NEURAL FOLDS

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November 1, 2025

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Primary Disciplinary Field(s): Developmental Biology, Embryology, Neuroscience

1. Core Definition

The **neural folds** are transient, yet critical, paired ridges of neuroectodermal tissue that arise during the initial stages of central nervous system (CNS) development in vertebrate embryos. They constitute the elevated lateral margins of the flat **neural plate**, which is itself a specialized region of the dorsal embryonic ectoderm. These folds are induced to form by complex signaling interactions with the underlying mesoderm, particularly the notochord. The primary biological role of the neural folds is to facilitate the process of neurulation--the morphogenetic movement during which the ectoderm is invaginated and internalized--culminating in the successful formation of the **neural tube**. This tube is the embryonic precursor to the entire brain and spinal cord. Their successful elevation and subsequent fusion are fundamental requirements for establishing the correct body plan and preventing congenital defects.

The composition of the neural folds is highly specialized, encompassing several distinct cell populations. The majority of the structure consists of the rapidly proliferating neuroepithelium, which will become the ventricular zone of the mature CNS. Crucially, the dorsalmost margins, or crests, of the neural folds harbor the **neural crest cells**. These cells are unique for their high migratory potential and multipotency, and they delaminate from the folds upon fusion to colonize distant sites throughout the embryo, giving rise to diverse cell types including sensory neurons, glial cells, melanocytes, and craniofacial skeletal components. The complexity of these folds necessitates highly coordinated molecular and mechanical regulation to ensure that the correct cells are internalized (neuroepithelium) while others are released (neural crest) at the precise moment of closure.

2. Etymology and Historical Development

The anatomical features of the neural folds and the sequence of neurulation were first described extensively by embryologists in the 19th century, marking a critical advance in understanding vertebrate morphogenesis. Pioneering work by figures such as Wilhelm His utilized meticulous histological techniques and cross-sectional analysis, particularly in chick embryos, to map the developmental fate of the embryonic germ layers. These observations established the fundamental concept that the CNS arises not through the condensation of scattered cells, but through the deliberate folding and sealing of an epithelial sheet. The term **neural fold** is thus a descriptive anatomical label denoting the bilateral elevation of the tissue.

Historical research initially focused heavily on the mechanics of folding, investigating how cells

change shape (e.g., apical constriction) to drive the bending moment. The 20th century witnessed a shift toward identifying the inductive signals responsible for initiating this process. Landmark experiments demonstrated that the underlying mesoderm, particularly the notochord, secretes factors necessary to transform the overlaying ectoderm into the neural plate--a process known as **neural induction**. This developmental understanding progressed significantly with the identification of specific molecular pathways, such as the inhibition of Bone Morphogenetic Proteins (BMPs) by signals like Noggin and Chordin, which are essential for establishing the neural plate territory and dictating the elevation and convergence of the neural folds. The modern view integrates these morphological descriptions with the precise genetic and molecular controls governing cell behavior at the fold margins.

3. Formation Process: Primary Neurulation

The formation of the neural folds is the folding stage of primary neurulation, a dynamic process involving complex cellular movements and changes in cell shape. This phase begins immediately after the establishment of the flat neural plate. First, the neural plate undergoes a shaping phase, elongating along the anterior-posterior axis via a mechanism called **convergent extension**. This movement narrows the plate and prepares the margins for elevation.

Folding is initiated primarily by the formation of the **Medial Hinge Point (MHP)**, located along the midline of the neural groove, directly above the notochord. Cells at the MHP respond to signaling molecules, such as Sonic Hedgehog (Shh) from the notochord, by changing their shape from tall columnar cells to wedge-shaped cells. This conversion is driven by the coordinated contraction of actin microfilaments anchored at the apical surface of the cells. The resulting apical constriction forces the neural plate to bend inward, creating the neural groove and causing the lateral edges to lift, thereby forming the neural folds.

As the folds continue to elevate and approach each other, secondary pivot points, known as the **Lateral Hinge Points (LHPs)**, form in the wider regions of the neural plate, especially in the prospective brain areas. LHP formation allows the folds to roll over the neural groove and facilitates the necessary convergence toward the midline. The precise coordination between MHP and LHP function--mediated by intrinsic neuroepithelial forces and extrinsic forces exerted by the surrounding ectoderm--is essential for the successful apposition of the opposing fold crests. Once contact is established, the final step involves the fusion of the apical membranes of the folds, sealing the neural tube beneath the surface ectoderm. This fusion process typically begins in the cervical region and zips both cranially and caudally.

4. Key Characteristics and Cellular Dynamics

The successful closure of the neural folds depends on precise biomechanical and cellular

characteristics:

Epithelial Integrity and Adhesion: The neural plate, and subsequently the folds, are a continuous pseudostratified epithelium. Fusion requires the opposing apical surfaces to recognize each other and adhere. This recognition is mediated by specific adhesion molecules, such as E-cadherin in the non-neural ectoderm and N-cadherin in the neuroepithelium. Correct spatiotemporal regulation of these cadherins dictates where fusion occurs and ensures that the neural tissue separates cleanly from the surface ectoderm.

Mechanical Force Generation: The elevation and bending of the folds are not passive movements. They rely heavily on the contractile machinery of the cells, specifically the apical cytoskeletal elements (actin and myosin) at the hinge points. Additionally, external forces, such as the pushing and proliferation of the surrounding non-neural tissue and the underlying mesenchyme, contribute significantly to the mechanical push required for the folds to close across the midline, especially in the wider cranial regions.

Neural Crest Delamination: The crests of the folds represent a temporary reservoir of pluripotent cells. As fusion completes, the change in the local signaling environment--specifically the cessation of BMP signaling that occurs when the neural crest is separated from the surface ectoderm--triggers the epithelial-to-mesenchymal transition (EMT) of these cells. This allows them to detach from the folds and begin their extensive migration, highlighting the folds as a temporary boundary structure pivotal to peripheral nervous system development.

5. Significance for CNS Patterning

Beyond simply forming a closed tube, the precise geometry established by the neural folds is fundamentally significant for the subsequent patterning of the CNS. The orientation of the neuroepithelium within the newly formed tube establishes the critical dorsal-ventral axis that dictates neuronal cell fate specification.

The ventral patterning is controlled largely by the floor plate, which is derived from the cells at the MHP and is heavily influenced by the notochord's secretion of **Sonic Hedgehog (Shh)**. High concentrations of Shh specify motor neuron fate in the ventral spinal cord. Conversely, the dorsal patterning is regulated by the roof plate, which develops at the site of fold fusion and secretes members of the Transforming Growth Factor-beta (TGF-β) superfamily, primarily **BMPs**. A gradient of these opposing signals--high Shh ventrally, high BMP dorsally--establishes distinct domains of progenitor cells, ensuring that the correct types of neurons (e.g., motor neurons, interneurons) are generated in the appropriate locations along the developing spinal cord. A delay or failure in fold closure not only leaves the tissue exposed but disrupts the establishment of these signaling centers, leading to profound errors in neuronal specification and circuitry.

6. Clinical Implications: Neural Tube Defects (NTDs)

The failure of the neural folds to complete their fusion anywhere along the anterior-posterior axis results in **Neural Tube Defects (NTDs)**, which are serious and relatively common congenital anomalies. The clinical outcome depends entirely on the location of the failure.

Failure of anterior neural fold closure leads to **anencephaly**, a condition characterized by the severe underdevelopment or absence of the forebrain and cranial vault, which is invariably lethal shortly after birth. Failure of the posterior neural folds to close results in **Spina Bifida**, where the spinal cord remains exposed or protrudes through a defect in the vertebral column. The most severe form, myelomeningocele, exposes the neural tissue, leading to irreversible damage that results in paralysis, hydrocephalus, and bladder/bowel dysfunction.

A major breakthrough in preventative medicine related to neural folds was the discovery that maternal nutritional status, specifically the intake of **folic acid** (Vitamin B9), is strongly correlated with NTD incidence. Folic acid is essential for nucleotide synthesis and methylation processes critical for rapid cell proliferation and differentiation, both of which are required for the massive cellular remodeling involved in neural fold movement and fusion. Public health campaigns promoting periconceptional folic acid supplementation have demonstrated a significant reduction in NTD cases globally, underscoring the subtle metabolic requirements of successful neurulation.

7. Debates and Variations in Neurulation

While the primary neurulation pathway involving the elevation and fusion of the neural folds is dominant in forming the forebrain and upper spinal cord, the development of the caudal spinal cord involves a distinct mechanism known as **secondary neurulation**. The recognition of these two distinct processes introduces complexity and is a focus of ongoing comparative embryological study.

Secondary neurulation, which forms the terminal portion of the spinal cord (caudal to the posterior neuropore), does not involve neural folds. Instead, the neuroepithelium condenses from a mass of cells (the caudal cell mass) located in the tailbud. This solid rod of tissue then undergoes canalization or cavitation, hollowing out to form a lumen that subsequently merges with the lumen of the primary neural tube. The exact molecular switch that transitions the embryo from primary (fold-mediated) to secondary (cavitation-mediated) neurulation is still under investigation, and defects in this transition zone can lead to complex caudal spinal anomalies, such as tethered cord syndrome or sacral agenesis. The neural folds, therefore, define the boundary and mechanism for CNS development rostral to this transition zone.

Further Reading

Neurulation (Wikipedia)
Neural fold (Wikipedia)
Neural Tube Defects (Centers for Disease Control and Prevention)
Neural crest (Wikipedia)