HBCI Abstract

The glymphatic system is a brain-wide pathway involving perivascular spaces that activates during sleep to facilitate cerebrospinal fluid-based clearance of toxic proteins and by-products from nervous tissue. A breakdown of brain clearance is a potential root cause of protein accumulation in dementias, a process already starting years before clinical diagnosis is established. The observation that glymphatic perivascular exchange in rodents is more rapid during sleep, and is impaired in the setting of aging, neurovascular and neurodegenerative pathology, strongly suggests that the impairment of this biology may underlie the development of neurodegenerative disease in humans. The glymphatic system is well studied in animals but due to the invasive nature of the methods involved, translation into methodology for human studies is challenging. Thus, no validated biomarker of glymphatic function in humans is yet available. This project will focus directly on this void and 1) Design and validate a set of imaging biomarkers sensitive to disturbances in brain clearance; the different biomarkers differ in level of invasiveness and technology readiness level. 2) Measure the influence of sleep (deprivation) on the developed biomarkers. 3) Demonstrate functionality of the biomarkers in characterizing brain clearance disturbances in idiopathic normal-pressure hydrocephalus (iNPH) and early Alzheimer's disease (AD). To approach these tasks, leading European teams on imaging technologies and brain clearance join forces. Between the five groups represented in the consortium, promising human MRI technologies have been proposed that will be advanced into validated biomarkers. By linking these human studies with the basic research by the world-leading group on brain clearance of Prof. Nedergaard, validation of the technologies to true gold standards will be achieved. By this project design, bi-directional translation of knowledge, i.e. from animal models of disease to in vivo human measurements and vice versa, is guaranteed. Clearance of intrathecally injected MRI contrast agent (gMRI), as pioneered by Dr. Ringstad, is widely considered as break-through technology that for the first-time provided us with insight into the human brain clearance system at work over a time span of days, and here this approach will be validated in mice. The second technique relies on intravenous injection of contrast agent and is therefore less invasive, albeit less established. The other biomarkers are purely non-invasive with the first exploiting ultra-high field MRI at 7 Tesla to allow CSF-specific, high spatial resolution imaging of CSF mobility in perivascular spaces. The second non-invasive technique is based on the presence of different frequencies in functional MRI signals especially in the fourth ventricle, whereas the last technique relies on diffusion weighted MRI. Clearance of CSF tracer assessed by gMRI and blood samples obtained through 2-3 days in humans and mice will serve as reference for validation of non-invasive MRI. Failure of effective clearance of amyloid-β and tau is thought to be an early and important pathological process in the two neurodegenerative diseases that we will study: iNPH and AD. However, an important difference between these two is that iNPH is a treatable disease via shunting and therefore offers the possibility to link changes in efficiency of brain clearance to cognitive improvement, thereby also proofing that our developed markers provide essential clinical information by making early disruptions of the brain clearance system visible. The validation of non-invasive imaging biomarkers in these two dedicated cohorts may catalyze the opening of brain clearance research to groups around the world, and to enable key step of deploying of these techniques into existing neuroimaging cohorts throughout Europe, and around the world, as well as to exploit data already available in large, well characterized open-source cohorts of healthy (UK Biobanking) and high risk (ADNI) subjects.