

Enlarged perivascular spaces (EPVS): a visual rating scale and user guide

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Section 1. Introduction

Enlarged perivascular spaces (EPVS, sometimes called Virchow-Robin spaces) surround the walls of vessels as they course from the subarachnoid space through the brain parenchyma.¹ EPVS appear in all age groups, but are only visualised clearly on T2-weighted brain magnetic resonance imaging (MRI) when enlarged.

Several EPVS rating scales have been described,²⁻⁷ but these are either limited in their anatomical location, in the range of EPVS that they describe, or in their method of assessing severity. Additionally, some scales were tested using specific MRI sequences rather than standard structural brain MRI. We reviewed existing EPVS visual rating scales,²⁻⁸ identified omissions or ambiguities in each, and used this combined knowledge to design improvements to one existing scale⁸ that already most closely met requirements for a comprehensive easy to use scale. We then tested this revised scale on 60 MRI scans chosen to demonstrate a full range of EPVS frequencies and designed a comprehensive user guide. Using the revised scale and the user guide, two observers showed similar intra-rater agreement for BG-, CS- and midbrain EPVS ranging from good to very good kappa values. Inter-rater agreement was moderate for CS- and MB-EPVS on both ratings although very good for BG-EPVS on the initial rating. Disagreements were mainly due to the counting of very small but just visible EPVS, which were a recognised source of difficulty prior to rating. Other main causes for disagreement were the presence of background white matter hyperintensities (WMH), particularly when confluent, and lacunes (in the CS and BG regions, respectively). The user guide was subsequently modified to help avoid residual sources of observer variation.

This revised EPVS rating scale includes the 3 major anatomical regions where EPVS are found: basal ganglia (BG), centrum semiovale (CS) and midbrain.¹ The development of a validated

rating scale, including a user guide with illustrations, will hopefully minimise inter-observer variation in studies of EPVS, enable cross-comparison between research groups and facilitate meta-analysis of EPVS studies.

Section 2. EPVS on brain MRI

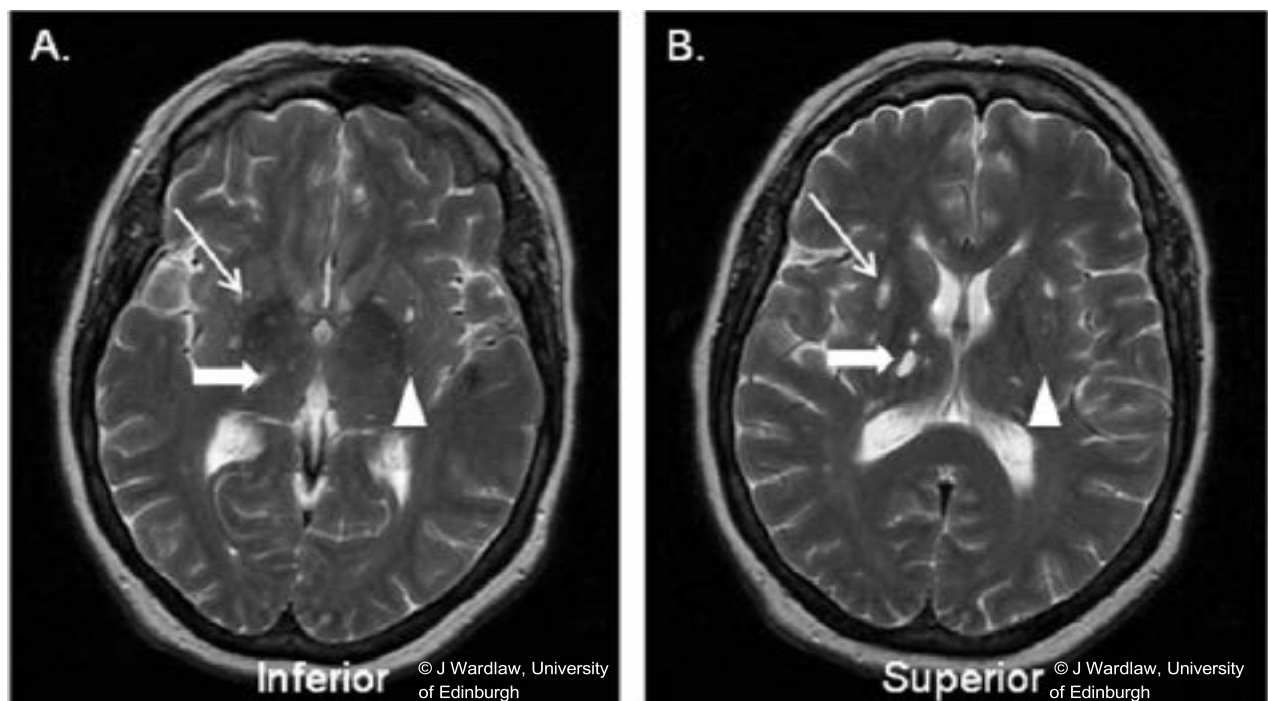
A. Definition

EPVS may be defined on MRI as 'small, sharply delineated structures of cerebrospinal fluid (CSF) intensity (or close to CSF intensity) measuring $<3\text{mm}$ following the course of perforating vessels'.

B. Visualisation of EPVS on MRI

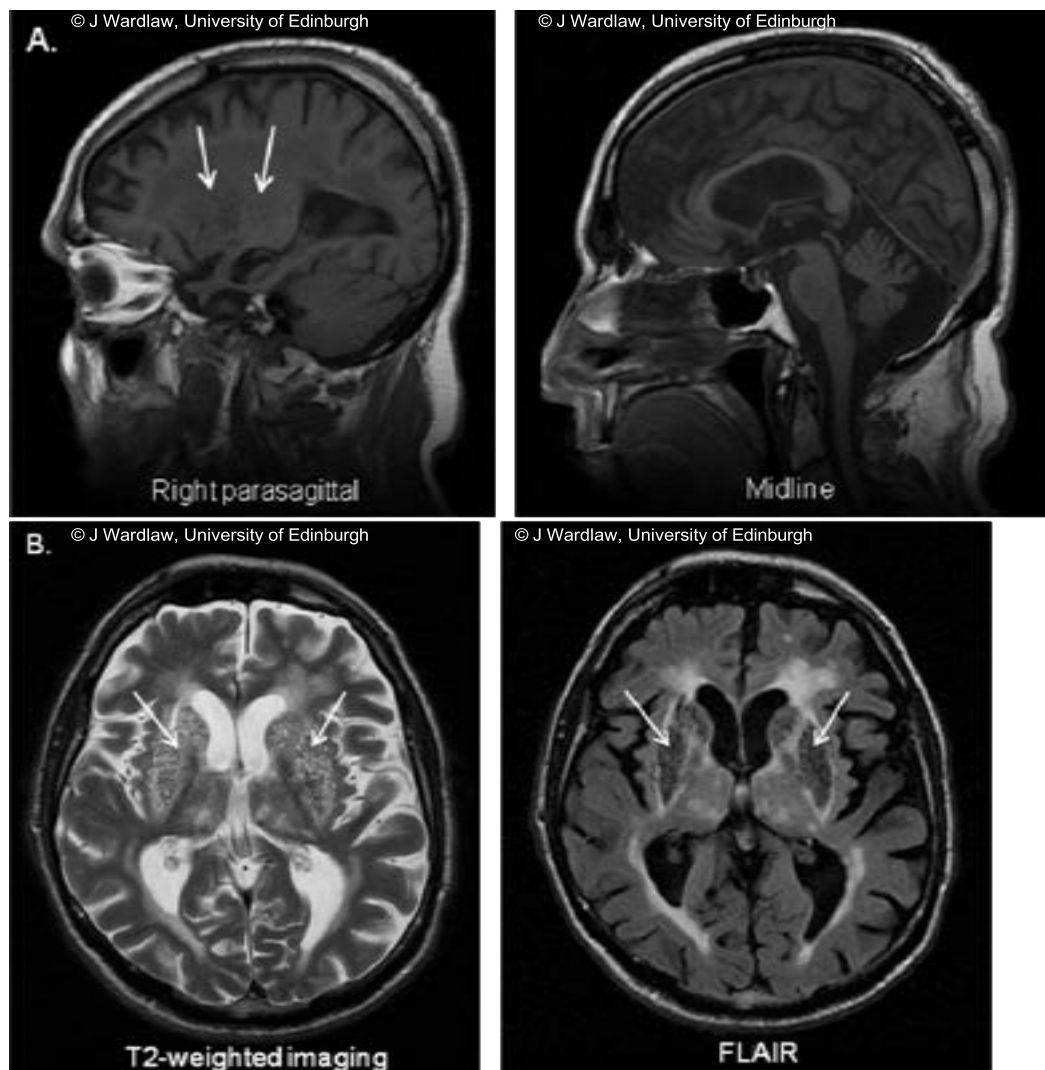
EPVS are most easily seen on T2-weighted imaging (T2WI), and may be distinguished from cavitated lacunes which contain CSF by the latter's large size ($>3\text{mm}$) and shape (spheroid; Fig 1); these features are often easier to see by reviewing adjacent slices.

Figure 1. Differentiating true EPVS (arrowhead) from lacunes containing CSF (thin and block arrows) in the basal ganglia using size and shape criteria



Although often described as hypointense structures on T1 and FLAIR, many EPVS will not be visible unless severe (Fig 2).

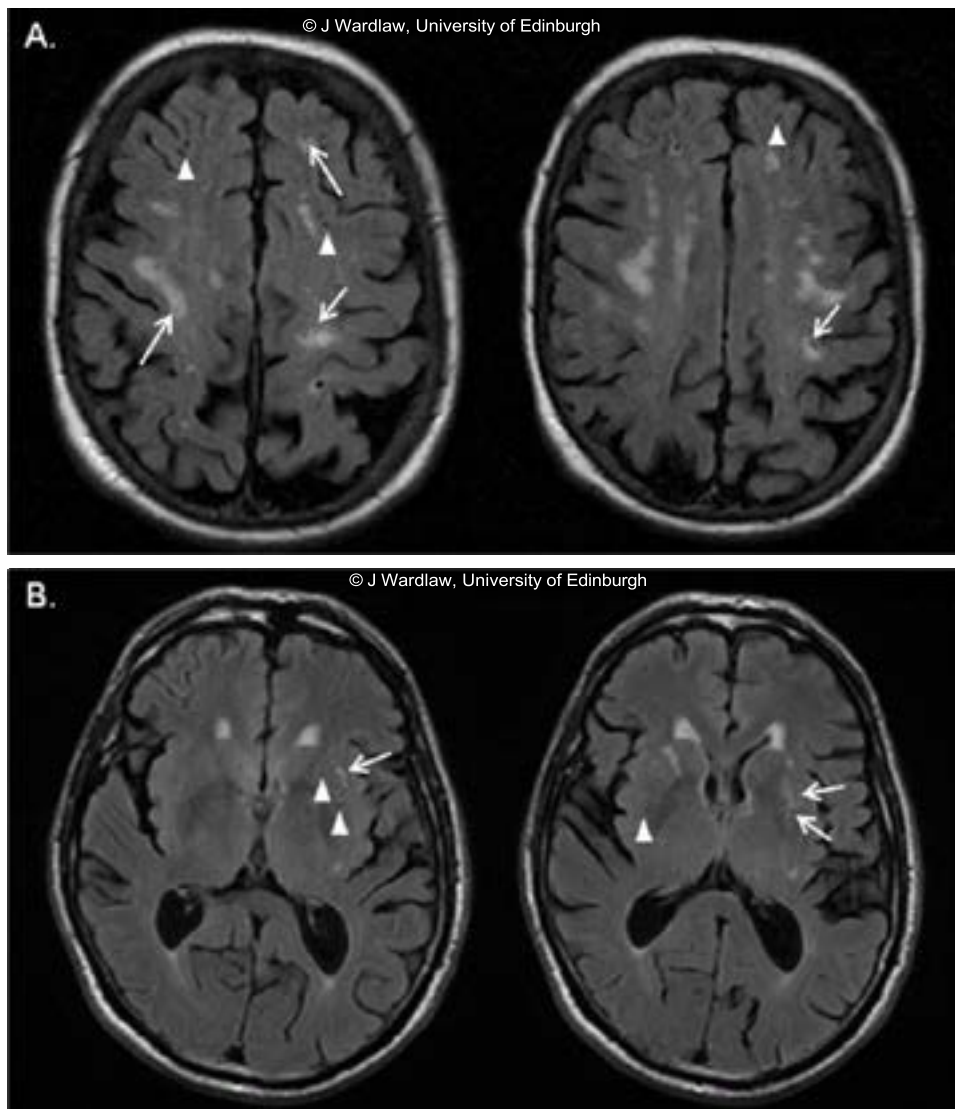
Figure 2. A. Sagittal T1 imaging showing severe EPVS in the basal ganglia (arrows). B. Axial T2 and equivalent FLAIR imaging showing a 'spongiform' appearance of the basal ganglia on both sides due to numerous EPVS



If EPVS are not identified on T2 images, it is very unlikely that they will be identified on other routine sequences. Thus, T2 images should always be reviewed first.

Although others have excluded EPVS with surrounding FLAIR hyperintensity when rating EPVS (Fig 3), these have been included in the current scale

Figure 3. Axial FLAIR MRI showing EPVS surrounded by white matter hyperintensities (WMH) in the centrum semiovale (A, arrows) and basal ganglia (B, arrows; different patient to A). EPVS without surrounding WMH are also visible in both regions (arrowheads).



C. Location of EPVS

EPVS are found throughout the brain, and are subpial spaces surrounding the perforating arteries, arterioles, veins and venules of the brain.

For EPVS rating, there are three primary areas to be considered: basal ganglia, centrum semiovale and midbrain. EPVS in these areas have been kept separate in the rating scale as it is possible that they may have different underlying pathophysiology.

For the basal ganglia, this will normally involve reviewing at least 3 slices, for the midbrain, 1- 2, and for the centrum semiovale, at least 3 slices.

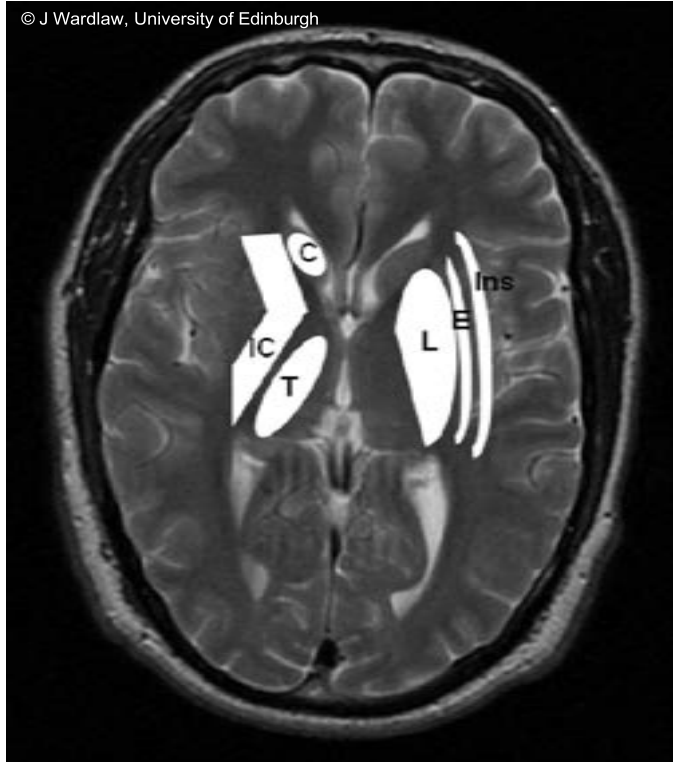
Each anatomical area will now be described in more detail.

D. Description of EPVS in each anatomical area

a. Basal ganglia EPVS

EPVS are seen in the basal ganglia along the paths of the perforating lenticulostriate arteries (arising from the middle cerebral artery), which enter the brain parenchyma inferiorly at the anterior perforated substance at the level of the anterior commissure, before coursing superiorly through the basal ganglia. However, EVPS in relation to perforating arteries in the insular cortex should be included in the basal ganglia EPVS rating.

Structures to be reviewed in basal ganglia rating are shown in the following diagram:



C	Caudate nucleus
IC	Internal capsule
T	Thalamus
L	Lentiform nucleus
E	External/extreme capsules
Ins	Insular cortex

On standard axial T2MR imaging, EPVS in the basal ganglia most commonly appear as rounded foci of high signal (Fig 4). In the insular cortex, EPVS often appear as short linear structures due to different orientation of vessels (Fig 5).

Figure 4. Basal ganglia EPVS appearing as multiple, rounded, sharply delineated foci of T2 high signal (arrowheads)

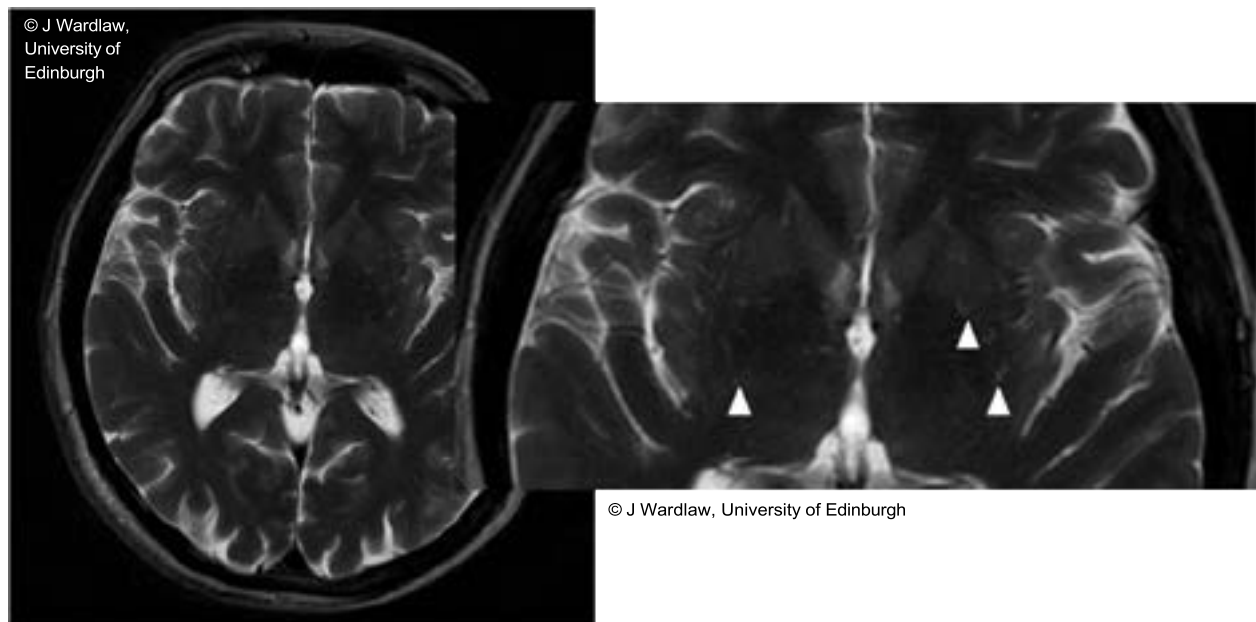
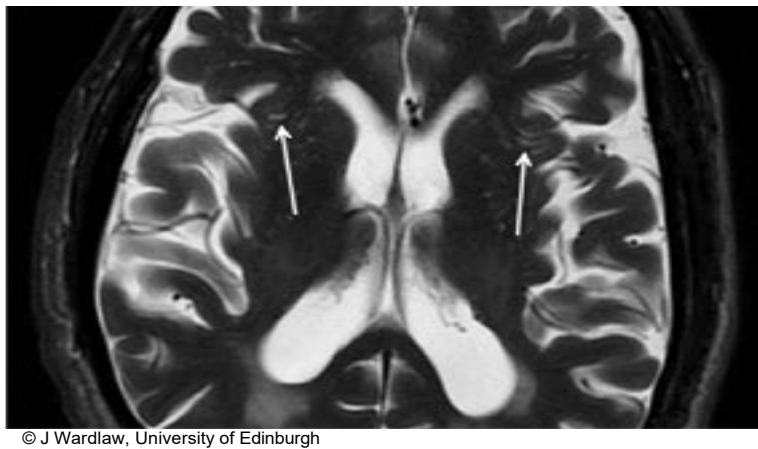
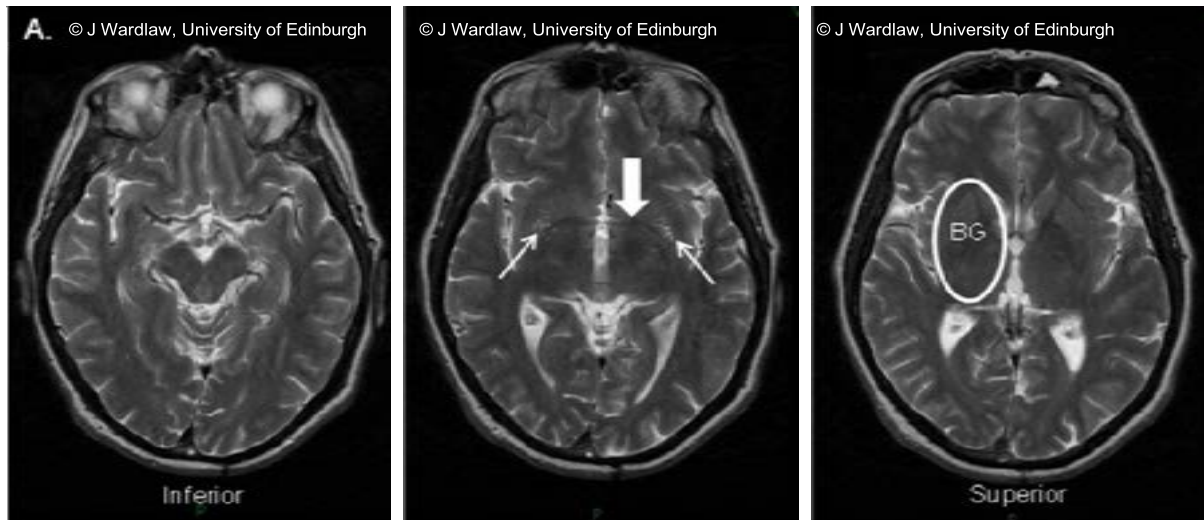


Figure 5. Linear EPVS following the course of perforating arteries in the insular cortex (arrows)

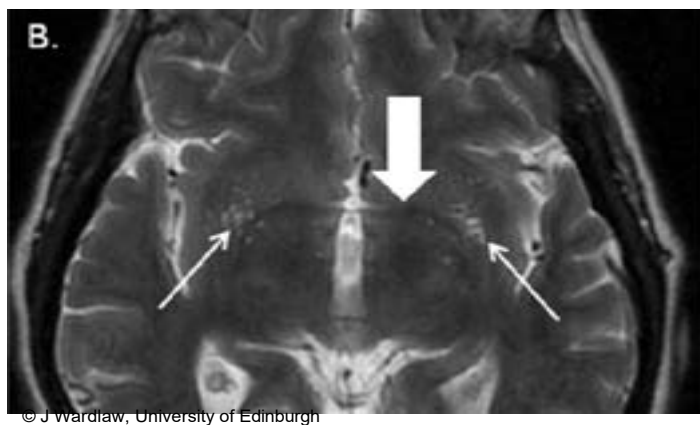


Inferior to the basal ganglia, at the level of the anterior perforated substance (or substantia innominata) most normal people will demonstrate EPVS (Fig 6). Rating of EPVS in the basal ganglia should therefore be done above this level: EPVS at the level of the anterior commissure should be excluded from the overall rating.

Figure 6. A. EPVS at the level of the anterior perforated substance (thin arrows), on the slice immediately above the upper midbrain (left image), and below the basal ganglia (circled, right image)



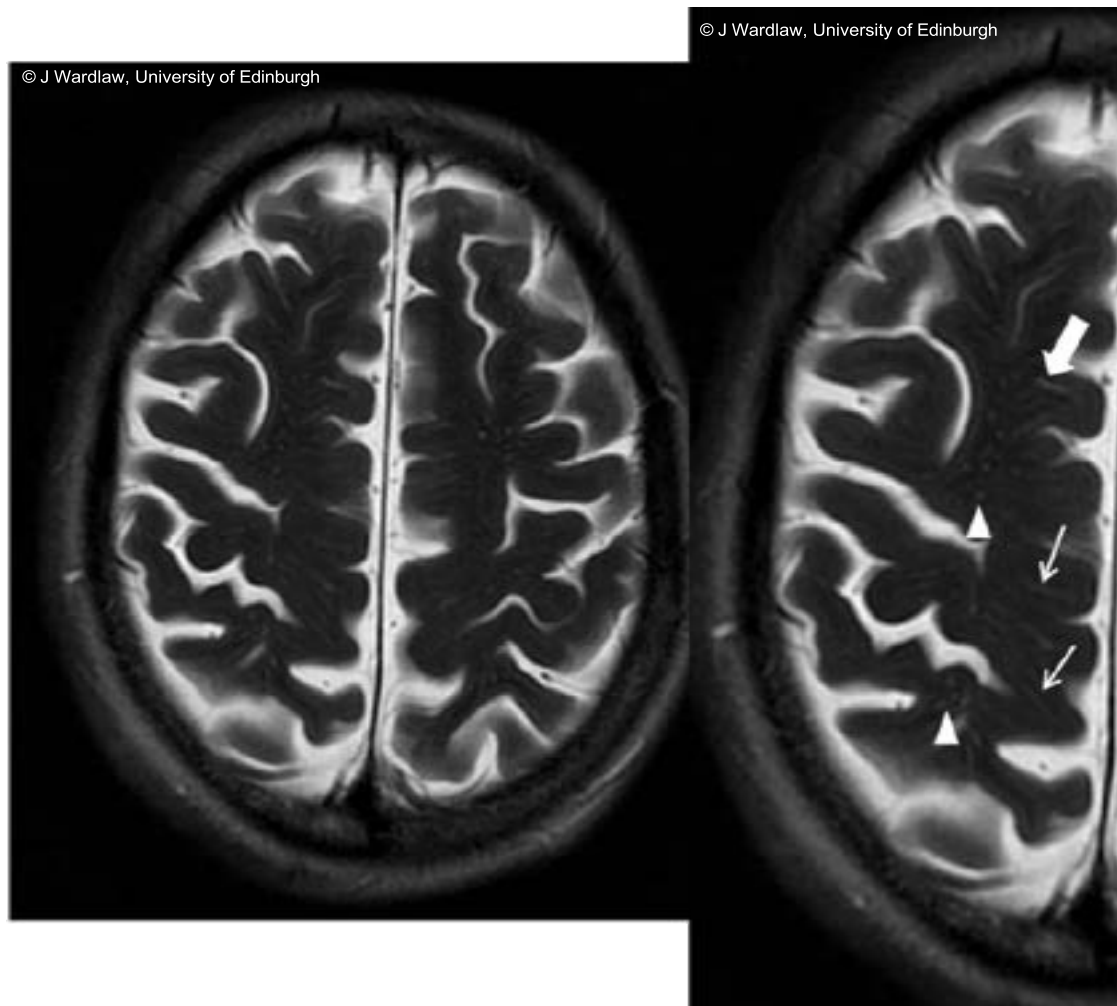
B. Magnified view showing EPVS at the level of the anterior perforated substance, where the anterior commissure is also seen (block arrow, pointing to anterior commissure (left side))



b. Centrum semiovale EPVS

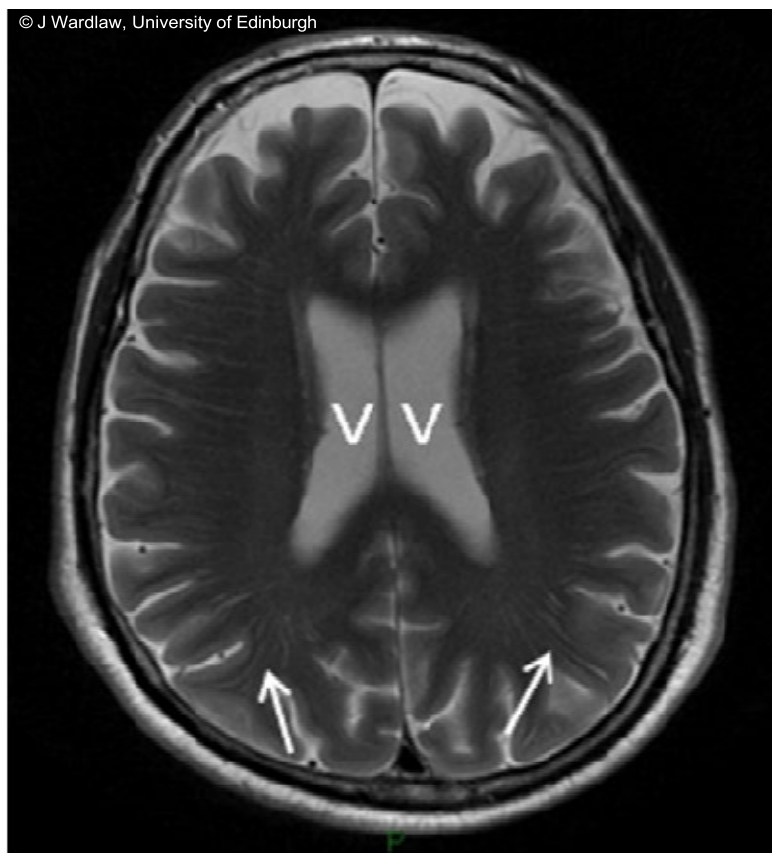
EPVS are seen in the centrum semiovale along the paths of the perforating medullary arteries as they enter the cortical gray matter over the high convexities and extend into the white matter. On standard axial T2MR imaging, EPVS in the centrum semiovale may have 3 different appearances depending on location scan orientation and perforator vessel orientation (Fig 7).

Figure 7. Varied configuration of EPVS in the centrum semiovale close to the vertex, with a combination of rounded (arrowheads), short linear (block arrow) and long linear (arrows) configurations



More inferiorly in the centrum semiovale, EPVS are frequently seen as linear, rather than rounded structures (Fig 8). Some scales separate EPVS in the centrum semiovale into round/oval and linear (Rouhl, 2008); in this scale, only 1 rating is given to EPVS in the centrum semiovale.

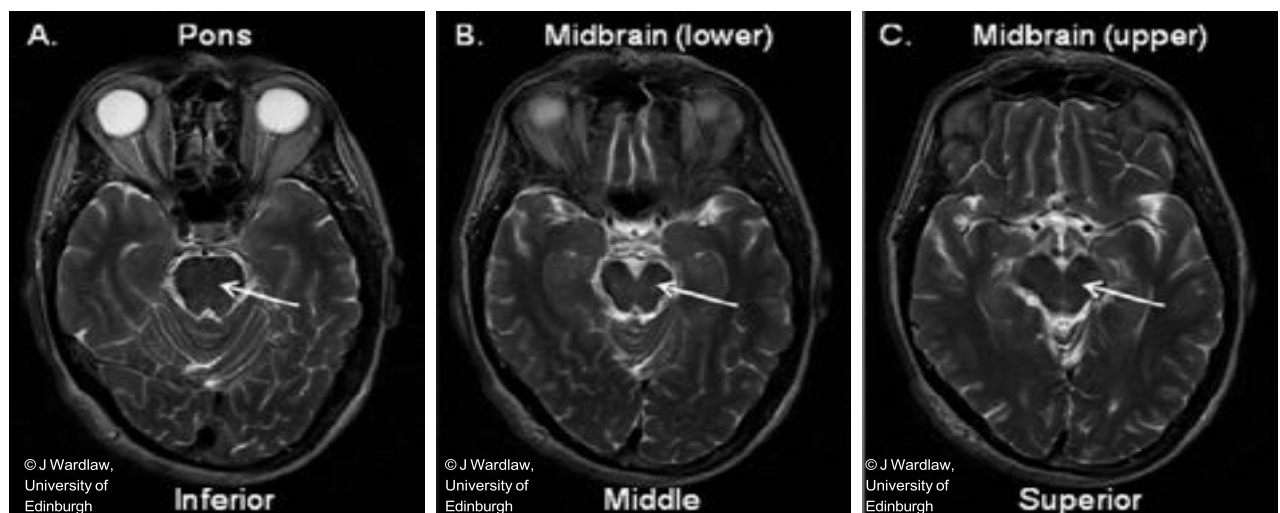
Figure 8. EPVS (arrows) visualised as linear structures in the centrum semiovale at the level of the bodies of the lateral ventricles (V)

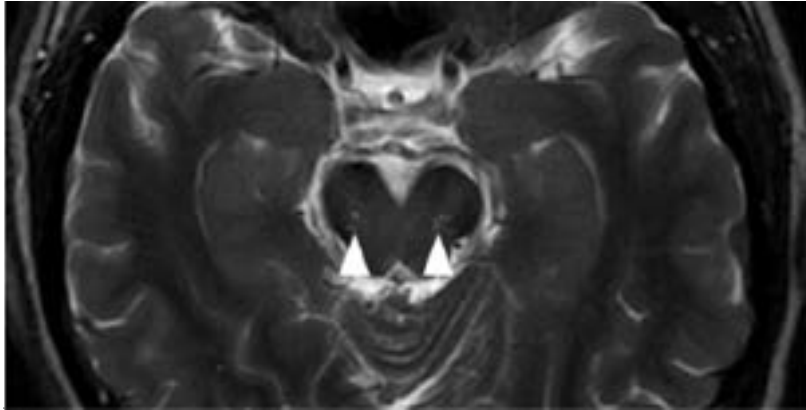


c. Midbrain EPVS

At the junction of the midbrain and pons (Fig 9), EPVS may be seen in relation to perforating arteries arising from the short paramedian (perforating) branches of the basilar artery. On standard axial T2MR imaging, EPVS in the midbrain normally appear as rounded foci of high signal. Normally, at least 2 slices should be reviewed when assessing midbrain EPVS.

Figure 9. A. Level of pons. B. Midbrain (at pons-midbrain junction), the third major site at which EPVS are seen. C. Slice above pons. A magnified view of the midbrain is also shown, demonstrating lower midbrain EPVS (arrowheads)





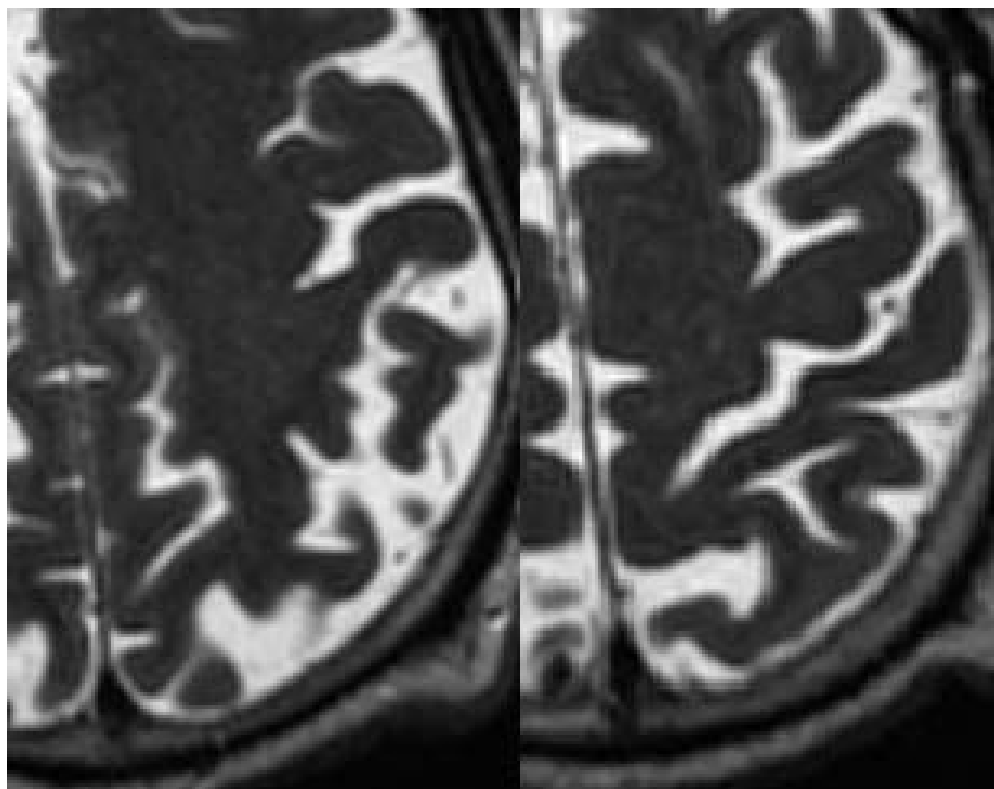
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Section 3. Potential difficulties in EPVS rating

A. Variations in EPVS visibility

With current MRI scanners, some EPVS may be seen as faint, indistinct high signal structures in the basal ganglia, centrum semiovale and midbrain rather than clear, very high – near-CSF signal – structures (Fig 10, 11). A general impression of the region being rated should be used to choose a category, using the ‘whole picture’ and matching as closely as possible with the categories provided.

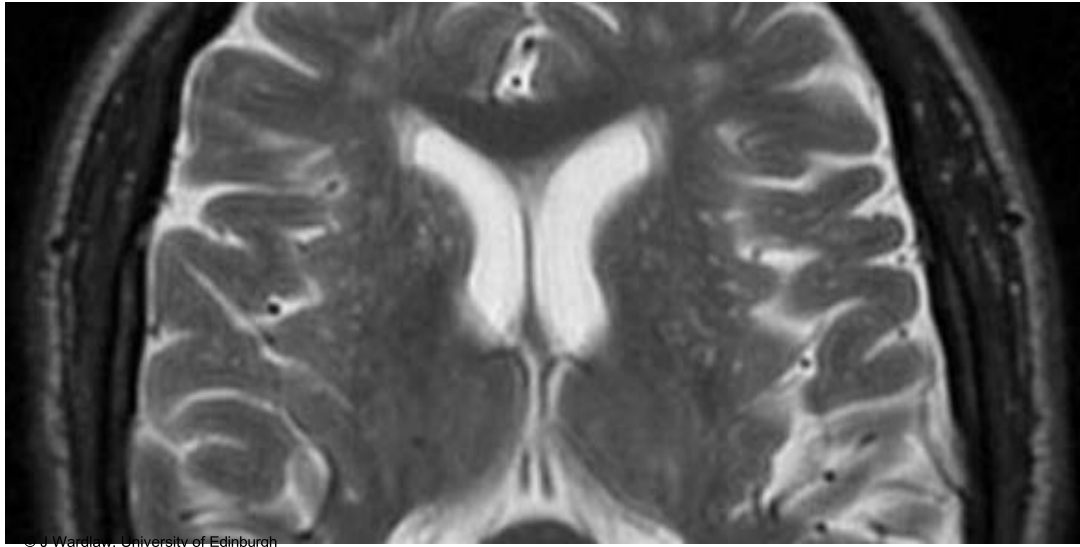
Figure 10. Multiple tiny EPVS visualised in the centrum semiovale, in a patient with additional movement artefact.



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Figure 11. Multiple tiny EPVS visualised in the basal ganglia, where other EPVS are also seen far more clearly.



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B. Background WMH

Where there are extensive WMHs, EPVS may be difficult to rate. In such cases, an estimate must be made of the closest rating category, using the appearance of non-involved white matter (where visible), and cortical gray matter. Review of all slices, including those at the vertex may be useful, where uninvolved white matter, and cortical gray matter, may be more easily visible (Fig 12). Some EPVS may also remain visible despite the presence of extensive WMH. Where WMH are non-confluent, rating may be more straightforward (Fig 13); in such cases, non-affected parenchyma should be used, and review of gray matter may also help.

Figure 12. Extensive deep WMHs in the centrum semiovale, extending to the vertex.

Appearances closer to the vertex (magnified image, bottom right image) suggest only mild

EPVS

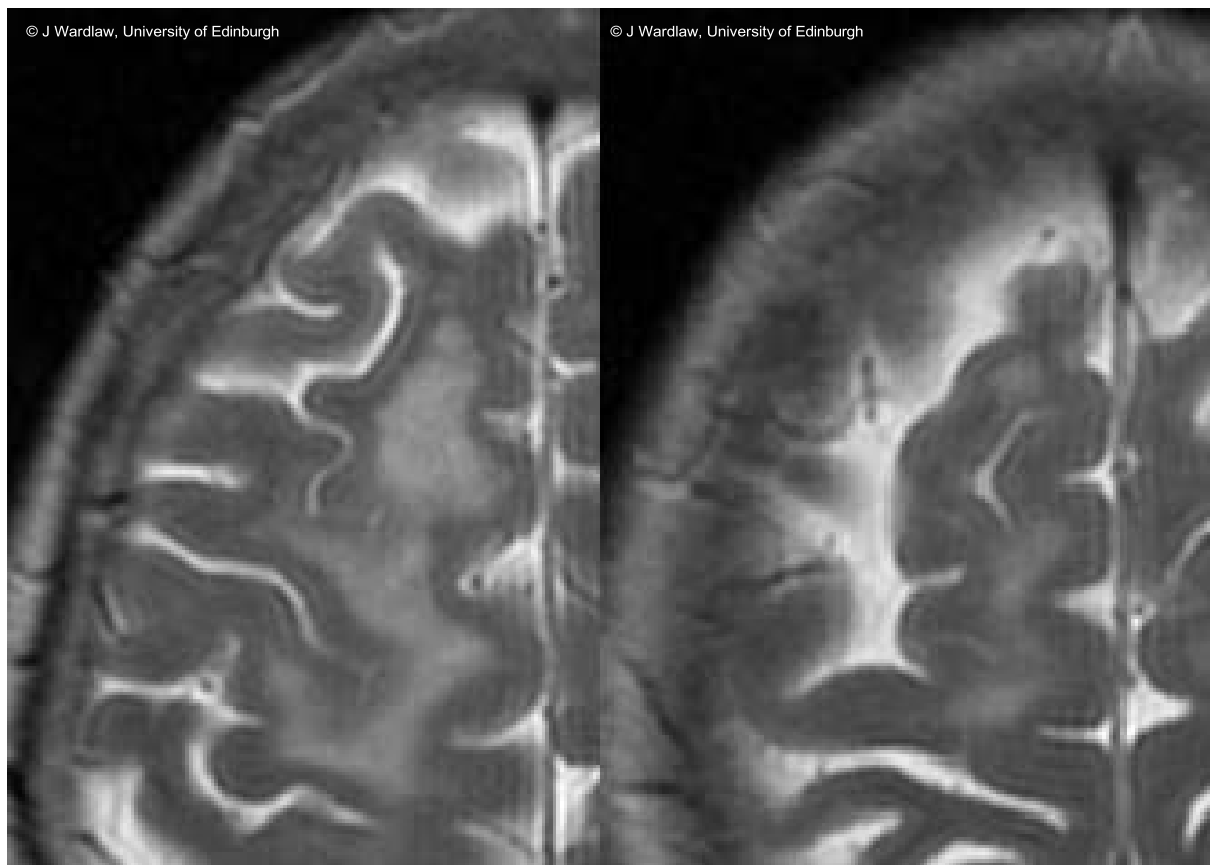
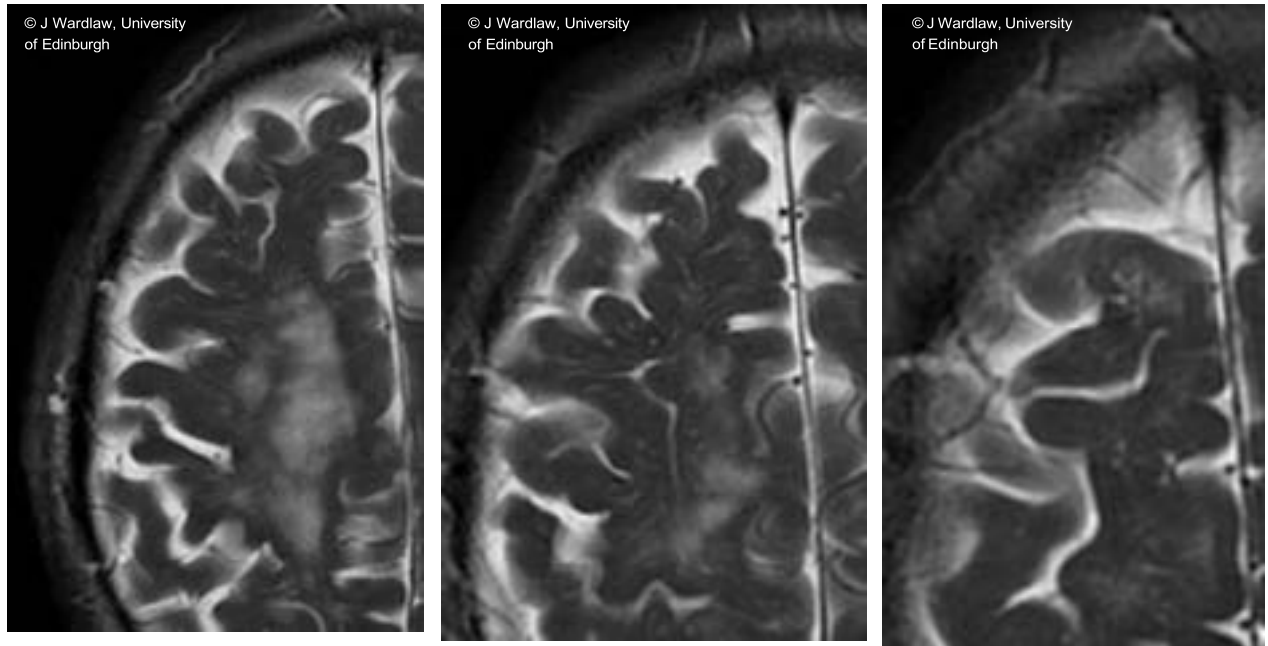


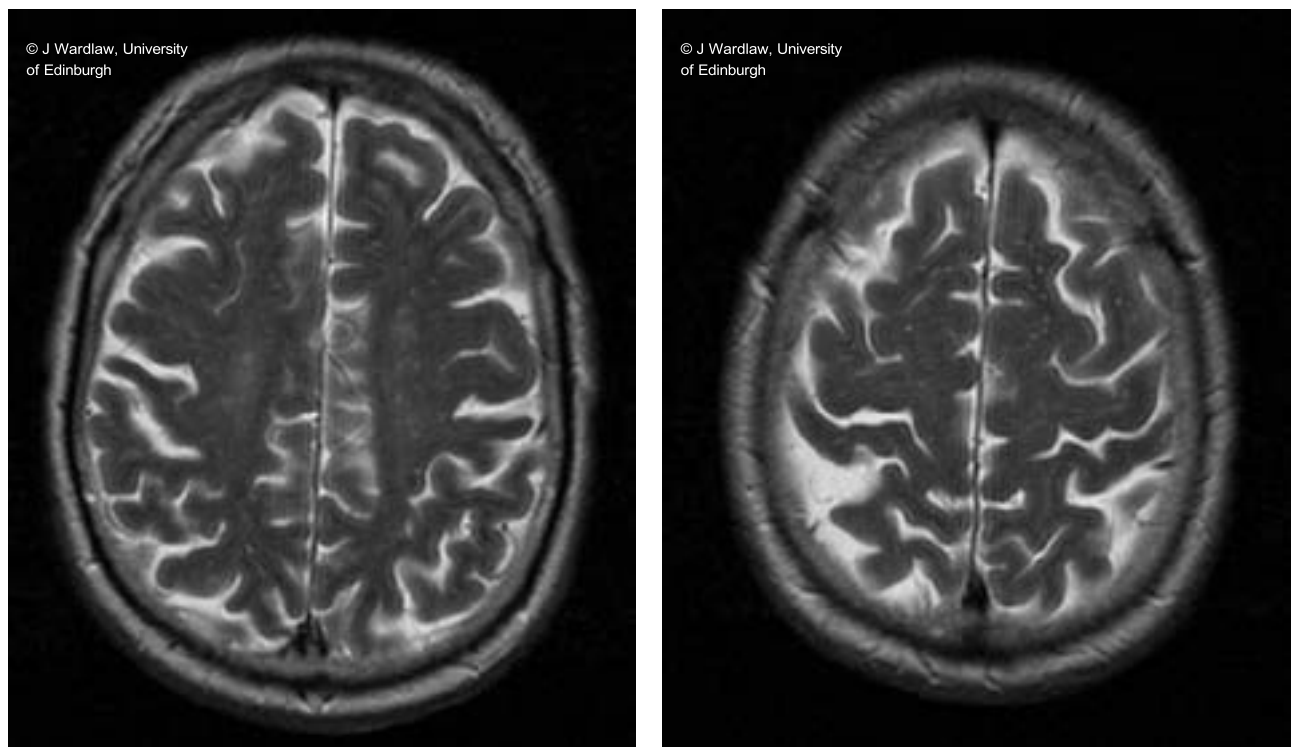
Figure 13.Non-confluent WMHs



C. Varying number of EPVS on different slices

The number of EPVS may vary depending on the slice selected. For example, in some patients, fewer EPVS will be visualised in the centrum semiovale at the level of the vertex compared to slices below this (Fig 14). After reviewing all relevant slices for the anatomical area being assessed, the highest number of EPVS should be recorded.

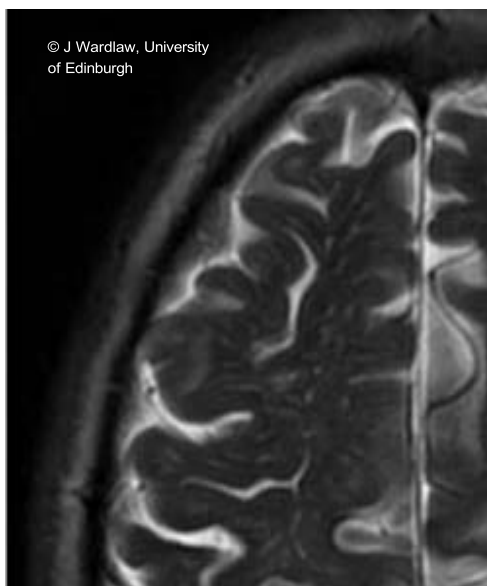
Figure 14. Axial T2-weighted images slices demonstrating varying numbers of EPVS at different levels of centrum semiovale, with fewer EPVS visible closer to the vertex (right image)



D. 'Double counting' of linear EPVS

Care should be taken to try to avoid counting linear EPVS twice, particularly in the centrum semiovale (Fig 15). Review of slices closer to the vertex – where EPVS are more often punctuate, rather than linear – may help in form an initial impression of the closest rating category. In all areas, review of adjacent slices can help reduce this potential problem.

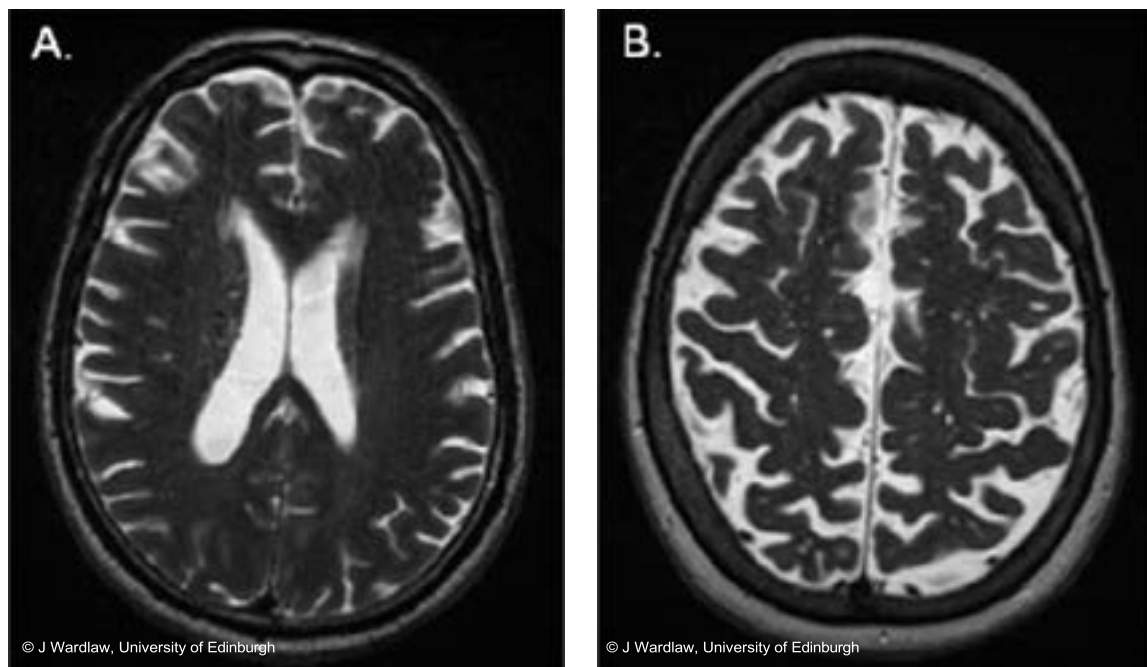
Figure 15. Illustration of potential pitfall of double counting EPVS in the centrum semiovale



E. Poor scan quality, including movement

In some cases, EPVS rating may be made more difficult due to limited scan quality, particularly in patients with mild/moderate EPVS (Fig 16A) rather than frequent/ severe EPVS (Fig 16B). In such cases, an estimate of the closing rating category should be made.

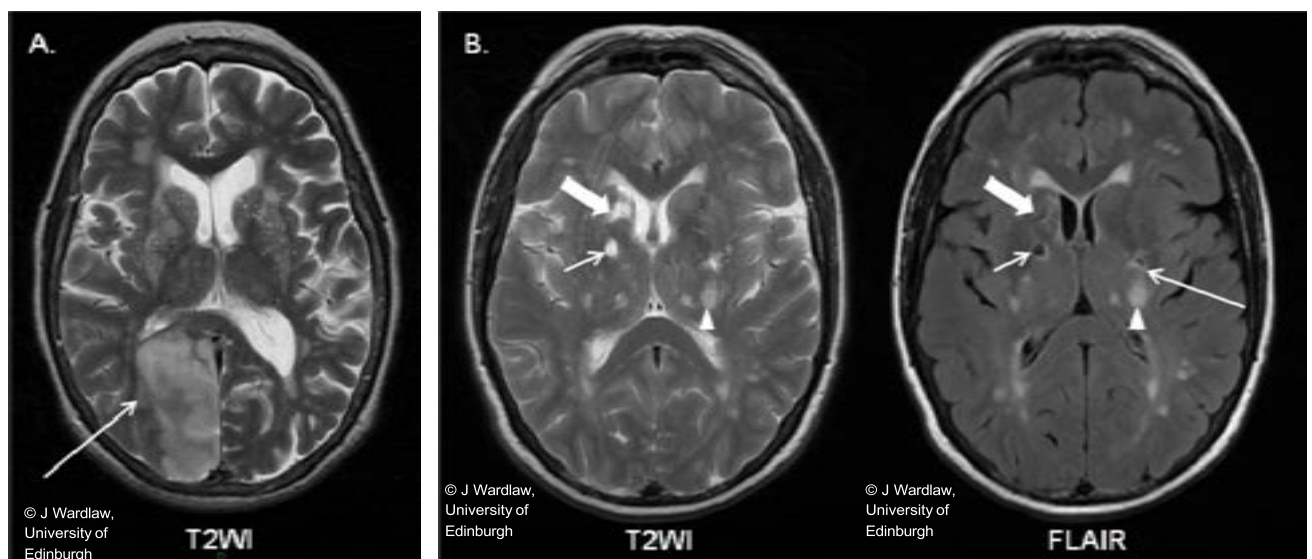
Figure 16. Limited MRI scan quality due to movement, making assessment of small structures more difficult, particularly where EPVS are mild (A) rather than frequent (B)



F. Asymmetry in background brain appearances

When background brain parenchyma is asymmetric due to the presence of another lesion, e.g. infarction (Fig 17A), EPVS should be rated on the other side where possible, or an estimate made of the closest category. Lacunes (fully, partially or non-cavitated) in the basal ganglia may also lead to difficulties in rating (Fig 17B); again, an estimate must be made of the closest category.

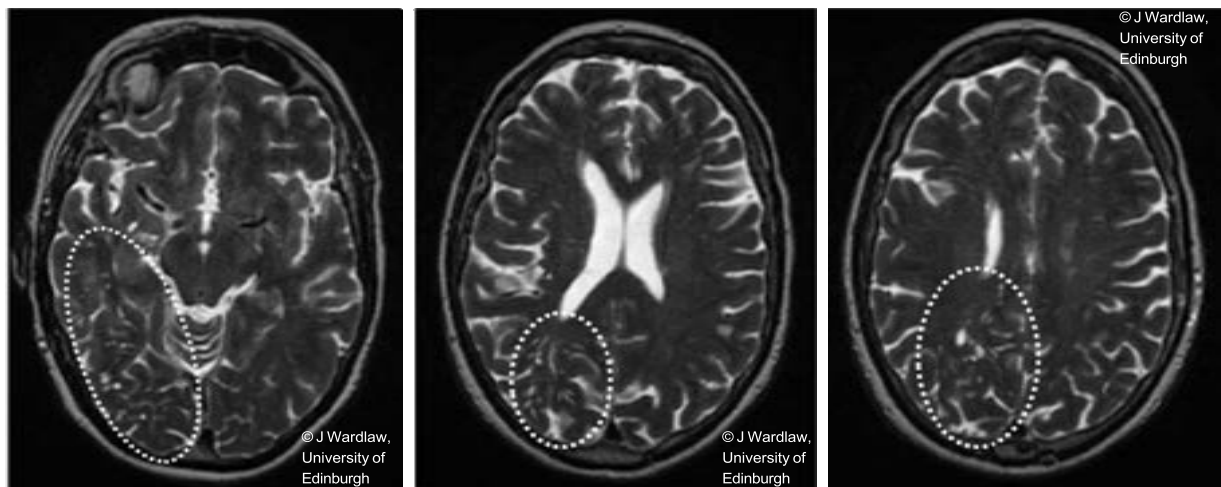
Figure 17. A. Asymmetry of background brain parenchyma due to an infarct in the right parieto-occipital lobe on T2-weighted MRI (arrow). B. Fully cavitated (short arrow), partially cavitated (thick arrow) and probably non-cavitated (arrowhead) lacunar lesions in the basal ganglia on T2 and FLAIR MRI. The exact nature of the lesion indicated by the long arrow is less certain - this could represent a cavitated lacune or EPVS with surrounding WMH



G. Asymmetry in EPVS

In some patients, EPVS may show significant asymmetry (Fig 18). In such cases, the side with the higher number should be counted

Figure 18. Marked asymmetry in EPVS, with a higher number of EPVS in the posterior cerebral artery territory on the right side (arrows)

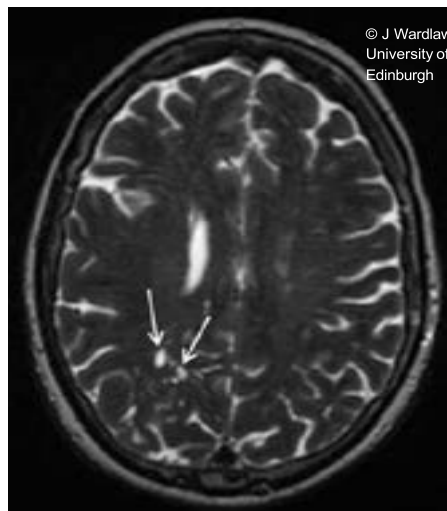


H. Focally dilated EPVS

In some patients, focally dilated EPVS will be seen amongst uniformly dilated EPVS (Fig 19).

The rating scale does not specifically take account of these.

Figure 19. Focally dilated EPVS (arrows) amongst uniformly dilated EPVS



I. Differentiating between the most severe categories of centrum semiovale EPVS

In many patient cohorts, the number of patients exhibiting the highest numbers/most severe degrees of EPVS in the centrum semiovale will be limited. Experience in rating the highest degrees of EPVS will thus be limited for the majority of people performing EPVS rating.

J. Variations in lesion load between cohorts

Rating of EPVS may vary with lesion load, as found in observer reliability testing for WMH⁹ intermittent review of the full range of EPVS which may be encountered in patients – as demonstrated in this guide – is advised in order to help raters 'recalibrate'. Differences in MRI

parameters may also contribute to observer differences, although this is a parameter which may be difficult to alter in the majority of cases.

Section 4. The EPVS scale

A. Rating categories & descriptions for each anatomical area

	Rating	Description
Basal ganglia and centrum semiovale	0	No EPVS
	1	1-10 EPVS (mild)
	2	11-20 EPVS (moderate)
	3	21-40 EPVS (frequent)
	4	>40 EPVS (severe)
Midbrain	0	No EVPS visible
	1	EPVS visible

Notes:

Review both sides of the brain for EPVS, but use the *highest number from 1 side only*

Review all relevant slices, but use the slice with the highest number of EPVS

In cases where rating is difficult (e.g. due to movement, extensive WMH or uncertainty due to variations in EPVS visibility), select the closest category

In cases of marked asymmetry (rare), record the score for the side of the brain with more EPVS

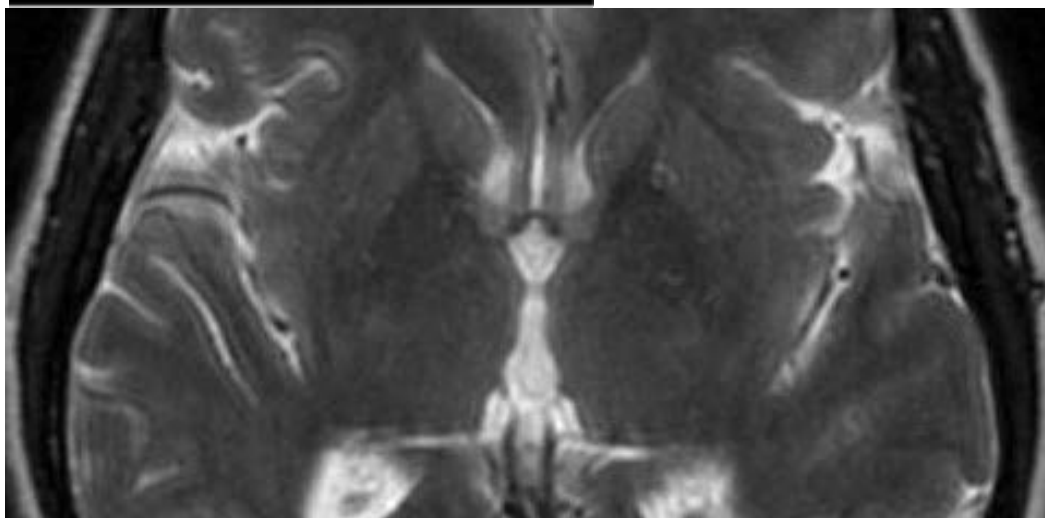
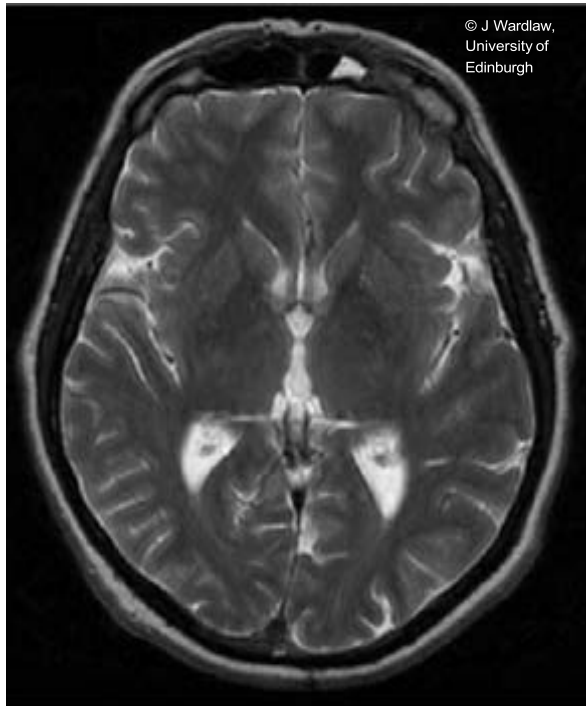
For basal ganglia EPVS, do not include EPVS in the anterior perforated substance (see above)

B. Imaging examples for rating categories

a. Basal ganglia

Basal ganglia

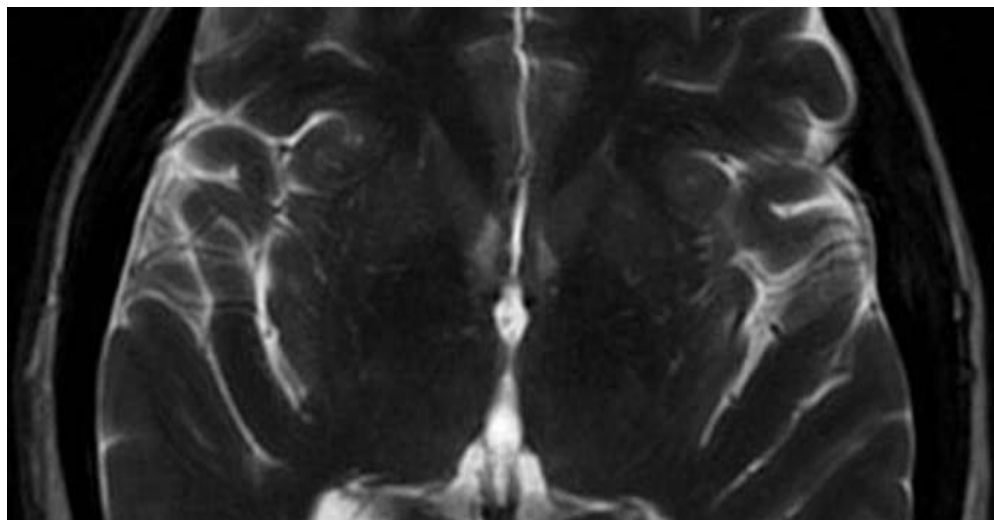
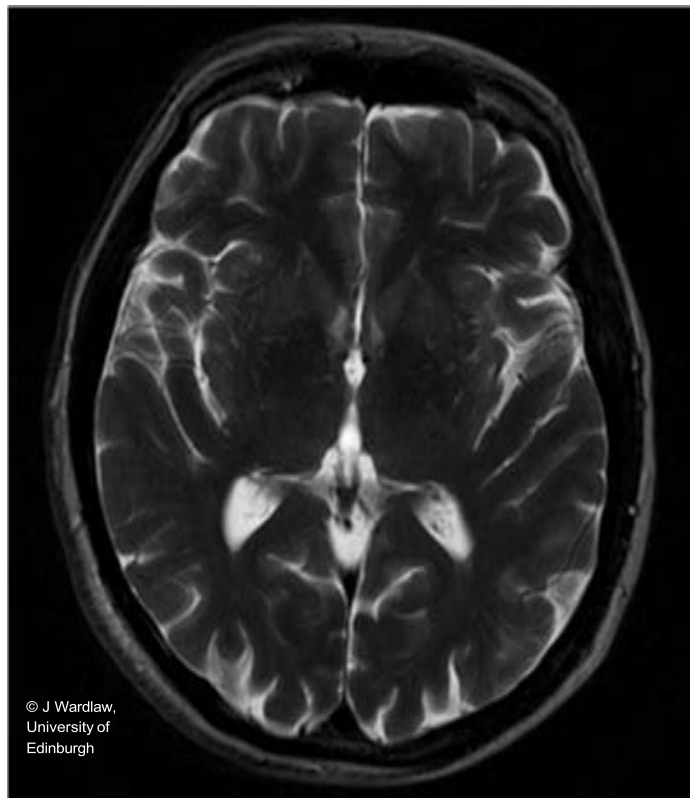
1-10 EPVS – category 1 (one example)



Basal ganglia

11-20 EPVS – category 2

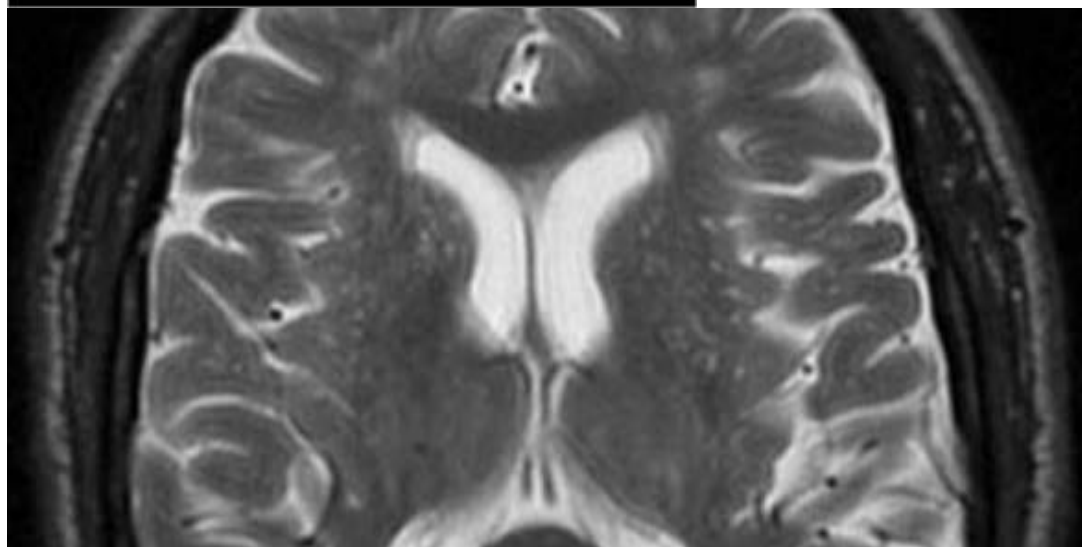
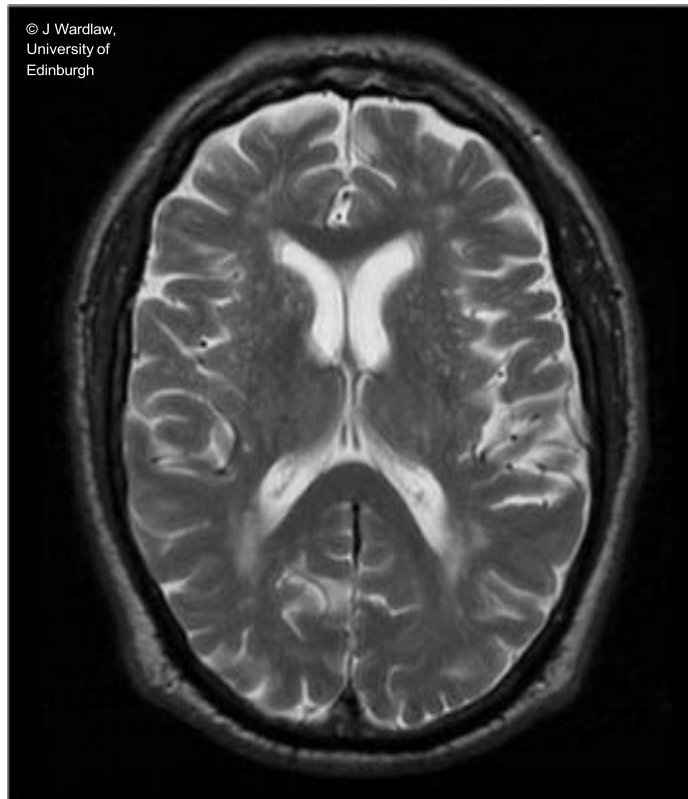
Example 1 of 2



Basal ganglia

11-20 EPVS – category 2

Example 2 of 2

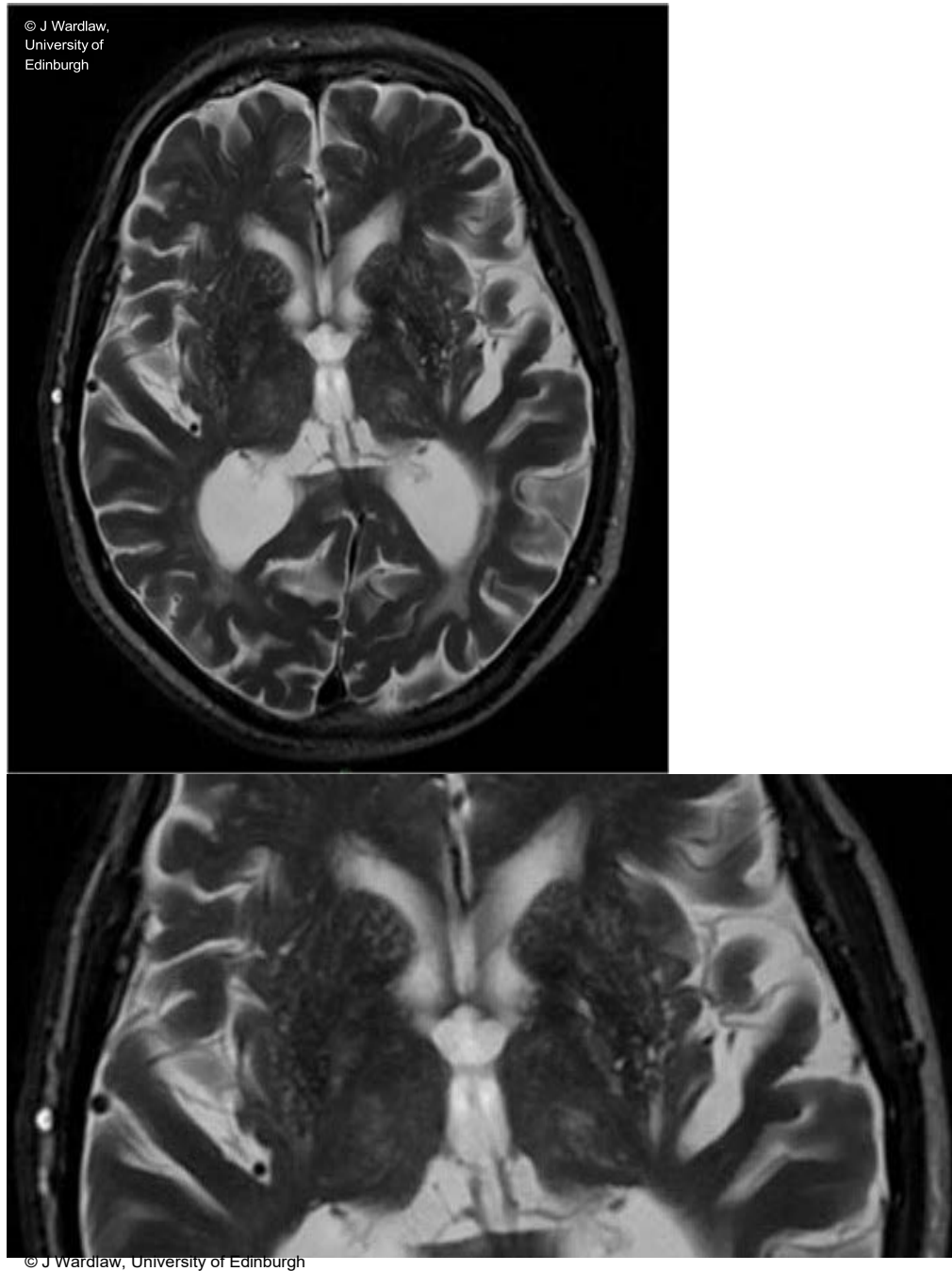


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Basal ganglia

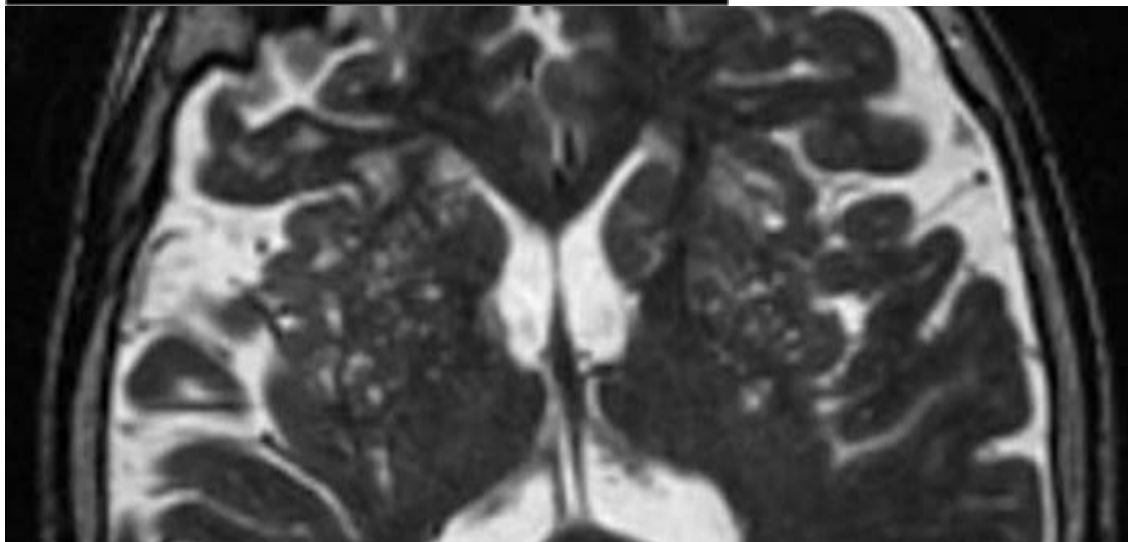
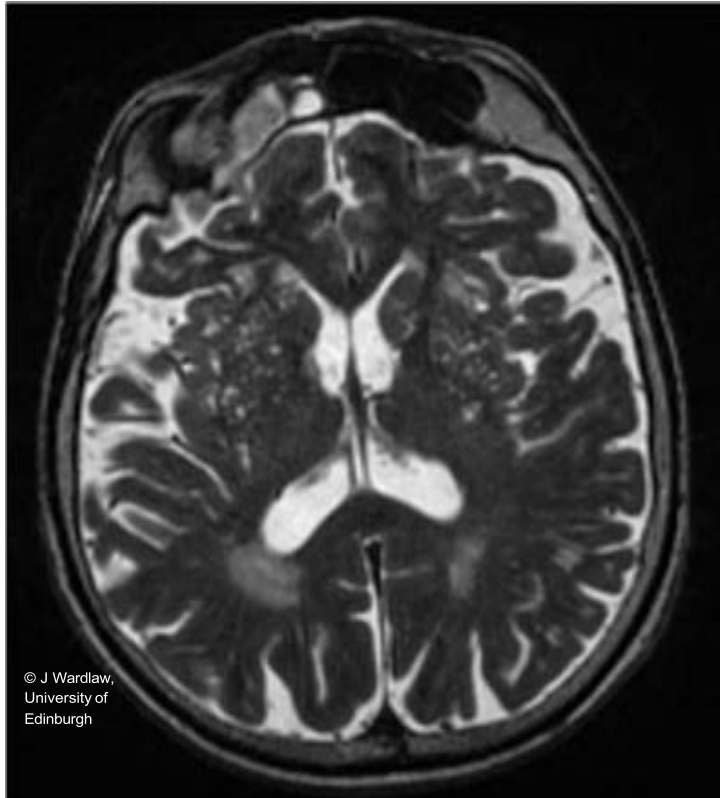
20-40 EPVS – category 3

Example 1 of 2



Basal ganglia

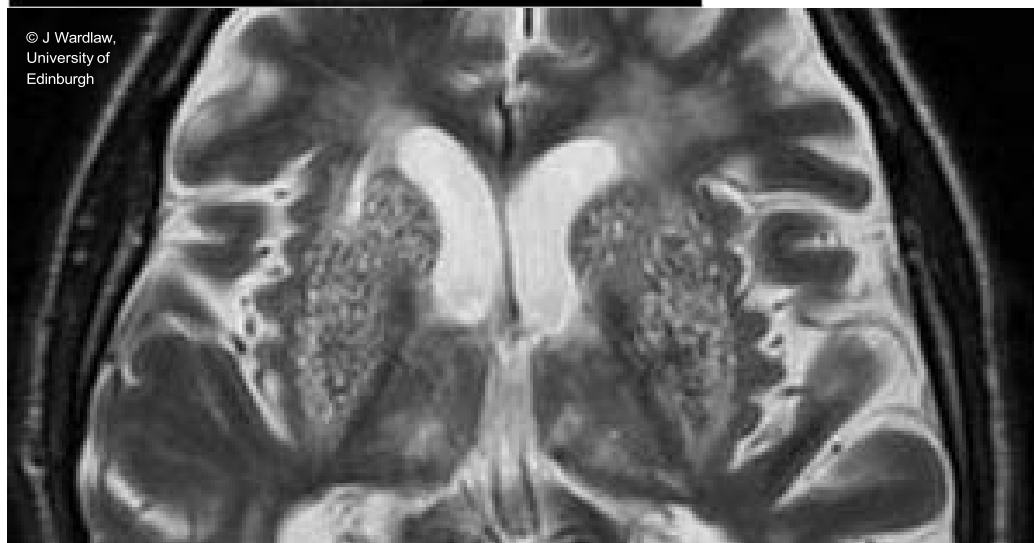
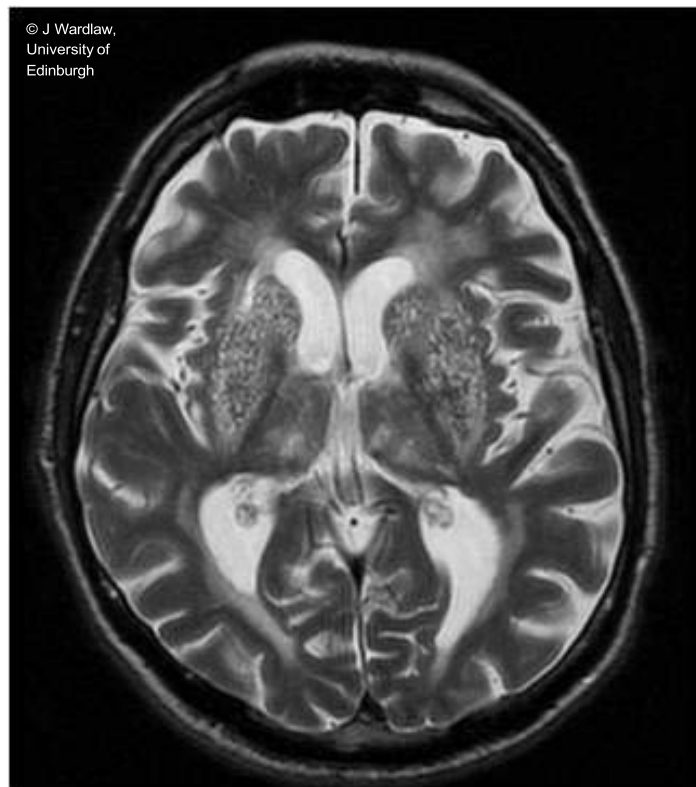
20-40 EPVS – category 3



Basal ganglia

>40 EPVS – category 4

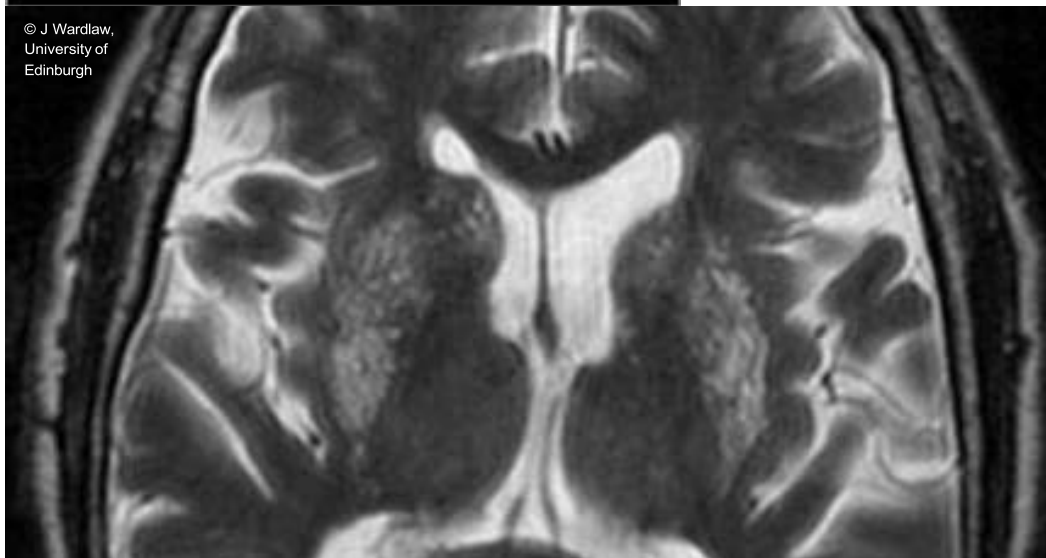
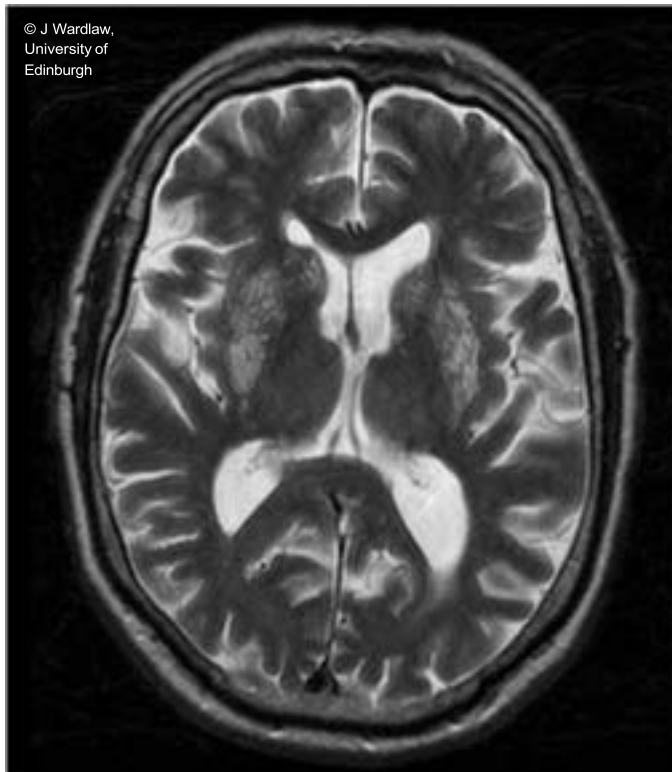
Example 1 of 2



Basal ganglia

>40 EPVS – category 4

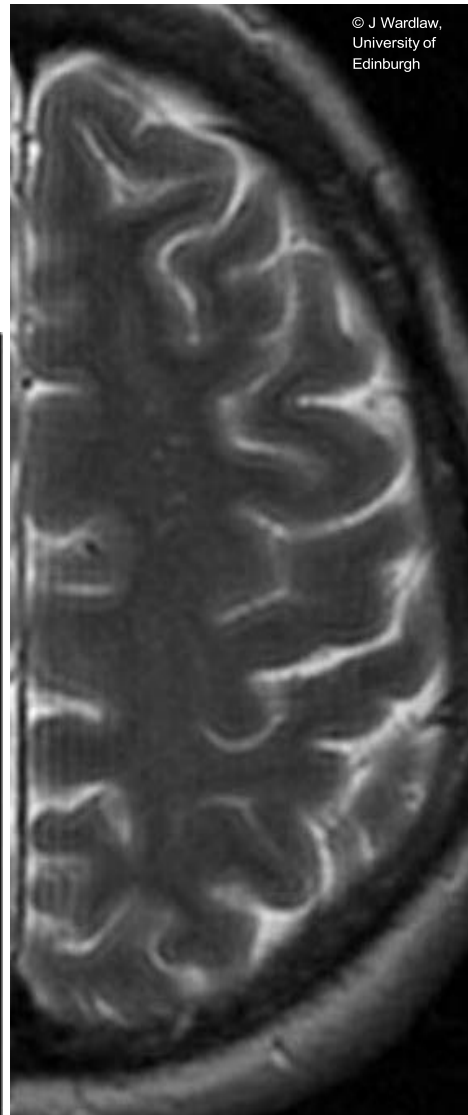
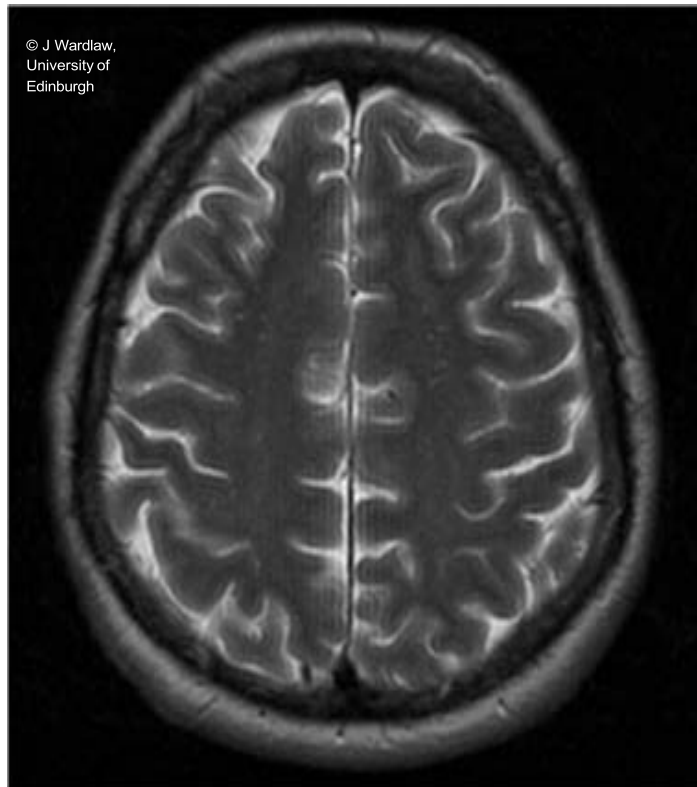
Example 2 of 2



b. Centrum semiovale

Centrum semiovale

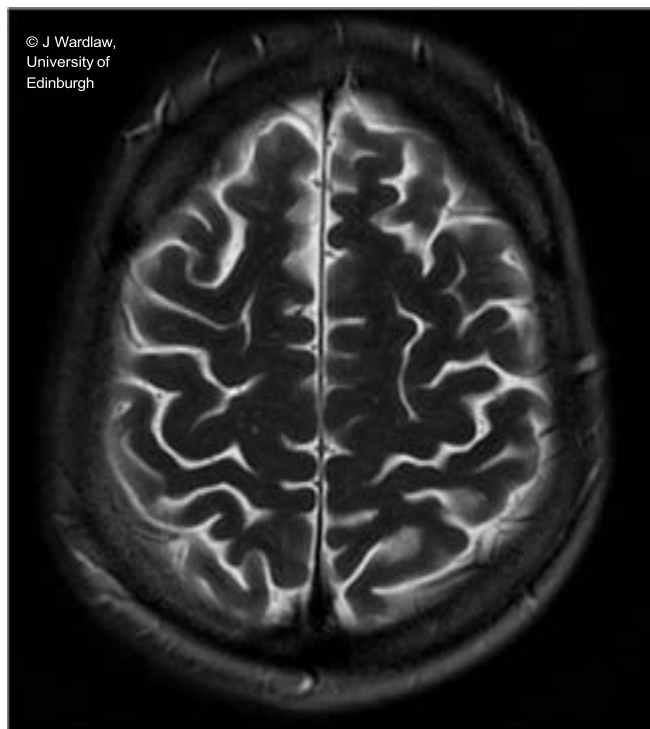
1-10 EPVS – category 1



Centrum semiovale

11-20 EPVS – category 2

Example 1 of 2



Centrum semiovale

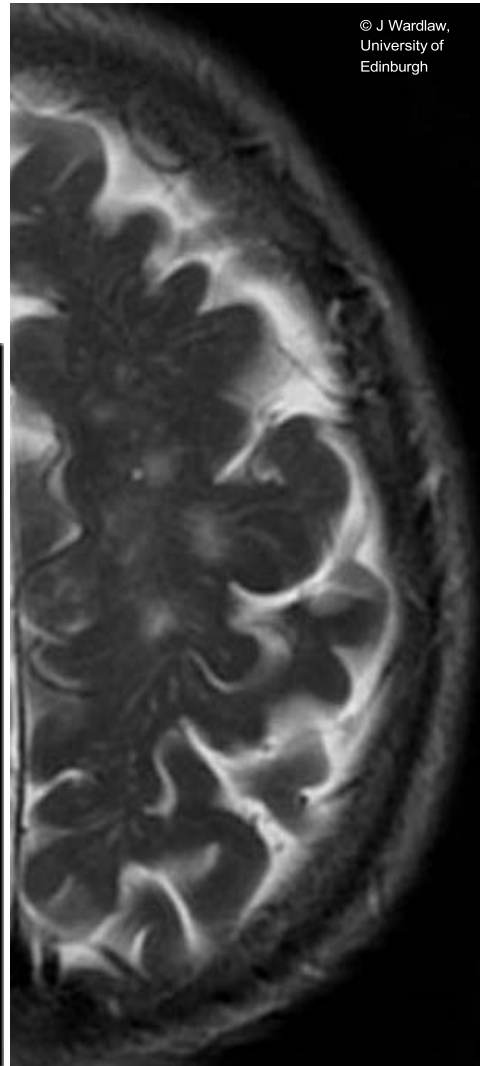
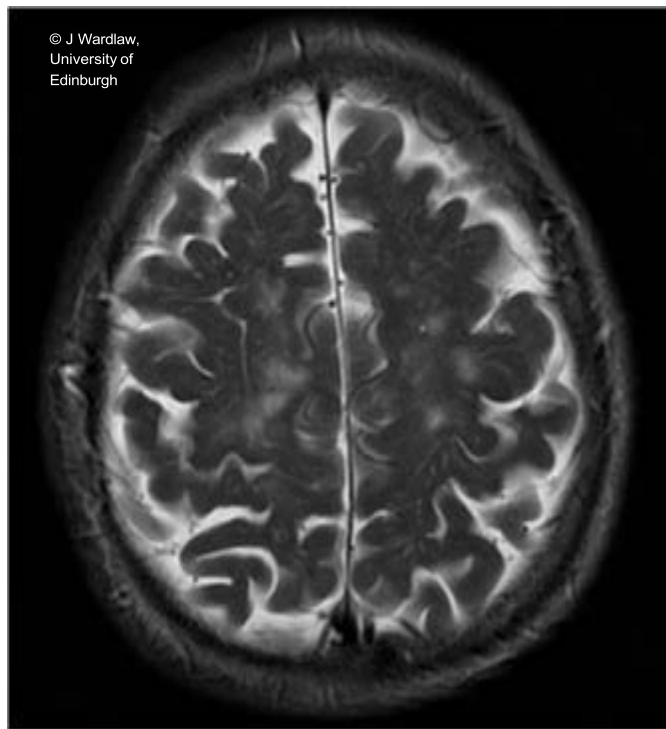
11-20 EPVS – category 2

Example 2 of 2



Centrum semiovale

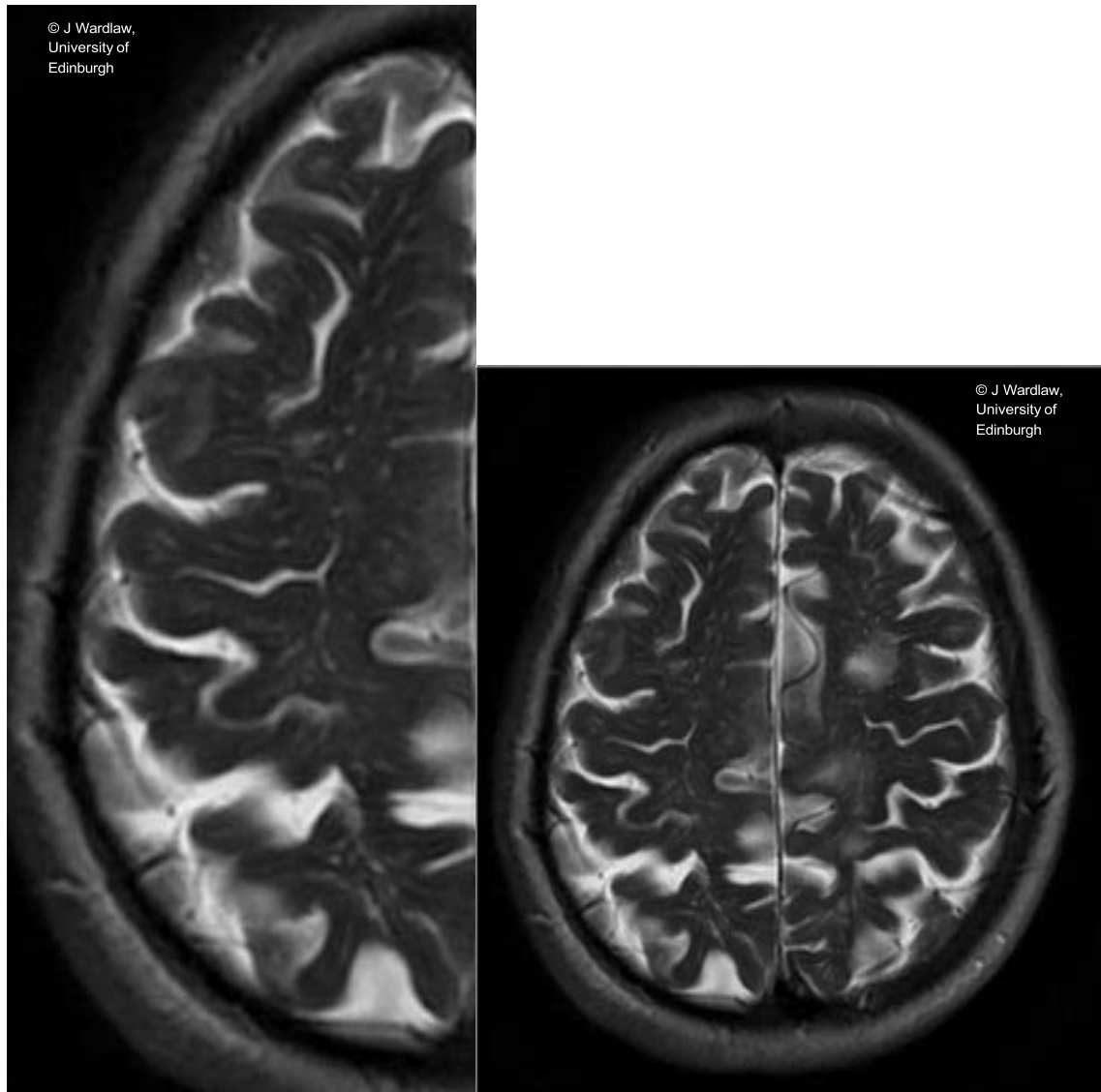
20-40 EPVS – category 3



Centrum semiovale

>40 EPVS – category 4

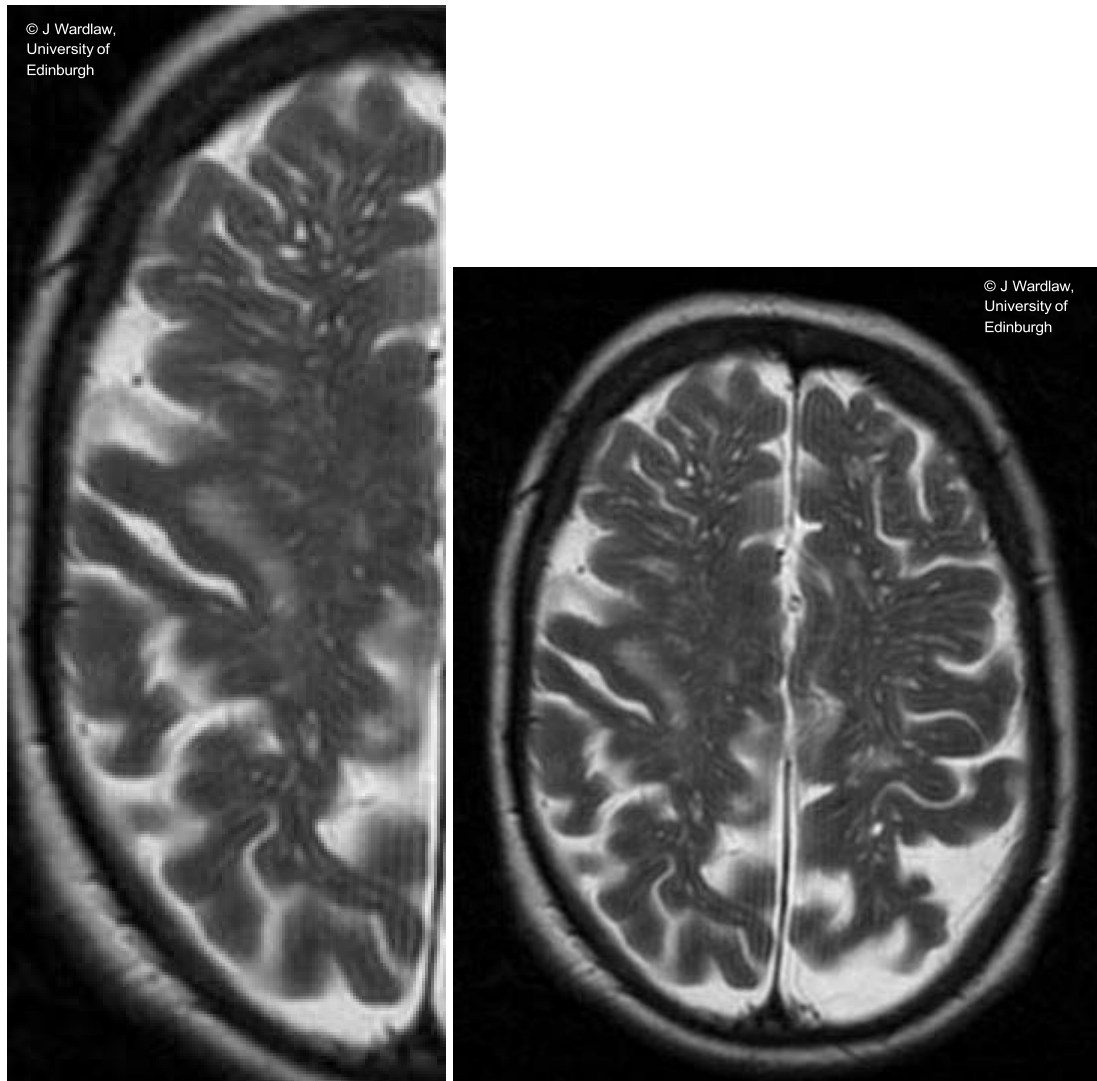
Example 1 of 2



Centrum semiovale

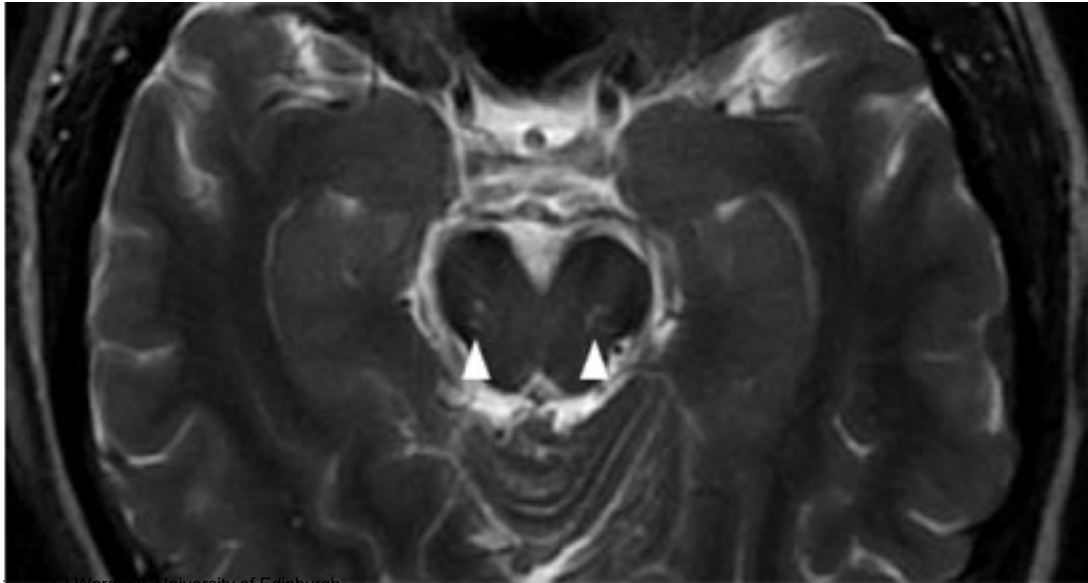
>40 EPVS – category 4

Example 2 of 2



c. Midbrain

EPVS visible – category 1



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Conclusion

Because the clinical implications of EPVS remain to be established, there is still an opportunity to improve the reliability of EPVS assessment by the use of the EPVS rating scale, so that adequately powered, well designed studies will be able to answer the outstanding clinical concerns about their diagnostic and prognostic value within the spectrum of cerebral small vessel disease, and whether EPVS should influence patient management. Although we have developed and tested a visual rating scale, automated EPVS measurement methods may be possible with improved image processing algorithms in future.