# Is the central nervous system enclosed by a mesothel?

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## Comment

Møllgård et al. recently described a novel mesothelial cell layer in mice brain which they propose to be a functional division of the subarachnoid space (Møllgård et al., 2023). After detailed comparison of their results with our own optical coherence tomography studies of the human meninges in vivo, prior electron microscopic studies by several other groups as well as daily neurosurgical and medical observations we consider an alternative interpretation of their highly relevant findings.

We assume that the entire central nervous system (CNS) is enclosed by a mesothel, which lies between the dura mater and the arachnoid mater. Here it acts as an immunological tissue and as a physiological shifting layer between the rigid dura mater and pulsating CNS - similar to other mesothelia of moving organs such as the pleura or pericardia. This concept would on the one hand solve numerous controversial physiological and pathophysiological uncertainties concerning the "subdural space" and on the other hand significantly contribute to the basic anatomic concept of the lymphatic system of the CNS.

After detailed comparison of Møllgård *et al.*[1] results with our own *in vivo* optical coherence tomographies (OCTs) of the human meninges, we assume (A) that the *in vivo* two-photon imaging in Prox1-EGFP+ reporter mice (Prox1, prospero homeobox protein 1; EGFP, enhanced green fluorescent protein) stained the priorly described neurothelial cells (REINA 98). These cells are described at multiple sites of the central nervous system (CNS) on the cranial and spinal level and are situated inferior to the dura mater and superior to the arachnoid mater – precisely inferior to the inner membrane of the dura mater and superior to the arachnoid barrier cell membrane. Neurothelial cells are described with a nuclear thickness of 0.5–1 µm and length of 100 µm and form 4 to 8 parallel rows leading to an approximate thickness of this layer of 5–7 µm$^2$ (see Figure 1).

These morphological characteristics and the neuroanatomic position are in clear conformity with the Prox1-EGFP+ stained cells of mesodermal and lymphatic origin described by Møllgård and colleagues.

For example, in Figure 1(a) Møllgård *et al.*[1] clearly depict that the cell layer is situated inferior to the dura mater and superior to the arachnoid mater. To be precise: Inferior to the dura mater and superior to the arachnoid barrier cell membrane. If the stained layer would be inside the arachnoid mater – like suggested by the authors – the arachnoid blood vessels need to be around them.

Here, it is to be noted that arachnoid vessels solely exist inside the subarachnoid space, which is physiologically enclosed by the arachnoid barrier cell membrane as clearly depicted by the first *in vivo* OCT of the human subarachnoid space by our own group[3] (see Figure 2).

Figure 1(b) and especially (c) of Møllgård *et al.*[1] further demonstrate the classic morphological character of neurothelial cells and again its position inferior to the dura mater and superior to the arachnoid blood vessels.

In the second experiment, the authors injected red fluorophore inferior to the dura mater and blue fluorophore at the position of the cisterna magna into the subarachnoid space of Prox1-EGFP+ reporter mice (see Figure 2(a)). Since

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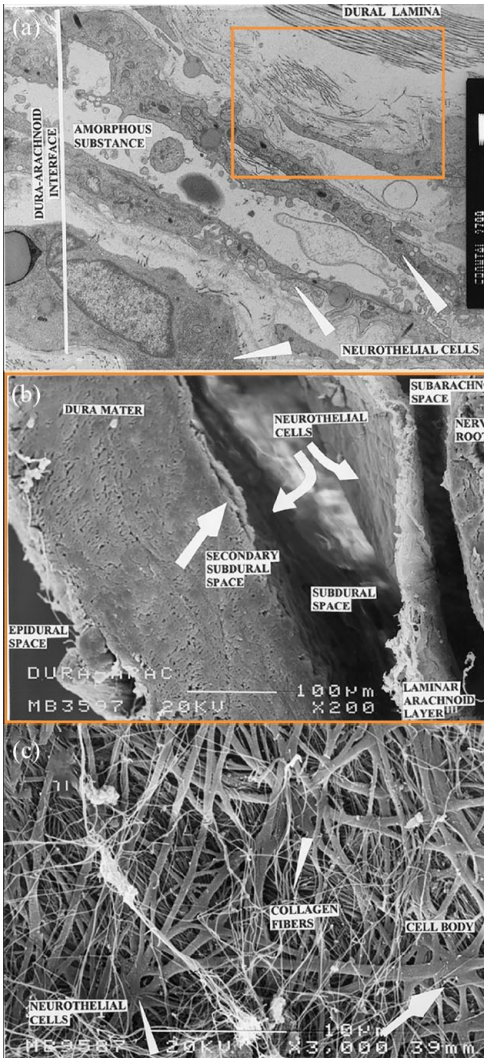


**Figure 1.** Electron microscopic imaging of neurothelial spinal cells. (a) Dura–arachnoid interface is seen below the dural lamina. The dura–arachnoid interface is filled with neurothelial cells and amorphous material. Here demonstrated with transmission electron microscopy (TEM), magnification 5000×, bar = 1 µm. Orange box indicates a probable scanning point for (b) Subdural space seen by scanning electron microscopy (SEM). The dura mater (thickness of 300 µm) is seen on the left, and the arachnoid barrier cell membrane or laminar arachnoid layer (thickness of 40 µm) is seen on the right. The internal surface of both membranes is covered with neurothelial cells. These lay inside the dura–arachnoid interface – the subdural space. (c) Dura–arachnoid interface. Neurothelial cells have a syncytial structure and show ramifications. They present an irregular diameter of approximately 1 µm and a smooth surface. Collagen fibers can also be seen which belong to the laminar portion of the dura mater. However, they are about a tenth in diameter, and they do not have ramifications (SEM, magnification 3000×, bar = 10 µm).

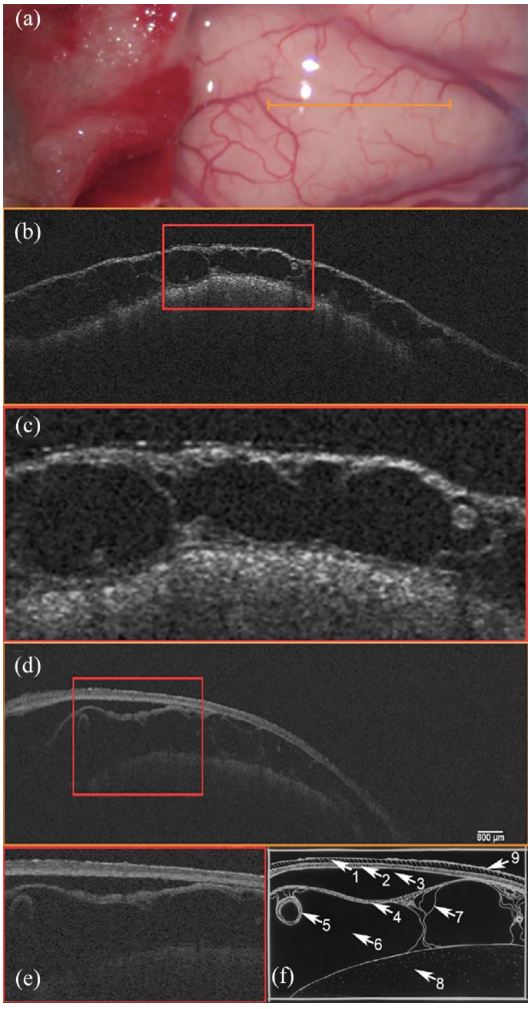


**Figure 2.** *In vivo* visualization of human subarachnoid space and cranial meninges with OCT. (a) Light microscopic image after right fronto-lateral craniotomy. Opened segment shows frontal brain cortex. Orange line indicates region of scan. (b) OCT scan of frontal arachnoid mater, pia mater, and cerebral cortex. (c) Enlarged excerpt demonstrating details of the subarachnoid space. Note that the arachnoid barrier cell membrane is covered by a slim inhomogeneous layer which might represent the neurothelial layer. Further note that the arachnoid vessels are inside the subarachnoid space which is enclosed by the arachnoid barrier cell membrane. (d) OCT scan of dura mater. During craniotomy, the dura was punctured leading to the formation of a subdural space by detaching of the flexible arachnoid barrier cell membrane from the rigid dura mater. (e) Enlarged excerpt demonstrating details of the dura mater, subdural space, and arachnoid mater. (f) Schematic drawing of microstructures: (1) + (2) dura mater, (1) outer endosteal layer, (2) inner meningeal layer, (3) subdural space, (4) arachnoid barrier cell membrane, (5) subarachnoid blood vessels, (6) subarachnoid space, (7) subarachnoid trabecular system, (8) brain cortex, and (9) reflection artifacts.

*in vivo* two-photon imaging then depicted red fluorescence superior to the green-stained cell layer and blue fluorescence inferiorly, the authors concluded that the green-stained cell layer states an impermeable membrane inside the subarachnoid space.

In contrast to the authors – we assume (B) that the injection separated the flexible arachnoid barrier cell membrane from the rigid dura mater leading to the formation of a priorly not existing subdural space. This is the typical mechanism during microneurosurgical dissections of the dura mater. If the red fluorophore was injected into the subarachnoid space – as postulated by the authors – the red fluorophore needed to be around the vessels of the subarachnoid space.

This described formation of a subdural space between the dura mater and arachnoid membrane was clearly depicted with OCT by our group (see Figure 2).[4]

If Møllgård *et al.* correctly described the mesothelial origin of cells and our two assumptions (A) and (B) are correct, the logic conclusion states that the CNS is covered and enclosed by a thin mesothelium which lies between the dura mater and arachnoid mater. The organogenesis could be analog to other organs via mesodermalic enfolding of the neural tube during embryogenesis.

This would not only solve the physiological question why the pulsating CNS is able to shift effortless in relation to the rigid dura mater – like the heart in relation to the pericard or the lung in relation to the thorax.

It might also solve numerous pathophysiological inadequacies concerning the formation of subdural spaces and its diseases:

Chronic subdural hematomas – most common intracranial bleeding, most common reason for cranial neurosurgery and recurrence rates of 10%–20% – show a growth without re-bleeding, an abundance of inflammatory cells and fluids which lead to an extended reorganization and septation of these hematomas. This would be explained if these hematomas would be situated in an inflammatoric active mesothelic cavity – similar to pleural hematomas.[5,6]

Subdural effusions or so-called 'hygromas' often develop slowly parallel to the presence of meningitides – in children, the incidence is 30%–39% – and tend to dissolve without surgical interventions with the decrease of the inflammatory process – similar to inflammatory pleural effusions during pneumonias, pericardial effusions during myocarditis or peritoneal effusions ascites during eneritis.[7–9]

Severe cerebritis or paranasal sinusitis can lead to subdural empyemas – similar to pleural empyemas in severe pneumonia.[10,11]

Symptomatic subdural hematomas or hygromas are trephined and drained with positive atmospheric pressure. This therapy often leads to inadequate evacuation and high recurrence rates of 10%–20% – if pleural effusions would be drained without suction and water sealing similar results could be expected.[12,13]

Finally, our described concept of an mesothelial engulfed CNS would clarify and rapidly progress the recent controversial discussion on the structure of the lymphatic system of the CNS with impact on the therapy of numerous neuroinflammatory diseases.[14]

Further investigations should now redefine the anatomic position of the mesothelial cell layer with, for example psOCT or speckle modulated OCT and focus on asservation of mesothelial cells at the subdural level when the arachnoid barrier cell membrane is a natomically still intact.[15]

## Declarations

### *Ethics approval and consent to participate*

All procedures performed in the primary OCT studies of our group involving human participants were in accordance with the ethical standards of the institutional and national, or both, research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was further approved by the local ethics committee (grant no. 3012-2016).

Informed consent was obtained from all individual participants included in the primary OCT studies of our group.

### *Consent for publication*

Consent for publication was obtained from all individual participants included in the primary OCT studies of our group study.

### *Author contributions*

**Karl Hartmann:** Conceptualization; Formal analysis; Investigation; Methodology; Project administration; Validation; Visualization; Writing – original draft; Writing – review and editing.

**Belal Neyazi:** Investigation.

**Klaus-Peter Stein:** Supervision.

**Aiden Haghikia:** Supervision.

**I. Erol Sandalcioglu:** Conceptualization; Supervision.

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### *Competing interests*

The authors have nothing to disclose and no competing interests. OptoMedical Technologies GmbH supported the primary OCT studies of our group with free equipment for iOCT.

### *Availability of data and materials*

OCT scans of our group can be made available on request.

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