The circulation of cerebrospinal fluid (CSF) plays a key role in maintaining the homeostasis of the central nervous system (CNS). Production of CSF occurs primarily at the choroid plexuses within the ventricles of the brain. The fluid and its solutes then flow within the sub-arachnoid spaces of the cranial and spinal compartments, where a tightly controlled exchange with the interstitial fluid of the CNS parenchyma occurs. Remarkably, the mechanisms of clearance for this important fluid are still incompletely understood. An intense debate about the main routes of CSF outflow that originated in the late 19th century has continued to the present day with some favouring a direct efflux through arachnoid villi to the dural venous sinuses or others proposing routes to lymphatic vessels located in proximity to exiting cranial nerves or within the subarachnoid spaces of the cranial and spinal compartments. The patients were injected with gadodiamide contrast agent and were given MRI scans before injection and at 4.5, 15 and 39 h after injection. In an unbiased approach, the authors assessed three potential CSF outflow pathways simultaneously: to the parasagittal dura, through the cribriform plate to the nasal turbinates and along the perineural space of the optic nerve, as well as accumulation of the contrast agent at the draining deep cervical lymph nodes. Significant contrast enhancement was found at each of these evaluated areas providing clinical evidence for multiple active sites of CSF outflow to the lymphatic system. Taking advantage of the large range of subjects, the authors performed correlation analysis between measurements of efflux and patient age and assessments of quality of sleep and cognitive decline (which were both determined by telephone survey). Interestingly, significant negative correlations were found between increasing age and clearance function at the peri-olfactory nerve and parasagittal dura regions. The authors also determined that impairments in sleep quality and cognitive function were most closely associated with a reduced clearance of contrast agent to the nasal turbinate regions, indicating that the peri-olfactory nerve pathway may be of particular importance.

One limitation of the study is that the resolution of the MRI technique does not allow direct visualization of contrast agent drainage within lymphatic vessels at the three assessed regions, thus the authors are correct to describe these routes as “putative” clearance pathways at this point. In addition, small molecular weight contrast agents are not ideal for the assessment of CSF clearance as significant diffusion into the CNS parenchyma or extracranial interstitial tissue may occur. However, clinically-approved macromolecular contrast agents are lacking at this time. Finally, other potential efflux routes from the basal skull or spine would need to be evaluated. This may require the development of whole-body scanning techniques, ideally with multiple timepoints in the hours immediately following injection.

These intriguing findings have provided more evidence for a concept of a decline in CSF turnover during physiological ageing, which may play a role in the accumulation of toxic metabolites such as amyloid beta.
More research would be necessary to determine at which stage a functional decline may occur in patients suffering from cognitive decline or if the frequent loss of olfactory function seen in early-stage Alzheimer’s disease may be related to a reduction of CSF clearance along olfactory nerves.

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S.T.P. is the sole author.

Declaration of interests
The author has no conflicts of interest to disclose.

References