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# THESIS
# MENTALIZATION AND EPIGENETIC CHANGES IN PSYCHOTHERAPY OF ADOLESCENTS DIAGNOSED WITH BORDERLINE PERSONALITY DISORDER

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*To María José and Amalia with whom I started, and to Augusto and Ramón who joined our family in the course of this venture.*

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## 3. SUMMARY

Genetic and early environmental factors are interwoven in the etiopathogenesis of Borderline Personality Disorder (BPD). Epigenetic mechanisms, allow the molecular machinery to adapt to environmental conditions. There are gaps in the knowledge of how epigenetic mechanisms are involved in the effects of early affective environment, development of BPD and psychotherapy response. This work aims to explore changes in DNA methylation of *FKBP5* gene, which encodes for a stress response protein, in relation to psychotherapy, on symptomatology and underlying psychological processes in a sample of 11 female adolescents diagnosed with BPD. For this purpose, measures of early trauma, borderline and depressive symptoms, psychotherapy outcome, mentalization and emotional regulation were studied longitudinally at baseline, 3 and 6 months. Percentage DNA methylation levels of *FKBP5* gene intron 7 were measured at the same times.

A significant reduction of borderline and depressive symptoms was found. No significant change was observed in emotional regulation and mentalization.

A reduction in the average DNA methylation was observed over time. Additionally, it was observed that this decrease in methylation occurred only in those individuals who reported the presence of early trauma and responded to psychotherapy.

The results support an effect of psychotherapy on epigenetic mechanisms associated with the stress response, specifically DNA methylation of *FKBP5*, which is concordant with previous studies in other phenotypes. The fact that the epigenetic change occurred only in the presence of early trauma is suggestive of a specific molecular mechanism of recovery.

The results should be taken with caution given the small sample size. Further research is needed to include covariates that modify DNA methylation and incorporate endocrinological markers and therapeutic process variables.

Psychotherapy focused on personality pathology could lead to changes in DNA methylation causing permanent reprogramming of phenotypic adaptation to the interpersonal environment.

## 2. INTRODUCTION

Borderline Personality Disorder (BPD) is a mental disorder characterized by a general pattern of instability in affect regulation, impulse control, interpersonal relationships and self-image. The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) study in the United States reports a lifetime prevalence between 2.7% and 5.9% (Tomko et al., 2014). Moreover, this may increase up to 10% in the case of outpatient psychiatric patients, and between 15 and 25% in hospitalized patients (Leichsenring et al., 2011).

The prevalence and stability of BPD over time is relatively similar in adolescent and adults. Adolescents with the most severe symptoms tend to persist with the disorder during the whole adolescence period (Guilé et al., 2018) and present acute BPD symptomatology, such as suicidal ideation, impulsive behaviors, and non-suicidal self-injury (NSSI) (Stead et al., 2019), substance abuse and sexual risk taking behavior (i.e. unprotected sex) (Sharp & Fonagy, 2015). Additionally, adolescents with more severe BPD symptoms have impaired social functioning and lower academic and occupational achievement from mid-adolescence through mid-adulthood (Winograd, et al., 2008).

Given the implications of BPD diagnosis on the functioning and mental health of adolescents, a better understanding of the interplay between genetic and environmental factors that contribute to their symptomatic expression is highly needed.

The development of BPD pathology implies a complex ethiopathogenic trajectory in which genes that confer sensitivity to the environment, in the presence of adverse early life events, can lead to the development over time of the BPD phenotype or its underlying traits (Gunderson & Lyons-Ruth, 2008; Bulbena-Cabre et al., 2018). However, evidence of the underlying molecular mechanisms is in the early stages of research. Studies of association with candidate genes have not shown conclusive results despite the high heritability of the disorder (Calati et al., 2013; Amad et al., 2014).

Epigenetic processes are sensitive to environmental conditions and can operate as mechanisms that allow early environmental experiences to trigger phenotypic modifications without modifying the genotype (Weaver, 2007). A limited number of studies have shown relationships between epigenetic methylations patterns with the presence of childhood stress in BPD phenotype. The genes involved were related to stress response and neuroplasticity (Perroud et al., 2013; Martín-Blanco et al., 2014).

Psychotherapy could be considered as an environmental stimulus that could modify the epigenetic profile. In this line, there are few and recent studies relating BPD and the potential epigenetic effect of psychotherapeutic treatments (Perroud et al., 2013; Roberts et al., 2015)

To date, there is no psychopharmacological treatment with robust evidence of efficacy for the treatment of BPD. On the other hand, various types of specialized psychotherapy have shown efficacy in reducing symptoms and improving functioning (Choi-Kain et al., 2017). The exploration of the association between the change produced at the level of symptoms or

personality functioning induced by psychotherapeutic interventions and changes at the molecular level is still very scarce (Jiménez et al., 2018). However, its development can contribute to the understanding of the biological basis for significant and sustained improvement over time in patients with severe personality disorders.

Accordingly, this thesis first discusses the development of BPD in adolescence and its impact on health and functioning. The current evidence of the involvement of genes and the early environment in the genesis of BPD is presented below. The epigenetic mechanisms are proposed as a mechanism that regulates the effects of the environment on the genetic expression in the configuration of the phenotype. Preliminary evidence that links psychotherapy with epigenetic changes in different mental disorders is described. The concept of mentalization as a capacity for the processing of the interpersonal context, its development from the early experiences of care and its participation as a possible common factor in the psychotherapy in BPD is exposed. Finally, the notion that subjective processing of the social environment can act on the genetic expression as mechanism of adaptation of the phenotype in sensitive periods of life is discussed.

The main objective of this study is to advance in knowledge of putative causal mechanisms in psychotherapy by exploring the potential relationship between two explanatory levels, changes in mentalization induced by psychotherapy and changes in the epigenetic regulation of genes involved in stress response. This will be done through the evaluation during the course of therapeutic processes of methylation levels in a candidate gene and levels of mentalization in a sample of adolescents with BPD. The results are expected to clarify some aspects of molecular mechanisms associated with changes produced by psychotherapy, in

particular, processes that may explain stable recovery beyond symptomatic relief in personality pathology.

## 3. EMPIRICAL AND THEORETICAL BACKGROUND

### 3.1 The onset of Borderline Personality Disorder during adolescence

BPD is characterized by a general pattern of instability in the regulation of affect, impulse control, interpersonal relationships, and self-image. The clinical signs of the disease include emotional dysregulation, impulsive aggression, repeated self-injury and chronic suicidal tendencies, making these patients frequent users of mental health care devices (Lieb et al., 2004). To the above, it should be added that it presents a high axis I comorbidity and is the most frequent of the personality disorders (Leichsenring et al., 2011).

Epidemiological studies worldwide indicate that its prevalence ranges from 0.7% to 1.8%, increasing to 10% in the case of outpatient psychiatric patients, and 20% in hospitalized patients (Lieb et al., 2004). In Chile there are no studies in general population. However, when studying a sample of hospitalized patients in a psychiatry unit, it is estimated that 47% of them meet their diagnostic criteria (López et al., 2010).

Although personality development begins in childhood, and traits begin to consolidate during adolescence, until recently the diagnosis of BPD under 18 years was controversial; on the one hand, the difficulty of establishing the differentiation between extreme personality traits and the emotional vicissitudes characteristic of the normative period, and on the other, the reluctance to permanently label with a stigmatizing and hopeless diagnosis (Kaess et al.,

2014). In this regard, a review of the empirical literature since 1980 that evaluated the reliability and validity of the diagnosis of BPD in adolescents, contributes evidence that the characteristics of this in adolescents are comparable to those of adults, with a more severe subgroup stable over time and one of less severity that moved within and outside the diagnostic criteria in adulthood (Miller et al., 2008; Guilé et al., 2018). Today there is a wider acceptance of the diagnosis of personality disorders at least in emerging adulthood, which is reflected in the Diagnostic and Statistical Manual for Mental Disorders, Fifth Edition (DSM-5) and the International Classification of Disease 11th edition (ICD-11) (Kaess et al., 2014). It has been suggested that a subthreshold criterion of BPD with 3 or more criteria may be clinically relevant, as it has been associated with increased psychiatric comorbidity, risk taking behaviors, self-injury and increased psychological distress (Kaess et al., 2017).

Adolescents with BPD have academic difficulties and social relationship problems (Kaess et al., 2014). Additionally, this disorder is a significant predictor of substance use and mood disorders (Chanen et al., 2008). Suicide attempts and self-injury are prevalent in adolescents with BPD. Moreover, the severity of self-injuries would be greater in adolescents than in adults with BPD (Goodman et al., 2017).

Early suicidal gestures or attempts are likely to occur in adolescence and the presence of these increases the risk of committing suicide before the age of 30. The suicide rate in the United States is 11.8 per 100,000, among 15- to 19-year-olds (Miron et al., 2019). The rate of suicide among adolescents in Chile has increased from 8.83 to 9.28 per 100,000 in the 10-24 age group between 1990 and 2005 (Ventura-Juncá, et al., 2010). Although, there is no national data, a substantial proportion of adolescents with suicide attempt(s) may have borderline personality disorder pathology or borderline personality traits.

### 3.2 Etiology of borderline personality disorder

According to the model proposed by Gunderson & Lyons-Ruth (2008), the development of the borderline phenotype is associated with an emerging pattern in early interactions with attachment figures. This interaction as it evolves over time becomes the characteristic interpersonal pattern of the disorder, in particular a hypersensitivity to interpersonal stress. This would occur in subjects with a psychobiological predisposition, which contributes to an ambivalent-disorganized form of attachment. In other words, it requires the participation of both, a genetically predisposed infant and caregivers who are predisposed to maladaptive, hostile, unreliable or not attuned responses, leading to an escalation of problematic transactions and consolidating in the development of the subject a pattern of dysfunctional interpersonal strategies.

This model is consistent with the accumulated evidence of the relationship between childhood adversity and the presence of the borderline phenotype in epidemiological, case-control, and prospective studies, being emotional abuse and neglect the subtypes of adversity most strongly associated with BPD (Porter et al., 2020). Prospective analyses of developmental trajectories show association between maltreatment background, disorganized attachment and parental hostility with behavioral alterations, disturbed relationships, emotional dysregulation and alterations in self-representation during adolescence and the subsequent development of borderline symptoms in adulthood (Carlson et al., 2009). These findings support the notion of the profound and deleterious impacts of various forms of childhood adversity on the organization of basic personality domains.

The genetic contribution to vulnerability to BPD is supported by several studies, including family aggregation, twin and association studies. One family aggregation study showed that the risk of BPD was 3.9 times higher in relatives of individuals with BPD than in relatives of individuals without BPD (Gunderson et al., 2011). Twin studies report heritability ranging from 35% (Reichborn-Kjennerud et al., 2013) to 67% (Torgersen et al., 2012). Additionally, candidate-gene association studies have identified genetic variants associated with serotonin system, dopamine system, the brain-derived neurotrophic factor (*BDNF*), the Arginine Vasopressin Receptor (*AVR1A*) *Neurexin 3*, that encodes for presynaptic cell adhesion proteins (Panagopoulos et al., 2013) and *SCN9* that encodes a voltage-gated sodium channel Nav1.7 that is expressed in sensory neurons. In contrast, a meta-analysis including 18 genes showed no significant associations between BPD and any of the investigated genetic variants including the serotonin transporter gene, the tryptophan hydroxylase 1 gene, or the serotonin 1B receptor gene (Amad et al., 2014).

Only two genome-wide studies have been performed in individuals with BPD. In the study conducted by Lubke et al. (2014), BPD was significantly associated with genotypic variation of the SERINC5 gene that encodes for a myelinization protein. A first case-control genome-wide association study (GWAS) found no significant associations in single marker analysis, however, in the gene-based analysis, that includes multiple markers to determine their joint effect, two genes were significant, *DPYD* and *PKP4* , previously associated with Bipolar Disorder and Schizophrenia (Witt et al., 2017).

Together, these findings suggest heritability similar to other mental health disorders and associated genetic variants related to molecular mechanisms of synaptic signaling. Yet, results of candidate gene association studies are not confirmed by meta-analysis and do not

overlap with GWAS analysis. The possible reasons for inconsistent results in candidate gene and genome-wide association studies include small number of studies, relatively small sample size and high phenotypic heterogeneity. Further research is needed for the discovery of newly identified molecular mechanisms specific for BPD and also common with other psychiatric disorders.

Several studies have found interactions between childhood sexual abuse(CSA) or Stressful Life Events and gene variants (polymorphisms) on BPD diagnosis, such as Brain Derived Neurotrophic Factor (*BDNF)* (Wagner et al., 2010), the catechol o-methyltransferase (COMT) (Wagner et al., 2009), Tryptophan Hydroxylase 1 (*TPH1*) (Wilson et al., 2012) and Tryptophan Hydroxylase 2 (*TPH2*) (Perez-Rodriguez et al., 2010).

In relation to the involvement of HPA axis genes in BPD etiology, several studies have focused on *FKBP5* gene, which encodes for FK506-binding protein 5. FK506-binding protein 5 is a glucocorticoid receptor co-chaperon whose levels are increased after stress exposure and, by changing the conformation of the glucocorticoid receptor complex, decrease the affinity of glucocorticoid receptor for corticoids creating an ultrashort negative feedback for Glucocorticoid receptor gene (*NR3C1*) activation (Binder, 2009; Zannas and Binder, 2014). Two *FKBP5* alleles (rs4713902-C and rs9470079-A) were more frequent in individuals with BPD with a history of physical or sexual abuse (Martín-Blanco et al., 2016). Another study carried out in children with borderline symptoms reported association with maltreatment history with the same gene, this association was moderated by gender and by the presence of minor alleles of *FKBP5* CATT haplotype (rs3800373, rs9296158, rs1360780, and rs9470080) (Cicchetti et al., 2014).

These findings support the interplay between Hypothalamic-Pituitary-Adrenal (HPA) axis genetic variants and early adverse events in the etiology of BPD, in particular, the involvement of *FKBP5* as a regulator of the stress response.

Recent studies have begun to measure the positive environment moderation of the effect of genotypes on the phenotype. This change has led to the formulation of what has been called differential susceptibility hypothesis that implies that genes confer greater or lesser sensitivity to both positive and negative environmental elements (Carpenter et al., 2013). For instance, in relation to oxytocin (OXT), a neuropeptide involved in social behavior. A significant moderating effect of *OXTR* rs53576 polymorphism was found on the quality of family relationships in the development of BPD symptoms. The findings were consistent with the model of differential sensitivity as the A allele carriers had more symptoms when they have experienced adverse family conditions and were less symptomatic when they have positive familiar atmosphere. In contrast, GG homozygotes had average levels of BPD symptoms regardless of their quality of the family environment (Hammen et al., 2015).

Together, the reported studies suggest the interaction of genes that encode for different signaling molecules with affective environmental conditions in the development of BPD. These signaling molecules are related to neurotransmission, response to stress, neuroplasticity and social bonding behaviors. More research is needed to define the involvement of molecular systems that increase sensitivity to the early affective environment, especially studies of gene-environment interaction that include the measurement of positive emotional environment.

It has been widely postulated that a biological mechanism of the interplay between early environment and genetic factors is the epigenetic regulation of gene expression. The relevance of epigenetic mechanisms for BPD is reviewed below.

### 3.3 Epigenetics as a mechanism of gene-environment interaction

Epigenetic modifications refer to stable alterations of potential gene expression during development and cell proliferation, that are held through cell divisions and do not alter the DNA sequence (Jaenisch & Bird, 2003). These correspond to heritable patterns of DNA methylation and hydroxymethylation, posttranslational histone modifications, and gene expression regulation by non-coding RNAs (Zannas et al., 2015). The combination of these changes determines a specific pattern of gene expression, which is highly dynamic and permeable to environmental influences. It is also heterogeneous in different organisms, tissues and cell types, and change according to the stages of development. Therefore, corresponds to a complex mechanism of "phenotypic plasticity" in response to environmental demands (Ecker et al., 2018).

Experimental models have studied the impact of early adversity as a function of maternal care. For instance, in rats the effect of care behavior like licking, grooming (LG) and back arch-nursing (ABN) over behavior of the offspring and DNA methylation in the glucocorticoid receptor gene (*NR3C1*) (Lutz & Turecki, 2014). Increased DNA methylation (hence more inactive chromatin and therefore lower transcription) in promoter regions of GR gene (*NR3C1*) in the hippocampus of adult rats reared by mothers with low levels of LG-ABN compared to offspring reared by mothers with high LG-ABN was observed. This lower GR expression was associated with less negative feedback in HPA axis and higher reactivity to stress (Lutz & Turecki, 2014).

In rats exposed to early stress (separation of mother and calf), increased secretion of corticosterone is observed and a persistent increase in Arginine Vasopressin (AVP) expression

in neurons of the paraventricular nucleus of the Hippocampus. AVP acts by enhancing the action of Corticotropin Releasing Hormone (CRH) under sustained stress situations. This increase is associated with hypomethylation in the regulatory region CGI3 of *AVP* gene and with altered behaviors of stress coping (Murgatroyd et al., 2009).

In humans, a number of studies have explored the relationship between early adverse environment and changes in methylation patterns, using candidate genes and epigenome-wide strategies. The epigenetic association studies of candidate genes explore DNA methylation in a number of a-priori selected genes and Epigenome Wide Association Studies (EWAS) explore DNA methylation across the whole genome.

Regarding studies linking candidate genes related to the stress response and adverse events in childhood, a correlation between the number of adverse events reported and one DNA methylation site (cg17860381, located in exon 1F) of *NR3C1* gene was found in lymphocytes of females who reported childhood adverse events, including physical, emotional and sexual abuse. Additionally, this pattern of adverse events and DNA methylation was correlated with borderline symptoms (Radtke et al., 2015).

The relation between reactivity of the cortisol in saliva, *FKBP5* (rs1360780) genotype, methylation levels and the attachment pattern using the Strange Situation Procedure (to observe attachment behavior between caregiver and child) were assessed in a sample of 14-month-old infants. Infants who were T allele carriers had a greater chance of increased cortisol reactivity, association that was moderated by high *FKBP5* DNA methylation levels. This modification was more pronounced in infants who displayed resistant attachment behavior (Mulder et al., 2017).

A systematic review conducted by Turecki and Meaney (2016) regarding the effects of social environment on *NR3C1* gene methylation showed that there was a consistent relationship (16 out of 17 reviewed studies) between early life adversity and increased exon 1F DNA methylation across different tissues (blood, saliva, buccal cells and brain tissue). However, the results are discordant when exploring the relationship between exon 1F methylation and psychopathology including Post-traumatic stress disorder and Depression. The results are also inconsistent when exploring methylation in other sites of exon 1 of the same gene, suggesting the need for further research to determine the permeability and stability of DNA methylation of each specific site.

Other candidate gene association studies include BDNF, OXT, and the serotonin transporter *5HTT*. A low level of maternal care in childhood, measured with the Parental Bonding Instrument (PBI) was associated with increased DNA methylation of *OXTR* and *BDNF* genes in peripheral blood cells in adult life. However, differences in DNA methylation were relatively small and only three target sequences of the two genes were included (Unternaehrer et al., 2015).

DNA methylation in the serotonin transporter gene 5HTT was evaluated in relation to the presence of unresolved trauma or loss in a sample of adopted individuals. DNA was obtained from lymphoblast cell lines. Higher levels of DNA methylation in the promoter region of 5HTT were associated with increased risk of unresolved trauma in carriers of phenotype l/l ("long allelles"). This is contrary to the protective effect of "l" alleles previously described. The authors suggest that a higher methylation impedes the usually protective effect of this allele and elevate the risk of unresolved loss or trauma (vanIJzendoorn et al., 2010).

In relation to EWAS, there are a limited number of studies. One study, assessed DNA methyation in buccal cells samples, using Infinium Human Methylation 450 BeadChip in children of orphanages in Romania (N = 49). Children who spend more than six months in the institutions had higher methylation at 9 CpG sequential sites in cytochrome P450 2E1 gene (*CYP2E1*) promoting region. The protein CYP2E1 is an enzyme involved in the metabolism of drugs and neurotoxins. The same methylation pattern was associated with lower performance in cognitive and theory of mind (ToM) tests. Due to the small sample size the study is under powered to evaluate if deprivation effects on sociocognitive processes are mediated by epigenetic effects (Kumsta et al., 2016).

An association between maltreatment and methylation in 2868 CpG sites of the 485k sites included in the array (Illumina 450K BeadChip) was found in a sample of 96 abused children compared to 96 demographically-matched control children, using DNA from saliva samples. The genes involved were related to cortical development, depression risk and substance dependence among others (Yang et al., 2013). An association was also found between physical maltreatment and sexual abuse and variation in methylation in different loci in a sample of 124 adolescents and young adults from deprived sectors of London. Some DNA methylation loci with altered methylation were specific to physical abuse and gene ontology analyses indicated enrichment for biological processes, including cardiovascular function or fear response. Others DNA methylation loci with altered methylation were common to all types of abuse such as regions linked to nervous system development like *HUWE1* and *CACNA2D4* (Cecil et al., 2016).

Interestingly, there was no overlap between the findings of these last two epigenome-wide studies. This may be due to different ways of assessing early adversity. In Yang's study,

parents and children were informants and protective services records were screened, while in Cecil's study, a self-report questionnaire was used. These studies also differed in age range (5-14 vs 16-24 years) and cell type (saliva in the first and buccal epithelial cells in the second).

Different types of early adversity including physical, emotional, or sexual abuse or institutional deprivation are associated with altered DNA methylation in specific sites of the epigenome, which seem to mediate the interaction between the environment and allelic variants in selected candidate genes. The epigenome wide studies that include a greater number of genetic loci, to date are scarce, the sample sizes are small, assess adverse events with different methods and their findings although positive are still inconsistent between them and with candidate genes studies.

### 3.4 Epigenetics in Borderline Personality Disorder

There is a limited number of studies that explore the relationship between borderline phenotype, adverse environment and DNA methylation patterns, using candidate genes and epigenome-wide strategies.

In relation to association studies with candidate genes associated with stress response, one study reports the association between higher DNA methylation in regions promoting the *NR3C1* gene in women with eating disorders, but only in those who were associated with a diagnosis of BPD or were suicidal compared to healthy subjects (Steiger et al., 2013). A positive correlation has been observed between the levels of DNA methylation of exon 1F the Glucocorticoid Receptor gene (*NR3C1*) promoting region in peripheral blood, child

maltreatment (physical abuse) and clinical severity in a sample of BPD subjects (Martín-Blanco et al., 2014).

Maternal stress during pregnancy can also operate as a significant stress factor. Prenatal stress measured with semistructured interview, predicts site-specific CpG hypermethylation of exon 1F of the *NR3C1* gene only in subjects with BPD compared to healthy controls (Schwarze et al., 2019). Together, these findings imply that this specific exonic region, highly expressed in the brain could mediate the epigenetic programming of traits such as impulsivity and emotional instability.

Other studies with candidate genes have explored the involvement of genes related to neurotransmission and neuroplasticity and the relationship between BPD diagnosis or severity and DNA methylation patterns.

DNA methylation in promoter regions of 14 genes, previously associated to neuropsychiatric disorders, in whole blood samples a significant increased average methylation (1.7%) was found in individuals with BPD. Additionally, an increase in DNA methylation in CpG sites of 5 genes associated with monoamine neurotransmission and stress response (*HTR2A, MAOA, MAOB, NR3C1,* and *S-COMT*) was found in a sample of 24 females with BPD and 11 female healthy controls, using Infinium HumanMethylation27 BeadChip (Dammann et al., 2011).

DNA methylation was significantly lower in promoter region and 5′ETS region of *rDNA* gene and higher for promoter region of PRIMA1 gene in in peripheral blood samples of BPD individuals compared to healthy controls (N=35). *PRIMA1* is related to cholinergic transmission and increased DNA methylation of promoter of *rDNA* has been found in the brain of suicide persons (Teschler et al., 2016)

Women with Bulimia Spectrum Disorder who also met diagnostic criteria for BPD had a higher level of DNA methylation in the promoter region of the *DRD2* gene compared to women without eating disorder in a sample of 72 female individuals, using blood samples. No association was found with early adverse events (Groleau et al., 2014).

Childhood maltreatment was associated with higher severity (number of mood episodes, suicide attempts and hospitalizations) and the effect was mediated by Serotonin 3A receptor gene (*5-HT3AR*) DNA methylation at two CpG sites in a sample of 346 subject with diagnosis of BPD, bipolar disorder and adult attention deficit hyperactivity disorders (Perroud et al., 2016).

Patients with BPD had lower DNA methylation compared with healthy controls at one CpG site in the promoter region of *COMT* gene after controlling for Val 108/158 Met genotype (Thomas et al., 2019).

Two studies explore the association with *BDNF* gene. Increased DNA methylation was observed in saliva, but not blood, in patients with BPD compared to healthy controls (N=82) (Thomas et al., 2018). The authors suggest that the discrepancies observed when using peripheral tissues, could be due to the presence of lymphocytes and epithelial cells that express *BDNF* in saliva. Other study in women with Bulimia Nervosa showed elevated DNA methylation at specific *BDNF* promoter region sites if they had BPD diagnosis or reported abuse during childhood (physical and sexual abuse) (Thaler et al., 2014).

One study compared subjects with Major Depressive Disorder (MDD) who reported low levels of maltreatment and subjects with BPD with high levels of child adversity (sexual abuse and abuse or emotional or physical neglect) through the Child Trauma Questionnaire (CTQ), using methylation analysis of whole genome of blood with cells. Differences in the

methylation patterns of various genes either by comparing diagnosis or level of abuse were found. An important result from a biological point of view was the higher DNA methylation of the region cg04927004 MicroRNA gene, *MiR124-3*. The micro RNA are short regions of RNA that regulate protein synthesis, are widely expressed in neurons and are associated with processes of neurogenesis and neuroplasticity, additionally could regulate the expression of genes related to the HPA axis as *NR3C1*, whose methylation status it has been correlated with BPD (Perroud et al., 2011).

The findings of these studies are heterogeneous. One study find relationships with the diagnosis of BPD, but not with childhood adversity (Groleau et al., 2014) and others with both (Thaler et al., 2014; Perroud et al., 2011; Perroud et al., 2016) Some studies find differences using blood cells (Gruleau et al., 2014; Thaler et al., 2014; Perroud et al., 2011; Perroud et al., 2016; Thomas et al., 2019), and one study find association in saliva, but not in blood samples (Thomas et al., 2018). One study analyzes clinical severity using a transdiagnostic approach by grouping BPD with Attention deficit hyperactivity disorder (ADHD) and Bipolar Disorder (Perroud et al., 2016) and two studies explore the comorbidity with BPD in eating disorders (Gruleau et al., 2014; Thaler et al., 2014).

To date, only a few studies used epigenome-wide techniques in individuals with BPD phenotype. A significantly increase in DNA methylation at CpG sites of *APBA2*, *APBA3*, *KCNQ1*, *MCF2* and *NINJ2* genes was found in BPD patients compared to healthy controls (N=35) using the HumanMethylation27 bead chip and confirmed by quantitative pyrosequencing. *APBA2* and *APBA3* are both neuronal adaptor proteins, NINJ2 adhesion molecule that promotes neurite outgrowth, *KCNQ1* gene encodes a voltage-gated potassium

channel and *MCF2/DBL* encodes an oncogenic guanine nucleotide exchange factor (Teschler et al., 2013).

In the second study, differences in methylation patterns of various genes either by comparing diagnosis or level of abuse were found (*IL17RA, miR124-3, KCNQ2, EFNB1, OCA2, MFAP2, RPH3AL, WDR60, CST9L, EP400, A2ML1, NT5DC2, FAM163A* and *SPSB2).* The study compared 93 patients with Major Depressive Disorder (MDD) who reported low levels of maltreatment with 96 individuals with BPD who reported high levels of child maltreatment (sexual abuse and emotional or physical neglect or abuse) through the Child Trauma Questionnaire (CTQ). (Prados et al., 2015).

In sum, studies so far suggest that individuals with BPD have altered patterns of DNA methylation in genes associated with neurotransmission, neuroplasticity and stress response. Moreover, this relationship seems to be moderated by the presence of early adverse events. Yet, to date, there is no concordance between candidate gene studies and EWAS studies. Replicability of these findings and standardization of assessment methods for psychopathology and DNA methylation is required.

### 3.5 Epigenetics changes and psychotherapy in BPD

Only a few studies address the potential link between epigenetic changes and the effect of psychotherapy over time across a limited range of mental disorders and candidate genes; in individuals with Post-traumatic stress Disorder, exposure therapy and DNA methylation change in *FKBP5* gene exon 1 (Yehuda et al., 2013), children with anxiety disorders, cognitive behavioral therapy (CBT) and DNA methylation change in *FKBP5* gene exon 1 (Roberts et al., 2015), Panic Disorder, CBT and DNA methylation change in monoamine

oxidase A (MAOA) gene (Ziegler et al., 2016), agoraphobia, CBT and DNA methylation change in promoter region and intron 7 of *FKBP5* gene (Roberts et al., 2019) and one longitudinal EWAS of CBT for Panic Disorder (Ziegler et al.,2019).

Psychotherapy have demonstrated to be an effective treatment for BPD. A recent meta-analysis concluded that specialized psychotherapy was associated with a decrease in the severity of BPD and self-injuries with a medium effect size. (Oud et al., 2018). A limited number of studies have explored the effect of psychotherapy on epigenetic changes in BPD. One study using a sample of 115 outpatients diagnosed with BPD (and 52 healthy controls) and extracting DNA from blood leukocytes measured CpG methylation of exons I and IV of the *BDNF* gene before and after 4 weeks of Intensive Dialectical Behavioral psychotherapy (DBT). Patients who responded to DBT, exhibited a decrease in DNA methylation of *BDNF* gene exons I and IV, whereas no association was found between BPD diagnosis and methylation levels (Perroud et al., 2013). In another study performed in 44 patients with BPD and 44 matched controls, DNA methylation of *APBA3* and *MCF2* genes was measured from blood samples. Individuals with BPD who respond to DBT therapy presented higher methylation in both genes after 12 weeks relative to non-responders. (Knoblich et al., 2017). *APBA 3* (neuronal adapter protein) is related to the production of β-amyloid, a component of amyloid plaques linked to Alzheimer's disease and *MCF2* is a guanine nucleotide exchange factor, involved in neurite outgrowth that has been associated with schizophrenia and autism-spectrum disorders (Piton et al., 2011).

A third study, involving a sample of 41 individuals with BPD ant 41 healthy controls and assessing candidate gene DNA methylation using pyrosequencing, reported higher methylation levels in promoter IV of *BDNF* gene in both saliva and blood samples of BPD

patients. Twenty-six patients completed DBT psychotherapy and after 12 weeks, a decrease in methylation levels was observed only in saliva samples (Thomas et al., 2018).

Some results are discordant, for example Perroud et al. (2013) study shows significant change after therapy in blood samples while Thomas et al. (2018), work does not. One possible explanation may be that the first study reported an average of methylation from exon IV while the second reported individual CpG methylation. There were also differences in the methylation evaluation technique (high resolution melt analysis vs. pyrosequencing).

These initial findings suggest that psychotherapy may have an effect on peripheral methylation levels and could be considered as a potential biomarker of psychotherapy improvement, however replication with larger cohorts is required.

Since BPD starts to manifest from the beginning of adolescence, it is necessary to understand the characteristics of epigenome changes at this stage of development.

### 3.6 The epigenome remains dynamic during adolescence, a critical period for personality development.

Adolescence is understood as a period of transition from childhood to adulthood, in which physical maturation and brain development take place along with a drive for greater independence and an increase in the relevance of peer relationships (Casey et al., 2010). Current evidence suggests that adolescence would be a period of permeability and change also at the epigenetic level. Adolescents show no differences in the methylation of *NR3C1* gene according to age or history of childhood stress but do show differences associated with stressful life events (SLE) occurred during adolescence, that included sexual and physical

abuse (Van Der Knaap et al., 2014). In an EWAS study, using Infinium Human Methylation 450 BeadChip (450K array), an association was found between behavioral reactivity and DNA methylation of two genes, *DLX5* (involved in neuron and craniofacial development) and *IGF2* (encodes a growth factor that promotes cell differentiation and proliferation). Adolescents with greater disinhibition, i.e. approach negativity, anger and externalizing behaviors, exhibited higher methylation compared with children with inhibition, fear, and internalizing symptoms. Interestingly, the association was maintained from adolescence into young adulthood, supporting the combined fixed and dynamic nature of DNA methylation and that certain genes relevant to the development of behavior may have stable methylation patterns over time (Goodman et al., 2018).

Using a genome-wide DNA methylation strategy in healthy adolescent monozygotic twins to explore stability of DNA methylation over 3-6 months, a study differentiated two types of methylation patterns, those that presented high variability among different individuals, but were stable in time ("*trait-like genes")* and a second group of genes that were hypervariable over time ("*state-like genes")*. A pathway analysis associated both groups to developmental processes, cellular mechanisms, tissue and cell morphology. These findings suggest that a portion of the methylome remains dynamic in adolescence (Levesque et al., 2014).

During adolescence, methylation maintains its potential for change, is permeable to influences from the social environment and correlates with markers of psychopathology such as behavioral reactivity. In addition, some changes in the levels of DNA methylation in this period may remain stable until adulthood. Current evidence regarding the stability of

epigenetic changes is limited. There is a clear need for longitudinal studies to explore the variability of methylation changes over time especially in critical developmental stages.

### 3.7 Importance of the choice of tissue for the study of DNA methylation

It should be noted that it is very difficult to study DNA methylation in the living brain. An attractive strategy is the use of peripheral tissue such as blood, buccal cells or saliva, the collection of which is less invasive. The use of peripheral tissue leads to the problem of to what extent peripheral methylation patterns are correlated with human brain and whether can be used as a proxy for brain processes. It also raises the discussion about the peripheral tissue of choice, which one is easier to collect, more stable in time, and which one best corresponds to central nervous tissue (Di Sante et al., 2018).

Exploring the correlation in methylation of temporal lobe biopsies from patients with epilepsy diagnosis and peripheral blood samples only 7.9% of all variable, brain-associated CpGs showed a statistically significant correlation between brain and blood which suggests that a small subset of peripheral methylation markers might be useful as a proxy for brain methylation (Walton et al., 2016).

A recent study used in vivo brain samples from patients undergoing surgery for refractory epilepsy. Blood, saliva and buccal samples were obtained at the same time and Genome-wide methylation was assessed Infinium HumanMethylation450 and HumanMethylationEPIC BeadChip arrays. Considering only variable CpGs for each peripheral tissue, 15.7% of CpGs in blood, 11.6% in buccal, and 8.8% in saliva were moderately correlated ($r > 0.5$) (Braun et al., 2019).

While there is evidence of correlation between brain tissue and surrogate tissues, it should be noted that the correlations are relatively small-moderate. Further research is needed to inform the choice of surrogate tissues and to take into account the specific correlation for each gene loci.

### 3.8 The mentalizing capacity

Mentalization can be understood as a mental activity that allows us to interpret human behavior in terms of intentional mental states (needs, desires, feelings, goals), constituting a form of social cognition (Fonagy & Luyten, 2009).

Through mentalization an individual is able to realize that he has a mind that can mediate his experience with the world, provide to the person the capacity to distinguish the inner reality of external reality and includes both, an intrapersonal mental context and emotional processes of interpersonal communication (Fonagy, Gergely, & Jurist, 2004).

Broadly speaking, mentalizing is a capability that allows a representation of the Self as an "agent", i.e., enables the sense of mastery over one's own behavior and thoughts. This capability is an achievement of development, a result of an evolutionary process, which in turn depends on early experiences and the emotional bond that is formed with a caregiver (Bateman & Fonagy, 2004). It is crucial for the development of mentalization, the quality of early attachment relationships, as they allow the internal states to be mirrored by an attentive and reliable caretaker, this process at the same time impacts on the processes of emotional regulation and self- control (Fonagy & Luyten, 2009).

The concept of mentalization presents considerable overlap with other concepts such as empathy, mindfulness, psychological mindedness and affect consciousness. They all involve

the unconscious or deliberate ability to grasp the affective aspects of the mental states of self and others (Choi-Kain & Gunderson, 2008). A recent meta-analysis that included 585 subjects with BPD and 501 healthy controls evidenced a lower performance in overall ToM in BPD subjects, additionally, BPD subjects did not present differences in the tasks of decoding mental states, but in those that evaluated the ability to reason about them, that means, it is not compromised the capacity to discriminate mental states but to integrate affective experiences and reflective knowledge (Németh et al., 2018).

### 3.9 Mentalization in Borderline Personality Disorder

According to this conceptualization, the various domains of symptomatic borderline pathology as emotional dysregulation and interpersonal difficulties could correspond to manifestations of an underlying core failure in the mentalizing process.

Specifically, BPD subjects show a decreased ability of mentalizing in interpersonal contexts of high emotional intensity, for example, in couple relationships. This means there is a lower threshold deactivation of explicit reflective processes and the reemergence of less sophisticated mental modes, that are normal in early stages of social-emotional development, called pre-mentalizing modes, for example, the mode of "psychic equivalence" in where subjective internal states are experienced as real (e.g. fear of abandonment lived as a real). This leads to the maintenance of self-destructive behavior given the extreme difficulty to organize painful mental states (Fonagy & Luyten, 2009).

While there is evidence linking a mentalization deficit with a wide range of psychiatric disorders, such as substance abuse, depression, or eating disorder, this is inconclusive

(Katznelson, 2014). A mentalization deficiency occurs in subjects with BPD in a clinical sample compared to a non-clinical sample and with subjects with other personality disorders, but only in the presence of child abuse (Fonagy et al., 1996). However, other studies show a superior capacity for mentalization in these patients. This may be because mentalization is a multidimensional construct and therefore, the expression of deficits could be in BPD, specifically activated in the context of attachment relationships under conditions of high emotional arousal (Antonsen et al., 2016), in which it increases the tendency to attribute mental states to others that exceed the information given by social cues (hypermentalization) (Sharp & Fonagy, 2015).

Less certainty about mental states as measured by the Reflective Functioning Questionnaire (RFQ) correlated with the severity of BPD in a study that included 154 healthy controls and 59 subjects with BPD (Morandotti et al., 2018). Moreover, subjects with BPD would not present difficulties in the processess of decoding mental states from observed behavior, but rather to make causal inferences and predictions that include context information and basic social knowledge (Nemeth et at., 2018; Nemeth et al., 2020). Lower values of mentalization measured with RFQ mediate the relationship between a diagnosis of BPD and insecure adult attachment, supporting the idea that the presence of negative internal work models reduces the ability to accurately distinguish the relationship between mental states and behavior (Badoud et al, 2018).

In adolescents, BPD subjects show lower mentalization as measured by the Reflective Functioning Questionnaire for Youth (RFQY) self-report questionnaire compared to normal controls. In addition, low mentalization was associated with hypermentalizing responses in the Movie Assessment of Social Cognition (MASC), consistent with the proposed tendency to

over-attribution of mental states (Ha et al., 2013; Quek et al., 2019). Moreover, one study suggests that difficulties in emotion regulation measured with the Difficulties in Emotion Regulation Scale (DERS) could mediate the relationship between overmentalization and borderline traits. The authors suggest that an overinterpretation of social cues can trigger a vicious circle of emotional deregulation and inability to stop anxious rumination (Sharp et al., 2011).

### 3.10 Mentalization in the treatment of Borderline Personality Disorder

The treatment specifically developed to increase mentalization, Mentalization Based Treatment (MBT) (Bateman & Fonagy, 2004) has proven to be effective compared to Structured Clinical Management in a sample of BPD subjects in both reducing self-injurious behaviors and hospitalizations and in reducing symptoms and improving interpersonal functioning (Bateman & Fonagy, 2009). Also, at an 8-year follow-up, subjects treated with MBT maintained a stable improvement over time compared with Treatment as Usual (TAU) (Bateman & Fonagy, 2008). In adolescents, a pilot study shows a reduction in the severity of symptoms and improvement in functioning 12 months after initiation of treatment (Laurenssen et al., 2014).

Increased mentalization using the Reflective Functioning Scale (RFS) in BPD patients treated with Transference Focused Psychotherapy (TFP) compared to Dialectical Behavioral Therapy and Supportive Psychotherapy after one year of treatment (Levy et al., 2006). Other study found no relation between mentalizing and outcome, which could be due to the fact that the therapies have a shorter duration (Karlsson & Kermott, 2006) or the validity of the RFS to

evaluate the change (Vermote et al., 2010). A single case study after 2.5 years of individual therapy showed an increase in total RFS score from 3 to 5 and exhibits a greater range of thoughts and feelings (Gullestad & Wilberg, 2011).

Using the Psychotherapy Process Q-Set, one study compares sessions of TFP, DBT and therapy focused on mentalization. Interestingly, the prototype mentalization response correlated with all therapies, with a greater emphasis on mentalizing the other (including the therapist) in TFP and more focused on the self in DBT (Goodman et al., 2015). These findings are in agreement with the statement that the development of mentalization corresponds to a common factor in BPD psychotherapies (Fonagy & Allison, 2014).

A systematic review which included 11 studies and 3 follow-up studies, showed that MBT was superior to well-established comparison treatments of BPD such as treatment as usual, standard psychiatric care, structured clinical management, and specialized clinical management in achieving a reduction in the severity of BPD symptoms. Further research is needed to determine whether MBT is able to elicit symptomatic improvement through the development of mentalization skills (Vogt & Norman, 2019).

### 3.11 Can subjective processes affect molecular mechanisms?

Can subjective processes such as mentalization modify the molecular machinery and determine phenotypic adaptations to the environment?

Kendler (2005) proposes that subjective or "first-person" experiences have causal efficacy in the organism and can be understood as highly elaborated forms of intentional

processes that eventually lead to action and that allow for achievements such as language, customs, technology and culture. Mental disorders emerge in the failure of these intentional states to exert effective action in the world (Spence, 1996).

Fonagy (2004) argues that the intrapsychic representational processes are able to moderate the effects of the environment on the phenotype, in other words, the interpretation of the social environment and not the mere physical environment acts on the genetic expression as mechanism of adaptation of the phenotype.

The subjective perception of the social environment (e.g. perception of isolation or social anxiety) can generate changes in different levels of the body's response systems, such as the central nervous system, hypothalamic pituitary adrenal axis, intracellular signals and finally transcription factors and genetic expression. This causal trajectory is called "Social Signal Transduction" (Slavich & Cole, 2013). An example of this is that the perception of social rejection in adolescents predicts the increase of inflammatory molecules (NF-κB and I-κB). Faced with a threat to the position in the social hierarchy, molecular mechanisms of response to a potential physical aggression are activated; this initially adaptive response causes a collateral increase in cardiovascular and affective disorders risk (Murphy et al., 2013).

Mentalization could then be understood as an evolutionarily valuable capacity for the proper navigation of the social world. Learning from one generation to another is constituted as another mechanism for the transmission of relevant information to survival, in parallel with the transmission of genetic material (Fonagy & Allison, 2014). At the same time, the epigenetic modifications can be an articulating mechanism between both forms.

The "Social Brain Network" (dorsal medial prefrontal cortex, temporoparietal junction, posterior superior temporal sulcus, and anterior temporal cortex) is associated with socio-

cognitive processes such as mentalizing, social emotion and peer evaluation, and remains in development until early adulthood (Blakemore, 2013). This makes adolescence a "sensitive period" open to social interactions that act as a critical input for human social development (Feldman, 2015). Epigenetic mechanisms are both permeable to environmental influences and stable over time so it is possible to argue that they can be a mechanism for long-term effects of both early experiences and significant emotional experiences, such as psychotherapy, in sensitive periods of life.

Consequently, this research aims to find preliminary evidence regarding the understanding of epigenetic changes in FKBP5, a gene relevant to stress response processes, whose genetic variants have been associated with BPD phenotype (Cichetti et al., 2014; Martín-Blanco et al., 2016) and response to psychotherapy. Change in methylation of this genes could be an underlying mechanism at the molecular level that of stable changes in time of mentalization capacity achieved with psychotherapy, and through these, significant and permanent changes in the ability to regulate emotions and better interpersonal functioning in adolescents with personality pathology.

## 4. OBJECTIVES

### 4.1 General objective

To assess the relationship between changes in levels of DNA methylation of FKBP5 gene and change of mentalization in adolescents with BPD across the psychotherapy process.

### 4.2 Specific objectives

1. To determine changes of Mentalization levels in a group of adolescents with BPD in psychotherapy.
2. To characterize the changes in symptoms, functioning and emotional regulation during the course of the psychotherapeutic process in a group of adolescents with BPD.
3. To evaluate changes in DNA methylation of FKBP5 gene in a group of adolescents diagnosed with BPD after receiving the psychotherapeutic treatment.
4. To establish the relationship between change in mentalization levels and DNA methylation of FKBP5 gene in a group of adolescents diagnosed with BPD.
5. To establish the relationship between changes in DNA methylation of FKBP5 gene and changes in symptoms and functioning in a group of adolescents diagnosed with BPD.
6. To establish the relationship between changes in DNA methylation of FKBP5 gene and emotion regulation in a group of adolescents diagnosed with BPD.

## 5. HYPOTHESES

H1: The DNA methylation pattern of FKBP5 gene change in adolescents with BPD after psychotherapy treatment.

H2: The improvement in mentalization and emotion regulation achieved in therapy in adolescents with BPD in psychotherapy is associated with changes in DNA methylation of FKBP5 gene.

## 6. METHODS

The design was a quasi-experimental, longitudinal, process-outcome study. Given that it was not possible to randomly assign patients to a no psychotherapy condition, a quasi-experimental design was chosen. Measurements were carried out in three times (at the beginning, in the middle and at the end of treatment) considering a time interval of 3 months. All the therapies had an approximate duration of 6 months (or 25 sessions).

### 6.1 Sample

Participants were female adolescent patients, aged 15 to 20 years, a BPD subthreshold cut-off of 3 or more criteria of the DSM IV-TR for BPD (Kaess et al., 2017) and who were starting a psychotherapeutic process with focus on difficulties in the development of their personality.

The exclusion criteria were the following psychosis, pervasive developmental disorder and unstable medical (non-psychiatric) disease.

A final sample of 11 patients was included in the study.

### 6.2 Procedure

A convenience sampling technique was used by contacting psychotherapists who work with adolescent populations and whose theoretical model and therapeutic approach includes the development of the mentalizing capacity, including psychodynamic psychotherapies and DBT (Goodman et al., 2015) applied in private practice and in public and private outpatient treatment centers of Santiago (previous authorization by the director of the respective center). Therapists were clinical psychologists or psychiatrists with therapeutic training. Principal Investigator (psychiatrist) or research assistants (psychiatry residents) assessed whether they meet the eligibility criteria, then interview the subjects and applied the screening instruments Mini International Neuropsychiatric Interview (M.I.N.I-Kid), Structured Clinical Interview for DSM-IV axis II Personality Disorders (SCID II), Childhood Trauma Questionnaire (CTQ) and Attachment Adolescent Questionnaire (AAQ). Once selected, the Brief Reflective Functioning Interview (BRFI) (Rudden et al., 2005) and Difficulties in Emotion Regulation Scale (DERS) was applied at 0, 3 and 6 months and the instruments of follow-up Youth Outcome Self-Report (Y-OQ-SR), Beck Depression Inventory (BDI-I), Borderline Symptom List (BSL-23), at 0, 3 months and 6 months. In addition, a blood sample was collected to perform the epigenetic analysis at 0, 3 and 6 months.

Verbal and written information about the research and subject participation were provided. All subjects must have submitted their consent and assent and the informed consent of the parents if they were underaged. Subjects could resign at any moment of the research with no consequences in the treatment. Subjects received compensation for time and effort

consisting in 2 cinema tickets. The project was submitted and approved by the ethics committee of Pontificia Universidad Católica de Chile.

### 6.3 Assessment

**6.3.1 Sociodemographic and Clinical Background record:** Sex, Age, School Level, Contraceptive, Tobacco and Medication use.

#### 6.3.2 Screening instruments

1. **Structured Clinical Interview for DSM-IV axis II Personality Disorders (SCID II)**: Semi structured interview evaluation (First et al., 1995). It contains 119 open questions, although we will use only the BPD subscale (15 questions). The Spanish validation was developed by First et al. (1999) and is been used in Chile (Echávarri et al., 2015; Florenzano et al., 2002). It has an interrater reliability of .91 (Cohen's Kappa) and an internal consistency of .71-.94 (Cronbach's $\alpha$).
2. **Mini International Neuropsychiatric Interview (M.I.N.I-Kid):** It is a structured diagnostic interview designed to determine current and past psychiatric disorders based on DSM-IV (Sheehan et al., 1998), the child and adolescent version was developed by Sheehan et al., (2010). Was validated in Chile for externalizing disorders (de la Peña et al., 2009). It will be used to detect psychosis exclusion criteria.

#### 6.3.3 Trauma and Attachment instruments

1. **Childhood Trauma Questionnaire (CTQ):** It is a 25 items retrospective self-report questionnaire designed to identify trauma history in adults and adolescents. It measures physical, sexual and emotional abuse including physical and emotional neglect (Bernstein et al.,1997). It has been validated in Spanish (Hernandez et al., 2013) and validated in Chile and has an internal consistency of .89 (Cronbach's α), with the exception of the physical negligence scale, the scales shows internal consistency in ranges suitable to excellent (Behn et al., 2020). A threshold of at least one subscale scoring in the moderate or severe trauma range was used to consider the presence of trauma (Tyrka et al., 2015).
2. **Attachment Adolescent Questionnaire (AAQ):** A self-report instrument of 9 items that evaluates the quality of early relationships, has three sub-scales a) Availability scale; b) Goal corrected Partnership scale and c) Angry distress scale. It was developed by West et al. (1998) and validated in Chile with a reliability of .52 - .77(Cronbach's $\alpha$) and same factorial structure as the English version (Morán et al., 2014). This instrument has been applied to explore the relationship between attachment patterns and personality features in adolescents (Ramos et al.,2016).

### 6.3.4 Process instruments

1. **Reflective Functioning Scale (RFS):** Coding system to measure the level of mentalization and rate narratives describing interactions between self and others in transcripts from the Adult Attachment Interview (AAI) (Main et al., 2003) and

rating them in a scale of 7 points ranging from negative RF (-1) to Exceptional (9) (Fonagy et al., 1998). The reliability of the RFS after training is high and pairs of raters have correlations between .81 and .94 (Bouchard et al., 2008). The RFS will be applied to BRFI transcripts.

2. **Brief Reflective Functioning Interview (BRFI):** Is a brief semiestructured interview about relationships with on parent and other important person in their current life. Participant responses should reflect RF capacity. Have 10 questions and an approximate duration of 25 minutes. The interview shows reliability (ICC = .79) and a high positive correlation with RFS scores from AAI (r = .71) (Rutimann & Meehan, 2012).
3. **Difficulties in Emotion Regulation Scale (DERS):** Developed by Gratz & Roemer (2004), is a self-report questionnaire with 28 items, assesses difficulties in emotional regulation and has the following 5 dimensions: Control, Awareness, Understanding and Acceptance of emotions. Was validated in Chilean population with a high reliability (Cronbach's $\alpha$=.92) and the factor structure is consistent with the Spanish version (Gomez-Simon et al., 2014).

### 6.3.5 Outcome Instruments

1. **Beck Depression Inventory (BDI-I):** Developed by Beck et al. (1961). This self-report inventory contains 21 questions that measures attitudes and symptoms of depression and was used as a screening of potential clinically significant symptoms (total score >9). The mean internal consistency estimate was 0.87.

(Cronbach's $\alpha$) and test-retest reliability greater than 0.60. (Beck et al., 1988). This instrument has been used in Chile (Alvarado et al., 2005; Ruiz et al., 2001).

2. **Youth Outcome Self-Report (Y-OQ-SR):** It is a self-administered Likert scale developed by Lambert, et al. (1996) to measure psychotherapeutic outcome. The adolescent version has 64 items to measure the following 6 dimensions: intrapersonal distress, behavioral dysfunction, somatic complaints, interpersonal relations, social problems and critical items. The Coefficient alpha for internal consistency is .95 and has a high test-retest correlation (r = .89, $p$< .001) (Ridge et al., 2009). The OQ-45.2 was validated in Chile by de la Parra et al. (2002) while the Y-OQ-SR is currently being validated (Cortés et al., 2018).

4. **Borderline Symptom List (BSL-23):** Developed by Bohus, et al. (2009) for assessing the symptom severity. Has 23 items distributed in three sub-scales: general symptoms, self-injurious behavior, and a visual analogue scale for subjective well-being during the past. Has a Spanish version that maintains the one-factor structure of the original version, has a high reliability (Cronbach's $\alpha$=.95) and good test-retest stability (n=74; r=.734; p<.01) (Soler, et al., 2013).

### 6.3.6 *FKBP5* Polymorphism (SNP rs1360780)

The technique used was allele-specific amplification by PCR which consists of two independent reactions that include the partition that in its 3' end carries the complementary base that recognizes the specific allele. The F6-R6 partition pair allows amplification of a 568-bp fragment that includes the position of the SNP rs1360780 and serves as an internal

PCR control (Ventura-Juncá et al., 2014).

### 6.3.7 *FKBP5* DNA Methylation levels

**Sample Extraction**: for each subject, a nurse collected 3 samples of 5 ml of venous blood. The genomic DNA of the subjects was extracted from 5mL leukocytes of peripheral venous blood using tubes with EDTA as an anticoagulant. The blood samples were kept at 4ºC for a maximum of 24 hours before the extraction of the DNA using the QIAamp DNA Blood Mini Kit QIAGEN. The extracted DNA was stored at -20ºC.

**Pyrosequencing Method:**

**Bisulfite treatment of gDNA:** For DNA methylation analysis, 500 ng of extracted genomic DNA was bisulfite treated using the EZ DNA Methylation kit (Zymo Research, Inc., CA). Bisulfite treated DNA was purified according to the manufacturer's protocol and eluted to a final volume of 46 μL.

**PCR:** PCRs were performed using 1 μL of bisulfite treated DNA and 0.2 μM of each primer. One primer was biotin-labeled and HPLC purified in order to purify the final PCR product using sepharose beads.

**Pyrosequencing:** PCR products were sequenced by Pyrosequencing on the PSQ96 HS System (Pyrosequencing, Qiagen) following the manufacturer's instructions.

The methylation status of 3 intron 7 CpG sites (ADS3828-FS2, ADS3828-FS1

and ADS6607-FS) was determined individually as an artificial C/T SNP using QCpG software (Pyrosequencing, Qiagen). The methylation level at each CpG site was calculated as the percentage of the methylated alleles divided by the sum of all methylated and unmethylated alleles. The mean methylation level was calculated using methylation levels of all measured CpG sites within the targeted region of each gene. Each experiment included non-CpG cytosines as internal controls to detect incomplete bisulfite conversion of the input DNA. In addition, a series of unmethylated and methylated DNA are included as controls in each PCR. Furthermore, PCR bias testing was performed by mixing unmethylated control DNA with in vitro methylated DNA at different ratios (0%, 5%, 10%, 25%, 50%,75%, and 100%), followed by bisulfite modification, PCR, and Pyrosequencing analysis (https://www.epigendx.com/d/service/pyrosequencing).

### 6.3.8 Psychotherapy response

To quantify the degree of change in clinical measures observed in this sample the Reliable Change Index (RCI) was calculated using pre and post treatment score, standard deviation and Cronbach alpha from the normative sample of the scale according to Jacobson and Truax formula (Bauer et al., 2014; Jacobson & Truax, 1991).

The RCI allows to identify if the differences are greater than expected due to random error. An RCI that is greater than 1,96 correspond to the 97,5 th percentile of a normal distribution and is equivalent to a statistically significant change ($p<.05$) (Jacobson & Truax, 1991).

### 6.4 Data Analytic procedure

Data analysis was performed using using R version 3.4.1 (RC Team, 2018) and the R packages *psych* for descriptive data (Revelle, 2016). Baseline features were summarized using descriptive statistics. Given multiple cases of data for each participant, a mixed-effect model was performed to assess the change in time of DNA methylation and clinical parameters that accounts for shared variance within subjects while modeling between-subject differences. The nlme package was used (Pinehiro et al., 2013).

A model with randomized intercept was used due to convergence failure for randomized slopes given the small sample size.

The dependent variable was transformed to its natural logarithm to normalize the distribution of the residues. Visual inspections were performed to check assumptions of heterocedasticity and normality of residues. Missing values were handled listwise.

## 7. RESULTS

A total of 11 individuals complete the study. The mean age was 16.77 ± 1.64 years. Two individuals were in their first year of college (18,2%) and 9 were in high school (81,8%). Three of them use tobacco (27,3%) with an average of 23 cigarettes per week. Two individuals use oral contraceptives (18,2%).

All individuals were on medication. Seven of them use antidepressants (63,6 %), six use an atypical antipsychotic (54,5%), three use benzodiazepines (27,3%) and one (9,1%) use a mood stabilizer (valproic acid). Six patients use more than 1 type of medication (54,5%).

Nine therapists were female (81,8%) and two were male (18,2%). The average age of the therapists was 36,9 ± 7,0 years and the average experience was 10,56 ± 7,33 years. Regarding the type of psychotherapy, eight performed psychodynamic psychotherapy (72,7%) and three dialectic behavioral therapy (27,3%). Main features of each participant are presented in table 1.

### 7.1 Baseline clinical characteristics

The patients' clinical characteristics at baseline are presented in table 2. Nine of the 11 patients fulfill the threshold of 5 BPD criteria and two patients fulfill the sub-threshold criteria with four symptoms.

BSL-23 average score placed the sample in between the two quarters of highest symptomatic severity based on correspondence with BDI-CGI (Clinical Global Impression for Borderlines) non-standardized scores according to Soler et al. (2013).

When analyzing baseline symptom intensity, it is observed that although there is wide variability among the answers of each individual in the different items, in all the questions the median ranges from rating their symptoms of the last week "a little" to "much" (figure 1).

All patients were above the cut-off score for the presence of depression (BDI-I) of 13 for Chilean population (Valdés et al., 2017) and the mean was in the range of severe depressive symptomatology (Beck et al.,1988) (Table 2).

The average total DERS score of was 89.36 ± 27.04 and was higher than the average score of a non-clinical sample of Spanish adolescents of similar age (Gómez-Simón et al., 2014) and higher than the 73 cut-off score proposed for Chilean adult population to differentiate high and low emotion difficulties groups (Guzmán-Gonzalez et al., 2020).

The average total Y-OQ-SR score was 96,18 ± 36,95 and was higher than the suggested clinical cut off of 47 (Wells et al., 2003).

The average values of the AAQ subscales *partnership* and *avalability* (6.09 ± 2.66 and 5.36 ± 1.69, respectively) are under the suggested normal range for adolescents in Chile (between 10 and 15 points and between 12 and 15 points respectively) (Morán et al, 2014). The angry distress subscale (6.64 ± 3.64) is within the suggested normal range (between 0 and 8 points).

The average CTQ values were within the range of “non to minimal” trauma according to Bernstein's classification (2003) for *Physical Abuse* and *Physical Neglect* subscales and “slight to moderate” trauma for *Emotional Abuse*, *Emotional Neglect* and *Sexual Abuse*

subscales. However, 7 participants (63.6%) had scores in the "moderate to severe" trauma range on at least one of the subscales.

**Table 1**

*Individual general, clinical and treatment features of the sample at baseline*

| Subject | Age | Educational level | Number of BPD symptoms | Psychotherapy type |
|---|---|---|---|---|
| 1 | 15 | 10th grade | 6 | PDT |
| 2 | 17 | 11th grade | 7 | PDT |
| 3 | 19 | 1st college | 5 | PDT |
| 4 | 16 | 11th grade | 5 | PDT |
| 5 | 16 | 10th grade | 7 | PDT |
| 6 | 14 | 8th grade | 4 | PDT |
| 7 | 16 | 10th grade | 9 | DBT |
| 8 | 15 | 10th grade | 9 | DBT |
| 9 | 17 | 9th grade | 4 | DBT |
| 10 | 19 | 1st college | 5 | PDT |
| 11 | 17 | 11th grade | 6 | PDT |

NOTE: PDT: Psychodynamic Therapy, DBT: Dialectic Behavioral Therapy

**Table 2**

*Means and SD of clinical characteristics of the sample at baseline*

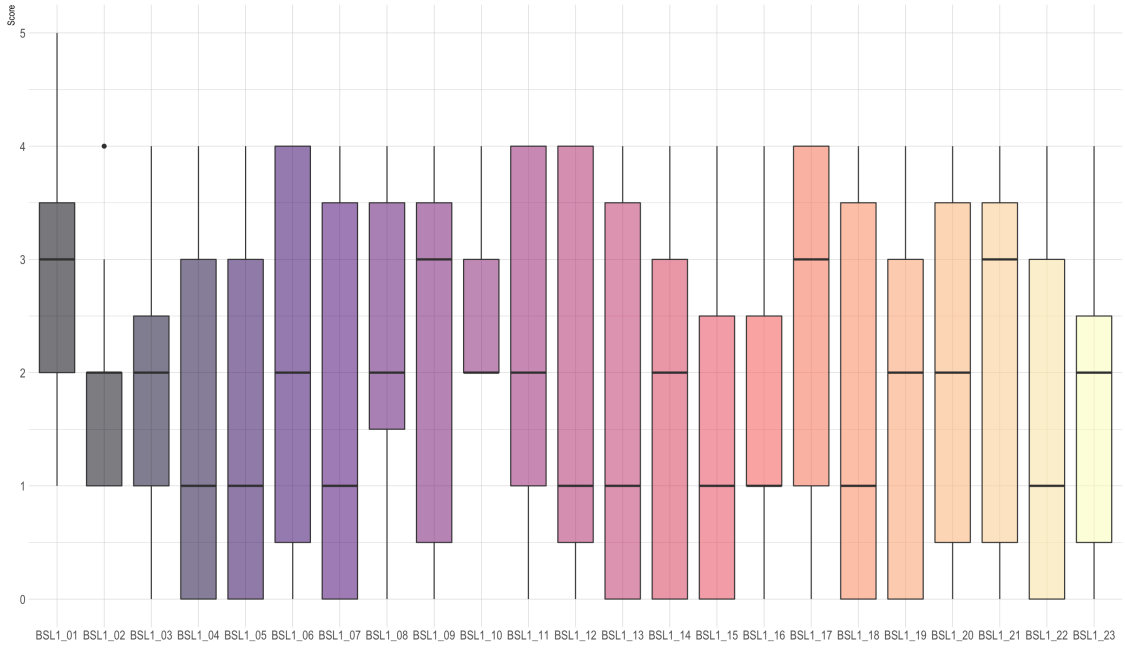
| Clinical Measures | Mean (SD) |
|---|---|
| BSL-23 | 1.99 (1.09) |
| BDI-I | 28.36 (15.13) |
| DERS | 89.36 (27.04) |
| Y-OQ-SR | 96.18 (36.95) |
| AAQ | |
| Availability | 6.09 (2.66) |
| Partnership | 5.36 (1.69) |
| Angry Distress | 6.64 (3.64) |
| CTQ | |
| Emotional Abuse | 10.82 (5.12) |
| Physical Abuse | 6.82 (3.16) |
| Emotional Neglect | 10 (2.72) |

| | |
|---|---|
| Physical Neglect | 6.09 (0.94) |
| Sexual Abuse | 7 (3.03) |

NOTE: BSL-23: Borderline Symptoms List, DERS: Difficulties in Emotion Regulation Scale, BDI-I: Beck Depression Inventory, Y-OQ-SR: Youth Outcome Self-Report, AAQ: Adolescent Attachment Questionnaire, CTQ: Child Trauma Questionnaire.

**Figure 1**

*Mean baseline score for each BSL-23 item*




## 7.2 Longitudinal change of clinical measures

To evaluate the change in the different symptomatic and functional domains during the course of therapy, individual trajectories were observed, as well as the change in the average values of each instrument over time.

The results for each patient borderline symptoms (BSL-23) are shown in figure 2. In general, a tendency to a reduction of the scores along the psychotherapy is observed in most of them, and 5 patients (45.5%) reach values corresponding to the quarter of less severity. When averaging the values (figure 3) a significant reduction is observed ($p = 0.003$).

In relation to depressive symptoms (BDI-I) a similar trend was observed and 6 (54.5%) patients reached values below the cut-off score for clinical depression (one of them being below the cut-off score at all three measurement times) (figure 4). Average values (figure 5) show a significant reduction over time ($p = 0.02$).

In the measurement of the psychotherapy response score (Y-OQ-SR), a tendency for the score to decrease over time was observed, although only three patients (27.3%) reached scores below the clinical threshold at the end of treatment (figure 6). The average scores show a significant reduction over time ($p=0.02$) (figure 7).

No significant change in emotion regulation (DERS) and mentalization (RFS) were observed (table 2).

**Table 3**

*Regression analyses of change in time of clinical measures*

| Instrument | BSL-23 | | BDI-I | | Y-OQ-SR | | DERS | | RF | |
|---|---|---|---|---|---|---|---|---|---|---|
| Parameter | β (S.E) | t | β (S.E) | t | β(S.E) | t | β(S.E) | t | β(S.E) | t |
| Fixed Effects | | | | | | | | | | |
| Intercept | 0.56(0.22)* | 2.49 | 3.21(0.27)** | 11.91 | 4.46(0.14)** | 30.99 | 4.44(0.10)** | 46.20 | 1.30(0.12)** | 10.97 |
| Time | 0.42(0.13)** | -3.31 | 0.44(0.12)** | -3.51 | 13.50(5.67)* | -2.46 | -0.10(0.05) | -1.98 | 0.084(0.05) | 1.7 |
| Random Effects | | | | | | | | | | |
| Intercept | 4.68e05 | | 0.00011 | | 3.17e05 | | 2.24e05 | | 0.34 | |
| Residual | 0,75 | | 0,89 | | 0.48 | | 0.32 | | 0.25 | |

NOTE 1: BSL-23: Borderline Symptoms List, DERS: Difficulties in Emotion Regulation Scale, BDI-I: Beck Depression Inventory, Y-OQ-SR: Youth Outcome Self-Report, RF: Reflective Functioning.
NOTE 2: Standard errors (S.E)(in parentheses). *p < .05, **p<.01.

**Figure 2**

*Individual borderline symptoms scores over time. Each facet represents one participant. The horizontal line represents the first quartile of symptom severity.*

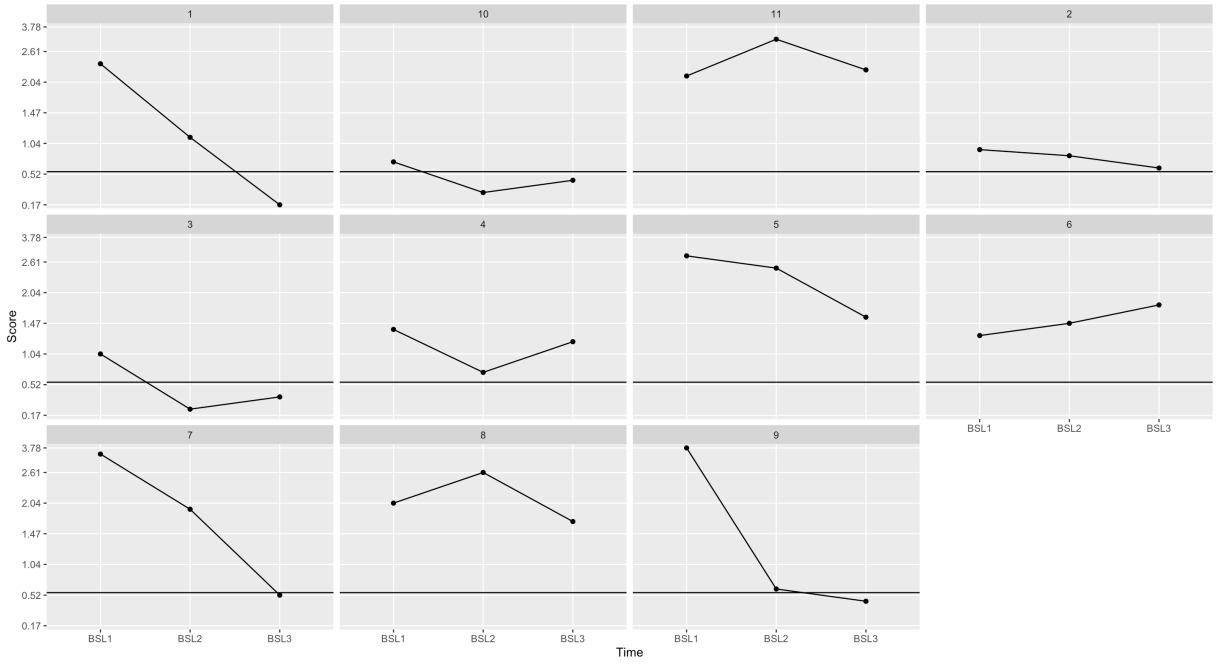


**Figure 3**

*Borderline symptoms scores over time. Individual values at each time and linear regression with confidence interval.*

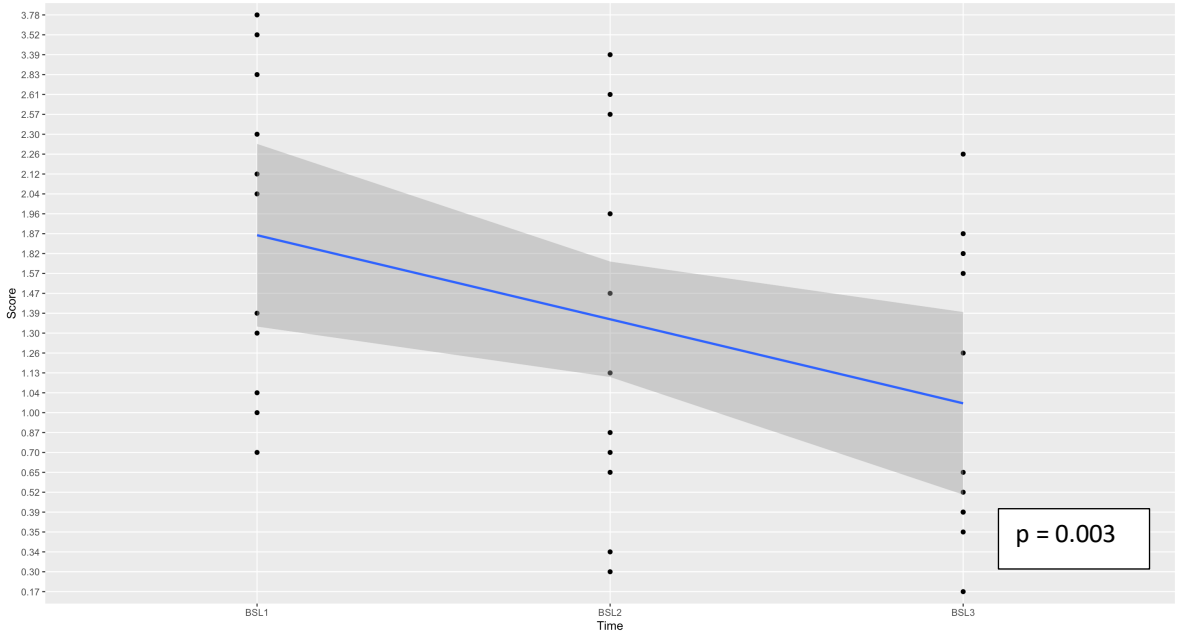


**Figure 4**

*Individual depressive symptoms scores over time. Each facet represents one participant. The horizontal line represents the clinical depression cut-off score.*

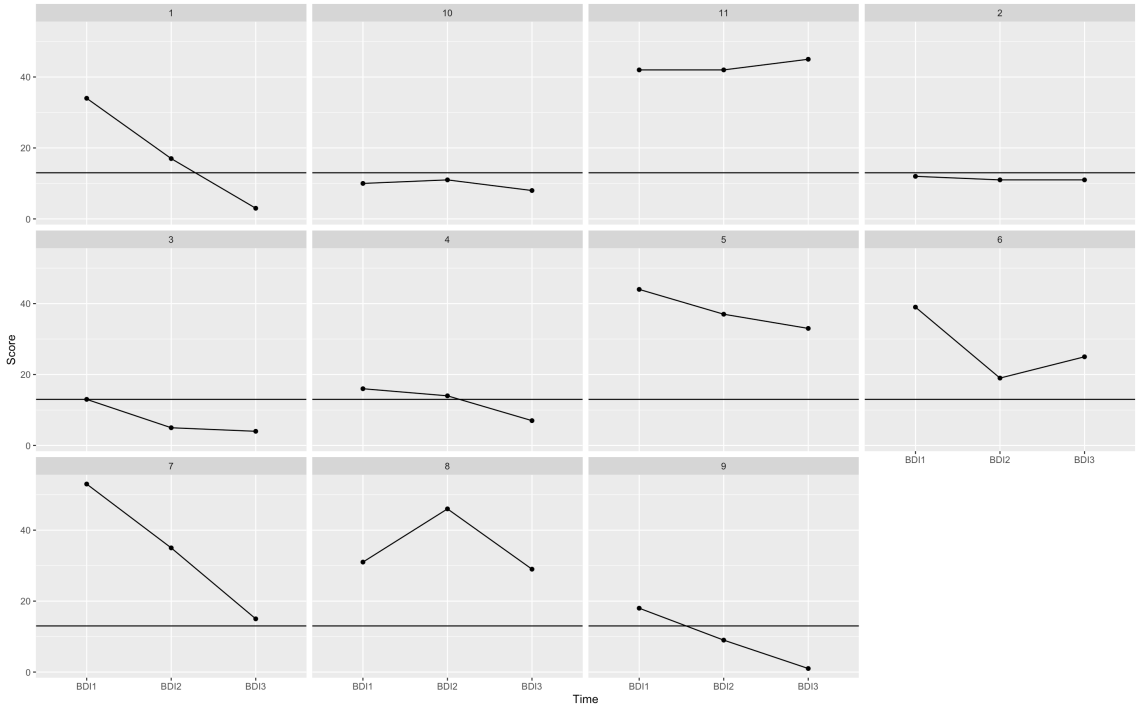


**Figure 5**

*Depressive symptoms scores over time. Individual values at each time and linear regression with confidence interval.*

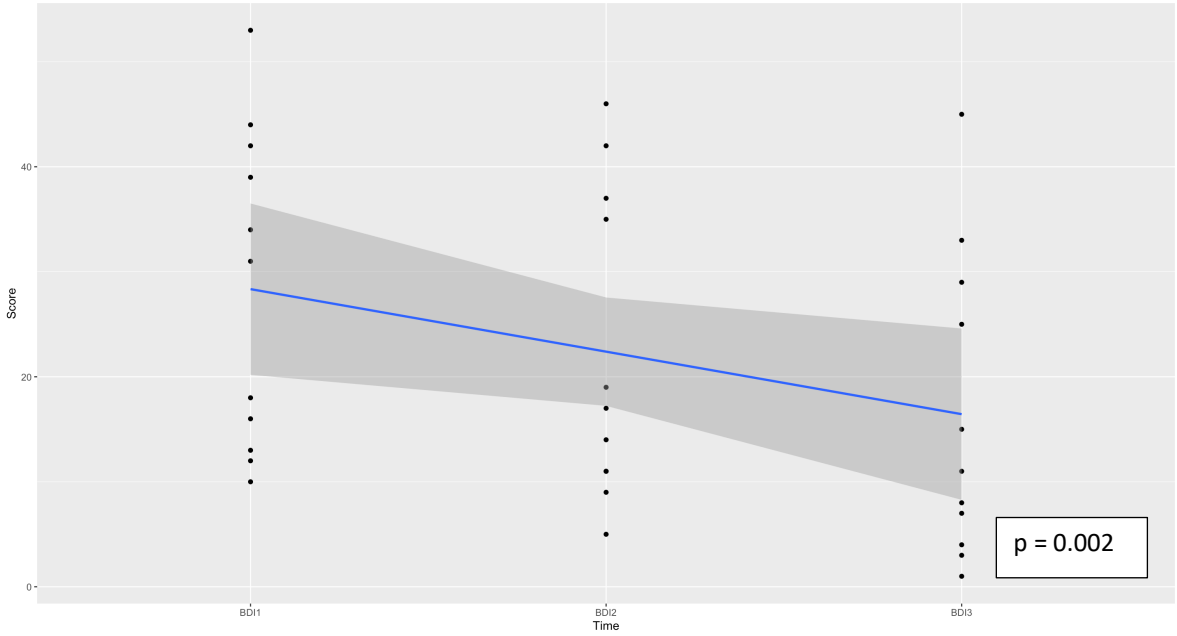


**Figure 6**

*Individual psychotherapy outcome scores over time. Each facet represents one participant. The horizontal line represents clinical cut-off score.*

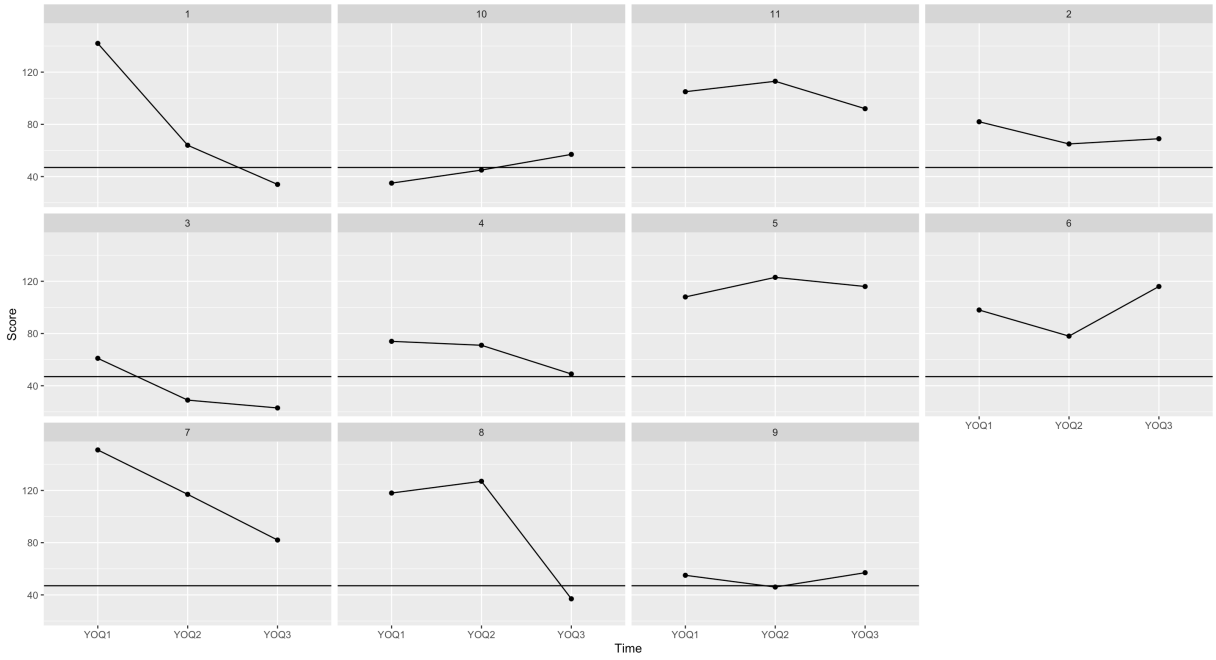
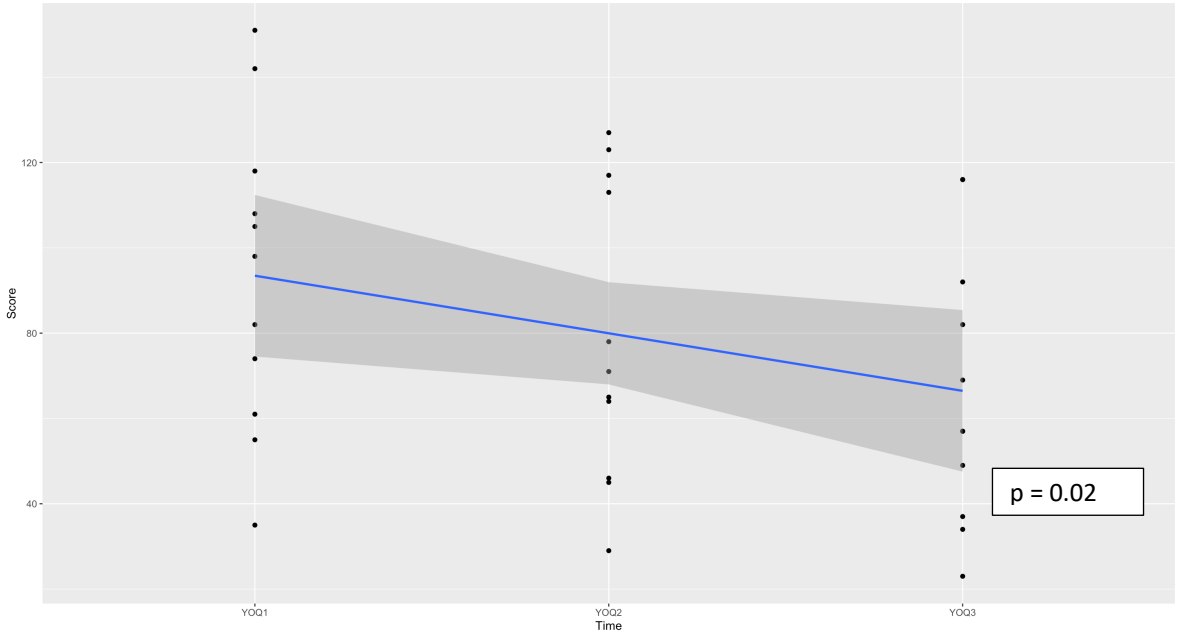



**Figure 7**

*Psychotherapy outcome scores over time. Individual values at each time and linear regression with confidence interval.*



### 7.3 *FKBP5* DNA methylation change over time and its relationship to clinical measures

The change over time of average and site-specific DNA methylation was assessed.

Mean *FKBP5* DNA methylation decrease over time (β=-0.93, SE = 0.92, p = .04) (see table 4 for the regression analysis, figure 8 for individual trajectories and figure 9 for linear trend). Fixed effects explain 0.06 of the variance (marginal $R^2$: 0.06, conditional $R^2$: 0.06). When analyzing each methylation site separately, no association was found.

**Table 4**

*Regression analyses of mean FKBP5 DNA methylation change in time*

| | β(S.E) | t |
|---|---|---|
| Parameter | | |
| Fixed Effects | | |
| Intercept | 78.60(0.92)* | 85.55 |
| Time | -0.93(0.41)* | -2.25 |
| Random Effects | | |
| Intercept | 0.00089 | |
| Residual | 3.05 | |

NOTE 1: Estimates and standard errors (in parentheses). *p < .05, **p<.01

**Figure 8**

*Individual mean FKBP5 DNA methylation over time. Each facet represents one participant.*

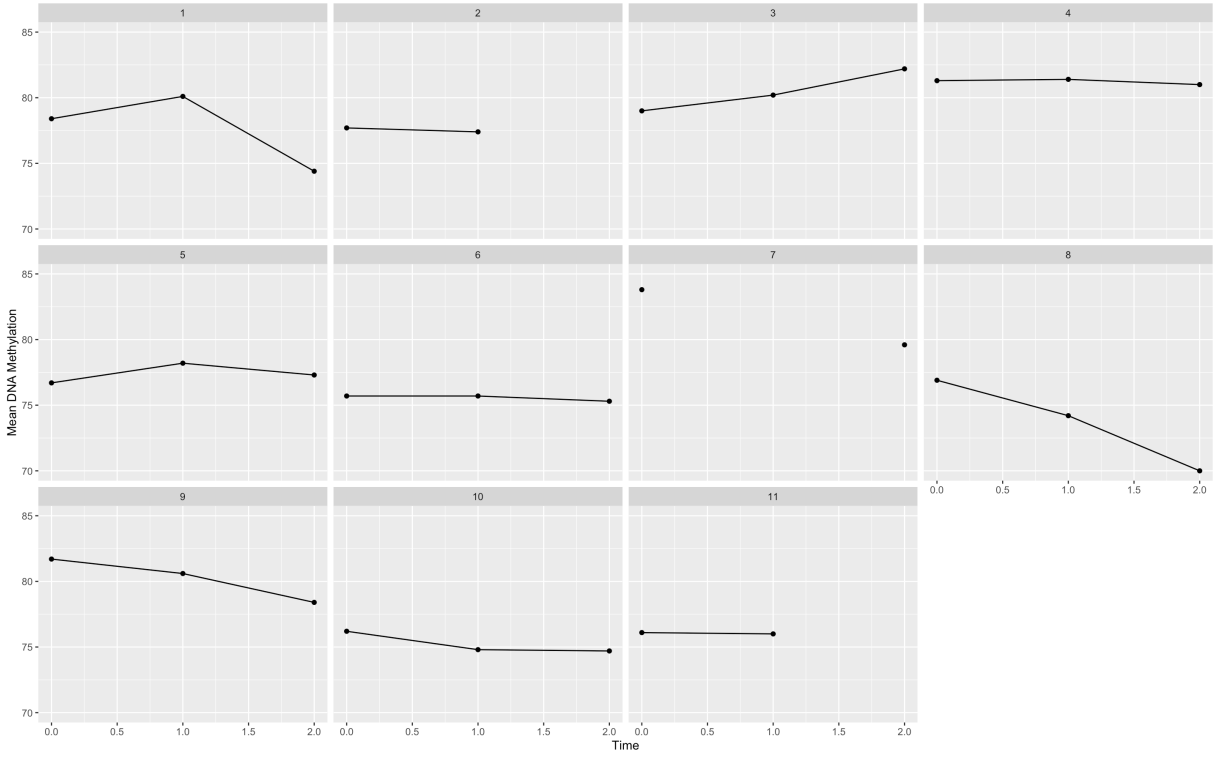
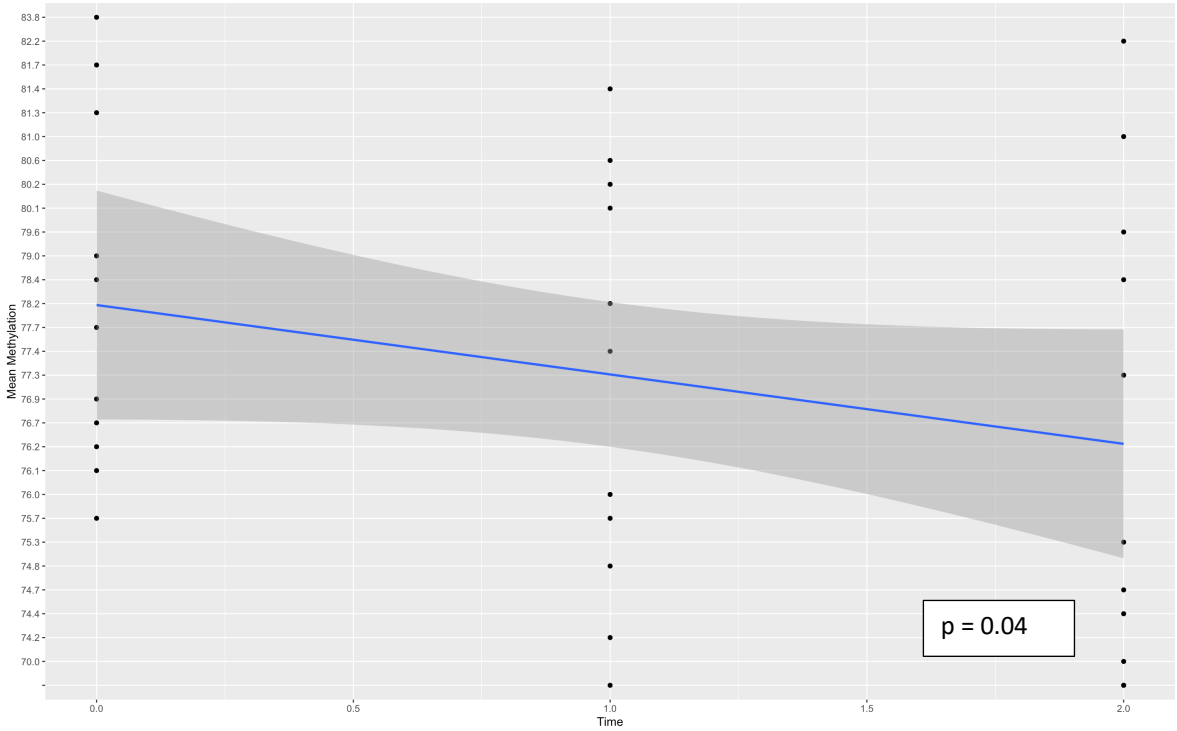


**Figure 9**

*FKBP5 mean DNA methylation over time. Individual values at each time and linear regression with confidence interval.*




The presence of childhood trauma was determined if at least one of the subscales of the CTQ scored above the threshold for moderate trauma. No significant differences in DNA methylation were found at baseline between individuals with and without the presence of childhood trauma (0.79 versus 0.78, p = .65).

Individuals who report trauma shows more decrease in *FKBP5* DNA methylation than the whole group (Figure 10), this reduction is also significant (β=-1.69, SE = 0.78, p = .04) (Table 4). In this model, fixed effects explain 0.18 of the variance (marginal $R^2$: 0.18, conditional $R^2$: 0.35).

Response to psychotherapy as measured by Y-OQ-SR and according to the Reliable Change Index was associated with a decrease in mean *FKBP5* DNA methylation only in those

participants who reported the presence of moderate to severe childhood trauma (β=-3.18, SE = 1.24, p = .04) (Table 5 and Figure 11). In this model, fixed effects explain 0.42 of the variance (marginal $R^2$: 0.42, conditional $R^2$: 0.81).

No significant relationship was observed between genotype, depressive symptoms, borderline symptoms, mentalization and emotional regulation and change in DNA methylation over time (data not shown).

**Table 5**

*Regression analyses of mean FKBP5 DNA methylation change in time according to trauma*

| | β(S.E) | t |
|---|---|---|
| Parameter | | |
| Fixed Effects | | |
| Intercept | 77.14(1.79)** | 43.14 |
| Time | 0.13(0.67) | 0.20 |
| Trauma | 0.97(1.95) | 0.50 |
| Genotype | 1.79(1.76) | 1.02 |
| Time x Trauma | -1.69(0.78) * | -2.18 |
| Random Effects | | |
| Intercept | 1.45 | |
| Residual | 2.75 | |

NOTE: Estimates and standard errors (in parentheses). *p < .05, **p<.01.

**Figure 10**

*Mean FKBP5 DNA methylation change in time according to trauma. (0 = No trauma).*

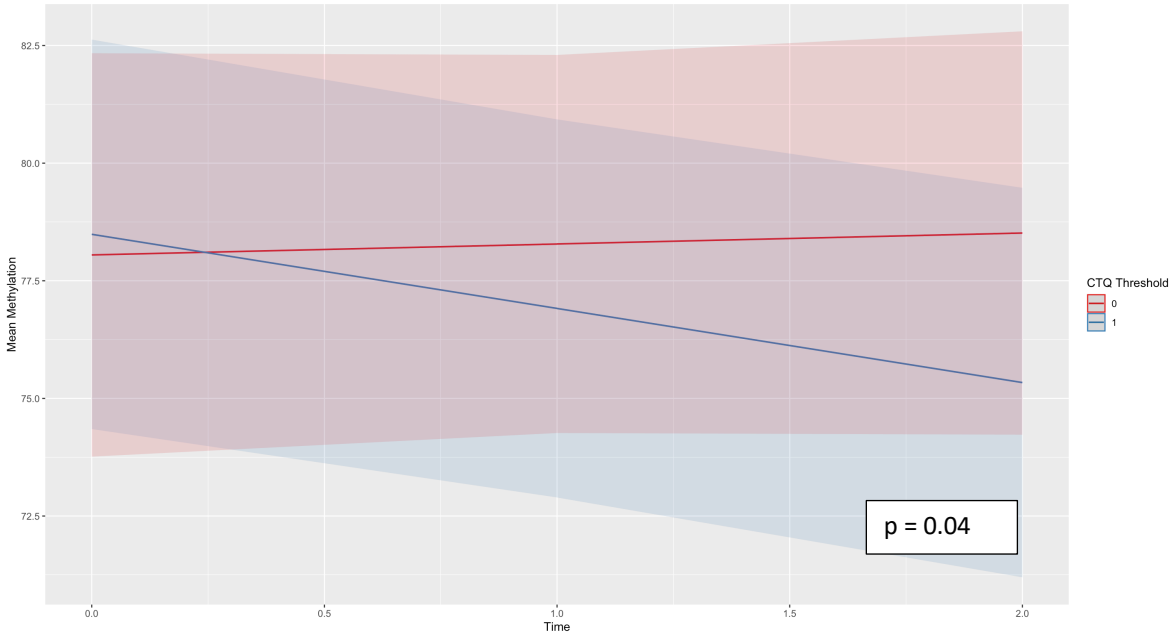



**Table 6**

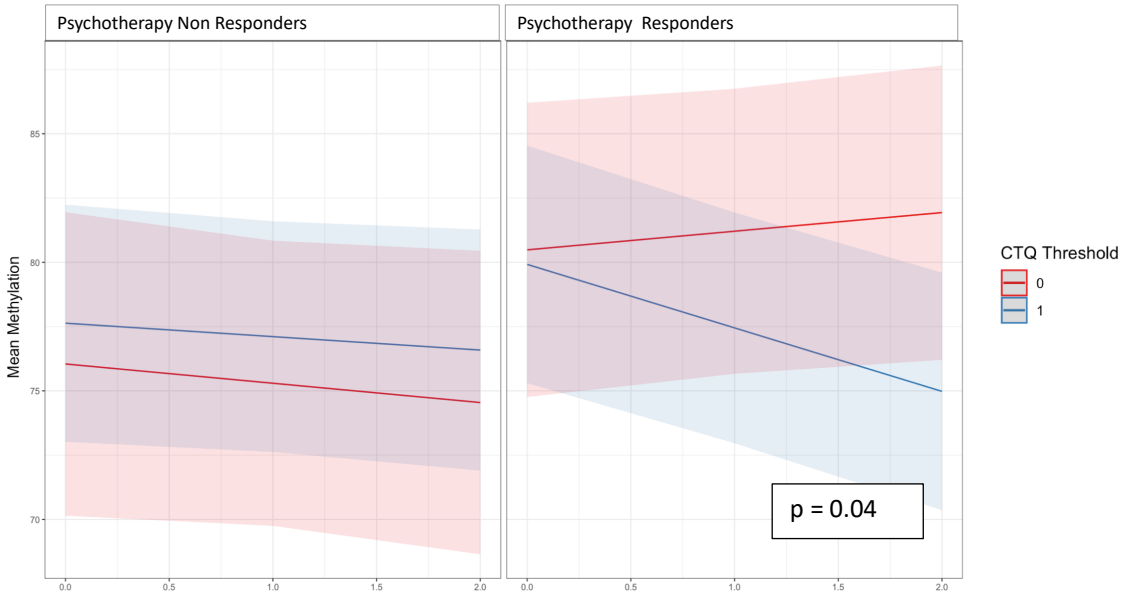
*Regression analyses of mean FKBP5 DNA methylation change in time according to trauma and psychotherapy response*

| | β(S.E) | t |
|---|---|---|
| Parameter | | |
| Fixed Effects | | |
| Intercept | 75.03(1.95)** | 38.45 |
| Time | -0.48(0.68) | -0.70 |
| Trauma | 2.27(2.22) | 1.02 |
| Psychotherapy Response | 4.24 (2.55) | 1.65 |
| Genotype | 1.73(1.47) | 1.17 |
| Time x Trauma | -0.14(0.89) | -0.02 |
| Trauma x Psychotherapy Response | 1.2(0.96) | -0.45 |
| Time x Trauma x Psychotherapy Response | -3.18(1.24) * | -2.57 |
| Random Effects | | |
| Intercept | 2.12 | |
| Residual | 1.46 | |

NOTE: Estimates and standard errors (in parentheses). *p < .05, **p<.01.

**Figure 11**

*Mean FKBP5 DNA methylation change in time according to trauma and psychotherapy response (0 = No trauma).*




## 7. DISCUSSION

Regarding hypothesis 1 which states that the DNA methylation pattern of *FKBP5* gene change in adolescents with BPD after psychotherapy treatment, the finding of decreased *FKBP5* DNA methylation associated with response to psychotherapy replicates the results of previous studies in PTSD treated with exposure therapy (Yehuda et al., 2013), children with anxiety disorders treated with cognitive behavioral therapy (Roberts et al., 2015) and individuals with Agoraphobia with or without panic disorder (Roberts et al., 2019). Bishop et al (2020) also report significant findings in individuals with PTSD treated with Mindfulness

Based Stress Reduction (MBSR) therapy, but in the opposite direction, responders have increased DNA methylation (intron 7, bin 2). This study found a decrease in *FKBP5* DNA methylation in BPD phenotype and with different types of psychotherapy (psychodynamic psychotherapy and dialectic behavior therapy) suggesting that psychotherapies in general can act as "environmental regulators" (Yehuda et al., 2013) through modification of expression of HPA-axis related genes across several mental disorders. DBT psychotherapy has previously been associated with DNA methylation change in other genes in BPD subjects, but not with *FKBP5* (Perroud et al., 2013; Knoblich et al., 2017 and Thomas et al., 2018).

The identification of plasticity genes can contribute to the advance in the identification of molecular markers of stable improvement in BPD. Interesting candidates are genes associated with HPA axis, *NR3C1* and *FKBP5*. Both showed stability in methylation for two years in healthy adults suggesting that it could be trait markers of stable changes and individual differences in stress response regulation (Di Sante et al., 2018). More research is needed to determine the patterns of variability and stability in time of methylation patterns of different genes, in different developmental periods and in clinical samples.

A relevant finding of this study is that only those who reported the presence of early trauma had a decrease in DNA methylation.

Although in this study no difference in DNA methylation of FKBP5 intron 7 was found at baseline and no effect of FKBP5 SNP1360780 risk T allele, several studies have reported a relationship between the presence of childhood trauma and decreased DNA methylation levels in this region across different populations, preschool children, low income adult population, holocaust offspring, postpartum women, subjects with MDD and subjects with psychotic disorders (Grasso et al, 2020; Klengel et al., 2013; Misiak et al, 2020; Tozzi et al., 2018;

Tyrka et al., 2015; Yehuda et al., 2013) in particular those subjects carrying the *FKBP5* SNP1360780 risk T allele, suggesting the impact of early emotional environment on stress response systems and development of psychopathology throughout life.

Regarding hypothesis 2 which states that the improvement in mentalization, emotion regulation achieved in therapy in adolescents with BPD in psychotherapy is associated with changes in DNA methylation of FKBP5 gene. No significant change in mentalization levels was observed, nor was an association found with response to psychotherapy or changes in DNA methylation. This is probably due to the difficulty of the instruments to detect changes in mentalizing capacity, which is highly context-dependent. In individuals with BPD faced with interpersonal situations that generate emotional arousal, mentalizing capacity is deactivated and less sophisticated behavioral and emotional patterns are activated (Fonagy & Bateman, 2008). Instruments that can assess mentalization emerging from dyadic interaction such as psychotherapy sessions (Talia et al., 2019) could be more accurate and ecologically valid in finding improvements in mentalization.

With respect to emotional regulation, no improvement was observed in response to psychotherapy, nor was there any association with changes in methylation. A previous study has shown improvements in emotional regulation, measured by DERS in response to DBT psychotherapy in adults BPD patients in a small sample (n= 22) (Goodman et al., 2014). To date and to our knowledge, no changes in emotional regulation associated with epigenetic changes have been reported.

In this study, only individuals who reported the presence of early trauma and who responded to psychotherapy exhibited a decrease in DNA methylation. Other studies have reported positive associations between the presence of early adverse events and response to

psychotherapy, adult individuals treated for chronic depression responded better to psychotherapy than to psychopharmacological treatment if they had a history of childhood abuse (Nemeroff et al, 2003). Similarly, adolescents with non-suicidal self-injury (NSSI) had a better response to psychotherapy in reducing the frequency of NSSI if they had reported adverse childhood experiences (Edinger et al., 2020). This differential response by the presence of early trauma is suggestive of specific mechanisms not only of symptomatology development but also of distinct mechanisms of recovery. In this sample, the differential response to psychotherapy at the level of DNA methylation may imply that some individuals are more permeable at the molecular level to both negative (early trauma) and positive influences (psychotherapy) from their affective environment.

According to the differential sensitivity model, individuals carrying "plasticity genes" who, faced with an early sub-optimal affective environment, would be more susceptible to develop psychopathology, but can be also more susceptible to respond to positive social environments (Hammen et al., 2015). Psychotherapeutic interventions, understood as a factor capable of modifying the relationship with the current social environment, may have a greater effect on individuals who carry plasticity genes (Jiménez et al., 2018; Leighton et al., 2017)

In accordance with the above, a GWAS study of twins reported a polygenic score based on differences in sensitivity to develop anxiety disorders according to positive or negative parenting. In a second sample, individuals with major differential sensitivity polygenic score responded better to individual cognitive behavioral therapy (Keers et al., 2016). These results suggest that those individuals who present a greater sensitivity to the environment present more emotional problems if they experienced negative parenting, but they will also be the

ones who will benefit most from more intensive forms of psychotherapy (Choi-Kain et al., 2017).

This study has several limitations; the sample size is small, the results should be interpreted with caution and require replication in larger samples. For the same reason, other concomitant environmental factors were not incorporated as covariates that may interact with DNA methylation such as physical factors, i.e., nutrition, alcohol, drugs, contraceptives and sleep deprivation (Gabbianelli & Damiani, 2018; Nilsson et al., 2016; Sarabi et al., 2017) and other social factors such as socioeconomic status (Maddock et al., 2018) should be taken into account.

The absence of healthy controls is another important limitation because in the childhood and adolescent population there may be methylation changes associated with development.

In this regard, studies exploring longitudinal changes using a genome-wide DNA methylation strategy in adolescents show that in a range of 3 to 6 months, there is one group of genes that is highly variable over time and another that varies between individuals, but remains stable over time (Levesque et al., 2014).

In this study, BPD symptomatology was assessed through an instrument based on symptom intensity according to the DSM-IV categorization (Bohus et al., 2009). The study of personality can be broadened by resorting to a dimensional approach in line with the Alternative Model of Personality Disorders of DSM-5 (American Psychiatric Association, 2013)and the International Classification of Diseases, 11th Revision (ICD-11, (ICD-11 - Mortality and Morbidity Statistics, accessed 2021)), for example characterizing the Functioning Levels of Personality, which include identity, self-direction, empathy and intimacy (Zimmermann et al., 2012). These dimensions of personality functioning are more

directly connected with the focus of the therapeutic work and, therefore, allow a greater understanding of the mechanisms of change in psychotherapy of personality.

Another limitation of the study is the absence of measurement of current contextual factors that could influence the change in DNA methylation. In this regard, a longitudinal study in preschoolers showed an interaction between early adversity and contextual stressors including household instability, inadequate feeding or clothing, or separation from caregivers on the change over time of DNA methylation in 2 CpG regions of intron 7 of FKBP5 highlighting the potential impact of current stress on epigenetic modifications (Parade et al., 2018). However, the current study did consider the evolution over time in different areas of the individual's functioning through the subscales of the Y-OQ-SR instrument that include intrapersonal distress, behavioral dysfunction, somatic complaints, interpersonal relations, social problems and critical items (suicidality, substance use among others). A larger sample size would allow to know the differential impact of distinct contextual stressors.

Along with outcome indicators, psychotherapy process measures such as emotional regulation and mentalization were included which has not been reported in previous studies. Other process measures can be incorporated, such as therapeutic alliance (Horvath et al., 2011), characteristics of the therapist (e.g. warmth) and the patient (e.g. expectations) (Wampold, 2015). Prospective, longitudinal studies designs with the use of repeated measures could allow to explore the interaction between and DNA methylation changes and different factors of the therapy process.

Blood samples were used as a tissue surrogate for epigenetic changes in the central nervous system, although several studies show a correlation between peripheral tissues and brain tissue, it should be noted that the correlations are relatively small-moderate (Braun et al.,

2019; Walton et al., 2016). Further evidence is required for the specificity of genes and loci that might be sensitive to change in the affective environment. With respect to FKBP5, a study in mice exposed to corticosteroid administration reported a high correlation between DNA methylation of intronic regions of FKBP5 in brain and blood. This correlation would be dependent on functional glucocorticoid signaling in both tissues and would suggest that blood DNA can be used to assess dynamic changes induced by stress in the brain (Ewald et al., 2014).

Functional inferences are not possible given that FKBP5 expression and endocrine markers of hypothalamic-pituitary-adrenal axis function were not measured. Yehuda et al., (2013) found that variation in FKBP5 DNA methylation was associated with treatment response and correlated with measures of plasma cortisol and glucocorticoid sensitivity, implying a functional impact at the HPA axis level of changes in DNA methylation.

Close human relations regulate optimal stimulation and modulate arousal levels and attenuate stress in order to improve the adaptation to the social environment. This phenomenon has been called "psychobiological attunement", has been explored in mother-child dyads and peer relations and can be observed from its behavioral, physiological and biochemical correlates (Field, 2012). For example, intrusive mothers can up regulate infants developing stress systems, increasing cortisol levels in saliva (Tarullo et al., 2017).

During the establishment of the therapeutic relationship, the formation of an alliance between patient and therapist can lead to the restoration of "epistemic trust", that is, to restore an individual's confidence in obtaining from another human being knowledge relevant to his or her adaptation to the social world (Fonagy & Allison, 2014). This would be particularly relevant with individuals with BPD, in whom insecure attachment patterns developed in sub-

optimal interaction with their caregivers would involve chronic epistemic mistrust, i.e., a deficiency in the trustworthiness and relevance of interpersonal communication with the concomitant development of deficient behavioral and emotional patterns for establishing cooperation and the ability to repair ruptures in relationships with others. (Fonagy et al., 2015; Orme et al., 2019).

Psychotherapy as a special form of human relationship, would then be constituted as a biologically embedded experience, capable of altering biological functions in a stable and long-term manner (Demetriou et al., 2015). Psychotherapy is constituted as a disrupter of the "external social recursion" that goes from the social environment to the neural systems, modifying the subjective perception of the interpersonal environment. At the same time, it is capable of changing the "internal physiologic recursion" that ranges from the Central Nervous System to gene expression, that includes hormonal systems, inflammatory molecules and intracellular signal transduction (Slavich and Cole, 2013).

Psychotherapy focused in personality pathology may lead to changes in DNA methylation causing not only a symptomatic improvement but a permanent reprogramming of the phenotypic adaptation to the interpersonal environment.

## 9. CONCLUSIONS

The results of this research show a change in DNA methylation at specific sites of the FKBP5 gene in adolescents with BPD after psychotherapy in agreement with the first hypothesis of the study. A change in DNA methylation was observed in relation to the outcome of psychotherapy, particularly in subjects who report early trauma, but not in relation to mentalization or emotional regulation, not supporting the second hypothesis.

The results highlight the role of psychotherapy as an environmental regulator capable of exerting actions at the epigenetic level on genes associated with stress response in individuals with BPD.

Replication of these findings in larger samples and the inclusion of functional markers of the stress response, variables of the psychotherapeutic process and other environmental variables that may cause changes in DNA methylation are required.

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## 11. ANNEXED: QUESTIONNAIRES AND INTERVIEW

SOCIODEMOGRAPHICS QUESTIONS

ENCUESTA SOCIODEMOGRÁFICA

NOMBRE:

1. ¿Cuál es tu sexo? –

a. Hombre b. Mujer

2. ¿Qué edad tienes? _____

3. ¿En que curso estás?_____

3. ¿En qué comuna vives? _____

4. ¿Qué nacionalidad tienes?

a. Chilena b. Otra(describa)_____

5. ¿Con quién vives?

a. Con ambos padres.

b. Con mi padre.

c. Con mi madre.

d. Con otro cuidador(describa)_____

6. ¿Tienes hermanos?

a. No b. Si (¿Cuántos?)_____

7. Si tienes hermanos ¿Qué numero de hermano eres?

a. Primero
b. Segundo
c. Tercero
d. Cuarto o más

8. ¿Vive alguien más en tu casa?

a. No

b. Si (¿Quién o quiénes?)_____

_____

BRIEF REFLECTIVE FUNCTIONING INTERVIEW

1. Tell me about one of your parents- what is that parent like?
2. How do you think he/she came to be that way? (if the subject says, "that is just their personality", or that "they are just like one of their parents", ask –do you think this came about genetically or in some other way? )
3. Can you tell me about your relationship- what is it like?
4. Do you have any thoughts about how your relationship came to be that way? (if the subject doesn't respond in much detail, you should add, "tell me how the relationship came to be… …", using the subject's words from question 3)
5. Can you tell me a specific memory of being with that parent between ages 5 and 12? (if a general memory is given, such as, "we used to always….,"then ask for a memory that is particular, something that happened on one occasion)
6. How has this relationship changed over time? Can you tell me about it?
7. What kind of impact has this parent had on your life?
8. Why do you think you chose to talk about this parent today?
9. Can you tell me about another person who is important in your life now?
10. Can you tell me about your relationship with that person?

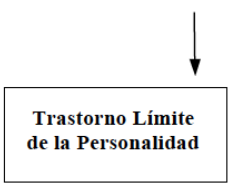
STRUCTURED CLINICAL INTERVIEW FOR DSM-IV AXIS II PERSONALITY DISORDERS (SCID II)

**SCID - II** **Trastorno Límite de la Personalidad**

**? = Inadecuado** **1 = Ausente o falso** **2 = Subumbral** **3 = Umbral o verdadero**

| | **Trastorno Límite de la Personalidad** | **Criterios para el Trastorno Límite de la Personalidad** | | | | | |
|---|---|---|---|---|---|---|---|
| | | Un patrón general de inestabilidad en las relaciones interpersonales, la autoimagen y la efectividad, y una notable impulsividad, que comienzan al principio de la edad adulta y se dan en diversos contextos, como lo indican cinco (o más) de los siguientes: | | | | | |
| 90 | ¿Se ha puesto frenético cuando alguien que le importaba lo iba a dejar?<br>¿Que fue lo que hizo?<br>(¿Lo amenazó o le suplicó?) | (1) Esfuerzos frenéticos para evitar un abandono real o imaginado (Nota: No incluir los comportamientos suicidas o de automutilación que se recogen en el criterio 5).<br>3 = Varios ejemplos. | **?** | **1** | **2** | **3** | **112** |
| 91 | ¿Las relaciones con la gente que le importa tienen muchos altibajos?<br>Platíqueme de ello<br>(¿Hubo momentos en los que pensó que ellos eran todo lo que usted deseaba y otros momentos en los que pensó que eran terribles? ¿Cuántas de sus relaciones han sido así?) | (2) Un patrón de relaciones interpersonales inestables e intensas caracterizado por la alternativa entre los extremos de idealización y devaluación.<br>3 = Ya sea una relación prolongada o varias relaciones breves en donde el patrón ocurre al menos dos veces. | **?** | **1** | **2** | **3** | **113** |
| 92 | ¿De forma repentina ha perdido el sentido de quien es y hacia donde se dirige?<br>Deme algunos ejemplos de esto | (3) Alteración de la identidad; autoimagen o sentido de sí mismo acusada y persistentemente inestable.<br>(Nota: No se incluyen la incertidumbre normal del adolescente). | **?** | **1** | **2** | **3** | **114** |
| 93 | ¿El sentido de quien es cambia de forma dramática?<br>Platíqueme de ello | 3 = Acepta la característica. | | | | | |
| 94 | ¿Se comporta diferente con distintas personas o diferentes situaciones por lo que en ocasiones ya no sabe quien es en realidad?<br>Deme algunos ejemplos de esto<br>(¿Se siente de esta forma muy seguido?) | | | | | | |
| 95 | ¿Han habido cambios repentinos en sus metas, planes de carrera, creencias religiosas, etc.?<br>Platíqueme de ello | | | | | | |
| 96 | ¿Con frecuencia hace cosas impulsivamente?<br>¿Qué clase de cosas?<br>(¿Qué acerca de...<br>...comprar cosas que no puede pagar?<br>...tener relaciones sexuales con | (4) Impulsividad en al menos dos áreas, que es potencialmente dañina para sí mismo (p.ej., gastos, sexo, abuso de sustancias, conducción temeraria, atracones de comida). (Nota: No incluir los comportamientos suicidas o automutilación que se recogen en el criterio 5).<br>3 = Varios ejemplos que indican un patrón de comportamiento impulsivo (no necesariamente limitado a los ejemplos expuestos | **?** | **1** | **2** | **3** | **115** |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | personas que no conoce muy bien o "sexo no seguro"?<br>...beber demasiado o consumir drogas?<br>...manejar sin precaución?<br>...comer sin control alguno?)<br>SI A CUALQUIERA DE LAS ANTERIORES:<br>Platíqueme de ello. ¿Con qué frecuencia ocurre? ¿Qué clase de problemas le ha causado? | anteriormente). | | | | | |
| 97 | ¿Ha tratado de lastimarse o suicidarse o ha amenazado con hacerlo? | (5) Comportamientos, intentos o amenazas suicidas recurrentes, o comportamientos de automutilación. | **?** | **1** | **2** | **3** | **116** |
| 98 | ¿alguna vez se ha cortado, quemado o lastimado a propósito?<br>Platíqueme de ello. | 3 = Dos o más eventos (cuando no ocurren en el curso de un episodio depresivo mayor) | | | | | |
| 99 | ¿Tiene muchos cambios repentinos de humor? | (6) Inestabilidad afectiva debida a una notable reactividad del estado de ánimo (p.ej. episodios de intensa disforia, irritabilidad o ansiedad, que suelen durar unas horas y rara vez unos días). | **?** | **1** | **2** | **3** | **117** |
| | Platíqueme de ello<br>(¿Cuánto dura su "mal" humor? ¿Con que frecuencia se dan estos cambios? ¿Que tan repentinamente cambian?) | 3 = Acepta la característica. | | | | | |
| 100 | ¿Con frecuencia se siente vacío por dentro?<br>Platíqueme de ello. | (7) Sentimientos crónicos de vacío.<br>3 = Acepta la característica. | **?** | **1** | **2** | **3** | **118** |
| 101 | ¿Con frecuencia tiene estallidos o se enoja a tal grado de perder el control? | (8) Ira inapropiada e intensa o dificultades para controlar la ira (p.ej., muestras frecuentes de mal genio, enfado constante, peleas físicas recurrentes). | **?** | **1** | **2** | **3** | **119** |
| | Platíqueme de ello | 3 = Acepta la característica y al menos da un ejemplo. | | | | | |
| 102 | ¿Con frecuencia golpea a la gente o arroja cosas cuando está enojado?<br>Platíqueme de ello<br>(¿Ocurre con frecuencia?) | | | | | | |
| 103 | ¿Aún las cosas pequeñas le enojan demasiado?<br>¿Cuándo ocurre esto?<br>(¿Ocurre con frecuencia?) | | | | | | |
| 104 | ¿Cuando está bajo mucho estrés, sospecha de otras personas o se siente sin espacio alguno?<br>Platíqueme de ello. | (9) Ideación paranoide transitoria relacionada con el estrés o síntomas disociativos graves<br>3 = Varios ejemplos que no ocurren exclusivamente durante un trastorno psicótico o afectivo con rasgos psicóticos | **?** | **1** | **2** | **3** | **120** |
| | | **AL MENOS CINCO REACTIVOS CODIFICADOS "3"** | | **1** | | **3** | **121** |



M.I.N.I KID PSYCHOTIC DISORDER AND DISOCIAL DISORDER

## R. TRASTORNOS PSICÓTICOS

(➡ SIGNIFICA: IR A LAS CASILLAS DIAGNÓSTICAS, CIRCULAR **NO** EN CADA UNA Y CONTINUAR CON EL SIGUIENTE MÓDULO)

**PIDA UN EJEMPLO PARA CADA PREGUNTA CONTESTADA AFIRMATIVAMENTE. CODIFIQUE SÍ** SOLAMENTE PARA AQUELLOS EJEMPLOS QUE MUESTRAN CLARAMENTE UNA DISTORSIÓN DEL PENSAMIENTO O DE LA PERCEPCIÓN O SI NO SON CULTURALMENTE APROPIADOS. ANTES DE CODIFICAR, INVESTIGUE SI LAS IDEAS DELIRANTES CALIFICAN COMO "EXTRAÑAS" O RARAS.

LAS IDEAS DELIRANTES SON "EXTRAÑAS" O RARAS SI: SON CLARAMENTE ABSURDAS, IMPROBABLES, INCOMPRENSIBLES, Y NO PUEDEN DERIVARSE DE EXPERIENCIAS DE LA VIDA COTIDIANA.

LAS ALUCINACIONES SON "EXTRAÑAS" O RARAS SI: UNA VOZ HACE COMENTARIOS SOBRE LOS PENSAMIENTOS O LOS ACTOS DE LA PERSONA DOS O MAS VOCES CONVERSAN ENTRE SÍ.

| | | Ahora te voy a preguntar acerca de experiencias poco usuales que algunas personas pueden tener. | | | EXTRAÑAS | |
|---|---|---|---|---|---|---|
| R1 | a | ¿Alguna vez, has creído que secretamente la gente te mira? ¿Alguna vez, has creído alguien te esta persiguiendo o trata de hacerte daño?<br>CODIFICAR SÍ, SI CONTESTÓ SÍ EN ALGUNA<br>**NOTA:** PIDA EJEMPLOS PARA DESCARTAR UN VERDADERO ACECHO | NO | SÍ | SÍ | 1 |
| | b | **SI SÍ:** ¿Actualmente crees esto? | NO | SÍ | SÍ ➡R6 | 2 |
| R2 | a | ¿Alguna vez, has creído que alguien estaba leyendo tu mente? ¿O que alguien podía escuchar tus pensamientos? ¿O tu podías leer lo que estaba en la mente de otra persona? ¿O podías escuchar lo que estaban pensando? | NO | SÍ | SÍ | 3 |
| | b | **SI SÍ:** ¿Actualmente crees esto? | NO | SÍ | SÍ ➡R6 | 4 |
| R3 | a | ¿Alguna vez ha creído, que alguien o algo puso pensamientos en tu mente que no eran los tuyos? ¿Has creído que alguien o algo te hizo actuar de una manera no usual en ti?<br>**NOTA**: PIDA EJEMPLOS Y DESCARTE CUALQUIERA QUE NO SEA PSICÓTICO | NO | SÍ | SÍ | 5 |
| | b | **SI SÍ:** ¿Actualmente crees esto? | NO | SÍ | SÍ ➡R6 | 6 |
| R4 | a | ¿ Alguna vez ha creído, que te enviaban mensajes especiales a través de el televisor o la radio? ¿A través de tus juguetes?<br>CODIFICAR SÍ, SI CONTESTÓ SÍ EN ALGUNA | NO | SÍ | SÍ | 7 |
| | b | **SI SÍ:** ¿Actualmente crees esto? | NO | SÍ | SÍ ➡R6 | 8 |
| R5 | a | ¿Alguna vez han considerado tus familiares o amigos que algunas de tus creencias son extrañas o poco usuales? Me puedes dar un ejemplo.<br>ENTREVISTADOR/A:. CODIFIQUE SÍ SOLO SI LOS EJEMPLOS SON **CLARAMENTE** IDEAS DELIRANTES Y NO HAN SIDO EXPLORADAS EN LAS PREGUNTAS DE R1 A R4, POR EJEMPLO, SOMÁTICOS O RELIGIOSOS O GRANDEZA, CELOS, CULPA, RUINA O DESTITUCIÓN, ETC. | NO | SÍ | SÍ | 9 |
| | b | **SI SÍ:** ¿Actualmente, creen los demás que tus ideas son extrañas? | NO | SÍ | SÍ | 10 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| R6 | a | ¿Alguna vez, has escuchado cosas que otras personas no pueden escuchar, como voces?<br>[LAS ALUCINACIONES SON CODIFICADAS COMO "EXTRAÑAS" SOLAMENTE SI EL PACIENTE CONTESTA SÍ A LO SIGUIENTE]:<br>**SI SÍ:** ¿Escuchaste una voz hablabando de ti? Escuchaste más de una voz hablando? | NO | SÍ | SÍ | 11 |
| | b | **SI SÍ:** ¿Has escuchado estas cosas en el pasado mes? | NO | SÍ | SÍ →R 8b | 12 |
| R7 | a | ¿Alguna vez, has tenido visiones o ha visto cosas que otros no pueden ver?<br>NOTA: INVESTIGUE SI ESTAS VISIONES SON CULTURALMENTE INAPROPIADAS | NO | | SÍ | 13 |
| | b | **SI SÍ:** ¿Ha visto estas cosas el pasado mes? | NO | | SÍ | 14 |
| | | **BAJO EL PUNTO DE VISTA DEL ENTREVISTADOR (A)**: | | | | |
| R8 | b | ¿PRESENTA EL PACIENTE ACTUALMENTE UN LENGUAJE, INCOHERENTE DESORGANIZADO, O CON MARCADA PÉRDIDA DE LAS ASOCIACIONES? | NO | | SÍ | 15 |
| R9 | b | ¿PRESENTA EL PACIENTE ACTUALMENTE UN COMPORTAMIENTO DESORGANIZADO O CATATÓNICO? | NO | | SÍ | 16 |
| R10 | b | ¿HAY SÍNTOMAS NEGATIVOS DE ESQUIZOFRENIA PROMINENTES DURANTE LA ENTREVISTA [UN APLANAMIENTO AFECTIVO INCAPACIDAD PARA INICIAR O PERSISTIR EN ACTIVIDADES CON UNA FINALIDAD DETERMINADA] ? | NO | | SÍ | 17 |

R11 ¿CODIFICÓ **SÍ** EXTRAÑO EN **1 O MÁS** PREGUNTAS « b »?

**O**

¿CODIFICÓ **SÍ** (EN VEZ DE **SÍ** EXTRAÑO) EN **2 O MÁS** PREGUNTAS « b »?

**NO** **SÍ**

***TRASTORNO PSICÓTICO* ACTUAL**

R12 ¿CODIFICÓ **SÍ** EXTRAÑO EN **1 O MÁS** PREGUNTAS « a »?

**O**

¿CODIFICÓ **SÍ** (EN VEZ DE **SÍ** EXTRAÑO) EN **2 O MÁS** PREGUNTAS « a »?

VERIFIQUE QUE LOS DOS SÍNTOMAS OCURRIERAN DURANTE EL MISMO PERÍODO DE TIEMPO

18

**NO** **YES**

***TRASTORNO PSICÓTICO* DE POR VIDA**

# CHILD TRAUMA QUESTIONNAIRE

CTQ [1]

Mientras iba creciendo...

| | Nunca | Rara vez | Algunas veces | Frecuentemente | Muy frecuentemente |
|---|---|---|---|---|---|
| 1. No tenía suficiente para comer | | | | | |
| 2. Yo sabía que había alguien para cuidarme y protegerme | | | | | |
| 3. Algunas personas de mi familia me decían cosas como "estúpido/a", "flojo/a", o "feo/a" | | | | | |
| 4. Mis padres estaban demasiado borrachos o drogados como para cuidar de la familia | | | | | |
| 5. Había alguien en mi familia que me ayudaba a sentirme importante o especial | | | | | |
| 6. Tenía que usar ropa sucia | | | | | |
| 7. Me sentía amado/a | | | | | |
| 8. Alguna vez pensé que mis padres desearon que yo jamás hubiese nacido | | | | | |
| 9. Alguna o algunas personas de mi familia me pegaron tan fuerte que tuve que ver un doctor o ir al hospital | | | | | |
| 10. No hubo nada que haya querido cambiar de mi familia | | | | | |
| 11. Algunas personas de mi familia me pegaban/golpeaban tan fuerte que me dejaban marcas o moretones | | | | | |
| 12. Era castigado con un cinturón, una palo, un cuerda o algún otro objeto duro | | | | | |
| 13. Las personas en mi familia nos cuidábamos lo unos a los otros | | | | | |
| 14. Algunas personas de mi familia me decían cosas hirientes o insultos | | | | | |
| 15. Yo creo que fui maltratado físicamente | | | | | |
| 16. Tuve una infancia perfecta | | | | | |
| 17. Fui tan fuertemente golpeado/a por alguien de mi familia que otras personas, como un profesor, un vecino o un médico, se dieron cuenta | | | | | |
| 18. Yo sentía que alguien en mi familia me odiaba | | | | | |
| 19. Las personas en mi familia se sentían cercanas entre ellas | | | | | |
| 20. Alguien intentó tocarme en una forma sexual, o trató que yo lo/la tocara | | | | | |
| 21. Alguien me amenazó con hacerme daño o decir mentiras acerca de mí a menos que yo hiciera algo sexual con el o ella. | | | | | |
| 22. Yo tenía la mejor familia del mundo. | | | | | |
| 23. Alguien intentó que yo hiciera cosas sexuales o que viera cosas sexuales | | | | | |
| 24. Alguien me acosaba /incomodaba | | | | | |
| 25. Yo creo que fui maltratado emocionalmente | | | | | |
| 26. Había alguien para llevarme al doctor si lo necesitaba | | | | | |
| 27. Yo creo que fui sexualmente abusado/a | | | | | |
| 28. Mi familia era una fuente de fuerza y apoyo | | | | | |

[1]Bernstein, D. P., Stein, J. A., Newcomb, M. D., Walker, E., Pogge, D., Ahluvalia, T., Zule, W. (2003). Development and validation of a brief screening version of the childhood trauma questionnaire. *Child Abuse & Neglect, 27*(2), 169-190. doi: 10.1016/S0145-2134(02)00541-0 Adaptado para Chile por Leighton, C.; Botto, A.; De la Cerda C.J.; Undurraga, C. (2013)

ADOLESCENT ATTACHMENT QUESTIONNAIRE

## Cuestionario de Apego en Adolescentes (AAQ)

**Curso** ☐ **Edad** ☐ **Sexo: Hombre** ☐ **Mujer** ☐

**Por favor, contesta las 9 preguntas que se muestran a continuación.**

1) Estas preguntas tienen que ver con lo que sientes sobre tu relación con la persona que más te crió desde que naciste.
2) En cada frase del cuestionario aparecerá un **espacio en blanco** que corresponde a la persona que tú reconoces como aquella que más te crió. **Deberás responder todas las preguntas pensando siempre en esa misma persona.**
3) Por favor, encierra con un círculo uno de los números del 1 al 5 que aparecen frente a cada frase. Mientras más cerca del 1 es porque NO estás de acuerdo con lo que dice la frase, y si el número es más cercano a 5, significa que SI estás de acuerdo con lo que dice la frase
4) No tienes que poner tu nombre en el cuestionario, y nadie va a saber que fuiste tú el/la que lo contestó.

| | | Muy en desacuerdo | En desacuerdo | Ni de acuerdo ni en desacuerdo | De acuerdo | Muy de acuerdo |
|---|---|---|---|---|---|---|
| 1. | Me hace sentir bien ser capaz de ayudar a _____ | 1 | 2 | 3 | 4 | 5 |
| 2. | A veces me siento enojado/a con_____ sin saber por qué | 1 | 2 | 3 | 4 | 5 |
| 3. | Estoy seguro/a que _____ me escuchará. | 1 | 2 | 3 | 4 | 5 |
| 4. | Me molesto con _____ porque pareciera que tengo que exigirle que me cuide y apoye. | 1 | 2 | 3 | 4 | 5 |
| 5. | Estoy seguro que _____ tratará de entender cómo me siento | 1 | 2 | 3 | 4 | 5 |
| 6. | Puedo ponerme en el lugar de _____ y entenderlo/a cuando se enoja. | 1 | 2 | 3 | 4 | 5 |
| 7. | Disfruto ayudando a _____ cada vez que puedo. | 1 | 2 | 3 | 4 | 5 |
| 8. | Hablo las cosas con _____ | 1 | 2 | 3 | 4 | 5 |
| 9 | Pareciera que _____ sólo me presta atención cuando estoy enojado/a | 1 | 2 | 3 | 4 | 5 |

¿Quién es la persona que elegiste para completar los espacios en blanco? ☐

DIFFICULTIES IN EMOTION REGULATION SCALE (DERS)

Terapia Psicológica 2014, Vol. 32, Nº 1, 19-29 Validez y Confiabilidad de la versión adaptada al español de la Escala de Dificultades de Regulación Emocional (DERS-E) en población chilena. Mónica Guzmán-González; Caterina Trabucco Alfonso Urzúa M., Lusmenia Garrido ,José Leiva

**Escala de Regulación emocional (Guzman-González et al, 2014)**

| Indique con qué frecuencia se le pueden aplicar las siguientes afirmaciones según la escala que aparece a continuación. | | | | | |
|---|---|---|---|---|---|
| | Casi Nunca | Algunas veces | La mitad de las veces | La mayoría de las veces | Casi Siempre |
| 1. Percibo con claridad mis sentimientos | 1 | 2 | 3 | 4 | 5 |
| 2. Presto atención a como me siento | 1 | 2 | 3 | 4 | 5 |
| 3. Vivo mis emociones como algo desbordante y fuera de control | 1 | 2 | 3 | 4 | 5 |
| 4. No tengo ni idea de cómo me siento | 1 | 2 | 3 | 4 | 5 |
| 5. Tengo dificultades para comprender mis sentimientos | 1 | 2 | 3 | 4 | 5 |
| 6. Estoy atento a mis sentimientos | 1 | 2 | 3 | 4 | 5 |
| 7. Doy importancia a lo que estoy sintiendo | 1 | 2 | 3 | 4 | 5 |
| 8. Estoy confuso sobre lo que siento | 1 | 2 | 3 | 4 | 5 |
| 9. Cuando me encuentro mal, reconozco mis emociones | 1 | 2 | 3 | 4 | 5 |
| 10. Cuando me encuentro mal, me enfado conmigo mismo por sentirme de esa manera | 1 | 2 | 3 | 4 | 5 |
| 11. Cuando me encuentro mal, me da vergüenza sentirme de esa manera | 1 | 2 | 3 | 4 | 5 |
| 12. Cuando me siento mal, tengo dificultades para completar trabajos. | 1 | 2 | 3 | 4 | 5 |
| 13. cuando me encuentro mal, pierdo el control | 1 | 2 | 3 | 4 | 5 |
| 14. Cuando me encuentro mal, creo que estaré así durante mucho tiempo | 1 | 2 | 3 | 4 | 5 |
| 15. Cuando me encuentro mal, creo que acabaré sintiéndome muy deprimido | 1 | 2 | 3 | 4 | 5 |
| 16. cuando me encuentro mal, me resulta difícil centrarme en otras cosas | 1 | 2 | 3 | 4 | 5 |
| 17. Cuando me encuentro mal, me siento fuera de control | 1 | 2 | 3 | 4 | 5 |
| 18. Cuando me encuentro mal, me siento avergonzado conmigo mismo por sentirme | 1 | 2 | 3 | 4 | 5 |

| | | | | | |
|---|---|---|---|---|---|
| de esa manera | | | | | |
| 19. Cuando me encuentro mal, me siento como si fuera una persona débil | 1 | 2 | 3 | 4 | 5 |
| 20. Cuando me encuentro mal, me siento culpable por sentirme de esa manera | 1 | 2 | 3 | 4 | 5 |
| 21. Cuando me encuentro mal, tengo dificultades para concentrarme | 1 | 2 | 3 | 4 | 5 |
| 22. Cuando me encuentro mal, tengo dificultades para controlar mi comportamiento | 1 | 2 | 3 | 4 | 5 |
| 23. Cuando me encuentro mal, me irrito conmigo mismo por sentirme de esa manera | 1 | 2 | 3 | 4 | 5 |
| 24. Cuando me encuentro mal, empiezo a sentirme muy mal sobre mí mismo | 1 | 2 | 3 | 4 | 5 |
| 25. Cuando me encuentro mal, creo que darme vueltas en ello es todo lo que puedo hacer | 1 | 2 | 3 | 4 | 5 |
| 26. Cuando me encuentro mal, pierdo el control sobre mi comportamiento | 1 | 2 | 3 | 4 | 5 |
| 27. Cuando me encuentro mal, tengo dificultades para pensar sobre cualquier otra cosa | 1 | 2 | 3 | 4 | 5 |
| 28. Cuando me encuentro mal, mis emociones parecen desbordarse | 1 | 2 | 3 | 4 | 5 |

BECK DEPRESSION INVENTORY (BDI-I)

NÚCLEO MILENIO
INTERVENCIÓN PSICOLÓGICA
Y CAMBIO EN DEPRESIÓN

| ID Participante | |
|---|---|
| Fecha | |

**BDI-I[1]**

En este cuestionario aparecen varios grupos de afirmaciones. Por favor, lea con atención cada una. A continuación, señale cuál de las afirmaciones de cada grupo describe mejor cómo se ha sentido **DURANTE ESTA ÚLTIMA SEMANA, INCLUIDO EL DIA DE HOY**. Encierre en un círculo el número que está a la izquierda de la afirmación que haya elegido. Si dentro de un mismo grupo hay más de una afirmación que considere aplicable a su caso puede marcarla también. **Asegúrese de leer todas las afirmaciones dentro de cada grupo antes de efectuar la elección.**

| A | F |
|---|---|
| 0. No me siento triste<br>1. Me siento triste<br>2. Me siento triste continuamente y no puedo dejar de estarlo<br>3. Ya no puedo soportar esta pena | 0. No siento que esté siendo castigado/a<br>1. Me siento como si fuese a ser castigado/o<br>2. Siento que me están castigando o que me castigarán<br>3. Siento que merezco ser castigado/a |
| **B** | **G** |
| 0. No me siento pesimista, ni creo que las cosas me vayan a salir mal<br>1. Me siento desanimado/a cuando pienso en el futuro<br>2. Creo que nunca me recuperaré de mis penas<br>3. Ya no espero nada bueno de la vida, esto no tiene remedio | 0. No estoy decepcionado de mí mismo/a<br>1. Estoy decepcionado de mí mismo/a<br>2. Estoy muy descontento/a conmigo mismo/a<br>3. Me odio, me desprecio |
| **C** | **H** |
| 0. No me considero fracasado/a<br>1. Creo que he tenido más fracasos que la mayoría de la gente<br>2. Cuando miro hacia atrás, sólo veo fracaso tras fracaso<br>3. Me siento una persona totalmente fracasada | 0. No creo ser peor que otras personas<br>1. Me critico mucho por mis debilidades y errores<br>2. Continuamente me culpo de todo lo que va mal<br>3. Siento que tengo muchos y muy graves defectos |
| **D** | **I** |
| 0. Las cosas me satisfacen tanto como antes<br>1. No disfruto de las cosas tanto como antes<br>2. Ya nada me llena<br>3. Estoy harto/a de todo | 0. No tengo pensamientos de hacerme daño<br>1. Tengo pensamientos de hacerme daño, pero no llegaría a hacerlo<br>2. Siento que estaría mejor muerto/a o que mi familia estaría mejor si yo me muriera<br>3. Me mataría si pudiera |
| **E** | **J** |
| 0. No me siento culpable<br>1. Me siento culpable en bastantes ocasiones<br>2. Me siento culpable en la mayoría de las ocasiones<br>3. Todo el tiempo me siento una persona mala y despreciable | 0. No lloro más de lo habitual<br>1. Ahora lloro más de lo normal<br>2. Ahora lloro continuamente, no puedo evitarlo<br>3. Antes podía llorar, ahora no lloro aunque quisiera |

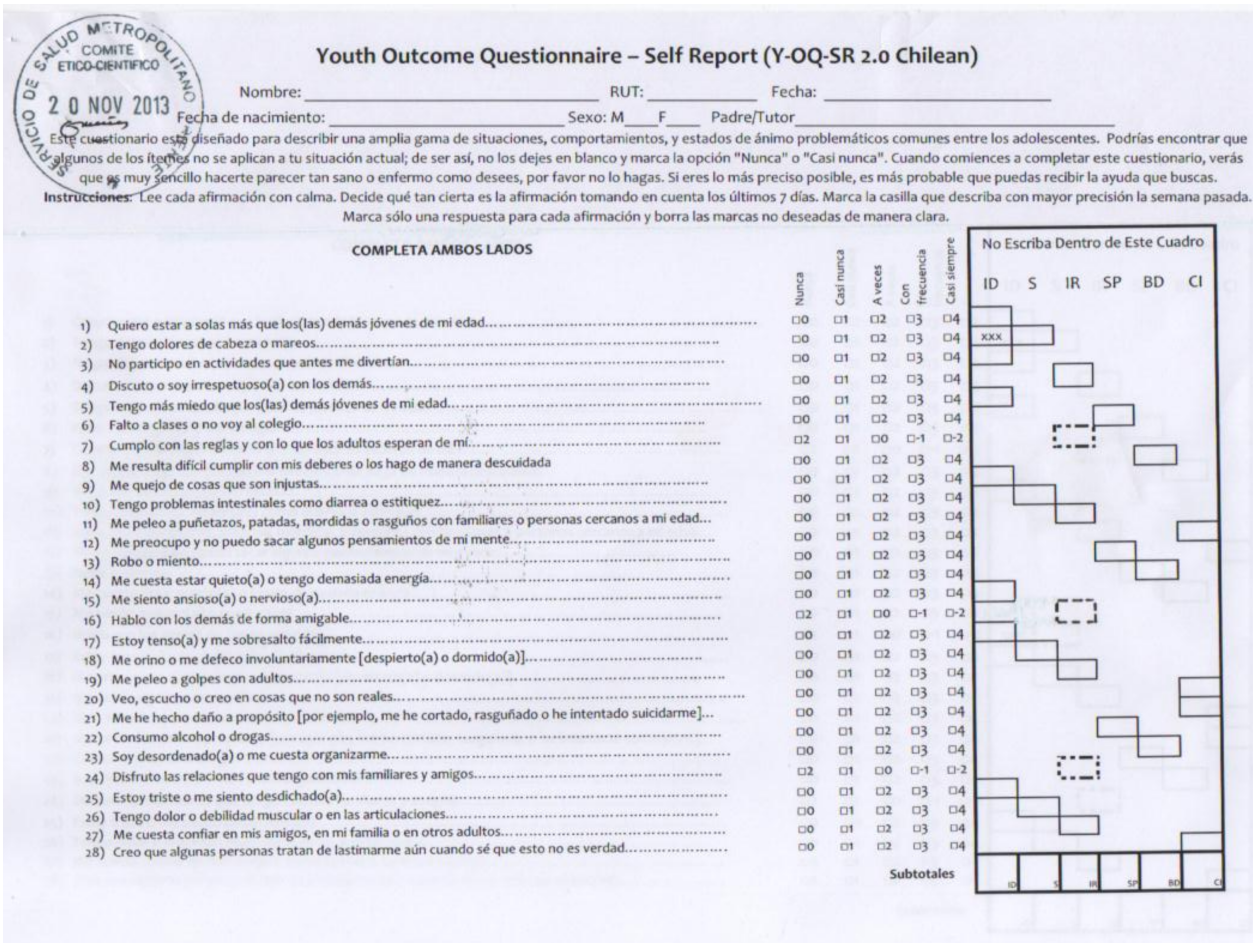
[1]Traducción basada en el original en inglés de Beck, Ward, Mendelson, Mock & Erbaugh (1961).

NÚCLEO MILENIO
INTERVENCIÓN PSICOLÓGICA
Y CAMBIO EN DEPRESIÓN

| ID Participante | |
|---|---|
| Fecha | |

| K | Q |
|---|---|
| 0. No estoy más irritable de lo normal<br>1. Me irrito o enojo con más facilidad que antes<br>2. Me siento irritado/a todo el tiempo<br>3. Las cosas que antes me irritaban ya ni siquiera me importan | 0. No me canso más de lo normal<br>1. Me canso más fácilmente que antes<br>2. Cualquier cosa que hago me cansa<br>3. Estoy demasiado cansado/a para hacer nada |
| **L** | **R** |
| 0. No he perdido el interés por los demás<br>1. Me intereso por la gente menos que antes<br>2. He perdido casi todo mi interés por los demás<br>3. Los demás no me importan en absoluto | 0. Tengo el mismo apetito de siempre<br>1. No tengo tan buen apetito como antes<br>2. Ahora tengo mucho menos apetito<br>3. He perdido totalmente el apetito |
| **M** | **S** |
| 0. Tomo mis decisiones como siempre<br>1. Estoy inseguro/a de mí mismo/a y evito tomar decisiones<br>2. Ya no puedo tomar decisiones sin ayuda<br>3. Ya no puedo tomar decisiones en absoluto | 0. No he perdido peso últimamente<br>1. He perdido más de 2 kilos<br>2. He perdido más de 5 kilos<br>3. He perdido más de 8 kilos<br><br>Estoy bajo dieta para adelgazar: SI NO |
| **N** | **T** |
| 0. No me siento con peor aspecto que antes<br>1. Me preocupa que ahora parezco más viejo/a o poco atractivo/a<br>2. Creo que se han producido cambios permanentes en mi aspecto que me hacen parecer poco atractivo/a<br>3. Creo que tengo un aspecto horrible | 0. No estoy más preocupado/a por mi estado de salud que lo habitual<br>1. Estoy preocupado/a por problemas físicos como dolores, molestias, malestar de estómago o estreñimiento<br>2. Estoy preocupado/a por mi salud y me es difícil pensar en otra cosa<br>3. Estoy tan preocupado/a por mis problemas de salud que soy incapaz de pensar en otra cosa |
| **O** | **U** |
| 0. Puedo trabajar tan bien como siempre<br>1. Tengo que hacer un esfuerzo especial para iniciar algo<br>2. Tengo que obligarme mucho para hacer algo<br>3. Soy incapaz de hacer algún trabajo | 0. No he notado ningún cambio en mi atracción por el sexo<br>1. Estoy menos interesado/a en el sexo que antes<br>2. Actualmente me siento mucho menos interesado/a en el sexo<br>3. He perdido todo mi interés por el sexo |
| **P** | |
| 0. Duermo tan bien como siempre<br>1. Me despierto más cansado/a por la mañana<br>2. Me estoy despertando una o dos horas más temprano de lo habitual y no puedo volver a quedarme dormido/a<br>3. Me despierto varias horas más temprano todas las mañanas y no logro dormir más de 5 horas | Subtotal Página 1<br>Subtotal Página 2<br>Total |

YOUTH OUTCOME SELF-REPORT (Y-OQ-SR)



SERVICIO DE SALUD METROPOLITANO COMITE ETICO-CIENTIFICO 20 NOV 2013

## Youth Outcome Questionnaire – Self Report (Y-OQ-SR 2.0 Chilean)

Nombre: _____ RUT: _____ Fecha: _____

Fecha de nacimiento: _____ Sexo: M____F____ Padre/Tutor_____

Este cuestionario está diseñado para describir una amplia gama de situaciones, comportamientos, y estados de ánimo problemáticos comunes entre los adolescentes. Podrías encontrar que algunos de los ítemes no se aplican a tu situación actual; de ser así, no los dejes en blanco y marca la opción "Nunca" o "Casi nunca". Cuando comiences a completar este cuestionario, verás que es muy sencillo hacerte parecer tan sano o enfermo como desees, por favor no lo hagas. Si eres lo más preciso posible, es más probable que puedas recibir la ayuda que buscas.

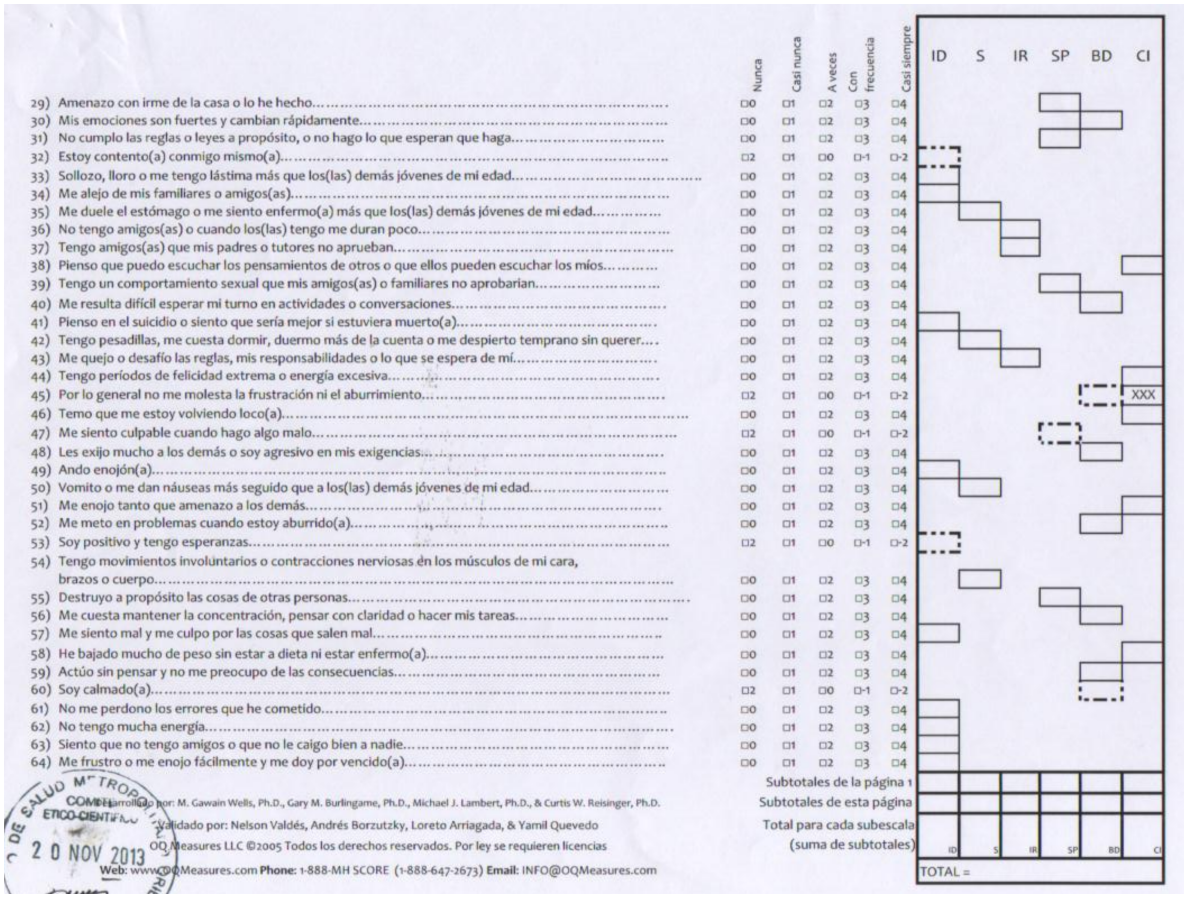
**Instrucciones**: Lee cada afirmación con calma. Decide qué tan cierta es la afirmación tomando en cuenta los últimos 7 días. Marca la casilla que describa con mayor precisión la semana pasada. Marca sólo una respuesta para cada afirmación y borra las marcas no deseadas de manera clara.

**COMPLETA AMBOS LADOS**

| | | Nunca | Casi nunca | A veces | Con frecuencia | Casi siempre |
|---|---|---|---|---|---|---|
| 1) | Quiero estar a solas más que los(las) demás jóvenes de mi edad | □0 | □1 | □2 | □3 | □4 |
| 2) | Tengo dolores de cabeza o mareos | □0 | □1 | □2 | □3 | □4 |
| 3) | No participo en actividades que antes me divertían | □0 | □1 | □2 | □3 | □4 |
| 4) | Discuto o soy irrespetuoso(a) con los demás | □0 | □1 | □2 | □3 | □4 |
| 5) | Tengo más miedo que los(las) demás jóvenes de mi edad | □0 | □1 | □2 | □3 | □4 |
| 6) | Falto a clases o no voy al colegio | □0 | □1 | □2 | □3 | □4 |
| 7) | Cumplo con las reglas y con lo que los adultos esperan de mí | □2 | □1 | □0 | □-1 | □-2 |
| 8) | Me resulta difícil cumplir con mis deberes o los hago de manera descuidada | □0 | □1 | □2 | □3 | □4 |
| 9) | Me quejo de cosas que son injustas | □0 | □1 | □2 | □3 | □4 |
| 10) | Tengo problemas intestinales como diarrea o estitiquez | □0 | □1 | □2 | □3 | □4 |
| 11) | Me peleo a puñetazos, patadas, mordidas o rasguños con familiares o personas cercanos a mi edad | □0 | □1 | □2 | □3 | □4 |
| 12) | Me preocupo y no puedo sacar algunos pensamientos de mi mente | □0 | □1 | □2 | □3 | □4 |
| 13) | Robo o miento | □0 | □1 | □2 | □3 | □4 |
| 14) | Me cuesta estar quieto(a) o tengo demasiada energía | □0 | □1 | □2 | □3 | □4 |
| 15) | Me siento ansioso(a) o nervioso(a) | □0 | □1 | □2 | □3 | □4 |
| 16) | Hablo con los demás de forma amigable | □2 | □1 | □0 | □-1 | □-2 |
| 17) | Estoy tenso(a) y me sobresalto fácilmente | □0 | □1 | □2 | □3 | □4 |
| 18) | Me orino o me defeco involuntariamente [despierto(a) o dormido(a)] | □0 | □1 | □2 | □3 | □4 |
| 19) | Me peleo a golpes con adultos | □0 | □1 | □2 | □3 | □4 |
| 20) | Veo, escucho o creo en cosas que no son reales | □0 | □1 | □2 | □3 | □4 |
| 21) | Me he hecho daño a propósito [por ejemplo, me he cortado, rasguñado o he intentado suicidarme] | □0 | □1 | □2 | □3 | □4 |
| 22) | Consumo alcohol o drogas | □0 | □1 | □2 | □3 | □4 |
| 23) | Soy desordenado(a) o me cuesta organizarme | □0 | □1 | □2 | □3 | □4 |
| 24) | Disfruto las relaciones que tengo con mis familiares y amigos | □2 | □1 | □0 | □-1 | □-2 |
| 25) | Estoy triste o me siento desdichado(a) | □0 | □1 | □2 | □3 | □4 |
| 26) | Tengo dolor o debilidad muscular o en las articulaciones | □0 | □1 | □2 | □3 | □4 |
| 27) | Me cuesta confiar en mis amigos, en mi familia o en otros adultos | □0 | □1 | □2 | □3 | □4 |
| 28) | Creo que algunas personas tratan de lastimarme aún cuando sé que esto no es verdad | □0 | □1 | □2 | □3 | □4 |
| | **Subtotales** | | | | | |

No Escriba Dentro de Este Cuadro

| ID | S | IR | SP | BD | CI |
|---|---|---|---|---|---|
| XXX | | | | | |



| | Nunca | Casi nunca | A veces | Con frecuencia | Casi siempre |
|---|---|---|---|---|---|
| 29) Amenazo con irme de la casa o lo he hecho | □0 | □1 | □2 | □3 | □4 |
| 30) Mis emociones son fuertes y cambian rápidamente | □0 | □1 | □2 | □3 | □4 |
| 31) No cumplo las reglas o leyes a propósito, o no hago lo que esperan que haga | □0 | □1 | □2 | □3 | □4 |
| 32) Estoy contento(a) conmigo mismo(a) | □2 | □1 | □0 | □-1 | □-2 |
| 33) Sollozo, lloro o me tengo lástima más que los(las) demás jóvenes de mi edad | □0 | □1 | □2 | □3 | □4 |
| 34) Me alejo de mis familiares o amigos(as) | □0 | □1 | □2 | □3 | □4 |
| 35) Me duele el estómago o me siento enfermo(a) más que los(las) demás jóvenes de mi edad | □0 | □1 | □2 | □3 | □4 |
| 36) No tengo amigos(as) o cuando los(las) tengo me duran poco | □0 | □1 | □2 | □3 | □4 |
| 37) Tengo amigos(as) que mis padres o tutores no aprueban | □0 | □1 | □2 | □3 | □4 |
| 38) Pienso que puedo escuchar los pensamientos de otros o que ellos pueden escuchar los míos | □0 | □1 | □2 | □3 | □4 |
| 39) Tengo un comportamiento sexual que mis amigos(as) o familiares no aprobarían | □0 | □1 | □2 | □3 | □4 |
| 40) Me resulta difícil esperar mi turno en actividades o conversaciones | □0 | □1 | □2 | □3 | □4 |
| 41) Pienso en el suicidio o siento que sería mejor si estuviera muerto(a) | □0 | □1 | □2 | □3 | □4 |
| 42) Tengo pesadillas, me cuesta dormir, duermo más de la cuenta o me despierto temprano sin querer | □0 | □1 | □2 | □3 | □4 |
| 43) Me quejo o desafío las reglas, mis responsabilidades o lo que se espera de mí | □0 | □1 | □2 | □3 | □4 |
| 44) Tengo períodos de felicidad extrema o energía excesiva | □0 | □1 | □2 | □3 | □4 |
| 45) Por lo general no me molesta la frustración ni el aburrimiento | □2 | □1 | □0 | □-1 | □-2 |
| 46) Temo que me estoy volviendo loco(a) | □0 | □1 | □2 | □3 | □4 |
| 47) Me siento culpable cuando hago algo malo | □2 | □1 | □0 | □-1 | □-2 |
| 48) Les exijo mucho a los demás o soy agresivo en mis exigencias | □0 | □1 | □2 | □3 | □4 |
| 49) Ando enojón(a) | □0 | □1 | □2 | □3 | □4 |
| 50) Vomito o me dan náuseas más seguido que a los(las) demás jóvenes de mi edad | □0 | □1 | □2 | □3 | □4 |
| 51) Me enojo tanto que amenazo a los demás | □0 | □1 | □2 | □3 | □4 |
| 52) Me meto en problemas cuando estoy aburrido(a) | □0 | □1 | □2 | □3 | □4 |
| 53) Soy positivo y tengo esperanzas | □2 | □1 | □0 | □-1 | □-2 |
| 54) Tengo movimientos involuntarios o contracciones nerviosas en los músculos de mi cara, brazos o cuerpo | □0 | □1 | □2 | □3 | □4 |
| 55) Destruyo a propósito las cosas de otras personas | □0 | □1 | □2 | □3 | □4 |
| 56) Me cuesta mantener la concentración, pensar con claridad o hacer mis tareas | □0 | □1 | □2 | □3 | □4 |
| 57) Me siento mal y me culpo por las cosas que salen mal | □0 | □1 | □2 | □3 | □4 |
| 58) He bajado mucho de peso sin estar a dieta ni estar enfermo(a) | □0 | □1 | □2 | □3 | □4 |
| 59) Actúo sin pensar y no me preocupo de las consecuencias | □0 | □1 | □2 | □3 | □4 |
| 60) Soy calmado(a) | □2 | □1 | □0 | □-1 | □-2 |
| 61) No me perdono los errores que he cometido | □0 | □1 | □2 | □3 | □4 |
| 62) No tengo mucha energía | □0 | □1 | □2 | □3 | □4 |
| 63) Siento que no tengo amigos o que no le caigo bien a nadie | □0 | □1 | □2 | □3 | □4 |
| 64) Me frustro o me enojo fácilmente y me doy por vencido(a) | □0 | □1 | □2 | □3 | □4 |



Subtotales de la página 1

Subtotales de esta página

Total para cada subescala (suma de subtotales)

ID S IR SP BD CI

TOTAL =



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Validado por: Nelson Valdés, Andrés Borzutzky, Loreto Arriagada, & Yamil Quevedo



Web: www.OQMeasures.com **Phone**: 1-888-MH SCORE (1-888-647-2673) **Email**: INFO@OQMeasures.com

BORDERLINE SYMPTOM LIST (BSL-23)

## Borderline Symptom List 23 (BSL-23)

**Code:** _____ **Date:** |__|__|. |__|__|. | 2 | 0 |__|__|

Por favor, siga estas instrucciones cuando responda el cuestionario: En la siguiente tabla encontrará una serie de dificultades y problemas que podrían describirle. Por favor, lea detenidamente el cuestionario y decida en qué grado le afectó cada problema durante la semana pasada. En el caso de que no sienta nada en este momento, por favor responda de acuerdo a cómo piensa *que podría haberse sentido.* Por favor responda con sinceridad.

**Todas las preguntas hacen referencia a la última semana. Si se ha sentido de diferente manera en diferentes momentos de la semana, haga una valoración promedio de cómo le fueron las cosas.**

**Por favor asegúrese de responder a todas las preguntas.**

| **Durante la última semana…** | | Nunca | Algo | Bastante | Mucho | Muchísimo |
|---|---|---|---|---|---|---|
| 1 | Me resultaba difícil concentrarme | **0** | **1** | **2** | **3** | **4** |
| 2 | Me sentí indefenso | **0** | **1** | **2** | **3** | **4** |
| 3 | Estuve ausente e incapaz de recordar que estaba haciendo en realidad | **0** | **1** | **2** | **3** | **4** |
| 4 | Sentí asco | **0** | **1** | **2** | **3** | **4** |
| 5 | Pensé en hacerme daño | **0** | **1** | **2** | **3** | **4** |
| 6 | Desconfié de los demás | **0** | **1** | **2** | **3** | **4** |
| 7 | No creía que tuviera derecho a vivir | **0** | **1** | **2** | **3** | **4** |
| 8 | Me sentía solo | **0** | **1** | **2** | **3** | **4** |
| 9 | Sentí una tensión interna estresante | **0** | **1** | **2** | **3** | **4** |
| 10 | Sentí mucho miedo de imágenes que me vinieron a la cabeza | **0** | **1** | **2** | **3** | **4** |
| 11 | Me odié a mí mismo | **0** | **1** | **2** | **3** | **4** |
| 12 | Quise castigarme | **0** | **1** | **2** | **3** | **4** |
| 13 | Sufrí de vergüenza | **0** | **1** | **2** | **3** | **4** |
| 14 | Mi humor oscilaba rápidamente entre la ansiedad, la rabia y la depresión. | **0** | **1** | **2** | **3** | **4** |
| 15 | Sufrí al oír voces y ruidos procedentes de dentro o fuera de mi cabeza | **0** | **1** | **2** | **3** | **4** |
| 16 | Las críticas tuvieron un efecto demoledor en mí | **0** | **1** | **2** | **3** | **4** |
| 17 | Me sentí vulnerable | **0** | **1** | **2** | **3** | **4** |
| 18 | La idea de morirme me causó una cierta fascinación | **0** | **1** | **2** | **3** | **4** |
| 19 | Nada parecía tener sentido para mí | **0** | **1** | **2** | **3** | **4** |
| 20 | Tuve miedo de perder el control | **0** | **1** | **2** | **3** | **4** |
| 21 | Me di asco a mí mismo | **0** | **1** | **2** | **3** | **4** |
| 22 | Tuve la sensación de salir de mí mismo | **0** | **1** | **2** | **3** | **4** |
| 23 | Sentí que no valía nada | **0** | **1** | **2** | **3** | **4** |

Ahora nos interesaría conocer además la calidad de su estado **general** a lo largo de la última semana. 0 % significa **absolutamente hundido**, 100% significa **excelente**. Por favor, señale el porcentaje que más se aproxime a su situación.

| 0% | 10% | 20% | 30% | 40% | 50% | 60% | 70% | 80% | 90% | 100% |
|---|---|---|---|---|---|---|---|---|---|---|
| (absolutamente hundido) ← | | | | | | | | | | → (excelente) |

## BSL - Supplement: Items for Assessing Behavior

| | **Durante la última semana…** | Nada | una vez | 2- 3 veces | 4-6 veces | Diariamente o más a menudo |
|---|---|---|---|---|---|---|
| 1 | Me hice daño cortándome, quemándome, estrangulándome, dándome golpes con la cabeza, etc. | **0** | **1** | **2** | **3** | **4** |
| 2 | Dije a otras personas que iba a matarme | **0** | **1** | **2** | **3** | **4** |
| 3 | Intenté suicidarme | **0** | **1** | **2** | **3** | **4** |
| 4 | Tuve atracones de comida | **0** | **1** | **2** | **3** | **4** |
| 5 | Me provoqué el vómito | **0** | **1** | **2** | **3** | **4** |
| 6 | Realicé deliberadamente conductas arriesgadas como conducir demasiado rápido o en dirección contraria, hacer equilibrios y juegos en lugares altos, en las vías de tren o con trenes en marcha, etc. | **0** | **1** | **2** | **3** | **4** |
| 7 | Me emborraché | **0** | **1** | **2** | **3** | **4** |
| 8 | Tomé drogas | **0** | **1** | **2** | **3** | **4** |
| 9 | Tomé medicación que no se me había recetado o si se me había prescrito, tomé más de la dosis recetada. | **0** | **1** | **2** | **3** | **4** |
| 10 | Tuve brotes de ira incontrolada o ataqué físicamente a otras personas | **0** | **1** | **2** | **3** | **4** |
| 11 | Tuve relaciones sexuales que no pude controlar, de las cuales más tarde me sentí avergonzado/a o enfadado/a. | **0** | **1** | **2** | **3** | **4** |

**Por favor, compruebe que ha contestado a todas las preguntas.**

**LE AGRADECEMOS MUCHO SU PARTICIPACIÓN!**
**POR FAVOR, DEVUELVA EL CUESTIONARIO A SU TERAPEUTA.**