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Age-related plasticity of the axon initial segment of cortical pyramidal cells in marmoset monkeys

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ABSTRACT

Structural plasticity of the axon initial segment (AIS), the site of action potential initiation, is observed as part of the normal early development of the cortex, as well as in association with injury and disease. Here, we show that structural AIS plasticity also occurs with normal aging in adult marmosets. Immunohistochemical techniques were used to reveal the extent of the AIS of layer 2/3A pyramidal cells in 8 neocortical areas. We found that the AIS length varied significantly between areas in young adult (2–3 years old) marmosets, with neurons in frontal area 14C having the longest AIS, and those in the primary visual cortex the shortest. Similar interareal differences were observed in aged (12–14 year old) monkeys, but the AIS was significantly shortened in many areas, relative to the corresponding length in young adults. Shortening of the AIS is likely to represent a compensatory response to changes in the excitation-inhibition balance, associated with the loss of GABAergic interneurons in the aged cortex.
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1. Introduction

The axon initial segment (AIS), which is characterized by a high density of voltage-gated Na^+ ion channels, is the site of action potential initiation in most neurons (Kole and Stuart, 2008). Previous studies have shown that AIS structural plasticity plays a major role in modification of neuronal excitability (Evans et al., 2015; Grubb and Burrone, 2010; Kuba et al., 2010) and have suggested that this plasticity represents a homeostatic response to alterations in the balance of excitatory and inhibitory synaptic inputs (Buffington and Rasband, 2011; Wefelmeyer et al., 2016). AIS structural plasticity is associated with different stages of development (Cruz et al., 2009; Fish et al., 2013; Gutzmann et al., 2014; Kuba et al., 2014), as well as pathophysiological conditions involving an excitation-inhibition imbalance, such as epilepsy and schizophrenia (Harty et al., 2013; Nozari et al., 2017; Yoshimura and Rasband, 2014).

Aging has been shown to affect brain plasticity at both the structural and behavioral levels (Burke and Barnes, 2006). For example, aging is linked to the loss of dendritic spines and synapses, leading to a reduction in the excitatory connectivity between neurons (Luebke et al., 2010; Peters et al., 2008) as well as changes in the structure of myelin sheaths, and alterations in neurotransmitters and receptors (Burke and Barnes, 2006; Luebke et al., 2010; Peters et al., 2008). Importantly, aging-associated decline in cognitive function is linked with region-specific reductions in the function of inhibitory neuron systems (Thomê et al., 2016). Even in the absence of specific neural pathologies, aging affects the density of GABAergic cortical neurons in a differential manner (Bu et al., 2003; Hua et al., 2008; Lehmann et al., 2012), leading to concomitant changes in excitation-inhibition balance and information-processing capacity (e.g., Hua et al., 2008; Schmolesky et al., 2000; Thomé et al., 2016; Yu et al., 2006). In light of the above, we hypothesized that systematic changes in AIS length, such as those observed during early maturation of cortical areas (Cruz et al., 2009; Fish et al., 2013; Gutzmann et al., 2014; Kuba et al., 2014), are likely to continue throughout life, and could become evident even in comparisons between sexually mature young adults or aged individuals of the same species.

However, a possible confound in this type of comparison is the fact that cortical areas undergo developmental changes at different rates, with primary sensory processing areas maturing earlier than high-order association areas, such as the prefrontal cortex (Amlien et al., 2016; Bourne and Rosa, 2006; Bourne et al., 2005; Conde et al., 1996; Elston and Fujita, 2014; Gogtay et al., 2004; Hill et al., 2010; Shaw et al., 2008). Given that the AIS of pyramidal neurons tends to shorten with postnatal age (Cruz et al., 2009), we also hypothesized that the average AIS would be longer in frontal association areas than in visual areas of individuals of the same age. There is

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Table 1
Details of sex, age, and areas analyzed in each subject

Subject	Sex	Age at perfusion (mo)	Area (number of sections) used
CJ162	F	28	Area 10 (n = 3), Area 14C (n = 2), Area 24a (n = 3), Area 25 (n = 3), Area 32 (n = 2)
CJ167	F	27	Area 10 (n = 3), Area 14C (n = 3), Area 24a (n = 3), Area 25 (n = 3), Area 32 (n = 3)
CJ170	M	27	V1 (n = 3), V2 (n = 3), V3 (n = 3)
CJ173	M	24	Area 10 (n = 3)
CJ178	F	27	Area 14C (n = 2), Area 32 (n = 2), V1 (n = 4), V2 (n = 3), V3 (n = 3)
CJ179	F	25	V1 (n = 4), V2 (n = 3), V3 (n = 3)
F1512	F	43	Area 10 (n = 3), Area 14C (n = 3), Area 24a (n = 3), Area 25 (n = 3), Area 32 (n = 3), V1 (n = 3), V2 (n = 3), V3 (n = 3)
WG1	F	164	Area 10 (n = 3), Area 14C (n = 3), Area 24a (n = 3), Area 25 (n = 3), Area 32 (n = 2)
WG2	F	162	V1 (n = 2), V2 (n = 3), V3 (n = 3)
WG3	F	144	Area 10 (n = 3), Area 14C (n = 2), Area 24a (n = 2), Area 25 (n = 3), Area 32 (n = 3), V1 (n = 3), V2 (n = 3), V3 (n = 4)
WG5	F	176	Area 10 (n = 3), Area 14C (n = 3), Area 24a (n = 3), Area 25 (n = 3), Area 32 (n = 3), V1 (n = 3), V2 (n = 3)

recent evidence that this is the case in the mouse cerebral cortex (Nozari et al., 2017), but the extent of such differences in the more complex primate brain is unknown.

In this study, we used immunohistochemical staining for ankyrin G (a protein needed for the clustering of voltage-gated Na^+ channels in AISs; Zhou et al., 1998) to reveal the morphology of the AIS in various prefrontal and visual areas of healthy young adult and aged marmosets. Marmosets are New World monkeys for which a wealth of anatomical and physiological information is available regarding cortical areas (e.g., Bakola et al., 2015; de la Mothe et al., 2006; Krubitzer and Kaas, 1990; Paxinos et al., 2012; Solomon and Rosa, 2014). Relative to the more commonly used macaque monkey, marmosets present distinctive advantages for aging studies, including a shorter lifespan, and a simpler brain morphology (which facilitates quantitative comparisons, as most cortical areas are located on the surface of the brain). The present study was designed to address 2 questions in parallel: do different areas show distinctive AIS lengths in the brain of monkeys of comparable ages, and is healthy aging linked to systematic changes in AIS length?

2. Materials and methods

2.1. Subjects

The materials used in this study were obtained from 11 marmosets (*Callithrix jacchus*), which included 7 young adult (24–43 month old) and 4 aged monkeys (144–176 month old; Table 1). The experiments were conducted in accordance with the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes, and all procedures were approved by the Monash University Animal Ethics Experimentation Committee, which also monitored the health and wellbeing of the animals

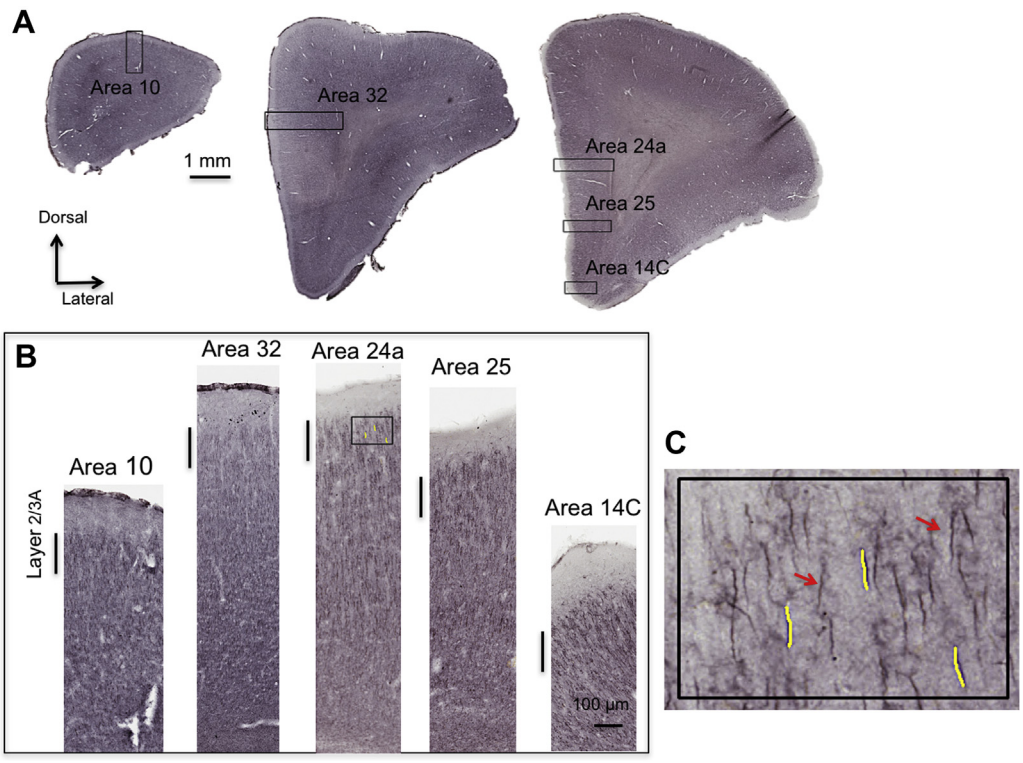

Fig. 1. Sampling of marmoset prefrontal cortex for AIS length analysis. (A) Examples of coronal sections from marmoset brain showing ankyrin G immunoreactivity in prefrontal areas 10 (corresponding to interaural level +18.50–19.00 mm), 32 (corresponding to interaural level +16.00–16.50 mm), 14C, 24a, and 25 (corresponding to interaural level +14.30–14.50 mm; Paxinos et al., 2012). Black arrows show section orientation. Scale 1 mm. (B) Areas within rectangles in A are shown at higher magnification. Scale 100 µm. (C) Individual AISs of layer 2/3A (from area 24a in B) are shown inside a rectangular frame (100 µm × 150 µm) used for length analysis. Red arrows point to AISs and yellow lines are drawings superimposed on AISs to show how AIS length was traced and measured. Abbreviation: AIS, axon initial segment. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

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