finding was not related with clinical outcome of ECT, telomere length or circulating levels of inflammatory markers *(Ryan et al., 2023).*

- Telomere length

  TL result influenced by psychotropic medications (especially lithium) *(Coutts et al., 2019) (Fries et al., 2020) (Martinsson et al., 2013) (Pisanu et al., 2020) (Squassina et al., 2020)* and it has been proven that TL at baseline can predict response to antidepressants *(Rampersaud et al., 2023) (Rasgon et al., 2016)*. Fewer studies to date, explored if TL may be used as predictive marker of ECT response in patients with TRD. Some of them showed no correlation between TL and effectiveness of ECT treatment *(Ryan et al., 2020)*; this result was confirmed by one of the studies that will be presented in this thesis *(Pisanu et al., 2021).*

2. Accelerated aging hypothesis

As already mentioned, patients with MDD have a reduced life expectancy compared to the general population, this is due to comorbid conditions such as cardiovascular and metabolic disorders, besides for suicide *(Chesney, Goodwin, & Fazel, 2014) (Kahl, Stapel & Frieling, 2019) (Musselman, Evans & Nemeroff, 1998)*. Also, TRD patients that have a decreased life expectancy due both to natural and unnatural causes *(Li et al., 2019)*. In general, many studies showed that people affected by severe mental disorders (SMDs), such as mood disorders and psychotic disorders, have also higher incidence of age-related disorders like cardiovascular diseases, metabolic disorders, stroke, dementia *(Brown, Varghese, & McEwen, 2004; Irwin & Miller, 2007; Pennix et al., 2013; Viron and Stern, 2010*) and their prevalence is even higher in patients with TRD *(Hare et al., 2014)*. Of course, this increased incidence can't be fully explained by a worse lifestyle compared to non-psychiatric individuals (such

diet, smoke, physical activity) *(Schulz et al., 2000),* but different hypotheses have been evaluated including a genetic predisposition and altered biological processes involved in response to stress and coping with allostatic load as mentioned before in this work *(Monroy-Jaramillo, Dyukova, & Walss-Bass, 2018) (Simon et al., 2006)*. These latter observations support the hypothesis that SMDs patients might be characterized by accelerated aging.

The accelerated aging hypothesis for MDD is corroborated by several studies aimed at identifying the biological moderators of this process. The proposed moderators are genetic, epigenetic and biochemical. The evaluation of these moderators is not a purpose of this work, but they involve glucocorticoids, neurosteroids, glucose and insulin regulation, immune function and inflammation, oxidation, and growth factors, in particular BDNF (*Wolkowitz et al., 2010) (Heuser, 2002).*

Both psychological and physiological stress may lead to premature cellular aging involving similar physical processes. In general, stressors trigger physiological responses but when these responses are disrupted or inappropriately prolonged, the endangering effects become more relevant than the protective ones. It is defined as allostatic load the cost of maintaining these physiological responses over prolonged time. In SMDs, this allostatic load results in chemical imbalances and perturbations other than changes in brain structures *(McEwen, 2000).*

Of course, in addition to this condition of chronic stress, genetic and epigenetic, psychological, and environmental circumstances favor the dysregulation of important effectors of the stress response: limbic-hypothalamic -pituitary adrenal (LHPA) axis and the locus coeruleus noradrenergic (NE) system *(Seeman et al., 2001) (Wong et al., 2000).*

2.1 Markers of cellular aging

For the possible implications of the accelerated aging in psychiatric disorders, in particular in MDD, it is of great relevance to find possible markers of this process *(Bersani et al., 2019).*

Structural magnetic resonance imaging (sMRI) markers *(Ahmed et al., 2022)*

- white matter hyperintensity (WMH) volume.
  Normally WMHs develop and worsen with aging, and in some studies resulted more severe in late life depression. A relationship between WMH severity and antidepressant treatment

response was also observed *(Park et al., 2015) (Taylor et al., 2005) (Gunning-Dixon et al., 2010) (Sheline et al., 2010).* Despite this evidence, there are also studies that did not confirm these results *(Sneed et al., 2007) (Salloway et al., 2002).* The inconsistency of results could be related to the heterogeneity of the samples or the modest effect of this structural abnormality.

- hippocampal volume loss.

Many studies support a critical role of hippocampus in depression *(Arnone et al., 2012)*. Hippocampus volume loss is normal with aging, but an accelerated atrophy of this brain structure is a marker of Alzheimer disease *(Jack et al., 2000).*

Epigenetic

Epigenetic mechanisms, such as DNA methylation, play several important roles during brain development and are dramatically modified during aging processes *(Jung and Pfeifer, 2015).* Epigenetic represents a reversible mechanism in regulating the function of the genome without altering the underlying DNA sequence of the genome; in response to environmental stimulation, the aging process is modulated by the epigenome, which links genotype to phenotype *(Wang et al., 2022)*. This mechanism is affected by environment and lifestyle behaviors (sleep, diet, smoking, exercise, etc.) *(Ciccarone et al., 2018) (Lu et al., 2019)*. DNA methylation is a biochemical process that consents the addition of a methyl group to a cytosine nucleotide, leading to the formation of a 5-methylcytosine (5mC). In humans and most other mammals, methylation is almost exclusively found on cytosine nucleotides followed by a guanine nucleotide (the so called CpG-sites). CpG sites are unevenly distributed across the genome but most of them cluster together in regions of around 1 kb with a higher density of CpG sites compared to the rest of the genome in CpG islands (CGIs) *(Illingworth et al., 2009)* Since many of these regions are collocated near promoter sites of known genes, their methylation is involved in several processes like gene activation, alternative splicing, nucleosome positioning, and the recruitment of transcription factors *(Jones, 2012).* The assessment of the CpGs sites methylation can be used to calculate Epigenetic Age which has been correlated with biological age *(Horvath, 2013)*.

Several measures of epigenetic aging, also called epigenetic clocks, have been developed, each one with specific properties and meanings. Two of these clocks are the Horvath and the Hannum clocks.

The Horvath clock was the first one developed based on the methylation of a set of 354 CpGs. It can predict chronological age and is strongly associated with biological aging processes *(Horvath, 2013)*. The Hannum clock assesses the extrinsic epigenetic aging and incorporates information on leukocyte populations that can change with aging *(Hannum et al., 2013).*

More recent epigenetic clocks are still correlated with chronological age but can also predict disease and mortality. These clocks were trained on both phenotypic age (clinical laboratory measures such as albumin, creatinine, C-reactive protein, and others associated with illnesses and mortality*) (Levine et al., 2015)*, on plasma proteins previously associated with mortality or morbidity (ex: plasminogen activator inhibitor-1 (PAI-1), cystatin C, leptin, and others) and on methylation changes related to cigarette smoking history ('DNAm GrimAge') *(Lu et al., 2019)*. Of course, the analysis of these findings in SMDs need to be very cautious because of small samples size, technical challenges, the often-insufficient phenotyping of the patients and the presence of comorbidities (medical or psychiatric), the tobacco/substance use and abuse, that add confounders into the studies. *(Morrison et al., 2019).*

Several studies link DNA methylation age and psychiatric or neurological disorders such as bipolar disorder (BD) and Alzheimer's disease *(De Paoli-Iseppi, et al. 2017) (Levine, et al. 2015)*. There are fewer studies on MDD but some of them evidenced higher epigenetic age in patients with this disorder compared to controls *(Han et al., 2018) (Protsenkoet al., 2021),* while some of them did not confirm this finding *(Li et al., 2018) (Declerck and Vanden, 2018).*

Inflammation

Mental illnesses are characterized by a persistent inflammatory state, a feature shared with other age-related disorders and this evidence led to the hypothesis that inflammation plays a key role in the pathophysiology of psychiatric disorders, including MDD *(Kiecolt-Glaser et al., 2016).* In fact, increased levels of circulating pro-inflammatory cytokines were found in mood disorders *(Young, et al., 2014) (Leboyeret al., 2016).* A dysfunction in the immune-inflammatory pathway in the pathophysiology of mood disorders is supported by several studies *(Mechawar and Savitz, 20166.) (Miller and Raison, 2016).*

It has been shown that low-grade inflammation is also linked with structural and functional changes on the brain through different mechanisms: passage of cytokines through leaky regions in the blood brain barrier, bid to peripheral afferent nerve fibers, stimulating ascending catecholaminergic fibers in the brain *(Miller and Raison, 2016) (Kohler et al., 2017).*

Inflammatory cytokines can also affect the synthesis and the synaptic availability of monoamines that are associated with the pathophysiology of MDD as previously discussed *(Neurauter et al., 2008) (Zhu et al., 2010).*

Wray and colleagues in a meta-analysis of genome-wide association study (GWAS) datasets implicated genes involved in cytokine and immune response in the etiopathology of MDD *(Wray et al., 2018).*

Also, the response to antidepressant treatment has been suggested to be modulated by low-grade inflammation *(Carvalho et al., 2013.) (Powell et al., 2013).* On the other hand, antidepressants decrease peripheral levels of inflammatory cytokines (such as IL-6, IL-10, TNF- alpha) *(Wiedlocha et al., 2018).*

Altered cytokine levels have been found in acute and chronically ill patients with different psychiatric disorders (schizophrenia, BD and MDD) with a certain grade of similarity among the diagnostic groups, suggesting a common contribution of inflammation and immune response and that these measures can be considered a transdiagnostic marker in psychiatry *(Goldsmith et al., 2016).*

Although a low level of chronic inflammation has been demonstrated in MDD and in general in SMDs, its role in biological aging have yet to be accurately studied in SMDs *(Fougere et al., 2017) (Xia et al., 2016).*

Recently Alpert and colleagues explored a novel biological aging marker called "IMM-AGE" that considers the relative abundance of 33 immune cell subsets consistently associated with age and the function of these cells to express certain genes and to produce and react to cytokines. This measure has yet to be assessed in SMDs but is promising and may be more accurate of epigenetic clocks to assess general mortality risk *(Alpert et al., 2019).*

For the purposes of the work presented in this thesis, the attention will be focused on two markers of biological aging: telomeres and mitochondrial DNA copy number.

Telomeres

Telomeres are specialized structures at the end of chromosomes *(Blackburn et al., 2006)*. In humans, they mainly consist of highly-conserved nucleotide-repeat regions containing 5'-TTAGGG-3' DNA tandem repeats and telomere-associated shelterin proteins *(Giardini et al., 2014).* Telomeres are crucial to maintain the integrity of the genome, to distinguish the natural termination of the chromosome from a possible termination due to double-strand DNA breaks, to protect the

chromosomes from end-to-end fusions, misrepairs and degradation; more in general they are responsible for the three-dimensional architecture of the DNA and its structural integrity.

In proliferating tissues, telomeres progressively shorten at each cell cycle until a critical minimum length that causes growth arrest of the cells as they enter in a senescent phase where they remain viable but do not divide *(Shay, 2016).*

The progressive shortening can be counteracted by the telomerase, an RNA-dependent DNA polymerase that adds telomeric repeat sequences at the end of chromosomes *(Blackburn et al., 2006)*. This enzyme is not present in most of somatic differentiated cells and is active only in subsets of proliferating somatic adult progenitor cells and in spermatogonia *(Shay and Wright, 2010.) (Wright et al., 1996).* The inhibition of telomere shortening (TS) may trigger the transition of cells to cancer cells *(Bojesen, 2013)*. Telomere shortening represents a biological marker of cellular aging. This physiological process can be accelerated by different factors such as oxidative stress, inflammation, hormones, but also genetic variants of genes involved in telomere biology *(Mangino et al., 2012)*.

Several factors that can induce accelerated telomere shortening, such as inflammation and oxidative stress, are also implicated in mood disorders and this supports the hypothesis of a complex interplay of these processes.

Telomere length inversely correlates with chronological age, as Leucocyte Telomere Length (LTL) shorten at an average rate of approximately 25–30 base pairs per year *(Muezzinler et al., 2013).*

Shortened LTL longitudinally predicts poor physical health and is significantly correlated with all-cause mortality *(Wang et al., 2018)*. Many studies found shorter telomeres in SMDs patients and in particular in MDD *(Ridout et al., 2016)*. The causative reasons of this shortening are still not completely known but inflammation, oxidative stress and stress hormones are prime candidates *(Lindqvist et al., 2015) (Lindqvist et al., 2019) (O'Donovanet al., 2011*). In particular a large study of Révész and coworkers in 2016, highlighted that the relationship between psychopathology and LTL was mediated by levels of inflammatory markers (CRO and IL-6 in particular) as well as other factors (triglycerides, high-density lipoprotein cholesterol and cigarette smoking), supporting the hypothesis of the interaction between factors involved in TS and inflammation in mood disorders *(Revesz et al., 2016).*

A prospective longitudinal study found that a diagnosis of MDD predicts LTL shortening over two years even if was not correlated with symptoms severity or duration *(Vance et al., 2018).*

It is clear that TS can be enhanced by stress and SMDs, but there is also the possibility that TS can be a risk factor for the development of SMDs and that TS and SMDs share common antecedents like

environmental factors and/or common genetic underpinnings *(Gotlib et al., 2015) (Puterman et al., 2013).*

Some studies affirm that telomere length is partly heritable, but heredity interacts with the environment to predict telomere length *(Hjelmborg et al., 2015) (Blackburn et al., 2015).* GWAS analyses found several single- nucleotide polymorphisms (SNPs) associated with LTL *(Prescott et al., 2011),* such as rs2736100, a variant of the telomerase reverse transcription (TERT) gene, which was associated with clinical depression *(Wei et al., 2016)*, rs10936599, a variant of the TERC gene, coding for the RNA component of telomerase, that was associated with higher risk for childhood-onset of MDD. Other studies did not confirm the association between genetic predisposition to shorter LTL and MDD *(Wium-Andersen et al., 2017)*.

Fewer studies explored the interplay between peripheral TL and TL in brain or brain structures. Wolkowitz and colleagues found a positive association between peripheral blood mononuclear cells (PBMC) telomerase activity, but not TL, and hippocampal volume in patients with MDD, while Mamdani et al highlighted a reduced TL in the hippocampus of MDD patients compared to controls in a postmortem brain study *(Mamdani, et al., 2016) (Wolkowitz et al., 2015).* Different single-cells population of the brain resulted also to have a different vulnerability to TS, in particular oligodendrocytes but not astrocytes from postmortem prefrontal cortex brain of MDD patients, had reduced TL compared to controls *(Szebeni et al., 2014).*

Mitochondria dynamics

Mitochondrial dysfunctions play a role in accelerated biological aging and have been studied in SMDs *(Picard and McEwe, 2018).*

Mitochondria are essential to regulate cellular metabolism and homeostasis due to their role in different biological processes: bioenergetics, generation of reactive oxygen species (ROS), anabolism and catabolism, heme biosynthesis, calcium and iron homeostasis, apoptosis, and signal transduction *(Nicholls, 2005) (Srivastava, 2016).* These organelles are essential for life and are involved in the response to cellular stress *(Liu and Butow, 2006).*

Their dysfunction is associated with different aspects of aging such as impaired oxidative phosphorylation activity, increased oxidative damage, decline in mitochondrial quality control, lower activity of metabolic enzymes, but also changes in mitochondrial morphology, dynamics, and biogenesis *(Kauppila et al., 2017).*

There is an intricate regulatory mechanism that consents a balance between mitophagy, the process that eliminates dysfunctional and damaged mitochondria, and mitochondria biogenesis; the coordination of these processes is critical for aging and longevity *(Palikaras et al., 2015).*

Perturbations in mitochondrial function, biogenesis and dynamics impair cellular homeostasis and trigger quality control mechanisms; an alteration of these mechanisms promotes accumulation of damaged mitochondria that contributes to aging and age-related disorders *(Srivastava, 2017).*

Even if most mitochondrial proteins are encoded in the nuclear genome, mitochondria have their own genome, the mitochondrial DNA (mtDNA), a legacy of their independent origin and essential for coupling oxidative phosphorylation to ATP synthesis *(Allen, 2003).* mtDNA is involved in different processes that lead to aging and age-related disorders, including changes in mtDNA copy number (mtDNAcn), epigenetic modifications and mtDNA mutations *(Chocron et al., 2019).*

Different types of damage or mutations can be present in disease and aging. Gu and colleagues showed that older people had higher levels of mutant mtDNA and this finding was associated with age-related blood physiological markers *(Zhang et al., 2017).* Both mutations and deletions in mtDNA were found during aging *(Michikawa et al., 1999) (Nekhaeva et al., 2002) (McInerny et al., 2009) (Fayet et al., 2002)*

mtDNA can be present in hundreds to thousands of copies that can contain different sequences, in fact mutated mtDNA can coexist with wild-type mtDNA in a condition called heteroplasmy. Different studies found an association between decreased mtDNAcn in whole blood and age or poorer health outcomes *(Mengel-From et al., 2014) (Lee et al., 2010).*

mtDNAcn is a marker of oxidative stress and biological aging and is correlated with mitochondrial biogenesis and functioning. It has been shown that increased inflammatory response and oxidative stress negatively impact on mitochondria by promoting, among other ways, the accumulation of point mutations *(Srivastava, 2017),* but how these processes have an impact on the mtDNAcn has not been clarified yet.

As regards to mitochondria dysfunction in psychiatric disorders, it is important to point out that the brain has high energetic demand, and the ATP produced by mitochondria, is essential for neural processes (such as ion transport, receptor function, neurotransmitter production and release, neural differentiation, synaptic plasticity etc.) *(Streck et al., 2014) (Marques-Aleixo et al., 2012) (Lopresti et al., 2013).*

Several studies reported abnormalities in mitochondrial function in psychiatric disorders (schizophrenia, BD and MDD) and stress exposure might play an important role in these association.

In fact, glucocorticoids both induce metabolic stress and have an effect on mitochondrial genes and nuclear genes that influence mitochondrial density and function *(Picard et al., 2014).* Stress is also able to enhance the excitatory transmission in the brain mediated by glutamate, leading to increased oxidative stress and possibly mitochondrial damage *(Atlante et al., 2001) (Toya et al., 2014).*

Studies exploring the correlation between mtDNAcn as a marker of aging, and mood disorders are controversial. While for patients with BD most of the studies report a decreased mtDNAcn compared to controls *(Wang et al., 2020) (Dong et al., 2018) (Tsujii et al., 2019) (Angrand et al., 2021),* for MDD many studies reported an increased mtDNAcn *(Ryan et al., 2023) (Chung et al., 2019) (Tyrka et al., 2015).* However, there are also studies that reported the opposite result or no differences (*Verhoeven et al., 2018) (Chang et al., 2015) (He et al., 2014) (de Sousa et al., 2013)*.

Tyrka and colleagues found that MDD patients with early stress and psychopathology had shorter telomeres but higher mtDNAcn, suggesting a co-regulation of these processes might play a compensatory role in adults *(Tyrka et al., 2016).* Further investigations in larger samples are needed to explore the role of this marker in MDD.

3. Aims

The general aim of this thesis was to explore markers of accelerated aging in patients with treatment resistant depression and in response to electroconvulsive therapy.

At this purpose, here I present two studies:

- In the first study we aimed to explore if leucocyte telomere length (LTL), a marker of cellular aging, is a marker of TRD by comparing patients with TRD with non-psychiatric controls (NPC), and to investigate whether baseline LTL (before ECT treatment) could predict response to ECT.

  Furthermore, we explored the role of genetic variance in this association by leveraging genome wide genotyping data from a sub-group of 107 TRD patients. Findings from this study have been recently published (PMID: 34834452).

- In the second longitudinal study we explored if LTL and mtDNAcn differ between TRD patients and controls and if they can be considered as predictive markers of response to ECT. Furthermore, measuring these markers before and after the ECT treatment, we aimed to correlate dynamic changes in molecular measures with response to ECT and changes in symptoms severity. Findings from this longitudinal investigation have been submitted for publication.

4. First study: LTL on TRD patients and response to ECT

4.1 Material and Methods

4.1.1 Sample

In accordance with the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) classification system criteria, 149 TRD patients (of whom 23 BD) referred to the Psychiatric Hospital "Villa Santa Chiara," Verona, Italy, were voluntarily enrolled in the study, which was approved by the local ethics committee (ethics committee of the province of Verona, No. 4997/09.11.01), and written informed consent was obtained. Diagnosis of unipolar or bipolar depression was confirmed using the Structured Clinical Interview for DSM-IV Axis 1 Disorders diagnostic structured interview. Exclusion criteria were: (i) mental retardation and cognitive disorders; (ii) a lifetime history of schizophrenic or schizoaffective disorder; (iii) personality disorders, obsessive-compulsive disorder, or posttraumatic stress disorder as primary diagnosis; and (iv) comorbidity with eating disorders. All the patients were evaluated as treatment resistant. Treatment-resistant depression was defined as at least the failure to respond to 2 or more adequate trials with 2 or more different classes of antidepressants and to an adequate trial of a tricyclic drug, referred to as stage III of Phase and Rush Staging Method *(Thase and Rush, 1997)*. All the patients were scheduled to undergo ECT. ECT was performed according to standard settings, with a bipolar brief pulse square wave and bilateral electrode placement. The ECT procedure has been described in detail elsewhere *(Minelli et al., 2011)*. Illness severity and the outcome of ECT were assessed using the MADRS before the treatment (T0), the day after the end of ECT (T1) and about 1 month after its end (T2). Patients were considered as responders if the MADRS reduction was >50% at T1 or T2. In addition, symptom improvement at both time points was defined as the % variation (Delta) of MADRS score compared to baseline computed as (((T2 score or T1 score) - T0 score)/T0 score) x 100. Patients were considered remitters if they presented a MADRS score > or = 10 at T2.

LTL was measured, before the ECT treatment, in patients with TRD and compared with LTL from 336 healthy controls without any personal or family history of psychiatric conditions recruited at the Lithium Clinic of the Clinical Psychopharmacology Centre of the University Hospital of Cagliari. The

research protocol was approved by the local Ethics Committee of the University of Cagliari, Italy. All participants signed informed written consent after a detailed description of the study procedures.

4.1.2 Methods

DNA Extraction

For TRD patients, genomic DNA was extracted from whole blood samples using the Gentra Puregene Blood kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions and the DNA quantification and quality evaluation were performed through spectrophotometric analysis (NanoDrop 2000, Thermo Scientific, Waltham, MA, USA).

For non-psychiatric controls, genomic DNA was extracted from peripheral blood leukocytes using the salting-out method starting from 10 ml of peripheral blood anticoagulated with EDTA (*Lahiri and Nurnberger, 1991*) and the DNA quantification and quality evaluation were performed through spectrophotometric analysis.

Measurements of Leukocyte Telomere Length with Quantitative PCR

The quantitative Polymerase Chain Reaction (qPCR) technique, according to Cawthon (Cawthon, 2002) was used to evaluate LTL.

Samples were processed in triplicates both for the telomere (Tel) and for the single-copy gene (hemoglobin-b, Hgb). For Tel and Hbg, Platinum® SYBR® Green qPCR SuperMix-UDG w/ROX (Thermo Fisher Scientific, Waltham, MA, USA) was used on a StepOnePlus ™ Real-Time PCR System (Thermo Fisher Scientific).

All samples were tested in triplicate to assess the reproducibility of the obtained data and a negative control was inserted in each experimental plate, in which DNA was replaced by sterile water. In addition, in each PCR plate, three wells were reserved for a reference DNA sample (calibrator) at the same sample concentration, necessary to normalize any differences between the different assays.

Table 3. Primer's Sequences

Primer	Sequence 5' → 3'
Tel-1	GGTTTTTGAGGGTGAGGGTGAGGGTGAGGGTGAGGGT
Tel-2	TCCCGACTATCCCTATCCCTATCCCTATCCCTATCCCTA
HBG-1	GCTTCTGACACAACTGTGTTCACTAGC
HBG-2	CACCAACTTCATCCACGTTCACC

The technique is based on the use of a fluorescent molecule, SYBR® Green I, part of the group of asymmetric cyanins, which binds to the minor groove of double-stranded DNA (dsDNA) *(Zipper et al., 2004*). The DNA-dye complex absorbs blue light at a maximum wavelength of 498 nm and emits green light at a wavelength of 522 nm. During the denaturing phase, the SYBR® Green is free in solution, while in the annealing phase of the primers it intercalates in a non-specific way in the minor groove of the dsDNA and begins to emit fluorescence. Finally, during the extension phase the emitted fluorescence increases proportionally to the number of copies of DNA produced.

The fluorescent signal emitted during the reaction is recorded at each cycle of PCR by the sensor of the instrument and reported in a system of Cartesian axes in which is represented in abscissa the number of cycles and in ordinate a logarithmic scale of the fluorescence emission associated with each cycle (expressed as ΔRn). This results in a typically sigmoidal curve with an exponential phase, a linear phase, and a plateau phase in which amplification terminates and fluorescence stabilizes at a regime value. At the end of the reaction a software calculates for each sample the threshold cycle (Ct) which represents the number of PCR cycles required for the fluorescence signal to exceed the reference line (threshold line), automatically set by the instrument at an intermediate point of the sample amplification curves. The value of the Ct is inversely proportional to the initial number of molecules present in the sample: the fewer cycles it takes to overcome the threshold, the greater the amount of starting DNA.

By binding in a non-specific manner to the minor groove of DNA, SYBR® Green can generate non-specific signals. Therefore, it is necessary to verify the specificity of the reaction through the analysis of the melting curve (dissociation curve), specific for each amplicon produced.

The amplification conditions for the telomeres and for the HBB gene involve a denaturation step at 95 °C for 3 min followed by 28 cycles of 95 °C for 15 s and 60 °C for 1 min for Tel, and 95 °C for 3 min followed by 32 cycles of 95 °C for 15 s and 60 °C for 1 min for Hgb.
Specificity was assessed through the dissociation curve included in each plate.

LTL was calculated using the 2−ΔΔCT method where ΔΔCT = ΔCT sample−ΔCT calibrator and ΔCT sample = CT Tel − CT Hgb.

4.1.3 Statistical Analysis

Normality of distribution was assessed using the Shapiro-Wilk test. Grubb's test was used to identify outliers. The association between LTL and quantitative or categorical variables was assessed using Spearman's correlation test or Mann-Whitney's U test, respectively. In addition, we conducted analyses adjusted for age using partial correlation test or rank analyses of covariance (Quade's test) to analyze the association between LTL and quantitative or categorical variables, respectively. Since patients and controls showed a significant difference in age, and this factor is known to be associated with LTL, we also repeated the analyses in a subsample of patients and controls matched using the Case Control Matching function in SPSS v. 26. A tolerance factor of 3 years was applied (this number was found to be the one able to minimize the loss of cases while still obtaining two subsamples of cases and controls that did not show a significant difference in age). Stratified analyses were conducted based on psychiatric diagnosis (BD or MDD). Analyses were conducted using GraphPad Prism v. 9 and SPSS v. 26.

Analysis of GWAS Data

For 107 TRD patients with LTL data, genome-wide genotyping data were available. Ninety-five patients were genotyped using Infinium Multi-Ethnic Genotyping Array, whereas twelve patients with the Infinium PsychArray-24 BeadChip (Illumina, San Diego, CA, USA). Quality control (QC) was performed for each dataset with PLINK v. 1.9 (Chang et al., 2015) in order to exclude SNPs with a minor allele frequency (MAF) < 0.05, a Hardy-Weinberg equilibrium (HWE) p-value < $1x\ 10^{-}6$, and a call rate < 0.95; also, individuals with unusual heterozygosity (<0.20 or >0.40), a call rate < 0.99, cryptic relatedness (p_hat > 0.20) and sex discrepancy were removed. Imputation was performed

based on the 1000 Genome data (Phase 3 Version 5) reference panel using Minimac 3 software through the Michigan Imputation Server, that provides genotype imputation service and an extensive quality control check for all uploaded datasets *(Das et al., 2016)*. After imputation, only biallelic variants with R2 ≥ 0.5, a genotype posterior probability (GP) > 0.9, MAF > 0.01 and in HWE ($p > 1 \times 10^{-}6$) were retained for statistical analyses. The single datasets were then merged to generate one dataset including all cases. To reduce the batch effect due to multiple platforms, we removed from both datasets any SNP showing significant association (false discovery rate, FDR < 0.05) with the genotyping batch. Finally, we removed outlier individuals based on the inspection of the first 5 genotyping principal components (PCs) computed using PLINK v. 1.9. The association between SNPs and categorical (response at T1 or T2) or quantitative variables (Delta MADRS % T0-T1, Delta MADRS % T0-T2 or LTL) was analyzed using binary logistic or linear regression, respectively, using PLINK v. 1.9 *(Chang et al., 2015)*. Analyses were also conducted at a gene-based level using MAGMA on the FUMA platform *(Watanabe et al., 2017)*.

We also checked whether SNPs associated with LTL in previous studies were associated with LTL or response to ECT in our sample. To this aim, we selected 60 SNPs associated with LTL in previous publications *(Li et al., 2020) (Codd et al., 2013)*, 22 of which were represented in our dataset (Table 12). Using the hypergeometric test, we also checked if SNPs/genes nominally associated with LTL showed over-representation of SNPs/genes nominally associated with response to ECT.

4.2 Results

After the exclusion of two outliers, the analysis was performed on 148 TRD patients (125 with unipolar depression and 23 with bipolar depression) and 335 non-psychiatric controls. The LTL was measured at baseline, before the ECT treatment. Table 4 reports demographic characteristics of the sample.

Table 4. Demographic characteristics of the sample

	Patients with TRD (n = 148)	**Controls (n = 335)**	**Statistics**	**p**
Age, median (IQR)	56 (20)	43 (22)	14,125 a	<0.0001
Gender (women, %)	67.6	53.1	8.76 b	0.004

a= Mann-Whitney U; b = Pearson's Chi-Square. Abbreviations: IQR, interquartile range.

In line with previous findings, LTL resulted negatively correlated with age (Spearman's correlation coefficient = -0.25, p < 0.0001) (Figure 1) but not associated with sex (defined as sex assigned at birth) (U = 25,835, p = 0.079).

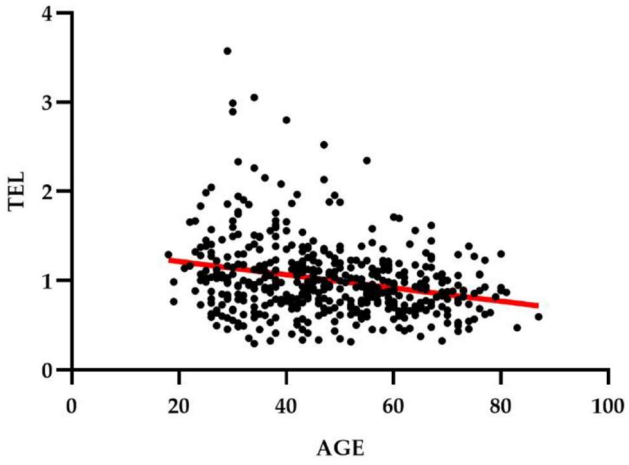


Figure 1. Negative correlation between LTL and age in the sample including 148 patients with TRD and 335 controls.

The correlation between LTL and other demographic and clinical variables was also evaluated (Table 5).

A trend for negative correlation between LTL and body mass index (BMI, Spearman's rho = -0.16, p = 0.067) was found and this association resulted significative after adjusting for age (partial correlation coefficient = -0.19, p = 0.027).

Patients with comorbid personality disorders showed longer LTL, but the association did not result significative after adjusting for age (Mann Whitney's U = 1456, p = 0.019; Model adjusted for age: Quade's F = 2.36, p = 0.13). No other clinical or demographic variable was significantly associated with LTL.

Table 5. Association between LTL and demographic and clinical variables.

Variable	Unadjusted Analyses		Analyses Adjusted for Age	
	Statistics	***p***	**Statistics**	***p***
Years of education, median (IQR): 8 (8)	0.14 [a]	0.10	0.01 [b]	0.90
BMI, median (IQR): 26.4 (6.7)	−0.16 [a]	0.067	**−0.19** [b]	**0.027**
Psychotic symptoms (70.9%)	2162 [c]	0.687	0.09 [d]	0.76
Smoking (35.1%)	2405 [c]	0.72	0.24 [d]	0.63
History of substance abuse (5.1%)	435 [c]	0.85	0.27 [d]	0.60
Comorbid alcohol abuse (2.7%)	244 [c]	0.60	0.10 [d]	0.75
Comorbid anxiety disorders (27.7%)	2030 [c]	0.48	1.64 [d]	0.20
Comorbid personality disorders (23.6%)	**1456** [c]	**0.019**	2.36 [d]	0.13
Comorbid cardiometabolic disorders (27.0%)	2055 [c]	0.65	1.74 [d]	0.19

a Spearman's rho; b partial correlation coefficient; c Mann-Whitney's U; d Quade's F Abbreviations: IQR, interquartile range.

LTL did not result different in patients treated with different medications: antidepressants, antipsychotics, mood stabilizers and benzodiazepines (Table 6), suggesting that pharmacological treatments mostly used for the management of MDD and TRD do not affect telomere dynamics.

Table 6. Association between LTL and medication intake.

Variable	Unadjusted Analyses		Analyses Adjusted for Age	
	U	*p*	Quade's F	*p*
Antipsychotics (76.2%)	1730	0.30	0.56	0.46
Antidepressants (95.2%)	378	0.31	0.11	0.19
Mood stabilizers (15.0%)	1258	0.53	0.15	0.70
Benzodiazepines (87.1%)	1150	0.34	1.05	0.31

LTL resulted shorter in patients with TRD compared to controls (U = 13,015, p < 0.0001), even after adjusting for age using rank analysis of covariance (Quade's F = 49.17, p < 0.0001) (Table 7, Figure 2). This result, in line with previous studies, point out that patients with TRD show signs of accelerated aging compared to non-psychiatric controls.

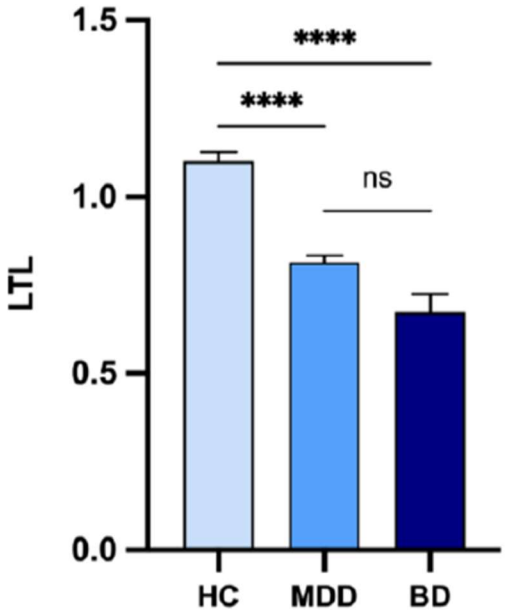
Table 7. Comparison between TRD patients and controls

		Unadjusted Analyses		Analyses Adjusted for Age	
	LTL, median (IQR)	U	p	Quade's F	*p*
Patients with TRD (*n* = 148)	0.77 (0.30)	13,015	<0.0001	49.17	<0.0001
Controls (*n* = 335)	1.03 (0.48)				

Abbreviations: corr. coeff., correlation coefficient; IQR, interquartile range; LTL, leukocyte telomere length; TRD, treatment-resistant depression.

When stratifying patients based on their diagnosis (MDD and BD), using Kruskal-Wallis analysis with post hoc tests, with Dunn's correction for multiple testing, both groups resulted having significantly shorter LTL compared to controls (MDD vs controls: U = 11.63, p < 0.0001, Quade's F = 35.18, p < 0.0001; BD vs controls, U = 1.39, p < 0.0001, Quade's F = 20.84, p < 0.0001)(Figure 2). Even if the sample of patients with bipolar TRD is underpowered, this result suggests that these signs of accelerated aging are common among different diagnostic groups.

Figure 2. LTL in patients with TRD is shorter compared to healthy controls (HC) stratifying for their diagnosis (MDD and BD)



Abbreviations: BD, bipolar disorder; HC healthy controls; MDD, major depressive disorder; ns, not significant.

*Barplots showing mean and standard error of the mean. ****p<0.0001.*

When repeating the analysis in a subsample of participants in which cases and controls were matched based on age, similar results were obtained (Table 8).

Table 8. Comparison of LTL between patients with TRD and controls in a subsample of patients and controls matched for age.

		Unadjusted analyses		**Analyses adjusted for age**	
	LTL, median (IQR)	**U**	**p**	**Quade's F**	**p**
Patients with TRD (n=147)	0.77 (0.30)	**5,567**	**< 0.0001**	**58.92**	**< 0.0001**
Controls (n=147)	1.03 (0.48)				
Patients with MDD (n=121)	0.79 (0.28)	**4,698**	**< 0.0001**	**47.91**	**< 0.0001**
Controls (n=147)	1.03 (0.48)				
Patients with BD (n=26)	0.70 (0.45)	**869**	**< 0.0001**	**22.81**	**< 0.0001**
Controls (n=147)	1.03 (0.48)				

Abbreviations: IQR, interquartile range; LTL, leukocyte telomere length; TRD, treatment-resistant depression.

LTL was compared between a subsample of 147 patients with TRD (median age: 56 years, IQR = 19 years) and 147 controls (median age: 54 years, IQR: 20 years) who were matched based on age using the Case Control Matching function in SPSS v. 26. A tolerance factor of 3 years was applied in order to minimize the loss of cases while still obtaining two groups of cases and controls that did not show a statistically significant difference in age (Mann Whitney's U = 9610, p = 0.10).

In the whole TRD sample, LTL measured before the ECT treatment was not significantly different between responders and non-responders both at T1 or T2 or between remitters and non-remitters (Table 9) and did not result correlated with improvement of symptoms defined as the variation on the Montgomery and Asberg Depression Rating Scale (MADRS) between either T1 or T2, suggesting that LTL at baseline can't be used as predictive marker of response to ECT.

Furthermore, baseline LTL was not correlated with MADRS scores at baseline or at any timepoint or with the number of ECT sessions (Table 9), suggesting the absence of a correlation between LTL and severity of depression.

Table 9. LTL and ECT response

		Unadjusted Analyses		Analyses Adjusted for Age	
	LTL, median (IQR)	**U**	***p***	**Quade's F**	***p***
Responders at T1 (*n* = 119)	0.77 (0.30)	777	0.68	0.04	0.85
Non-Responders at T1 (*n* = 14)	0.85 (0.34)				
Responders at T2 (*n* = 65)	0.77 (0.34)	767	0.34	0.54	0.46
Non-Responders at T2 (*n* = 27)	0.88 (0.27)				
Remitters (*n* = 53)	0.75 (0.32)	769	0.18	1.50	0.23
Non-remitters (*n* = 35)	0.88 (0.29)				
	Median (IQR)	**Spearman's rho**	***p***	**partial corr. coeff.**	***p***
Delta % MADRS T1-T0	75 (77)	−0.11	0.23	−0.12	0.17
Delta % MADRS T2-T0	78 (118)	−0.16	0.13	−0.18	0.10
MADRS scores at T0	33 (36)	0.03	0.73	0.03	0.76
MADRS scores at T1	8 (7)	0.11	0.20	0.13	0.15
MADRS scores at T2	7.5 (18)	0.17	0.12	0.17	0.12
Number of ECT sessions	7 (3)	0.03	0.71	0.02	0.79

Abbreviations: corr. coeff., correlation coefficient; IQR, interquartile range; LTL, leukocyte telomere length; MADRS, Montgomery Asberg Depression rating scale.

When stratifying patients based on psychiatric diagnosis, similar results were obtained (Table 10).

Table 10. LTL between Responders and Non responders in TRD patients stratified based on psychiatric diagnosis.

		Unadjusted analyses		Analyses adjusted for age	
	LTL, median (IQR)	**U**	**p**	**Quade's F**	**p**
Patients with MDD					
Responders at T1 (n=102)	0.79 (0.27)	598	0.57	0.30	0.59
Non-Responders at T1 (n=13)	0.86 (0.25)				
Responders at T2 (n=59)	0.77 (0.31)	598	0.17	0.94	0.34
Non-Responders at T2 (n=25)	0.89 (0.24)				
Remitters (n=47)	0.75 (0.30)	605	0.10	1.93	0.17
Non remitters (n=33)	0.88 (0.26)				
Patients with BD					
Responders at T1 (n=17)	0.65 (0.33)	5	0.67	0.39	0.54
Non-Responders at T1 (n=1)	-				
Responders at T2 (n=6)	0.76 (0.44)	3	0.43	0.47	0.52
Non-Responders at T2 (n=2)	0.60 (-)				
Remitters (n=6)	0.76 (0.44)	3	0.43	0.47	0.52
Non remitters (n=2)	0.60 (-)				
	Median (IQR)	**Spearman's rho**	**p**	**partial corr. coeff.**	**p**
Patients with MDD					
Delta % MADRS T1-T0	75.00 (21.22)	-0.13	0.15	-0.15	0.11
Delta % MADRS T2-T0	74.08 (55.75)	-0.19	0.09	-0.18	0.12
Patients with BD					
Delta % MADRS T1-T0	79.22 (31.16)	0.15	0.56	0.18	0.50
Delta % MADRS T2-T0	94.17 (41.81)	0.22	0.60	0.19	0.69

Abbreviations: BD, bipolar disorder; corr. coeff, correlation coefficient; IQR, interquartile range; LTL, leukocyte telomere length; MADRS, Montgomery Asberg Depression rating scale; MDD, major depressive disorder.

For 107 TRD patients, genome-wide genotyping data were available. No SNP or gene was associated with response to ECT or LTL at a genome wide threshold (data not shown).

Among 185,410 SNPs and 885 genes nominally associated with LTL, there was no significant enrichment for SNPs or genes nominally associated with response to ECT (Table 11).

Table 11. Assessment of overrepresentation between SNPs and genes associated with response to ECT and LTL

Number of SNPs nominally associated with LTL	**Number of SNPs nominally associated with response**	**Overlap between SNPs associated with LTL and response**	**p**
SNP associated with LTL: 185,410	SNPs associated with response at T1: 128,228	6,021	p = 1
	SNPs associated with response at T2: 144,770	6,222	p = 1
	SNPs associated with remission: 145,795	6,803	p = 1
	SNPs associated with Delta % T0-T1: 179,239	8,312	p = 1
	SNPs associated with Delta % T0-T2: 177,725	8,134	p = 1
Number of genes nominally associated with LTL	**Number of genes nominally associated with response**	**Overlap between genes associated with LTL and response**	**p**
Genes associated with LTL: 885	Genes associated with response at T1: 608	39	p = 0.11
	Genes associated with response at T2: 651	26	p = 0.93
	Genes associated with remission: 602	26	p = 0.85
	Genes associated with Delta % T0-T1: 849	45	p = 0.44
	Genes associated with Delta % T0-T2: 810	48	p = 0.17

Abbreviations: LTL, leukocyte telomere length; SNP, single nucleotide polymorphism.

Finally, among SNPs previously associated with LTL, we observed only few SNPs showing a nominal association with response to ECT (Table 12). Specifically, the G allele of rs8105767 (closest gene: ZNF208) was associated with reduced symptom improvement at T1, the A allele of rs60160057 (DCLK2) with reduced improvement and lower odds of response at T2 and the C allele of rs7194734

(MPHOSPH6) was associated with increased LTL in the current sample but lower odds of response to ECT at T2.

Table 12. Association between SNP previously associated with LTL and response to ECT

				Response at T1		Delta % T0-T1		Response at T2		Remission		Delta % T0-T2		LTL in current sample	
Chr	**SNP**	**Closest gene**	**A1**	**OR**	**P**	**Beta**	**P**	**OR**	**P**	**OR**	**P**	**Beta**	**P**	**Beta**	**P**
1	rs3219104	*PARP1*	A	0.95	0.93	0.80	0.81	0.64	0.33	0.78	0.58	-7.37	0.33	-0.03	0.41
3	rs2613954	*RP11-572M11.4*	C	1.26	0.72	2.97	0.35	2.47	0.10	1.48	0.38	12.70	0.09	-0.02	0.60
3	rs10936600	*LRRC34 (TERC)*	T	0.55	0.21	-0.29	0.91	0.69	0.33	0.65	0.26	-2.64	0.69	0.00	0.94
4	rs60160057	*DCLK2*	A	2.33	0.26	3.80	0.18	**0.41**	**0.045**	0.42	0.06	**-16.63**	**0.02**	0.00	0.94
4	rs4691895	*NAF1*	G	0.76	0.63	0.40	0.90	2.20	0.12	1.34	0.51	-0.90	0.90	-0.02	0.68
5	rs2853677	*TERT*	G	1.20	0.71	-3.55	0.15	1.38	0.37	1.72	0.13	4.87	0.38	-0.01	0.61
6	rs2736176	*PRRC2A*	C	1.22	0.69	0.32	0.90	0.53	0.11	0.84	0.64	-9.44	0.12	-0.01	0.86
7	rs59294613	*POT1*	A	1.15	0.76	2.70	0.26	1.11	0.77	1.25	0.51	3.61	0.50	-0.02	0.47
8	rs57415150	*CSMD1*	A	1.00	1.00	-5.07	0.39	0.92	0.92	1.53	0.64	-4.57	0.75	0.00	0.97
10	rs9419958	*STN1 (OBFC1)*	T	0.47	0.13	-4.60	0.14	1.38	0.52	1.20	0.69	4.37	0.54	-0.06	0.08
11	rs228595	*ATM*	G	1.79	0.23	2.36	0.33	0.78	0.49	0.82	0.56	-2.28	0.69	0.05	0.11
12	rs7311314	*SMUG1*	A	3.45	0.06	-0.16	0.95	1.41	0.39	1.67	0.18	4.41	0.46	0.01	0.74
14	rs2302588	*DCAF4*	C	0.59	0.36	-6.87	0.05	1.28	0.64	1.09	0.86	-1.56	0.85	0.03	0.49
15	rs12909131	*ATP8B4*	T	0.61	0.38	-1.38	0.68	0.79	0.60	0.88	0.78	-7.73	0.30	0.00	0.92
16	rs3785074	*TERF2*	G	0.60	0.31	-4.29	0.13	1.26	0.60	0.95	0.90	1.35	0.84	0.00	0.92
16	rs7194734	*MPHOSPH6*	C	1.36	0.58	4.23	0.12	**0.39**	**0.032**	0.72	0.42	-13.05	0.05	**0.07**	**0.04**
18	rs2124616	*TYMS*	A	1.03	0.97	3.43	0.44	0.59	0.42	0.74	0.64	-2.49	0.82	0.01	0.88
19	rs8105767	*ZNF208*	G	0.44	0.07	**-7.19**	**0.003**	0.73	0.41	0.49	0.07	-11.26	0.07	0.01	0.78
20	rs75691080	*STMN3*	T	1.39	0.69	0.60	0.88	2.00	0.27	3.37	0.05	13.68	0.13	0.01	0.76
20	rs932827	*ZBTB46*	T	0.85	0.76	2.30	0.43	0.72	0.46	0.60	0.25	-0.79	0.91	-0.04	0.29
20	rs73624724	*ZBTB46*	C	*NA*	*NA*	0.99	0.86	0.29	0.09	0.32	0.13	-19.26	0.12	0.07	0.31

Abbreviations: A1, effect allele; Chr, chromosome; LTL, leukocyte telomere length; NA, not available, OR, odds ratio; SNP, single nucleotide polymorphism.

5. Second study: longitudinal evaluation of LTL and mtDNAcn in TRD patients treated with ECT

5.1 Material and methods

5.1.1 Sample

The study sample included 31 TRD patients longitudinally followed-up and sampled at the Psychiatric Hospital "Villa Santa Chiara," Verona, Italy. These patients are a sub-group of a cohort of individuals included on the previously described study: diagnostic criteria and exclusion criteria are the same of the previously described study (Section 4.1.1). Illness severity and the outcome of ECT were assessed using the MADRS scores before the treatment (T0), the day after the end of ECT (T1) and about 1 month after its end (T2). Patients were considered responders if the MADRS reduction was >50%, and remitters if MADRS was < = 9. LTL and mtDNAcn were only measured at T2 and T0 since at T1 only 1 patient was "non-responder" to ECT. The sample also included a cohort of 65 sex and age matched healthy controls recruited by word of mouth among the hospital staff, their families, and university students. Individuals were included if between 18 and 65 years of age and if a standard medical, laboratory test assessment as well as clinical interview confirmed the absence of psychiatric disorders diagnosed according to the DSM-5 as well as of neurological or other severe unregulated medical conditions.

The study protocol was approved by the local Ethics Committees (Province of Verona, 4997/09.11.01; University Hospital Agency of Cagliari, PG/2019/6277) and written informed consent was obtained for all individuals in compliance with the Helsinki Declaration.

Demographic and clinical characteristics of this sample are reported in Table 13.

Table 13. Demographic and clinical characteristics of the sample

Variable	Group			
	R (n=23)	**NR (n=8)**	**NPC (n=65)**	**p**
Age (mean ± SD)	56.9 ± 15.6	56.4 ± 12.2	52.6 ± 6.8	ns
Sex (M/F)	5/18	4/4	24/41	ns
Years of education (mean ± SD)	7.9 ± 3.1	8.1 ± 1.9	na	ns
Psychotic symptoms (Y/N)	16/7	6/2	/	ns
Comorbidity with Personality Disorders (Y/N)	3/20	3/5	/	ns
Comorbidity with Anxiety disorders (Y/N)	3/20	0/8	/	ns
Other medical comorbidities (Y/N)	8/15	3/5	/	ns
BMI (mean ± SD)	26.7 ± 5.9	27.1 ± 4.3	23.7 ± 3.1	0.002*
Smoke (Y/N)	7/16	3/5	35/30	ns
Number of ECT sessions (mean ± SD)	7.2 ± 1.7	8.1 ± 3.4	/	ns
MADRS baseline (mean ± SD)	33.2 ± 7.3	34.1 ± 9.3	/	ns
MADRS T2 (mean ± SD)	5.5 ± 3.9	25.9 ± 5.9	/	<0.001
1st generation antipsychotics (Y/N)	9/14	3/5	/	ns
2nd generation antipsychotics (Y/N)	13/10	6/2	/	ns
SSRI (Y/N)	15/8	6/2	/	ns
SNRI (Y/N)	8/15	3/5	/	ns
TCA (Y/N)	7/16	3/5	/	ns
Benzodiazepines (Y/N)	21/2	6/2	/	ns
Mood stabilizers (Y/N)	1/22	1/7	/	ns

**Significant against non-psychiatric controls.*

Abbreviations: R, responders; NR, non-responders; NPC, non-psychiatric controls; SD; standard deviation; M, male; F, female; Y, yes; N, no; BMI, body mass index; MADRS, Montgomery and Asberg Depression Rating Scale; SSR, selective serotonin ruptake inhibitors; SNRI, serotonin and norepinephrine reuptake inhibitors; TCA, trcyclic antidepressants

5.1.2 Methods

The DNA extraction was performed as described in section 4.1.2.

The quantitative Polymerase Chain Reaction (qPCR) technique, according to Cawthon *(Cawthon, 2002)* was used to evaluate LTL, while for the mitochondrial DNA copy numbers a modified protocol from Tyrka and colleagues was used *(Tyrka, et al. 2016) (Bai and Wong 2005)*.

Samples were processed in triplicates both for the telomere (Tel), mitochondrial DNA copy number (mtDNAcn) and for the single-copy gene (hemoglobin-b, Hgb). For Tel and Hbg, Platinum® SYBR® Green qPCR SuperMix-UDG w/ROX (Thermo Fisher Scientific, Waltham, MA, USA) was used, while for mtDNAcn and Hbg SYBR® Select Master Mix (Life Technologies, Carlsbad, CA, USA), both on a StepOnePlus ™ Real-Time PCR System (Thermo Fisher Scientific).

All samples were tested in triplicate to assess the reproducibility of the obtained data as described in section 4.1.2.

Table 3. Primer's Sequences

Primer	Sequence 5' → 3'
Tel-1	GGTTTTTGAGGGTGAGGGTGAGGGTGAGGGTGAGGGT
Tel-2	TCCCGACTATCCCTATCCCTATCCCTATCCCTATCCCTA
HBG-1	GCTTCTGACACAACTGTGTTCACTAGC
HBG-2	CACCAACTTCATCCACGTTCACC
mtDNA-1	CATCTGGTTCCTACTTCAGGG
mtDNA-2	TGAGTGGTTAATAGGGTGATAGA

The amplification conditions for the telomeres and for the HBB gene involve a denaturation step at 95 °C for 3 min followed by 28 cycles of 95 °C for 15 s and 60 °C for 1 min for Tel, and 95 °C for 3 min followed by 32 cycles of 95 °C for 15 s and 60 °C for 1 min for Hgb.

The amplification conditions for mtDNAcn and for the HBB gene involve a denaturation step at 95 °C for 10 min followed by 32 cycles of 95 °C for 15 s and 60 °C for 1 min for mtDNAcn, and 95 °C for 10 min followed by 38 cycles of 95 °C for 15 s and 60 °C for 1 min for Hgb.

Specificity was assessed through the dissociation curve included in each plate.

LTL and mtDNAcn were calculated using the 2−ΔΔCT method where ΔΔCT = ΔCT sample−ΔCT calibrator and ΔCT sample = CT Tel/mtDNAcn − CT Hgb.

5.1.3 Statistics

The normality of distribution was tested using the Kolmogorov-Smirnov test. Presence of outliers was tested with the Grubb's test. Differences in demographic and clinical variables among studied groups were tested with the chi-square or t-test. Correlation between continuous variables was tested with Pearson's or Spearman correlation or partial correlation controlling for age. Difference between TRD and controls was tested with a general linear model including age as a covariate. A general linear model for repeated measures was used to test the association between changes in LTL or mtDNAcn and response to ECT between baseline and T2. The predictive significance of LTL and mtDNAcn was calculated with a binary logistic model. A Receiving Operator Characteristics (ROC) curve was built for each separate molecular measure and for the two measures combined by using predicted probabilities from a logistic regression model including LTL and mtDNAcn as predictive variables. Analyses were performed with SPSS (v. 28) and GraphPad Prism (v. 9).

5.2 Results

LTL and mtDNAcn resulted normally distributed and were not correlated with each other. In literature the correlation between these two markers is controversial and it seems that their regulation shares common dynamics *(Billard et al., 2019) (Zheng et al., 2019) (Tyrka et al., 2016)*.

As in the first study, LTL resulted inversely correlated with age both at baseline (Pearson's r=-0.31, p=0.003) and after a month from the ECT (T2) (Pearson's r=-0.54, p=0.002), while mtDNAcn and age did not result to be significantly correlated.

When analyzing differences between cases and controls at baseline, the logistic regression model including age as a covariate was highly significant (model chi-square = 50.91, p=5.11e-11), with a

significant contribution of both markers (LTL, B=-2.60, p=0.027; mtDNAcn, B=-5.64, p=0.000002; table 14), suggesting that both markers are significant predictors of TRD.

Table 14. Binary logistic regression model for LTL and mtDNAcn for TRD patients versus controls

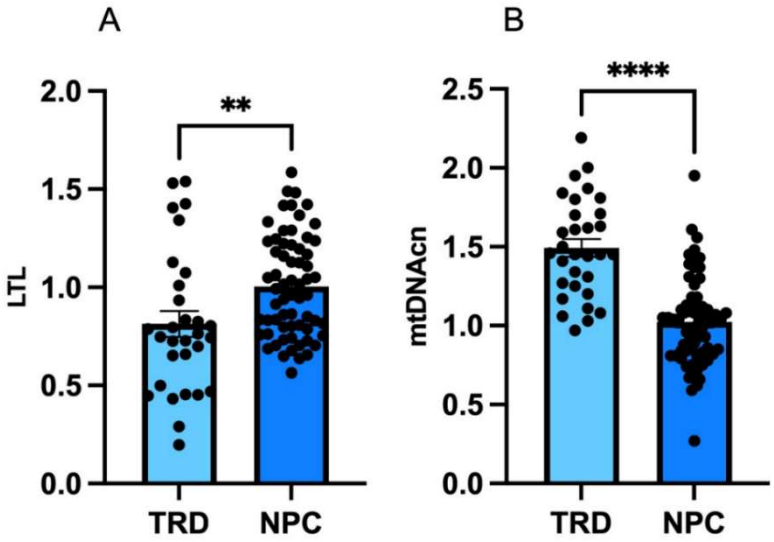
Model statistics	**Chi-square**	**Df**	**p value**	
	50.911	3	5.11 E-11	
Variables	B	S.E.	Wald	p value
LTL baseline	2.598	1.171	4.919	**0.027**
mtDNAcn baseline	-5.643	1.182	22.78	**2.00 E-05**
Age	-0.050	0.031	2.661	0.103

Abbreviations: LTL, leukocyte telomere length; mtDNAcn, mitochondrial DNA copy number; Df, degree of freedom; S.E. standard error

LTL was found to be significantly shorter in TRD patients compared to controls, in line with previous studies suggesting accelerated cellular aging in patients with psychiatric disorders and specifically in MDD and with the precedent study described in this thesis (Figure 3).

mtDNAcn resulted to be higher in patients with TRD compared to controls (Figure 3). While controversial, this result is in line with several other studies and will be further commented on the Discussions (Section 6).

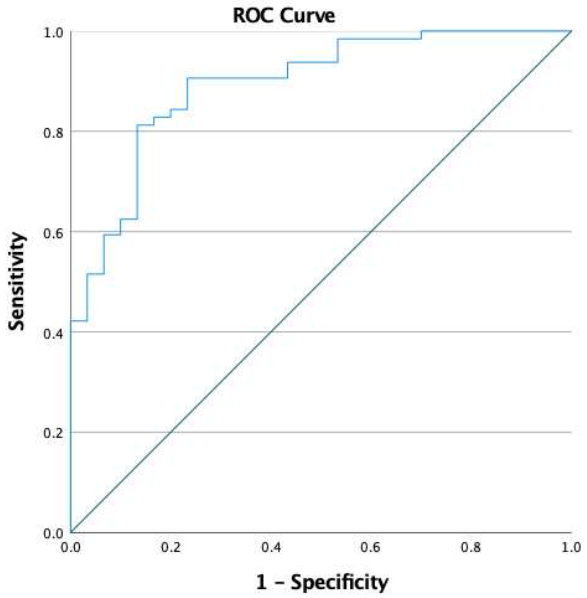
Figure 3. Leukocyte telomere length (A) and mitochondrial DNA copy number (B) in patients with treatment resistant depression and non-psychiatric controls.



*The p value refers to the pairwise comparison between the two groups. ** p value is lower than 0.005; *** p value is lower than 0.001*

The ROC curve including both measures (LTL and mtDNAcn) showed better performance than each of the two measures alone, with an area under the curve (AUC) of 0.89 (C.I. 0.83-0.96), sensitivity of 85% and specificity of 80%, suggesting that these two markers together can discriminate better between the two diagnostic groups and therefore that LTL and mtDNAcn can be considered as markers of diagnosis.

Figure 4. Receiving Operator Characteristics (ROC) Curve

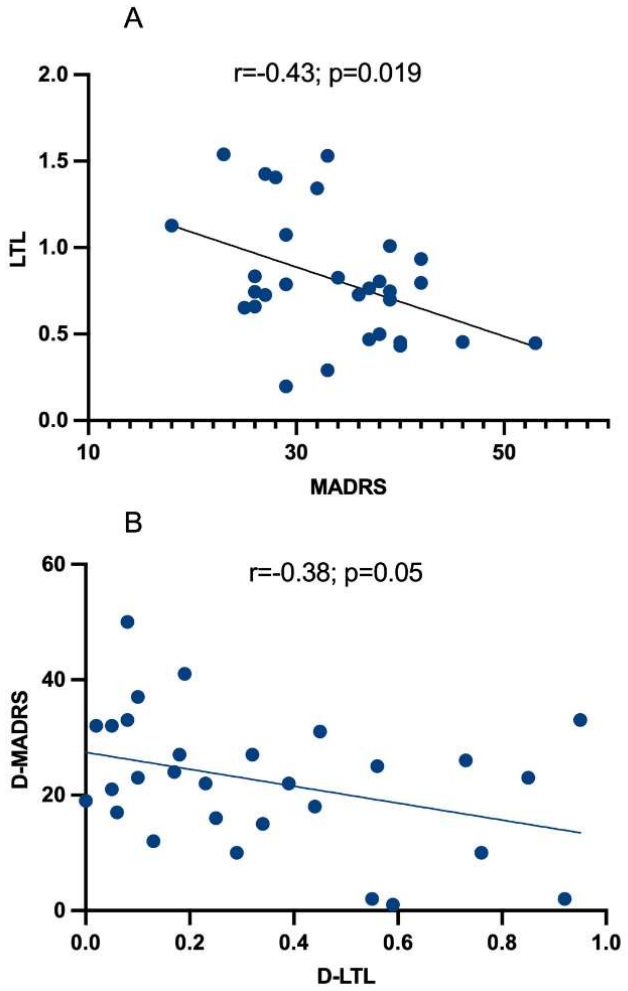


In the TRD sample, 23 patients were responders and 8 were non-responders to ECT at T2.

The two groups did not differ for any of the tested variables, while they both differed from controls for BMI (table 13).

LTL was influenced by comorbid personality disorders (t=-2.87, p=0.008) and was inversely correlated with MADRS scores at baseline (partial correlation controlling for age, r =- 0.38; p=0.042), suggesting that patients with worse symptomatology at baseline had also shorter telomeres and consequently more signs of accelerated aging (Figure 5A).

Figure 5. A: correlation between LTL and MADRS score at baseline. B: correlation between difference between the difference in LTL and MADRS score between baseline and T2.



Abbreviations: D-MADRAS: difference in MADRS scores between baseline and one month after the ECT sessions; D-LTL: difference in leukocyte telomere length between baseline and one month after the ECT sessions.

Figure 5B shows the inverse correlation between the difference in telomere length and MADRS scores between baseline and T2 (before ECT treatment and one month after ECT sessions). This trend suggests that patients with better improvement in symptoms show smaller shortening in LTL after ECT.

Neither LTL or mtDNAcn resulted correlated with sex (defined as the sex assigned at birth), BMI, comorbidity with alcohol disorder, anxiety, comorbid medical disorders, smoke, number of ECT sessions, classes of antidepressants, and comedication with mood stabilizers (Table 13).

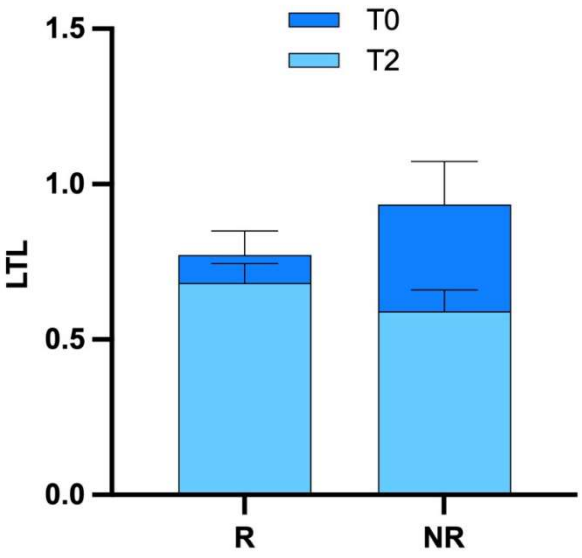
In the logistic regression analysis including comorbid personality disorder, neither LTL nor mtDNAcn at baseline resulted significant predictors of response to ECT or remission.

LTL resulted shorter at T2 compared to baseline (F=6.453, p=0.017), but no significative differences were found for mtDNAcn, suggesting an effect of ECT treatment in telomere, but not mitochondrial, dynamics.

Furthermore, there was not a significant interaction between response to ECT and LTL (F=2.207, p=0.149; Figure 6). Similar results were obtained when remission at T2 was considered as the outcome (effect of LTL, F=5.820, p=0.023; LTL*Remission, F=2.374, p=0.135).

A non-significant trend for a larger reduction of LTL in non-responders than in responders can be observed, suggesting a greater effect of ECT on telomere dynamics in patients with worse improvement of symptoms, supported also by the significant inverse correlation of changes in LTL and in MADRS scores between baseline and T2 (partial correlation controlling for age; r =-0.40, p=0.03. Figure 5B).

Figure 6. Difference in leukocyte telomere between response groups and timepoints



Abbreviations: R: responders to electroconvulsive therapy; NR: non responders to electroconvulsive therapy; LTL, leukocyte telomere length

6. Discussion and conclusions

The aim of this thesis was to explore if LTL and mtDNAcn, two markers of biological aging, could be involved in TRD and in response to ECT.

In both studies presented here, we found that baseline LTL was shorter in TRD patients compared to controls, supporting the hypothesis of accelerated cellular aging in depression *(Squassina et al., 2019) (Lindqvist et al., 2019) (Muneer and Minhas, 2019).*

This hypothesis originated from the evidence that affected individuals present higher incidence of age-related disorders, such as cardiovascular diseases, metabolic disorders, stroke, and dementia *(Brown et al., 2004) (Musselman et al., 1998),* other than a reduced life expectancy compared to the general population *(Chesney et al., 2014).* While this could be the consequence of a lower health-related quality of life associated with the disease, the predisposing role of biological players of cellular aging has been largely explored and their involvement supported by several findings *(Monroy-Jaramillo et al., 2018) (Simon and Smoller, 2006).* Telomere length has been the most widely studied aging biomarker in MDD *(Schroder et al., 2022),* but other aging biomarkers have been investigated and proved to be associated with this mood disorder: DNA methylation age *(Wang et al., 2023)*, functional brain data *(Luo et al., 2022)* and others *(Cole et al., 2021) (Shindo et al., 2023)*, all supporting the hypothesis of accelerated biological aging in depression. There is also a small number of published controversial findings on the role of mtDNAcn in depression, with studies reporting higher *(Lindqvist et al., 2018)*, lower *(Kageyama et al., 2018)* or no difference between cases and controls *(Chung et al., 2019) (Tyrka et al., 2016).*

It is acknowledged that there are significant differences in telomere biology and length in different tissues of the human body, but several studies suggest that LTL is highly correlated with region-specific and total brain volume *(Gampawar et al., 2020).* It has been suggested that a reduction of the hippocampus's size is significantly correlated with shorter LTL (*King et al., 2014).* Mood disorders are associated with significant reduction of the hippocampus, a crucial structure in the limbic system that is involved in multiple cognitive functions *(Haukvik et al., 2020).* Recent findings have suggested that there is a correlation between decreased telomere length, accelerated brain aging, and the hippocampus *(Fries et al., 2020).* Several studies indicate that the thalamus and the pulvinar nucleus play a critical role in the aging brain, which is characterized by altered neural circuits at different levels *(Zhang et al., 2018) (Fredericks et al., 2019).* Patients with schizophrenia showed reduced

functional connectivity in several regions of the brain compared to healthy controls, including the pulvinar nucleus, the hippocampus, and the anterior cingulate cortex, as shown by a recent study *(Penner et al., 2018).* TL has been linked to extensive connectivity changes in the brain, especially in the cingulum, a key component of the limbic system that consists of a bundle of white fibers that connects to the frontal, parietal, middle temporal, and subcortical regions *(Yu et al., 2020).*

Furthermore, some structural connectivity changes could offer a partial explanation for the connection between TL and executive function, a neuropsychological correlate that is highly reported to be impaired in mood disorder patients *(Cotrena et al., 2016)*. These data indicate that telomere shortening may play a role in the accelerated brain aging reported in mood disorder patients, and it may involve various brain regions and both functional and structural connectivity processes.

In the first study, we did not observe a correlation between LTL and severity of depression based on the MADRS score at baseline or at any time point evaluated. Although this finding is consistent with previous research *(Hartmann et al., 2010),* a recent study on patients with late-life depression revealed a negative correlation between LTL and the severity of depressive symptoms measured with the Hamilton Depression Rating Scale *(Mendes-Silva et al., 2021).* The differences in the findings could be due to various factors, such as differences in the scales used to assess the severity of symptoms and demographic characteristics (in our study, the median age of participants was 56 years, whereas the previous study only included patients with late-life depression). Moreover, while the Hartmann and colleagues' study *(Hartmann et al., 2010)* included MDD patients with no stratification based on resistance to treatments, all participants included in our study had a diagnosis of TRD.

We also found that LTL was negatively correlated with BMI, after adjusting for age. Increased levels of CRP may play a role in this correlation, but it's important to investigate this relationship further since increased BMI is also associated with telomere attrition through non-inflammatory mechanisms *(Gao et al., 2021).*

The role of telomeres in response to pharmacological and non-pharmacological treatments has yet to be elucidated, but some studies showed that TL predicts response to antidepressants or that TL is affected by treatment with antidepressants *(Rampersaud et al., 2023) (Rasgon et al., 2016) (da Silva et al., 2022) (Hough et al., 2016)* while the few studies published so far suggest no involvement of telomeres in response to ECT *(Ryan et al., 2020).* Both our studies did not support the role of LTL in predicting response to ECT in patients with TRD. These results are in line with a previous study that found no correlation between whole blood TL and response to ECT, remission, or cognitive side

effects in a sample of 100 patients with severe depression, where improvement was evaluated using the Hamilton rating scale for depression-24 item *(Ryan et al., 2020).*

Considering the cross-sectional nature of previous studies, this lack of evidence only suggests that TL could not be considered a predictive marker of response to ECT but does not exclude its implication in its mechanism of action or in modulating response to ECT.

In the analysis of GWAS data of the first study, we observed no significant enrichment between genetic variants associated with LTL and variants nominally associated with response to ECT. Although LTL is a highly heritable trait, and shorter genetically predicted TL has been associated with increased risk of some disorders, such as coronary artery disease and other cardiovascular disorders *(Hayflick, 1980) (Li et al., 2020*), previous studies aiming to assess the presence of an enrichment between genetic variants associated with LTL and psychiatric phenotypes mostly yielded negative results (*Pisanu et al., 2020) (Wium-Andersen et al., 2017) (Verhoeven et al., 2019)*.

The main strength of the second study was its longitudinal design with multiple time-points, which allowed, for the first time, to explore the correlation between dynamic changes in LTL and mtDNAcn in response to ECT.

While we reported no correlation between baseline LTL and response to ECT, in our longitudinal study we showed reduced LTL after ECT and an inverse correlation between changes in MADRS scores and in LTL after ECT, suggesting that, while a certain degree of telomere shortening might be involved in ECT, a larger decrease would be present in those individuals with minor improvement in symptoms. These findings provide some evidence that TL could be indeed affected by ECT through unknown mechanisms. One of the hypotheses is that telomere shortening could be induced by increased inflammation. While most studies have shown that ECT decreases neuro-inflammation *(Maffioletti et al., 2021),* some have suggested that it may actually cause inflammation and DNA damage to some extent *(Karayagmurlu et al., 2022) (van Buel et al., 2015).* It has been suggested that a mild and transient neuro-inflammatory response may be essential for proper brain functioning *(DiSabato et al., 2016).* In fact, the acute release of cytokines right after the ECT seems to stimulate neurotrophins release, such as BDNF, involved in the hippocampal neurogenesis and the clinical response *(van Buel et al., 2015) (Yrondi et al., 2018) (Rush et al., 2016).* Conversely, chronic inflammation could lead to mood disorders and damage to telomeres *(Miller, 2020) (Zhang et al., 2016).* However, the inflammation caused by ECT appears to be temporary, as the levels of inflammatory markers return to normal after weeks from the ECT course *(Gay et al., 2021) (Kruse et al., 2018).* Thus, we could only speculate that the telomere shortening observed in our study might be a marker of ECT treatment,

but it is still unclear if it is caused by an induced inflammation, if this shortening is transient as it is proved for the increasing of the cytokine's levels and lastly if this consequence could be negative or inversely contribute to the efficacy of ECT.

To date, the involvement of mtDNAcn in response to ECT and in TRD has been scarcely investigated. Our findings showed highly significant differences in baseline mtDNAcn between TRD patients and controls, but no involvement in response to ECT.

The biological importance of changes in mtDNAcn is still not completely clear, and therefore the larger mtDNAcn we observed in TRD needs further investigation and interpretation. It has been suggested that stressors that cause mitochondrial damage may cause mtDNA to leak out of cells, which would result in an increase in mtDNAcn in whole blood *(Klinedinst and Regenold, 2015).* Mood disorders have been associated with increased mitochondria turnover, apoptosis, and oxidative stress *(Gimenez-Palomo et al., 2021).* It has been suggested that stress is responsible for dysregulated energy homeostasis and could be a predisposing and trigger factor for depression *(Ostergaard et al., 2018).* The larger mtDNAcn found in TRD may be a result of compensatory mitochondrial biogenesis and replication to compensate for deficient energy supply from stressors, as evidenced by findings in rats *(Picard and McEwen, 2018).*

Our results must be interpreted in light of several limitations. The studies included a limited number of participants and in the first study the number of BD patients was particularly underpowered. Moreover, in the first study, we applied a cross-sectional design, which did not allow exploring the causative role of telomere shortening or the correlation between longitudinal changes in telomere length and variations in the MADRS scores.

Furthermore, we did not measure circulating levels of inflammatory markers, and therefore the hypothesis of an effect of ECT on LTL or mtDNAcn through modulation of inflammatory response could only be postulated. Another limitation was the lack of a sample of patients not treated with ECT, and the lack of data on blood cell types in our sample. In fact, studies suggest differences in mtDNA and LTL across blood cells *(Lin et al., 2016) (Picard, 2021).*

Moreover, the time difference between baseline and the evaluation of response to ECT could be too short to sensitively detect changes in either LTL or mtDNAcn. However, considering that ours is the first study of this kind and due to lack of data, to date, it is not possible to exclude that an intensive treatment such as ECT may determine telomere shortening or changes in mtDNA number of in a short period of time. A study by Fries and colleagues *(2020)* showed that in vitro treatment of

lymphoblastoid cell lines of BD patients with lithium for a week determined statistically significant changes in telomere length between before and after a week of treatment. Furthermore, Lee and colleagues showed that in rats 3 weeks treatment with glucocorticoids to induce stress, resulted in a reduction of telomere length of 43.2% measured in DNA extracted from the dentate gyrus *(Lee et al., 2021).*

In conclusion, our results support previous findings suggesting premature cell senescence in patients with severe psychiatric disorders, in particular with TRD and that LTL and mtDNAcn may constitute disease biomarkers for TRD, confirming the involvement of aging and oxidative factors in depression. LTL (and genetic variants affecting it) and mtDNAcn cannot be considered predictive biomarkers of response to ECT but treatment with ECT may correlate with telomere shortening, suggesting a potential implication of telomere dynamics. Nevertheless, our limited understanding of the biological significance of mtDNAcn and the limits of our study require further investigation to better delineate the involvement of aging markers in MDD and response to ECT.

7. Future Directions

Future studies should extend the analyses to a larger set aging and oxidative stress markers, and mitochondrial dysfunction markers in general, as well as to inflammatory pathways. Moreover, to better understand the involvement of telomere and mitochondria dynamics in response to ECT it would be essential to include samples of TRD patients not treated with ECT. It is also important to further study the role of mtDNAcn cross-disorder, and to evaluate if the differences between different pathologies implicate a specific involvement of mitochondrial dysfunction, and if this dysfunction is a consequence or a causative factor of the symptomatology or of response to treatments.

Moreover, it would be interesting to measure LTL and mtDNAcn in the same cohort of patients at a later timepoint (such as one year after ECT treatment) to explore if the differences observed changed or persisted, or if there are different patterns of changes that were not observed after one month. This approach would allow answering the many open questions, including the possible negative implications of ECT on aging markers.

Future directions of this line of research will lead to better understanding the role of cellular aging in MDD, especially in treatment resistance and in the response to pharmacological and non-pharmacological therapies, such as ECT. In fact, it would be extremely important to find predictive biomarkers to allow us to know in advance if treatments, especially invasive and prolonged ones, would be effective or deleterious for a specific patient, in order to ultimately personalize the management of this disorder and reach a better compliance, increase efficacy and reduce side effects.

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