PERSPECTIVES: NEUROSCIENCE

Switching On the Infant Brain

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It is hard to tell whether a baby can see or hear properly. The usual tests do not work well because of babies' limited attention span and their inability to comprehend the cognitive aspects of a behavioral test. Yet, especially in infants with sensory or motor disabilities, it is essential to reliably measure their abilities, so that remedial measures can be implemented without delay. The report by Maurer and her colleagues on page 108 of this issue (*1*) demonstrates that in infants born with an opaque lens (cataract) in one or both eyes—which usually leads to blindness—even a very brief period of visual exposure sets the stage for rapid development of the visual system.

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The visual world of the newborn human infant is unbelievably poor. The visual field consists of a narrow tunnel around the line of vision, and the ability to resolve visual details is roughly 40 times poorer than that of adult humans. What is more, newborns have no means to appreciate depth, and their eyes move in an uncoordinated manner.

Within weeks, newborn vision improves dramatically, and by 4 months of age, the ability to appreciate stereoscopic depth emerges. The field of view expands progressively, becoming equivalent to that in adults by the end of the first year of life. Visual acuity of the newborn improves steadily, changing rapidly during the first 6 months of life, and then more slowly thereafter. The ability to fix, follow, and focus on objects of interest improves daily from birth. Around a baby's first birthday, its visual world differs only slightly from that of a normal adult (*2*, *3*).

In rare cases, the amazing process of visual development fails. About 1 in 10,000 newborns first see the world through partially or completely clouded lenses (congenital cataracts). In this serious condition, vision never develops normally. If both eyes are affected, the child will grow up with a brain that cannot handle any visual images (binocular visual deprivation). If the affected lenses are not removed at once, the child's visual acuity, field of vision, and ability to use both eyes will remain at the level of a healthy newborn. But far more dramatic is the situation in which a child is born with a cataract in only one eye. In this child, vision in the affected eye is prevented from developing through active suppression by the nonaffected eye. Clearly, the two eyes compete for a glimpse of the outer world. If left untreated, vision in the affected eye, and the ability to use both eyes for binocular vision, will be permanently lost.

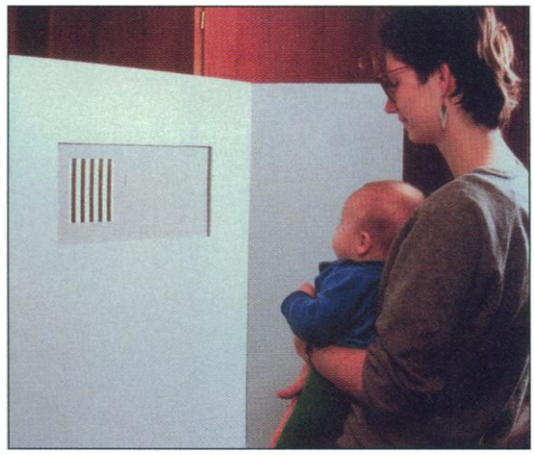
It is not actually the eye that suffers, but the brain. Lack of proper visual exposure prevents the developing human brain from establishing the exquisite, bewilderingly complex network of connections that form the basis of our ability to receive and interpret light reflected by the objects around us (*4*, *5*). Fortunately, cataracts can be diagnosed at birth. Removal of the affected lens and its replacement by a clear, artificial one gives the brain a chance to receive sharp, contrasted images—then, vision, even at a suboptimal level, can be achieved. But how much visual input is enough? Does the infant brain need hundreds of hours of visual experience (possibly accompanied by the enforced use of the affected eye) to resume the job of seeing, or is it merely a matter of seconds?

The Maurer study provides us with the long-awaited answer to this question. The investigators persuaded 28 human infants treated for congenital cataracts in one or both eyes (and their mothers) to participate in a psychophysical test designed to measure the infants' visual acuity (see the figure). This test capitalizes on the innate tendency of young human subjects to orient toward objects that contain more pattern than their surroundings—for example, a black-and-white striped patch on a gray background of identical mean luminance. Watching the infants' responses to stripes of increasing density (increasing spatial frequency) gives the researchers the opportunity to estimate their visual acuity (*6*, *7*).

Using this test, Maurer and colleagues found that, within a few minutes after exposure to the patterns, visual acuity was no better than that of normal newborns. As expected, acuity improved significantly over the next month. Remarkably, however, improvement was apparent after as little as 1 hour of cumulative visual exposure (for some infants this meant several hours during which short waking periods were interrupted by naps). Preventing vision in the treated eye by covering it with a patch did not result in any improvement.

It appears that lack of visual exposure maintains the visual cortex of infants at the newborn level. But, even a 1-hour exposure to the visual world sets the stage for rapid visual improvement. In these early stages, it makes no difference whether deprivation was monocular or binocular. In both cases, the lack of previous visual experience is what counts. Only at later stages does unfair competition between the healthy and affected eye result in additional effects.

The results of this careful study parallel recent findings in kittens. Here too, lack of visual input by artificial visual deprivation maintains the brain structures at a rudimentary state, characterized by diffuse connections and a lower level of activity. Onset of visual stimulation triggers an abrupt recovery in the kittens, which appears to be driven exclusively by neural activity (*8*, *9*).



Seeing is believing. An example of a visual acuity test on a human infant. The infant faces a card that displays a patch of black-and-white vertical stripes, embedded in a gray surround of matched average luminance. An observer—naïve to the side of presentation of the pattern—watches the reaction of the infant through a small peephole in the center of the card. The highest spatial frequency that the infant is deemed to see is taken as a measure of visual acuity.

How applicable are these findings to the plasticity of other sensory modalities? Does a sudden onset of, say, acoustic stimulation after a period of silence in a congenitally deaf child serve as a signal for rapid development of the brain structures concerned with the analysis of sound? Indeed, this is what happens: Congenitally deaf children in whom acoustic stimulation is provided by cochlear implants show

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a dramatic recovery, leading to nearly perfect acoustic communication and language competence. The neural basis of this improvement was reported several weeks ago in *Science* (*10*) by Klinke and his colleagues. They fitted congenitally deaf kittens with cochlear implants, which conveyed acoustic stimulation directly to the brain, circumventing the damaged sensory hair cells of the inner ear. These previously acoustically deprived kittens showed dramatic improvements: Field potentials of higher amplitudes were produced during cortical activity, the activated area of the auditory cortex expanded, and long-latency neural responses (indicative of intracortical information processing) developed and showed more synaptic efficacy than they did in naïve, unstimulated deaf cats. A similar recruitment of the auditory cortex might form the basis of hearing acquisition in prelingually deaf infants after cochlear implantation. It is quite likely that a similar "awakening" of the visual cortex takes place in congenitally blind infants newly exposed to visual information after cataract removal and the fitting of an artificial lens.

The Maurer study demonstrates the amazing plasticity of the young human brain, and underscores the importance of complete, balanced early sensory input for guiding subsequent brain development. It also shows how a simple psychophysical test can be used as a powerful tool for early diagnosis and for monitoring subsequent therapy for a rare, but devastating, human ailment.

References and Notes

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RNA CATALYSIS

Chemical Diversity in RNA Cleavage

Eric Westhof

Ribozymes are RNA molecules that possess a catalytic activity and, thus, behave as enzymes. Those that occur in nature can catalyze the formation of a phosphodiester bond between two nucleotides or can break that bond. The ribozymes from plant pathogens or the human hepatitis delta virus (HDV) are self-cleaving RNAs that undergo an intramolecular reaction (called transesterification), leading to 5′-hydroxyl group and 2′,3′-cyclic phosphate products. The self-cleaving reactions are necessary for replication of the single-stranded RNA genome of viral pathogens (*1*). Despite the similarities in products, the three-dimensional architectures of the characterized self-cleaving ribozymes (*2, 3*) do not appear to be similar. The distinct dependence of cleavage efficiency on the presence of metal ions or other organic molecules (*4, 5*) suggests that there is also chemical diversity in the mechanisms of cleavage. Now, a report on page 123 of this issue by Perrotta *et al.* (*6*) presents clear evidence for a unique catalytic cleavage pathway in the HDV ribozyme. They show that this ribozyme is capable of a process called base catalysis during self-cleavage. This discovery sheds new light not only on the mechanisms of RNA catalysis, but also on the chemical evolution of RNA in a hypothetical prebiotic RNA world. Possibly, it could also lead to other yet undiscovered biological enzymatic activities effected by RNA molecules.

The mechanism for RNA self-cleavage entails activating a specific ribose 2′-hydroxyl group for attacking the adjacent phosphodiester bond (*7*). Such a nucleophilic reaction demands an increase in negative charge on the attacking oxygen atom and an increase in positive charge on the phosphorus atom to be attacked. This is the reason why RNA is randomly cleaved and degraded into its constituent nucleotides at basic pHs: Hydroxide ions abstract the proton from the ribose 2′-hydroxyl group, whereas protons are transferred to the departing 5′-group. This catalytic mechanism is called specific acid-base catalysis. In the protein universe, the ribonucleases cleave RNAs using amino acids such as histidine, which carries an imidazole side chain that has a nitrogen atom with a pK_a around 6 (where K_a is the acid constant). During acid-base catalysis, the nitrogen of a histidine attacks the ribose hydroxyl, whereas another histidine gives off a proton to the departing 5′-hydroxyl group (see the figure). Acid-base catalysis is most efficient when the catalysts have pK_a's around 7 (a pK_a similar to that of the imidazole ring) (*7*). However, nucleic acids do not possess chemical groups that can be ionized around neutral pH. The best candidates are the ring nitrogens N1 of adenine (A) or N3 of cytosine (C) (with pK_a values of 3.9 and 4.5, respectively). But nucleic acids, because of the negative charges they carry, regularly require metal ions for folding and stabilization, and metal ions can be a good source of hydroxide ions at neutral pH. Ribozymes have therefore been considered as metalloenzymes that use metal ion catalysis, with the magnesium ion (which has strong affinity for phosphate oxygens) being the most common catalytic metal ion (*8*). It is this latter consensus that Perrotta and co-workers (*6*) now fracture.

Indeed, following hints from crystallography (*3*), they convincingly suggest that in the HDV ribozyme, a C residue acts as a general base catalyst. Although previously debated (*5*), this extension of the repertoire of catalytic mechanisms that are open to RNA brings forth anew the amazingly efficient parsimony of biological evolution, which takes advantage of every physicochemical characteristic of the four natural nucleic acid bases. Furthermore, this observation also points to a meaningful functional partition of the four bases into two groups: the amino bases, A and C, which could sustain general base catalysis, and the keto bases, guanine (G) and uracil (U), which could not because they carry an imino proton on the pyrimidine ring. But RNA functions foremost for maintenance and exchange of genetic information and, therefore, a certain degree of chemical lethargy is a valuable asset. In this respect it is worth noting that, during the editing of RNA, the modifications occur essentially from amino to keto bases, C to U or A to inosine (I), a keto purine (*9*).

For their demonstration, Perrotta and colleagues (*6*) introduce a method that is sure to become popular in the RNA field. It has long been known that cytidine C75 of the genomic HDV ribozyme (an infectious RNA) is essential for catalysis (*10*). In the antigenomic HDV ribozyme, a replicative intermediate, the equivalent cytosine (C76) could be mutated into A with a loss in catalytic efficiency of three orders of magnitude. But it could not be

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