

The distribution of plaques in the cerebrum in multiple sclerosis

Betty Brownell and J. Trevor Hughes

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Subtitle: One of the major steps in deciphering multiple sclerosis was the description of exact lesion topography made over 50 years ago.

Published 58 years ago this seminal work, from Oxford has been cited nearly 600 times.¹ What did it describe and why is it considered so important?

Multiple sclerosis (MS) remains an enigmatic disease (or syndrome), reluctant to give up its secrets: visualised on MRI, an inflammatory vapour trail in the CSF, characteristic in its clinical manifestations and now partially responsive to therapeutic intervention. However the exact causality (genetic/environmental) remains hidden behind the curtain. One way to try to coax it onto the stage is neuropathology, where the 'caught in the act' actors are captured and their ruinous works see light – even though of course, they are frozen from the time of death and represent the accumulated sacking of the central nervous system over many decades.

The article commences by describing the quandary faced in the middle of the 20th century with MS neuropathology. Whilst the literature was immense,² there was no work which mapped out the 'position of the plaques in the cerebrum with any exactitude', though a spinal cord study of 8 cases found spinal plaques with some regional consistency.³ The task set here, was to 'determine with some precision the position and relative frequency of plaques seen macroscopically in the cerebral hemispheres'. The underlying manifesto of course, was that this could shine some light on the secrets of the disease process.

The experimental stage chosen was 22 unselected MS cases (the clinical details were not given) accumulated from 1958-1961. The fixed hemispheres were cut coronally at 1cm intervals (the first cut in front of the mammillary bodies) and the slices photographed in life size prints. On the prints, each plaque was outlined in ink and its position transposed onto the outline of a normal brain. A dot represented the plaque centre and the combined dots were assigned to

their respective cerebral geographies. The categories were: left/right hemispheres; and then: cortex, white matter, central grey matter and junctional cortex/white matter [juxtacortical]. These were then divided into lobes and ultimately gyri.

Around 1600 plaques were counted, with an average of 72 per case. The leading regions were: periventricular (40%), frontal lobe (22%), parietal (15%), and temporal (12%). Other areas (eg occipital, corpus callosum, hypothalamus) were low single figures. Adjusting for area with a planimeter, the incidence/cm² was not significantly different. Around three-quarters were white matter distributed, 17% junction of the cortex and white matter, cortex and central grey matter about 5% each. There was enormous variation in the absolute numbers of plaques per case with a range from 3-225. Cortical plaques were particularly seen from the three patients with the largest numbers of plaques overall (180, 220 and 225). Plaques were commonest around the lateral ventricles: anterior, inferior and posterior horns.

The study concluded that to an extent, all areas of the cerebrum were vulnerable once regional size was accounted for. Although the white matter plaques were most conspicuous they were seen junctionally and in the internal nuclei. However 'stand-out' areas were periventricular in the lateral ventricle (as opposed to the third ventricle, say), and in detail these were the: supero-lateral angles of the anterior horns, bodies of the lateral ventricles, inferior and posterior horns (but not the infero-medial aspects). However there seemed to be some sparing of certain large periventricular areas: caudate nucleus, thalamus and corpus callosum.

Apart from the beautiful microscopic detail, which resonates with MRI work decades later, what pathogenic insights did the authors discuss?

Firstly, they felt that the asymmetry in the deeper recesses of the paraventricular structures mitigated against soluble diffusing factors. They did however support the concept of a vascular basis which had been put forward and then debated in 1863 (for), 1942 (against) and 1950 (against) in particular. Their stand was nuanced against a large vasculopathy, but they felt that there was 'some more subtle peculiarity of the circulation in certain cerebral areas'. What they especially highlighted was that these periventricular areas were situated on boundary zones between major cerebral arteries, and that these were relatively avascular.⁴ For example, the white matter at the lateral angle of the lateral ventricle was at the limits of supply of two large rivers: anterior and middle cerebral; or the lateral angle of the posterior horn (anterior, middle and posterior cerebral). They contrast this with regions which although adjacent to the lateral ventricles, have adequate supply, and were not unduly susceptible, for example: thalamus, caudate nucleus and hippocampus. The thesis also extended to the junction of the cortex and white matter.

Their work was dedicated and exhaustive. Their conjectures stimulating. How did the next half-century of medical scientists view their contributions? One way, is consider how the top five articles which cite this work, frame their contribution.

Kutzelnigg (2005) highlights cortical pathology.. ' the presence of cortical demyelination ..has been previously recognised [from this work].'⁵ Trapp (2008) considers the grey matter involvement and says..'whilst recent reports of cortical demyelination were a surprise to many in the MS community, cortical demyelination has been reported in the MS literature for decades [from this work].'⁶ Peterson (2001) uses this work to point out that ..'while the density of myelin in the cortex is less than in the white matter, demyelinated lesions have

been identified in the cerebral cortex of MS brains [from this work]'.⁷ Magliozzi (2007) cites Brownell and Hughes ..'previous neuropathological studies have shown the presence of demyelination, axonal damage and neuronal loss, in the cortical and deep grey matter of multiple sclerosis patients.'⁸ Kidd (1999) describe in some detail the distribution of the lesions given in this paper in their introduction to their work on cortical lesions.⁹

A different compass to use is McAlpine's Multiple Sclerosis and its progeny, with a roll call of distinguished MS investigators over half a century. The original was published prior to this publication (1955) and the 1965 and 1972 editions carry little in the way of comment. It is in 1985 that a full chapter is devoted to neuropathology and our paper is well described in a rich section on plaque topography. Five years later, the essence of the work is again well detailed, with Ian McDonald's chapter (1998) pointing out that the later accumulation of disability probably reflects the multiplicity of lesions involving the cortex as described by this work. The most recent edition in 2005 highlights again the original contribution in demonstrating that demyelinated plaques may be present in all areas of the grey matter.

Modern MRI techniques are increasingly being used to visualise grey matter pathology and the current McDonald classification of multiple sclerosis specifically highlights cortical lesions to enable dissemination in space, as well as the other characteristic topographies described in this paper.¹⁰

The legacy was clearly immense and is, and was, a fundamental clue to the task of trying to edge closer to a truer understanding of the hidden secrets of

multiple sclerosis. We remain truly grateful to the insights from the work of Brownell and Hughes.

It is appropriate now to honour the two individuals who carried out this work by briefly describing their lives.

Betty Brownell (figure 1) was born in Dublin of Huguenot descent. She had an illustrious pathological career centred on Bristol and Oxford as well as deep involvement in the Royal College of Pathologists, especially related to training and the establishment of neuropathology as a sub-speciality. Her research work was wide: muscle, peripheral nerve, Creutzfeldt-Jakob disease and spinal cord.¹¹



Figure 1: Betty Brownell in 1975

Trevor Hughes talks about his life in a number specially recorded videos.¹² He had an extremely busy neuropathological career in Oxford and Stoke Mandeville, culminating in his book the Pathology of the Spinal Cord. But it was also hugely varied from a love of natural history (spiders in particular) to intense University and Hospital administration (he was also the Senior Bursar and then acting Warden of Green Templeton College) to biography (Thomas Willis).

A final symmetry to this paper was their marriage, but sadly Betty Brownell died only a few years later.

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