plate. Cdk5 and p35 (a neuronal-specific activator of Cdk5) are required. Both molecules are present in migrating neurons, and inactivation of either of them produces a phenotype somewhat similar to reeler in that cells are positioned in an outside-in gradient.

However, by contrast to the adult reeler, in Cdk5−/p35 mutants there is a relatively normal layer I below the subpial layer,

suggesting that in this mutant cortical plate cells respond normally to Reelin.

An interesting observation is that in the Cdk5−/− mutant, the subplate remains within the cortical plate during development; that is, early-born cortical plate cells are able to traverse the subplate, but late-born cells become positioned below the subplate, forming an underplate. This does not occur in the p35−/− mutant, in which all or most cortical plate cells are able to cross the subplate. It is possible that late-born cortical plate cells require Cdk5 to cross the subplate, but are activated by a factor other than p35 (perhaps p39).

An additional point is that the defect in p35−/− mutants is more severe in dorsomedial cortex, but lateral and ventrolateral cortices are less affected by the mutation, again suggesting that in the latter regions there might be other factors, in addition to p35, that activate Cdk5.

Based on these observations, I proposed a hypothesis suggesting that Cdk5 was a key factor in the evolutionary origin of the isocortical inside-out gradient.

This hypothesis postulated that in the cortical plate of the Cdk5/p35 mutant, and perhaps in that of an ancestral mammal-like reptile with an underplate. This does not occur in the adult reeler, in Cdk5−/− mice. It is possible that late-born cortical plate cells require Cdk5 to cross the subplate, but are activated by a factor other than p35 (perhaps p39).

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in the coordinates of the respective stimulus space in order to explore cooperative processes.

To explore the contribution of many cells to a common stimulus representation across visual space, we constructed dynamic population-RF's. A Gaussian interpolation procedure (for technical details see Refs 8,9) was used to depict the entire temporal structure of neural responses of nearly 200 single cells recorded in area 17. The population dynamics were captured using the time-slice technique, which is frequently used for calculation of single-cell dynamic RFs (time-slicing and reverse correlation are identical assuming the use of simple on-off stimuli). However, the spatio-temporal evolution of population-RF's differed compared with single-cell RFs. First, the time-scale of population RFs was much shorter: population activity was characterized by a gradual build-up and decay lasting only 40–50 ms, whereas single-cell dynamics typically vary over much longer periods.

Second, the profile of the population RFs indicated a remarkable spatio-temporal coherence across visual space (Fig. 1).

To understand these differences one has to recall how the construction of population RFs was achieved: because our main goal was to study the population response to a common stimulus (i.e. the contributions of all neurons responding to the given stimulus), its position was kept fixed irrespective of the location or specific properties of each RF analyzed. This procedure becomes intuitively clear when taking into account the fact that under natural viewing conditions, stimuli are similarly distributed in arbitrary ways across RFs. What is the impact of this procedure?

Using the common-response plane technique for assessment of RF dynamics, different positions within the RF of a cell are stimulated: when the time course of each position reveals substantial and systematic differences, the cell is said to be spatio-temporally non-separable. Assuming that about 50% of V1 neurons are non-separable and that our population response is a representative sample of V1, we would expect that separable and non-separable cells contribute in approximately equal proportions. However, the complex spatio-temporal behavior that is characteristic for non-separable cells appeared not to be preserved in our population dynamics. We therefore argue that, at the level of populations, each position in the visual field is well-represented by a large pool of neurons that respond maximally to any potential stimulus configuration.

Consequently, the structure of single-cell RF dynamics, characterized by highly complicated distributions of activity in space and time, transforms into much simpler spatio-temporal activity patterns (Fig. 1). A comparable coherence of overall response dynamics has also been observed for somatosensory cortical populations.

The transformation of the diversified spatio-temporal behavior of single cells into coherent ensemble dynamics might indicate a qualitative step of time-variant processing from microscopic into mesoscopic (e.g. population) levels in which the aspect of non-separability might become obsolete.

Such a lack of separability and complexity in response to stimuli that are very simple in shape and timing, however, does not necessarily imply that the single-cell dynamics are meaningless. Indeed, we assume that the detailed, idiosyncratic time structure is a consequence of cooperative processes that, in turn, are generated by non-linear time-dependent interaction effects across the entire neural network. At the population level, consistent coherent dynamics become observable that allow a direct link between physiological and psychophysical phenomena. Conceivably, the utilization of more complicated and demanding spatio-temporal stimulus configurations might allow a better understanding of cortical function. In fact, recent evidence from our laboratory indicates that moving stimuli are represented as coherently moving waves of population activity and that these waves emerge from active processes underlying lateral pre-activation and integration across the entire population.

Interestingly, the representations of moving stimuli were characterized by significantly shorter latencies compared with representations of a flash (D. Jancke et al. unpublished observations). Psychophysically, a flashed and a moving stimulus presented at the same location are perceived as being displaced. It is therefore tempting to speculate that the latency differences observed for populations contribute to the so-called 'flash-lag' effect.

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Glia-neuronal culture models - do we need to change the paradigms?

The review by Fields and Stevens was welcome in its much-needed emphasis on the roles of the neuregulin in the CNS and PNS, in this case focusing on how the important extracellular signaling molecule, ATP, might direct glia-neuron interactions. Several studies suggesting intriguing possibilities were described. However, a major deficiency that is apparent from this review is that almost all the studies, so far, have been carried out in various culture or co-culture systems or easily accessible PNS systems. There is a reasonably abundant body of work indicating differences between astroglial and other CNS glial properties in culture and in situ, and also similarities. The problem with this situation is that the similarities or differences are unpredictable so one always needs in situ knowledge of the property in question. Similarities and differences are also probably a function of how probing the questions are. So what systems should be used to get the reliable information that is required to know that our ideas of how the CNS or PNS works will not be forever flawed because it is not known what the ‘glia’ are actually doing? Currently the most reliable systems are tissue slices and freshly isolated cells (which provide information on the individual properties without the changes in gene expression that occur as a result of the culture environment), and of course the classical histological techniques with all their remarkable up-dates. Another feature that is well known but needs to be considered more rigorously is that glia refers to three major classes of different cells in the CNS with further subtypes, which in turn might shelter an unknown number of functional variants.

Resolution of these issues only appears possible by a shift of emphasis of a critical mass of productive laboratories from neuron to glial studies. This could be instituted by targeting funds to the glial field, but at whose behest and with what justification would we violate the principle of investigator-initiated science with its demonstrated creativity? To paraphrase Newton we still support the view that it is not for one group to direct the studies of another investigator. However, we all know that peer review, the litmus test of scientific merit, is in fact does this all the time, but in a reactive rather than proactive manner. The smallness of the ‘glia’ field and that technically easy, rather than harder and more reliable, experiments are mainly carried out, are both the cause and effect of the size of the field and the low amounts of reliable data. So when the cell neuron neuroscientists ask their poor country glial colleagues ‘so what do glia actually do?’, all we can say is ‘we’re working on it as best we know how. Well I have some answers for you as soon as we can.’

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Reference

*But he knows well ye it is not for one man to prescribe Rules to ye studies of another. ’From 1672 letter by Newton to Henry Oldenburg, secretary to the Royal Society, concerning the despised Robert Hooke.

Response:

Glia-neuronal culture models - do we need to change the paradigms?

Kimelberg raises several important points concerning studies of purinergic receptors in glia. Sensitivity to the importance of potential differences

References
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