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Review

Epigenetic and Mental Diseases: The Role of Psychotherapy

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Abstract: It is well known that mental illness is often the result of genetic susceptibility combined with environmental factors. In this context, it is useful to consider the role that changes in DNA expression, known as epigenetic, can play in the development and progression of psychiatric disorders. Accordingly, psychotherapy, a form of pharmacological strategy that often targets dysfunctional emotions and behaviors, may also improve the symptoms of mental illness via epigenetic changes. This article reviews the current literature on epigenetic changes induced by psychotherapy in psychiatric disorders, pointing out encouraging findings for borderline personality disorder (BPD), post-traumatic stress disorder (PTSD), anxiety disorders and obsessive–compulsive disorder (OCD). It focuses on genes that are more commonly associated with epigenetic changes and paves the way for further research.

Keywords: epigenetic; psychotherapy; PTSD; OCD; BPD; anxiety

1. Introduction

It is known that psychiatric illnesses have a genetic basis. Meanwhile, genes usually interact with environmental elements such as poverty, migration, alcohol consumption, microbiota and stress factors such as the activation of the hypothalamic–pituitary–adrenal axis, which are epigenetic factors [1]. In addition, links between a specific epigenetic change, such as DNA methylation, and an increased risk of mental illness have been established. In particular, schizophrenia and depression [2] have been linked to the methylation of genes involved in neuronal, neuroendocrine and immunological processes [3]. This gene methylation, in turn, has been reported as a useful biomarker for treatment-resistant schizophrenia [4]. Specifically, histone acetylation and microRNAS (miRNAS) have been associated with schizophrenia, and it has been suggested that interventions altering the gut microbiota through novel prebiotics may be as helpful to patients as other pharmacological interventions [5]. The modulatory role of epigenetics has also been noted in other mental diseases, such as autism spectrum disorder [6–8], BPD [9], PTSD [10], alcohol consumption and dependence [11], OCD [12] and attention deficit hyperactivity disorder [13]. In this framework, psychotherapy seems to exert a significant role in the epigenetics of mental diseases [14,15]. In this review, two main forms of psychotherapy are discussed: cognitive behavioral therapy (CBT) and dialectical behavior therapy (DBT). CBT consists of behavioral interventions to reduce dysfunctional emotions and behaviors. To achieve this result, therapists work on individual appraisals and thinking patterns with the aim of altering behaviors themselves or modifying cognitive alterations. CBT is often employed for the treatment of psychiatric diseases such as depression, psychosis and suicidal ideation [16–18].

DBT is instead a psychotherapeutic approach moving from a dialectical philosophy that aims to target the whole emotion system, coping, distress and social skills of the patients by considering not only individuals' behaviors but also the environmental context external to the patient [15,19]. A recent review pointed out that psychotherapy, as well as environmental stimuli, can play an important role in the epigenetic development of mental diseases [20]. A potential epigenetic effect of CBT was suggested by Bleker et al.

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(2020), who reported changes in DNA methylation levels in children whose mothers had been administered CBT in the antenatal period [14]. Promising results also came from DBT in the epigenetics of BPD, where DBT seems to reduce amygdala activation after negative stimuli [15].

Starting from these premises, the aim of this study is to review the existing literature on the role of psychotherapy in DNA changes underlying mental disorders.

2. Results

In our search and after-study selection, we came across psychotherapy and epigenetic modification of the following disorders: BPD, PTSD, anxiety, mood disorders and OCD. In each paragraph, we will report the effects of psychotherapy on the epigenetics of the above-mentioned diseases, making a brief mention of the main implicated genes' functions.

2.1. Psychotherapy and the Epigenetics of BPD

The main genes implicated in the epigenetic effect of psychotherapy in borderline personality disorder are *BDNF* [21], *APBA3* [22], *MCF2* [22] and *FKBP5* [23].

2.1.1. BDNF

Brain-derived neurotrophic factor (BDNF) encodes for neurotrophins, members of the family of growth factors. It is crucial for apoptosis, neuronal differentiation, the outgrowth of neurites, cell survival and synaptic strengthening [24]. Perroud and colleagues examined 115 subjects with BPD and 52 controls who underwent intensive dialectical behavior therapy (I-DBT) for 4 weeks. Participants had their *BDNF* methylation levels assessed at baseline and at the end of the treatment. The results showed that the BPD subjects had a significantly higher methylation status in both *CpG* regions than the controls, which in turn was positively correlated with a higher number of childhood traumas. Equally, higher *BDNF* methylation levels were found in maltreated children. When analyzing the role of I-DBT in BPD, *BDNF* methylation increased after the treatment, but this change was not associated with the response to I-DBT. In fact, the respondents presented lower DNA methylation levels over time. Furthermore, changes in methylation were positively correlated with depression scores, hopelessness scores and impulsivity. The authors concluded that psychotherapeutic approaches may modify the epigenetic markers of diseases and, in turn, cognitive functions [21].

2.1.2. *APBA3* and *MCF2*

APBA3 is a gene encoding for an amyloid beta A4 precursor protein-binding family A member, a protein involved in signal transduction processes and purported to be implicated in Alzheimer's disease [25]. *MCF2* encodes for the DBL proto-oncogene protein. Murine models showed that this gene was expressed not only in the brain but also in the kidneys, intestines and testes. Additionally, it is implicated in different cellular signaling pathways [26].

APBA3 and *MCF2* have been reported to be potential biomarkers of the DBT outcome in people with BPD, as suggested by a study carried out in 44 BPD individuals and 44 matched controls analyzed for DNA methylation of these genes. Even if significant DNA methylation differences emerged between the patients and controls, the authors reported higher levels of *APB3* and *MCF2* methylation in patients responding to DBT therapy compared to the controls [22].

2.1.3. *FKBP5*

FKBP5 encodes for FK506, a glucocorticoid receptor co-chaperone whose levels are increased after stress exposure. In addition, the ability of the glucocorticoid receptor to bind cortisol and to translocate into the nucleus is down-regulated by FK506, thus exerting negative feedback for glucocorticoid receptor (*NR3C1*) activation, a gene implicated in stress responses [27,28].

FKBP5 methylation seems to be significantly associated with psychotherapy in BPD. A pilot study by Quevedo et al. (2022) examined 11 females with BPD for changes in peripheral DNA methylation of *FKBP5* at 0, 3 and 6 months after psychotherapeutic treatment. It was found that only responders to psychotherapy who had early trauma showed lower levels of *FKBP5* methylation, thus suggesting the presence of a specific molecular mechanism of recovery that justifies these specific epigenetic changes [23] (Table 1).

Table 1. Psychotherapy and epigenetics of BPD.

REFERENCE	SAMPLE	INTERVENTION	GENES ASSESSED	PSYCHIATRIC SCALES	MAIN FINDINGS
[21]	115 individuals with BPD (M = 7, F = 108, mean age = 30.36 ± 9.19 years) and 52 controls (M = 28, F = 24, mean age = 40.65 ± 12.04 years).	Patients underwent DBT consisting of daily group and individual therapy for 4 weeks.	*BDNF* methylation levels were collected 1 week before the intervention and on the last day of DBT	BDI-II was used to assess severity of depression, the BHS the degree of pessimism and negativity about the future, the BIS-10 impulsivity, the CTQ traumatic childhood experiences.	BPD subjects had a significantly higher methylation status in both *CpG* regions than the controls ($p < 0.05$); maltreated children had higher *BDNF* methylation levels than the controls ($p = 0.05$); *BDNF* methylation increased after the treatment.
[22]	44 BPD individuals (M = 7, F = 37, mean age = 29.5 ± 8,4 years) and 44 matched controls (M = 37, F = 7, mean age = 29.7 ± 8.8 years)	Participants underwent DBT for 12 weeks.	*APBA3* and *MCF2* methylation levels	Participants were assessed using the CTQ for traumatic experiences, the SCL90 for global severity of their symptoms and the BLS23 for borderline symptoms.	Higher levels of *APB3* ($p = 0.04$) and *MCF2* ($p = 0.003$) methylation were detected in patients responding to DBT therapy compared to the controls.
[23]	11 females with BPD (mean age = 16.77 ± 1.64 year)	Participants underwent psychodynamic orientation psychotherapy (N = 3) and DBT (N = 8), globally lasting 6 months.	*FKPB5* methylation levels was assessed at 0, 3 and 6 months	Childhood trauma was assessed by CTQ; attachment patterns by the AAQ; Affective symptoms were assessed by the Y-OQ-SR, DERS, BDI-I and BSL-23.	Lower levels of *FKBP5* methylation were only found in responders to psychotherapy with moderate to severe early trauma in childhood ($p = 0.04$).

Abbreviations: DBT: dialectical behavior therapy; BDI-II: Beck Depression Inventory II; BHS: the Hopelessness Scale; BIS-10: the Barrat Impulsiveness Scale; CTQ: Childhood Trauma Questionnaire; p: p-value; AAQ: Attachment Adolescent Questionnaire; DERS: Difficulties in Emotion Regulation Scale; BDI-I: Beck Depression Inventory-I; BLS-23: Borderline Symptom List-23; SCL-90-R: Symptom Checklist SCL-90-R Questionnaire.

2.2. Psychotherapy and the Epigenetics of PTSD

The main genes implicated in the epigenetic effect of psychotherapy in PTSD are *ZFP57* [29], *NR3C1* [30], *FKBP5* [31], *NR4A*] [3], *AUTS2* [3] and *TFAM* [3].

2.2.1. *ZFP57*

Zinc finger transcription factor (*ZFP57*) is a gene expressed very early in embryogenesis and deregulated upon the differentiation of embryonic stem cells [32] and is also involved in imprinted establishment [33]; thus, alterations in *ZFP57* expression could have important effects on regular embryo neurodevelopment [34].

A study conducted in soldiers who achieved or did not achieve remission from PTSD examined changes in the genome-wide DNA methylation levels in their blood to find differentially methylated regions (DMRs) 6–8 months after trauma-focused psychotherapy. In addition, the authors enrolled a group of traumatized military controls and screened 85 soldiers for 12 different DMRs of the *APOB*, *MUC4*, *EDN2*, *ZFP57*, *GPX6*, *CFAP45*, *AFF3*, *TP73*, *UBCLP1* and *RPL13P* genes and indicated that *ZFP57* changes in methylation were related to differences in PTSD symptoms. Meanwhile, psychotherapy appeared to increase *ZFP57* methylation independently of symptom reduction. This sheds new

light on candidate genomic regions potentially relevant to the etiology and treatment of stress-related disorders such as PTSD [29].

2.2.2. *NR3C1* and *FKBP5*

NR3C1, also known as the glucocorticoid receptor gene, is involved in hypothalamic–pituitary axis responses, as well as in reactivity to stress [35], and has been implicated in epigenetic alterations leading to neurobehavioral and mental health outcomes [36].

Wilker and colleagues investigated the effects of narrative exposure therapy on *NR3C1* methylation in 153 survivors from Northern Uganda with PTSD. Patients were assessed before treatment and 4 and 10 months after the completion of treatment and had their salivary DNA analyzed for methylation changes at 38 *CpG* sites via *NR3C1* at the three measurement time points. A negative correlation was found between DNA methylation at the *CpG* site *cg25535999* and PTSD symptoms. Thus, a significant increase in DNA methylation was observed after narrative exposure therapy (NET), with lower methylation before treatment predicting a greater improvement in symptoms [30].

Similarly, work carried out in 16 veterans with PTSD investigated the epigenetic biomarkers of improvement after psychotherapy. Participants were investigated in terms of the relationship between cytosine methylation of their *NR3C1* and *FKBP51* genes. A group of veterans who responded to prolonged exposure (PE) psychotherapy and another group of non-responders had their blood drawn before treatment and 4 and 10 months after the completion of treatment and their lymphocyte DNA extracted to assess *NR3C1* and *FKBP5* methylation. It was found that despite no significant alteration, the psychotherapy outcome pre-treatment was predicted by the methylation of the GR gene (*NR3C1*) exon 1F promoter. Moreover, the authors pointed out a subset of participants in which a higher expression of *FKBP5* was registered in treatment responders compared to non-responders, concluding that epigenetic state may be influenced by psychotherapy [31].

2.2.3. *NR4A2*, *AUTS2* and *TFAM*

NR4A2 encodes for a nuclear receptor and transcriptional factor playing an important role in the maintenance of the dopaminergic neurons. NR4A2, in fact, regulates the expression of genes implicated in dopamine synthesis and catabolism [37]. *AUTS2* encodes for a transcriptional factor which regulates neuronal gene expression, migration and neurite extension [38] and has also been implicated in behavioral processing underlying substance abuse [39]. *TFAM* encodes for a member of the mitochondrial transcription initiation complex that plays a central role in the repairment and replication of the mitochondria and consequently in supporting neuronal processes [40].

It is worth reporting a study investigating the epigenetic signatures of psychotherapy for PTSD and appetitive aggression symptoms (AAS) in South African men with chronic trauma exposure. The participants were divided into three distinct groups based on the treatment received, narrative exposure therapy for the rehabilitation of offenders (FORNET), cognitive behavioral therapy (CBT) and a waitlist control group receiving no treatment, and had their DNA analyzed for methylation in 22 gene promoter regions. The FORNET group showed a lower severity of symptoms of PTSD and AAS behavior at 8 and 16 months compared to the baseline. Specifically, the participants in the FORNET group were found to have increased methylation of *NR4A2* and *AUTS2*. In addition, *TFAM* methylation appears to be positively correlated with AAS [3] (Table 2).

Table 2. Psychotherapy and epigenetics of PTSD.

REFERENCE	SAMPLE	INTERVENTION	GENES ASSESSED	PSYCHIATRIC SCALES	MAIN FINDINGS
[29]	21 soldiers who obtained remission from PTSD (mean age = 34.7 ± 9.3 years) and 23 who did not achieve remission (mean age = 40.8 ± 9.1 years) + 23 traumatized military controls (mean age = 38.03 ± 10.70 years)	Participants underwent trauma-focused psychotherapy for 6–8 months.	DNA methylation levels of *APOB*, *MUC4*, *EDN2*, *ZFP57*, *GPX6*, *CFAP45*, *AFF3*, *TP73*, *UBCLP1* and *RPL13P* were assessed 6–8 months after treatment.	Diagnosis and PTSD severity were assessed by the CAPS while PTSD symptoms over the previous 4 weeks by the SRIP.	Differences in PTSD symptoms were related to *ZFP57* changes in methylation; psychotherapy increased *ZFP57* methylation independently of symptom reduction ($p = 0.001$).
[30]	153 individuals (M = 55, F = 98, mean age= 32.45 ± 8.77 years) with PTSD	Participants underwent 12 sessions of narrative exposure therapy. Each session lasted about 1–2 h.	Methylation of *NR3C1* was assessed before treatment and 4 and 10 months after the completion of treatment.	PTSD symptoms were assessed by the PDS and depressive symptoms by the HSCL	Lower DNA methylation before treatment predicted greater improvements in symptoms ($p = 0.003$); after treatment, an increase in *NR3C1* methylation was registered.
[31]	A group of Veterans who responded (N= 8, mean age= 41.25 ± 17.82 years) to PE psychotherapy and another group of non responders (N= 8, mean age = 57.88 ± 7.45 years)	Participants underwent PE and MA psychotherapy for 12 weeks.	*NR3C1* and *FKBP51* methylation levels were assessed at pre-treatment, after 12 weeks of psychotherapy (post-treatment) and after a 3-month follow-up.	Symptom severity of PTSD was assessed by the CAPS; self-report PTSD symptoms by the PSS-SR; early trauma by the CTQ; military and civilian life events pre- and post-deployment by the DRRI.	Methylation of the GR gene (*NR3C1*) exon 1F promoter predicted the psychotherapy outcome at pre-treatment. In a subset of participants, higher expression of *FKBP5* was registered in treatment responders compared to non-responders ($p < 0.05$).
[3]	A group receiving forensic offender rehabilitation (N = 10), another cognitive behavioral therapy group (N = 10) and a control group (N = 9).	Participants were administered CBT, conducted at several three-week camps, each hosting twelve to fourteen participants.	DNA methylation levels were assessed.	PTSD symptoms were assessed by the PSSI, desire to commit violent acts by the AAS and trauma exposure at baseline and 8- and 16-month follow-up by the CECV.	Increased methylation of *NR4A* and *AUTS2* was found in the group receiving narrative exposure therapy; *TFAM* methylation positively correlated with AAS. ($p < 0.05$)

Abbreviations= PTSD: post-traumatic stress disorder; CAPS: Clinician-Administered PTSD Scale-IV; SRIP: 22-item Self-Report Inventory for PTSD; PE: prolonged exposure; MA: minimal attention; PSS-SR: PTSD Symptom Scale—Self-Report Version; CTQ: Childhood Trauma Questionnaire; DRRI: Deployment Risk and Resiliency Inventory; p: p-value; PSSI: DSM-5 Posttraumatic Stress Symptom Interview; PHQ-9: Patient Health Questionnaire-9; AAS: Appetitive Aggression Symptoms; CECV: Childhood Exposure to Community Violence Checklist; PDS: Posttraumatic Diagnostic Scale; HSCL: Hopkins Symptom Checklist.

2.3. Psychotherapy and the Epigenetics of Anxiety and Mood Disorders

FKBP5 [41,42], *MAOA* [43], *5-HTTLPR* [44], *HTR3A* [45] and *ARG1* [45] are the main genes involved in epigenetic modifications induced by psychotherapy in anxiety and mood disorders.

2.3.1. *FKBP5*

In analyzing the role of psychotherapy in epigenetic anxiety disorders, a study by Roberts and colleagues found the hypothalamic–pituitary–adrenal (HPA) axis to be crucial for stress-related psychiatric diseases, as well as for anxiety disorders. Of a group of 98 individuals, a subset had their DNA methylation at the *FKBP5* and *GR* promoter regions measured before and after CBT. The results showed that treatment response were positively correlated with changes in *FKBP5* DNA methylation. Specifically, the higher the reduction in symptom severity, the greater the decrease in DNA methylation was, thus shedding light

on the association between DNA methylation changes and the response to psychological therapies [41]. Another study examining *FKPB* in psychotherapy for anxiety disorder was carried out in 111 individuals who received exposure-based cognitive behavioral therapy (CBT) for agoraphobia with or without panic disorder or specific phobias and had their DNA measured for the methylation levels of the promoter region and intron 7 of *FKBP5*. It was found that there was an association between the reduction in the severity of the diseases and the change in the percentage of DNA methylation at one *CpG* site of intron 7; specifically, a greater response to therapy was negative correlated with DNA methylation [42].

2.3.2. *MAOA*

Monoamine oxidase A (*MAOA*) encodes for an enzyme implicated in the degradation of biogenic amines such as serotonin and dopamine and is supposed to play an important role in panic disorders (PDs) [46].

Hypomethylation of *MAOA* has been implicated in the epigenetic effect of psychotherapy on panic disorder. To examine the epigenetic processes underlying fear extinction after psychotherapy, a study was carried out in 28 females with PDs and in 28 healthy controls assessed for *MAOA* methylation at baseline and after 6 weeks of CBT. Lower *MAOA* methylation was found at the baseline in females with panic disorder compared with the healthy controls. In addition, the CBT responders had higher levels of *MAOA* methylation, while non-responders had lower levels of gene methylation. Altogether, these findings pointed out *MAOA* hypomethylation as a risk marker for panic diseases, as well as the reversibility of *MAOA* hypomethylation as a potential epigenetic correlate of the response to CBT [43].

2.3.3. *5-HTTLPR*, *HTR3A* and *ARG1*

The serotonin 5-hydroxytriptamine (5-HT) transporter (5-HTT) gene-linked polymorphic region (*5-HTTLPR*) is a variable number of tandem repeats (VNTR) located in the promoter region of the human *5-HTT*-encoding gene *SLC6A4*. Variants in *SLC6A4* expression have been related to different neuropsychiatric diseases [47]. *HTR3A* encodes for a subunit of the serotonin 3 receptors (5-HT3s), ligand-gated channel receptors associated with learning, memory and emotions [48]. *ARG1* encodes for an enzyme, arginase 1, that converts the amino acid arginine into ornithine and urea [49]. It is expressed not only in peripheral tissues but also in the brain, thus regulating different neuronal processes [50].

Schiele and colleagues conducted a meta-analysis examining the therapy–genetic effects of the gene *5-HTTLPR* in moderating the response to CBT. The *5-HTTLPR* gene was examined in patients with primary anxiety disorders, and it was concluded that there is insufficient evidence to date that the gene plays a moderating role in the response to CBT [44]. In this framework, Moser et al. (2022) investigated the DNA methylation and immune cell type composition of patients with panic disorder during CBT and therapeutic exposure interventions to clarify possible biomarkers of treatment success. DNA methylation and the composition of the immune cell types during CBT and therapeutic exposure interventions were investigated to decipher their biological correlates and identify possible biomarkers for treatment success. A specific gene sequence, *cg01586609*, located in a *CpG* island and annotated to serotonin receptor 3 A (*HTR3A*), was found to be differentially methylated during anxiety exposure and between remitters and non-remitters, and *cg01699630*, annotated to *ARG1*, underwent long-lasting methylation changes during therapy. Overall, the results supported the association between long-term CBT and changes in serotonin receptor 3 A methylation and expression during anxiety exposure, with the latter as a possible marker of treatment success [45].

A review by Uher (2011) suggested that different genetic polymorphisms could influence responses to psychotherapy in depressive disorders. Particularly, epigenetic mechanisms such as DNA methylation may be mediated by environmental exposures in early life, including childhood maltreatment, as well as by pharmacological and psychological treat-

ments. Meanwhile, studies conducted on animal models pointed out that environmental stressor impacts may be modified by epigenetic interventions [51] (Table 3).

Table 3. Psychotherapy and epigenetics of anxiety diseases.

REFERENCE	SAMPLE	INTERVENTION	GENES ASSESSED	PSYCHIATRIC SCALES	MAIN FINDINGS
[41]	From 1152 individuals (M = 568, F = 584, mean age = 9.8 years, age range = 5–18 years), a group of 98 participants was selected for DNA analysis	Participants underwent 16 sessions of CBT over 12 weeks.	Polymorphisms of *FKBP5* and *GR* were analyzed in a subset of 98 individuals before and after CBT	Anxiety was assessed by the ADIS-IV-C/P before and after treatment and at follow-up (3, 6 or 12 months after the conclusion of treatment).	Reduction in symptom severity was negatively correlated with *FKBP5* DNA methylation level ($p < 0.05$)
[42]	111 individuals (age range = 19–68 years, F = 75, M = 36)	Participants underwent one of four exposure therapy or exposure-based-CBT programs for about 14 months.	Methylation of *FKBP5* was assessed	CGI-S scale was used to assess clinical outcome.	Greater response to therapy was negative correlated with DNA methylation ($p < 0.05$)
[43]	28 females (mean age= 34.57 ± 8.51 years) with PD and 28 healthy controls (mean age= 34.96 ± 9.02 years)	Participants were administered CBT consisting of six semi-standardized sessions over 6 weeks.	*MAO-A* methylation was assessed at baseline and after 6 weeks of CBT	CAPI-WHO-CIDI was used for diagnosis.	Patients showed lower *MAOA* methylation than controls; higher levels of methylation were also found in CBT responders compared with non-responders ($p = 0.01$)
[45]	42 patients (M = 15, F = 27, mean age of 32 ± 10 years) with anxiety disorder	Participants were administered 12 sessions of CBT over 6–8 weeks at baseline and 2 booster sessions after 2 and 4 months of treatment.	Methylation level of *HTR3A* was detected	Panic diagnosis and anxiety level were, respectively, assessed by the DSM-IV and the HARS.	Long-term CBT was associated with changes in *HTR3A* methylation and expression during anxiety exposure ($p < 0.05$)

Abbreviations: CBT: cognitive behavioral therapy; ADIS-IV-C/P: Anxiety Disorders Interview Schedule for DSM-IV; *p*: *p*-value; CGI-S: Clinical Global Impression Severity; PD: panic disorder; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; CAPI-WHO-CIDI: standardized computer-administered face-to-face interview; HARS: Hamilton Anxiety Rating Scale.

2.4. Psychotherapy and the Epigenetics of OCD

We report three genes being involved in the epigenetics of psychotherapy in OCD: *MAOA* [52], *OXTR* [53] and *SLC6A4* [54].

2.4.1. *MAOA*

Schiele and colleagues assessed 12 women with untreated obsessive–compulsive disorder and 14 age- and sex-matched healthy controls for *MAOA* promoter methylation at baseline and after 8 to 10 weeks of semi-standardized, obsessive–compulsive–specific cognitive behavioral therapy. Methylation at the *MAOA* site was found to correlate with a decrease in OCD symptoms and severity [52].

2.4.2. *OXTR*

Oxytocin receptor *(OXTR)* is a gene associated with individual differences in social and emotional abilities, as well as the genesis of psychopathology. In addition, it has been reported that its effects are both direct and mediated by the environment [55], thus opening avenues for epigenetic modifications of the gene induced by psychotherapy [56].

A study conducted on 113 inpatients with OCD and 113 age- and sex-matched healthy controls who underwent OCD-specific cognitive behavioral psychotherapy analyzed their *OXTR* exon III methylation levels. It was found that *OXTR* hypermethylation was associated with a poorer response to psychotherapy for compulsions but not for obsessions [53].

2.4.3. *SLC6A4*

Schiele and colleagues investigated 112 patients (M = 55, F = 57, mean age = 34.31 ± 11.57 years) with primary OCD who underwent OCD-specific cognitive behavioral treatment. Participants had their *SLC6A4* promoter methylation levels measured at baseline. The authors found that a lower treatment response was predicted by lower baseline *SLC6A4* promoter methylation levels, thus shedding new light on *SLC6A4* methylation's role as a potential biomarker in predicting medical changes by psychotherapy treatment [54] (Table 4).

Table 4. Psychotherapy and epigenetics of OCD.

REFERENCE	SAMPLE	INTERVENTION	GENES ASSESSED	PSYCHIATRIC SCALES	MAIN FINDINGS
[52]	12 women (mean age = 33.71 ± 12.60 years) with untreated obsessive–compulsive disorder and 14 age- and sex-matched healthy controls (mean age = 33.0 ± 11.2 years)	Participants were administered 8 to 10 weeks of CBT, including psychoeducation, exposure and response prevention/management	*MAOA* promoter methylation was assessed at baseline and after 8 and 10 weeks of CBT	OCD severity was evaluated by the Y-BOCS	Levels of *MAOA* methylation correlated with a decrease in Y-BOCS score ($p = 0.046$)
[53]	113 inpatients with OCD (M = 56, F = 57, mean age = 34.31 ± 11.57 years) and 113 age- and sex-matched healthy controls (M = 56, F = 57, mean age: 33.63 ± 10.12 years)	Participants were administered 8- to 10-week semi-standardized CBT comprising psychoeducation, exposure and response prevention/management	*OXTR exon III* methylation levels were analyzed at baseline and after treatment phases I and II	Participants were assessed by the Y-BOCS at baseline and after 10 weeks of treatment.	*OXTR* hypermethylation was associated with a poorer response to psychotherapy for compulsions but not for obsession ($p < 0.05$)
[54]	112 patients (M = 55, F = 57, mean age = 34.31 ± 11.57 years) with OCD	Participants were administered OCD-specific CBT for about 8 months	*SLC6A4* promoter methylation levels were assessed at baseline	OCD severity was assessed by the Y-BOCS at baseline and before and after the in vivo exposure phase	*SLC6A4* promoter methylation levels predicted a lower treatment response ($p = 0.02$)

Abbreviations: CBT: cognitive behavioral therapy; OCD: obsessive–compulsive disorder; Y-BOCS: Yale–Brown Obsessive–Compulsive Scale; *p*: *p*-value.

3. Discussion

Our work addresses the role of psychotherapy in epigenetics and, specifically, in DNA methylation. Four disorders in particular have been reported to benefit significantly from the epigenetic effect of psychotherapy: BPD, PTSD, anxiety and OCD.

In the epigenetics of borderline personality disorder, the role of psychotherapy has been referred to in terms of its capacity to modulate *BDNF* [21], *APBA3* [22], *MCF2* [22] and *FKPB* expression [23].

Regarding PTSD, it has been studied in soldiers [29] and in survivors of war situations [30], with *NR3C1*, *FKBP5*, *NR4A*, *AUTS2* and *TFAM* among the main genes involved. Accordingly, Yang et al. (2021) identified the methylation of *FKBP5* as a good clinical biomarker for predicting clinical recovery in PTSD and potential applications of treatment effects [57]. Similarly, epigenetic changes in *NR3C1* and *FKBP5* seem to be associated with hypocortisolemic patterns in PTSD that may be ameliorated by trauma-focused cognitive behavioral therapy (TF-CBT) [58]. In keeping with these results, a study carried out in children and individuals chronically exposed to traumatic experiences identified 62 genes associated with both clinical/social outcomes and treatment, emphasizing that gene regulatory processes involved in memory formation, as well as changes in the glucocorticoid and aldosterone systems, can be altered by NET [59]. These findings confirm previous literature on the role of psychoanalysis in attenuating psychological trauma through epigenetic modifications of DNA [60], as well as the importance of trauma-focused psychotherapy for treatment-resistant depression [61]. Consistent with these findings,

Post and Kegan reported the good effects of cognitive behavioral therapy in reversing the recurrence of affective episodes, anxiety and drug abuse related to PTSD [62]. Despite this body of evidence, some authors have pointed out the need for more studies regarding the potential epigenetic and transgenerational effects of dialectical behavior therapy on PTSD symptoms in specific conditions, such as pregnancy [63].

About anxiety disorders, encouraging results supported epigenetic modifications in the *5-HTTLPR* and *ARG1* genes and in the sequence *cg01586609*, which is located in a *CpG* island of serotonin receptor 3 A (HTR3A) [45].

When dealing with OCD, there is evidence for the role of *MAOA* hypomethylation [52] and *OXTR* [53] and *SLC6A4* promoter methylation [54] in predicting the response to psychotherapy.

By and large, our results are in line with other existing literature dealing with the role of psychotherapy in the epigenetics of mental illness. Indeed, Piotrkowicz et al. (2021) analyzed individuals with borderline personality disorder, major depression, anorexia nervosa, bulimia nervosa and post-traumatic stress disorder who underwent psychotherapy and showed a decrease in *BDNF* methylation after treatment [64]. In addition, encouraging results have also been reported on the effects of cognitive remediation on DNA methylation and brain connectivity changes in schizophrenia [65], also in the framework of a bio-psychosocial–behavioral treatment model [66]. Meanwhile, Castro-Vale and Carvalho (2020) supported the HPA axis's central role as a useful biomarker to assess the response to psychotherapy in post-traumatic stress disorder (PTSD) [67].

Recently, growing literature has focused on the connection between changes in epigenetics and brain function in relation to neuropsychiatric disorders. Particularly, some authors have suggested the role of electrical stimulation, a form of brain stimulation based on an electric field, in DNA demethylation of the retinal ganglion cells in murine models [68]. Additionally, Trenado et al. (2023) presented focus ultrasound (FU), a technology employing sound waves to target brain regions with specificity and without the need for incision and radiation, as a promising treatment for mental diseases [69].

This work has several limitations. First, most of the studies reported on PTSD were conducted on soldiers, veterans or people living in war situations. Therefore, it is not clear whether our findings on psychotherapy for PTSD are applicable in other contexts. Second, this study is based on the currently available literature, which is limited to four main disorders, namely BPD, anxiety, PTSD and OCD. Third, the reported studies generally had only a few participants, with a global prevalence of females. Fourth, from the studies discussed, as well as from the literature, a clear consensus about the role of the psychotherapy duration or demographic variables in the treatment response did not emerge. According to the works analyzed in this review, for BPD, the duration of treatment ranged from about 1 to 6 months, for PTSD, from about 3 to 8 months, and for anxiety disorders, from 3 to 14 months, and for OCD, two studies pointed out the effectiveness of CBT for 8–10 weeks.

If considering demographic influences on the psychotherapy response, all the studies discussed in this work showed a female prevalence, particularly for BPD, thus not allowing for appropriate gender differences in the treatment response. For age, no definite correlation was pointed out between the age of the participants and their response to treatment. It is noteworthy that the participants' ages differed among the groups of diseases, with significant variability even within the same group. Fifth, a large part of the studies discussed were conducted in western countries, making it difficult to generalize the results to different people from other parts of the world. Sixth, for OCD, the works discussed were carried out only by a single group of authors, with the participants undergoing only CBT; consequently, it has not been possible to make comparisons with other researchers' findings, as well as with other psychotherapeutic approaches.

However, there are also some strengths. First, the papers reviewed usually not only reported the names of the genes but sometimes also the exact gene locus affected by the epigenetic alteration. Second, different forms of psychotherapies involved in epigenetics

were proposed, not just one form. Finally, the age of the participating individuals shows a wide range, from 5 to 65 years.

Globally, even if promising findings have been shown, according to our opinion, other points should be taken into account to better investigate the role of psychotherapy in the epigenetics of mental diseases, as well as to drive future research: (1) extending research to other countries and to people with different lifestyles and in different professional situations; (2) analyzing more psychiatric conditions, including, for example, psychotic, mood and neurodevelopmental disorders; (3) stating criteria for the therapeutic duration; and (4) making the demographic characteristics more homogeneous among groups. Meanwhile, defining guidelines for standard diagnostic and therapeutic protocols is surely urgent, not only to help clinicians make more accurate diagnoses but also to establish a proper treatment, considering the contribution of epigenetics to the response to psychotherapy.

4. Materials and Methods

To find the existing literature dealing with epigenetic changes caused by psychotherapy in mental disorders, we conducted a literature search using mainly the "PubMed" database. We specifically focused on works dealing with the role of psychotherapy in the epigenetics of mental diseases. The keywords used were "epigenetic", "psychotherapy", "mental illness", "mood disorders", "anxiety", "psychotic disorders", "schizophrenia", "PTSD", "ADHD", "ASD", "OCD", "personality disorders" and "substance use disorders". The inclusion criteria were (1) based on the type of article, original research, reviews, meta-analyses and short communications were included; (2) studies carried out in humans and (3) works written in English. The exclusion criteria were (1) works not specifically regarding the role of psychotherapy as an epigenetic modulator of mental diseases; (2) articles not written in English and (3) studies carried out in animals. We conducted our search from February 2024 to April 2024.

5. Conclusions

In this paper, we have specifically investigated the ability of psychotherapy to modulate epigenetic changes in DNA, pointing to promising results for BPD, PTSD, anxiety disorders and OCD. As only a limited amount of literature is available so far, further studies are needed to shed new light on the potential role of psychotherapy in epigenetic changes underlying various mental disorders.

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