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Aberrant grey matter volume in responsive and treatment-resistant patients with Major Depressive Disorder: two coordinate based meta-analyses of whole-brain sMRI studies

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Riassunto

Il Disturbo Depressivo Maggiore (MDD) è una malattia mentale il cui esordio può essere causato da molteplici fattori di natura psicosociale, biologica ed anche genetica, ma, nonostante gli importanti progressi ottenuti da decenni di ricerca nel campo delle neuroscienze cliniche, la sua eziopatogenesi non è ancora stata del tutto compresa. Inoltre, non tutti i pazienti rispondono al trattamento farmacologico, ad oggi la terapia di prima scelta nei casi di MDD; nello specifico, l'etichetta diagnostica "Depressione resistente al trattamento" (TRD) si riferisce all'assenza di risposta ad un adeguato regime terapeutico. Per indagare i correlati neurali di MDD e TRD, un approccio estremamente efficace, non invasivo e in vivo è costituito dalle tecniche di neuroimmagine. Fra queste, la risonanza magnetica strutturale (sMRI), in particolare, permette di identificare le alterazioni morfologiche presenti a livello di volume di materia grigia (GMV), consentendo di far luce sulla fisiopatologia del MDD e sui meccanismi che collegano il disturbo, le anomalie strutturali e la reattività al trattamento.

La presente tesi si compone di due metanalisi *coordinated based* su studi che, ricorrendo alla tecnica *whole-brain voxel-based morphometry* (VBM), hanno indagato anomalie strutturali in pazienti con MDD e TRD rispetto a controlli sani (HC), ponendo particolare attenzione alla responsività al trattamento. La suddetta tecnica, completamente automatizzata e ad oggi ben consolidata, consente di confrontare a livello statistico le differenze anatomiche rilevabili fra gruppi diversi, creando mappe cerebrali parametriche.

È stata condotta una ricerca sistematica della letteratura presente in PubMed fino a Gennaio 2022, da cui sono stati selezionati sessantasette studi per la prima metanalisi, e sette per la seconda. I campioni confrontati consistevano in 3532 pazienti con MDD aventi atrofia *vs*. 4224 HC, 1846 pazienti con MDD aventi ipertrofia *vs*. 2483 HC, e 245 pazienti con TRD *vs*. 258 HC. Allo scopo di identificare le alterazioni strutturali comuni nei pazienti, sono stati utilizzati il metodo ALE (*activation likelihood estimation*) e l'approccio *coordinate-based mapping*.

Dalla prima metanalisi sono emerse sia una riduzione significativa del GMV nel giro fusiforme e nel declive, sia un'ipertrofia a livello di giro paraippocampale in pazienti depressi rispondenti al trattamento. I pazienti con TRD, invece, presentavamo solo atrofia

nel cingolato anteriore. Abbiamo dunque formulato un'ipotesi sulle cause attribuibili alle differenze strutturali rilevate tra pazienti rispondenti e refrattari al trattamento.

Lo scopo del presente lavoro è di contribuire all'identificazione delle anomalie più comunemente rintracciabili nel MDD, e di chiarire come tali alterazioni differiscono tra pazienti che rispondono e non rispondono alla terapia – un campo di ricerca in cui i risultati sono ancora inconsistenti.

Abstract

Major Depressive Disorder (MDD) is a mental disease caused by many complex factors (psycho-social, biological, genetic factors), but, despite decades of research, its etiopathogenesis has not yet been fully elucidated. Moreover, not all patients respond to the pharmacological treatment, which is the first-choice therapy for MDD. Treatment-resistant depression (TRD) is the diagnostic label for the occurrence of an inadequate response to an adequate antidepressant therapy. To investigate the neural correlates of MDD and TRD, neuroimaging techniques represent a powerful, in vivo, and noninvasive approach; in particular, structural Magnetic Resonance Imaging (sMRI) can identify morphological alterations in Grey Matter Volume (GMV) underpinning the pathophysiology of MDD and can help to shed light on the still unclear mechanisms linking depression, structural abnormalities, and treatment responsiveness.

The present thesis consists of two coordinate based meta-analyses of whole-brain voxel-based morphometry (VBM) studies on GMV structural alterations occurring in MDD and TRD patients with respect to healthy controls (HC) with a particular focus on treatment responsiveness. VBM is a well-established, whole-brain, automatic, and unbiased tool that allows comparisons of focal differences in brain anatomy between groups, using the statistical approach of parametric mapping.

A systematic literature search was performed in PubMed up to January 2022. Sixty-seven studies were included in the first meta-analysis, and seven in the second one. Comparisons were the followings: 3532 MDD patients showing GMV atrophy *vs.* 4224 HC; 1846 MDD patients showing GMV hypertrophy *vs.* 2483 HC; 245 TRD patients *vs.* 258 HC.

An activation likelihood estimation (ALE) analysis and a coordinate-based mapping approach were used to identify common brain structural alterations among patients.

GMV was significantly reduced in the fusiform gyrus and the declive in respondent MDD patients, and in the anterior cingulate in TRD ones. We only found hypertrophy in MDD patients located in the parahippocampal gyrus. A hypothesis for structural differences between respondent and refractory patients has been suggested.

The project aims to contribute to identify consistent GMV anomalies in MDD, and to elucidate the difference in these alterations between patients who respond and who don't respond to drug treatment, for which findings are yet inconsistent.

CHAPTER 1 - MAJOR DEPRESSIVE DISORDER: AN OVERVIEW OF THE MOST PREVALENT MENTAL DISEASE ACROSS ITS COMPLEXITY

Introduction

Depression is the most common mental disorder [1], with approximately 280 million people suffering from it [2]; it is estimated it affects 5.0% of the adult population [2]. It is nonetheless a leading cause of disability worldwide and it greatly contributes to the overall global burden of disease [2].

In order to understand its nature and recognize its severity, distinguishing depression from sadness is a first essential step. The features and the extent of depressive symptomatology allow for a clear distinction between them: while sadness refers to "*an emotional state of unhappiness, ranging in intensity from mild to extreme and usually aroused by the loss of something that is highly valued"* [3], depression is a disease characterized by "*a negative affective state, ranging from unhappiness and discontent to an extreme feeling of sadness, pessimism, and despondency, that interferes with daily life*" [3]. The impact on everyday life can manifest in form of cognitive, emotional, behavioral, social, and physical alterations (e.g., lack of interest and pleasure in previously pleasurable activities, inability to concentrate or make decisions, feelings of worthlessness or excessive guilt, poor social functionality, altered eating or sleeping habits, lack of energy and tiredness) [1], and frequent thoughts of death can occur too, leading to suicide in the worst case; as recently reported, depression has a role in more than one-half of suicide attempts [4].

Acknowledging the extent to which depression differs from a low mood state or short-lived emotional responses to life events is necessary to assist people in getting the help they need adequately. Depression is actually treatable and, as appropriate, both psychological and pharmacological therapies are available and effective, such as Cognitive-behavioral therapy and antidepressant medications (e.g., Selective Serotonin Reuptake Inhibitors) [5]. Unfortunately, in low- and middle-income countries services for depression are often absent still today, while depressive people are often not correctly diagnosed even in countries with a high-level income [2].

As can be deduced from the abovementioned symptomatology, depression is a multifaceted illness, and so is its etiology. Indeed, it can be caused by many complex psychological, social, and biological factors [2], often resulting in the "downward spiral" typically referred by affected people. Stressful events, family history, biochemical imbalance, personality traits, substance misuse, and another illness are all elements that can catalyze depression onset and contribute to its maintenance [6].

Depression can also vary in severity. The three main factors determining the degree of its severity are symptoms (in terms of number, frequency, and intensity), duration, and impact on personal and social functioning [5]. The combinations of these elements have led to four categories: subthreshold, mild, moderate, and severe [5]. Especially when recurrent or long-lasting and with moderate-to-severe intensity, depression may become a serious medical condition [2], also known as Major Depressive Disorder.

1. Major Depressive Disorder

Major Depressive Disorder (MDD), also termed Major Depression or Clinical Depression, is the most severe form of this disease [7]. Within the depressive disorders group (Disruptive Mood Dysregulation Disorder, Major Depressive Disorder -including major depressive episode-, Persistent Depressive Disorder, Premenstrual Dysphoric Disorder, Substance/Medication-Induced Depressive Disorder, Depressive Disorder Due to Another Medical Condition, Other Specified Depressive Disorder, and Unspecified Depressive Disorder), it represents the classic condition [7].

According to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5), major depression essential features are discrete episodes lasting no less than two weeks, although most episodes have a considerably longer duration, and even if it is possible to diagnose MDD based on one single episode, the disorder tends to be mostly recurrent [7]. The International Classification of Diseases 11th Revision (ICD-11) considers two weeks as the minimum duration of one depressive episode too, and it distinguishes between Single Episode Depressive Disorder and Recurrent Depressive Disorder, the latter being marked by at least two depressive episodes separated by several months without significant mood disturbance [8]. The two core symptoms of a major

depressive episode (MDE) are depressed mood and anhedonia, which can occur together or alone [7,8].

Depressed mood may take the form of various changes in affect, like persistent sadness, pessimism or overly negativism, hopelessness or discouragement, but also exaggerated irritability or anger [3,7]; moreover, a person can either report these feelings or somatize them through physical symptoms, such as bodily pains [7]. In some other cases, depressed mood could be denied, but it can be inferred from facial expressions or behavior [7]. The key feature of depressed mood is its constant deflection, which never alternates with abnormally elevated mood (i.e., manic or hypomanic episode) in Major Depressive Disorder; from here, the definition of MDD as Unipolar Depression, to distinguish it from Bipolar Disorder, in which the mood switch is crucially present [9].

Anhedonia is defined as the loss of experiencing interest or pleasure in many, if not all, activities that were once considered rewarding or enjoyable [7,8], and because of its pervasiveness it is one of the first signs of depression onset/recurrence. This cardinal symptom is heterogeneous: it can be referred to as *social anhedonia* when it affects the interpersonal sphere in the form of a lack of pleasure in social situations, with typical manifestations such as great difficulty in interactions or withdrawal from social activities [10]; instead, *physical anhedonia* refers to an inability of enjoying physical sensations or to feel tactile pleasures, such as eating, touching, or sex [11]. In recent years, it was reported that almost 70% of MDD patients showed clinically significant levels of anhedonia [12].

These two key symptoms, together with other important changes in cognition, emotions, and neurovegetative and physical functions (see paragraph 1.1), determine clinically significant functional consequences: whether it is mild or serious, impairment in relevant areas of functioning always accompanies a major depressive episode [7]. Patients typically report impairments in the occupational domain, like a reduction of work capacity/productivity or difficulty in maintaining their role [13], the factor that contributes for the largest portion (61%) to the economic burden of depression in the U.S., which was estimated to account in total for $326.2 billion in 2018 [14]. Other compromised domains are family, school, and leisure [13]. At its worst range, depressed people lose the capacity to meet their self-care needs, or they can even become mute or catatonic [7]. Assessing and treating functional impairment in patients with MDD is

clinically critical because it was found to be associated with the severity of symptoms and, nonetheless, to persist even after a marked symptomology improvement; thus, residual functional deficit has been linked with a higher risk of relapse and recurrence of depression [15].

Ultimately, the presence of depressed mood and/or anhedonia, and clinically significant distress are essential for the diagnosis of MDD, but not exhaustive; indeed, some other elements must be present for a correct diagnosis. The diagnostic criteria for major depression are provided by DSM-5 and ICD-11, the two principal classification systems for psychiatric disorders, and reported in the following paragraphs. In addition, the Research Domain Criteria framework for depression developed by the U.S. National Institute of Mental Health (NIMH) will be also discussed.

1.1 Diagnostic Criteria

1.1.1 Definition of Major Depressive Disorder according to DSM-5

DSM-5 is published by the American Psychiatric Association (APA), and it offers a valid and complete description of symptoms and other criteria for diagnosing Major Depressive Disorder following a categorical, nomothetic, and a-theoretical approach, being its main aims to provide a common language for clinicians and researchers, and to establish consistent and reliable diagnoses for mental disorders [7,16]. Once the diagnosis is made, DSM-5 also includes further characterizations using various specifiers, which allow to grade the severity (mild, moderate, or severe), the course (single or recurrent episode), and the remission status (in partial or full remission), and to define the presence of additional features, e.g., psychotic, melancholic, or anxious features [7,16].

MDD diagnostic criteria are listed in Table 1.

Table 1. DSM-5 diagnostic criteria for Major Depressive Disorder [7].

Major Depressive Disorder
Diagnostic Criteria
A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning: at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. **Note**: Do not include symptoms that are clearly attributable to another medical condition. 1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful). (**Note**: In children and adolescents, can be irritable mood.) 2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation). 3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. (**Note**: In children, consider failure to make expected weight gain.) 4. Insomnia or hypersomnia nearly every day. 5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down). 6. Fatigue or loss of energy nearly every day. 7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick). 8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others). 9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.
B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
C. The episode is not attributable to the physiological effects of a substance or to another medical condition.
Note: Criteria A-C represent a major depressive episode.
Note: Responses to a significant loss (e.g., bereavement, financial ruin, losses from a natural disaster, a serious medical illness or disability) may include the feelings of intense sadness, rumination about the loss, insomnia, poor appetite, and weight loss noted in Criterion A, which may resemble a depressive episode. Although such symptoms may be understandable or considered appropriate to the loss, the presence of a major depressive episode in addition to the normal response to a significant loss should also be carefully considered. This decision inevitably requires the exercise of clinical judgment based on the individual's history and the cultural norms for the expression of distress in the context of loss.
D. The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.
E. There has never been a manic episode or a hypomanic episode. **Note:** This exclusion does not apply if all of the manic-like or hypomanic-like episodes are substance-induced or are attributable to the physiological effects of another medical condition.

Together with the above-described depressed mood and anhedonia (see paragraph 1), some symptoms of a different order characterize major depression, according to DSM-5, which recur nearly every day for at least two weeks and represent a clear-cut worsening from the previous level of functioning. They are categorizable into physical-neurovegetative and affective-cognitive alterations.

The firsts refer to criteria 3 to 6 (Table 1), and they contribute to the definition of MDD as a full-fledged heterogeneous disease; indeed, criteria 3, 4, and 5 describe

symptoms of opposite polarity, whose combinations elucidate how much the disorder can be phenotypically different [17]. In particular, depressed people could gain or lose weight, have increased or reduced appetite, suffer from insomnia or hypersomnia, or experience agitation or retardation at psychomotor level. Attempts to define which profiles are typical and atypical have been done, resulting in a general agreement in considering the occurrence of the atypical one when the reversed subtype symptoms are present (i.e., increased appetite and/or weight gain and hypersomnia) [17]. The physical sign with one single polarity is decreased energy, in the form of tiredness and/or fatigue (criterion 6), which is critical to distinguish between Unipolar and Bipolar Depression [9]. Of note, neurovegetative symptoms are well known to be linked in reciprocal associations with somatic conditions, such as heart failure, headache, and back pain [18].

The second alteration category refers to criteria 7, 8, and 9 (Table 1). Self-criticism and self-blaming emotional and moral biases, such as self-hate or excessive guilt (criterion 7), play a central role in the negative feelings sphere characterizing depression [19]. Thoughts like "*I am a failure, therefore I hate myself*" or "*I am the only one responsible for my relatives' discontent*" are very common among MDD patients, and they were found to be closely associated with core depressive symptoms like depressed mood and high distress [19], as well as being more frequent than negative emotions towards others [20,21]. "*The sense of worthlessness or guilt (...) may include unrealistic negative evaluations of one's worth or guilty preoccupations or ruminations over minor past failings*" DSM-5 reports, adding that they can even reach delusional proportions [7].

Impaired ability to think, be or remain concentrated, or make decisions, even the minor ones, are great-impact cognitive signs mentioned in criterion 8 because they are reported by many individuals. Unfortunately, cognition in MDD can be much more widely disrupted; the disease can indeed affect attention, memory, learning, information processing, problem-solving, cognitive flexibility, and, more in general, executive functioning [22]. It has been shown that cognitive dysfunction is a mediator of daily-life functional disability in MDD, especially in the workplace [23], and that its persistence tends to go beyond the resolution of the acute phase, making it one of the more common residual complaints among patients who achieve symptomatic remission [23,24]. Special attention must be reserved for elderly people to not mistake cognitive difficulties for signs of dementia, but also because, on the opposite, a major depressive episode may be

sometimes the prodromal phase of dementia, whose early recognition can make the difference in treatment choices [7,25].

Finally, criterion 9 defines the presence of death thoughts and suicidal behaviors, both ideations and attempts, symptoms that must never be underestimated. In 2015 it was estimated that up to 50% of the 800000 suicides per year worldwide were committed during a depressive episode [26], while a meta-review reported that MDD patients were 20-fold more likely to die by suicide than the general population [27]. There are several diseases that might increase the risk of suicidal behaviors when interacting with depression, such as the co-occurrence of alcohol and drug abuse, panic disorder, or post-traumatic stress disorder, but also individual factors like early-life adversity, family history, impulsive aggression personality trait or belonging to a minority (e.g., sexual minority) [28]. Lots can be done to prevent suicides, but this is possible, World Health Organization (WHO) says, only with the cooperation of as many social sectors as possible, from public health to education, politics, and media [29].

In summary, DSM-5 requires for MDD diagnosis at least five of the above-written symptoms, one of which must be depressed mood or loss of interest or pleasure, to be simultaneously present for a period lasting no less than 2 weeks; they must represent a change in the individual functioning, as well as be the cause of functional impairment. Symptoms must not be attributable to another medical condition, effects of substance use, or any psychotic disorders, must not be mistaken with consequences of a significant loss, and must not be interspersed with manic/hypomanic phases unless they are induced by a substance or another medical condition.

1.1.2 ICD-11 criteria for Depressive Episode

In the public health overview, ICD is the global standard for diagnostic information of human diseases provided by the WHO, which aims to provide worldwide healthcare professionals with statistically based standardized methods of tracking and recording illnesses, including mental ones [30]. In particular, Depressive disorders belong to the Mood disorders category, which is itself part of the Mental, behavioral or neurodevelopmental disorders category in ICD-11, the latest version of ICD which came into effect in January 2022.

A difference from DSM-5 immediately noticeable is that the Major Depressive Disorder label is not present in ICD-11; in its place, Single Episode Depressive Disorder and Recurrent Depressive Disorder definitions can be found, where the first one corresponds to a major depressive episode as described in DSM-5, whereas the second one is more properly associable to MDD because its course is mostly recurrent (see paragraph 1.2.2). Thus, the presentation and the symptomology of Single Episode Depressive Disorder are the same as those of Recurrent Depressive Disorder apart from a history of prior depressive episodes [8].

The diagnostic features of a depressive episode according to ICD-11 are listed in the following table and divided into three different clusters (Table 2), specifying that they must occur most of the day, nearly every day, for minimum 2 weeks with a significant impact on the individual's functioning, that at least five out of ten must be concurrently present and that one of them must belong to the affective cluster; in addition, symptoms cannot be explained as a consequence of either bereavement, another medical condition, or substance intake, and no manic, hypomanic, or mixed episodes must have occurred before because they would indicate the presence of a bipolar disorder [8].

Table 2. ICD-11 Diagnostic Requirements for Depressive Episode [8].

Depressive Episode
Essential (Required) Features

• The concurrent presence of at least five of the following characteristic symptoms occurring most of the day, nearly every day during a period lasting at least 2 weeks. At least one symptom from the Affective cluster must be present. Assessment of the presence or absence of symptoms should be made relative to typical functioning of the individual.
• *Affective cluster:*
  ○ Depressed mood as reported by the individual (e.g., feeling down, sad) or as observed (e.g., tearful, defeated appearance). In children and adolescents depressed mood can manifest as irritability.
  ○ Markedly diminished interest or pleasure in activities, especially those normally found to be enjoyable to the individual. The latter may include a reduction in sexual desire.
• *Cognitive-behavioural cluster:*
  ○ Reduced ability to concentrate and sustain attention to tasks, or marked indecisiveness.
  ○ Beliefs of low self-worth or excessive and inappropriate guilt that may be manifestly delusional. This item should not be considered present if guilt or self-reproach is exclusively about being depressed.
  ○ Hopelessness about the future.
  ○ Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation (with or without a specific plan), or evidence of attempted suicide.
• *Neurovegetative cluster:*
  ○ Significantly disrupted sleep (delayed sleep onset, increased frequency of waking during the night, or early morning awakening) or excessive sleep.
  ○ Significant change in appetite (diminished or increased) or significant weight change (gain or loss).
  ○ Psychomotor agitation or retardation (observable by others, not merely subjective feelings of restlessness or being slowed down).
  ○ Reduced energy, fatigue, or marked tiredness following the expenditure of only a minimum of effort.
• The symptoms are not better accounted for by bereavement.
• The symptoms are not a manifestation of another medical condition (e.g., a brain tumour) and are not due to the effects of a substance or medication on the central nervous system (e.g., benzodiazepines), including withdrawal effects (e.g., from stimulants).
• The clinical presentation does not fulfil the diagnostic requirements for a Mixed Episode.
• The mood disturbance results in significant impairment in personal, family, social, educational, occupational, or other important areas of functioning. If functioning is maintained, it is only through significant additional effort.

The harmonization between DSM and ICD criteria has been pursued both by APA and WHO to improve clinical utility, increase global applicability and facilitate scientific investigations on mental health [31]. This process results in consistent compatibility in the diagnostic guidelines, especially for depression, whose definitions in ICD-11 and DSM-5 are nearly the same (see Table 1 and Table 2).

There are only two differences between them: the first is the inclusion in ICD of hopelessness as a discrete symptom, while it is considered as an example of a subjective report of depressed mood in DSM. The rationale for the ICD approach of giving more relevance to hopelessness (i.e., "*the feeling that one will not experience positive emotions or an improvement in one's condition*" [3]) is because it has proven to be strongly

effective in differentiating depressed individuals from those who are not, more than about half of the other symptoms [32,33].

The second regards bereavement: ICD-11 made an effort to give guidance less vague as possible for diagnosing a depressive episode during the grieving process, indicating that "*A Depressive Episode should not be considered to be present if the individual is exhibiting normal grief symptoms (...) and the individual has experienced the death of a loved one within the past 6 months, or longer if a more extended period of bereavement is consistent with the normative response for grieving within the individual's religious and cultural context. (...) However, a Depressive Episode can be superimposed on normal grief. The presence of a Depressive Episode during a period of bereavement is suggested by persistence of constant depressive symptoms a month or more following the loss (...), severe depressive symptoms such as extreme beliefs of low self-worth and guilt not related to the lost loved one, presence of psychotic symptoms, suicidal ideation, or psychomotor retardation.*" [8]. Instead, DSM-5 just states that "*The presence of a major depressive episode in addition to the normal response to a significant loss* - including bereavement- *should be carefully considered.*", and then reports some differences between grief and MDE in a footnote; thus, the decision is up to the clinicians' judgment [7]. In this case too, ICD choice is supported by evidence: some studies longitudinally document that people who reported a single depressive episode related to grief at baseline had a lower risk of further depressive episodes than those who experienced non-bereavement-related depression, and there were no differences between the bereaved group and general population with no baseline depression history [34,35].

Apart from the discrepancies described above, similarities between the two systems' ways to define a depressive episode are glaring, including the ICD-11 adoption of qualifiers, which are analogous to DSM-5 specifiers (see paragraph 1.1.1); these descriptors allow to indicate the eventual presence of psychotic symptoms, panic attacks, melancholia, seasonal pattern, or prominent anxiety symptoms, and to rate the episode on a mild, moderate or severe level based on the number and severity of the symptoms, as well as the impact on the individual's functioning [8,36].

Unfortunately, the assessment of depression grade severity is still considered unsatisfactory in ICD-11 and DSM-5 [36], a fact that represents a prominent issue in everyday health care reality, and that is reflected in the more general problem of the lack

of dimensionality in both diagnostic systems. Despite important changes from their previous editions (e.g., the introduction of a dimensional model for personality disorder assessment and diagnosis) [37], the categorical approach is still undeniably dominant in the two principal classification systems, and the main reason why they still adopt it can be found in its great clinical and administrative utility, such as providing standardized diagnosis and treatment, helping clinicians to make dichotomous decisions, facilitating communication among specialists, and monitoring care systems [38]. At the same time, however, there is a general agreement on considering mental disorders more accurately described as dimensional phenomena, rather than strict polythetic-categorical constructs [39]. Therefore, a major challenge for DSM and ICD is to include dimensional components, in order to reconcile the complex nature of mental illness with their categories [37,38].

The importance of adopting a dimensional perspective on mental disorders has been fully recognized by NIMH, which responded to the increasing necessity of a framework to investigate multiple aspects operating in psychopathology by developing the Research Domain Criteria (RDoC) project [40].

1.1.3 Research Domain Criteria framework for Depression

RDoC is a theoretical research framework provided by NIMH to investigate mental illness as a product of several interrelated mechanisms, traceable to varying levels of dysfunction in psychological, biological, physiological, and behavioral systems [40]. Although the project was launched in 2009 in response to the increasing discontent with the conventional classifications of mental disorders [41], RDoC is not a diagnostic guide and it does not aim to replace DSM and ICD, but at the same time, the perspective adopted by NIMH diverges markedly from that one followed by APA and WHO in the realization of the major current diagnostic systems [37]. The ultimate goal of RDoC is to deepen the knowledge about the basis of psychopathology, and therefore to develop a precision medicine approach to mental disorders [41].

The framework consists of an organizational structure with four major components: neurodevelopmental and lifespan changes in behavioral and biological aspects of functioning; environmental factors (e.g., physical environment, cultural components,

social determinants of health); six main functional domains; different constructs of each of the six domains, studied along eight units of analysis [37,40]. The two latter components are organized in a matrix as follows: every higher-level domain (i.e., negative valence systems, positive valence systems, cognitive systems, social processes, arousal and regulatory systems, and sensorimotor systems) is defined by specific constructs and subconstructs, and each of those is characterized by genes, molecules, cells, circuits, physiology, behavior, self-report, and paradigms used to study it [40] (see Table 3 for an example).

Table 3. Negative Valence Systems Construct of Loss, adapted from [42].

Negative Valence Systems Construct of Loss					
Units of Analysis					
Genes	**Molecules**	**Circuits**	**Physiology**	**Behavior**	**Self-Reports**
MAOA; COMT; DAT1; 5-HTTLPR	Downregulation of Glucocorticoid Receptors; Estrogens; Androgens; Oxytocin; Vasopressin; Inflammatory Molecules	Sustained Amygdala Reactivity; Decreased DLPFC Recruitment; Increased Insula Activation; Increased Posterior Cingulate Activity; Increased Default Mode Activity; Dysregulated Reward Circuitry	ANS, HPA, & Neuroimmune Dysregulation; Prolonged Psychophysiological Reactivity	Rumination; Withdrawal; Worry; Crying; Sadness; Loss-relevant Recall Bias; Shame; Guilt; Morbid Thoughts; Psychomotor retardation; Deficits in Executive Function; Loss of Drive (Sleep, Appetite, Libido)	Change in Attributional style; Hopelessness

Abbreviations: MAOA= Monoamine oxidase A; COMT= Catechol-O-methyltransferase; DAT1= Dopamine transporter gene; 5-HTTLPR=serotonin-transporter-linked promoter region; DLPFC= Dorsolateral prefrontal cortex; ANS= Autonomic nervous system; HPA= Hypothalamic-pituitary- adrenal.

Several studies have been conducted to integrate RDoC into depression research, which lends itself well to the application of the framework, being such a heterogeneous disorder from etiological, pathophysiological, neurobiological, and phenotypic points of view. For example, Woody and Gibb (2015) realized a matrix for the negative valence systems construct of loss in the depressive state by reviewing the literature on the matter [42], starting from the definition of loss offered by NIMH: "*A state of deprivation of a motivationally significant con-specific, object, or situation. Loss may be social or non-*

social and may include permanent or sustained loss of shelter, behavioral control, status, loved ones, or relationships. The response to loss may be episodic (e.g., grief) or sustained." [40]. Their study clearly shows how neuroscientific contributors are essential to understand specific features such as loss in this case (Table 3).

Other works focused on specific depressive symptoms. Dillon et al. (2013) investigated threat responses and reward processing in light of RDoC conceptualization, integrating well-established findings at genetic, molecular, circuit, and behavioral levels [43], while Mao and Yuan (2021) demonstrated that anhedonia consists of a series of impairments in the RDoC positive valence systems (anticipatory pleasure, incentive motivation/effort, and reward learning), emphasizing the role of dopaminergic system abnormalities, altered cerebral structures and functional networks underlying reward systems modifications in the pathogenesis of anhedonia [44].

Using the specific RDoC constructs to identify different phenotypes of the same disease is another interesting modality to apply the framework to research. This is the procedure followed in an exploratory study promoted by the Mood Disorders Precision Medicine Consortium [45], where four major depression phenotypes have been defined by selecting the items from the Hamilton Depression Rating Scale and Quick Inventory of Depressive Symptomatology which matched with RDoC constructs, under the expert review and consensus. *'Core Depression'* is the first phenotype, identified by the presence of feelings of sadness and loss of pleasure or motivation; thus, it is in line with the RDoC construct of loss [42]. The second one is named *'Anxiety'*, because it highlights the anxious spectrum of symptoms often associated with depression (agitation, psychological anxiety, somatic anxiety, and hypochondriasis). This phenotype is consistent with the RDoC construct of potential threat, described as the "*activation of a brain system in which harm may potentially occur but is distant, ambiguous, or low/uncertain in probability, characterized by a pattern of responses such as enhanced risk assessment (vigilance)*", adding that "*these responses to low imminence threats are qualitatively different than the high imminence threat behaviors that characterize fear*." [40]. The last two align with the matrix's arousal and regulatory systems; indeed, they are the Neurovegetative Symptoms of Melancholia phenotype, characterized by insomnia and hypophagia, and the Neurovegetative Symptoms of Atypical Depression phenotype, which manifests, on the contrary, through hypersomnia and increased appetite.

Similarly to the previous work, Gunzler et al. (2020) found a four-factor model to describe different depressive phenotypes by fitting the patient health questionnaire (PHQ)-9, a common tool used for depression screening, for RDoC domains [46]. The model consists of traits reflecting RDoC negative valence systems and externalizing (anhedonia and depression), negative valence systems and internalizing (depression, guilt, and self-harm), arousal and regulatory systems (sleep, fatigue, and appetite), and cognitive and sensorimotor systems (concentration and psychomotor). Authors found a high level of intercorrelation between these phenotypes, which also turned out to be significantly influenced by age, sex, ethnicity, and the number of comorbidities.

Studies such as the above [42-46] have a central role in research on depression, firstly because they clarify how RDoC accounts for the multidimensionality of the disorder, and this benefits both research and clinical practice; indeed, a common factor shared by RDoC-inspired works is the pursuit of the clinical goal to develop an individualized and precision medicine for depression from the diagnosis to the treatment choice. The NIHM project, with its potential to be constantly updated by gathering worldwide efforts, is, therefore, one of the most complete tools to keep up with the recent advances in the understanding of depression.

In conclusion, the Research Domain Criteria initiative represents the cutting-edge dimensional approach to mental health, whose integration with the traditional categorical systems looks essential for diagnosis. Furthermore, studies conducted with its approach extensively contribute to the biological analysis of clinical components, and therefore to the investigation of psychopathology etiology, a field in which research on biomarkers has become increasingly important. Finally, characterizing biological factors of disease could impact treatment, providing for example new targets for drug development or discovering whether pharmacological treatment outcomes differ between phenotypes.

1.2 Epidemiology

1.2.1 Prevalence

According to the U.S. National Institute of Mental Health, Major Depressive Disorder affects an estimated 6.7% of the United States population over the age of 18

every year; in 2020 about 21 million adults in the U.S. had at least one major depressive episode, and about 14.8 million adults had at least one major depressive episode with severe impairment [47] (Figure 1).

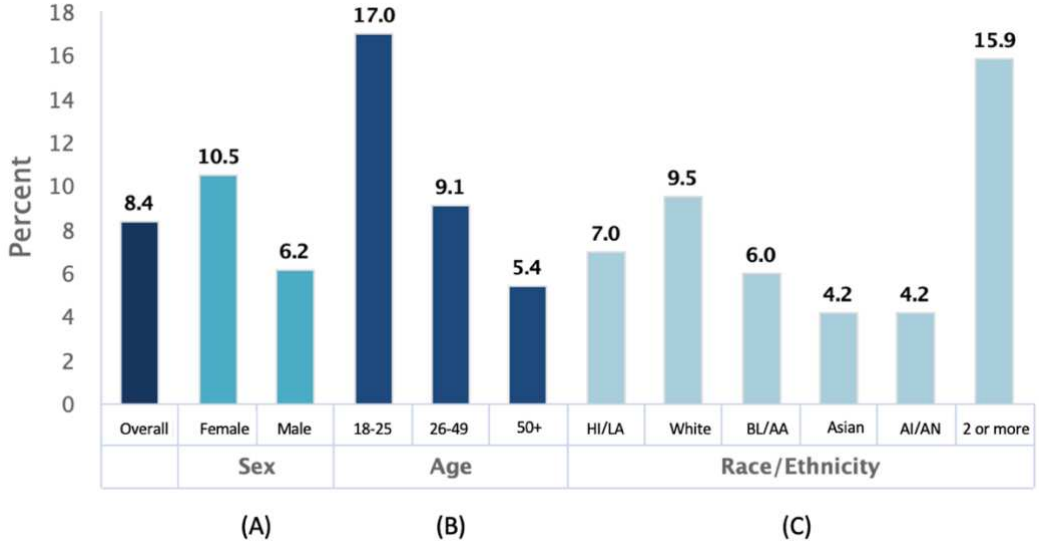

Figure 1. Prevalence of major depressive episode among U.S. adult population in 2020 divided for sex (A), age (B), and race/ethnicity (C) [47].
Abbreviations: HI/LA= Hispanic/Latino; BL/AA= Black/African American; AI/AN= American Indian/Alaskan Native.

10.5% of U.S. adult females experienced a major depressive episode in 2020 compared to 6.2% of males [47] (Figure 1A), a fact that corroborates the most reproducible finding in the MDD epidemiology: women are more likely than men to experience major depression, with a 1.5- to 3-fold higher incidence rate [7] and a lifetime prevalence approximately twice as high [8].

Among adolescents, 17.0% of the U.S. population aged 12 to 17 was estimated to experience at least one major depressive episode in 2020 [47], and among elderly people, even if the prevalence in 18- to 29-year-old individuals is three times higher than the prevalence in 60 years or older population (Figure 1B), an onset in late life is not uncommon [7]. A current issue is that MDD is frequently undiagnosed and untreated in children, teens, and older adults [48].

Finally, the prevalence was higher among multiracial people in 2020 comparing different ethnicities [47] (Figure 1C). Socio-demographic correlates, such as gender, age of onset, and marital status, severity, and symptom profile of MDD are mostly

comparable between countries, although the prevalence estimates could vary because of discrepancies in methodological processes and study-design factors [49]. Cultural differences play a role too: reporting biases are often caused by the diverse perception of depression depending on cultural norms [8], and in many cases stigma is the reason why symptoms are under-detected; widespread shame experienced by depressed people is an urgent issue [50]. Clinicians should be aware of the unrecognition of the majority of depression cases in most countries [7] as a fundamental step to facilitate symptomatology reports, access to primary care settings and treatment acceptability.

1.2.2 Disease course

A consistent age-related feature of MDD is that the disorder may first appear at any time, from childhood to old age, but on average the prevalence increases at puberty, and the onset usually occurs during the late teens to mid-20s (Figure 2) [47,51,52].

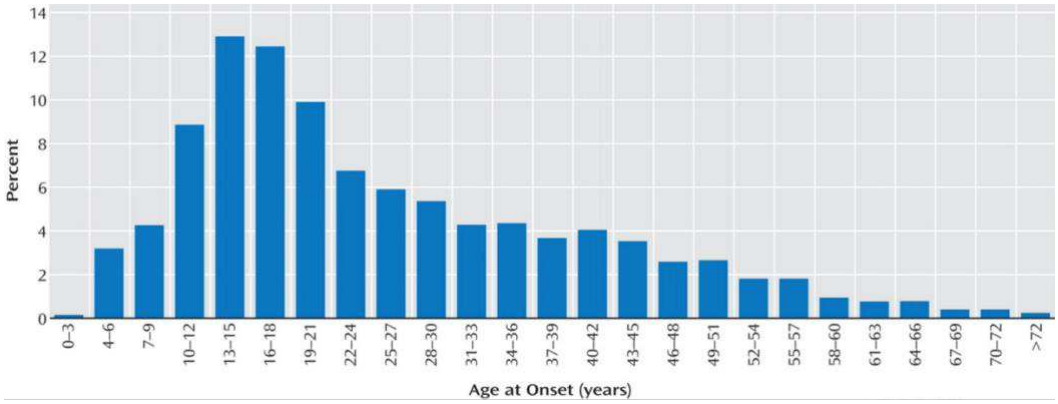

Figure 2. Age-of-onset data of 3,896 participants enrolled in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, the mean age of Major Depressive Disorder onset was 26 years [52].

In such cases of early onset, individuals often continue to suffer from major depressive episodes throughout adulthood as well; indeed, for many people, MDD is a lifelong disorder with multiple relapses, requiring long-term prophylactic treatment [53]. It has been shown that most patients have a recurring-remitting course with 5 lifetime episodes on average, and with a 3–6 times higher recurrence risk after a first MDE [54]. Particularly concerning is the scenario emerging from care settings data: in a follow-up study with an outpatient-based sample (n = 767), one out of four patients with nonchronic

MDD progressed to a chronic disorder, while >50% of patients still had MDD after 4 years [55]. Hopefully, the disease course looks more favorable when studies conducted on the general population are taken into account, like the one providing results from the Netherlands Mental Health Survey and Incidence Study (NEMESIS) on 7076 adults, according to which half of those affected recovered within 3 months [56]; however, almost 20% of the participants had not recovered at 24 months [56]. This evidence poses the critical challenge for clinicians and researchers to identify predictors of persistence and recurrence of major depression; among these, the severity of the depressive illness, the severity of psychiatric and other physical comorbidities, and a failure to seek treatment were found to be crucial independent predictive factors at baseline, both for persistence and recurrence [53].

The consequence of the high rates of chronicity is that remission is uncommonly achieved. It was estimated that almost two out of three patients with major depression did not remit in 23 psychiatric and 18 primary care settings, even after a well-delivered 12- to 14-week trial of optimally dosed antidepressant drugs [57], and a recent meta-analysis shows that short-term remission from depression without treatment is rare too, with about only 12.5% of untreated people remitting within 12 weeks [58]. In addition, residual symptoms and functional impairment in form of psychosocial disability often remain after individuals remit from a major depressive episode [59].

Nevertheless, it is important to point out that remission rates could vary depending on the considered conditions under which it is supposed to be achieved. A useful tool is the report on remission in Major Depressive Disorder realized by the American College of Neuropsychopharmacology (ACNP) Task Force, according to which remission in MDD refers to a period of at least 3 consecutive weeks characterized by a virtual absence of the DSM core criterion symptom domains, with the exclusion of daily function [60]. This state ends in case of relapse (i.e., a return of the index MDE) or recurrence (i.e., a new MDE) [60]. Factors capable of affecting the chance of attaining remission and its duration identified by the Task Force are type, dose, and duration of treatment or its resistance, baseline symptom severity, presence of comorbidities, environmental supports and stressors, previous course of the disease, and individual genetic vulnerability [60].

The epidemiological studies briefly reviewed suggest that if major depression is itself an extremely severe condition, its troubled course tends to make it worsen. But this

does not mean depression is untreatable; on the contrary, it highlights the magnitude of the necessity to focus on interventions, with prevention as the ultimate goal, and remission/recovery as objectives once the disease has arisen, taking advantage of the progress made in psychotherapeutic and pharmacotherapeutic treatments.

1.2.3 Risk factors

The field of psychiatric epidemiology has identified various putative risk factors for Major Depressive Disorder, including a variety of genetic, psychological, and environmental contributors. Although there is no evidence for causality, the association of some of them with the onset of MDD is well-documented and widely supported [53,61]. In particular, the factors described below are those that stand out for their great level of consistency in the research on the risk for depression [53].

Being female is usually referred to as first because of its highest level of epidemiological replicability [7]: a key finding of the National Center for Health Statistics (NCHS) is that 10.4% of American women had depression during 2013-2016, while the prevalence drops to 5.5% among males (Figure 3) [62].

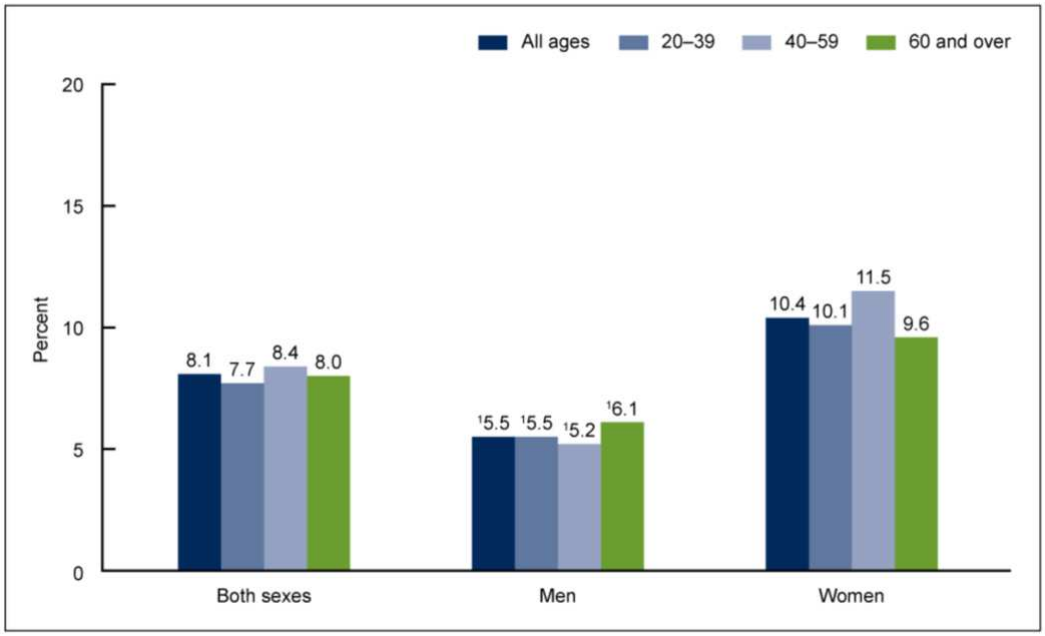

Figure 3. Percentage of persons aged 20 and over with depression, by age and sex: United States, 2013–2016 [62].
[1]Significantly different from females in the same age group.

A few theories as to why this is the case have been proposed, from the experience of more stress and higher rates of trauma in females, to the occurrence of major life events such as pregnancy, and a role played by hormones, like a decrease in estrogens [63]. However, the underlying mechanisms of this gender discrepancy remain unclear, thus research efforts become increasingly necessary, especially for developing women-specific treatments.

It has long been known that genetic influences on depression onset are critical too, as indicated by family, twin, and adoption studies [64]. It is a fact that MDD runs in families: indeed, a person with a first-degree relative suffering from major depression is likely to have a 2- or 3-times greater risk of developing the same illness compared with the general population [62]. Through decades of studies, researchers have estimated heritability for this disorder as probably 40-50%, a quantity that might be even higher for severe depression [65]; it is important to point out that family and twin studies report a higher level of heritability than single-nucleotide polymorphism-based estimates from genome-wide association studies (GWAS), which suggests that other genetic variables, such as rare mutations, could contribute to MDD risk [61]. In fact, it is still not certain which are the specific genetic mechanisms mainly involved in MDD and to what extent they are associated with environmental factors. Although several potential candidate genes have been identified, such as the serotonin transporter gene (SLC6A4) and the brain-derived neurotrophic factor (BDNF) [66], to date, what seems more realistic is that combinations of genetic changes (and not one single defective gene) can predispose to become depressed [65] and that MDD does not arise from either genetic or environmental influences alone, but rather from both [64].

Regarding the environment, the determinants with more consensus are attributable to socially disadvantaged conditions, like belonging to a low social class, job loss, or marital difficulties, and to negative life events, such as adverse childhood experiences (in particular sexual, physical, or emotional abuses), illness, or loss of close personal relationships [53,62]. Among all of them, it clearly emerges how stress is a common factor, whose role comprehension, according to the authoritative opinion of Hammen (2018), "*is the central challenge in understanding the etiology of most forms of depression*" [67]. Notably, studies over the last 50 years show that dysfunction of the HPA axis (i.e., the interaction between the Hypothalamus, Pituitary gland, and Adrenal

glands which plays a vital role in how the body handles stress) is manifested in most depressive patients [68]. Given the widely recognized importance of both environment and genetics, trying to understand how they interact in determining depression onset has become essential over the years; thus, it is not surprising that one of the most popular explanations for the etiology of depression is nowadays the diathesis-stress model, a paradigm operationalizable as a gene by environment interaction (GxE) [72]. The term "diathesis" refers to the biological/genetic predisposition to the development of a certain disorder, whereas "stress" indicates the set of environmental or existential conditions that disturbs a person. Therefore, the synergy between diathesis and stress is such that whether genotypes lead to the actual phenotypic manifestation of the disorder or not depends on the environment and personal experiences of the individual. In other words, stress can activate an already existing vulnerability, transforming the potential of predisposition into the actuality of depression [72].

One last risk factor with the best evidence is "neuroticism" [53], a stable personality trait "*characterized by a chronic level of emotional instability and proneness to psychological distress"* [3], which covers different facets defined by Costa and McCrae as anxiety, angry hostility, self-consciousness, impulsiveness, vulnerability to stress and, precisely, depression [69]. Based on the Big Five personality model, a meta-analysis by Kotov et al. (2010) showed that patients with depression scored higher than non-clinical samples on Neuroticism, and that MDD and unipolar depression emerged as the strongest correlates of neuroticism among other psychiatric disorders [70]. These results have been replicated by recent work, confirming the existence of a personality profile in depressed individuals characterized by high levels of neuroticism and by high scores on most facets of the neuroticism domain [71].

Overall, all the risk factors discussed above can seriously contribute to depression to varying degrees, but as is true in general for psychopathology, also the risk of MDD is not likely determined by a single cause, but rather by the combined effects of multiple risk factors that may have a heavier impact on different people – yet another demonstration of how depression is a complex heterogeneous psychiatric disorder with multiple factors weighing in. An optimal model that encompasses the multiplicity of the etiopathogenesis of depression is the biopsychosocial model, which interprets the onset of mental illness as coming from the interaction between biological (e.g., altered levels

of monoamine neurotransmitters 5-hydroxytryptamine/5-HT/serotonin), psychological (e.g., dysfunctional cognitive schemas and negative automatic thoughts) and social factors (e.g., weak social networks). Greatly fitting with the diathesis-stress paradigm (see above), this model does not limit itself to describing the symptoms that deviate from the norm, but it evaluates the complex experience of disturbance that results from the combination of various factors, in order to understand the etiological mechanisms, the risk factors, and the protective ones [73]. The value of the biopsychosocial frame, therefore, lies also in its capacity of providing a theory-driven basis for treatment planning, especially when the combination of pharmacotherapy and psychotherapy is necessary, because it requires interdisciplinary teamwork and the integration of biological, psychological, and social theories of depression [73].

1.3 Treatment

Worldwide, depression is a seriously disabling public health problem, not only because of its intrinsic symptomatology features and its serious consequences, like decreased quality of life, increased suicidal risk, and intensified health care use, but also because of its strong relation with physical illnesses (e.g., coronary artery disease, diabetes, cancer) [74]. The magnitude of the problem highlights the importance of treating depressed patients with the most effective, evidence-based therapy choices.

Considering the whole spectrum of depression gravity, from the mildest subthreshold form to the most severe one, the National Institute for Health and Care Excellence (NICE) guidelines represent a great value instrument to orient patients and practitioners in making treatment decisions [5]. The proposed method is a stepped-care model, which provides an access to the less intensive and most effective treatment in the initial phase, and then establishes clear and explicit criteria for the transition to and between the different levels of care based on both the benefits that patients derive, and the severity of the symptomatology referred by them [5]. A summarizing representation of the model is shown in Figure 4.

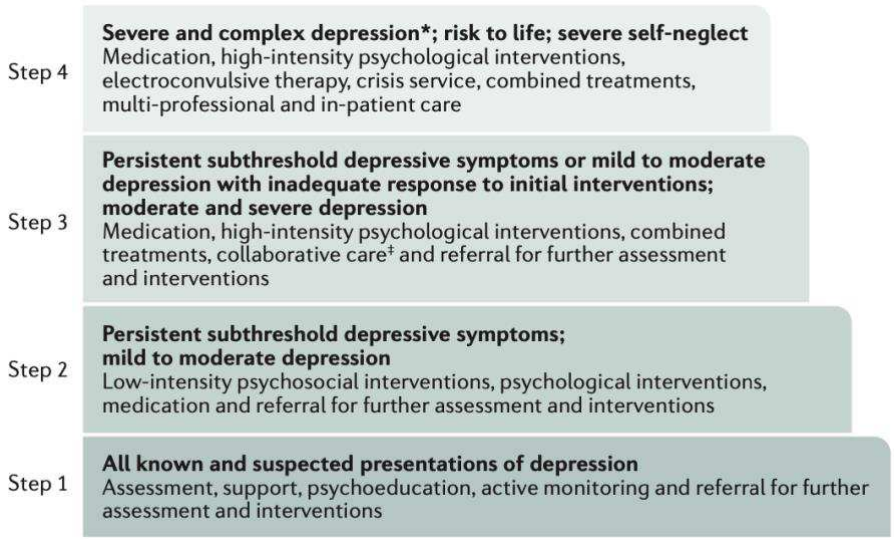

Figure 4. The stepped-care model in the management of depression proposed by NICE guidelines [61].
*Complex depression includes depression that shows an inadequate response to multiple treatments, is complicated by psychotic symptoms and/or is associated with considerable psychiatric comorbidity or psychosocial factors.
‡Only for depression in which the person also has a chronic physical health problem and associated functional impairment.

As mutually agreed by the various major American and European guidelines published in the past decades, when it comes specifically to the management of Major Depressive Disorder, clinicians have two main treatment options: pharmacotherapy and psychotherapy [75]. In particular, the first-line approaches for moderate-to-severe major depression are antidepressant monotherapy, evidence-based psychotherapy, and/or a combination of both [75].

Antidepressants are a first-line treatment for major depression of moderate and greater severity in adults, with response rates of about 48–50% compared with 30–32% on placebo, irrespective of environmental factors and symptom profile, but the choice of the drug must match, as far as possible, to the individual needs of the patient, considering likely short-term and long-term effects [76]

First-generation antidepressants include two classes of drugs, tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), the introduction of which followed the monoaminergic hypothesis of depression that the disorder is due to a relative deficiency of serotonin and noradrenaline (a pathophysiological interpretation currently recognized as too simplistic) [77]. Indeed, TCAs block the presynaptic receptor protein

carrying the neurotransmitters norepinephrine and serotonin, while MAOIs bind and block the monoamine oxidase enzyme, allowing an increase in the levels of monoaminergic transmitters [77]. Both classes of drugs are effective in the treatment of major depression, but they cause particularly adverse side effects (e.g., sedation, impaired memory and cognitive functions, heart problems) [78] and this has prompted research on new antidepressants, equivalent in efficacy, but better tolerated and less toxic.

The lack of anticholinergic and cardiac effects, a high therapeutic index, and the ease of administration are responsible for the success of selective serotonin reuptake inhibitors (SSRIs) in displacing first-generation antidepressants [61]; their main neuronal effect consists in making a greater quantity of serotonin available in the synaptic space – a condition that activates all postsynaptic receptors for serotonin [77]. A systematic review comparing some of the most authoritative clinical practice guidelines for the pharmacological treatment of depression has been recently released, and it shows that all of them recommend SSRIs as first-line treatment [79]. Like with any other drug, some side effects are associated with SSRIs too, and the most reported ones are the so-called serotonin syndrome (a series of cognitive disorders, restlessness, dysfunctions of the autonomic nervous system, and neuromuscular impairment caused by the accumulation of serotonin), sexual dysfunctions, consequences due to long-term use (such as sleep disorders, hyponatremia, and osteoporosis), and a disabling withdrawal syndrome, which occurs in about 60% of patients following abrupt cessation of use [77].

Unfortunately, the largest and longest study ever conducted to evaluate depression pharmacological treatment, the NIMH-funded Sequenced Treatment Alternatives to Relieve Depression (STAR*D) [80], showed that among a huge sample (n = 2876) monitored over 7 years in a 4-levels randomized trial, only a minority reached remission status (remission rates for treatment levels 1 to 2 and 3 to 4 were 18% to 30% and 7% to 25%, respectively), highlighting the serious problem of managing patients resistant to therapy [81], but also shedding light on important treatment-strategies-related features. As well clarified by APA, because the effectiveness of antidepressant medications is generally comparable, the initial selection of an antidepressant must be based on the anticipated side effects, the safety or tolerability of these side effects for the individual patient, pharmacological properties of the medication (e.g., half-life, other drug

interactions), and additional factors such as medication response in prior episodes, cost, and patient preferences [82].

A large and constantly increasing number of randomized controlled trials and meta-analyses show that psychotherapy is effective in treating MDD; actually, psychotherapy produces effects that are mostly equivalent to pharmacotherapy and, more in particular, available evidence suggests no difference in treatment effects of second-generation antidepressants and cognitive behavioral therapies, either alone or in combination [83].

Different approaches and techniques are available, among which Cognitive-behavioral therapy (CBT) and Interpersonal psychotherapy (IPT) are the elective ones for depression according to the NICE guidelines [5].

CBT is a structured, evidenced-based, delivered in line with current treatment manuals and goal-oriented therapy, focused on resolving current issues by working on how thoughts, beliefs, attitudes, feelings, and behavior interact, and by teaching coping skills to deal with things in life differently [5]. The great value of CBT is to be the most researched and best-studied type of therapy for adult depression, with numerous data supporting its effectiveness; for example, a meta-analysis on 115 studies showed its superiority over all control groups (waiting list, care-as-usual, and placebo) and it found that its combination with pharmacotherapy was superior to drug therapy alone for the treatment of depression [84], results supported also by a review on numerous other meta-analyses [85].

Scientific evidence is available for IPT too, an approach that turned out to be somewhat more efficacious in a metanalytic comparison between the major types of psychological treatment for mild to moderate adult depression (cognitive-behavior therapy, nondirective supportive treatment, behavioral activation treatment, psychodynamic treatment, problem-solving therapy, interpersonal psychotherapy, and social skills training) [86].

IPT is structured and in line with current manuals as well, but, differently from CBT, it focuses on identifying how interpersonal relationships or circumstances are related to feelings of depression, exploring emotions, and changing interpersonal responses, in order to modify relationship patterns rather than directly targeting associated depressive thoughts [5].

Regardless of the type of approach, as with patients undergoing pharmacotherapy, patients receiving psychotherapy should be carefully and systematically monitored on a regular basis to assess their response to treatment [82].

Nowadays, after decades of applied clinical research, it seems possible to affirm that the most consistent and supported results are in favor of the combination of pharmacotherapy and psychotherapy to treat MDD [87,88,89]. Indeed, different meta-analyses concluded that the combined treatment is more effective than drug [87] or psychological [88] treatment alone, in terms of better outcomes, higher improvement rates, and greater adherence in cases of longer therapies.

Despite the therapeutic potential of these treatments, unfortunately there are patients who derive insufficient or no benefit from them. It is the case of treatment-resistant depression, a chronic, severe, disabling, and not rare condition affecting people who try to cope with MDD, but to which standard medications tend to provide little to no relief [90].

1.4 Treatment-resistant depression

Treatment-resistant (or refractory) depression (TRD) is the diagnostic label for the occurrence of an inadequate response to an adequate antidepressant therapy, in terms of dosage, duration, and compliance, among patients suffering from unipolar major depressive disorder [90,91].

The central issue with TRD is the lack of uniformity in the criteria used to define what an inadequate response is constituted of. Although it might have been possible to argue that inadequate response is basically the failure to achieve remission with the consent of most experts [90], a more systematic and standardized definition has become necessary over the years, primarily for the consequences on the epidemiological level. Indeed, it has recently been reported that the lack of a universally accepted definition of TRD is one of the causes of the inaccurate and widely different (12%-55%) estimates of the disorder prevalence [92]; moreover, it seems evident that up to 60% of patients initially classified as suffering from TRD fall into the category of pseudoresistance, that is still a form of nonresponse but, this time, to an inadequate treatment [91].

At present, the most common and with general sense definition is that a patient has clinically significant TRD if a current episode of depression has not benefited from at

least two adequate trials of different classes of antidepressants, and there is confirmation of prior adequate dose, duration, and compliance [93]. These indications were initially promoted by the European Staging Method, which distinguishes among three groups: nonresponse, treatment-resistant depression, and chronic resistant depression (Table 4) [94]. Thus, the European approach recognizes the lack of response to a first trial as a clinical issue that differs from responsive MDD, but it makes the TRD label more specific and progressive, with further staging (from 1 to 5) depending on the duration of treatment with adequate medication doses; when the resistance condition goes beyond 12 months, it is indicated as chronic resistant depression [94].

Table 4. The European Staging Method of treatment resistance for major depression [94].

Staging of treatment resistance		
Resistance: Major depression with lack of response to an adequate antidepressant trial		
(A)	Non Responder (NR) to	TCA SSRI MAOI SNRI ECT Other
	– Non response to one adequate antidepressant trial	
	– Duration of trial: 6–8 weeks	
(B)	Treatment Resistant Depression (TRD)	
	–Resistance to 2 or more adequate antidepressant trials	
	– Duration of trial(s):	TRD 1: 12–16 weeks TRD2: 18–24 weeks TRD3: 24–32 weeks TRD4: 30–40 weeks TRD5: 36 weeks–1 year
(C)	Chronic Resistant Depression (CRD)	
	– Resistance to several antidepressant trials, including augmentation strategy.	
	– Duration of trial(s): at least 12 months	

Abbreviations: TCA= Tricyclic Antidepressants; SSRI= Selective Serotonin Reuptake Inhibitors; MAOI= Monoamine Oxidase Inhibitors; SNRI= Serotonin and Norepinephrine Reuptake Inhibitors; ECT= Electroconvulsive Therapy.

Epidemiological data about TRD are of concern. An up-to-date cross-sectional study detect treatment-resistant patients among those pharmaceutically treated in two large U.S. databases, Humana (n= 296055) and Optum (n= 277941), and it found that 17640 (6.0%) and 16131 (5.8%) of them, respectively, experienced failure of treatment with at least 2 antidepressants with ≥ 4 weeks of adequate treatment [95], a shorter period than that indicated by the European approach (see Table 4), but still indicative of the pervasiveness of non-responsivity.

In 2021 a cost model to estimate the economic burden of TRD in the United States was developed, taking into account patients who initiate a third antidepressant treatment course after changing 2 antidepressant courses of adequate dose and duration [92]. The model shows that the annual incremental burden carried by TRD in health care, productivity, and unemployment costs was $25.8 billion, $9.3 billion, and $8.7 billion, respectively, contributing in total to 47.2% of the total annual incremental burden incurred by adults with medication-treated MDD [92].

Together with the definition of structured, feasible, and shared criteria for TRD diagnosis, another field of research that can concretely help in setting up timely interventions and developing new therapeutic strategies is the one looking for non-responsiveness predictors. Since 1999, the European Group for the Study of Resistant Depression (GSRD) has sought to identify clinical, epidemiological, socio-demographic, and genetic correlates of treatment outcomes in patients with MDD, and an overview of their research advances in the last two decades has been recently released [96]. In accordance with other numerous works [e.g., 97,98,99], it suggests that the most relevant and informative predictors are the severe intensity of depressive symptoms, suicidal thoughts and behavior, comorbid anxiety, and recurrent episodes lifetime, but it also listed other noteworthy factors, such as early age of onset, previous hospitalizations, psychotic and melancholic features, low socioeconomic status, and novel associations of single nucleoid polymorphisms within the PPP3CC, ST8SIA2, CHL1, GAP43, and ITGB3 genes [96].

Setting up timely interventions and implementing individualized treatment plans is possible for TRD thanks to great research advances.

Psychopharmacological approaches include the following choices [100]: the optimization of the current medication dose, by increasing it at least to standard maximal doses as tolerated; the combination of two or more antidepressants, typically from two different mechanistic classes; the augmentation, that is the addition to a tolerated antidepressant of a non-antidepressant medication, such as atypical antipsychotics or lithium; the switching from the primary antidepressant drug to another of the same or of a different class.

Psychotherapy is also effective, with CBT as the most studied and commonly utilized approach in TRD [61]. Compared with treatment as usual (TAU) alone, which was mainly a continuation of ongoing pharmacotherapy, a meta-analysis published in 2018 found that

psychotherapy added to ongoing TAU had a moderate effect size in producing a significant improvement in treatment-resistant patients [101]. These results are in line with another meta-analysis, which also shows that remission rate was nearly twice as likely with adjunctive psychotherapy compared to antidepressants alone [102].

Important signs of progress in TRD knowledge are the emerging somatic treatments available for its management, such as transcranial magnetic stimulation, magnetic seizure therapy, transcranial direct current stimulation, vagus nerve stimulation, deep brain stimulation, and novel therapeutic drugs, like ketamine and psilocybin [103]. Nevertheless, the most widely used, the most effective acute treatment and, therefore, the established best option for TRD still remains Electroconvulsive Therapy (ECT) [104].

Compared with many interventions (placebo and different drugs) ECT elicits fast-acting and prominent antidepressant effects by triggering a brain seizure through a controlled amount of current during short general anesthesia [105], a process that turned out to be more efficacious than drugs in severe depressive cases [104]. Despite the use of ECT being limited because of safety risks (e.g., heart complications), high relapse rates, and, most concerning, cognitive side effects, especially anterograde and retrograde amnesia [106], the scientific community agrees on considering ECT generally safe based on the results of various randomized controlled trials, and its use for severe treatment-resistant depression, especially in urgent and emergency situations, is consistent with recommendations in multiple practice guidelines [5,76,82,107]. However, the treatment is still stigmatized, and this can be partially attributed to its mechanisms of action still being largely unknown [108]. Consequently, "*increased knowledge gained through scientific investigations can reduce stigmata and inform patients and health care providers to make appropriate use of ECT (...), may help patients to cope with side effects and contribute to the development of new treatment options*" [109]. This can be done, for example, by applying state-of-the-art radiology through advanced magnetic resonance imaging (MRI) techniques, to investigate the structural and functional brain effects of ECT [109].

More in general, neuroimaging techniques, among which MRI plays a major role, have demonstrated their capacity to improve the understanding of psychiatric diseases over the past three decades, facilitating the diagnosis and the development of new medications [110]. Psychoradiology, translational psychiatry, and precision medicine for mental

disorders are now realities thanks to the neuroscientific contribution, which offers adequate tools to look at what concretely happens in a brain affected by psychopathology.

CHAPTER 2 - STRUCTURAL MAGNETIC RESONANCE BRAIN IMAGING AND ITS OBJECTIVE EVALUATION THROUGH VOXEL-BASED MORPHOMETRY

Introduction

Neuroimaging is the discipline concerned with the in vivo, noninvasive, depiction of the anatomical structure and function of the central nervous system in health and disease, whose application in different fields has brought invaluable progress, including neurosciences, psychology, and several clinical areas (e.g., radiology, nuclear medicine, neurology, neurosurgery, psychiatry) [111]. Practitioners can make use of a set of techniques, which fall into two broad categories, structural and functional imaging [112].

Structural MRI, computed tomography, and diffusion tensor imaging are examples of structural neuroimaging used to quantify brain structure, visualize the architectural integrity of various systems, and eventually evaluate intracranial abnormalities [113]. Differently, functional neuroimaging provides volumetric and spatially localized measurements of neural activity across the brain and time, through techniques like functional MRI, magnetoencephalography, or positron emission tomography [113].

Capturing data about cerebral structures, such as white versus gray matter tissues density, and functions (e.g., metabolism or blood flow) not only has contributed to the creation of brain maps, but also has propelled the cognitive neurosciences in the understanding of the biological basis of behavior, and, driven by clinical aims, has yielded important insights on translational neuroscience and psychiatry [114]. Indeed, what has been produced by the application of neuroimaging in psychiatry over the past thirty years was revolutionary: the chance of identifying neural correlates of mental disorders became real [115]. Thus, "*It is no hyperbole to suggest that advances (...) in neuroimaging have provided the most powerful tools to date for advancing human systems-level brain science*", and psychopathology in particular [115].

For all these reasons, and with constantly emerging future directions, neuroimaging approaches comprise a powerful method to investigate the neurobiological mechanisms underpinning psychiatric disorders [110], potentially looking for biomarkers (even though up today none of the imaging features has reached the required sensitivity and

specificity to qualify as a diagnostic marker [116]). Moreover, both functional and structural neuroimaging are key methodologies for their clinical applications in diagnosis and treatment: they can help to redefine diagnostic boundaries [116] and to disambiguate the occurrence of psychiatric symptoms when caused by neurological diseases [110]; they may provide markers of prognosis, and monitor therapies, in an attempt to identify neural system abnormalities characterizing treatment-relevant endophenotypes, that is subgroups of individuals who respond best to different treatment modalities [117]; finally, they can provide the rationale for the development of specific neurostimulation approaches [115].

Among the above-named techniques, structural MRI (sMRI) has played a pivotal role in providing tangible evidence of the neurobiological manifestations of mental diseases in the form of brain anomalies, especially in illnesses like schizophrenia, anxiety, and depression [118]; regarding this latter, last decades have witnessed to an increasing body of literature on structural changes of various neuroanatomical brain regions in depressed individuals, with important relations to clinical features, such as duration and severity of disease, and the response to therapies [118]. The following paragraphs are firstly dedicated to sMRI operating description and to its contribution to both normal and diseased brain anatomy study, and then to one of the most important techniques used to analyze it, known as Voxel-based morphometry. Finally, the last paragraphs will be dedicated to the state-of-the-art knowledge on morphological abnormalities occurring in Major Depressive Disorder and Treatment-resistant depression elucidated by an in vivo, non-invasive, and paradigm-free technical tool such as sMRI.

2. Structural Magnetic Resonance Imaging

Structural magnetic resonance imaging is a powerful imaging technique that constructs three-dimensional detailed anatomical images by exploiting the interaction of magnetic fields, hydrogen ions, and radiofrequency pulses [119,120].

Briefly, during an MRI scan, protons of hydrogen, which act as small dipole magnets because of their intrinsic properties (i.e., the nuclear spin and the electric charge), align in the direction of the machine's magnetic field; then, a radiofrequency signal is applied to change the direction of alignment of the protons, and finally, when the radio waves are

turned off, the protons realign through various relaxation processes releasing a signal that is received by specific coils (Figure 5) [119,120].

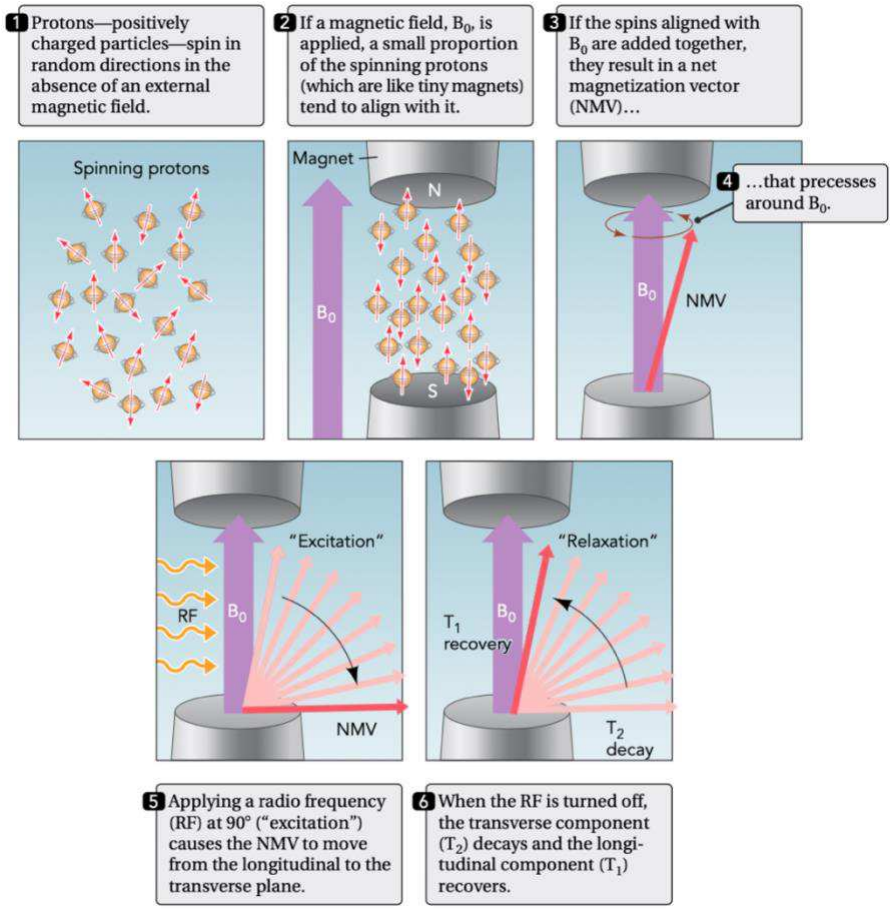

Figure 5. Basic description of MRI steps, adapted from [121].

This is the signal used to create the MR images by applying the Fourier transform, a mathematical process that converts the spatial frequencies contained in the signal to corresponding intensity levels in sectional images along a gray scale from dark (low intensity) to bright (high intensity) [119,120]. The strength of the signal depends on the type of tissue that the hydrogen ions are in: this difference in signal strength from one region to another constitutes the basis of tissue contrast and forms the substrate for image interpretation [119,120].

MRI signal is also influenced by two types of protons relaxation (the process by which hydrogen nuclei return to their low-energy state and their magnetic moments diphase), T1 and T2 [119,120].

T1 relaxation is also named “longitudinal recovery” or “spin-lattice relaxation” because it is caused by hydrogen nuclei giving up their energy to the surrounding molecular lattice so that they can recover their longitudinal magnetization. The time constant associated with this process is called “T1 recovery time” and it corresponds to the time it takes for 63% of the longitudinal magnetization to recover in a tissue, thus it represents an intrinsic contrast parameter inherent to the type of scanned tissue [119,120]; for example, in the brain, the typical T1 recovery times of water and fat are 2500 ms and 200 ms, respectively [119].

T2 relaxation is caused by the magnetic fields of neighboring hydrogen nuclei interacting with each other, and it is usually referred to as “decay” due to the loss of coherent transverse magnetization because spins transfer energy to other spins rather than into the lattice (“transverse relaxation time” is indeed another term for it) [119,120]. Spin-spin interactions are inherent to the tissue, but dephasing is also caused by inhomogeneities in the external magnetic field strength [119,120]. “T2 decay time” is the time constant occurring in this phase, which corresponds to the time necessary for the transverse magnetization to decay to 37% of its value. Water T2 decay time in the brain is typically 2500 ms, while fat’s is 100 ms [119].

Summarizing, different proton densities in addition to variation in T1 and T2 times for different tissues are what make the contrasts in MR images [119,120]. In particular, if an image has a T1 contrast, this means that contrast is derived from differences in the T1 recovery time, while T2 contrast is determined by differences in the T2 decay time of the tissue [119,120]. T1 contrast is dependent on “repetition time” (TR), the intercurrent duration between the start of one radiofrequency pulse to the application of the next pulse for each slice; for good T1 contrast, the TR must be short, to make sure that both fat and water have not recovered all their longitudinal magnetization [119,120]. Instead, T2 contrast is controlled by the “echo time” (TE), which is the time from the start of a radiofrequency pulse to the peak of a signal induced in the receiver coil, and a long TE is necessary to get good T2 contrast, so that both fat and water have enough time to decay [119,120].

In addition, a third modality of contrast that is always present is the proton density one, which refers – as its name suggests – to differences in signal intensity between tissues

due to their number of hydrogen protons per unit volume; a high signal is present in tissues with a high proton density [119,120].

The selection of the appropriate extrinsic parameters from the up-listed mechanisms serves to weight the images toward intrinsic contrast parameters, to avoid mixed-appearance images [119,120]. Hence, in a T1-weighted image the contrast mainly depends on the differences in the T1 recovery times between fat and water, with a combination of short TR and short TE [119,120]; fat, which has the shortest T1 relaxation time, appears bright in this kind of image (Figure 6A). Diversely, the contrast in a T2-weighted image predominantly relies on the differences in the T2 decay times between fat and water, and TE and TR must be long [119,120]; this time, water appears bright, because it has the longest T2 decay time (Figure 6B).

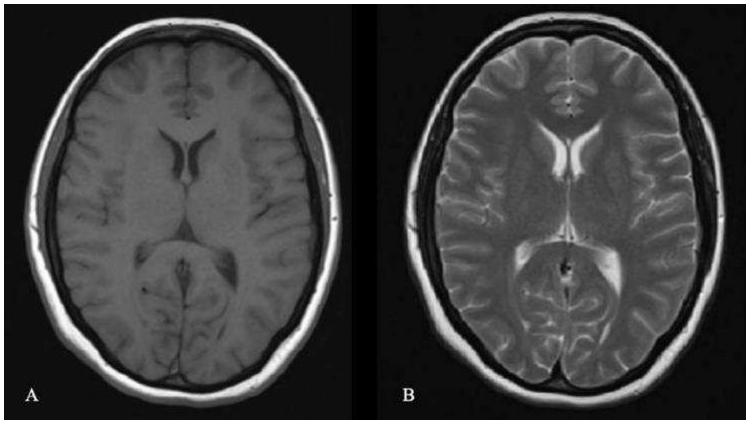

Figure 6. T1-weighted brain image (A) and T2-weighted brain image (B) [122].

T1 Weighted images are more commonly used to show anatomy, while T2-weighted images are used to image pathology, because most tissues involved in a pathologic process have a higher water content than normal [119,120].

2.1 Brain structural MRI

Living human brain morphology, function, and metabolism are all accessible thanks to MR scanners [123]. In-depth research on brain anatomy is made possible by the sMRI capacity to spatially encode the water tissue MR-signal so that images can be made. Indeed, structural MRI takes advantage of the fact that different neural tissue types contain varying proportions of water, which impact their signal [124]; for example, grey matter (GM) is about 80% water, white matter (WM) is about 70%, and cerebrospinal

fluid (CSF) is about 99% [124]. Because tissue contrast observed in any MR scans arises from an interplay between the intrinsic tissue properties and the extrinsic pulse sequence parameters employed to generate the image, with structural MRI it is feasible to manipulate the excitation of water protons to yield intensity variations between distinct brain tissues and, therefore, to map brain neuroanatomy differentiating gray matter, white matter, and CSF, whose T1 and T2 relaxation times are consequently diverse too (Table 5) [123].

Table 5. Typical T1 and T2 values for the normal tissues when imaging the brain at 1.5 Tesla [123].

Tissue	Gray matter	White matter	CSF
T1 (ms)	700–900	550–750	2000–5000
T2 (ms)	80–100	60– 80	1000–2000

Abbreviations: CSF= Cerebrospinal fluid.

CSF tends to have long T1 and T2 times given the unrestricted movement of its water molecules, on the other hand, gray and white matter have shorter relaxation times as their water molecules frequently interact with macromolecules [125].

Hence, in a T1-weighted image (where structures mostly made of fat appear brighter) CSF looks black, GM gray, and WM white, while a T2-weighted image (which best depicts structures with a high amount of water) shows CSF as white, GM as gray, and WM as darker gray (Figure 7) [125].

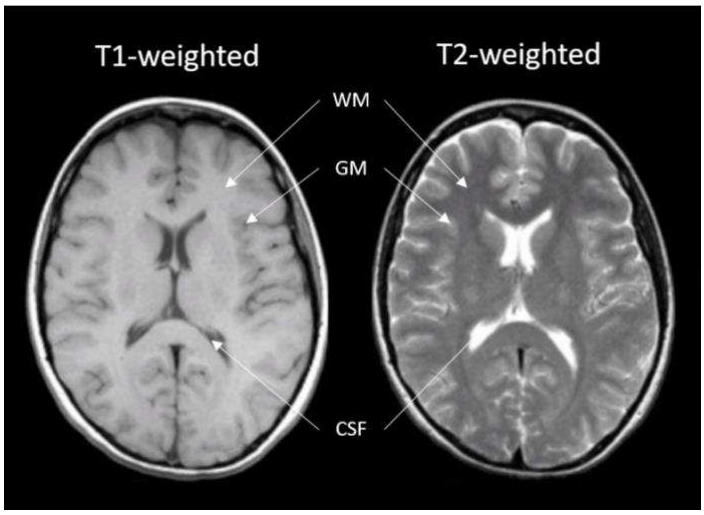

Figure 7. A T1-weighted image (left) and a T2-weighted image (right) of the brain highlighting contrast differences in the various tissue types [126].
Abbreviations: WM= White matter; GM= Grey matter; CSF= Cerebrospinal fluid.

In other words, the difference between a T1- and a T2-weighted image is that in the first one, the ventricles appear darker than the brain parenchyma, and in the second one the ventricles appear brighter than the white matter, therefore the various structures can be distinguished more clearly [125].

A great advantage of MRI is that images of the brain sections can be generated on each of the three orientations of the human head: the axial plane (also known as the horizontal plane) is an X-Y plane parallel to the ground, which separates the superior from the inferior (Figure 8A); the coronal plane (also known as the frontal plane) is perpendicular to the ground and it goes from front to back, constituting an X-Z plane (Figure 8B); the sagittal plane (also known as the median plane) separates left from right sides perpendicularly to the ground, thus it is a Y-Z plane (Figure 8C) [127]. When interpreting axial and coronal views, it is important to appreciate that the image is viewed from the feet upwards, so the image's left-hand side refers to the patient's right (and vice versa) [127].

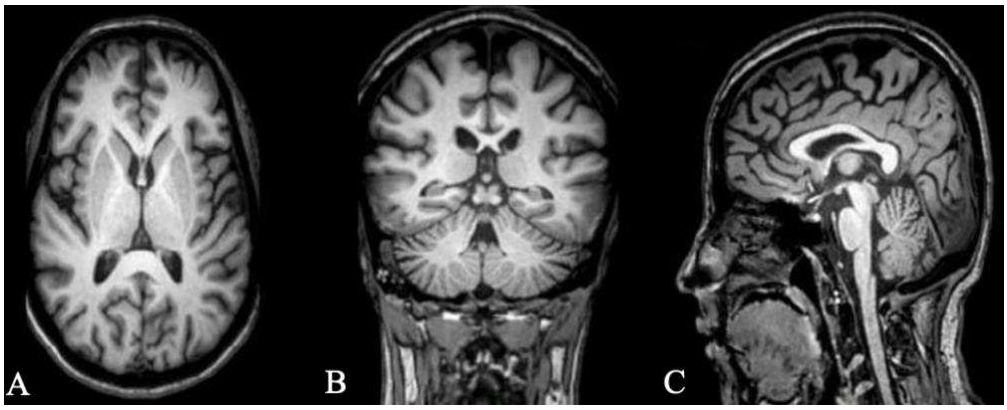

Figure 8. MRI planes for the head scan (A) Axial (B) Coronal (C) Sagittal [128].

Structural MRI has inescapably changed the way of studying brain, both normal and diseased, first because its operating mechanisms allow getting brain maps in vivo, in situ, non-invasively, in patients or normal volunteers of any age. With these properties, it has opened a window in the living human brain: cerebral morphology can be visualized in three-dimensions with a submillimetric resolution, great details and variety because of its sensitivity to soft tissues, systematic studies on brain development, aging, and plasticity are possible, as well as understanding of how brain structures mediate with functions, including the crucial evaluation of the links between a lost function and the localization of a lesion [129]. Specifically focusing on brain anatomy study, the primary

sMRI contribution can be summed up as its capacity to classify each element in the image into one of the three main tissue types, i.e., gray matter, white matter, and cerebrospinal fluid; the results of this segmentation can be further used in different applications, such as for detecting and analyzing anatomical structures, for surgical planning, and for studying pathological regions [130].

Over the last decades, sMRI has proved to be a tremendously useful tool within the clinical setting for brain pathologies, representing neuroimaging's first choice to assess neurologic disorders [131]. The advances in several automated techniques for the analysis of the scans, such as the development of computational technologies for the quantitative assessment of brain volumes, have enabled the investigation of morphometric differences improving the detection of focal and subtle brain pathology automatically, before overt degeneration or atrophy are visually apparent [125,131].

In the context of neurodegenerative diseases, the brain atrophy detected by structural MRI (mainly in the medial temporal lobe [132]) is to all effects a valid marker of Alzheimer's disease (AD) and its progression, even at the stage of prodromal/earliest manifestations, and of non-AD dementias too, such as vascular dementia, frontotemporal degeneration, and dementia with Lewy bodies [133]. For Parkinson's disease (PD) diagnosis as well, MRI has proved its capacity showing evidence for promising candidate biomarkers at various levels of the central nervous system, including the substantia nigra volume alterations and the reduction patients' cortex volume and thickness [134]; however, with regard to PD, the most probably important role of sMRI is the identification of secondary parkinsonism resulting from structural lesions, including vascular parkinsonism, neoplasms and multiple sclerosis [135].

Multiple sclerosis (MS) is a chronic inflammatory disease of the nervous system known to be highly heterogeneous in its clinical expressions and course, which are mirrored by the heterogeneity of neuropathology findings [136]. MRI provides various approaches to phenotype patients with MS, such as lesion-based measures to monitor the disease course or atrophy-based measures to determine the topography of tissue damages and, interestingly, to explore their associations with specific functional impairments [137].

For structural imaging of epilepsy MRI is again the preferred technique [138], especially in cases of symptomatic generalized or focal seizures, but also with apparent generalized epilepsies or benign partial seizures [139]; notably, sMRI enables to detect the most

frequently encountered cause of refractory temporal lobe epilepsy, that is the presence of a firm, atrophic hippocampus (i.e., hippocampal sclerosis/mesial temporal sclerosis) [138,139].

Other examples of sMRI essential application in brain pathologies comprise the detection of cerebrovascular diseases [140], traumatic brain injuries [141], and, certainly, brain tumors [142].

Unlike neurological pathologies, psychiatric disorders either do not cause macroscopic brain changes [110, 115] and produce disruptions in mental processes (emotions, behavior, cognition, and perception) which have long been challenging to link with cerebral substrates [115]. Moreover, the prominent role of the alteration in neurotransmitters and receptors in this class of disorders has caused many radiologists to be skeptical of using a tool without neurochemical specificity, such as structural MRI, to identify biomarkers of mental disorders [116]. Because of these limitations, together with substantial interindividual disparities in MRI findings [118], imaging-based accurate diagnosis and differential diagnosis of psychiatric disorders are not yet possible [116,118].

However, with the fast growth of MR neuroimaging techniques and their application to psychiatric disorders in the past decades, particularly quantitative structural imaging [110], the burgeoning literature shows an increasingly enlightened understanding of brain circuit abnormalities in mental illnesses, providing evidence for definite neuropathologic bases [115,118]. Indeed, despite the highly heterogenic manifestations in the affected individuals remaining a milestone of psychopathology, many structural abnormalities findings have been duplicated by several groups, which may serve as MR signatures [110,118]; for instance, some of those associated with a choice of the major psychiatric disorders are listed in the following table (Table 6), while paragraphs 2.1.2. and 2.1.3. are fully and extensively dedicated to the state-of-the-art knowledge on morphological abnormalities occurring in Major Depressive Disorder and Treatment-resistant depression, for which consistent results are available, shedding light on the possible etiology of the disease, its course, and its responsivity to treatment [143,144].

Table 6. Most reported structural MRI Findings of major psychiatric disorders [118].

Disorder	Structural MR Imaging Findings
Schizophrenia	• Decreased frontal lobe, temporal lobe, cerebellum, and total brain volumes • Increased lateral ventricular volume • Unchanged or decreased prefrontal cortex, striatum, and thalamus volumes • Cortical gray matter thinning
Bipolar disorder	• Decreased subgenual anterior cingulate cortex and prefrontal cortex volumes • Increased T2-weighted hyperintensity in white matter • Increased lateral ventricular and third ventricular volumes • Increased amygdala and striatum volumes • Cortical gray matter thinning
Major depressive disorder	• Decreased prefrontal cortex, subgenual anterior cingulate cortex, medial temporal lobe, amygdala, hippocampus, striatum, and basal ganglia volumes • Increased high-signal-intensity white matter regions
Anxiety disorders	• Decreased hippocampus and medial prefrontal cortex volumes in patients with PTSD and those with GAD • Decreased medial temporal lobe volume in patients with Panic disorder
ADHD	• Decreased anterior cingulate cortex, prefrontal cortex, striatum, and cerebellum volumes • Cortical gray matter thinning

Abbreviations: ADHD= Attention deficit–hyperactivity disorder; PTSD= Post-traumatic stress disorder; GAD= Generalized anxiety disorder.

Nowadays, 40 years after the first MRI studies were performed on psychopathology, it is possible to conclude that objective documentation of structural differences in the brains of psychiatric patients has been widely provided by research, laying a foundation for progress in the treatment of such complex disorders; the study on psychotropic drugs and brain stimulation techniques, but also on psychotherapy plastic changing outcomes [145], have in fact benefited greatly from it [146].

In pursuing the aim of precision medicine for psychiatric disorders, the development of automated processing methods for structural imaging analysis able to extract quantitative measurements, mainly across large populations, has represented a breakthrough [147], because they allow the detection of subtle morphometric variations that might not be perceptible upon ocular inspection, or anyway without the need for time-consuming manual measurements, avoiding the issue of subjective visual assessments [125]. Among these, Voxel-based morphometry (VBM) is an objective technique that provides an even-handed evaluation of anatomical differences throughout the brain, whose importance over the years has become predominant [148]. With its potential to identify both mechanisms underlying normal brain processes and structural abnormalities in a variety of diseases, it has contributed enormously to the development of cognitive

neuroscience and the clinic [149], particularly for understanding multifaceted pathologies such as MDD.

2.1.1 Voxel-based morphometry

Digital images obtained through magnetic resonance are quantitative, and therefore measurable, because made up of building units called pixels, the governors of spatial resolution [119]. The brightness of each pixel depends on the MRI signal generated by the concerned tissue, which is, in turn, divisible into units of volume named voxels [119]. Hence, the relation between pixel and voxel is such that voxel dimensions are determined by the pixel bidimensional area and the slice thickness, which provides the voxel with a certain depth (Figure 9) [119]. In this way, the entire image can be considered as a spatially distributed matrix of values [150].

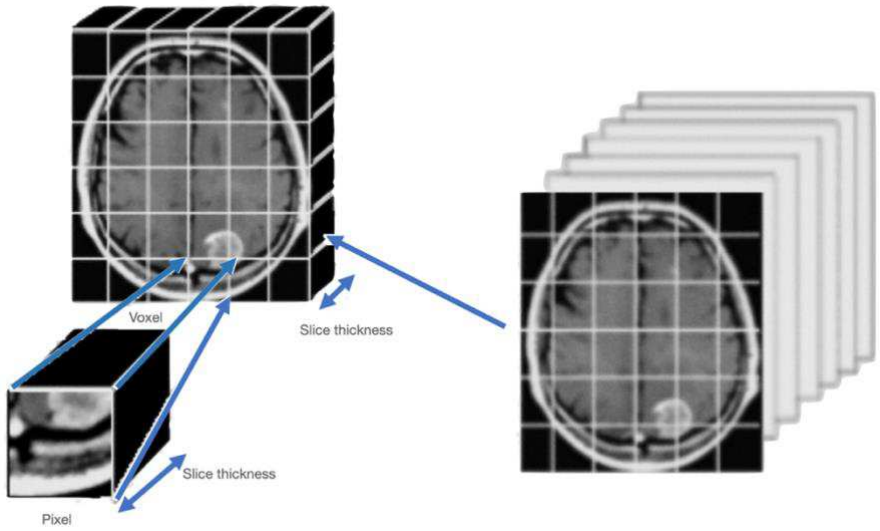

Figure 9. Illustration of the voxel, whose volume is determined by the pixel bidimensional area and the slice thickness [151].

The most common method to analyze specific brain components within an MR image consists of manually tracing regions of interest (ROIs), definable as a hand-crafted capture of the features of interest (e.g., color, texture, and shape) so that spatial information is retained while at the same time ensuring tractability [152]; in particular, the use of a mask establishes different ROI values based on its pixels to separate the selected region from surrounding tissue [152], and statistical information about the

chosen set of pixel values are immediately available, like their number, mean, and volume [153]. Namely, ROIs contain the key information the experts need for further steps, and they are used both for brain atlas formation and clinical purposes [130]. In any case, the level of accuracy in their extraction must be high, so that they can empower the detection and classification of anatomy and pathological signs [154].

Due to the difficulty in reliably delineating structures in medical images because of their intrinsic complexity, the manual method is generally believed to be the most accurate, thanks to its well-established great anatomical validity [130]. However, it is not exempt from limitations, therefore its adequacy must be assessed on a case-by-case basis. First, the procedure is laborious and time-consuming, especially when the ROI appears in multiple thin slices [153,155]; to extract the target structure, a specialist typically must examine about eighty images, slice by slice [130]. Then, results are difficult to reproduce in longitudinal or different studies because it is almost impossible to manually segment the exact same imaging geometries [130,153]. Also, in cases of lack of knowledge about the location of a disease, a priori ROI accurate selection represents an issue [155] that cannot be solved by increasing its extension, because doing so means adding irrelevant pixels and therefore lowering the spatial specificity and the statistical power [153]. Finally, as demonstrated by various studies testing the intra- and inter-rater variability, this technique is prone to mistakes, especially when the target structure has complicated boundaries or is unusually small [130,153,155].

The essential problem of ROI measurements can be summed up as being operator-dependent. Helpfully, advances in computer technologies have led to the development of a class of image processing methods, whose full automated algorithms marked a turning point in the management of huge amounts of radiological data, for which visual inspection could not be sufficient [153], therefore excluding the obstacle of subjective inaccuracies [155]. Their collective name is Voxel-wise (or -based) analysis, because they share the capacity to make multiple image comparisons and statistical inferences on the minimum level basis, the voxel [153].

Different MRI techniques require different voxel-wise analyses; for example, in Diffusion Tensor Imaging (DTI), an MR application to measure the diffusivity of water in tissue, voxel-based analysis methods (e.g., Tract-based spatial statistics) permit the investigation of voxel-wise diffusion differences in every voxel across the whole brain

[156]; else, Voxel-mirrored homotopic connectivity is a method employed to analyze functional MRI data, by providing a voxel-wise measure of connectivity between hemispheres [157]; also structural MR images are processable in a computational and automatic manner within the individual voxels, thanks to approaches like Deformation-based morphometry and Voxel-based morphometry [147,158].

In detail, Voxel-based morphometry is a fully automated technique that compares the local concentration of gray and white matter at the voxel level to discover significant morphometric differences between two or more subject groups [148]. The sequential steps it is made of are the followings: spatial normalization, segmentation, smoothing, and statistical analysis [148,149].

Spatial normalization consists in registering all the individuals' images to the same brain template to guarantee that a specific voxel is in the same anatomical position across subjects (Figure 10), after having minimized the gross shape differences but preserving the distinctive features, which is the reason why there is no exact match between the subjects' brains and the template [148,149]; in other words, what is done in practice is to transform every data to the same stereotactic space, while simultaneously decreasing the residual sum of squared differences between brains and template and enhancing the deformation smoothness (see below the smoothing phase) [148,149]. The two main stereotactic spaces are the Talairach coordinates and the Montreal Neurological Institute (MNI) coordinate system [159], with the latter by now displacing the former since it is the template -created from 152 T1-weighted images, collected in a 1.5-T scanner- used by Statistical parametric mapping (SPM), the most used software to implement a VBM pipeline [160].

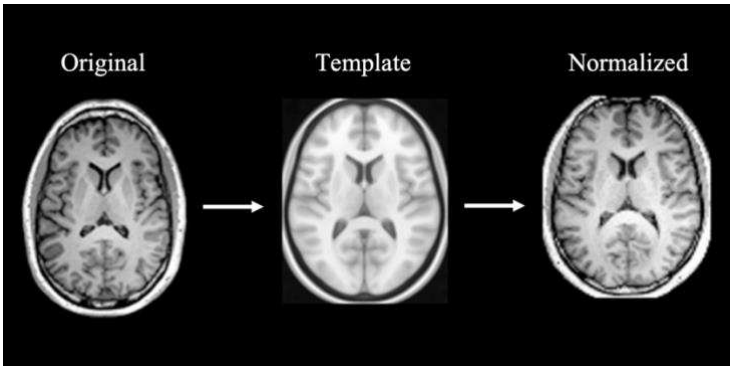

Figure 10. Example of spatial normalization in structural MRI preprocessing adapted from [161].

Once the images are spatially normalized, neural tissues can be segmented and classified based on voxel intensities [148,149]. This procedure involves the integration of several a priori probability maps, by employing a Bayesian image segmentation algorithm, with a mixture model cluster analysis, whereby the consolidated knowledge of the spatial distribution of different tissues in healthy individuals is combined with the identification of the actual voxel intensity spread across different tissue types [148,149]. It was pointed out that prior probability maps may be more unbiased if created from the specific sample under study [162].

The next step is smoothing the images, a process that ensures that the intensity of each voxel is replaced with the weighted average concentration of gray or white matter (according to the tissue of interest) from the surrounding voxels [148,149]. The region around each voxel is defined by the isotropic Gaussian kernel, so that data are more normally distributed, the validity of parametric statistical tests is increased, and intersubjective variability is decreased (diminishing properly the variance across individuals raises the sensitivity to detect changes [161]) [163]. The optimum range for smoothing kernels has been suggested to be 12 mm [148,149,163].

It should be noted that what has been described so far aims to compare the GM or WM concentrations (or densities) in the spatially normalized images; if, however, the object of interest for the measurement is the volume, a further step is necessary, called modulation, which entails the multiplication of the spatially normalized tissue by its relative volume before and after the spatial normalization [149]. Density and volume are indeed different concepts when talking about structural images analysis [149]: density is a unitless, scalar metric derived from the partitioning process and related to T1 signal intensity [164] that displays the ratio of gray or white matter to all other tissue types within a particular area [149], whereas volume is the absolute, total amount of a gray or white matter structure [149] measured in cubic millimeters [164]. It is very important to examine these values separately, as demonstrated by some studies in which GM density (GMD) and GM volume (GMV) contribute differently to results [164,165]. If it is true that these measures are complementary, and it is good practice to include both in an experiment [164,165], the problem with GMD is that the real neuronal density cannot be determined by any in vivo tool: indeed, what MRI provides is a probabilistic value coming

from segmentation, while GMV is a more direct measure, which is why it is the main readout of VBM studies [166].

Finally, statistical analysis can be run [148,149]. First, the standard parametric procedures (e.g., t test and F test) are used to check the hypotheses assuming data are normally distributed [148,149]; in case this assumption cannot be done, it is better to apply nonparametric testing [148,149]. Then, general linear models, together with the theory of Gaussian random fields to correct for multiple comparisons for avoiding type I error (false positive results), are employed to test whether regions of GM or WM concentration differ significantly across groups, but also if they are related to covariates of interest (e.g., sex, age, severity of disease) [148,149]. Now, the voxels refuting the null hypothesis (i.e., no difference in tissue concentrations between the groups) with correspondent p-values below the user-selected significance threshold are displayed colored in a statistical parametric map (Figure 11) [162].

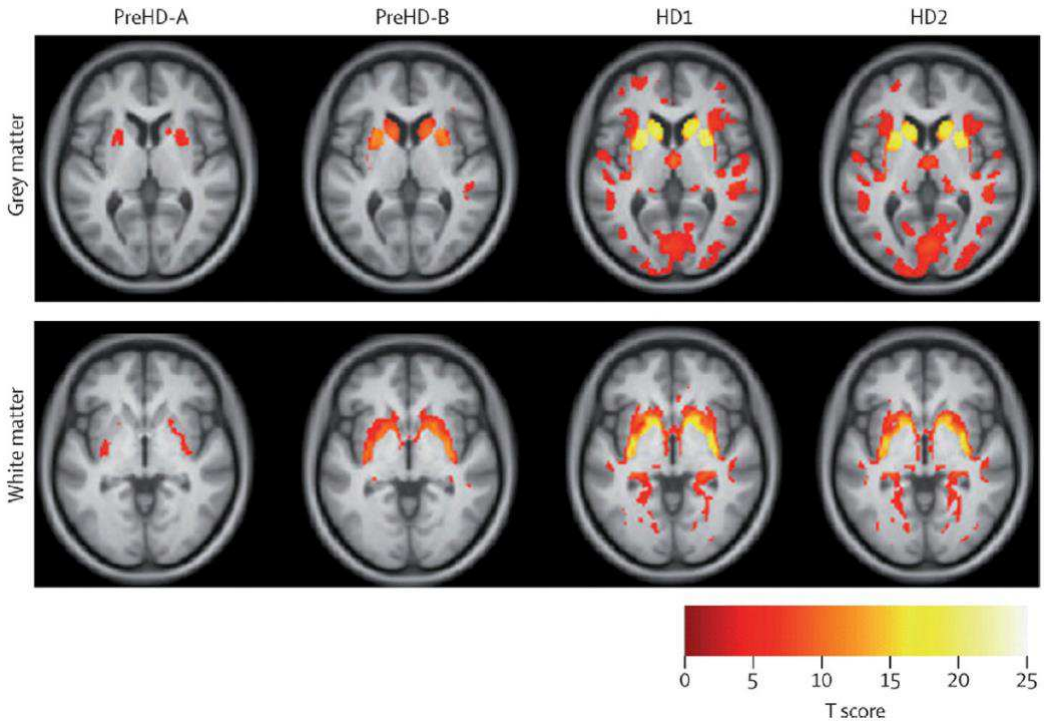

Figure 11. An example of statistical parametric maps showing reduced gray and white matter volume across different stages of Huntington's disease when compared to controls [167]. *Abbreviations: PreHD-A= individuals further from predicted diagnosis age; PreHD-B= individuals nearer to predicted diagnosis age; HD1= patients at stage 1; HD2= patients at stage 2.*

Since its introduction, VBM has gained much interest from the neuroscientific community, which has widely recognized its potential. The fact that it is fully automated

makes it relatively easy to use and time-saving [162], which are already themselves important advantages. Then, the automation together with its functioning at a whole-brain level lead to another great value: it is unbiased, and it is so because, differently from the ROI approach, it does not require to be guided by a priori anatomical knowledge and constraints [168]; as a consequence, it does not limit itself to evaluating only clearly defined areas, but it is capable of objectively detecting those focal subtle differences that may be beyond the eye inspection [168].

However, various limitations have been highlighted, even by its own creators, such as the strict need to collect all the images with the same scanner and MR sequence, so that resulting structural differences cannot be misinterpreted [149].

One of the most frequent objections is about the validity of the spatial normalization process, as according to the critics of the method, it produces anatomical deformations which render the results unreliable [168,169]. Nevertheless, the advances in segmentation and, indeed, spatial normalization techniques, including modulation (see above), achieved over the years have remedied this issue to a significant degree by the implementation of high-resolution warps [149], which have therefore improved registration accuracy and statistical power [168]. A demonstration of this is that a growing literature shows VBM to have an accuracy comparable with manual volumetry (still regarded as the gold standard) [168,170,171].

A last limitation to stress is VBM is not validated for single-subject studies, although some researchers are trying this path [172], because its strength derives from its statistical nature, hence from its efficiency to run group analyses [162]. The flip side is it provides high validity information across big samples, which is a prerequisite for assessing the treatment effects in pharmacological trials [162], but also in the attempt to characterize the common changes occurring in patients suffering from neurological or psychiatric disorders. For these diseases, the application of VBM has produced a wealth of evidence, especially regarding the alterations of gray matter, as white matter changes are better assessable with techniques like DTI [162].

Major depression is certainly one of the psychiatric disorders to which VBM has contributed the most, and all the studies on the matter present in the last twenty years of literature, showing alterations of GMV at the whole-brain level, have been systematically searched and meta-analyzed in the novel coordinate based meta-analyses described in the

third chapter of the present thesis, with a particular focus on treatment responsiveness. Before moving to the project, an overview of the structural alterations identified so far through whole-brain VBM and ROI approaches in both MDD and TRD is provided in the following two paragraphs.

2.1.2 Structural MRI findings in Major Depressive Disorder

Major Depressive Disorder affects the brain, and structural MRI is a greatly powerful tool researchers have at their disposal to non-invasively assess its neuroanatomical correlates [143]. To date, after almost thirty years of sMRI cross-sectional and longitudinal studies investigating regional brain volumes in depressed patients [173], it is possible to affirm that MDD is closely related to brain structural abnormalities [174].

Grey matter volume reductions in fronto-temporo-limbic areas and white matter hyperintensities are, so far, the most replicated structural findings in MDD [175], involving both subcortical (Figure 12) and cortical (Figure 13) regions. Among these, the most consistent evidence is in support of hippocampus atrophy [176].

A wealth of literature, including independent meta-analyses, demonstrates the presence of decreased hippocampal volume in chronic, recurrent, and remitted patients, as well as in first-episode and drug-naïve cases, [175] with confirmations coming from ROI [e.g.,177] and whole-brain VBM [e.g.,178] investigations. According to the latest work by the ENIGMA (enhancing neuroimaging genetics through meta-analysis) MDD Consortium, which meta-analyzed data from 45 MDD study cohorts from 14 countries across six continents, significantly lower hippocampal volume is associated with increased frequency of episodes or longer illness duration [179]. Given the neurochemical nature of the hippocampus, a hypothesis about its volume loss that has received a great consensus argues that the hypercortisolemia induced by chronic stimulation of the hypothalamus-pituitary-adrenal axis due to stressful conditions, such as those characterizing depression (see paragraph 1.2.3), is the cause of glutamatergic neuronal apoptosis and, consequently, atrophy in the hippocampus [180].

As an essential part of the limbic system and a key player in affective management (especially for negative emotions), memory and learning processes, reward mechanisms,

and social behavior [181], not surprisingly the amygdala has been found to be altered in its GMV in depressed patients, but with a certain amount of heterogeneity [182]. Indeed, some studies found increased volumes [e.g.,183], while many others showed the occurrence of atrophy [e.g., 184]. A possible explanation for this discrepancy might be the difficulty in manually tracing clear delineations between amygdala and hippocampus, being the first close to the head of the second [175,182], a fact that could prove in favor of automated segmentation.

Other subcortical areas consistently reported to be abnormal in MDD are the midline brain structures such as caudate and putamen (and more in general basal ganglia), and thalamus [185], with the volume reductions in bilateral putamen and left thalamus being suggested as potential trait markers since they were found to be present in first-episode and untreated patients [186].

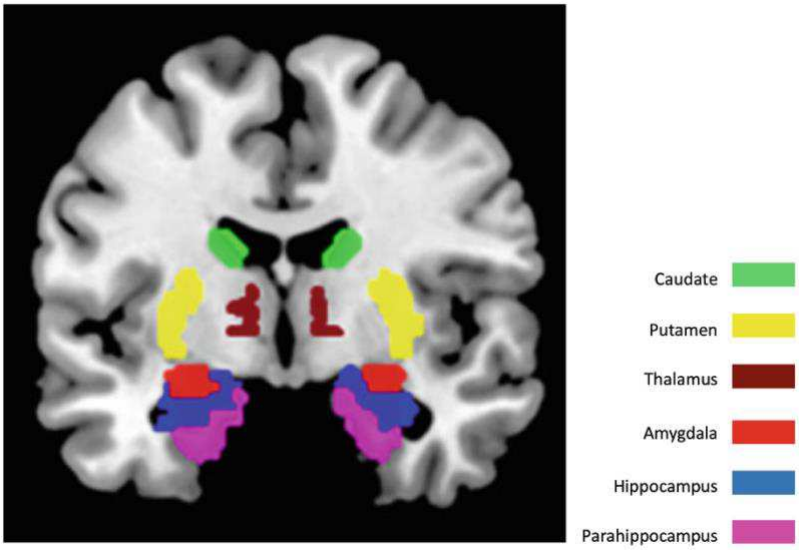

Figure 12. Subcortical regions consistently found to be altered and involved in Major Depressive Disorder [175].

Among the cortical alterations in major depression, those documented in the volume of the anterior cingulate cortex (ACC) in terms of reduction are particularly reliable [e.g.,187,188], as well as data revealing its thinner structure [189]. Interestingly, Frodl et al. (2008) found that an opposite pattern may be a predictor of good clinical outcomes: indeed, in comparison with patients with smaller ACC volumes, larger right ACC volumes were correlated with lower depression severity symptoms and larger left ACC volumes with fewer previous hospitalizations [190].

Frontal and prefrontal atrophies are other crucial changes in MDD, which have been mainly localized at the levels of dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), and orbitofrontal cortex (OFC) [175], the latter in particular turning out to be characteristic of geriatric depression [191]. These areas have also been taken as a reference point by some theoretical models of MDD pathophysiology [192], such as the one by Hamilton and colleagues (2012) illustrating the critical role of DLPFC in decreasing the ability to contextually process and reappraise the over-salient negative information [193].

Insula, precuneus, and posterior cingulate cortex are other three cortical regions whose anomalies have been linked with major depression, also by the influential worldwide ENIGMA Working Group [189].

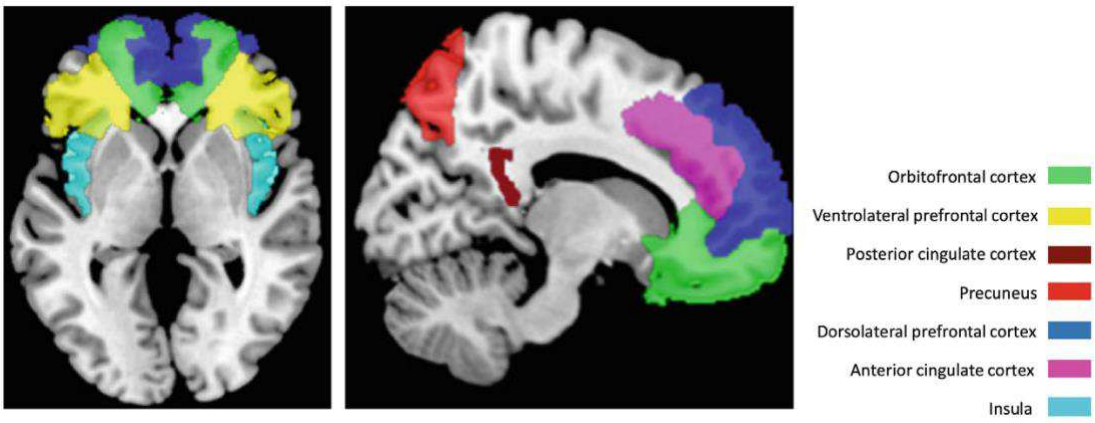

Figure 13. Cortical regions consistently found to be altered and involved in Major Depressive Disorder [175].

Finally, thanks to an increasing number of studies conducted with VBM and especially DTI, white matter hyperintensity (i.e., WM lesions appearing as increased signal intensity on T2 weighted images) has been demonstrating its potential as a biological sign of depression, most of all in cases of late life, and, to a greater extent, late-onset cases, suggesting a likely difference in its etiology compared to early-onset depression [194].

2.1.3 Structural MRI findings in Treatment-resistant depression

As previously seen in paragraph 1.4, not all people suffering from MDD benefit from proper pharmaceutical treatment, and those who do not respond to at least two

adequate different classes of antidepressants are labeled, as generally agreed, treatment-resistant depressed patients [93]. Therefore, just as it is important to boost the research on the biomarkers of MDD to accurately diagnose the disease as soon as possible, it has become equally essential to look for the brain correlates that can give us information on the differential response to treatment. Yet, a premise must be made: not much is known about the structural alterations occurring in TRD [144] as evidenced by the less literature available on the subject. Many reasons can be responsible for this, such as a difference in the size of samples between resistant and not-resistant MDD patients (according to the most recent estimates, 2.76 million against 8.95 million U.S. adults, respectively [92]) with the risk that small samples lead to false positives, and a still missing uniform definition of treatment resistance which could make research more systematic [144].

Aware of this limitation, the first and, to date, the only review of structural brain changes in TRD has been recently released, which analyzed whole-brain VBM and ROI studies, but also Magnetization Transfer Imaging (MTI) (an MRI technique that quantitatively measures macromolecular structural integrity [195]) and DTI ones, comparing TRD patients (for a total of 455 subjects if considered altogether) with healthy controls, and in some cases also with depressed patients responding to treatment [196]. The results highlighted by this review can be considered the state of the art in the knowledge of structural anomalies occurring in TRD.

Findings were divided into those that seem to specifically differentiate TRD from "milder forms" of MDD (i.e., non-refractory MDD) and those that seem to have no discriminative properties, depending on whether studies show alteration patterns that are absent in the literature exclusively on MDD, or findings are placeable in a shared continuum between responsiveness and no-responsiveness that does not allow separation in different entities [196].

The first category includes grey matter volume reduction in the caudate nucleus and putamen (which were stated to be altered also in MDD but only moderately [197]), and the inferior frontal gyrus, precentral gyrus, angular- and post-central gyri [196]. In addition, it has been found in a clinical trial that smaller volumes in frontal and prefrontal regions at baseline could reliably predict the subset of patients who did not remit after an acute treatment with three commonly used antidepressants [198].

The fitting of these results has laid the groundwork for the hypothesis that frontostriatal atrophy is a hallmark of TRD, which could constitute a substrate for the dysregulation of reward mechanisms if cell atrophy would affect mostly dopaminergic layers [199]. This theory is very interesting, especially for the contributions it could make in understanding the processes underlying non-responsiveness to psychopharmacology, but it is still purely speculative and more evidence is needed.

The second category includes GMV atrophy in the hippocampus, ACC, right cerebellum, insula, corpus callosum, and superior/medial frontal gyrus [196]. All these areas are known for having a particular involvement in major depression [e.g.,192], whereby, when alterations are found in these areas in TRD samples, the data end to converge with those, much more conspicuous, regarding MDD. However, this does not imply that these alterations do not play a key role in refractory depression; in fact, as a part of a continuum, they could help the diagnostic process in clarifying the progression of the disease from a responsive to a no responsive phase [196], and they can provide essential information when monitored before and after different therapeutic strategies. An example above all is the consistently observed increase in the hippocampal volume following Electroconvulsive Therapy (ECT), whose amount of evidence brought arguments in favor of the neurogenic theory of depression, which postulates that depression inhibits neurogenesis in the hippocampus and ECT might be able to reverse this effect [200].

In conclusion, due to the aforesaid limitations and a basic lack of convergence among the reviewed studies, also because of their different imaging analysis protocols, [196] it clearly emerges how findings on different alterations between patients who respond and those who don’t respond to drug treatment are yet inconsistent. Therefore, further studies on TRD are needed, hopefully paying special attention to defining the resistance to treatment with a uniform criterion. Then, to make the studies more systematic, several other variables can be taken into account and controlled for, such as the severity and duration of the symptoms, the age of the patients, the drug usage history, and, given its brain modulatory effects, the inclusion of ECT in the therapeutic plan.

CHAPTER 3 – THE RESEARCH: ABERRANT GREY MATTER VOLUME IN RESPONSIVE AND TREATMENT-RESISTANT PATIENTS WITH MAJOR DEPRESSIVE DISORDER

Introduction

Major Depressive Disorder, the most severe form of depression, is a debilitating mental illness defined by the two principal classification systems for psychiatric disorders, DSM-5 and ICD-11, as characterized by at least one discrete depressive episode lasting no less than two weeks, during which evident changes in mood, interests, and pleasure, together with cognitive and vegetative alterations, occur [7,8]. It is estimated to affect 6.7% of the United States adult population every year [47], with females being almost twice as likely as men to experience the disorder [62]; adolescents and the elderly are heavily affected too [47].

The symptomatology burdensome severity, the consequent functional impairment in everyday life areas (family, work, school, leisure) [13], the disorder tendency to have a recurring-remitting course [54], its widespreadness [47], and the high association with suicide attempts [4] are some of the main reasons why MDD was acknowledged as the second major contributor to global disease burden in 2013 [201] and currently represents a leading cause of disability worldwide [2]. Nevertheless, this disorder is curable, and consistent evidence is in favor of the combination of pharmacotherapy and psychotherapy as the gold-standard treatment [87].

Major depression is known to be heterogeneous in its manifestations, as well elucidated by the dimensional framework RDoC (see paragraph 1.1.3), and so is its etiopathogenesis. In fact, many complex factors have been identified as potential contributors to explaining MDD onset and maintenance, such as trauma, stress, psycho-social/biological/genetic factors [6], but, despite decades of basic science, clinical neuroscience, and psychiatric research, the etiology and pathophysiology of MDD have not yet been fully understood.

Heterogeneity also regards responsiveness to treatment, which is a crucial issue in dealing with depression: the most recent estimates refer to 2.76 million U.S. adults who fail to respond or achieve remission after at least two trials of drug treatment of adequate dose and duration [92]. This condition is named Treatment-resistant depression, and little is

known about its nature, such as whether it represents a more serious form of depression, and therefore it needs more invasive interventions (e.g., Electroconvulsive Therapy), or it owns specific features which make it clearly distinguishable from non-refractory MDD. This and many other questions can be investigated with the powerful approach of neuroimaging, the discipline concerned with depicting the anatomical structure and function of the central nervous system in vivo, non-invasively, in both health and disease [111].

Over the past three decades, the contribution of neuroimaging techniques in exploring the neurobiological mechanisms underpinning MDD has been invaluable and MRI, in particular, has been widely applied to identify the key brain regions implicated in its pathophysiology [110], a field of research that can allow for considerable progress in clinical diagnosis and treatment.

Structural MRI uses the responses of hydrogen in tissue molecules to strong magnetic impulses to construct three-dimensional detailed anatomical images of body organs [119], and its application to the brain materializes into neuroanatomical mapping, systematic studies on cerebral development, aging, plasticity, and the mediation between structure and function, and assessing tool of brain pathologies. Among these latter, for psychiatric disorders, even if not characterized by macroscopic brain changes [115], a burgeoning literature based on quantitative imaging provides evidence for structural neuropathologic bases [118].

A fundamental step in gaining neural findings as objective as possible has been represented by the development of automated processing methods for structural imaging analysis; these techniques enable the detection of subtle morphometric variations that might not be visible through visual inspection, eliminating the need for laborious manual measurements and the problem of subjective ocular assessments [125]. A category belonging to this approach comprises full automated algorithms capable of making multiple image comparisons and statistical inferences based on the minimum volume unit of the digital images obtained through magnetic resonance, the voxel [153]. In particular, Voxel-based morphometry is the technique that compares the local concentration of gray and white matter volumes at the voxel level to discover significant morphometric differences between two or more subject groups, which is of extraordinary importance

for allowing to get high validity unbiased information across big samples also in a whole-brain manner [148].

Thanks to the wealth union of studies carried out with both whole-brain VBM and ROI (a hand-crafted capture of the features of interest, the actual gold-standard measurement [152]) methodologies, the hypothesis that MDD affects the brain has received definite supporting proof. Regarding specifically grey matter volume, its reductions in fronto-temporo-limbic areas, both subcortical and cortical, are so far the most replicated structural findings in major depression [175], even though up today none of these alterations has reached the required sensitivity and specificity to qualify as a diagnostic biomarker [116].

Morphological anomalies have been found in treatment-resistant depressive patients too [196], but these MRI results are much more controversial, and the main issue is represented by the difficulty in understanding whether findings are ascribable to the specific condition of resistance to treatment, or they do not have discriminative properties because originated from the underlying presence of depression [196]. A cause for this can be traced to the still missing uniformly adopted definition of treatment resistance [144].

The contribution made by every single neuroimaging study in identifying the key brain regions implicated in the pathophysiology of MDD and TRD is priceless and must be fully recognized; however, these works are not exempt from limitations: on one hand, because of clinical practice inherent problems, they are inevitably characterized by the availability of small samples in most cases – a fact that causes the loss of results and forces the use of thresholding parameters that increase false positives [202]; on the other hand, the multitude of studies makes it challenging to keep track of all their results [203]. The meta-analytic approach is a powerful method to merge the plethora of neuroimaging results in an unbiased fashion, and it is optimal to respond to the request for robust and consistent data [204].

Several meta-analyses on GMV alterations in major depression have already been published, of which most took into consideration ROI structural MRI studies, whereby they focus on those brain regions of primary theoretical importance or whose tracing on anatomical scans is simple [188]. To overcome the problem of subjective operator dependency, a meta-analysis of whole-brain VBM studies is a greatly useful tool for identifying GMV group differences [188], but reliable data can be obtained only by

proceeding systematically. In this sense, some confounding factors must be pointed out in the meta-analyses of whole-brain voxel-based morphometry studies on MDD present in the literature, such as the inclusion of patients with comorbidity [e.g., 188], the lack of attention in distinguishing grey matter volume from grey matter density or concentration [e.g., 205], or the non-exclusion of studies performing small volume correction (SVC) [e.g., 206] (this procedure is formally a violation of whole-brain investigation because it restricts the search area to a given region of interest).
Regarding TRD, only one meta-analysis of whole-brain VBM studies has been released in 2016, taking into account five studies, one of which performed SVC [207]; then, up today, some other works came out.

In an attempt to contribute systematically to shed light on the complicated and still not fully elucidated pathophysiology of major depression and to fill the lack of consistent knowledge on TRD brain correlates, overcoming the methodologic inaccuracies contained in previous works, this chapter is dedicated to the presentation of two novel meta-analyses, the first on MDD and the second on TRD. Both of them have been carried out focusing exclusively on the technique that allows analyzing the brain morphology in an unbiased and objective way, whole-brain voxel-based morphometry, and extreme attention has been paid to rigorously meeting several strict inclusion criteria. To the best of our knowledge, this procedure results in the most complete and systematic meta-analyses of Major Depressive Disorder and Treatment-resistant depression.

3.1 Methods

3.1.1 Inclusion criteria and studies selection

A systematic and extensive literature search was carried out in Pubmed between January 2000 and January 2022 to identify potential studies according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines (PRISMA) [208].

The following keywords were used for the first meta-analysis: 1) (major depression OR major depressive disorder OR MDD) AND (voxel) AND (morphometry), 2) (major depression OR major depressive disorder OR MDD) AND (structural MRI OR sMRI), 3)

(major depression OR major depressive disorder OR MDD) AND (gray matter volume OR grey matter volume). The procedure returned 1937 records.

The keywords used for the second meta-analysis were: 1) (resistant depression OR resistant major depressive disorder OR resistant MDD OR refractory depression OR TRD) AND (voxel) AND (morphometry), 2) (resistant depression OR resistant major depressive disorder OR resistant MDD OR refractory depression OR TRD) AND (structural MRI OR sMRI), 3) (resistant depression OR resistant major depressive disorder OR resistant MDD OR refractory depression OR TRD) AND (gray matter volume OR grey matter volume). 179 studies resulted at the time of the access, 126 of which were duplicates compared with the first meta-analysis, from which they were therefore removed.

Studies were included if they met these inclusion criteria: 1) they were written in English; 2) they compared MDD or TRD patients with healthy controls (HC); 3) they reported grey matter volume (GMV) abnormalities using structural MRI (studies with no significant results were excluded, as well as studies investigating GM concentration or density); 4) they performed whole-brain VBM analysis (nor ROI or Small Volume Correction analyses were included); 5) they reported stereotactic coordinates in MNI or Talairach space; 6) they included patients with no overt physical or psychic comorbidities (patients with any comorbid anxiety disorders too were excluded, but not those with anxiety symptoms).

The flowcharts summarize the inclusion process for the first (Figure 14) and the second (Figure 15) meta-analysis.

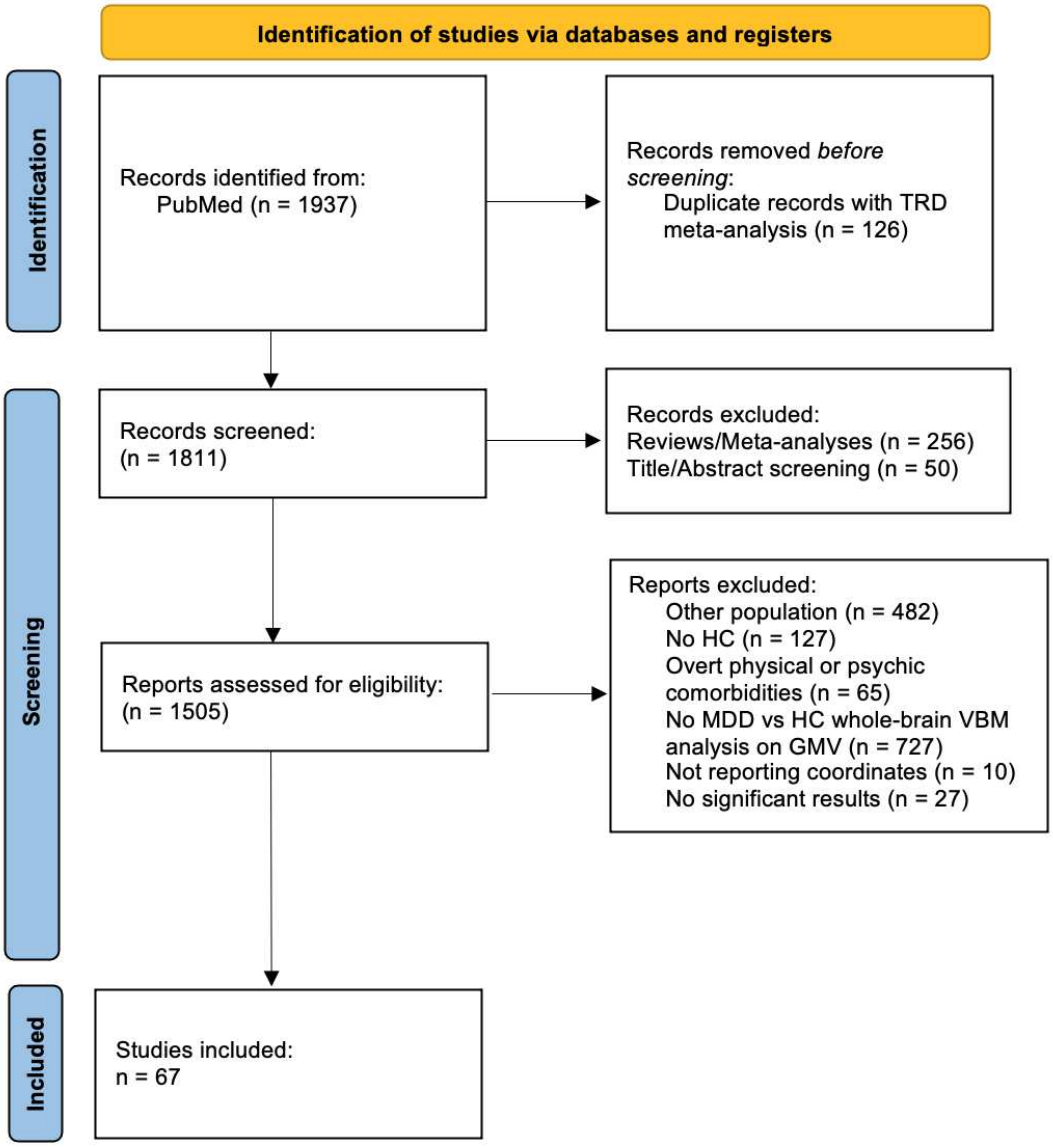

Figure 14. PRISMA flow diagram for meta-analysis on Major Depressive Disorder, adapted from [208].
Abbreviations: TRD= Treatment-resistant depression; HC= healthy controls; MDD= Major Depressive Disorder; VBM= Voxel-based morphometry; GMV= grey matter volume.

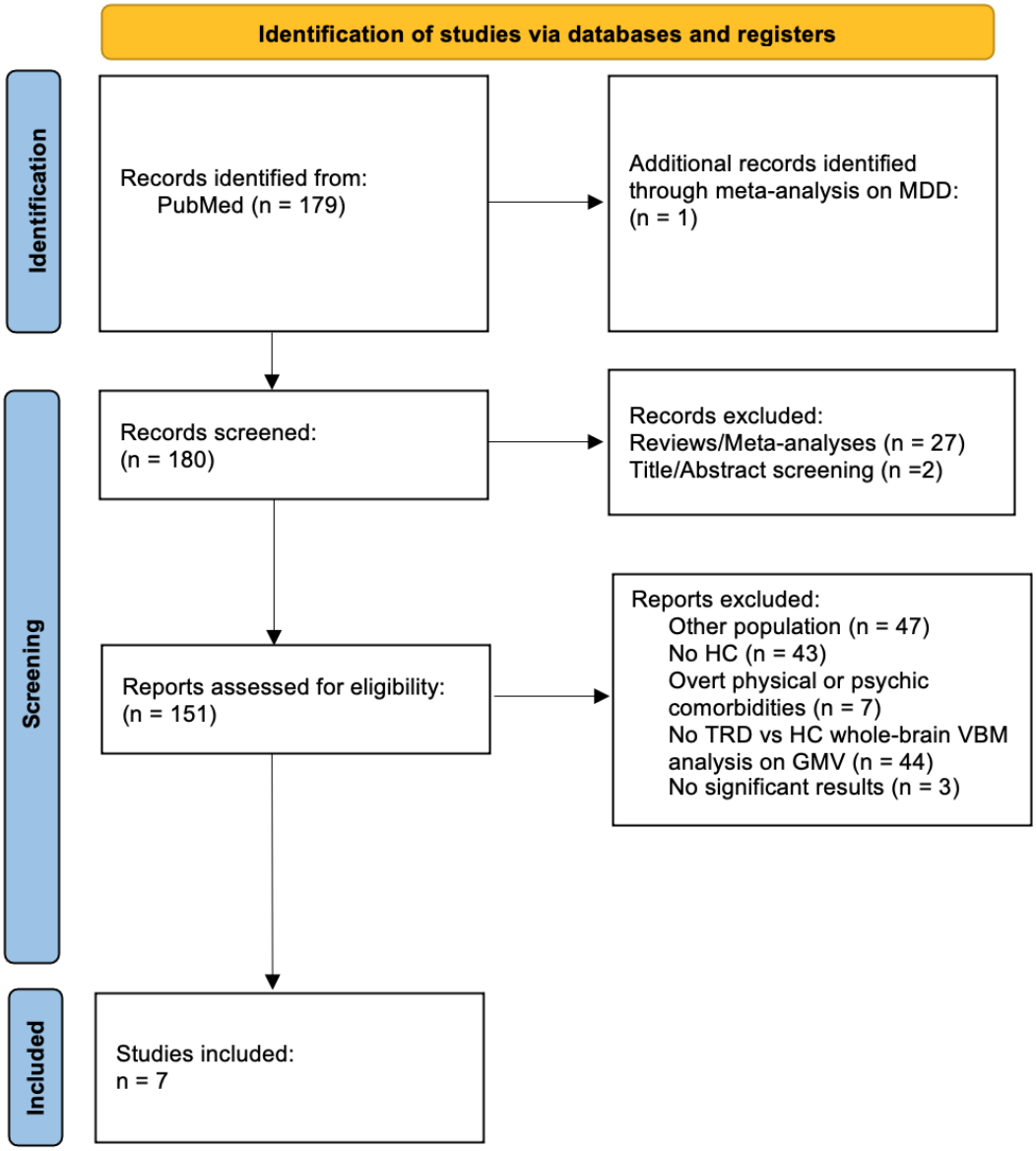

Figure 15. PRISMA flow diagram for meta-analysis on Treatment-resistant depression, adapted from [208].
Abbreviations: MDD= Major Depressive Disorder; HC= healthy controls; TRD= Treatment-resistant depression; VBM= Voxel-based morphometry; GMV= grey matter volume.

The final pool of works consisted of sixty-seven studies in the first meta-analysis (Table 7), and seven studies (Table 8) in the second meta-analysis. Selected studies reported either decreases or increases in GMV, or both in some cases.

Table 7. Studies included in the first meta-analysis.

First meta-analysis: GMV alterations in MDD patients with respect to healthy controls					
Study	**MDD patients**	**Healthy controls**	**Study**	**MDD patients**	**Healthy controls**
Kim et al. (2008) [209]	22	25	Ozalay et al. (2016) [241]	24	24
Wagner et al. (2008) [210]	15	16	Qiu et al. (2016) [242]	12	15
Leung et al. (2009) [211]	17	17	Shen et al. (2016) [243]	147	130
Mak et al. (2009) [212]	17	17	Wang et al. (2016) [244]	25	35
Zou et al. (2009) [213]	23	23	Igata et al. (2017) [245]	27	44
Cheng et al. (2010) [214]	68	68	Yang et al. (2017) [246]	82	82
Hwang et al. (2010) [215]	70	26	Zhao et al. (2017) [247]	37	41
Scheuerecker et al. (2010) [216]	13	15	Zhuo et al. (2017) [248]	45	48
Amico et al. (2011) [187]	33	30	Chang et al. (2018) [249]	108	156
Salvadore et al. (2011) [217]	58	107	Chen et al. (2018) [250]	36	47
Wagner et al. (2011) [218]	30	30	Lu et al. (2018) [251]	76	86
Ma et al. (2012) [219]	17	17	Zaremba et al. (2018) [252]	37	54
Wang et al. (2012) [220]	18	18	Zhou et al. (2018) [253]	144	111
Grieve et al. (2013) [192]	102	34	Gong et al. (2019) [254]	92	122
Chaney et al. (2014) [221]	37	46	Hellewell et al. (2019) [255]	229	66
Guo et al. (2014) [222]	44	44	Kandilarova et al. (2019) [256]	39	42
Jung et al. (2014) [223]	24	29	Li et al. (2019) [257]	56	56
Kong et al. (2014) [224]	28	28	Liu et al. (2019) [258]	45	30
Lai et al. (2014) [225]	38	27	Peng et al. (2019) [259]	161	160
Modinos et al. (2014) [226]	23	46	Straub et al. (2019) [260]	42	43
Nakano et al. (2014) [227]	36	54	Chen et al. (2020) [261]	22	22
Peng et al. (2014) [228]	38	28	Liu et al. (2020) [262]	58	27
Qi et al. (2014) [229]	18	28	Nan et al. (2020) [263]	166	166
Qiu et al. (2014) [230]	46	46	Meng et al. (2020) [264]	159	53
Cai et al. (2015) [231]	23	23	Zhang et al. (2020) [265]	53	50
Dannlowski et al. (2015) [232]	171	512	Yang et al. (2020) [266]	187	103
Fang et al. (2015) [233]	20	19	Jiang et al. (2021) [267[	20	30
Vasic et al. (2015) [234]	43	29	Liu et al. (2021) [268]	484	446
Lai et al. (2015) [235]	53	54	Ma et al. (2021) [269]	52	65
Watanabe et al. (2015) [236]	29	45	Takamiya et al. (2021) [270]	48	52
Yang et al. (2015) [237]	50	50	Zhang et al. (2021) [271]	20	20
Yang et al. (2015) [238]	51	51	Zhou et al. (2021) [272]	109	163
Chen et al. (2016) [239]	27	28	Zhang et al. (2022) [273]	26	35
Opel et al. (2016) [240]	20	20			

Table 8. Studies included in the second meta-analysis.

Second meta-analysis: GMV alterations in TRD patients with respect to healthy controls		
Study	**TRD patients**	**Healthy controls**
Ma et al. (2012) [219]	18	17
Serra-Blasco et al. (2013) [274]	22	32
Jung et al. (2014) [223]	26	29
Machino et al. (2014) [275]	29	29
Johnston et al. (2015) [276]	20	21
Wang et al. (2017) [277]	25	23
Camilleri et al. (2020) [278]	85	86

3.1.2 Meta-analyses

In compliance with the meta-analysis guidelines by Müller and colleagues (2018) [204], two different meta-analyses were run in the GingerALE software [279]. The first one regarding MDD was in turn subdivided into two meta-analyses performed separately, one for GMV decreases (i.e., atrophy) and the other for GMV increases (i.e., hypertrophy) in patients compared to HC. The second analyzed TRD, and due to the presence of only one single work exhibiting GMV hypertrophy in patients with respect to HC, this study was combined with all the others showing GMV atrophy for completeness.
To prevent terms confusion, from now on the meta-analysis on GMV atrophy in MDD patients compared to controls will be referred to as "A", the one on GMV hypertrophy in MDD patients compared to controls as "B", and the last one on TRD as "C".

To weight studies contributions, GingerALE uses sample sizes and coordinates, which must be expressed in the same stereotactic space; therefore, the first step consisted in converting Talairach coordinates into MNI space.

Then, the activation likelihood estimation (ALE) method [280,281] was performed under the software to quantitatively assess the inter-study concordance. ALE approach assesses spatial convergence of reported coordinates across the experiments against the null hypothesis that findings follow a random spatial distribution. The coordinates, or foci, are treated as three-dimensional Gaussian probability distributions centered at the given coordinates to generate per-experiment modeled atrophy/hypertrophy maps, which are subsequently joined in a union map [282,283]. For each Gaussian distribution, the algorithm derives full-width half-maximum by considering the sample size of every single study. Finally, ALE tests for above-chance spatial convergence through a range of available thresholding options. In all three meta-analyses, statistical ALE maps were thresholded for significance using cluster-level family-wise error (FWE) correction at $p<0.05$ (5000 permutations), with cluster-forming threshold of $p<0.01$. Forasmuch as each coordinate referred to the contrast between two groups (patients *vs.* healthy controls), the analysis relied on the *n* of the smaller of the two samples to yield a more conservative activation likelihood estimation [284].

3.2 Results

3.2.1 Patients' characteristics

Sixty-six comparisons between 3532 patients suffering from MDD showing GMV atrophy with respect to 4224 healthy controls were conducted in meta-analysis A. Patients were 36.52 years old on average, the diagnosis of MDD was mostly made on the basis of the DSM [7] (only three studies resorted to ICD [8]), and they had no overt comorbidities. The severity of depression was assessed with Hamilton Rating Scale for Depression [285] in most cases, but also Beck's Depression Inventory [286] and Montgomery–Åsberg Depression Rating Scale [287] were sometimes administered. In some instances, anxious symptomatology -which did not reach the diagnostic threshold for an anxiety disorder- was present too and typically measured with Hamilton Anxiety Rating Scale [288]. In general, in the selected studies it was reported that healthy controls matched the depressed patients demographically (mean HC age= 35.53).

A total of 1846 MDD patients and 2483 controls were compared in twenty-eight contrasts analyzing GMV hypertrophy in meta-analysis B. Patients, all meeting the DSM criteria for MDD [7], were 34.7 years old on average and their symptomatology was screened with Hamilton Rating Scale for Depression [285], Beck's Depression Inventory [286], and Self-Rating Depression Scale [289]. Every overt comorbidity was excluded, while anxiety symptoms, when present, were assessed with Hamilton Anxiety Rating Scale [288]. The demographics of healthy subjects and depressed individuals were similar (mean HC age= 34.2).

Finally, meta-analysis C is based on eight comparisons, seven of which outline GMV atrophy in TRD patients *vs.* HC, and only one GMV hypertrophy; this latter was included for completeness and to not lose data. Overall, treatment-resistant subjects were n=245 and 44.3 years old on average, and controls, matched for demographics, were n=258 and 40.5 years old on average. Patients were diagnosed with depression exclusively according to DSM [7], and in this case too Hamilton Rating Scale for Depression [285], Beck's Depression Inventory [286], and Montgomery–Åsberg Depression Rating Scale [287] quantified symptoms severity.

Regarding the resistance to treatment, it was defined as non-responsiveness to at least two adequate trials of different classes of antidepressants in the majority of the studies [219,274,275,276,277]; in one case the non-responder group was defined as showing <50% reduction in the Hamilton Depression Rating Scale after the treatment [223]; one last study reported the diagnosis of treatment-resistant unipolar depression was made according to either ICD and DSM IV [278].

3.2.2 Grey matter atrophy in MDD patients vs. healthy controls

Meta-analysis A was conducted on sixty-six experiments that compared GMV atrophy between MDD patients (n= 3532) and healthy adults (n= 4224), and it included 332 foci. The minimum size for a cluster to be considered statistically significant was 2080 mm^3. Our results revealed a region of convergence of 2184 mm^3 (~2 ml) centered in the left Fusiform Gyrus (MNI coordinates: X = −34.7, Y = −60.1, Z = −11.4, corresponding to Brodmann area [BA] 19), with five peaks. Figure 16 shows that the significant cluster was lateralized in the left hemisphere and that it included the Fusiform Gyrus and the Declive. The maximum ALE value (0.0182, p = 0.00008; z = 3.79) was found within the left Fusiform Gyrus (MNI coordinates: X = −24, Y = −62, Z = −6, corresponding to BA 19).

A summary of all significant results is provided in Table 9.

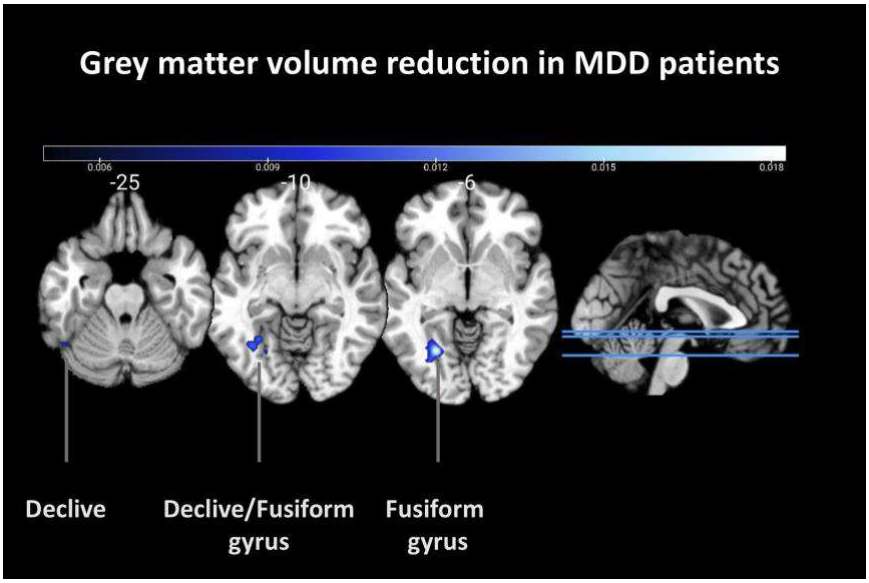

Figure 16. Significant cluster of GMV atrophy in MDD patients *vs.* healthy controls.

Table 9. Significant results of the five peaks belonging to the cluster of GMV atrophy in MDD patients *vs.* healthy controls.

	Grey matter volume reduction in MDD patients						
Peak	X	Y	Z	ALE	p	z	Label
1	-24	-64	-6	0.0182	0.00008	3.79	Fusiform Gyrus (BA 19)
2	-46	-58	-20	0.0148	0.00006	3.26	Declive
3	-34	-60	-10	0.0116	0.00289	2.76	Declive
4	-30	-54	-10	0.0112	0.00352	2.69	Declive
5	-30	-72	-6	0.0111	0.00371	2.68	Fusiform Gyrus (BA 19)

3.2.3 Grey matter hypertrophy in MDD patients vs. healthy controls

Meta-analysis B was conducted on twenty-eight experiments that compared GMV hypertrophy between 1846 MDD patients and 2483 healthy controls, including 62 foci. The minimum size for a cluster to be considered statistically significant was 1672 mm^3. Our results revealed two clusters of convergence. The first cluster of 1704 mm^3 (~1.7 ml) was centered in the left Parahippocampal Gyrus (MNI coordinates: X = −14.7, Y = −4.2, Z = −15.5) with three peaks. The maximum ALE value (0.0121, p = 0.00006; z = 3.85) was found within the left Parahippocampal Gyrus (MNI coordinates: X = −14, Y = −8, Z = −16, corresponding to corresponding to BA 28). The second cluster of 1688 mm^3 was centered in the right Parahippocampal Gyrus (MNI coordinates: X = 22.4, Y = −1.3, Z = −16.8) with three peaks, and the maximum ALE value (0.0156, p = 0.000006; z = 4.39) was found within the right Parahippocampal Gyrus (MNI coordinates: X = 22, Y = 2, Z = −16, corresponding to corresponding to BA 34).

Figure 17 shows that the significant cluster including the left and right Parahippocampal Gyri, while a summary of all significant results is provided in Table 10.

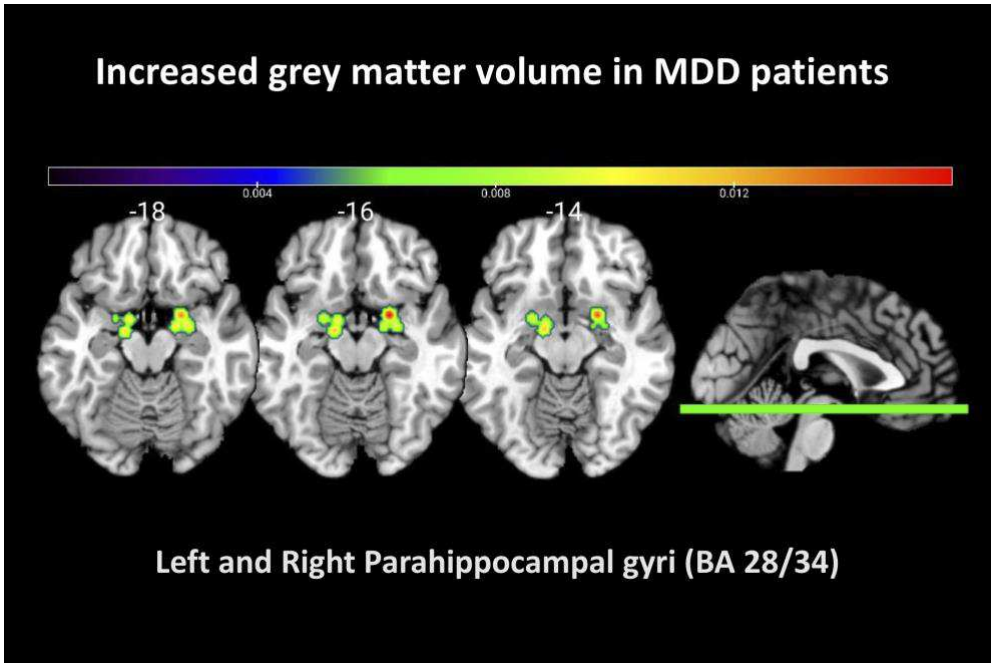

Figure 17. Significant clusters of GMV hypertrophy in MDD patients *vs.* healthy controls.

Table 10. Significant peaks' results of the two clusters of GMV hypertrophy in MDD patients *vs.* healthy controls.

		Grey matter volume increase in MDD patients						
Cluster	Peak	X	Y	Z	ALE	p	z	Label
1	1	-14	-8	-16	0.0121	0.00006	3.85	Parahippocampal Gyrus (BA 28)
1	2	-12	0	-18	0.0108	0.0001	3.65	Parahippocampal Gyrus (BA 34)
1	3	-20	0	-14	0.0096	0.0004	3.34	Parahippocampal Gyrus (BA 34)
2	1	22	2	-16	0.0156	0.000006	4.39	Parahippocampal Gyrus (BA 34)
2	2	26	-4	-18	0.0109	0.00012	3.68	Parahippocampal Gyrus
2	3	18	-6	-18	0.0108	0.00013	3.66	Parahippocampal Gyrus (BA 28)

3.2.4 Grey matter atrophy in TRD patients vs. healthy controls

We conducted meta-analysis C on eight experiments, for a total of 64 foci, comparing GMV between 245 TRD patients and 258 healthy controls. The minimum size for a cluster to be considered statistically significant was 1384 mm^3 (~1.4 ml). Our results revealed a region of convergence of 1400 mm^3 centered in the Anterior Cingulate (MNI coordinates: X = 1.7, Y = 33.2, Z = −7.7), with two peaks. The maximum ALE value (0.0121, p = 0.00003; z = 4.03) was found within the Anterior Cingulate (MNI coordinates: X = 2, Y = 34, Z = −10, corresponding to BA 24). Notably, Ginger ALE

report revealed that the study showing greater GMV in patients compared to controls [276] did not contribute.

Figure 18 shows the significant cluster, and a summary of significant peaks' results is provided in Table 11.

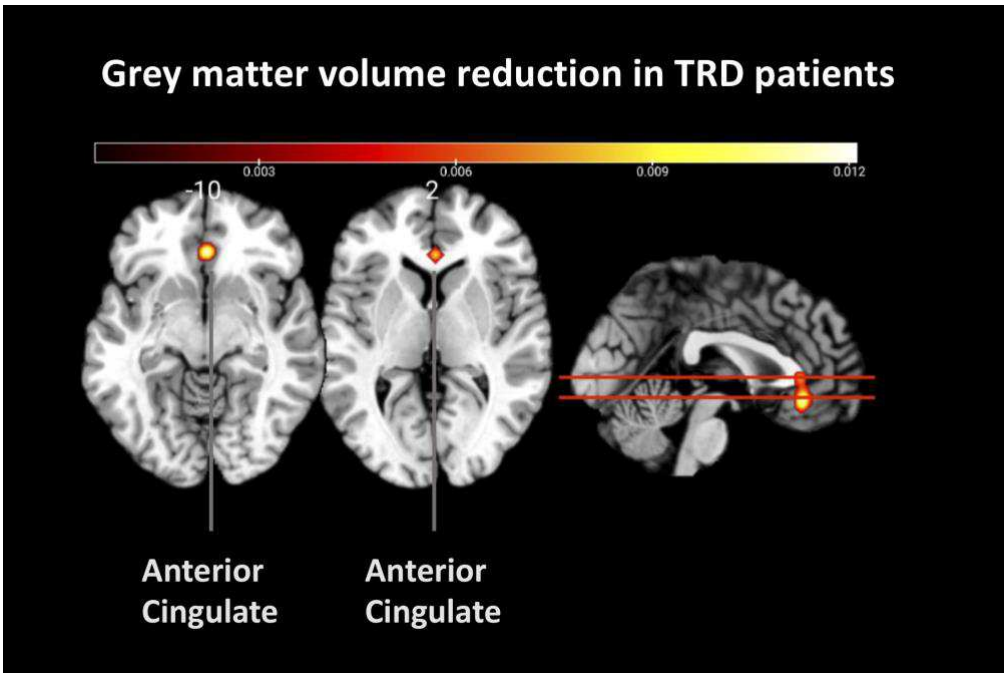

Figure 18. Significant cluster of GMV atrophy in TRD patients *vs.* healthy controls.

Table 11. Significant results of the two peaks belonging to the cluster of GMV atrophy in TRD patients *vs.* healthy controls.

		Grey matter volume reduction in TRD patients					
Peak	X	Y	Z	ALE	p	z	Label
1	2	34	-10	0.0121	0.00002	4.03	Anterior Cingulate (BA 24)
2	2	32	2	0.0086	0.0003	3.4	Anterior Cingulate (BA 24)

CHAPTER 4 – DISCUSSION

This study aimed to evaluate the grey matter volume abnormalities in patients affected by Major Depressive Disorder who were responsive or resistant to treatment. Hence, we performed two different meta-analyses, one on MDD studies and the other on TRD ones. They were run in the GingerALE software, a program that allows applying the ALE method to calculate the result that statistically converges between all data entries (i.e., the coordinates/foci extracted from every study).

A first outcome that stands out is that in both kinds of patients GMV alterations occurred, but they steadily took the forms of either increases or reductions only in MDD cases, while non-responders showed broadly atrophy with respect to healthy controls, and only one work reported hypertrophy (which, moreover, did not even contribute to the ALE analysis) [276]. This first difference between the two groups could be due precisely to the fact that one, unlike the other, does not respond to treatment. A possible interpretation for that, as already formulated by Liu and colleagues (2017) [207], is that MDD patients might benefit from an antidepressants' neurotrophic effect [290], which, evidence suggests, can lead to the recovery of morphological changes and the restoration of GMV [e.g., 291,292] potentially through synaptic plasticity [293]; this acting, on the other hand, seems to not take place in the case of refractoriness.

In this regard, it is important to specify that the grey matter data of resistant patients considered in the present thesis were related to a pre-ECT phase, when this was the therapy implemented in the clinical studies [277,278]. It is indeed known that ECT is an invasive technique which, acting directly on the brain by triggering seizures through a controlled amount of current [105], determines cerebral modulation [294] with mechanisms of action still largely undiscovered [108]. Thus, to prevent these ECT-induced (and not attributable to the pathology) effects from confusing the results and to allow more precise interpretability, alterations detected post-ECT were not taken into account. However, of note, Camilleri et al. (2020) found that patients, who before ECT showed only GMV reductions, after the therapy had both a cluster of atrophy and hypertrophy compared to healthy controls, the latter located in areas of the hippocampus and amygdala extending into the thalamus, and a significant widespread GMV increase emerged from the post-ECT-patients>pre-ECT-patients contrast [278]. Wang's study

(2017) also revealed that ECT caused volume augmentation in undergoing patients, with findings mainly showing GMV hypertrophy in the left superficial nucleus of the amygdala [277]. These results are in line with the literature, which highlights incrementally consistent data in favor of the increase in GMV as a consequence of ECT [e.g., 295,296].

In conclusion, an explanation of the difference between MDD and TRD groups could be that, in responding patients, greater GMV might be a sign of the treatment efficacy and, vice versa, the lack of hypertrophy in resistant individuals may signal that standard therapy is not effective; capable of determining increases on the brain of TRD patients is instead the ECT, a more invasive technique than drugs, that seems to have the sufficient power to produce a neurotrophic effect in case of refractoriness.

We now focus on the results obtained in each of the three meta-analyses (A, B, C) carried out.

Our first coordinate based meta-analysis comparing patients suffering from MDD showing GMV atrophy with respect to healthy controls returned two convergent atrophic areas: the left fusiform gyrus (BA 19) and the left declive, a vermian lobule in the cerebellum.

The fusiform gyrus (FFG) has been found to have a smaller volume also in other meta-analyses on whole-brain VBM studies [205,297,298,299], suggesting that this area – which is overlooked in ROI studies because it is not among those known to be particularly involved in depression, as are instead the hippocampus [177] or the amygdala [182] – might emerge when an unbiased approach is used. Indeed, it has been widely emphasized that the ROI method is guided by a priori anatomical knowledge and that it tends to provide insights only for those regions considered worthy of labeling [168], whereas whole-brain voxel-based morphometry is the optimal choice to go beyond the limited focus on regions of primary theoretical importance, thus to proceed objectively in the discovery of depressed brain's alterations [148].

Despite the evident underestimation in literature records, the structural alteration of the FFG is not by chance, rather it could be grounded in its functional involvement in depressive symptomatology. The fusiform gyrus, the largest part of the ventral temporal cortex, is involved in emotional regulation [299], and, by its fusiform face area, is well-recognized to be responsible for face-specific processing, hence for the recognition of

different emotions [300]. In compliance with that, it has been shown that structural and functional abnormalities occurring in this region are linked to alexithymia [301,302], the "*inability to express, describe, or distinguish among one's emotions*" [3]; this disturbance, whether it is a state reaction or a risk factor, is highly relevant in Major depression [303]. Very interestingly, a recent study found that higher alexithymia scores were associated with lower fusiform gyrus GMV in patients with MDD compared to healthy controls [304], fitting in the wake of previous functional works, such as the classic one by Surguladze et al. (2005) which proved the positive correlation between depressive symptoms severity and the magnitude of response within FFG to sad expressions (and the opposite pattern to the happy ones) [305], or the research by Ho et al. (2016) showing the association between significantly reduced responses in FFG and a deficit in the perceptual processing of facial emotions in a depressed sample [306].

These data have demonstrated not only that the fusiform gyrus is associated with alexithymia and disruption in emotional responses, but also that it is crucially involved in depression in such a way that the morphological atrophy in FFG might be associated with its functional impairment, resulting precisely in the depressed people's difficulties to first recognize, and then to regulate emotions. Notably, one of the aforementioned whole-brain VBM meta-analyses found the left fusiform gyrus reduced in GMV in patients with first-episode MDD, namely an alteration detectable since the earliest stages of the disorder [298]; in other words, FFG could be a potential target for early diagnosis and clinical intervention and therefore deserves further and in-depth studies.

What has been said so far becomes even more interesting if we consider that also the declive, the second outcome of meta-analysis A, is a cerebellar area whose increased activation in healthy people has been associated with the processing of faces, both emotional and neutral [307], even in case of dynamic moving expressions [308]. These psychological processes underlie a cascade effect, whereby they are essential for perceiving and recognizing emotions, which are, in turn, needful for social interactions [307,308]. Alterations in these mechanisms in forms of alexithymia (see above) and impaired social life are characteristic of MDD [307], and they are traceable to a cognitive theory according to which negative biases in information processing play a key role in the development, course, and maintenance of depression [309]. Consequently, the fact that two areas sharing the same function relevant to MDD phenotype were found to be

atrophic in our research, both objectively detected by other various studies (another whole-brain VBM meta-analysis found GMV reduction in declive in depressed patients [299]), might lead us towards a more complete understanding of the disorder, shedding light on the important structural (and probably functional) involvement of areas that until now have not received much attention, such as the declive and the fusiform gyrus.

The hypothesis that functional deterioration and morphological atrophy are associated is supported by Arnone and colleagues (2016) too, who stated that a smaller declive volume in MDD patients is a sign of its involvement in emotion dysregulation, even more when considering the extensive connectivity of the cerebellum with limbic and cortical associative areas [299], whose role in affective processes are well known [310].

For completeness, it is important to point out that, as every cerebellar component, declive too is involved in motor functioning [311]; a fascinating proposal for a link between this regional implication in both motor and emotional processing suggests that a cerebellar ability might consist in estimating possible changes in facial expression through the recording of spatial sequences, and the subsequent updating of information about perceptual features of a face [308].

Finally, given that cerebellar areas are highly interconnected with each other and with the cerebellum as a whole [312], further evidence supporting the involvement of declive at a structural level in MDD comes from other meta-analyses showing clusters with reduced volume in the cerebellum [205,297], highlighting its non-negligible role in affective processes, both in healthy and diseased brain [205]. Interest in cerebellar contributions to major depression is growing, also thanks to compelling results such as those concerning the connection between less GMV in the cerebellum and the persistence of cognitive deficits in MDD patients [313], or the longer disease duration correlated with atrophy in the left cerebellum (and in the fusiform gyrus too) [205], or even the damage in cerebellar subregions which interact with the cortical networks supporting cognitive and self-referential functions [314]. In conclusion, although future studies are needed, data suggests that the cerebellum may play a more important role in depression than has been recognized so far, and that declive with its specific function in emotion regulation might be, within the cerebellar structures, the one that reaches the level of potential disease trait marker.

Moving to meta-analysis B, we found increased GMV in bilateral Parahippocampal Gyri (PHG) in MDD patients compared to healthy controls. This result diverges from the majority of meta-analyses on the matter [e.g., 299,315,316], which, taken together, have led to argue that PHG tends to be atrophic in depression. This finding from other studies is not surprising, being the PHG an important source of input to the hippocampus, that, as many lines of work suggest, represents the most frequently replicated structural abnormality in MDD [176,317]. Different potential causes of volumetric loss detected in the hippocampus and in the areas closest to it, including the PHG, have been investigated, such as the depletion of glial cells that increases sensitivity to glutamate neurotoxicity or the stress-related decrease in neurotrophic factors and neurogenesis [318]. Currently, one of the most accredited theories explains that the hypercortisolemia induced by chronic stimulation of the hypothalamus-pituitary-adrenal axis due to stressful conditions, such as those characterizing depression, is the cause of glutamatergic neuronal apoptosis and, consequently, atrophy in the hippocampus and closest neighbors [180].

In contrast with these damaging mechanisms, the use of antidepressants produces cellular and molecular reactions, resulting in an increase in neuroplasticity and structural remodeling through signal transduction pathways [319]. Evidence shows that this is particularly true for the hippocampus: in this region, it has been elucidated that drugs have a reversing effect on morphological damages in form of restoration of grey matter volume, as demonstrated by Frodl and colleagues (2008), whose longitudinal study returned a significantly increased hippocampal volume among medicated patients during 3 years of follow-up [320]; moreover, they found a favorable therapeutic response and a low relapse rate to be linked to greater hippocampus GMV [320]. Being our sample treatment-respondent, this might be the reason why we did not find atrophic hippocampus, unlike other existing meta-analyses [e.g.,176,317]. Or even, various past meta-analyses have not been stringent in excluding comorbidities in the same way as we did, especially with anxiety disorders, and therefore they had more spurious samples; we might speculate that the hippocampus is more critical for those depressive conditions in which there is also a strong anxious and rumination mechanisms component [205].

Going back to the initial explanatory hypothesis of our work, according to which hypertrophy might be a sign of treatment efficacy in respondent depressed patients (see above), and given that hippocampus and parahippocampal gyrus are, due to their

anatomical nature, closely connected (the hippocampus is a convex elevation of grey matter tissue within the parahippocampal gyrus inside the temporal lobe [321]), it is reasonable to assume that the finding of parahippocampal hypertrophy may be attributed to the neurotrophic effect of antidepressants occurring in responsive MDD patients. As proof of this, Malykhin et al. (2010) found that unmedicated patients with major depression had grey matter reductions in the parahippocampal regions compared with MDD patients under drug therapy (which had instead a significantly larger hippocampal body volume bilaterally) [322], while the first-ever whole-brain VBM meta-analysis showed atrophy in parahippocampal gyrus GMV in drug-free samples, but not in chronic patients [188]. In addition, some functional investigations reported interesting insights in line with our hypothesis. A research on antidepressants' cerebral effects in clinical depression meta-analyzed fMRI and PET studies conducted in patients following pharmacological therapy during emotional processing tasks, and they found a pattern of decreased activation in several limbic and paralimbic regions, including the parahippocampal gyrus, specifically in response to negative stimuli after drugs administration [323]; consequently, authors formulated the hypothesis that antidepressants could decrease the hypersensitivity to negative emotional stimuli in MDD patients in an adaptive way, targeting functionally crucial areas, such as the PHG [323]. Another following meta-analysis uncovered a similar antidepressants' effect in healthy volunteers, in which repeated administration increased activity in the parahippocampus in response to positive emotions and caused its hypoactivation in reaction to negative ones [324].

Altogether, when focusing selectively on studies showing GMV hypertrophy in depressed brains, these results might suggest an important significance of increased parahippocampal gyrus volume, as a positive sign of responsiveness to treatment.

At last, our meta-analysis on Treatment-resistant depression identified GMV reduction in the Anterior Cingulate Cortex (ACC), confirming one of the results previously obtained by the only other meta-analysis of whole-brain VBM studies existing on TRD [207]. The convergence of these data might stand in support of the hypothesis that lower ACC volume is peculiar to the most severe forms of depression, including the treatment-refractory one. Indeed, assuming the perspective according to which major depression might be placeable in a disease gravity continuum (where responsive MDD is

considered a milder form of depression and TRD a more severe one) [325], it is possible to refer to studies showing that the improvement/remission of symptoms is associated with higher GMV in ACC [326,327], and larger right ACC volumes are correlated with lower depression severity symptoms [190], while its decrease tends to occur mostly in multi-episode samples, longer illness duration cases [188] and treatment-resistant patients [207]. However, this hypothesis is not yet widely accepted; indeed, the unique systematic review of structural brain changes in TRD supports the theory that GMV reduction of the ACC might be a stage (and severity)-independent trait marker of the disease, since its manifestations have been detected in early phases and in vulnerable individuals too [196]. More studies are needed to understand which hypothesis to lean toward, but so far data suggest that the anterior cingulate is involved in TRD, with the further support of our meta-analysis. Then, an important insight provided by this thesis is that only ACC was found to have significantly lower GMV in TRD patients compared to healthy controls, differently from the work of Liu et al. (2017) which also showed a reduction in the superior frontal gyrus [207]. A possible explanation could be that, by increasing the sample thanks to the inclusion of new studies, and excluding the one performing small volume correction [328] to comply with stringent inclusion criteria, a more reliable analysis was conducted, to which only the most representing finding for TRD survived, precisely the anterior cingulate cortex. As corroborating data, the functional involvement of ACC in emotional and mood dysregulation in major depression has been described [329] and the presence in non-remitters of lower 5-HTT binding in the ACC than responders has been proved [330], which is of note considering that current antidepressant drugs act mainly through the serotonergic system [77].

Limitations and future directions

The present study has some limitations.

In meta-analyses A and B, we did not consider important variables, like the type of drug or how long the patients had been treated (we include first-episode patients too), precluding exploration of their impact on our results. Since our work seems to show some differences between MDD and TRD patients attributable to the effect of antidepressants,

further studies might run specific sub-analyses to investigate the role of different medications and the contribution of the length of treatment.

However, it must be pointed out that we performed a meta-analysis including also cross-sectional studies, therefore our hypothesis that the hypertrophy found only in responding patients could be caused by the neurotrophic effect of drugs is purely speculative. Longitudinal studies monitoring brain alterations in medicated subjects are crucial to deepen the neural mechanisms underlying the responsiveness to treatment.

Meta-analysis C has a small sample, due to the presence of few studies in the literature on Treatment-resistant depression meeting our inclusion criteria; more in general, not many research on TRD have been conducted so far, for an effective smaller number of patients, when compared with individuals suffering from MDD, but also for the complex clinical features of this disorder that make it often not easy to retrieve data.

Another issue is the lack of uniformity in defining the resistance to treatment: although the majority of the included studies recruited patients non-responsive to at least two adequate trials of different classes of antidepressants, two other works have not adapted to this definition, which is however the most commonly adopted, and with general sense in clinical settings.

The small sample and the absence of consistent definition limit the generalizability of our result, therefore new studies with larger populations, and a more systematic approach to refractoriness are needed to get solid information on this disabling disorder.

Finally, although we adopted strict inclusion criteria regarding patients' clinical profiles, such as the exclusion of every overt comorbidity and each kind of depression-related disease diverse from Major Depressive Disorder (e.g., subthreshold depression, secondary depression, psychotic depression, bipolar depression, premenstrual dysphoric disorder, peri-partum/post-partum depression, seasonal affective disorder, dysthymic disorder), we did not check for differences in age, gender, and symptomatology features, which make our sample quite heterogeneous, with the risk of reduced power and increase false negatives. We prearranged this proceeding to get a greater ecological exploration, being heterogenicity an inherent feature of MDD: future research might start from our results to conduct studies with a different approach to our coordinate-based dataset to further support (and cross validate) the findings obtained using an ALE approach, e.g., using a more conservative permutation of subject images (PSI) with a seed-based d

mapping (SDM-PSI software), also focusing on specific subgroups based on the age of onset, gender differences, and symptomatic manifestations.

REFERENCE LIST

[1] American Psychological Association, Depression, Accessed 4 July 2022 [Online]. Available: https://www.apa.org/topics/depression.

[2] World Health Organization, Depression, Accessed 4 July 2022 [Online]. Available: https://www.who.int/news-room/fact-sheets/detail/depression.

[3] APA Dictionary of Psychology [Online]. Available: https://dictionary.apa.org/.

[4] Medscape, Depression: Practice Essentials, Background, Pathophysiology, Accessed 4 July 2022 [Online]. Available: https://emedicine.medscape.com/article/286759-overview#a6.

[5] Recommendations | Depression in adults: Treatment and management | Guidance | NICE, Accessed 4 July 2022 [Online]. Available: https://www.nice.org.uk/guidance/ng222/chapter/Recommendations#recognition-and-assessment.

[6] Nhs.Uk., Causes—Clinical depression, Accessed 4 July 2022 [Online]. Available: https://www.nhs.uk/mental-health/conditions/clinical-depression/causes/.

[7] American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington: American Psychiatric Publishing.

[8] World Health Organization. (2019). *International Statistical Classification of Diseases and Related Health Problems* (11th ed.). [Online]. Available: https://icd.who.int/browse11/l-m/en.

[9] Hirschfeld, R. M. (2014). Differential diagnosis of bipolar disorder and major depressive disorder. *Journal of Affective Disorders*, *169 Suppl 1*, S12-16.

[10] Enneking, V., Krüssel, P., Zaremba, D., Dohm, K., Grotegerd, D., Förster, K., Meinert, S., Bürger, C., Dzvonyar, F., Leehr, E. J., Böhnlein, J., Repple, J., Opel, N., Winter, N. R., Hahn, T., Redlich, R., & Dannlowski, U. (2019). Social anhedonia in major depressive disorder: A symptom-specific neuroimaging approach. *Neuropsychopharmacology, 44*(5), 883–889.

[11] Billones, R. R., Kumar, S., & Saligan, L. N. (2020). Disentangling fatigue from anhedonia: A scoping review. *Translational Psychiatry, 10*(1), 1–11.

[12] Ritsner, M. S. (2014). *Anhedonia: A Comprehensive Handbook Volume I: Conceptual Issues And Neurobiological Advances*. Springer.

[13] Sheehan, D. V., Nakagome, K., Asami, Y., Pappadopulos, E. A., & Boucher, M. (2017). Restoring function in major depressive disorder: A systematic review. *Journal of Affective Disorders, 215*, 299–313.

[14] Greenberg, P. E., Fournier, A.-A., Sisitsky, T., Simes, M., Berman, R., Koenigsberg, S. H., & Kessler, R. C. (2021). The Economic Burden of Adults with Major Depressive Disorder in the United States (2010 and 2018*). PharmacoEconomics, 39*(6), 653–665.

[15] Hammer-Helmich, L.; Haro, J. M.; Jönsson, B.; Tanguy Melac, A.; Di Nicola, S.; Chollet, J.; Milea, D.; Rive, B.; Saragoussi, D. (2018). Functional Impairment in Patients with Major Depressive Disorder: The 2-Year PERFORM Study. *Neuropsychiatric Disease and Treatment, 14*, 239–249.

[16] Uher, R.; Payne, J. L.; Pavlova, B.; Perlis, R. H. (2014). Major Depressive Disorder in DSM-5: Implications for Clinical Practice and Research of Changes from DSM-IV. *Depression and Anxiety, 31*(6), 459–471.

[17] Toenders, Y. J.; Schmaal, L.; Harrison, B. J.; Dinga, R.; Berk, M.; Davey, C. G. Neurovegetative Symptom Subtypes in Young People with Major Depressive Disorder and Their Structural Brain Correlates (2020*). Translational Psychiatry, 10*(1), 1–11.

[18] Bekhuis, E., Schoevers, R., van Borkulo, C., Rosmalen, J., & Boschloo, L. (2016). The network structure of major depressive disorder, generalized anxiety disorder and somatic symptomatology. *Psychological Medicine, 1*, 1–10.

[19] Zahn, R., Lythe, K. E., Gethin, J. A., Green, S., Deakin, J. F. W., Young, A. H., & Moll, J. (2015). The role of self-blame and worthlessness in the psychopathology of major depressive disorder. *Journal of Affective Disorders, 186*, 337–341.

[20] Green, S., Moll, J., Deakin, J. F. W., Hulleman, J., & Zahn, R. (2013). Proneness to decreased negative emotions in major depressive disorder when blaming others rather than oneself. *Psychopathology, 46*(1), 34–44.

[21] Zahn, R., Lythe, K. E., Gethin, J. A., Green, S., Deakin, J. F. W., Workman, C., & Moll, J. (2015). Negative emotions towards others are diminished in remitted major depression. *European Psychiatry, 30*(4), 448–453.

[22] Hammar, Å., & Årdal, G. (2009). Cognitive functioning in major depression—A summary. *Frontiers in Human Neuroscience, 3*, 26.

[23] Lam, R. W., Kennedy, S. H., McIntyre, R. S., & Khullar, A. (2014). Cognitive Dysfunction in Major Depressive Disorder: Effects on Psychosocial Functioning and Implications for Treatment. *Canadian Journal of Psychiatry*, *59*(12), 649–654.

[24] McIntyre, R. S., Cha, D. S., Soczynska, J. K., Woldeyohannes, H. O., Gallaugher, L. A., Kudlow, P., Alsuwaidan, M., & Baskaran, A. (2013). Cognitive deficits and functional outcomes in major depressive disorder: Determinants, substrates, and treatment interventions. *Depression and Anxiety, 30*(6), 515–527.

[25] Byers, A. L., & Yaffe, K. (2011). Depression and Risk of Developing Dementia. *Nature Reviews. Neurology, 7*(6), 323–331.

[26] Bachmann, S. (2018). Epidemiology of Suicide and the Psychiatric Perspective. *International Journal of Environmental Research and Public Health, 15*(7), 1425.

[27] Chesney, E., Goodwin, G. M., & Fazel, S. (2014). Risks of all-cause and suicide mortality in mental disorders: A meta-review. *World Psychiatry, 13*(2), 153–160.

[28] Turecki, G., & Brent, D. A. (2016). Suicide and suicidal behaviour. *The Lancet, 387*(10024), 1227–1239.

[29] World Health Organization, Suicide, Accessed 8 July 2022 [Online]. Available: https://www.who.int/news-room/fact-sheets/detail/suicide.

[30] World Health Organization, International Classification of Diseases (ICD), Accessed 8 July 2022 [Online]. Available: https://www.who.int/standards/classifications/classification-of-diseases.

[31] First, M. B., Gaebel, W., Maj, M., Stein, D. J., Kogan, C. S., Saunders, J. B., Poznyak, V. B., Gureje, O., Lewis-Fernández, R., Maercker, A., Brewin, C. R., Cloitre,

M., Claudino, A., Pike, K. M., Baird, G., Skuse, D., Krueger, R. B., Briken, P., Burke, J. D., … Reed, G. M. (2021). An organization- and category-level comparison of diagnostic requirements for mental disorders in ICD-11 and DSM-5. *World Psychiatry, 20*(1), 34–51.

[32] First, M. B., Gaebel, W., Maj, M., Stein, D. J., Kogan, C. S., Saunders, J. B., Poznyak, V. B., Gureje, O., Lewis-Fernández, R., Maercker, A., Brewin, C. R., Cloitre, M., Claudino, A., Pike, K. M., Baird, G., Skuse, D., Krueger, R. B., Briken, P., Burke, J. D., … Reed, G. M. (2021). An organization- and category-level comparison of diagnostic requirements for mental disorders in ICD-11 and DSM-5. *World Psychiatry: Official Journal of the World Psychiatric Association (WPA), 20*(1), 34–51.

[33] McGlinchey, J. B., Zimmerman, M., Young, D., & Chelminski, I. (2006). Diagnosing Major Depressive Disorder VIII: Are Some Symptoms Better Than Others? *The Journal of Nervous and Mental Disease, 194*(10), 785–790.

[34] Mojtabai, R. (2011). Bereavement-related depressive episodes: Characteristics, 3-year course, and implications for the DSM-5. *Archives of General Psychiatry, 68*(9), 920–928.

[35] Wakefield, J. C., & Schmitz, M. F. (2012). Recurrence of depression after bereavement-related depression: Evidence for the validity of DSM-IV bereavement exclusion from the Epidemiologic Catchment Area Study. *The Journal of Nervous and Mental Disease, 200*(6), 480–485.

[36] Stein, D. J., Szatmari, P., Gaebel, W., Berk, M., Vieta, E., Maj, M., de Vries, Y. A., Roest, A. M., de Jonge, P., Maercker, A., Brewin, C. R., Pike, K. M., Grilo, C. M., Fineberg, N. A., Briken, P., Cohen-Kettenis, P. T., & Reed, G. M. (2020). Mental, behavioral and neurodevelopmental disorders in the ICD-11: An international perspective on key changes and controversies. *BMC Medicine, 18*(1), 21.

[37] Clark, L. A., Cuthbert, B., Lewis-Fernández, R., Narrow, W. E., & Reed, G. M. (2017). Three Approaches to Understanding and Classifying Mental Disorder: ICD-11, DSM-5, and the National Institute of Mental Health's Research Domain Criteria (RDoC). *Psychological Science in the Public Interest, 18*(2), 72–145.

[38] First, M. B., & Westen, D. (2007). Classification for clinical practice: How to make ICD and DSM better able to serve clinicians. *International Review of Psychiatry (Abingdon, England), 19*(5), 473–481.

[39] Haslam, N., Holland, E., & Kuppens, P. (2012). Categories versus dimensions in personality and psychopathology: A quantitative review of taxometric research. *Psychological Medicine, 42*(5), 903–920.

[40] National Institute of Mental Health (NIMH), Research Domain Criteria (RDoC), Accessed 10 July 2022 [Online]. Available: https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc.

[41] Insel, T. R. (2014). The NIMH Research Domain Criteria (RDoC) Project: Precision Medicine for Psychiatry. *American Journal of Psychiatry*, *171*(4), 395–397.

[42] Woody, M. L., & Gibb, B. E. (2015). Integrating NIMH Research Domain Criteria (RDoC) into Depression Research. *Current Opinion in Psychology, 4*, 6–12.

[43] Dillon, D. G., Rosso, I. M., Pechtel, P., Killgore, W. D. S., Rauch, S. L., & Pizzagalli, D. A. (2014). Peril and Pleasure: An Rdoc-Inspired Examination of Threat Responses and Reward Processing in Anxiety and Depression. *Depression and Anxiety, 31*(3), 233–249.

[44] Mao, J., & Yuan, J. (2021). Anhedonia and its intervention in depressive adults: New developments based on Research Domain Criteria (RDoC) in mental illnesses. *Stress and Brain, 1(*1).

[45] Ahmed, A. T., Frye, M. A., Rush, A. J., Biernacka, J. M., Craighead, W. E., McDonald, W. M., Bobo, W. V., Riva-Posse, P., Tye, S. J., Mayberg, H. S., Flavin, D. H., Skime, M. K., Jenkins, G. D., Wang, L., Krishnan, R. R., Weinshilboum, R. M., Kaddurah-Daouk, R., & Dunlop, B. W. (2018). Mapping Depression Rating Scale Phenotypes onto Research Domain Criteria (RDoC) to Inform Biological Research in Mood Disorders. *Journal of Affective Disorders, 238*, 1–7.

[46] Gunzler, D., Sehgal, A. R., Kauffman, K., Davey, C. H., Dolata, J., Figueroa, M., Huml, A., Pencak, J., & Sajatovic, M. (2020). Identify depressive phenotypes by applying RDOC domains to the PHQ-9. *Psychiatry Research, 286*, 112872.

[47] National Institute of Mental Health (NIMH), Major Depression, Accessed 13 July 2022 [Online]. Available: https://www.nimh.nih.gov/health/statistics/major-depression.

[48] WebMD, An Overview of Clinical Depression, Accessed 13 July 2022 [Online]. Available: https://www.webmd.com/depression/guide/major-depression.

[49] Kessler, R. C., & Bromet, E. J. (2013). The epidemiology of depression across cultures. *Annual Review of Public Health, 34*, 119–138.

[50] Yakeley, J. (2018). Shame, culture and mental health. *Nordic Journal of Psychiatry, 72*(sup1), S20–S22.

[51]American Psychiatric Association, Psychiatry.org-What Is Depression?, Accessed 13 July 2022 [Online]. Available: https://psychiatry.org:443/patients-families/depression/what-is-depression.

[52] Zisook, S., Lesser, I., Stewart, J. W., Wisniewski, S. R., Balasubramani, G. k., Fava, M., Gilmer, W. S., Dresselhaus, T. R., Thase, M. E., Nierenberg, A. A., Trivedi, M. H., & Rush, A. J. (2007). Effect of Age at Onset on the Course of Major Depressive Disorder. *American Journal of Psychiatry, 164*(10), 1539–1546.

[53] Fava, M., & Kendler, K. S. (2000). Major Depressive Disorder. *Neuron, 28*(2), 335–341.

[54] Hoertel, N., Blanco, C., Oquendo, M. A., Wall, M. M., Olfson, M., Falissard, B., Franco, S., Peyre, H., Lemogne, C., & Limosin, F. (2017). A comprehensive model of predictors of persistence and recurrence in adults with major depression: Results from a national 3-year prospective study. *Journal of Psychiatric Research, 95*, 19–27.

[55] Boschloo, L., Schoevers, R. A., Beekman, A. T. F., Smit, J. H., Hemert, A. M. van, & Penninx, B. W. J. H. (2014). The Four-Year Course of Major Depressive Disorder: The Role of Staging and Risk Factor Determination. *Psychotherapy and Psychosomatics, 83*(5), 279–288.

[56] Spijker, J., Graaf, R. D., Bijl, R. V., Beekman, A. T. F., Ormel, J., & Nolen, W. A. (2002). Duration of major depressive episodes in the general population: Results from the

Netherlands Mental Health Survey and Incidence Study (NEMESIS). *The British Journal of Psychiatry, 181*(3), 208–213.

[57] Trivedi, M. H., Rush, A. J., Wisniewski, S. R., Nierenberg, A. A., Warden, D., Ritz, L., Norquist, G., Howland, R. H., Lebowitz, B., McGrath, P. J., Shores-Wilson, K., Biggs, M. M., Balasubramani, G. K., & Fava, M. (2006). Evaluation of Outcomes With Citalopram for Depression Using Measurement-Based Care in STAR*D: Implications for Clinical Practice. *American Journal of Psychiatry, 163*(1), 28–40.

[58] Mekonen, T., Ford, S., Chan, G. C. K., Hides, L., Connor, J. P., & Leung, J. (2022). What is the short-term remission rate for people with untreated depression? A systematic review and meta-analysis. *Journal of Affective Disorders, 296*, 17–25.

[59] Ormel, J., Oldehinkel, A. J., Nolen, W. A., & Vollebergh, W. (2004). Psychosocial Disability Before, During, and After a Major Depressive Episode: A 3-Wave Population-Based Study of State, Scar, and Trait Effects. *Archives of General Psychiatry, 61*(4), 387–392.

[60] Rush, A. J., Kraemer, H. C., Sackeim, H. A., Fava, M., Trivedi, M. H., Frank, E., Ninan, P. T., Thase, M. E., Gelenberg, A. J., Kupfer, D. J., Regier, D. A., Rosenbaum, J. F., Ray, O., & Schatzberg, A. F. (2006). Report by the ACNP Task Force on Response and Remission in Major Depressive Disorder. *Neuropsychopharmacology, 31*(9), 1841–1853.

[61] Otte, C., Gold, S. M., Penninx, B. W., Pariante, C. M., Etkin, A., Fava, M., Mohr, D. C., & Schatzberg, A. F. (2016). Major depressive disorder. *Nature Reviews Disease Primers, 2*(1), 1–20.

[62] National Center for Health Statistics (NCHS), Products—Data Briefs—Number 303—February 2018. Accessed 13 July 2022 [Online]. Available: https://www.cdc.gov/nchs/products/databriefs/db303.htm.

[63] Albert, P. R. (2015). Why is depression more prevalent in women? *Journal of Psychiatry & Neuroscience: JPN*, *40*(4), 219–221.

[64] Sullivan, P. F., Neale, M. C., & Kendler, K. S. (2000). Genetic Epidemiology of Major Depression: Review and Meta-Analysis. *American Journal of Psychiatry, 157*(10), 1552–1562.

[65] Standford Medicine, Major Depression and Genetics, Genetics of Brain Function, Accessed 16 July 2022 [Online]. Available: https://med.stanford.edu/depressiongenetics/mddandgenes.html

[66] Lohoff, F. W. (2010). Overview of the Genetics of Major Depressive Disorder. *Current Psychiatry Reports, 12*(6), 539–546.

[67] Hammen, C. (2018). Risk Factors for Depression: An Autobiographical Review. *Annual Review of Clinical Psychology, 14*, 1–28.

[68] Pariante, C. M., & Lightman, S. L. (2008). The HPA axis in major depression: Classical theories and new developments. *Trends in Neurosciences, 31*(9), 464–468.

[69] Costa Jr., P. T., & McCrae, R. R. (2008). The Revised NEO Personality Inventory (NEO-PI-R). In The SAGE handbook of personality theory and assessment, Vol 2: Personality measurement and testing (pp. 179–198). Sage Publications, Inc.

[70] Kotov, R., Gamez, W., Schmidt, F., & Watson, D. (2010). Linking "big" personality traits to anxiety, depressive, and substance use disorders: A meta-analysis. *Psychological Bulletin, 136*(5), 768–821.

[71] Jourdy, R., & Petot, J.-M. (2017). Relationships between personality traits and depression in the light of the "Big Five" and their different facets. *L'Évolution Psychiatrique, 82*(4), e27–e37.

[72] Colodro-Conde, L., Couvy-Duchesne, B., Zhu, G., Coventry, W. L., Byrne, E. M., Gordon, S., Wright, M. J., Montgomery, G. W., Madden, P. a. F., Ripke, S., Eaves, L. J., Heath, A. C., Wray, N. R., Medland, S. E., & Martin, N. G. (2018). A direct test of the diathesis–stress model for depression. *Molecular Psychiatry, 23*(7), 1590–1596.

[73] Schotte, C. K. W., Van Den Bossche, B., De Doncker, D., Claes, S., & Cosyns, P. (2006). A biopsychosocial model as a guide for psychoeducation and treatment of depression. *Depression and Anxiety, 23*(5), 312–324.

[74] Goldberg, D. (2010). The detection and treatment of depression in the physically ill. *World Psychiatry, 9*(1), 16–20.

[75] Davidson, J. R. T. (2010). Major Depressive Disorder Treatment Guidelines in America and Europe. *The Journal of Clinical Psychiatry, 71*(suppl E1), 27767.

[76] Cleare, A., Pariante, C., Young, A., Anderson, I., Christmas, D., Cowen, P., Dickens, C., Ferrier, I., Geddes, J., Gilbody, S., Haddad, P., Katona, C., Lewis, G., Malizia, A., McAllister-Williams, R., Ramchandani, P., Scott, J., Taylor, D., & Uher, R. (2015). Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2008 British Association for Psychopharmacology guidelines. *Journal of Psychopharmacology, 29*(5), 459–525.

[77] Julien, Robert M. (2011). A Primer of Drug Action (12th ed.). New York: Worth Publishers.

[78] Santarsieri, D., & Schwartz, T. L. (2015). Antidepressant efficacy and side-effect burden: A quick guide for clinicians. *Drugs in Context, 4*, 212290.

[79] Gabriel, F. C., Melo, D. O. de, Fráguas, R., Leite-Santos, N. C., Silva, R. A. M. da, & Ribeiro, E. (2020). Pharmacological treatment of depression: A systematic review comparing clinical practice guideline recommendations. *PLOS ONE, 15*(4), e0231700.

[80] National Institute of Mental Health (NIMH), Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Study. Accessed 20 July 2022 [Online]. Available: https://www.nimh.nih.gov/funding/clinical-research/practical/stard.

[81] Sinyor, M., Schaffer, A., & Levitt, A. (2010). The sequenced treatment alternatives to relieve depression (STAR*D) trial: A review. *Canadian Journal of Psychiatry. Revue Canadienne De Psychiatrie, 55*(3), 126–135.

[82] Gelenberg, A. J., Freeman, M. P., Markowitz, J. C., Rosenbaum, J. F., Thase, M. E., Trivedi, M. H., Rhoads, R. S. V., Reus, V. I., DePaulo, J. R., Fawcett, J. A., Schneck, C. D., & Silbersweig, D. A. (2010). Practice guideline for the treatment of patients with major depressive disorder Third edition. *The American journal of psychiatry, 157*(4 Suppl), 1–45.

[83] Amick, H. R., Gartlehner, G., Gaynes, B. N., Forneris, C., Asher, G. N., Morgan, L. C., Coker-Schwimmer, E., Boland, E., Lux, L. J., Gaylord, S., Bann, C., Pierl, C. B., &

Lohr, K. N. (2015). Comparative benefits and harms of second generation antidepressants and cognitive behavioral therapies in initial treatment of major depressive disorder: Systematic review and meta-analysis. *BMJ (Clinical research ed.), 351*, h6019.

[84] Cuijpers, P., Berking, M., Andersson, G., Quigley, L., Kleiboer, A., & Dobson, K. S. (2013). A Meta-Analysis of Cognitive-Behavioural Therapy for Adult Depression, Alone and in Comparison with other Treatments. *The Canadian Journal of Psychiatry, 58*(7), 376–385.

[85] Hofmann, S. G., Asnaani, A., Vonk, I. J. J., Sawyer, A. T., & Fang, A. (2012). The Efficacy of Cognitive Behavioral Therapy: A Review of Meta-analyses. *Cognitive Therapy and Research, 36*(5), 427–440.

[86] Cuijpers, P., van Straten, A., Andersson, G., & van Oppen, P. (2008). Psychotherapy for depression in adults: A meta-analysis of comparative outcome studies. *Journal of Consulting and Clinical Psychology, 76*(6), 909–922.

[87] Pampallona, S., Bollini, P., Tibaldi, G., Kupelnick, B., & Munizza, C. (2004). Combined pharmacotherapy and psychological treatment for depression: A systematic review. *Archives of General Psychiatry, 61*(7), 714–719.

[88] Cuijpers, P., van Straten, A., Warmerdam, L., & Andersson, G. (2009). Psychotherapy versus the combination of psychotherapy and pharmacotherapy in the treatment of depression: A meta-analysis. *Depression and Anxiety, 26*(3), 279–288.

[89] Cuijpers, P., Dekker, J., Hollon, S. D., & Andersson, G. (2009). Adding psychotherapy to pharmacotherapy in the treatment of depressive disorders in adults: A meta-analysis. *The Journal of Clinical Psychiatry, 70*(9), 1219–1229.

[90] Fava, M. (2003). Diagnosis and definition of treatment-resistant depression. *Biological Psychiatry, 53*(8), 649–659.

[91] Berlim, M. T., & Turecki, G. (2007). Definition, Assessment, and Staging of Treatment-Resistant Refractory Major Depression: A Review of Current Concepts and Methods. *The Canadian Journal of Psychiatry, 52*(1), 46–54.

[92] Zhdanava, M., Pilon, D., Ghelerter, I., Chow, W., Joshi, K., Lefebvre, P., & Sheehan, J. J. (2021). The Prevalence and National Burden of Treatment-Resistant Depression and Major Depressive Disorder in the United States. *The Journal of Clinical Psychiatry, 82*(2), 29169.

[93] Gaynes, B. N., Lux, L., Gartlehner, G., Asher, G., Forman-Hoffman, V., Green, J., Boland, E., Weber, R. P., Randolph, C., Bann, C., Coker-Schwimmer, E., Viswanathan, M., & Lohr, K. N. (2020). Defining treatment-resistant depression. *Depression and Anxiety, 37*(2), 134–145.

[94] Souery, D., Amsterdam, J., de Montigny, C., Lecrubier, Y., Montgomery, S., Lipp, O., Racagni, G., Zohar, J., & Mendlewicz, J. (1999). Treatment resistant depression: Methodological overview and operational criteria. *European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology, 9*(1–2), 83–91.

[95] Liu, X., Mukai, Y., Furtek, C. I., Bortnichak, E. A., Liaw, K.-L., & Zhong, W. (2021). Epidemiology of Treatment-Resistant Depression in the United States. *The Journal of Clinical Psychiatry, 83*(1), 21m13964.

[96] Bartova, L., Dold, M., Kautzky, A., Fabbri, C., Spies, M., Serretti, A., Souery, D., Mendlewicz, J., Zohar, J., Montgomery, S., Schosser, A., & Kasper, S. (2019). Results of the European Group for the Study of Resistant Depression (GSRD)—Basis for further research and clinical practice. *The World Journal of Biological Psychiatry: The Official Journal of the World Federation of Societies of Biological Psychiatry, 20*(6), 427–448.

[97] Carter, G. C., Cantrell, R. A., Victoria Zarotsky, Haynes, V. S., Phillips, G., Alatorre, C. I., Goetz, I., Paczkowski, R., & Marangell, L. B. (2012). Comprehensive review of factors implicated in the heterogeneity of response in depression. *Depression and Anxiety, 29*(4), 340–354.

[98] Iniesta, R., Hodgson, K., Stahl, D., Malki, K., Maier, W., Rietschel, M., Mors, O., Hauser, J., Henigsberg, N., Dernovsek, M. Z., Souery, D., Dobson, R., Aitchison, K. J., Farmer, A., McGuffin, P., Lewis, C. M., & Uher, R. (2018). Antidepressant drug-specific prediction of depression treatment outcomes from genetic and clinical variables. *Scientific Reports, 8*(1), 5530.

[99] Chekroud, A. M., Zotti, R. J., Shehzad, Z., Gueorguieva, R., Johnson, M. K., Trivedi, M. H., Cannon, T. D., Krystal, J. H., & Corlett, P. R. (2016). Cross-trial prediction of treatment outcome in depression: A machine learning approach. *The Lancet. Psychiatry, 3*(3), 243–250.

[100] Ionescu, D. F., Rosenbaum, J. F., & Alpert, J. E. (2015). Pharmacological approaches to the challenge of treatment-resistant depression. *Dialogues in Clinical Neuroscience, 17*(2), 111–126.

[101] Bronswijk, S. van, Moopen, N., Beijers, L., Ruhe, H. G., & Peeters, F. (2019). Effectiveness of psychotherapy for treatment-resistant depression: A meta-analysis and meta-regression. *Psychological Medicine, 49*(3), 366–379.

[102] Ijaz, S., Davies, P., Williams, C. J., Kessler, D., Lewis, G., & Wiles, N. (2018). Psychological therapies for treatment-resistant depression in adults. *The Cochrane Database of Systematic Reviews, 5*, CD010558.

[103] Voineskos, D., Daskalakis, Z. J., & Blumberger, D. M. (2020). Management of Treatment-Resistant Depression: Challenges and Strategies. *Neuropsychiatric Disease and Treatment, 16*, 221–234.

[104] UK ECT Review Group (2003). Efficacy and safety of electroconvulsive therapy in depressive disorders: A systematic review and meta-analysis. (2003). *The Lancet, 361*(9360), 799–808.

[105] Pagnin, D., de Queiroz, V., Pini, S., & Cassano, G. B. (2004). Efficacy of ECT in depression: A meta-analytic review. *The Journal of ECT*, *20*(1), 13–20.

[106] Andrade, C., Arumugham, S. S., & Thirthalli, J. (2016). Adverse Effects of Electroconvulsive Therapy. *The Psychiatric Clinics of North America, 39*(3), 513–530.

[107] Milev, R. V., Giacobbe, P., Kennedy, S. H., Blumberger, D. M., Daskalakis, Z. J., Downar, J., Modirrousta, M., Patry, S., Vila-Rodriguez, F., Lam, R. W., MacQueen, G. M., Parikh, S. V., Ravindran, A. V., & CANMAT Depression Work Group. (2016). Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 4.

Neurostimulation Treatments. *Canadian Journal of Psychiatry. Revue Canadienne De Psychiatrie, 61*(9), 561–575.

[108] Sienaert, P. (2014). Mechanisms of ECT: Reviewing the science and dismissing the myths. *The Journal of ECT, 30*(2), 85–86.

[109] Oltedal, L., Kessler, U., Ersland, L., Grüner, R., Andreassen, O. A., Haavik, J., Hoff, P. I., Hammar, Å., Dale, A. M., Hugdahl, K., & Oedegaard, K. J. (2015). Effects of ECT in treatment of depression: Study protocol for a prospective neuroradiological study of acute and longitudinal effects on brain structure and function. *BMC Psychiatry, 15*(1), 94.

[110] Masdeu, J. C. (2011). Neuroimaging in Psychiatric Disorders. *Neurotherapeutics: The Journal of the American Society for Experimental NeuroTherapeutics, 8*(1), 93–102.

[111] Fulham, M. J. (2004). Neuroimaging. In L. R. Squire (Ed.), *Encyclopedia of Neuroscience* (pp. 459–469). Academic Press.

[112] Sharma, A., & Weintraub, A. (2017). Neuroimaging. In J. Kreutzer, J. DeLuca, & B. Caplan (Eds.), *Encyclopedia of Clinical Neuropsychology* (pp. 1–5). Springer International Publishing.

[113] Noggle, C. A., & Davis, A. S. (2021). Advances in Neuroimaging. In R. C. D'Amato, A. S. Davis, E. M. Power, & E. C. Eusebio (Eds.), *Understanding the Biological Basis of Behavior: Developing Evidence-Based Interventions for Clinical, Counseling and School Psychologists* (pp. 107–137). Springer International Publishing.

[114] Marková, I. S. (2018). Translational neuroscience and psychiatry: A conceptual analysis. *Journal of Evaluation in Clinical Practice, 24*(4), 791–796.

[115] Silbersweig, D. A., & Rauch, S. L. (2017). Neuroimaging in Psychiatry: A Quarter Century of Progress. *Harvard Review of Psychiatry, 25*(5), 195–197.

[116] Linden, D. E. J. (2012). The Challenges and Promise of Neuroimaging in Psychiatry. *Neuron, 73*(1), 8–22.

[117] Phillips, M. L. (2007). The Emerging Role of Neuroimaging in Psychiatry: Characterizing Treatment-Relevant Endophenotypes. *American Journal of Psychiatry, 164*(5), 697–699.

[118] Agarwal, N., Port, J. D., Bazzocchi, M., & Renshaw, P. F. (2010). Update on the use of MR for assessment and diagnosis of psychiatric diseases. *Radiology, 255*(1), 23–41.

[119] Westbrook, C., & Talbot, J. (2018). *MRI in Practice* (5th ed.). John Wiley & Sons.

[120] Brown, M. A., & Semelka, R. C. (2003). *MRI: Basic Principles and Applications* (3rd ed.). John Wiley & Sons.

[121] Westbrook, C., & Kaut, C. (1998). *MRI in Practice* (2nd ed.). Oxford, UK: Blackwell.

[122] MRI, Radiology at St. Vincent's University Hospital. Accessed 1 August 2022 [Online]. Available: http://www.svuhradiology.ie/diagnostic-imaging/mri/

[123] Talos, I.-F., Mian, A. Z., Zou, K. H., Hsu, L., Goldberg-Zimring, D., Haker, S., Bhagwat, J. G., & Mulkern, R. V. (2006). Magnetic resonance and the human brain:

Anatomy, function and metabolism. *Cellular and Molecular Life Sciences: CMLS, 63*(10), 1106–1124.

[124] Rosenbloom, M. J., & Pfefferbaum, A. (2008). Magnetic Resonance Imaging of the Living Brain. *Alcohol Research & Health, 31*(4), 362–376.

[125] Yousaf, T., Dervenoulas, G., & Politis, M. (2018). Chapter Two—Advances in MRI Methodology. In M. Politis (Ed.), *International Review of Neurobiology* (Vol. 141, pp. 31–76). Academic Press.

[126] Magnetic Resonance Imaging. Accessed 5 August 2022 [Online]. https://www.cookchildrens.org/services/neurosciences-research/technology/mri/

[127] Westbrook, C. (2014). *Handbook of MRI technique* (4th ed.). John Wiley & Sons.

[128] Padmanaban, S., Thiruvenkadam, K., T., P., Thirumalaiselvi, M., & Kumar, R. (2020). A Role of Medical Imaging Techniques in Human Brain Tumor Treatment. *International Journal of Recent Technology and Engineering, 8*, 565–568.

[129] Le Bihan, D. (2020). How MRI Makes the Brain Visible. In Y. Toyama, A. Miyawaki, M. Nakamura, & M. Jinzaki (Eds.), *Make Life Visible* (pp. 201–212). Springer.

[130] Despotović, I., Goossens, B., & Philips, W. (2015). MRI Segmentation of the Human Brain: Challenges, Methods, and Applications. *Computational and Mathematical Methods in Medicine, 2015*, e450341.

[131] Giorgio, A., & De Stefano, N. (2013). Clinical use of brain volumetry. *Journal of Magnetic Resonance Imaging, 37*(1), 1–14.

[132] Duara, R., Loewenstein, D. A., Potter, E., Appel, J., Greig, M. T., Urs, R., Shen, Q., Raj, A., Small, B., Barker, W., Schofield, E., Wu, Y., & Potter, H. (2008). Medial temporal lobe atrophy on MRI scans and the diagnosis of Alzheimer disease. *Neurology, 71*(24), 1986–1992.

[133] Frisoni, G. B., Fox, N. C., Jack, C. R., Scheltens, P., & Thompson, P. M. (2010). The clinical use of structural MRI in Alzheimer disease. *Nature Reviews Neurology, 6*(2), 67–77.

[134] Pyatigorskaya, N., Gallea, C., Garcia-Lorenzo, D., Vidailhet, M., & Lehericy, S. (2014). A review of the use of magnetic resonance imaging in Parkinson's disease. *Therapeutic Advances in Neurological Disorders, 7*(4), 206–220.

[135] Politis, M. (2014). Neuroimaging in Parkinson disease: From research setting to clinical practice. *Nature Reviews Neurology, 10*(12), 708–722.

[136] Lassmann, H., Brück, W., & Lucchinetti, C. (2001). Heterogeneity of multiple sclerosis pathogenesis: Implications for diagnosis and therapy. *Trends in Molecular Medicine, 7*(3), 115–121.

[137] Bakshi, R., Thompson, A. J., Rocca, M. A., Pelletier, D., Dousset, V., Barkhof, F., Inglese, M., Guttmann, C. R., Horsfield, M. A., & Filippi, M. (2008). MRI in multiple sclerosis: Current status and future prospects. *The Lancet Neurology, 7*(7), 615–625.

[138] Deblaere, K., & Achten, E. (2008). Structural magnetic resonance imaging in epilepsy. *European Radiology, 18*(1), 119–129.

[139] Kuzniecky, R. I. (2005). Neuroimaging of epilepsy: Therapeutic implications. *NeuroRx: The Journal of the American Society for Experimental NeuroTherapeutics, 2*(2), 384–393.

[140] Gupta, A., Nair, S., Schweitzer, A. D., Kishore, S., Johnson, C. E., Comunale, J. P., Tsiouris, A. J., & Sanelli, P. C. (2012). Neuroimaging of Cerebrovascular Disease in the Aging Brain. *Aging and Disease, 3*(5), 414–425.

[141] Bigler, E. D. (2001). Quantitative Magnetic Resonance Imaging in Traumatic Brain Injury. *The Journal of Head Trauma Rehabilitation, 16*(2), 117–134.

[142] Mabray, M. C., Barajas, R. F., & Cha, S. (2015). Modern Brain Tumor Imaging. *Brain Tumor Research and Treatment, 3*(1), 8–23.

[143] Lorenzetti, V., Allen, N. B., Fornito, A., & Yücel, M. (2009). Structural brain abnormalities in major depressive disorder: A selective review of recent MRI studies. *Journal of Affective Disorders, 117*(1), 1–17.

[144] Klok, M. P. C., van Eijndhoven, Philip. F., Argyelan, M., Schene, A. H., & Tendolkar, I. (2019). Structural brain characteristics in treatment-resistant depression: Review of magnetic resonance imaging studies. *BJPsych Open,* 5(5), e76.

[145] Hasse Karlsson, M. A. (2011). How Psychotherapy Changes the Brain. *Psychiatric Times, 28*(8), 6.

[146] Huang, X., Gong, Q., Sweeney, J. A., & Biswal, B. B. (2019). Progress in psychoradiology, the clinical application of psychiatric neuroimaging. *The British Journal of Radiology, 92*(1101), 20181000.

[147] Forkel, S. J., & Catani, M. (2018). Structural Neuroimaging, *Research Methods in Psycholinguistics*. Wiley & Sons.

[148] Ashburner, J., & Friston, K. J. (2000). Voxel-Based Morphometry—The Methods. *NeuroImage, 11*(6), 805–821.

[149] Mechelli, A., Price, C. J., Friston, K. J., & Ashburner, J. (2005). Voxel-Based Morphometry of the Human Brain: Methods and Applications. *Current Medical Imaging Reviews, 1*(2), 105–113.

[150] Seeram, E. (2019). Digital Image Processing Concepts. In E. Seeram (Ed.), *Digital Radiography: Physical Principles and Quality Control* (pp. 21–39). Springer.

[151] Villegas, L., & Bloch, I. (2014). Segmentation of Magnetic Resonance Images of newborn brains: Functionalities implemented in a matlab interface.

[152] Elsayed, A., Coenen, F., García-Fiñana, M., & Sluming, V. (2012). Region Of Interest Based Image Classification: A Study in MRI Brain Scan Categorization, *Data Mining Applications in Engineering and Medicine*. IntechOpen.

[153] Astrakas, L. G., & Argyropoulou, M. I. (2010). Shifting from region of interest (ROI) to voxel-based analysis in human brain mapping. *Pediatric Radiology, 40*(12), 1857–1867.

[154] Sun, S., & Zhang, R. (2017). Region of interest extraction of medical image based on improved region growing algorithm. In: *2017 International Conference on Material Science, Energy and Environmental Engineering (MSEEE 2017)* (pp. 471-475). Atlantis Press.

[155] Giuliani, N. R., Calhoun, V. D., Pearlson, G. D., Francis, A., & Buchanan, R. W. (2005). Voxel-based morphometry versus region of interest: A comparison of two methods for analyzing gray matter differences in schizophrenia. *Schizophrenia Research, 74*(2), 135–147.

[156] Van Hecke, W., Leemans, A., & Emsell, L. (2016). DTI Analysis Methods: Voxel-Based Analysis. In W. Van Hecke, L. Emsell, & S. Sunaert (Eds.), *Diffusion Tensor Imaging: A Practical Handbook* (pp. 183–203). Springer.

[157] Wei, J., Wei, S., Yang, R., Yang, L., Yin, Q., Li, H., Qin, Y., Lei, Y., Qin, C., Tang, J., Luo, S., & Guo, W. (2018). Voxel-Mirrored Homotopic Connectivity of Resting-State Functional Magnetic Resonance Imaging in Blepharospasm. *Frontiers in Psychology*, *9*, 1620.

[158] Ashburner, J., & Friston, K. (2003). Morphometry, *Human Brain Function* (pp. 707–722). Academic Press.

[159] Mandal, P. K., Mahajan, R., & Dinov, I. D. (2012). Structural Brain Atlases: Design, Rationale, and Applications in Normal and Pathological Cohorts. *Journal of Alzheimer's Disease: JAD, 31*(0 3), S169–S188.

[160] SPM - Statistical Parametric Mapping. Accessed 10 August 2022 [Online]. https://www.fil.ion.ucl.ac.uk/spm/

[161] Martínez-Murcia, F. J., Górriz, J. M., & Ramírez, J. (2016). Computer-Aided Diagnosis in Neuroimaging. In *Computer-aided Technologies—Applications in Engineering and Medicine*. IntechOpen.

[162] Whitwell, J. L. (2009). Voxel-Based Morphometry: An Automated Technique for Assessing Structural Changes in the Brain. *Journal of Neuroscience, 29*(31), 9661–9664.

[163] Salmond, C. H., Ashburner, J., Vargha-Khadem, F., Connelly, A., Gadian, D. G., & Friston, K. J. (2002). Distributional Assumptions in Voxel-Based Morphometry. *NeuroImage, 17*(2), 1027–1030.

[164] Gennatas, E. D., Avants, B. B., Wolf, D. H., Satterthwaite, T. D., Ruparel, K., Ciric, R., Hakonarson, H., Gur, R. E., & Gur, R. C. (2017). Age-Related Effects and Sex Differences in Gray Matter Density, Volume, Mass, and Cortical Thickness from Childhood to Young Adulthood. *The Journal of Neuroscience, 37*(20), 5065–5073.

[165] Yankowitz, L. D., Yerys, B. E., Herrington, J. D., Pandey, J., & Schultz, R. T. (2021). Dissociating regional gray matter density and gray matter volume in autism spectrum condition. *NeuroImage: Clinical, 32*, 102888.

[166] Weinberger, D. R., & Radulescu, E. (2016). Finding the Elusive Psychiatric "Lesion" With 21st-Century Neuroanatomy: A Note of Caution. *American Journal of Psychiatry, 173*(1), 27–33.

[167] Tabrizi, S. J., Langbehn, D. R., Leavitt, B. R., Roos, R. A., Durr, A., Craufurd, D., Kennard, C., Hicks, S. L., Fox, N. C., Scahill, R. I., Borowsky, B., Tobin, A. J., Rosas, H. D., Johnson, H., Reilmann, R., Landwehrmeyer, B., Stout, J. C., & TRACK-HD investigators. (2009). Biological and clinical manifestations of Huntington's disease in the longitudinal TRACK-HD study: Cross-sectional analysis of baseline data. *The Lancet. Neurology, 8*(9), 791–801.

[168] Focke, N. K., Trost, S., Paulus, W., Falkai, P., & Gruber, O. (2014). Do Manual and Voxel-Based Morphometry Measure the Same? A Proof of Concept Study. *Frontiers in Psychiatry, 5*, 39.

[169] Bookstein, F. L. (2001). 'Voxel-based morphometry' should not be used with imperfectly registered images. *NeuroImage, 14*(6), 1454–1462.

[170] Davies, R. R., Scahill, V. L., Graham, A., Williams, G. B., Graham, K. S., & Hodges, J. R. (2009). Development of an MRI rating scale for multiple brain regions: Comparison with volumetrics and with voxel-based morphometry. *Neuroradiology, 51*(8), 491–503.

[171] Seyedi, S., Jafari, R., Talaei, A., Naseri, S., Momennezhad, M., Moghaddam, M. D., & Akbari-Lalimi, H. (2020). Comparing VBM and ROI analyses for detection of gray matter abnormalities in patients with bipolar disorder using MRI. *Middle East Current Psychiatry, 27*(1), 69.

[172] Mühlau, M., Wohlschläger, A. M., Gaser, C., Valet, M., Weindl, A., Nunnemann, S., Peinemann, A., Etgen, T., & Ilg, R. (2009). Voxel-Based Morphometry in Individual Patients: A Pilot Study in Early Huntington Disease. *American Journal of Neuroradiology, 30*(3), 539–543.

[173] Zhuo, C., Li, G., Lin, X., Jiang, D., Xu, Y., Tian, H., Wang, W., & Song, X. (2019). The rise and fall of MRI studies in major depressive disorder. *Translational Psychiatry, 9*(1), 1–14.

[174] Dai, L., Zhou, H., Xu, X., & Zuo, Z. (2019). Brain structural and functional changes in patients with major depressive disorder: A literature review. *PeerJ, 7*, e8170.

[175] Dusi, N., Delvecchio, G., Rovera, C., Altamura, C. A., & Brambilla, P. (2018). Voxel-Based Morphometry Imaging Studies in Major Depression. In G. Spalletta, F. Piras, & T. Gili (Eds.), Brain Morphometry (pp. 385–402). Humana Press, New York, NY.

[176] Cole, J., Costafreda, S. G., McGuffin, P., & Fu, C. H. Y. (2011). Hippocampal atrophy in first episode depression: A meta-analysis of magnetic resonance imaging studies. *Journal of Affective Disorders, 134*(1), 483–487.

[177] Campbell, S., Marriott, M., Nahmias, C., & MacQueen, G. M. (2004). Lower Hippocampal Volume in Patients Suffering From Depression: A Meta-Analysis. *American Journal of Psychiatry, 161*(4), 598–607.

[178] Stratmann, M., Konrad, C., Kugel, H., Krug, A., Schöning, S., Ohrmann, P., Uhlmann, C., Postert, C., Suslow, T., Heindel, W., Arolt, V., Kircher, T., & Dannlowski, U. (2014). Insular and Hippocampal Gray Matter Volume Reductions in Patients with Major Depressive Disorder. *PLoS ONE, 9*(7), e102692.

[179] Schmaal, L., Pozzi, E., C. Ho, T., van Velzen, L. S., Veer, I. M., Opel, N., Van Someren, E. J. W., Han, L. K. M., Aftanas, L., Aleman, A., Baune, B. T., Berger, K., Blanken, T. F., Capitão, L., Couvy-Duchesne, B., R. Cullen, K., Dannlowski, U., Davey, C., Erwin-Grabner, T., … Veltman, D. J. (2020). ENIGMA MDD: Seven years of global neuroimaging studies of major depression through worldwide data sharing. *Translational Psychiatry, 10*(1), 1–19.

[180] Lee, A. L., Ogle, W. O., & Sapolsky, R. M. (2002). Stress and depression: Possible links to neuron death in the hippocampus. *Bipolar Disorders, 4*(2), 117–128.

[181] Baxter, M. G., & Murray, E. A. (2002). The amygdala and reward. *Nature Reviews Neuroscience, 3*(7), 563–573.

[182] Bellani, M., Baiano, M., & Brambilla, P. (2011). Brain anatomy of major depression II. Focus on amygdala. *Epidemiology and Psychiatric Sciences, 20*(1), 33–36.

[183] Tebartz van Elst, L., Woermann, F., Lemieux, L., & Trimble, M. R. (2000). Increased amygdala volumes in female and depressed humans. A quantitative magnetic resonance imaging study. *Neuroscience Letters, 281*(2), 103–106.

[184] Sheline, Y. I., Gado, M. H., & Price, J. L. (1998). Amygdala core nuclei volumes are decreased in recurrent major depression. *NeuroReport, 9*(9), 2023–2028.

[185] Kempton, M. J., Salvador, Z., Munafò, M. R., Geddes, J. R., Simmons, A., Frangou, S., & Williams, S. C. R. (2011). Structural neuroimaging studies in major depressive disorder. Meta-analysis and comparison with bipolar disorder. *Archives of General Psychiatry, 68*(7), 675–690.

[186] Lu, Y., Liang, H., Han, D., Mo, Y., Li, Z., Cheng, Y., Xu, X., Shen, Z., Tan, C., Zhao, W., Zhu, Y., & Sun, X. (2016). The volumetric and shape changes of the putamen and thalamus in first episode, untreated major depressive disorder. *NeuroImage: Clinical, 11*, 658–666.

[187] Amico, F., Meisenzahl, E., Koutsouleris, N., Reiser, M., Möller, H.-J., & Frodl, T. (2011). Structural MRI correlates for vulnerability and resilience to major depressive disorder. *Journal of Psychiatry & Neuroscience: JPN, 36*(1), 15–22.

[188] Bora, E., Fornito, A., Pantelis, C., & Yücel, M. (2012). Gray matter abnormalities in Major Depressive Disorder: A meta-analysis of voxel based morphometry studies. *Journal of Affective Disorders, 138*(1–2), 9–18.

[189] Schmaal, L., Hibar, D. P., Sämann, P. G., Hall, G. B., Baune, B. T., Jahanshad, N., Cheung, J. W., van Erp, T. G. M., Bos, D., Ikram, M. A., Vernooij, M. W., Niessen, W. J., Tiemeier, H., Hofman, A., Wittfeld, K., Grabe, H. J., Janowitz, D., Bülow, R., Selonke, M., … Veltman, D. J. (2017). Cortical abnormalities in adults and adolescents with major depression based on brain scans from 20 cohorts worldwide in the ENIGMA Major Depressive Disorder Working Group. *Molecular Psychiatry, 22*(6), 900–909.

[190] Frodl, T., Jäger, M., Born, C., Ritter, S., Kraft, E., Zetzsche, T., Bottlender, R., Leinsinger, G., Reiser, M., Möller, H.-J., & Meisenzahl, E. (2008). Anterior cingulate cortex does not differ between patients with major depression and healthy controls, but relatively large anterior cingulate cortex predicts a good clinical course. *Psychiatry Research: Neuroimaging, 163*(1), 76–83.

[191] Lai, T., Payne, M. E., Byrum, C. E., Steffens, D. C., & Krishnan, K. R. (2000). Reduction of orbital frontal cortex volume in geriatric depression. *Biological Psychiatry, 48*(10), 971–975.

[192] Grieve, S. M., Korgaonkar, M. S., Koslow, S. H., Gordon, E., & Williams, L. M. (2013). Widespread reductions in gray matter volume in depression. *NeuroImage: Clinical, 3*, 332–339.

[193] Hamilton, J. P., Etkin, A., Furman, D. J., Lemus, M. G., Johnson, R. F., & Gotlib, I. H. (2012). Functional Neuroimaging of Major Depressive Disorder: A Meta-Analysis and New Integration of Baseline Activation and Neural Response Data. *American Journal of Psychiatry, 169*(7), 693–703.

[194] Herrmann, L. L., Masurier, M. L., & Ebmeier, K. P. (2008). White matter hyperintensities in late life depression: A systematic review. *Journal of Neurology, Neurosurgery & Psychiatry, 79*(6), 619–624.

[195] van, B. M., & Tofts, P. S. (2000). Magnetization transfer imaging. *Neuroimaging Clinics of North America, 10*(4), 771-88 ,ix.

[196] Klok, M. P. C., Eijndhoven, P. F. van, Argyelan, M., Schene, A. H., & Tendolkar, I. (2019). Structural brain characteristics in treatment-resistant depression: Review of magnetic resonance imaging studies. *BJPsych Open, 5*(5), e76.

[197] Koolschijn, P. C. M. P., van Haren, N. E. M., Lensvelt-Mulders, G. J. L. M., Hulshoff Pol, H. E., & Kahn, R. S. (2009). Brain volume abnormalities in major depressive disorder: A meta-analysis of magnetic resonance imaging studies. *Human Brain Mapping, 30*(11), 3719–3735.

[198] Korgaonkar, M. S., Rekshan, W., Gordon, E., Rush, A. J., Williams, L. M., Blasey, C., & Grieve, S. M. (2015). Magnetic Resonance Imaging Measures of Brain Structure to Predict Antidepressant Treatment Outcome in Major Depressive Disorder. *EBioMedicine, 2*(1), 37–45.

[199] Shah, P. J., Glabus, M. F., Goodwin, G. M., & Ebmeier, K. P. (2002). Chronic, treatment-resistant depression and right fronto-striatal atrophy. *The British Journal of Psychiatry, 180*(5), 434–440.

[200] Oltedal, L., Narr, K. L., Abbott, C., Anand, A., Argyelan, M., Bartsch, H., Dannlowski, U., Dols, A., van Eijndhoven, P., Emsell, L., Erchinger, V. J., Espinoza, R., Hahn, T., Hanson, L. G., Hellemann, G., Jorgensen, M. B., Kessler, U., Oudega, M. L., Paulson, O. B., … Dale, A. M. (2018). Volume of the Human Hippocampus and Clinical Response Following Electroconvulsive Therapy. *Biological Psychiatry, 84*(8), 574–581.

[201] Vos, T., Barber, R. M., Bell, B., Bertozzi-Villa, A., Biryukov, S., Bolliger, I., Charlson, F., Davis, A., Degenhardt, L., Dicker, D., Duan, L., Erskine, H., Feigin, V. L., Ferrari, A. J., Fitzmaurice, C., Fleming, T., Graetz, N., Guinovart, C., Haagsma, J., … Murray, C. J. (2015). Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: A systematic analysis for the Global Burden of Disease Study 2013. *The Lancet, 386*(9995), 743–800.

[202] Button, K. S., Ioannidis, J. P. A., Mokrysz, C., Nosek, B. A., Flint, J., Robinson, E. S. J., & Munafò, M. R. (2013). Power failure: Why small sample size undermines the reliability of neuroscience. *Nature Reviews. Neuroscience, 14*(5), 365–376.

[203] Radua, J., & Mataix-Cols, D. (2012). Meta-analytic methods for neuroimaging data explained. *Biology of Mood & Anxiety Disorders, 2*, 6.

[204] Müller, V. I., Cieslik, E. C., Laird, A. R., Fox, P. T., Radua, J., Mataix-Cols, D., Tench, C. R., Yarkoni, T., Nichols, T. E., Turkeltaub, P. E., Wager, T. D., & Eickhoff, S.

B. (2018). Ten simple rules for neuroimaging meta-analysis. *Neuroscience and Biobehavioral Reviews, 84*, 151–161.

[205] Serra-Blasco, M., Radua, J., Soriano-Mas, C., Gómez-Benlloch, A., Porta-Casteràs, D., Carulla-Roig, M., Albajes-Eizagirre, A., Arnone, D., Klauser, P., Canales-Rodríguez, E. J., Hilbert, K., Wise, T., Cheng, Y., Kandilarova, S., Mataix-Cols, D., Vieta, E., Via, E., & Cardoner, N. (2021). Structural brain correlates in major depression, anxiety disorders and post-traumatic stress disorder: A voxel-based morphometry meta-analysis. *Neuroscience and Biobehavioral Reviews, 129*, 269–281.

[206] Sha, Z., & Banihashemi, L. (2022). Integrative omics analysis identifies differential biological pathways that are associated with regional grey matter volume changes in major depressive disorder. *Psychological Medicine, 52*(5), 924–935.

[207] Liu, J., Xu, X., Luo, Q., Luo, Y., Chen, Y., Lui, S., Wu, M., Zhu, H., Kemp, G. J., & Gong, Q. (2017). Brain grey matter volume alterations associated with antidepressant response in major depressive disorder. *Scientific Reports, 7*(1), 10464.

[208] Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., … Moher, D. (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ, 372*, n71.

[209] Kim, M. J., Hamilton, J. P., & Gotlib, I. H. (2008). Reduced caudate gray matter volume in women with major depressive disorder. Psychiatry Research, 164(2), 114–122.

[210] Wagner, G., Koch, K., Schachtzabel, C., Reichenbach, J. R., Sauer, H., & Schlösser Md, R. G. M. (2008). Enhanced rostral anterior cingulate cortex activation during cognitive control is related to orbitofrontal volume reduction in unipolar depression. *Journal of Psychiatry & Neuroscience: JPN, 33*(3), 199–208.

[211] Leung, K.-K., Lee, T. M. C., Wong, M. M. C., Li, L. S. W., Yip, P. S. F., & Khong, P.-L. (2009). Neural correlates of attention biases of people with major depressive disorder: A voxel-based morphometric study. Psychological Medicine, 39(7), 1097–1106.

[212] Mak, A. K. Y., Wong, M. M. C., Han, S.-H., & Lee, T. M. C. (2009). Gray matter reduction associated with emotion regulation in female outpatients with major depressive disorder: A voxel-based morphometry study. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 33*(7), 1184–1190.

[213] Zou, K., Deng, W., Li, T., Zhang, B., Jiang, L., Huang, C., Sun, X., & Sun, X. (2010). Changes of brain morphometry in first-episode, drug-naïve, non-late-life adult patients with major depression: An optimized voxel-based morphometry study. *Biological Psychiatry, 67*(2), 186–188.

[214] Cheng, Y.-Q., Xu, J., Chai, P., Li, H.-J., Luo, C.-R., Yang, T., Li, L., Shan, B.-C., Xu, X.-F., & Xu, L. (2010). Brain volume alteration and the correlations with the clinical characteristics in drug-naïve first-episode MDD patients: A voxel-based morphometry study. *Neuroscience Letters, 480*(1), 30–34.

[215] Hwang, J.-P., Lee, T.-W., Tsai, S.-J., Chen, T.-J., Yang, C.-H., Lirng, J.-F., & Tsai, C.-F. (2010). Cortical and subcortical abnormalities in late-onset depression with history

of suicide attempts investigated with MRI and voxel-based morphometry. *Journal of Geriatric Psychiatry and Neurology, 23*(3), 171–184.

[216] Scheuerecker, J., Meisenzahl, E. M., Koutsouleris, N., Roesner, M., Schöpf, V., Linn, J., Wiesmann, M., Brückmann, H., Möller, H.-J., & Frodl, T. (2010). Orbitofrontal volume reductions during emotion recognition in patients with major depression. *Journal of Psychiatry & Neuroscience: JPN, 35*(5), 311–320.

[217] Salvadore, G., Nugent, A. C., Lemaitre, H., Luckenbaugh, D. A., Tinsley, R., Cannon, D. M., Neumeister, A., Zarate, C. A., & Drevets, W. C. (2011). Prefrontal cortical abnormalities in currently depressed versus currently remitted patients with major depressive disorder. *NeuroImage, 54*(4), 2643–2651.

[218] Wagner, G., Koch, K., Schachtzabel, C., Schultz, C. C., Sauer, H., & Schlösser, R. G. (2011). Structural brain alterations in patients with major depressive disorder and high risk for suicide: Evidence for a distinct neurobiological entity? *NeuroImage, 54*(2), 1607–1614.

[219] Ma, C., Ding, J., Li, J., Guo, W., Long, Z., Liu, F., Gao, Q., Zeng, L., Zhao, J., & Chen, H. (2012). Resting-state functional connectivity bias of middle temporal gyrus and caudate with altered gray matter volume in major depression. *PloS One, 7*(9), e45263.

[220] Wang, L., Dai, W., Su, Y., Wang, G., Tan, Y., Jin, Z., Zeng, Y., Yu, X., Chen, W., Wang, X., & Si, T. (2012). Amplitude of low-frequency oscillations in first-episode, treatment-naive patients with major depressive disorder: A resting-state functional MRI study. *PloS One, 7*(10), e48658.

[221] Chaney, A., Carballedo, A., Amico, F., Fagan, A., Skokauskas, N., Meaney, J., & Frodl, T. (2014). Effect of childhood maltreatment on brain structure in adult patients with major depressive disorder and healthy participants. *Journal of Psychiatry & Neuroscience: JPN, 39*(1), 50–59.

[222] Guo, W., Liu, F., Yu, M., Zhang, J., Zhang, Z., Liu, J., Xiao, C., & Zhao, J. (2014). Functional and anatomical brain deficits in drug-naive major depressive disorder. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 54*, 1–6.

[223] Jung, J., Kang, J., Won, E., Nam, K., Lee, M.-S., Tae, W. S., & Ham, B.-J. (2014). Impact of lingual gyrus volume on antidepressant response and neurocognitive functions in Major Depressive Disorder: A voxel-based morphometry study. *Journal of Affective Disorders, 169*, 179–187.

[224] Kong, L., Wu, F., Tang, Y., Ren, L., Kong, D., Liu, Y., Xu, K., & Wang, F. (2014). Frontal-subcortical volumetric deficits in single episode, medication-naïve depressed patients and the effects of 8 weeks fluoxetine treatment: A VBM-DARTEL study. *PloS One, 9*(1), e79055.

[225] Lai, C.-H., & Wu, Y.-T. (2014). Frontal-insula gray matter deficits in first-episode medication-naïve patients with major depressive disorder. *Journal of Affective Disorders, 160*, 74–79.

[226] Modinos, G., Allen, P., Frascarelli, M., Tognin, S., Valmaggia, L., Xenaki, L., Keedwell, P., Broome, M., Valli, I., Woolley, J., Stone, J. M., Mechelli, A., Phillips, M. L., McGuire, P., & Fusar-Poli, P. (2014). Are we really mapping psychosis risk?

Neuroanatomical signature of affective disorders in subjects at ultra high risk. *Psychological Medicine, 44*(16), 3491–3501.

[227] Nakano, M., Matsuo, K., Nakashima, M., Matsubara, T., Harada, K., Egashira, K., Masaki, H., Takahashi, K., & Watanabe, Y. (2014). Gray matter volume and rapid decision-making in major depressive disorder. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 48*, 51–56.

[228] Peng, H., Wu, K., Li, J., Qi, H., Guo, S., Chi, M., Wu, X., Guo, Y., Yang, Y., & Ning, Y. (2014). Increased suicide attempts in young depressed patients with abnormal temporal-parietal-limbic gray matter volume. *Journal of Affective Disorders, 165*, 69–73.

[229] Qi, H., Ning, Y., Li, J., Guo, S., Chi, M., Gao, M., Guo, Y., Yang, Y., Peng, H., & Wu, K. (2014). Gray matter volume abnormalities in depressive patients with and without anxiety disorders. *Medicine, 93*(29), e345.

[230] Qiu, L., Lui, S., Kuang, W., Huang, X., Li, J., Li, J., Zhang, J., Chen, H., Sweeney, J. A., & Gong, Q. (2014). Regional increases of cortical thickness in untreated, first-episode major depressive disorder. *Translational Psychiatry, 4*, e378.

[231] Cai, Y., Liu, J., Zhang, L., Liao, M., Zhang, Y., Wang, L., Peng, H., He, Z., Li, Z., Li, W., Lu, S., Ding, Y., & Li, L. (2015). Grey matter volume abnormalities in patients with bipolar I depressive disorder and unipolar depressive disorder: A voxel-based morphometry study. Neuroscience Bulletin, 31(1), 4–12.

[232] Dannlowski, U., Kugel, H., Grotegerd, D., Redlich, R., Suchy, J., Opel, N., Suslow, T., Konrad, C., Ohrmann, P., Bauer, J., Kircher, T., Krug, A., Jansen, A., Baune, B. T., Heindel, W., Domschke, K., Forstner, A. J., Nöthen, M. M., Treutlein, J., … Witt, S. H. (2015). NCAN Cross-Disorder Risk Variant Is Associated With Limbic Gray Matter Deficits in Healthy Subjects and Major Depression. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology, 40*(11), 2510–2516.

[233] Fang, J., Mao, N., Jiang, X., Li, X., Wang, B., & Wang, Q. (2015). Functional and Anatomical Brain Abnormalities and Effects of Antidepressant in Major Depressive Disorder: Combined Application of Voxel-Based Morphometry and Amplitude of Frequency Fluctuation in Resting State. *Journal of Computer Assisted Tomography, 39*(5), 766–773.

[234] Vasic, N., Wolf, N. D., Grön, G., Sosic-Vasic, Z., Connemann, B. J., Sambataro, F., von Strombeck, A., Lang, D., Otte, S., Dudek, M., & Wolf, R. C. (2015). Baseline brain perfusion and brain structure in patients with major depression: A multimodal magnetic resonance imaging study. *Journal of Psychiatry & Neuroscience: JPN, 40*(6), 412–421.

[235] Lai, C.-H., & Wu, Y.-T. (2015). The gray matter alterations in major depressive disorder and panic disorder: Putative differences in the pathogenesis. *Journal of Affective Disorders, 186*, 1–6.

[236] Watanabe, K., Kakeda, S., Yoshimura, R., Abe, O., Ide, S., Hayashi, K., Katsuki, A., Umene-Nakano, W., Watanabe, R., Nakamura, J., & Korogi, Y. (2015). Relationship between the catechol-O-methyl transferase Val108/158Met genotype and brain volume in treatment-naive major depressive disorder: Voxel-based morphometry analysis. *Psychiatry Research, 233*(3), 481–487.

[237] Yang, X., Ma, X., Li, M., Liu, Y., Zhang, J., Huang, B., Zhao, L., Deng, W., Li, T., & Ma, X. (2015). Anatomical and functional brain abnormalities in unmedicated major depressive disorder. *Neuropsychiatric Disease and Treatment, 11*, 2415–2423.

[238] Yang, X., Ma, X., Huang, B., Sun, G., Zhao, L., Lin, D., Deng, W., Li, T., & Ma, X. (2015). Gray matter volume abnormalities were associated with sustained attention in unmedicated major depression. *Comprehensive Psychiatry, 63*, 71–79.

[239] Chen, Z., Peng, W., Sun, H., Kuang, W., Li, W., Jia, Z., & Gong, Q. (2016). High-field magnetic resonance imaging of structural alterations in first-episode, drug-naive patients with major depressive disorder. Translational Psychiatry, 6(11), e942.

[240] Opel, N., Zwanzger, P., Redlich, R., Grotegerd, D., Dohm, K., Arolt, V., Heindel, W., Kugel, H., & Dannlowski, U. (2016). Differing brain structural correlates of familial and environmental risk for major depressive disorder revealed by a combined VBM/pattern recognition approach. *Psychological Medicine, 46*(2), 277–290.

[241] Ozalay, O., Aksoy, B., Tunay, S., Simsek, F., Chandhoke, S., Kitis, O., Eker, C., & Gonul, A. S. (2016). Cortical thickness and VBM in young women at risk for familial depression and their depressed mothers with positive family history. *Psychiatry Research. Neuroimaging, 252*, 1–9.

[242] Qiu, H., Li, X., Zhao, W., Du, L., Huang, P., Fu, Y., Qiu, T., Xie, P., Meng, H., & Luo, Q. (2016). Electroconvulsive Therapy-Induced Brain Structural and Functional Changes in Major Depressive Disorders: A Longitudinal Study. *Medical Science Monitor: International Medical Journal of Experimental and Clinical Research, 22*, 4577–4586.

[243] Shen, Z., Cheng, Y., Yang, S., Dai, N., Ye, J., Liu, X., Lu, J., Li, N., Liu, F., Lu, Y., Sun, X., & Xu, X. (2016). Changes of grey matter volume in first-episode drug-naive adult major depressive disorder patients with different age-onset. *NeuroImage. Clinical, 12*, 492–498.

[244] Wang, Y., Yang, S., Sun, W., Shi, Y., & Duan, H. (2016). Altered functional interaction hub between affective network and cognitive control network in patients with major depressive disorder. *Behavioural Brain Research, 298*(Pt B), 301–309.

[245] Igata, N., Kakeda, S., Watanabe, K., Ide, S., Kishi, T., Abe, O., Igata, R., Katsuki, A., Iwata, N., Yoshimura, R., & Korogi, Y. (2017). Voxel-based morphometric brain comparison between healthy subjects and major depressive disorder patients in Japanese with the s/s genotype of 5-HTTLPR. *Scientific Reports, 7*(1), 3931.

[246] Yang, X., Peng, Z., Ma, X., Meng, Y., Li, M., Zhang, J., Song, X., Liu, Y., Fan, H., Zhao, L., Deng, W., Li, T., & Ma, X. (2017). Sex differences in the clinical characteristics and brain gray matter volume alterations in unmedicated patients with major depressive disorder. *Scientific Reports, 7*(1), 2515.

[247] Zhao, Y., Chen, L., Zhang, W., Xiao, Y., Shah, C., Zhu, H., Yuan, M., Sun, H., Yue, Q., Jia, Z., Zhang, W., Kuang, W., Gong, Q., & Lui, S. (2017). Gray Matter Abnormalities in Non-comorbid Medication-naive Patients with Major Depressive Disorder or Social Anxiety Disorder. *EBioMedicine, 21*, 228–235.

[248] Zhuo, C., Zhu, J., Wang, C., Qu, H., Ma, X., & Qin, W. (2017). Different spatial patterns of brain atrophy and global functional connectivity impairments in major depressive disorder. *Brain Imaging and Behavior, 11*(6), 1678–1689.

[249] Chang, M., Womer, F. Y., Edmiston, E. K., Bai, C., Zhou, Q., Jiang, X., Wei, S., Wei, Y., Ye, Y., Huang, H., He, Y., Xu, K., Tang, Y., & Wang, F. (2018). Neurobiological Commonalities and Distinctions Among Three Major Psychiatric Diagnostic Categories: A Structural MRI Study. *Schizophrenia Bulletin, 44*(1), 65–74.

[250] Chen, L., Wang, Y., Niu, C., Zhong, S., Hu, H., Chen, P., Zhang, S., Chen, G., Deng, F., Lai, S., Wang, J., Huang, L., & Huang, R. (2018). Common and distinct abnormal frontal-limbic system structural and functional patterns in patients with major depression and bipolar disorder. *NeuroImage. Clinical, 20*, 42–50.

[251] Lu, X.-W., Guo, H., Sun, J.-R., Dong, Q.-L., Zhao, F.-T., Liao, X.-H., Zhang, L., Zhang, Y., Li, W.-H., Li, Z.-X., Liu, T.-B., He, Y., Xia, M.-R., & Li, L.-J. (2018). A shared effect of paroxetine treatment on gray matter volume in depressive patients with and without childhood maltreatment: A voxel-based morphometry study. *CNS Neuroscience & Therapeutics, 24*(11), 1073–1083.

[252] Zaremba, D., Dohm, K., Redlich, R., Grotegerd, D., Strojny, R., Meinert, S., Bürger, C., Enneking, V., Förster, K., Repple, J., Opel, N., Baune, B. T., Zwitserlood, P., Heindel, W., Arolt, V., Kugel, H., & Dannlowski, U. (2018). Association of Brain Cortical Changes With Relapse in Patients With Major Depressive Disorder. *JAMA Psychiatry, 75*(5), 484–492.

[253] Zhou, R., Wang, F., Zhao, G., Xia, W., Peng, D., Mao, R., Xu, J., Wang, Z., Hong, W., Zhang, C., Wang, Y., Su, Y., Huang, J., Yang, T., Wang, J., Chen, J., Palaniyappan, L., & Fang, Y. (2018). Effects of tumor necrosis factor-α polymorphism on the brain structural changes of the patients with major depressive disorder. *Translational Psychiatry, 8*(1), 217.

[254] Gong, Q., Scarpazza, C., Dai, J., He, M., Xu, X., Shi, Y., Zhou, B., Vieira, S., McCrory, E., Ai, Y., Yang, C., Zhang, F., Lui, S., & Mechelli, A. (2019). A transdiagnostic neuroanatomical signature of psychiatric illness. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology, 44*(5), 869–875.

[255] Hellewell, S. C., Welton, T., Maller, J. J., Lyon, M., Korgaonkar, M. S., Koslow, S. H., Williams, L. M., Rush, A. J., Gordon, E., & Grieve, S. M. (2019). Profound and reproducible patterns of reduced regional gray matter characterize major depressive disorder. *Translational Psychiatry, 9*(1), 176.

[256] Kandilarova, S., Stoyanov, D., Sirakov, N., Maes, M., & Specht, K. (2019). Reduced grey matter volume in frontal and temporal areas in depression: Contributions from voxel-based morphometry study. *Acta Neuropsychiatrica, 31*(5), 252–257.

[257] Li, Y., Wang, C., Teng, C., Jiao, K., Song, X., Tan, Y., Xiao, C., Zhang, N., & Zhong, Y. (2019). Hippocampus-driving progressive structural alterations in medication-naïve major depressive disorder. *Journal of Affective Disorders, 256*, 148–155.

[258] Liu, P., Li, G., Zhang, A., Sun, N., Kang, L., Yang, C., Wang, Y., & Zhang, K. (2019). The prognosis and changes of regional brain gray matter volume in MDD with gastrointestinal symptoms. Neuropsychiatric Disease and Treatment, 15, 1181–1191.

[259] Peng, W., Jia, Z., Huang, X., Lui, S., Kuang, W., Sweeney, J. A., & Gong, Q. (2019). Brain structural abnormalities in emotional regulation and sensory processing regions associated with anxious depression. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 94*, 109676.

[260] Straub, J., Brown, R., Malejko, K., Bonenberger, M., Grön, G., Plener, P. L., & Abler, B. (2019). Adolescent depression and brain development: Evidence from voxel-based morphometry. Journal of Psychiatry & Neuroscience: JPN, 44(4), 237–245.

[261] Chen, M.-H., Kao, Z.-K., Chang, W.-C., Tu, P.-C., Hsu, J.-W., Huang, K.-L., Su, T.-P., Li, C.-T., Lin, W.-C., Tsai, S.-J., & Bai, Y.-M. (2020). Increased Proinflammatory Cytokines, Executive Dysfunction, and Reduced Gray Matter Volumes In First-Episode Bipolar Disorder and Major Depressive Disorder. *Journal of Affective Disorders, 274*, 825–831.

[262] Liu, P., Li, G., Zhang, A., Yang, C., Liu, Z., Sun, N., & Kerang, Z. (2020). Brain structural and functional alterations in MDD patient with gastrointestinal symptoms: A resting-state MRI study. *Journal of Affective Disorders, 273*, 95–105.

[263] Nan, D., Yuqi, C., Zonglin, S., Chenglong, D., Na, L., Fang, L., Cong, Z., & Xiufeng, X. (2020). Association of a SIRT1 polymorphism with changes of gray matter volume in patients with first-episode medication-naïve major depression. *Psychiatry Research. Neuroimaging, 301*, 111101.

[264] Meng, Q., Zhang, A., Cao, X., Sun, N., Li, X., Zhang, Y., & Wang, Y. (2020). Brain Imaging Study on the Pathogenesis of Depression & Therapeutic Effect of Selective Serotonin Reuptake Inhibitors. *Psychiatry Investigation, 17*(7), 688–694.

[265] Zhang, T., Zhao, B., Shi, C., Nie, B., Liu, H., Yang, X., Sun, Y., Li, P., Lin, L., Yang, X., Li, J., Gao, X., Feng, S., Li, X., Sun, X., Pan, T., Feng, T., Bao, T., & Shan, B. (2020). Subthreshold depression may exist on a spectrum with major depressive disorder: Evidence from gray matter volume and morphological brain network. *Journal of Affective Disorders, 266*, 243–251.

[266] Yang, Y., Chattun, M. R., Yan, R., Zhao, K., Chen, Y., Zhu, R., Shi, J., Wang, X., Lu, Q., & Yao, Z. (2020). Atrophy of right inferior frontal orbital gyrus and frontoparietal functional connectivity abnormality in depressed suicide attempters. *Brain Imaging and Behavior, 14*(6), 2542–2552.

[267] Jiang, X., Wang, X., Jia, L., Sun, T., Kang, J., Zhou, Y., Wei, S., Wu, F., Kong, L., Wang, F., & Tang, Y. (2021). Structural and functional alterations in untreated patients with major depressive disorder and bipolar disorder experiencing first depressive episode: A magnetic resonance imaging study combined with follow-up. *Journal of Affective Disorders, 279*, 324–333.

[268] Liu, P.-H., Li, Y., Zhang, A.-X., Sun, N., Li, G.-Z., Chen, X., Bai, T.-J., Bo, Q.-J., Chen, G.-M., Chen, N.-X., Chen, T.-L., Chen, W., Cheng, C., Cheng, Y.-Q., Cui, X.-L., Duan, J., Fang, Y.-R., Gong, Q.-Y., Guo, W.-B., … Zhang, K.-R. (2021). Brain structural alterations in MDD patients with gastrointestinal symptoms: Evidence from the REST-meta-MDD project. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 111*, 110386.

[269] Ma, M., Zhang, Y., Zhang, X., Yan, H., Zhang, D., & Yue, W. (2021). Common and Distinct Alterations of Cognitive Function and Brain Structure in Schizophrenia and Major Depressive Disorder: A Pilot Study. *Frontiers in Psychiatry, 12,* 705998.

[270] Takamiya, A., Vande Casteele, T., Koole, M., De Winter, F.-L., Bouckaert, F., Van den Stock, J., Sunaert, S., Dupont, P., Vandenberghe, R., Van Laere, K., Vandenbulcke, M., & Emsell, L. (2021). Lower regional gray matter volume in the absence of higher cortical amyloid burden in late-life depression. *Scientific Reports, 11*(1), 15981.

[271] Zhang, Y.-N., Li, H., Shen, Z.-W., Xu, C., Huang, Y.-J., & Wu, R.-H. (2021). Healthy individuals vs patients with bipolar or unipolar depression in gray matter volume. World Journal of Clinical Cases, 9(6), 1304–1317.

[272] Zhou, R., Chen, J., Zhao, G., Wang, Z., Peng, D., Xia, W., Mao, R., Xu, J., Wang, F., Zhang, C., Wang, Y., Yuan, C., Su, Y., Huang, J., Yang, T., Wang, C., Cui, L., Wang, J., Palaniyappan, L., & Fang, Y. (2021). Neural biomarker of functional disability in major depressive disorder: A structural neuroimaging study. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 111*, 110337.

[273] Zhang, C., Ni, P., Liang, S., Li, X., Tian, Y., Du, X., Wei, W., Meng, Y., Wei, J., Ma, X., Deng, W., Guo, W., Li, M., Yu, H., Zhao, L., Wang, Q., Pak, S. C., & Li, T. (2022). Alterations in CRY2 and PER3 gene expression associated with thalamic-limbic community structural abnormalities in patients with bipolar depression or unipolar depression. *Journal of Affective Disorders, 298*(Pt A), 472–480.

[274] Serra-Blasco, M., Portella, M. J., Gómez-Ansón, B., de Diego-Adeliño, J., Vives-Gilabert, Y., Puigdemont, D., Granell, E., Santos, A., Alvarez, E., & Pérez, V. (2013). Effects of illness duration and treatment resistance on grey matter abnormalities in major depression. *The British Journal of Psychiatry: The Journal of Mental Science, 202*, 434–440.

[275] Machino, A., Kunisato, Y., Matsumoto, T., Yoshimura, S., Ueda, K., Yamawaki, Y., Okada, G., Okamoto, Y., & Yamawaki, S. (2014). Possible involvement of rumination in gray matter abnormalities in persistent symptoms of major depression: An exploratory magnetic resonance imaging voxel-based morphometry study. *Journal of Affective Disorders, 168*, 229–235.

[276] Johnston, B. A., Steele, J. D., Tolomeo, S., Christmas, D., & Matthews, K. (2015). Structural MRI-Based Predictions in Patients with Treatment-Refractory Depression (TRD). *PloS One, 10*(7), e0132958.

[277] Wang, J., Wei, Q., Bai, T., Zhou, X., Sun, H., Becker, B., Tian, Y., Wang, K., & Kendrick, K. (2017). Electroconvulsive therapy selectively enhanced feedforward connectivity from fusiform face area to amygdala in major depressive disorder. *Social Cognitive and Affective Neuroscience, 12*(12), 1983–1992.

[278] Camilleri, J. A., Hoffstaedter, F., Zavorotny, M., Zöllner, R., Wolf, R. C., Thomann, P., Redlich, R., Opel, N., Dannlowski, U., Grözinger, M., Demirakca, T., Sartorius, A., Eickhoff, S. B., & Nickl-Jockschat, T. (2020). Electroconvulsive therapy modulates grey matter increase in a hub of an affect processing network. *NeuroImage. Clinical, 25*, 102114.

[279] Brainmap.org | GingerALE, Accessed 1 September 2022 [Online]. Available: http://www.brainmap.org/ale/

[280] Eickhoff, S. B., Bzdok, D., Laird, A. R., Kurth, F., & Fox, P. T. (2012). Activation Likelihood Estimation meta-analysis revisited. *Neuroimage, 59*(3), 2349–2361.

[281] Turkeltaub, P. E., Eickhoff, S. B., Laird, A. R., Fox, M., Wiener, M., & Fox, P. (2012). Minimizing within-experiment and within-group effects in Activation Likelihood Estimation meta-analyses. *Human Brain Mapping, 33*(1), 1–13.

[282] Eickhoff, S. B., Laird, A. R., Grefkes, C., Wang, L. E., Zilles, K., & Fox, P. T. (2009). Coordinate-based activation likelihood estimation meta-analysis of neuroimaging data: A random-effects approach based on empirical estimates of spatial uncertainty. *Human Brain Mapping, 30*(9), 2907–2926.

[283] Laird, A. R., Fox, P. M., Price, C. J., Glahn, D. C., Uecker, A. M., Lancaster, J. L., Turkeltaub, P. E., Kochunov, P., & Fox, P. T. (2005). ALE meta-analysis: Controlling the false discovery rate and performing statistical contrasts. *Human Brain Mapping, 25*(1), 155–164.

[284] Ramsay, I. S. (2019). An Activation Likelihood Estimate Meta-analysis of Thalamocortical Dysconnectivity in Psychosis. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 4*(10), 859–869.

[285] Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery, and Psychiatry, 23*, 56–62.

[286] Beck, A. T., Ward, C. H., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An inventory for measuring depression. *Archives of General Psychiatry, 4*, 561–571.

[287] Montgomery, S. A., & Asberg, M. (1979). A new depression scale designed to be sensitive to change. *The British Journal of Psychiatry: The Journal of Mental Science, 134*, 382–389.

[288] Hamilton M. (1959). The assessment of anxiety states by rating. *Br J Med Psychol, 32*:50–55.

[289] ZUNG, W. W. K. (1965). A Self-Rating Depression Scale. *Archives of General Psychiatry, 12*(1), 63–70.

[290] Castrén, E. (2004). Neurotrophic effects of antidepressant drugs. *Current Opinion in Pharmacology, 4*(1), 58–64.

[291] Arnone, D., McKie, S., Elliott, R., Juhasz, G., Thomas, E. J., Downey, D., Williams, S., Deakin, J. F. W., & Anderson, I. M. (2013). State-dependent changes in hippocampal grey matter in depression. *Molecular Psychiatry, 18*(12), 1265–1272.

[292] Fossati, P., Radtchenko, A., & Boyer, P. (2004). Neuroplasticity: From MRI to depressive symptoms. *European Neuropsychopharmacology, 14*, S503–S510.

[293] Manji, H. K., & Duman, R. S. (2001). Impairments of neuroplasticity and cellular resilience in severe mood disorders: Implications for the development of novel therapeutics. *Psychopharmacology Bulletin, 35*(2), 5–49.

[294] Sackeim, H. A. (2020). The impact of electroconvulsive therapy on brain grey matter volume: What does it mean? *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation, 13*(5), 1226–1231.

[295] Ota, M., Noda, T., Sato, N., Okazaki, M., Ishikawa, M., Hattori, K., Hori, H., Sasayama, D., Teraishi, T., Sone, D., & Kunugi, H. (2015). Effect of electroconvulsive

therapy on gray matter volume in major depressive disorder. *Journal of Affective Disorders, 186*, 186–191.

[296] Brancati, G. E., Brekke, N., Bartsch, H., Evjenth Sørhaug, O. J., Ousdal, O. T., Hammar, Å., Schuster, P. M., Oedegaard, K. J., Kessler, U., & Oltedal, L. (2021). Short and long-term effects of single and multiple sessions of electroconvulsive therapy on brain gray matter volumes. Brain Stimulation, 14(5), 1330–1339.

[297] Zacková, L., Jáni, M., Brázdil, M., Nikolova, Y. S., & Marečková, K. (2021). Cognitive impairment and depression: Meta-analysis of structural magnetic resonance imaging studies. *NeuroImage. Clinical, 32*, 102830.

[298] Zheng, R., Zhang, Y., Yang, Z., Han, S., & Cheng, J. (2021). Reduced Brain Gray Matter Volume in Patients With First-Episode Major Depressive Disorder: A Quantitative Meta-Analysis. *Frontiers in Psychiatry, 12*, 671348.

[299] Arnone, D., Job, D., Selvaraj, S., Abe, O., Amico, F., Cheng, Y., Colloby, S. J., O'Brien, J. T., Frodl, T., Gotlib, I. H., Ham, B.-J., Kim, M. J., Koolschijn, P. C. M., Périco, C. A.-M., Salvadore, G., Thomas, A. J., Van Tol, M.-J., van der Wee, N. J. A., Veltman, D. J., … McIntosh, A. M. (2016). Computational meta-analysis of statistical parametric maps in major depression. *Human Brain Mapping, 37*(4), 1393–1404.

[300] McCarthy, G., Puce, A., Gore, J. C., & Allison, T. (1997). Face-specific processing in the human fusiform gyrus. *Journal of Cognitive Neuroscience, 9*(5), 605–610.

[301] Xu, P., Opmeer, E. M., van Tol, M.-J., Goerlich, K. S., & Aleman, A. (2018). Structure of the alexithymic brain: A parametric coordinate-based meta-analysis. *Neuroscience & Biobehavioral Reviews, 87*, 50–55.

[302] van der Velde, J., Servaas, M. N., Goerlich, K. S., Bruggeman, R., Horton, P., Costafreda, S. G., & Aleman, A. (2013). Neural correlates of alexithymia: A meta-analysis of emotion processing studies. *Neuroscience and Biobehavioral Reviews, 37*(8), 1774–1785.

[303] Honkalampi, K., Hintikka, J., Laukkanen, E., & Viinamäki, J. L. H. (2001). Alexithymia and Depression: A Prospective Study of Patients With Major Depressive Disorder. Psychosomatics, 42(3), 229–234.

[304] Förster, K., Enneking, V., Dohm, K., Redlich, R., Meinert, S., Geisler, A. I., Leehr, E. J., Kugel, H., Baune, B. T., Arolt, V., Zwitserlood, P., Grotegerd, D., & Dannlowski, U. (2020). Brain structural correlates of alexithymia in patients with major depressive disorder. *Journal of Psychiatry and Neuroscience, 45*(2), 117–124.

[305] Surguladze, S., Brammer, M. J., Keedwell, P., Giampietro, V., Young, A. W., Travis, M. J., Williams, S. C. R., & Phillips, M. L. (2005). A differential pattern of neural response toward sad versus happy facial expressions in major depressive disorder. *Biological Psychiatry, 57*(3), 201–209.

[306] Ho, T. C., Zhang, S., Sacchet, M. D., Weng, H., Connolly, C. G., Henje Blom, E., Han, L. K. M., Mobayed, N. O., & Yang, T. T. (2016). Fusiform Gyrus Dysfunction is Associated with Perceptual Processing Efficiency to Emotional Faces in Adolescent Depression: A Model-Based Approach. *Frontiers in Psychology, 7*.

[307] Fusar-Poli, P., Placentino, A., Carletti, F., Landi, P., Allen, P., Surguladze, S., Benedetti, F., Abbamonte, M., Gasparotti, R., Barale, F., Perez, J., McGuire, P., & Politi,

P. (2009). Functional atlas of emotional faces processing: A voxel-based meta-analysis of 105 functional magnetic resonance imaging studies. *Journal of Psychiatry & Neuroscience: JPN, 34*(6), 418–432.

[308] Zinchenko, O., Yaple, Z. A., & Arsalidou, M. (2018). Brain Responses to Dynamic Facial Expressions: A Normative Meta-Analysis. *Frontiers in Human Neuroscience, 12*.

[309] Foland-Ross, L. C., & Gotlib, I. H. (2012). Cognitive and Neural Aspects of Information Processing in Major Depressive Disorder: An Integrative Perspective. *Frontiers in Psychology, 3*, 489.

[310] Taylor, S. F., & Liberzon, I. (2007). Neural correlates of emotion regulation in psychopathology. *Trends in Cognitive Sciences, 11*(10), 413–418.

[311] Park, I. S., Lee, N. J., & Rhyu, I. J. (2018). Roles of the Declive, Folium, and Tuber Cerebellar Vermian Lobules in Sportspeople. *Journal of Clinical Neurology (Seoul, Korea), 14*(1), 1–7.

[312] Jörntell, H. (2017). Cerebellar physiology: Links between microcircuitry properties and sensorimotor functions. *The Journal of Physiology, 595*(1), 11–27.

[313] Depping, M. S., Schmitgen, M. M., Bach, C., Listunova, L., Kienzle, J., Kubera, K. M., Roesch-Ely, D., & Wolf, R. C. (2020). Abnormal Cerebellar Volume in Patients with Remitted Major Depression with Persistent Cognitive Deficits. *The Cerebellum, 19*(6), 762–770.

[314] Depping, M. S., Schmitgen, M. M., Kubera, K. M., & Wolf, R. C. (2018). Cerebellar Contributions to Major Depression. *Frontiers in Psychiatry*, *9*.

[315] Du, M.-Y., Wu, Q.-Z., Yue, Q., Li, J., Liao, Y., Kuang, W.-H., Huang, X.-Q., Chan, R. C. K., Mechelli, A., & Gong, Q.-Y. (2012). Voxelwise meta-analysis of gray matter reduction in major depressive disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 36*(1), 11–16.

[316] Huang, K., Kang, Y., Wu, Z., Wang, Y., Cai, S., & Huang, L. (2021). Asymmetrical alterations of grey matter among psychiatric disorders: A systematic analysis by voxel-based activation likelihood estimation. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 110*, 110322.

[317] Arnone, D., McIntosh, A. M., Ebmeier, K. P., Munafò, M. R., & Anderson, I. M. (2012). Magnetic resonance imaging studies in unipolar depression: Systematic review and meta-regression analyses. *European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology, 22*(1), 1–16.

[318] Sheline, Y. I., Mittler, B. L., & Mintun, M. A. (2002). The hippocampus and depression. *European Psychiatry, 17*(S3), 300s–305s.

[319] Duman, R. S. (2004). Neural plasticity: Consequences of stress and actions of antidepressant treatment. *Dialogues in Clinical Neuroscience, 6*(2), 157–169.

[320] Frodl, T., Jäger, M., Smajstrlova, I., Born, C., Bottlender, R., Palladino, T., Reiser, M., Möller, H.-J., & Meisenzahl, E. M. (2008). Effect of hippocampal and amygdala volumes on clinical outcomes in major depression: A 3-year prospective magnetic resonance imaging study. *Journal of Psychiatry & Neuroscience : JPN, 33*(5), 423–430.

[321] Fogwe, L. A., Reddy, V., & Mesfin, F. B. (2022). *Neuroanatomy, Hippocampus*. Treasure Island (FL): StatPearls Publishing.

[322] Malykhin, N. V., Carter, R., Seres, P., & Coupland, N. J. (2010). Structural changes in the hippocampus in major depressive disorder: Contributions of disease and treatment. *Journal of Psychiatry & Neuroscience: JPN, 35*(5), 337–343.

[323] Delaveau, P., Jabourian, M., Lemogne, C., Guionnet, S., Bergouignan, L., & Fossati, P. (2011). Brain effects of antidepressants in major depression: A meta-analysis of emotional processing studies. *Journal of Affective Disorders, 130*(1), 66–74.

[324] Ma, Y. (2015). Neuropsychological mechanism underlying antidepressant effect: A systematic meta-analysis. *Molecular Psychiatry, 20*(3), 311–319.

[325] Balestri, M., Calati, R., Souery, D., Kautzky, A., Kasper, S., Montgomery, S., Zohar, J., Mendlewicz, J., & Serretti, A. (2016). Socio-demographic and clinical predictors of treatment resistant depression: A prospective European multicenter study. *Journal of Affective Disorders, 189*, 224–232.

[326] Phillips, J. L., Batten, L. A., Tremblay, P., Aldosary, F., & Blier, P. (2015). A Prospective, Longitudinal Study of the Effect of Remission on Cortical Thickness and Hippocampal Volume in Patients with Treatment-Resistant Depression. *The International Journal of Neuropsychopharmacology, 18*(8), pyv037.

[327] Costafreda, S. G., Chu, C., Ashburner, J., & Fu, C. H. Y. (2009). Prognostic and Diagnostic Potential of the Structural Neuroanatomy of Depression. *PLOS ONE, 4*(7), e6353.

[328] Li, C.-T., Lin, C.-P., Chou, K.-H., Chen, I.-Y., Hsieh, J.-C., Wu, C.-L., Lin, W.-C., & Su, T.-P. (2010). Structural and cognitive deficits in remitting and non-remitting recurrent depression: A voxel-based morphometric study. *NeuroImage, 50*(1), 347–356.

[329] Drevets, W. C., Savitz, J., & Trimble, M. (2008). The Subgenual Anterior Cingulate Cortex in Mood Disorders. *CNS Spectrums, 13*(8), 663–681.

[330] Miller, J. M., Oquendo, M. A., Ogden, R. T., Mann, J. J., & Parsey, R. V. (2008). Serotonin transporter binding as a possible predictor of one-year remission in major depressive disorder. *Journal of Psychiatric Research, 42*(14), 1137–1144.