Review article

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Measuring the spatial arrangement patterns of pathological lesions in histological sections of brain tissue

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Abstract

The development of abnormal protein aggregates in the form of extracellular plaques and intracellular inclusions is a characteristic feature of many neurodegenerative diseases such as Alzheimer's disease (AD), Creutzfeldt-Jakob disease (CJD) and the fronto-temporal dementias (FTD). An important aspect of a pathological protein aggregate is its spatial topography in the tissue. Lesions may not be randomly distributed within a histological section but exhibit spatial pattern, a departure from randomness either towards regularity or clustering. Information on the spatial pattern of a lesion may be useful in elucidating its pathogenesis and in studying the relationships between different lesions. This article reviews the methods that have been used to study the spatial topography of lesions. These include simple tests of whether the distribution of a lesion departs significantly from random using randomized points or sample fields, and more complex methods that employ grids or transects of contiguous fields and which can detect the intensity of aggregation and the sizes, distribution and spacing of the clusters. The usefulness of these methods in elucidating the pathogenesis of protein aggregates in neurodegenerative disease is discussed.

Key words: *spatial topography, neurodegenerative disease, protein aggregate, clustering, poisson distribution, variance/mean ratio*

Introduction

There has been a considerable increase in the application of methods designed to quantify features in histological sections of brain tissue [1,6]. Image analysis systems have enabled images to be captured and enhanced on a computer screen so that particular histological features can be quantified rapidly and more objectively [40]. In tissue sections, histological features often appear as discrete objects or profiles such as cell perikarya, cell nuclei, blood vessels, or lesions that are formed in the brain as a result of pathological processes. In neurodegenerative disorders such as Parkinson's disease (PD), Pick's disease (PiD) and dementia with Lewy bodies (DLB), abnormal protein aggregates in the form of inclusion bodies may be observed within the perikarya of vulnerable groups of neurons, while in Alzheimer's disease (AD) and Creutzfeldt-Jakob disease (CJD), extracellular deposits of abnormal protein aggregates occur in the form of discrete senile plaques [16]. In many neurodegenerative diseases, understanding the formation of these pathological lesions has become critical in elucidating the pathogenesis of the disease [17].

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An important property of a pathological lesion is its spatial arrangement pattern or topography in the tissue [17]. A lesion may not be randomly scattered throughout a histological section but exhibit a spatial pattern, i.e., a departure from randomness towards regularity or clustering. For example, in AD there is evidence that both the β-amyloid (Aβ) protein deposits, an important constituent of senile plaque (SP) [25], and the intracellular neurofibrillary tangles (NFT) are clustered in the cerebral cortex [1,36]. In many regions, these clusters are regularly distributed along the cortex parallel to the pia mater. Information on spatial pattern may be valuable in understanding both the relationships between different lesions, e.g., the relationship of Aβ protein deposits to neurofibrillary tangles (NFT) [8,13], and between lesions and the anatomical features of the brain, e.g., the relationship between Aβ deposits and neuronal perikarya [5] or blood vessel profiles [3,10].

This review describes the methods that have been used to study the spatial topography of abnormal protein aggregates in neurodegenerative disease. These methods range from simple methods that employ randomized points or sample fields to more complex methods based on grids or transects of contiguous fields. Each method has strengths and limitations and an appreciation of these qualities is essential for their successful application. Methods based on point patterns that have not been extensively used to date to study protein aggregates have been reviewed previously [9].

Types of spatial pattern

A pathological lesion such as a protein deposit or cellular inclusion may be distributed randomly, regularly, or it may be aggregated into clusters. Spatial pattern is defined as a statistically significant departure from a random distribution. The most commonly observed departure from randomness exhibited by brain lesions is towards aggregation or clustering [17]. If a feature is clustered, then the distribution of the clusters themselves may be regular or random. Clustering may occur at two or more scales in a section, e.g., small and larger-scale clusters may be present and smaller clusters may be aggregated into larger clusters. Two important features of a clustered pattern are its "intensity" and "grain" [37]. Intensity is the ratio of the density of an object at the centre of the clusters to that of the adjacent spaces or to regions of lower density. A feature may be distributed in dense clusters separated by distinct gaps (high intensity pattern) or there may be a more gradual transition from regions of high to low density (lower intensity pattern). By contrast, the "grain" of a pattern relates to the size and spacing of the clusters. Large clusters, which are widely spaced in the tissue, form a coarse-grained pattern, while small clusters, more closely spaced, form a fine--grained pattern. Information on some or all of these aspects of spatial pattern may be relevant in individual studies. However, each method only provides information on certain aspects of spatial pattern. Successful application of a particular method requires first, a clear hypothesis and second, an appreciation of the advantages and limitations of each method.

"Plotless" methods

Many of the methods of studying spatial pattern rely on counting the number of lesions in defined sample fields or plots. Measuring a spatial pattern, however, is dependent on the shape and size of the sample fields used [1]. Hence, a good alternative is to use a "plotless" method, i.e., a sampling method based on the use of randomized points.

Holgate's method

In Holgate's method [29], a number of randomly selected points ("n" at least 50) are superimposed over the area of the section to be sampled (Fig. 1A). From each point, the distance to the nearest lesion of interest (d) is measured and the distance to the second nearest lesion (d_1). The index of aggregation (A_1) (Table I) is zero for a random distribution, greater than zero for a contagious distribution, and less than zero for a uniform distribution.

Hopkin's method

In Hopkin's method (Fig. 1B) [30], a number of points are superimposed at random over the section and the distance of each point to the nearest lesion measured (d). Second, a total of "n" lesions are selected at random and the distance from each to the nearest profile measured (d_1). The index of aggregation A_2 (Table I) is zero for a random distribution, greater than zero for a contagious distribution, and less than zero for a uniform distribution. A_2 is more difficult to determine than A_1 since the selection of random

Table I. Summary of formulae and significance tests for studying spatial pattern in histological sections

Method	Statistic	Significance test	Data
Holgate's index (A_1)	$A_1=\Sigma\ (d^2/d_1^2)/n-0.5$	$t=\lvert A_1\rvert/(\sqrt{n}/12)$	Distance
Hopkin's index (A_2)	$A_2=\Sigma d^2/\Sigma d_1^2-1$	$t=2\lvert(A_2+1)/(A_2+2)-0.5\rvert\sqrt{(2n+1)}$	Distance
Poisson	–	$\chi^2=\Sigma\ (O-E)^2/E$	Frequency
Poisson	V/M	$t=\lvert V/M-1.0\rvert/\sqrt{2}(n-1)$ $\chi^2=\{(n-1)(V)\}/M$	Density
Index of aggregation (k)	$p^k(1-q)^{-k}$; p=k/k+μ and q=1–p	–	Density
Morisita's index (I_d)	$I_d=n\ (\Sigma X^2-N)/N(N-1)$	$\chi^2=(n\Sigma X^2/N)-N$	Density
Spatial pattern analysis (grid, transect)	V/M	$t=\lvert V/M-1.0\rvert/\sqrt{2}(n-1)$ $\chi^2=\{(n-1)(V)\}/M$	Density
Spatial pattern analysis (grid, transect)	V	–	Any
Regression	β (b)	$t=b/s_b$	Any
Fourier analysis	f(x)=f(An, Bn)	ANOVA	Any

ANOVA – analysis of variance; V – variance; X – individual observations; M – mean of densities; n – number of observations or plots; N – total number of individuals counted on all "n" plots; d – distance measure; t – student's "t"; p, q – probability of an individual event; β – regression coefficient; b – sample regression coefficient; s_b – standard error of b; O – observed frequency; E – expected frequency.

lesions can be a tedious procedure. In addition, it is not valid to consider the lesion nearest a random point to be a randomly selected lesion. One method would be to assign a number to each lesion in the area of interest and select a random sample using a random numbers table.

Methods based on randomised sample fields

A number of methods of determining spatial pattern are based on the use of sample fields in which various histological features are counted [1]. Individual fields may be located at random within a region of interest or a more systematic sampling regime may be employed involving the use of grids or transects.

The Poisson distribution

Methods based on the Poisson distribution are the most commonly used to test the degree of departure from randomness. Any type of sampling employing sample fields can be used to fit the Poisson distribution to data but the most usual method employs a random distribution of individual fields. If spatial pattern of the lesion is random then the probability (P) that the fields contain 0, 1, 2, 3, ..., n, individuals is given by the Poisson distribution. The Poisson distribution can be used to calculate the expected number of fields containing 0, 1, 2, 3, ..., n, individuals and deviations of the observed from the expected frequencies tested using either a Kolmorogorov-Smirnov or chi-square (χ^2) test.

An example of the use of this method to determine whether NFT were randomly distributed in the frontal cortex of a case of AD is shown in Fig. 2.

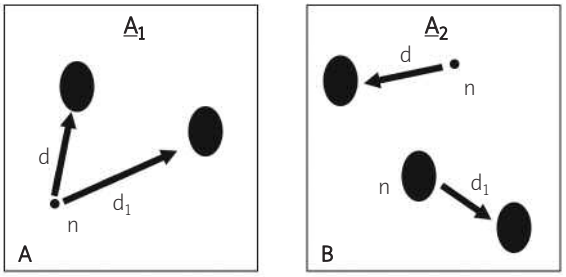

Fig. 1. Different methods of point sampling: **A)** Holgate's method based on the distances of randomly selected points (n) to the nearest and second nearest profile, **B)** Hopkin's method based on the distance of both random points to the nearest profile and randomly selected profile to nearest neighbour

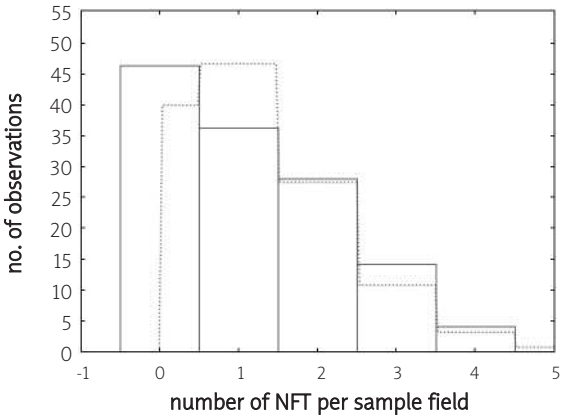

Fig. 2. Fitting the Poisson distribution to the frequency distribution of the numbers of neurofibrillary tangles (NFT) in a case of Alzheimer's disease (AD) (continuous line = observed frequencies, dashed line = expected frequencies, chi-square (χ^2)=4.46, P=0.216)

Tissue sections were stained with the Gallyas method to reveal the NFT and 128, 200 x 1000 µm sample fields positioned at random within the section. The number of NFT was counted in each sample field and a frequency distribution constructed of the number of fields containing 0, 1, 2, 3, ..., n, NFT (Fig. 1). A Poisson distribution was fitted to this discrete distribution which in this case fitted the data adequately (χ^2=4.46, P=0.216). Hence, there was no evidence in the frontal cortex that the NFT deviated significantly from a random distribution. However, Pearson et al. [36] and Myers et al. [35] used this method to determine the spatial pattern of SP and NFT respectively in patients with AD. Significant degrees of clustering of the SP and NFT were observed, leading to the conclusion that the lesions developed in relation to the cortico-cortical projections of the brain, i.e., those anatomical pathways that connect cortical gyri [23,28], and that the pathology may spread gradually from a point of origin in the temporal lobe to affect most other areas of the brain via these projections [36].

The negative binomial distribution

Methods of studying spatial pattern based on the Poisson distribution test the hypothesis that an observed pattern does not differ significantly from an expected random distribution. Such a test, however, does not give a good description of the intensity of aggregation.

The negative binomial distribution can be fitted to a variety of clustered patterns and may give a more accurate estimate of the intensity of aggregation. The negative binomial is a two--parameter distribution defined by the mean density of the histological feature (µ) and the binomial exponent "k" (Table I). The value of "k" is generally between 0.5 and 3.0 and decreases as the degree of aggregation increases, and hence the reciprocal of "k" can be used as an index of the degree of aggregation. Care must be taken in comparing different populations, however, since they may differ in both mean density and in aggregation, the relationship between "k" and density being more complex [41,42]. The procedure for fitting the negative binomial to data is given by [21]. Essentially, any sample information about the numbers of a histological feature in space can be analysed as long as the mean number of individuals per sample is low and plot size is adjusted to reflect this limitation. Data are grouped as a frequency distribution to show the number of samples (f) containing various numbers of individuals (X). The mean number of individuals per plot is then calculated and "k" estimated by an iterative procedure. The expected frequencies of samples containing various numbers of individuals can then be calculated and compared with the observed distribution to test whether the negative binomial is an adequate fit to the data.

Morisita's index of dispersion

Morisita's index of dispersion [34] is an alternative to the use of the Poisson and negative binomial distributions and has the additional advantage that the index of clustering is unaltered if objects have disappeared at random from the original clusters. This may be especially relevant in the analysis of cell populations and of pathological lesions since losses of these entities may occur during aging and disease pathogenesis in the brain [31,38]. Morisita's index of clustering (I_d) (Table I) is unity for a random distribution, zero for a perfectly uniform distribution, and equal to "n" when individuals are maximally aggregated. The significance of I_d can be tested by a chi-square test (Table I).

Other methods based on the Poisson distribution and the V/M ratio include David & Moore's test [22] that can be used as an index of clustering and to compare whether similar degrees of clustering were present in different areas, and Lloyd's method [33] based on the calculation of a "mean crowding index" or "index of patchiness".

Methods based on grids or transects

A disadvantage of the Poisson method of determining spatial pattern is that the results are markedly affected by field size. To overcome this problem, if contiguous samples or grid-sampling is used, quantitative measures in adjacent fields can be added together successively to provide the data for increasing field sizes up to a size limited by the length or area of the section sampled [1,4,26,27,32]. The starting position of the transect relative to the tissue section or the location of the grid should be determined randomly. There are two main methods of analyzing data from this type of sampling regime, viz., the variance/mean (V/M) method and spatial pattern analysis by regression.

The V/M method

This method is an extension of the Poisson distribution to grids and transects. If a transect is employed, then the numbers of profiles of the histological feature of interest in adjacent plots can be added together successively to obtain counts for larger field sizes, i.e., two unit blocks made up of adding together data from the original plots (field size 2), four unit blocks (field size 4), eight unit blocks (field size 8), etc., up to a size limited by the length of the sample transect. In a Poisson distribution, the variance (V) is equal to the mean (M) and hence the V/M ratio is unity. The V/M ratio (Table I), also known as the "coefficient of dispersion" or "the relative variance", can be used as an index of spatial pattern, uniform distributions having a V/M ratio less than unity and contagious distributions greater than unity. The significance of departure of the V/M ratio from unity can be tested by a "t"-test or by a chi-square test [19]. In fitting a Poisson distribution, the mean number of individuals per plot should not exceed 10 and should preferably be less than 5, field size being adjusted to achieve this outcome. The V/M ratio is calculated at each field size and a graph plotted of the relationship between V/M and field size. If the distribution of a lesion is random, then V/M will not rise significantly above or below unity. If V/M increases with field size reaching a plateau or asymptotic value, this indicates that the clusters are distributed randomly. The field size at which V/M reaches its asymptotic value provides an estimate of cluster size. If V/M increases to a significant peak, then a regular distribution of clusters is present, the location of the peak indicating the cluster size. Whether a significant peak is present can be tested either by a t-test or a chi-square test (Table I) as described previously [19]. The height of a V/M peak is a measure of the intensity of clustering, i.e., the ratio of density in the clusters to that in the adjacent spaces. Finally, if V/M increases with field size neither reaching a plateau nor a peak, then this is an indication of the presence of clustering on a large scale, i.e., the total length of the transect may only include part of a single large cluster.

This method can be extended to non-density data such as areas or volumes but in this case it would not be valid to use the Poisson distribution. Instead, the data can be analysed by analysis of variance (ANOVA) [32] in which the total sums of squares is partitioned between the various field sizes, the within field sizes mean squares being considered to be a comparable measure to the V/M ratio.

An example of the use of the V/M method is shown in Fig. 3 and shows the spatial pattern of the diffuse and florid prion protein (PrP) deposits in the frontal cortex in a case of variant CJD (vCJD). A transect of contiguous 50 x 200 µm sample fields, commencing at a random location, was set up parallel to the pia mater in the frontal cortex, the short dimension of the sample field aligned with the surface of the cortex. The number of the diffuse and florid PrP deposits per sample field was counted using an exclusion rule that stated that more than 50% of the area of the deposit should fall into a field before it can be included. A plot of V/M against field size for the resulting data is shown in Fig. 3. The V/M ratio of the florid deposits reached a peak at a field size of 400 µm, suggesting the presence of clusters of florid plaques, 400 µm in diameter, distributed with a regular periodicity parallel to the pia mater. By contrast, the V/M ratio of the diffuse deposits was significantly lower than unity at each field size, suggesting a regular or uniform distribution of deposits.

This type of analysis has been used extensively to study the spatial patterns of abnormal protein aggregates in diseased brain [17]. However, the method does have limitations. First, although

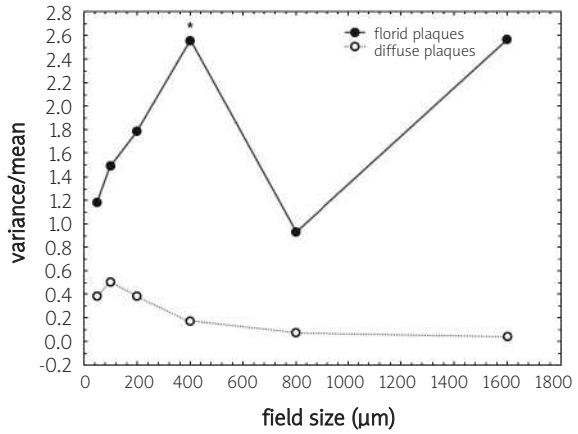

Fig. 3. Spatial pattern analysis using the variance/mean (V/M) method of the florid and diffuse prion protein deposits (PrP) in a case of variant Creutzfeldt-Jakob disease. (* – indicates significant V/M peak)

confidence intervals [27] and tests of significance [19] can be calculated for the V/M ratio, if non--density data are obtained then variance ratio (F) tests cannot be performed because the calculated mean squares are not independent of each other [32]. Hence, there is no objective test of the statistical significance of a variance peak with non--density data. The occurrence of the same peak in replicate samples taken from the same brain region could be used to assess the significance of a peak. However, this is unlikely to be satisfactory because spatial patterns of the same feature may vary significantly in closely parallel sections [12]. Second, most forms of this analysis add together in pairs adjacent density values successively to produce data for the larger field sizes. As a result, no information is available on the scale of spatial pattern between field sizes and this may create a significant error in estimating the size of larger clusters since field size increases geometrically. Third, the analysis may select the clusters, the intervening spaces, or one--half of the cluster plus space size as the significant unit of pattern [24,37]. Careful interpretation of the original data may be necessary to confirm that a V/M peak actually represents the cluster size. If the pattern present has a low intensity this distinction may be difficult to make. Fourth, no information is provided as to the spacing or "periodicity" of the clusters of a histological feature along the transect or within the grid.

Spatial pattern analysis by regression

A disadvantage of the V/M method is that it is based on the Poisson distribution and can only be applied to data in the form of counts or frequencies. Non-density data such as area of an object or "load" cannot be analysed using this method [1,4]. An alternative method of analysis, based on a linear regression model, has been described by Yarranton [43] and can be used on any quantitative measure obtained from the sample fields. As in the V/M method, a measure of a histological feature is made in a series of contiguous sample fields. This type of analysis is based on the observation that if lesions are distributed in discrete clusters and regularly distributed along the transect, the amount of a lesion in adjacent sample fields (comprising the X and Y variables of the analysis) will be high in both fields if they are sampling a cluster and low if they sample an intervening space. If the spacing between the sample fields is increased (e.g., if X and Y are the first and third fields, second and fourth fields, etc.), the probability increases that there will be pairs of values such that one member of the pair will fall within a cluster and the other within an adjacent space. Hence, the degree of positive correlation between the sample pairs should decrease as the spacing increases. In theory, the correlation between sample pairs should become significantly negative when the spacing between the X and Y variables corresponds to the average size of the clusters. Moreover, when the spacing between the X and Y variables corresponds to the distance between regularly distributed clusters, a significant positive correlation should be found. This occurs because the pairs of values are now so widely spaced that they sample adjacent clusters or spaces. Hence, linear regression coefficients (β, sample coefficient "b") (Table I) are calculated between pairs of adjacent values and then with increasing degrees of separation (i.e., separated by 1, 2, 3, 4, 5, ..., n units). The regression coefficient is plotted as a function of the degree of separation of the pairs of samples. A "t" test of the regression coefficient [39] can be used to test the significance of the positive and negative peaks.

An example of this analysis using simulated data is shown in Fig. 4. The simulated data contain three regularly spaced clusters of a feature of size 5 units separated by spaces of 11 units. Regression coefficients were calculated for adjacent pairs of

values and then with increasing degrees of separation up to a separation of 12 units. A plot of β against degree of separation reveals a negative peak at 5–6 units corresponding to cluster size, and a positive peak at 11 units corresponding to the spacing between the centres of adjacent clusters. This method was used by Armstrong and Wood [11] to study the spatial pattern of clusters of Aβ deposits in the cerebral cortex in patients with AD. Regularly spaced clustering of Aβ deposits parallel to the pia mater was detected and the analysis also estimated the spacing between the clusters to be in the range 2,200–11,800 μm. The regression method also was able to detect the presence of clusters of Aβ deposits at scales not detected by the V/M method [11].

Methods based on Fourier analysis

Bruce et al. [20] described a method of determining the spatial pattern of histological features across the different laminae of the cerebral cortex of the brain. The data comprised measurements of the amount or "load" of amyloid at different levels in the cortex. A Fourier series was calculated as a series of harmonic components (Table I) and ANOVA was used to determine the presence of significant harmonics. If no significant harmonics are found, this indicates that the distribution was random. The number of significant harmonics may indicate the number of clusters present and the curve of best fit can be used to describe the "grain" of the pattern. Significant harmonics were detected in the parahippocampal gyrus (PHG), suggesting the presence of clustering of Aβ deposits in relation to particular laminae [20].

Discussion

Successful studies of spatial pattern in brain tissue require that the objectives have been explicitly defined and translated into precise questions or hypotheses to be tested. The study population should then be carefully defined, e.g., a histological feature in a particular lobe or lamina of the cerebral cortex and a random sampling regime employed so that quantitative estimates of the feature of interest can be obtained.

Sampling regime

The first decision to be made in a study of spatial pattern is the type of sampling regime to be employed

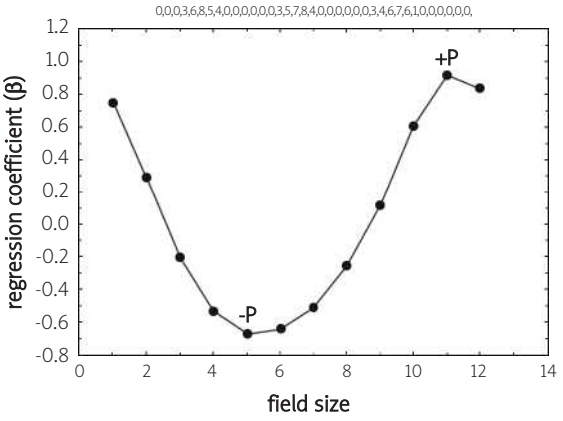

Fig. 4. Pattern analysis by regression: an example using a simulated data set comprising 37 contiguous fields (listed at top of graph) and which includes three clusters

[6]. Methods based on the distances of points to the nearest lesion may provide only limited information on spatial pattern. If a plot-based method is chosen, the size, shape, the number of the sample fields, and their spatial arrangement should then be considered. In general, rectangular fields may give the best estimates of a quantitative measure. Many of the methods of determining spatial pattern are dependent on field size and this size should be determined by consideration of the density and the scale of pattern to be detected. The number of fields measured used may be estimated by examining the precision required and the degree of variability between plots. The sampling strategy may also involve fields arranged at random, in a grid, or in a contiguous transect. In the cerebral cortex, transect sampling parallel to the pia mater or vertically across the laminae is often a useful method of studying features in the cerebral cortex because there is often significant variation in pathological features in these specific directions [6]. Where sampling is involved, transect starting position or location of the grid should be randomly determined.

Quantitative measurements

The next decision that needs to be made is the quantitative measure to be obtained from each field. Profile density provides a reliable measure of abundance of a histological feature in histological sections. In some circumstances, however, individual objects cannot be identified, e.g., certain types of diffusely distributed protein deposits, and estimates of

the area or load may be a more appropriate measure. Finally, the statistical method of determining spatial pattern needs to be selected. If the objective of the study is simply to test whether a population in a particular area departs from randomness, then a variety of methods based on points or lines are available. To test more complex hypotheses, however, methods that measure cluster dimension, the arrangement of clusters or the correlation between two different histological entities [7] may be required.

Application to neurodegenerative disease

A major application of spatial pattern analysis has been to the study of the spatial distribution of cellular inclusions and protein deposits in neurodegenerative disease [17]. In diseases such as AD and CJD, randomly distributed lesions are rare and, within a particular disorder, usually comprise less than 6% of tissue sections analysed. A randomly distributed pattern is most likely to be found when the density of a lesion is low and individuals are widely scattered [17]. Regularly distributed lesions are also uncommon in brain tissue and occur either when the density of objects is low and lesions are widely spaced or when the density of a lesion is high. Pathological lesions are rarely regularly distributed but neuronal cell bodies within normal control brain are often distributed evenly parallel to the pia mater. In the neurodegenerative diseases studied to date, including AD, CJD and the various forms of FTD, the most common spatial pattern observed is clustering [17]. Clusters that are randomly distributed are rare, although the degree of vacuolation ("spongiform change") in patients with sporadic CJD may show this pattern in some cortical areas [16]. In the majority of tissues examined, clustering takes two forms. First, the most common type of distribution is of clusters that are regularly distributed parallel to the tissue boundary. In some circumstances, smaller aggregations of lesions are clustered together to form larger aggregations and clustering may therefore occur at two or more scales in the tissue. Hence, such methods as the V/M method applied to grids or transects will be essential to reveal these patterns in brain tissue. Second, lesions occur in large clusters, usually greater than 6400 µm in diameter, and a single cluster may occupy a considerable portion of the sampled area. Within such large clusters, individual lesions may be randomly or uniformly distributed.

Comparison of the frequencies of the different types of spatial patterns reveals similarities both between lesions and disorders, especially in the cerebral cortex [17]. First, Aβ protein aggregates exhibit a similar range of spatial patterns in AD [13], DLB [15], and in Down's syndrome [2]. Second, PrP aggregates in CJD show essentially the same types of distribution as the Aβ deposits in AD [14,18]. Third, cellular inclusions in AD, DLB, PiD, and corticobasal degeneration (CBD) exhibit a similar range of spatial topographies [17]. Hence, despite their morphological and molecular diversity, different lesions often exhibit a common type of spatial distribution in the brain. A possible explanation is that the lesions all develop as a result of the degeneration of specific neuroanatomical pathways. In the cerebral cortex, the cells of origin of the long and short cortico-cortical projections are clustered and occur in bands that are distributed along the cortical strip. In the primate brain, for example, individual bands of cells associated with a particular projection are 500–800 µm in width and traverse the cortical laminae [28]. There is a regular distribution of bands along the cortex although there is also a complex pattern of branching and rejoining of the groups of cells. The spaces between the bands of cells are occupied by afferent or efferent connections with different cortical sites or with subcortical regions. In the disorders studied to date, the estimated width of the lesion clusters and their planar distribution along the cortex is consistent with their development in relation to these cell clusters [17]. This suggests that the most common explanation for the regularly distributed clustering observed in the cerebral cortex is that the lesions develop in association with degeneration of the cortico-cortical pathways and that this pattern of degeneration is common to many forms of neurodegenerative disease. Hence, despite differences in morphology and molecular diversity, pathological lesions often exhibit similar spatial patterns, implying a degree of overlap between the different disorders and shared pathological mechanisms [17].

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