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EDITORIAL COMMENTARY

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Morphological Bases of Neuronal Hyperexcitability in Neurodegeneration

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Alzheimer's disease (AD) is characterized by neuronal degeneration at cellular level and dementia at cognition level. The cellular mechanism of neural circuit transmission dysfunction, however, is not fully understood. A The recent study combined *in vivo* electrophysiology recording, ultrastructural imaging, and computational simulation paradigms to explain the morphological bases responsible for the dysregulated firing pattern of hippocampal neuron in AD (Figure 1).

Dendritic geometry determines the neuronal integration of synaptic inputs and functional outputs [1,2]. The morphological plasticity of dendrites during neuronal development or pathological condition therefore alters the functional consequences of information processing by the neuron.

Since 1990s, the reduced dendrite length and complexity have been reported in the brain samples of AD patients and animal models [3,4]. How these changes alter the synaptic integration and neuronal excitability remains unsolved. More specifically, are morphological changes of the dendrites sufficient to reshape the neuronal firing patterns, even in the absence of protein expression changes? Combining *in vivo* whole-cell patch-clamp recording, ultrastructural imaging, and computational simulation, Siskova et al. identified morphological pathology as the important mechanism underlying spiking alterations of neurons in the brain of a mouse AD model [5].

Siskova et al. identified neuronal hyperexcitability in the hippocampal region of CA1 in aged APP/PS1 mice, a well-established animal model of AD. CA1 pyramidal neurons in the AD mice exhibited increased probability of burst firing, and elevated firing frequency during *in vivo* recording [5]. Consistently, local field potential (LFP) recording revealed increased bursting activities at the network level. These changes were explained by intrinsic hyperexcitability, reflected by increased numbers of spikes in response to current injection. The authors further examined the morphological changes of CA1 pyramidal neurons in AD mice using confocal and stimulated emission depletion (STED) microscopy, and they have discovered a series of significant alterations, such as reduced dendritic length and branching points, as well as reduced numbers of spines on apical tuft of the dendrite.

To explore the potential link between morphological alterations and intrinsic excitability changes, Siskova et al. modeled CA1 neurons by manipulating the morphological variables of the dendrites. They found that the total membrane capacitance might decrease by 30% in neurons when simulated with the parameters of the AD animals, and the input resistance increased in the neurons of AD neuron-like morphologies. These changes in the electrophysiological constants make more efficient synaptic integration to the neurons and thus lead to the decreased rheobase and increased firing frequency in response to simulated current injection. These results confirmed that morphological modifications are sufficient for neuronal hyperexcitability. In a complementary experiment, Siskova et al. simulated excitatory synaptic inputs by injecting excitatory postsynaptic potentials (EPSPs) to these modeled neurons, and they reported higher voltage responses in neurons with AD mice parameters, which were in consistence with their *in vivo* recording findings on spontaneous EPSPs. In addition, when the synaptic input was simulated at theta frequency, the common input pattern to CA1 neuron in behaving animals, the neurons with AD mice parameters exhibited increased bursting firing pattern [5]. All these results support the conclusion that morphological changes are sufficient to induce alterations on the information processing ability of neurons.

It has been reported that dendritic length and complexity could alter the intrinsic excitability and integration of synaptic inputs, based on a simplified model of pyramidal neuron with merely eight segments in the model [6]. Siskova et al. was the first to investigate the effect of "AD mice" parameters on neuronal functions with the full modeling of all dendrites obtained from morphological analyses. Their results speak to the debate about the

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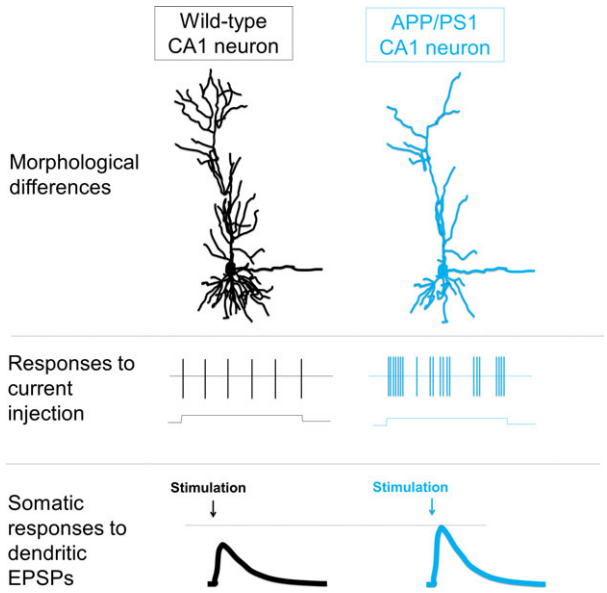

Figure 1 Morphological bases of neuronal dysfunction in the mice model of Alzheimer's disease (AD). Upper: morphologies of two CA1 pyramidal neurons from wild-type mice (Black) and APP/PS1 mouse model of AD (Blue), respectively. Middle: the differential responses of the neurons to current injection. The CA1 neuron from AD mice exhibited increased firing frequency and bursting firing probability. Lower: the differential responses of the neurons to dendritic EPSP integration. The CA1 neuron from AD mice exhibited increased EPSPs at soma.

origins of neuronal dysfunctions during AD. In particular, are the higher firing rates in AD due to morphological changes, or decreased potassium channel function/increased excitatory transmission? The fact that morphological changes were sufficient to induce the cellular hyperexcitability suggested that the dendrite geometry should be considered as the important pathological mechanisms underlying neurodgeneration, rather than merely the outcome. However, experimenters could also be conducted to measure the receptor and channel functions on the neuronal dendrites from AD animals, to provide a full picture of dendrite computational changes in AD.

The next step will be to model the alterations of whole brain network activities in AD progression, such as with large population of simulated neurons in one network (e.g. >1,000,000). In addition, modeling the interneuron in the diseased brain would further improve the fidelity of the computer model when simulating a degenerating brain.

Understanding the morphological bases of neuronal hyperexcitability in AD raises a new set of questions to study. As the aberrant hyperactivity is prevalent in different types of neurodegeneration, even without unambiguous neural inputs [7,8], the neurons undergo remodeling during neurodegeneration [9]. Whether the hyperactivity is the cause or consequence of morphological remodeling in other neurodegenerative disease is still elusive. Moreover, the hyperactivity increases the neural noises and thus masks the natural signals [10]. Whether the cognitive and behavioral dysfunctions are due to the impaired signal transmission is also to be understood, in which case pharmacological inhibition of hyperactivity may help ameliorate the symptom.

The study by Siskova et al. provides more knowledge to understand the functional diversity based on morphological classification. For instance, retina contains more than 60 neuronal types; roughly, 20 types are with known functions, while the rest of the types are defined by location and morphology [11]. Previous efforts to functionally separate these cells included genetic labeling with fluorescence proteins, electron microscopy reconstruction, and high throughput electrophysiological recording (e.g., with microchip). Employing computerized simulation would therefore provide a fast and convenient approach in dissecting the potentially functional differences of different retinal neurons. Eventually, the success of the retina analysis will be insight to dissect the functional circuitry of the brain.

Last but not the least, this study also sheds some insights into studies investigating dendrite development. The molecular mechanisms underlying dendrite growth and spine formation have been extensively studied in past decades [12], with accumulating data on accompanying electrophysiological characteristic of developing neurons (including adult new neurons) [13]. It will be interesting to simulate neuronal morphological development to correlate the potential changes of electrical functions. Such investigations are important to understand functional changes of neurons during developmental neuropathies, such as epilepsy. Stabilizing cytoskeleton as well as dendrite therefore could be one therapeutic strategy against some neurological disorders.

Simulating the physiological functions of neurons using morphological characteristics therefore represents a new connection from neuroanatomical studies to functional evaluations. The dendritic morphology has a critical function in determining the potential firing pattern of the neuron, while the neuronal activities are able to refine the dendritic development as well. Electrophysiology, in combination with anatomical studies and computational neuroscience, would provide better elucidation of cognitive dysfunction in brain diseases.

Conflicts of interest

The authors declare no conflict of interest.

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References

1. Hausser M, Spruston N, Stuart GJ. Diversity and dynamics of dendritic signaling. *Science* 2000;**290**:739–744.
2. Spruston N. Pyramidal neurons: Dendritic structure and synaptic integration. *Nat Rev Neurosci* 2008;**9**:206–221.
3. Ferrer I. Neurons and their dendrites in frontotemporal dementia. *Dement Geriatr Cogn Disord* 1999;**10**(Suppl 1):55–60.
4. Spires TL, Hyman BT. Neuronal structure is altered by amyloid plaques. *Rev Neurosci* 2004;**15**:267–278.
5. Siskova Z, Justus D, Kaneko H, et al. Dendritic structural degeneration is functionally linked to cellular hyperexcitability in a mouse model

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of Alzheimer's disease. *Neuron* 2014;**84**: 1023–1033.
6. van Elburg RA, van Ooyen A. Impact of dendritic size and dendritic topology on burst firing in pyramidal cells. *PLoS Comput Biol* 2010;**6**: e1000781.
7. Margolis DJ, Newkirk G, Euler T, Detwiler PB. Functional stability of retinal ganglion cells after degeneration-induced changes in synaptic input. *J Neurosci* 2008;**28**:6526–6536.
8. Borowska J, Trenholm S, Awatramani GB. An intrinsic neural oscillator in the degenerating mouse retina. *J Neurosci* 2011;**31**:5000–5012.
9. Strettoi E, Pignatelli V. Modifications of retinal neurons in a mouse model of retinitis pigmentosa. *Proc Natl Acad Sci U S A* 2000;**97**:11020–11025.
10. Toychiev AH, Ivanova E, Yee CW, Sagdullaev BT. Block of gap junctions eliminates aberrant activity and restores light responses during retinal degeneration. *J Neurosci* 2013;**33**:13972–13977.
11. Masland RH. The neuronal organization of the retina. *Neuron* 2012;**76**:266–280.
12. Santiago C, Bashaw GJ. Transcription factors and effectors that regulate neuronal morphology. *Development* 2014;**141**:4667–4680.
13. Elston GN, Fujita I. Pyramidal cell development: Postnatal spinogenesis, dendritic growth, axon growth, and electrophysiology. *Front Neuroanat* 2014;**8**:78.

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