



REVIEW ARTICLE

# Neurocosmetics and Longevity: Shaping the Future of Well-Being

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## ABSTRACT

Cosmetic science is undergoing a paradigm shift, moving beyond superficial and narrowly defined anti-aging targets toward holistic and longer-term interventions designed as an integral part of daily lifelong self-care, and addressing the fundamental biological processes underlying skin health and beauty together with overall user well-being in the wider context of longevity. Neurocosmetics, positioned at the critical interface between the skin and the nervous system, represents a unique opportunity as a tool for such holistic interventions, and has been making remarkable progress of its own in recent years. We explain the reframing around longevity and briefly review the biological foundations of neurocosmetics, centering on the bidirectional skin-brain communication network through which topical neurocosmetic interventions may benefit both dermatological outcomes and psychophysiological states, improving visible skin appearance while also promoting positive psychological effects such as stress reduction, mood enhancement, and improved sleep quality. We explore advanced measurement tools, including functional magnetic resonance imaging, electroencephalography, and artificial intelligence that have enabled objective assessment of holistic conscious and unconscious neurocosmetic effects, progressing the field beyond superficial or subjective evaluations. We pause to address critical ethical, safety, and regulatory considerations that this field will need to observe, in particular around avoiding the trap of addiction-promoting product development or promotion strategies, and ensuring the transparency that informed consumer choice requires. We review holistic formulation approaches including tactile perception, olfactory stimulation, and multisensory integration, and active ingredients including neuropeptides and neuroactive botanicals. This review aims to provide a framework for positioning neurocosmetics as a scientifically grounded approach to promoting holistic well-being in longevity.

## 1 Introduction

### 1.1 Cosmetic Science: Evolving from Aesthetics to Holistic Well-Being, from Anti-aging to Longevity, and from Symptom Management to Root Cause Intervention

The history of cosmetics and the personal care industry has included repeated paradigm shifts, each induced by deeper changes in scientific advancement, evolving consumer awareness, and approaches to broader health and healthcare. Dating back millennia, cosmetic interventions had focused primarily on decorative or surface cosmetic effects, and social signaling. Traditional anti-aging strategies have primarily focused on a repair and after-the-fact protection approach, and emphasizing the cosmetic remediation or masking, through topical interventions, of 'visible signs of aging' such as wrinkles, age spots, dry skin, and loss of elasticity and firmness [cite historical review of cosmetic science across civilizations]. Cosmetics became increasingly industrialized and medicalized over the 20<sup>th</sup> century. This included the emergence of modern cosmeceuticals, positioning topical products at the intersection of cosmetics and pharmaceuticals<sup>1-2</sup>. Over this period, cosmetics increasingly used scientifically validated claims and powerful bioactive ingredients (iconic examples include alpha-hydroxy acids, retinoids, vitamins C and E, botulinum toxin, and peptides) which demonstrably altered the skin's structure and function beyond strictly superficial effects<sup>3-6</sup>. The promise offered was that topical creams alone could deliver youthful skin health and appearance – and that this represented the key to well-being and self-esteem for the aging user. Throughout, the skin, and indeed the user, was considered for the most part as a passive recipient or an object of work. This approach thus retained a narrow character, treating skin aging as a strictly local dermatological phenomenon amenable to topical intervention aimed at isolated biological targets and outcome parameters, and often largely ignoring the complex interplay between skin health and beauty, systemic physiology, psychological states, and overall aging<sup>7-12</sup>. The traditional "anti-aging" paradigm, which has dominated until very recent years, conceptualized aging primarily as an issue to be delayed, reversed, or concealed, focusing on its visible signs such as wrinkles, hyperpigmentation, and textural changes<sup>13-15</sup>.

In contrast, a more sophisticated and integrative framework has emerged more recently, referred here as "longevity", which conceptualizes aging not as system failure but as a natural process whose healthspan can be extended through evidence-based, multifaceted interventions<sup>16-24</sup>. This paradigm shift has been driven by advances in the science of aging, revealing new biological hallmarks and mechanisms of aging<sup>21-22</sup>, growing consumer awareness of holistic wellness and preventive health as promoters of well-being in longevity<sup>25-26</sup>, increasing recognition of the complex interconnections between psychological stress and biological aging<sup>27-31</sup>, and mounting evidence for holistic or multi-system aging interventions<sup>9,32-33</sup>. The longevity paradigm thus shifts the focus both deeper and wider: towards deeper biological and molecular root causes of aging (rather than its outwardly visible signs only), ultimately aiming to modulate the aging process itself

and thereby extend the skin's "healthspan" (defined as the period during which skin maintains healthy structural and functional integrity)<sup>15,34-37</sup>; and, reframes this consideration within a wider context of holistic well-being in aging.

In the fields of dermatology and cosmetic science, this has thus meant an increasing recognition that skin aging cannot be adequately understood, and should not be addressed, in isolation from systemic well-being factors. Terms including chronic inflammation ("inflammaging")<sup>38-41</sup>, oxidative stress<sup>42-44</sup>, mitochondrial aging<sup>45-47</sup>, glycation<sup>48-49</sup>, hormonal aging<sup>10,50-51</sup>, circadian disruption<sup>52-54</sup>, the skin and gut microbiota<sup>55-58</sup>, nutritional status<sup>59-61</sup>, and psychophysiological stress<sup>62-64</sup> all make this point.

The landscape of cosmetic science, and with it the cosmetics industry, is thus now undergoing one more such paradigm shift, one which may turn into a fundamental transformation, moving beyond the superficial treatment of visible aging signs toward a more integrative understanding of skin health as one intrinsically connected part in overall well-being and longevity. This ongoing evolution in thinking and language in the cosmetics field, from "anti-aging" to "longevity" or "pro-longevity", represents more than a mere semantic refinement. This shift in terminology signals a fundamental reconceptualization of aging in general, and skin aging in particular – including its place within a newly holistic aging picture, and how skin aging should be understood and addressed in that new holistic landscape. This new approach rejects the idea that skin aging is merely an aesthetic concern, and reframes it as part of a complex biological process involving the whole person. Beyond reactive / repair and even simply protective interventions, a longevity approach will look to more proactive or even preventive and anticipated health, wellness, and youth maintenance. The longevity approach will also be more deeply mechanistically oriented, addressing root causes of aging at the cellular and molecular levels, and again seeking to intervene before damage becomes irreversible<sup>18,21-22,24</sup>. This approach will use the language of "healthspan", defined as the period of life spent in good health and function, rather than only lifespan or appearance. In the context of skin, this translates *inter alia* to maintaining barrier integrity, immune competence, regenerative capacity, structural resilience, and functional homeostasis throughout an extended healthspan.

Critically, the longevity approach will need to be explicitly holistic, recognizing that optimal aging requires concerted attention to multiple interconnected systems, including biological ones such as metabolism, immune function, stress responses, sleep, nutrition; but also psychological / emotional and self-image facets of wellness, such as social connection and psychological well-being<sup>9,65-67</sup>. In this manner, the longevity approach will be able to reach past the often limited and transient benefits of narrower paradigms. This will also involve seeing both the skin and the user as a more active part of the process. Potentially, the longevity approach in skin care will lead to lifelong self-care discipline, one potentially including both topical and systemic (or at least nutritional) aspects,

and one started at younger age ranges. Within this holistic framework, the bidirectional skin-brain axis will emerge as a critical, if previously neglected, target. Psychological stress accelerates multiple aging processes, increasing oxidative stress and inflammation, shortening telomeres, impairing autophagy, disrupting circadian rhythms, and compromising immune function, with direct consequences for skin aging<sup>29-31,68</sup>. Conversely, interventions that reduce stress, improve emotional well-being, enhance sleep quality, and support psychological resilience may slow biological aging and extend healthspan<sup>69-72</sup>.

The emerging field of neurocosmetics is fully part of this latest paradigm shift in cosmetic science, towards well-being in longevity: an interdisciplinary domain bridging neuroscience, dermatology, and experiential psychology to recruit skin-brain communication towards user well-being, offering new possibilities to address well-being in longevity through the mind-skin connection. By simultaneously improving skin structure and function while also reducing stress, enhancing mood, promoting relaxation, and supporting sleep, all through topical treatment, neurocosmetic formulations could theoretically achieve synergistic pro-longevity effects beyond what conventional topical or psychological interventions alone could achieve<sup>62,73-75</sup>. This convergence of neuroscience and dermatology has the potential to enable both new modes of intervention and investigation, actively including the conscious and unconscious human experience of cosmetic use, and thus pave the way for a new generation of highly science-based skin care with psychophysiological impact – thus potentially representing a truly transformative concept in clinical and cosmetic dermatological practice<sup>73-47,76-78</sup>.

## 1.2 Neurocosmetics: A New Integrative Frontier

Neurocosmetics has been emerging as a potentially transformative element of this shift toward more integrative approaches. Unlike classical cosmetics targeting superficially visible or structural skin parameters, neurocosmetics engages the cutaneous nervous system, local neuropeptide signaling, and skin-central nervous system communication to influence peripheral dermatological and central (e.g. psychological, emotional) outcomes<sup>73-77</sup>. Neurocosmetics integrates several established scientific fields, including psychodermatology, psychoneuroimmunology, neuroscience, and neuroendocrinology.

### 1.2.1 The Skin as a Neuroendocrine Organ

Far from being a mere passive physicochemical barrier, the skin is and functions as a complex immunologically and endocrinologically active, richly innervated organ capable of producing and responding to hormones, neurotransmitters, and neuropeptides<sup>50,79-85</sup>.

The skin expresses key elements of the hypothalamic-pituitary-adrenal (HPA) axis, including corticotropin-releasing hormone (CRH) and its receptors, proopiomelanocortin and its derivatives (adrenocorticotrophic hormone,  $\alpha$ -melanocyte-stimulating hormone,  $\beta$ -endorphin), and glucocorticoid receptors. The skin also produces melatonin and expresses melatonin receptors, participating in circadian regulation. The skin

also synthesizes and responds to oxytocin, often termed the "love/bonding hormone", which plays a role in mediating stress and social-emotional regulation. These neuroendocrine mediators and receptors suggest para-, auto-, and intracrine mechanisms of action<sup>80-81,83,86-100</sup>.

Psychological stress activates the HPA axis and downstream signaling pathways, leading to systemic release of CRH, cortisol, catecholamines, and other mediators that affect cutaneous immunity, inflammation, barrier function, and cellular biology<sup>62,93,101-103</sup>. Psychodermatology and psychoneuroimmunology study the complex bidirectional relationships between psychological factors and skin conditions; wherein dermatological conditions affect mental and emotional health (psychosocial impact) and psychological states influence skin physiology (psychosomatic mechanisms)<sup>104-107</sup>. Conditions such as psoriasis, atopic dermatitis, acne, vitiligo, and chronic urticaria all show well-documented associations with psychological distress, anxiety, and depression, as well as stress-related exacerbations<sup>63,108-109</sup>. Honeyman comprehensively reviewed psychoneuroimmunological aspects of skin, demonstrating that the nervous, immune, endocrine, and integumentary systems interact bidirectionally in both health and disease<sup>110</sup>. This again confirms that addressing skin health, beauty, and well-being in longevity in a more holistic fashion will require attending to this complex interplay of psychological, neural, immune, and dermatological mechanisms. These disciplines have helped establish that interventions targeting psychological factors (such as cognitive-behavioral therapy, stress management, meditation, and mindfulness) can improve dermatological outcomes<sup>111-113</sup>. Foundational work by Ader, Felten, and Pert *inter alia* showed that the nervous, immune, and endocrine systems form an integrated bidirectional communication network<sup>114-118</sup>. The skin is also the body's largest sensory organ, containing a wide range of mechanoreceptors, thermoreceptors, nociceptors, and more, continuously recording environmental information for the central nervous system<sup>119-122</sup>.

The skin also possesses autonomous neurochemical systems capable of synthesizing, releasing, and responding to diverse neurotransmitters (such as acetylcholine, catecholamines, serotonin, GABA, and neuropeptides such as substance P, calcitonin gene-related peptide, neuropeptide Y, vasoactive intestinal peptide, and the proopiomelanocortin family)<sup>79,83,85,90,119,123-124</sup>. These neurotransmitters regulate a wide range of biological functions in skin, including cellular proliferation and differentiation, melanogenesis, immune responses, vascular tone, barrier function, sensory signaling, and more, contributing to local homeostasis and systemic communication<sup>90,125</sup>. Keratinocytes, melanocytes, fibroblasts, and immune cells within the skin all participate in this neuroendocrine signaling network. In skin, serotonin (best known for its role as a central nervous system neurotransmitter) affects local cutaneous functions including proliferation, differentiation, and immune responses, while also potentially influencing mood and behavior through systemic pathways<sup>125-126</sup>. Substance P, calcitonin gene-related peptide (CGRP), vasoactive intestinal peptide,

and neuropeptide Y regulate diverse processes including vascular tone, immune cell activation, melanogenesis, hair growth, wound healing, and inflammatory responses<sup>79-81,90</sup>. Cutaneous nerve fibers release these neurotransmitters and neuropeptides in response to various stimuli, leading to rapid local modulation of skin function.

Recent research has elucidated specialized C-tactile (CT) afferents, low-threshold mechanoreceptors sensitive to low-force, low-speed touch, linked to brain regions involved in emotional processing as opposed to purely discriminative touch perception<sup>127-135</sup>. CT afferents are thought to mediate hedonic and emotional aspects of touch perception, contributing to social bonding, stress reduction, and emotional well-being<sup>136-138</sup>. This neurobiology is relevant to the sensory experience of cosmetic use (including variables such as texture, temperature, application mode, residual feel after application, and more), which can influence psychological states in ways quite independent of the biological effects of the formulation's active ingredients on the local skin biology itself<sup>75,139-142</sup>.

Each of these pathways provides potential biological targets for neurocosmetic interventions. Neurocosmetics thereby represents an innovative category of cosmetic products aimed at leveraging the intimate connection between the integumentary and central nervous systems to enhance not only skin health but also sensorial and emotional well-being<sup>73-74,76-78,126</sup>. Neurocosmetic topical formulations have thus claimed activity on the cutaneous nervous system or local mediators, thereby combining dermatological benefits with a psychophysiological impact.

### **1.2.2 Biological Foundations: The Skin-Brain Axis, Embryological Origins, and Bidirectional Communication**

The skin-brain axis describes the bidirectional communication network operating through neural, endocrine, immune, and possibly other pathways between the skin and the central nervous system, allowing sensory information from cutaneous receptors to reach the brain, and enabling the skin to respond to brain-produced neurotransmitters and hormones<sup>73-74,143-145</sup>. This bidirectional interface allows environmental stressors affecting the skin to influence brain function and, conversely, enables psychological states to manifest in cutaneous responses. The connection between skin and the nervous system originates at the earliest stages of embryonic development, as both skin and nervous tissues derive from the same ectoderm germ layer, from which the neural plate gives rise to the central nervous system while adjacent cells differentiate into epidermis<sup>143,146-147</sup>. This shared origin underlies continued molecular, structural, and functional interconnections.

The bidirectional nature of skin-brain communication operates through multiple interconnected mechanisms. In the afferent direction (inward, skin to brain), the skin functions as a major sensory interface. Specialized sensory neurons transduce mechanical, thermal, chemical, and noxious stimuli into electrical signals conveyed to somatosensory cortices, as well as to limbic and emotional processing regions including the insula, anterior cingulate

cortex, and amygdala<sup>128,132,134,148-149</sup>. These cutaneous sensory fibers can also communicate changes in local conditions such as pH or the presence of inflammatory mediators. These neural pathways can modulate stress responses and influence emotional states<sup>91,145</sup>. Cutaneous sensory input can modulate autonomic nervous system activity, HPA axis activation, and emotional states<sup>136,138,150-151</sup>. Beyond neural signaling itself, cytokines, chemokines, and other immune mediators released in the skin during inflammation or barrier disruption can also take part in "peripheral-to-central immune signaling"<sup>62,125-155</sup>. In the efferent direction (outward, brain to skin), psychological and central nervous system states such as stress, anxiety, or emotional arousal stress can activate the HPA axis and the sympathetic-adrenal medullary system, leading to the release of CRH, adrenocorticotropic hormone, cortisol, and other mediators into the bloodstream<sup>81,143</sup>. The skin, stimulated through respective receptors for these mediators, responds with changes in vascular tone, immune function, barrier function, sebum production, cellular proliferation and differentiation, gene expression, and more<sup>79-80</sup>. Additionally, peripheral sympathetic nerve fibers innervating skin can release neuropeptides (e.g., neuropeptide Y) that directly influence cutaneous cells<sup>119,156-158</sup>. This bidirectional communication creates feedback loops, where the status of the skin can influence psychological states, and vice-versa, in some cases even potentially establishing vicious feedback cycles. This is observable in disease states such as atopic dermatitis, psoriasis, and acne, which have some association with psychological distress, including the possibility of stress-related aggravation<sup>105,159-161</sup>. Recent work has also thrown light on the role of dopamine and serotonin in psoriasis<sup>125</sup>.

### **1.3 Current State of Neurocosmetics: Opportunities and Knowledge Gaps**

Despite growing scientific and industrial commercial interest, neurocosmetics retains some significant knowledge gaps and methodological challenges. Products claiming neurocosmetic effects have been marketed, often based on neuropeptides, neuromodulatory botanical extracts, sensorially targeted formulations, or aromatherapeutic components; the scientific basis for some of these claims remains limited, while others are better-established<sup>73-77</sup>.

Several aspects of this field still hold vast room for improvement and knowledge expansion. While the biological basis for bidirectional skin-brain communication is now well-established, much remains to explore regarding which specific molecular targets, pathways, and mechanisms might be effectively modulated by topical neurocosmetic ingredients to achieve neurodermatological outcomes supporting well-being in longevity<sup>73-77</sup>. Uncertainty remains around the ability of cutaneous neurochemical modulation to meaningfully influence the user's holistic wellbeing experience. The development and adoption of appropriate methods to objectively quantify the results of proposed interventions, and validate their clinical significance, remains a main challenge. Traditional cosmetic clinical trials focus on objective dermatological parameters (such as the 'Big Four': wrinkle counts and

dimensions, skin barrier function, skin pigmentation, and skin biomechanics) and subjective self-assessments of appearance. Leveraging neurocosmetics to deliver well-being via topical regimens will require additional routes to assess psychological and emotional outcomes, while still facing traditional complexities including placebo effects, expectation bias, and subjectivity. Objective neurophysiological measurements (such as electroencephalography, cortisol levels, or neuroimaging) are still rarely employed in cosmetic research, but are likely the key to validating neurocosmetic effects. On the other hand, the intentional modulation of nervous function, even peripheral, potentially raises important safety and ethical considerations in addition to those involved in traditional cosmetics. Concerns may go as far as a potential for habituation, unintended psychological effects, and interactions with medications or underlying psychological conditions; ethical implications of products influencing emotional states, artificially enhancing user well-being, must be included in the discussion.

#### **1.4 Goals and Scope - Neurocosmetics in the Paradigm Shift Towards Holistic Intervention for Well-Being in Longevity.**

Neurocosmetics emerges at the convergence of multiple contemporary trends: the holistic wellness movement, increasing mental health awareness, and the demand for science-backed, multifunctional interventions<sup>162-164</sup>. Modern consumers, particularly those prioritizing self-care and mental health, increasingly seek products that offer benefits beyond superficial aesthetics, valuing emotional balance and experiential quality alongside visible results.

This makes neurocosmetics a natural fit for the new longevity framework, shifted from purely external, appearance-focused interventions to holistic strategies recognizing the interconnected nature of skin health, emotional well-being, and whole-person well-aging.

In this context, neurocosmetic formulations can potentially achieve dual outcomes: improving skin appearance and function while simultaneously promoting positive psychological outcomes such as stress reduction, mood enhancement, improved sleep quality, and overall emotional resilience. This integrative approach acknowledges that skin health and beauty cannot be handled in isolation from other integrated factors, if the goal is now to address the whole person's well-being in longevity.

Beyond cosmetic concerns *per se*, by alleviating emotional stress, improving sleep quality, and supporting the skin's neuroendocrine balance, these formulations may help prevent stress-accelerated aging and maintain the skin's structural and functional integrity over time. Rather than compensating for aging signs, neurocosmetics can aim to extend the skin's healthspan by addressing the psychophysiological factors that contribute to accelerated aging.

This convergence of neuroscience, psychology, immunology, endocrinology, and dermatology has the potential to grow beyond an incremental advance in

cosmetic science, and become part of a fundamental reconceptualization of skin and personal care: beyond appearance, promoting holistic well-being in longevity. Neurocosmetics here becomes an integral component of a complete longevity strategy, recognizing that the skin's health and overall physical and psychological well-being are mutually integral, and that nurturing the skin-nervous system axis may offer unique opportunities to enhance quality of life in longevity.

Given neurocosmetics' potential contribution to holistic longevity strategies, alongside knowledge gaps and challenges which remain, a need exists for comprehensive, critical review synthesizing current knowledge, evidence, and best practices, and charting possible directions for future research. The aim of this review is thus to provide an evidence-based framework for understanding neurocosmetics as a scientifically grounded approach to integrate skin health and psychophysiological well-being in the context of promoting longevity. Beyond mere marketing narratives, we wish to build a starting point for systematic evaluation of biological foundations, mechanisms of action, evidence for efficacy, and ethical considerations. Specific objectives of this review include: Establishing biological foundations, describing the relevant aspects of skin neurobiology and neurochemical pathways, skin-brain communication lines, and mechanisms behind observed neurocosmetic effects, as a first step to providing mechanistic rationales; Reviewing some of the latest advancements in measurement methodologies, including advanced tools and techniques for objectively assessing neurocosmetic effects, including neurophysiological measurements (including electroencephalography and functional magnetic resonance imaging), stress biomarkers, and more; Addressing ethical and regulatory concerns, including some potential risks and ethical implications of neuromodulatory cosmetics, as a first step to proposing principles for responsible development and marketing; Evaluating active ingredients and formulation strategies, reviewing the evidence for specific neurocosmetic ingredients (neuropeptides, neuromodulatory botanicals, aromatherapeutic compounds) and formulation approaches (sensory design, texture optimization, delivery systems), and distinguishing well-supported interventions from more speculative ones; Exploring integrative approaches, including how neurocosmetics can be brought into synergy with other holistic well-being dimensions, such as multisensory formulation design; and finally, suggesting some possible future directions, research priorities, and the interdisciplinary collaborations necessary to advance neurocosmetics from an emerging concept to a mature, evidence-based field.

This review is intended for diverse audiences, including academic researchers in dermatology, neuroscience, psychology, and cosmetic science; preclinical and clinical model developers; ingredient and product developers and formulators in the cosmetics industry; clinicians interested in integrative approaches to skin health and psychodermatology; regulatory scientists; and informed consumers seeking to understand the scientific basis for emerging neurocosmetic claims.

The scope of this review includes topical cosmetic and cosmeceutical products shown to modulate skin-central nervous system communication, neurochemical signaling in skin, or psychophysiological aspects of user experience, through topical application. Sensory dimensions of formulation design, integral to the user experience, are also discussed. We explicitly situate neurocosmetics within the broader context of well-being in longevity, emphasizing holistic well-being rather than isolated or superficial outcome parameters.

Following this introduction, Section 2 will examine some of the latest tools and methodologies for researching and demonstrating neurocosmetic effects, including neuroimaging, electrophysiology, and artificial intelligence applications. Section 3 will address some of the specific ethical and regulatory considerations involved in neurocosmetics. Section 4 will explore holistic formulation approaches, emphasizing multisensory design principles. Section 5 will evaluate some active ingredients in the neurocosmetic space, including neuropeptides and neuroactive botanicals. Finally, Section 6 will conclude by identifying future research directions, and offer perspectives on positioning neurocosmetics within comprehensive longevity strategies.

By providing this review, we hope to assist the maturation of neurocosmetics from an intriguing concept into a rigorous, evidence-based discipline that can meaningfully contribute to holistic well-being in longevity.

## 2. A New World, with New, More Holistic Tools

The evolution of neurocosmetics research has been propelled by the rapid development of practically applicable measurement methodologies, assisting the move beyond the narrow, monochrome lens of isolated biomarker analysis and toward more holistic, multidimensional assessment of skin health, the skin-brain-emotion axis, and the user's well-being experience. Future research might embrace multidimensional measurement strategies to better capture the user's well-being experience. These include sophisticated neuroimaging, electrophysiological, and artificial intelligence-driven tools. As Diwoux and coworkers<sup>75</sup> emphasized in their systematic review, the use of cosmetics is inherently a holistic, multisensory experience, necessitating measurement approaches that honor this complexity; functional neuroimaging in particular has emerged as a critical tool for validating neurocosmetic mechanisms and understanding consumer-product relationships. These methods align with emerging trends in consumer neuroscience, where they join an array of biometric assessments – including heart rate variability, galvanic skin response, and facial electromyography – to help evaluate psychophysiological responses to product exposure<sup>165</sup>. Additionally, where earlier methods (such as the widespread use of questionnaires) were in most cases both subjective and focused on the user's conscious and verbalized experience, some of these newer methods enable more quantitative measures, as well as broadened access to subconscious as well as conscious components of the user's wellbeing experience.

### 2.1 Functional Magnetic Resonance Imaging: Neuroimaging Brain-Skin Connectivity

Functional magnetic resonance imaging (fMRI) has emerged as a powerful tool for objectively mapping the neural correlates of cosmetic product use and tactile skin stimulation – whether that be in the context of the product application itself, or of its short- and longer-term effects on skin sensoriality. fMRI investigations have revealed that cosmetic application activates brain regions associated with pleasure and reward, including the nucleus accumbens, ventral pallidum, and hippocampus. Notably, the left ventral pallidum shows enhanced activation during use of preferred cosmetic products, correlating with product attachment and anthropomorphic attribution<sup>166</sup>. Querleux and others demonstrated that fMRI could distinguish brain activation patterns when subjects touched cosmetic-treated skin versus untreated skin, revealing differential activation patterns in specific somatosensory cortex areas for the physical and emotional components of physical component of tactile perception, opening the door for objectivation of the psychological dimensions of cosmetic experience<sup>167-168</sup>. This methodology has enabled the field to move beyond the constraints of subjective self-report, offering quantifiable signatures of the sensory and emotional effects of cosmetic interventions.

### 2.2 Electroencephalography and Real-Time Emotional Assessment

Electroencephalography (EEG) has proven particularly valuable for assessing emotional responses to cosmetic products and their sensory attributes in real-time, with reduced bias compared to explicit self-report methodologies<sup>169-170</sup>, and offering temporal resolution that complements fMRI's spatial precision. As with fMRI, this method's scope can potentially cover attributes of the immediate experience of product use, as well as changes in skin sensoriality and associated emotional valence resulting from product use over the short or longer term. EEG is also noticeably easier to implement in clinical research than fMRI, as well as considerably less costly.

Gabriel and coworkers<sup>140</sup> demonstrated that EEG could successfully differentiate between cosmetic products based on emotional valence and arousal measured during application (based on alpha and beta wave activity). Wang<sup>170</sup> further showed that EEG-based emotional valence assessment could distinguish between different cosmetic creams across multiple sensory dimensions (olfactive, vision, and feel during and after application), drawing a more comprehensive profile of the emotional experience during product use. Diwoux and coworkers<sup>79</sup> recently reviewed neurophysiological approaches to cosmetic research, identifying frontal alpha asymmetry as a particularly useful indicator of positive emotional states, albeit with a remaining need for more robust and standardized protocols. These EEG methodologies represent a significant advance over traditional (subjective) sensory panels, providing objective, quantifiable data on the psychobiological in-use impact and experience, as well as post-use and long-term benefits, of cosmetic interventions.

## 2.3 Digital Technology and Artificial Intelligence Integration

The rapid rise and adoption of new technologies including artificial intelligence and machine learning, wearable sensors, and personalization algorithms is also expanding the range of possibilities for skin and well-being research, and the holistic design of neurocosmetic products aimed at well-being in longevity.

The applications of artificial intelligence-powered platforms, able to process unprecedented volumes of information at speed, are increasingly employed for predictive analytics, are ballooning at ever-increasing rates. Eventually, these tools may be able to utilize historical user skin health and beauty data, combined with environmental, nutritional, health and other parameters, to forecast potential concerns and provide proactive recommendations at the level of populations and individuals. Wearable devices capable of real-time monitoring of simple parameters such as skin hydration, UV exposure, and other physiological metrics enable real-time data integration with artificial intelligence systems to deliver contextualized skincare guidance based on real-life activities and conditions. Advanced personalization devices, such as artificial intelligence-driven individual user formulation systems, might analyze individual skin characteristics and preferences to create customized on-demand products, using algorithms to optimize formulations iteratively as user data accumulates<sup>171</sup>. As the field advances, neurocosmetics may come to incorporate increasingly sophisticated understanding of individual variation in skin-brain axis function, potentially leveraging artificial intelligence and personalized medicine approaches to tailor interventions.

In dermatological image analysis, deep learning algorithms are already achieving diagnostic accuracy that meets or exceeds that of trained dermatologists. Li and coworkers<sup>172</sup> reviewed current developments in artificial intelligence-based dermatology image analysis, highlighting some systems' performance in analysis of skin lesions and conditions. A new review by the McMullen group examined machine learning methods for determining skin age, noting that that artificial intelligence models achieved a striking mean error range of 2-8 years (based most often on facial image analysis, but also including some biomarker-based analyses)<sup>173</sup>. Notably, the incorporation of dynamic facial expressions was found to improve the accuracy of age estimations, suggesting that artificial intelligence could capture subtle emotional markers, overlooked so far in more traditional assessments. For emotional analysis, artificial intelligence-driven facial expression recognition systems have also advanced dramatically. Recent deep learning approaches have shown promise for highly accurate, real-time emotion detection in real-world conditions<sup>174</sup>. These systems will likely provide an increasing contribution to a nuanced understanding of emotional states, to complement instrumental / physiological measurements.

These all represent both a potential deepening and broadening of the scope of holistic well-being interventions – by providing more, richer, and more precise data, correlated to a real user in real life and

real time. The natural integration of emotional / affective parameters would then represent a new opportunity for the neurocosmetic approach.

## 3. A Note of Caution: Ethical, Safety, and Regulatory Considerations

As the emerging field of neurocosmetics bridges neuroscience, dermatology, and cosmetic science, it will need to carefully navigate complex regulatory landscapes and uphold the highest standards of consumer protection and ethical practice. While this can and should be the topic of a full-length review in its own right, here we will only broach very briefly some of the considerations that must guide responsible development and marketing of neurocosmetic products.

### 3.1 Current Regulatory Landscape; and Avoiding Drug Territory.

In the European Union, Regulation (EC) No 1223/2009 defines a cosmetic product as "any substance or mixture intended to be placed in contact with the external parts of the human body...with a view exclusively or mainly to cleaning them, perfuming them, changing their appearance, protecting them, keeping them in good condition". Similarly, the US Modernization of Cosmetics Regulation Act of 2022 defines cosmetics as "articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body...for cleansing, beautifying, promoting attractiveness, or altering the appearance"<sup>175-178</sup>.

The working definition of neurocosmetics as products aiming to modulate the neuro-cutaneous interface while emphasizing local, topical action without systemic absorption or systemic effects aims to maintain a clear position within the cosmetic regulatory sphere, without straying into the pharmaceutical domain. The Scientific Committee on Consumer Safety's ongoing guidance on ingredient safety assessment, requiring comprehensive evaluation of potential hazards, exposure levels, and risks to consumer health, should be observed<sup>179</sup>.

Concerns have also been raised around products that may produce systemic effects, warning that such products raise both safety and regulatory issues, particularly as regards psychologically vulnerable patients (a common comorbidity in the context of skin disease in particular)<sup>73-74,76-78,180</sup>. Neurocosmetics must therefore embrace a strategy of smart, local, minimalistic interventions that produce holistic well-being ripple effects through local mechanisms without crossing into systemic activity – as it were, "peripheral modulation for holistic well-being" - leveraging skin-nervous system signaling without directly altering central nervous system chemistry, thereby maintaining cosmetic status while delivering meaningful benefits<sup>74</sup>.

### 3.2 Ethical Considerations: Avoiding the Addiction Trap

The history of consumer product industries offers plentiful cautionary tales about the ethical perils of a model reliant on leveraging reward systems. The tobacco and food industries provide particularly relevant examples<sup>181</sup>. In both cases, products relied on the

dopamine reward system to drive product consumption – sometimes ignoring the accompanying risk of addiction<sup>182-184</sup>. Recent research on ultra-processed foods demonstrates that non-drug products can exhibit addictive potential when engineered to produce exaggerated dopamine responses<sup>185-186</sup>. Neurocosmetics should explicitly and intentionally reject this hazard. Products and formulations designed to modulate the skin-brain axis for well-being not only should not be engineered to drive consumption in this manner and thus potentially create dependency, compulsive use, or withdrawal symptoms – they should be tested over the long term to ensure this is not taking place. This will likely involve avoiding products that produce acute, intense reward responses or that could otherwise drive compulsive use behaviors; designing for sustainable, balanced effects rather than the dramatic highs and lows common in addictive substance patterns; implementing rigorous safety assessments specifically addressing addiction potential, particularly for products targeting stress, mood, or emotional states; and adopting ethical marketing practices that avoid exploiting psychological vulnerabilities or promoting excessive use. Like the new longevity approach itself, this ethical framework should be proactive rather than reactive. As in so many other scientific, industrial, and policy fields, the key question of neuroethics<sup>187</sup>, is not one of what can be done, but of whether what can be done, should be done. For neurocosmetics, this means establishing higher industry standards, matching holistic well-being longevity claims with genuinely prioritized long-term consumer well-being.

### 3.3 Transparency and Consumer Education to Enable Informed Choice.

The principle of informed consent, foundational to medical ethics, may be seen as applying equally to consumer products. While cosmetics purchase decisions differ from medical procedures, the underlying ethical principle of respect for autonomy through provision of adequate information remains key. Pseudoscientific language should be avoided throughout.

In the specific context of neurocosmetics, this transparency may include multiple levels of disclosure. Claims for cosmetic products should be supported by adequate, truthful, and verifiable evidence<sup>188</sup>; this evidence should not be overstated, and claims should not imply pharmaceutical-level efficacy. Transparency around the mechanism of action should provide consumers clear, accessible explanations of how neurocosmetic products work, and educate by distinguishing between local effects on direct neurobiological targets, indirect well-being effects mediated through the skin-brain axis, and subjective sensory experiences. Transparent disclosure of safety data and potential risks will also be essential, particularly for vulnerable populations; neurocosmetic products should clearly identify any contraindications for individuals with psychological conditions, those taking psychoactive medications, or any other at-risk groups.

Neurocosmetics offer genuine potential to enhance well-being through the skin-brain axis, but realizing this potential requires unwavering commitment to ethical principles, regulatory compliance, and consumer protection. The industry must chart a course characterized

by smart, minimalistic interventions; explicit rejection of addiction-promoting design; rigorous safety assessment; and transparent, evidence-based communication that empowers informed consumer choice.

## 4. Towards a Holistic Formulation Approach.

Just as anti-aging thinking evolves towards a holistic paradigm of well-being in longevity, applied neurocosmetics should widen to encompass holistic formulation approaches: ones integrating active and functional ingredients into a complete well-being and sensory experience designed to support and enhance the developing longevity routine. This integrated approach might leverage multiple sensory modalities, including touch but also sight, smell, and even sound, to fully bring the bidirectional skin-brain axis to bear and simultaneously deliver both dermatological and psychological well-being outcomes. Multisensory contributions to the experience of contact with cosmetic formulations have been reviewed by Spence and Zhang<sup>189</sup>, who observed that “The complex interaction between the particular skin site stimulated and the multisensory attributes of the product (...) can exert a number of effects on an individual’s mood, their emotions, as well as on their self-perception (and self-confidence) ... .” And beyond sensoriality itself, Hirao and coworkers<sup>190</sup> showed that contextual cues, such as luxury, can enhance the reward value of the tactile experience. Active ingredients will directly target local neurocosmetic biology; functional ingredients will both deliver the actives and also deliver amplifying sensorial experiences and enhance the user’s sensorial receptivity to the product concept; and sensorial ingredients such as perfume will serve to reinforce the experience and its emotional component. The experience with the product will benefit from being conceptualized and designed as a whole, considering chassis functionals, actives, and perfumes as working together to deliver a global well-being and sensorial experience.

### 4.1 Tactile Perception and Product Texture

Skin tactile perception during and following application of cosmetic formulations engages complex neurophysiological mechanisms mediated by distinct receptor populations (including mechanoreceptors and thermal receptors) in the skin. The affective aspect of tactile perception also engages distinct systems<sup>191</sup>: A-β fibers are responsible for discriminating fine spatial / textural detail<sup>121,192</sup>, while emotional aspects are mediated by unmyelinated C-tactile afferents, more responsive to slow, gentle stimulation (characteristic of pleasant sensation<sup>148,193</sup>). The latter signal to the posterior insula and cingulate and prefrontal cortex, all involved in emotional valence<sup>129,132-133,194</sup>. This has suggested that contact with a cosmetic formulation may engage sensory and emotional systems simultaneously.

Touch is the central element in the multimodal sensory experience of texture<sup>195-196</sup>, such as that of a cosmetic product<sup>170</sup>, from first contact in dispensing from the container (or indeed, with the container itself and even its secondary packaging), to product application itself, and the no less important post-application sensations. This

"after-feel" (described using terms like stickiness, oiliness, smoothness) has long been used as the critical focal point of sensorial analysis in evaluating formulation texture and user experience after the penetration of the formula<sup>197-198</sup>.

However, emotional evaluation of this experience has been relatively rare. Emotions triggered by tactile experiences can, nevertheless, be objectively assessed using physiological or neuroimaging methods such as functional near-infrared spectroscopy<sup>199</sup> or EEG<sup>140,200</sup>. fMRI studies of the emotional valence of touch have consistently implicated brain areas linked to reward and social processing<sup>132,201</sup>. Pleasant touch engages the orbitofrontal cortex, putamen, and pregenual anterior cingulate cortex, which code for reward value and hedonic experience<sup>133,135,202</sup>.

Our own investigations<sup>191</sup> employing functional magnetic resonance imaging (fMRI) further highlighted a hierarchical integration of tactile input, from simple sensory encoding up to higher-order affective valuation, by showing that tactile experiences delivered by cosmetic formulations enhanced with an emulsifier derived from Quinoa starch (marketed by Lucas Meyer Cosmetics as Pickmulse™) can activate not only touch-encoding somatosensory regions (which were shown to be also activated using a reference cream or under no-cream touch stimulation control conditions), but also areas involved in affective / wellbeing and reward processing in the brain, including the orbitofrontal cortex, nucleus accumbens, amygdala, and putamen. This phenomenon may involve C-tactile afferent pathways, known to be involved in affective tactile signals, and suggests that intentionally designed cosmetic formulations can positively leverage the emotional salience of touch – potentially recentering a new, broader understanding of touch sensoriality as part of a holistic neurocosmetic longevity wellbeing approach.

These findings have further highlighted the influence of functional ingredients (usually, as opposed to the active ingredients), defined as ingredients responsible for the formulation's physical and sensorial properties, or for its ability to deliver active ingredients – including thickening agents, emollients, emulsifiers, and the like - on the emotional valence of the formulation's in-use experience.

It should be noted that it may be useful to fully take into account cultural differences in the experience of tactile stimulation, and in its verbal communication. Cross-cultural studies have identified differences in haptic evaluation of facial skin, with distinct patterns observed across Asian, European, and North American populations<sup>203-204</sup>. These findings may point to a need to formulate cosmetic products' sensory profiles to align with culturally-specific tactile preferences and exploration behaviors.

#### 4.2 Olfactory Stimulation, Mood, and Stress Response

The olfactory system provides direct neural pathways to limbic structures involved in emotional processing, making fragrance a powerful tool for modulating psychological states. Neuroimaging studies have confirmed activation of the piriform cortex, insula, amygdala,

parahippocampal gyrus, and superior temporal gyrus inter alia in response to odor stimulation<sup>205</sup>. Clinical studies using EEG and autonomic nervous system measurements have demonstrated that specific aromatic oils significantly reduce mood disturbances. For example, white musk aromatherapy showed significant decreases in Fatigue-Inertia, Tension-Anxiety, and Total Mood Disturbance scores on the Profile of Mood States assessment<sup>206</sup>. Other work with olfactory stimulation (for example, by Choi and coworkers<sup>207</sup>) shows effects on enhanced relaxation states. The value of olfactory stimulation as part of a holistic neurocosmetic approach to well-being in longevity is thus self-evident.

Beyond the value of emotional-psychological effects as such, Angelucci and coworkers<sup>208</sup> have reviewed the physiological effects of olfactory stimulation, and found that influences on a wide range of parameters, including stress biomarkers, oxidative stress, dopamine, and direct skin function indicators including skin barrier, sebum secretion, and cutaneous immune function. Whether these are direct actions, or indirect (that is, mediated by the emotional valence of olfactory stimulation), the value of such interventions may well yet be mostly untapped.

#### 4.3 Visual Design and Multisensory Integration

The relationship between aesthetic perception and purchasing decisions has been widely studied, including in consumer product contexts. For example, Chattaraman and others<sup>209</sup> report on fMRI investigations showing the neurological chain involved – a key component of which is the emotion-linked amygdala and the reward network.

More broadly, properly considered holistic sensory experience extends beyond individual sense modalities, to the overall experience these interacting modalities generate, and encompasses product and signaling aesthetics – including packaging design. Research on multisensory packaging demonstrates that color, texture, ambient scent, and unboxing interactions operate synergistically rather than in isolation to shape consumer perception, emotional responses, and product appraisal. Xiao and coworkers<sup>210</sup> showed that multisensory packaging design for chocolate can influence emotional responses, willingness to pay, and even taste perception itself. A review of multisensory food packaging design by Spence<sup>211</sup> broadens this picture.

In the skin care area, Rodriguez and coworkers<sup>212</sup> recently published a review of multisensory design, highlighting its potential to drive user engagement, loyalty, and treatment adherence – the latter especially, seeming to hold possible value in the context of designing a potentially lifelong holistic well-being regimen.

## 5. Active Ingredients

In a world where cosmetic formulations will now be expected to deliver well beyond a narrowly defined anti-aging benefit, the central active ingredients whose design was up to now narrowly targeted at one biological target or parameter will now be expected, not to activate one target, but as it were, to activate the user's well-being itself.

## 5.1 Neuropeptides and their Applications in Skin Care

Neuropeptides, small molecules involved in neural signaling, represent a potentially valuable class of bioactive molecules for delivering well-being in longevity skin care. They play a role in regulating diverse physiological processes including inflammation, wound healing, collagen synthesis, and barrier function<sup>73,77,36,213</sup>.

A native set of skin neuropeptides orchestrates critical functions in tissue homeostasis and aging. Substance P, CGRP, vasoactive intestinal peptide, and neuropeptide Y are among the most extensively studied<sup>213</sup>. Substance P and CGRP, co-released from nociceptive C-fibers, play pivotal roles in neurogenic inflammation and wound healing. Schlereth and coworkers elucidated the respective role of Substance P and CGRP in vasodilation<sup>214</sup>, and Kim and Granstein reviewed the roles of CGRP in skin, including its crucial function in regulating cutaneous immune responses and keratinocyte proliferation<sup>215</sup>. Xing and coworkers<sup>213</sup> reviewed the role of neuropeptides in cutaneous wound healing, demonstrating their influence on immune cells, repair cells, and the growth factor network. Al Mamun and coworkers recently reviewed the role of neuroregulation in wound healing, explaining that neuropeptides, neurotransmitters, and neurotrophic factors are critical for regulating angiogenesis, inflammation, and tissue repair processes<sup>216</sup>.

In the cosmetic field, some synthetic peptide analogs have been developed to replicate or modulate endogenous neuropeptide actions, be those stimulatory or inhibitory interactions with receptors or enzymes.

For example, Acetyl hexapeptide-8 exemplifies this approach, mimicking the N-terminal region of synaptosomal-associated protein 25 (SNAP-25), which plays a key role in neuromuscular junctions. Wang evaluated the anti-wrinkle efficacy of Acetyl hexapeptide-8 in a clinical study, demonstrating its effectiveness in reducing wrinkle appearance. Zdrada-Nowak and coworkers published a comprehensive review of Acetyl hexapeptide-8, indicating it may reduce wrinkle depth, improve skin elasticity, and enhance hydration, although they emphasized that the precise biological mechanisms – and the peptide's ability to effectively reach neuromuscular junctions when applied topically – remain incompletely understood<sup>217-219</sup>. The Draelos team conducted a 14-week clinical trial testing a peptide treatment serum containing gamma-aminobutyric acid and several other peptides with neurotransmitter inhibiting and cell signaling properties, demonstrating statistically significant improvements in expression lines, eye wrinkles, and overall skin appearance<sup>220</sup>.

Based on evidence that proopiomelanocortin-derived neuropeptides exert anti-inflammatory activity in the skin through activation of the melanocortin-1 receptor, Lucas Meyer Cosmetics developed a lipopeptide derived from the  $\alpha$ -melanocyte-stimulating hormone sequence, sold under the name Neutrazen™, which demonstrated a high binding affinity for melanocortin-1 receptor and anti-inflammatory benefits<sup>221</sup>. The Fatemi group documented this peptide's inhibition of capsaicin-induced sensory

irritation, and hypothesized that this effect proceeds through a limitation in substance P and IL-8 release<sup>222</sup>.

## 5.2 Neuroactive Botanicals and Mechanisms of Action

### 5.2.1 Oxytocin Signaling

The hypothalamic neuropeptide oxytocin (OXT) enjoys a well-known connection to social bonding, reproduction, and psychological health<sup>223-226</sup>. It is also produced locally in the skin. Both oxytocin and its receptor (OXTR) are expressed in human dermal fibroblasts and epidermal keratinocytes<sup>10</sup>. OXTR is a G-protein coupled receptor (GPCR), and initiates multiple intracellular signaling cascades mediating diverse physiological responses beyond its classical role in social bonding and reproduction. This suggests that topical interventions activating oxytocin signaling may deliver benefits beyond dermatological improvement, potentially influencing emotional states through the skin-neuronal axis.

Recent research shows OXT signaling's role in skin homeostasis and aging. Cho (2019) demonstrated that oxytocin alleviates cellular senescence in human dermal fibroblasts through OXTR-mediated signaling; OXT suppressed senescence-associated secretory phenotype (SASP)-induced senescence in normal human dermal fibroblasts, suggesting that OXT and OXTR agonists could serve as clinically promising agents for ameliorating age-associated skin aging<sup>227</sup>.

Oxytocin also promotes cell proliferation, and enhances the density of sensory neurons in skin tissue, thereby heightening receptivity to pleasant tactile sensations; simultaneously, oxytocin inhibits nociceptive nerve sensitivity, reducing discomfort – thereby overall influencing skin sensoriality and generating a more pleasant sensory experience<sup>228</sup>. These dual effects, enhancing pleasant sensations while at the same time dampening pain perception, are a hallmark of oxytocin as a key mediator of skin comfort and psychological well-being.

Our own recently published work<sup>228</sup> shows the potential of a *Hyacinthus orientalis* (hyacinth) bulb extract (commercialized as GlowCytocin™ by Lucas Meyer Cosmetics) to activate OXTR and deliver oxytocin-like downstream benefits in skin beauty and sensorial well-being. Our *in-vitro* and organ-on-a-chip studies showed that this extract increases fibroblast proliferation and promotes sensory innervation, while decreasing nociceptive signaling. This was validated clinically, in a placebo-controlled trial involving 60 mixed-ethnicity volunteers aged 19-65 years. Twice-daily application of 1% *Hyacinthus* bulb extract for 28 days yielded statistically significant improvements in multiple key parameters of skin health and beauty, including increased skin luminosity and healthy glow, reduced wrinkle count, and improved skin elasticity. No less importantly, these visible improvements were accompanied by enhanced sensitivity to pleasant touch sensations, as evidenced by EEG recordings taken during gentle touch stimulation, which showed selective left-side frontal alpha-wave activation, indicating pleasant sensation. We also showed reduced nociception

triggered by both heat and capsaicin stimuli. These results show this *Hyacinthus* extract acting as a well-being mimic, as it were, and locally delivering the peripheral benefits of well-being via OXTR signaling, on skin condition and sensoriality – and thus demonstrating the extract's value for holistic solutions enhancing the skin's receptivity to pleasant sensations and promoting well-being in longevity. While some other botanical substances have been reported to activate OXTR or otherwise have oxytocin-like effects<sup>229-230</sup>, or increase OXT levels or OXTR expression in skin<sup>231-232</sup>, to our knowledge our work with the *Hyacinthus* bulb extract remains a leading example of leveraging OXT signaling for these ends.

### 5.2.2 Psychological Stress and the Stress Response Mechanisms

Chronic psychological stress can profoundly impact the skin through interconnected pathways; cortisol is a primary mediator of these effects. Under stress, the hypothalamus releases CRH, which stimulates pituitary adrenocorticotropic hormone, triggering adrenal cortisol release<sup>233</sup>. In addition, and interestingly, human skin expresses elements of the HPA axis, including CRH, CRH receptors (including CRH-R1), steroidogenic enzymes, and glucocorticoid synthesis<sup>234</sup>.

Chronically elevated cortisol can exert deleterious effects on dermal tissue through multiple mechanisms. The Oikarinen team demonstrated that topical glucocorticoid treatment causes a 70-80% decrease in type I and III collagen propeptides<sup>235</sup>, and indicated this decrease originated at the transcriptional level. Matrix metalloproteinase expression may also be variably affected, potentially accelerating favoring collagen degradation<sup>236</sup>. Choe and coworkers<sup>237</sup> further elucidated that psychological stress deteriorates skin barrier function through activation of the HPA axis in the epidermis, with stratum corneum (SC) cortisol levels primarily regulated by activation of 11 $\beta$ -hydroxysteroid dehydrogenase type 1 (whose activity has been shown to also increase in skin with age, leading to elevated local glucocorticoid generation and adverse age-related changes<sup>238</sup> in epidermal keratinocytes. Conversely, topical application of 11 $\beta$ -hydroxysteroid dehydrogenase type 1 inhibitors has shown promise in reducing glucocorticoid-mediated skin atrophy<sup>239</sup>.

Stress also causes skin to produce CRH locally, activating CRH-R1 receptors expressed by skin cells including keratinocytes, mast cells, and immune cells<sup>92,240</sup>. CRH-R1 activation stimulates nuclear factor-kappa B (NF- $\kappa$ B), a master regulator of inflammation. CRH-induced NF- $\kappa$ B activation drives production of pro-inflammatory cytokines including interleukin-6 (IL-6), interleukin-1 $\beta$  (IL-1 $\beta$ ), and tumor necrosis factor-alpha, creating a state of chronic low-grade inflammation termed "neurogenic inflammation"<sup>241</sup>. This inflammatory cascade triggers mast cell degranulation and vascular permeability changes, and also generates reactive oxygen species that damage cellular components including DNA, proteins, and lipids, directly contributing to cellular senescence and accelerated aging<sup>240</sup>. Again, aging also exacerbates these phenomena. Zouboulis showed age-

associated upregulation of CRH in sebaceous glands and CRH-R1 in hair follicles and the epidermis, as well as downregulation of CRH inhibitor Corticotropin-releasing hormone-binding protein<sup>242</sup>. This pattern suggests aged skin is, as it were, in a continuous stress-like state, or at least that with aging, skin becomes more vulnerable to stress-induced tissue damage.

Telomeres, protective DNA structures capping chromosome ends, which shorten with each cell division and thus have been suggested as biomarkers of cellular aging<sup>243-244</sup>, also connect stress and longevity. Epel and coworkers showed telomeres shorter (meaning, more aged) by the equivalent of at least a decade in women undergoing high stress levels<sup>245</sup>. Conversely, Lin, Epel, and Blackburn reviewed how lifestyle factors including stress management can influence telomere length, with stress buffering behaviors (exercise, adequate sleep, healthy diet) protecting against stress-induced telomere shortening<sup>246</sup>. One controlled study also demonstrated that comprehensive lifestyle changes (diet, activity, stress management, and social support) increased relative telomere length over a five-year period<sup>247</sup>.

Interventions targeted at stress and its outcomes should thus address, not only downstream inflammatory effects but also ideally be directed at the initial stress signaling cascade itself. Adaptive stress response systems include sirtuin activation, Adenosine monophosphate-activated protein kinase signaling, and nuclear factor erythroid 2-related factor 2 antioxidant pathways, all of which decline with chronic stress and aging<sup>248-251</sup>. Targeting receptors and signaling factors upstream in the stress cascade (CRH-R1, glucocorticoid receptors, 11 $\beta$ -hydroxysteroid dehydrogenase type 1) may offer opportunities to prevent inflammatory aging in the first place.

### "Pseudo-Neurocosmetic" Actives and Stress-Induced Skin Aging

While some cosmetic products claim to address stress-induced aging, and thereby belong to the class of neurocosmetics, we suggest that a distinction should be made between actives which modulate stress signaling pathways, and more conventional ingredients that only address the downstream consequences of stress and/or inflammation signaling. The latter might be termed "pseudo-neurocosmetics". Traditional anti-aging active ingredients such as antioxidants or anti-inflammatories (for example, vitamins C / E, polyphenols, coenzyme Q10, niacinamide, resveratrol, green tea extracts) certainly can provide benefits by suppressing oxidative species and inflammatory mediators. However, these arguably represent symptom alleviation more closely than root cause interventions. A standard topical antioxidant may scavenge free radicals already generated by stress-induced processes, but cannot prevent the continued stress and inflammatory signaling which drives the ongoing generation of oxidative species. This creates an all-too common therapeutic scenario analogous to continuously mopping water from a flooded room without first closing the overflowing faucet responsible for the flood.

### ***Cistus incanus* Extract: Intervening Through the Stress Signaling Cascade**

Our group demonstrated the potential of a *Cistus incanus* (also known as hoary rock rose / pink rock rose) extract as a botanical neurocosmetic active, intervening in the stress signaling cascade rather than merely treating its symptoms. In our work<sup>241</sup>, we showed that an extract of *Cistus incanus* aerial parts (commercialized as IBR-Chill™ by Lucas Meyer Cosmetics) can block psychological stress signaling at the CRH-R1 receptor, and reduce neurogenic inflammation. The *Cistus incanus* extract prevented CRH-induced NF-κB activation, and suppressed production of inflammatory mediators interleukin-6, interleukin-1β, and tumor necrosis factor-alpha. The extract was shown to contain myricitrin, a naturally-occurring flavonoid glycoside of myricetin with documented antioxidant, anti-inflammatory, and anxiolytic effects<sup>252-258</sup>. Myricetin was shown to regulate the HPA axis activity<sup>259</sup>. This work also included a randomized, placebo-controlled clinical study evaluating the *Cistus incanus* extract in participants with elevated stress levels (as assessed by psychological questionnaires and salivary cortisol dosage). In this trial, topical application of a formulation containing the extract for 28 days resulted in statistically significant reductions in skin wrinkling in the high-stress cohort. This was, to the best of our knowledge, the first such demonstration of a botanical extract directly interrupting psychological stress signaling via CRH-R1 receptor blockade in skin – distinguishing this extract from more conventional, strictly anti-inflammatory or antioxidant ingredients that only address the downstream consequences of stress signaling. By interrupting the stress signaling cascade, this *Cistus incanus* extract could thus be said to deliver the effects of psychological well-being in a local manner.

The following represent three additional salient examples of botanical extracts which may qualify as authentic neurocosmetic actives to address stress-induced aging: *Withania somnifera* (Ashwagandha): This Ayurvedic adaptogen has been extensively studied for cortisol-reducing effects. *Withania somnifera* was shown to significantly decrease serum cortisol levels and clinically relevant Perceived Stress Scale scores in mentally stressed adults<sup>260</sup>. In a randomized clinical trial, topical application of *Withania somnifera* extract significantly improved markers of photoaged skin including wrinkles, pores, hydration, brightness, and pigmentation<sup>261-262</sup>. It has been suggested that these effects may involve HPA axis modulation [136]. *Rhodiola rosea* (Golden root): Traditionally used in Russian and Scandinavian medicine to combat fatigue and enhance stress resilience, *Rhodiola* contains rosavins, salidroside, and other phenylpropanoid compounds that modulate stress response pathways<sup>260,263</sup>. Some of the available clinical evidence supports *Rhodiola*'s ability to reduce cortisol levels and improve stress adaptation, though useful studies of topical applications appear to remain somewhat limited. Cannabidiol from *Cannabis sativa*: cannabidiol interacts with cannabinoid receptors 1 and 2 and Transient receptor potential vanilloid 1 channels involved in neuroinflammation, demonstrating anti-inflammatory, antioxidant, and stress-modulating properties<sup>264-265</sup>. While promising, the neurocosmetic

mechanisms and possible downsides do require further elucidation.

The above represents, at the least, proof of concept for additional neurocosmetic botanical actives with similar or complementary mechanisms. Screening programs evaluating plant extracts for activity at specific nodes in the stress signaling chain (Corticotropin-releasing hormone receptors 1 and 2, glucocorticoid receptors, 11β-hydroxysteroid dehydrogenase type 1, NF-κB, mitogen-activated protein kinases, and more) could yield novel promising materials. The distinction between authentic neuromodulatory ingredients and symptomatic treatments should guide both research and marketing claims towards greater scientific integrity.

## **6. Conclusion**

Positioned at the interface between the skin and the nervous system, the critical junction connecting the body's inner biology to the outside world; as well as its literal connection with the psychophysiological dimension of skin health, wherein conscious and unconscious emotional well-being and dermatological outcomes mutually influence each other, neurocosmetics is ideally poised to converge with the Industry's paradigm shift into longevity care, transcending purely surface aesthetic considerations to embrace holistic well-being in longevity. As bidirectional communication within the skin-brain axis becomes increasingly well-characterized through neurocutaneous and neuroimmune research, the integration of neurocosmetic strategies into a comprehensive longevity framework seems to show ever more compelling potential<sup>34,74,266</sup>.

The understanding that while aging may be unavoidable, it is nevertheless a modifiable process: one shaped *inter alia* by genetic predisposition and lifestyle factors, but nevertheless one whose trajectory a well-designed, broader approach might also be more positively directed by a well-thought strategy targeted at the holistic process of aging, rather than at some of its narrow surface outcomes. The concept of "healthspan", properly applied to the skin context, provides a framework for incorporating neurocosmetic interventions within broader longevity strategies. New intervention approaches will likely be multi-tiered, employing multiple product vectors (packaging, formulation sensoriality, and multiple targeted actives) and showing benefits on multiple levels (direct efficacy at the molecular cellular level; measurable and user-perceptible skin health, beauty, and well-being benefits in real-life use). These interventions will likely also broaden across time, starting earlier in life and becoming part of a lifelong routine of investment in holistic self-care to foster well-being in longevity.

The promise of neurocosmetics should be translated into proven clinical applications embracing a holistic evaluation of skin beauty, skin health, but also overall user physical and psychophysiological well-being, including both conscious and unconscious aspects, over the long term – certainly, much longer than the field has usually considered to date. To achieve this, several underexplored research areas still require attention.

Robust, long-term multimodal studies are needed to properly establish the efficacy and safety of neurocosmetic interventions in the context of well-being in longevity. The role of the skin microbiome in mediating skin responses linked to emotion and psychophysiological well-being may be such an avenue, for one example. The development of next-generation, more sophisticated biomarkers (and multimodal combinations of multiple such biomarkers) for assessing aging processes on a more holistic basis, both at the systemic and local (skin tissue) levels, should enable more relevant evaluations of neurocosmetic interventions in this context. The integration of rapidly rising artificial intelligence and big-data technologies, along with increasingly implementable real-time, wearable personal digital monitoring – if these were to be ethically and responsibly implemented – offers unprecedented opportunities for personalization, and allows us to envision dynamic, neuro-responsive strategies targeted to individual skin and emotional needs and profiles<sup>15,267-268</sup>.

This realization of the full potential of neurocosmetics to deliver well-being in longevity depends, by definition, on well-functioning interdisciplinary collaboration and

information-sharing, connecting biologists, dermatologists, neuroscientists, psychologists, ethicists, industry players, and regulatory bodies. Such collaboration will be needed essential to ensure that these innovations serve skin health and emotional well-being in an ethical and responsible manner, and deliver authentic and meaningful benefits to the end user. The field of psychodermatology, for example, shows great promise, and also persistent knowledge gaps around the link between psychological stress and skin diseases<sup>269</sup>. Multidisciplinary education, updated clinical guidelines, and seamless collaboration between scientists, clinicians, AI systems, bioinformaticians, industrials, and patients themselves will be necessary to genuinely and responsibly advance personalized longevity interventions beyond the academic research stages. As longevity research continues to progress, and as industry growth continues to be driven by both biotechnological innovations and consumer demand for genuinely efficacious, safe, and responsible interventions to extend healthspan and deliver well-being in longevity<sup>270</sup>, the field of neurocosmetics could potentially contribute very high value, and thus may have a very bright future ahead.

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