endocrines

MDPI

Review

A Scoping Review of Potential Biological Mechanisms and Predictors of Interpersonal Psychotherapy

Victoria Papke [1], Hopewell Hodges [2], Kristina Reigstad [3], Meredith Gunlicks-Stoessel [3] and Bonnie Klimes-Dougan [1,*]

[1] Department of Psychology, University of Minnesota, 75 East River Road, Minneapolis, MN 55455, USA
[2] Institute of Child Development, University of Minnesota, 51 East River Road, Minneapolis, MN 55455, USA
[3] Department of Psychiatry and Behavioral Sciences, University of Minnesota, 606 24th Ave S, Minneapolis, MN 55454, USA
* Correspondence: klimes@umn.edu

Abstract: Social dysfunction plays a critical role in the development and maintenance of depression in both adolescents and adults. Interpersonal psychotherapy (IPT) and interpersonal psychotherapy for depressed adolescents (IPT-A) are effective, evidence-based, and time-limited treatments for depression that aim to mitigate depressive symptoms by strengthening an individual's interpersonal relationships and skills. Though the efficacy of IPT/IPT-A has been well established, we are just beginning to know how biological systems are implicated in its success. In this scoping review, we examine the extant literature on biological mechanisms and predictors of IPT/IPT-A treatment efficacy. Overall, seven studies were identified that consider biological processes in the context of evaluating IPT/IPTA, and the studies that were conducted are typically preliminary in nature. Notably, there is some evidence showing that the hypothalamic–pituitary–adrenal axis, various frontal and limbic brain regions, and behavioral indexes that represent brain functioning are associated with changes in IPT/IPT-A or predictive of IPT/IPT-A outcomes. We also consider consequences for treatment and future research. The hope is that a better understanding of how and for whom IPT/IPT-A works can optimize the success of the treatment in reducing an individual's depressive symptoms.

Keywords: IPT; IPT-A; biological mechanisms; personalization; MRI; HPA axis; treatment mechanisms

Citation: Papke, V.; Hodges, H.; Reigstad, K.; Gunlicks-Stoessel, M.; Klimes-Dougan, B. A Scoping Review of Potential Biological Mechanisms and Predictors of Interpersonal Psychotherapy. *Endocrines* **2023**, *4*, 742–756. https://doi.org/10.3390/endocrines4040054

Academic Editor: Sharon DeMorrow

Received: 11 August 2023
Revised: 18 November 2023
Accepted: 23 November 2023
Published: 1 December 2023

1. Introduction

Social dysfunction plays a crucial role in major depressive disorder (MDD) and other depressive disorders, acting as a causal factor, an effect of the disease process, and a maintenance factor for other symptoms [1]. Interpersonal psychotherapy (IPT) emerged as a response to these observations: A manualized and time-limited treatment for MDD in adults, IPT aims to attenuate patients' depressive symptoms by strengthening their interpersonal relationships and skills. Over the years, IPT has accumulated substantial empirical support through trials, meta-analyses, and systematic reviews [2,3]. Though most commonly used to treat depression, IPT has been adapted in recent years as an intervention for many psychiatric diagnoses, such as borderline personality disorder, bipolar disorder, and posttraumatic stress disorder [4–6]. Due to the significance of social dysfunction in depression, research on mechanisms of change in IPT has generally centered on psychosocial factors [7], and as with other psychotherapies, there is a paucity of literature examining IPT using a biological approach [8]. Given that neurological and physiological correlates of depression sequelae are well documented [9], it is critically important to consider the biological mechanisms underlying this social dysfunction, their malleability to change by IPT, and the ways in which these processes can be further leveraged to predict treatment response and improve treatment outcomes. This chapter reviews the burgeoning field of research on possible biological mechanisms and predictors of IPT.

1.1. Interpersonal Psychotherapy: Overview and Adaptation for Adolescents

IPT is an evidence-based, manualized, and time-limited treatment for MDD in adults. Early conceptualization of IPT began in 1969 under the leadership of Gerald Klerman, Myrna Weissman, and their colleagues, drawing heavily on foundational research on the attachment and interpersonal difficulties associated with depression [10]. The first IPT manual was created using these theoretical principles and published in 1984 [11]. IPT is generally administered over the course of 12–16 weekly sessions and consists of three main phases: the initial phase (1–4 sessions), the middle phase, and the termination phase (the final 2–3 sessions) [12]. The therapist uses the initial phase to diagnose depression and identify how interpersonal difficulties manifest in the individual's depression. They also work with the individual to identify the most prominent interpersonal difficulty, which will be the focus of treatment in the middle phase. Throughout the middle phase of treatment, the therapist employs specific techniques to validate the individual's struggles; teaches them skills to express their emotions and to cope with their difficulties; and helps the individual plan for future interpersonal difficulties. The final, or termination, phase consists of preparing the individual to end IPT, identifying the new skills they have developed for use in future interpersonal difficulties, and celebrating their accomplishments from the process.

In the 1990s, Laura Mufson and colleagues initiated a developmental adaptation of IPT that became known as Interpersonal Psychotherapy for Depressed Adolescents (IPT-A) [13]. The adaptation process involved an increased focus on specific social stressors most relevant to teenagers, such as peer pressure, friendship challenges, and changes in parent–child relationships resulting from new identity explorations [14]. It also included guidelines for addressing environmental experiences relevant to teenagers' interpersonal functioning: life in single-parent families, abusive or neglectful caregiving relationships, school refusal, and involvement with child protective services [15]. Developmental modifications included optional joint sessions with caregivers, greater emphasis on perspective-taking skills, and the use of tools such as mood-rating scales. Like IPT, IPT-A can be administered with or without concurrent medication treatment. IPT-A has shown efficacy similar to other evidence-based psychotherapies (e.g., cognitive behavioral therapy [CBT]) in addressing depressive disorders and other psychiatric conditions among teenagers [16]. IPT-A's time-limited nature and focus on interpersonal improvement often make it especially appealing to adolescent patients [13].

Both IPT and IPT-A target specific problem areas that contribute to and proceed from depression symptoms. These problem areas include grief, role disputes, role transitions, and interpersonal deficits [11,13]. When addressing grief, the therapist provides support for the mourning process and assists the patient in developing strategies to avoid or shift out of atypical reactions. In the case of role disputes, such as disagreements between the patient and a significant person in their life (e.g., spouse, parent), the therapist and patient work together to explore the conflict, identify interpersonal patterns, and improve communication skills. Role transitions include life changes such as losing a job, beginning parenthood, or, for adolescents specifically, beginning a new school or becoming sexually active. If a role transition is identified as the primary problem area, the focus is on assisting the patient in adjusting to the new role and acquiring the necessary skills for a successful transition. Interpersonal deficits include challenges with starting and maintaining relationships, or with social and emotional communication. In addressing interpersonal deficits, the therapist works towards reducing social withdrawal, enhancing relationship quality, improving communication skills, and fostering the development of social support networks.

1.2. Predictors and Mechanisms of Treatment Response

Empirical evidence strongly supports the effectiveness of IPT and IPT-A as treatments for depression [17,18]. However, similar to other evidence-based treatments, IPT does not improve depressive symptoms for a sizeable proportion of patients (30–50%) [17,19]. Given the heterogeneous nature of depression, which has multiple underlying causes, it

is unsurprising that treatments elicit varying responses among adults and adolescents alike [20,21]. Clinicians may use various strategies to optimize treatment outcomes, such as increasing treatment frequency or incorporating approaches from other treatment modalities. They may also consider what treatment might be effective for a specific individual. However, there is currently limited evidence to guide the selection of appropriate evidence-based treatments for patients with depression. As a result, providers often rely on clinical judgment and a trial-and-error process. Unfortunately, poor response to initial treatment options often leads to reduced treatment-seeking behavior in the future [22] and may also damage a person's optimism about treatment utility. Robust algorithms based on clinical data, rather than subjective clinical impressions, could equip clinician–client dyads to select interventions and strategies that are most likely to be effective at treating depression (e.g., [23,24]).

Personalization, also known as precision medicine, may significantly enhance the effectiveness of established interventions by matching individuals with the treatments that are likely to yield the maximum benefits based on patients' personal characteristics, including biological processes [25]. One component of personalization involves identifying and characterizing subgroups of patients who might respond favorably to different treatment approaches. This involves identifying moderators of treatment—that is, patient characteristics that are present prior to treatment, are independent of the type of treatment the patient receives, and have an interactive effect with the type of treatment on outcome [26]. Some of these moderators may be characteristics that one would not expect to change with treatment (e.g., demographic variables), and others reflect processes that could change with and may even be targets for treatment. While it is often assumed that an intervention will be most effective for individuals with the greatest difficulties in the areas targeted by the intervention, known as the compensation model of personalization, this assumption is just one of two positions on treatment personalization. In contrast, the capitalization model proposes that an intervention will be most effective if it builds on the individual's strengths [27]. The first step is often to identify predictors of treatment response. However, for personalization to be effective, different treatments must be rigorously evaluated through randomized controlled trials (RCT) that identify and measure characteristics that, when assessed at baseline, can predict the success of one treatment over another. These may be as diverse as gender, clinical characteristics, performance on a behavioral measure, the magnitude of hormonal fluctuations during stress, or patterns of brain functioning.

Effective personalization also requires an understanding of the mechanisms of depression treatments—that is, what are the underlying processes that occur during each treatment to bring about change? Why and how does each treatment work? All evidence-based therapies propose theoretically grounded mechanisms of action but often lack compelling evidence as to whether the theoretical treatment targets serve as the actual mechanism of action. While most clinical trials have shown that the intervention being studied affects the proposed mechanism of action (e.g., IPT-A produces a significant improvement in adolescents' interpersonal functioning [28]), they have failed to demonstrate that altering the target mechanism results in the intended clinical effect. To provide stronger evidence for a potential causal mechanism, studies must establish that changes in the treatment target (e.g., improved interpersonal relationships) preceded changes in the clinical outcome [29,30]. Identifying treatments' mechanisms of action can further knowledge of personalization in two ways. First, when a treatment target that is known to the field is identified as a treatment's mechanism of action, this can inform guidelines for delivering that treatment to a patient with that treatment target. Second, identifying a treatment's mechanism of action can also lead to the identification of new treatment targets, previously unknown to the field. These new treatment targets can then be evaluated as moderators of treatment outcomes in future trials to determine whether the capitalization or compensation model applies.

With robust knowledge of mechanisms and predictors, clinician–client dyads would have the tools to select the treatments and approaches that are most appropriate for a given patient's disorder process and, based on patient characteristics, are most likely to offer

favorable outcomes. Though there is a small body of work that identifies demographic and clinical predictors of IPT/IPT-A response [31], this review primarily focuses on the biological predictors and mechanisms—including neurological, behavioral, and physiological correlates—of IPT/IPT-A that hold potential in optimizing treatment effectiveness.

2. Methods

For this scoping review, the included articles were clinical trials published in the last two decades that examined IPT/IPT-A and the assessment of a biological predictor or mechanism. Studies published in languages other than English were excluded. Further, studies that were not peer-reviewed journal articles and studies that did not present original data (e.g., literature reviews, editorials) were excluded. Google Scholar, APA PsychInfo, and PubMed were the primary databases searched. Both backward and forward citation strategies were additionally used. Examples of search terms included "IPT", "IPT-A", "biological correlates", "treatment response", "mechanisms", "neuroimaging", "physiological", and "neurological". A total of 7 primary sources were identified (Table 1).

3. Results

3.1. Neurological Correlates of IPT Response

When we consider biological predictors and mechanisms of IPT/IPT-A, an important question arises: Where do we start? Indeed, the array of possible targets that may ultimately serve as predictors or mechanisms of treatment is nearly infinite. Biological correlates of depression alone may include biological changes that take place as an individual's symptoms improve or get worse and biological correlates of stressful interpersonal processes. To assess which processes may be relevant in the context of IPT/IPT-A treatment response, researchers and clinicians can look to the National Institute of Mental Health's Research Domain Criteria (RDoC), a research classification system for mental health disorders based on varying dimensions of neurobiology and behavior [32]. Specifically, when considering processes of change in treating depression, relevant domains that have undergone considerable examination include Negative Valence Systems (e.g., the stress response system) and Cognitive Systems. The Negative Valence System involves heightened responsiveness to negative stimuli and implicates key limbic structures including the amygdala, hippocampus, and insula. Cognitive control deficits typically implicate the prefrontal cortex and are associated with impairments in inhibition, attention, and decision-making processes. These networks are integral in determining salient characteristics of emotion regulation, social functioning, and which inputs warrant attention, particularly when defending the self from threats to social-emotional well-being [33]. So far, cognitive control deficits have yielded valuable insights into the mechanisms underlying depressive symptoms. Additionally, the anterior cingulate cortex (ACC) is part of the limbic system, serving as a critical bridge between cortical and limbic structures involved in detecting conflict and regulating emotions. This region is commonly implicated in depressive disorders and within the context of treatment [34,35].

Neurological research on depression has examined these frontal and limbic regions, both through resting state and task-based analysis (with most studies focusing on brain function rather than structure), and has shown evidence for atypical functioning in and across these regions [33]. However, there is a very limited amount of research that considers neurological predictors of treatment response in a rigorous manner or how common treatments for depression bring about changes in these networks (i.e., mechanisms). Noted below is the available research that focuses on neural, behavioral, and physiological correlates of IPT/IPT-A treatment. Table 1 summarizes the results of the reviewed articles.

In the last two decades, non-invasive magnetic resonance imaging (MRI) technology—suitable for studying the developing brain—has been used to investigate IPT-A predictors. Embedded within the larger SMART study [36], researchers examined a subgroup of teenage participants who voluntarily participated in an additional protocol that considered neuroimaging indexes of brain functioning [37]. Specifically, this sub-analysis examined

neurological systems involved in threat processing as potential predictors of IPT-A response. One area of interest included the ACC, which regulates attention to threats and modulates amygdala responses [38]. In the study, among a group of 15 adolescents diagnosed with depressive disorders, greater baseline activation in the ACC (assessed during an emotion-matching task) and greater baseline resting-state functional connectivity between the amygdala and ACC were associated with greater improvements in depression symptoms [37]. These findings offer preliminary evidence of neurological correlates that may predict IPT-A responders, supporting the capitalization model with regard to these neural markers. However, they do not directly address treatment personalization in terms of favoring one treatment over another. Individuals who benefit from IPT-A may also benefit from other evidence-based treatments such as cognitive-behavioral therapy (CBT) or psychopharmacological interventions. Nonetheless, these initial results stimulate the consideration of alternative avenues, including methodologies and analytic techniques to assess differential responses to a range of treatments, which would be pertinent to the concept of personalization (e.g., [24]).

Research has also explored alterations in brain structure, activation, and connectivity associated with stress system functioning as potential mechanisms of IPT and IPT-A treatment response. Some foundational studies utilizing positron imaging technology examined neural mechanisms of IPT in adults [39,40]. A study by Martin et al. [39] compared cerebral blood flow, a metric of brain metabolism, in 28 adults with depression using sequential single-photon emission computed tomography (SPECT) scans at baseline and after 6 weeks. Participants were randomly assigned to either weekly sessions of IPT or twice-daily doses of the antidepressant venlafaxine hydrochloride, a serotonin and norepinephrine reuptake inhibitor (SNRI), for 6 weeks of treatment. In both treatment groups, depressive symptoms improved, but more so with venlafaxine. However, only the IPT group showed increased metabolism in limbic areas, while both treatments demonstrated increased metabolism in the basal ganglia [39]. Though this study had a small sample size and lacked a control group, it highlights some potential neurological mechanisms underlying IPT, which appear to differ from the mechanisms of some psychotropic medication.

In a similar study by Brody et al. [40], 24 adults with MDD and 16 adult control subjects underwent positron emission tomography (PET) scanning at baseline and after 12 weeks. Between scans, participants with MDD were treated with either paroxetine (a selective serotonin reuptake inhibitor, or SSRI) or IPT, while controls received no treatment. Notably, the MDD participants were not randomly assigned to treatment groups but were assigned based on their personal preferences. Following treatment, paroxetine-treated MDD participants had a greater mean decrease in depressive symptoms (61.4%) than did the MDD participants treated with IPT (38.0%). However, both subgroups showed increases in normalized left temporal lobe metabolism and decreases in left anterior cingulate gyrus metabolism. Both groups also showed decreases in normalized prefrontal cortex metabolism, though bilaterally in paroxetine-treated MDD participants and only in the right in IPT-treated MDD participants [40]. These neural alterations allude to potential mechanisms underlying IPT, which critically occur in regions pertinent to socialization.

Looking beyond IPT as a treatment for depression, a recent study examined neurological correlates of change associated with a revised adaptation of IPT for patients with borderline personality disorder (IPT-BPD-R) [4]. In this study, 43 adults with borderline personality disorder (BPD) were randomly assigned to receive either IPT-BPD-R or be put on a waiting list with clinical management. IPT-BPD-R was administered over the course of 10 months, split into two phases of 22 and 20 sessions. Participants in both groups underwent functional magnetic resonance imaging (fMRI) testing before and after treatment. IPT-BPD-R was shown to be effective in treating BPD symptoms; furthermore, researchers found that the IPT-BPD-R-treated participants showed significantly decreased activity in the right ACC and the right temporoparietal junction [4]. While these results suggest potential mechanisms of change in IPT, they may not be wholly generalizable

to understanding IPT for depression, as mechanisms of MDD and BPD may share some similarities but may also differ in certain regards.

3.2. Behavioral Correlates of IPT Response

To further assess which biological predictors and mechanisms may be relevant in the context of IPT treatment response, one study focused on behavioral indices of executive functioning (EF) that are primarily undergirded by the frontal brain regions. EF encompasses higher-level cognitive processes such as inhibition, attention, goal setting, planning, and organizing. It has been observed that adolescent depression is associated with subtle deficits in EF [41]. In a subsample of the previously noted SMART trial [36], executive functioning was assessed in 25 adolescents aged 12–17 years, utilizing cognitive measures that evaluated cognitive flexibility, inhibitory control, attention, and specific attention networks such as alerting, orienting, and conflict. Supporting the compensatory model, the findings revealed that lower EF as measured prior to the start of the intervention predicted a higher likelihood of early symptom decline and remission upon completing IPT-A treatment [42]. Importantly, social-emotional functioning is directly targeted in IPT-A, as it is often impaired in depression [1], and EF plays a crucial role in social-emotional functioning [43]. While these findings do not provide evidence that would aid in the goal of treatment selection per se, these preliminary findings offer evidence that EF may serve as a potential predictor of favorable outcomes in IPT-A, highlighting the need for further research to dive deeper into this relationship. Also, the enhanced feasibility of administering behavioral tasks (e.g., compared to MRI) for the purpose of treatment selection is potentially advantageous. Notably, no studies to date examine whether EF changes while receiving treatment, so it is unclear whether it also acts as a mechanism, which may be apt for future work to consider.

3.3. Physiological Correlates of IPT Response

Understanding how brain and body systems operate during stressful interpersonal interactions and emotional experiences may provide valuable insights into the underlying mechanisms of mental health challenges and therapeutic progress. The exploration of physiological systems has indeed yielded valuable insights into the mechanisms underlying depressive symptoms, though there is room to expand our research to explore these mechanisms in the context of therapeutic interventions. Extant literature largely focuses on the hypothalamic–pituitary–adrenal (HPA) axis, which plays a pivotal role in the body's stress response system, releases hormones that regulate stress and emotions, and often interacts with frontolimbic regions of the brain. Dysregulation of the HPA axis has been consistently associated with mood disorders. For example, adults with depression have been found to show heightened arousal in the HPA axis [44–46], a pattern also evident in adolescents with depression [47,48]. Notably, this altered stress sensitivity has even been observed prior to the onset of the first depressive episode [49]. The HPA axis is crucial for the regulation of basal body function and survival in the face of external threats [50]. In response to an external stressor, interactions among cortico-limbic regions of the brain culminate in the release of cortisol, a glucocorticoid hormone, from the adrenal glands. The release of cortisol, via a cascade of biochemical interactions, activates the paraventricular nucleus, hippocampus, and medial prefrontal cortex, which in turn down-regulate activity in the HPA axis [51]. Together, these regions facilitate the integration of the physical and cognitive resources required to manage the environmental threat.

There is reason to believe that the HPA axis is particularly relevant to mental health outcomes during adolescence. Social stress is known to trigger the activation of the HPA axis, evidenced by physiological changes such as an increase in cortisol production [52]. Within the daily lives of adolescents, social stress can arise from various interpersonal difficulties, including those addressed in IPT-A (e.g., peer pressure, friendship challenges, and changes in parent–child relationships resulting from new identity exploration; [14]). Adolescents with depression tend to exhibit elevated cortisol levels in response to a social

stressor compared to their non-depressed peers [52]. This underscores the HPA axis's significant role in adolescent depression, particularly in response to social stressors, and therefore, the potential importance of this system in mechanism and prediction research.

While no studies have directly compared HPA axis functioning before and after IPT treatment for depression (i.e., examining HPA axis functioning as a mechanism of change in reducing depressive symptoms), there is some evidence suggesting it predicts treatment response. One study examined cortisol levels during parent–adolescent conflict as a predictor of treatment response to IPT-A [53]. The study included 15 adolescents (ages 12–17) diagnosed with depression, primarily from low-income Latine families. They were randomly assigned to receive either standard IPT-A or IPT-A with enhanced parental involvement. Prior to treatment initiation, salivary cortisol samples were collected before, during, and after a conflict discussion between parents and adolescents. This method of social stress induction is likely to be ecologically valid compared to other paradigms (e.g., Trier Social Stress Test; [52]), given that parent–adolescent conflict is common during this developmental stage and has been linked to the development and recurrence of depression in youth [54]. The study reported that high cortisol levels were associated with more severe pre-treatment depression and predicted greater improvements in depressive symptoms following IPT-A treatment, suggesting that cortisol responses to social stress align with compensatory models of treatment response. Despite the limitations of this study, such as the small sample size and restricted focus on parent–adolescent conflict, these results suggest a potential predictor of treatment response, while also implicating the HPA axis as a critical mechanism of action in IPT-A. Future research should further explore the role of the HPA axis throughout the course of IPT-A treatment, potentially by measuring cortisol levels in response to specific social or interpersonal stressors.

One study compared pre- and post-treatment cortisol levels (in response to a cognitive stressor) in adult women who were victims of intimate partner violence [55]. Fifty adult women were randomly assigned to receive either Acceptance and Commitment Therapy (ACT) or IPT, which was adapted to focus on women's empowerment. Compared to their baseline levels, both the IPT and ACT groups showed decreased cortisol levels in response to a cognitive stressor post-treatment [55]. This supports the idea that HPA axis functioning may be a critical mechanism of change in psychotherapies, including IPT. A notable strength of this study was the RCT, and while the mechanisms of ACT and IPT may prove to be similar, larger studies would be required to provide convincing evidence of the null hypothesis.

Table 1. Biological correlates of IPT: review of results.

Study	Correlate	System/Region/ Function	Context of Treatment Response	Participants	Study Design	Results
Klimes-Dougan et al., 2022 [36]	Neurological	MRI: Anterior cingulate cortex, amygdala	Predictor	n = 15 adolescents with depression	Random assignment to early or late decision points for determining treatment responsiveness; if non-responsive, random assignment to either the addition of fluoxetine or more IPT-A sessions.	Greater baseline activation in the ACC and greater baseline resting-state functional connectivity between the amygdala and ACC were associated with greater improvements in depression symptoms following IPT-A.

Table 1. *Cont.*

Study	Correlate	System/Region/ Function	Context of Treatment Response	Participants	Study Design	Results
Martin et al., 2001 [39]	Neurological	PET: Brain metabolism in the limbic region and basal ganglia	Mechanism	*n* = 28 adults with depression	Random assignment to either IPT or venlafaxine hydrochloride for 6 weeks.	Depressive symptoms improved in both treatment groups (IPT or antidepressant) but more so in the antidepressant group. IPT group showed increased metabolism in the limbic region, while both treatments demonstrated increased metabolism in the basal ganglia.
Brody et al., 2001 [40]	Neurological	PET: Brain metabolism in temporal lobe, anterior cingulate gyrus, prefrontal cortex	Mechanism	*n* = 24 adults with depression, N = 16 adult controls	Patient preference-based assignment to either IPT or paroxetine for 12 weeks.	Depressive symptoms improved in both treatment groups (IPT or antidepressant) but more so in the antidepressant group. Both groups showed changes in metabolism.
Bozzatello et al., 2021 [4]	Neurological	fMRI: Anterior cingulate cortex, temporopari-etal junction	Mechanism	*n* = 43 adults with borderline personality disorder	Participants were randomly assigned to receive either IPT-BPD-R or be put on a waiting list with clinical management.	Compared to the waitlist group, participants treated with IPT-BPD-R showed decreased activity in the right anterior cingulate cortex and right temporoparietal junction.
Wagner et al., 2022 [42]	Behavioral	Executive functioning	Predictor	*n* = 25 adolescents with depression	Random assignment to early or late decision points for determining treatment responsiveness; if non-responsive, random assignment to either the addition of fluoxetine or more IPT-A sessions.	Lower baseline executive functioning predicted a higher likelihood of early symptom decline and remission upon completing IPT-A.

Table 1. *Cont.*

Study	Correlate	System/Region/ Function	Context of Treatment Response	Participants	Study Design	Results
Gunlicks-Stoessel et al., 2013 [53]	Physiological	HPA axis	Predictor	n = 15 adolescents with depression	Random assignment to early or late decision points for determining treatment responsiveness; if non-responsive, random assignment to either the addition of fluoxetine or more IPT-A sessions.	High HPA axis activation predicted greater improvements in depressive symptoms following IPT-A.
Cerda-Molina & Biagini-Alarcón, 2023 [55]	Physiological	HPA axis	Mechanism	n = 50 adult women who were victims of domestic violence	Random assignment to either IPT or Acceptance Commitment Therapy.	Both treatment groups showed decreased HPA axis activation following treatment

Notes: Studies are listed in the order they are presented throughout the review. ACC: Anterior Cingulate Cortex. IPT: Interpersonal psychotherapy. IPT-A: Interpersonal psychotherapy for depressed adolescents. IPT-BPD-R: Revised Interpersonal Psychotherapy for patients with borderline personality disorder. HPA axis: Hypothalamic–Pituitary–Adrenal axis; MRI: Magnetic Resonance Imaging; PET: Positron Emission Tomography; fMRI: functional Magnetic Resonance Imaging.

4. Discussion

The extant literature on IPT and IPT-A supports its efficacy and effectiveness in treating depression among adults and adolescents by addressing social dysfunction and interpersonal stressors. However, the current understanding of the biological predictors and mechanisms by which IPT/IPT-A reduces depressive symptoms remains limited, and more research exploring these questions is needed. Additionally, the work that has been conducted typically involves small sample sizes, often without a comparison group.

Fortunately, it appears that some momentum is building, as many reviewed articles here were published in the last 5 years (which is especially notable considering that most of the seminal IPT/IPT-A efficacy studies were conducted over two decades ago, e.g., [2,14]). Some preliminary evidence suggests that biological factors, including brain structure and connectivity, behavioral manifestations of brain functioning (executive functioning), and HPA axis functioning may all be relevant predictors of treatment response. Furthermore, some potential mechanisms of changes underlying IPT/IPT-A treatment response have been identified, such as changes in the neural activity and metabolism of limbic regions, as well as decreased HPA axis reactivity. These initial findings provide direction for what future research may evaluate as moderators of treatment outcomes. Treatment research should further examine whether these potential moderators pertain to compensation or capitalization models of personalization. The field will benefit from future studies being modeled after larger-scaled RCTs (e.g., [56]). While this field of research is yet in its infancy, there are promising glimpses of how this line of inquiry may benefit those who are suffering from depression and other psychological problems.

The reviewed literature provided some evidence that is beneficial for a foundational understanding of predictors and mechanisms of treatment response. The array of potential biological factors to consider is exceedingly vast, so perhaps it is surprising that the handful of studies to date have yielded any notable findings. Given the extent of potentially perti-

nent biological factors, researchers may find guidance in the RDoC framework, as there are more avenues to examine. For example, most research considers measures relevant to Negative Valence and Cognitive Domains. Social Processes and Positive Valence systems may also be highly relevant to depression, particularly when considering interpersonal aspects of depression; there is evidence of reward-system dysfunction in adolescents with depression, which has been proposed to generate interpersonal stress [34,57]. Additionally, most studies using the HPA axis have considered stress-reactive activation patterns. There is some emerging evidence, too, to suggest patterns of diurnal activation—the daily circadian rhythm of the HPA axis can also be dysregulated in depression; for example, a study found that children with depression and a history of maltreatment had lower morning cortisol levels and showed a rise in levels throughout the day, rather than the expected pattern of higher morning cortisol levels that decrease throughout the day [58]. Therefore, examining diurnal cortisol in the context of IPT/IPT-A may be an important direction. Also, considering the interplay between these various systems is crucial. Promising approaches include employing a multilevel analysis approach that has been used with adolescents as well as adults (e.g., [59,60]). Future work using multilevel analysis could further benefit from implementing innovative methodologies to better address personalization. For example, a recent study used machine-learning techniques to develop an algorithm that successfully identified adolescents with depression who responded favorably to specific types of treatments [24].

Much of the extant literature we reviewed focuses on either predictors of treatment response or mechanisms underlying change throughout IPT/IPT-A, rather than both. Though these are two distinct concepts, predictors may offer insights into potential mechanisms. Future work should assess change in these predictors throughout administrations of IPT/IPT-A to assess whether they reveal mechanisms of treatment. Of note, although some mechanisms and predictors of treatment response may remain consistent across the lifespan, there are biological differences between adolescents and adults that may cause recovery processes to vary by developmental stage.

Embedding this literature within a developmental framework is important when considering the biological processes across the lifespan and should be considered in future research. Importantly, adolescence is both a time of risk and of opportunity. Adolescence, marked by neural plasticity, is characterized by rapid shifts in brain development and interactions with the environment that can amplify risk or resilience factors [61]. Interpersonal stress, highly influential in shaping psychological outcomes during adolescence, coincides with increased cognitive and emotional demands as youths navigate rewards and threats in their environment [62–65]. Through IPT-A, adolescents may develop skills to manage and cope with interpersonal stress, reducing depression severity. Furthermore, leveraging neuroplasticity and neurogenesis during this phase can potentially prevent future mental health issues. The biological continuum of brain development extends into adulthood, where notable changes persist; neurogenesis, though it declines with age, reflects the adult brain's continuing plasticity [66].

Given that the focus of IPT/IPT-A is on interpersonal functioning, considerations of developmental social context are also paramount. Accordingly, the common themes that need to be addressed as potential threats to the self may vary by patients' developmental stages. IPT-A holds appeal for teenagers, as it aligns with their increasing emphasis on peer relationships—and decreasing time spent with caregivers—and provides tools to navigate interpersonal challenges, building up protective and promotive factors [67,68]. Interpersonal dynamics evolve as individuals move through adulthood as well; while social networks may shrink, the quality of remaining relationships typically improves, influenced by strategies that optimize positivity and minimize conflicts [69–72]. Despite these improvements, older adults encounter unique challenges, such as grief or role transitions like retirement or relocation, necessitating continued consideration of mental health interventions. Learning more about how these common interpersonal stressors are processed in

the brain in the body will provide a better understanding of possible biological mechanisms of treatment.

A greater array of treatments will need to be considered in the future. As with other evidence-based treatments, investigating the interplay between IPT/IPT-A and medications may offer valuable insights into the benefits of combination therapies for individuals with depression and support more successful personalization. Furthermore, comparative studies between IPT/IPT-A and other interventions are also essential for improving treatment choice and personalization. Many of the reviewed findings provide preliminary evidence of predictors of favorable response to IPT/IPT-A. However, without comparing IPT/IPT-A to other treatment modalities, it remains unclear who will most benefit from one treatment approach over another. This literature review reveals the need for more RCTs that directly compare IPT/IPT-A against other well-validated psychotherapeutic or psychopharmacological interventions for optimizing treatment outcomes. While moderate-scale RCTs have yet to be employed for IPT research, Helen Mayberg's team has found that CBT and escitalopram (an SSRI) are associated with post-treatment differences in glucose metabolism in cingulate and limbic structures of the brain (e.g., insula, amygdala) [73], providing evidence that these methodologies are feasible for IPT/IPT-A and other forms of psychotherapy. Moreover, RCTs have been used to examine the effects of other psychotherapies, such as CBT, on the HPA axis; for example, some RCTs showed that participants who completed treatment had differences in cortisol levels (in response to a stressor) compared to the waitlist groups [74–76]. It will also be important to continue advancing the line of evidence by Bozzatello et al. [4] by addressing questions of whether biological mechanisms are similar across different forms of psychotherapy. Furthermore, there is a paucity of studies exploring the effectiveness of IPT or IPT-A in combination with medication. However, in the previously noted SMART trial [36], different treatment plans for insufficient responders were implemented by augmenting IPT-A with either increased therapy frequency (twice per week) or adding fluoxetine. The results demonstrated that both augmentation methods were similarly effective. Given that monotherapy is less frequently employed for those with moderate or severe depression, the next step to consider is identifying biological correlates of combination therapy, such as IPT/IPT-A in combination with medication.

Considering other methods to optimize treatment for depression is promising. Indeed, there are a multitude of approaches to consider. Continuing to examine demographic and psychosocial, as well as biological predictors, is warranted. Increasing the dose of standard treatment schedules may also be useful [36]. Additionally, cultural adaptations will undoubtedly be needed to most effectively treat those with depression using IPT/IPT-A. This process is already underway, with global efficacy studies having been conducted in several countries outside of the United States, such as Taiwan and Uganda [77]. However, much more work is needed to keep up with the increasing drive for cultural adaptation within mental health interventions. Finally, IPT/IPT-A may have especially relevant clinical utility due to recent dramatic societal shifts such as the COVID-19 pandemic and global patterns of forced displacement due to the intensification of climate threats, economic shocks, and armed conflict. Continuing research that seeks to understand the processes underlying IPT/IPT-A is especially critical to address these changing social landscapes.

5. Conclusions

IPT and IPT-A, already well-supported as effective treatments for adolescents and adults with depression, can be further improved through research that uses biomarkers to evaluate the mechanisms and predictors associated with treatment response. Extant literature suggests that differences in brain structure and connectivity, executive functioning, and HPA axis activation may be especially important markers of treatment response, though more research is warranted. Conducting randomized controlled trials with larger and more diverse samples can strengthen the evidence base and guide more personalized and effective treatment approaches for individuals with depression. Continued research in the field of IPT/IPT-A holds significant promise for advancing mental healthcare for

adult and adolescent individuals, enhancing their well-being and resilience in the face of depression and its related interpersonal challenges.

Author Contributions: Conceptualization, B.K.-D., H.H., K.R., M.G.-S. and V.P.; methodology, V.P.; writing—original draft preparation, B.K.-D., H.H. and V.P.; writing—review and editing, B.K.-D., H.H., K.R., M.G.-S. and V.P. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Hirschfeld, R.M.; Montgomery, S.A.; Keller, M.B.; Kasper, S.; Schatzberg, A.F.; Möller, H.J.; Healy, D.; Baldwin, D.; Humble, M.; Versiani, M.; et al. Social Functioning in Depression: A Review. *J. Clin. Psychiatry* **2000**, *61*, 268–275. [CrossRef] [PubMed]
2. de Mello, M.F.; de Jesus Mari, J.; Bacaltchuk, J.; Verdeli, H.; Neugebauer, R. A Systematic Review of Research Findings on the Efficacy of Interpersonal Therapy for Depressive Disorders. *Eur. Arch. Psychiatry Clin. Neurosci.* **2005**, *255*, 75–82. [CrossRef]
3. Barth, J.; Munder, T.; Gerger, H.; Nüesch, E.; Trelle, S.; Znoj, H.; Jüni, P.; Cuijpers, P. Comparative Efficacy of Seven Psychotherapeutic Interventions for Patients with Depression: A Network Meta-Analysis. *Focus* **2016**, *14*, 229–243. [CrossRef] [PubMed]
4. Bozzatello, P.; Morese, R.; Valentini, M.C.; Rocca, P.; Bellino, S. How Interpersonal Psychotherapy Changes the Brain: A Study of fMRI in Borderline Personality Disorder. *J. Clin. Psychiatry* **2021**, *83*, 38075. [CrossRef] [PubMed]
5. Goldstein, T.R.; Fersch-Podrat, R.; Axelson, D.A.; Gilbert, A.; Hlastala, S.A.; Birmaher, B.; Frank, E. Early Intervention for Adolescents at High Risk for the Development of Bipolar Disorder: Pilot Study of Interpersonal and Social Rhythm Therapy (IPSRT). *Psychotherapy* **2014**, *51*, 180–189. [CrossRef] [PubMed]
6. Graf, E.P.; Markowitz, J.C. Interpersonal Psychotherapy for Posttraumatic Stress Disorder (PTSD). In *Casebook Interpers*; Oxford University Press: Oxford, UK, 2012.
7. Lipsitz, J.D.; Markowitz, J.C. Mechanisms of Change in Interpersonal Therapy (IPT). *Clin. Psychol. Rev.* **2013**, *33*, 1134–1147. [CrossRef] [PubMed]
8. Etkin, A.; Pittenger, C.; Polan, H.J.; Kandel, E.R. Toward a Neurobiology of Psychotherapy: Basic Science and Clinical Applications. *J. Neuropsychiatry Clin. Neurosci.* **2005**, *17*, 145–158. [CrossRef]
9. Trifu, S.C.; Trifu, A.C.; Aluaş, E.; Tătaru, M.A.; Costea, R.V. Brain Changes in Depression. *Rom. J. Morphol. Embryol.* **2020**, *61*, 361–370. [CrossRef]
10. Weissman, M.M. A Brief History of Interpersonal Psychotherapy. *Psychiatr. Ann.* **2006**, *36*, 553–557.
11. Klerman, G.L.; Weissman, M.M.; Rounsaville, B.J.; Chevron, E.S. *Interpersonal Psychotherapy of Depression 1984 New York*; Basic Books: New York, NY, USA, 1984.
12. Markowitz, J.C.; Weissman, M.M. Interpersonal Psychotherapy: Principles and Applications. *World Psychiatry* **2004**, *3*, 136–139.
13. Mufson, L. *Interpersonal Psychotherapy for Depressed Adolescents*; Guilford Press: New York, NY, USA, 2004.
14. Mufson, L.; Weissman, M.M.; Moreau, D.; Garfinkel, R. Efficacy of Interpersonal Psychotherapy for Depressed Adolescents. *Arch. Gen. Psychiatry* **1999**, *56*, 573–579. [CrossRef] [PubMed]
15. Russ, S.W.; Ollendick, T.H. *Handbook of Psychotherapies with Children and Families*; Springer Science & Business Media: Berlin/Heidelberg, Germany, 2013.
16. Eckshtain, D.; Kuppens, S.; Ugueto, A.; Ng, M.Y.; Vaughn-Coaxum, R.; Corteselli, K.; Weisz, J.R. Meta-Analysis: 13-Year Follow-up of Psychotherapy Effects on Youth Depression. *J. Am. Acad. Child Adolesc. Psychiatry* **2020**, *59*, 45–63. [CrossRef] [PubMed]
17. Cuijpers, P.; Geraedts, A.S.; van Oppen, P.; Andersson, G.; Markowitz, J.C.; van Straten, A. Interpersonal Psychotherapy for Depression: A Meta-Analysis. *Am. J. Psychiatry* **2011**, *168*, 581–592. [CrossRef]
18. David-Ferdon, C.; Kaslow, N.J. Evidence-Based Psychosocial Treatments for Child and Adolescent Depression. *J. Clin. Child Adolesc. Psychol.* **2008**, *37*, 62–104. [CrossRef]
19. Mufson, L.H.; Dorta, K.P.; Olfson, M.; Weissman, M.M.; Hoagwood, K. Effectiveness Research: Transporting Interpersonal Psychotherapy for Depressed Adolescents (IPT-A) from the Lab to School-Based Health Clinics. *Clin. Child Fam. Psychol. Rev.* **2004**, *7*, 251–261. [CrossRef]
20. Cuijpers, P.; Karyotaki, E.; Weitz, E.; Andersson, G.; Hollon, S.D.; van Straten, A. The Effects of Psychotherapies for Major Depression in Adults on Remission, Recovery and Improvement: A Meta-Analysis. *J. Affect. Disord.* **2014**, *159*, 118–126. [CrossRef] [PubMed]

21. Curry, J.; Rohde, P.; Simons, A.; Silva, S.; Vitiello, B.; Kratochvil, C.; Reinecke, M.; Feeny, N.; Wells, K.; Pathak, S.; et al. Predictors and Moderators of Acute Outcome in the Treatment for Adolescents with Depression Study (TADS). *J. Am. Acad. Child Adolesc. Psychiatry* **2006**, *45*, 1427–1439. [CrossRef]
22. Simon, G.E.; Perlis, R.H. Personalized Medicine for Depression: Can We Match Patients with Treatments? *Am. J. Psychiatry* **2010**, *167*, 1445–1455. [CrossRef]
23. Grove, W.M.; Zald, D.H.; Lebow, B.S.; Snitz, B.E.; Nelson, C. Clinical versus Mechanical Prediction: A Meta-Analysis. *Psychol. Assess.* **2000**, *12*, 19–30. [CrossRef]
24. Gunlicks-Stoessel, M.; Klimes-Dougan, B.; VanZomeren, A.; Ma, S. Developing a Data-Driven Algorithm for Guiding Selection between Cognitive Behavioral Therapy, Fluoxetine, and Combination Treatment for Adolescent Depression. *Transl. Psychiatry* **2020**, *10*, 321. [CrossRef]
25. Ng, M.Y.; Weisz, J.R. Personalizing Evidence-Based Psychotherapy for Children and Adolescents in Clinical Care. In *Evidence-Based Psychotherapies for Children and Adolescents*, 3rd ed.; Guilford Press: New York, NY, USA, 2018; Volume 3, pp. 501–519.
26. Kraemer, H.C.; Wilson, G.T.; Fairburn, C.G.; Agras, W.S. Mediators and Moderators of Treatment Effects in Randomized Clinical Trials. *Arch. Gen. Psychiatry* **2002**, *59*, 877–883. [CrossRef] [PubMed]
27. Rude, S.S.; Rehm, L.P. Response to Treatments for Depression: The Role of Initial Status on Targeted Cognitive and Behavioral Skills. *Clin. Psychol. Rev.* **1991**, *11*, 493–514. [CrossRef]
28. Mufson, L.; Dorta, K.P.; Wickramaratne, P.; Nomura, Y.; Olfson, M.; Weissman, M.M. A Randomized Effectiveness Trial of Interpersonal Psychotherapy forDepressed Adolescents. *Arch. Gen. Psychiatry* **2004**, *61*, 577–584. [CrossRef] [PubMed]
29. Kazdin, A.E.; Nock, M.K. Delineating Mechanisms of Change in Child and Adolescent Therapy: Methodological Issues and Research Recommendations. *J. Child Psychol. Psychiatry* **2003**, *44*, 1116–1129. [CrossRef]
30. Kazdin, A.E. Mediators and Mechanisms of Change in Psychotherapy Research. *Annu. Rev. Clin. Psychol.* **2007**, *3*, 1–27. [CrossRef]
31. Carter, J.D.; Crowe, M.T.; Jordan, J.; McIntosh, V.V.W.; Frampton, C.; Joyce, P.R. Predictors of Response to CBT and IPT for Depression; the Contribution of Therapy Process. *Behav. Res. Ther.* **2015**, *74*, 72–79. [CrossRef] [PubMed]
32. Cuthbert, B.N.; Insel, T.R. Toward the Future of Psychiatric Diagnosis: The Seven Pillars of RDoC. *BMC Med.* **2013**, *11*, 126. [CrossRef]
33. Kaiser, R.H.; Andrews-Hanna, J.R.; Wager, T.D.; Pizzagalli, D.A. Large-Scale Network Dysfunction in Major Depressive Disorder: A Meta-Analysis of Resting-State Functional Connectivity. *JAMA Psychiatry* **2015**, *72*, 603–611. [CrossRef]
34. Pizzagalli, D.A. Frontocingulate Dysfunction in Depression: Toward Biomarkers of Treatment Response. *Neuropsychopharmacology* **2010**, *36*, 183–206. [CrossRef]
35. Corrigan, F.M. Psychotherapy as Assisted Homeostasis: Activation of Emotional Processing Mediated by the Anterior Cingulate Cortex. *Med. Hypotheses* **2004**, *63*, 968–973. [CrossRef]
36. Gunlicks-Stoessel, M.; Mufson, L.; Bernstein, G.; Westervelt, A.; Reigstad, K.; Klimes-Dougan, B.; Cullen, K.; Murray, A.; Vock, D. Critical Decision Points for Augmenting Interpersonal Psychotherapy for Depressed Adolescents: A Pilot Sequential Multiple Assignment Randomized Trial. *J. Am. Acad. Child Adolesc. Psychiatry* **2019**, *58*, 80–91. [CrossRef] [PubMed]
37. Klimes-Dougan, B.; Başgöze, Z.; Mueller, B.; Wiglesworth, A.; Carosella, K.A.; Westlund Schreiner, M.; Bortnova, A.; Reigstad, K.; Cullen, K.R.; Gunlicks-Stoessel, M. Structural and Functional Neural Correlates of Treatment Response for Interpersonal Psychotherapy for Depressed Adolescents. *J. Clin. Med. Res.* **2022**, *11*, 1878. [CrossRef] [PubMed]
38. Bishop, S.; Duncan, J.; Brett, M.; Lawrence, A.D. Prefrontal Cortical Function and Anxiety: Controlling Attention to Threat-Related Stimuli. *Nat. Neurosci.* **2004**, *7*, 184–188. [CrossRef] [PubMed]
39. Martin, S.D.; Martin, E.; Rai, S.S.; Richardson, M.A.; Royall, R. Brain Blood Flow Changes in Depressed Patients Treated with Interpersonal Psychotherapy or Venlafaxine Hydrochloride: Preliminary Findings. *Arch. Gen. Psychiatry* **2001**, *58*, 641–648. [CrossRef] [PubMed]
40. Brody, A.L.; Saxena, S.; Stoessel, P.; Gillies, L.A.; Fairbanks, L.A.; Alborzian, S.; Phelps, M.E.; Huang, S.C.; Wu, H.M.; Ho, M.L.; et al. Regional Brain Metabolic Changes in Patients with Major Depression Treated with Either Paroxetine or Interpersonal Therapy: Preliminary Findings. *Arch. Gen. Psychiatry* **2001**, *58*, 631–640. [CrossRef]
41. Klimes-Dougan, B.; Garber, J. Regulatory Control and Depression in Adolescents: Findings from Neuroimaging and Neuropsychological Research. *J. Clin. Child Adolesc. Psychol.* **2016**, *45*, 1–5. [CrossRef] [PubMed]
42. Wagner, A.C.; Ozturk, S.; Thai, M.; Westervelt, A.; Reigstad, K.; Cullen, K.R.; Gunlicks-Stoessel, M.; Klimes-Dougan, B. Executive Functioning as a Predictor of Response to Interpersonal Psychotherapy in Adolescents with Depression: A Pilot Study. *J. Affect. Disord. Rep.* **2022**, *10*, 100376. [CrossRef]
43. Riggs, N.R.; Jahromi, L.B.; Razza, R.P.; Dillworth-Bart, J.E.; Mueller, U. Executive Function and the Promotion of Social–emotional Competence. *J. Appl. Dev. Psychol.* **2006**, *27*, 300–309. [CrossRef]
44. Chrousos, G.P.; Gold, P.W. The Concepts of Stress and Stress System Disorders. Overview of Physical and Behavioral Homeostasis. *JAMA* **1992**, *267*, 1244–1252. [CrossRef]
45. Belvederi Murri, M.; Prestia, D.; Mondelli, V.; Pariante, C.; Patti, S.; Olivieri, B.; Arzani, C.; Masotti, M.; Respino, M.; Antonioli, M.; et al. The HPA Axis in Bipolar Disorder: Systematic Review and Meta-Analysis. *Psychoneuroendocrinology* **2016**, *63*, 327–342. [CrossRef]
46. Pariante, C.M.; Lightman, S.L. The HPA Axis in Major Depression: Classical Theories and New Developments. *Trends Neurosci.* **2008**, *31*, 464–468. [CrossRef]

47. Guerry, J.D.; Hastings, P.D. In Search of HPA Axis Dysregulation in Child and Adolescent Depression. *Clin. Child Fam. Psychol. Rev.* **2011**, *14*, 135–160. [CrossRef]
48. Klimes-Dougan, B.; Begnel, E.; Almy, B.; Thai, M.; Schreiner, M.W.; Cullen, K.R. Hypothalamic-Pituitary-Adrenal Axis Dysregulation in Depressed Adolescents with Non-Suicidal Self-Injury. *Psychoneuroendocrinology* **2019**, *102*, 216–224. [CrossRef] [PubMed]
49. Wichers, M.; Geschwind, N.; Jacobs, N.; Kenis, G.; Peeters, F.; Derom, C.; Thiery, E.; Delespaul, P.; van Os, J. Transition from Stress Sensitivity to a Depressive State: Longitudinal Twin Study. *Br. J. Psychiatry* **2009**, *195*, 498–503. [CrossRef] [PubMed]
50. Selye, H. Forty Years of Stress Research: Principal Remaining Problems and Misconceptions. *Can. Med. Assoc. J.* **1976**, *115*, 53–56. [PubMed]
51. Herman, J.P.; Cullinan, W.E. Neurocircuitry of Stress: Central Control of the Hypothalamo–pituitary–adrenocortical Axis. *Trends Neurosci.* **1997**, *20*, 78–84. [CrossRef] [PubMed]
52. Kirschbaum, C.; Pirke, K.-M.; Hellhammer, D.H. The "Trier Social Stress Test"—A Tool for Investigating Psychobiological Stress Responses in a Laboratory Setting. *Neuropsychobiology* **1993**, *28*, 76–81. [CrossRef] [PubMed]
53. Gunlicks-Stoessel, M.; Mufson, L.; Cullen, K.R. A Pilot Study of Depressed Adolescents' Cortisol Patterns during Parent–adolescent Conflict and Response to Interpersonal Psychotherapy (IPT-A). *J. Affect. Disord.* **2013**, *150*, 1125–1128. [CrossRef] [PubMed]
54. Sander, J.B.; McCarty, C.A. Youth Depression in the Family Context: Familial Risk Factors and Models of Treatment. *Clin. Child Fam. Psychol. Rev.* **2005**, *8*, 203–219. [CrossRef]
55. Cerda-Molina, A.L.; Biagini-Alarcón, M. Comparison of Two Psychotherapies in Cortisol Response and Their Efficacy in Reducing Symptoms of Anxiety and Depression in Women Victims of Intimate Partner Violence. *Salud* **2023**, *46*, 137–146.
56. Williams, L.M.; Rush, A.J.; Koslow, S.H.; Wisniewski, S.R.; Cooper, N.J.; Nemeroff, C.B.; Schatzberg, A.F.; Gordon, E. International Study to Predict Optimized Treatment for Depression (iSPOT-D), a Randomized Clinical Trial: Rationale and Protocol. *Trials* **2011**, *12*, 4. [CrossRef] [PubMed]
57. Auerbach, R.P.; Admon, R.; Pizzagalli, D.A. Adolescent Depression: Stress and Reward Dysfunction. *Harv. Rev. Psychiatry* **2014**, *22*, 139–148. [CrossRef]
58. Hart, J.; Gunnar, M.; Cicchetti, D. Altered Neuroendocrine Activity in Maltreated Children Related to Symptoms of Depression. *Dev. Psychopathol.* **1996**, *8*, 201–214. [CrossRef]
59. Williams, L.M.; Phillips, M.L.; Brammer, M.J.; Skerrett, D.; Lagopoulos, J.; Rennie, C.; Bahramali, H.; Olivieri, G.; David, A.S.; Peduto, A.; et al. Arousal Dissociates Amygdala and Hippocampal Fear Responses: Evidence from Simultaneous fMRI and Skin Conductance Recording. *Neuroimage* **2001**, *14*, 1070–1079. [CrossRef] [PubMed]
60. Klimes-Dougan, B.; Westlund Schreiner, M.; Thai, M.; Gunlicks-Stoessel, M.; Reigstad, K.; Cullen, K.R. Neural and Neuroendocrine Predictors of Pharmacological Treatment Response in Adolescents with Depression: A Preliminary Study. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2018**, *81*, 194–202. [CrossRef] [PubMed]
61. Wiglesworth, A.; Fiecas, M.B.; Xu, M.; Neher, A.T.; Padilla, L.; Carosella, K.A.; Roediger, D.J.; Mueller, B.A.; Luciana, M.; Klimes-Dougan, B.; et al. Sex and Age Variations in the Impact of Puberty on Cortical Thickness and Associations with Internalizing Symptoms and Suicidal Ideation in Early Adolescence. *Dev. Cogn. Neurosci.* **2023**, *59*, 101195. [CrossRef]
62. Owens, S.A.; Helms, S.W.; Rudolph, K.D.; Hastings, P.D.; Nock, M.K.; Prinstein, M.J. Interpersonal Stress Severity Longitudinally Predicts Adolescent Girls' Depressive Symptoms: The Moderating Role of Subjective and HPA Axis Stress Responses. *J. Abnorm. Child Psychol.* **2019**, *47*, 895–905. [CrossRef]
63. Rudolph, K.D. Gender Differences in Emotional Responses to Interpersonal Stress during Adolescence. *J. Adolesc. Health* **2002**, *30* (Suppl. 4), 3–13. [CrossRef]
64. Casey, B.J.; Getz, S.; Galvan, A. The Adolescent Brain. *Dev. Rev.* **2008**, *28*, 62–77. [CrossRef]
65. Ernst, M.; Pine, D.S.; Hardin, M. Triadic Model of the Neurobiology of Motivated Behavior in Adolescence. *Psychol. Med.* **2006**, *36*, 299–312. [CrossRef]
66. Galvan, V.; Jin, K. Neurogenesis in the Aging Brain. *Clin. Interv. Aging* **2007**, *2*, 605–610. [CrossRef] [PubMed]
67. Hartup, W.W. Social Relationships and Their Developmental Significance. *Am. Psychol.* **1989**, *44*, 120–126. [CrossRef]
68. Bowker, J.C.; Weingarten, J. Temporal Approaches to the Study of Friendship: Understanding the Developmental Significance of Friendship Change during Childhood and Adolescence. *Adv. Child Dev. Behav.* **2022**, *63*, 249–272. [CrossRef]
69. Cumming, E.; Henry, W.E. *Growing Old: The Process of Disengagement*; Basic Books: New York, NY, USA, 1961.
70. Fingerman, K.L.; Hay, E.L.; Birditt, K.S. The Best of Ties, the Worst of Ties: Close, Problematic, and Ambivalent Social Relationships. *J. Marriage Fam.* **2004**, *66*, 792–808. [CrossRef]
71. Fingerman, K.L.; Turiano, N.A.; Davis, E.; Charles, S.T. Social and Emotional Development in Adulthood. In *Gerontology: Perspectives and Issues*; Springer: Berlin/Heidelberg, Germany, 2013; pp. 127–148.
72. Luong, G.; Charles, S.T.; Fingerman, K.L. Better with Age: Social Relationships Across Adulthood. *J. Soc. Pers. Relat.* **2011**, *28*, 9–23. [CrossRef] [PubMed]
73. Mayberg, H.S.; Brannan, S.K.; Mahurin, R.K.; Jerabek, P.A.; Brickman, J.S.; Tekell, J.L.; Silva, J.A.; McGinnis, S.; Glass, T.G.; Martin, C.C.; et al. Cingulate Function in Depression: A Potential Predictor of Treatment Response. *Neuroreport* **1997**, *8*, 1057–1061. [CrossRef] [PubMed]

74. Gaab, J.; Blättler, N.; Menzi, T.; Pabst, B.; Stoyer, S.; Ehlert, U. Randomized Controlled Evaluation of the Effects of Cognitive–behavioral Stress Management on Cortisol Responses to Acute Stress in Healthy Subjects. *Psychoneuroendocrinology* **2003**, *28*, 767–779. [CrossRef] [PubMed]
75. Hammerfald, K.; Eberle, C.; Grau, M.; Kinsperger, A.; Zimmermann, A.; Ehlert, U.; Gaab, J. Persistent Effects of Cognitive-Behavioral Stress Management on Cortisol Responses to Acute Stress in Healthy subjects—A Randomized Controlled Trial. *Psychoneuroendocrinology* **2006**, *31*, 333–339. [CrossRef]
76. Denson, T.F.; Creswell, J.D.; Terides, M.D.; Blundell, K. Cognitive Reappraisal Increases Neuroendocrine Reactivity to Acute Social Stress and Physical Pain. *Psychoneuroendocrinology* **2014**, *49*, 69–78. [CrossRef]
77. Duffy, F.; Sharpe, H.; Schwannauer, M. Review: The Effectiveness of Interpersonal Psychotherapy for Adolescents with Depression—A Systematic Review and Meta-Analysis. *Child Adolesc. Ment. Health* **2019**, *24*, 307–317. [CrossRef]