Extensive migration of young neurons into the infant human frontal lobe

Mercedes F. Paredes, David James, Sara Gil-Perotin, Hosung Kim, Jennifer A. Cotter, Carissa Ng, Kadelyn Sandoval, David H. Rowitch, Duan Xu, Patrick S. McQuillen, Jose-Manuel Garcia-Verdugo, Eric J. Huang,* Arturo Alvarez-Buylla*

INTRODUCTION: Inhibitory interneurons balance the excitation and inhibition of neural networks and therefore are key to normal brain function. In the developing brain, young interneurons migrate from their sites of birth into distant locations, where they functionally integrate. Although this neuronal migration is largely complete before birth, some young inhibitory interneurons continue to travel and add to circuits in restricted regions of the juvenile and adult mammalian brain. For example, postnatally migrating inhibitory neurons travel from the walls of the lateral ventricle, along the rostral migratory stream (RMS) into the olfactory bulb. In humans, an additional ven- triculoposterior migratory stream (MMS), takes young neu- rons into the medial prefrontal cortex. It has been suggested that recruitment of neurons during postnatal life could help shape neural circuits according to experience. Specifically, inhibitory interneuron maturation during postnatal development is associated with critical periods of brain plasticity. We asked whether neuronal recruitment continues into early childhood in the frontal lobe, a region of the human brain that has greatly increased in size and complexity during evolution.

RATIONALE: Migrating young neurons persist for several months after birth in an extensive region of the subventricular zone (SVZ) around the anterior lateral ventricles in the human brain. Are all these young neurons migrating into the RMS and MMS, or do they have other destinations? Using high-resolution magnetic resonance imaging (MRI), histology, and time-lapse confocal microscopy, we observed the migration of many young inhibitory interneurons around the dorsal anterior walls of the lateral ventricle and into multiple cortical regions of the human frontal cortex. We determined the location and orientation of these young neurons, demonstrated their active translocation, and inferred their fates in the postnatal anterior forebrain.

RESULTS: A large collection of cells expressing doublecortin (DCX), a marker of young migrating neurons, traveled and integrated within the infant frontal lobe. This migratory stream, which was most prominent during the first 2 months after birth and persisted until at least 5 months, formed a caplike structure surrounding the anterior body of the lateral ventricle. We refer to this population of young neurons as the Arc. This structure could also be visualized by brain MRI. Young neurons in the Arc appeared to move long distances in distinct regions around the ventricular wall and the developing white matter. The orientation of elongated DCX+ cells suggested that migratory neurons closer to the ventricular wall dispersed tangentially. In contrast, migratory neurons within the developing white matter tended to be orientated toward the overlying cortex. These cells expressed markers of inter-neurons, and their entry into the anterior cingulate cortex (a major target of the Arc used for quantification) was correlated with the emergence of specific subsets of γ-aminobutyric acid (GABA)–expressing interneurons (neuropeptide Y, somatostatin, calretinin, and calbindin). Expression of transcription factors associated with specific sites of origin suggested that these neurons arise from ventral telencephalon progenitor domains.

CONCLUSION: Widespread neuronal migration into the human frontal lobe continues for several months after birth. Young neurons express markers of cortical inhibitory inter-neurons and originate outside the cortex, likely in the ventral forebrain. The postnatal recruitment of large populations of inhibitory neurons may contribute to maturation and plasticity in the human frontal cortex. Defects in the migration of these neurons could result in circuit dysfunctions associated with neurodevelopmental disorders.

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The first few months after birth, when a child begins to interact with the environment, are critical to human brain development. The human frontal lobe is important for social behavior and executive function; it has increased in size and complexity relative to other species, but the processes that have contributed to this expansion are unknown. Our studies of postmortem infant human brains revealed a collection of neurons that migrate and integrate widely into the frontal lobe during infancy. Chains of young neurons move tangentially close to the walls of the lateral ventricles and along blood vessels. These cells then individually disperse long distances to reach cortical tissue, where they differentiate and contribute to inhibitory circuits. Late-arriving interneurons could contribute to developmental plasticity, and the disruption of their postnatal migration or differentiation may underlie neurodevelopmental disorders.

Fig. 1. Migrating young neurons in the infant frontal lobe are widely distributed in four tiers. (A) Serial Nissl-stained sections (taken at birth) reveal cell-dense collections around the anterior body of the lateral ventricle (black arrows, defined here as the Arc); LV, lateral ventricle. (B and C) The cells in these densities (yellow arrows) and next to the ventricular wall express DCX. (D) Coronal sections (38 GW) showing cell densities close to the ventricular wall (eyebrow-shaped, black arrows). (E) Dense aggregates of DCX+ cells around the walls of the lateral ventricles (white arrows), around blood vessels (red arrowhead), and in the parenchyma within the Arc (gray arrows). (F to I) DCX+ cells also express PSA-NCAM; (F) and (G) show cells within the Arc; (H) and (I) show cells next to the ventricular walls. (J and K) Schematic drawings of traced DCX+ cells (in green) illustrating how cells within the Arc are organized into four tiers (see text). Blood vessels are shown in red; light green clusters correspond to DCX+ cellular densities seen in (B) and (E). Scale bars, 2 mm [(A and (B)], 50 μm (C], 1 mm (D], 25 μm [(F to (I)].
These densities were adjacent to the anterior body of the lateral ventricle and within the neighboring subcortical white matter, forming a distinct arched structure in sagittal sections or an eyebrow-shaped extension in coronal sections (Fig. 1, A and D, black arrows). The majority of cells within these regions coexpressed double-cortin (DCX) and polysialylated neural cell adhesion molecule (PSA-NCAM), markers of young migrating neurons (Fig. 1, B, C, and E, and fig. S1B) (21, 22). Many of these cells displayed migratory morphology, with an elongated cell body and a leading process that was occasionally bifurcated (23–25). DCX+ cells did not express Olig2 (see below), which marks oligodendrocytes and their precursor cells, but the astrocytic markers glial fibrillary acidic protein (GFAP) and Aldh1L1 (Fig. S1 and fig. S2, K and L).

In postmortem brains collected at birth and at 1 month, these putative migrating young neurons were organized into four layers, or tiers, around the anterior body of the lateral ventricles (Fig. 1, J and K, and fig. S1F). Tier 1 corresponded to a cell-dense SVZ band of DCX+ cells next to the walls of the lateral ventricle; between 6 and 12 months, tier 1 is depleted of young neurons, becoming a hypocellular gap layer (26). Tier 2 contained a more dispersed collection of DCX+ cells. Tier 3 was an intermediate region with many DCX+ cells within clusters, frequently around blood vessels, and dispersed DCX+ cells around these clusters (fig. S3). Tier 4 contained a group of DCX+ cells dispersed within areas of the developing white matter. Many cells in tier 4 were organized around radial finger-like extensions of triangular shape (Fig. 1B, yellow arrows). We analyzed these tiered regions in 1-day-old and 28-day-old brains by electron microscopy. Cells with the ultrastructure of young migrating neurons were found throughout tiers 1 to 4. Migrating young neurons were organized as chains (27) or as individual cells (Fig. 2, A to D, and fig. S4, C and G). Those within chains had adherent junctions similar to those observed in the RMS (fig. S4, C and G). Confocal and electron microscopy showed that chains of migrating neurons were flanked by cells rich in intermediate filaments containing GFAP (Fig. 2F, fig. SIC, and movie S1).

To generate a multiplanar representation of migratory streams of cells, we used high-resolution magnetic resonance imaging (MRI) to image intact hemispheres from postmortem human brains between birth and 2 months of age, including a premature case born at 34 gestational weeks (GW) (table S1). MRI analysis revealed a T2 hyperintense signal adjacent to the anterior horn of the lateral ventricle (fig. S5, A and B, red shading). Three-dimensional rendering of the segmented areas of T2 signal in brains at 34 GW and at birth showed that this structure formed a cap around the anterior horn of the lateral ventricle (fig. S5D). In sagittal MRI planes, this cap structure had an arc shape (fig. S5, A and G), running parallel to the anterior cingulate cortex and extending caudally to approximately the level of the central sulcus. This arc was also observed in live MRI images of the developing human brain (fig. S5, H and I). The T2 hyperintense signal was localized to ventricular regions densely populated by DCX+ cells (fig. S1, E to G). Given the organization we observed in both histological and radiographic images, we refer to these streams of cells as the “Arc.”

Migratory features of young neurons in the human infant brain

To confirm that these cells were in fact actively migrating, we obtained human neonatal brain samples (table S1) with short postmortem intervals and infected them with adenovirus carrying green fluorescent protein (adenoGFP) for time-lapse confocal microscopy. Elongated GFP+ cells (n = 18) with leading processes were identified, and we studied their behavior for 24 to 48 hours (Fig. 3C). As shown (movies S2 and S3), these cells actively migrated in coronal and sagittal slice cultures, displaying leading process extension, nucleokinesis, and retraction of trailing process. These features were indistinguishable from the migratory behavior of neurons in the
fetal brain (24, 26, 27). Active migration was also observed within clusters of cells (movies S3 and S4) at the dorsal lateral ventricular edge, but because of their high cellular density, the behavior of individual cells was often not evident. In one of these clusters, we captured a labeled cell escaping the cluster to begin individual migration (movie S4). Immunostaining of these brain slices after time-lapse imaging confirmed that the migrating cells were DCX⁺ (Fig. 3B). Thus, neurons in the newborn brain within the Arc and immediate surroundings are actively migrating.

Using fixed tissue, we inferred possible migratory trajectories from the orientation of the leading process of DCX⁺ young neurons. We defined a vector from the center of the cell body in the direction of the leading process (see supplementary materials). We applied this analysis to DCX⁺ cells in coronal and sagittal sections at birth and 1.5 months of age in periventricular and subcortical white matter regions in the frontal lobe (Fig. 3, D and E). We observed that the vector orientation of the cells changed depending on the region. The leading process of DCX⁺ cells could not be discerned in tier 1 because of the high cellular density, but the majority of cells in tier 2 appeared to be migrating tangentially, parallel to the ventricle wall. In the sagittal plane, cells were oriented ventrally and dorsally. In tier 3, the orientation remained largely tangential, but cellular direction was more variable than in tier 2. Lastly, in tier 4 and at the gray matter–white matter junction, more cells were oriented toward the developing cortex (Fig. 3, D and E, and figs. S6 and S7). A similar pattern of vector orientation was also observed in the coronal plane of the frontal lobe at 1.5 months (fig. S8).

We next mapped the distribution of young migratory neurons adjacent to the ventricular wall and in the overlying cortices at birth and...
Fig. 4. Interneuron and subpallial marker expression in migrating DCX+ cells in the infant brain. (A) Schematic of coronal section indicating the Arc area that was analyzed at the dorsolateral edge of the ventricle; see fig. S2 for marker expression next to the walls of the lateral ventricle. (B to D) DCX+ cells express GAD67, GABA, and the cytokine receptor CXCR4 present in migrating interneurons. (E to H) Subpopulations of DCX+ cells express different transcription factors associated with ventral telencephalic origin, including Sp8, COUP-TFIi, Nkx2.1, or Lhx6 associated with the CGE or MGE. (I) Quantification of DCX+ cells expressing Sp8, COUP-TFIi, Nkx2.1, and Lhx6. Bars show means ± SEM of counts performed on three or four individual cases.  (J and K) DCX+ cells do not express Olig2 or Sox2. Scale bar, 20 μm.

Fig. 5. Interneuron subtype development in the cingulate gyrus. (A to E) Many DCX+ cells in the neonatal cingulate cortex express GAD67 (A), and subpopulations also coexpress interneuron subtype markers: calbindin (CalB) (B), neuropeptide Y (NPY) (C), somatostatin (SST) (D), and calretinin (CalR) (E). DAPI, 4′,6-diamidino-2-phenylindole. Yellow arrows point to DCX+ cells that coexpress the indicated subtype markers. (F) Spatiotemporal distribution of interneuron subtypes from birth to 24 years. NPY+ and SST+ cells are located primarily in the white matter at birth but shift to the cortex over time. CalR+ and CalB+ are already expressed in cells throughout the cortex at all ages, but their number continues to increase during the first five postnatal months. (G) Stereological quantification of interneuron subtypes in the cingulate cortex from birth to 24 years. The number of NPY+, SST+, CalB+, and CalR+ cells increases between birth and 5 months, coinciding with the arrival of DCX+ cells in the cingulate cortex (see Fig. 3G). Scale bars, 50 μm [(A) to (E)], 2 mm [(F), 1 day to 6 years], 1 mm [(F), 24 years]. Directional axes: D, dorsal; L, lateral.

GAD67 DCX DAPI
CalB DCX DAPI
NPY DCX DAPI
SST DCX DAPI
CalR DCX DAPI

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at 1.5, 3, 5, and 7 months. At and immediately after birth, elongated DCX+ cells were found at the dorsal ventricular wall and in the mantle region of the developing white matter (Fig. 3F). By 1.5 months, DCX+ cells were mainly found in the dorsal cortex in the superior and middle frontal gyri and the cingulate cortex, but many remained in the developing white matter. The total number of DCX+ cells with migratory morphology decreased between 1.5 and 7 months of age (Fig. 3, F and G; for representative DCX+ cells at 5 and 7 months, see fig. S9). The entry of DCX+ cells into the anterior cingulate gyrus was correlated with an increase in the number of cells expressing NeuN, a marker of mature neurons (fig. S10B). We also examined the cingulate cortex at 2, 6, and 15 years of age. Four to six DCX+ cells were observed per section in the 2-year-old sample, but these cells did not have a clear migratory morphology. None were detected at 6 or 15 years. Sagittal sections mapped at birth also demonstrated migrating young neurons moving into the anterior pole of the developing human brain (fig. S11). These observations indicate that postnatal neuronal migration in the human frontal lobe, in the Arc and beyond, occurs primarily within the first 3 months after birth, with a few DCX+ elongated cells persisting at 7 months.

Postnatally migrating neurons differentiate into interneurons

We sought to determine which types of neurons the DCX+ cells in the Arc become. DCX+ cells in all tiers at birth and at 1.5 months expressed γ-aminobutyric acid (GABA), the main inhibitory neurotransmitter in the adult brain; GAD67, an enzyme involved in the production of GABA; and the chemokine receptor CXCR4, seen in migrating interneurons (Fig. 4, B to D). Within tiers 1 and 2 (close to the ventricular wall), 92.5 ± 2.9% (SD) of DCX+ cells were GAD67+ and 96.1 ± 2.4% were GABA+. Farther away, within tiers 3 and 4, 91.2 ± 4.4% of DCX+ cells were GAD67+ and 94.8 ± 5.8% were GABA+. Because cortical interneurons primarily arise from the MGE and CGE (3, 5, 19, 22), we asked whether DCX+ cells in the Arc expressed Nkx2.1 or Lhx6 (transcription factors associated with the MGE), or Sp8 and COUP-TFI (associated with the CGE and possibly the lateral ganglionic eminence [LGE]). At birth, about 10% of DCX+ cells were Nkx2.1+ and 28% were Lhx6+ (Fig. 4, G to I, and fig. S2, A and G). Sp8 and COUP-TFI were expressed in 24% and 22% of DCX+ cells, respectively (Fig. 4, E, F, and I, and fig. S2, D and E). DCX+ cells did not express Sox2 or Tbr2, transcription factors associated with early and intermediate progenitor cells, respectively (Fig. 4K and fig. S2), nor did they express Emx1, CTIP2, or SATB2, transcription factors associated with excitatory neurons (fig. S2). In tiers 1 to 4 at birth, we found very few cells positive for Ki67, a marker of proliferating cells (fig. S12). Most of these Ki67+ cells were also Olig2+ and none were DCX+. Thus, DCX+ cells in the
postnatal frontal lobe correspond to postmitotic migrating young inhibitory interneurons, likely derived from the developing ganglionic eminences (CGE, MGE, and possibly LGE).

The interneuron subtype composition in the anterior cingulate cortex changes postnatally

To address how the Arc might contribute to developing cortical circuits, we mapped and quantified the total number of cells, neurons, and interneuron subtypes from birth until adulthood. We focused on the anterior cingulate cortex, which runs parallel to the Arc and had many DCX+ cells during the first postnatal months. The cell number and volume of the cingulate cortex increased between birth and 5 months of age (Fig. S10, A and C). The neuronal population in the cingulate cortex, as identified by NeuN expression, also increased during this time. These population changes followed the peak in the total number of DCX+ cells, at ~1.5 months, suggesting that the cingulate cortex receives young migratory neurons up to 5 months after birth. Most DCX+ cells found postnatally in the cingulate cortex white matter expressed GAD67, and a subpopulation expressed interneuronal subtype markers [neuroepitpeptide Y (NPY), somatostatin (SST), calretinin (CalR), or calbindin (CalB)] (Fig. 5, A to E). If these different subtypes of migrating young neurons enter the cingulate cortex, we hypothesized that its interneuron subtype composition would change over time. Indeed, by quantifying the abundance of different interneuron subtypes in this region, we found that the number of cells expressing NPY, SST, CalR, and CalB increased during the first 5 months after birth (Fig. 5, F and G). The number of parvalbumin-expressing cells also changed with age (from ~20,000 cells per cingulate segment at 3 months to ~70,000 cells at 24 years), but we do not know whether this increase is due to cell addition or due to their late maturation (28, 29). These data suggest that DCX+ cells from the Arc contribute to interneuron subtype populations within the infant cingulate cortex.

Discussion

We have identified a large, heterogeneous population of late-migrating neurons in the infant human brain that targets an extensive region of the anterior prefrontal cortex, including the cingulate gyrus and prefrontal cortex. In the motor cortex, a population of CGE-derived young migrating neurons continues to migrate into the cortex within the first few weeks of postnatal life (16, 17, 30). The population of young migrating neurons in the frontal lobe of postnatal humans appears to include this population but also others, including SST, NPY, and CalB. This assortment of subtypes, along with the expression of the regionally specific transcription factors Nkx2.1, Lhx6, COUP-TFII, and SP8, suggests that cells within the Arc derive from various progenitor zones in the ventral forebrain. The extensive tangential migration in the SVZ and periventricular region of the infant brain (Fig. 6 and movie S5) could allow for mixed populations of interneurons from distinct progenitor zones (3f) to reach appropriate cortical regions. The precise time and birthplace of young migrating neurons within the postnatal human frontal lobe remains to be determined.

Because migrating neurons from the Arc reach cortical circuits during postnatal life, sensory experience could shape their recruitment and possibly their connectivity (32–36). Periods of plasticity are tightly linked to the time course of inhibitory interneuron maturation; thus, the late incorporation of inhibitory neurons into the cingulate cortex could also be associated with the extension and delay in periods of plasticity during postnatal human development (37–39). Given the large numbers of young neurons that continue to migrate in the human brain at birth and during the first few months of life, injuries during this time (e.g., hypoxic ischemia) could affect neuronal recruitment from the Arc (40, 41) and may contribute to sensorimotor handicaps and neurocognitive deficits, including those seen in epilepsy, cerebral palsy, and autism spectrum disorders (42, 43).

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SUPPLEMENTARY MATERIALS
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Editor's Summary

Building the human brain
As the brain develops, neurons migrate from zones of proliferation to their final locations, where they begin to build circuits. Paredes et al. have discovered that shortly after birth, a group of neurons that proliferates near the ventricles migrates in chains alongside circulatory vessels into the frontal lobes (see the Perspective by McKenzie and Fishell). Young neurons that migrate postnatally into the anterior cingulate cortex then develop features of inhibitory interneurons. The number of migratory cells decreases over the first 7 months of life, and by 2 years of age, migratory cells are not evident. Any damage during migration, such as hypoxia, may affect the child's subsequent physical and behavioral development.

Science, this issue p. 81; see also p. 38

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