Dermatology Reports
https://journals.pagepress.net/dr

eISSN 2036-7406

Please cite this article as:

Cassalia F, Danese A, Del Fiore P. Neurocutaneous system: Is the skin a big eye with deep brain connections? *Dermatol Rep 2026 [Epub Ahead of Print] doi: 10.4081/dr.2026.10930*

Received: 2 May 2026; Accepted: 24 August 2026.

Neurocutaneous system: Is the skin a big eye with deep brain connections?

Fortunato Cassalia,[1] Andrea Danese,[2] Paolo Del Fiore[1]

[1]Soft-Tissue, Peritoneum and Melanoma Surgical Oncology Unit, Veneto Institute of Oncology IOV-IRCCS, Padua; [2]Section of Dermatology, Department of Medicine, University of Verona, Italy

Correspondence: Fortunato Cassalia, MD, Soft-Tissue, Peritoneum and Melanoma Surgical Oncology Unit, Veneto Institute of Oncology IOV-IRCCS, 35128 Padua, Italy. E-mail: fortunato1287@gmail.com

Key words: neurocutaneous system; skin-brain axis; cutaneous neurogenic inflammation; psychodermatology; Koebner phenomenon; somatosensory system.

Conflict of interest: the authors have no conflict of interest to declare.

Contributions: All authors have contributed significantly to this publication. All authors have read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Traditionally recognised as the body's largest organ, the skin acts as a protective barrier and primary sensory interface with the external environment.[1] Recent advances in dermatology and neuroscience have revealed a sophisticated neuroendocrine network within the skin, suggesting that the skin's role extends far beyond mere protection and sensation.[2]

In this article, we propose an innovative perspective by conceptualising the skin as a "big eye" in close communication with the central nervous system (CNS). Central to this concept is the idea that all nerve endings in the skin converge into a single extended nerve, like the optic nerve, which we can imagine as a "cutaneous nerve". This nerve could act as a conduit for the transmission of sensory and emotional information from the skin to the CNS.

By analogy with the visual pathway, in which retinal ganglion cell axons partially decussate at the optic chiasm before continuing within the optic tracts, the hypothetical cutaneous pathway could include central relay and integration points, potentially involving midbrain structures, before

information is conveyed to the cerebral cortex.[3] This neural architecture hypothesises a highly integrated system between the skin and the CNS.

This hypothesis is based on several well-established anatomical and physiological considerations. During embryonic development, the skin and nervous system share a common ectodermal origin. The surface ectoderm gives rise to the epidermis, whereas the neuroectoderm forms the neural tube, from which the CNS develops, and the neural crest.[4] Neural crest cells migrate extensively and give rise to melanocytes and multiple components of the peripheral nervous system, among other specialised cell types. Melanocytes populate the basal layer of the epidermis, whereas CNS neurons and glial cells arise predominantly from the neural tube.[5]

Traditionally known for their role in pigment production and UV protection, melanocytes also have complex interactions with keratinocytes and the nervous system, suggesting their involvement in sensory and neuroendocrine functions.[6] These cells express opsins, light-sensitive proteins found in the retina, which enable them to respond to both ultraviolet and visible light. This photoreceptive capacity allows melanocytes to dynamically modulate melanin production in the same way that retinal photoreceptors use phototransduction to process visual information.

Anatomically, melanocytes are strategically positioned close to the skin surface for optimal interaction with incoming light. This arrangement mirrors the organisation of photoreceptors in the retina, facilitating rapid and efficient responses to changes in light intensity.

The idea is that the cutaneous neural network could be connected to a type of associative cortical area, a hypothetical ancestral cortical structure closely linked to the limbic system, which serves as an integrative hub responsible for processing sensory and emotional information, both conscious and unconscious, in a similar way to how the cerebral cortex interprets visual data from the retina. Located close to the limbic areas, this structure would facilitate the integration of sensory input from the skin with emotional and physiological responses, allowing the skin to participate in the response to external stimuli by influencing mood, anxiety levels and overall emotional well-being. In this sense, this integration could see the skin as a primordial, sophisticated organ of communication between the external and internal worlds.

Psychodermatology, an emerging field that combines dermatology and psychology, exemplifies the clinical relevance of this integrative perspective.[7] It recognises that emotional and psychological factors have a significant impact on skin health. Chronic conditions such as psoriasis and eczema are not only manifestations of immune dysregulation, but also reflect underlying neuroendocrine imbalances influenced by emotional states.[8] Differences in perceptions of skin condition between people with psoriasis and controls have also been reported, further underscoring the subjective dimension of cutaneous disease.[9]

Experimental neuroscience provides further support for bidirectional skin-brain communication. In mice, Yu *et al.* showed that social touch-like tactile stimulation activates a tachykinin 1-oxytocin pathway linking somatosensory input to central circuits involved in affective and social responses.[10] Although these findings do not demonstrate the existence of a dedicated "cutaneous tract" in humans, they provide proof of principle that sensory signals originating at the skin can engage defined central neuropeptidergic circuits.

At the peripheral level, cutaneous neurogenic inflammation may represent a complementary mechanism: activation of sensory nerve endings and transient receptor potential channels promotes the release of neuropeptides, including substance P and calcitonin gene-related peptide, which interact with keratinocytes, mast cells, endothelial cells and immune cells, thereby amplifying local inflammation.[11] Exogenous stimuli such as rubbing or trauma and endogenous neuroendocrine or emotional signals may therefore converge on neuroimmune pathways within the skin, potentially contributing to the preferential localisation or exacerbation of inflammatory dermatoses.

From a historical and purely conceptual perspective, Rosenfeld's psychoanalytic notion of "psychotic islands" may be viewed as an early attempt to describe the compartmentalisation of emotional tension.[12] This construct should not be interpreted as biological evidence, but it offers a historical parallel to contemporary attempts to understand how emotional and somatosensory processes may become spatially expressed at the body surface.

The peculiar distribution of skin lesions in inflammatory skin diseases such as psoriasis, atopic dermatitis or vitiligo, which are usually bilateral and symmetrical, suggests a topographical distribution – a kind of cortical homunculus upon which neurocutaneous inflammatory stimuli depend. It could be hypothesised that within this homunculus, the dorsal surface of our body is represented on one side and the ventral surface on the other, like an anatomical-physiological trait inherited from our quadrupedal ancestors, in which dorsal and ventral skin reactions were triggered by different emotional stimuli. This would explain why some skin pathologies affect the extensor surfaces while others affect the skin folds, almost as if our skin responds autonomously to external stimuli, like a chameleon adapted to modern society.

Another indication is the Koebner phenomenon, in which new skin lesions form at sites of trauma in susceptible individuals.[13] Within the framework proposed here, this phenomenon may represent a clinical example in which local neuroimmune signalling contributes to a spatially restricted cutaneous response. Mechanical trauma can activate sensory nerves and promote the release of neuropeptides capable of modulating local immune responses and inflammation.[11,13]

In addition, palmar-plantar hyperhidrosis could reinforce this model, acting as an epiphenomenon resulting from the integration of emotional stimuli reaching the limbic areas closely linked to this hypothetical associative cortical area, leading to effector stimuli with topographical distribution.

Moreover, cutaneous oncology could find more explanations if this theory is validated. For example, melanoma cells have been shown to exhibit strong neurotropism, allowing melanoma cells to navigate the peripheral nervous system towards the CNS.[14] Studying this neurotrophic migration could also be crucial to understanding melanoma's ability to metastasise in a zosteriform pattern – where tumour cells spread along peripheral nerves following dermatomal distribution, mimicking the spread of herpes zoster infections.[15] This phenomenon would not only complicate diagnosis and treatment, but also explain the similarities between melanoma and CNS neoplasms.

Neurofibromatosis type 1 (NF1) is another compelling example of a neurocutaneous genodermatosis that intricately links the skin and nervous system, reinforcing the concept of the skin as a "big eye" with integrated neural functionality. One of the defining features of NF1 is the presence of Lisch nodules: benign, pigmented hamartomas located on the iris of the eye. These nodules illustrate the shared embryological and molecular pathways between skin and eye tissues. Derived from neural crest cells that give rise to both melanocytes in the skin and various cell types in the eye, Lisch nodules reflect underlying genetic mutations in the *NF1* gene that disrupt normal cell differentiation and proliferation. This dual manifestation in the skin and eye highlights the neurotropic nature of NF1, where genetic changes predispose cells to migrate and form tumours along neural pathways.[16]

A hypothetical "cutaneous sensory associative cortex" would play a fundamental role in processing and integrating sensory and emotional information, allowing the skin to independently interpret and respond to environmental and emotional stimuli, thereby enhancing the body's ability to maintain homeostasis and emotional balance. This ancestral communication system, closely linked to the limbic system, would be able to process external sensory inputs to modulate emotional outputs and physiological responses.

In summary, conceptualising the skin as a "big eye" connected to the CNS offers a transformative perspective for understanding skin neurophysiology. Drawing parallels between the skin and the ocular system, particularly through a hypothetical associative area of the cerebral cortex responsible for integrating information from the skin with the ancestral limbic system, provides a novel framework. However, it is important to recognise that these ideas remain largely theoretical, and this hypothesis requires rigorous scientific validation using advanced imaging techniques, molecular biology and interdisciplinary research to explore and confirm these proposed links.

References

1. Gravitz L. Skin. Nature 2018;563:S83.
2. Vidal Yucha SE, Tamamoto KA, Nguyen H, et al. Human Skin Equivalents Demonstrate Need for Neuro-Immuno-Cutaneous System. Adv Biosyst 2019;3:e1800283.
3. Mehra D, Moshirfar M. Neuroanatomy, Optic Tract. 2023. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024.
4. Pispa J, Thesleff I. Mechanisms of ectodermal organogenesis. Dev Biol 2003;262:195-205.
5. Brombin A, Patton EE. Melanocyte lineage dynamics in development, growth and disease. Development 2024;151:dev201266.
6. Hara M, Toyoda M, Yaar M, et al. Innervation of melanocytes in human skin. J Exp Med 1996;184:1385-95.
7. Ait Oussous S, Jafferany M, Chakiri R. Psychodermatology knowledge, awareness and patterns of practice among Moroccan dermatologists: a national survey study. Clin Exp Dermatol 2023;48:1152-4.
8. Zhang H, Wang M, Zhao X, et al. Role of stress in skin diseases: A neuroendocrine-immune interaction view. Brain Behav Immun 2024;116:286-302.
9. Cassalia F, Cazzaniga S, Ofenloch R, et al. Comparison of Perceptions of Skin Condition, Product Use and Allergen Reactivity Between People with Psoriasis and Controls in the European Dermato-Epidemiology Network (EDEN) Fragrance Study. Acta Derm Venereol 2024;104:adv23513.
10. Yu H, Miao W, Ji E, et al. Social touch-like tactile stimulation activates a tachykinin 1-oxytocin pathway to promote social interactions. Neuron 2022;110:1051-67.e7.
11. Marek-Jozefowicz L, Nedoszytko B, Grochocka M, et al. Molecular Mechanisms of Neurogenic Inflammation of the Skin. Int J Mol Sci 2023;24:5001.
12. Rosenfeld HA. Psychotic States: A Psychoanalytical Approach. London: The Hogarth Press and the Institute of Psycho-Analysis; 1965.
13. Sanchez DP, Sonthalia S. Koebner Phenomenon. 2022. In: StatPearls[Internet]. Treasure Island (FL): StatPearls Publishing; 2024.
14. Hughes TA, McQueen IN, Anstey A, et al. Neurotropic malignant melanoma presenting as a trigeminal sensory neuropathy. J Neurol Neurosurg Psychiatry 1995;58:381-2.
15. Morgado-Carrasco D, Fernández-Sartorio C, Carrera C. Zosteriform Cutaneous Distant Metastases as Onset of Relapsing Melanoma. Dermatol Pract Concept 2019;10:e2020007.

16. Goetsch Weisman A, Weiss McQuaid S, Radtke HB, et al. Neurofibromatosis- and schwannomatosis-associated tumors: Approaches to genetic testing and counseling considerations. Am J Med Genet A 2023;191:2467-81.