Choroid plexuses at the interface of peripheral immunity and tissue repair in multiple sclerosis

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Purpose of review
Choroid plexuses (ChPs) are key actors of the blood-to-cerebrospinal-fluid barrier and serve as brain immune checkpoint. The past years have seen a regain of interest about their potential involvement in the physiopathology of neuroinflammatory disorders like multiple sclerosis (MS). This article offers an overview of the recent findings on ChP alterations in MS, with a focus on the imaging tools able to detect these abnormalities and on their involvement in inflammation, tissue damage and repair.

Recent findings
On MRI, ChPs are enlarged in people with MS (PwMS) versus healthy individuals. This size increase is an early event, already detected in presymptomatic and pediatric MS. Enlargement of ChPs is linked to local inflammatory infiltrates, and their dysfunction selectively impacts periventricular damage, larger ChPs predicting the expansion of chronic active lesions, smoldering inflammation and remyelination failure in tissues surrounding the ventricles. ChP volumetry may add value for the prediction of disease activity and disability worsening.

Summary
ChP imaging metrics are emerging as possible biomarkers of neuroinflammation and repair failure in MS. Future works combining multimodal imaging techniques should provide a more refined characterization of ChP functional changes, their link with tissue damage, blood to cerebrospinal-fluid barrier dysfunction and fluid trafficking in MS.

Keywords
choroid plexus, MRI, multiple sclerosis, PET, remyelination

INTRODUCTION

The choroid plexuses (ChPs) are highly vascularized veil-like structures running along the ventricles of the brain [1]. Microscopically, they are made of connective stroma, rich in fenestrated capillaries, surrounded by a layer of ciliated epithelial cells interconnected by tight junctions and facing the cerebrospinal fluid (CSF), forming the blood-CSF barrier (BCSFB) [2]. Beyond their primary function of CSF production, which reaches a rate of 0.3–0.4 ml/min [3], ChPs are involved in brain solute clearance [4] and regulate inflammatory cell transit between the blood and the CSF compartment, acting as key neuroimmune checkpoint within the central nervous system [2]. Given this immune-related function, an increasing body of literature over the past few years has focused on their potential involvement in neurological diseases, with a particular focus on those having a neuro-inflammatory component.

THE CHOROID PLEXUS: FROM BIOLOGY TO TRANSLATIONAL NEUROLOGY

ChPs are very reactive structures that can sense peripheral inflammation and subsequently adapt their function. This could be mediated by the release into the CSF by epithelial cells of extracellular vesicles containing proinflammatory microRNAs that can reach central nervous system (CNS) resident cells and upregulate inflammatory targeted genes [5]. In addition, resident macrophages in the ChP stroma dynamically surveil the fenestrated

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KEY POINTS

- ChPs are a key neuroimmune interface between peripheral immunity and central nervous system disease.
- In-vivo imaging studies have recently shown ChP structural and inflammatory modifications in people with MS (PwMS), particularly during the relapsing-remitting phase of the disease.
- ChP alterations are associated with chronic lesion expansion, smoldering inflammation and remyelination failure in the periventricular region of PwMS.
- Future multimodal imaging approaches are needed to disentangle the contribution of ChP changes, dysfunction of the blood-cerebrospinal fluid barrier and fluid trafficking changes to the pathophysiology of tissue damage and repair in MS.

blood vessels and may exhibit functional modifications in response to peripheral events, such as changes in the gut microbiota [6]. In the context of experimental intestinal inflammation, which is associated with an increase in gut permeability, the BCSFB of ChPs was shown to be transiently close, potentially locking down the entrance of immune cells from the blood into the brain [7▪▪].

Immune cell trafficking through ChPs is considered to play a crucial role in neuro-inflammatory diseases. In the experimental autoimmune encephalomyelitis (EAE) multiple sclerosis (MS) models, a seminal work highlighted that ChPs grant the initial access of pathogenic T-helper 17 lymphocytes into the CNS, a process that may precede the appearance of parenchymal infiltrates and myelin loss [8]. The cellular and molecular mechanisms underlying this cell trafficking remain partly unknown but could involve a CCR6-CCL20 axis for Th17 entrance in EAE [8]. *In vitro*, T lymphocytes were shown to cross the BCSFB barrier in ChPs [9], and preactivated memory B cells sampled from people with MS had enhanced chemotactic properties, being able to migrate through the ChP using both paracellular and transcellular pathways [10▪]. Of note, traffic via ChPs is not limited to cells but also involves serum proteins, such as immunoglobulins, that could pass in both directions through different mechanisms of trans-BCSFB diffusion, making these structures an efflux path and a clearance system to recycle immunoglobulins to the circulation [11].

A few post-mortem studies have investigated ChP abnormalities in tissues from people with MS (PwMS), mostly reflecting the end-stage processes taking place at the BCSFB level. Infiltrates of T lymphocytes and antigen-presenting cells, and increased expression of vascular adhesion molecules, were described in ChPs from PwMS and viral encephalitis but not amyotrophic lateral sclerosis, supporting the possible role of ChPs as immune cell route in both acute and chronic neuroinflammation [12]. Recent investigations have corroborated this hypothesis, showing an excess of macrophages, dendritic cells, CD8+ tissue-resident memory T cells, and granulocytes in ChP stroma and vessels of people with progressive MS compared with healthy controls [13]. The presence of activated $CD56^{bright}$ natural killer (NK) cells in both ChPs and periventricular lesions of MS, which seems to be disease-specific compared with other neurological disorders [14], further highlights a possible immunoregulatory role of this subset of NK cells as a modulator of brain neuroinflammation. Transcriptomic analysis of ChPs from people with progressive MS revealed hypoxic modifications as well as altered neuroprotective and secretory properties, suggesting a global dysregulation of immune control and brain protection [15].

In vivo, translational explorations of ChPs abnormalities have been performed jointly in immune-mediated (EAE) and nonimmune mediated (cuprizone intoxication) models of CNS demyelination [16▪▪]. Surprisingly, in both models, ChPs showed lymphocytic and innate immune cell infiltration at the acute stage, which was associated with ChP enlargement on MRI [16▪▪]. In both settings, transcriptomic analysis at the peak of the disease confirmed that enlarged ChPs had an inflammatory signature related to genes regulating leukocyte migration, activation and differentiation [16▪▪], together with an up-regulation of mitochondria-related pathways [16▪▪,17]. MRI quantification of ChP volume in mouse models could therefore be used as a proxy of neuroinflammation and offers the possibility to explore the mechanisms underlying ChP transformation during inflammation [17].

IN VIVO ANALYSIS OF CHOROID PLEXUSES IN HUMAN: THE IMAGING TOOLS AND THEIR INTERPRETATION

Thanks to its high spatial resolution and spontaneous tissue contrast, MRI has emerged as a powerful tool for ChP morphometric analysis [18]. Disorders in which ChP volumetric changes have been described span from psychiatric (autism spectrum disorder, psychosis, depression) [18–20] to neurodegenerative (Alzheimer's, Parkinson's) [21,22] and infectious (e.g. CNS cryptococcosis, neurotuberculosis) diseases [23,24]. In the last couple of years, converging results from independent research groups have further demonstrated that ChPs are enlarged in PwMS compared with healthy controls

[16▪▪,25▪,26▪▪,27▪], raising interest on these structures as potential novel MRI biomarker of neuroinflammation [28].

A comprehensive and comparative interpretation of studies investigating volumetric changes of ChPs would imply the discussion of common methodological approaches for volume quantification. ChP MRI segmentation is classically performed on structural three-dimensional T1-weighted sequences [17]. On nonenhanced acquisitions, ChP signal intensity is comparable with that of the grey matter [17]. On contrast-enhanced images, injected agents yield a higher contrast between ChPs and the surrounding CSF [29]. Fluid-attenuated inversion recovery (FLAIR) sequences have also been proposed for ChP annotation [27▪], but validation and reproducibility studies are still awaited. FLAIR offers the advantage of better estimate the proper ChP tissue compartment and to identify adult ChP cystic abnormalities, which may contribute to volumetric increase [30,31].

Independently of the selected sequence, the gold standard method for segmentation on MRI remains manual annotation that is reproducible across operators [25▪], despite being extremely time-consuming. The delimited structures are usually the ChPs of the lateral ventricles, while those of the third and fourth ventricles are generally not included due to their partial and inconstant visualization [32]. *FreeSurfer*, to date the most widely applied software for brain segmentation, showed only poor correlation with manual ChP annotation [25▪]. Alternative automatic segmentation methods are emerging, showing better performances in healthy controls, but validation on larger groups and in disease conditions is needed [33,34].

Methodologically, the analysis of ChP volumetric differences between patients and healthy controls should take into account the volume of lateral ventricles, which correlates with ChP size, both in normal and disease conditions [25▪]. Adjusting for this metric is therefore recommended to minimize segmentation and atrophy biases, particularly in diseases with a neurodegenerative component. Several additional parameters have been identified as modulators of ChPs size: sex – the enlargement being greater in females in healthy controls, psychiatric disorders and pediatric MS [35,36▪▪] – aging [37], adiposity and obesity [36▪▪,38].

The pathophysiological correlates of ChP size changes in humans remain enigmatic and may involve various processes, including perfusion changes, inflammatory infiltrates, BCSFB dysfunction. Beyond conventional MRI, these mechanisms might be partly disentangled *in vivo* using combinations of advanced MRI or PET imaging tools.

Perfusion proxies within the ChPs can be generated by contrast-enhanced MRI sequences, by arterial spin labeling (ASL) or by PET. A decreased perfusion in aging individuals was found on dynamic susceptibility contrast MRI [39,40]. In Alzheimer's disease, an impaired blood flow that correlated with cognitive decline was demonstrated in comparison with healthy controls [21,41▪▪]. Avoiding the infusion of contrast agent, ASL can quantify ChP apparent blood flow [42]. To overcome its poor temporal resolution, which implies a long acquisition time, a pseudo-continuous version of ASL based on a short radiofrequency pulse coupled with a fast imaging sequence has been proposed [43] and has confirmed that ChP is hypoperfused in aging individuals [37,44]. These MRI tools for perfusion assessment have not yet been applied to PwMS, but the quantification of the early component of time activity curves from dynamic PET acquisitions, which represents a proxy of perfusion, suggested that perfusion was not impaired in ChPs of MS [25▪].

Molecular imaging by PET offers the opportunity to quantify inflammatory infiltrates within ChPs [25▪,45]. Applying translocator protein (TSPO) tracers that mostly bind to innate immune cells, a neuroinflammatory component has been demonstrated in ChPs of people with temporal lobe epilepsy and MS at different disease stages [25▪,46▪,47]. Beyond PET, an increase in pseudo-T2 mapping on MRI, which is a simplification of T2 mapping, was also found in MS ChPs and interpreted as a proxy of inflammation [27▪]. However, this interpretation has not yet been supported by pathological validation.

Finally, while we still lack data in PwMS, imaging metrics reflecting BCSFB permeability could be of great interest to explore the physio-pathological background of ChP structural abnormalities. Diffusion-weighted imaging has showed an increased water diffusion during aging and in obesity [37,38], but this approach lacks specificity [48]. The dynamic measurement of contrast agent distribution from ChPs into the CSF, either through sequential MRI acquisitions after contrast administration [49,50] or through dynamic PET, may generate more specific proxies of BCSFB permeability.

THE IMAGING SIGNATURE OF CHOROID PLEXUSES IN MULTIPLE SCLEROSIS: INSIGHT INTO NEUROINFLAMMATION AND REMYELINATION FAILURE

Two pioneer studies have recently shown that ChPs are significantly enlarged in PwMS compared with healthy controls [16▪▪,25▪]. Using complementary approaches, they both highlighted that ChP volume

was linked to the inflammatory component of the disease. Through a combination of MRI and TSPO PET with ^{18}F-DPA-714, Ricigliano *et al.* [25▪] found an association between enlargement and innate immune cell Infiltration, as reflected by increased ^{18}F-DPA-714 uptake in the ChPs of PwMS, the correlation being more pronounced at the relapsing-remitting stage. The relationship between higher ^{18}F-DPA-714 uptake and innate immune cell infiltration was further attested on post-mortem samples, where a subset of immune cells coexpressing TSPO and the CD163 marker was identified in ChPs of PwMS but not of control individuals [46▪]. Using an original translational approach, Fleischer *et al.* [16▪▪] corroborated the link between ChP enlargement and inflammatory content, both in the EAE and in the cuprizone-mediated demyelinating model. Of great interest, a large infiltrate of adaptive and innate immune cells was found within enlarged ChPs at the acute stage of each model, which was reversible following remyelination in the cuprizone model [16▪▪].

Whether ChP changes are consequence of tissue damage or play a causative role in mouse models and in PwMS remains unclear. Noteworthy, their enlargement also informs about brain parenchymal inflammation and tissue damage. Indeed, ChP volume showed an association with focal white matter lesion load [16▪▪,25▪], gadolinium-positive lesions on MRI [25▪], the extent of neuroinflammation in the thalami and normal-appearing white matter on PET [25▪], and brain atrophy [16▪▪,25▪].

Significantly, when analyzed more in-depth using multimodal imaging approaches, the influence of ChP dysfunction was found to be regionalized within the brain and to mainly impact on periventricular areas in MS. Indeed, converging MRI studies have demonstrated that periventricular regions exhibit a greater microstructural damage, which decreases according to the distance from ventricles [51–53]. A similar periventricular gradient of immune cell density was unraveled by TSPO PET [53], pointing at a possible deleterious effect of CSF composition [53,54], which could act both on deep and superficial brain surfaces and explain the gradient of microstructural damage. In addition, we recently discovered that white matter lesion remyelination selectively failed in proximity to ventricular CSF, this failure driving regional cortical atrophy through structural connectivity [55▪].

ChPs, therefore, emerged as a possible explanatory factor for the regionalization of persisting neuroinflammation and repair failure in MS (Fig. 1). Supporting this hypothesis, their enlargement was shown to predict the slow expansion of chronic active periventricular lesions on MRI [56▪▪]. On TSPO-PET, a similar correlation was found between ChP enlargement and the percentage of chronic MS lesions containing a smoldering inflammatory component, the strength of the association being higher in periventricular white matter [57▪]. Finally, our group recently reported that greater ChP size was associated with lower periventricular remyelination ($r = -0.79$, $P = 0.0018$) in two independent cohorts of PwMS [55▪]. Although the biological mechanisms underlying these correlations still needs to be elucidated, these novel findings convincingly support the role of ChPs in the persistence of neuroinflammation and the failure of myelin repair in the tissues facing ventricular CSF, the two processes being closely interconnected. We can speculate that BCSFB dysfunction at the ChP level may generate a harmful proinflammatory environment, potentially involving cytokines, deleterious antibodies, exosomes or other mediators, such as fibrin or ceramide, that sustain smoldering inflammation and in turn, prevent repair via impairment of metabolism, survival or differentiation within remyelinating cells [55▪,58–60].

CLINICAL RELEVANCE OF CHOROID PLEXUS ENLARGEMENT IN MULTIPLE SCLEROSIS

Although the clinical use at the individual level of ChP volumetric analysis may be hampered by the overlap of values between PwMS and healthy controls, this imaging metric may bring novel insights for patient diagnosis or prognosis.

In a comparative study between PwMS, neuromyelitis optica spectrum disorder (NMOSD), migraine and healthy controls, only PwMS patients were characterized by ChP enlargement, possibly reflecting the different role of these structures in the pathogenesis of MS and NMOSD, and encouraging investigation on ChP changes as a disease-specific marker in the diagnostic workup of inflammatory demyelinating diseases [26▪▪]. Converging studies have further explored the timing of ChP changes during the course of MS. They unraveled that these alterations are one of the earliest signs that can be detected on MRI, being identifiable in presymptomatic MS (where ChP inflammation may precede parenchymal infiltrates) [46▪], clinically isolated syndrome [61] and pediatric MS [36▪▪].

How ChP volumetric assessment could help, disease course prediction is an active field of investigation. Indeed, relapsing-remitting MS patients with larger ChPs showed higher annualized relapse rates over 4 years [25▪], strengthening the relationship between ChP volume and clinical metrics of inflammation (Fig. 1). Whether ChP size also

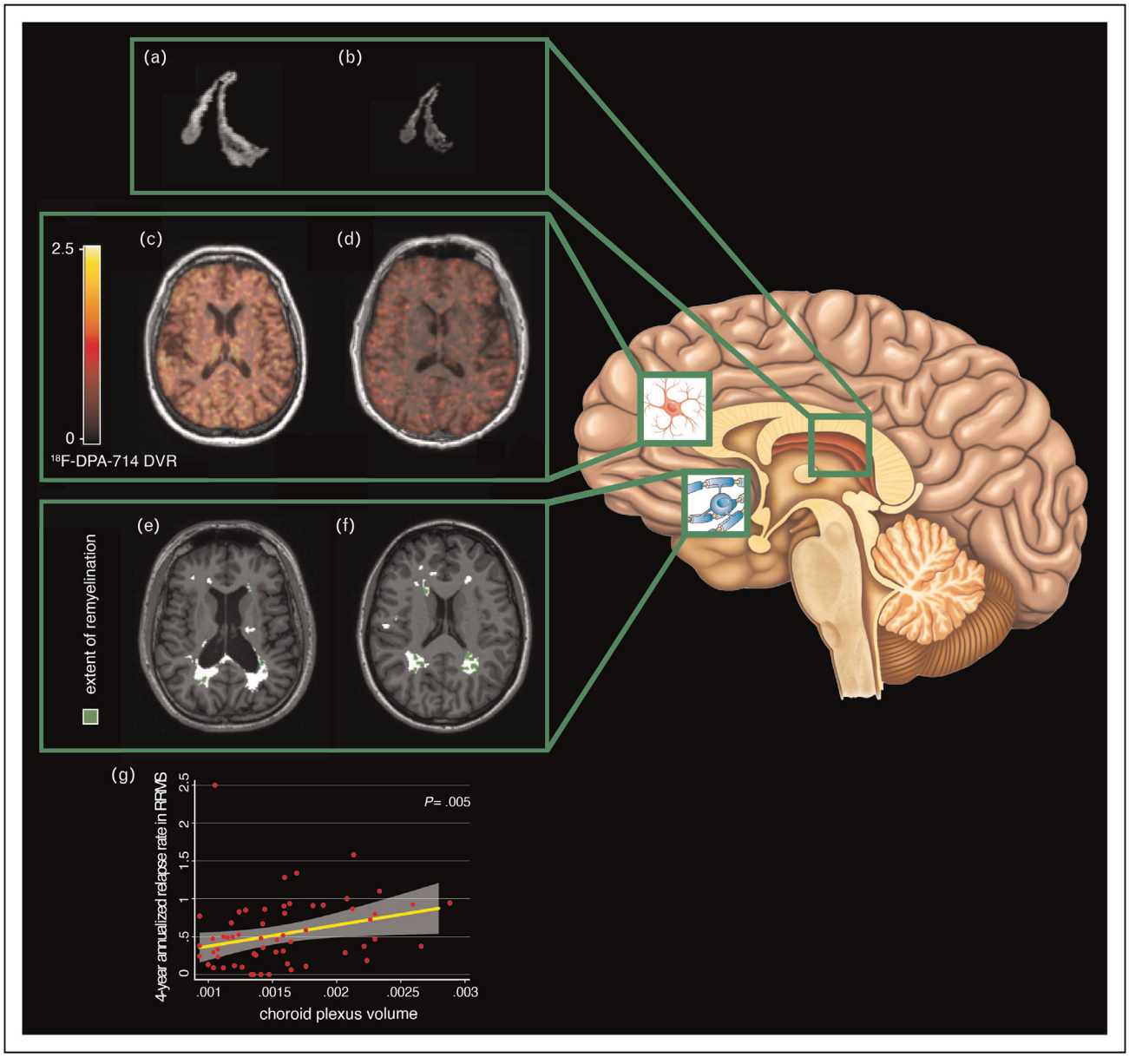

FIGURE 1. Choroid plexus enlargement is associated with higher innate immune cell activation and lower periventricular remyelination. The image on the right illustrates a sagittal view of the brain, including a focused zoom on three key players: choroid plexus, activated microglia (cell in red) and oligodendrocyte (cell in light blue). (a and b). Choroid plexus volumes were selected from the three-dimensional-T1-weighted images of two individuals with relapsing-remitting multiple sclerosis, one with large (a) and the other with smaller (b) choroid plexus. (c and d). Axial slices illustrating the brain expression of translocator protein (reflecting the density of innate immune cells) assessed with ^{18}F-DPA-714 PET and quantified as distribution volume ratio maps, which were registered onto the three-dimensional-T1 image. The subject shown in (c) is the same as the one from part (a) and displayed higher distribution volume ratio parenchymal values compared with the subject shown in (d), who was the one shown in part (b) (both individuals had a mixed-affinity binding genotype for translocator protein). (e and f) Individual maps of remyelination within multiple sclerosis lesions from two individuals with relapsing-remitting multiple sclerosis. Maps were obtained from dynamic ^{11}C-PIB PET and were registered onto the three-dimensional-T1 magnetic resonance images [55▪]. The subject shown in (e) displayed a low extent of remyelination and large choroid plexus, whereas the subject shown in (f) displayed more remyelination and smaller choroid plexus. Lesional voxels are indicated in white, while remyelinated voxels are indicated in green. (g) Scatterplot illustrating the positive association between 4-year annualized relapse rate and choroid plexus volume in a group of individuals with relapsing-remitting multiple sclerosis [25▪]. All volumes were normalized according to total intracranial volume. Confidence interval is represented by the gray area on the graph, while the fit line is indicated in yellow. DVR, distribution volume ratio; RRMS, relapsing-remitting multiple sclerosis; $P = P$ value of the multivariable linear regression model.

predicts disability worsening remains unclear since studies reported discrepancies, some finding no association between ChP enlargement and Expanded Disability Status Scale (EDSS) scores [25▪,36▪▪], while others identifying a positive correlation with both baseline and 4-year longitudinal EDSS [16▪▪]. These contrasting results might be explained by differences in study power or demographics between cohorts but also by the statistical approaches employed. Indeed, a close relationship between ChP and ventricular size has been described [25▪,27▪], suggesting that, beyond inflammation, brain atrophy may influence the measured size of ChPs. This bias may be more pronounced for PwMS at advanced progressive stages [25▪]. Part of the predictive value of ChP enlargement might therefore be linked to the atrophy component, and future studies should adjust for this confounding variable. A recent study has further highlighted that baseline ChP microstructural abnormalities, explored through pseudo-T2 mapping on MRI, may have a stronger value compared with ChP size for the prediction of subsequent 5-year disability progression [27▪]. However, the relationship between T2 mapping and inflammation in ChPs still has to be proven.

FUTURE PERSPECTIVES/CONCLUSION

Larger scale ChP volumetric analysis will benefit from the development of accurate and time-saving techniques for automatic annotation [62▪,63]. Algorithms obtained through deep learning approaches have recently been proposed and yielded promising results [33,34], opening the perspective of a systematic quantification of these metrics in daily practice. However, ChP enlargement has been detected in several brain disorders and may traduce distinct biological processes depending on the pathological condition or disease stage. As an example, ChP enlargement is more closely associated with inflammatory infiltrates at early stages of MS, such as presymptomatic or relapsing-remitting MS, whereas brain atrophy may increasingly impact at later progressive phases [25▪,46▪]. This justifies additional multimodal imaging approaches to disentangle the respective contribution of ChP immune infiltration, perfusion changes, permeability and brain atrophy to ChP dilation. Integrating dynamic PET with MRI-based techniques should further allow to explore jointly ChP's BCSFB function, fluid trafficking through the brain glymphatic and lymphatic systems, parenchymal neuroinflammation and repair, opening a novel window of investigation in the physiopathology of MS.

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Conflicts of interest

The authors report no conflicts of interest related to this work.

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