

# LIS-less neurons don't even make it to the starting gate

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The manuscript by Tsai et al. (935–945) is a tour de force analysis of a controversial issue in developmental neurobiology, namely the molecular basis of the devastating human brain malformation, type I lissencephaly (*Lis1*) (Jellinger, K., and A. Rett. 1976. *Neuropadiatrie*. 7:66–91). For several decades, defects in neuronal migration have been assumed to underlie all defects in cortical histogenesis. In the paper by Tsai et al., the authors use a variety of elegant approaches, including the first real-time imaging of cortical neurons with reduced levels of LIS1, to demonstrate that LIS1 and dynactin act as regulators of dynein during cortical histogenesis. A loss of LIS1 results in both a failure to exit the cortical germinal zone and abnormal neuronal process formation. Thus, the primary action of the mutation is to disrupt the production of neurons in the developing brain as well as their migration.

Lissencephaly (from the Greek “lissos” for smooth and “enkefalos” for brain) is a developmental malformation characterized by the absence of convolutions (Fig. 1). The classic study of Bielschowsky (1923) defined the architectonic features of abnormal cerebral cortex in type I lissencephaly (*Lis1*). At birth, although children with LIS1 mutations have “normal” head size, a surrogate for brain weight, the values almost always fall below the 50th percentile. The cerebral cortex of these children contains four layers, rather than the usual six. Layer I, the superficial layer, corresponds to the molecular or plexiform layer of normal brain. Layer II is a thin layer dominated by neurons that should normally be located in the deeper layers of normal brain, layers IV–VI, and includes some “upside-down” layer I and layer II cells. Layer III is a thin ribbon of white matter and Layer IV is a generally wide layer of heterotopic cells (Stewart et al., 1975). The relative absence of the neurons that are produced in the later cell cycles of cortical histogenesis suggests a failure of neural production as cortical development proceeds.

The relationship of neurogenesis and the formation of neural layers in developing cortex emerged from the pioneering

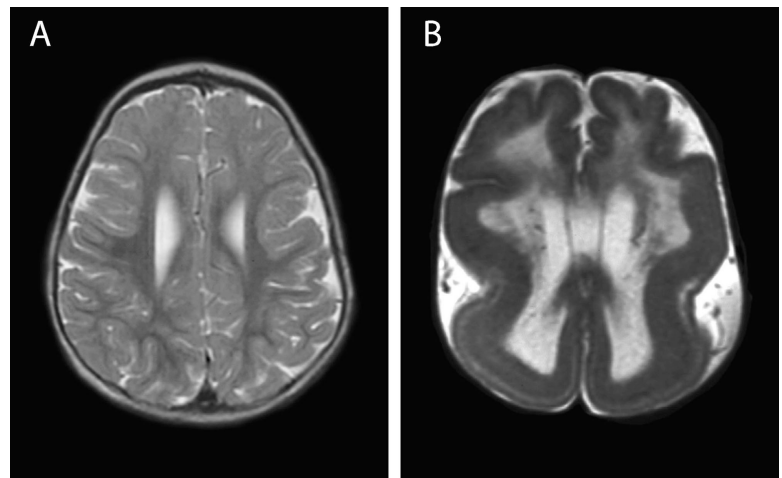
work of Richard Sidman on thymidine “birthdating” (Sidman, 1970). The discovery of directed neuronal migration along glial fibers by Pasko Rakic in the 1970's (Rakic, 1972; Sidman and Rakic, 1973) set the stage for a period of intense focus on the process of neuronal migration in cortical histogenesis (Fig. 2). Rakic's review of neuronal migration in the human neocortex demonstrated that directed migrations establish the principal neuronal layers by the end of the second trimester (Sidman and Rakic, 1982). The studies on the architectonics of human cortical malformations revealed populations of heterotopic cells and suggested that pathogenic processes disrupted normal glial-guided neuronal migration. The hypothesis that cortical malformations resulted from migration defects became even more attractive with the analysis of spontaneously occurring neurological mutations (Caviness and Rakic, 1978; Rakic and Caviness, 1995). Cell and molecular studies of identified neurons from the cerebellar cortex and hippocampal formation provided real-time imaging of neuronal migration along glial fibers (Edmondson and Hatten, 1987; Gasser and Hatten, 1990b). In addition, MRI studies of children with a range of brain malformations demonstrated the high frequency of neuronal ectopias in childhood epilepsies (Kuzniecky, 1994). All of these studies underscored the critical role of neuronal migration in brain development.

Relatively few studies have compared mechanisms of neurogenesis during normal and abnormal cortical histogenesis. Detailed cell cycle analyses by Caviness et al. (2003) demonstrate that the murine neocortex is generated over an epoch of 11 cell cycles. Work by Marin-Padilla (Marin-Padilla and Marin-Padilla, 1982), McConnell (McConnell et al., 1989; McConnell and Kaznowski, 1991), Shatz (Shatz et al., 1990), O'Leary (De Carlos and O'Leary, 1992), and Ghosh (Whitford et al., 2002) and colleagues demonstrated that the normal architectonics of the cortex requires the generation of a “pre-plate” in the initial cell cycles, followed by the formation of the cortical plate, which contains the immature pyramidal neurons destined for layers V and VI as well as a smaller population of interneurons. As development proceeds, directed migrations of pyramidal neuron precursors along the radial glial fibers establish layers IV, II, and I with vast populations of interneurons (80%) entering the cortex tangentially from their site of origin in basal forebrain (Anderson et al., 2001). Recently, Kriegstein (an author of the Tsai et al., 2005 paper) and colleagues (Noctor et al., 2001) showed that later generated neurons thought to establish the outer layers missing in type I lissencephaly are generated in substantial numbers from the radial glia, which are stem cells in addition to substrates for radial migrations.

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Abbreviations used in this paper: CNS, central nervous system; *Lis1*, type I lissencephaly; *nud*, nuclear distribution gene; SVZ, subventricular zone; VZ, ventricular zone.

Figure 1. **Comparison of MRI images of normal and LIS1 human brain.** The MRI in B has reduced gyration of the cerebral surface and increased thickness of the cortex, compared with the image of normal brain in A. Image B is from a boy with a deletion of LIS1 by FISH. The size of the deletion is given in Cardoso et al. (2003) (Brain Malformation Research Project number LP99-086; courtesy of Dr. William Dobyns, University of Chicago, Chicago, IL).



Efforts to provide a molecular explanation of the *Lis1* birth defect were informed by the genetic studies of Dobyns and colleagues to map the *Lis1* gene (Dobyns, 1989), which culminated in the cloning of *Lis1* in 1993 (Reiner et al., 1993). LIS1 encodes a 45-kD protein with seven WD40 repeats that binds microtubules. The gene is expressed in neural progenitors within the ventricular zone as well as in differentiated neurons, suggesting a function during multiple stages of neu-

ral development. As mice lacking *Lis1* die before birth, neurons from heterozygous *Lis1* (+/-) have been used to provide a bioassay for loss of function (Hirotsumi et al., 1998). Initial functional assays using dissociated cerebellar cells showed defects in neurite outgrowth and neuronal migration. Biochemical studies demonstrate that Lis1 binds to microtubules (Sasaki et al., 2000), suggesting a role in cytoskeletal dynamics of migrating neurons.

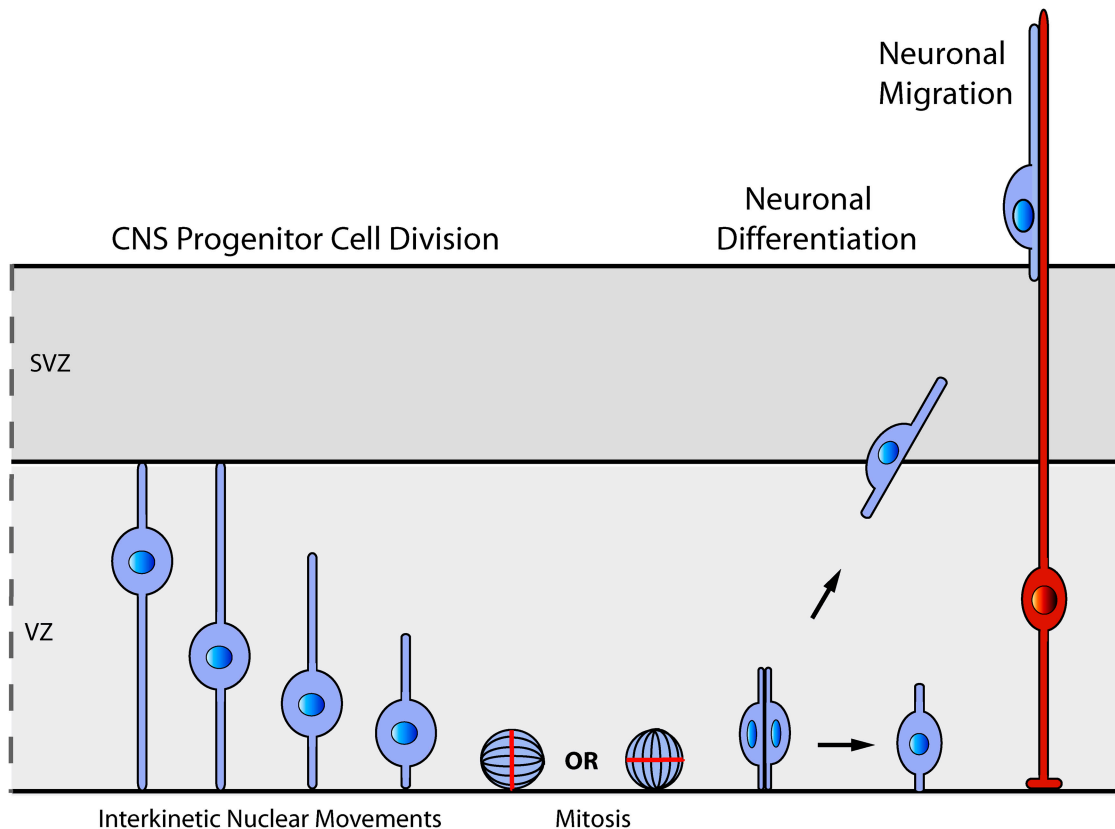
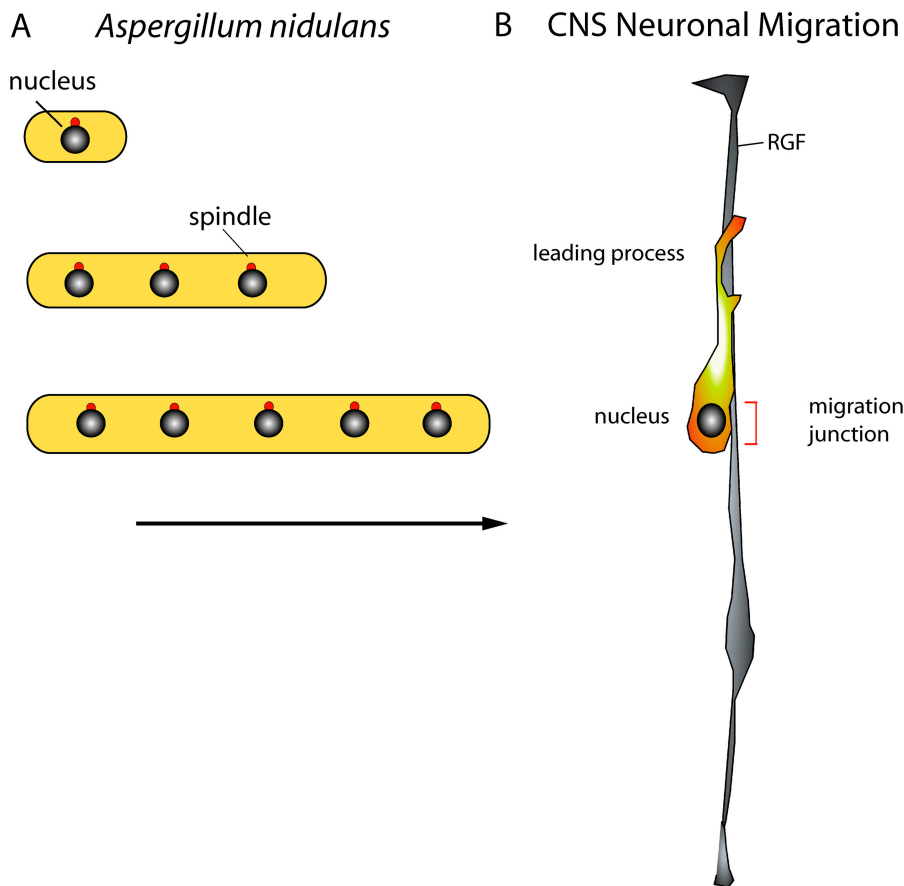


Figure 2. **Possible functions of LIS1 in mammalian cortical histogenesis.** Neuronal progenitor cells in the vertebrate VZ undergo cell cycle-dependent nuclear translocations. During mitosis, progenitor cells drop to the basal surface of the VZ, dividing parallel to the ventricular plane in the case of asymmetric divisions. After an asymmetric division, one cell remains in the VZ as a neural progenitor and recapitulates the series of interkinetic nuclear movements illustrated at left. The other cell exits the cell cycle and moves through the VZ and SVZ by a mechanism that involves the establishment of neuronal polarity and the translocation of the nucleus through the cytoplasm of the cell. Near the upper boundary of the SVZ, the young neuron binds to the fibers of radial glia (red) and migrates past earlier born neurons through the thickening wall of the cerebral cortex.

The first *Lis1* related gene discovered in other organisms was the nuclear distribution gene (*nud*) *nudF* in the mold *Aspergillum nidulans*. Indeed a comparison of the coding regions of *Lis1* and *nudF* suggested that the two genes are orthologues (Xiang et al., 1995). Mutations in a series of *nud* genes that included *nudF* caused smaller colonies, via a failure of cytoplasmic dynein function. As illustrated in Fig. 3 A, the hypha of *Aspergillum* are elongated syncytia that extend by the addition of nuclei. This extension requires dynein for cell cycle progression and movement of the nucleus (Yamamoto and Hiraoka, 2003). The growth arrest in filamentous mold, caused by a failure of dynein-mediated events in mitosis and organelle transport, was used as support for the hypothesis that LIS1 functions in neuronal translocation in mammalian central nervous system (CNS) migration. According to this model, the nucleus of the migrating neuron moved freely into the leading process of the migrating neuron. This view prevailed in spite of three decades of EM studies on cortical, hippocampal, and cerebellar neurons, live imaging of all of these types of neurons (Rakic, 1971, 1972; Nowakowski and Rakic, 1979; Gasser and Hatten, 1990a,b), and correlated EM and live imaging of cerebellar migration along glial fibers (Gregory et al., 1988), showing that the nucleus remained in the posterior aspect of the migrating cell as the cell soma moved along the glial fiber (Fig. 3 B).

Evidence for a role for LIS1–dynein interactions in the binding of microtubules to the cell cortex of mammalian CNS neurons and generation of cellular machinery for neuronal division has come from experiments by Vallee and colleagues. They showed that LIS1 binds cytoplasmic dynein and dynactin, and localizes to the cell cortex and to mitotic kinetochores (Faulkner et al., 2000). They went on to demonstrate that perturbation of LIS1 in cultured mammalian cells interferes with mitotic progression and leads to spindle disorientation. The mechanism of spindle defects appeared to be related to the attachment of chromosomes to the metaphase plate, leading to chromosome loss. Thus, their previous study suggested an alternative hypothesis to the migration-centric view of LIS1 function, namely that LIS1 regulates the division of neuronal progenitor cells in the germinal zones of brain. This idea is consistent with recent, elegant studies by Feng and Walsh (2004) on mice lacking *Nude-1*, a vertebrate protein isolated in yeast two-hybrid binding assays with LIS1 (Feng et al., 2000), where severe aberrations in spindle orientation and laminar fate lead to defects in laminar architecture (Feng and Walsh, 2004). Recent loss-of-function studies in invertebrate systems are also consistent with this view. In the slime mold *Dictyostelium*, reduced levels of *DdLIS1* perturb the mitotic spindle and organelle transport, but not cell movement (Rehberg et al., 2005). To examine the role of the *Caenorhabditis elegans* Lis-1 in cell



**Figure 3. Comparison of nuclear movements in *A. nidulans* and mammalian CNS migration along glial fibers.** (A) Growth of the filamentous mold *A. nidulans* by nuclear division. Nuclear division and distribution toward the growing tip regulates the growth of *A. nidulans*. A series of mutations that disrupt nuclear distribution (the *nud* or nuclear distribution genes) slow the growth of the *A. nidulans* colonies. Genetic and biochemical studies indicate that most of the *nud* mutants (*nudA–nudF*) encode components of tubulin, cytoplasmic dynein motors, or associated proteins such as LIS1 (*nudF*) or dynactin, revealing the critical role of dynein motors in the distribution of nuclei within the syncytia. Using GFP labeling, NUDF, NUDE, and dynein/dynactin subunits localize in *A. nidulans* to comet-like structures corresponding to the ends of dynamic cytoplasmic microtubules (Xiang et al., 1995; Yamamoto and Hiraoka, 2003). The functional, NUDF-binding NH<sub>2</sub>-terminal coiled coil of NUDE does not localize to growing ends of microtubules. Instead, the COOH-terminal domain, which is dispensable for the biological activity of NUDE, binds to microtubules indirectly by binding to NUDF (for review see Yamamoto and Hiraoka, 2003). (B) CNS neuronal migration along glial fibers. After the immature, post-mitotic neuron traverses the SVZ (see Fig. 2), it binds to the processes of radial glial fibers (RGF, gray) extending from the ventricular surface to the outer surface of the brain. The neuron (yellow) migrates in a saltatory cadence, as it forms and releases a broad junction with the glial fiber beneath the cell soma. A highly motile leading process extends in the direction of migration, spiraling

around the glial fiber by extending short (1–5 mm) filopodia and lamellipodia. The nucleus remains in the posterior of the cell soma, and the neuron moves for ~3 min between the release of the adhesion with the glial fiber and formation of a new junction, migrating at a rate of ~20–50 mm/h (drawing after that by Dr. Pasko Rakic, Yale University School of Medicine, New Haven, CT).

division, Cockell et al. (2004) showed that apparent null alleles of *lis-1* result in defects identical to those observed after inactivation of the dynein heavy chain *dhc-1*, including defects in centrosome separation and spindle assembly. Mosaic analysis using a *Lis-1* null mutation in *Drosophila* provides evidence that *Lis1* is essential for neuroblast proliferation and cytoplasmic dynein-mediated organelle transport (Liu et al., 2000).

The current paper by Vallee, Kreigstein, and colleagues (Tsai et al., 2005) uses in utero electroporation of *Lis1* small interfering RNA and dominant-negative forms of *LIS1* or dynactin to test the role of *Lis1* and dynein in live explants of embryonic brain. This approach allowed the first real-time imaging of cortical cell progenitors lacking *LIS1* or dynactin function. The results of these experiments were surprising and dramatic, as the primary effect of a loss of *LIS1* function(s) was a perturbation of the earliest steps of cortical histogenesis—the progression of neural progenitors through the cell cycle in the ventricular zone (VZ). This failure caused a reduction in neuronal progenitor cell proliferation. In addition, defects in neuronal process outgrowth appeared to block the passage of post mitotic precursors through the subventricular zone (SVZ) onto the radial glial pathways. The accumulation of multipolar progenitor cells within the SVZ was the most dramatic effect of *LIS1* or dynactin disruption. The classic interkinetic nuclear oscillation normally observed in radial glial progenitors was also abolished, perhaps contributing to disruptions in the outer cortical layers normally populated by these cells.

These results underscore long-neglected aspects of neural production and disposition in the developing neocortex, namely the control of polarity signaling in both mitotic and post-mitotic cells (Fig. 2). In dividing cells, polarity is essential for asymmetric divisions to occur, as evidenced by the Partition-defective mutants (*Par*) in *C. elegans* (Schneider and Bowerman, 2003). As early as the 1950's, Sauer and Walker (1959) observed specific interkinetic movements of the nuclei of dividing neural progenitors in germinal zones, a process that is required for the nucleus to move through the cell to the basal surface where cell mitosis occurs. As observed for more than two decades in electron microscopic studies (Rakic, 1972, 1978; Rakic and Caviness, 1995) and in real-time imaging of neuronal migration along glial fibers, the nucleus does not undergo kinetic movements during migration. Rather it is held in the rear of the cell by a perinuclear cage of tubulin (Solecki et al., 2004).

Several other lines of evidence point to a distinct mode of locomotion of newly post mitotic neurons from the VZ through the SVZ onto the glial system. First and foremost, in live imaging experiments, Nadarajah et al. (2001) provided evidence that interkinetic nuclear movement is prominent in cells as they extend a migratory process and develop the polarity required to move from the VZ through the SVZ. Second, neuron–glial adhesion ligand systems shown to function in glial-guided migration, but not in axon extension, such as *Astn1* (Zheng et al., 1996), are not expressed in the SVZ. Third, EM experiments by Rakic (1972) did not describe close interactions between early post-mitotic neurons and glial fibers; rather, the cells appeared to commence migration as they left the SVZ. The coordinated

movements of the nucleus during mitosis, the development of cell polarity through the positioning and function of the centrosome and cytoskeleton, and the transition needed to ready the young neuron for migration along the glial fibers are all profoundly disrupted in cells lacking *LIS1*. As cytoplasmic dynein motors are critical to all of these events, the current findings underscore the role of a *LIS1* and dynactin in the dynein-dependent functions needed to support neurogenesis during the development of the mammalian neocortex.

These results have profound implications for understanding mechanisms of brain development, as they underscore the importance of neurogenesis relative to neuronal migration, and emphasize the urgent need to discover the mechanisms that control the development of proper neuronal polarity in the early steps of neuronal differentiation. As first suggested by Susan McConnell (McConnell, 1988; McConnell and Kaznowski, 1991), cell cycle timing and spindle orientation are critical to the acquisition of proper laminar fate, by mechanisms that are not yet understood. Clearly the remarkable migrations of neurons to establish the laminae are part of this process, but they are only one step, a step that is dependent on an earlier complex program of neural production and polarity cues needed to establish normal cortical circuitry.

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