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Biopsychological assessment of resilience in depression from the perspective of Positive Psychiatry

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Contents

Abstract

Background: Positive psychiatry is the science and practice of psychiatry that seeks to understand and promote well-being through assessments and interventions aimed at enhancing positive psychosocial factors such as resilience.

Aim: The aim of this study was to better understand the associations between biological and psychological aspects of resilience in patients with depression from the perspective of positivepsychiatry. Hypothesis 1a: Patients with higher scores in positive coping strategies tend to have lower depression symptomatology. Hypothesis 1b: Patients with higher scores in negative coping strategies tend to have higher depression symptomatology. Hypothesis 2: Patients with higher levels of general resilience have lower depression scores. Hypothesis 3a: Morning plasma cortisol shows a negative association with positive coping strategies. Hypothesis 3b: ACTH/cortisol response to the Dex/CRH-test is inversely associated with positive coping strategies. Hypothesis 4: Childhood trauma and cumulated life events have a negative impact on coping strategies and resilience, and increase the severity of depression.

Methods: The analyses were performed within a sample of 397 depressed in-patients of the Munich Antidepressant Response Signature (MARS) study and assessments used in this analysis include depression severity (Hamilton Depression Rating Scale. HAM-D), resilience-related coping and general resilience (Stress Coping Style Questionnaire, SVF-78, and the Resilience Scale (RS-11), life events and childhood trauma (Event List and Childhood Trauma Questionnaire, CTQ), and the regulatory function of the HPA axis (Dex-CRH test).

Results: The severity of depression shows a significant negative correlation with positive coping strategies and the level of general resilience, and a significant positive correlation with negative coping strategies. The cortisol response in terms of the total and net AUC showed a negative association with subscales minimization and situation control. The subscales distraction and situation control have a significant positive correlation with basal morning cortisol. The net AUC of the cortisol response was linked to the subscale rumination, in addition to factors devaluation and control. A significant association was found between the subscale situation control and factor control and ACTH. ACTH baseline was linked to the subscale response control and resignation. The uncategorized subscales need for social support

was positively associated with ACTH AUC and ACTH AUCnet. Of note, the ACTH and cortisol response to the Dex/CRH test at admission was positively associated with depression severity.

A significant negative association was found between the childhood trauma and level of psychological resilience and positive coping strategies, whereas a significant positive association was observed with negative coping strategies, stressful life events and severity of depression. These results are largely consistent with our hypotheses.

Conclusion: This study shows that a low level of resilience seems to be a risk factor for residual depression symptoms after inpatient treatment and that some parameters of HPA axis regulation might be potential biomarkers for resilience. Improving the understanding of the biological basis of resilience may help to find new biomarkers for depression, as one of the goals of positive psychiatry, which seeks to find biomarkers for positive psychological factors.

Zusammenfassung

Hintergrund: Positive Psychiatrie ist eine Disziplin und Herangehensweise in der Psychiatrie, die versucht, das Wohlbefinden durch Beurteilungen und Interventionen, die darauf abzielen, positive psychosoziale Faktoren wie Resilienz zu verbessern, zu verstehen und zu fördern.

Ziel: Ziel dieser Studie war es, die Zusammenhänge zwischen biologischen und psychologischen Aspekten der Resilienz bei Patienten mit Depression aus der Perspektive der positiven Psychiatrie besser zu verstehen. Hypothese 1a: Patienten mit höheren Werten bei positiven Bewältigungsstrategien neigen dazu, eine geringere Depressionssymptomatik zu haben. Hypothese 1b: Patienten mit höheren Werten bei negativen Bewältigungsstrategien neigen dazu, eine höhere Depressionssymptomatik zu haben. Hypothese 2: Patienten mit einem höheren Grad an allgemeiner Resilienz haben niedrigere Depressionswerte. Hypothese 3a: Morgendlicher Plasmacortisolspiegel zeigt eine negative Assoziation mit positiven Bewältigungsstrategien. Hypothese 3b: Die ACTH/Cortisol-Reaktion auf den Dex/CRH-Test ist invers assoziiert mit positiven Bewältigungsstrategien. Hypothese 4: Kindheitstraumata und kumulierte Lebensereignisse wirken sich negativ auf Bewältigungsstrategien und Belastbarkeit aus und verstärken den Schweregrad einer Depression.

Methoden: Die Analysen wurden an einer Stichprobe von 397 depressiven Patienten der Munich Antidepressant Response Signature (MARS) Studie durchgeführt. Zu den in dieser Analyse berücksichtigten Erhebungen gehören der Schweregrad der Depression (Hamilton Depression Rating Scale. HAM-D), resilienzbezogene Bewältigung und allgemeine Belastbarkeit (Stressverarbeitungsfragebogen (SVF-78), und Resilience Scale (RS-11), Lebensereignisse und Kindheitstraumata (Event List und Childhood Trauma Questionnaire, CTQ) und die regulatorische Funktion der HPA-Achse (Dex-CRH-Test, ACTH und Cortisol, Gesamt-Reaktion als Fläche unter der Konzentrationskurve (Gesamt-AUC), Baselinebereinigte Fläche unter der Konzentrationskurve (Netto-AUC)). Ergebnisse: Der Schweregrad der Depression zeigt eine signifikant negative Korrelation mit positiven Bewältigungsstrategien und dem Grad der allgemeinen Belastbarkeit sowie eine signifikante positive Korrelation mit negativen Bewältigungsstrategien. Die Cortisolreaktion in Bezug auf die Gesamt- und Netto-AUC zeigte eine negative Assoziation mit den SVF78 Subskalen Minimierung, Situationskontrolle und Bedürfnis nach sozialer Unterstützung. Die Subskalen Ablenkung und

Situationskontrolle haben eine signifikante positive Korrelation mit dem basalen Morgencortisol. Die Netto-AUC der Cortisolreaktion war mit der Subskala Gedankliche Weiterbeschäftigung verknüpft, zusätzlich zu den Faktoren Abwertung und Kontrolle. Es wurde eine signifikante Assoziation zwischen der Subskala Situationskontrolle und dem Faktor Kontrolle und der ACTH-Reaktion festgestellt. Der ACTH-Basiswert war mit der Subskala Reaktionskontrolle und Resignation verknüpft. Die nicht kategorisierten Subskalen Bedürfnis nach sozialer Unterstützung waren positiv mit ACTH verknüpft. Bemerkenswert ist, dass die ACTH- und Cortisolreaktionen im Dex/CRH-Test bei Studieneinschluss positiv mit dem Schweregrad der Depression verknüpft waren. Es wurde ein signifikant negativer Zusammenhang zwischen Kindheitstraumata, dem Grad der psychischen Belastbarkeit und positiven Bewältigungsstrategien festgestellt, während ein signifikanter positiver Zusammenhang mit negativen Bewältigungsstrategien, belastenden Lebensereignissen und der Schwere der Depression beobachtet wurde. Diese Ergebnisse stimmen weitgehend mit unseren Hypothesen überein. Schlussfolgerung: Diese Studie zeigt, dass ein niedriges Maß an Resilienz ein Risikofaktor für verbleibende Depressionssymptome nach einer stationären Behandlung zu sein scheint und dass einige Parameter der HPA-Achsenregulierung potenzielle Biomarker für Resilienz sein könnten. Ein besseres Verständnis der biologischen Grundlagen der Resilienz könnte dazu beitragen, neue Biomarker für positive psychologische Faktoren bei Depressionen zu finden, was eines der Ziele der positiven Psychiatrie ist.

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1. INTRODUCTION

Let us assume that we have two patients. Both of them were diagnosed according to their psychopathology with moderate depression and treated successfully with the same medication and psychotherapy methods. However, when we assess psychological resilience at the end of the treatment period, we may find that one patient is more resilient than the other. So, in this situation, the required assistance for the patients to maintain remission might be different.

1.1. Stress and stress response

The stress response is necessary for maintaining homeostasis in response to perceived obstacles. Physiological adaptations encompass heightened cardiovascular and respiratory rates, as well as moderate metabolic activation. These adaptations also involve the suppression of specific vegetative functions like as digestion and immunity (Habib et al., 2001). The hypothalamic-pituitary-adrenal (HPA) axis serves as the primary stress response system in situations of severe or persistent stress. The term refers to a complex system involving the hypothalamus, pituitary gland, and adrenal glands, which interact with each other and regulate various bodily functions (Heaney 2013). The stress response is regulated by the neuroendocrine system, which includes the release of corticotropin-releasing hormone (CRH), ACTH, and cortisol (Besnier et al., 2017). An excessive or prolonged activation of the HPA axis is associated with several physiological and psychological disorders (Stefanaki et al., 2018).

Acute stress triggers the activation of the HPA axis, which leads to various psychological and physiological reactions, such as heightened concentration, increased energy levels, and enhanced motivation (McEwen 2007). Acute stress can be interpreted as a pleasurable experience, which is referred to as "eustress". Conversely, "distress" arises when stress is viewed as menacing or becomes long-lasting, leading to changes in the control of the HPA axis function and, consequently, the ability to cope with stress (Bienertova-Vasku et al., 2020).

The glucocorticoid receptors located in the hypothalamus and pituitary gland have a crucial function in regulating the HPA axis response by providing feedback mechanisms that halt the reaction once the stressor has ceased (Herman et al., 2016). If there is a malfunction in this inhibitory feedback process, it can lead to the development of many diseases and disorders (Smith et al., 2006). When the body experiences stress, the paraventricular nucleus of the hypothalamus releases corticotropin-releasing factor (CRF) into the anterior pituitary gland. It binds to the receptor on pituitary corticotropes, causing the release of adrenocorticotropic

hormone (ACTH) into the bloodstream (Herman et al., 2016; Smith et al., 2006). The adrenal cortex is the site that circulating ACTH acts upon, triggering the production and release of glucocorticoids (Smith et al., 2006). Glucocorticoids, such as cortisol, are steroid hormones that play a significant role in regulating several biological and behavioral processes in humans (Charmandari et al., 2005). Increased concentrations of glucocorticoids in the bloodstream, as a result of stress, suppress the functioning of the hypothalamus and pituitary gland in the HPA axis (Smith et al., 2006). Furthermore, many limbic system structures also contribute to the activation of the HPA axis (Herman et al., 2016; Smith et al., 2006).

1.2. Dexamethasone/corticotrophin-releasing-hormone (dex/CRH) test

Assessment of the hypothalamic-pituitary-adrenal (HPA) axis can be done by static and dynamic tests, as described by Yo et al. in 2014. The HPA axis regulates the generation and release of cortisol and other stress hormones (Herman et al., 2016). Cortisol is essential in regulating the body's reaction to stress (van der Valk et al., 2018). In addition, it has played a role in overseeing several activities such as metabolic regulation, the inflammatory response, and immunological function (Thau et al., 2019). Various circumstances can influence cortisol levels. Timing the cortisol test is crucial due to the diurnal variation in cortisol levels. Typically, cortisol levels increase in the early morning and can be measured using a morning serum cortisol test. They then decline in the evening and throughout the early stages of sleep (Weitzman et al., 1971).

The integrated DEX/CRH test has been formulated to evaluate neuroendocrine dysregulations of the hypothalamic-pituitary-adrenal (HPA) axis and the stress response system. Research has demonstrated that the hormonal reaction to the combined DEX/CRH test serves as an indicator of the disruption of the regulation of the hypothalamic-pituitary-adrenal (HPA) axis (Heuser et al., 1994). The index serves as a measure of the glucocorticoid feedback regulation of the HPA axis and is highly effective in detecting dysregulation of the HPA axis in depressed individuals (Heuser et al., 1994, Hennings et al., 2009). The Dex/CRH test detects anomalies in the signaling of the glucocorticoid receptor (GR) at the pituitary level, as well as excessive secretion of CRH and vasopressin in the paraventricular nucleus (Holsboer, 2000, Holsboer and Ising 2021). Zobel and colleagues (1999) reported that patients diagnosed with remitted major depression who have elevated cortisol levels in response to the DEX/CRH test are more likely to experience a recurrence of depression. The dysregulation of the HPA-axis was influenced by the frequency of mood episodes (Kunzel et al., 2003, Hennings et al., 2009). According to Ising

et al. (2005, 2007), the DEX-CRH test is regarded as the most effective method for identifying abnormalities in the hypothalamic-pituitary-adrenal (HPA) axis in cases of acute depression. Furthermore, it has been seen that the HPA axis returns to normal functioning following successful therapy.

1.3. Depressive episodes

Depressive episode (ICD 10-F32) is a prevalent medical condition that has a detrimental impact on person's emotions, cognition, and behavior. It can lead to disabilities that hinder or restrict the ability to perform daily activities. Depression hampers psychosocial functioning and reduces the quality of life (Malhi and Mann, 2018). Depression is currently classified as the third most significant contributor to disability-adjusted life years, according to the World Health Organization. It is anticipated that by 2030, depression would surpass all other causes and become the leading contributor. Depression is influenced by various elements, including biochemistry, genetics, personality, environmental circumstances, and stressful life events (Sadock, 2007). The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) states that a depressive episode diagnosis necessitates the presence of five or more symptoms over a span of two weeks. This criterion is also supported by the International Classification of Diseases (ICD-10). The primary symptoms include a persistent feeling of sadness, a lack of interest or enjoyment in activities, or both. Anhedonia may manifest as a pervasive absence of enjoyment in nearly all or the majority of activities during the day. The secondary symptoms encompass substantial fluctuations in weight, either through a notable decrease or increase, as well as alterations in appetite. Sleep disturbances may manifest as a decrease or increase in sleep duration. Psychomotor agitation or retardation may occur, alongside a decrease or loss of energy. Individuals may experience a pervasive sense of worthlessness and excessive or inappropriate guilt. Additionally, there may be a decline in cognitive abilities and concentration, along with recurrent thoughts of death. Suicidal ideation, with or without a specific plan, or even a suicide attempt, may also be present (American Psychiatric Association, 2013). The severity of a depressive episode can be categorized as severe, moderate, or minor, based on the quantity of symptoms and the level of impaired functioning. In order to receive a diagnosis of depression, the symptoms must result in substantial impairment in one's ability to work, engage in social activities, or perform other important tasks. There are other choices available, such as psychopharmacotherapy, primarily including the use of antidepressants, and psychotherapy. Electroconvulsive therapy (ECT) is

indicated for individuals who have not achieved a satisfactory response to alternative therapies (Sadock, 2007). Depression can lead to limitations or disruptions in doing daily activities. Depression restricts psychosocial functioning and reduces the overall quality of life (Malhi and Mann, 2018). The involvement of the hypothalamic-pituitary-adrenal (HPA) axis in depression studies has been thoroughly examined (Malhi and Mann, 2018).

1.4. Positive psychological characteristics

Positive psychological traits are crucial factors for preventing illness and improving health (Vahia et al., 2011a). These factors encompass attributes such as self-assurance, sagacity, ingenuity, tenacity, positive outlook, perceived ability to achieve goals, diligence, self-control, expertise, and devotion to spirituality and religion. The aforementioned factors are linked to improved physical and mental well-being (Jeste and colleagues, 2015). The research are centered around comprehending the biological foundation of psychopathology, whereas positive psychiatry concentrates on the biological foundation of positive psychological traits in order to provide a biological evaluation and therapies (Jeste and Palmer 2015).

Studies indicate that positive psychological traits are associated with beneficial outcomes in mental health (Dimtry et al., 2010). According to Moore et al. (2018), they positively impact the cognitive aging process in older patients who have HIV/AIDS. Additionally, Heisel et al. (2016) found that they decrease the risk of suicide among older persons. Furthermore, McCanlies et al. (2014) discovered that they alleviate symptoms of posttraumatic stress disorder. Patients with schizophrenia who possess a high level of wisdom demonstrate enhanced cognitive function, as indicated by research conducted by Van Patten et al. in 2019. Optimism has a significant impact on how individuals deal with difficult situations and pressure, as stated by Carver et al. (2010). Additionally, it demonstrates improved health outcomes in individuals suffering from chronic angina (Fanaroff et al., 2019) and those afflicted with migraines (Peres et al., 2019). Furthermore, it is linked to a reduced occurrence of depression, enhanced quality of life and contentment (Zeng and Shen 2010), and improved immune function (Rasmussen et al., 2009).

1.4. Resilience

Resilience refers to the ability to effectively cope with and bounce back from difficult situations and stressors, while yet maintaining one's mental and physical well-being (Russo et al., 2012; Rutter et al., 2012; Wu et al., 2013). It pertains to the ability to positively adjust, personal traits, and a dynamic process of adjusting to challenges. Resilience refers to the capacity to bounce back from or adjust to stress or challenging circumstances (Ong et al., 2006). Resilience is a crucial factor in the process of turning stressful events into posttraumatic growth. It involves retaining a positive outlook on life and having the belief that problems can be overcome (Toukhsati et al., 2017). It functions as a protective barrier that shields individuals from the adverse impacts of stress and adversity. Resilience is the synergistic interplay of skills and traits that enable individuals to effectively rebound and adapt to stress or challenges (Rutter, 1993). Within the realm of literature, resilience can be divided into two distinct components: the psychological aspects related to coping and the physiological aspects associated with stress management (Tusaie et al., 2004). According to Olsson et al. (2003), it is regarded as both a result and a procedure. Psychological resilience refers to the ability to effectively manage and adapt to stress, as well as the potential for personal growth, development, and learning in the face of adversity (Reid, 2016). Psychological resilience encompasses various attributes, elements, or origins, such as acknowledging the truth, confronting realities, and embracing the aspects that are beyond one's control (Coutu 2002, Meredith et al., 2011, Rice et al., 2016).

Research suggests numerous aspects that contribute to the improvement of resilience. As stated by Rutter (2012), the factors are as follows: Enhanced cognitive ability, self-worth, interpersonal competence, optimism, regard for others, perceived personal agency, attributing trauma to external factors, willingness to seek and accept help, positive peer relationships and recreational activities, and engagement in creative endeavors. Insufficient levels of resilience can be seen as a potential risk factor for the emergence of psychopathology (Ziaian et al., 2012). Assessing resilience can serve as a valuable tool for identifying and preventing mental diseases, creating therapies, and establishing fundamental requirements for mental health (Siriwardhana et al., 2013, Backer et al., 2015). Resilience can be viewed as a safeguard against prenatal anxiety and depression (Ma et al., 2019). Physical health improvement (Stewart and Yuen 2011), well-being (Lamond et al., 2008), and reduced pain (Tomás et al., 2012) are all linked to it.

The biological stress system plays a crucial role in comprehending resilience mechanisms, as it serves as the mechanistic site where environmental inputs are converted into enduring

biological effects (Elbau et al., 2019). Gaining a more comprehensive comprehension of the biological foundation of resilience could offer valuable insights for the creation of novel psychological and pharmacological interventions aimed at bolstering positive mental health. Based on the research, there exist certain possible biomarkers that indicate resilience (Jeste and Palmer, 2015). Neurochemicals have a significant impact on resilience and the ability to adjust to stress, both in the short-term and long-term (Wu et al., 2013). These stress hormones include CRH (Manji et al., 2001), ACTH (Dallman et al., 1987), and cortisol (Nemeroffet et al., 2005), as well as copeptin (Dobša et al., 2013), alpha-amylase (Koh et al., 2014), and other steroids such as dehydroepiandrosterone (DHEA) (Rasmussonet et al., 2010) and testosterone (Morganet al., 2000). Furthermore, potential markers for resilience include neuropeptides such as neuropeptide Y (Morgan et al., 2002) and neurotransmitters (Ranabir et al., 2011; Konstandi et al., 2000; Harvey et al., 2012), cytokines (TNF-α, IL-6, IL-10) and CRP (Walker et al., 2011), brain-derived neurotrophic factor (BDNF) (Lakshminarasimhan et al., 2012), and telomere length (Epel et al., 2006).

Brain imaging is crucial in investigating resilience. Functional magnetic resonance imaging (fMRI) has been employed in numerous resilience studies that have specifically examined the areas and networks responsible for regulating emotions and behavior. These include the amygdala, hippocampus, anterior cingulate cortex, hypothalamic-pituitary-adrenal (HPA) axis, reward circuitry, and somatic nervous system (Jeste et al., 2015). Some research have indicated that specific genetic characteristics may play a role in the process of resilience (Jeste and Palmer, 2015).

1.5. Positive Psychiatry

The notion of positive mental health is not novel. During the early 1900s, William James, a medical doctor and psychologist, discussed the concept of positive ideas, beliefs, and emotions. Subsequently, the concept was further developed and disseminated through the field of humanistic psychology, spearheaded by Ibrahim Maslow and his associates. The reference citation is from Messias et al., (2020). Positive psychotherapy was established in 1977 by Nossrat Peseschkian and his associates. The notion of positive psychology, initially introduced by Martin Seligman in 1998 (Messias et al., 2020), has steadily gained momentum over time. Subsequently, the literature encompassed a multitude of scientific investigations and research projects, leading to the establishment of numerous organizations. Positive psychiatry was established by Dilip Jeste in 2013, as documented by Jeste et al. (2013).

Psychiatry is a medical specialty focused on the identification, management, and prevention of mental, emotional, and behavioral disorders. Positive psychiatry is a field of psychiatry that focuses on studying and improving well-being by examining and intervening in positive psychosocial factors like resilience, optimism, and social engagement. It is particularly concerned with individuals who have or are at a high risk for mental or physical illnesses (Jeste et al., 2015). According to the World Health Organization, health is defined as a condition of whole physical, mental, and social well-being, rather than just the absence of disease or weakness. Positive psychiatry emphasizes the promotion of positive psychosocial characteristics, such as wisdom, optimism, resilience, posttraumatic growth, creativity, confidence, perceived self-efficacy, conscientiousness, personal mastery, and spirituality, in order to improve overall health rather than solely treating mental illness. Psychiatry focuses on evaluating and treating mental disorders, while positive psychiatry integrates this with evaluating and enhancing positive psychosocial traits through psychological, behavioral, and biological therapies. Positive psychiatry and positive psychology have common ground, as do psychiatry and clinical psychology. While there may be overlapping thoughts and objectives, each individual possesses distinct abilities and perspectives. Positive psychiatry is a field of study that examines the biological foundations of positive psychological characteristics, such as neurocircuitry, neurochemistry, and hereditary factors. It also aims to identify biomarkers associated with these traits (Jeste and Palmer, 2015).

Multiple studies have identified positive psychological interventions that aim to enhance resilience and reduce stress in individuals, regardless of whether they have mental problems or not (Creswell et al., 2012; Adler et al., 2015). Interventions encompass many activities such as physical exercise, meditation, yoga, and maintaining a nutritious diet. Engaging in physical activity can serve as a preventive measure against depression, as stated by Mammen et al. in 2015. According to Yin et al. (2014), meditation has been found to reduce anxiety and improve positive emotions. Yoga is linked to enhanced immune function and decreased stress levels (Arora and Bhattacharjee 2008, Yadav et al. 2012). Multiple studies have established a correlation between a nutritious diet and a decrease in the likelihood of experiencing severe depression (O'Neil et al., 2014).

From the perspective of positive psychiatry, we tried in this study to find answers regarding the associations between general resilience and depression and association between resilience-related positive coping and depression. In addition, we asked whether the ACTH/cortisol response to the Dex/CRH-test can be considered as biomarkers for resilience-related positive coping, general resilience and depression, and whether childhood trauma and/or the number and summarized burden of experienced life events affect coping strategies, resilience, and the severity of depression.

2. METHODS

2.1. Sample

The analyses were conducted using a sample of depressive individuals who took part in the Munich Antidepressant Response Signature (MARS) study (Hennings et al., 2009). The purpose of the MARS project was to determine the parameters that can predict the response to antidepressant drugs and to identify specific groups of patients with similar conditions who are likely to benefit from personalized treatment. The Max-Planck-Institute of Psychiatry (MPI-P) in Munich, Germany conducted the experiment from 2000 to 2008. Data on depressed inpatients have been gathered longitudinally from three clinical facilities in Southern Bavaria, namely MPI-P in Munich, Bezirkskrankenhaus Augsburg, and Klinikum Ingolstadt. The study design was naturalistic, meaning that the treatment and duration of hospitalization were not impacted by the study protocol. This was done to create a setting that accurately represents the ordinary clinical scenario (Hennings et al, 2009).

2.2. **Assessments**

Assessments used in this analysis included depression severity (Hamilton Depression Rating Scale (HAM-D), resilience-related coping (Stress Coping Style Questionnaire, SVF-78) and general resilience, (Resilience Scale, RS-11), life events and childhood trauma (Event List and Childhood Trauma Questionnaire, CTQ), and the regulatory function of the HPA axis (Dex-CRH test).

2.2.1. Hamilton Depression Rating Scale (HAM-D)

The Hamilton Depression Rating Scale was developed by Max Hamilton to assess the effectiveness of the first generation of antidepressants and was initially published in 1960 (Hamilton,1960). It is considersed as a standard tool to measure depression severity for clinical trials of antidepressants and is a commonly used measurement for depression (Endicott et al., 1981). It contains 21 variables items that represent the symptoms of the depressive episodes. The items are depressed mood, feelings of guilt, suicide, insomniainitial, insomnia- middle, insomnia-delayed, work and interests, retardation, agitation, anxiety-psychic, anxiety-somatic, somatic symptoms-gastrointestinal, somatic symptomsgeneral, genital symptoms, hypochondriasis, weight loss, insight, diurnal variation derealisation and depersonalization,

paranoid symptoms and obsessional symptoms (Hamilton,1960). The HAM-D was rated on admission then weekly until week 6 and biweekly until week 12 and at discharge.

2.2.2. Stress Coping Style Questionnaire (SVF-78)

In positive psychiatry, a low level of perceived stress and how the patients cope with stress are considered an important outcome parameter (Jeste et al.,2015), and maladaptive or negative coping strategies can lead to an impaired resilience (Hurley, 2018). To assess coping strategies, we used the Stress Coping Style Questionnaire (SVF-78), a short version of the SVF120 (Ising et al., 2001; Erdmann and Janke, 2008). It contains 78 items and measures the individual strategies that the subject uses in response to life stress. It is divided into 13 subscales to be answered on a five-point scale (not at all- hardly-possibly-probably-very probably), and each subscale is demonstrating a particular way of responding to a stressful situation. According to (Höhne et al.,2014), the subscales are clustered into four categories, and three categories are assigned as positive strategies: Devaluation/Defense, including subscales of minimization and guilt denial, distraction from stress comprising the subscales of distraction and substitute gratification, and control including the subscales situation control, response control, and positive self-instruction (Höhne et al.,2014). The category of Negative strategies contains the subscales avoidance, escape, rumination, resignation, and self-blame (Ising et al., 2001). The subscales Need for social support cannot be assigned to one of the categories and remain unclassified.

As resilience is positively related to adaptive (positive) coping and negatively to maladaptive (negative) coping (Macía et. al 2021), we used the Stress Coping Style Questionnaire (SVF-78) as a proxy to evaluate resilience (see Tabel 1). The SVF-78 was assessed shortly prior to discharge of the patients.

Table 1: Stress Coping Style Questionnaire (SVF-78)

Stress Coping Style subscales (SVF-78)
positive strategies
Positive strategies (total score)
- Devaluation/Defense (Positive 1)
- - Minimization
- - Guilt denial
- Distraction (Positive 2)
- - Distraction
- - Substitute Gratification
- Control (Positive 3)
- - Situation Control
- - Response Control
- - Positive self-instruction
Need for social support
Negative strategies
Negative strategies (total score)
- - Avoidance
- - Escape
- - Rumination
- - Resignation
- - Self-blame

2.2.3. Resiliance Scale 11 (RS-11)

The Resilience Scale is utilized to assess the level of general resilience (Wagnild et al., 1993, Abiola et al., 2011). The RS-11 is a technique used to assess resilience using an 11-item questionnaire, which is a condensed version of the RS-25 (Leppert et al., 2008). Schumacher et al. (2005) have validated the RS-11. In the RS-11, resilience is defined as a beneficial psychological attribute that is linked to a robust ability to handle stress in social and psychological contexts. This is measured using a 7-point Likert scale, ranging from '1' indicating strong disagreement to '7' indicating strong agreement. The RS-11 has demonstrated its reliability and validity as a tool for economically evaluating resilience in a community sample of N = 2,031 individuals (Schumacher et al., 2005; von Eisenhart Rothe, 2013). Evaluations using the RS-11 were conducted at admission, after a period of six weeks, and

before the patient's discharge. RS-11 data is exclusively accessible among a small subset of individuals participating in the study.

2.2.4. Event list

The "Event List" (Ising et al., 2003), a German version of the Social Readjustment Scale developed by Holmes and Rahe (1967), was used to evaluate personal life events. The event list comprises 37 questions that evaluate the incidence and frequency (once, twice, several times) of particular life events, such as marriage, separation, changes in living conditions and behaviors, and the loss of close family members and friends. Each item was also evaluated based on personal valency, ranging from extremely positive to very negative, and burden, ranging from not burdensome at all to quite burdensome, using a 5-item Likert scale. The study involved calculating a total life events score and a weighted total life event score based on 37 items. These scores represent the overall frequency of all life events and the overall life events frequency weighted by the individual burden score, respectively. The assessment of the Even List occurred alone at the time of discharge.

2.2.5. Childhood trauma questionnaire (CTQ)

The German version of the childhood trauma questionnaire (CTQ) (Wingenfeld et al. 2010) was used to assess emotional, sexual and physical abuse, as well as emotional and physical neglect experiences during childhood until puberty. The CTQ is the most frequently used screening instrument to assess potential maltreatment in childhood and adolescence. The scale consists of 34 items and has five subscales: emotional abuse, sexual abuse, physical abuse, physical neglect and emotional neglect. The CTQ was assessed at discharge only. CTQ data are available only in a subgroup of participants.

2.2.6. Dex/CRH - test

The dex/CRH test was conducted according to the methodology outlined by Heuser et al. (1994). In summary, a dose of 1.5 mg of dexamethasone was taken orally at 11 p.m. the day prior to being stimulated with 100µg of human CRH. Blood samples were collected at 3:00, 3:30, 3:45, 4:00, and 4:15 p.m. on the day of the test. The CRH is administered intravenously within a time frame of 30 seconds, immediately following the collection of the 3:00 p.m.

sample. The participants remained in a supine position during the exam. Immunometric assays were utilized to quantify the levels of plasma ACTH and cortisol. The hormone levels in the initial sample collected at 3:00 p.m. indicate the inhibitory impact of the dexamethasone treatment administered at 11 p.m. the previous day, and are referred to as baseline ACTH and cortisol. The remaining samples demonstrate the reaction to the CRH while being influenced by the inhibitory properties of dexamethasone (Ising et al. 2005). The AUC was computed to represent the cumulative response for ACTH and cortisol. Furthermore, the netAUC, which represents the entire area under the curve minus the baseline equivalent to accurately depict the effects of CRH, was computed. The basal fasting morning cortisol level was determined prior to the administration of dexamethasone. The Dex/CRH test was administered to a subset of study participants soon after they were admitted and before they were discharged.

2.3. Research questions and hypotheses

The analysis addressed four research questions evaluating associations of coping-related and general resilience with depression symptoms and HPA-axis regulation.

1. Are there reciprocal associations between positive vs. negative coping strategies and depression symptomatology at the end of hospitalization (before discharge)?

Hypothesis 1a: Patients at discharge with higher scores in positive coping strategies tend to have lower depression symptomatology.

Hypothesis 1b: Patients at discharge with higher scores in negative coping strategies tend to have higher depression symptomatology.

2. Is there an association between general resilience and depression symptomatology before discharge?

Hypothesis 2: Patients at discharge with higher level of general resilience have lower depression scores.

2. Can basal plasma cortisol levels in the morning and/or the ACTH/cortisol response to the

Dex/CRH-test be considered as biomarkers for positive coping strategies at the end of hospitalization (before discharge)?

Hypothesis 3a: Morning plasma cortisol before discharge shows a negative association with positive coping strategies.

Hypothesis 3b: ACTH/cortisol response to the Dex/CRH-test before discharge is inversely associated with positive coping strategies.

4. Do childhood trauma and/or the number und summarized burden of experienced life events affect coping strategies, resilience and severity of depression?

Hypothesis 4: Childhood trauma and cumulated life events have a negative impact on coping strategies and resilience, and increase severity of depression.

2.4. Statistical analysis

All statistical analyses were performed using SPSS for Windows, version 25 (IBM, Chicago, IL). Descriptive statistics were used to report demographic and clinical characteristics variables in addition to the factors and subscales of the German Stress Coping Questionnaire SVF-78. The mean and standard deviation were calculated for each variable. Pearson's correlation coefcients were used to determine the relationship between total coping strategies SVF-78 (resilience) and severity of depression (HAM-D) at admission and before discharge.

Spearman correlation coefcients were used to evaluate the correlation between the severity of depression (HAM-D) and general resilience, the correlation between individual coping strategies SVF-78 (resilience) and cortisol and ACTH, the correlation between the number of depressive episodes, cortisol, and ACTH, in addition to the relationships between individual coping strategies and age, gender, number of depressive episode stressful life events and age of onset.

A multiple regression analysis was conducted to identify the most critical factors linked to the total negative and positive strategies as dependent variables. The independent variables entered in the regression analysis were life event score, gender, age, age of onset, the severity of depression measured by the Hamilton Depression Rating Scale, and the number of depressive episodes.

SVF-78 and RS-11, the questionnaires used in the analysis, comprise together five independent factors (SVF-78: POS1, POS2, POS3, NEG + RS-11). These scales were associated with the ACTH and cortisol outcome of the dex/CRH-test, which are highly correlated as they reflect the activity of the same system, the HPA axis, from difference perspectives. Therefore, we applied a Bonferroni-correction for five independent dimensions that are part of the analyses. Thus, the adjusted level of significance was reduced to $p < .01$ (= .05/5).

An explorative analysis was performed between RS-11 and the dex/CRH test response, which included only seven subjects. Given the small samples size and the explorative character of this analysis, no correction for multiple testing was applied in this case.

3. RESULTS

3.1. Demographic and clinical characteristics of the study sample

In total, 397 hospitalized patients with depression were included in the analysis. Demographic characteristics are shown in Table 2. The mean age of the sample was 46.7 years. 50.3% were female, 48.6% were married, and 61%. were employed. Patients diagnosed with depression disorders represented 88.6%, bipolar disorder 5.8%, and 5.6% represented other mental illnesses that a depressive syndrome was dominating also in these patients. Patients with recurrent depressive disorder were significantly older than patients with a single major depressive disorder and bipolar disorder.

Moreover, patients with recurrent depressive disorder had the lowest employment rate due to the higher retirement rate. Family history was higher among patients diagnosed with bipolar disorder than other groups. Two-third of the patients had a high level of psychosocial stress. Anxiety disorder was the most frequent comorbid psychiatric illness, and patients with major depressive disorder had the highest rate.

Table 2: Demographics of the study sample.

	N	Total	
		Mean	SD
General	397	%	
Gender (ratio male: female)		200:197	
Age (years)		46.7	12.4
Partenership	397		
Single		30.5%	
Married		48.6%	
Separated		13.6%	
Widowed		3.3%	
Employment	397		
Employed		61%.	
Unemployment		7.8%	
Retired		31.2%	

3.2. Descriptive analysis of factors and subscales of the Stress Coping Questionnaire and associations with descriptive and clinical factors.

Mean scores and standard deviations of the all subscales of the SVF-78 and of the (sub-) categories of positive and negative coping strategies are shown in Table 3.

Table 3: Descriptive analysis of factors and subscales of the Stress Coping Questionnaire SVF-78. N=395.

Stress Coping strategies	M	SD
Minimization	7,38	4,15
Guilt denial	10,83	4,28
Distraction	11,82	3,80
Substitute Gratification	8,60	4,51
Situation Control	15,14	3,89
Response Control	15,27	3,96
Positive self-instruction	14,06	4,64
Need for social support	13,62	5,32
Avoidance	14,84	4,55
Escape	11,65	5,55
Rumination	16,53	5,13
Resignation	11,68	5,19
Self-blame	12,88	5,38
Positive 1 (Devaluation)	9,11	3,64
Positive 2 (Distraction)	10,21	3,59
Positive 3 (Control)	14,83	3,46
Total Positive strategies	11,40	2,80
Total Negative strategies	13,19	4,59

There are several associations between coping strategies measured by SFV-78 and demographic and clinical variables. Age was linked to the total score of positive coping (r 0.158**), whereas stressful life events were linked to total score of negative coping (r 0.122*). Gender was associated with the total score of negative coping (r 0.125*) and all other negative coping subscales except subscale (escape).

The number of depressive episodes has a significant association with total negative coping strategies (r 0.144**) and all negative subscales except avoidance. In contrast, there was no association with positive coping strategies.

The age of onset of the disorder has a positive correlation with the total score of positive coping (r 0.212**) and several positive coping subscales and associated with the total score of negative coping and all other negative coping strategies subscales except avoidance.

3.3. Relations between positive and negative coping strategies (SVF-78) and severity of depression (HAM-D) at admission and prior to discharge

As shown in Table 4, the severity of depression measured by the Hamilton Depression Rating Scale (HAM-D) prior to discharge shows a significant negative correlation with total positive coping strategies measured with the SVF-78 and a significant positive correlation with total negative coping strategies. Subscales of positive strategies except substitute gratification and need for social support were negatively associated as well, while significant positive associations were observed for the negative strategies subscales except avoidance. Interestingly, the severity of depression at admission did not show any correlations with total and individual positive coping strategies. However, there was a positive association with total negative strategies and the subscales rumination and self-blame.

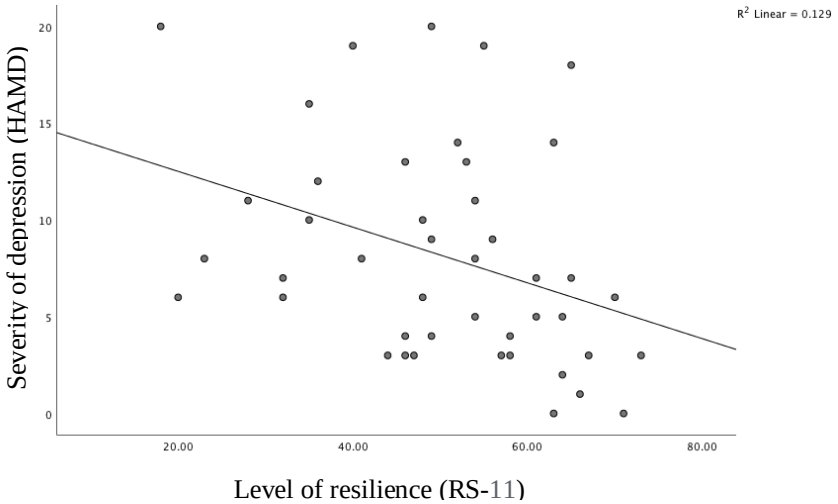
Table 4: Relations between positive and negative coping strategies (SVF-78) and severity of depression (HAMD) at admission and prior to discharge. Pearson correlation, (N=381)

Coping Strategy	Severity of depression (HAMD)	
	At admission	*Before discharge*
positive strategies		
Total positive strategies	-0.023	**-0.187 * ***
- Positive 1 (Devaluation)	-0.066	**-0.149 * ***
- - Minimization	-0.056	**-0.134 * ***
- - Guilt denial	-0.060	**-0.124 ***
- Positive 2 (Distraction)	-0.034	**-0.112 ***
- - Distraction	0.023	**-0.109 ***
- - Substitute Gratification	-0.074	-0.086
- Positive 3 (Control)	0.027	**-0.190 * ***
- - Situation Control	-0.031	**-0.158 * ***
- - Response Control	-0.085	**-0.105 ***
- - Positive self-instruction	-0.044	**-0.206 * ***
Need for social support	0.081	-0.070
Negative strategies		
Total negative strategies	**0.109 ***	**0.248 * ***
- - Avoidance	0.067	0.065
- - Escape	0.055	**0.209 * ***
- - Rumination	**0.140 * ***	**0.209 * ***
- - Resignation	0.052	**0.221 * ***
- - Self-blame	**0.132 * ***	**0.219 * ***

3.4. Relation between general resilience (RS-11) and severity of depression (HAMD) before discharge

A significant negative association was found between the severity of depression measured with the HAMD before discharge and the level of general resilience measured with the RS-11. Spearman r = -0.408 (p = 0.006) (N=44) (see Figure 1).

Figure 1: Correlation between severity of depression and level of resilience prior to discharge. Spearman r-0.408, *P*=0.006 (N=44)



3.5. Relations between positive and negative coping strategies (SVF-78) and ACTH and cortisol response to the Dex/CRH test at admission

The relationship between positive and negative coping strategies measured with the SVF-78 and ACTH and cortisol responses to the Dex/CRH test at admission was examined. In addition, associations with basal fasting morning cortisol the day before the Dex/CRH test were additionally evaluated (Table 5).

The cortisol response in terms of the total and net AUC showed a negative association with subscale minimization. The subscales distraction and situation control have a significant positive correlation with basal morning cortisol. The net AUC of the cortisol response was linked to the subscale rumination, in addition to factors devaluation and control. A significant association was found between the subscale situation control and factor control and ACTH (baseline, AUC, and AUCnet).

ACTH baseline was linked to the subscale response control and resignation. The uncategorized subscales need for social support was positively associated with ACTH AUC and ACTH AUCnet. Of note, the ACTH and coprtisol response to the Dex/CRH test at admission was positively associated with HAMD depression severity (ACTH baseline, ACTH AUC, cortisol AUC, $p < 0.05$). No associations were observed between positive and negative coping strategies and the ACTH and cortisol response to the Dex/CRH test at discharge (see Table 6).

Table 5: Correlation between individual coping strategies SVF-78 (resilience) and cortisol and ACTH at admission. Spearman correlation.

Coping Strategy	Cortisol morning *(N=343)*	(Dex/CRH) - Test					
		Cortisol baseline *(N=336)*	Cortisol AUC *(N=300)*	Cortisol AUCnet *(N=300)*	ACTH baseline *(N=382)*	ACTH AUC *(N=346)*	ACTH AUCnet *(N=346)*
Positive strategies							
Total positive strategies	0.080	0.078	0.082	0.032	0.029	0.039	0.030
-Positive1(Devaluation)	0.030	0.056	-0.055	**-0.110***	-0.006	-0.054	-0.067
- -Minimization	0.042	0.022	**-0.111***	**-0.157****	-0.049	-0.096	-0.096
- - Guilt denial	0.006	0.075	0.015	-0.033	0.040	0.005	-0.016
-Positive 2 (Distraction)	0.084	0.022	0.086	0.097	-0.066	0.019	0.038
- -Distraction	**0.115***	0.046	0.088	0.077	0.006	0.041	0.041
- -Substitute Gratification	0.035	0.003	0.057	0.080	-0.091	0.001	0.031
-Positive 3 (Control)	0.063	0.095	**0.162****	**0.116***	**0.142****	**0.160****	**0.135***
- -Situation Control	**0.139****	0.094	**0.165****	**0.153****	**0.141****	**0.165****	**0.152****
- -Response Control	-0.021	0.028	0.101	0.062	**0.111***	0.105	0.077
- -Positive self-instruction	0.054	**0.105***	0.110	0.051	0.091	0.110	0.087
Need for social support	0.099	0.064	**0.152****	**0.181****	0.098	**0.163****	**0.150****
Negative strategies							
Total negative strategies	-0.052	-0.044	0.008	0.059	-0.060	0.048	0.025
- -Avoidance	-0.045	0.012	0.049	0.071	0.012	-0.042	-0.046
- -Escape	-0.055	-0.037	-0.038	0.008	-0.095	-0.083	-0.047
- -Rumination	-0.068	0.003	0.074	**0.107***	0.002	0.015	0.026
- -Resignation	-0.056	-0.083	-0.044	0.013	**-0.110***	-0.080	-0.043
- -Self-blame	-0.006	-0.029	0.042	0.083	-0.004	0.006	0.002

Note: statistically significant data shown in bold. p* <0.05 p**<0.01.

Table 6: Correlation between individual coping strategies (resilience) and cortisol and ACTH prior to discharge.

Spearman correlation

		(Dex/CRH) - Test					
Coping Strategy	Cortisol morning *(N=14)*	Cortisol baseline *(N=17)*	Cortisol AUC *(N=170)*	Cortisol AUCnet *(N=170)*	ACTH baseline *(N=171)*	ACTH AUC *(N=170)*	ACTH AUCnet *(N=170)*
Positive strategies							
Total positive strategies	-0.042	0.005	0.056	0.030	-0.021	0.036	0.062
-Positive 1 (Devaluation)	-0.043	0.011	0.008	-0.045	0.015	0.030	0.056
- - Minimization	0.038	-0.003	-0.008	-0.034	0.012	0.021	0.049
- - Guilt denial	-0.122	0.031	0.023	-0.038	0.029	0.038	0.041
- Positive 2 (Distraction)	-0.052	-0.027	0.074	0.089	-0.051	0.040	0.039
- - Distraction	0.000	0.048	0.116	0.082	0.055	0.071	0.062
- - Substitute Gratification	-0.079	-0.091	0.006	0.057	-0.103	0.002	0.010
- Positive 3 (Control)	-0.040	0.014	0.046	0.046	0.005	0.050	0.084
- - Situation Control	0.080	-0.018	0.064	0.099	0.061	0.082	0.098
- - Response Control	0.000	0.079	0.057	0.022	-0.010	0.073	0.067
- - Positive self-instruction	-0.142	0.011	-0.013	-0.026	-0.043	-0.019	0.043
Need for social support	0.015	-0.001	-0.006	0.032	0.019	0.003	-0.024
Negative strategies							
Total negative strategies	0.056	0.062	0.040	0.076	-0.060	0.048	0.025
- - Avoidance	-0.003	0.114	0.097	0.103	0.001	-0.010	-0.065
- - Escape	0.034	0.028	0.022	0.068	-0.018	0.006	-0.036
- - Rumination	0.010	0.082	0.054	0.066	0.072	0.023	-0.065
- - Resignation	0.074	0.037	-0.008	0.023	-0.041	-0.044	-0.083
- - Self-blame	0.110	0.055	0.079	0.121	0.063	0.039	-0.027

Note: statistically significant data shown in bold. p* <0.05 p**<0.01.

3.6. Relationship of childhood trauma (CTQ) and cumulative life events (Event list) with coping strategies, resilience and severity of depression

A significant negative association was found between childhood trauma measured with the CTQ and the level of psychological resilience measured by (RS-11). Also, a significant negative association was found between childhood trauma and positive coping strategies, whereas a significant positive association was observed with negative coping strategies. A significant positive association was found between childhood trauma and severity of depression measured by the (HAM-D) (see Table 7).

Table 7: Relationship between childhood trauma and coping strategies, resilience, stressful life events and severity of depression. Spearman correlation.

	Positive Coping Strategies	Negative Coping Strategies	Resilience	Severity of depression
Childhood Trauma	**-0.237***	**0.241***	**-0.311***	**0.452****
Significant	0.018	0.016	0.040	0.002
N	100	100	44	44

Note: statistically significant data shown in bold. p* <0.05 p**<0.01

3.7. Multivariate analysis

As various factors were significantly related to the total score of negative strategies, a multiple regression analysis was performed to identify the most critical factors linked to the total score of negative strategies as dependent variables, respectively. As independent variables, life event score, gender, age, age of onset, the severity of depression measured by the (HAM-D) before discharge, and the number of depressive episodes were included in the regression analysis. All requested variables were simultaneously entered in the regression analysis. The most influential

factors connected with the total negative strategies total score were gender and severity of depression measured by the Hamilton Depression Rating Scale before discharge. (see Table 8).

Table 8: Factors related to the total score of negative coping strategies

Model	Regressors	*B*	SE	t.	Significance
1.	Life Event score	0.030	0.020	0.522	0.602
	Gender	0.167	0.500	2.983	**0.003**
	Age	0.065	0.028	0.837	0.403
	Age of onset	-0.205	0.026	-2.521	**0.012**
	Sseverity of depression	0.224	0.044	3.973	**0.000**
	Number of depressive episode	0.031	0.040	0.501	0.617
	ANOVA F=6,941 df=296 p<0.000				

4. DISCUSSION

The purpose of this study was to better understand the associations between biological and psychological aspects of resilience in patients with depression.

The analyses were performed with a sample of depressed in-patients having participated in the Munich Antidepressant Response Signature (MARS) study (Hennings et al. 2009). The MARS study was carried out to find factors that (1) are anticipating for antidepressant drug response, (2) determine the homogeneous subgroups of patients with a common pathology likely to benefit from individualized treatment. Assessments used in this analysis include depression severity (Hamilton Depression Rating Scale. HAM-D), resilience-related coping and general resilience (Stress Coping Style Questionnaire, SVF-78, and the Resilience Scale (RS-11), life events and childhood trauma (Event List and Childhood Trauma Questionnaire, CTQ), and the regulatory function of the HPA axis (Dex-CRH test). Positive coping is assumed as a specific aspect of resilience related to an appropriate and positive way in coping with stress, while the RS-11 assesses general resilience in a broader sense.

The study addressed four research questions:

First: Are there reciprocal associations between positive vs. negative coping strategies and depression symptomatology at the end of hospitalization (before discharge)?

In agreement with our hypothesis, residual depression symptoms in depressed patients at the end of the hospitalization period showed a negative association with positive coping strategies and a positive correlation with negative coping strategies measured by Stress Coping Style Questionnaire SVF-78. Thus, positive coping strategies related with resilience are accompanied by a low amount of residual symptoms in depressed patients at the end of inpatient treatment, while negative coping strategies are associated with more residual symptoms despite inpatient treatment.

Second: Is there an association between general resilience and depression symptomatology before discharge?

In agreement with our hypothesis, patients with a higher level of psychological resilience showed less residual depression symptoms at the end of inpatient treatment.

Third: Can basal plasma cortisol levels in the morning and/or the ACTH/cortisol response to the Dex/CRH-test be considered as biomarkers for positive coping strategies at the end of hospitalization (before discharge)?

Our study partly supports our hypothesis: Cortisol response to the Dex/CRH test in terms of the total and net AUC showed a negative association with subscale minimization. The subscales distraction and situation control have a significant positive correlation with basal morning cortisol. The net AUC of the cortisol response was linked to the subscale rumination, in addition to factors devaluation and control.

Also, the ACTH response to the dex/CRH test showed a solid significant negative association with general resilience indicating that a dysregulated HPA axis at the level of the pituitary at the end of in-patient treatment is associated with a lack of resilience. While this finding is in agreement with previous findings A significant association was found between the subscale situation control and factor control and ACTH (baseline, AUC, and AUCnet). ACTH baseline was linked to the subscale response control and resignation. The uncategorized subscales need for social support was positively associated with ACTH AUC and ACTH AUCnet. Of note, the ACTH and coprtisol response to the Dex/CRH test at admission was positively associated with HAMD depression severity (ACTH baseline, ACTH AUC, cortisol AUC, $p < 0.05$). However, it is to be noted that the number of patients with dex/CRH test data and data on general resilience was very low with only seven patients constituting the observed association between ACTH response and resilience.

Fourth: Do childhood trauma and/or the number und summarized burden of experienced life events affect coping strategies, resilience and severity of depression?

Our results support the hypothesis that childhood trauma and cumulated life events have a negative impact on coping strategies and resilience, and increase severity of depression. Where was found a significant negative association between the childhood trauma measured with the CTQ and level of psychological resilience measured by (RS-11). Also, a significant negative association was found between the childhood trauma and positive coping strategies, whereas a significant positive association was observed with negative coping strategies. A significant positive association was found between childhood trauma and severity of depression. These results are in agreement with the literature (Zheng et al., 2022).

Our findings are in agreement with previous evidence indicating an important role of positive psychological factors like resilience for successful interventions in depression (Jeste & Palmer 2015). Jeste and colleagues (2015) mentioned that one goal of positive psychiatry is understanding the neurobiological basis for positive psychological factors as a step to develop pharmacological, biological, and psychosocial interventions and that resilience is associated with less HPA-axis activation to stress. Hölzel and colleagues (2011) showed that the 8-week

Mindfulness-Based Stress Reduction (MBSR) program reduces the level of distress. (Creswell et., al 2012) mentioned that Mindfulness-Based Stress Reduction can be considered to reduce loneliness and related pro-inflammatory gene expression in older adults. Vahia and colleagues (2011) noted that people with a high level of positive psychological factors tend to have healthier lives.

The pattern of this study's results is consistent with the previous literature. Orzechowska and colleagues (2013) indicating that depression may be a factor of a negative assessment of one's ability to cope with difficult situations and tend to perceive stressful events as overwhelming.

Our findings highlight how resilience as an important aspect of positive psychology plays a prominent role in depression outcomes. This suggests that it could be valuable to integrate elements of positive psychology into depression treatment. Several studies support these findings. Maekawa and colleagues (2017) showed that patients experiencing their first episode of major depressive disorder have low resilience levels. Toukhsati and colleagues (2017) indicated that low resilience was associated with depression in patients with cardiovascular disease. Ziaian and colleagues (2012) showed adolescents with a lower level of psychological resilience suffering from depressive symptoms. Ma and colleagues (2019) pointed out that resilience could be a protective factor for prenatal depression.

There are at least two limitations that should be taken into consideration for the generalization of the study results. The first limitation is that the sample consists only of patients with depressive symptoms, while patients with other mental illnesses and healthy controls were not considered. The second limitation is that the primary assessment tool for resilience Stress Coping Style Questionnaire SVF-78 has been developed for measuring coping strategies rather than resilience. However, we can argue that resilience is reflected by positive coping with stress and how we can grow, develop, and learn (Reid 2016). Therefore, the positive coping subscale of the SVF-78 can be regarded as an assessment tool for specifically stressrelated aspects of resilience, while the Resilience Scale 11(RS-11), unfortunately available only for a small subsample, can be regarded as an assessment tool for general resilience.

Despite these limitations, the present study enhances our understanding of the relationship between resilience, depression, and stress response regulation markers contributing to a growing body of evidence suggesting the importance of biological and psychological assessment of positive psychological factors. We hope that the current study stimulates further research in this important area extending the current findings by adding more parameters such

as neuroimaging, neuropsychology, inflammatory markers, psychophysiology, and omics markers.

In conclusion this study shows that a low level of resilience seems to be a risk factor for residual depression symptoms after inpatient treatment and that some parameters of HPA axis regulation might be potential biomarkers for resilience. Improving the understanding of the biological basis of resilience may help to find new biomarkers for depression.

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I hereby declare, that the submitted thesis entitled Biopsychological assessment of resilience in depression from the perspective of Positive Psychiatry

is my own work. I have only used the sources indicated and have not made unauthorised use of services of a third party. Where the work of others has been quoted or reproduced, the source is always given.

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