*sophila* cells with an RNA virus triggers strong virus RNA silencing and that the same virus is equipped with an effective silencing suppressor essential for infection. These data provide direct evidence that RNA silencing naturally acts as an adaptive antiviral defense in animal cells. The specificity mechanism of this adaptive defense is based on nucleic acid base pairing between siRNA and its target RNA (*1*, *2*) and thus is distinct from cellular and humoral adaptive immunity based on peptide recognition (*19*). A prediction from our work is that heterologous sequences inserted into a replicating virus genome will lead to the production of a population of siRNAs capable of silencing other viral and cellular RNAs in trans that are homologous to the insert. Indeed, recent studies showed that viral sequences inserted in alphavirus vectors give rise to virus resistance in mosquitoes, which is dependent on the inserted RNA sequence rather than on its protein product (*20*, *21*). It will be of interest to determine if RNA silencing also plays a role in observed protection against mammalian viruses, derived similarly from heterologous expression of RNA sequences from a replicating RNA virus vector (*22*).

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fig. S1

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# Is Face Processing Species-Specific During the First Year of Life?

**Olivier Pascalis,[1*] Michelle de Haan,[2] Charles A. Nelson[3]**

**Between 6 and 10 months of age, the infant's ability to discriminate among native speech sounds improves, whereas the same ability to discriminate among foreign speech sounds decreases. Our study aimed to determine whether this perceptual narrowing is unique to language or might also apply to face processing. We tested discrimination of human and monkey faces by 6-month-olds, 9-month-olds, and adults, using the visual paired-comparison procedure. Only the youngest group showed discrimination between individuals of both species; older infants and adults only showed evidence of discrimination of their own species. These results suggest that the "perceptual narrowing" phenomenon may represent a more general change in neural networks involved in early cognition.**

At first glance the development of the ability to recognize faces appears to follow a typical trajectory: rapid change during infancy, followed by more gradual improvement into adolescence (*1*). This pattern contrasts with some aspects of language development. For example, speech perception is characterized by a loss of ability with age, such that 4- to 6-month-olds can discriminate phonetic differences that distinguish syllables in both their native and unfamiliar languages, whereas 10- to 12-month-olds can only discriminate the phonetic variations used in their native language (*2*, *3*). Here we describe a similar phenomenon for face recognition: Specifically, we demonstrate that 6-month-old infants are equally good at recognizing facial identity in both human and nonhuman primates, whereas 9-month-old infants and adults show a marked advantage for recognizing only human faces.

Nelson (*4*) has proposed that the ability to perceive faces narrows with development, due in large measure to the cortical specialization that occurs with experience viewing faces. In this view, the sensitivity of the face recognition system to differences in identity among the faces of one's own species will increase with age and with experience in processing those faces. By adulthood the extensive experience with human faces can be mentally represented as a prototype that is "tuned" to the face inputs most frequently observed (human faces), with individual faces encoded in terms of how they deviate from the prototype (*5*). Because infants begin to show evidence of forming face prototypes by 3 months of age (*6*), their face recognition should become more "human face specific" some time after this. This leads to the prediction that younger infants, who possess less experience with faces than older infants and adults, should be better than older infants or adults at discriminating between individual faces of other species.

This hypothesis is indirectly supported by several lines of research. For example, human adults are far more accurate in recognizing individual human than monkey faces; the opposite is true for monkeys (*7*). Such species-specificity may be due to the differential expertise in the two groups: monkeys are more familiar with monkey than human faces, whereas humans are more familiar with human than monkey faces. Human infants, of course, likely have no experience with monkey faces and relatively little experience with human faces. This may confer upon them a more broadly tuned face recognition system and, in turn, an advantage in recognizing facial identity in general (i.e., regardless of species). This prediction is supported by a preliminary study (*8*) in which it was demonstrated using event-related potentials (ERPs) that young infants, but not adults, could discriminate monkey face identity across changes in facial orientation. A second ERP study examined the influence of stimulus inversion, a manipulation that in behavioral studies impairs adults' recognition of identity of human faces

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more than objects (*9*). In adults, inversion affected only the processing of human faces and not monkey faces, whereas in 6-month-olds, inversion affected the ERPs similarly for human and monkey faces (*10*). This suggests that infants were processing facial identity in the two species comparably. It is noteworthy that this was not because they failed to detect the difference between the two species, as the early-latency sensory components of the ERP differed for human and monkey faces for both ages. None of these studies directly tested the discrimination abilities of older and younger infants and adults in the same experimental procedure. We compared the ability of 6- and 9-month-old infants and adults to process human and monkey faces with the same visual paired-comparison procedure. We hypothesized that if face recognition follows the same developmental pattern as language, the ability to process other species' faces will be present only in the youngest age group studied. A similar development (tuning period) for face recognition and for language may indicate a more general sensitive or tuning period for various cognitive functions. A visual paired-comparison procedure (VPC) was used to assess recognition in both infants and adults. VPC indexes the relative interest in the members of a pair of visual stimuli made of one novel item and one item already seen in a prior familiarization period. Recognition is inferred from the participant's tendency to fixate the novel stimulus significantly longer. The stimuli were colored pictures (Fig. 1) of human Caucasian (male and female faces from our collection) and monkey faces (*Macaca fascicularis*) [details of materials and methods (*11*)].

Eleven adult participants with no special expertise in monkey face recognition were tested (*11*). For human face stimuli, the average looking time toward the novel stimulus during the 5-s recognition tests was significantly longer (2.79 s) than that toward the familiar stimulus (1.63 s) (paired two-tailed $t$ test, $t = 3.93$, df = 10; $P < 0.01$). By contrast, for monkey face stimuli, participants looked as long at the novel stimulus (2.42 s) as at the familiar stimulus (2.31 s) (paired two-tailed $t$ test, $t = 0.30$, df = 10; $P > 0.05$).

Infant participants were 30 healthy, full-term 6-month-old infants and 30 healthy, full term 9-month-old infants. No differences were found in the amount of time required to reach the familiarization time between age groups nor between species of face (*11*). In 6-month-olds, for human face stimuli, the average looking time toward the novel stimulus during the 10-s recognition test for human face stimuli was significantly longer (4.55 s) than that toward the familiar face (3.57 s) (paired two-tailed $t$ test, $t = 2.67$, df = 14; $P < 0.05$). During the parallel test for monkey face stimuli, 6-month-olds looked at the novel face significantly longer (4.04 s) than at the familiar face (2.31 s) (paired two-tailed $t$ test, $t = 3.78$, df = 14; $P < 0.05$). During the 10-s test for human face stimuli, 9-month-old infants looked significantly longer toward the novel stimulus (4.50 s) than toward the familiar stimulus (3.63 s) (paired two-tailed $t$ test, $t = 3.44$, df = 14; $P < 0.05$). In contrast, for monkey face stimuli, 9-month-olds looked as long at the novel stimulus (3.86 s) as at the familiar stimulus (3.74 s) (paired two-tailed $t$ test, $t = 0.35$, df = 14; $P > 0.05$).

Our results with adults support our prediction and are consistent with prior findings (*7*). It is important to note that this failure to recognize monkey face identity is not due to the lack of explicit instruction to do so. Our previous work shows that even in a classic forced-choice task, human adults are worse at recognizing monkey faces (55%) than human faces (73%) (*12*).

The infants' results support our predictions: 9-month-olds showed a pattern similar to that of adults, whereas 6-month-olds showed a preference for the novel facial identity both when tested with human faces and with monkey faces. The results of 6-month-olds and adults are also consistent with previous electrophysiological studies showing a difference in the specificity of face processing between these ages (*8*, *10*). Our experiments support the hypothesis that the perceptual window narrows with age and that during the first year of life the face processing system is tuned to a human template (*4*). This early adjustment does not rule out the possibility that later in life individuals can learn how to discriminate a new class of stimuli on a perceptual basis (*13*). As is the case for speech perception, our evidence with face processing indicates the existence of an early tuning period that is likely dependent on experience. Although it is difficult to compare directly the tuning of speech perception with the tuning of face perception, there may be overlap between these systems. By 3 months of age infants are already relating these two types of information, as they are able to associate faces with voices (*14*). Systems for processing faces and for processing speech may thus develop in parallel, with a similar timing and a mutual influence. One possibility is that there is a general perceptuo-cognitive tuning apparatus that is not specific to a single modality and that can be described as an experience-expectant system [for discussion see (*15*)]. Alternatively, the concordance in age may simply be a developmental coincidence, thus reflecting a modality-specific, experience-dependent process. Distinguishing between these views will be facilitated by further developmental and comparative studies.

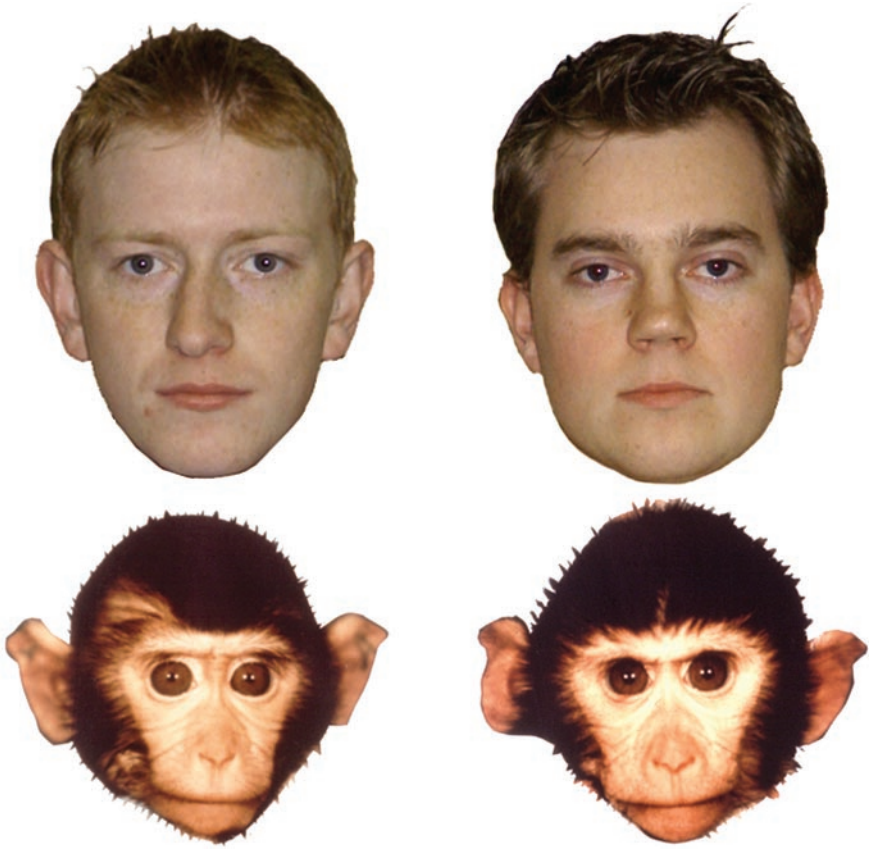

**Fig. 1.** Examples of stimuli used (*11*).


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# Direct Recognition of Cytomegalovirus by Activating and Inhibitory NK Cell Receptors

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**Natural killer (NK) cells express inhibitory receptors for major histocompatibility complex (MHC) class I antigens, preventing attack against healthy cells. Mouse cytomegalovirus (MCMV) encodes an MHC-like protein (m157) that binds to an inhibitory NK cell receptor in certain MCMV-susceptible mice. In MCMV-resistant mice, this viral protein engages a related activating receptor (Ly49H) and confers host protection. These activating and inhibitory receptors are highly homologous, suggesting the possibility that one evolved from the other in response to selective pressure imposed by the pathogen.**

Natural killer (NK) cells mediate innate immunity against viruses, bacteria, parasites, and tumors by using an array of cell surface receptors that regulate their response (*1*). In rodents, the *Ly49* family of genes encodes both activating and inhibitory NK cell receptors (*2*). The inhibitory Ly49 receptors recognize major histocompatibility complex (MHC) class I and suppress NK cell attack against healthy cells but permit a response against cells that have lost class I expression (*3*). The function of the activating Ly49 receptors has remained elusive. However, recent reports have implicated the activating Ly49H receptor that is expressed on NK cells from mouse cytomegalovirus (MCMV)–resistant mice [strain C57BL/6 (B6)] in immune protection against MCMV infection (*4–6*).

We considered several possibilities to explain Ly49H-mediated protection against MCMV. Because other Ly49 receptors recognize mouse H-2 class I proteins, Ly49H might recognize self H-2 presenting a viral peptide. Alternatively, Ly49H may recognize a host MHC class I protein that is induced after viral infection of cells, in a manner similar to the NKG2D receptor, which recognizes the stress-induced class I–like molecule MIC in human CMV (HCMV)–infected cells (*7*). Finally, Ly49H could directly bind to an MCMV-encoded protein.

In order to test these possibilities, we transfected a mouse T cell hybridoma carrying a NFAT–green fluorescent protein (GFP) reporter construct with Ly49H and the DAP12 signaling adapter protein (*8*). Cross-linking with monoclonal antibody (mAb) to Ly49H induced GFP expression, confirming that the receptor was functional (*9*). When these Ly49H reporter cells were cocultured for 18 hours with mouse NIH-3T3 cells infected with MCMV Smith strain or with the K181 strain (*9*), they turned green, indicating the presence of a Ly49H ligand (Fig. 1A). Ly49H reporter cells cultured with uninfected NIH-3T3 cells or parental T hybridoma cells

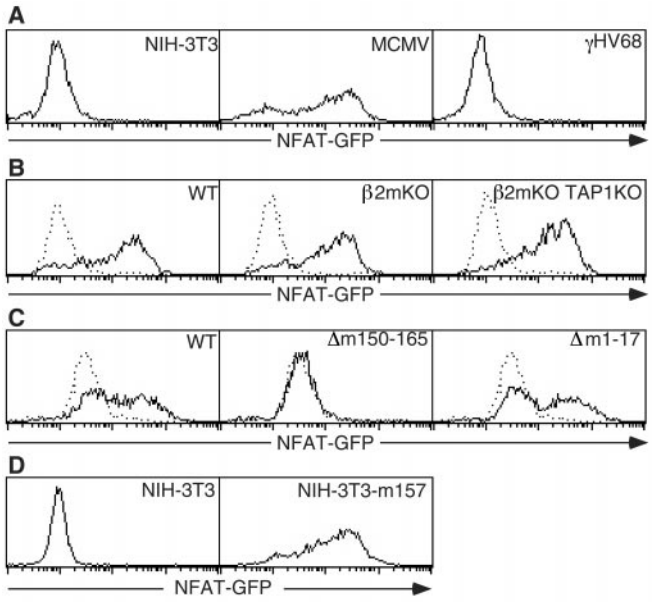


**Fig. 1.** Activation of Ly49H reporter cells by MCMV-infected cells. (**A**) Ly49H reporter cells were cocultured with MCMV or γ-herpesvirus 68–infected NIH-3T3 cells for 18 hours, and GFP expression was analyzed by flow cytometry with a FACSCaliber flow cytometer (Becton Dickinson, San Jose, CA). (**B**) β2 microglobulin–deficient, β2 microglobulin– and TAP-deficient, or wild-type mouse SV40-transformed embryonic fibroblasts were infected with MCMV and cocultured with Ly49H reporter cells for 2 days. GFP expression was analyzed by flow cytometry. Histograms of Ly49H reporter cells cocultured with uninfected cells (dotted lines) are superimposed over histograms of MCMV-infected cells (solid lines). KO, knockout. (**C**) NIH-3T3 cells were infected with wild-type MCMV or ΔMS 94.5 (m150-m165 deletion mutant) or with ΔMS 94.7 (m1-m17 deletion mutant) MCMV. Thereafter, Ly49H reporter cells were cocultured with the infected (solid lines) or uninfected (dotted lines) cells, and GFP expression was analyzed. (**D**) Ly49H reporter cells were cocultured with parental NIH-3T3 cells or NIH-3T3 cells transduced with m157, and GFP expression was analyzed.

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