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Biological Underpinnings of Anxiety and Well-Being

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Abstract:

While well-being has emerged as a crucial factor in determining resilience and health, anxiety disorders are among the most common mental health diseases in the world, significantly increasing disability and associated risk. In order to investigate the common and unique neurobiological underpinnings of anxiety and wellbeing across biomarkers, brain circuits, genetic factors, and intervention outcomes, this study synthesises research from after 2019. While dopaminergic reward pathways and striatal activity promote well-being through positive affect and resilience, anxiety is caused by amygdala hyperactivity, HPA axis instability, and decreased prefrontal control. Their orientations differ—vigilance versus reward engagement—despite having similar corticolimbic networks. Dopaminergic polymorphisms are linked to wellbeing, while serotonergic and Hypothalamic-Pituitary-Adrenal (HPA) variations are linked to anxiety, according to genetic data. System plasticity is demonstrated by interventions like mindfulness, Cognitive Behavioral Therapy (CBT), and Selective Serotonin Reuptake Inhibitors (SSRIs). The findings, which are backed by longitudinal, cross-cultural, and developmental studies, collectively imply that anxiety and well-being are related but separate, highlighting the potential of precision medicines that lessen threat sensitivity while increasing reward responsiveness.

Keywords: Anxiety Disorders, Psychological Well-being, Neurobiological Mechanisms.

1 Introduction

Anxiety disorders remain among the most prevalent and disabling mental health conditions worldwide, contributing substantially to the global burden of disease. Recent epidemiological estimates indicate a rising prevalence across diverse populations, accompanied by significant increases in disability-adjusted life years (DALYs) and economic costs [1]. Beyond their immediate psychological impact, anxiety disorders are associated with heightened risks for comorbid depression, cardiovascular disease, and impaired immune function, underscoring their broad public health significance. Parallel to these concerns, the

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concept of well-being—encompassing both subjective and psychological dimensions—has gained prominence as a critical determinant of population mental health, influencing not only quality of life but also physical health outcomes and resilience against stress [2]. The World Health Organization and related bodies now emphasize that mental health strategies should aim not only to reduce psychopathology but also to actively promote well-being at individual and societal levels.

In light of these developments, there is a growing need to integrate the study of anxiety and well-being within a unified neurobiological framework. While traditionally considered opposing ends of a single emotional continuum, recent evidence suggests that they rely on partially overlapping but distinct neural networks, including the prefrontal cortex (PFC), amygdala, anterior cingulate cortex (ACC), mesolimbic reward pathways, and systems regulating stress hormones and neuroplasticity [3]. Examining these constructs side by side allows for a deeper understanding of how shared and divergent biological mechanisms shape emotional health, and offers the potential to identify intervention targets that can simultaneously reduce maladaptive threat processing and enhance adaptive reward sensitivity. Such a comparative approach aligns with emerging transdiagnostic models in affective neuroscience and can bridge the gap between clinical symptom reduction and the promotion of flourishing.

This review synthesizes post-2019 peer-reviewed studies identified from PubMed, Web of Science, and Scopus, prioritizing high-quality meta-analyses, systematic reviews, and rigorous empirical research spanning molecular markers, brain networks, and behavioral outcomes. It outlines theoretical foundations, examines biological correlates, and integrates comparative insights to clarify neurobiological intersections between anxiety and well-being while highlighting pathways for personalized interventions and global prevention strategies.

2 Theoretical Foundations

2.1 Anxiety: Definitions, Typologies, and Measurement

Anxiety is increasingly recognized as a multidimensional construct involving the interplay of emotional, physiological, and cognitive dysregulation. From the perspective of categorical nosology, the DSM-5 delineates discrete anxiety disorders such as generalized anxiety disorder (GAD) and social anxiety disorder (SAD) based on symptom patterns, chronicity, and functional impairment. However, dimensional models have gained prominence in recent years, reframing anxiety as a continuum that spans subclinical worry to clinically significant psychopathology, and emphasizing the shared neurobiological substrates across diagnostic categories. Meta-analytic evidence suggests that trait anxiety, in particular, is associated with structural alterations in brain regions critical for neurocognitive control and emotion regulation, including the prefrontal cortex, anterior cingulate cortex, and amygdala, thereby underscoring the role of both cortical and limbic circuitry in its pathophysiology [4].

The conceptual shift towards dimensionality has been paralleled by advances in psychometric assessment. Traditional measures often provided a global severity score, offering limited insight into the qualitative differences between cognitive and somatic symptoms or between transient and enduring forms of anxiety. In contrast, more recent instruments such as the State–Trait Inventory for Cognitive and Somatic Anxiety (STICSA) offer a refined two-by-two structure that separately indexes cognitive and somatic manifestations within both state and trait domains [5]. This distinction aligns closely with neuroimaging evidence indicating that state and trait anxiety rely on overlapping but partially dissociable neural mechanisms. For instance, Saviola et al. demonstrated that state anxiety is characterized by transient shifts in limbic–prefrontal functional connectivity, whereas trait anxiety is linked to more stable patterns of cortical–subcortical coupling [6].

Emerging functional connectivity studies have further elaborated on these trait-related neural signatures. De la Peña-Arteaga et al. reported that higher trait anxiety is associated with altered resting-state integration within attentional control networks, even in the absence of explicit threat cues [7]. Such findings suggest that trait anxiety reflects a persistent bias in attentional allocation and threat monitoring, whereas state anxiety may be more sensitive to environmental contingencies. When considered together, these psychometric and neurobiological data converge on a model in which anxiety is best understood as a multifaceted phenomenon, characterized by distinct temporal dynamics, symptom topography, and neural circuitry.

Research on anxiety remains constrained by inconsistent definitions, limited cross-cultural validation, and scarce longitudinal neuroimaging, highlighting the need for integrative, culturally diverse, and multimodal approaches to clarify its mechanisms and trajectories.

2.2 Well-Being Models in Contemporary Psychology

Well-being is now widely conceptualized as a multidimensional construct encompassing both hedonic and eudaimonic dimensions. The hedonic approach, often operationalized as subjective well-being (SWB), emphasizes

the experience of positive affect, life satisfaction, and the absence of negative affect. In contrast, the eudaimonic approach, frequently captured through psychological well-being (PWB) measures, focuses on meaning, self-realization, and the pursuit of one's potential. Building on these two pillars, recent theoretical developments—sometimes referred to as the "third wave" of positive psychology—have sought to integrate additional dimensions such as resilience, social connectedness, and purpose, thereby broadening the conceptual scope of well-being to better reflect its complexity and contextual variability [8].

Empirical research increasingly supports the neural validity of these models. Systematic reviews of neuroimaging studies indicate that both hedonic and eudaimonic well-being are associated with activity in overlapping yet partially distinct brain networks, particularly involving the prefrontal cortex, anterior cingulate cortex, and reward-related subcortical structures [9]. Functional MRI studies have demonstrated that hedonic well-being tends to be linked with increased activation in brain regions implicated in reward anticipation and positive affect, such as the ventral striatum and orbitofrontal cortex, whereas eudaimonic well-being more strongly engages areas related to self-referential processing, perspective-taking, and goal-directed behavior, including the medial prefrontal cortex and posterior cingulate cortex [10]. These findings suggest that while both forms of well-being share common neural substrates, they are supported by partially specialized neurocognitive mechanisms.

Recent scoping reviews have extended this line of inquiry to encompass emotional well-being more broadly, highlighting consistent associations between positive emotional functioning and neural markers across diverse methodological approaches, including task-based functional Magnetic Resonance Imaging (fMRI), resting-state connectivity, and structural imaging [11]. Importantly, such studies underscore the predictive validity of well-being measures for mental and physical health outcomes, lending support to the argument that well-being is not merely a subjective state but is underpinned by identifiable and measurable biological processes.

Current research on well-being is limited by a lack of cross-cultural validation of measurement tools and scarce longitudinal neuroimaging studies, underscoring the need for integrative, culturally sensitive, and multimodal approaches to clarify its psychological and neural trajectories.

3 Biological Correlates of Anxiety

3.1 Cortisol and HPA Axis Dysregulation

The hypothalamic–pituitary–adrenal (HPA) axis plays a central role in the neuroendocrine regulation of stress and emotion, integrating inputs from limbic, hypothalamic, and brainstem structures to coordinate systemic responses to perceived threat. Dysregulation of this axis has been consistently implicated in the pathophysiology of anxiety disorders, with mounting evidence that it represents both a marker and a potential driver of maladaptive emotional states. Post-2020 studies confirm that individuals with chronic anxiety frequently exhibit elevated basal cortisol concentrations, prolonged diurnal cortisol release, and exaggerated cortisol reactivity under sustained or repeated stress exposures [12]. These alterations reflect a maladaptive shift in neuroendocrine homeostasis that can reinforce hyperarousal, disrupt circadian rhythm stability, and impair the fine-tuned feedback loops necessary for adaptive stress recovery. Such persistent cortisol elevations are thought to contribute to compromised hippocampal integrity, reduced prefrontal inhibition of limbic threat circuits, and heightened vulnerability to stress-related comorbidities, including depression and metabolic disorders. Salivary cortisol, owing to its non-invasive collection, high temporal resolution, and sensitivity to both acute and chronic fluctuations, has emerged as a practical biomarker for indexing emotional dysregulation, cumulative stress burden, and therapeutic response trajectories.

Beyond static associations, recent research has shifted attention toward the modifiability of HPA axis function through targeted psychosocial and behavioral interventions. For example, Lange and Erhardt-Lehmann report that cognitive behavioural therapy (CBT) in patients with anxiety disorders can partially normalize diurnal cortisol slope and attenuate exaggerated reactivity to standardized stress paradigms [13]. Such findings suggest that improvements in cognitive–emotional regulation achieved through CBT may be accompanied by parallel recalibration of neuroendocrine set points, potentially restoring more adaptive feedback sensitivity within the HPA axis. These effects are not restricted to CBT; mindfulness-based stress reduction, aerobic exercise, and structured social support interventions have also been shown to induce measurable shifts in cortisol dynamics, supporting the concept that HPA axis dysregulation is a plastic and potentially reversible process rather than an immutable trait marker.

Further, the link between HPA axis dysfunction and neuroinflammation adds a critical mechanistic layer to people's understanding of anxiety's biological underpinnings. Lei et al. detail how chronic stress-induced HPA hyper-

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activity interacts with inflammatory cascades—particularly involving cytokine release and microglial activation within the hippocampus and medial prefrontal cortex—to amplify synaptic remodeling, neuronal vulnerability, and functional network disruptions that exacerbate affective dysregulation [14]. This bidirectional interplay between endocrine and immune systems not only accelerates structural brain changes but may also perpetuate a feed-forward loop, in which inflammatory mediators further dysregulate HPA axis control. These observations underscore the need for integrated models of anxiety pathogenesis that bridge neuroendocrinology, neuroimmunology, and affective neuroscience, and that incorporate systemic factors such as gut–brain axis signaling and metabolic regulation.

Taken together, findings from other studies converge on the consensus that HPA axis dysregulation—characterized by elevated basal output, heightened stress reactivity, and impaired negative feedback—is a core biological signature of anxiety [12-14]. Cortisol findings in anxiety remain inconsistent across subtypes, stages, and sex, underscoring the need for harmonized longitudinal, cross-cultural, and biomarker-integrated studies to clarify causal pathways and identify neuroendocrine targets for precision intervention.

3.2 Amygdala Hyperactivity and Functional Circuits

Converging evidence from neuroimaging meta-analyses demonstrates that anxiety disorders are consistently characterized by heightened amygdala reactivity to threat-related cues, accompanied by attenuated top-down regulatory control exerted by the prefrontal cortex (PFC). This imbalance is embedded within a broader dysregulation of salience network structures, notably the anterior cingulate cortex (ACC) and insula, which coordinate the detection, appraisal, and prioritization of emotionally salient stimuli [15]. The overactivation of the amygdala, particularly in response to socio-emotional threat cues, amplifies defensive vigilance, while the under-recruitment of dorsolateral and ventromedial PFC regions undermines adaptive reappraisal processes. These functional patterns compromise the brain's capacity to downregulate exaggerated threat responses, perpetuating hypervigilance, heightened arousal, and maladaptive coping strategies observed across multiple anxiety phenotypes. Shackman and Fox situate this profile within the broader construct of "dispositional negativity," emphasizing that such neural signatures may not simply reflect transient state anxiety but instead represent stable, trait-like individual differences that confer vulnerability to chronic affective dysregulation and comorbid mood disorders.

Extending this framework, Langhammer et al. provide a comprehensive systematic review and meta-analysis of resting-state functional connectivity in anxiety disorders, revealing a robust and reproducible pattern of amygdala hyperconnectivity with salience network hubs—including the dorsal ACC, anterior insula, and midcingulate cortex—alongside hypoconnectivity with regulatory prefrontal regions such as the medial and lateral PFC [16]. This network-level reorganization appears to be transdiagnostic, persisting across generalized anxiety disorder, social anxiety disorder, and panic disorder, and is evident even in the absence of acute threat exposure. The persistence of these patterns at rest underscores their potential role as trait markers, reflecting enduring functional architecture rather than transient neural responses to situational stressors. Importantly, this resting-state signature may encode a predisposition toward threat-biased attentional allocation and reduced cognitive control over affective responses, thereby shaping the day-to-day emotional landscape of affected individuals.

Varkevisser et al. critically appraise the methodological landscape of amygdala fMRI research, noting that heterogeneity in task paradigms (e.g., explicit versus implicit emotion processing), definitions of regions of interest, and statistical thresholding complicates the comparability of findings across studies [17]. Nonetheless, their synthesis reaffirms the reliability of amygdala hyperactivation in anxiety, particularly when evoked by ecologically valid socio-emotional threat stimuli such as fearful or angry faces. They further advocate for integrating multimodal imaging approaches—such as coupling functional MRI with diffusion tensor imaging (DTI)—to map the white matter tracts, including the uncinate fasciculus and cingulum bundle, that structurally support functional dysregulation. Such multimodal strategies could clarify how microstructural integrity constrains or enables functional communication between limbic and prefrontal systems.

Taken together, findings from other studies converge on the consensus that amygdala hyperactivity, coupled with disrupted PFC–amygdala functional coupling, constitutes a central neurobiological signature of anxiety disorders [15-17]. However, substantial gaps remain in understanding the temporal dynamics of these alterations—whether they emerge as precursors to disorder onset, evolve with chronicity, or represent enduring scars of past psychopathology. Further, the degree to which these network abnormalities are modifiable by targeted interventions, such as cognitive-behavioral therapy, mindfulness training, or neuromodulation techniques, remains incompletely understood. Addressing these questions will require longitudinal, mechanistically driven studies employing harmonized imaging protocols, multimodal neuroimaging, and experi-

mental intervention designs. Only through such approaches can the field disentangle causality from correlation, determine the prognostic value of circuit-level biomarkers, and advance toward precision-targeted treatments that restore adaptive balance between defensive vigilance and regulatory control.

3.3 Serotonin and SSRI Mechanisms

Advances in cognitive-affective neuroscience have substantially deepened people's understanding of the serotonergic system's role in modulating emotional processing, particularly within the context of anxiety disorders. The serotonergic system, originating largely from the raphe nuclei, exerts widespread influence over corticolimbic circuits that govern threat detection, emotional regulation, and behavioral adaptation. Selective serotonin reuptake inhibitors (SSRIs)—the most widely prescribed class of antidepressants—exert therapeutic effects through a dual time course: gradual neurochemical modulation over weeks to months, and rapid, early-stage changes in affective bias. These early alterations involve a measurable redirection of attention and interpretative processes away from negative, threat-congruent stimuli and toward neutral or positively valenced information, thereby attenuating maladaptive threat monitoring. Godlewska et al. demonstrated that such changes can emerge within the first two weeks of treatment, preceding overt clinical improvement, and are accompanied by functional connectivity shifts between the amygdala and medial prefrontal cortex (mPFC) [18]. This suggests that SSRIs may rapidly engage top-down regulatory pathways, enhancing inhibitory control over limbic hyperactivity and setting the stage for longer-term symptom reduction.

Neuroimaging evidence reinforces the centrality of these early network-level effects for SSRI efficacy. Kotoula et al., in a systematic review of fMRI applications in psychopharmacology, highlight convergent findings across task-based and resting-state paradigms showing SSRI-induced normalization of hyperactive limbic regions—particularly the amygdala—alongside enhanced recruitment of dorsolateral and ventromedial PFC regions during emotional appraisal tasks [19]. Such functional rebalancing within corticolimbic networks is posited to underlie improvements in emotional resilience, stress reappraisal capacity, and the attenuation of pathological anxiety. Importantly, these authors emphasize that neuroimaging biomarkers could serve as early predictors of treatment response, enabling personalized pharmacotherapy that minimizes the trial-and-error period currently inherent in SSRI prescription.

Complementary evidence from Yang et al. extends this mechanistic picture to the connectome-wide level, showing that antidepressant treatment recalibrates amygdala connectivity not only with prefrontal regulatory regions but also with hippocampal and parahippocampal structures, key nodes in memory encoding and contextual modulation of emotional responses [20]. This broader network-level modulation implies that SSRIs do not solely dampen threat reactivity but also enhance the integration of contextual memory and emotion regulation, potentially supporting adaptive decision-making in emotionally salient contexts. Furthermore, the distributed nature of these changes suggests that SSRIs may act through coordinated modulation of both emotion regulation and memory-related pathways, fostering more flexible cognitive control over affective states while reducing maladaptive fear conditioning and threat generalization.

Taken together, findings from other studies converge on the consensus that SSRIs achieve their anxiolytic effects through early and sustained modulation of serotonergic pathways that reconfigure corticolimbic connectivity [18-20]. This reconfiguration appears to be multi-layered, encompassing both rapid engagement of prefrontal inhibitory circuits and longer-term remodeling of hippocampal–amygdala–PFC interactions. However, critical gaps remain. Treatment response is heterogeneous, with some patients showing minimal benefit despite robust serotonergic modulation, and the full clinical benefit often lags behind the onset of neurobiological changes. Moreover, mechanistic data from longitudinal, multimodal imaging—integrating fMRI, magnetic resonance spectroscopy, and PET imaging of serotonin transporter occupancy—remain scarce, limiting people's capacity to link molecular changes to network-level adaptations and clinical trajectories. Addressing these challenges will require integrative approaches that combine advanced neuroimaging, computational modeling of network dynamics, and pharmacogenetic profiling to map the precise neurobiological pathways that distinguish responders from non-responders, ultimately informing precision-based interventions in anxiety treatment.

4 Neurobiological Basis of Well-Being

4.1 Dopaminergic Reward Processing and Positive Affect

The experience of well-being is deeply rooted in the brain's reward chemistry, with dopamine emerging as a central neuromodulator in this relationship. Far from being a mere "pleasure molecule," dopamine operates as a key regulator of motivational drive, reward valuation, and affective tone. Evidence from large-scale neuroim-

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aging syntheses, including the meta-analysis by Radua et al., consistently reveals a recurring pattern: individuals who report higher levels of positive affect, greater life satisfaction, and stronger eudaimonic engagement exhibit increased activation in dopamine-rich hubs such as the ventral striatum and nucleus accumbens [21]. These regions function as integrative nodes within the mesolimbic reward pathway, orchestrating the convergence of sensory input, value assessment, and goal-directed behavior. Their activity supports not only transient moments of enjoyment but also the sustained sense of flourishing and purpose that characterizes high well-being states.

What is particularly striking is that dopamine's role extends well beyond the hedonic impact of reward consumption. As Weinstein emphasizes, a substantial proportion of ventral striatal activity is observed in the anticipatory phase of reward processing—before the reward is actually obtained [22]. This predictive function implicates dopamine in shaping the cognitive-emotional landscape of expectation, enabling individuals to mentally simulate positive outcomes and prepare adaptive responses. Anticipatory reward processing has been linked to resilience mechanisms, wherein the ability to look forward to, and plan for, future positive events helps buffer against stress, maintain mood stability, and promote proactive coping strategies. In this way, well-being is sculpted as much by what people aspire to and anticipate as by what they tangibly experience in the present.

These circuits are also dynamic and highly plastic. Calabro et al. provide compelling evidence that dopamine release within the striatum actively supports reinforcement learning processes, facilitating the updating of internal "reward maps" in light of new experiences [23]. This means that the brain continuously recalibrates its valuation system, preferentially reinforcing patterns of thought, attention, and behavior that have historically yielded positive emotional states. Over time, individuals with more efficient dopaminergic learning mechanisms may not only experience rewards more vividly but also become more adept at seeking out and engaging with contexts that promote well-being. This creates a positive feedback loop in which successful reward prediction strengthens motivational systems, which in turn increases the likelihood of future rewarding experiences, amplifying both hedonic and eudaimonic dimensions of well-being.

Taken together, the lines of evidence from converge on the view that the dopaminergic system plays a pivotal role in scaffolding the mental architecture of well-being [21-23]. It sustains motivation over time, sharpens the capacity to anticipate and prepare for positive experiences, and reinforces adaptive behavioral strategies that maintain emotional balance. When these mechanisms falter—whether through neurochemical disruption, maladaptive learning, or diminished reward sensitivity—the consequences extend beyond a simple reduction in pleasure. They can manifest as a pervasive dampening of life's forward momentum, erosion of goal-directed engagement, and a narrowing of the cognitive-emotional repertoire needed to sustain resilience. Understanding these mechanisms offers a promising avenue for interventions aimed at enhancing well-being, whether through behavioral strategies, neurofeedback training, or pharmacological modulation of dopaminergic pathways.

4.2 Genetic Polymorphisms and Dopamine Receptors

Variation in genes regulating the dopaminergic system offers a compelling biological thread linking brain chemistry to subjective well-being. Genome wide association studies increasingly pinpoint alleles whose influence extends beyond psychiatric vulnerability to shape everyday emotional tone and motivational style. Wingo et al. report that polymorphisms in dopamine receptor genes—particularly DRD2—are associated with greater recruitment of mesolimbic reward circuitry during positive affect, implying that receptor-related differences in postsynaptic signaling can scale the vigor of approach behavior and the subjective salience of rewarding cues [24]. Individuals carrying such alleles appear better able to sustain high levels of well being under stress, consistent with the idea that genetically tuned dopaminergic tone functions as a built in buffer that stabilizes mood and goal pursuit.

The functional implications of these variants are heterogeneous. Synthesizing decades of evidence, Tunbridge et al. distinguish polymorphisms with demonstrable physiological effects from those with minimal impact, emphasizing variants that alter receptor binding affinity, transporter efficiency, or synaptic clearance as most relevant to affective phenotypes [25]. Mechanistically, such variants are expected to shift the balance of tonic–phasic dopamine signaling, reshape prediction error coding, and modify reinforcement learning parameters (e.g., learning rates, choice stochasticity). In imaging genetics work, these molecular shifts map onto individual differences in ventral striatal responsivity and prefrontal engagement during reward anticipation and outcome evaluation—precisely the phases that track well being and motivational persistence.

Broadening the lens from receptors to metabolism, Baetu and Neguţ show that common variation in COMT, DRD1, and DRD2 influences not only the vigor with which people pursue rewards but also the executive functions that sustain pursuit [26]. For instance, COMT Val158Met—by modulating cortical dopamine availability—has been

linked to working memory updating, cognitive control, and reward learning, cognitive endophenotypes that scaffold eudaimonic engagement. In combination, receptor level and enzymatic variants likely shape efficient "gatekeeping" between prefrontal control systems and mesolimbic valuation circuits, thereby influencing both the quality of positive emotion and the durability of goal directed behavior.

At the same time, important caveats remain. Effect sizes for single variants are small, and many findings are sensitive to task design, sample size, and population stratification. Most studies are cross sectional and culturally narrow, limiting inference about causality, sensitive developmental windows, and gene–environment interplay (e.g., stress exposure, social context) that can potentiate or mute genetic effects. Moving forward, the field will benefit from polygenic approaches that aggregate small effects across loci, preregistered imaging genetics in large, diverse cohorts, and longitudinal designs that track how dopaminergic genotypes shape the maturation of reward circuitry from adolescence into adulthood. Together, evidence from other studies indicates that dopamine related polymorphisms do more than subtly tweak chemistry—they calibrate how efficiently the brain encodes, values, and learns from rewarding experience, with downstream consequences for resilience and well being [24-26].

4.3 Neuroplasticity and Social-Mindfulness Interventions

Emerging research increasingly supports the proposition that well-being is not a fixed trait but a trainable neurobiological skill, and that structured mindfulness and compassion-based interventions can act as powerful catalysts for both structural and functional brain reorganization. In a multi-month longitudinal trial, Kok et al. demonstrated that social mindfulness-based stress reduction (MBSR) enhances connectivity within the default mode network (DMN) and salience network (SN)—two large-scale systems central to affect regulation, self-referential thought, and socio-emotional integration [27]. Crucially, these connectivity gains were accompanied by measurable improvements in interpersonal awareness and empathy, suggesting that prosocial mindfulness practices can generate durable network-level adaptations that sustain psychological well-being beyond the intervention period.

Structural neuroimaging evidence corroborates these functional shifts. Hölzel et al. reported that participation in MBSR was associated with significant increases in gray matter density in key hubs implicated in learning, memory consolidation, and emotion regulation, including the hippocampus, posterior cingulate cortex, and temporo-parietal junction. [28] The rapidity of these changes—emerging within as little as eight weeks—underscores the brain's capacity for experience-dependent plasticity, even in mature adults, and suggests that targeted contemplative practice can recalibrate neural substrates in ways directly supportive of adaptive emotional processing and cognitive flexibility.

More recent findings extend these insights across the lifespan. Yue et al. demonstrated that mindfulness-based therapy in older adults enhanced the efficiency of brain functional reconfiguration, a network-level property reflecting the capacity to dynamically adapt neural architecture in response to cognitive and affective demands [29]. This efficiency gain persisted despite age-related declines in structural integrity and co-occurring sleep difficulties, and it was strongly linked to improvements in emotional stability, attentional control, and cognitive agility. Such results highlight the potential of mindfulness interventions not only for bolstering well-being in healthy populations but also for mitigating age-related vulnerabilities and maintaining resilience in the face of neurodegenerative risk factors.

Taken together, the convergent evidence from positions mindfulness and related social-mental training paradigms as potent, biologically grounded tools for enhancing neuroplasticity [27-29]. By reshaping both functional networks (e.g., DMN, SN) and structural substrates (e.g., hippocampal volume, cortical density), these interventions appear to support a virtuous cycle in which improved affect regulation fosters prosocial engagement, which in turn reinforces neural adaptability. Nevertheless, critical questions remain regarding the durability and generalizability of these neural changes, their dose–response characteristics, and the extent to which individual differences—such as baseline connectivity, genetic polymorphisms, or cultural context—moderate intervention efficacy. Addressing these gaps will require well-powered, longitudinal, multimodal studies integrating neuroimaging, behavioral measures, and biological markers to map the precise causal pathways from mental training to sustained well-being.

5 Comparative Analysis and Synthesis

A comparative reading of the literature on anxiety and well-being reveals both striking overlaps and meaningful divergences in their neurobiological substrates. Prior study synthesizes these relationships across four key dimensions—neural circuitry, neurotransmitter systems, genetic markers, and intervention-linked plasticity—providing a concise visual framework to orient the reader before delving into a more detailed discussion. The table underscores the presence of a shared core network—comprising the

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prefrontal cortex (PFC), amygdala, and anterior cingulate cortex (ACC)—that serves as an integrative hub for affective appraisal, salience detection, and emotion regulation in both conditions. However, it also maps the clear asymmetry between the threat-oriented dominance of salience network activity in anxiety and the reward-centered mesolimbic activation in well-being, pointing to divergent priorities in neural resource allocation.

At the systems level, convergent findings from functional neuroimaging repeatedly implicate this core PFC–amygdala–ACC network as central to the processing of both negative and positive affective states. In anxiety, the prevailing pattern involves heightened amygdala reactivity to threat cues, attenuated top-down control from the PFC, and disrupted ACC-mediated conflict monitoring [15–17]. Such dysregulation manifests as persistent hypervigilance, an exaggerated salience signal for potential danger, and diminished cognitive flexibility in reappraising emotional stimuli. By contrast, well-being is typically associated with more balanced PFC–amygdala interactions, alongside robust ACC engagement during contexts of reward anticipation, prosocial behavior, and self-referential processing [21–23, 27–29], supporting adaptive reappraisal and greater emotional stability.

The functional asymmetry between these constructs is most pronounced in two domains: threat reactivity and reward sensitivity. Anxiety states bias neural processing toward rapid detection of potential danger, often over-recruiting salience networks even in the absence of explicit threat [15–17]. In contrast, high well-being states correlate with amplified mesolimbic reward responsiveness—particularly in dopamine-rich nodes such as the ventral striatum and nucleus accumbens—during both positive affective experiences and reward anticipation [21–23]. This divergence reflects not merely opposing affective poles but fundamentally distinct motivational orientations: defensive vigilance versus approach-driven goal pursuit. Importantly, emotional regulation capacity also differs: anxiety frequently involves weakened connectivity between regulatory PFC nodes and limbic regions, while well-being appears to rely on strong, flexible coupling in these circuits that sustains positive mood and supports rapid recovery from negative affect [8–11, 27–29]. Cross-domain comparisons further reveal several critical moderating factors. Cross-cultural investigations suggest that sociocultural norms shape both the behavioral expression of anxiety and the subjective valuation of well-being, potentially influencing the degree to which core affective circuits are engaged in specific emotional contexts. Gender differences have also been observed, with some evidence indicating that women may exhibit stronger PFC–amygdala coupling during positive emotional states—potentially conferring advantages in social-emotional integration—but also heightened vulnerability to stress-induced dysregulation [1–3, 21–23]. Across developmental stages, the trajectory of both anxiety vulnerability and well-being potential is shaped by maturational changes in PFC and subcortical architecture, with adolescence emerging as a critical period of heightened neuroplasticity but also increased susceptibility to maladaptive circuitry reorganization under chronic stress.

A key point of consensus is that anxiety and well-being are not simply inverse points on a single emotional continuum. Rather, they draw upon partially overlapping but functionally distinct neural architectures, with unique circuit dynamics supporting defensive vigilance on the one hand and approach-oriented reward engagement on the other. This conceptual distinction carries direct implications for intervention design: targeting both threat reactivity reduction and reward sensitivity enhancement in parallel could yield synergistic benefits, simultaneously alleviating anxiety symptoms and strengthening well-being capacity.

Nevertheless, limitations in the current evidence base temper these conclusions. Longitudinal neuroimaging studies capable of tracking within-subject neural changes over time remain sparse, constraining causal inference regarding whether observed circuitry patterns are antecedents or consequences of the affective state. Similarly, mechanistically driven intervention trials that integrate multimodal imaging, behavioral metrics, and biological markers are rare, making it difficult to determine how circuit-level changes translate into durable clinical or functional gains. Future progress will require cross-disciplinary collaboration, harmonized imaging protocols, and culturally diverse cohorts, as well as an explicit focus on developmental windows where neuroplasticity can be harnessed most effectively to promote resilience and flourishing.

6 Discussion and Future Directions

Synthesizing findings across biomarkers, neuroimaging, genetic analyses, and intervention studies reveals a converging picture of anxiety and well-being as interconnected yet partially independent constructs underpinned by overlapping corticolimbic and reward-related networks. Biomarkers such as salivary cortisol provide accessible indices of HPA axis function [9–11]. Functional and structural neuroimaging consistently implicates the PFC, amygdala, and ACC as central hubs for both maladaptive threat processing and adaptive emotion regulation [12–14, 18–20]. Genetic evidence further refines this picture, showing that polymorphisms in dopamine receptor and metabolism genes influence the efficiency of reward

circuitry engagement and emotional resilience [21–23]. Intervention research—ranging from pharmacological modulation of serotonergic tone to mindfulness-based programs that reshape network connectivity—demonstrates the malleability of these systems, reinforcing the potential for targeted, circuit-informed approaches [15-17, 24-26].

This integrative framework highlights the design of individualized interventions that simultaneously reduce threat reactivity and enhance reward responsivity, guided by biomarkers, neuroimaging, and genetic profiles. Therapeutic strategies may include cognitive reappraisal, mindfulness, neuromodulation, behavioral activation, or dopaminergic enhancement, tailored to baseline affective profiles. Future priorities include cross-cultural affective neuroscience, longitudinal youth studies targeting sensitive developmental windows, and neurofeedback technologies that enable direct modulation of neural circuits. Together, these directions advance precision models of affective health capable of predicting who benefits from which interventions, ultimately reducing anxiety and fostering well-being across populations and life stages.

7 Conclusion

Elucidating the shared and distinct neurobiological foundations of anxiety and well-being has profound clinical and public health implications. Clinically, mapping the hypothalamic–pituitary–adrenal axis, corticolimbic circuitry, reward dynamics, and genetic polymorphisms supports precision interventions. Such approaches may dampen hyperactive salience networks while strengthening prefrontal regulation, and enhance reward responsiveness via mesolimbic activation and dopaminergic learning. This integration moves beyond symptom relief toward restoring balance across affective networks.

At the population level, neurobiological insights inform scalable prevention programs, including school curricula on emotional regulation, workplace strategies to reduce chronic stress, and community initiatives that foster resilience. Translating biomarkers into mobile health platforms, biosensors, and digital phenotyping enables early detection and timely, culturally adaptable interventions.

Advancing these goals requires cross-disciplinary integration of neuroscience, psychology, genetics, epidemiology, and digital health. Combining neuroimaging, computational modeling, cohort studies, and adaptive trials will generate a robust evidence base for personalized yet contextually responsive approaches.

Finally, resilience emerges as a dynamic, trainable capacity. Early interventions promoting emotional literacy, and later-life practices such as mindfulness, exercise, and prosocial engagement, can reinforce adaptive neural plasticity. A sustained global commitment to resilience may simultaneously reduce anxiety and strengthen well-being for future generations.

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