20. S. E. Blumstein, E. Baker, H. Goodglass. Neuropsychologia 15, 19 (1977). L. B. Taylor in Functional Neuropsychology. T. Rasmussen and R. Marino, Eds. Raven, New York, 1979, pp. 165–180 (G. Ojemann and C. Mather, Science 205, 1401 (1979)) also reported an association between impairments in phoneme identification and sequential orofacial movements during electrical stimulation of left perisylvian cortex. Further converging evidence comes from a study (R. J. Zatorre, unpublished observations) of a patient with surgical excision of a tumor in Broca’s area who was tested with exactly the same task used in this study. This patient, though not globally aphasic, was unable to perform the phonemic discrimination task (52% correct, a level not distinguishable from chance) but was able to perform the pitch discrimination (66% correct, significantly above chance (2 = 4.03, P < 0.0001)), albeit not as well as young normal subjects.

21. Reports of Broca’s area activation during subvocalization (6) (H. Chertkow, D. Bub, A. Evans, E. Meyer, S. Marrett, Neurology 41 (suppl. 1), 300 (1991)) support this hypothesis. Our task, however, required only a perceptual judgment.


24. This conclusion is supported by reports of dissociations between disturbances of speech perception and comprehension in aphasia (S. E. Blumstein, in Motor and Sensory Processes of Language, E. Keller and M. Gopnik, Eds. (Erlbaum, Hillsdale, NJ, 1987), pp. 257–275 (222)).


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REFERENCES


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Reports

Neocortex Development and the Cell Cycle

S. K. McConnell and C. E. Kaznowski report (1) that environmental factors can determine the laminar fate of forebrain neocortical neurons during the last mitotic division of their ventricular zone precursors. They suggest that the decision of a cortical ventricular zone precursor to generate a deep-layer neuron is made in late S-phase near the transition into G2 of the cell cycle. There is an alternative explanation for the data that is consistent with other findings that suggest a laminar fating of earlier ventricular zone precursors to the neocortex.

McConnell and Kaznowski find that, among migrating neurons, 90% of E29 cells labeled with [3H]thymidine and transplanted 2 hours later into the neonatal host ventricular zone migrate to the superficial (2/3) neocortical layers. However, 90% of these cells transplanted 6 hours later (removed after 4 hours and transplanted 2 hours after that) migrate to the deep (5/6/subplate) layers. Thus, within a 4-hour period near the end of S-phase, 90% of cortical cells must change their laminar fate. If these cells have an S-phase of 8 hours and an unsynchronized cell cycle as stated in (1), then only the 25% of the cells that are in the first 2 hours of S-phase and transplanted 2 hours after labeling [rather than the observed 90% in (1), figure 2A] should have escaped the deep-layer decision phase in the last 4 hours of S-phase. If the deep-layer decision phase of the cell cycle happened later in S-phase or in G2, then fewer cells transplanted at 6 hours after labeling should have reached the decision phase before transplantation.

Only 20% or less of the transplanted E29 cells actually migrate out of the host ventricular zone into the host neocortical lamina [as detailed by McConnell (2)]. It is possible that one of the dissociation, culturing, or transplantation procedures used in (1) selected for different 20% subpopulations to migrate among the cells transplanted 2 hours, rather than 6 hours, after labeling. This explanation implies that there were heterogeneous ventricular zone populations among which to select. Heterogeneous ventricular zone populations have been revealed by combining retroviral lineage tracing and [3H]thymidine autoradiography (3). In addition, data about cortical genotype ratios in mice produced from blas toxoyt chimeras have suggested that separate precursor populations may give rise to deep and superficial layer cortical neurons (4). We have recently found (5) through retroviral lineage tracing of the progeny of individual ventricular zone cells that many mammalian neocortical neuronal clones are restricted to deep, rather than superficial, layers. However, these studies (3–5) test for fate or specification of cells, but not if the cells are irreversibly committed to a phenotype; nor do they test whether the commitment can be overcome by environmental cues.

McConnell and Kaznowski also find that most cells lightly labeled with [3H]thymidine (that have presumably divided more than once in the host tissue) migrate to superficial cortical lamina. Once again, these cells may represent a selected subpopulation that is already fated to produce superficial cortical neurons. One would expect continued division by these cells, although the postnatal host tissue environment may artificially limit the total number of divisions by these precursors.

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S-phase, then cells lightly labeled with $[^3]H$-thymidine (which have therefore gone through an additional round of cell division after transplantation) should always change their fate and migrate to the upper layers, regardless of the time interval between thymidine labeling and transplantation. In contrast, if precommitted precursor cells are transplanted, lightly labeled cells should migrate to a mixture of upper and deep layers. We found that lightly labeled cells migrated to the upper layers, adopting the fate typical of their new environment, regardless of the time interval. This finding is incompatible with the selection hypothesis of van der Kooy.

Van der Kooy argues that the distributions of cells in the cell cycle do not perfectly match the timing of the commitment event, which he has assigned to mid-S-phase despite the fact that our data suggest it to be near the S to G2 transition (1). We have not identified the exact point in the cell cycle when laminar commitment occurs, but we did not make any strong claims to this effect. Furthermore, our data are consistent with the hypothesis that a cell cycle–dependent event controls determination, for three reasons.

First, cell cycle progression may be most accurately measured not linearly, in hours, but by actual progression through S-phase, as measured by cellular DNA contents. It is well known from studies of cultured cell lines (3) that rates of progression through S-phase are variable. Van der Kooy does not appear to take into account the possibility that progression through S-phase proceeds nonlinearly and that the important decision point is related not to time spent in S-phase but to progression through the cycle, as measured by DNA replication.

Second, as we explained in our paper (1), 0-hour cells were labeled with $[^3]H$-thymidine in vitro rather than in vivo, so there was less time (roughly an hour) between cell labeling and transplantation at this time point. The actual time that cells had to progress through the cell cycle when one compares the 0-hour and 4-hour time points was closer to 5 hours than the 4-hour period cited by van der Kooy.

Third, our estimate of the length of S-phase is rough and, without knowing the variability in the fractions of cells that migrate to the deep layers at different times, there may be no significant statistical differences between van der Kooy’s projections and our data.

Van der Kooy argues that cell lineage experiments reveal “that many mammalian neocortical clones are restricted to deep, rather than superficial, layers.” We await the publication of these data and warn that conclusions derived from studies of cortical cell lineages that use single retrovirus vectors have been called into question by recent work of Walsh and Cepko (4), who have shown that spatial clustering cannot be used to accurately determine clonal boundaries in the cortex. As van der Kooy points out, cell lineage studies reveal only the normal fates of cells and do not test their developmental potential. The latter was and remains the goal of our studies.

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REFERENCES AND NOTES
2. Our experiments were designed to distinguish between two hypotheses, (i) that laminar fate was determined by cell cycle position and (ii) that the ventricular zone contains a mixture of precommitted cells. In previous work [S. K. McConnell, J. Neurosci. 8, 945 (1988)], cells transplanted after a mixture of time intervals from 1 to 4 hours after labeling migrated to a mixture of the upper and deep layers. We reasoned that either the precursor cell population was heterogeneous, in which case the exact interval between labeling and transplantation should be irrelevant to the laminar fates of daughter cells, or the precursor cells were homogeneous but were receiving temporally mixed cues, in which case one should be able to find time points at which cells behave homogeneously. Indeed we found the latter to be the case.

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AAAS–Newcomb Cleveland Prize
To Be Awarded for an Article or a Report Published in Science

The AAAS–Newcomb Cleveland Prize is awarded to the author of an outstanding paper published in Science. The value of the prize is $5000; the winner also receives a bronze medal. The current competition period began with the 7 June 1991 issue and ends with the issue of 29 May 1992.

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Throughout the competition period, readers are invited to nominate papers appearing in the Reports or Articles sections. Nominations must be typed, and the following information provided: the title of the paper, issue in which it was published, author’s name, and a brief statement of justification for nomination. Nominations should be submitted to the AAAS–Newcomb Cleveland Prize, AAAS, Room 924, 1333 H Street, NW, Washington, D.C. 20005, and must be received on or before 30 June 1992. Final selection will rest with a panel of distinguished scientists appointed by the editor of Science.

The award will be presented at the 1993 AAAS annual meeting. In cases of multiple authorship, the prize will be divided equally between or among the authors.
Response
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