Title: Surface-in pathology in multiple sclerosis: A new view on pathogenesis?

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Abstract
While multiple sclerosis can affect any part of the central nervous system, it does not do so evenly. In white matter it has long been recognised that lesions tend to occur around the ventricles, and grey matter lesions mainly accrue in the outermost (subpial) cortex. In cortical grey matter, neuronal loss is greater in the outermost layers. This cortical gradient has been replicated in-vivo with magnetisation transfer ratio and similar gradients in grey and white matter magnetisation transfer ratio are seen around the ventricles, with the most severe abnormalities abutting the ventricular surface. The cause of these gradients remains uncertain, though soluble factors released from meningeal inflammation into the cerebrospinal fluid has the most supporting evidence. In this Update, we review this “surface-in” spatial distribution of multiple sclerosis abnormalities and consider the implications for understanding pathogenic mechanisms and treatments designed to slow or stop them.

Keywords
Multiple sclerosis; magnetisation transfer ratio; neuropathology, meningeal inflammation; B cell follicle
**Introduction**

Since its first description multiple sclerosis (MS) has predominantly been considered an inflammatory demyelinating disease of central nervous system (CNS) white matter (WM), but it is now clear that no part of the CNS is spared. The detailed molecular pathogenesis of MS still eludes us, but the uneven nature of MS pathology may provide important clues. WM lesions, the most visible feature of MS, tend to form adjacent to the ventricles (Dawson, 1916) and GM lesions also usually form close to the brain surface (Kutzelnigg et al., 2005). Extra-lesional abnormalities are also most marked at the inner (periventricular) and outer (subpial) brain surfaces. Recent MRI studies have shown that “surface-in” abnormality gradients are associated with clinical outcomes in MS, independently of WM lesions, and can predict treatment response. The presence of these gradients has potentially important therapeutic implications, as it implicates CSF as being a likely mediator of this, yet many drugs used to treat MS do not readily enter the intrathecal space. In this Update, we review the “surface-in” spatial distribution of MS abnormalities and consider the implications for understanding pathogenic mechanisms and treatments.

**White matter lesions**

Classic active lesions, present in greater numbers at earlier stages and in the most rapidly progressive cases, have perivascular and parenchymal infiltrates of lymphocytes and abundant macrophages throughout (Prineas and Wright, 1978). In progressive MS half of all lesions seen still have features suggesting activity (termed chronically active, smouldering or slowly expanding lesions) characterised by an inactive core surrounded by a rim of activated microglia and macrophages with on-going tissue injury (Prineas et al., 2001; Frischer et al., 2009; Lassmann, 2011). Virtually all WM lesions form around a vein (for example (Ribbert, 1882)) and using 7T MRI a central vein is visible in 87% of WM lesions (Tallantyre et al., 2009). WM lesions also tend to occur around the ventricles (Dawson, 1916), and on MRI there is a high lesional density around the lateral ventricles (which have a high density of veins draining towards them) but low density surrounding the fourth ventricle (which has few veins draining towards it) (Wang et al., 2010; Pardini et al., 2016). Lesions also occur in the outer cervical cord, again around small veins (Oppenheimer, 1978). These data collectively suggest that most, if not all, WM lesions in MS are venocentric.

Lesion formation around veins may be due to factors originating from the blood (see later) or perivascular space. Perivascular spaces are continuous with the subarachnoid space (Ichimura et al., 1991), though they collapse at post-mortem making them difficult to study. Perivascular spaces are significantly larger in people with MS (independent of atrophy) and increase in size and number at
the time of lesional contrast enhancement, suggesting some inflammatory association (Wuerfel et al., 2008). Perivenular hypoxia may also be a relevant factor (Martinez Sosa and Smith, 2017): veins normally supply oxygen to surrounding brain tissue (Vovenko, 2009), but under conditions of hypoxia, venous blood becomes deoxygenated, draining oxygen from it (Ivanov et al., 1999). In a cross sectional comparison, WM lesions in secondary progressive MS were most prevalent in areas of low cerebral perfusion while in early relapsing-remitting MS, lesions were also seen in well perfused regions (Holland et al., 2012). Longitudinal assessment is needed, but this finding suggests a differential repair capacity within the human brain influenced by cerebral perfusion. Distinguishing this from a CSF-derived factor impairing repair is however difficult as most areas of low perfusion lie close to the ventricles.

It is also worth noting that even amongst lesions their pathology varies by location: endogenous remyelination (Patrikios et al., 2006) and recovery of T1-hypointensity on MRI (a putative marker of remyelination (Papadopoulou et al., 2014)) are markedly limited in lesions close to the lateral ventricles.

**Grey matter lesions**

In long-standing MS, lesions account for a quarter of cortical GM compared to 6% of the WM (Bo et al., 2003). GM lesions are seen in the spinal cord (Fog, 1950); deep GM (predominantly in the inner layers closest to the ventricles (Haider et al., 2014)); and cortical GM (most frequently in the outermost (subpial) layer (Kutzelnigg et al., 2005; Maglioetti et al., 2007)). While evident early (Lucchinetti et al., 2011; Bevan et al., 2018) subpial lesions become more prevalent in progressive disease (Kutzelnigg et al., 2005) accounting for two thirds of all cortical lesions (Bo et al., 2003). If active, subpial lesions in progressive disease occur close to focal areas of meningeal inflammation (Howell et al., 2011) which predominantly occur in cortical sulci (Maglioetti et al., 2007; Haider et al., 2016), suggesting that these lesions might arise from soluble factors released by meningeal inflammation, which diffuses across the CSF and damages CSF-bathed tissue (perhaps via microglial activation) (Kutzelnigg et al., 2005; Howell et al., 2011).

**Extralesional WM**

Extralesional WM - regions free of lesions seen using conventional (PD/T2-weighted and FLAIR) MRI - are abnormal when assessed with magnetisation transfer ratio (MTR) and diffusion tensor imaging (DTI), both of which correlate with myelin intensity and axonal count (Schmierer et al., 2008).
2004; Schmierer et al., 2007). Structural changes at the nodes of Ranvier associated with microglial activation might also contribute to such abnormalities (Howell et al., 2010).

However, extralesional abnormalities are not uniform. First, perilesional tissue is abnormal for up to 4mm from the T2-defined lesion edge (Vrenken et al., 2006). Second, periventricular changes: in healthy controls, WM MTR is highest adjacent to the lateral ventricles and decreases with distance from them; in all types of MS, extralesional WM MTR is lowest (most abnormal) at the ventricular edge, increases over the first ~5 mm (Fig. 1) before mirroring patterns seen in healthy controls (Liu et al., 2015; Brown et al., 2017; Brown et al., 2019a). This periventricular MTR gradient surrounds supratentorial and infratentorial ventricles (Pardini et al., 2016) and has been replicated with DTI where the gradient is most marked in people with oligoclonal bands (Pardini et al., 2019). Another diffusion technique, the restricted signal fraction (FR) from the Composite Hindered and Restricted Model of Diffusion (CHARMED), appears more sensitive to axons (Assaf and Basser, 2005) though to the best of our knowledge this has not been confirmed in pathological studies. While the FR is lowest at the ventricular edge in early MS - and differences between healthy controls and people with early MS also appear greatest at the ventricular edge - no significant interaction was found between disease group and distance from the ventricles (De Santis et al., 2019). It remains unclear whether this disparity reflects differences in statistical approaches, a smaller sample size (n=22 compared to n=71 (Brown et al., 2017)), or that the periventricular gradient is more heavily driven by demyelination than axonal loss.

The extralesional periventricular WM MTR gradient appears independent of lesions: the severity is the same in those with and without T2 or enhancing lesions, and remains unchanged after excluding perilesional tissue; gradients and lesions have differing distributions (gradients surround the fourth ventricle (despite low lesion density)); and gradients occur within lesional tissues (Pardini et al., 2016; Brown et al., 2017; Pardini et al., 2019). Outside-in MTR gradients are also seen in cervical cord WM (Kearney et al., 2014). Taken together this suggests different mechanisms may underlie lesion formation and gradients within extralesional (and lesional) tissue.

The pathologic substrate underlying periventricular WM gradients remains under-explored, but a PET study has shown a periventricular gradient of microglial activation in extralesional WM and GM (Poirion et al., 2017).

**Extralesional GM**
Extralesional cortical and thalamic GM show significant axonal loss compared to healthy controls (Cifelli et al., 2002; Choi et al., 2012; Bevan et al., 2018). Neuronal loss appears relatively independent of demyelination (Magliozzi et al., 2010) and no differences in axonal density were seen between demyelinating cortical lesions and extralesional GM (Klaver et al., 2015). Cortical demyelination has typically been quantified in terms of demyelinating lesions, but extralesional reductions in myelin density are seen (Bevan et al., 2018), in part reflecting areas of incomplete remyelination (Albert et al., 2007).

Significantly greater neuronal loss is seen in the outermost cortical layers in some patients with SPMS (Magliozzi et al., 2010), respect to healthy controls. This abnormality is related to an elevated level of meningeal inflammation (Fig. 2) and accompanied by substantial gradient of microglial activation in the most external cortical layers (Magliozzi et al., 2010) in different cortical grey matter regions (Fig 2), including motor cortex and hippocampus. Preliminary neuropathology studies in progressive MS found a thalamic surface-in gradient of neuronal loss and microglial activation, maximal near the ependyma (Magliozzi et al., 2018a) and most marked in cases where meningeal lymphoid aggregates were found in the cortex (Fig. 2). Similar increases in MHCII+cell density associated with significant axonal/dendritic loss and neuronal dystrophy was observed in subependymal lesions along the ventricular surface (Mahajan et al., 2020), further supporting an “ependyma-in” pattern that may mirror the “pial-in” one of cortical injury (Magliozzi et al., 2010). This study also demonstrated the presence of ovoid perivascular lesions contributing to thalamic injury, but with perivascular axons relatively preserved (Mahajan et al., 2020). It may therefore be hypothesized that intrathecal inflammation, compartmentalized in the CSF and possibly in the leptomeninges, may drive and or enhance superficial cortical and subcortical GM damage.

Notwithstanding MRI’s limited lesional sensitivity [even at 7T only about a third of GM lesions are seen (Kilsdonk et al., 2016)], mean GM MTR is decreased in all disease stages (Fernando et al., 2005). Surface-in GM MTR gradients are seen in all types of MS, both in the cortex (where the MTR is lowest at the outer cortical surface (Samson et al., 2014; Brown et al., 2019a) and the deep GM (where the MTR is lowest at the inner periventricular surface (Pardini et al., 2016), Fig. 1). A corresponding gradient of thalamic atrophy, maximal at the CSF boundary and lessening with increasing distance from it, is visible in early paediatric MS (Fadda et al., 2019) but not in monophasic acquired demyelinating syndromes (mono-ADS) studied in parallel. T2*, which inversely correlates with myelin and iron content, also shows surface-in cortical gradients from clinical onset (Mainero et al., 2015). Periventricular and cortical MTR gradients are more severe in SPMS compared to
RRMS (Samson et al., 2014; Liu et al., 2015) and worsen with increasing disease duration (Brown et al., 2019a).

What causes surface-in gradients?

The cause of periventricular and cortical gradients – and if they reflect the same processes – remains unclear. The correlations between the severity of (i) periventricular and cortical MTR gradients; (ii) periventricular DTI gradients and cortical lesion loads; and (iii) periventricular lesion loads and cortical atrophy suggests a common cause (Jehna et al., 2015; Pardini et al., 2016). A spatially consistent feature is proximity to the CSF compartment, which can carry both cellular and soluble factors.

Meningeal inflammation

While most pronounced in progressive disease, meningeal inflammation is seen histopathologically in all types of MS (Maglioizzi et al., 2007; Lucchinetti et al., 2011; Choi et al., 2012; Bevan et al., 2018) and in multiple anatomical locations (Howell et al., 2011; Howell et al., 2015; Reali et al., 2020). Such ‘compartmentalised inflammation’ may attract and retain further inflammatory cells, that together with immune cells circulating in the CSF may facilitate a microenvironment where inflammation may persist within this relatively sequestered compartment (Krumbholz et al., 2006; Meinl et al., 2008). Although lesions and surface-based gradients may arise from different mechanisms, identical antigen-experienced B-cell clones have been found in meningeal aggregates and WM perivascular spaces (presumably trapped from perivascular infiltrates) (Lovato et al., 2011), suggesting a common origin.

A common molecular pattern of proinflammatory cytokines (IFNγ, TNF, IL2 and IL22) and molecules promoting sustained B-cell activity and lymphoid neogenesis (CXCL13, CXCL10, LTα, IL6 and IL10) is found in the CSF of patients with MS, both at disease onset (where it strongly correlates with cortical lesion number on MRI (R² = 0.88)) and in patients with SPMS at post-mortem (where it correlates with the percentage of demyelinated cortex; and is also seen in the meninges) (Maglioizzi et al., 2018b). This supports the hypothesis that meningeal inflammation may represent the principal source of CSF inflammatory mediators (Gardner et al., 2013). Neither subpial cortical and or thalamic demyelination nor this inflammatory profile are seen in other conditions characterised by meningeal and CSF inflammation, suggesting it is MS-specific (Maglioizzi et al., 2018b; Junker et al., 2020). Soluble CSF factors inhibiting remyelination and cell/tissue repair mechanisms might be also involved in an MS-specific, surface-in pattern injury, but this has yet to be investigated.
Until recently, MRI detection of meningeal inflammation relied on surrogates (principally cortical lesions), with poor sensitivity and inter-rater reliability (Geurts et al., 2011; Seewann et al., 2012). Postcontrast T2 FLAIR has recently identified changes that might represent leptomeningeal enhancement (LME) in up to half of patients with MS, particularly in those with SPMS, older age, longer disease duration and more disability (Absinta et al., 2015; Eisele et al., 2015; Zivadinov et al., 2017). In two patients proceeding to post-mortem (both with PPMS), areas of LME on T2 FLAIR corresponded to regions of meningeal inflammation overlying cortical demyelination (Absinta et al., 2015). However, LME is not specific for meningeal inflammation - subarachnoid veins, dural venous sinuses and basal meninges all enhance on postcontrast T2 FLAIR (Zurawski et al., 2017). LME correlates with cortical GM atrophy, but not with neocortical CLs (Ighani et al., 2019), suggesting an association with neurodegenerative processes, rather than focal lesion development. It is unclear whether the compartmentalised inflammation that is seen in the leptomeninges, including the build up of lymphoid-like cell aggregates, would be accompanied by LME.

**Lymphoid tissues**

The most striking form of meningeal inflammation – lymphoid tissue formation – is seen in about 40% of patients with SPMS at post-mortem (Magliozzi et al., 2007; Howell et al., 2011), and similar proportions of patients that died following their first MS presentation (Bevan et al., 2018). Lymphoid-like tissues are topographically related to subpial cortical demyelinating lesions, but also occur alongside areas of reduced myelin density suggesting partial demyelination or remyelination (Magliozzi et al., 2010; Bevan et al., 2018). Their presence is associated with cortical gradients of damage: greater neuronal and astrocyte loss, accompanied by increased microglial density, occurs close to the CSF/pia surface which lessens through inner cortical layers (Magliozzi et al., 2010).

The absence of lymphoid-like structures in PPMS might reflect the lower numbers of tissue blocks examined from a smaller number of patients or that aggregates are not an absolute requirement for surface-based gradients (simply worsening them when present). Diffuse meningeal inflammation was associated with both cortical lesions and increased clinical progression rates in a subgroup of PPMS patients (Choi et al., 2012). Lymphoid-like structures have also been found in the spinal cord in MS cases with cerebral meningeal lymphoid-like structures (Reali et al., 2020) and the severity of extralesional spinal WM axonal loss clearly correlates with the degree of both extralesional WM microglial/macrophage activation and the density of meningeal T-cells (Androdias et al., 2010).
**Choroid plexus**

Inflammatory cells may enter the CSF via the choroid plexus, particularly in early disease, influenced by the expression of a specific acute cytokine/chemokine pattern (Engelhardt et al., 2001; Reboldi et al., 2009). The concentration of the tight-junction protein claudin-3 (responsible for maintaining the blood-CSF barrier) is significantly lower in patients with MS (Kooij et al., 2014).

**CSF cytokines and other soluble factors**

CSF from people with MS has been shown to cause axonal damage and oligodendroglial and neuronal death in-vitro (Menard et al., 1998; Alcazar et al., 2000; Vidaurre et al., 2014). The finding of elevated proinflammatory CSF cytokines suggests that neuronal dysfunction and death arise from cytokine-induced synaptic hyperexcitability, glutamate-dependent neurotoxicity or direct cytokine induced death receptor signalling, again pointing to an inflammatory origin (Rossi et al., 2012; Rossi et al., 2014). In support of the latter, an increase in TNF/TNF receptor 1 expression, together with all the downstream signaling pathway genes leading to necroptotic cell death, occurs in MS cortical grey matter in cases with high levels of meningeal infiltrates (Magliozzi et al., 2019). In addition, persistently elevated levels of TNF and IFNγ in the rat subarachnoid space leads to meningeal inflammation, subpial demyelination, microglial activation and neuronal loss, that is similar to that seen in the cortical GM in MS (James et al., 2020). In RRMS, an association found between leptomeningeal enhancement, cortical and thalamic lesion numbers (Zurawski et al., 2020) also supports the hypothesis that CSF-related inflammation links cortical and thalamic injury.

Ceramides are sphingolipids, and the elevated CSF levels seen in patients with MS (Vidaurre et al., 2014; Wentling et al., 2019) particularly C24, probably reflect WM destruction or exosome release from membranes of mature oligodendrocytes. Ceramides may signal via similar pathways to TNF: both impair mitochondrial function, decrease neuronal energy production and increase reactive oxygen species and free radical production, culminating in neuronal damage. In progressive (but not relapsing-remitting) MS, ceramides accentuate this neurotoxicity by decreasing glucose bioavailability, culminating in ‘virtual hypoglycosis’ in these patients’ CSF (Wentling et al., 2019). It could be proposed that, rather than a single CSF factor, a particular combination of inflammatory and cytotoxic mediators may mediate the MS-specific surface-in damage.

**Other contributory factors**

Some factors may augment the effects of a CSF-mediated process. In progressive MS the cortical glia limitans is compromised (Magliozzi et al., 2010), allowing greater molecular diffusion into the
underlying cortex. A similar compromise of the ependymal layer has not been investigated, but granular ependymitis is seen in some patients with MS at post-mortem (Adams et al., 1987). The periventricular venous watershed predisposes the region to hypoperfusion and hypoxia (Andeweg, 1996; Dewar et al., 2003; Varga et al., 2009; Beggs, 2013), though a similar watershed has not been demonstrated in the well-perfused cortex.

**Clinical relevance of surface-based gradients in MS**

Surface-in gradients occur early in MS (Samson et al., 2016; Brown et al., 2017; Fadda et al., 2019), within 5 months of a clinically-isolated syndrome (even in those without WM lesions), and independently predict a further relapse within 2 years (OR 61.7, p=0.02), Fig. 1, dwarfing the predictive effect of more established metrics like T2 lesions (OR 8.5, p=0.07, (Brown et al., 2017)). Unlike other radiological markers (Wattjes, 2015), the periventricular WM gradient independently predicts on-treatment relapses following alemtuzumab (Brown et al., 2019b), though larger corroboratory studies are required. Surface-based gradients in the cortex (Mainero et al., 2015; Brown et al., 2019a), periventricular WM (Brown et al., 2019a) and spinal cord WM (Kearney et al., 2014) all correlate with disability. In support, post mortem studies noted the most aggressive disease-course during life was associated with more severe gradients of cortical neuronal loss and the most marked meningeal inflammation (Magliozzi et al., 2007; Magliozzi et al., 2018b). Taken together, this suggests that surface-in gradients are related to clinical outcomes independently of WM lesions, and so the process that causes them may represent an important and independent therapeutic target. They also have prognostic value, again independent of WM lesions, however at present the clinical utility of periventricular MTR gradients is limited by the need for offline MRI scan processing.

**Insights from treatment effects on surface-based pathology**

There have only been a few studies on treatment effects on putative markers of intrathecal inflammation. In one study, LME persisted for up to 5.5 years despite (unspecified) disease-modifying therapy (Absinta et al., 2015). If LME does reflect meningeal inflammation, this suggests it might not be affected by current MS treatments. However, more recently, periventricular MTR gradients have been ameliorated with two monoclonal antibodies, alemtuzumab (Brown et al., 2019b) and GNbAC1 (Hartung et al., 2017). If the periventricular MTR gradient reflects intrathecal inflammation then its diminuation following alemtuzumab and GNbAC1 suggests that these processes may originate, or at least be sustained, by factors from the periphery (as alemtuzumab does not cross the blood brain barrier (Moreau et al., 1994)). Further, given that the MTR gradient showed continued improvement two years after the last dose of alemtuzumab, aggressive peripheral
immunodepletion may have an enduring effect (Brown et al., 2019b). Importantly, the effect alemtuzumab had on the MTR gradient was related to the risk of further relapses following treatment, demonstrating that an effect on the processes underlying the gradient is associated with an effect on clinical outcomes. However, treatment of an intrathecal process is likely to be slower or diminished unless a treatment is able to penetrate the CSF, and current MS disease modifying treatments (and in particular the more potent monoclonal antibody agents) have not been designed with this in mind. The discrepancy between LME and periventricular MTR findings may indicate that meningeal inflammation is not actually associated with periventricular gradients (although it has been directly linked with gradients in underlying cortical pathology), or that meningeal inflammation and periventricular gradients respond to treatment in different ways or at different rates. However, it should be noted that LME results from increased permeability of meningeal blood vessels and does not indicate a build-up of large immune cell aggregates in the meningeal space. Alternatively, disease duration may significantly modulate treatment effects, and the mean disease duration in Absinta et al. (Absinta et al., 2015) was 11 years, versus 1.6 years in Brown et al. (Brown et al., 2019b).

**Conclusions**

Outside-in gradients in lesional and extrallesional tissue are seen in all types of MS, can manifest at the earliest stages of the disease, show clear clinical correlations, and have prognostic value. The underlying process(es) represent an attractive treatment target, and appear at least partially distinct from those leading to demyelinating lesion formation. We now need to know the molecular and histopathological substrates underlying MRI-visible periventricular gradients, particularly whether or not they are pathologically equivalent to cortical gradients. A CSF-mediated process, secondary to meningeal intrathecal inflammation, currently represents one of the best explanations for cortical and periventricular gradients.

Potential biomarker candidates - cortical lesions, leptomeningeal enhancement, MTR gradients and CSF molecular profiling - require optimisation, standardisation and a systematic examination of their response to therapies. Subsequent comparisons with traditional metrics may then identify any true additional value, thereby contributing to more personalised prognostication and therapy in MS. MRI surrogates must also be sought in different diseases with meningeal inflammation to ensure, like the intrathecal CSF pattern (Magliozzi et al., 2018b), they are specific to multiple sclerosis.
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Figure Legends

Figure 1
Brain segmentation into concentric bands between the ventricular walls and pial surfaces. **Inset A**: periventricular extralesional white matter (WM) MTR in each band comparing people with RRMS, SPMS, PPMS and healthy controls. Mean ± 2 standard errors. MTR is given in per cent units (pu).

**Inset B**: periventricular extralesional WM MTR in each band comparing healthy controls to patients 4.6 months after a clinically isolated optic neuritis (ON) divided into those who did convert to clinically definite MS (CDMS) (yellow) and those that did not (green). **Inset C**: periventricular grey matter (GM) MTR in each band comparing patients with RRMS, SPMS, PPMS and healthy controls.

**Inset D**: periventricular lesional white matter MTR in each band in patients with RRMS, SPMS and PPMS. **Inset E**: cortical GM MTR in each band comparing people with relapsing-remitting multiple sclerosis (RRMS), secondary progressive multiple sclerosis (SPMS), primary progressive multiple sclerosis (PPMS) and healthy controls.

Figure 2
Gradient of demyelination (**A, D, G**), microglia activation (**C, E, H**) and axonal loss (**F**), evident in the motor cortex (**A-C**), thalamus (**D-F**) and hippocampus (**G, H**) in post-mortem progressive MS. Extensive subpial cortical demyelination (**A**) is often associated with increased meningeal inflammation, diffuse or aggregated in lymphoid-like aggregates (**B**). Substantial increase of MHC-class II+ activated microglia/macrophages density is observed in the external cortical layers in close proximity to the pial surface (**C**) but not in the internal cortical layers, close to the white matter, according to a surface-in gradient.

Similar gradient of demyelination (**D, G**) and increased density of MHC-class II+ activated microglia/macrophages is seen in the thalamus (**D-F**) and hippocampus (**G-H**), in close proximity to the ependyma surface. Surface-in gradient of axonal loss (**F**) as visualized by Bielschowsky staining, is also observed in a thalamic lesion (**D**) in the external areas close to the ependyma.

Figure 3
While meningeal and ependymal factors may explain local gradients in pathology, alone they do not readily link gradients seen in both grey and white matter. Instead, proximity to CSF provides a more plausible unifying explanation, but also means that anything that can diffuse into the CSF may be relevant, including constituents arising from the brain’s extracellular fluid or blood (via the choroid plexus). It also complicates the search for a cause for meningeal and ependymal inflammation, as this
may not necessarily be the source of the factor responsible for surface-in gradients in brain pathology, but instead be another consequence of it.