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ANALYSIS OF DENDRITIC SPINES MORPHOLOGY: FROM CLASSICAL DIVISION TO TYPES TOWARD ALTERNATIVE APPROACHES

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This article provides a brief overview of the existing methods and approaches to analyzing the dendritic spines morphology playing an important role in the functioning of synaptic plasticity and memory formation mechanisms. Both various mathematical algorithms that classify spines according to their shape (thin, mushroom and stubby) and emerging alternative approaches have been considered. The reported scientific results point to uniform distribution of the main morphological parameters of dendritic spines; a number of authors cast some doubt on the often used division of spines into types and argue in favor of the existence of a shape continuum. Relying on this, a new approach to an analysis of dendritic spines morphology and to data presentation was advanced. It combines classification with the study of the distribution of dendritic spines by key morphological parameters.

Keywords: neuronal morphology, mushroom spine, thin spine, stubby spine, headed spine

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ПЕРЕХОД ОТ КЛАССИЧЕСКОГО ДЕЛЕНИЯ ДЕНДРИТНЫХ ШИПИКОВ НЕЙРОНОВ НА ТИПЫ К АЛЬТЕРНАТИВНЫМ МЕТОДАМ АНАЛИЗА

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В статье представлен краткий обзор существующих методов и подходов к анализу морфологии дендритных шипиков, которые играют важную роль в функционировании механизмов синаптической пластичности и формировании памяти. Рассмотрены как различные математические алгоритмы, подразделяющие шипики на классы по признаку их формы (тонкие, грибовидные и пеньковые), так и новые альтернативные подходы. Результаты опубликованных исследований указывают на нормальный характер распределения основных морфологических параметров дендритных шипиков, ряд авторов ставят под сомнение часто используемое разделение шипиков на типы и свидетельствуют в пользу существования континуума форм. На этом основании в статье предложен новый подход к анализу морфологии дендритных шипиков и представлению данных. Он объединяет классификацию с изучением распределения дендритных шипиков по ключевым морфологическим параметрам.

Ключевые слова: морфология нейрона, грибовидный шипик, тонкий шипик, пеньковый шипик, филоподия

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Introduction

A synapse is commonly understood as the zone of specialized contact between two neurons, serving to transmit information from cell to cell. An intrinsic property of neurons is that they can form synaptic connections, transmitting signals through them by means of electrical impulses that trigger the release of neurotransmitters. Most synapses form between the axonal bouton and the dendritic spine, which is a specialized protrusion from the dendritic membrane.

Dendritic spines come in a variety of shapes and sizes, differing greatly across different brain areas, cell types, and animal species [1]. The dendritic spine is an active element of synaptic transmission, capable of functional and morphological rearrangements in response to changes in the incoming signal. Synapses can modulate the efficiency of information transfer; for this reason, they are believed to serve as sites for memory formation and storage, initiating memory consolidation through mechanisms of potentiation and depression of synaptic activity [2–5]. Detailed analysis of synaptic morphology, reflecting the functional state of neurons, is an important task for neurobiology.

Dendritic spines are traditionally grouped into four large classes according to their morphological features: mushroom, thin, stubby and filopodia (Fig. 1).

Mushroom spines have a large head and a small neck, are relatively stable, form strong synaptic connections and supposedly act as memory storage sites [3, 6].

Thin spines have a small head and a long narrow neck, are more dynamic and are believed to be "learning spines", responsible for forming new memories [3].

Stubby spines typically do not have a neck. They are known to be the predominant type in early stages of postnatal development but are also still found in small amounts in adulthood, where they are likely formed due to disappearance of mushroom spines [7].

Filopodia are long, thin spines without a clear head, commonly observed in developing neurons. These spines may also be found in mature neurons, but under specific conditions, for example, induction of plasticity after

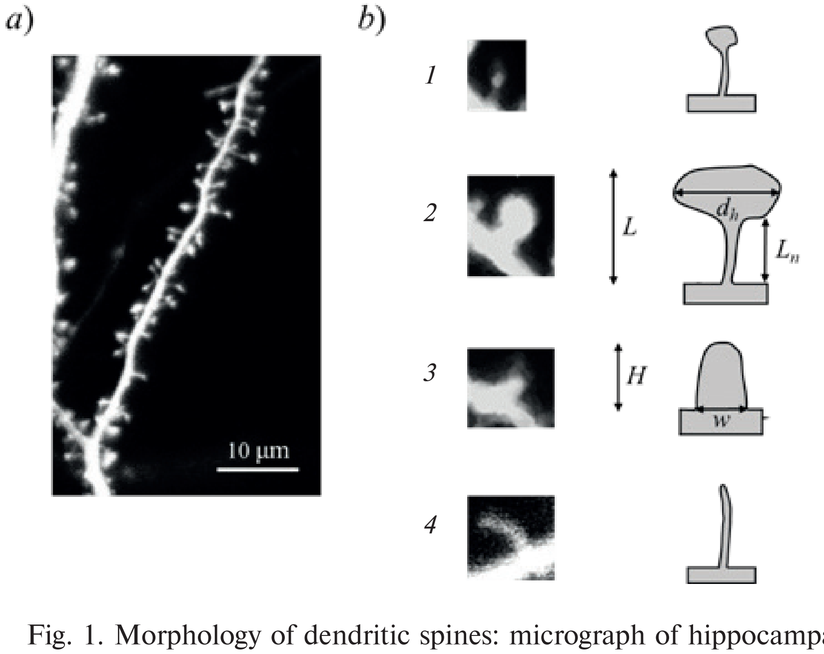

Fig. 1. Morphology of dendritic spines: micrograph of hippocampal neuron *in vitro* (confocal microscopy, ×60) (*a*); schematic representations of main types of dendritic spines with key morphological parameters (*b*).
Types of spines: thin (*1*), mushroom (*2*), stubby (*3*), filopodia (*4*); L, L_n are the lengths of the spine and its neck, respectively; d_h is the head width; H and w are the height and width of the base of the stubby spine

different types of brain injury [8]. Compared to other types of dendritic spines, filopodia are very mobile and flexible structures with a short lifetime. Electron micrographs show that filopodia mostly lack postsynaptic density and the apposing axon terminal contains only a few synaptic vesicles. Because of this, it was proposed to exclude filopodia from spine counts used to estimate synaptic density [9].

The morphology of the dendritic spine corresponds to its functional role and developmental stage at a given time, and the changes in its shape and size reflect changes in the activity of the given synaptic connection or in the environment surrounding the neuron and physiological processes in the neuron.

Various psychiatric and neurodegenerative diseases, such as Alzheimer's disease (AD) [10, 11], Parkinson's disease [12], Huntington's disease [13], schizophrenia [14], autism [15], depression [16], etc., are characterized by changes in the density and shape of dendritic spines of neurons in brain areas affected by these diseases. For example, it is believed that Huntington's chorea stems from dysfunction of the corticostriatal pathway [17]. Progressive memory loss in Alzheimer's disease is associated with a decrease in the number of mushroom spines in brain areas involved in memory formation, such as the hippocampus and the cortex [18].

Notably, synaptic degeneration is the initial stage of irreversible changes in the affected neuron, followed by atrophy of neurites and subsequent cell death. A recent study found that the number of mushroom and thin spines in pyramidal neurons of the prefrontal cortex was significantly lower in patients with Alzheimer-type dementia than in cognitively normal controls with AD pathology [19]. It was suggested that such spine morphology helps prevent the onset of dementia, despite the presence of characteristic AD pathology in the brain. These data are another argument supporting the position that using pharmacological agents to restore or stabilize dendritic spines in AD patients can prevent memory loss [18, 20–22].

Analysis of the number and shape of dendritic spines can provide insights into molecular mechanisms and signaling pathways involved in formation and functioning of synapses, the functional state of neurons, and mechanisms of neurodegenerative diseases, serving as a tool for assessing the effectiveness of pharmacological agents for treating these diseases [23–27]. Developing methods that can make this analysis accurate and quick is of key importance.

This paper provides a brief overview of the existing methods and approaches to studies of morphology of dendritic spines and suggest a new approach to classification of spines and presentation of the data obtained.

Review of existing methods for analysis of synaptic morphology

Analysis of morphology of dendritic spines is important for neurobiological studies, as it can shed light on the relationship between the structure of synaptic contacts and their function. There is currently no reliable automated software yielding accurate results, which means that experimenters have to resort to manual analysis of neuron images. This method is extremely time-consuming, and also completely depends on the opinion of the expert performing the analysis, which means that it lacks objectivity. In view of this, attempts were made to develop semi-automated and automated algorithms for analysis and subsequent classification of dendritic spines on images obtained by both confocal and multiphoton laser scanning microscopy [28–34].

One of the first attempts at automated classification of spines with software methods was undertaken in 2002, when advances in technologies for laser scanning microscopy made it possible to obtain high-resolution images of neurons on a spatial scale sufficient to visualize such small cell structures as dendritic spines [28]. The proposed approach to classification of spines [28] was based on the results discussed in [35], performing manual analysis of synaptic morphology on a series of slices of spine images obtained by electron microscopy. The authors found that neck diameter d_n, head width d_h and spine length L (see Fig. 1) were the most important morphological characteristics for classifying the spine into a specific category. The classification was based on the assumption that the length of thin spines is much greater than the diameter of their neck ($L >> d_n$), while head width cannot be substantially greater than neck diameter. Head width should be considerably larger than neck diameter ($d_h >> d_n$) for mushroom spines, and neck diameter is comparable to spine length ($d_n \approx L$) for stubby spines. Ratios L/d_n and L/d_h were used as criteria in the algorithm developed by the authors for assigning spines to one of four classes [28].

Later, another research group developed the NeuronStudio software, classifying spines using a decision tree based on parameters such as the aspect ratio, head-to-neck ratio, and head diameter [29]. This software module subsequently became part of Neurolucida 360, a commercial package for analyzing the morphology of neuron cells [30]. Another classification based on a decision tree used such spine parameters as neck diameter, head diameter, shape criterion, area, spine length and perimeter [31]. The 2dSpAn software [32] also uses a set of rules incorporated in the decision tree for classification; the key parameters are neck length, the ratio of the locally deepest point to spine length and the ratio of base-to-head distance L_n/L to spine length. Notably, the authors excluded thin spines from consideration, regarding them as an intermediate type, but included spine-head protrusions as a separate type, combining them with filopodia in subsequent analysis. The software was later improved with a new algorithm for spine segmentation and extraction of morphometric data, but the principle of classification remained unchanged [33].

An algorithm for analyzing spines proposed in 2014 was based on semi-supervised learning (SSL) [34]. In this approach, spines are first segmented in three-dimensional space using wavelet functions, with the object's boundary defined as the position where the response of the wavelet on the spine section changes quickly. Spine parameters such as length, volume, neck and head diameters, etc., constituting the matrix of parameters, are calculated after segmentation. To form a training set, a neurobiology expert decides which class a small portion of the total number of detected spines belongs to, and the system sorts each of the remaining spines into the given classes at the final stage following training. One of the benefits of this approach is that it requires minimal operator intervention (only at the training stage), so, accordingly, the errors resulting from the experimenter's personal assessment of spine types that we have mentioned earlier are eliminated. However, a drawback of this approach is that the method's accuracy and performance strongly depend on the size of the training set and on the parameters included in the training vector.

Another new approach to classical methods of morphological analysis described above is classification of dendritic spines by appearance and shape [1]. Spine shape was represented in parametric form as a result of segmentation of the dendrite image using the recently proposed disjunctive normal shape model (DNSM). A histogram of oriented gradients (HOG) was used to extract the appearance parameters. The authors suggested kernel density estimation for classification based on the selected parameters, calculating three non-parametric density estimates for three spine classes based on the training set assigned by the expert. The accuracy of classification using a similar combination of methods significantly exceeded that of the above-mentioned classical approaches [28, 29, 32]. The highest accuracy, which was 87%, was obtained by combining DNSM segmentation and HOG with a classification using a neural network.

To validate the accuracy of their approach, the authors compared spine types detected by the program with the labels manually assigned to the spines by one or several experts [1, 29, 31, 32]. Notably, there was significant variation in classifications of spines made by different experts. In some cases, the expert had difficulties in assigning the type of spine; moreover, the same expert could assess the given sample differently on different days (the percentage of coincidences is 82.9%) [29]. This is to say that it is difficult to estimate the accuracy of classification algorithms due to lack of objective reference.

Continuum of spine shapes

The common approach to analysis of morphology of dendritic spines is dividing spines into the subgroups described above: stubby, thin, mushroom, and filopodia. Even though this classification is used in many studies, the question remains open whether there are actually different classes of spines or whether they should be modeled using a continuum of shape variations. It is also important to note that the existing classification of spine shapes does not provide a clear standardized definition for each group. Experimenters are free to select their own criteria, which introduces significant uncertainty to interpreting the data obtained by different research groups.

The study carried out by Yuste et al. [36]), analyzing the morphology of neurons in layers II and III of mouse visual cortex, found that a continuous distribution rather than several discrete peaks (which would have been an argument in favor of separate classes of spines) was observed for each of the morphological parameters of the spines. Another study analyzing the morphology of neurons in cortical layer III [37] also found a continuous and smooth distribution of spine length and head diameter in the sample.

The authors of [38], where clustering of parameters which could be indicative of distinct spine types was not detected (similar to the above-mentioned works), suggested that classical categories of spines are just typical examples from a continuum of shapes. A recent review [9] also concluded based on data on the dynamics of dendritic spines that the shapes of synaptic contacts are a continuum; the stability of the spine and the strength of the synaptic connection it forms increase with increasing spine size. A multi-method study of the link between spine shape and compartmentalization of synapses [39] also observed a great diversity in spine morphology, which is further evidence against standard classification systems.

A radically new approach to analysis of spine shapes was proposed in 2016 based on these data. The authors applied a clustering method to study subpopulations of spines. Spines were not divided into predefined types; instead, spine groups (clusters) with similar features were detected by mathematical methods, and the distribution of their morphological parameters was analyzed.

To get a full picture, the authors of [40] used the data given in literature to compose a set of eleven most frequently used morphological parameters, which were reduced, using the method of principal components, to two parameters that were a linear combination of the initial ones. The first parameter included the components describing spine size and, accordingly, it was interpreted as a generalized size descriptor. Similarly, the second parameter was interpreted as the contour descriptor. After all spines from the sample were distributed into a two-dimensional orthogonal space formed by descriptors, hierarchical clustering was performed. Ten clusters were obtained, including both small peripheral clusters and clusters with insufficient separation. The authors selected three images of spines from each cluster, most closely reflecting the empirical morphological features of this group, to illustrate the results. Predictably, the clusters corresponding to the classical thin and mushroom types turned out to be the most dense and poorly separated, and stubby spines were represented by a single cluster with only a few spines. Importantly, the number and composition of the clusters obtained strongly depend on the chosen clustering algorithm and the properties of the initial data. The authors also proposed a model for analyzing the transitions between clusters under chemically stimulated long-term potentiation. Thus, it was proved mathematically that there are might be much more groups of spines similar in morphological structure than the four classical types. While the approach proposed in [40] can be extremely useful for fundamental study of synapses, it is ill-suited for wide practical use, where analysis of synaptic morphology is part of general analysis of the functional state of neurons, since presenting and interpreting data can be difficult. In view of the above, we can conclude that developing alternative automated methods for classification is an urgent task.

New approach to collection and presentation of numerical data on morphology of dendritic spines

Since an increasing number of studies indicate that there is a continuum of spine shapes, it is important to develop a new simple method of analysis for practical purposes that could be used to present the experimental data most fully, reliably and clearly.

Most errors in classification of spines happen in separating thin and mushroom spines, as these two types have the same shape and the only critical parameter by which they can be differentiated is the size of the head. Studies indicate that head size is directly proportional to the area of postsynaptic density and is correlated with the number of postsynaptic receptors and synaptic strength [36, 41–43], while neck length and width of the spines are directly related to the magnitude of postsynaptic potential [39]. The morphology of synapses varies depending on the strength of synaptic contact. Changes in synaptic strength during long-term potentiation and long-term depression are associated, respectively, with enlargement or shrinkage of the spine head [44, 45]. Thus, the shape of the dendritic spine determines the strength of synaptic connections; changes in spine shape are believed to be involved in coding information and storing memory in the brain.

As discussed above, the head size distribution has a continuous shape [9, 36–39], which casts doubt on whether such classes as thin and mushroom spines actually exist. For this reason, we propose to categorize all spines with a pronounced head in a separate group called “headed spines”. According to our observations, confirmed by another research group [32], one of the potential critical parameters for this type of spines is the ratio L_n/L of neck length to total spine length. This parameter is of interest because the proportion of the neck from total spine length is more often smaller in spines with large heads than in spines with smaller heads.

Stubby spines have a pronounced shape, completely lacking a neck, and thus stand out clearly among diverse synaptic morphologies. This is confirmed by results of cluster analysis carried out earlier in [40], where stubby spines could be clearly detected as a separate group. It is difficult to determine the head width of the stubby spine because of this shape, since its widest part coincides with the base in most cases. We assume that spine length L and base width b_w can serve as critical parameters for stubby spines, and we plan to test this hypothesis in future studies. Electron microscopy of synapses revealed another structure, the filopodia, which are thin hair-like protrusions of the dendritic membrane [9]. As filopodia are characterized by very rapid changes in shape and do not form active synaptic contacts, there are probably no critical parameters for their morphology. In view of this, methods of intravital microscopy should be used for focused analysis of morphology of this type of dendritic spines, allowing to analyze their behavior in dynamics. Notably, the total content of stubby spines and filopodia in mature neurons does not exceed 10%, according to estimates [9], and, therefore, synaptic contacts of this type are few in number.

A histogram is obtained by dividing spines into classical groups, showing either the percentage of spines of a certain type or their density. Standard methods like the *t*- test or ANOVA are used to identify statistically significant differences between the control and experimental groups. A reasonable question, then, would be how to visualize the data, since they are characterized by a continuous distribution.

We propose to combine a pie chart (Fig. 2), where the size of the sector corresponds to the percentage of the group it contains, with a plotted distribution by parameters, which makes it possible to represent the most important parameter that is the change in the size of spine heads as a continuum. It is proposed for spines with pronounced heads to plot the head width d_h normalized to the average value along the inner circumference, and the point corresponding to the ratio L_n/L (neck length to total spine length) in the range from 0 to 1 along the radius. If there are enough spines without necks (stubby type), their distribution can be also represented as follows: spine height H is plotted along the inner circumference, and the point corresponding to the ratio H/w (spine height to base width) along the radius. Another sector should correspond to filopodia (if there are any). We also propose to introduce a sector reflecting the percentage of spines with

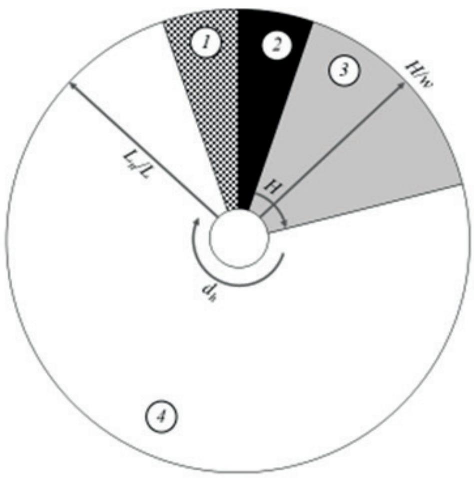

Fig. 2. Proposed model for presentation of experimental data, showing percentage of different types of dendritic spines and their distribution by key morphological parameters (see the explanations in the text)

Types of spines: filopodia (*1*), stubby (*2*), headed (*3*), with anomalous shape (*4*) anomalous shapes that cannot be classified as any of the types by algorithm.

We offer the software tool we have developed for detecting and recording the metric of dendritic spines. At the first stage of its operation, the image is processed using the Otsu filter to eliminate noise and noisy areas. At the second stage, a neuron stem model is constructed using binarization and subsequent skeletonization of the image, while spine detection is performed by subtracting the resulting stem model from the filtered image with the necessary correction determined algorithmically. The obtained data on the morphology of dendritic spines is used to perform classification with help of a previously trained neural network. We plan to use the opinion formulated in consultation with a group of neuroscientists to generate a training set and monitor the performance and accuracy of the algorithm. Such critical morphological parameters as head size, neck length and neck height are carried out after classification using mathematical algorithms specially adapted to a certain type of spines, which should reduce potential errors. Subsequent manual analysis of the shape of anomalous spines recorded in experiments with the control and experimental groups might reveal new processes and changes in the morphology of synapses that could not be detected in studies using rigid classification methods. The diagram in Fig. 2 illustrates our model for representing the experimental data; its efficiency and practical value are to be assessed in forthcoming studies.

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