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EFFECT OF CHILDHOOD MALTREATMENT ON THE ENDOCRINE, CEREBRAL, CARDIAC AND METABOLIC SYSTEMS. REVIEW AND META-ANALYSIS.

EFFETTI DEI MALTRATTAMENTI INFANTILI SUL SISTEMA ENDOCRINO, CEREBRALE, CARDIACO E METABOLICO. REVIEW E META-ANALISI.

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Abstract

The main objectives of this thesis are to describe the phenomenon of violence against children, to review the current scientific literature about the effects of childhood psychophysical abuse on the dysregulation of the HPA axis, and to undertake a meta-analysis assessing the effect of childhood maltreatment on cortisol response to social stress, or to the awakening response. Current literature supports the relationship between the experiences of child abuse and blunted cortisol levels, however, the data are not consistent. To investigate this issue, this thesis undertook two different meta-analyses. The first evaluation estimated the standardized mean difference between the control subjects and the subjects with a history of childhood maltreatment. The second evaluation estimated the standardized mean difference between the control subjects and the subjects with a history of childhood maltreatment, that also took into account a diagnosis of a psychological disorder. The 59 papers included in the meta-analysis contained 79 records, which involved 6364 participants of different ages (3165 subjects for the experimental group and 3199 subjects for the control group). The two meta-analyses showed a small but significant overall effect (g_1 = -0.14, 95% CI_1 = [-0.21; -0.08], p-value$_1 < 0.001$; g_2 = -0.14, 95% CI_2 = [-0.21; -0.06], p-value$_2 < 0.001$). The heterogeneity was high and significant, but this result decreased if the records outliers are excluded. In conclusion, this work may further confirm the theory of the attenuation of cortisol levels with chronic stress brought on by childhood maltreatment and abuse.

Contents

Introduction

The goals of the thesis are:

- Describing the phenomenon of violence against children.
- Reviewing the scientific literature about the effects of childhood psychophysical abuse on the dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis.
- Showing a meta-analysis.

The discussion has this structure:

- Introduction.
- Overview childhood maltreatment: defining violence and describing demographic prevalence and impact on the psychophysical health of the early adverse experience.
- Methodological issue: describing the way to study the dysregulation of the HPA axis. What are the methods to induce stress in a laboratory setting and what are the endocrine, cardiac, cerebral and weight measures.
- Review: showing outcomes of recent scientific literature.
- Meta-analysis: showing a meta-analysis of the effects of childhood psychophysical abuse on the cortisol levels.
- Conclusion.

Chapter 1

Overview childhood maltreatment

The aim of this chapter is to give an overview on the phenomenon of childhood maltreatment. I'm presenting the definition of violence and the different types of psychophysical violence according to the classification of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, DSM-5® (see § 1.1). I'm also showing a description of the prevalence of violence against children in the world (see § 1.2), and I'm concluding with the major effects on the psychophysical health of children and adults (see § 1.3).

1.1 Different types of psychophysical violence

On the 18^{th} of April 2011 the Committee on the Rights of the Child (CRC) defined *violence* as "all forms of physical or mental violence, injury or abuse, neglect or negligent treatment, maltreatment or exploitation, including sexual abuse." (CRC, 2011, pag. 4).

The different types of psychophysical violence under the classification of the DSM-5® (American Psychiatric Association, 2013, pag. 717–719) are:

Child Physical Abuse is nonaccidental physical injury to a child - ranging from minor bruises to severe fractures or death - occurring as a result of punching, beating, kicking, biting, shaking, throwing, stabbing, choking, hitting (with a hand, stick, strap, or other object), burning, or any other method that is inflicted by a parent, caregiver, or other individual who has responsibility for the child. Such injury is considered abuse regardless of whether the caregiver intended to hurt the child. Physical discipline, such as spanking or paddling, is not considered abuse as long as it is reasonable and causes no bodily injury to the child.

Child Sexual Abuse encompasses any sexual act involving a child that is intended to provide sexual gratification to a parent, caregiver, or other individual who has responsibility for the child. Sexual abuse includes activities such as fondling a child's genitals, penetration, incest, rape, sodomy, and indecent exposure. Sexual abuse also includes noncontact exploitation of a child by a parent or caregiver - for example, forcing, tricking, enticing, threatening, or pressuring a child to participate in acts for the sexual gratification of others, without direct physical contact between child and abuser.

Child Neglect is defined as any confirmed or suspected egregious act or omission by a child's parent or other caregiver that deprives the child of basic age-appropriate needs and thereby results, or has reasonable potential to result, in physical or psychological harm to the child. Child neglect encompasses abandonment; lack of appropriate supervision; failure to attend to necessary emotional or psychological needs; and failure to provide necessary education, medical care, nourishment, shelter, and/or clothing.

Child Psychological Abuse is nonaccidental verbal or symbolic acts by a child's parent or caregiver that result, or have reasonable potential to result, in significant psychological harm to the child (Physical and sexual abusive acts are not included in this category). Examples of psychological abuse of a child include berating, disparaging, or humiliating the child; threatening the child; harming/abandoning - or indicating that the alleged offender will harm/abandon - people or things that the child cares about; confining the child (as by tying a child's arms or legs together or binding a child to furniture or another object, or confining a child to a small enclosed area [e.g., a closet]); egregious scapegoating of the child; coercing the child to inflict pain on himself or herself; and disciplining the child excessively (i.e., at an extremely high frequency or duration, even if not at a level of physical abuse) through physical or nonphysical means.

To study the demographic prevalence of these events it is necessary to have an evaluation assessment. Table 1.1 shows the comparison between areas of concern in three main scales, cited in scientific literature:

- Childhood Trauma Questionnaire (CTQ) (Bernstein, Fink, Handelsman, & Foote, 1998)
- Traumatic Experiences Checklist (TEC) (Nijenhuis, Van der Hart, & Vanderlinden, 1999)
- Juvenile Victimization Questionnaire (JVQ) (Hamby, Finkelhor, Ormrod, & Turner, 2004).

CTQ	TEC	JVQ
Physical abuse	Physical abuse Bodily threat from a person Intense pain	Maltreatment Peer and sibling victimization Conventional Crime
Sexual abuse	Sexual abuse Sexual harassment	Sexual victimization
Emotional abuse	Emotional abuse	Witnessing and other exposure to violence
Emotional neglect	Emotional neglect	

Table 1.1: Comparison between areas in: Childhood Trauma Questionnaire (CTQ), Traumatic Experiences Checklist (TEC), and Juvenile Victimization Questionnaire (JVQ).

1.2 Prevalence of childhood maltreatment

Childhood maltreatment is widely extended and with high variability. There are different studies that try to explain what the dimension of this phenomenon is and the differences between categorical variables (e.g., gender, education, socioeconomic status, etc.).

A systematic review of Hillis, Mercy, Amobi, and Kress (2016) used a triangulation approach to get minimum regional prevalences of childhood maltreatment in a population aged 2-17 years old. Authors analyzed 38 studies from January 2014 to August 2015. They estimated a minimum of 50% or more of children have had experiences with severe violence in 2014 in Asia, Africa, and North America (see graph 1.1). Furthermore violence against children is rising quickly. A longitudinal study done in the UK (Chandan et al., 2020) on a population of 3045456 (under 18 years old) between 1997 and 2017, showed a dramatic increase in the percentage of maltreatment cases (see fig. 1.2).

These data demonstrate an urgent need to take action to protecting children.

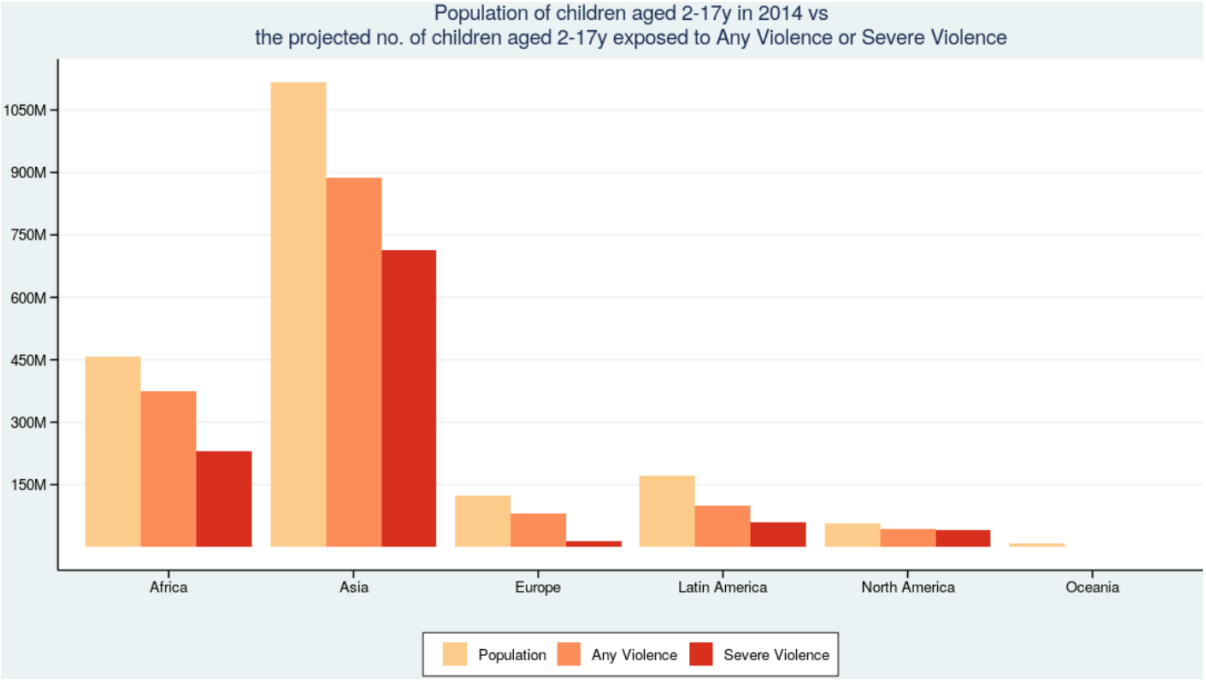

Figure 1.1: Comparison between the population aged 2–17 years old and the population exposed to severe violence (such as kicking, choking, smothering, burning, scaling, branding, beating repeatedly, or hitting with an object) and any violence (including exposure to one or more of the following: physical violence, emotional violence, sexual violence, bullying, or witnessing violence) (data source Hillis et al., 2016).

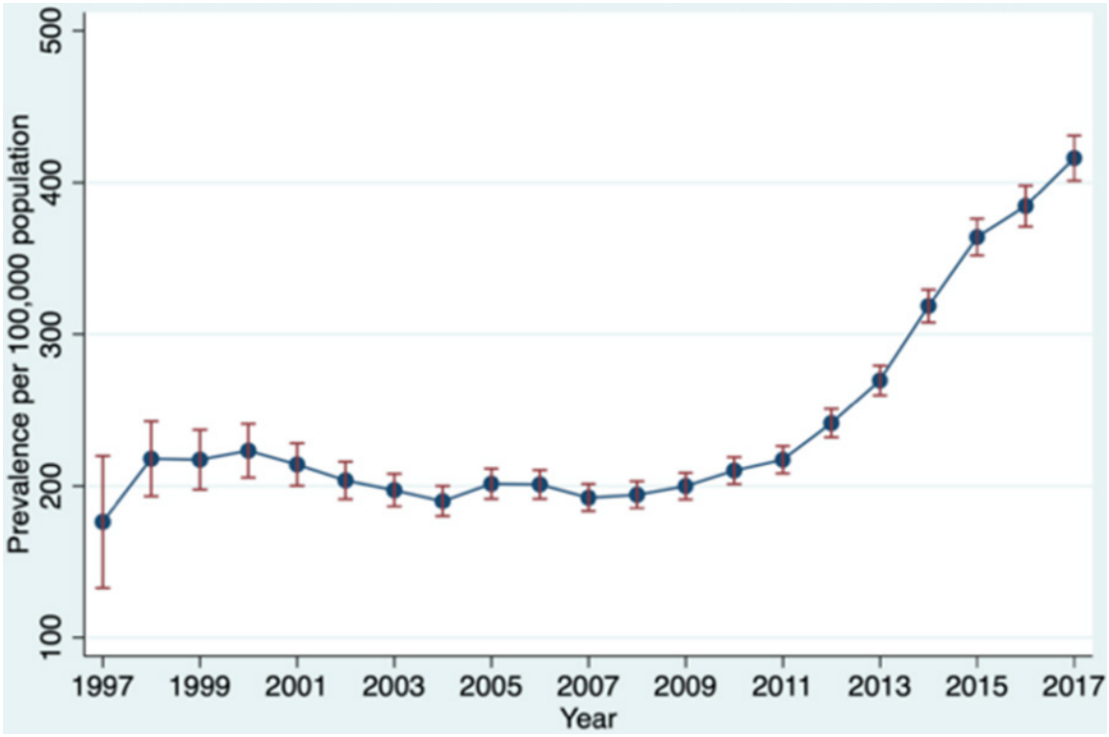

Figure 1.2: Prevalence of childhood maltreatment: 1997–2017 (Chandan et al., 2020).

As previously mentioned, it's important to explore the phenomenon between categorical variables. In this context, the most important categorical variable is gender. The difference in the demographic prevalence between males and females helps the researches to investigate the relation with psychological disorders and variables.

Studying scientific papers, it is evident that females are more favorable victims of sexual abuse. United Nations International Children's Emergency Fund (UNICEF) titled a chapter of his report Hidden in plain sight: "Sexual Violence: Not limited to girls" (UNICEF, 2017, page 60). A US study (Scher, Forde, McQuaid, & Stein, 2004) with the sample of 967 adult men and women combined, showed that the preference of victims in regards to sex, found female victims to be 3.75 times more preferred than male victims (OR = 3.75, 95% CI = [1.83; 7.72], p-value < 0.001). A Brazilian study (de Azeredo et al., 2020) with the sample of 83 children (mean age 10.84 years old) showed the module of sexual victimization in JVQ is significantly different between males and females in "S1 Sexual assault by know adult" and "S4 Rape: attempted or completed", with the prevalence for females: 72.7% in the 1st case (p-value = 0.038) and 77.8% in the 2nd case (p-value = 0.030). I have summarized in table 1.2, statistically significant difference between males and females of a study of the Crimes Against Children Research Center (Finkelhor, Turner, Shattuck, & Hamby, 2013). This research gathered the experiences of 4503 children and youth aged 1 month to 17 years old. The authors showed that females are the preferred sex compared to males, for sexual abuse victims.

1.3 Association with Psychiatric Disorders and risky behaviors

Childhood maltreatment is a risk factor for numerous mental disorders and dysfunctional behavior.

A recent German study (Struck et al., 2020) showed the prevalence of: emotional abuse, physical abuse, sexual abuse, emotional neglect, physical neglect in a sample of patients with schizophrenia/schizoaffective disorder (107 subjects), bipolar disorder (103 subjects), depression (604 subjects), and in healthy controls (715 subjects). There is a statistically significant difference ($p < 0.001$) in the prevalence of the abuses in patients with mental disorders than controls, the histogram 1.3 shows this trend.

Victimization type	Victimizations %		
	All Victims	Male	Female
Assaults and Bullying			
Any physical assault	41.2	45.2	37.1
Assault with weapon	6.2	7.4	5.1
Assault with injury	10.1	13.0	7.1
Assault with no weapon or injury	29.8	33.0	26.4
Assault by peer, nonsibling	17.9	22.8	12.8
Assault by gang or group	1.7	2.5	0.9
Genital assault	5.2	9.3	1.0
Dating violence	3.2	1.9	4.7
Relational aggression	36.5	31.9	41.4
Sexual Victimization			
Any sexual victimization	5.6	3.8	7.5
Sexual assault	2.2	1.0	3.5
Rape, attempted or completed	1.3	0.6	2.1
Sexual assault by known adult	0.5	0.1	0.9
Sexual assault by peer	1.6	0.9	2.2
Sexual harassment	3.2	1.8	4.7
Unwanted internet sex talk	3.0	1.3	4.8
Maltreatment by a Caregiver			
Physical abuse	3.7	4.5	2.9
Sexual abuse	0.1	0.0	0.3

Table 1.2: Rates of exposure to victimization for one year. Red numbers are percentage with standardized residuals are over 1.96 of χ^2 test (data source Finkelhor et al., 2013).

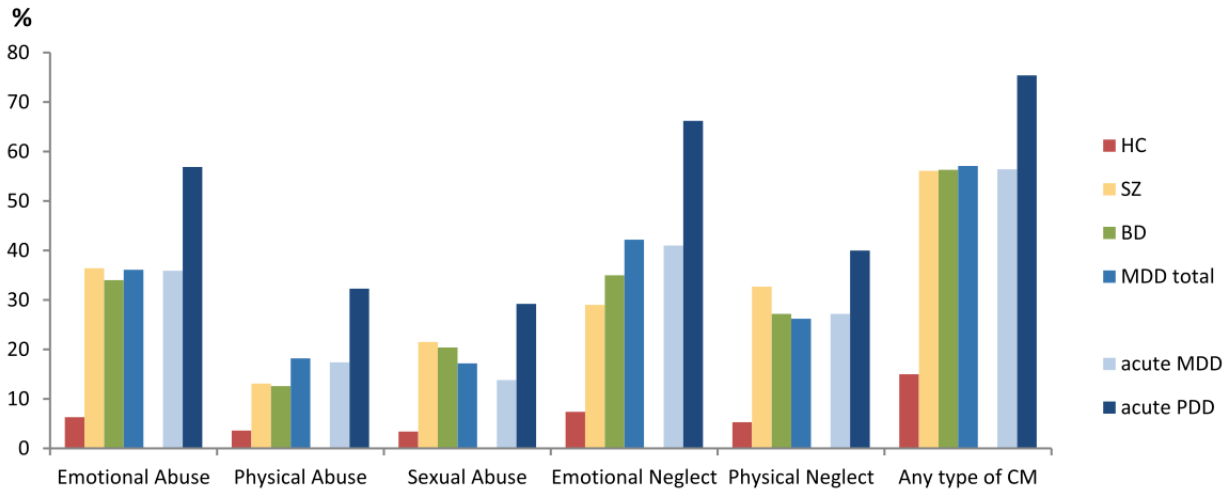

Figure 1.3: Percentage of the childhood maltreatment forms in patients with schizophrenia/schizoaffective disorder (SZ), bipolar disorder (BD), depression (MDD total), acute depression (acute MDD), persistent depressive disorder (PDD), and in healthy controls (HC) (Struck et al., 2020).

A meta-analysis investigated the relation between childhood maltreatment and depression (Nanni, Uher, & Danese, 2012). The analysis gathered 16 epidemiological studies and 10 clinic trials. Epidemiological studies summarized data from 23 544 participants, and they suggested an elevated risk of developing recurrent and persistent depressive episodes (OR = 2.27, 95% CI = [1.80; 2.87]; see forest plot 1.4). Furthermore clinic trials (3098 participants) revealed a resistance to treatment (OR = 1.43, 95% CI = [1.11; 1.83]).

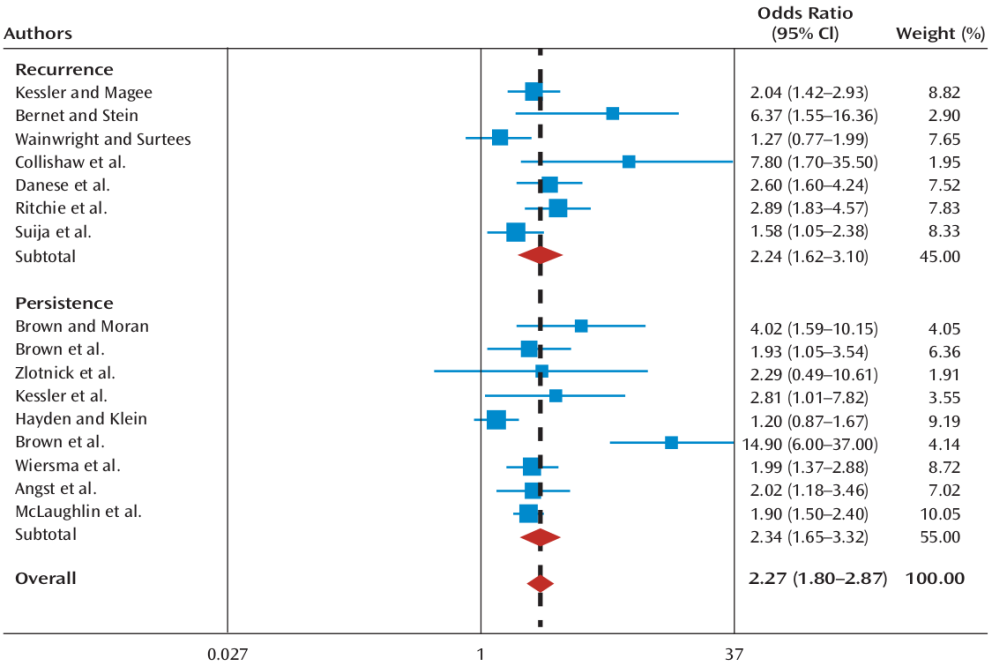

Figure 1.4: Odds ratio between people with history of childhood maltreatment and controls to estimate the risk of recurrent and persistent depressive episodes. The red diamonds show the effect sizes for each category and the overall effect size of the meta-analysis (Nanni et al., 2012).

A meta-analysis studied the association between different types of childhood maltreatment and suicidality (Angelakis, Gillespie, & Panagioti, 2019). The study pooled 261 660 adults with history of childhood abuse and at least one suicide attempt, and for a part of the sample was evaluated suicide ideation. All different types of childhood maltreatment (except physical neglect) have a higher probability of suicide attempts (see table 1.3).

Each type of abuse was associated with an increased risk for suicide attempts, but it's important to note that "complex abuse (repetitive incidents) in childhood showed the strongest association (increased the risk five times) with suicide attempts" (Angelakis et al., 2019, pag. 1059). One key point when studying the impact on the health of the adverse childhood experiences, is the frequency of traumatic episodes.

Childhood maltreatment	Suicide attempts			Suicide ideation		
	Subjects	Odds Ratio	95% CI	Subjects	Odds Ratio	95% CI
Sexual abuse	210 763	3.17	[2.76; 3.64]	112 626	2.15	[1.77; 2.62]
Physical abuse	109 627	2.52	[2.09; 3.04]	32 083	2.43	[1.85; 3.18]
Emotional abuse	33 857	2.49	[1.64; 3.77]	5936	2.10	[1.51; 2.94]
Any child abuse	14 574	2.09	[1.67; 2.60]	21 201	2.66	[1.93; 3.68]
Emotional neglect	1777	2.29	[1.79; 2.94]	2176	1.40	[1.02; 1.93]
Physical neglect	955	1.51	[0.87; 2.62]	2176	1.44	[1.06; 1.95]
Complex abuse	101 929	5.18	[2.52; 10.63]	-	-	

Table 1.3: Number of subjects, odds ratio and confidence intervals between people with history of childhood abuses and controls divided by types of childhood maltreatment and suicidality. The red numbers are OR with statistically significant difference, all p-value < 0.001 excepted for: physical neglect in suicide attempts (p-value = 0.14), emotional neglect in suicide ideation (p-value = 0.04) and physical neglect in suicide ideation (p-value = 0.02) (data source Angelakis et al., 2019).

The polyvictimization is a risk factor for different behavioral problems. The study of de Azeredo et al. (2020) showed that children and youth aged from 6 to 18 years old with a history of repetitive victimization had greater scores in different behavioral problems of the Child Behavior Checklist (CBCL) (Achenbach & Edelbrock, 1991) (see graph 1.5).

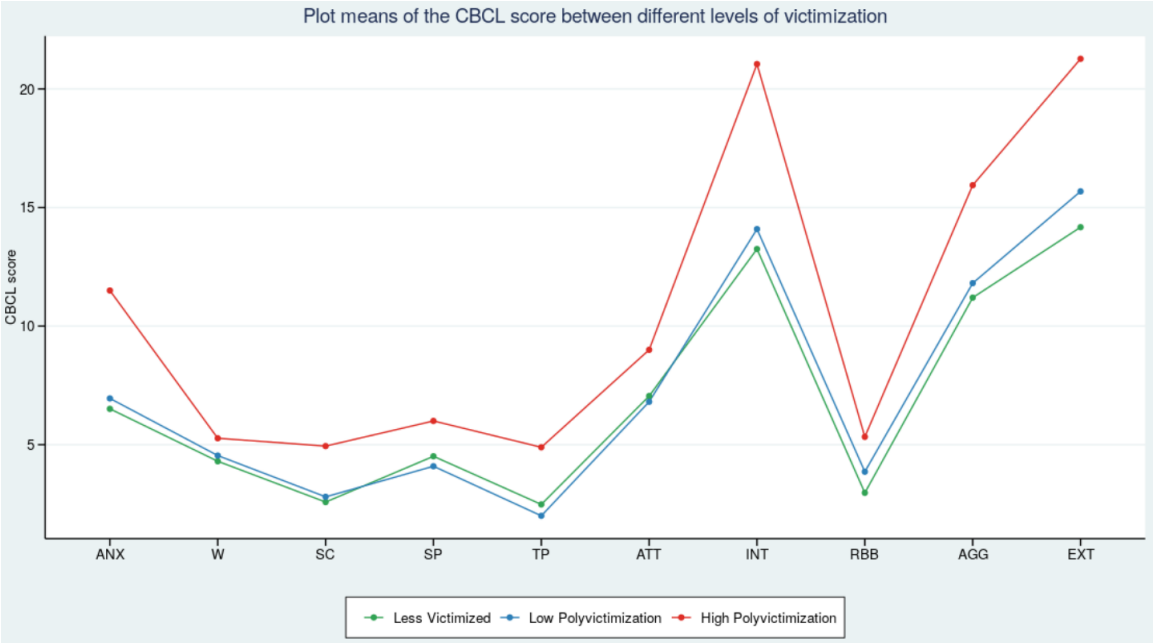

Figure 1.5: The plotting means of the scores of the Child Behavior Checklist in these areas: anxiety/depression (ANX), withdrawn (W), somatic complaints (SC), social problems (SP), thought problems (TP), attention problems (ATT), internalizing problems (INT), rule-breaking behavior (RBB), aggressive behavior (AGG), externalizing problems (EXT) (data source de Azeredo et al., 2020).

The subjects with high levels of victimization (evaluated with JVQ) showed a statistically significant difference in these areas: anxiety/depression ($F_{(2)}$ = 6.006, p-value = 0.004), somatic complaints ($F_{(2)}$ = 4.417, p-value = 0.015), thought problems ($F_{(2)}$ = 4.351, p-value = 0.016), internalizing problems ($F_{(2)}$ = 4.255, p-value = 0.018), rule-breaking behavior ($F_{(2)}$ = 3.806, p-value = 0.027), externalizing problems ($F_{(2)}$ = 3.174, p-value = 0.047).

A Chinese meta-analysis (Wang, Hu, Yu, & Yang, 2019) studied the association between childhood maltreatment and risky sexual behaviors. The analysis summarized data from 74 557 participants. Authors studied the association with four types of risky sexual behaviors: early sexual debut (OR = 2.22, 95% CI = [1.64; 3.00], p-value $<$ 0.001, I^2 = 81%), multiple sexual partners (OR = 2.22, 95% CI = [1.78; 2.76], p-value $<$ 0.001, I^2 = 91%), transactional sex (OR = 3.05, 95% CI = [1.92; 4.86], p-value $<$ 0.001, I^2 = 84%) and unprotected sex (OR = 1.59, 95% CI = [1.22; 2.09], p-value $<$ 0.001, I^2 = 88%) (see forest plot 1.6). Furthermore authors studied the relation between the type of abuse and the risky sexual behaviors: child sexual abuse (OR = 3.59, 95% CI = [1.95; 6.62], p-value $<$ 0.001, I^2 = 86%) had stronger association than child physical abuse (OR = 1.54, 95% CI = [0.94; 2.51], p-value $=$ 0.09, I^2 = 67%) and child neglect (OR = 1.58, 95% CI = [1.03; 2.43], p-value $=$ 0.03, I^2 = 59%).

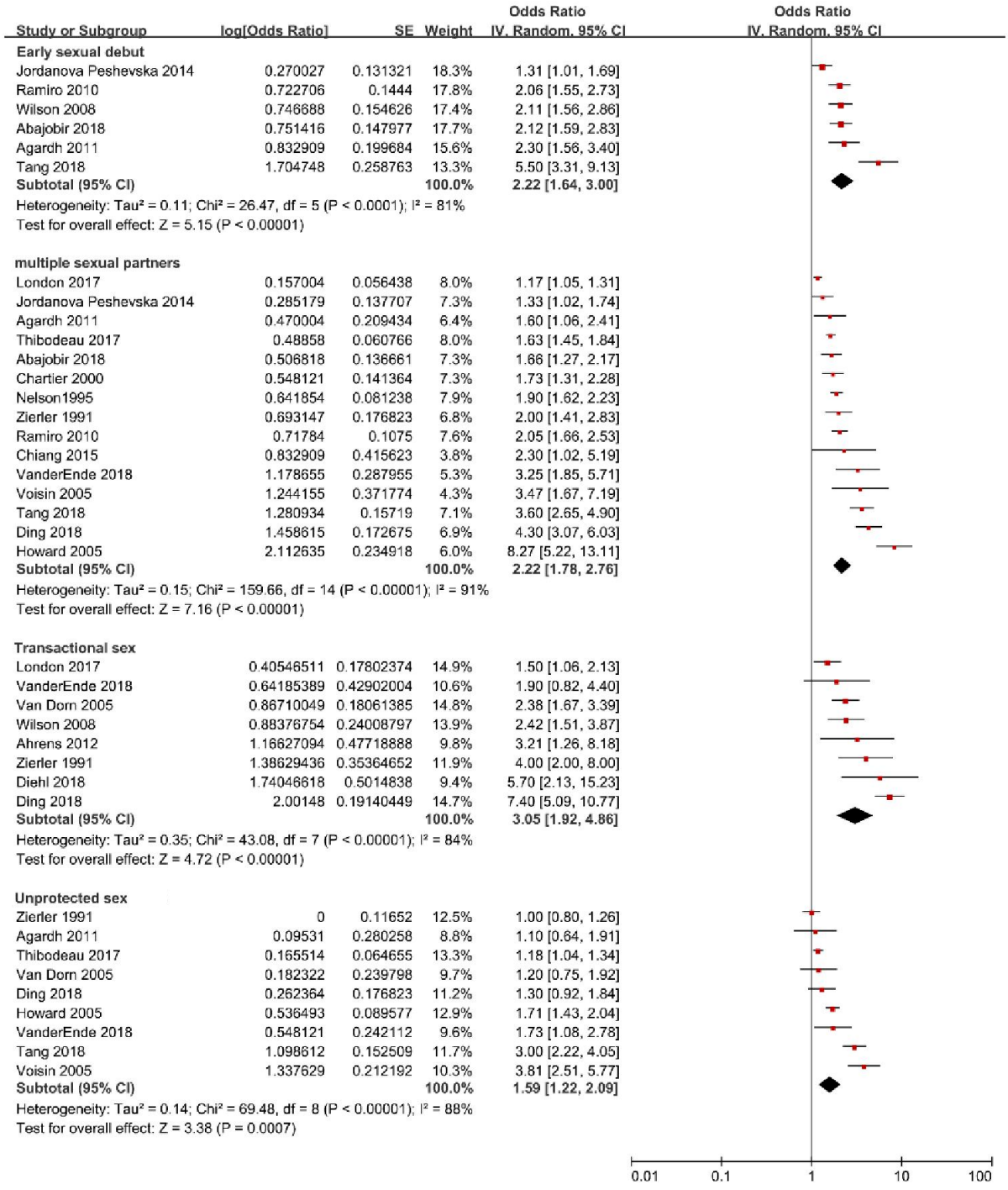

Figure 1.6: Odds ratio between people with history of childhood maltreatment and controls divided by risky sexual behaviors (Wang et al., 2019).

Chapter 2

Methodological issue

2.1 How to study the physiological effects of chronic stress

In § 1 I presented some important associations between childhood maltreatment, psychiatric disorders and behavioral problems. I will present how these powerful stressors have been studied by scientific research.

The model of Selye (1936) was the first to explain the effect of stress on the body. The author associated stress with the activation of the hypothalamic–pituitary–adrenal (HPA) axis and the release of cortisol from the adrenal grands. Scientific research widely studied the association between stress and increased cortisol secretion. From these few considerations, we expected that the pathology or disorders associated with stress, could be the consequences of high cortisol levels, but paradoxically there is evidence of a decrease (Heim, Ehlert, & Hellhammer, 2000). This decrease is a phenomenon known as hypocortisolism.

The first challenge model to assess the role of the HPA axis in the stress response, was for post traumatic stress disorder (PTSD). International Classification of Diseases 11th Revision (ICD-11) included PTSD in the category of Disorders specifically associated with stress, and defined this category as "Disorders specifically associated with stress are directly related to exposure to a stressful or traumatic event, or a series of such events or adverse experiences".

Neuroscientist Yehuda conducted the first studies to establish the relation between cortisol levels and PTSD. She studied Vietnam veterans (Yehuda, Boisoneau, Mason, & Giller, 1993; Yehuda et al., 1990; Yehuda, Teicher, Trestman, Levengood, & Siever, 1996) and Holocaust survivors (Yehuda, Boisoneau, Lowy, & Giller, 1995) with PTSD. She not only studied cor-

tisol levels, but also: glucocorticoid receptors (GRs), adrenocorticotropic hormone (ACTH), corticotropin-releasing hormone (CRH). A German review (Heim, Ehlert, & Hellhammer, 2000) summarized combined findings and defined that neuroendocrine correlates of PTSD are:

- low baseline cortisol secretion
- increased GRs binding in lymphocytes
- suppression of cortisol by dexamethasone
- blunted ACTH response to CRH
- increased CRH concentrations in the cerebrospinal fluid.

This model has been questioned from other studies. The conclusions of a further meta-analysis (Meewisse, Reitsma, De Vries, Gersons, & Olff, 2007, pag. 387) were: "low cortisol levels in PTSD are only found under certain conditions. Future research should elucidate whether low cortisol is related to gender or abuse and depends on the measurement methods used.". The forest plot 2.1 shows the standardized mean difference (SMD) in cortisol level being less than zero (SMD = -0.12, 95% CI = [-0.32; 0.08], p-value = 0.24) with a large heterogeneity (I^2 = 71%, p-value $<$ 0.001), so the variation across studies can be attributed to heterogeneity rather than chance. The forest plot 2.2 shows statistically significant differences for these variables: gender (p-value = 0.003), trauma type (p-value = 0.005), years since trauma (p-value = 0.038) and exposure controls (p-values = 0.015).

The model that relates lower levels of cortisol with high stress, is inconsistent. A more complex model is necessary to take into account different variables and the relation of the HPA axis with other systems.

I have presented to date, studies that demonstrate the involvement of the HPA axis in stressful situations, but the stress system also includes the autonomic, metabolic and immune systems. Consequentially it's not a surprise that hypocortisolism is not an idiosyncratic correlate of psychological disorders, but rather, also presents in stress-related bodily disorders (such as: chronic fatigue syndrome, fibromyalgia, rheumatoid arthritis, asthma, and allergies) (Heim, Ehlert, & Hellhammer, 2000).

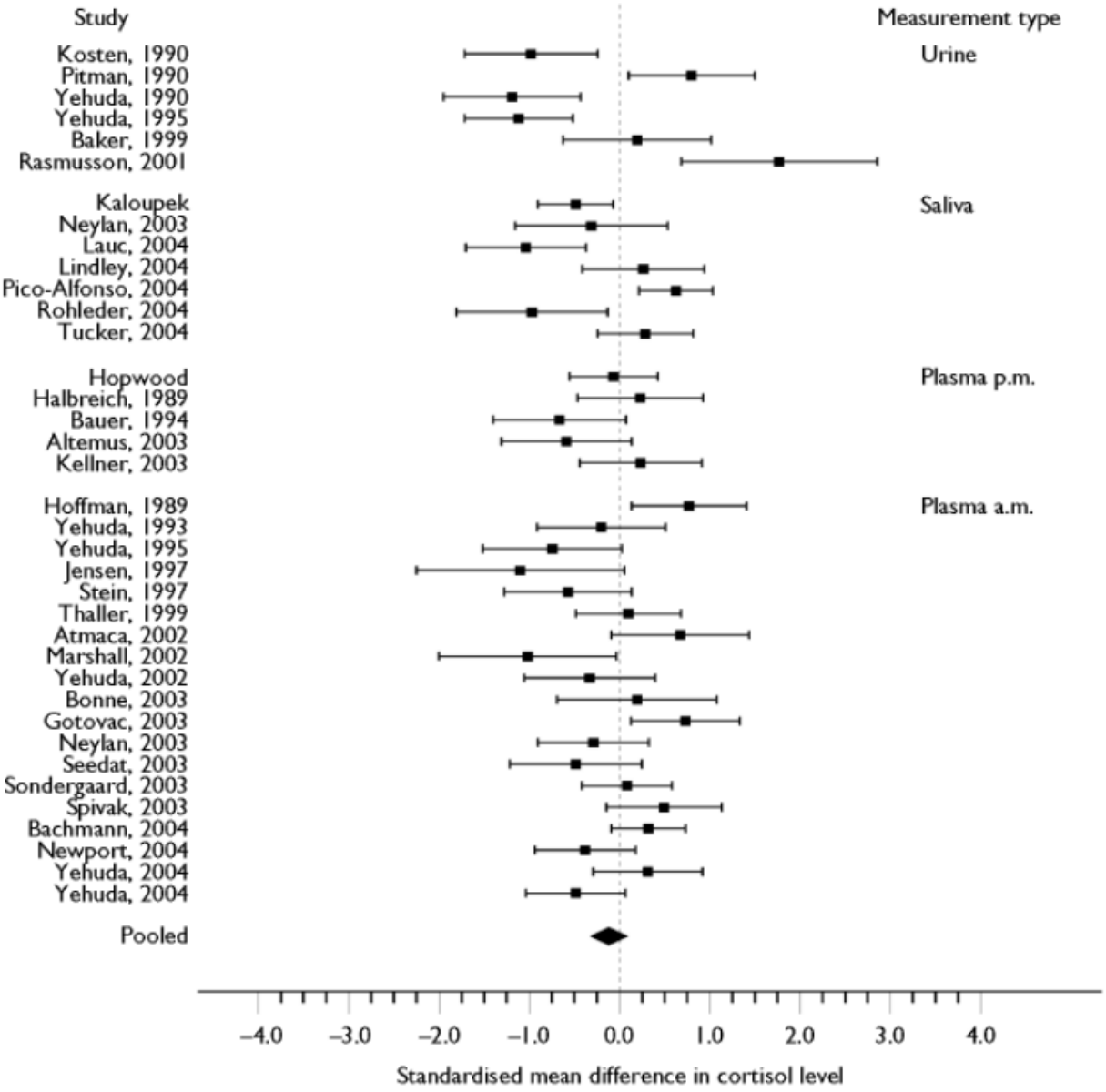

Figure 2.1: Standardized mean difference of cortisol levels between people with post traumatic stress disorder (PTSD) and controls sectioned by: measurement type (Meewisse et al., 2007).

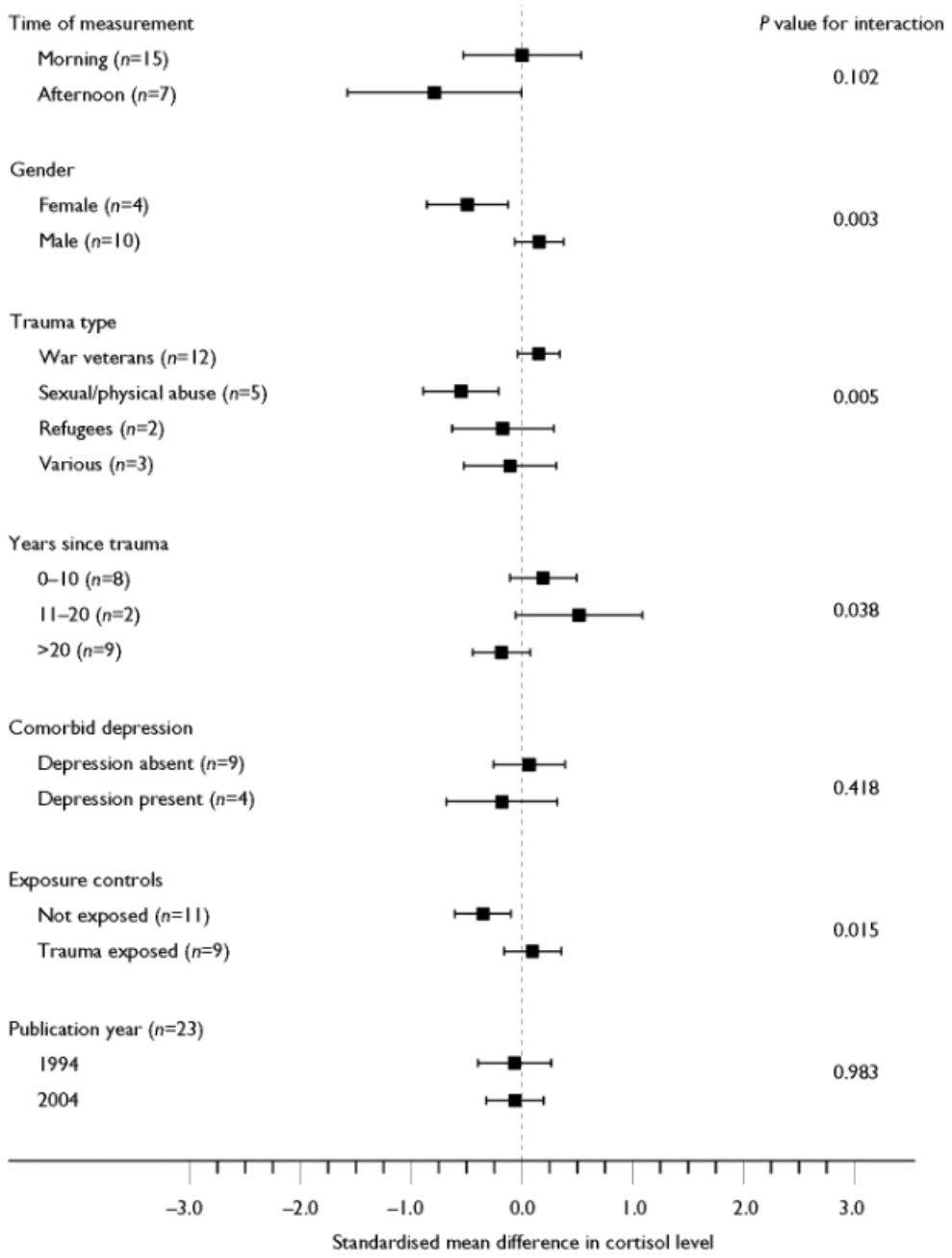

Figure 2.2: Standardized mean difference of cortisol levels between people with post traumatic stress disorder (PTSD) and controls sectioned by: time of measurement, gender, trauma type, years since trauma, comorbid depression, exposure controls, publication year (Meewisse et al., 2007).

To understand the mutual relation between these systems, it is useful to describe what happens during acute stress. Stress-related HPA activation, begins in the hypothalamus that secretes CRH under the influence of serotonin from the amygdala. CRH stimulates the pituitary gland to release ACTH, which in turn circulates through the bloodstream to the adrenal cortex. The adrenal gland produces and releases glucocorticoids (Kyrou & Tsigos, 2009).

As previously mentioned, other major systems respond to stress such as the autonomic nervous system, the immune system and the metabolic system. The HPA axis affects their function and viceversa (see figure 2.3).

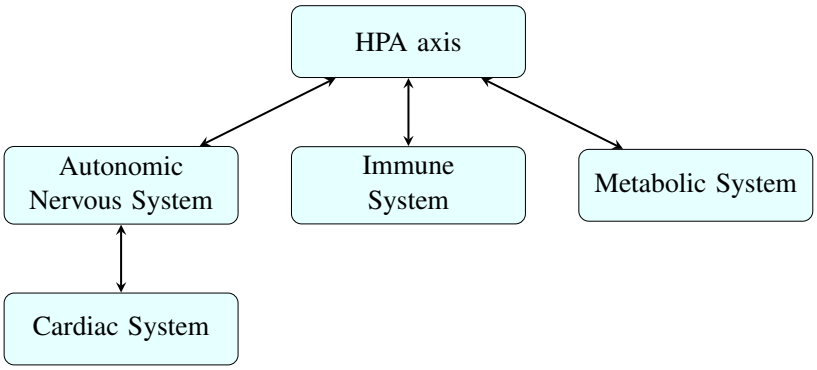

Figure 2.3: Relation between the HPA axis and other systems involved in the stress response.

The response to stress is a feedback response. The responsiveness of the HPA axis to stress, is also determined by GRs at various levels of the system, such as the pituitary glands, the hypothalamus, the hippocampus and the frontal cortex (Lupien, McEwen, Gunnar, & Heim, 2009) (see fig. 2.4).

These effects on the cerebral system have different impacts on the stages of ontological development (see fig. 2.5), because the brain regions mature at different times:

Prenatal stress: there are many brain regions that are involved in regulating the HPA axis, including the amygdala, the frontal cortex and the hippocampus.

Postnatal stress: the hippocampus is the most vulnerable area to effect stress.

Stress in adolescence: the frontal cortex is increasing its volume and it is sensitive to stress exposure.

Stress in adulthood and in aging: different regions may be vulnerable because they are undergoing a decline as a result of aging (Lupien et al., 2009).

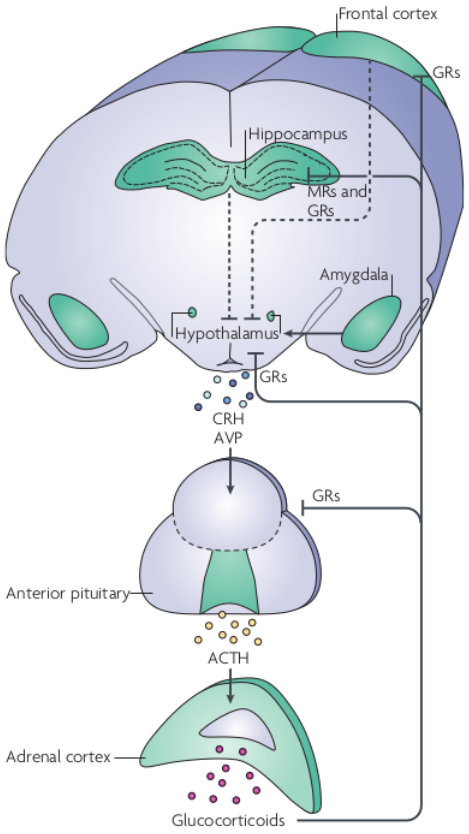

Figure 2.4: The stress system. In the situation of stress, the hypothalamus releases corticotropin-releasing hormone (CRH). CRH stimulates adenohypophysis (anterior pituitary gland) to release adrenocorticotropic hormone (ACTH) into the bloodstream. Subsequently, ACTH stimulates the adrenal cortex to produce glucocorticoids. Glucocorticoids will be gathered by glucocorticoids receptors (GRs) in different areas, such as: the pituitary glands, the hypothalamus, the hippocampus and the frontal cortex (Lupien et al., 2009).

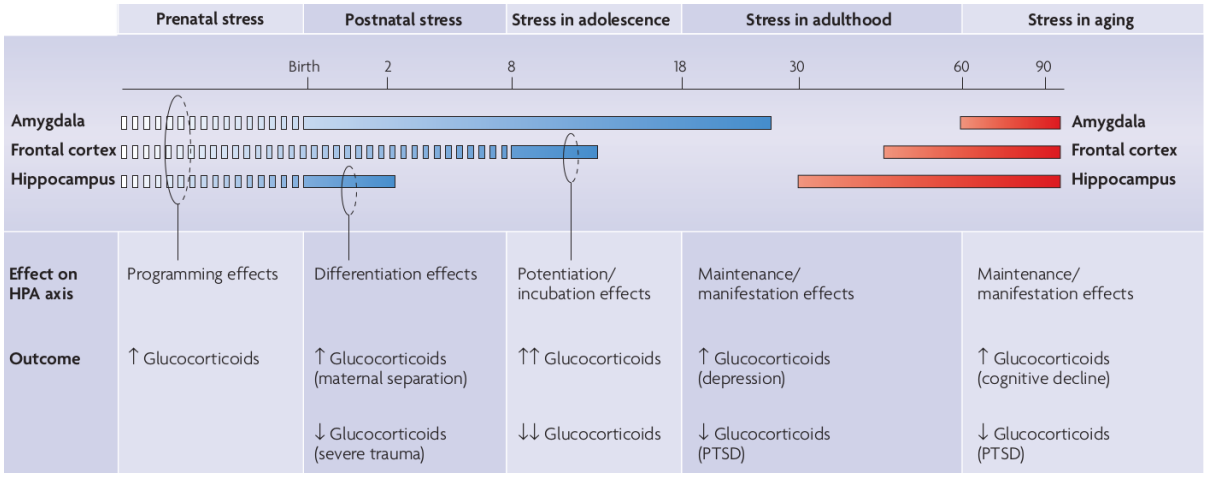

Figure 2.5: The life cycle model of stress. The exposure to stress has different effects on the HPA axis and the outcome in relation to the stage of development (Lupien et al., 2009).

The relation between the HPA axis and the autonomic nervous system is supported by the Polyvagal Theory (Porges, 2001). The subdiaphragmatic vagus may influence the adrenal glands, and therefore it controls the cortisol secretion. Furthermore there is a correlation between increases in cortisol and decreases in respiratory sinus arrhythmia (see § 2.5). According to the Polyvagal Theory, the hypocortisolism associated with chronic stress disorders "may reflect a neural strategy associated with immobilization (e.g., passive avoidance, death feigning, dissociative states) that would require a reduction in energy resources" (Porges, 2001, pag. 137).

Metabolic effects of the dysregulation of the HPA axis are particularly evident in obesity. In animal and human models, cortisol promotes the accumulation of fat cells and weight gain (Björntorp, 2001; Björntorp & Rosmond, 2000) (see fig. 2.6). Cortisol's rule in fat physiology is very complex, and scientific literature agrees that studying the direction of the dysregulation of the HPA axis is very important in adipocyte biology and it is the key to explain the etiology of obesity (Rodriguez et al., 2015). This issue will be discussed during the thesis (see § 2.6 and § 3.4).

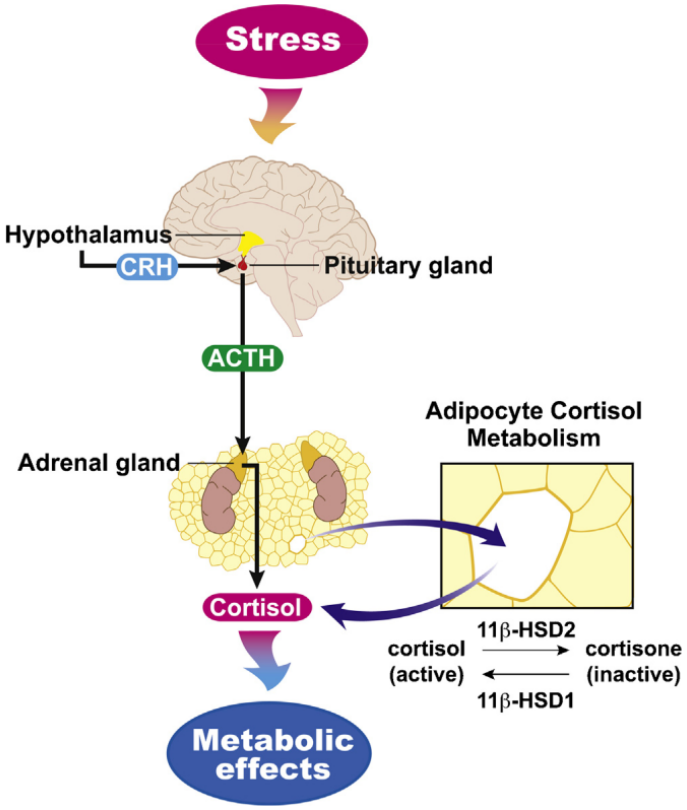

Figure 2.6: The stress system. The HPA axis acts on the adipocyte cortisol metabolism (Rodriguez et al., 2015).

2.2 Methods to induce stress in a laboratory setting

In this section I will present the paradigms that have been used to stimulate the HPA axis, and how they provoke the stress response in a laboratory setting.

2.2.1 Non-Pharmacological stress challenges

Non-Pharmacological stress challenges are natural tasks. The subjects have to follow a behavioral protocol, and meanwhile at different intervals, saliva and/or blood samples are gathered. The most common stress tasks used are: the Cold Pressor Test and the Trier Social Stress Test (McRae et al., 2006).

The Cold Pressor Test (CPT) consists of submerging the hand or the arm in cold water. The duration of the submersion depends on the tolerance of the subject. The methodology can change from different authors between these variables: temperature, circulation of water, submerged part of body and number of immersions (see table 2.1).

Author	Year	Temperature (C)	Circulated?	Arm/Hand	No. of immersion
Rosenbaum	1980	1° – 2°	No	Arm	1
Worthington and Shumate	1981	0° – 1°	Yes	Hand	2
McCaul and Haugtvedt	1982	7°	No	Hand	1
Ashton et al.	1984	0°	Not stated	Hand	6
Farthing et al.	1984	1° – 2°	Yes	Hand	2
Johnson et al.	1989	0°	Not stated	Hand	6
Hodes et al.	1990	0° – 1°	No	Arm	2
Levine and deSimone	1991	0° – 1°	No	Hand	1
Rainville et al.	1992	5°	Yes	Hand	3
McCaul et al.	1992	1° – 3°	No	Hand	1
Hekmat and Hertel	1993	0° – 1°	Yes	Hand	2
Weisenberg et al.	1995	1°	Yes	Arm	6
Johnson and Petrie	1997	4°	Not stated	Hand	1
Compton	1998	0° – 2°	No	Hand	1
Freeman et al.	2000	2°	Yes	Hand	3
Keogh et al.	2000	3°	Yes	Hand	1
Stevens et al.	2000	3°	Yes	Arm	1
Enggaard et al.	2001	4°	Yes	Hand	1
Myers et al.	2001	1° – 3°	Yes	Hand	1
deWied and Verbaten	2001	2°	Yes	Hand	1
Feldner and Hekmat	2001	0° – 1°	Not stated	Hand	1
Keogh and Hertenfeldt	2002	1° – 2°	Yes	Hand	2

Table 2.1: These studies show the different ways in which the Cold Pressor Test had been conducted (Mitchell et al., 2004).

The response of thermal and nociceptor afferents increases orthosympathetic nervous system and HPA axis activity (McRae et al., 2006).

The Trier Social Stress Test (TSST) (Kirschbaum, Pirke, & Hellhammer, 1993) consists of two different tasks with the first part involving speech and the second part involving the performance of mental arithmetic in the presence of an audience. Both of these tasks also involve the gathering of blood and/or saliva samples. In the first task, the subjects have to prepare and give a free speech trying to convince an audience to hire them for a vacant job placement (simulating a job interview environment). In the second task, the subjects have to serially subtract the number 13 from 1022 as best as they can (Kirschbaum et al., 1993). A US study (McRae et al., 2006) showed that the CPT and the TSST have a statistically significant difference in the ACTH ($F_{(4,120)} = 5.5$, p-value < 0.01) and cortisol ($F_{(4,120)} = 13.1$, p-value < 0.01) levels. Shown in fig. 2.7, the means trend of ACTH is linear and cortisol is quadratic, which explains a preference for the TSST rather than the CPT.

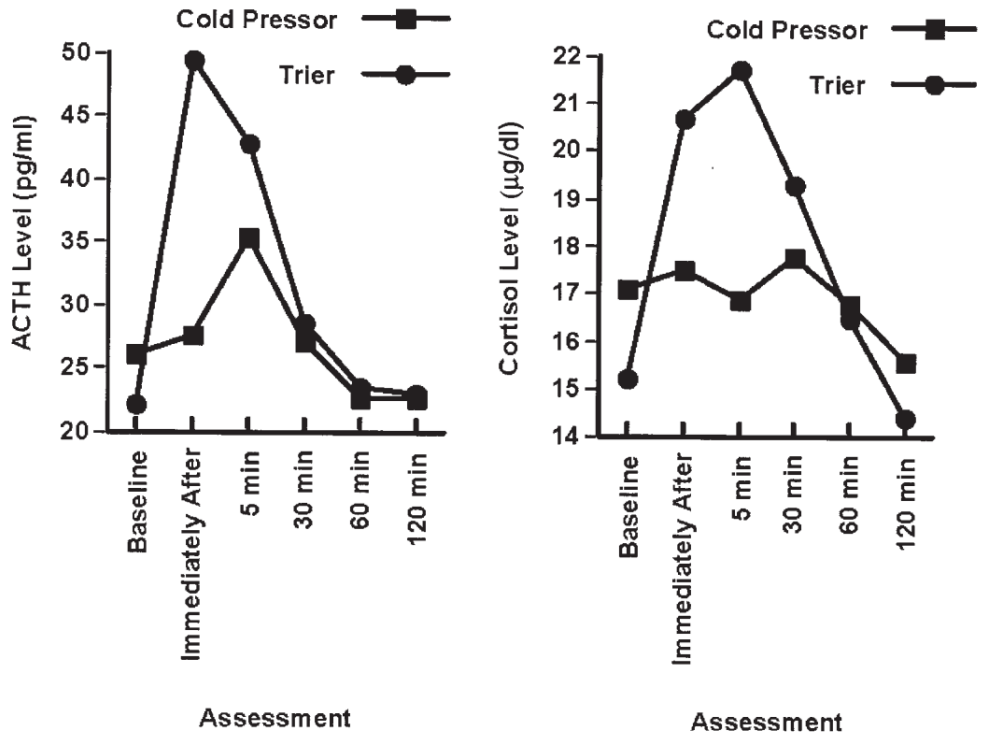

Figure 2.7: Comparison between the adrenocorticotropic hormone (ACTH) and the cortisol levels at different stages of the Cold Pressor Test and the Trier Social Stress Test (McRae et al., 2006).

2.2.2 Pharmacological stress challenges

CRH challenge

The CRH challenge consists of the administration of CRH by bolus injection, the common dose being 100 μg. After the injection, blood samples are repeatedly taken to measure the ACTH and cortisol at regular time intervals. In healthy individuals, the ACTH increases at 5 to 15 min intervals and cortisol increases at 30 to 60 min intervals after administration. Coincidently, adrenal responsivity can be assessed as the ratio between the ACTH and the cortisol levels. For example, a downregulation of the CRH receptors, as in the PTSD, determines a blunted hormonal response, and it's possible to apply this principle to subjects with chronic stress experiences (De Kloet et al., 2006).

ACTH challenge

The ACTH challenge, known as the rapid stimulation test, was developed for the clinical testing of the ACTH response in the therapy of Cushing disease. Cosyntropin is a synthetic version of ACTH. The administration of 0.25 *mg* of Cosyntropin, determines an increase of cortisol within 30 min. If there is an adverse alteration in the release of cortisol, it's evidently likely to presume problems with adrenal functioning, GRs affinity and feedback inhibition by cortisol (De Kloet et al., 2006).

Dexamethasone Suppression Test

The Dexamethasone Suppression Test was developed for the clinical testing of Cushing disease. Dexamethasone is a synthetic version of cortisol. The administration of 0.5 *mg* to 1 *mg* of dexamethasone, determines a modest suppression of the HPA axis activity. If there is a dysregulation of the HPA axis, it is possible to differentiate between normal and augmented suppression. A common procedure protocol involves administering the injection at 11 p.m., and the measure of cortisol happens during the following morning or afternoon (De Kloet et al., 2006). Neuroscientist Yehuda trialed the use of the 0.5 *mg* dose and she reported an important correlations. Firstly, the number of years since the most recent trauma is correlated with the log-transformed cortisol ratio (r = 0.42, p-value = 0.027) (Yehuda, Halligan, Golier, Gross-

man, & Bierer, 2004), and secondly, symptom severity is also positively correlated with cortisol suppression (r = 0.44, p-value < 0.01) (Yehuda, Golier, Halligan, Meaney, & Bierer, 2004).

Dexamethasone–CRH challenge

The Dexamethasone–CRH challenge is a combination between the CRH challenge and the Dexamethasone suppression test. Holsboer, Von Bardeleben, Wiedemann, Müller, and Stalla (1987) developed this procedure to study the regulation of the HPA axis in psychiatric disorders. It consists of the oral administration of 1.5 *mg* of dexamethasone the night before the CRH test, and then the following day 100 μg of CRH is administered by bolus injection in the afternoon. The advantage of this procedure is that by the time the second administration is given, the HPA axis is already downregulated and it is possible to check the cortisol response before and after the CRH injection (De Kloet et al., 2006). The fig. 2.8 shows an example of the application of this technique, in the afternoon of the day after the dexamethasone injection where the HPA activity was shown to be suppressed in the participants, but with the administration of the CRH injection, it was clearly visible, the difference between women with history of childhood trauma and controls.

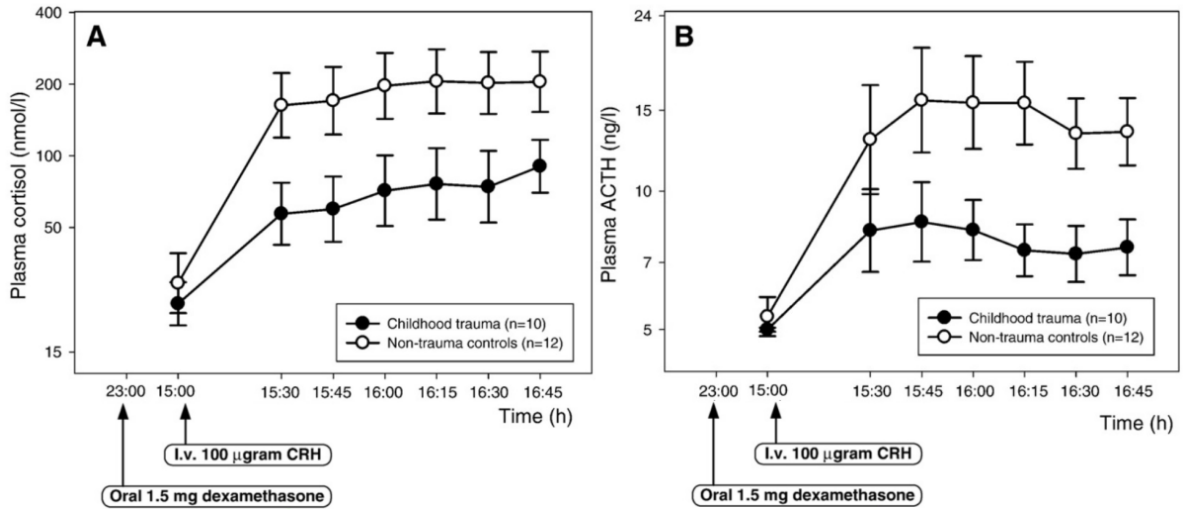

Figure 2.8: The plotting measures of plasma cortisol levels (A) and plasma ACTH levels (B) throughout the day with the combined dexamethasone / corticotrophin realizing hormone (Klaassens et al., 2009).

Glucocorticoid receptors studies

The study of the GRs is relatable to chronic stress, because the glucocorticoids bind to the intracellular receptors, and these determine the "up or down regulation" in the expression of genes. The leukocytes are the most accessible cells to study GRs, but the leukocytes belong in the immune system, therefore making the interpretation difficult. It is however, possible to study the GRs by vitro procedure, measuring the inhibitory effect of dexamethasone on the immune system. If the GRs are more functional, they determine an inhibition of the immune system (De Kloet et al., 2006). For example, the study by Yehuda, Golier, Yang, and Tischler (2004) showed that subjects with PTSD had a greater sensitivity to GRs than control group (significantly lower mean concentration of dexamethasone at which 50% of lysozyme activity is inhibited; $F_{(2,40)} = 6.6$, p-value = 0.003).

2.3 HPA activity measures

There are a variety of ways to assess the HPA activity. The most common method is to measure the cortisol. The cortisol can be assessed in the biologically active form i.e., unbound to carrier proteins (in the saliva) or in the biologically active and inactive form i.e., bound and unbound to proteins (such as: blood, urine and cerebrospinal fluid), therefore the salivary free cortisol reflects the amount of free cortisol in plasma (B. M. Kudielka & Kirschbaum, 2005). The cortisol levels in saliva or blood, show the HPA activity in the past 10-60 min, and for this reason, they are assessed within the stress challenges. Cortisol levels have a diurnal rhythm as well. The cortisol rhythm is high after awakening and low in the evening. So it is necessary to collect samples at multiple times throughout the day to describe a profile or to calculate a slope (Miller, Chen, & Zhou, 2007).

The cortisol level is not the only way to measure the HPA activity. The CRH level and the ACTH level are both additional indicators. As previously mentioned, the CRH challenges study the adenohypophysis function and it can be assessed by cerebrospinal fluid. The ACTH challenges study the sensitivity of the adrenal glands and it can be assessed by blood (Miller et al., 2007).

The collection of samples, and the extraction of cortisol, can be done in the following ways:

- Blood samples are obtained from a catheter at 15 min intervals before, during, and after the stress exposure (stopping at 90 min post stress test) or at different times of the day. The blood tubes are then placed on ice and centrifuged at 4°C for 10 min at 3000 revolutions per minute (RPM). Plasma is then separated and stored at −80°C, and then cortisol or ACTH concentrations are analyzed using radioimmunoassay techniques (Heim, Newport, et al., 2000).

- Salivary cortisol samples are obtained from a Salivette device. This device is a cotton roll which participants have to place under their tongue for 3 minutes. The saturated roll is refrigerated for no longer than 16 hours, and then centrifuged to extract saliva. Samples are frozen at −80°C until they are analysed. The cortisol is then measured using a high sensitivity salivary cortisol immunoassay kit (Gruenewald, Kemeny, Aziz, & Fahey, 2004).

- Urine samples are obtained throughout the day (24-h urinary free cortisol [UFC]) and they are often used to describe the trend of cortisol. The urine samples are mixed with an organic solvent (e.g., dichloromethane), and after, the urinary cortisol is then measured in one of the following ways: radioimmunoassay, enzyme-linked immunoassay or chemiluminescent assay (El-Farhan, Rees, & Evans, 2017).

- Hair samples are obtained by cutting hair strands from the posterior vertex position of the subjects' heads with surgical scissors. The hair samples are then stored at room temperature. Subsequently, the samples are cut up into approximately 1 mm pieces. It's important to note that, unlike blood and saliva, each hair segment should represent cumulative cortisol for the last month. Powdered hair is prepared in methanol and incubated in a water bath, and after 24 hours, the liquid solution contains the cortisol extract. With high-sensitivity, salivary cortisol enzyme-linked immunosorbent is present to analyze the hair cortisol levels (de Azeredo et al., 2020). This measure is a little used, even though it is a promising method for examining long-term cortisol output (Stalder & Kirschbaum, 2012).

I'm concluding this section with a list of the main variables to evaluate cortisol levels:

Peak is the highest (or lowest) level measured, out of repeat measures during the lab stressor. (Heim, Newport, et al., 2000)

Basal cortisol is the average of different levels measured throughout the day (Rodriguez et al., 2015).

Total daily output is a cumulative measure throughout the day (Rodriguez et al., 2015).

Reactive cortisol is the difference between the average level measured during the lab stressor and the average basal measure (Murali & Chen, 2005).

Cortisol awakening response (CAR) is the peak in cortisol concentration exhibited just after awakening (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003).

Area under curve ground (AUC_g) is the area of a plotting measures from the connected line of measures to the ground (Pruessner et al., 2003) (see left fig. 2.9).

Area under curve increment (AUC_i) is the area of plotting measures from the connected line of measures to the horizontal line of the first measure, which is the lowest (Pruessner et al., 2003) (see right fig. 2.9).

Area under curve ground for cortisol awakening response (AUC_gCAR) is AUC_g calculated for different measures around awakening time (Pruessner et al., 2003).

Diurnal slope is the daily pattern of cortisol concentrations (Rodriguez et al., 2015). In standard conditions this pattern is a negative slope, because cortisol increase sharply increases upon awakening and then declines throughout the day (Pruessner et al., 2003).

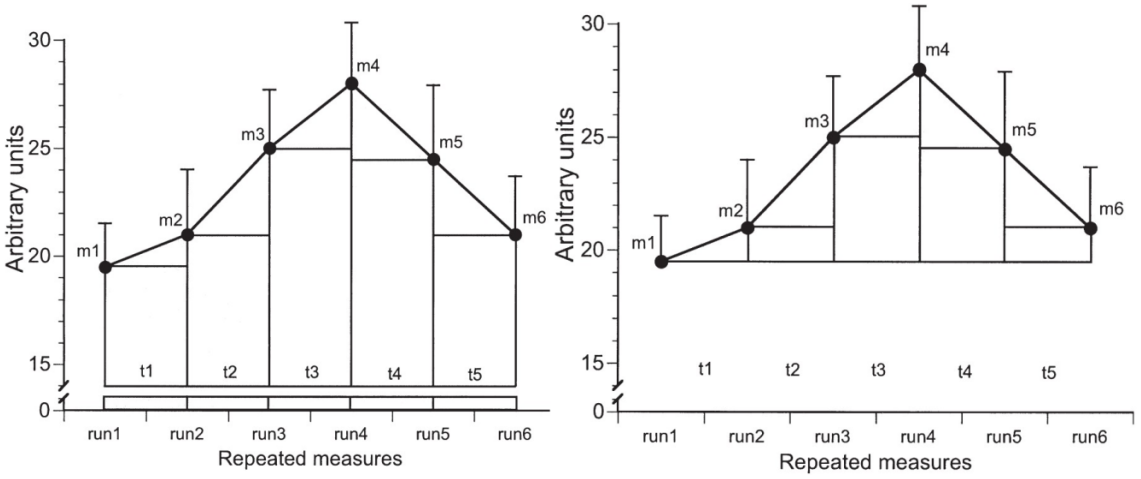

Figure 2.9: Example of six measures (m_1 to m_6) in six times (t_1 to t_6). The graph on the left shows the area under the curve with respect to the ground (AUC_g) and the graph on the right shows the area under the curve with respect to the increase (AUC_i). The measure of the variable is the sum of the triangles and rectangles area in their own illustration composition (Pruessner et al., 2003).

2.4 Cerebral measures

As mentioned in section 2.1, there is a relation between the HPA axis activity and brain development, so it's important that research considers studying brain morphology in subjects with history of childhood maltreatment.

The most common neuroimaging technology, is the magnetic resonance imaging (MRI) or functional magnetic resonance imaging (fMRI). An approach to analyze fMRI data, is the extraction of signals from specified regions of interest (ROI). The variables that are studied are: activated region, surface area, thickness and volume.

Another way to get data from the brain, is by studying the electrical activity in the brain by electroencephalogram (EEG). Electrical activity of the frontal region is related with stress vulnerability (Coan & Allen, 2004). Miskovic, Schmidt, Georgiades, Boyle, and MacMillan (2009) reported a pattern of frontal EEG alpha asymmetry reflecting:

- the bias to experience positive or negative emotion (see fig. 2.10)
- the individual differences in an affective style
- the psychiatric risk across development.

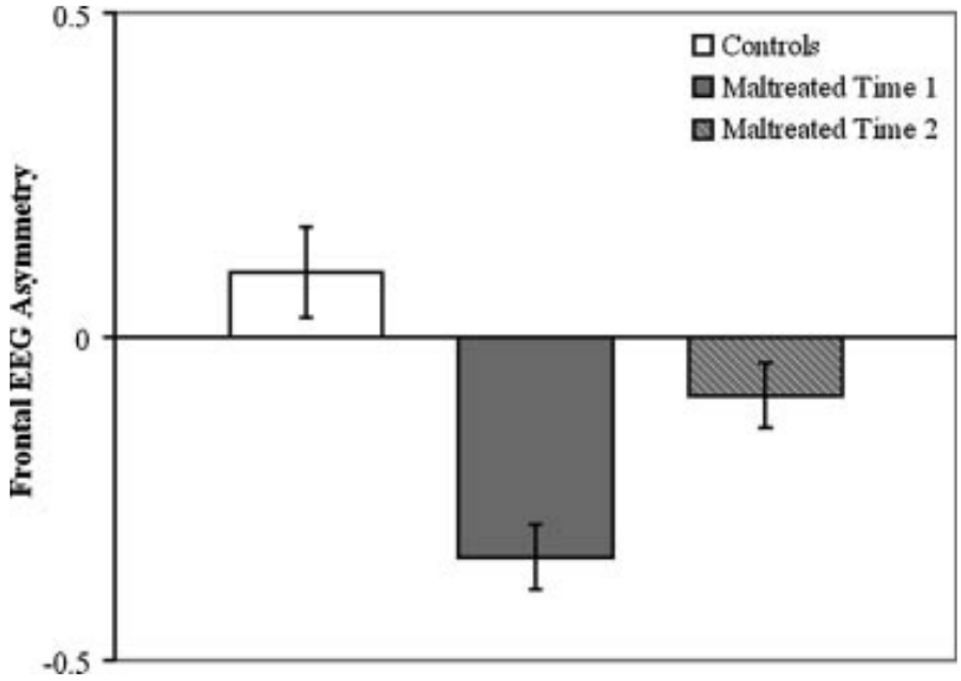

Figure 2.10: The mean differences between a group of adolescent females exposed to child maltreatment at two different times (n = 38, mean age = 14.47) and a group of adolescent females non-maltreated (n = 25; mean age = 14.00) with resting frontal EEG asymmetry. A positive mean indicates greater relative left frontal EEG activity and a negative mean indicates greater relative right frontal EEG activity. The bars represent standard errors (Miskovic et al., 2009).

2.5 Cardiac measures

The interest towards the cardiac measures increased after the Polyvagal Theory (see § 2.1). As a consequence of this theory, the cardiac vagal tone is considered a physiological marker of stress vulnerability (removal of the vagal brake and stimulation of the orthosympathetic nervous system).

During the measure, electrodes are placed on the chest and abdomen of each participant during the electrocardiography (ECG). The vagal tone is obtained using a polynomial method from the interbeat interval on a range of 30 seconds in two situations: relaxation period (Vagal relax, V_{relax}) and during the lab stressor (Vagal stressor, $V_{stressor}$). Changes in vagal tone are indicated as Vagal withdrawal (V_w), calculated as the difference between the vagal tone from the relaxation condition and the vagal tone from the stressor condition ($V_w = V_{relax} - V_{stressor}$). This difference (see fig. 2.11) is an indication of the reduction in parasympathetic influence over cardiac activity during a stress situation (Shenk, Noll, Putnam, & Trickett, 2010).

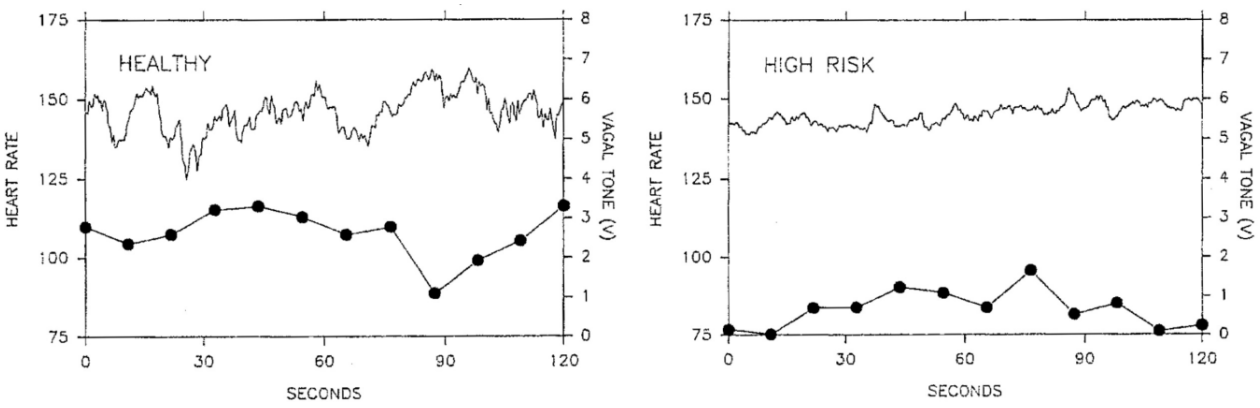

Figure 2.11: The difference between the heart rate (left y axis) and the cardiac vagal tone (right y axis) in two different neonates. The left panel shows the data from a healthy normal full-term neonate, and the right panel shows the data from a high risk preterm neonate (Porges, 1992).

Vagal tone is measured by the amplitude of respiratory sinus arrhythmia (RSA). RSA combines two measures: the rhythmic variability in heart rate and the frequency of respiration (Miskovic et al., 2009).

During inspiration, the vagal tone influences the heart by decreasing vagal activity. During expiration, the vagal tone influences the heart by increasing basal activity (see fig. 2.12). This cycle allows to monitor the degree of the individual vagal inhibition of the heart rate recovery. In a stressful condition, there is a rapid withdrawal of the vagus on the heart, to raise the heart rate to support the increased metabolic demands. This process is labeled as the release of the vagal brake (Dale et al., 2009).

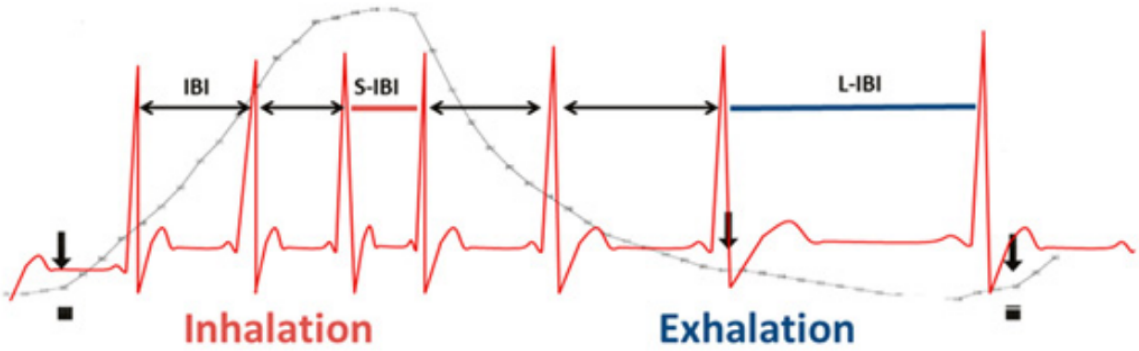

Figure 2.12: Respiratory sinus arrhythmia (RSA). During inhalation, the interbeat interval gets shorter (S-IBI) and the heart rate increases. During exhalation, the interbeat interval gets longer (L-IBI) and the heart rate decreases (Nederend et al., 2016).

It is therefore important to pair the heart rate to the respiratory rate. The respiratory rate measure can be done by spirometer, capnometry, and impedance pneumography (Liu, Allen, Zheng, & Chen, 2019).

Among other cardiac measures used to evaluate the effect of chronic stress on the body, it is possible to mention daytime systolic blood pressure (SBP) and nighttime diastolic blood pressure (DBP). Documented evidence shows:

- Significant positive correlations between DBP and exposure to violence (r = 0.32, p-value < 0.05) (Wilson et al., 1998).
- Significant positive regression in the levels of SBP ($\beta = 0.49$, p-value < 0.01) and DBP ($\beta = 0.42$, p-value < 0.01) in children exposed to a harsh parenting style and high violence (Krenichyn, Saegert, & Evans, 2001).
- Significant positive correlations between SBP and the frequency of exposure to violence (r = 0.26, p-value ≤ 0.05), and DBP and the frequency of exposure to violence (r = 0.31, p-value ≤ 0.05) (Murali & Chen, 2005).

2.6 Weight measures

In § 2.1, I mentioned the importance of the relation between the HPA axis dysregulation and the fat biology.

Understanding this aspect, it's important to briefly draw a concept of the adipocyte cortisol metabolism. The adipocyte metabolism functions through:

- The 11β-hydroxysteroid-dehydrogenase enzyme type 1 (11β-HSD1) that catalyzes the intracellular regeneration of cortisol from the inactive cortisone.
- The 11β-hydroxysteroid-dehydrogenase enzyme type 2 (11β-HSD2) that catalyzes the rapid conversion of active cortisol to inactive cortisone (Rodriguez et al., 2015) (see fig. 2.6).

Therefore a method to study weight gain, is to evaluate the relation between 11β-HSD1 and 11β-HSD2 concentrations in visceral adipose tissue (see § 3.4) and anthropometric measures (Desbriere et al., 2006; Engeli et al., 2004; Wake et al., 2003).

In this context, the most common anthropometric measures used are:

Body mass index (BMI) is body mass divided by the square of the body height.

Waist-to-hip ratio (WHR) is "the ratio of the minimum circumference value between the iliac crest and the lateral costal margin or the circumference at the umbilicus to the maximum circumference value over the buttocks" (Rodriguez et al., 2015, pag. 303).

Waist circumference is a measure of circumference of the abdomen at the level of the umbilicus.

Sagittal diameter is the distance from the small of the back to the front of the body (Rodriguez et al., 2015).

Common classifications such as "obesity" and "generalized obesity" are defined when BMI is over 30 and the "abdominal obesity" when WHR is over 1 (Rodriguez et al., 2015).

Chapter 3

Review

The aim of this chapter is to review the scientific literature on the relation between childhood maltreatment and the variables that I have described in § 2. It will include the main outcomes from single papers and also from meta-analysis.

3.1 Endocrine outcomes

It's not easy to establish a relation between childhood abuse and endocrine measures, because there are different moderator levels such as: cortisol relations, stress relations, population relations and potential confounding variables, that can render the reading of the outcomes difficult. In § 2.1, its stated that "the model that relates lower levels of cortisol with high stress, is inconsistent" (see page 18), I will show the results of three meta-analysis to support this. In chronological order they are:

- Maltreatment and diurnal cortisol regulation: a meta-analysis (Bernard, Frost, Bennett, & Lindhiem, 2017).
- Early-life adversity and cortisol response to social stress: a meta-analysis (Bunea, Szentágotai-Tătar, & Miu, 2017).
- Early life stress and cortisol: a meta-analysis (Fogelman & Canli, 2018).

The study of Bernard et al. (2017) gathered data from a sample of 3858 healthy people with three cortisol quantifications: wake-up cortisol level, cortisol awakening response and diurnal cortisol slope. This meta-analysis did not detect an association between maltreatment and the indicators of diurnal cortisol (see forest plot 3.1)

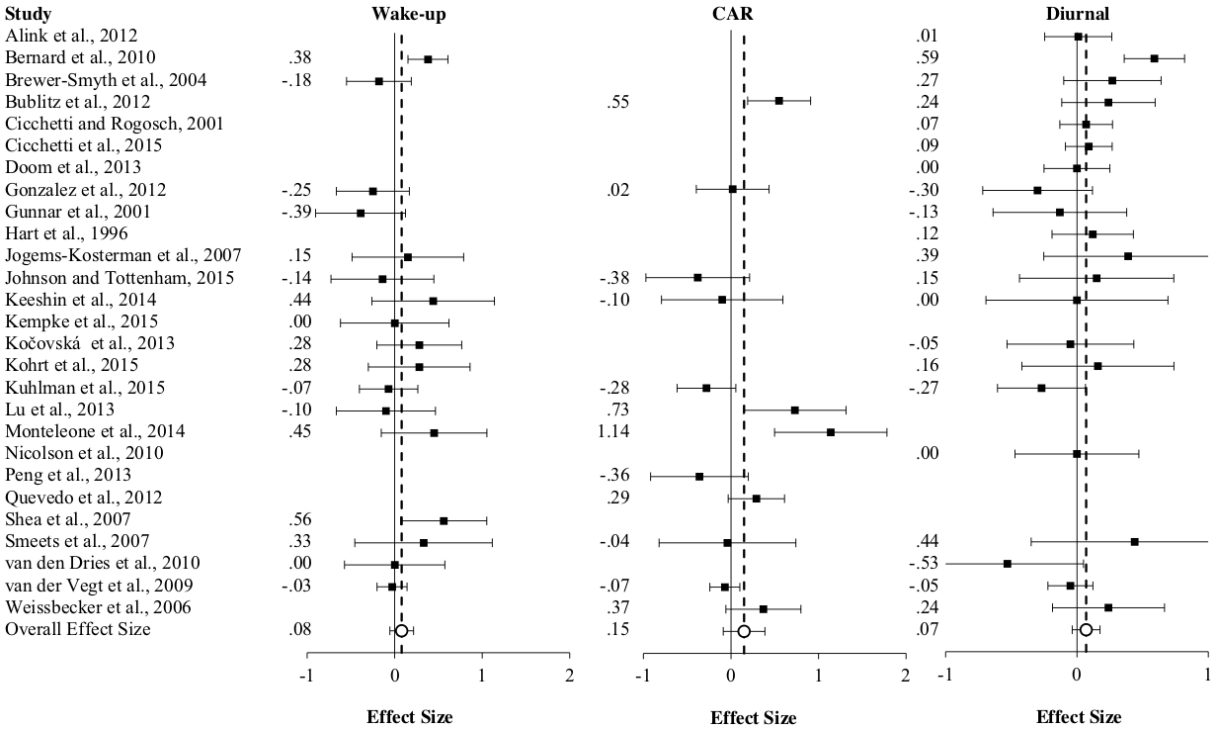

Figure 3.1: Effect sizes (Hedges' g) for wake-up cortisol levels (g = 0.08, p-value = 0.26), cortisol awakening response (CAR; g = 0.15, p-value = 0.20), and diurnal cortisol slope (g = 0.07, p-value = 0.18) (Bernard et al., 2017).

The study of Bunea et al. (2017) gathered data from a sample of 4292 healthy people in regards to their salivary cortisol levels after a stress test. This meta-analysis indicated a moderate alteration in overall cortisol levels (see forest plot 3.2). Moreover, the authors suggested that Bernard et al. (2017) failed to find the effect of childhood maltreatment because they focused on resting cortisol measures instead of reactivity to social stressors.

The study of Fogelman and Canli (2018) gathered data from a sample of 6828 healthy people with four cortisol quantifications: cortisol awakening response, baseline, non-stressed cortisol over time and reactivity. The results did not show any significant effect size for any measures (see forest plot 3.3). The authors concluded, that they did not demonstrate blunted cortisol levels in a population with history of childhood maltreatment, and they can attribute this relation by studying psychopathologic samples.

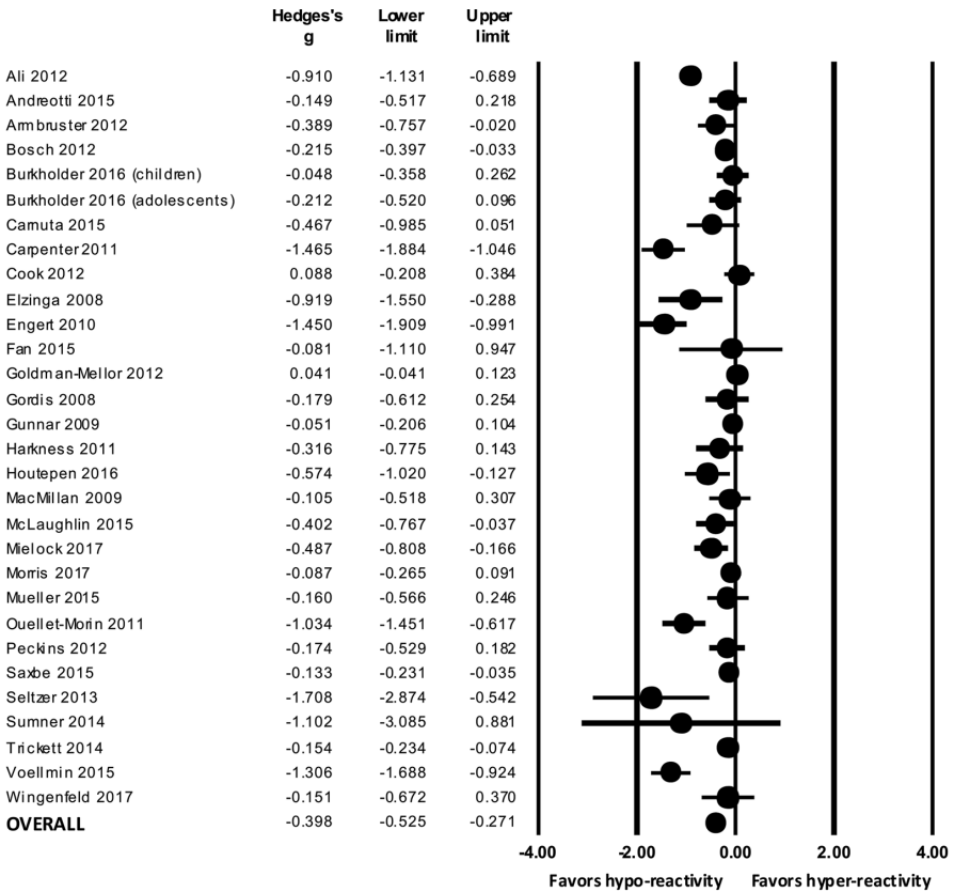

Figure 3.2: Effect sizes (Hedges' g) for the recovery cortisol measure after stress test (g = -0.39, 95% CI = [-0.53; -0.27], I^2 = 0.87) (Bunea et al., 2017).

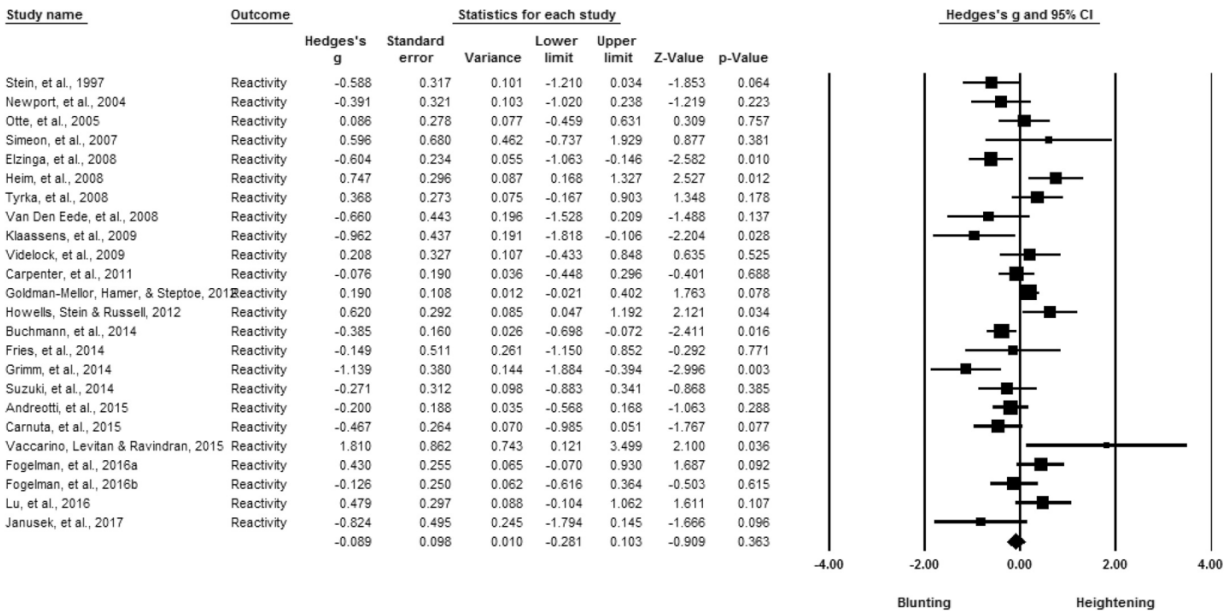

Figure 3.3: Effect sizes (Hedges' g) for the reactive cortisol (g = -0.09, 95% CI = [-0.28; -0.10], p-value = 0.363, I^2 = 0.66) (Fogelman & Canli, 2018).

After intensively studying these meta-analysis, there are two important issues of concern that are apparent:

1. Under which conditions is it possible to see the blunted cortisol levels in abuse victims?
2. What is the correct way to study this topic?

According to the scientific method, it is important to find confirmed results between different studies, in order to build a solid theory. Subsequently if it is true that childhood abuse leads to a dysregulation of the HPA axis, this should be visible in different meta-analysis, but as its shown previously, it's not clear or defined. Fogelman and Canli (2018) wanted to also bring to attention, the necessity to use standardization in regards to stress and cortisol measuring techniques. This is an issue for multiple scientific researchers since the literature continues to evolve (see histogram 3.4), and there are huge volumes of data that paradoxically may not be able to be synthesized.

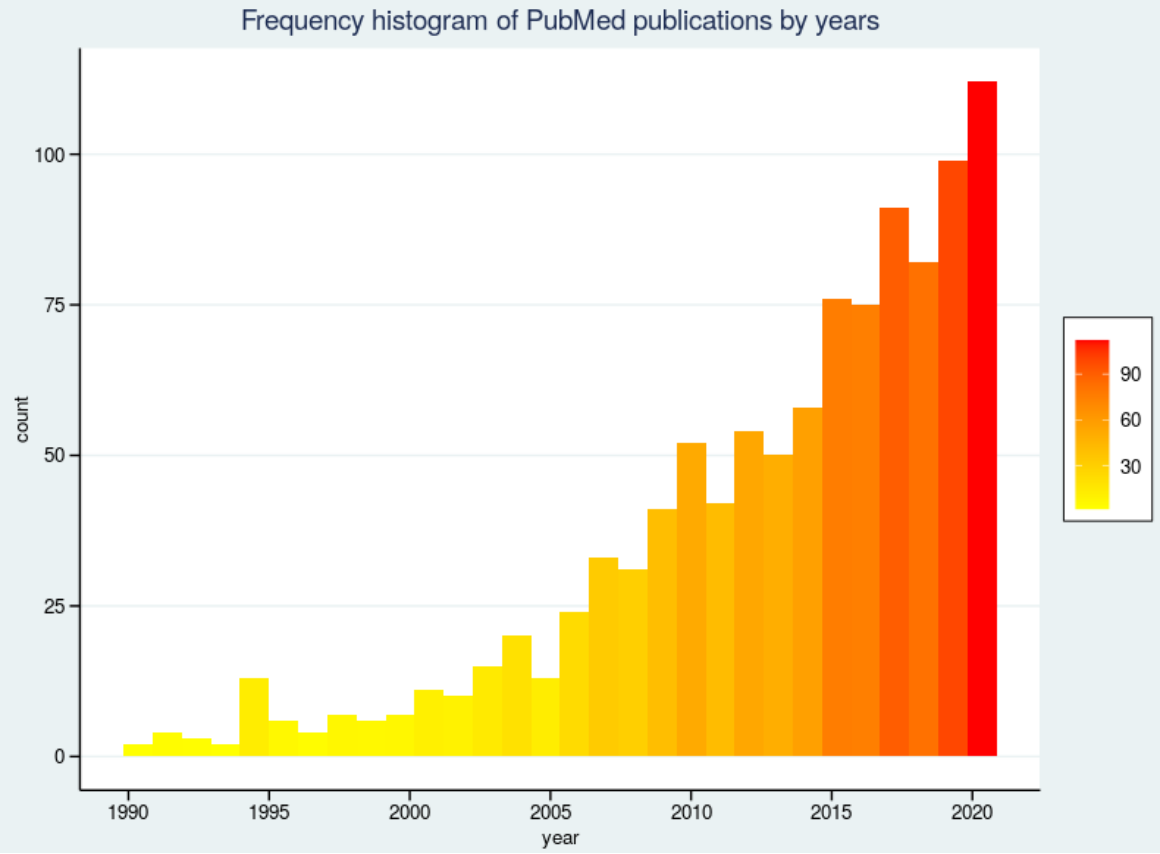

Figure 3.4: Numbers of PubMed publications regarding the topic of relationships between childhood maltreatment and cortisol (see table 4.1 for search criteria). After year 2010, there are approximately 50 publications per year, after year 2015 there are approximately over 75 publications per year.

A method to address the study of the dysregulation of the HPA axis, is by using evolutionary perspective. The figure 3.5, for example, schematizes four situations:

A: Children without history of abuse as an adult can be resilient upon exposure to severe trauma.

B: Children without history of abuse as an adult can develop psychopathology upon exposure to severe trauma.

C: Children with history of abuse as an adult can be resilient upon exposure to severe trauma.

D: Children with history of abuse as an adult can develop psychopathology upon exposure to severe trauma.

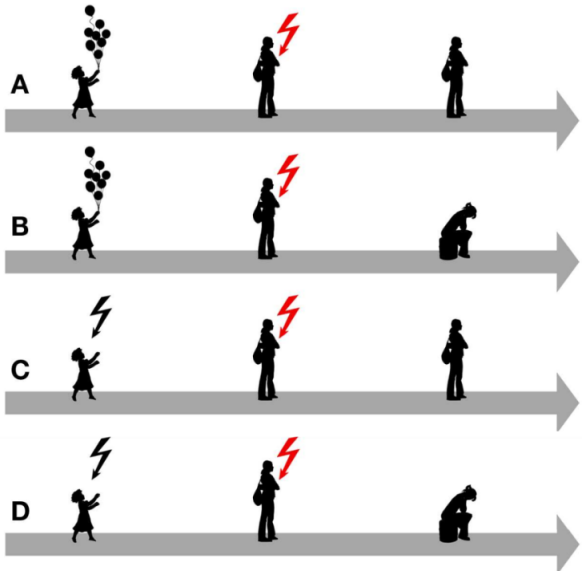

Figure 3.5: Different directions of trauma development in children without history of childhood maltreatment (situation A and B) and in children with history of childhood maltreatment (situation C and D). The adult can be resilient (situation A and C) or can develop psychopathology (situation B and D) upon exposure to severe trauma (Raabe & Spengler, 2013).

In this context, longitudinal studies are very important because they can give repeated and progressive information and offer possibilities to see changes over time.
Bunea et al. (2017) indicated that the effect on the cortisol response to social stress, in people with histories of childhood maltreatment, is minimal in children and adolescents, and therefore it is difficult to identify, but rather the effect is greater in adulthood. A longitudinal study (Trickett, Noll, Susman, Shenk, & Putnam, 2010) over the duration of 19 years with the samples

of 84 females with histories of sexual abuse, showed this trend: a period of HPA hyperactivity followed by a period of HPA hypoactivity (see fig. 3.6). Subsequently, it is interesting to notice that there are significant differences within the age group of 20 to 32 years of age (p-value = 0.01), but in the subjects that developed psychopathology, a significant difference is evident in the age group of 6 to 13 years of age (children with depression diagnosis, p-value = 0.04; children with trait anxiety diagnosis, p-value = 0.03).

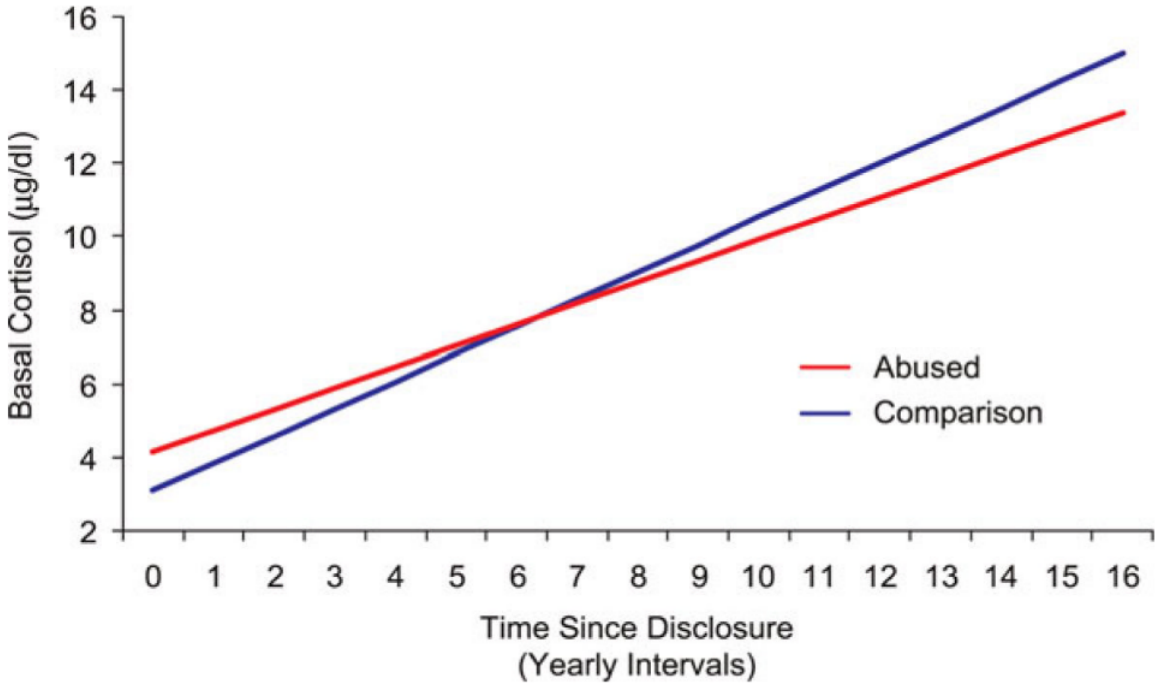

Figure 3.6: Regression line: basal cortisol predicted by the time of disclosure of sexual abuse. Sexually abused females showed attenuation of cortisol (Trickett et al., 2010).

I combined the outcomes in the model shown in figure 3.7. If we assume an ideal situation without prenatal stress (e.g., preterm birth or substance abuse in pregnancy), a child can be born with the ability to regulate the stress with a feedback system. On the contrary, adverse life experiences can lead to hypercortisolism (typically of situations of high allostatic load) or hypocortisolism (typically of psychopatological populations).

This model is only explanatory, therefore it does not have the presumption to extensively explain a very complex phenomenon like this. On the basis of observations shown in this thesis (see § 1.3), I would like to emphasize the importance of studying the dysregulation of the HPA axis during ontological development, especially in people with high risk of developing psychological or psychiatric disorders.

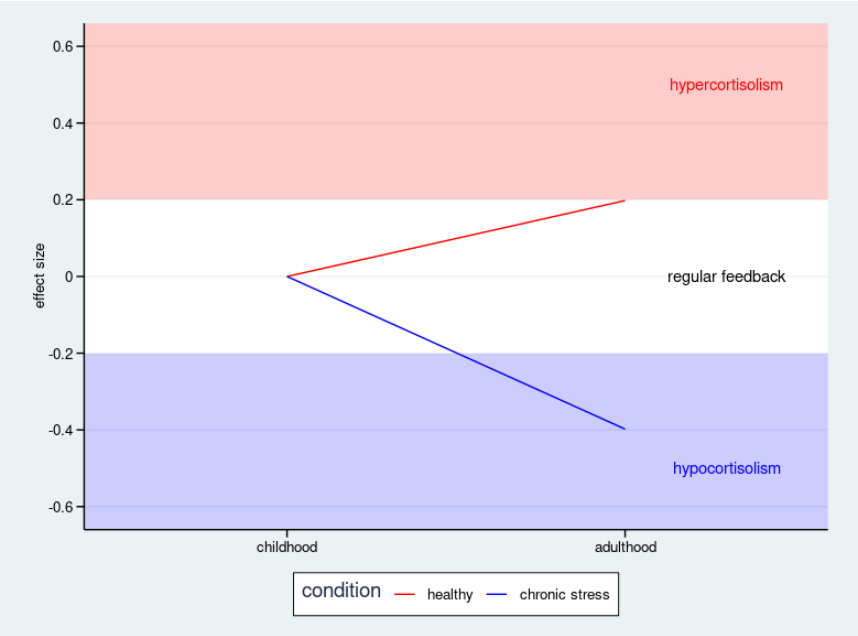

Figure 3.7: Hypothesis of a model with a dysregulation of the HPA axis. At birth (in absence of prenatal stress), a child is in a condition of regular feedback of corticosteroids (white zone). The following adverse stress conditions, can lead towards hypercortisolism (red zone) or hypocortisolism (blue zone). Childhood maltreatment is a risk factor for hypocortisolism and the development of psychopathology (blue line).

3.1.1 Sex differences in HPA axis responses to stress

The topic of sex differences in responses to childhood maltreatment, is complex to outline because of a lack of scientific literature. In § 1.2, I talked about the sex differences in terms of prevalence, but it is difficult to investigate the cause, or to describe the sex differences in regards to the direction of the dysregulation of HPA axis. A way to study this topic, is by observing the responses to general stress, and to also reference the relevant scientific literature pertaining to animal models, as its more consistent than human models. Although human data is more contradictory than the evidence from animal literature, gonadal steroids also seem to exert important modulatory effects on the functioning of the HPA axis in humans (see fig. 3.8). In this subsection, I will describe some results from the points of view of ontological development.

Evidence for sex differences in HPA axis activity are not clearly delineated in the infants and children (Goel, Workman, Lee, Innala, & Viau, 2011). B. Kudielka, Buske-Kirschbaum, Hellhammer, and Kirschbaum (2004), for example, reported no differential HPA responsivity to the Trier Social Stress Test (TSST) at this age.

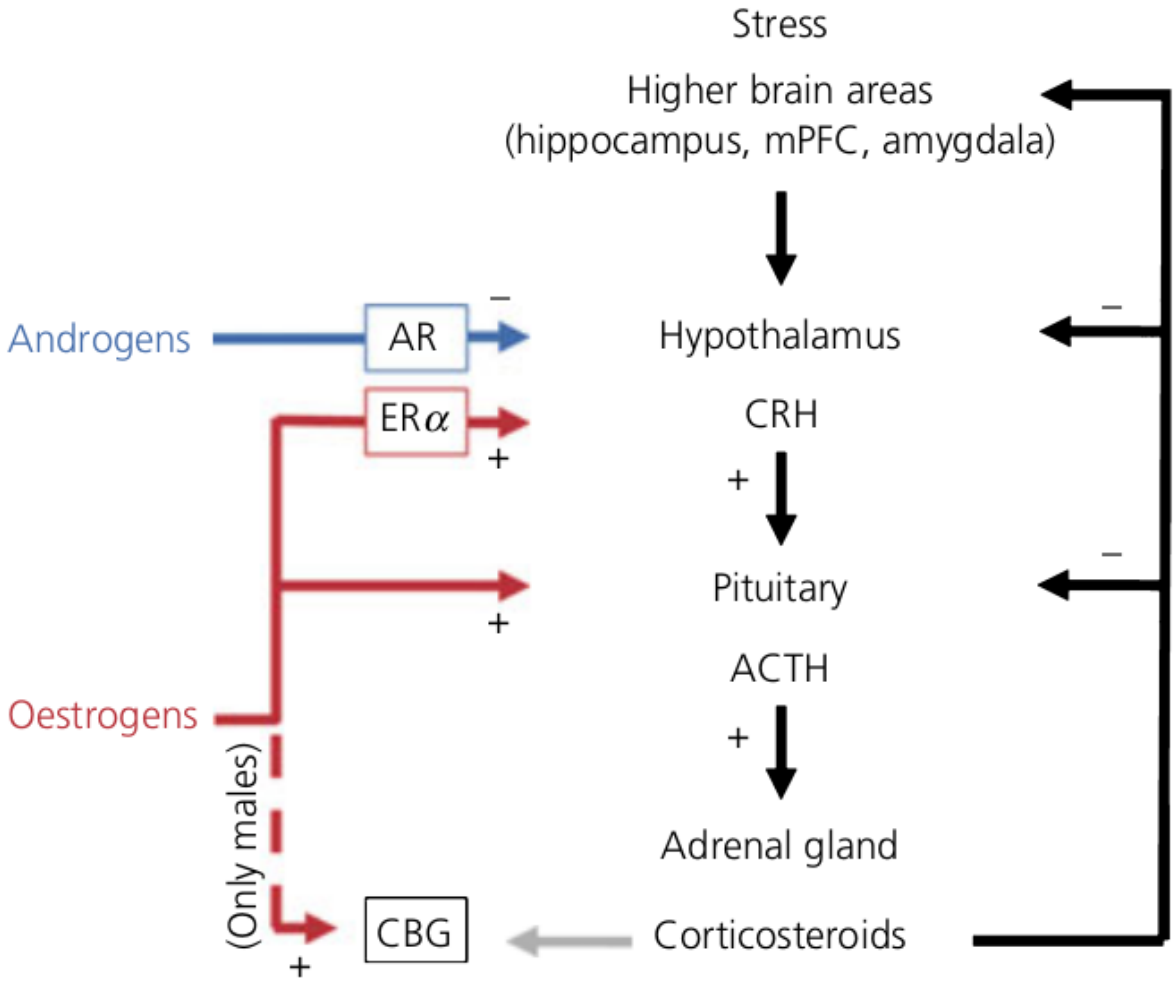

Figure 3.8: Schematic description of interrelation between regular negative feedback of corticosteroids (black line) and the role of sex steroids (blue line for androgens and red line for estrogens). Cortisol acts on the brain areas (hippocampus, medial prefrontal cortex [mPFC] and the amygdala) and reduce corticotropin-releasing hormone levels (CRH) in the hypothalamus and adrenocorticotrophic hormone levels (ACTH) in pituitary gland. Ovarian steroids and estrogen receptors (ERα) up-regulate the HPA activity in women, while in men, androgen and the respective receptors (AR) downregulate the HPA activity, and the estradiol increases corticosteroid-binding globulin (CBG) (Naninck et al., 2011).

The adolescent period is critical, to see the hormonal effects on sex differences. The elevated levels of gonadal hormones may influence the HPA axis, and this may also contribute to the emergence of sex differences in the HPA axis functionality (Goel et al., 2011). Adverse life experiences in this period, are an important factor to consider, because it may also contribute towards the hyperfunctioning or hypofunctioning of the HPA axis (Panagiotakopoulos & Neigh, 2014), but as mentioned in the previous section, there is need for additional evidence to determine the cause of hyporesponsive period.

During adult maturity, it is possible to study the response of the HPA axis in females between different menstrual-cycle phases, because free cortisol responses systematically vary (B. M. Kudielka, Hellhammer, & Kirschbaum, 2000). Kirschbaum, Kudielka, Gaab, Schommer, and Hellhammer (1999) measured the free cortisol after a social stress test in 81 young adults. The men had higher salivary free cortisol levels than their women counterparts regardless of menstrual cycle phase or use of oral contraceptives (p-value < 0.03). Subsequently, between the women, the highest free cortisol values were recorded during the luteal phase when the estrogen levels are at their highest (p-value < 0.03) (see fig. 3.9).

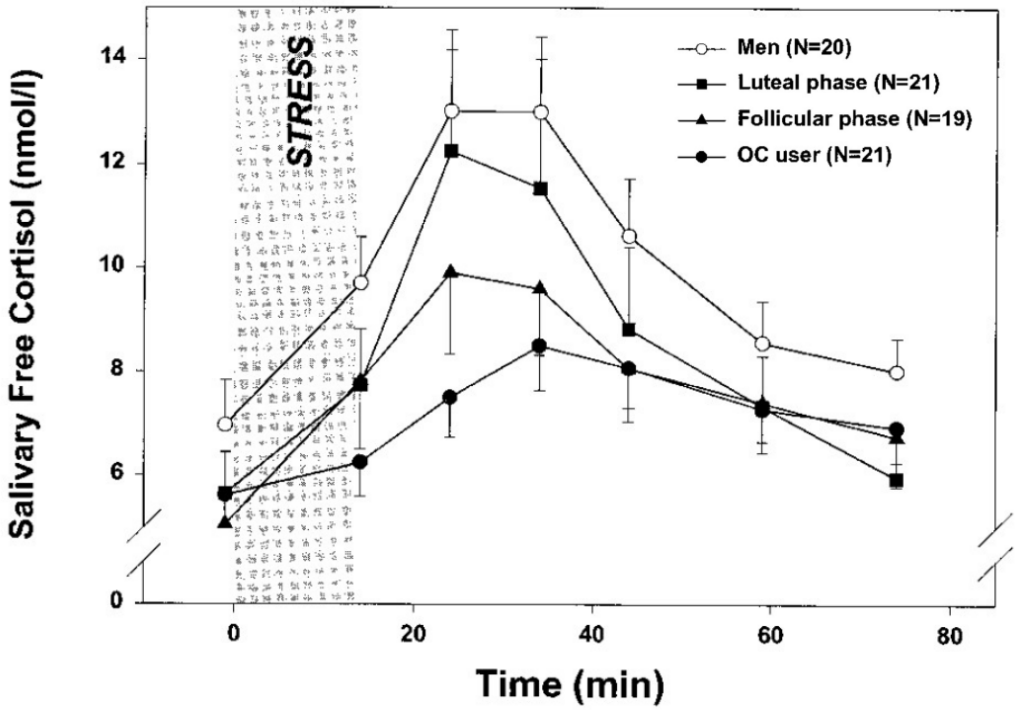

Figure 3.9: Salivary free cortisol values before and after stress test between: men, women in luteal phase, women in follicular phase and women used to oral contraceptives (Kirschbaum et al., 1999).

Finally a meta-analysis (Otte, Hart, et al., 2005) has shown a statistically significant difference between males and females in regards to the cortisol response in advancing age. The analysis included a combination of 45 studies and gathered data from a sample of 1225 people (625 older subjects and 670 young controls). Elderly women, rather than elderly men, showed three times greater cortisol response to dexamethasone suppression test (d_{women} = 0.66, 95% CI = [0.34; 0.97], d_{men} = 0.24, 95% CI = [0.02; 0.47], p-value = 0.003; see barplot 3.10). The result is robust in regards to heterogeneity (Q = 36.5, p-value = 0.26).

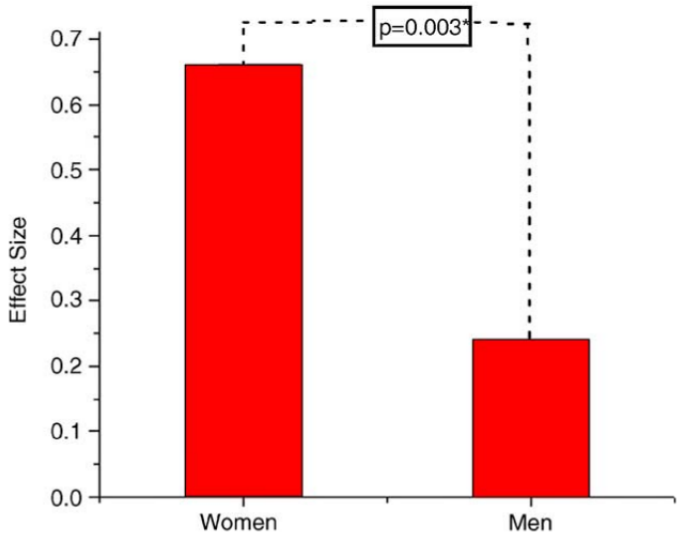

Figure 3.10: The differences of Cohen's d (effect size) regarding the effect of age on cortisol response in women and men (Otte, Hart, et al., 2005).

3.2 Cerebral outcomes

Childhood maltreatment causes structural brain changes that are associated with altered neurocognitive function, such as: threat processing, reward processing, and emotion regulation (Zhong et al., 2020). The research using brain morphometry and magnetic resonance imaging (MRI) in adults reporting childhood abuse, indicated reduced volume in these areas:

- medial prefrontal cortex (mPFC) (van Harmelen et al., 2010)
- anterior cingulate cortex (aCC) and caudate (Cohen et al., 2006)
- hippocampus (Dannlowski et al., 2012).

This data is not consistent in literature, and there are studies that did not detect decreased hippocampal volume (Cohen et al., 2006; Zhong et al., 2020). As I reported in on page 21, brain regions mature at different times and so it is possible that event-related anatomo-functions can be seen in different stages of life. The methodological issue that I mentioned on page 41 recurs equally. It's important to undertake a developmental approach with longitudinal studies or to standardize the variables with particular attention to the onset of the maltreatment (see on page 39). McCrory, De Brito, and Viding (2012, pag. 153) expressed their opinion in this way: "Unfortunately, most brain imaging studies have not systematically considered the age at which different kinds of abuse have occurred. From a clinical perspective it would be helpful for

further research to systematically investigate the relative susceptibility of different brain regions at different ages to different forms of early adversity.”.

Showing the importance of this aspect, I want to mention this article of Andersen et al. (2008): Preliminary evidence for sensitive periods in the effect of childhood sexual abuse on regional brain development. The authors made a cross-sectional study between children and teenagers with history of sexual abuse. Victims compared to control subjects, showed different structural brain alterations in relation to the onset of violence:

3–5 years: reduced hippocampal volume (regression analysis: β = -0.566, p-value < 0.001)

9–10 years: reduced corpus callosum volume (β = -0.422, p-value = 0.03)

11–13 years: reduced hippocampal volume (β = -0.308, p-value = 0.054)

14–16 years: reduced frontal cortex volume (β = -0.386, p-value = 0.009).

Ming et al. (2017) found a strong relation between ventromedial prefrontal cortex (vmPFC) and the HPA-axis activity in the stress-response regulation. During the Montreal Imaging Stress Task (mental arithmetic tasks), depressed and remitted patients, showed reduced activation of vmPFC compared to the healthy control subjects (control depressed: $t_{(70)} = 4.11$, p-value = 0.007; control remitted: $t_{(67)} = 5.02$, p-value < 0.001), and this is negatively correlated with cortisol increases in all three groups (control group: r = –0.35, p-value = 0.037; depressed group: r = –0.37, p-value = 0.026; remitted group: r = –0.40, p-value = 0.022; see fig. 3.11).

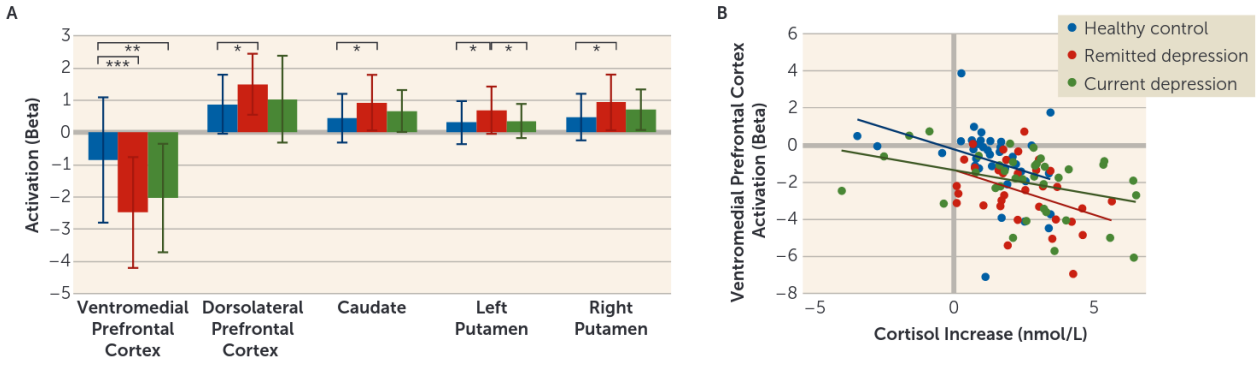

Figure 3.11: Left: Brain activation during a stress task, between healthy subjects and depressed/remitted patients. Asterisks indicate statistically significant differences between the groups. Right: Scatter plot with regression line between the ventromedial prefrontal cortex activation, and the increase of cortisol (Ming et al., 2017).

Zhong et al. (2020) claimed that the hypoactivation of vmPFC in the subjects with childhood maltreatment experiences, indicates hypersensitivity to stress. This confirms that the individuals with childhood traumatic stress and depression have dysregulation of the HPA axis and emotional alterations in response to stress (Heim, Newport, et al., 2000).

The corpus callosum is a white matter structure that controls inter-hemispheric communication, and it is implicated in arousal, emotion, and higher cognitive abilities (McCrory et al., 2012). Jackowski, De Araújo, De Lacerda, de Jesus Mari, and Kaufman (2009), in a brief review, reported that a reduced corpus callosum volume had been associated in maltreated children compared to the controls (see fig. 3.12). A meta-analysis (Karl et al., 2006) confirmed, that children with post traumatic stress disorder (PTSD) exhibited significantly smaller corpus callosum and frontal lobe volumes compared to the controls (d = -0.28, 95% CI = [-0.40; -0.16], data obtained from graph).

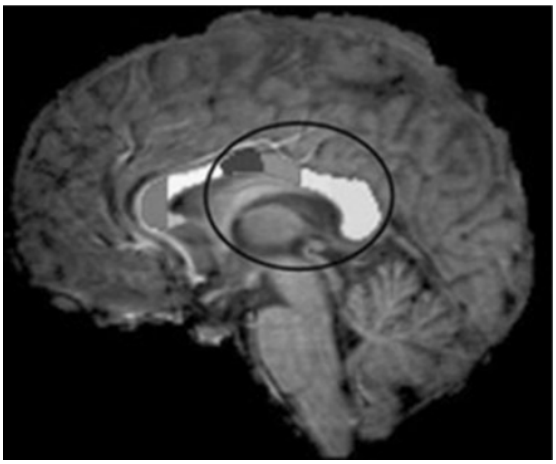

Figure 3.12: MR image of midsagittal section of brain from a subject with history of trauma exposure. The circle indicates reduced callosal areas (Jackowski et al., 2009).

The limbic system is a fundamental region involved in motivational behaviours. The major structures included in this system are: the cingulate cortex, amygdala, hippocampus, fornix, mammillary bodies and the septum (Pinel, 2011). The hippocampus is structure involved in the memory function, and as I mentioned on page 21 it is particularly vulnerable to stress in the postnatal and adulthood periods (Lupien et al., 2009). For this reason it is not a surprise if the literature relative to the evidence of smaller hippocampal volume after trauma, is consistent in adults, but in children and adolescents is reported to have an absence of reductions in hippocampal volume (Jackowski et al., 2009).

The amygdala is a key structure in evaluating threatening stimulus, fear conditioning and emotional processing (McCrory et al., 2012). Tottenham et al. (2010) observed that the scientific evidences suggest that there is a relation between childhood abuse and atypical amygdala development, and the consequence is greater reactivity to emotional information. Dannlowski et al. (2012), for example, reported hyperresponsiveness of amygdala (see fig. 3.13), during an emotional face matching paradigm designed to activate the amygdala in response to threat-related faces.

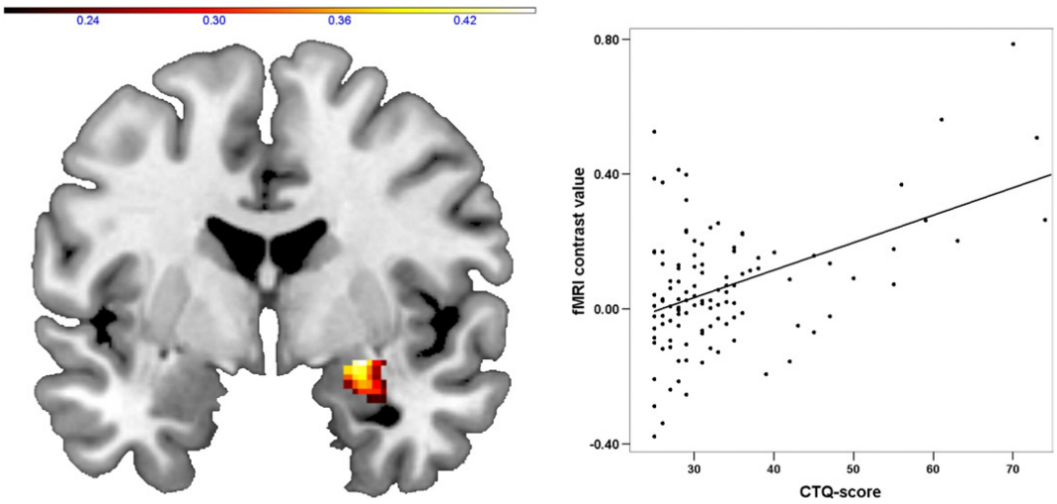

Figure 3.13: Left: Coronal view of functional magnetic resonance imaging (fMRI) of a subject while watching negative facial expressions. The color bar indicates the correlation coefficient of Pearson. It is evident to see the responsiveness of the right amygdala. Right: Scatter plot with a regression line linking the fMRI value and the score obtained in the childhood trauma questionnaire (CTQ). There is a significant positive regression ($\beta = 0.49$, p-value < 0.001) (Dannlowski et al., 2012).

The insula is a structure interconnected with the PFC and limbic system, and it is fundamental in processes such as interoceptive awareness and emotion processes (Craig, 2002). The insula is a part of the salience network and it is vital for triggering appropriate control signals to regulate emotional responses (Menon & Uddin, 2010). Given the relation between the salience network and reward sensitivity, Marusak, Etkin, and Thomason (2015) found an indirect effect of childhood maltreatment on reward sensitivity. Trauma exposure drives to increase the salience network connectivity within the insula, and this determines a diminished reward sensitivity (see fig. 3.14). Therefore trauma-exposed children or teenagers are very susceptible to stress and this correlates with higher fronto-insular responses and the activation of the salience network (Marusak et al., 2015).

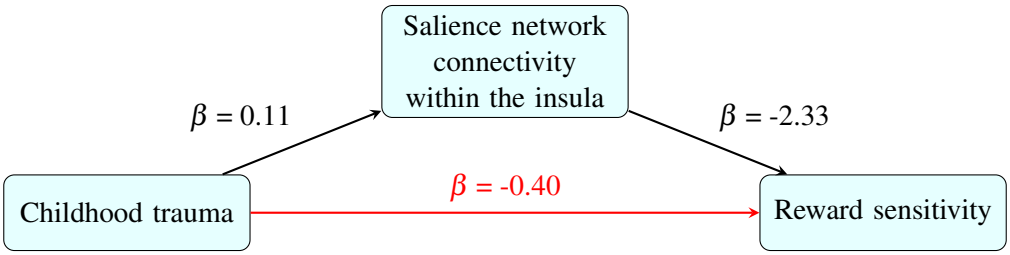

Figure 3.14: The chart shows the relationship between trauma exposure, salience network and reward sensitivity. On the arrows, the numerical values shown indicate the regression coefficients. The red arrow shows an indirect effect from the bootstrap-mediation analysis (β = -0.40, 95% CI =[-0.89; -0.01], p-value $<$ 0.05) (data source Marusak et al., 2015).

According to Zhong et al. (2020), this finding suggests that impaired processing in stress system, is a marker of vulnerability and this may be implicated in the etiopathogenesis of psychiatric disorders.

3.3 Cardiac outcomes

In § 2.1, I mentioned the relation between the HPA axis and the autonomic nervous system (ANS) in accordance with the Polyvagal Theory (Porges, 2001). In this section I will show the main outcomes on populations with history of childhood maltreatment, taking into account the cardiovascular reactivity.

Heart rate (HR) and heart rate variability (HRV) are two common variables to study, in regards to the responses of the heart in stress situations. HRV, in particular, represents the hearts ability when acting towards environmental stimuli (Acharya, Joseph, Kannathal, Lim, & Suri, 2006). Murali and Chen (2005) studied how exposure to violence in adolescents, affects cardiac reactivity measures, such as: HR, HRV, systolic blood pressure (SBP), and diastolic blood pressure (DBP). They found a decreased cardiovascular reactivity after the stress test (HR: β = -0.21, p-value $<$ 0.05; SBP: β = -0.27, p-value $<$ 0.05; no significant differences in β of predictors: HRV and DBP). Even in this case, the data is not consistent in literature. For example, MacMillan et al. (2009) showed a blunted cortisol response, but no difference in the HR after a psychosocial stressor.

The issue of blunted cardiovascular reactivity can be interpreted from an ontological point of view. The age may be a variable that explains the differences between studies. The children and teenagers did not always show a blunted response (cardiovascular or neuroendocrine levels) after the stress test or at the baseline, while in the studies with adults or elders, it's more easy to see this outcome (Phillips, Ginty, & Hughes, 2013).

To get a better understanding of the phenomenon of blunted reactivity after chronic stress, it's better to consider the relation between the HR and the ANS, also taking into account that the HR is also the result of the balancing action between the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS). As I mentioned on page 33, it's possible to use vagal tone to describe the cardiac and sympathetic response to a stress. The vagal tone prevails under resting conditions when the parasympathetic nerves are in a stable state. In a stress situation, the sympathetic nerves are more active, and therefore the vagal brake is removed. Chronic stress may break this balance, and lead towards dysregulation of the autonomic nervous control of the cardiovascular system. This is important also in pathology such as: coronary artery disease and ventricular arrhythmias (Kjellgren & Gomes, 1993; Sztajzel et al., 2004).

A way to study the effects of the vagal tone in subjects with early adverse experiences, is by using the respiratory sinus arrhythmia (RSA) (see on page 33). An Italian study (Ardizzi et al., 2013) evaluated the RSA suppression during a facial emotion recognition task in boys of Sierra Leone who live alone on the street without any type of parental/social care. The control group showed RSA suppression during the recognition task of anger, demonstrating an efficient release of the vagal brake. The experimental group showed RSA suppression during the recognition task of non-threatening stimuli (fear, sadness and joy), but not during the observation of anger. More so, the experimental group was also slower to recover an adequate vagal tone after the task (see fig. 3.15).

This research shows the dysregulation of the autonomic system and the effects on the social responses. The research of an Italian group in Sierra Leone (Ardizzi et al., 2015, 2013, 2016; Umiltà, Wood, Loffredo, Ravera, & Gallese, 2013) showed that childhood maltreatment effects, in regards to emotion recognition, decay quickly, whereas, the effects for facial expressions and autonomic regulation, decay progressively. Long-term childhood trauma modulates physiological mechanisms that support intersubjective abilities.

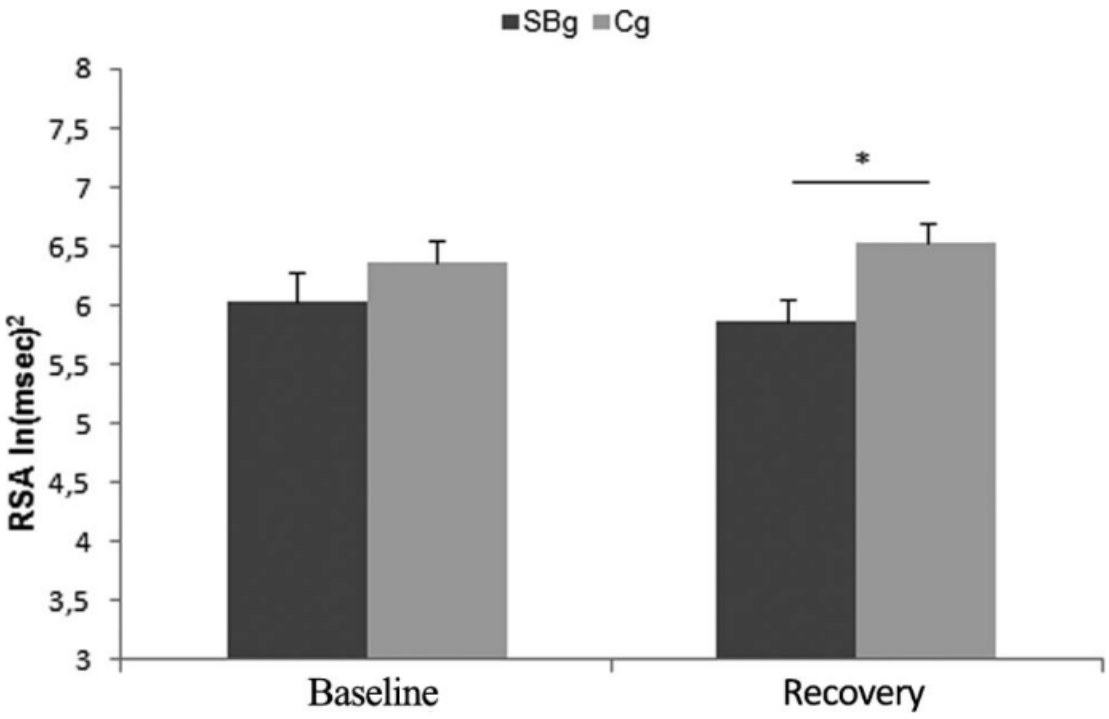

Figure 3.15: Baseline and recovery RSA values for experimental group (SBg: Street-Boys group) and control group (Cg). The asterisks indicate statistically significant differences between the groups, in the recovery phase, the experimental group showed lower RSA values ($t_{(34)}$ = -2.72, p-value $<$ 0.012) (Ardizzi et al., 2013).

The hypothesis is, that childhood maltreatment would "retune" the ANS. The adverse experiences may drive towards blunted cardiovascular reactivity and a lower vagal tone, and this disfacilitates socially trusting behaviors and facilitates vigilant states, to prepare for the flight or fight behaviors (Dale et al., 2009).

3.4 Metabolic outcomes

The relation between the dysregulation of the HPA axis and the metabolic system, is particularly evident in obesity, because childhood maltreatment is associated with a significant obesity risk (Hemmingsson, Johansson, & Reynisdottir, 2014). As showed in the forest plot (fig. 3.16), Hemmingsson et al. (2014) found that the following types of childhood abuse were associated with increased obesity risk: physical abuse (OR = 1.28, 95% CI = [1.13; 1.46], p-value $<$ 0.001, I^2 = 68%), emotional abuse (OR = 1.36, 95% CI = [1.08; 1.71], p-value $<$ 0.01, I^2 = 59%), sexual abuse (OR = 1.31, 95% CI = [1.13; 1.53], p-value $<$ 0.001, I^2 = 41%), general abuse (OR = 1.45, 95% CI = [1.24; 1.45], p-value $<$ 0.001, I^2 = 76%).

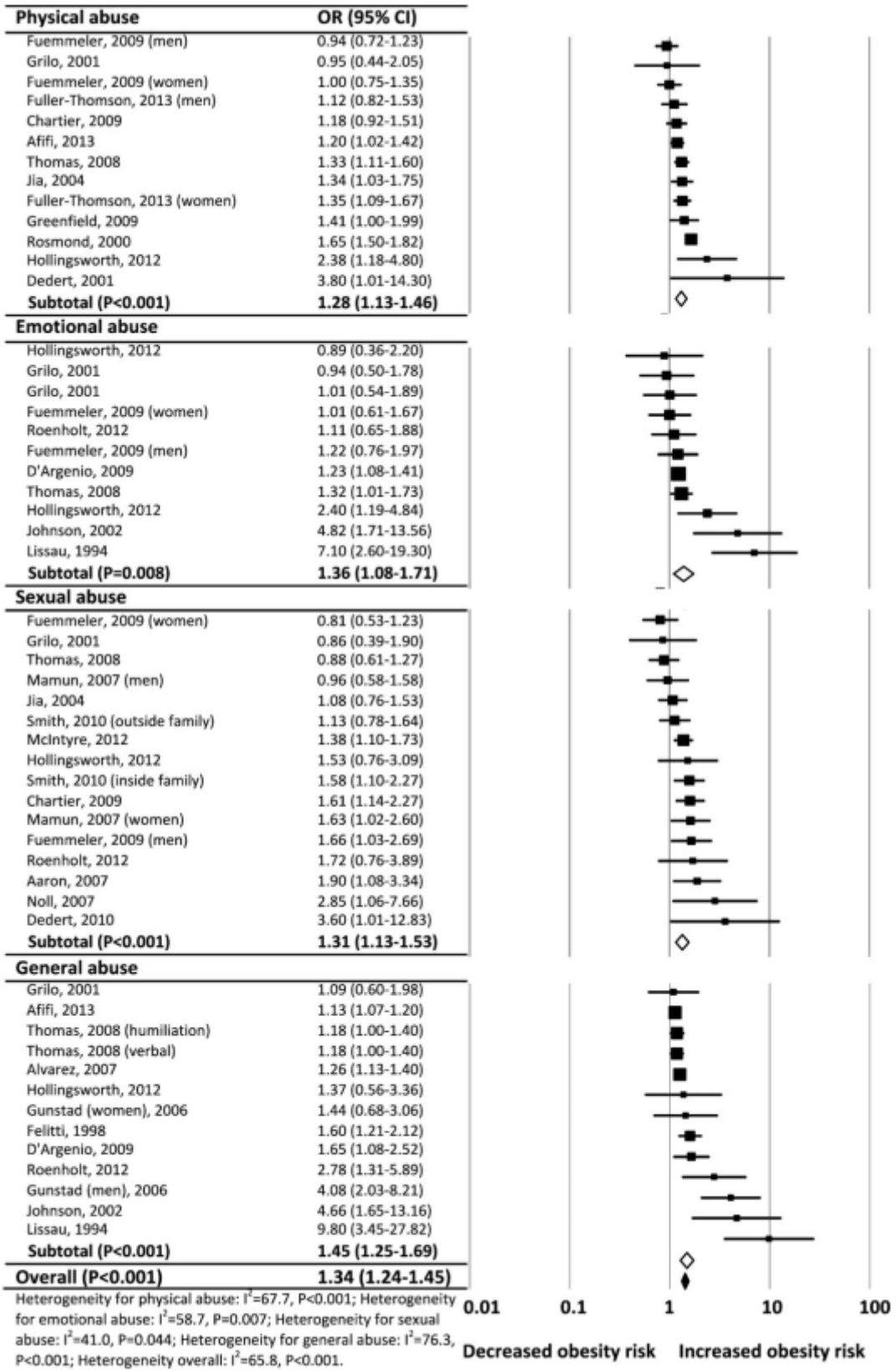

Figure 3.16: Odds ratio between people with history of childhood maltreatment and controls to estimate the obesity risk (Hemmingsson et al., 2014).

A developmental approach clarifies the evolution of this phenomenon. A longitudinal British study (Power, Pereira, & Li, 2015) measured the association between childhood maltreatment and body mass index (BMI). The group study recorded at seven time-points, the different types of abuse (such as: physical, psychological, sexual, neglect) and the BMI in the 1958 birth cohort (almost 15000 subjects). Participants with experiences or history of physical abuse, sexual abuse (only in the women) and neglect, showed normal BMI in childhood, but increased BMI gain and obesity in adulthood (see table 3.1). This result was adjusted for potential covariates (such as: parental BMI, prenatal/infancy factors, education, etc.).

	Men 50 years old		Women 50 years old	
Child maltreatment	Odds Ratio	95% CI	Odds Ratio	95% CI
Physical abuse	1.50	[1.13; 1.99]	1.73	[1.28; 2.32]
Psychological abuse	1.36	[1.06]; 1.74	1.44	[1.15; 1.80]
Sexual abuse	1.44	[0.53; 3.89]	1.75	[1.13; 2.71]
Neglect	1.35	[1.14; 1.61]	1.54	[1.28; 1.86]

Table 3.1: Odds ratio (OR) and confidence intervals between people with history of childhood abuse and control subjects, divided by types of childhood maltreatment and gender to estimate the obesity risk. The red numbers are the OR with a statistically significant difference (data source Power et al., 2015).

A longitudinal study of Baldwin et al. (2016) followed 2232 subjects from the ages of 10 years old to 18 years old. The authors assessed bullying victimization and categorically measured the obesity, BMI, and the waist-hip ratio. They found an association in chronically bullied children between victimization and obesity in young adulthood compared to non-bullied children (OR = 1.69, 95% CI = [1.21; 2.35]). This approach shows that childhood maltreatment is associated with a progressive increase in obesity risk during the life-course (Baldwin & Danese, 2019).

Given the association between childhood maltreatment and obesity risk, I will describe some possible causes of this phenomenon. In the early stages of maltreatment, children under chronic stress may eat high-calorie foods to reduce anxiety (Prasad & Prasad, 1996) and, consequently, to reduce HPA axis activation (Pecoraro, Reyes, Gomez, Bhargava, & Dallman, 2004). This behavior will affect reward processing and the neuroendocrine stress system. The relation between the endocrine and metabolic hormones, may be evident in leptin deficiency. The leptin promotes lipolysis and this increases the breakdown of fat into energy (Baldwin & Danese,

2019). Different authors have shown, low basal and stimulated levels of leptin, in subjects who have histories and experiences with childhood maltreatment (Danese et al., 2014; Panagiotaropoulos et al., 2004).

As I mentioned in § 2.6, it's important to study the contribution of 11β-HSD1 and 11β-HSD2 enzymes in the fat biology. The enzyme 11β-HSD1 catalyzes the conversion of the inactive cortisone to active cortisol, the consequence is the amplification of cortisol action in different areas, such as: liver, muscle and adipose tissue (Alberti et al., 2007; Baudrand et al., 2010). An over-expression of 11β-HSD1 in these tissues may dramatically increase weight leading towards obesity (Baudrand & Vaidya, 2015). There are many findings support this result. For example, Wake et al. (2003) found a positive regression between adipose 11β-HSD1 expression and BMI ($\beta = 0.48$, p-value < 0.05). Mariniello et al. (2006) found a 13-fold higher 11β-HSD1 mRNA expression in obese subjects compared to a control group (p-value < 0.01).

The enzyme 11β-HSD2 inactivates cortisol and turns it into the inactive cortisone, the consequence is the reduction of active cortisol concentrations in tissues. Thereby this trade-off between cortisol activation (role of 11β-HSD1) and inactivation (role of 11β-HSD2) may be essential in understanding the ethology of obesity. When this balance is skewed towards increased cortisol levels, the obesity risk is higher.

3.5 Inflammation outcomes

In § 2.1, I showed the relation between the HPA axis and other systems involved in the stress response (such as the autonomic nervous system, immune system and metabolic system). I will conclude this chapter by considering the relation of childhood maltreatment with the inflammatory response. The Inflammatory response is part of the immune system, and it represents the reaction to infection and physical injury.

Childhood maltreatment may be associated with chronic low-grade inflammation, consequently for high levels of inflammation biomarkers, such as: C-reactive protein (CRP), pro-inflammatory cytokines and interleukin 6 (IL-6) (Baldwin & Danese, 2019). Even in this case, it's useful to adopt a developmental approach. The long-term effects of maltreatment can predict high inflammation levels in midlife (Takizawa, Danese, Maughan, & Arseneault, 2015).

For example, children exposed to different types of abuse, showed higher levels of CRP compared to non-maltreated children at age 32 (Danese, Pariante, Caspi, Taylor, & Poulton, 2007) (see left fig. 3.17). More so, if children are exposed to multiple victimization types (Baldwin et al., 2018) or there is a morbidity with a psychopathology (like a depression; see Danese et al., 2010), the dysregulation of the inflammation response, can then arise during adolescence (see right fig. 3.17).

As discussed in the previous section, maltreated children have an elevated obesity risk. There is a relation between obesity and the inflammatory state, and this is due to the production of pro-inflammatory cytokines from adipose tissue (Gregor & Hotamisligil, 2011).

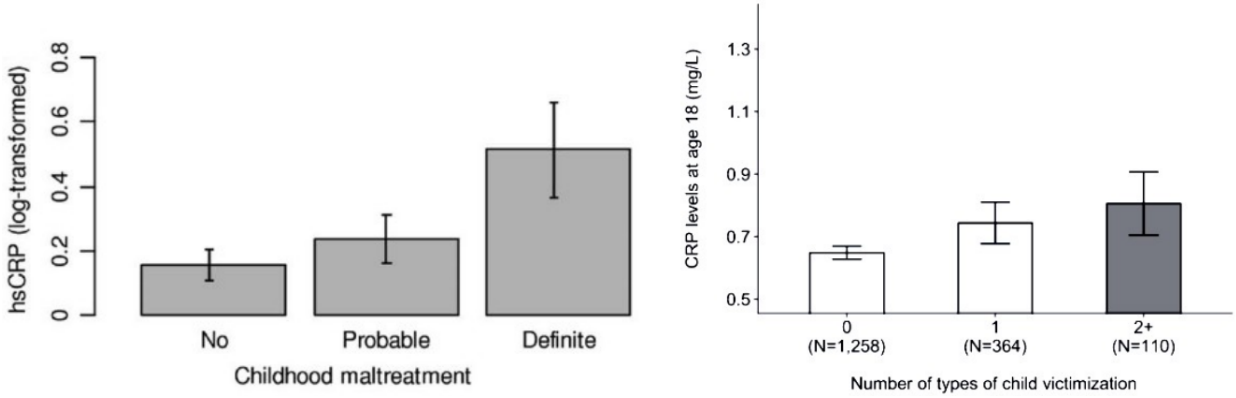

Figure 3.17: Left: The barplot shows the logarithm of the mean levels of high-sensitivity C-reactive Protein (hs-CRP) in adults with different levels of childhood maltreatment. There is a significant difference between the groups (p-value = 0.028) (Danese et al., 2007). Right: The barplot shows the mean levels of serum-equivalent C-reactive Protein in teenagers with histories of different childhood victimization. Authors found a positive linear regression, between exposure to childhood victimization and CRP levels at age 18 (β = 0.15, 95% CI = [0.03; 0.27], p-value = 0.018) (Baldwin et al., 2018). The lines across the barplot represent the standard error.

Chapter 4

Meta-analysis

In this chapter I will show two meta-analyses. The aim of these meta-analyses is to estimate the effect of childhood maltreatment in regards to the cortisol to social stress response, or to the awakening response. If the "attenuation hypothesis" is true (Gunnar & Vazquez, 2001; Heim, Newport, Mletzko, Miller, & Nemeroff, 2008; Susman, 2006), then what is the strength of the effect of the downregulating cortisol secretion, as a consequence of adapting to sustained periods of hypersecretion due to a history of abuse? To analyze this question, I evaluated the following:

1. The standardized mean difference between the subjects with a history of childhood maltreatment (μ_1) and the control subjects (μ_2) in the first meta-analysis.

2. The standardized mean difference between the subjects with a history of childhood maltreatment, which also took into account a diagnosis of a psychological disorder (μ_1), and the control subjects (μ_2) in the second meta-analysis.

The standardized mean difference is an index that allows the outcomes to be comparable across studies, when the scale of measurement differs from study to study. The standardized mean difference (δ) is obtained by dividing the mean difference ($\mu_1 - \mu_2$) in each study, by that study's standard deviation (σ) (Borenstein, Hedges, Higgins, & Rothstein, 2009), as defined in the following equation:

$$\delta = \frac{\mu_1 - \mu_2}{\sigma}$$

4.1 Materials and methods

4.1.1 Identification of studies

The phase of identification of studies occurred in April 2021. I used three electronic databases: PsycInfo, PubMed and Web of Science. The keywords used in all databases were: childhood (truncated term), different types of maltreatment and cortisol or HPA axis (see table 4.1). I excluded papers from other meta-analyses and reviews because they did not report original data. I also excluded papers from dissertations and theses because they were not subject to peer review. I selected papers dated from 1990 until the present, and this excluded 35 papers that would not have been included in the meta-analysis because 34 were not related to the research hypothesis and one did not have a control group. No language criteria was used.

	Search criteria
1	child*
2	maltreatment OR violence OR adversity OR trauma OR abuse OR victimization OR emotional abuse OR emotional neglect OR physical abuse OR physical neglect OR sexual abuse
3	cortisol[tiab] OR HPA axis
4	MR interview OR MR literature review OR MR systematic review OR MR meta analysis OR PZ dissertation OR PT book
5	Books and Documents[Publication Type] OR Meta-Analysis[Publication Type] OR Review[Publication Type] OR Systematic Review[Publication Type]
PsycInfo	1 AND 2 AND 3 NOT 4
PubMed	1 AND 2 AND 3 NOT 5
Web Of Science	1 AND 2 AND 3

Table 4.1: Search criteria for the identification of the papers included in the phase of screening of the meta-analyses.

4.1.2 Inclusion and exclusion criteria

The inclusion criteria of the meta-analysis were as follows:

1. the experimental group consisted of subjects with a history of childhood maltreatment
2. the sample involved human participants of all ages

3. the procedure provided an assessment of cortisol.

I focused my study on the forms of abuse that occurred during childhood (early or middle), and the experimental procedure characterized by assessment of cortisol as measure of stress responses or rest condition (e.g., awaking response).

The exclusion criteria of the meta-analysis were as follows:

1. experimental group involving subjects with onset of abuse experience starting after childhood
2. the sample involving animal models
3. procedures providing assessment of stress different than cortisol
4. procedures providing assessment of hair cortisol
5. lack of control participants (i.e., subjects below the cutoff of the scale or having no experience with childhood maltreatment)
6. subjects exposed to prenatal stress (such as maternal substance abuse)
7. pregnant women
8. drug abusers (e.g., alcohol or cocaine)
9. the presence of a medical condition (such as diabetes or chronic fatigue)
10. review papers and other meta-analysis studies
11. papers that were not written in English
12. papers that did not report data in the form of a table or graph
13. papers which are behind a paywall.

The first three exclusion criteria were used because they were strongly related with the research hypothesis and were complementary to inclusion criteria. The forth exclusion criteria was due to the fact that hair cortisol provides long-term cortisol output (see § 2.3) and the attenuation hypothesis was not verified for this assessment. The fifth exclusion criteria was necessary because without the control sample output, I could not calculate the standardized mean

difference. The exclusion criteria from sixth to ninth were necessary because they were conditions that could explain a dysregulation of the cortisol level besides childhood maltreatment. The tenth exclusion criteria was introduced because not all papers had the correct meta-data and the filter used in the identification step did not remove all requested records. The eleventh exclusion criteria was used because English is generally considered to be the language of the scientific community and it's most likely to get a peer review. The twelfth exclusion criteria was necessary to download data. The thirteenth and final exclusion criteria was used because I downloaded papers from my University account, and therefore I excluded 12 papers, 7 of which have been included in the eligibility step.

The screening phase has been made based on the title, abstract, table and graph. The eligible studies were assessed based on full text.

4.1.3 Risk of bias criteria

The risk of bias (RoB) was evaluated in included studies within three domains that were selected a priori:

selection bias: the risk of bias relative to the selection of research participants

performance bias: the risk of bias relative to the experimental procedure

attrition bias: the risk of bias relative to the publication of research data.

After the selection of the domains, I explicated the questions in order to evaluate if the RoB was either low, unclear or high (in accordance with Higgins et al., 2019). The questions were:

1. What is the risk of bias that comes from the selection of the experimental group? This selection bias was evaluated as low if the study used a standardized method to establish the entity of the abuse or the trauma (such as the Childhood Trauma Questionnaire, CTQ; Bernstein et al., 1998).

2. What is the risk of bias that comes from the selection of the participants for the research? This selection bias was evaluated as low if the paper indicated clearly the inclusion criteria.

3. What is the risk of bias that comes from the selection in the experimental group of subjects with a psychological disorder? This selection bias was evaluated as low if, for the

evaluation of the disorders, the diagnostic criteria was taken from the Diagnostic and Statistical Manual of Mental Disorders - DSM-IV (American Psychiatric Association, 1994) or DSM-5® (American Psychiatric Association, 2013).

4. What is the risk of bias that comes from the experimental procedure? This performance bias was evaluated as low if the description of the procedure was clear, and particularly if the assessment of cortisol provided at least three samples with an assessment in the first 30 min following the stress-test onset or the awakening.

5. What is the risk of bias that comes from the publication of research data? This attrition bias was evaluated as low if the data presentation was in tabular form with a clear explanation of the meaning of the variables.

For the 1st meta-analysis, I evaluated the questions numbered 1, 2, 4 and 5. For the 2nd meta-analysis, I evaluated the questions numbered 1, 2, 3, 4 and 5. After doing so, I established the following criteria: the overall RoB was low, if the research had at least three RoB that were considered low in the 1st meta-analysis and at least four RoB that were considered low in the 2nd meta-analysis.

4.1.4 Moderators

The moderators gathered for this meta-analysis are:

Categorical moderators:

- participants' gender: only females, only males, both;
- age: developmental stage at the time of assessment (early childhood - from 2 to 5 years, middle childhood - from 6 to 10 years, adolescence - from 11 to 19 years, youth - from 19 to 30 years, adulthood - over 30 years);
- cortisol: type of cortisol measure (plasma, salivary);
- abuse type: type of abuse suffered by the subjects of the experimental group (neglect, sexual, war, mixed);

- disorder type (2^{nd} meta-analysis): type of disorder diagnosed to the subjects of the experimental group in the second meta-analysis (attention deficit hyperactivity disorder - ADHD, anxiety, attachment, depression, eating, personality, post traumatic stress disorder - PTSD, schizophrenia);
- world region: region in which the research was conducted (Asia, Europe, Middle East, North America, South America);
- maltreatment assessment: method used to assess the maltreatment of the experimental group (standardized scale, - such as Adverse Childhood Experiences, Childhood Trauma Questionnaire, etc., versus no standardized scale);
- stress test: type of stress test (pharmacological, non-pharmacological, no stress test);
- RoB: risk of bias of the research (low, high).

Continuous moderators:

- female frequency: relative frequency of female participants in the experimental group for each study.

4.1.5 Statistical analysis

As I mentioned on page 56, I used the standardized mean difference (δ) as a population parameter for describing the size of effects relative to the difference in cortisol level between two populations. The most common sample estimate of the standardized mean difference is the Cohen's d (Borenstein et al., 2009). However, Cohen's d overestimates the absolute value of δ in small samples, so Hedges proposed a correction (J) in order to get an unbiased estimate of the standardized mean difference called Hedges' g (Hedges, 1981). The correction factor (J), the effect size (g) and the standard error (se_g) calculate by Hedges are:

$$J = 1 - \frac{3}{4(n_1 + n_2 - 2) - 1}$$

$$g = J \cdot d$$

$$se_g = \sqrt{J^2 \cdot var_d}$$

where:

- n_1 and n_2 are the size of the two samples,
- d is Cohen's d and
- var_d is variance of Cohen's d.

For each meta-analysis I did the following evaluation:

- power analysis: the estimation of how many papers were needed for the meta-analysis;
- main effect: the estimation of the overall effect;
- publication bias: the evaluation of the funnel plot asymmetry using Egger's test (Egger, Smith, Schneider, & Minder, 1997);
- outliers: the calculation of the outliers papers and the following analysis of the main effects after their exclusion;
- subgroup analysis: the estimation of the effects for each level of the categorical moderators;
- multimodel inference: the evaluation of the fit of the model and the relative importance of the singles moderators;
- meta-regression: the evaluation of the regression model between the main effects and a continuous moderator.

I used two software for meta-analysis:

Engauge Digitizer: to extract data from the graph. It's an open source software, available on GitHub.

R studio: to analyze data. It's a free software based on the GNU General Public License for the programming language R. I used this version: 4.1.0 and, more precisely, its following packages:

metapower (Griffin, 2020): to compute and visualize statistical power analysis;

meta (Balduzzi, Rücker, & Schwarzer, 2019): to calculate the statistical parameters, such as: Hedges' g, standard error, confidence interval, etc.;

dmetar (Harrer, Cuijpers, Furukawa, & Ebert, 2019a): to calculate publication bias, outliers, subgroup analysis, multimodel inference, and meta-regression;

metaviz (Kossmeier, Tran, & Voracek, 2020): to create the forest plots and funnel plots;

ggplot2 (Wickham, 2016) and **ggthemes** (Arnold, 2021): to create graphs for the moderators importance and for meta-regression.

4.1.6 Power analysis

According with Hedges and Pigott (2001), computing of statistical power needs three parameters previously estimated: number of participants of the research study, total number of studies and heterogeneity.

The heterogeneity is the variability in outcomes between studies, and the parameter I^2 describes the percentage of variability across the studies (Higgins & Thompson, 2002). If I^2 is high and statistically significant, it means that the variability across the studies is due to heterogeneity rather than chance. Contrarily, if I^2 is low, it means that the variability across the studies is due to chance, therefore the effect can be explained with a real difference between groups (Hedges & Pigott, 2001). The heterogeneity can then be expressed as the inconsistency of the studies' results (Higgins, Thompson, Deeks, & Altman, 2003).

In this meta-analysis, I hypothesized the following:

- expected effect size: 0.3 (small effect)
- expected study size: 40
- expected number of studies: 50
- heterogeneity: 80% (high heterogeneity).

The power analysis produced these results:

- fixed-effects model: 99%
- random-effects model: 85%

Therefore if I had an average study size of 40 participants and a number of studies of 50, I may get a robust effect (see graph 4.1).

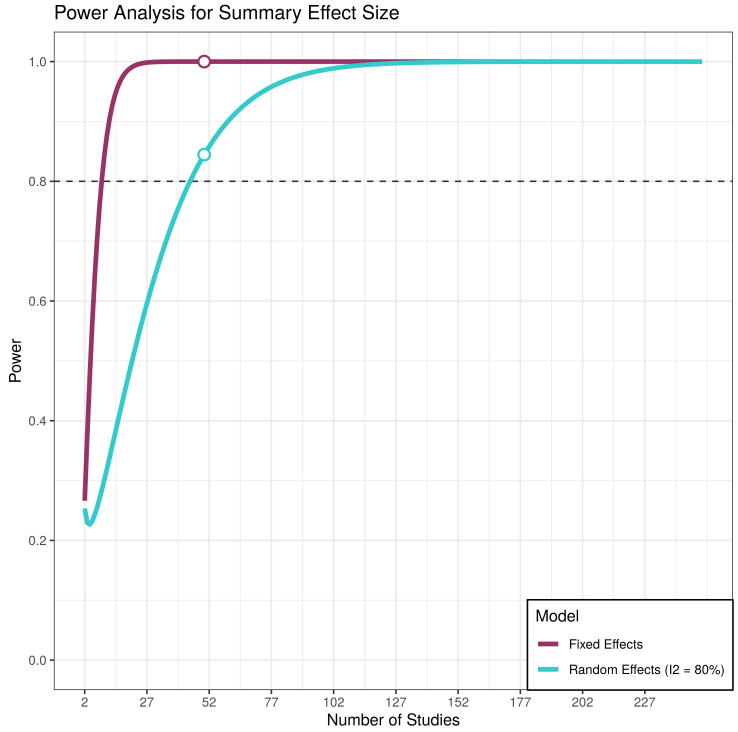

Figure 4.1: The power analysis function for the fixed-effects model (purple line) and for the random-effects model (light blue line). The white dots represent the number of studies that I hypothesized (50 studies) prior to the collection of data. Both these dots are above the dashed line (power = 80%), which indicates that, in these conditions, I may get a robust effect from the meta-analysis regardless of the heterogeneity.

4.2 Results

4.2.1 Study selection and data download

The study selection took place in four steps (see fig. 4.2):

1. Identification of the papers according to the criteria described in § 4.1.1.

2. Screening of 1605 papers according to inclusion and exclusion criteria (§ 4.1.2) and also the removal of duplicate papers.

3. Evaluation of 219 papers based on full text. This step showed that 160 did not comply with one or more of the exclusion criteria (e.g., the control group had participants with a

diagnosis of psychological disorder, the cutoff of the scale to establish if participants had experienced childhood maltreatment was not clear, etc.).

4. Selection of 59 papers to include in meta-analysis.

After the papers selection, I downloaded data in two datasheets, one for each meta-analysis. I got 46 records for the first meta-analysis and 33 records for the second meta-analysis (see fig. 4.3).

The included papers are listed in tables A1 (§ Appendix I) and A4 (§ Appendix II).

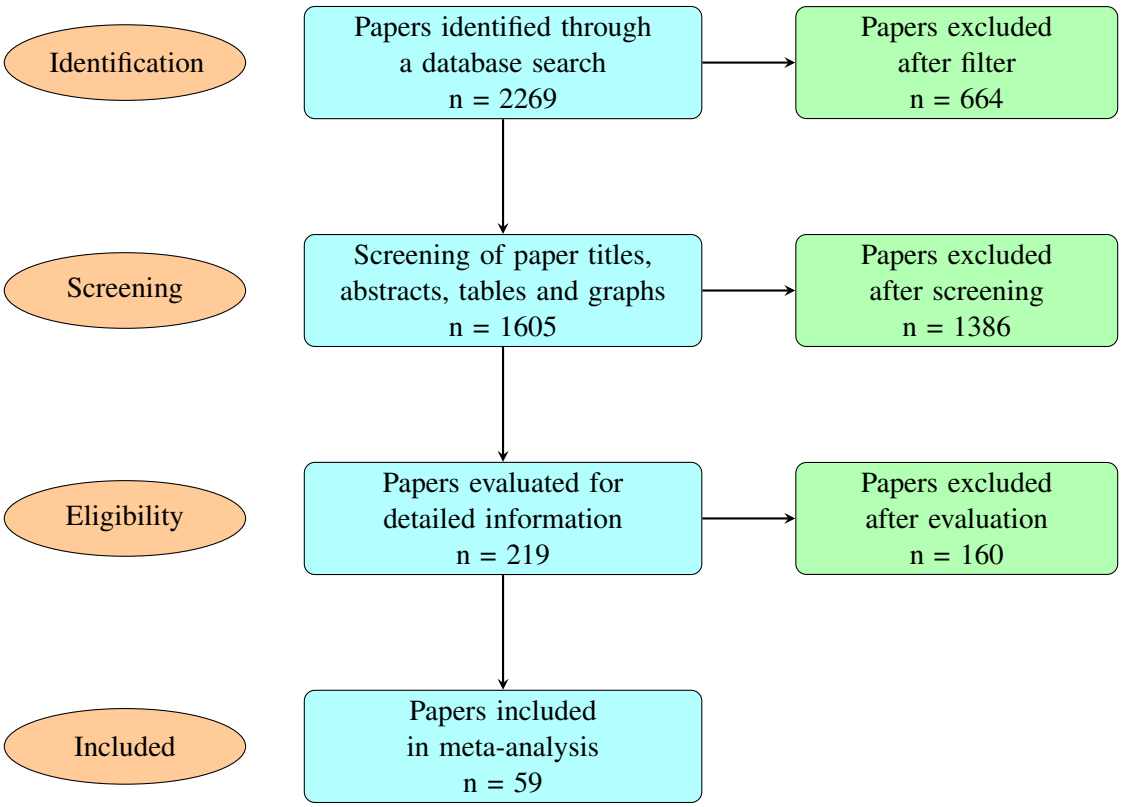

Figure 4.2: Study selection flowchart. The diagram depicts the articles included for each step of the study selection.

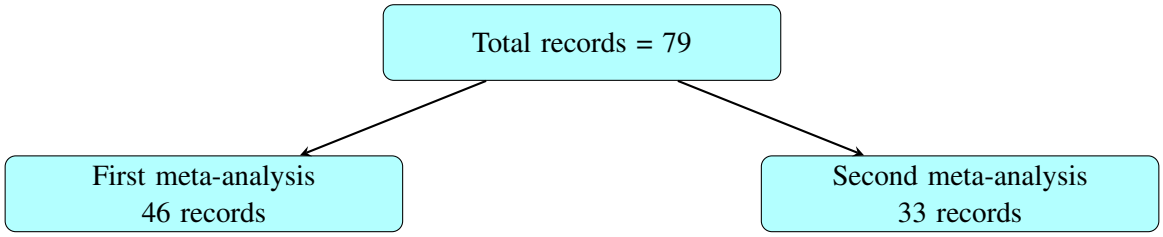

Figure 4.3: The chart shows the division of records between the two meta-analyses.

4.2.2 Post Hoc Power analysis

For the post hoc power calculation on true data, I used, for each meta-analysis, the median of samples size as estimator of the expected study size, and the number of records as estimator of expected number of studies. I kept constant the data of the expected effect size (0.3) and the heterogeneity (80%), than the prior power analysis.

The post hoc power in the first meta-analysis (experimental group without ongoing psychopathology) produced these results:

- fixed-effects model: 99%
- random-effects model: 65%

The post hoc power in the second meta-analysis (experimental group with ongoing psychopathology) produced these results:

- fixed-effects model: 98%
- random-effects model: 47%

The number of records (46 in the first meta-analysis and 33 in the second meta-analysis), in both cases, had sufficient power to detect a significant effect size, nevertheless the heterogeneity may be a limiting factor (see fig. 4.4 and 4.5).

4.2.3 Studies characteristics

The 59 papers included in the meta-analysis contained 79 records (see fig. 4.3), which involved 6746 participants (3165 subjects for the experimental group and 3581 subjects for the control group).

In table 4.2, I summarized the number of records in seven categorical moderators for each meta-analysis. The majority of the studies investigated the effect of childhood maltreatment on the salivary cortisol response to stress (both pharmacological and non-pharmacological). In the datasheet, I also specified the type of variable of cortisol, such as: peak after 30 min (or similar time) from the stress test or the awakening, the Area Under Curve, or the Cortisol Awakening Response. In most studies, the non-pharmacological stress test was induced

through the Trier Social Stress Test (21 studies); in the remaining studies, the stress was induced through verbal interaction, interview, or the Cold Pressure Test. The Pharmacological stress test was induced through the Dexamethasone Suppression Test (5 studies), the Dexamethasone–CRH challenge (3 studies), the CRH challenge (1 study), the Cortisol challenge (1 study), the meta-chlorophenylpiperazine challenge (1 study) and the L-5-Hydroxytryptophan challenge (1 study).

In table A1 (§ Appendix I), I listed the papers included in the first meta-analysis. I reported for each paper: the sample size, the average age of the experimental group, the percentage of female subjects of the experimental group, the type of cortisol measure, the type of abuse and stress test.

In table A4 (§ Appendix II), I listed the papers included in the second meta-analysis. I reported for each paper the same parameters as seen in table A1, with the addition of the type of disorder. The majority of papers studied subjects with a diagnosis of Major depressive disorder (14 studies), and the remaining studies included: Post Traumatic Stress Disorder (7 studies), Eating Disorder (3 studies), Personality Disorder (3 studies), Schizophrenia (1 study), Attention Deficit Hyperactivity Disorder (1 study), Anxiety Disorder (1 study), and Attachment (1 study).

4.2.4 Risk of bias evaluation

The risk of bias (RoB) was evaluated according to the criteria indicated in § 4.1.3.

In tables A2 (§ Appendix I) and A5 (§ Appendix II), I reported the evaluation of the RoB of first and second meta-analysis, respectively. Both meta-analyses showed that the frequency of studies with a low RoB was greater than the frequency of studies with a high RoB ($p\text{-value}_1 = 0.002$; $p\text{-value}_2 = 0.04$).

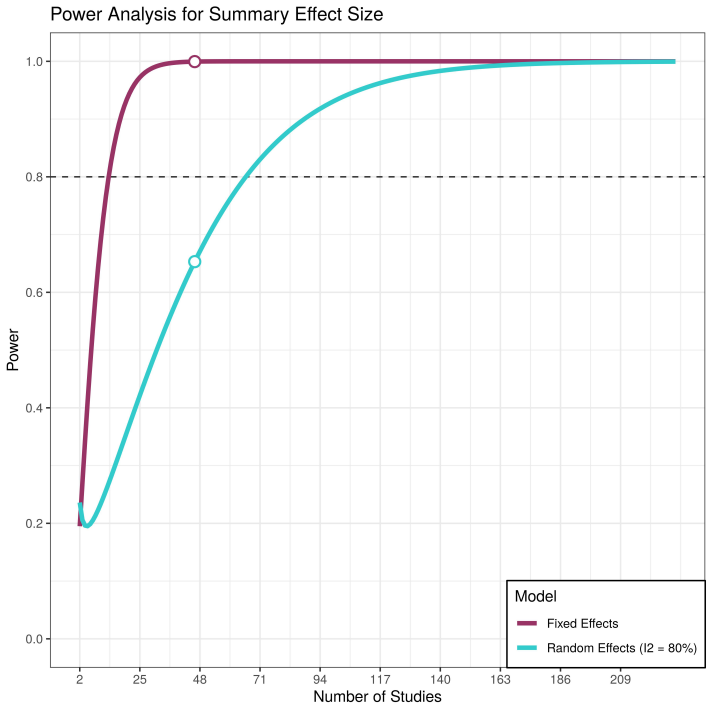

Figure 4.4: Post hoc power analysis of the first meta-analysis. With a number of records equal to 46 (represent by white dots), the power is over the threshold value (80%) in the fixed-effects model, but not in the random-effects model.

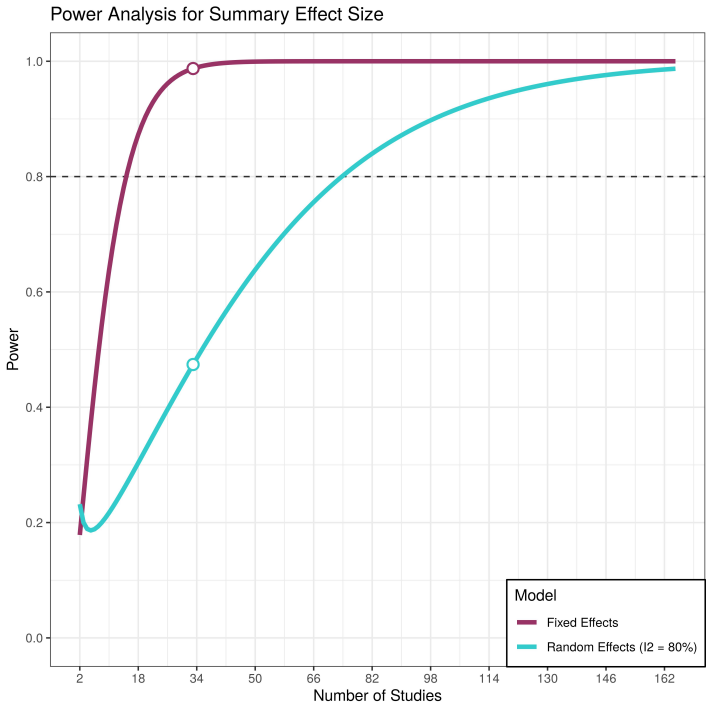

Figure 4.5: Post hoc power analysis of the second meta-analysis. With a number of records equal to 33 (represent by white dots), the power is over the threshold value (80%) in the fixed-effects model, but not in the random-effects model.

Description of the studies					
	Participants				
	Experimental	Control			
I:	1543	1949			
II:	1622	1632			
	Gender				
	Females	Males	Both		
I:	18	7	21		
II:	16	2	15		
	Stage of life				
	Early childhood	Middle childhood	Adolescence	Youth	Adulthood
I:	3	3	8	16	16
II:	1	2	4	12	14
	Cortisol measure				
	Plasma	Salivary			
I:	8	38			
II:	8	25			
	Type of abuse				
	Mixed	Neglect	Sexual	War	
I:	32	5	7	2	
II:	25	1	6	1	
	Maltreatment assessment*				
	No test	CTQ	Other		
I:	14	21	11		
II:	13	14	6		
	Stress test				
	No stress test	Pharmacological	Non-pharmacological		
I:	10	9	27		
II:	11	11	11		
	Region				
	Asia	Europe	Middle East	North America	South America
I:	3	17	4	22	0
II:	2	18	2	10	1

Table 4.2: Number of records for seven categorical moderators for each meta-analysis
* "No test": studies not using a standardized test; "CTQ": studies using the Childhood Trauma Questionnaire; "Other": studies using a different standardized test.

4.2.5 Main analysis

The analysis of the overall effect was conducted before and after deducting the outliers (6 out of 46 in the first meta-analysis and 16 out of 33 in the second meta-analysis).

In table 4.3, I summarized the following variables: the number of record (k), the Hedges' g (g), its confidence interval (95% CI_g) and p-value ($p\text{-value}_g$), the heterogeneity (I^2), its confidence interval (95% CI_{I^2}) and p-value ($p\text{-value}_{I^2}$).

Both meta-analyses showed a significant overall effect, but only the second meta-analysis showed the net of the outliers effect being more robust than the heterogeneity, even if this result may have been affected by the large number of records removed from the total. The overall effect was small in the direction of hypocortisolism and had the same value between first and second meta-analysis. The confidence interval was relatively narrow and the top end of the interval was always less than zero. This may be a point in favor of the attenuation hypothesis, and so, by repeating the analysis, the true effect should also confirm what I found.

A possible explanation of the large number of outliers can be attributed to the structure of the second meta-analysis, including experimental groups composed of participants who associated different types of psychological disorder with a history of childhood maltreatment. This implies that the sample probably has a strong variability. This issue will return in the subgroup analysis and the evaluation of moderators (see § 4.2.7).

Parameters	First meta-analysis	Second meta-analysis	First meta-analysis without outliers	Second meta-analysis without outliers
k	46	33	40	17
g	-0.14	-0.14	-0.18	-0.18
95% CI_g	[-0.21; -0.08]	[-0.21; -0.06]	[-0.25; -0.11]	[-0.31; -0.05]
$p\text{-value}_g$	< 0.001	< 0.001	< 0.001	< 0.01
I^2	61%	84%	44%	0%
95% CI_{I^2}	[46%; 72%]	[79%; 88%]	[18%; 61%]	[0%; 51%]
$p\text{-value}_{I^2}$	< 0.001	< 0.001	< 0.01	0.51

Table 4.3: Overall effect and heterogeneity for each meta-analysis (with and without outliers). The red numbers are the p-value with a statistically significant difference.

The thick forest plots (see fig. 4.6 and 4.7), a variant of the forest plot proposed by Schild and Voracek (2015), show: the effect found in each study as a dot, its confidence interval as a line and the weight of the study within the meta-analysis as the thickness of this line.

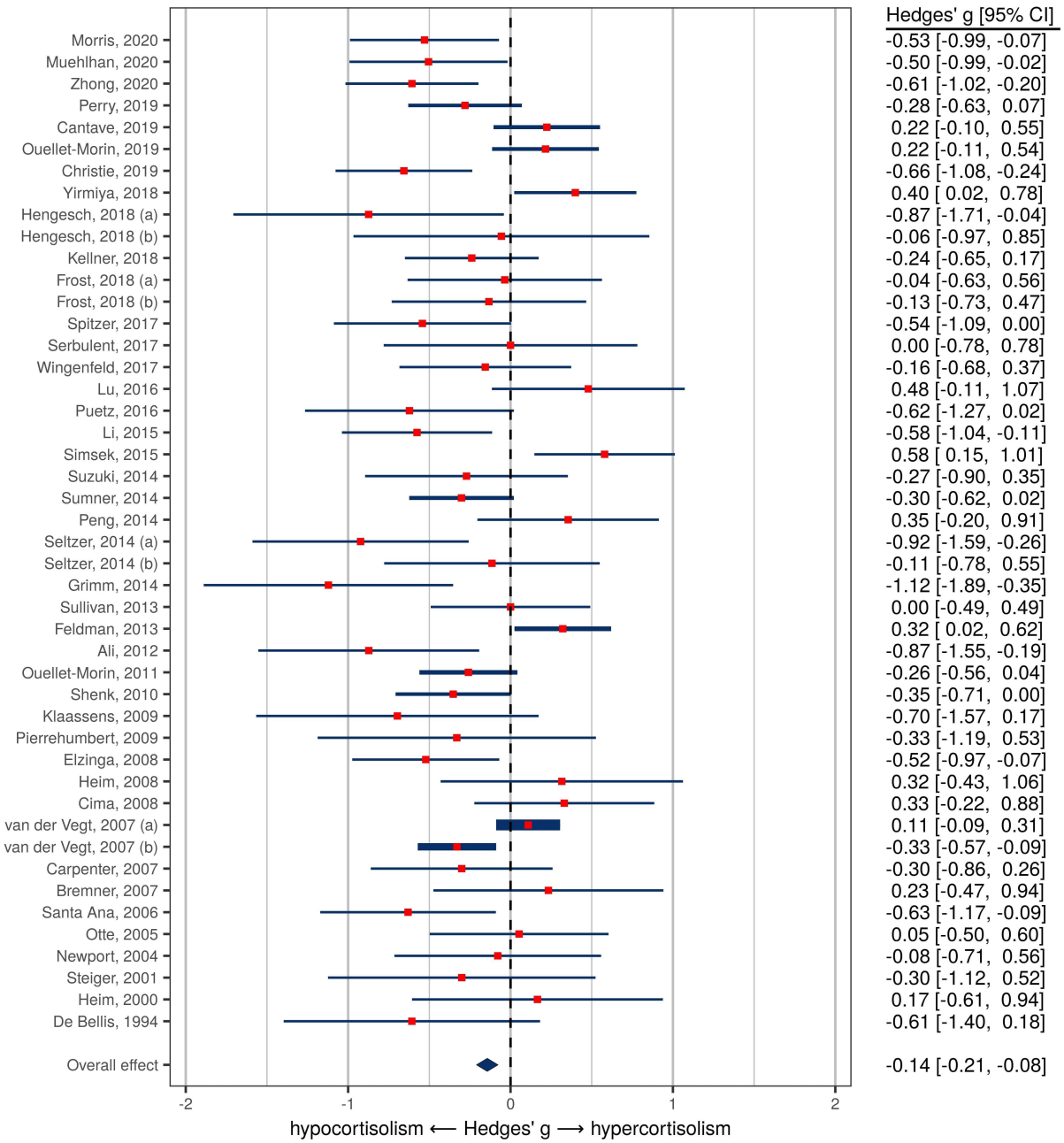

Figure 4.6: Thick forest plot of the first meta-analysis. The Hedges'g represents the effect size of the standardized mean difference in cortisol levels between experimental and controls subjects. The blue diamond on the bottom, left of the zero, indicates the overall effect to be hypocortisolism.

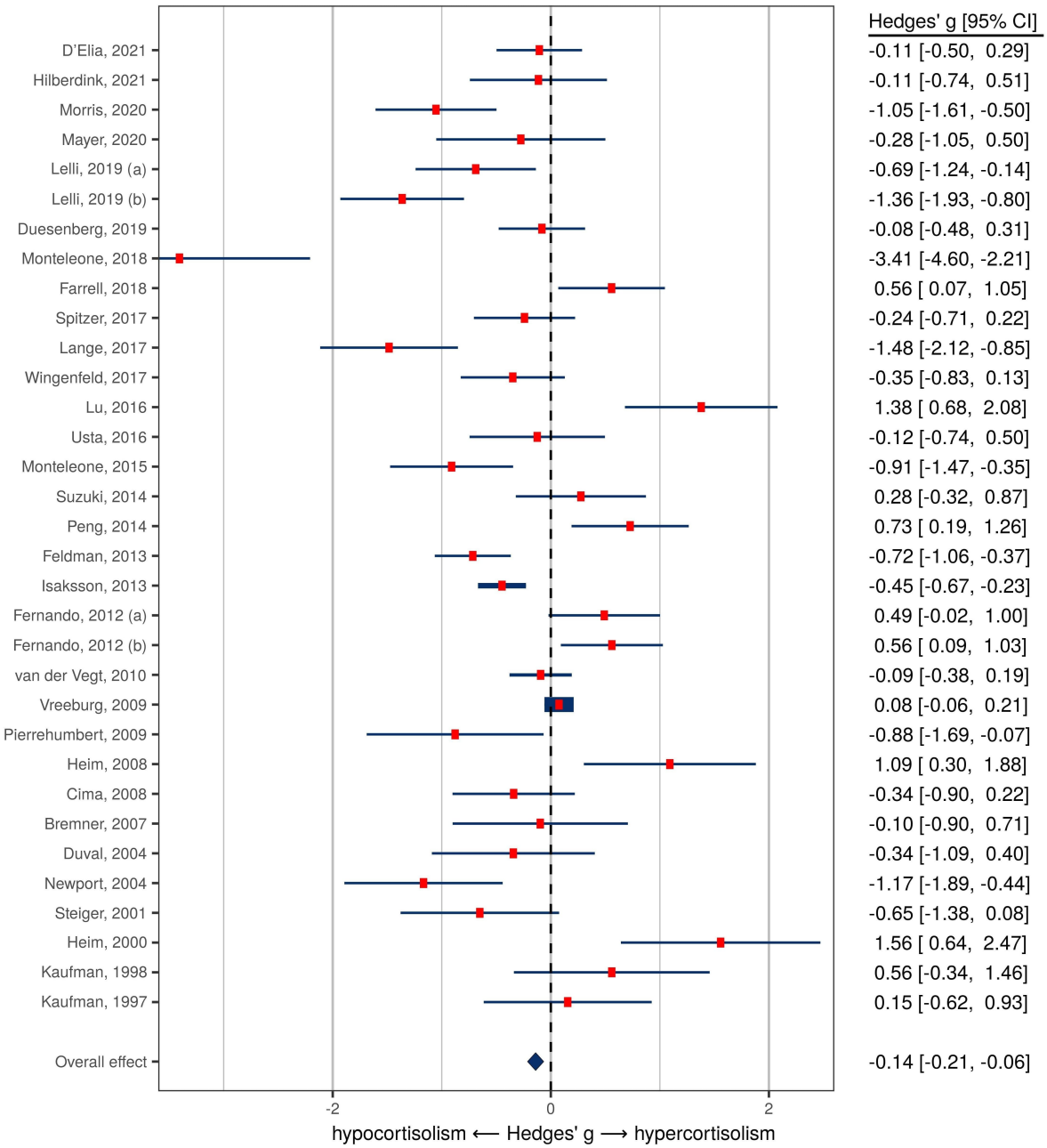

Figure 4.7: Thick forest plot of the second meta-analysis. The Hedges' g represents the effect size of the standardized mean difference in cortisol level between experimental subjects and controls. The blue diamond on the bottom left of the zero, indicates the overall effect to be hypocortisolism.

4.2.6 Publication bias

According to the definition of Dickersin (1990, pag. 1385), the publication bias is defined as "the tendency on the parts of investigators, reviewers, and editors to submit or accept manuscripts for publication based on the direction or strength of the study findings".

Publication bias was evaluated using the Eggers' test (Egger et al., 1997), that did not result statistically significant for both meta-analyses (t_1 = -1.83, $p - value_1$ = 0.07; t_2 = -0.85, $p - value_2$ = 0.41): therefore, the meta-analyses were not subject to publication bias, demonstrating a correct selection of studies.

Describing the publication bias, I also took into account the funnel plots (see fig. 4.8). Both meta-analyses showed that most of studies had a statistical power less than 0.50, a standard error greater than 0.20 and a weak right asymmetry. It seems that, according to Sedgwick (2013), the evaluation of the funnel plot asymmetry is a poor method to investigate the publication bias, because other kinds of reporting bias could affect the interpretation.

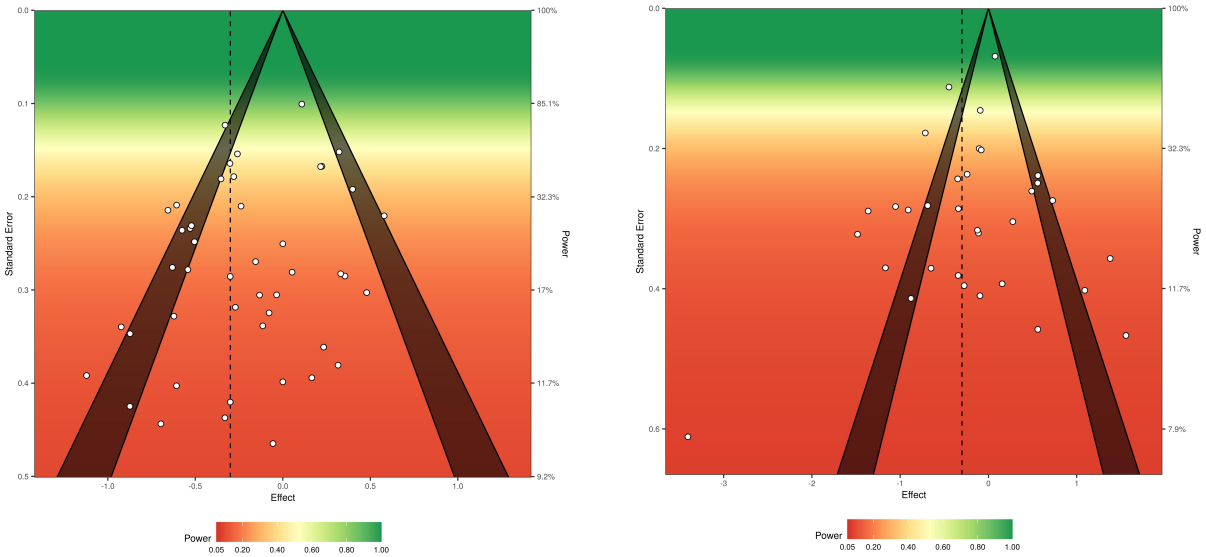

Figure 4.8: Funnel plots of the first (left) and second (right) meta-analysis. The dashed line represents the overall effect of the meta-analysis and the internal region of the inverted V defines an area where the studies that fell within the triangular region (external line) have 95% probability to have no biases or heterogeneity. In the first funnel plot, most of the studies fall inside the triangular region, and more than half of them are to the right of the overall effect (dashed line). In the second funnel plot, about one third of the studies fall outside the triangular region, and more than half of them are to the right the overall effect.

4.2.7 Evaluation of moderators and subgroup analysis

The subgroup analysis is the evaluation of the effect size between the levels of a categorical moderator. It was conducted by using a mixed-effect model (Borenstein & Higgins, 2013) to test the subgroup differences and to show the effect size for each subgroup.

Mixed-effects model is a regression model which contain fixed and random components (Harrer, Cuijpers, Furukawa, & Ebert, 2019b). It is often used in a meta-analysis because in addition to the effects of fixed levels, there are two other types of independent errors which explain the heterogeneity. The first one is the sampling error, and the second one is the error due to the fact that the overall effect of meta-analysis gets from the effect sizes of the studies (Harrer et al., 2019b).

I estimated the best combinations of moderators to predict the effect size and the relative importance for each moderator (see table 4.6 and fig. 4.9). A common rule of thumb is to consider a predictor as important when its importance value is greater than 0.8. In the first meta-analysis between 64 (= $2^{moderators} = 2^6$) fitted models the best model is represented by the combination of gender and type of abuse (see table 4.4). In the second meta-analysis between 128 (= 2^7) fitted models the best model is represented by the type of disorder (see table 4.5).

abuse	cortisol	gender	risk of bias	stress test	logLik	AICc	delta	weight
x		x			-14.45	45.80	0.00	0.39
x		x		x	-11.44	45.90	0.03	0.38
		x			-19.95	48.09	3.04	0.08
x	x	x			-14.58	49.10	3.22	0.08
x		x	x		-14.61	49.10	3.27	0.08

Table 4.4: The table reported the evaluation of the best five models of the first meta-analysis.

cortisol	disorder type	risk of bias	stress test	logLik	AICc	delta	weight
	x			-25.74	77.30	0.00	0.48
	x	x		-24.15	78.30	1.00	0.29
x	x			-25.24	80.50	3.17	0.10
	x		x	-23.17	80.90	3.60	0.08
x	x	x		-23.65	81.90	4.56	0.05

Table 4.5: The table reported the evaluation of the best five models of the second meta-analysis.

Moderators	First meta-analysis	Second meta-analysis
Gender	0.91	0.17
Stage of life	0.01	0.01
Cortisol measure	0.17	0.18
Type of abuse	0.79	0.03
Stress test	0.44	0.17
Risk of Bias	0.18	0.34
Type of disorder	-	0.82

Table 4.6: The table reported the moderators importance (see fig. 4.9). The red numbers are the values > 0.8.

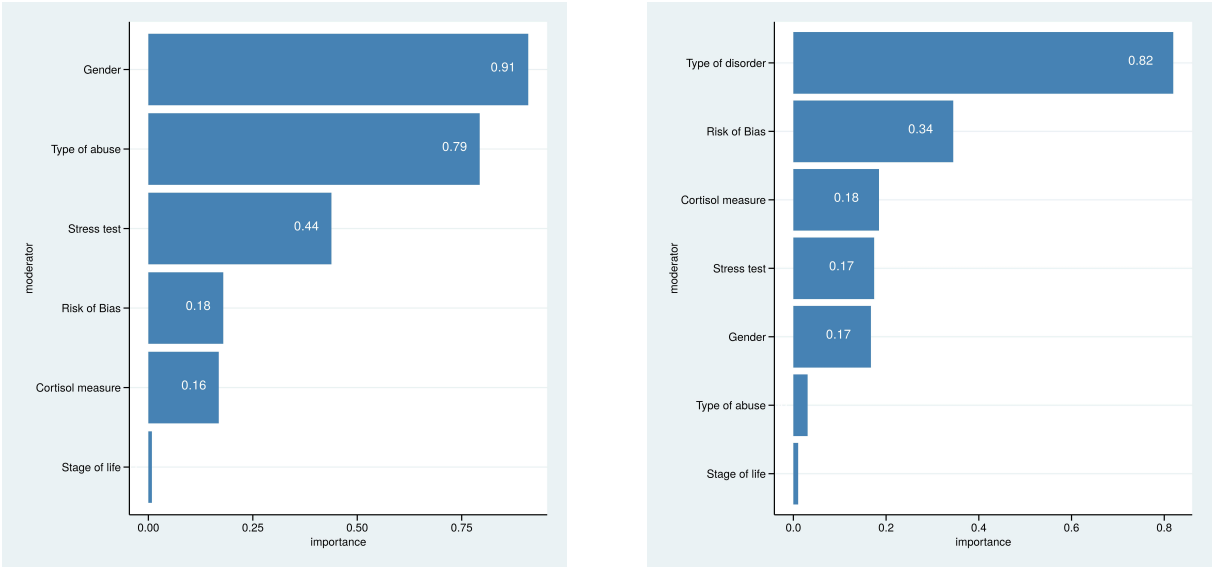

Figure 4.9: Barplot of the first (left) and of the second (right) meta-analysis, indicating the moderators importance.

In tables A3 (§ Appendix I) and A6 (§ Appendix II), I summarized the p-value of the test for the subgroup differences (p-value$_{subgroup}$), number of records (k), the effect size (Hedges' g, 95% CI$_g$, p-value$_g$), and the heterogeneity (I^2, p-value$_{I^2}$) of the subgroups for each moderator.

The moderators showing a statistically significant difference are gender and type of abuse; the subgroup with the strongest effects are: females and mixed type of abuse (see fig. 4.10).

In the second meta-analysis, the significant moderators were: gender, stage of life, type of abuse, stress test, and type of disorder (see red numbers). The subgroups with the strongest effects were: females, adolescence, sexual type of abuse, non-pharmacological stress assessment, depression, eating disorders and PTSD (see fig. 4.11).

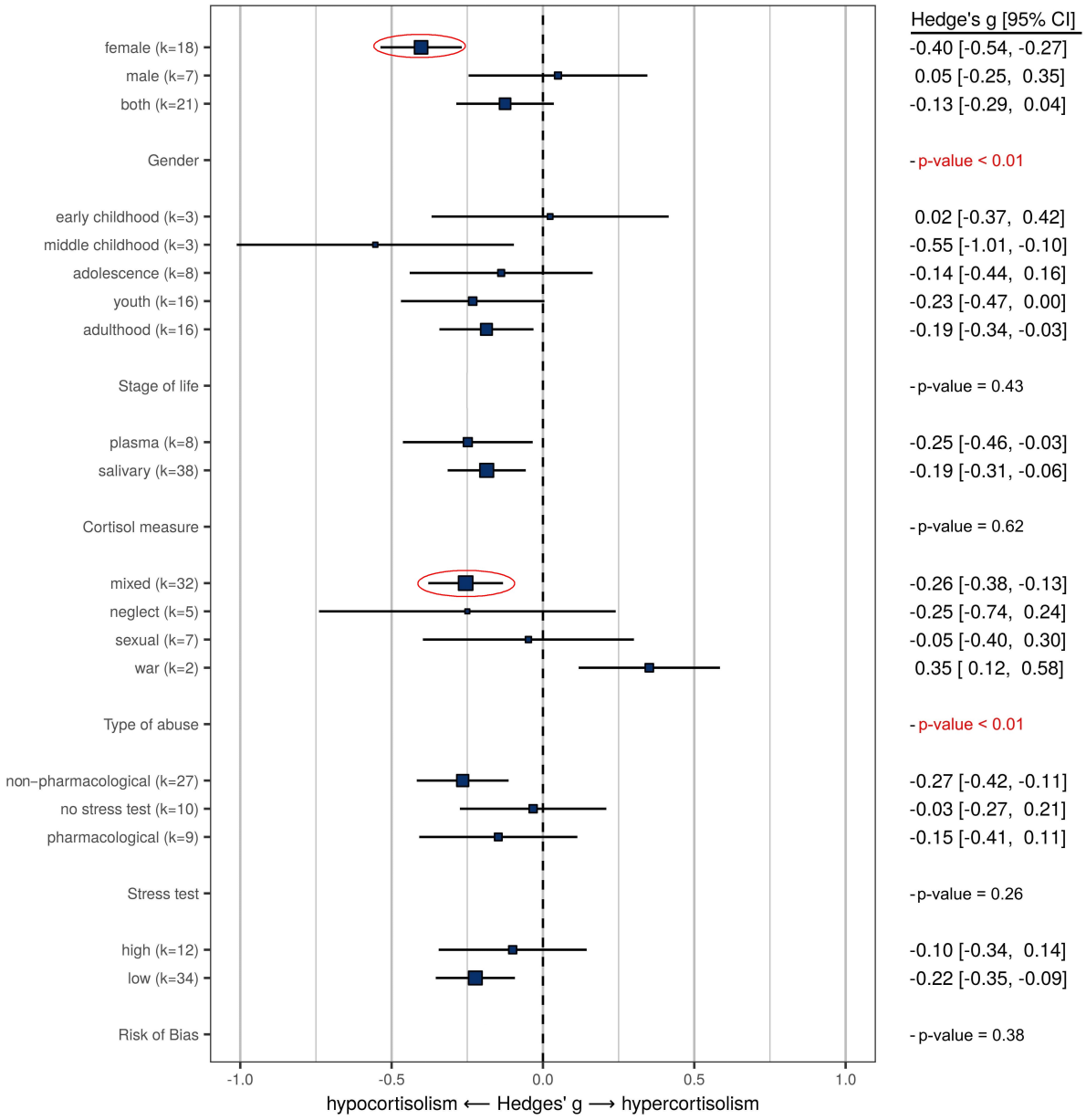

Figure 4.10: Forest plot for subgroup analysis of the first meta-analysis. The Hedges' g represents the effect size of the standardized mean difference in cortisol levels between subjects with history of childhood maltreatment and the controls. The dimension of the squares is in relation to the weight of the subgroup in the meta-analysis. Most of the subgroup effects are to the left of the nil effect (dashed line), in the direction of hypocortisolism. The red ellipses indicate the subgroups with the strongest effects.

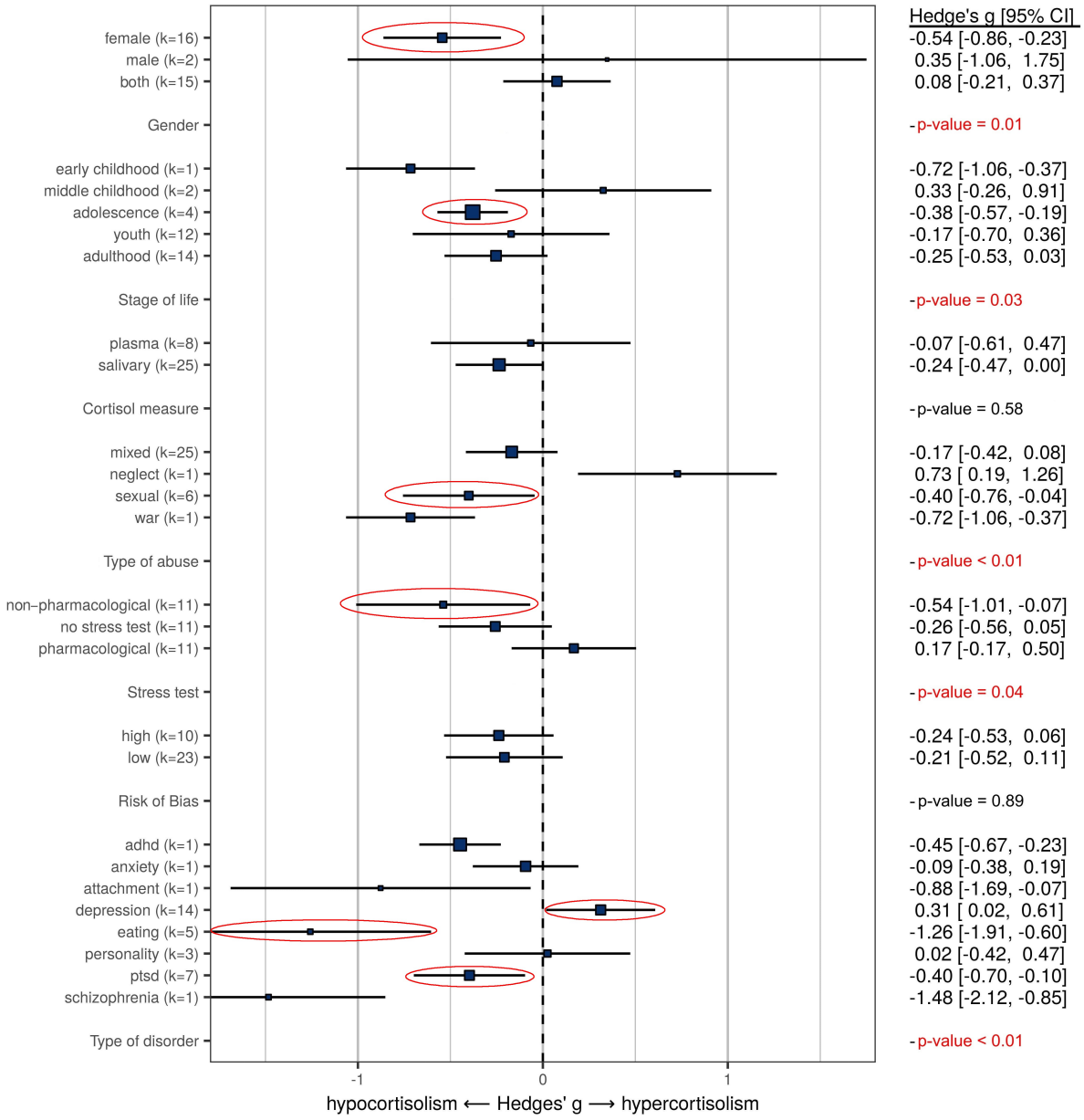

Figure 4.11: Forest plot for subgroup analysis of the second meta-analysis.

4.2.8 Meta-regression

I concluded the meta-analysis with a meta-regression. Considering the outcome of the moderator gender in the subgroup analysis, I evaluated if the relative frequency of female subjects in the experimental group was a predictor of the effect size. I expected a greater relative frequency of female subjects in the research to push the effect size more strongly in the direction of hypocortisolism rather than research with a low relative frequency.

The meta-regression confirmed my hypothesis (see fig. 4.12): in both meta-analyses, the relative frequency of female subjects was a statistically significant predictor of the effect size with negative slope (p-value$_1 < 0.01$, m_1 = -0.39, 95% CI_1 = [-0.70; -0.08], p-value$_{m_1}$ = 0.01; p-value$_2 < 0.01$, m_2 = -0.79, 95% CI_2 = [-1.51; -0.08], p-value$_{m_2}$ = 0.03).

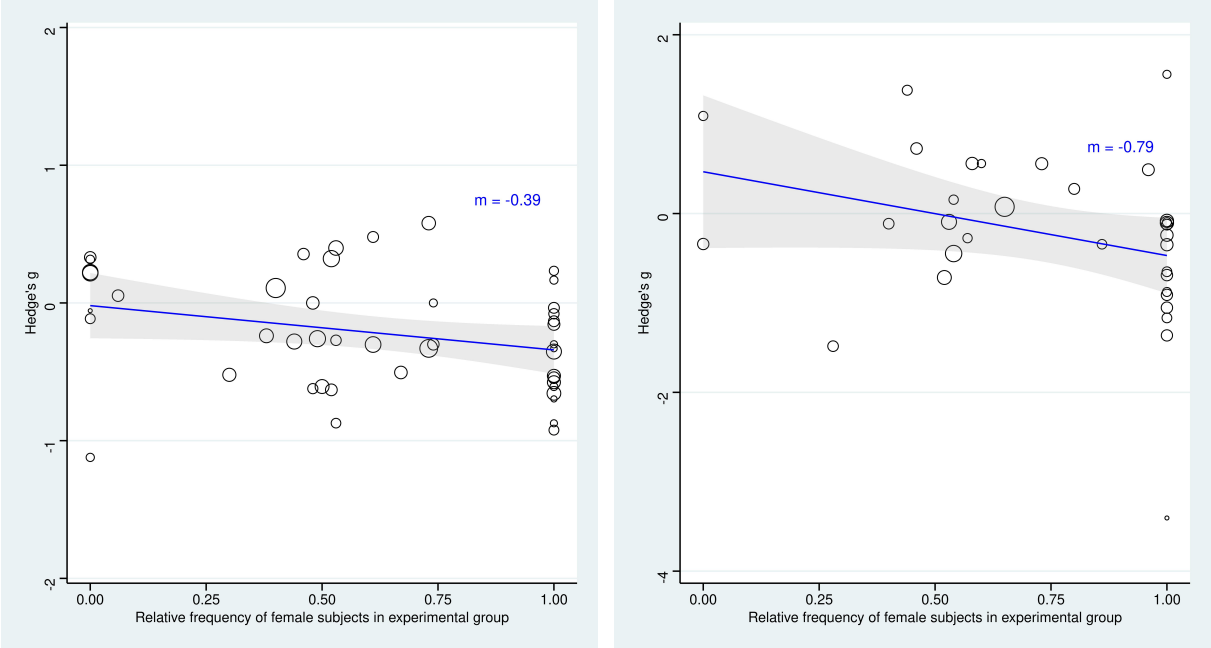

Figure 4.12: Meta-regression line and 95% confidence interval in the first (left) and second (right) meta-analysis: effect size predicted by relative frequency of female subjects in the experimental group. The bubbles represent the papers; their size is equal to $\frac{1}{\sqrt{\text{standard error}}}$.

4.3 Discussion

The two meta-analyses showed small but significant overall effects. This may confirm the expectations of the "attenuation hypothesis". The heterogeneity was high and significant in both meta-analyses, but this result decreased if the records outliers were excluded, and exclusively in the second meta-analysis, the heterogeneity was low and not significant, showing that the effect in the cortisol levels between a population with and a population without history of childhood maltreatment and psychological disorder, should be genuine (the variability is due to chance).

Between the moderators, the gender had an important role. The subgroup analysis showed a bigger effect in the subgroup with only women, and a meta-regression also showed that the ma-

jor presence of female participants in the experimental group, pushed towards a bigger effect.

This analysis may confirm the results of Bunea et al. (2017) (see § 3.2) and the hypothesis of Fogelman and Canli (2018), in which the blunted cortisol levels should be more evident in populations with history of childhood maltreatment and with an ongoing psychopathology (see § 3.1). Nevertheless it is necessary to contextualize this result. As I mentioned in § 4.2.5 the second meta-analysis got a large number of outliers (16 on 33 records), but this is not consistent with the definition of outlier.

In the second meta-analysis the presence of disorders in the experimental group was a better moderator (plausibility = 0.82) compared to all others (gender, type of abuse, risk of bias, etc.). This may support the evidence of the importance of working on a pathological group, as suggested by Fogelman and Canli (2018). Nevertheless, even in this case, it's important to remember the structure of the moderator. The type of psychological disorder is a variable characterized by extreme variability, and this may explain the error components of the heterogeneity in the mixed-effect model. This variability of disorder type therefore needs further investigation in conjunction with other meta-analyses.

The hypothesis of Bunea et al. (2017) is partially confirmed (see § 3.1). In the first meta-analysis there was no statistically significant difference in the subgroup analysis of the moderator stress test (no stress test, pharmacological and non-pharmacological). In the second meta-analysis there was a statistically significant difference, in particular reference to the non-pharmacological stress test (such as the Trier Social Stress Test) showed a strong effect size.

4.3.1 Limitations

The most significant limitation of this meta-analysis was that I've worked alone. Usually the selection of papers, the evaluation of the risk of bias and the data extraction, are steps that are performed by at least two independent authors. The lack of this critical aspect exposed the result to bias.

Other limitations are relative to the moderators. For example, disorder type was a moderator with a high variability, therefore a different disorder may lead towards different dysregulation of the cortisol level, so future meta-analyses should focus on different forms of a specific diagnosis like PTSD, depression, etc. Moreover, it was difficult to work on types of abuse suffered by the

subjects of the experimental group; because, in most cases, it consisted of different types of maltreatment. If the research standardized this variable, for example, adopting the Childhood Trauma Questionnaire (CTQ) and reporting in the paper (or in external link) the scores for each subscale (physical abuse, sexual abuse, emotional abuse, emotional neglect), it would be possible to obtain a better fit of the model.

There are two important variables that have been reported uncommonly: the frequency of abuse and the age of the onset of abuse. In the meta-analysis of which I've referred, the papers that had data regarding the frequency of abuse were: Frost et al. (2018) and van der Vegt, van der Ende, Kirschbaum, Verhulst, and Tiemeier (2009). The paper that had data regarding the age of the onset of abuse was only De Bellis et al. (1994). There is simply not enough data to work with these variables. In my opinion, it's important that scientific research agrees on a method to use, to gather this information to get a better understanding and clarity of this phenomenon.

The issue of the lack of standardization regarding the variables relative to cortisol measures and the description of childhood maltreatment, is cited often in the meta-analyses relative to this topic (Fogelman & Canli, 2018; McCrory et al., 2012; Molendijk, Hoek, Brewerton, & Elzinga, 2017). It is also important to note the growth of the scientific literature (see fig. 3.4); as it would be possible to get a lot of cumulative data over a period of a few years, therefore the future meta-analyses will offer strong evidence supporting a range of different topics.

Conclusion

This thesis outlines the phenomenon of childhood maltreatment in relation to the dysregulation of the HPA axis, with particular attention to the adoption of an ontological point of view.

After studying this topic, I report a robust evidence in the scientific literature showing a dysregulation of the HPA axis in the direction of hypocortisolism in the subjects with a history of childhood abuse, though there was no common agreement regarding this issue by the authors (see § 2.1).

A possible reason to explain why the literature is inconsistent, is due to the lack of standardized methods in the planning phase of the research design, such as: choosing variables and showing data, etc. As I mentioned before, several authors have complained about this aspect (see § 3.1 and § 3.2). For example, the onset of trauma may be a critical variable to consider, but I didn't find enough consistent research reporting this finding during the screening phase of meta-analysis.

A possible hypothesis emerging from the review of the literature and the meta-analysis that I carried out is that the dysregulation of the HPA axis may provide an important breakdown of the processes regarding the basis of the morphostructural and physiological changes following childhood maltreatment, or more generally, the post-maltreatment chronic and severe stress. The step forward for psychobiological research to implement is to systematize the methods to obtain a robust theoretical framework with a better description of risk factors and therapeutic interventions, in order to contribute to reduce the huge impact of this phenomenon.

Limitations of this study

I'm concluding this thesis with a criticism pertaining the limitations of my dissertation work. A thesis as part of this degree of this course has many elements to factor in, such as the resources

and the time. For example, as mentioned in § 4.3.1, the meta-analysis is a group based work, and disregarding the imperative reviews by my thesis advisers, I have hence worked alone and this casts doubt on the accuracy of some points of the analysis.

Another point that I would like to reflect on, in relation to § 3, is that I would have preferred to show a systematic review of each topic discussed, but a systematic review is, again, a job that needs the work of a group of researchers, to guarantee proper methods and consistent timing for the meta-analysis. For this reason, I have decided to include a brief consideration on the most recent outcomes and references.

A major limit of this thesis is unfortunately the lack of analysis in regards to the topic of gene-environment interaction. As shown in § 3.1, there are situations that suggest the development of psychopathology, but the disorder does not actually occur. The study of functional polymorphism in different genes, can moderate the effects of maltreatment, and to explain why some children who are maltreated, then grow up to develop psychopathology, in comparison to others that do not (see fig. 5.1).

There is a plethora of findings that show the relation between genes and childhood maltreatment, and it is my opinion, that this is a very specific field that deserves separate recognition and research. More so, this topic requires genetic specific expertise, that is unfortunately beyond my reach. I would like to highlight some articles that I have found during the screening phase of the meta-analysis that I perfomed in this thesis, and the diagram shown below:

- Gene-environment interactions between HPA-axis genes and childhood maltreatment in depression: a systematic review (Normann & Buttenschøn, 2020).
- A functional variant of CB2 receptor gene interacts with childhood trauma and FAAH gene on anxious and depressive phenotypes (Lazary, Eszlari, Juhasz, & Bagdy, 2019).
- Association of childhood trauma and genetic variability of CRH-BP and FKBP5 genes with suicidal behavior in bipolar patients (Segura et al., 2019).
- Effect of CRHR1 and CRHR2 gene polymorphisms and childhood trauma in suicide attempt (Sanabrais-Jiménez et al., 2019).

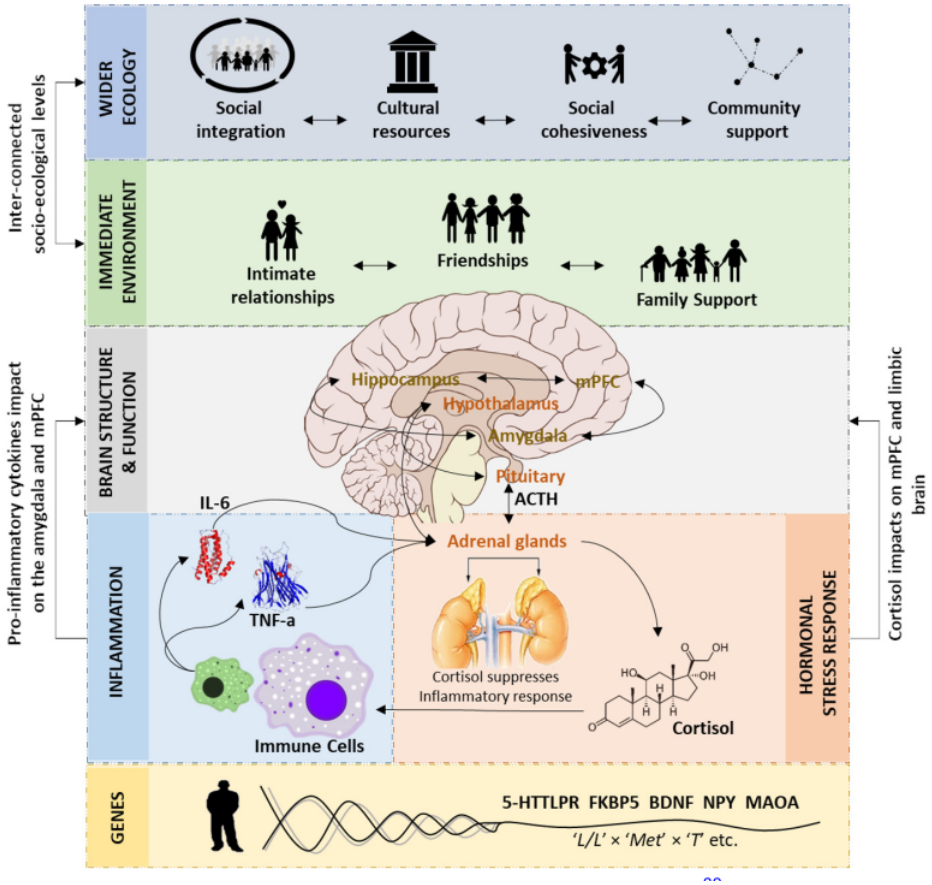

Figure 5.1: The complex neurobiology of resilience after childhood maltreatment. The psychopathology is the result of the interaction of different systems: genes, hormonal stress response, inflammation, brain structure and function, immediate environment and wider ecology. The genetic structure is on the base of model. The study of genetic predictors, such as: serotonin-transporter-linked polymorphic region (5-HTTLPR), brain-derived neurotrophic factor (BDNF), FK binding protein 5 (FKBP5), monoamine oxidase A (MAOA), neuropeptide-Y(NPY) (Ioannidis et al., 2020).

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Appendices

Appendix I

	Sample size	Average age	Females (%)	Cortisol measure	Type of Abuse	Stress test
Morris, 2020	76	23.80	100	salivary	mixed	non-pharmacological
Muehlhan, 2020	68	45.17	67	salivary	mixed	non-pharmacological
Zhong, 2020	96	22.67	50	salivary	mixed	non-pharmacological
Perry, 2019	127	2.25	44	salivary	mixed	no stress test
Cantave, 2019	156	24.09	0	salivary	mixed	non-pharmacological
Ouellet-Morin, 2019	155	24.10	0	salivary	mixed	non-pharmacological
Christie, 2019	92	18.90	100	salivary	mixed	non-pharmacological
Yirmiya, 2018	111	11.76	53	salivary	war	non-pharmacological
Hengesch, 2018 (a)	25	22.50	100	salivary	neglect	non-pharmacological
Hengesch, 2018 (b)	19	22.50	0	salivary	neglect	non-pharmacological
Kellner, 2018	92	39.60	38	plasma	mixed	non-pharmacological
Frost, 2018 *(a)	60	31.40	100	salivary	mixed	pharmacological
Frost, 2018 *(b)	60	28.10	100	salivary	mixed	pharmacological
Spitzer, 2017	58	34.80	100	salivary	mixed	pharmacological
Serbulent, 2017	27	12.30	74	salivary	sexual	no stress test
Wingenfeld, 2017	49	36.50	100	salivary	mixed	non-pharmacological
Lu, 2016	45	21.50	61	salivary	mixed	pharmacological
Puetz, 2016	40	10.60	48	salivary	mixed	no stress test
Li, 2015	75	39.70	100	salivary	mixed	no stress test
Simsek, 2015	86	13.10	73	salivary	sexual	no stress test
Suzuki, 2014	41	44.30	53	salivary	mixed	non-pharmacological
Sumner, 2014	158	15.30	61	salivary	mixed	non-pharmacological
Peng, 2014	51	28.37	46	salivary	neglect	no stress test
Seltzer, 2014 (a)	49	9.00	100	salivary	mixed	non-pharmacological
Seltzer, 2014 (b)	35	9.00	0	salivary	mixed	non-pharmacological
Grimm, 2014	31	29.50	0	salivary	mixed	non-pharmacological
Sullivan, 2013	64	3.49	48	salivary	neglect	non-pharmacological
Feldman, 2013	176	2.75	52	salivary	war	non-pharmacological
Ali, 2012	37	25.95	53	salivary	neglect	non-pharmacological
Ouellet-Morin, 2011	190	12.00	49	salivary	mixed	non-pharmacological
Shenk, 2010	139	18.54	100	salivary	sexual	non-pharmacological
Klaassens, 2009	22	47.80	100	salivary	mixed	pharmacological
Pierrehumbert, 2009	22	32.70	100	salivary	sexual	non-pharmacological
Elzinga, 2008	80	21.79	30	salivary	mixed	non-pharmacological
Heim, 2008	28	31.40	0	salivary	mixed	pharmacological
Cima, 2008	51	30.40	0	salivary	mixed	no stress test
van der Vegt, 2007 *(a)	443	31.50	40	salivary	mixed	no stress test
van der Vegt, 2007 *(b)	380	31.30	73	salivary	mixed	no stress test
Carpenter, 2007	50	35.00	74	plasma	mixed	non-pharmacological
Bremner, 2007	32	32.20	100	plasma	sexual	no stress test
Santa Ana, 2006	56	26.60	52	plasma	mixed	non-pharmacological
Otte, 2005	77	27.00	6	salivary	mixed	non-pharmacological
Newport, 2004	38	33.30	100	plasma	sexual	pharmacological
Steiger, 2001	23	23.95	100	plasma	mixed	pharmacological
Heim, 2000	26	30.00	100	plasma	mixed	non-pharmacological
De Bellis, 1994	26	11.20	100	plasma	sexual	pharmacological

Table A1: Study characteristics of the papers included in the first meta-analysis (experimental group without diagnosis of an ongoing psychopathology). The percentage of the females is relative to the experimental group.
* Hengesch et al. (2018); van der Vegt et al. (2009): (a) some, (b) severe.

	RoB 1	RoB 2	RoB 4	RoB 5	Risk of Bias
Morris, 2020	🟢	🟢	🟢	🔴	low
Muehlhan, 2020	🟢	🟢	🟢	🔴	low
Zhong, 2020	🟢	🟢	🟢	🔴	low
Perry, 2019	🔴	🟡	🟢	🔴	high
Cantave, 2019	🟢	🟢	🟢	🟢	low
Ouellet-Morin, 2019	🟢	🟢	🟢	🔴	low
Christie, 2019	🟢	🟢	🟢	🔴	low
Yirmiya, 2018	🔴	🟢	🟢	🟢	low
Hengesch, 2018 (a)	🟡	🟢	🟢	🟢	low
Hengesch, 2018 (b)	🟡	🟢	🟢	🟢	low
Kellner, 2018	🟢	🟢	🟢	🟢	low
Frost, 2018 *(a)	🟢	🟢	🟢	🟢	low
Frost, 2018 *(b)	🟢	🟢	🟢	🟢	low
Spitzer, 2017	🟢	🟢	🟢	🟢	low
Serbulent, 2017	🔴	🔴	🔴	🔴	high
Wingenfeld, 2017	🟢	🟢	🟢	🟢	low
Lu, 2016	🟢	🟢	🟢	🔴	low
Puetz, 2016	🟢	🟢	🟢	🟢	low
Li, 2015	🟢	🟢	🟢	🔴	low
Simsek, 2015	🔴	🟢	🟡	🟢	high
Suzuki, 2014	🟢	🟢	🟢	🟢	low
Sumner, 2014	🟢	🟢	🟢	🔴	low
Peng, 2014	🟢	🟢	🟢	🟢	low
Seltzer, 2014 (a)	🟡	🟢	🟢	🔴	high
Seltzer, 2014 (b)	🟡	🟢	🟢	🔴	high
Grimm, 2014	🟢	🟢	🟢	🔴	low
Sullivan, 2013	🟡	🔴	🟢	🔴	high
Feldman, 2013	🔴	🟢	🔴	🟢	high
Ali, 2012	🟡	🔴	🟢	🔴	high
Ouellet-Morin, 2011	🟡	🔴	🟢	🔴	high
Shenk, 2010	🟡	🟢	🟢	🟢	low
Klaassens, 2009	🟢	🟢	🟢	🟢	low
Pierrehumbert, 2009	🟢	🟢	🟢	🟢	low
Elzinga, 2008	🟢	🟢	🟢	🔴	low
Heim, 2008	🟢	🟢	🟢	🟢	low
Cima, 2008	🟢	🟢	🟢	🔴	low
van der Vegt, 2007 *(a)	🔴	🟢	🟢	🟢	low
van der Vegt, 2007 *(b)	🔴	🟢	🟢	🟢	low
Carpenter, 2007	🟢	🟢	🟢	🟢	low
Bremner, 2007	🟢	🟢	🟢	🟢	low
Santa Ana, 2006	🟢	🟢	🟢	🔴	low
Otte, 2005	🔴	🔴	🔴	🔴	high
Newport, 2004	🟢	🟢	🟢	🟢	low
Steiger, 2001	🔴	🟢	🔴	🔴	high
Heim, 2000	🟢	🟢	🔴	🔴	high
De Bellis, 1994	🟢	🟢	🟢	🟢	low

Table A2: Risk of bias (RoB) evaluation in the first meta-analysis.
The red bullets indicate a high RoB, the yellow bullets indicate an unclear RoB, the green bullets indicate a low RoB.
* Hengesch et al. (2018); van der Vegt et al. (2009): (a) some, (b) severe.

Moderators	k	Hedges' g	95% CI_g	p-$value_g$	I^2	95% CI_{I^2}	p-$value_{subgroup}$
Gender							< 0.01
female	18	-0.40	[-0.54; -0.29]	< 0.01	0%	[0%; 50%]	
male	7	0.05	[-0.25; 0.35]	0.74	51%	[0%; 79%]	
both	21	-0.13	[-0.29; 0.04]	0.12	69%	[51%; 80%]	
Stage of life							0.43
early childhood	3	0.02	[-0.37; 0.42]	0.90	70%	[0%; 91%]	
middle childhood	3	-0.55	[-1.01; -0.10]	0.02	31%	[0%; 93%]	
adolescence	8	-0.13	[-0.44; 0.16]	0.37	76%	[51%; 88%]	
youth	16	-0.23	[-0.47; 0.01]	0.06	67%	[44%; 80%]	
adulthood	16	-0.19	[-0.34; -0.03]	0.02	38%	[0%; 66%]	
Cortisol measure							0.62
plasma	8	-0.25	[-0.46; -0.03]	0.02	0%	[0%; 68%]	
salivary	38	-0.19	[-0.32; -0.06]	< 0.01	66%	[52%; 76%]	
Type of abuse							< 0.01
mixed	32	-0.26	[-0.38; -0.13]	< 0.01	56%	[34%; 70%]	
neglect	5	-0.25	[-0.74; 0.24]	0.32	63%	[2%; 86%]	
sexual	7	-0.05	[-0.40; 0.30]	0.78	57%	[0%; 81%]	
war	2	0.35	[0.12; 0.59]	< 0.01	0%	-	
Stress test							0.26
non-pharmacological	27	-0.27	[-0.42; -0.11]	< 0.01	63%	[44%; 76%]	
no stress test	10	-0.03	[-0.27; 0.21]	0.79	70%	[42%; 84%]	
pharmacological	9	-0.15	[-0.41; 0.11]	0.27	27%	[0%; 66%]	
Risk of Bias							0.38
high	12	-0.10	[-0.35; 0.14]	0.42	64%	[34%; 81%]	
low	34	-0.22	[-0.35; -0.09]	< 0.01	60%	[42%; 72%]	

Table A3: Subgroup analysis of the first meta-analysis. The numbers within the highlighted light blue background indicate the p-values of the test of the subgroup differences. In the highlighted red background, it outlines the subgroups and their statistically significant effect sizes. The red numbers are the statistically significant p-values. See the relative forest plot 4.10.

Appendix II

	Sample size	Average age	Females (%)	Disorder	Cortisol measure	Type of Abuse	Stress test
D'Elia, 2021	102	24.60	100	ptsd	salivary	sexual	no stress test
Hilberdink, 2021	39	14.25	40	ptsd	salivary	mixed	non-pharmacological
Morris, 2020	62	23.80	100	ptsd	salivary	mixed	non-pharmacological
Mayer, 2020	26	37.50	57	depression	plasma	mixed	non-pharmacological
Lelli, 2019 *(a)	88	24.80	100	eating	salivary	mixed	no stress test
Lelli, 2019 *(b)	89	25.70	100	eating	salivary	mixed	no stress test
Duesenberg, 2019	98	28.70	100	personality	salivary	mixed	non-pharmacological
Monteleone, 2018	29	24.00	100	eating	salivary	mixed	non-pharmacological
Farrell, 2018	67	28.27	73	depression	salivary	mixed	no stress test
Spitzer, 2017	72	35.20	100	depression	salivary	mixed	pharmacological
Lange, 2017	50	38.30	28	schizophrenia	salivary	mixed	non-pharmacological
Wingenfeld, 2017	69	34.20	100	depression	salivary	mixed	non-pharmacological
Lu, 2016	40	23.70	44	depression	salivary	mixed	pharmacological
Usta, 2016	40	15.40	100	ptsd	salivary	sexual	no stress test
Monteleone, 2015	54	31.35	100	eating	salivary	mixed	no stress test
Suzuki, 2014	44	52.10	80	depression	salivary	mixed	non-pharmacological
Peng, 2014	57	28.87	46	depression	salivary	neglect	no stress test
Feldman, 2013	140	2.75	52	ptsd	salivary	war	non-pharmacological
Isaksson, 2013	325	11.90	54	adhd	salivary	mixed	no stress test
Fernando, 2012 **(a)	65	26.92	96	personality	salivary	mixed	pharmacological
Fernando, 2012 **(b)	74	33.42	58	depression	salivary	mixed	pharmacological
van der Vegt, 2010	429	30.90	53	anxiety	salivary	mixed	no stress test
Vreeburg, 2009	1009	42.00	65	depression	salivary	mixed	pharmacological
Pierrehumbert, 2009	26	33.81	100	attachment	salivary	sexual	non-pharmacological
Heim, 2008	29	32.30	0	depression	salivary	mixed	pharmacological
Cima, 2008	50	30.40	0	personality	salivary	mixed	no stress test
Bremner, 2007	24	36.50	100	ptsd	plasma	sexual	no stress test
Duval, 2004	28	16.20	86	ptsd	plasma	sexual	pharmacological
Newport, 2004	35	32.40	100	depression	plasma	sexual	pharmacological
Steiger, 2001	36	24.60	100	eating	plasma	mixed	pharmacological
Heim, 2000	25	30.00	100	depression	plasma	mixed	non-pharmacological
Kaufman, 1998	20	10.30	60	depression	plasma	mixed	pharmacological
Kaufman, 1997	26	9.60	54	depression	plasma	mixed	pharmacological

Table A4: Study characteristics of the papers included in the second meta-analysis (experimental group with diagnosis of an ongoing psychopathology). The percentage of the females is relative to the experimental group.

* Lelli et al. (2019): (a) anorexia, (b) bulimia.

** Fernando et al. (2012): (a) borderline, (b) depression.

	RoB 1	RoB 2	RoB 3	RoB 4	RoB 5	Risk of Bias
D'Elia, 2021	🔴	🟢	🟢	🟢	🔴	high
Hilberdink, 2021	🟡	🟢	🟢	🟢	🔴	high
Morris, 2020	🟢	🟢	🟢	🟢	🔴	low
Mayer, 2020	🟢	🟢	🟢	🟢	🔴	low
Lelli, 2019 *(a)	🔴	🟢	🟢	🟢	🟢	low
Lelli, 2019 *(b)	🔴	🟢	🟢	🟢	🟢	low
Duesenberg, 2019	🟢	🟢	🟢	🟢	🔴	low
Monteleone, 2018	🟢	🟢	🟢	🟢	🔴	low
Farrell, 2018	🟢	🟢	🟢	🟢	🔴	low
Spitzer, 2017	🟢	🟢	🟢	🟢	🟢	low
Lange, 2017	🟢	🟢	🟢	🟢	🟢	low
Wingenfeld, 2017	🟢	🟢	🟢	🟢	🟢	low
Lu, 2016	🟢	🟢	🟢	🟢	🔴	low
Usta, 2016	🟡	🔴	🟢	🔴	🟢	high
Monteleone, 2015	🟡	🟢	🟢	🟢	🔴	high
Suzuki, 2014	🟢	🟢	🟢	🟢	🟢	low
Peng, 2014	🟢	🟢	🟢	🟢	🟢	low
Feldman, 2013	🔴	🟢	🟡	🔴	🟢	high
Isaksson, 2013	🔴	🟢	🟡	🟢	🟢	high
Fernando, 2012 **(a)	🟢	🟢	🟢	🟢	🟢	low
Fernando, 2012 **(b)	🟢	🟢	🟢	🟢	🟢	low
van der Vegt, 2010	🔴	🟢	🟢	🟢	🟢	low
Vreeburg, 2009	🔴	🔴	🟢	🔴	🟢	high
Pierrehumbert, 2009	🟢	🟢	🟢	🟢	🟢	low
Heim, 2008	🟢	🟢	🟢	🟢	🟢	low
Cima, 2008	🟢	🟢	🟢	🟢	🔴	low
Bremner, 2007	🟢	🟢	🟢	🟢	🟢	low
Duval, 2004	🔴	🔴	🟢	🟢	🔴	high
Newport, 2004	🟢	🟢	🟢	🟢	🟢	low
Steiger, 2001	🔴	🟢	🟢	🔴	🔴	high
Heim, 2000	🟢	🟢	🟢	🔴	🔴	high
Kaufman, 1998	🔴	🟢	🟢	🟢	🟢	low
Kaufman, 1997	🔴	🟢	🟢	🟢	🟢	low

Table A5: Risk of bias (RoB) evaluation in the second meta-analysis.
* Lelli et al. (2019): (a) anorexia, (b) bulimia.
** Fernando et al. (2012): (a) borderline, (b) depression.

Moderators	k	Hedges' g	95% CI_g	p-$value_g$	I^2	95% CI_{I^2}	p-$value_{subgroup}$
Gender							0.01
female	16	-0.54	[-0.86; -0.23]	< 0.01	81%	[70%; 88%]	
male	2	0.35	[-1.06; 1.75]	0.63	88%	[54%; 97%]	
both	15	0.08	[-0.21; 0.37]	0.61	85%	[77%; 90%]	
Stage of life							0.03
early childhood	1	-0.72	[-1.06; -0.37]	< 0.01	-	-	
middle childhood	2	0.33	[-0.26; 0.91]	0.27	0%	-	
adolescence	4	-0.38	[-0.57; -0.19]	< 0.01	0%	[0%; 85%]	
youth	12	-0.17	[-0.70; 0.36]	0.53	91%	[86%; 94%]	
adulthood	14	-0.25	[-0.53; 0.03]	0.07	80%	[67%; 88%]	
Cortisol measure							0.58
plasma	8	-0.07	[-0.61; 0.47]	0.81	73%	[45%,; 87%]	
salivary	25	-0.24	[-0.47; 0.00]	0.05	87%	[81%; 90%]	
Type of abuse							< 0.01
mixed	25	-0.17	[-0.42; 0.08]	0.18	86%	[81%; 90%]	
neglect	1	0.72	[0.19; 1.27]	< 0.01	-	-	
sexual	6	-0.40	[-0.76; -0.05]	0.03	44%	[0%; 78%]	
war	1	-0.72	[-1.06; -0.37]	< 0.01	-	-	
Stress test							0.04
non-pharmacological	11	-0.54	[-1.01; -0.07]	0.02	86%	[76%; 91%]	
no stress test	11	-0.26	[-0.56; 0.05]	0.10	80%	[66%; 89%]	
pharmacological	11	0.17	[-0.17; 0.50]	0.33	78%	[61%; 88%]	
Risk of Bias							0.89
high	10	-0.24	[-0.53; 0.06]	0.11	82%	[68%; 90%]	
low	23	-0.21	[-0.52; 0.11]	0.20	86%	[80%; 90%]	
Type of disorder							< 0.01
adhd	1	-0.45	[-0.67; -0.23]	< 0.01	-	-	
anxiety	1	-0.09	[-0.38; 0.19]	0.52	-	-	
attachment	1	-0.88	[-1.69; -0.07]	0.03	-	-	
depression	14	0.31	[0.02; 0.61]	0.04	78%	[64%; 87%]	
eating	5	-1.26	[-1.91; -0.60]	< 0.01	69%	[50%; 91%]	
personality	3	0.02	[-0.42; 0.47]	0.91	61%	[0%; 89%]	
ptsd	7	-0.40	[-0.70; -0.10]	< 0.01	53%	[0%; 80%]	
schizophrenia	1	-1.48	[-2.12; -0.85]	< 0.01	-	-	

Table A6: Subgroup analysis of the second meta-analysis. The red numbers are the statistically significant p-values. See the relative forest plot 4.11.