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Original Article

Complex and dynamic expression of cadherins in the embryonic marmoset cerebral cortex

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Cadherin is a cell adhesion molecule widely expressed in the nervous system. Previously, we analyzed the expression of nine classic cadherins (*Cdh4*, *Cdh6*, *Cdh7*, *Cdh8*, *Cdh9*, *Cdh10*, *Cdh11*, *Cdh12*, and *Cdh20*) and T-cadherin (*Cdh13*) in the developing postnatal common marmoset (*Callithrix jacchus*) brain, and found differential expressions between mice and marmosets. In this study, to explore primate-specific cadherin expression at the embryonic stage, we extensively analyzed the expression of these cadherins in the developing embryonic marmoset brain. Each cadherin showed differential spatial and temporal expression and exhibited temporally complicated expression. Furthermore, the expression of some cadherins differed from that in rodent brains, even at the embryonic stage. These results suggest the possibility that the differential expressions of diverse cadherins are involved in primate specific cortical development, from the prenatal to postnatal period.

Key words: cadherin, embryo, gene expression, marmoset, neocortex.

Introduction

The neocortex (NCX) consists of many functional areas, and is indispensable for multiple complex cognitive functions. It has been recently shown that various genes are involved in cortical area formation (Rakic 2009; Krubitzer & Seelke 2012; Sun & Hevner 2014). Mounting evidence has been presented for molecular mechanisms of rodent NCX development. However, it has been recently demonstrated that the primate NCX has various distinct features compared with the rodent NCX (Lui *et al.* 2011; LaMonica *et al.* 2012; Zeng *et al.* 2012; Miller *et al.* 2014; Dehay *et al.* 2015). In addition, how each cortical area is established in the primate NCX and how cortical areas differ among mammalian species remains to be determined.

Cadherins are transmembrane glycoproteins originally isolated as cell adhesion molecules (Takeichi 2007; Hirano & Takeichi 2012). Currently, more than 100 proteins belong to the cadherin superfamily. Cadherins are widely expressed in the nervous system, and play multiple roles in neural development and function through homo- or heterotypic interactions (Hirano & Takeichi 2012; Redies *et al.* 2012). Among the family members, type II cadherins show area-specific expression in relation to neural circuits (Suzuki *et al.* 1997; Suzuki & Takeichi 2008). Gain and loss-of-function analyses have revealed that type II cadherins are involved in neural patterning, cell migration, axon guidance, synapse formation, and synapse function (Nakagawa & Takeichi 1998; Manabe *et al.* 2000; Inoue *et al.* 2001; Price *et al.* 2002; Treubert-Zimmermann *et al.* 2002; Suzuki *et al.* 2007; Barnes *et al.* 2010; Matsunaga *et al.* 2011a,b; Osterhout *et al.* 2011; Williams *et al.* 2011; Kuwako *et al.* 2014). Type II cadherin expression is spatially and temporally regulated during development and is species-specific (Hatta & Takeichi 1986; Nakagawa & Takeichi 1998; Price *et al.* 2002; Ju *et al.* 2004; Matsunaga & Okanoya 2008, 2011, 2014; Neudert *et al.* 2008; Takahashi & Osumi 2008; Etzrodt *et al.* 2009; Krishna-K *et al.* 2009; Barnes *et al.* 2010; Mashiko *et al.* 2012; Matsunaga *et al.* 2013). Thus, the expression of diverse cadherins

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might have been involved in brain evolution and diversity.

The common marmoset (*Callithrix jacchus*) is a small new world monkey found in the forests of Brazil. The marmoset uses various vocal communications and is able to learn complex cognitive tasks (Pistorio *et al.* 2006; Yamazaki *et al.* 2011). Because marmosets are easy to breed in the laboratory facility, it is easier to obtain embryos and juveniles at various developmental stages compared with other primates. Furthermore, genetic manipulation technologies in marmosets have been developed (Sasaki *et al.* 2009; Kishi *et al.* 2014). Thus, the marmoset is an emerging animal model for studying primate-specific neural development and cognitive disorders.

Previously, we used the common marmoset as a model of primate NCX development, and performed *in situ* hybridization to analyze the expression of cadherins in the postnatal NCX and perinatal visual NCX (Matsunaga *et al.* 2013, 2014). We found that the expression of various cadherins differed between rodents and primates and was dynamically regulated, and in some cases, was related to the formation of primate-specific visual circuits (Matsunaga *et al.* 2013, 2014). Here, to explore whether primate specific expression of cadherins is seen even in the embryonic stage, we performed a more extensive spatial and temporal analysis of cadherin expressions in the developing embryonic NCX.

Material and methods

Ethics

Research protocols were approved by the Animal Care and Use Committee of RIKEN and conform to the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Animals and sample preparation

Parental marmosets were purchased from the Research Resource Center (RRC) of RIKEN, and kept on a 12–12 h light–dark cycle, at 27°C with 50% humidity; they had *ad libitum* access to water and a standard marmoset diet (CMS-1; Clea, Tokyo, Japan) with supplements. The dam was anesthetized by ketamine (15 mg/kg), followed by isoflurane, and embryonic marmosets were collected by cesarean section. After fixation in phosphate buffered saline (PBS, pH 7.4) with 4% paraformaldehyde, embryos were dissected and the brains were immersed in PBS with 20% sucrose. Brains were embedded in Tissue-Tek optimal cutting temperature compound (Sakura Fine Technical, Tokyo, Japan) and frozen on dry ice. Serial sections (10–16 μm) were cut using a cryostat (Leica Microsystems, Wetzlar, Germany). Sections were used for either *in situ* hybridization or stained with thionine, for neuroanatomical reference. We used 2 gestational week (GW)10, 3 GW12, 2 gestational month (GM) 3.5 (around GW15), and 4 GM4 (around GW16 or 17) embryos of either sex. The stage of the embryos were estimated by the morphology of the forelimb or brain according to the reference (Hikishima *et al.* 2013).

In situ hybridization

The probes and procedure of *in situ* hybridization were as described previously (Matsunaga *et al.* 2013). Accordingly, we used the sense probe for *Cdh10* as control, because longer probes induce stronger background signals in general and the probe length is the largest among the analyzed cadherins (we could not find any clear signals above the background staining with all cadherin sense probes.)

Results

We performed *in situ* hybridization analyses of nine classic cadherins (*Cdh4*, *Cdh6*, *Cdh7*, *Cdh8*, *Cdh9*, *Cdh10*, *Cdh11*, *Cdh12*, and *Cdh20*) and T-cadherin (*Cdh13*) in the marmoset NCX from GW10 to GM4 (Figs 1–6).

Expression of each cadherin in the NCX

Cdh4. *Cdh4* expression was weakly detected in the ventricular zone (VZ) of the NCX at GW10 (Fig. 1A). Its expression was strongly observed in the medial NCX, but faintly in the lateral NCX at GW10–12 (Figs 1A, 2A, 3A, arrows). By GM3.5 (around GW15), strong *Cdh4* expression was broadly seen in the upper layer of the NCX (Figs 4A, 5A, arrows). The strong expression in the upper layer continued into the neonatal stage (Fig. 6A; Matsunaga *et al.* 2013).

Cdh6. *Cdh6* expression was not seen in the VZ, but seen in the cortical plate (CP) at GW10 (Fig. 1B, arrowheads). At GW12 (GM3), *Cdh6* expression was seen in the subplate (SP) and the deep layer of CP of the NCX (Figs 2B, 3B, arrowhead and arrow, respectively). At GM3.5, *Cdh6* expression was seen in the deep layer of NCX (Figs 4B, 5B, arrow). Clear *Cdh6* expression was seen in the deep layer of the temporal NCX (Fig. 5B, arrow). Around GM4, *Cdh6* expression started to be seen in the middle layer of some brain areas such as the middle temporal

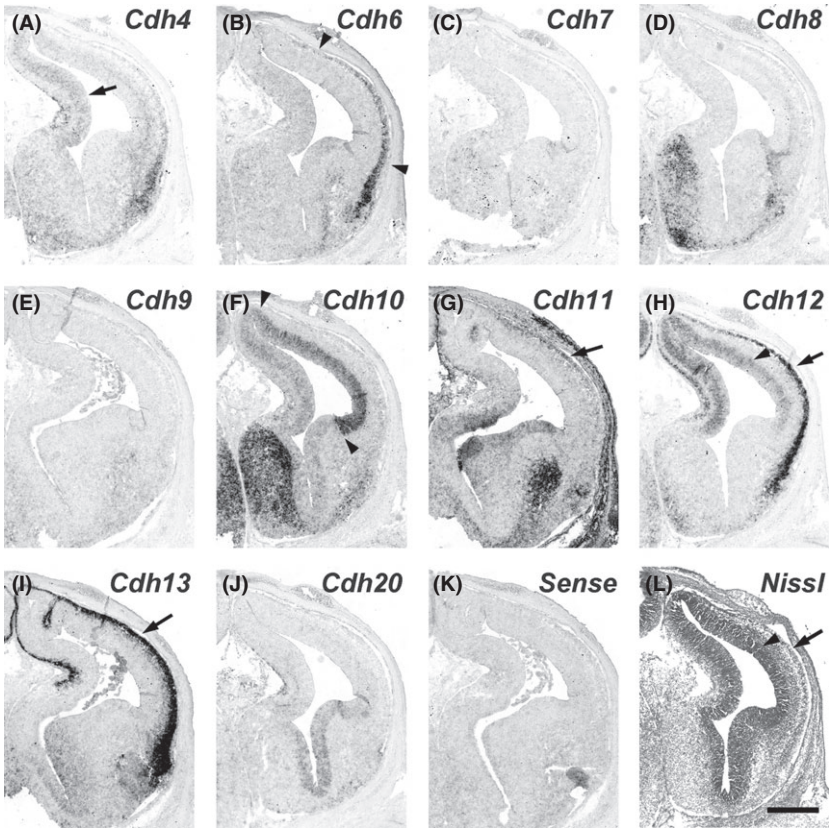

Fig. 1. Expression patterns of cadherins in the gestational week 10 marmoset neocortex (NCX). *In situ* hybridization for cadherins on serial transverse sections of the GW10 marmoset brain. *Cdh4* expression in the ventricular zone (VZ) (A, arrow). *Cdh6* expression in the cortical plate (CP) (B, arrowheads). *Cdh10* expression in the VZ (F, arrowheads). *Cdh11* expression in the CP (G, arrow). *Cdh12* expression in the VZ and CP (H, arrowhead and arrow, respectively). *Cdh13* expression in the CP (I, arrow). The VZ and CP in a Nissl stained section (L, arrowhead and arrow, respectively). Scale bar is 500 μm (L).

visual area (MT) (data not shown; Matsunaga *et al.* 2014).

Cdh7. No clear *Cdh7* expression in the NCX was seen at GW10–12 (Figs 1C, 2C, 3C), although its expression was seen in the thalamus (Fig. 3C, arrow). By GM3.5, *Cdh7* expression started to be seen in the temporal NCX (Fig. 5C, arrowhead), although its expression was area-specific (Figs 4C, 5C). By GM4, *Cdh7* expression was visible in the motor cortex in addition to the temporal cortex (data not shown).

Cdh8. Clear *Cdh8* expression in the NCX was first seen in the CP at GW12 (Fig. 3D). Its expression was area-specific (Figs 2D, 3D, arrow). At GM3.5, *Cdh8* expression was seen in the middle layer of the dorsal NCX (Fig. 5D, arrowhead) with a complementary expression to *Cdh6* and *Cdh7* (Fig. 5B, C, arrowheads). However, only faint expression was seen in the anterior NCX (Fig. 4D). By GM4, strong *Cdh8* expression was also seen in the ventral region of the anterior NCX (data not shown).

Cdh9. Similar to *Cdh7*, no clear *Cdh9* expression was seen at GW10 (Fig. 1E). At GW12, *Cdh9* expression was still lacking in the NCX (Figs 2E, 3E). At GM3.5, *Cdh9* expression was detected in the temporal area (Fig. 5E, arrow) but not in other cortical areas (Fig. 4E), similar to *Cdh7*. However, in contrast to *Cdh7*, by the neonatal stage, *Cdh9* expression was broadly seen in the NCX (Matsunaga *et al.* 2013).

Cdh10. *Cdh10* was strongly expressed in the VZ of the lateral NCX and weakly expressed in the medial NCX at GW10 (Fig. 1F, arrowheads). Its expression in the VZ was maintained at GW12 (Figs 2F, 3F, arrows). *Cdh10* was also sparsely expressed in the deep layer of the CP (Figs 2F, 3F). By GM3.5, *Cdh10* expression was seen from the upper to the deep layer of NCX (Figs 4F, 5F). Its expression continued into the neonatal stage (Fig. 6F; Matsunaga *et al.* 2013).

Cdh11. Sparse *Cdh11* expression was seen in the CP at GW10 (Fig. 1G, arrow). At GW12, *Cdh11* expres-

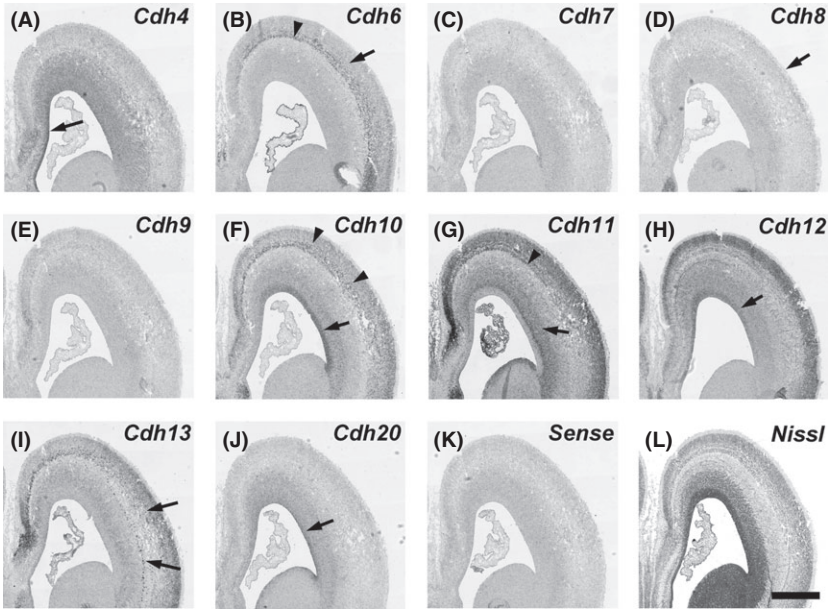

Fig. 2. *In situ* hybridization for cadherins on serial transverse sections of the anterior part of gestational week 12 marmoset neocortex (NCX). Expression patterns of cadherins in the ventricular zone (VZ) (A, F, H, J, arrows) and subventricular zone (SVZ) (G, arrow). Expression of cadherins in the subplate (SP) (B, G, arrowhead). Expression of cadherinsin the cortical plate (CP) (B, arrow; F, arrowheads). No clear *Cdh8* expression in the CP (D, arrow). Sparsely distributed cadherin-expressing cells (I, arrows). Scale bar is 1 mm (L).

sion was widely seen in the subventricular zone (SVZ) and CP (Fig. 2G). Clear *Cdh11* expression was seen in the SVZ (arrow), SP (arrowhead), and CP (Figs 2G, 3G). At GM3.5, *Cdh11* was broadly expressed both in the upper and deep layer of the dorsal NCX, but only in the upper layer of the ventral NCX (Figs 4G, 5G, arrowhead). By GM4, *Cdh11* expression was broadly seen in both the upper and deep layer of the NCX (Fig. 6G).

Cdh12. Expression of *Cdh12* was detected in the VZ of NCX at GW10 (Fig. 1H, arrowhead). Clear *Cdh12* expression was also seen in the CP (Fig. 1H, arrow). At GW12, *Cdh12* expression was seen in the VZ (arrow) and CP including the SP (arrowhead) (Figs 2H, 3H). At GM3.5, *Cdh12* showed a graded expression in the deep layer of NCX in a dorsal-high and ventral-low manner (Figs 4H, 5H, arrows). At GM4, *Cdh12* expression in the deep layer was maintained but its expression in the middle layer started to appear from the ventral part of the NCX (Fig. 6H). The *Cdh12* expression in the middle layer (presumptive layer IV) was seen in the temporal or occipital NCX, as previously described (Matsunaga *et al.* 2014), but not in the parietal NCX. However, by the neonatal stage, *Cdh12* expression in layer IV became clear in the parietal NCX (Matsunaga *et al.* 2013).

Cdh13. *Cdh13* was strongly expressed in the CP at GW10 (Fig. 1I, arrow). At GW12, *Cdh13* expressing cells were sparsely distributed in the SVZ and CP (Figs 2I, 3I, arrows). By GM3.5, *Cdh13* was expressed from the upper to the deep layer in the neonatal brain (Figs 4I, 5I; Matsunaga *et al.* 2013).

Cdh20. No clear *Cdh20* expression was detected in the NCX at GW10 (Fig. 1J). By GW12, *Cdh20* expression was seen in the VZ and SVZ (Fig. 3J, arrow). At GM3.5, *Cdh20* expression in the CP was seen only in a small part of the anterior NCX (data not shown). By GM4, *Cdh20* expression was evident in the deep layer (the presumptive layer V) of the anterior NCX (Fig. 6J). Its expression in other areas was evident by the neonatal stage (Matsunaga *et al.* 2013).

Cadherin expression in the hippocampal area

By GW12, clear *Cdh4*, *Cdh8*, *Cdh9*, *Cdh10*, *Cdh11*, and *Cdh13* expression was detected in the cortical hem, the presumptive area of the hippocampus (Fig. 3A,D,E,F,G,I). Weak *Cdh12* and *Cdh20* expression was also visible by this stage (Fig. 3H,J).

Discussion

In the present study, we analyzed the expression of 10 cadherins in the developing embryonic NCX and found complex and diverse cadherin expression pat-

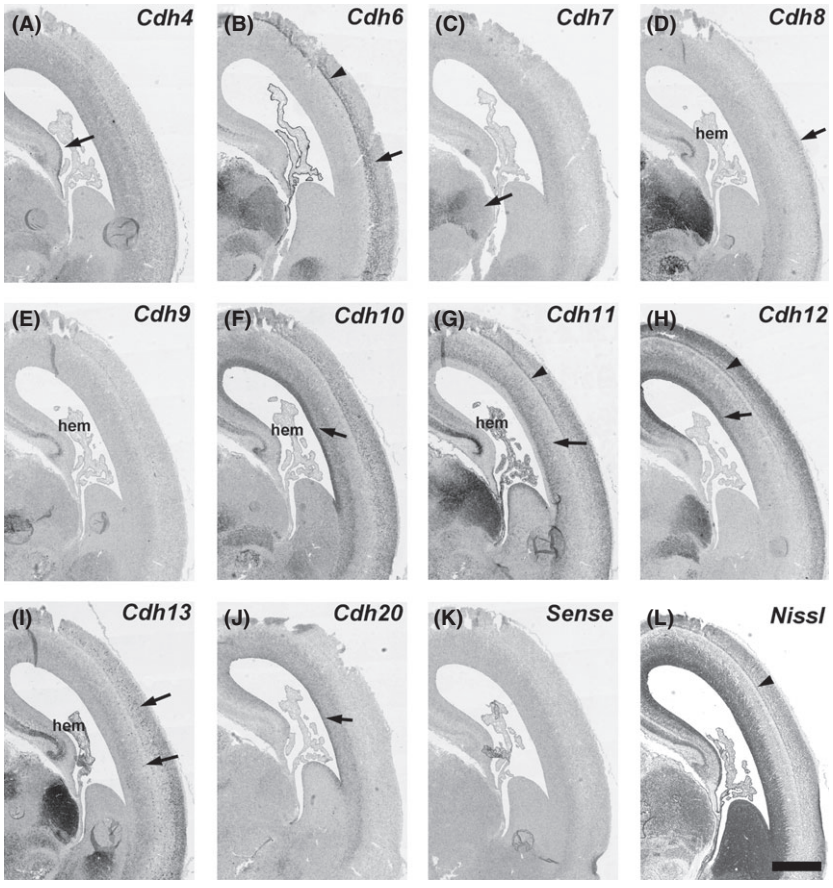

Fig. 3. *In situ* hybridization for cadherins on serial transverse sections of the middle part of gestational week 12 marmoset neocortex (NCX). Expression patterns of cadherins in the ventricular zone (VZ) (A, F, H, J, arrows), subventricular zone (SVZ) (G, arrow), subplate (SP) (B, G, H, arrowheads), and cortical plate (CP) (B, D, arrows). *Cdh7* expression in the thalamus (C). *Cdh13*-expressing cells in the SVZ and CP (I, arrows). SP in a Nissl stained section (L, arrowhead). Scale bar is 1 mm (L).

terns. The expression patterns are summarized in Figure 7.

Complex regulation of various cadherins in embryonic marmosets

Cadherin expression patterns are divided into at least four types (Fig. 7): (i) expression commencing from anterior to posterior (*Cdh4*, *Cdh13, Cdh20*), (ii) starting from dorsal to ventral (*Cdh11*), (iii) initiating from middle ventral region (temporal cortex) (*Cdh7*, *Cdh9*), and (iv) complicated regulation of expression (others). For example, *Cdh12* expression in the deep layer starts from the dorsal NCX by GW10, whereas *Cdh12* expression in the middle layer starts from the ventral region at around GM4. It appears that there are at least two mechanisms controlling *Cdh12* expression. First, expression in the deep layer may expand from dorsal to ventral by the signal from the cortical hem. Second, expression in the middle layer may expand from ventral to dorsal by the signal form the anti-hem. It has been suggested that some neurons migrate tangentially, such as the GABAergic neurons and some populations of subplate neurons from the ventral region outside the NCX (Hoerder-Suabedissen & Molnár 2013; Kessaris *et al.* 2014). Further analysis involving identification of individual cadherin-expressing cells with various cell-type specific markers is needed to examine whether *Cdh12*-expressing cells in the deep layer and middle layer are derived from the same origin.

It has been suggested that cortical areas are formed by the combination of various signals from the anterior neural ridge (ANR), cortical hem, and anti-hem (Alfano & Studer 2013). Interestingly, expression of *Cdh7* and *Cdh9* started to be seen in the middle part of the

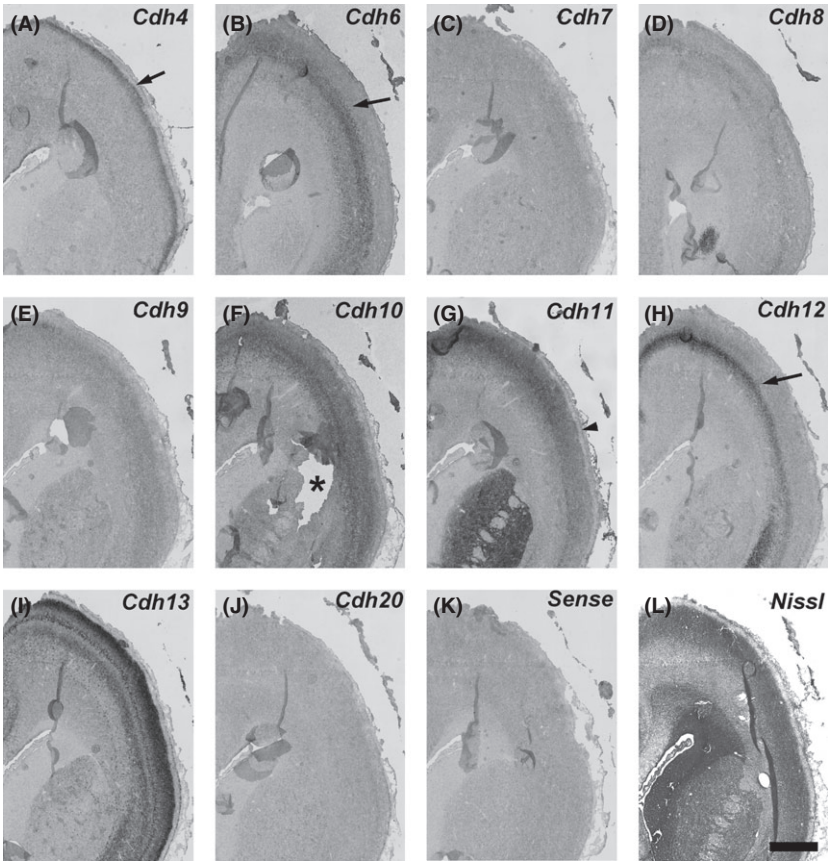

Fig. 4. Expression patterns of cadherinsin the anterior part of gestational month 3.5 marmoset neocortex (NCX). Cadherin expressions in the upper layer of cortical plate (CP) (A, arrow) and deep layer of CP (B, H, arrows). The asterisk indicates the disintegrating part of the section (F). Strong *Cdh11* expression in the dorsal NCX(G, arrowhead). *Cdh12* shows a dorsal-high and ventral-low graded expression (H, arrow). Scale bar is 1 mm (L).

NCX, an area surrounding the lateral sulcus (LS), noticeable in the primate brain. It is possible that a signal center exists in the presumptive area of LS, which induces temporal area-specific expression of cadherins.

Species differences in cadherin expression

Previously, we examined expression of various cadherins in the postnatal marmoset cerebral cortex and found differences in their expression between mouse and marmoset NCX. In this study, we found distinct expression of cadherins already in the embryonic stage. For example, expression of cadherins in the VZ differed between the mouse and marmoset NCX. In contrast to previously reported expression of cadherins in the mouse NCX (Inoue *et al.* 1998; Lefkovics *et al.* 2012), no clear *Cdh6*, *Cdh7*, and *Cdh9* expression was seen in the marmoset VZ. In the rodent brain, both *Cdh7* and *Cdh9* expression was already broadly seen in the NCX before the start of corticogenesis (Takahashi & Osumi 2008; Lefkovics *et al.* 2012). However, in the marmoset brain, *Cdh7* and *Cdh9* expression started only after the initiation of NCX differentiation and that too in a limited area. Such differential expression of cadherins may result in formation of distinct brain structures and function in rodents and primates.

Some type II cadherins share homologous sequences (Fig. S1), and it has been demonstrated that type II cadherins are capable of heterotypic binding and show functional redundancy among some family members (Shimoyama *et al.* 2000; Lefkovics *et al.* 2012). Therefore, a lack of specific expression of cadherins in the embryonic stage may be rescued by other cadherin expressions, and therefore, differential cadherin expressions in the embryonic stage may only have subtle effects on brain development. However,

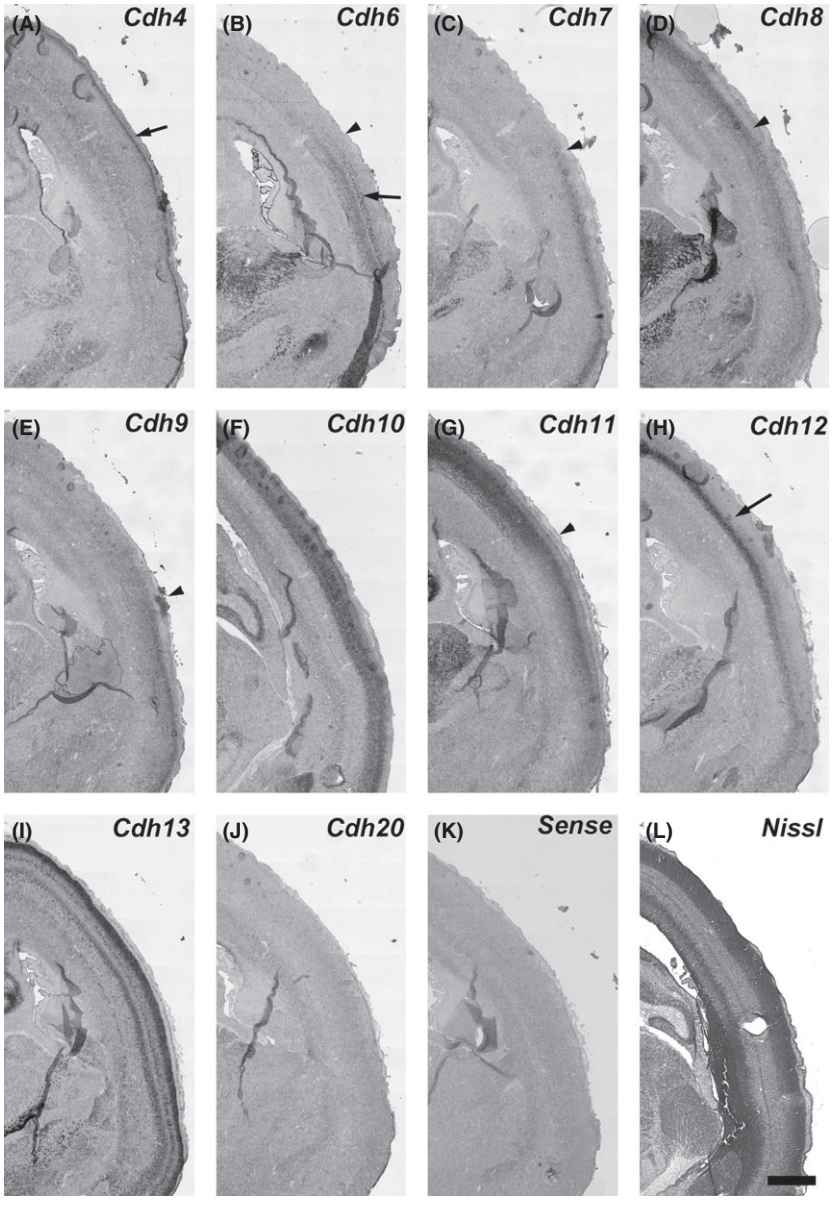

Fig. 5. Expression patterns of cadherins in the middle part of gestational month 3.5 marmoset neocortex (NCX). *Cdh4* expression in the upper layer of CP (A, arrow). *Cdh6* expression in the deep layer of the CP (arrow); Cdh6 is strongly expressed in the ventral part of the CP (temporal cortex) (B). *Cdh7* and *Cdh9* expression in the ventral part of the CP (C, E). *Cdh8* shows a complementary expression to *Cdh6*, *Cdh7*, and *Cdh9* (B–E, arrowheads). *Cdh11* expression in the middle and deep layer is strongly seen in the CP of the dorsal NCX (G, arrowhead). *Cdh12* shows a dorsal-high and ventral-low graded expression in the deep layer (H, arrow). Scale bar is 1 mm (L).

since expression of cadherins in the marmoset NCX tend to segregate during postnatal development (Matsunaga *et al.* 2013), expression of diverse cadherins may gradually cause differences in neural connections and electrophysiological properties during the later developmental stages, for example, the formation of intracontico-cortical connections, that is highly evolved in the primate NCX.

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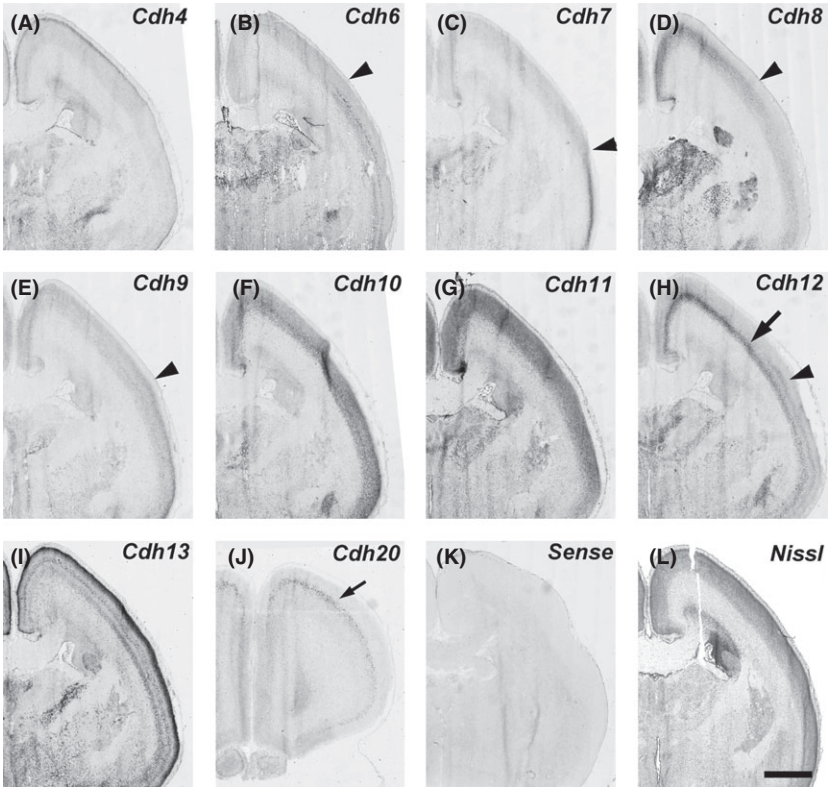

Fig. 6. Expression patterns of cadherins in the middle part of gestational month 4 marmoset neocortex (NCX). Complementary expressions of *Cdh6*, *Cdh7*, *Cdh9,* and *Cdh8* (B–E, arrowheads). *Cdh12* shows a dorsal-high and ventral-low expression in the deep CP (arrow) and a ventral-high expression in the middle CP (arrowhead) (H). *Cdh20* expression in the anterior NCX (J, arrow). Scale bar is 2 mm (L).

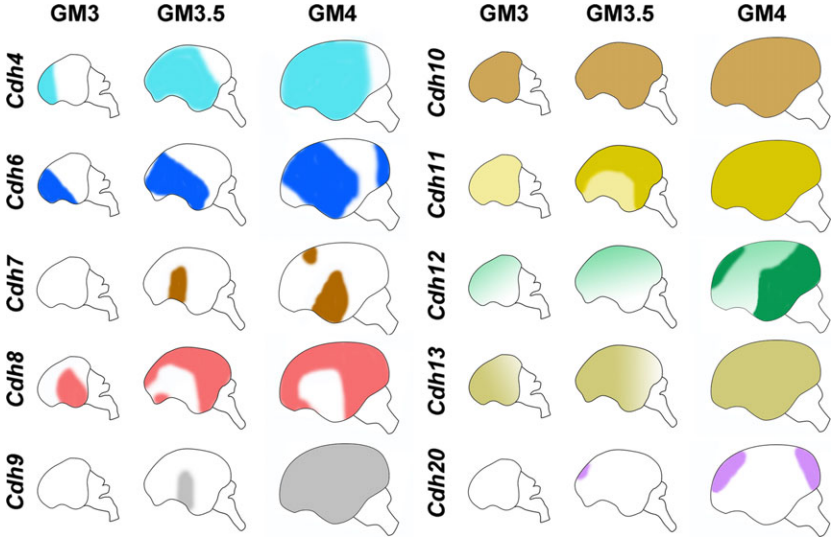

Fig. 7. Schematic representation of expression patterns of cadherins in the developing cortical plate of embryonic marmosets at gestational month (GM)3, GM3.5, and GM4. *Cdh11* expression in the upper layer was broadly seen in the whole neocortex (NCX) at GM3 (light yellow), whereas *Cdh11* expression in the deep CP is seen in the dorsal NCX at GM3.5 (dark yellow). *Cdh12* expression in the deep CP shows a dorsal-high and ventral low graded expression (light green) whereas *Cdh12* expression in the middle CP shows a strong expression in the ventroposterior NCX (dark green).

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web-site:

Fig. S1. Phylogenetic tree of mouse (m) or marmoset (cj) coding sequence of each cadherin gene.