

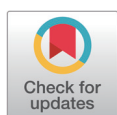
Effects of canine-assisted intervention on stress and depression in humans

Yujin Song¹, Youngwook Jung¹, Yeonju Choi¹, Minjung Yoon^{1,2,3*}

¹Department of Animal Science and Biotechnology, Kyungpook National University, Sangju 37224, Korea

²Department of Horse, Companion, and Wild Animal Science, Kyungpook National University, Sangju 37224, Korea

³Research Institute for Innovative Animal Science, Kyungpook National University, Sangju 37224, Korea



Received: Nov 21, 2024

Revised: Jan 3, 2025

Accepted: Jan 4, 2025

*Corresponding author

Minjung Yoon

Department of Animal Science and Biotechnology, Kyungpook National University, Sangju 37224, Korea
Tel: +82-54-530-1233

E-mail: mjyoon@knu.ac.kr

Copyright © 2025 Korean Society of Animal Science and Technology.
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ORCID

Yujin Song

<https://orcid.org/0009-0004-7273-9311>

Youngwook Jung

<https://orcid.org/0000-0002-7829-0349>

Yeonju Choi

<https://orcid.org/0000-0003-4956-554X>

Minjung Yoon

<https://orcid.org/0000-0001-9112-1796>

Competing interests

No potential conflict of interest relevant to this article was reported.

Abstract

The demand for mental health support systems has been increasing because of the rising prevalence of mental health issues globally. These challenges related to mental health have been addressed through animal-assisted intervention. This approach has gained recognition as an effective method that enhances emotional stability and fosters social bonds. Canine-assisted intervention, a subset of animal-assisted intervention that involves dogs, is recognized for its effectiveness in managing stress and depression in humans. Despite the development of various canine-assisted intervention programs, there is insufficient scientific data evaluating the efficacy of each program. Customized programs that target individuals' symptoms and needs are necessary to effectively manage stress and depression. As such, generalizing the effects of canine-assisted intervention across diverse situations continues to be a challenge. This review aims to identify the most effective canine-assisted intervention programs for various target groups and suggest strategies that maximize the effects of canine-assisted intervention programs by consolidating various biometric indicators and physiological evaluation tools and by analyzing the effects of canine-assisted intervention through multiple approaches. It examines current studies demonstrating how interactions with therapy dogs lead to remarkable psychological and physiological changes, including measurable reductions in stress indicators (such as cortisol levels and heart rates) and notable improvements in overall mood and emotional well-being. Furthermore, this paper evaluates the effectiveness of canine-assisted intervention in various settings, highlighting its potential as a therapeutic intervention and preventive measure in mental health care. Based on previous findings, this review provides a comprehensive overview of the role of canine-assisted intervention in enhancing human mental health and its potential for broader implementation across diverse environments.

Keywords: Canine-assisted intervention, Stress, Depression, Well-being

INTRODUCTION

Psychological and emotional crises, including stress and depression, have been rising significantly. They

Funding sources

This research was supported by the National Institute of Agricultural Sciences, Rural Development Administration, Korea (RS-2023-00232319).

Acknowledgements

The authors would like to Dr. Heejun Jung, Dr. Shakeel Hafiz Muhammad, Junyoung Kim, Geumhui Lee, Yubin Song, Taelang Kim and Jaewoo Choi from Kyungpook National University, Korea, for their help with temperament assessment.

Availability of data and material

Upon reasonable request, the datasets of this study can be available from the corresponding author.

Authors' contributions

Conceptualization: Song Y, Jung Y, Choi Y, Yoon M.

Methodology: Song Y.

Validation: Song Y.

Writing - original draft: Song Y.

Writing - review & editing: Song Y, Jung Y, Choi Y, Yoon M.

Ethics approval and consent to participate

This article does not require IRB/ACUC approval because this is review article.

are closely associated with increasing suicide rates, posing a significant societal challenge on a broader societal level [1].

Addressing these crises necessitates more diverse and specialized support programs. For instance, animal-assisted intervention (AAI) has emerged as an effective approach to addressing these challenges [2]. It facilitates the development of emotional stability and social bonds through human-animal interactions. Such interactions are key to overcoming psychological crises [2–6]. AAI is a broad concept that includes all activities involving various animals in beneficial ways to enhance human health and welfare [7]. These interventions span multiple fields, including healthcare, education, and social welfare, thereby providing individuals with physical, psychological, social, and cognitive benefits [8]. Therefore, animal-related activities have been recognized for their contributions to helping enhance humans' psychological stability and social functions.

Canine-assisted intervention (CAI), a type of AAI, involves dogs during the intervention. It is categorized into three types: canine-assisted therapy (CAT), canine-assisted education (CAE), and canine-assisted activities (CAA) [9]. CAT is conducted by professional therapists, who integrate dogs into therapeutic processes to enhance cognitive, psychological, physical, or social functions. Their effectiveness has been demonstrated in adults and children with mental disorders or developmental disabilities [3]. CAE is a program that utilizes dogs to support children's educational achievement [9]. CAA is a broader concept that is not confined to structured, goal-specific programs. It is implemented in diverse settings and can be performed by both professionals and nonprofessionals [9].

An increasing number of studies have demonstrated the effectiveness of interventions such as CAT, CAE, and CAA in addressing mental health challenges. These interventions are specifically used as coping strategies for stress or depression [10–14]. However, further studies should be performed to more comprehensively understand the effects of CAI and determine its appropriate applications. Therefore, this paper examines the effects of CAI, specifically its impacts on stress and depression. This review also highlights the practical contributions of CAI-based mental health programs and offers valuable insights into their clinical practice and future research directions by evaluating the current state of CAI studies.

CANINE-ASSISTED INTERVENTION

CAI offers unique advantages compared with general AAI. Unlike general AAI, CAI involves dogs that can form strong bonds with humans and are particularly known for providing emotional stability. They are highly attuned to human emotions, promoting positive interactions [15]. Additionally, they are versatile in a wide range of activities because of their high intelligence and trainability; as a result, they can be trained for specific therapeutic goals [16,17]. As such, their use in therapy provides comfort and familiarity, which can help enhance therapeutic outcomes [18]. For example, reading programs that involve dogs help alleviate anxiety and nervousness among students with a fear of public speaking [19].

Certain dog breeds are suitable for CAI because of their temperament, sociability, and trainability. The most commonly selected dog breeds for therapy work include Golden Retrievers, Labrador Retrievers, Poodles, Pugs, Cavalier King Charles Spaniels, and Beagles [20–22]. In a previous study, the suitability of different dog breeds for therapy roles was evaluated using the Canine Behavior Assessment and Research Questionnaire; its results showed that the most commonly used breeds for therapy by the Hokkaido Volunteer Dog Association are Labrador Retrievers, Golden Retrievers, and Toy Poodles. Other breeds with calm and friendly temperaments may also be effective as therapy dogs [23].

CANINE-ASSISTED INTERVENTION PROGRAMS

CAI programs consist of various forms categorized by target population, activity characteristics, and duration. Specifically, target populations are categorized based on the human life cycle and provided with customized programs. Individuals are categorized into three life stages: children (0–18 years), adults (19–64 years), and the elderly (65 years and above) [24]. During childhood, they undergo rapid physical growth and brain development. Their linguistic abilities, social skills, and emotional regulation abilities also develop during this time. Their socialization processes and the formation of their self-identity are crucial. As such, their CAI programs should focus on enhancing social skills and providing emotional support. During adulthood, adults need to maintain their physical health and manage stress. They encounter various social responsibilities and relationships. They may also develop mental health issues such as depression and anxiety. Therefore, their CAI programs should cover stress reduction and mental health support initiatives. During old age, the elderly may experience chronic illness and decreased physical functions. They may also feel isolated and lonely. Their risk of cognitive decline and dementia increases. Thus, their CAI programs should include initiatives that reduce social isolation and activities that stimulate cognitive functions [24,25].

CAI programs can also be categorized based on the characteristics of their activities. They are divided into two types: dynamic and static activities. Dynamic activities involve active physical movement and interaction. They aim to enhance physical functioning, improve athletic abilities, and allow for energy expenditure. Their effects include stress reduction caused by energy expenditure and the development of athletic abilities. Static activities focus on promoting emotional exchange, stimulating cognitive abilities, and enhancing emotional well-being. For instance, reading programs involving dogs effectively enhance a child's confidence. Additionally, incorporating dogs into psychological counseling can reduce individual stress and anxiety. Each activity must be selected based on the age, physical condition, and psychological needs of participants [26–31].

CAI can be categorized into two types based on duration: short- and long-term CAI [26]. Short-term CAI programs last from a few minutes to a few weeks. They aim to alleviate temporary stress and provide immediate emotional support. For instance, one-off CAI sessions can reduce anxiety and stress in students during exam periods and offer a change of scenery for patients in hospitals [32–34]. Short-term CAI does not require complex planning or long-term resource input and can be implemented in various environments. Long-term CAI programs last from a few months to several years. They focus on encouraging long-term behavioral changes, providing continuous emotional support, and achieving therapeutic goals [35]. For instance, individuals with mental health problems undergo continuous therapy sessions and use CAI in rehabilitation therapy [36]. The effects of long-term CAI include enhanced social skills, obtained treatment goals, and improved quality of life. Long-term CAI requires a professional therapeutic plan with set goals; it also needs certified therapists and the continuous involvement of experts [37].

Dog-mediated programs can be used for non-therapeutic activities to reduce stress, anxiety, and fear [38] and improve the overall well-being of people [39]. For example, the presence of a dog in a classroom enhances the concentration and motivation of students during classes [40]. Additionally, interactions with dogs remarkably reduce stress among university students during midterm or final exams [41]. Therefore, CAI has been proven to be an effective method for managing mental health issues such as anxiety, stress, and depression and for promoting overall well-being [38–41]. The ability of dogs to provide emotional stability and their high trainability positively affect not only therapeutic settings but also educational and non-therapeutic environments. With these benefits, CAI is a valuable alternative approach to mental health care.

STRESS IN PHYSIOLOGY

Stress is defined as a state of mental or emotional strain caused by adverse or demanding circumstances. A moderate amount of stress can help individuals perform daily activities. However, excessive stress can cause mental health problems, including anxiety disorders, depression, and panic disorders [42–44], accompanied by a range of negative emotions. Excessive stress can also lead to physical symptoms such as headaches, body aches, and sleep disturbances [42,43]. Therefore, methods should be developed to manage stress efficiently.

Physiologically, stress affects various body systems, including the nervous, endocrine, and immune systems, and is not limited to emotional responses. When stressors are present, the neuroendocrine system triggers the release of stress hormones such as cortisol and adrenaline. Cortisol, secreted by the adrenal cortex, increases blood sugar levels to provide quick energy and suppresses immune functions to reduce inflammation. Its secretion is regulated by the hypothalamic–pituitary–adrenal (HPA) axis [45,46]. Adrenaline and noradrenaline, secreted by the adrenal medulla, increase heart rate and blood pressure to prepare the body for a “fight-or-flight” response. Their secretion is regulated by the sympathetic–adrenal–medullary (SAM) axis [47].

Stressors induce the secretion of corticotropin-releasing hormone, which stimulates the release of adrenocorticotrophic hormone (ACTH) from the anterior pituitary gland. ACTH stimulates the adrenal cortex and increases cortisol secretion. Cortisol enhances energy supply by increasing blood sugar levels and promoting protein and fat breakdown. Additionally, it maintains homeostasis through negative feedback mechanisms that regulate hormone secretion from the hypothalamus and pituitary gland [48].

Although cortisol plays an important role in acute stress, chronic stress results in the overactivation of the HPA axis and induces the excessive secretion of cortisol. A chronic increase in cortisol levels may elicit negative effects, such as decreased immune function, metabolic disorders, and increased risk of cardiovascular disease [49,50]. Chronic stress can also contribute to depression and anxiety disorders. It induces constant adrenaline and noradrenaline secretion through the SAM axis, causing symptoms such as increased heart rate, increased blood pressure, and hypervigilance [47].

Because of these negative effects, the importance of stress management is emphasized. Meditation, exercise, psychological counseling, and social support networks can alleviate stress and improve physical and psychological health [51,52]. Additionally, CAI is recognized as an effective method for managing stress [53].

MEASUREMENT OF STRESS LEVELS

Various physiological and psychological indicators can be used to evaluate stress levels. Accurate and objective assessment requires multiple methods. The main assessment methods used are enzyme-linked immunosorbent assay (ELISA) for cortisol, functional magnetic resonance imaging (fMRI), Hematological analysis for the neutrophil/lymphocyte ratio (NLR), electroencephalogram (EEG), heart rate variability (HRV), and self-report measures. Each method assesses different aspects of stress responses (Table 1).

ELISA is a precise analytical technique used to quantitatively measure specific protein or hormone concentrations in biological samples. In studies on stress, ELISA is primarily used to evaluate cortisol levels. Cortisol, a major hormone that responds to stress, can be measured in the blood, saliva, and urine [46]. Cortisol levels obtained through ELISA serve as reliable physiological indicators of stress levels [54]. ELISA can detect small amounts due to its high sensitivity and

specificity, and quick results can be obtained through relatively simple experimental procedures. Because of these functions, it is widely utilized in clinical and research settings.

fMRI is a non-invasive imaging technology that visualizes activation patterns of the brain in real time. fMRI measures blood oxygen level-dependent signals to indirectly detect changes in neural activity. In stressful situations, fMRI can detect changes in the activation of brain regions such as the amygdala and prefrontal cortex. It can also identify functional changes in specific regions and help understand stress-related neural circuits [55,56]. It is mainly used to study the physiological mechanisms of the brain involved in psychological stress [57]. However, it entails high costs, requires specialized equipment that limits accessibility, and exhibits sensitivity to the movement of subjects, imposing constraints on experimental conditions [56].

The NLR is used as an indicator of stress and inflammatory responses; it is calculated by comparing the levels of neutrophils and lymphocytes in the blood [58]. Hematological analysis for the NLR is a technique that can quickly and accurately assess inflammation and stress responses. Although it is primarily used in animal studies, it can also be applied to human stress research [59]. The NLR is useful for evaluating physiological responses to stress because it increases under high-stress conditions [60]. It can be measured using Hematological analysis to evaluate stress and inflammation through simple blood examinations, allowing for immediate on-site results. Hematological analysis is a particularly cost-effective technique suitable for repeated measurements.

Brain waves reflect the brain's overall activity and can be measured in real time through an EEG. They are divided into five main types and appear in different states: Delta waves (0.5–4 Hz) appear in deep sleep, theta waves (4–8 Hz) appear in shallow sleep or deep meditation, and alpha waves (8–13 Hz) appear in relaxed states. Beta waves (13–30 Hz) are detected in concentration, cognitive work, and stress conditions, especially high beta waves (20–30 Hz) reflecting stress-related neural activities. Gamma waves (30 Hz or higher) are associated with high-dimensional cognitive functions and complex information processing. In stressful situations, beta waves increase activity, particularly high beta waves. Through EEG, changes in brain waves can be detected to assess stress levels [61].

The HRV measures the variation in time intervals between heartbeats, reflecting autonomic nervous system balance and stress levels [61,62]. Under stress, it decreases because of sympathetic nervous system activation. It is non-invasive and easy to measure, making it widely used in stress-related research.

Self-report measures involve individuals personally assessing their stress levels. Common tools include the Perceived Stress Scale (PSS) and the Visual Analog Scale (VAS) [63,64]. These self-reports are simple and quick to administer; therefore, they are suitable for large population studies.

Table 1. Measurements of stress

Measurements	Description
ELISA	Used to evaluate cortisol levels.
fMRI	Mainly used to study the physiological mechanisms of the brain involved in psychological stress.
Hematological analysis for NLR	Useful for evaluating physiological responses to stress because the NLR increases under high-stress conditions.
EEG	In stressful situations, beta waves have an increased activity, particularly high beta waves (20–30 Hz).
HRV	Under stress, the HRV decreases because of sympathetic nervous system activation.
Self-report	Perceived Stress Scale, Visual Analog Scale

ELISA, enzyme-linked immunosorbent assay; fMRI, functional magnetic resonance imaging; NLR, neutrophil/lymphocyte ratio; EEG, electroencephalogram; HRV, heart rate variability.

EFFECTS OF CANINE-ASSISTED INTERVENTION ON STRESS IN THE NON-ELDERLY

CAI can be an effective method for reducing stress in humans. Various studies have demonstrated the beneficial effects of CAI on stress across different age groups. For instance, CAI programs can be particularly beneficial for addressing stress in children. A study has demonstrated that interactions with dogs during classes significantly reduce stress levels in neurotypical and neurodivergent children requiring special educational care. For example, children in the dog intervention group exhibited significant reduction in average salivary cortisol levels (pre-intervention: $M = 0.1482 \mu\text{g/dL}$, $SD = 0.05$; post-intervention: $M = 0.0853 \mu\text{g/dL}$, $SD = 0.02$; $t(8) = 4.157$, $p = 0.003$, $d = 1.39$) compared with those in the control group, which exhibited no significant changes (pre-intervention: $M = 0.1486 \mu\text{g/dL}$, $SD = 0.05$; post-intervention: $M = 0.1468 \mu\text{g/dL}$, $SD = .06$; $t(14) = 0.487$, $p = 0.634$, $d = 0.13$) [10]. This result suggests that dog interventions can attenuate stress levels in school children. Additionally, short-term interactions with dogs significantly reduce stress levels and enhance the mobility and mood of children in pediatric critical care and acute care units, suggesting the benefits of CAI application to highly stressed children (Table 2).

For instance, children who participated in an AAI program demonstrated a significantly higher activity level 3 hours after the visit compared to children who did not participate ($B = 9.825$, $SE = 3.760$, $p < 0.001$; $\beta = 0.689$). Moreover, mood levels improved significantly in the AAI group, as indicated by a strong interaction effect between mood and group ($F(1,45) = 79.05$, $p < 0.001$). Regarding stress levels, children in the AAI group exhibited a significant decrease in cortisol levels over time, whereas the control group demonstrated an increase [65].

This animal support system can help ease the anxiety and stress experienced by children

Table 2. Effects of CAI on stress in non-elderly

Target group (n)	Application of CAI	Measurement methods and results	References
Children (n = 134)	Randomized controlled trials involving AAI aimed to reduce stress levels in general education children (n = 90) and special education children (n = 44) during school activities. Conducted AAI sessions twice a week for 20 minutes each over 4 weeks.	Salivary cortisol levels were measured in both general education children and special education children. For general education children, cortisol levels decreased significantly compared to the control group. Similarly, special education children also showed a significant reduction in cortisol levels during intervention sessions, highlighting the effectiveness of AAI in reducing stress for both groups.	[10]
Children in acute care settings (n = 80)	Randomly assigned to the Dog-assisted intervention (DAI) group (n = 44) or waitlist control group (n = 36). Therapy dog visits were conducted for the DAI group. The CAI group received dog visits for 5–10 minutes while the control group did not.	Stress was measured via salivary cortisol samples. Activity levels were also recorded. The CAI group showed increased interaction with the therapy dog and reduced stress levels compared to the control.	[66]
Sexually abused children (n = 42)	Children were assigned to an intervention group (AAI with therapy dog, n = 19) or a control group (standard interview protocol, n = 23). In the intervention group, children could pet and talk to the therapy dog during the forensic interview.	Cardiac assessments included blood pressure (BP), heart rates (HR), and saliva samples for cortisol and immunoglobulin A (IgA). The control group had significantly higher HR before the interview, indicating higher stress. Significant decreases in BP were observed in an intervention group. The intervention group showed lower HR and BP, indicating reduced physiological stress. No significant differences in cortisol or IgA were found.	[67]
College students (n = 48)	Interaction with therapy dogs for 15 minutes during final exams.	Stress levels were assessed using the Perceived Stress Scale (PSS), visual analog scales (VAS), vital signs, and salivary cortisol measurements before and after the intervention. Significant reductions were observed in all measures except diastolic blood pressure.	[68]
College student (n = 78)	Therapy dog intervention was conducted 1 week before final exams. Each session lasted for 15 minutes.	Stress was measured using the PSS, stress visual analog scale (SVAS), saliva for nerve growth factor, and alpha amylase (sAA). SVAS scores significantly decreased after intervention, indicating reduced perceived stress. No significant differences in physiological measures (sAA).	[69]

CAI, Canine-assisted intervention; AAI, animal-assisted intervention.

traumatized by serious abuse. For example, studies have indicated that therapy dogs' presence during forensic interviews substantially reduces physiological stress markers in sexually abused children. Specifically, children in the intervention group who interacted with therapy dogs exhibited decreased systolic blood pressure ($t(16) = -2.551, p = 0.021$) and diastolic blood pressure ($t(16) = -3.019, p = 0.008$) compared to those who did not. Heart rate prior to the forensic interview was notably lower in the intervention group ($M = 82.68, SD = 12.37$) compared to the control group ($M = 91.57, SD = 15.51; t(40) = 2.020, p = 0.050$). While cortisol levels in the intervention group did not show significant changes, the control group demonstrated a notable decrease in cortisol levels after the AAI interview ($t(20) = 2.346, p = 0.029$). These findings suggest that therapy dogs provide consistent emotional and physiological support, potentially alleviating the discomfort and stress of children during forensic interviews [66].

The development of stress-coping programs via CAI has shown its advantages in adults, such as college students. Two studies have explored the effects of CAI on students' stress levels. In one study, self-reported stress scores and vital signs were used to evaluate the stress levels of college students who were allowed to interact freely with a therapy dog for 15 minutes during their final exams. Self-reported data showed significant reductions in stress levels, with the PSS scores decreasing from 34.75 to 31.47 (mean difference = 3.28, $SD = 3.22, p = 0.001$). VAS measures also revealed notable decreases, including stress (70.97 to 41.71, mean difference = 29.26, $p = 0.001$), sadness (34.49 to 12.29, mean difference = 22.20, $p = 0.001$), confusion (31.29 to 14.57, mean difference = 16.71, $p = 0.001$), and anger (25.31 to 10.34, mean difference = 14.97, $p = 0.001$). Physiological assessments corroborated these findings, indicating reductions in systolic blood pressure (131.09 mm Hg to 122.79 mm Hg, mean difference = 8.30 mm Hg, $p = 0.001$) and pulse rate (80.68 bpm to 76.83 bpm, mean difference = 3.85 bpm, $p = 0.039$), although diastolic blood pressure changes were not significant (81.72 mm Hg to 80.02 mm Hg, $p = 0.104$). Additionally, salivary cortisol levels decreased significantly from 0.26 to 0.21 $\mu\text{g/dL}$ (mean difference = 0.057, $SD = 0.157, p < 0.015$) [67]. This result is supported by another study with a comparable methodology, which revealed that one-off meetings with therapy dogs mediated the stress levels of students before final exams [68]. Specifically, the students interacted with a therapy dog for 15 minutes in a single session and self-reported their stress scores. The stress scores of students who interacted with the dog markedly declined with those in the control group.

For instance, in one study, students who participated in the therapy dog session reported a mean reduction of 3.6 points in their Stress VAS scores ($SD = 2.35, p < .001, d = 1.57$), indicating a large effect size. Conversely, students in the control group experienced a slight increase in stress scores, with a mean increase of 1.2 points ($SD = 2.89, d = 0.40$), which reflected a medium effect size. These findings suggested that short-term CAI programs may be used as an economical and easily accessible way to enhance the well-being of students [68].

Studies have explored the effects of CAI on children and young people and suggested that CAI effectively reduces human stress. However, these studies are limited by the narrow age range of subjects and limitations of the methods used to measure stress. Self-reporting surveys are among the most common methods for measuring stress, but their reliability is limited due to subjectivity. Physiological indicators, such as cortisol [46,69,70] and heart rates [71,72], have been used to supplementary measures to validate the effects of CAI on stress levels. Nonetheless, more diverse measures (e.g., various hormones like oxytocin or electroencephalography to more precisely validate brain activities) can enhance the accuracy of stress measurement. Therefore, further studies should be performed to diversify the age range of subjects and assess the effects of CAI by using various measurements to optimize its effectiveness.

DEPRESSION IN PHYSIOLOGY

Depression is defined as a loss of pleasure in activities or a depressive mood that is more severe and lasts longer than a general emotional response [73]. It adversely impacts approximately 280 million people worldwide, or about 5% of adults [73]; consequently, this condition affects all aspects of life, including relationships with family, friends, and communities, and causes problems at school and work. The risk of depression is highest in adults aged over 60 years, with a prevalence rate of 5.7% [74]. Depressive disorders in seniors are characterized by diagnostic complexity, which is often accompanied by challenging clinical outcomes and a high risk of disability [75]. Therefore, developing the most effective treatments for patients suffering from depression is crucial.

Depression is associated with an imbalance of neurotransmitters and hormones. One of the major causes of depression is a decrease in neurotransmitters such as serotonin [76,77]. Such biochemical changes are crucial for understanding the mechanisms of depression and developing therapeutic strategies. Therefore, understanding the underlying causes of depression is essential for creating effective therapeutic methods [78].

Serotonin is a neurotransmitter that regulates various physiological functions in the central and peripheral nervous systems [79]. It is primarily synthesized in the raphe nuclei in the brainstem and widely distributed throughout the neural network [80]. It participates in mood regulation, sleep, appetite, digestion, learning, memory, and other functions. It is also involved in emotion and mood stabilization [81,82].

A serotonin imbalance is a major cause of depression. Decreased serotonin levels in the brain can result in depressive symptoms such as low mood, lethargy, and insomnia [77,83]. These biochemical changes are crucial in understanding the mechanisms of depression and developing effective therapeutic strategies. Therefore, disturbances in the serotonin system are associated with mental disorders such as anxiety disorders and obsessive-compulsive disorders [83].

In the treatment of depression, selective serotonin reuptake inhibitors (SSRIs) inhibit the reuptake of serotonin in presynaptic neurons, thereby increasing serotonin levels. Through this mechanism, SSRIs enhance the efficacy of neurotransmission and alleviate depressive symptoms [84,85]. This medical treatment is based on the neurobiological role of serotonin and has demonstrated effective therapeutic results in many patients.

Consequently, current studies focus on non-invasive treatments such as CAI as potential alternatives or complements to medication [86].

MEASUREMENT OF DEPRESSION LEVELS

Depression levels can be evaluated using various physiological and psychological indicators [87]. These indicators can be accurately and objectively assessed using different methods, including ELISA for serotonin, fMRI, hematological analysis of the NLR, positron emission tomography (PET) scans, retinal imaging, EEG, and self-report measures. Each method assesses different aspects of depression (Table 3).

ELISA is a precise analytical technique used to measure specific protein or hormone concentrations in biological samples quantitatively. Serotonin, a neurotransmitter closely associated with depression, can be measured in blood, saliva, or other biological samples. In studies on depression, serotonin levels are used to evaluate neurotransmitter imbalances and monitor the effects of treatment [77].

fMRI is a crucial tool for visualizing the functional changes in the brain in studies on depression. It is used to observe short-term and acute stress responses in stress measurements; in depression

Table 3. Measurements of depression

Measurements	Description
ELISA	Used to evaluate serotonin levels.
fMRI	fMRI is utilized to analyze changes in connectivity between the default mode network and the executive function network.
Hematological analysis for NLR	The NLR primarily indicates the inflammatory responses related to acute stress in stress assessments; in depression assessments, the NLR quantifies chronic inflammation.
EEG	Increased delta wave activity and alpha asymmetry may be associated with depression; however, relying solely on EEG as an indicator lacks scientific robustness.
PET	PET scans are applied to elucidate the neurobiological mechanisms of the brain and evaluate the diagnosis and therapeutic effects in depression studies.
Retinal imaging	Retinal imaging is a non-invasive technique that captures accurate images of the retina, which is the light-sensitive layer located behind the eye.
Self-report	Beck Depression Inventory, Hamilton depression rating scale, geriatric depression scale

ELISA, enzyme-linked immunosorbent assay; fMRI, functional magnetic resonance imaging; NLR, neutrophil/lymphocyte ratio; EEG, electroencephalogram; HRV, heart rate variability.

studies, fMRI is primarily used to examine functional changes in brain regions such as the prefrontal cortex, hippocampus, and amygdala [88,89]. For example, patients with depression may exhibit a decreased activation of the prefrontal cortex and an overactivation of the amygdala [88,90]. fMRI is used to assess structural changes, such as reduced volume of the hippocampus. In particular, it is utilized to analyze changes in connectivity between the default mode network (DMN) and the executive function network (EFN); it is also used to assess their association with overactivation or hypoactivation related to self-referential thinking [91]. Brain network connectivity is crucial in understanding the neurobiological mechanisms underlying depression. Changes in connectivity within the DMN and EFN are closely related to overactivation or hypoactivation related to self-referential processing, and these changes affect mood control and cognitive function in patients with depression [88,89,91]. Analyzing these connectivity changes, fMRI contributes to the diagnosis of depression, evaluates therapeutic effects, and aids in developing individualized therapy strategies [91].

Hematological analysis measures the NLR to evaluate changes in inflammation responses and immune function in depression studies. The NLR primarily indicates the inflammatory responses related to acute stress in stress assessments; in depression assessments, the NLR quantifies chronic inflammation. Chronic inflammation is closely associated with depression and can cause depressive symptoms by affecting neurotransmitter metabolism and neuroplasticity. A high NLR may be related to increased inflammatory cytokines, and the increase in inflammatory cytokines helps elucidate the pathophysiology of depression. The NLR can be compared before and after antidepressant treatments to estimate the therapeutic effects and changes in inflammatory responses [92, 93].

PET scans are applied to elucidate the neurobiological mechanisms of the brain and evaluate the diagnosis and therapeutic effects in depression studies [94]. They help reveal the complex characteristics of depression by estimating the activation of neurotransmitter systems, brain metabolic activity, and changes in connectivity within intracerebral networks. Specifically, they directly estimate the activation of neurotransmitter systems, such as serotonin and dopamine [95,96]. For example, the density of serotonin receptors or the activity of dopamine-related targets can be analyzed to assess their association with depression. However, prudence is required in their clinical application because of the high cost, radiation exposure, and time consumption associated with PET scans.

Retinal imaging is a non-invasive technique that captures accurate images of the retina, which is the light-sensitive layer located behind the eye [97]. The retina shares the same embryonic origin as the brain; thus, neurobiological changes associated with mental disorders can be indirectly observed

by monitoring retinal changes [98,99]. Depression includes various neurobiological alterations, such as neuroinflammation, neurodegeneration, and changes in neurotransmitter systems [100]. These changes manifest in the retina, reflecting similar processes occurring in the brain [101]. For instance, the retina can undergo structural and functional changes because of chronic inflammation and oxidative stress, which are commonly observed in depression [102]. Retinal imaging techniques are mostly painless and do not require surgery [103]. Additionally, the detailed images of retinal structures can be used as a basis for the early detection of diseases. However, these techniques are costly and require expert interpretation.

The EEG is a non-invasive technique that records the electrical activities of the brain. It is used to identify potential neural biomarkers and understand neurobiological mechanisms. It is a useful tool for understanding the neurobiological characteristics of depression. However, there is a lack of consistency among studies. Increased delta wave activity and alpha asymmetry may be associated with depression; however, relying solely on EEG as an indicator lacks scientific robustness [99,104]. Therefore, further studies should investigate EEG for evaluating depression. Future research should involve larger sample sizes and apply EEG in conjunction with other biometric indicators, such as hormone levels.

Self-report measures for depression include the Beck Depression Inventory (BDI), Hamilton depression rating scale, and Geriatric Depression Scale (GDS) for the elderly. These questionnaires assess the severity and range of symptoms associated with depression [105–107].

EFFECTS OF CANINE-ASSISTED INTERVENTION ON DEPRESSION IN ELDERLY

As depression is recognized as a medical condition, studies on depression have focused on a limited range of subjects in specific situations. One study demonstrated that CAT alleviates depressive symptoms in elderly patients with psychosis, as assessed using the GDS. The findings revealed a significant reduction in GDS scores among participants in the pet group, decreasing from 5.9 ± 4.7 to 2.7 ± 3.1 ($p = .013$), indicating a marked improvement in depressive symptoms [108]. These findings suggest that CAT is effective in alleviating depression among older adults with psychosis. Another study has explored the effects of CAI on residents of long-term care facilities [14]. The treatment group interacted with a therapy dog once a week for 6 weeks. Depression was assessed using the BDI. The results indicated that the average self-report scores of the treatment group significantly improved, with BDI scores decreasing from 15.4 ± 4.2 to 10.7 ± 3.8 ($p = 0.017$), whereas the scores of the control group did not have significant changes [14]. Therefore, CAI may be beneficial to residents of long-term care facilities. This finding is supported by several studies that highlight the effects of CAI in reducing depressive symptoms in individuals with dementia [13]. They demonstrated that depression levels significantly decreased in participants with severe dementia after the CAI program. For instance, in one study, depression levels measured by the DMAS showed a mean decrease of 4.5 points from baseline ($p < 0.001$) in the CAI group, while the control group exhibited a significant increase of 4.9 points ($p < 0.001$) [13]. Thus, CAI positively affects depression in people with dementia, especially in later stages (Table 4).

In addition, qualitative studies emphasize the significant role of dogs in enhancing the physical and psychological well-being of elderly individuals with chronic illnesses. Interactions with companion animals encourage physical activity, foster emotional bonding, and provide companionship, thereby contributing to the management of depressive symptoms. For example, engaging in caregiving activities such as walking or grooming pets not only increases physical activity but also boosts self-efficacy and fosters a sense of purpose. Moreover, companion animals

Table 4. Effects of CAI on depression in elderly

Target group (n)	Application of CAI	Measurement methods and results	References
Elderly inpatients (n = 21)	6-week intervention in a nursing home, 90 minutes once a week for the pet group (n = 10). Participants interacted with therapy dogs (holding, walking, talking, playing) under supervision. The control group (n = 11) observed but did not interact.	Cognitive function was measured using a Mini-Mental State Examination (MMSE), and depression was measured using the Geriatric Depression Scale (GDS). GDS scores improved by 50% within the pet group, and MMSE scores increased. Quality of life was also reported to have improved.	[109]
Residents in long-term care (n = 16)	AAA group (n = 8) received 30-minute visitations once a week for 6 weeks. The control group (n = 8) residents never saw the therapy dog until after the post-measures were done.	Depression and anxiety were measured using the Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI) pre-and post-intervention. Significant reduction in depression (BDI) in the AAA group, and no significant changes in anxiety (BAI).	[14]
Nursing home residents with dementia (n = 54)	Participants (n = 54) were randomly assigned to the AAT group (n = 27) and control group (n = 27). AAT was conducted for 10 weeks (once a week, 45 minutes) in a nursing home after preparation with the therapy center. The control group received their usual pharmacologic and nonpharmacologic treatments without AAT.	Symptoms of agitation/aggression and depression were assessed using the Cohen-Mansfield Agitation Inventory and Dementia Mood Assessment Scale. The control group showed increased symptoms over 10 weeks. The intervention group maintained constant levels of symptoms.	[13]

CAI, Canine-assisted intervention; AAA, animal-assisted activity; AAT, animal-assisted therapy.

act as sources of comfort and joy, helping to alleviate feelings of loneliness and isolation. In this respect, incorporating companion animals into therapeutic programs for the elderly can effectively alleviate depressive symptoms and improve overall quality of life [109].

Depressive symptoms often accompany chronic pain and a loss of interest in activities; these symptoms can exacerbate in terms of duration, pain intensity, and functional impairment [110], particularly in older adults. Dogs contribute to pain management by bringing joy and laughter [109]. Furthermore, activities involving therapy dogs, such as brushing or walking them, can increase physical activity in patients; thus, their self-efficacy can be enhanced by enabling them to provide meaningful care during older adulthood. For instance, a study reported that patients who participated in therapy dog-related activities demonstrated a significant increase in daily physical activity levels, walking an additional average of 1,500 steps per day compared to the baseline ($p < 0.05$). These findings suggest that therapy dog interactions not only promote physical activity but also foster a sense of purpose and capability in older adults [111].

The majority of studies have demonstrated that CAIs effectively alleviate depressive symptoms. As such, they show potential for therapeutic applications in mental health care to manage depression. Additionally, implementing CAIs in nursing homes or community spaces with seniors may be beneficial in the long term because it involves participation in recreational activities that improve the physical, mental, and social well-being of older adults. However, further studies should explore the long-term effects of CAIs, diversify the range of participants, and investigate the specific mechanisms through which CAIs exert their therapeutic benefits for depression.

To maximize the therapeutic potential of CAIs, developing customized programs tailored to individuals' symptoms and needs is essential. Such programs could enhance the effectiveness of CAIs in managing stress and depression, particularly in diverse populations. As a result, generalizing the effects of CAIs across diverse situations is challenging. Therefore, this review aims to establish optimized CAI programs for various subjects and maximize the effects of CAI in managing depression and stress. To achieve this objective, this review integrates various biometric indicators and physiological evaluation tools to analyze the effects of CAI through multiple approaches.

CONCLUSION

This review explores the effectiveness of CAI in managing stress and depression in humans. Various studies show that CAI provides substantial advantages, including emotional support, physical interaction, and social engagement, which enhance mental health outcomes across diverse age groups. Vulnerable populations, such as the elderly and individuals with psychiatric conditions, particularly benefit from CAI because of the unique therapeutic bond formed with therapy dogs. Despite these promising outcomes, CAI has several limitations, including lack of standardized protocols, limited long-term studies, and variability in program implementations. Additionally, the mechanisms through which CAI exerts its effects are not fully understood. As such, further research is needed to bridge these gaps. Future studies should elucidate the underlying mechanisms of CAI, expand the diversity of participant groups, and conduct longitudinal assessments to evaluate the sustained effect of CAI. Moreover, integrating CAI with other therapeutic modalities may enhance its benefits. Therefore, CAI offers relevant clinical advantages in the field of mental health, serving not only as an effective tool for alleviating the symptoms of depression and stress but also as an efficient technique to improve the overall quality of life of individuals experiencing these challenges. Integrating CAI into mainstream mental health care practices has the potential to enhance therapeutic outcomes and provide a holistic approach to mental well-being.

References

1. WHO (World Health Organization). Depression and other common mental disorders: global health estimates [Internet]. WHO; 2017 [cited 2023 Aug 17]. <https://www.who.int/publications/i/item/depression-global-health-estimates>
2. Liguori G, Costagliola A, Lombardi R, Paciello O, Giordano A. Human-animal interaction in animal-assisted interventions (AAI)s: zoonosis risks, benefits, and future directions—a one health approach. *Animals*. 2023;13:1592. <https://doi.org/10.3390/ani13101592>
3. Friedmann E, Son H. The human–companion animal bond: how humans benefit. *Vet Clin North Am Small Anim Pract*. 2009;39:293–326. <https://doi.org/10.1016/j.cvsm.2008.10.015>
4. DeSchraver MM, Riddick CC. Effects of watching aquariums on elders' stress. *Anthrozoös*. 1990;4:44–8. <https://doi.org/10.2752/089279391787057396>
5. Bert F, Gualano MR, Camussi E, Pieve G, Voglino G, Siliquini R. Animal assisted intervention: a systematic review of benefits and risks. *Eur J Integr Med*. 2016;8:695–706. <https://doi.org/10.1016/j.eujim.2016.05.005>
6. Kamioka H, Okada S, Tsutani K, Park H, Okuizumi H, Handa S, et al. Effectiveness of animal-assisted therapy: a systematic review of randomized controlled trials. *Complement Ther Med*. 2014;22:371–90. <https://doi.org/10.1016/j.ctim.2013.12.016>
7. AVMA (American Veterinary Medical Association). Animal-assisted interventions: definitions [Internet]. AVMA; 2025 [cited 2023 Aug 16]. <https://www.avma.org/resources-tools/avma-policies/animal-assisted-interventions-definitions>
8. Jegatheesan DB. The iaahio definitions for animal assisted intervention and guidelines for wellness of animals involved [Internet]. IAHAIO; 2018 [cited 2023 Aug 16]. <https://iahaio.org/wp/wp-content/uploads/2017/05/iahaio-white-paper-final-nov-24-2014.pdf>
9. Meers LL, Contalbrigo L, Samuels WE, Duarte-Gan C, Berckmans D, Laufer SJ, et al. Canine-assisted interventions and the relevance of welfare assessments for human health, and transmission of zoonosis: a literature review. *Front Vet Sci*. 2022;9: 899889. <https://doi.org/10.3389/fvets.2022.899889>

10. Meints K, Brelsford VL, Dimolareva M, Maréchal L, Pennington K, Rowan E, et al. Can dogs reduce stress levels in school children? Effects of dog-assisted interventions on salivary cortisol in children with and without special educational needs using randomized controlled trials. *PLOS ONE*. 2022;17:e0269333. <https://doi.org/10.1371/journal.pone.0269333>
11. Malinowski K, Yee C, Tevlin JM, Birks EK, Durando MM, Pournajafi-Nazarloo H, et al. The effects of equine assisted therapy on plasma cortisol and oxytocin concentrations and heart rate variability in horses and measures of symptoms of post-traumatic stress disorder in veterans. *J Equine Vet Sci*. 2018;64:17–26. <https://doi.org/10.1016/j.jevs.2018.01.011>
12. Rodriguez KE, Bryce CI, Granger DA, O'Haire ME. The effect of a service dog on salivary cortisol awakening response in a military population with posttraumatic stress disorder (PTSD). *Psychoneuroendocrinology*. 2018;98:202–10. <https://doi.org/10.1016/j.psyneuen.2018.04.026>
13. Majić T, Gutzmann H, Heinz A, Lang UE, Rapp MA. Animal-assisted therapy and agitation and depression in nursing home residents with dementia: a matched case-control trial. *Am J Geriatr Psychiatry*. 2013;21:1052–9. <https://doi.org/10.1016/j.jagp.2013.03.004>
14. Le Roux MC, Kemp R. Effect of a companion dog on depression and anxiety levels of elderly residents in a long-term care facility. *Psychogeriatrics*. 2009;9:23–6. <https://doi.org/10.1111/j.1479-8301.2009.00268.x>
15. Gfk. Man's best friend: global pet ownership and feeding trends [Internet]. NIQ; 2016 [cited 2023 Aug 17]. <https://nielseniq.com/global/en/insights/report/2016/mans-best-friend-global-pet-ownership-and-feeding-trends/>
16. Davis TN, Scalzo R, Butler E, Stauffer M, Farah YN, Perez S, et al. Animal assisted interventions for children with autism spectrum disorder: a systematic review. *Educ Train Autism Dev Disabil*. 2015;50:316–29. <https://www.jstor.org/stable/24827513>
17. Shubert J. Dogs and human health/mental health: from the pleasure of their company to the benefits of their assistance. *US Army Med Dep J*. 2012;21–9.
18. Guillen Guzmán E, Sastre Rodríguez L, Santamarina-Perez P, Hermida Barros L, García Giralt M, Domenec Elizalde E, et al. The benefits of dog-assisted therapy as complementary treatment in a children's mental health day hospital. *Animals*. 2022;12:2841. <https://doi.org/10.3390/ani12202841>
19. Brelsford VL, Meints K, Gee NR, Pfeffer K. Animal-assisted interventions in the classroom—a systematic review. *Int J Environ Res Public Health*. 2017;14:669. <https://doi.org/10.3390/ijerph14070669>
20. Pawsinwork. What breeds make good therapy dogs? [Internet]. Puppy Welfare; 2022 [cited 2023 Aug 17]. <https://www.pawsinwork.com/blog/which-dog-breeds-make-the-best-therapy-dogs>
21. Focus Care. The 10 best dog breeds for pet therapy [Internet]. Focus Care; 2021 [cited 2023 Aug 17]. <https://focuscare.com.au/blog/the-10-best-dog-breeds-for-pet-therapy>
22. US Service Animals. The 14 best therapy dog breeds [Internet]. US Service Animals; 2025 [cited 2023 Aug 17]. <https://usserviceanimals.org/blog/best-therapy-dog-breeds/>
23. Sakurama M, Ito M, Nakanowataru Y, Kooriyama T. Selection of appropriate dogs to be therapy dogs using the C-BARQ. *Animals*. 2023;13:834. <https://doi.org/10.3390/ani13050834>
24. Berk LE. Development through the lifespan. 6th ed. Pearson; 2018.
25. Erikson EH, Erikson JM. The life cycle completed (extended version). New York: W. W. Norton; 1998.
26. Kruger KA, Serpell JA. Animal-assisted interventions in mental health: definitions and theoretical foundations. In: Fine AH, editor. *Handbook on animal-assisted therapy: theoretical foundations and guidelines for practice*. 3rd ed. London: Elsevier; 2010. p. 33–48.

27. Johnson RA, Meadows RL. Dog-walking: motivation for adherence to a walking program. *Clin Nurs Res*. 2010;19:387-402. <https://doi.org/10.1177/1054773810373122>
28. Schofield G, Mummery K, Steele R. Dog ownership and human health-related physical activity: an epidemiological study. *Health Promot J Austr*. 2005;16:15-9. <https://doi.org/10.1071/HE05015>
29. Friesen L. Exploring animal-assisted programs with children in school and therapeutic contexts. *Early Child Educ J*. 2010;37:261-7. <https://doi.org/10.1007/s10643-009-0349-5>
30. Marcus DA. The science behind animal-assisted therapy. *Curr Pain Headache Rep*. 2013;17:322. <https://doi.org/10.1007/s11916-013-0322-2>
31. Fine AH. Incorporating animal-assisted interventions into psychotherapy: guidelines and suggestions for therapists. In: Fine AH, editor. *Handbook on animal-assisted therapy: foundations and guidelines for animal-assisted interventions*. 4th ed. London: Academic Press; 2015. p. 141-55.
32. Hunt MG, Chizkov RR. Are therapy dogs like Xanax? Does animal-assisted therapy impact processes relevant to cognitive behavioral psychotherapy? *Anthrozoös*. 2014;27:457-69. <https://doi.org/10.2752/175303714X14023922797959>
33. Barker SB, Dawson KS. The effects of animal-assisted therapy on anxiety ratings of hospitalized psychiatric patients. *Psychiatr Serv*. 1998;49:797-801. <https://doi.org/10.1176/ps.49.6.797>
34. Shiloh S, Sorek G, Terkel J. Reduction of state-anxiety by petting animals in a controlled laboratory experiment. *Anxiety Stress Coping*. 2003;16:387-95. <https://doi.org/10.1080/1061580031000091582>
35. Nimer J, Lundahl B. Animal-assisted therapy: a meta-analysis. *Anthrozoös*. 2007;20:225-38. <https://doi.org/10.2752/089279307X224773>
36. Berget B, Braastad BO. Animal-assisted therapy with farm animals for persons with psychiatric disorders. *Ann Ist Super Sanita*. 2011;47:384-90.
37. Chandler CK. *Animal assisted therapy in counseling*. 2nd ed. New York: Routledge; 2012.
38. Barker SB, Pandurangi AK, Best AM. Effects of animal-assisted therapy on patients' anxiety, fear, and depression before ECT. *J ECT*. 2003;19:38-44. <https://doi.org/10.1097/00124509-200303000-00008>
39. Barak Y, Savorai O, Mavashev S, Beni A. Animal-assisted therapy for elderly schizophrenic patients: a one-year controlled trial. *Am J Geriatr Psychiatry*. 2001;9:439-42. <https://doi.org/10.1097/00019442-200111000-00013>
40. Beetz A, Uvnäs-Moberg K, Julius H, Kotrschal K. Psychosocial and psychophysiological effects of human-animal interactions: the possible role of oxytocin. *Front Psychol*. 2012;3:234. <https://doi.org/10.3389/fpsyg.2012.00234>
41. Crossman MK, Kazdin AE. Animal visitation programs in colleges and universities: an efficient model for reducing student stress. In: Fine AH, editor. *Handbook on animal-assisted therapy: foundations and guidelines for animal-assisted interventions*. 4th ed. San Diego, CA: Academic Press; 2015. p. 333-7.
42. Baum A. Stress, intrusive imagery, and chronic distress. *Health Psychol*. 1990;9:653-75. <https://doi.org/10.1037/0278-6133.9.6.653>
43. Kuhlmann S, Piel M, Wolf OT. Impaired memory retrieval after psychosocial stress in healthy young men. *J Neurosci*. 2005;25:2977-82. <https://doi.org/10.1523/JNEUROSCI.5139-04.2005>
44. WHO (World Health Organization). Stress [Internet]. WHO; 2023 [cited 2023 Aug 19]. <https://www.who.int/news-room/questions-and-answers/item/stress>
45. Levine A, Zagoory-Sharon O, Feldman R, Lewis JG, Weller A. Measuring cortisol in

- human psychobiological studies. *Physiol Behav.* 2007;90:43-53. <https://doi.org/10.1016/j.physbeh.2006.08.025>
46. Nicolson NA. Measurement of cortisol. In: Luecken LJ, Gallo LC, editors. *Handbook of physiological research methods in health psychology*. Thousand Oaks, CA: Sage Publications; 2008. p. 37-74.
 47. Ulrich-Lai YM, Herman JP. Neural regulation of endocrine and autonomic stress responses. *Nat Rev Neurosci.* 2009;10:397-409. <https://doi.org/10.1038/nrn2647>
 48. Smith SM, Vale WW. The role of the hypothalamic-pituitary-adrenal axis in neuroendocrine responses to stress. *Dialogues Clin Neurosci.* 2006;8:383-95. <https://doi.org/10.31887/DCNS.2006.8.4/ssmith>
 49. Sapolsky RM. Stress hormones: good and bad. *Neurobiol Dis.* 2000;7:540-2. <https://doi.org/10.1006/nbdi.2000.0350>
 50. Tsigos C, Chrousos GP. Hypothalamic-pituitary-adrenal axis, neuroendocrine factors and stress. *J Psychosom Res.* 2002;53:865-71. [https://doi.org/10.1016/S0022-3999\(02\)00429-4](https://doi.org/10.1016/S0022-3999(02)00429-4)
 51. Kabat-Zinn J. Mindfulness-based interventions in context: past, present, and future. *Clin Psychol Sci Pract.* 2003;10:144-56. <https://doi.org/10.1093/clipsy.bpg016>
 52. Salmon P. Effects of physical exercise on anxiety, depression, and sensitivity to stress: a unifying theory. *Clin Psychol Rev.* 2001;21:33-61. [https://doi.org/10.1016/S0272-7358\(99\)00032-X](https://doi.org/10.1016/S0272-7358(99)00032-X)
 53. Gatti R, De Palo EF. An update: salivary hormones and physical exercise. *Scand J Med Sci Sports.* 2011;21:157-69. <https://doi.org/10.1111/j.1600-0838.2010.01252.x>
 54. Wang J, Rao H, Wetmore GS, Furlan PM, Korczykowski M, Dinges DF, et al. Perfusion functional MRI reveals cerebral blood flow pattern under psychological stress. *Proc Natl Acad Sci USA.* 2005;102:17804-9. <https://doi.org/10.1073/pnas.0503082102>
 55. Dedovic K, D'Aguir C, Pruessner JC. What stress does to your brain: a review of neuroimaging studies. *Can J Psychiatry.* 2009;54:6-15. <https://doi.org/10.1177/070674370905400104>
 56. Pruessner JC, Dedovic K, Pruessner M, Lord C, Buss C, Collins L, et al. Stress regulation in the central nervous system: evidence from structural and functional neuroimaging studies in human populations - 2008 Curt Richter Award Winner. *Psychoneuroendocrinology.* 2010;35:179-91. <https://doi.org/10.1016/j.psyneuen.2009.02.016>
 57. Forget P, Khalifa C, Defour JP, Latinne D, Van Pel MC, De Kock M. What is the normal value of the neutrophil-to-lymphocyte ratio? *BMC Res Notes.* 2017;10:12. <https://doi.org/10.1186/s13104-016-2335-5>
 58. Brinn A, Stone J. Neutrophil-lymphocyte ratio across psychiatric diagnoses: a cross-sectional study using electronic health records. *BMJ Open.* 2020;10:e036859. <https://doi.org/10.1136/bmjopen-2020-036859>
 59. Arwas N, Shvartzman SU, Goldbart A, Bari R, Hazan I, Horev A, et al. Elevated neutrophil-to-lymphocyte ratio is associated with severe asthma exacerbation in children. *J Clin Med.* 2023;12:3312. <https://doi.org/10.3390/jcm12093312>
 60. Thayer JF, Åhs F, Fredrikson M, Sollers JJ 3rd, Wager TD. A meta-analysis of heart rate variability and neuroimaging studies: implications for heart rate variability as a marker of stress and health. *Neurosci Biobehav Rev.* 2012;36:747-56. <https://doi.org/10.1016/j.neubiorev.2011.11.009>
 61. Kim HG, Cheon EJ, Bai DS, Lee YH, Koo BH. Stress and heart rate variability: a meta-analysis and review of the literature. *Psychiatry Investig.* 2018;15:235-45. <https://doi.org/10.30773/pi.2017.08.17>
 62. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *J Health Soc Behav.* 1983;24:385-96. <https://doi.org/10.2307/2136404>

63. Lesage FX, Berjot S, Deschamps F. Clinical stress assessment using a visual analogue scale. *Occup Med.* 2012;62:600-5. <https://doi.org/10.1093/occmed/kqs140>
64. Jennings ML, Granger DA, Bryce CI, Twitchell D, Yeakel K, Teaford PA. Effect of animal assisted interactions on activity and stress response in children in acute care settings. *Compr Psychoneuroendocrinol.* 2021;8:100076. <https://doi.org/10.1016/j.cpnec.2021.100076>
65. Krause-Parello CA, Gulick EE. Forensic interviews for child sexual abuse allegations: an investigation into the effects of animal-assisted intervention on stress biomarkers. *J Child Sex Abuse.* 2015;24:873-86. <https://doi.org/10.1080/10538712.2015.1088916>
66. Delgado C, Toukonen M, Wheeler C. Effect of canine play interventions as a stress reduction strategy in college students. *Nurse Educ.* 2018;43:149-53. <https://doi.org/10.1097/nne.0000000000000451>
67. Barker SB, Barker RT, McCain NL, Schubert CM. A randomized cross-over exploratory study of the effect of visiting therapy dogs on college student stress before final exams. *Anthrozoös.* 2016;29:35-46. <https://doi.org/10.1080/08927936.2015.1069988>
68. Kirschbaum C, Hellhammer DH. Salivary cortisol in psychobiological research: an overview. *Neuropsychobiology.* 1989;22:150-69. <https://doi.org/10.1159/000118611>
69. Groöschl M. Current status of salivary hormone analysis. *Clin Chem.* 2008;54:1759-69. <https://doi.org/10.1373/clinchem.2008.108910>
70. Everson SA, Lynch JW, Kaplan GA, Lakka TA, Sivenius J, Salonen JT. Stress-induced blood pressure reactivity and incident stroke in middle-aged men. *Stroke.* 2001;32:1263-70. <https://doi.org/10.1161/01.STR.32.6.1263>
71. Das S, O'Keefe JH. Behavioral cardiology: recognizing and addressing the profound impact of psychosocial stress on cardiovascular health. *Curr Atheroscler Rep.* 2006;8:111-8. <https://doi.org/10.1007/s11883-006-0048-2>
72. WHO (World Health Organization). Depressive disorder (depression) [Internet]. WHO; 2023 [cited 2023 Aug 23]. <https://www.who.int/news-room/fact-sheets/detail/depression>
73. GBD 2019 Healthcare Access and Quality Collaborators. Assessing performance of the Healthcare Access and quality index, overall and by select age groups, for 204 countries and territories, 1990–2019: a systematic analysis from the Global Burden of Disease Study 2019. *Lancet Glob Health.* 2022;10:E1715-43. [https://doi.org/10.1016/S2214-109X\(22\)00429-6](https://doi.org/10.1016/S2214-109X(22)00429-6)
74. Taylor WD. Depression in the elderly. *N Engl J Med.* 2014;371:1228-36. <https://doi.org/10.1056/NEJMcp1402180>
75. Krishnan V, Nestler EJ. The molecular neurobiology of depression. *Nature.* 2008;455:894-902. <https://doi.org/10.1038/nature07455>
76. Cowen PJ, Browning M. What has serotonin to do with depression? *World Psychiatry.* 2015;14:158-60. <https://doi.org/10.1002/wps.20229>
77. Millan MJ. Multi-target strategies for the improved treatment of depressive states: conceptual foundations and neuronal substrates, drug discovery and therapeutic application. *Pharmacol Ther.* 2006;110:135-370. <https://doi.org/10.1016/j.pharmthera.2005.11.006>
78. Berger M, Gray JA, Roth BL. The expanded biology of serotonin. *Annu Rev Med.* 2009;60:355-66. <https://doi.org/10.1146/annurev.med.60.042307.110802>
79. Hornung JP. The human raphe nuclei and the serotonergic system. *J Chem Neuroanat.* 2003;26:331-43. <https://doi.org/10.1016/j.jchemneu.2003.10.002>
80. Lucki I. The spectrum of behaviors influenced by serotonin. *Biol Psychiatry.* 1998;44:151-62. [https://doi.org/10.1016/S0006-3223\(98\)00139-5](https://doi.org/10.1016/S0006-3223(98)00139-5)
81. Young SN. How to increase serotonin in the human brain without drugs. *J Psychiatry Neurosci.* 2007;32:394-9.

82. Fava M, Kendler KS. Major depressive disorder. *Neuron*. 2000;28:335-41. [https://doi.org/10.1016/S0896-6273\(00\)00112-4](https://doi.org/10.1016/S0896-6273(00)00112-4)
83. Stahl SM. Mechanism of action of serotonin selective reuptake inhibitors: serotonin receptors and pathways mediate therapeutic effects and side effects. *J Affect Disord*. 1998;51:215-35. [https://doi.org/10.1016/S0165-0327\(98\)00221-3](https://doi.org/10.1016/S0165-0327(98)00221-3)
84. Owens MJ, Morgan WN, Plott SJ, Nemeroff CB. Neurotransmitter receptor and transporter binding profile of antidepressants and their metabolites. *J Pharmacol Exp Ther*. 1997;283:1305-22. [https://doi.org/10.1016/S0022-3565\(24\)37161-7](https://doi.org/10.1016/S0022-3565(24)37161-7)
85. Schooten AV, Peters-Scheffer N, Enders-Slegers MJ, Verhagen I, Didden R. Dog-assisted therapy in mental health care: a qualitative study on the experiences of patients with intellectual disabilities. *Eur J Investig Health Psychol Educ*. 2024;14:540-53. <https://doi.org/10.3390/ejihpe14030036>
86. Hasler G. Pathophysiology of depression: do we have any solid evidence of interest to clinicians? *World Psychiatry*. 2010;9:155-61. <https://doi.org/10.1002/j.2051-5545.2010.tb00298.x>
87. Sheline YI, Barch DM, Price JL, Rundle MM, Vaishnavi SN, Snyder AZ, et al. The default mode network and self-referential processes in depression. *Proc Natl Acad Sci USA*. 2009;106:1942-7. <https://doi.org/10.1073/pnas.0812686106>
88. Evans JW, Szczepanik J, Brusché N, Park LT, Nugent AC, Zarate CA Jr. Default mode connectivity in major depressive disorder measured up to 10 days after ketamine administration. *Biol Psychiatry*. 2018;84:582-90. <https://doi.org/10.1016/j.biopsych.2018.01.027>
89. Martens MAG, Filippini N, Harmer CJ, Godlewska BR. Resting state functional connectivity patterns as biomarkers of treatment response to escitalopram in patients with major depressive disorder. *Psychopharmacology*. 2022;239:3447-60. <https://doi.org/10.1007/s00213-021-05915-7>
90. Cole MW, Repovš G, Anticevic A. The frontoparietal control system: a central role in mental health. *Neuroscientist*. 2014;20:652-64. <https://doi.org/10.1177/1073858414525995>
91. Demir S, Atli A, Bulut M, İbiloğlu AO, Güneş M, Kaya MC, et al. Neutrophil-lymphocyte ratio in patients with major depressive disorder undergoing no pharmacological therapy. *Neuropsychiatr Dis Treat*. 2015;2015:2253-8. <https://doi.org/10.2147/NDT.S89470>
92. Mazza MG, Lucchi S, Tringali AGM, Rossetti A, Botti ER, Clerici M. Neutrophil/lymphocyte ratio and platelet/lymphocyte ratio in mood disorders: a meta-analysis. *Prog Neuropsychopharmacol Biol Psychiatry*. 2018;84:229-36. <https://doi.org/10.1016/j.pnpbp.2018.03.012>
93. Drevets WC, Frank E, Price JC, Kupfer DJ, Holt D, Greer PJ, et al. PET imaging of serotonin 1A receptor binding in depression. *Biol Psychiatry*. 1999;46:1375-87. [https://doi.org/10.1016/S0006-3223\(99\)00189-4](https://doi.org/10.1016/S0006-3223(99)00189-4)
94. Meyer JH, Wilson AA, Sagrati S, Hussey D, Carella A, Potter WZ, et al. Serotonin transporter occupancy of five selective serotonin reuptake inhibitors at different doses: an [¹¹C]DASB positron emission tomography study. *Am J Psychiatry*. 2004;161:826-35. <https://doi.org/10.1176/appi.ajp.161.5.826>
95. Hannestad J, DellaGioia N, Gallezot JD, Lim K, Nabulsi N, Esterlis I, et al. The neuroinflammation marker translocator protein is not elevated in individuals with mild-to-moderate depression: a [¹¹C]PBR28 PET study. *Brain Behav Immun*. 2013;33:131-8. <https://doi.org/10.1016/j.bbi.2013.06.010>
96. Satue M, Obis J, Rodrigo MJ, Otin S, Fuertes MI, Vilades E, et al. Optical coherence tomography as a biomarker for diagnosis, progression, and prognosis of neurodegenerative

- diseases. *J Ophthalmol.* 2016;2016:8503859. <https://doi.org/10.1155/2016/8503859>
97. Almonte MT, Capellán P, Yap TE, Cordeiro MF. Retinal correlates of psychiatric disorders. *Ther Adv Chronic Dis.* 2020;11:1-21. <https://doi.org/10.1177/2040622320905215>
 98. Yılmaz U, Küçük E, Ülgen A, Özköse A, Demircan S, Ulusoy DM, et al. Retinal nerve fiber layer and macular thickness measurement in patients with schizophrenia. *Eur J Ophthalmol.* 2016;26:375-8. <https://doi.org/10.5301/ejo.5000723>
 99. Lee CS, Apte RS. Retinal biomarkers of Alzheimer disease. *Am J Ophthalmol.* 2020;218:337-41. <https://doi.org/10.1016/j.ajo.2020.04.040>
 100. Sönmez İ, Köşger F, Aykan Ü. Retinal nerve fiber layer thickness measurement by spectral-domain optical coherence tomography in patients with major depressive disorder. *Noro Psikiyatr Ars.* 2017;54:62-6. <https://doi.org/10.5152/npa.2015.10115>
 101. Burkholder BM, Osborne B, Loguidice MJ, Bisker E, Frohman TC, Conger A, et al. Macular volume determined by optical coherence tomography as a measure of neuronal loss in multiple sclerosis. *Arch Neurol.* 2009;66:1366-72. <https://doi.org/10.1001/archneurol.2009.230>
 102. Kennedy KG, Mio M, Goldstein BI, Brambilla P, Delvecchio G. Systematic review and meta-analysis of retinal microvascular caliber in bipolar disorder, major depressive disorder, and schizophrenia. *J Affect Disord.* 2023;331:342-51. <https://doi.org/10.1016/j.jad.2023.03.040>
 103. Bruder GE, Fong R, Tenke CE, Leite P, Towey JP, Stewart JE, et al. Regional brain asymmetries in major depression with or without an anxiety disorder: a quantitative electroencephalographic study. *Biol Psychiatry.* 1997;41:939-48. [https://doi.org/10.1016/S0006-3223\(96\)00260-0](https://doi.org/10.1016/S0006-3223(96)00260-0)
 104. Dozois DJA, Covin R. The Beck depression inventory-II (BDI-II), Beck hopelessness scale (BHS), and Beck scale for suicide ideation (BSS). In: Hilsenroth MJ, Segal DL, editors. *Comprehensive handbook of psychological assessment. vol. 2: personality assessment.* Hoboken, NJ: John Wiley & Sons; 2004. p. 50-69.
 105. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry.* 1960;23:56. <https://doi.org/10.1136/jnnp.23.1.56>
 106. Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, et al. Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res.* 1982;17:37-49. [https://doi.org/10.1016/0022-3956\(82\)90033-4](https://doi.org/10.1016/0022-3956(82)90033-4)
 107. Moretti F, De Ronchi D, Bernabei V, Marchetti L, Ferrari B, Forlani C, et al. Pet therapy in elderly patients with mental illness. *Psychogeriatrics.* 2011;11:125-9. <https://doi.org/10.1111/j.1479-8301.2010.00329.x>
 108. Janevic MR, Shute V, Connell CM, Piette JD, Goesling J, Fynke J. The role of pets in supporting cognitive-behavioral chronic pain self-management: perspectives of older adults. *J Appl Gerontol.* 2020;39:1088-96. <https://doi.org/10.1177/0733464819856270>
 109. Adams LM, Turk DC. Central sensitization and the biopsychosocial approach to understanding pain. *J Appl Biobehav Res.* 2018;23:e12125. <https://doi.org/10.1111/jabr.12125>
 110. Pachana NA, Ford JH, Andrew B, Dobson AJ. Relations between companion animals and self-reported health in older women: cause, effect or artifact? *Int J Behav Med.* 2005;12:103-10. https://doi.org/10.1207/s15327558ijbm1202_8