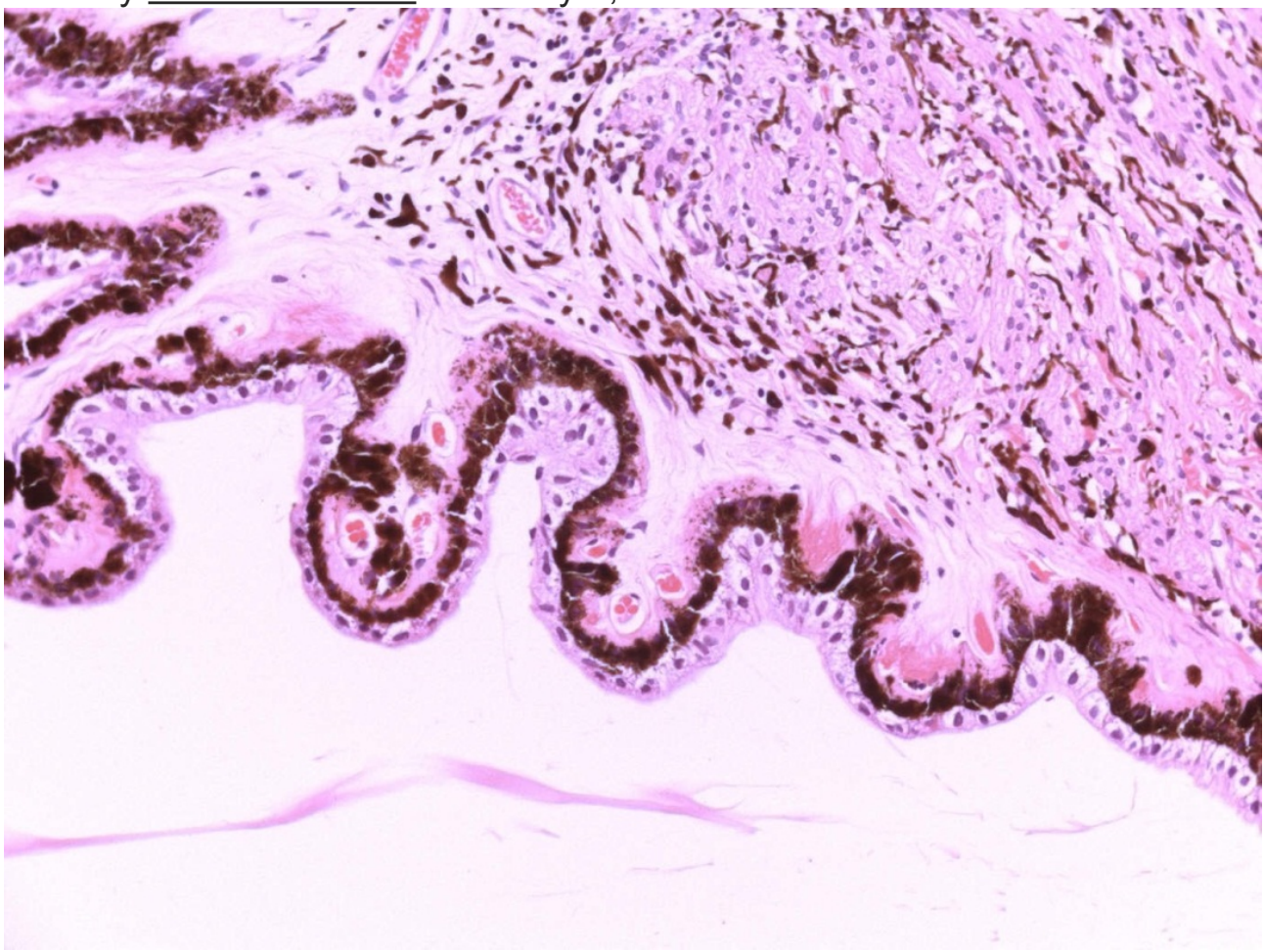
New insights in movement of cerebrospinal fluid in relation to craniosacral therapy (Part 2)

by Willem P. Visser February 5, 2019



After showing in the first post the development of the traditional understanding of cerebrospinal fluid physiology. In this post I will discuss the latest scientific breakthroughs and debates around cerebrospinal fluid. I will show the fluid exchange around brain capillaries and ventricles. Further the latest insights of how fluid and waste is drained from the brain, with introducing the glymphatic system. Finally I will show the picture of the (possible) ways and

directions fluid is moving through the brain and spine. First I share new discoveries about the role of the choroid plexus.

Relative role of choroid plexus in cerebrospinal fluid production

As shown in the previous post the choroid plexus is traditional understood to be the place where cerebrospinal fluid (CSF) is produced. There is no question if there is cerebrospinal fluid produced in the choroid plexus. There are though debates of how important the role of choroid plexus in the fluid production. There are two Croatian scientists, Orešković and Klarica who say the role of choroid plexus in cerebrospinal fluid physiology is highly overemphasised (3). Hydrocephalus is historically the background of a lot of the research and knowledge around the cerebrospinal fluid circulation. In non-communicating hydrocephalus the CSF can not reach the subarachnoid space. This is caused by a blockage in either the intraventricular foramena, the outflow of the 4th ventricle or mostly in the cerebral aqueduct between third and fourth ventricle. The, in the previous post mentioned, neurosurgeon Dandy introduced in the early 20th century the surgical removal of the choroid plexus (choroid plextomy) as a cure of hydrocephalus. Looking at the traditional understanding of CSF flow you expect this should indeed cure hydrocephalus. This wasn't the case and the treatment was abonded by neurosurgeons. Klarica and Orešković argue that: "the failure of choroid plexectomy to cure hydrocephalus is evidence enough that the CPs are not the main source of active CSF formation".

Klarica and Orešković also refer to a case study of a woman with hydranencephaly and macrocephaly who didn't have a visible choroid plexus (4). Furthermore they refer to another case study of a woman who had a blocked cerebral aquaduct without any CSF through flow for five years without creating a hydrocephalus (3). Similar in some sharks with isolated brain ventricles no hydrocephalus of extreme pressure is created due to CSF production by the choroid plexus (3). Another study shows reverse net flow through the aquaduct from the fourth to the third ventricle in infants (5). From this we can conclude that the choroid plexus *can*

not be the only place where CSF fluid is produced and that there is *not always a unidirectional flow* from the ventricles system towards the subarachnoid spaces. This is also shown in recent scientific reviews of cerebrospinal fluid movement through the brain (1,6). The review from Brinker et al questions the choroid plexus as main source of CSF production and challenges the traditional understanding of cerebrospinal fluid circulation(1). The second review of Hladky and Barrand (6) discusses the option of different CSF sources, but keep closer to the traditional understanding. Both reviews come with different new hypotheses of CSF circulation. Klarica and Orešković also have a new hypothesis (7). I come back to this later after I review other places where CSF fluid might be produced and where the fluid is secreted.

Recently it has been shown that respiration is the main regulation for the CSF flow within the ventricles (12). The flow fluctuated largely, shown in MRI images, in resonance with the inspiration, but the main direction was down from the main ventricles towards the fourth ventricle. The cardiac cycle only had a small influence on the flow. As mentioned earlier the flow is in some individual cases and in infants not always towards the fourth ventricle. Another recent research shows the flow in the ventricles is more complex (13). Cilia cells, that lay like hairs in the third ventricle, collectively alter the flow patterns spatially and periodically. This give rise to higly complex flow patterns that may control substance distribution in the third ventricle.

The intelligent choroid plexus

As we have shown the choroid plexus probably is not the only place where CSF is produced. We should though revise our understanding of the choroid plexus as a sort of pump producing CSF. There is more to the choroid plexus. First look at first stages of embryonic development of the choroid plexus in the below picture. In the first stage it is still a flat lining, just like in some amphibians and fishes. The cells already have microvilli, which looks like a brush on top of the cell and multiplies their surface within the CSF fluid. These microvilli increase the surface of the Choroid Plexus

surface of humans to 200cm². In the second stage a first primary fold and the nuclei of the ependymal cell move from the centre to the tip of the pointed structure. In the third stage the folds of the tissue becomes bigger, the nuclei move a bit to the center and the cells become flatter. In the last stage the nuclei move to the bottom of the cell, such that the top of the cell can likely interact more with the CSF. In the fourth stage the folds also become multiple and more complex. Between the adjacent cells junctions are found which form barriers to stop solutes moving from blood into CSF (8).

The function of epithelial cells of the choroid plexus is more than the production of CSF fluid. Choroid plexus epithelial cells secrete proteins into the CSF. In the different ventricles different proteins are found. In the fourth ventricle even different protein gradients are found in the bottom compared to the top. This again undermines the traditional understanding of the CSF circulation, it shows the stream and mixing within the ventricles can't be that strong. The different protein gradients across the ventricles are caused by local different protein secretion by the cells of the choroid plexus. About the choroid plexi of the lateral and fourth ventricle they even state "telencephalic and hindbrain choroid plexi are transcriptionally and functionally distinct tissues"(8).

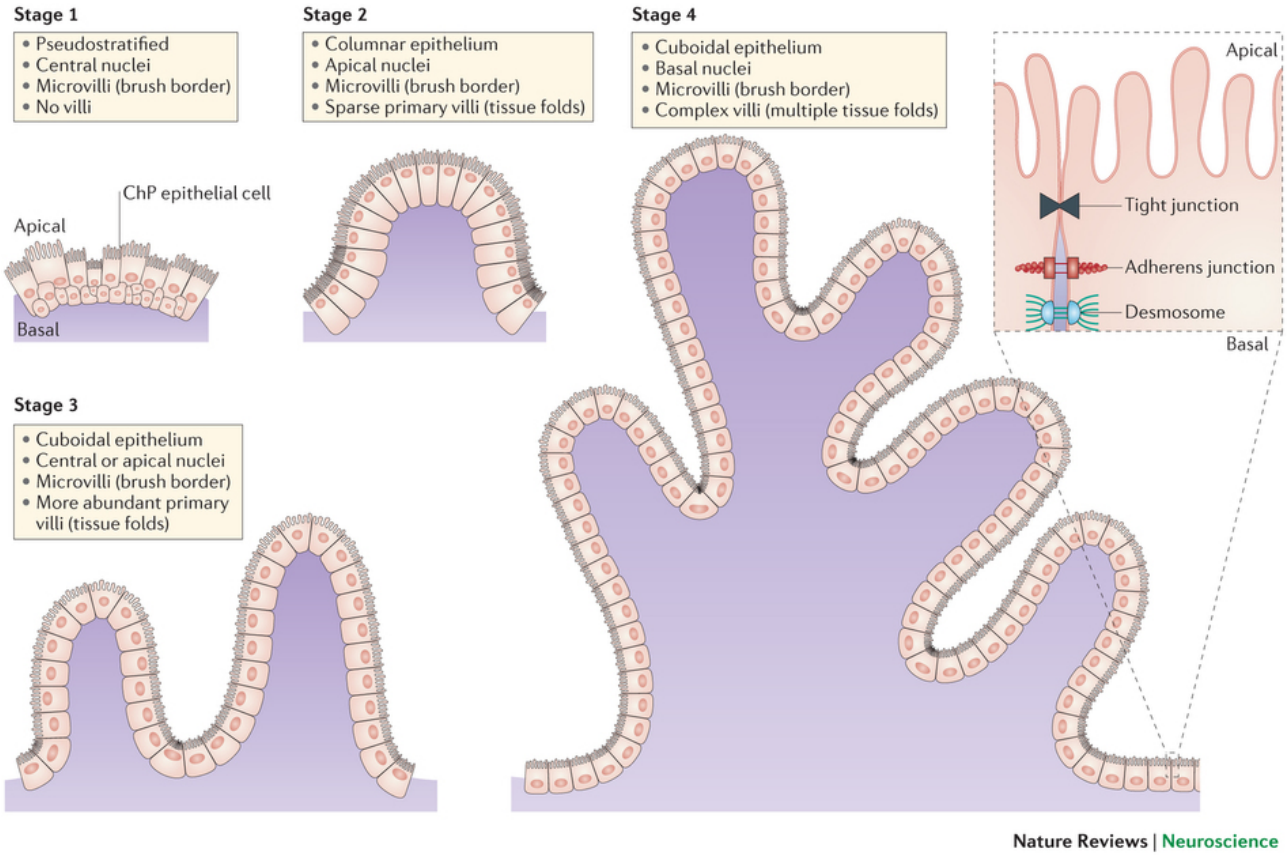


Figure 1: The four stages of fetal development of the choroid plexus.

The choroid plexus cells also play a role in the regulation of production of stem cells in the brain, which are produced in the subventrical zones of the lateral ventricles. Further they play an important role in the immunesystem of the brain. They regulate what immune cells enter the CSF fluid, which they do by picking up signals from the CSF fluid with receptors on their micro-villi. They so form a window between the brain and the immune system. Previously it was assumed that the central nervous system was largely devoid of immune cells, the microglia (a macrophage like cell) being an exception. If there were more immune entities found in the central nervous system, it was perceived as part of the pathology. Research in last decades mainly on diseases like MS have shown that immune cells do travel from blood to the central nervous system. The choroid plexus is together with meningeal bloods vessels the most likely place where they enter the ventricles. Where the choroid plexus with its receptors also appears to be the main communicator to the immune system about which immune cells are needed within the central nervous system (9). Read more about the intelligent choroid plexus in this excellent article.

In the below video you can see the choroid plexus floating inside the ventricles during an operation where an choroid plexus cyst in the third ventricle was removed.

Fluid exchange with brain

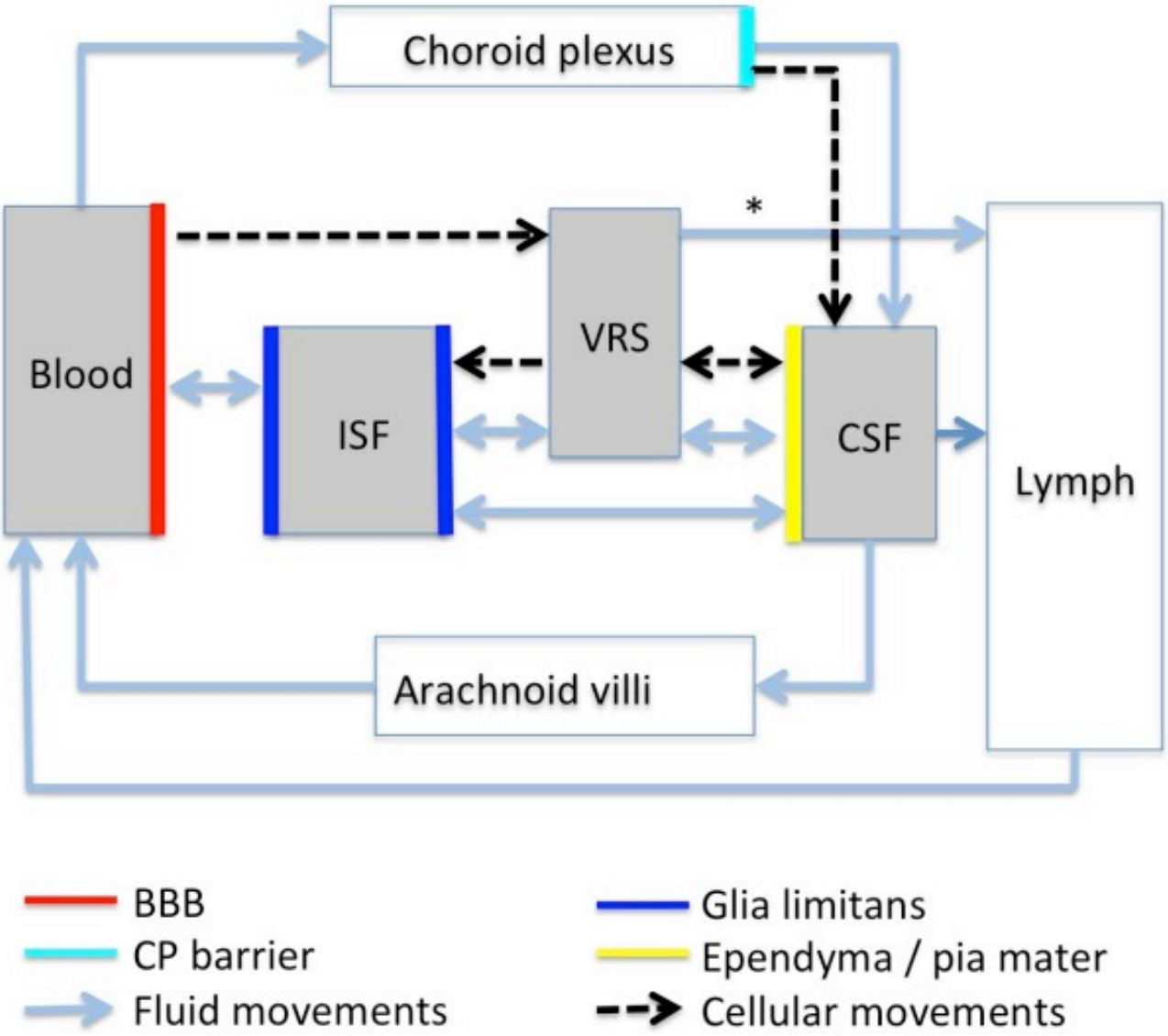


Figure 2: Schematic representation of the glymphatic system (8)
From subarachnoid spaces CSF fluid goes along arteries into the brain in the para arterial spaces. Small arterioles entering the cortex

from subarachnoid space, actually carry on an extension of the subarachnoid space, until the point they become capillaries. The exact lay out of these spaces around arteries into the brain is still under discussion. These space are also known as Virchow Robin spaces. There is a pial sheet around these arteries, which then joins with the pia mater of the cortex. Around the junction the pial sheet is said to have small openings allowing CSF fluid going along the arteries into the brain.

Glymphatic System

One of the hypotheses recently discovered is the so called “glymphatic system”. The hypothesis says that fluid from peri-arterial spaces diffuses through the pia membrane with the help of the cell membrane protein aquaporin-4 into the brain parenchyma (extracellular space of the brain). The fluid washes the brain parenchyma picking up waste products. The fluid is then drained back into the the CSF fluid through the perivenenous spaces. Figure 2 shows the glymphatic system. (9) The cardiac pressure causes the vessels to contract and expand, which likely helps the absorption into the perivascular spaces.

Since brain tissue doesn’t have a lymphatic system like the rest of the body, the “glymphatic system” is critical for the brain to get rid of waste. Interesting is as well that been shown that the washing of the brain increases during night. It correlated with an increase of 60% of the interstitial space of the brain. This resulted in a increased exchange of interstitial brain fluid with CSF fluid (10). This is very interesting, because it has never been proven why humans and animals need to sleep. The washing of the brain from (toxic) waste could be a plausible reason for the need to sleep. Next to getting rid of waste, the glymphatic system is also used to deliver molecules from the CSF to the brain. Recent research showed that a certain protein (Apolipoprotein E (apoE)) was delivered to the brain through the glymphatic system as the proteins were found around the arteries. It was also shown that the inflow of CSF with apoE was severely suppressed during sleep deprivation. (11)

Blood Brain Barrier

The blood brain barrier is another place where fluid and particles come into the brain. The blood brain barrier is the semipermeable layer of endothelial cells at the capillary bed of the blood circulation in the central nervous system. It was thought that this was the place where interstitial brain fluid was secreted into the brain. Next to that some molecules crucial to the brain like glucose were also transported to the brain through the blood brain barrier. Larger molecules and immune cells were traditionally understood to not be able to cross the blood brain barrier. Recently it has been discovered that the blood brain barrier is “in fact the result of a highly regulated and complex cellular and molecular transport processes, which allows for the transport of water, solutes, molecules and even cells” (1). It was also shown that cells surrounding the capillaries like astrocytes, microglia and even neurons can *control* and *modulate* the functioning of the blood brain barrier (1). It is also likely that cells move through the blood brain barrier first into the perivascular spaces.

Drainage of CSF

The classical hypothesis was that most of the CSF fluid is drained through the arachnoid granulations into the venous sinuses. This path is unlikely for immune cells, macromolecules and waste products, because they don’t normally leave tissue through reverse migration into blood vessels (9). So the understanding was that these particles would leave the brain along olfactory nerves and then drain from the nasal lymphatics into the deep cervical lymph nodes. Recently the existence of meningeal lymphatics, connected to the deep cervical lymph nodes, were discovered (9). They were then suggested as a direct route to drain waste products from the CSF fluid. It was also shown that for example the eye was drained by small lymphatic vessels. The endothelial cells that form the boundary of these vessels have many molecules in common with other cells in the central nervous system. At the moment it’s hard to say how extensive this system is and if it even grows into the brain.

Another theory is that this system only starts to grow during inflammation to form functional lymphatic vessels.

CSF Fluid along the spine

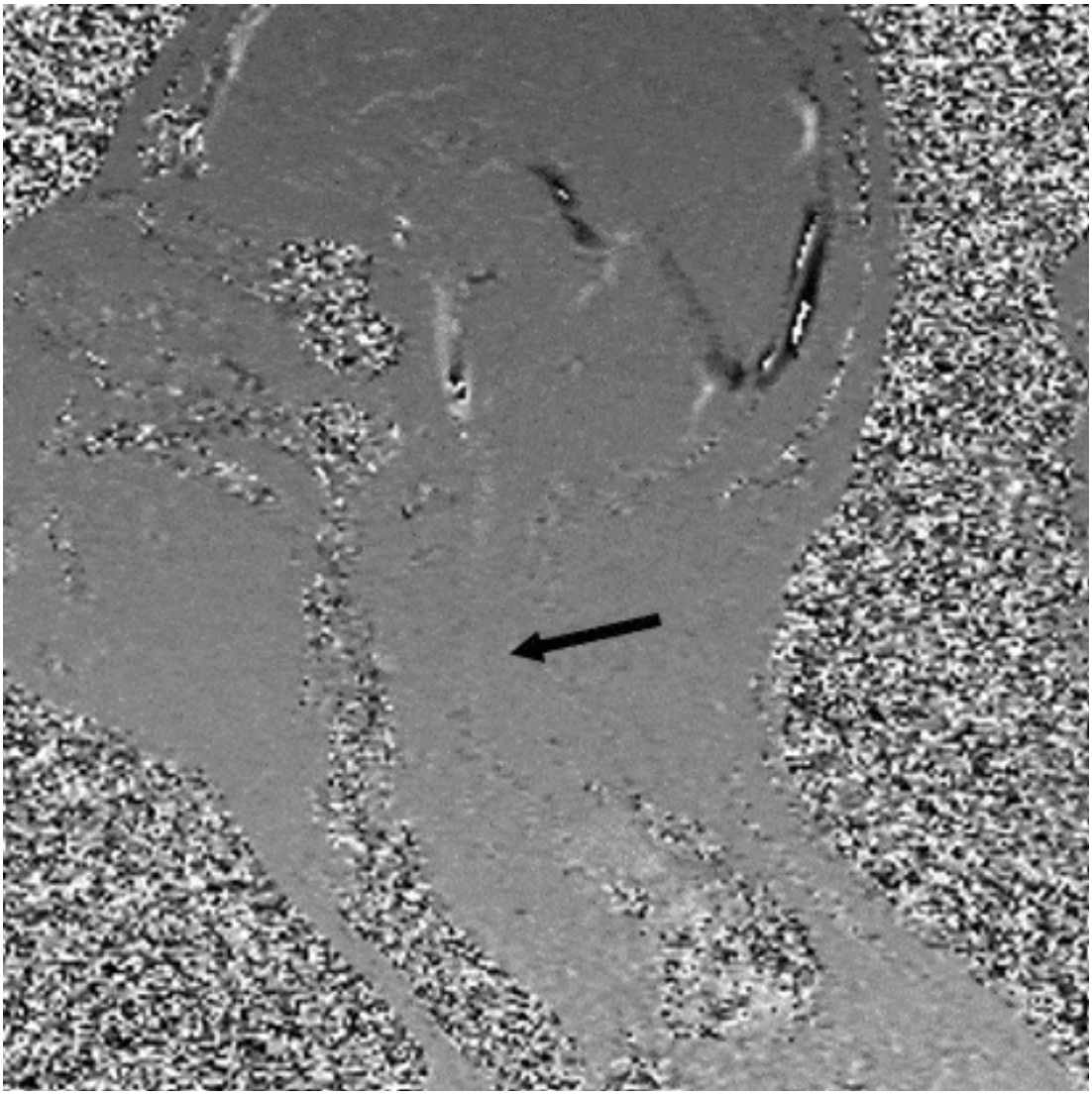


Figure 3: Animated MRI scans show CSF fluid along the spine, indicated by the pulsing dark (Source: https://www.regenexx.com/craniosacral-therapy-research/)

Different than in the cranium the spinal dura mater is only losely attached to the spinal vertebrae. Compared to research of CSF fluid in the brain there haven't been a lot of studies of CSF fluid around the spine the last decades. There have been some interesting studies with MRI scans that show fluid flowing along the spine. Longitudinal and transverse motions occur in the CSF fluid along the spinal cord, but also in the spinal cord itself (16).

Research (15) from 2001 with sequenced MRI scans show that the velocity of CSF fluid down the spine is higher than the velocity of fluid to the cranium. The highest velocity was measured at the thoraic spinal canal compared to the cervical and lumbar region. This is caused, because of the smaller diameter of the spinal canal at the thorax. Patients with stenosis of the spinal canal had a significantly higher velocity of CSF fluid at the place of narrowing and even 70cm further in the spine. The researchers concluded in general that there was a high interindividual variability of results, even under the healthy participants (15).

Figure 4: Streamline plots of CSF fluid around the spine for healthy case with fine structures (left) and without fine structures (right). On the left vortexes can be seen around the fine structures. (17)

There are also scientists who made a computer simulation of the CSF flow around the spine. As an input they use the physical laws of fluid dynamics and an anatomical 3D model of the spinal cord. With a lot of computer power the flow around the spine can then be predicted. A study from 2014 for example showed impact on the flow of the nerve roots and denticulate ligaments that come out of the spinal cord through the spinal subarachnoid space. It was shown that these ligaments change the flow and cause small vortexes. See the picture on the left. This likely improves the mixing of fluid and solutes in the spine (17).

The epidural space, the space between the dura mater and the spinal vertebrae, which is filled with fatty tissue and veins. Klarica and Orešković state that due to this the CSF space in cervical and lumbar region can be significantly altered due to respiration or pressure applied to the abdomen (7).

New concept of CSF movement

So how do all these new or improved concepts now fit together in the bigger picture. First of all we might be better of speaking of a movement of fluids, than a circulation of CSF fluid, like Oreskovic

and Klarica also suggest (7). Further what they also say and is important to note is that the movement of water, which is 99% of CSF fluid is different than the movement of solutes in the CSF (7). The below diagram from Brinker (1) summarizes the current understanding of the flow of CSF fluid the best in my opinion.

Figure 5: Diagram of CSF "circulation". This diagram summarizes fluid and cellular movements across the different barriers of the brain compartments (blood, interstitial fluid (ISF), Virchow Robin space (VRS), cerebrospinal fluid space comprising the cerebral ventricles, basal cisterns and cortical subarachnoid space).

In the picture is shown that at most boundaries a bi-directional flow might take place. So the net flow of soluters or water accross boundaries might be small, but the exchange of fluid might be bigger than expected. Previously it was understood that the interstitial fluid (ISF) around the brain cells was stagnant. It now has been shown fluids enter the brain through the blood brain barrier (BBB), Virchow Robin Spaces (VRS) and from CSF spaces. Cellular movement including inflammatory cells from blood may reach the brain through Virchow Robin Spaces or Choroid Plexus. Fluid movements are dependent on the cardiac pulse, especially at the blood brain barrier this seems obvious. In the ventricles and also along the spine respiration is the main regulator of the CSF flow (12).

So Figure 5 shows how fluids and solutes move through the CSF system. Question remains in what quantities fluid and solutes are moved over the boundaries and where is the biggest net transport? There is still a lot of debate about this. What is the relative importance of the glymphatic system or the choroid plexus? As discussed earlier Klarica and Orešković claim CSF isn't predominantly produced by the choroid plexus. Their hypothesis is that "CSF is permanently produced and absorbed inside the entire CSF system, as a consequence of water filtration and reabsorption through the capillary walls into the interstitial fluid (ISF) of the surrounding brain tissue" (6). Other researchers have and an understanding that is more in line with the traditional understanding

although they also incorporate the more complex transport accross the bloodbrain barrier and Virchow Robin spaces in their theories.

The other question is how the diagram in Figure 5 translates to an anatomical picture of the flow. As shown before the direction of flow from third to fourth ventricles doesn't hold for infants and certain pathologies. Next tot that it's still a question what the influence of posture is on the movement of CSF fluid in human (14). Gravity definitely seems to have a crucial influence on CSF as astronauts have eyesight problems, because the pressure of CSF fluid is different in space due to the low gravity. This is even one of the big problems for the NASA to overcome, to be able to send people to Mars. Not suprisingly long time space flights give astronauts back problems, see link.

So these days we know a little bit more about how CSF moves through the body and spine. Especially in the brain, prompted by a increasing popularity in neurology, a lot of discoveries have been made in the last decades. This showed the movement of fluid through the brain is way more complex than previously understood. As shown in this post there are still debates going on how these pieces fit together. Hopefully in the next years many new breakthroughs will be made about the function and movement of cerebrospinal fluid.

New insights in movement of cerebrospinal fluid in relation to craniosacral therapy

The movement of CSF fluid from sacrum to the to the cranium in plays a crucial role in the theory of craniosacral therapy. So how do these new insights in the movement of cerebrospinal fluid relate to craniosacral therapy? First the anatomy classes of most craniosacral therapy courses might need to be revised. Often the traditional understanding of CSF circulation is taught, just like in most anatomy classes of other medical courses and schools. More interesting is though how these new discoveries fit together with the philosophies behind craniosacral therapy. Does it support "primary

respiration” theory by, the founder of craniosacral therapy, Sutherland? What about the craniosacral rhythm? How does it relate to the theories by the other important figures in history of craniosacral therapy like Upledger and Sills? In my next post I will try to find the answer to these questions.

References

1. Brinker T, Stopa A, Morrison J and Klinge P: **A New Look at cerebrospinal fluid circulation** *Fluids and Barriers of the CNS* 2014 **11**:10 http://www.ncbi.nlm.nih.gov/pubmed/24817998

2. Melody P. Lun, Edwin S. Monuki & Maria K. Lehtinen: **Development and functions of the choroid plexus–cerebrospinal fluid system** *Nature Reviews Neuroscience* 2015 16: 445–457 http://www.nature.com/nrn/journal/v16/n8/full/nrn3921.html

3. Darko Orešković, Marijan Klarica: **The controversy on choroid plexus function in cerebrospinal fluid production in humans: how long could different views be neglected?** *Croatian Medicine Journal* 2015 56: 306-310

4. Milan Radoš, Marijan Klarica, Branka Mučić-Pucić, Ines Nikić, Marina Raguž, Valentina Galkowski, Dora Mandić, and Darko Orešković: **Volumetric analysis of cerebrospinal fluid and brain parenchyma in a patient with hydranencephaly and macrocephaly – case report** *Croat Med J.* 2014 55: 388–393. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4157378/

5.Kapsalaki E, Svolos P, Tsougos I, Theodorou K, Fezoulidis I, Fountas KN: **Quantification of normal CSF flow through the aqueduct using PC-cine MRI at 3T.** *Childs Nerv Syst.* 2012 28(1):55-63

6. Hladky SB, Barrand MA: **Mechanisms of fluid movement into, through and out of the brain: evaluation of the evidence.** *Fluids Barriers CNS.* 2014 11(1):26 http://www.ncbi.nlm.nih.gov/pubmed/25678956

7. Darko Orešković and Marijan Klarica: **A new look at cerebrospinal fluid movement** *Fluids and Barriers of the CNS* 2014, 11:16 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4118619/pdf/2045-8118-11-16.pdf

8. Melody P. Lun, Edwin S. Monuki and Maria K. Lehtinen: **Development and functions of the choroid plexus-cerebrospinal fluid** *Nature Reviews Neuroscience* 2015 16:445-457 http://www.nature.com/nrn/journal/v16/n8/full/nrn3921.html

9. Kipnis, J. **Multifaceted interactions between adaptive immunity and the central nervous system** *Science* 2016 353(6301):766-771

10. Lulu Xie, Hongyi Kang, Qiwu Xu, Michael J. Chen, Yonghong Liao, Meenakshisundaram Thiyagarajan, John O'Donnell, Daniel J. Christensen, Charles Nicholson, Jeffrey J. Iliff, **Sleep Drives Metabolite Clearance from the Adult Brain** *Science* 2013 342: 373-377

11. Thiyagaragan M. Achariyar, Baoman Li, Weiguo Peng, Philip B. Verghese, Yang Shi, Evan McConnell, Abdellatif Benraiss, Tristan Kasper, Wei Song, Takahiro Takana, David M. Holtzman, Maiken Nedergaard, and Rashid Deane **Glymphatic distribution of CSF-derived apoE into brain is isoform specific and suppressed during sleep deprivation** *Mol Neurodegener.* 2016; 11: 74. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5146863/

12. Dreha-Kulaczewski S., Joseph AA, Merboldt KD, Ludwig H., Gärtner J., and Frahm J., **Inspiration Is the Major Regulator of Human CSF Flow**, *Neurobiology of Disease* 2015 35(6):2485–2491

13. Faubel R, Westendorf C, Bodenschatz E, Eichele G., **Cilia-based flow network in the brain ventricles**, *Science* 2016 353:176-8 http://science.sciencemag.org/content/353/6295/176.long

14. Klarica M, Rados M, Erceg G, Petos G, Jurjevic , Oreskovic D., **The Influence of Body Position on Cerebrospinal Fluid Pressure Gradient and Movement in Cats with Normal and Impaired Craniospinal Communication** *PLOS ONE* 2014 9(4) http://europepmc.org/articles/PMC3991613

15. Freund M, Adwan M, Kooijman H, Heiland S, Thomsen M, Hahnel S, Jensen K, Gerner HJ, Sartor K, ***[*Measurement of CSF flow in the spinal canal using MRI with an optimized MRI protocol: experimental and clinical studies]** *Rofo* 2001 173(4):306-14 https://www.ncbi.nlm.nih.gov/pubmed/11367838

16. Levy LM, **MR imaging of cerebrospinal fluid flow and spinal cord motion in neurologic disorders of the spine,** *Magn Reson Imaging Clin N AM.* 1999 7(3):573-87 https://www.ncbi.nlm.nih.gov/pubmed/10494536

17. Pahlavian SH, Yiallourou T., Tubbs S, Bunck AC, Loth F., Goodin M., Raisee M., Martin BA, **The Impact of Spinal Cord Nerve Roots and Denticulate Ligaments on Cerebrospinal Fluid Dynamics in the Cervical Spine,** *PLOS* 2014 april 7th https://doi.org/10.1371/journal.pone.0091888