giving a statistic image for each contrast. P values for activations in the amygdala were corrected for the volume of brain analysed (specified as a sphere with radius 8 mm)[29]. Anatomical localization for the group mean-condition-specific activations are reported in standard space[28]. In all cases, the localization of the group mean activations was confirmed by registration with the subject's own MRIs.

In an initial conditioning phase immediately before scanning, subjects viewed a sequence of greyscale images of four faces taken from a standard set of pictures of facial affect[30]. Images of a single face were presented on a computer monitor screen for 75 ms at intervals of 15–25 s (mean 20 s). Each of the four faces was shown six times in a pseudorandom order. Two of the faces had angry expressions (A1 and A2), the other two being neutral (N1 and N2). One of the angry faces (CS+) was always followed by a 1-s 100-dB burst of white noise. In half of the subjects A1 was the CS+ face; in the other half, A2 was used. None of the other faces was ever paired with the noise. Before each of the 12 scanning windows, which occurred at 8-min intervals, a shortened conditioning sequence was played consisting of three repetitions of the four faces. During the 90-s scanning window, which seamlessly followed the conditioning phase, 12 pairs of faces, consisting of a target and mask, were shown at 5-s intervals. The target face was presented for 30 ms and was immediately followed by the masking face for 45 ms (Fig. 1). These stimulus parameters remained constant throughout all scans and effectively prevented any reportable awareness of the target face (which might be a neutral face or an angry face).

There were four different conditions (Fig. 1), masked conditioned, non-masked conditioned, masked unconditioned, and non-masked unconditioned. Throughout the experiment, subjects performed the same explicit task, which was to detect any occurrence, however fleeting, of the angry faces. Immediately before the first conditioning sequence, subjects were shown the two angry faces and were instructed, for each stimulus presentation, to press a response button with the index finger of the right hand if one the angry faces appeared, or another button with the middle finger of the right hand if they did not see either of the angry faces.

Throughout the acquisition and extinction phases, subjects' SCRs were monitored to index autonomic conditioning. SCRs were measured with Biodata galvanic skin response equipment using Ag/AgCl electrodes attached to the palmar surface of the middle phalanges of the index and middle fingers of the left hand. We took readings of skin conductance (in μS) every 500 ms and stored them digitally on computer. All SCRs were square-root-transformed to attain statistical normality. Using the SCR in the 4-s period before presentation as a baseline, the maximal SCR deflection in the period 0.5–4 s after a face was presented was assigned as the value for the SCR to that face. The mean SCRs for the CS+ and CS− angry faces were calculated for both the masked and the unmasked conditions, and the differences between the means were tested using a paired Student's t-test.

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The human amygdala in social judgment

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Studies in animals have implicated the amygdala in emotional[1–3] and social[4–6] behaviours, especially those related to fear and aggression. Although lesion[7–10] and functional imaging[11–13] studies in humans have demonstrated the amygdala's participation in recognizing emotional facial expressions, its role in human social behaviour has remained unclear. We report here our investigation into the hypothesis that the human amygdala is required for accurate social judgments of other individuals on the basis of their facial appearance. We asked three subjects with complete bilateral amygdala damage to judge faces of unfamiliar people with respect to two attributes important in real-life social encounters: approachability and trustworthiness. All three subjects judged unfamiliar individuals to be more approachable and more trust-worthy than did control subjects. The impairment was most striking for faces to which normal subjects assign the most negative ratings: unapproachable and untrustworthy looking individuals. Additional investigations revealed that the impairment does not extend to judging verbal descriptions of people. The amygdala appears to be an important component of the neural systems that help retrieve socially relevant knowledge on the basis of facial appearance.

Data from three subjects with complete bilateral amygdala damage (subjects SM, JM and RH) and seven with unilateral amygdala damage were compared to those from normal and from brain-damaged control subjects (see Table 1 and Methods). Ratings of approachability and of trustworthiness were analysed separately for the 50 faces to which normal controls assigned the most negative ratings, and for the 50 most positive faces. Subjects with bilateral amygdala damage rated the 50 most negative faces more positively than did either normal controls ($P < 0.01$) or brain-damaged controls ($P < 0.05$; Mann–Whitney U-tests on subjects' mean ratings, Bonferroni corrected) (Fig. 1). Groups with unilateral amygdala lesions did not differ from controls on either rating. All subject groups gave similar ratings to the 50 most positive faces.

Subject SM spontaneously commented during the experiment that, in real life, she would not know how to judge if a person were trustworthy, consistent with her tendency to approach and engage in physical contact with other people rather indiscriminately[7,14]. All subjects with bilateral amygdala damage had normal ability to discriminate faces (Table 1), clear evidence that there were no visuoperceptual impairments that might account for the above findings.

Data from subjects with bilateral amygdala damage showed two effects: the subjects tended to rate all faces more positively than did controls, and they also showed the largest deviation from control ratings specifically when rating the most negative faces (Fig. 2). This suggests an overall positive bias, as well as a disproportionate impairment in rating the most negative faces. To establish the independence of these two effects, we carried out a detailed two-alternative forced-choice task with JM, RH and SM, using the same 100 face stimuli. We asked JM and RH to choose the more approachable face in pairwise comparisons between an anchor face that received a mean normal rating of 0.0 and each of the remaining 99 faces. We compared subjects' choices on this task to the choices that would be expected from the mean approachability ratings given to the faces in each pair by normal controls. JM and RH consistently made more incorrect choices when making comparisons to very negative faces, than when making comparisons to very positive faces (Fig. 3a). By contrast, the small number of errors made by normal controls occurred in the opposite direction, with positive rather than with negative faces (Fig. 3a), indicating that the impairments seen in amygdala subjects cannot be explained by stimulus difficulty.

In subject SM, we carried out forced-choice tasks with a total of five anchor faces, including faces normally rated very negatively and very positively. Each anchor face was paired with the remaining 99 faces, for a total of $5 \times 99 = 495$ pairwise comparisons. SM made the largest number of incorrect choices in comparisons involving those of the five anchor faces that normally receive the most negative
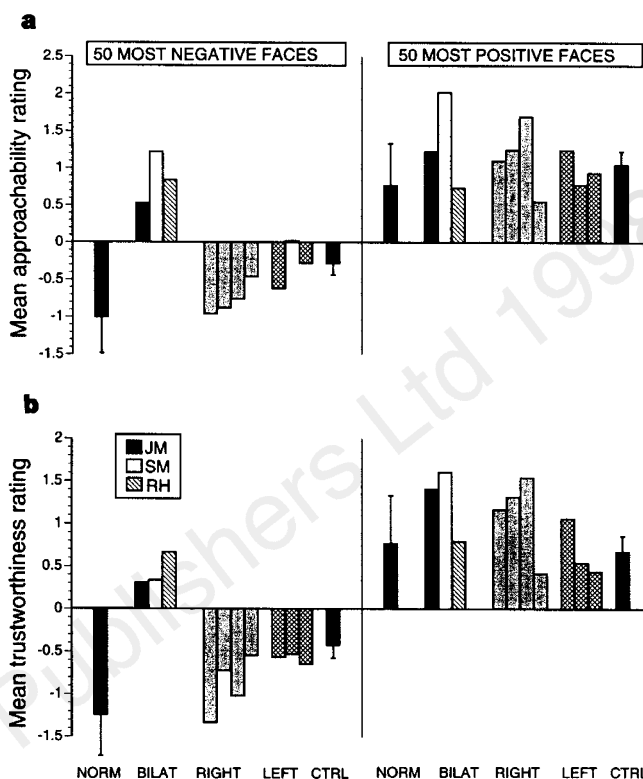

Figure 1 Mean judgments. **a**, Approachability; **b**, trustworthiness of the faces of 100 unfamiliar people, shown for the 50 faces that received the most negative (left) and most positive (right) mean ratings from normal controls. Data are shown from 46 normal controls (NORM; means and s.d.), 3 subjects with bilateral amygdala damage (BILAT; individual means), 4 subjects with unilateral right (RIGHT) and 3 with unilateral left (LEFT) amygdala damage, and 10 brain-damaged controls with no damage to amygdala (CTRL; means and s.e.m.).
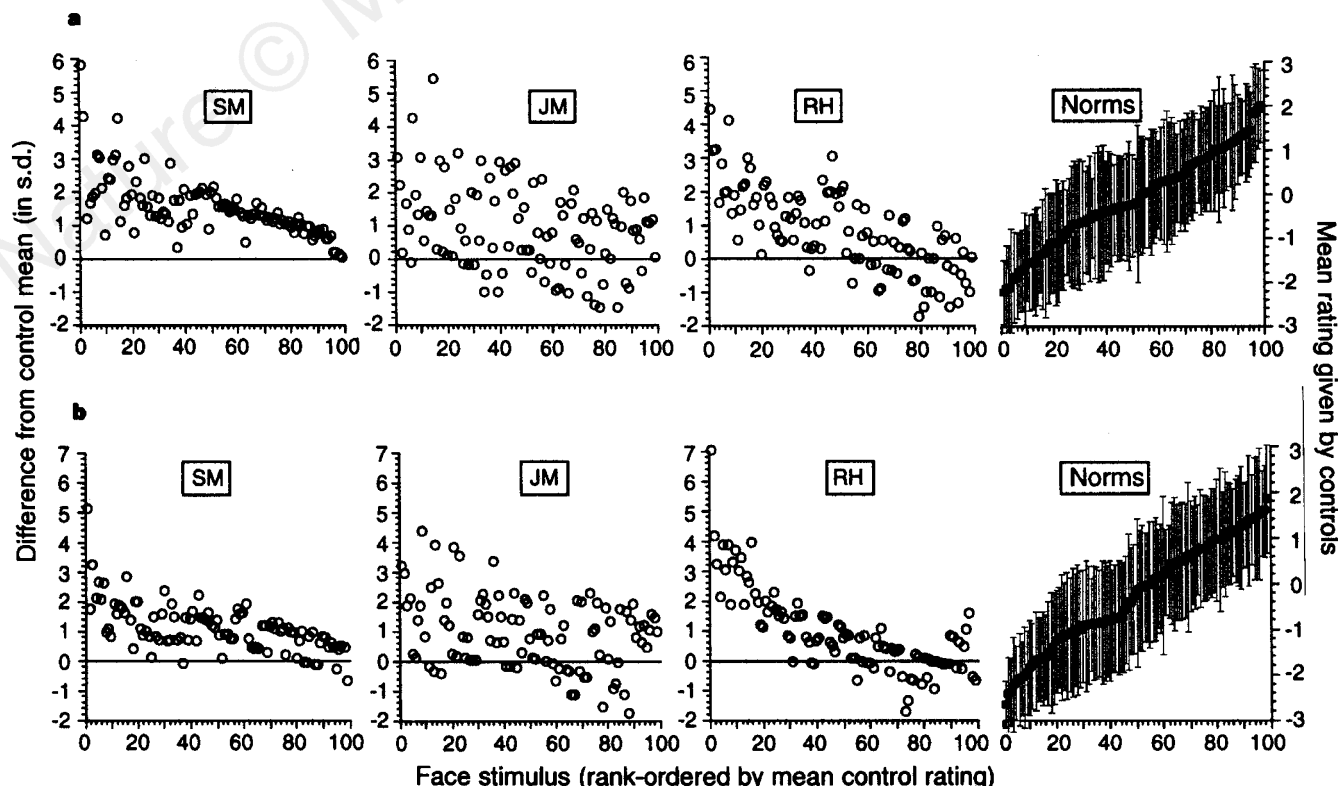

Figure 2 Deviations from normal judgments. **a**, Approachability; **b**, trustworthiness given by subjects with bilateral amygdala damage (circles; left y-axis). Units are standard deviations of the normal control ratings. Stimuli are rank-ordered on the x-axis according to the ratings normal controls gave them (squares; far right y-axis; means and s.d.).

ratings, a performance that was highly abnormal compared to control subjects' forced-choices in the same task (Fig. 3b). The findings from the forced-choice tasks cannot be explained solely on the basis of a general positive bias, and confirm that judgments given by subjects with bilateral amygdala damage are disproportionately impaired relative to individuals who are normally classified as unapproachable.

Might the impairment seen in subjects with bilateral amygdala damage extend to judging people from word descriptions rather than from faces? We asked subjects to rate the likeability of different individuals based on short verbal biographies or on single words (adjectives describing people). All three subjects with bilateral amygdala damage made entirely normal judgments when the stimuli were verbal (Fig. 4). This critical dissociation supports the
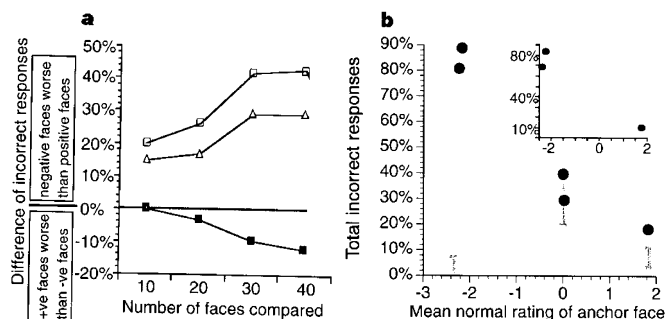
following interpretation. The amygdala appears necessary to trigger the retrieval of information on the basis of prior social experience or innate bias in regard to certain classes of faces[15]. The retrieved information might be either covert or overt, or both (compare with ref. 16). The failure due to amygdala damage thus occurs after basic visual processing has taken place, by blocking the retrieval of information normally linked either to negative past experiences with similar stimuli, or to innately specified feature configurations. By contrast, sentences and words evoke a broad sweep of information directly, without the need for the amygdala's assistance, thus providing a sufficient basis for performing judgments normally.

A further question concerns the specific facial cues that would normally engage the amygdala in social judgment. Might amygdala lesions impair judgments based only on certain facial features? This does not seem to be the case, as subjects with bilateral amygdala lesions gave idiosyncratic ratings to specific negative faces (Fig. 2; intersubject Spearman rank correlations of ratings given by subjects with bilateral amygdala lesions for the 50 most negative faces: $-0.23 < r < 0.31$). We further explored this complex issue by choosing the 10 faces to which SM had given the most abnormal ratings of approachability (all rated very negatively by controls), and systematically manipulating individual features in each face. We showed subjects 109 pairs of faces in which each pair showed the same individual differing by only one single feature. We manipulated direction of gaze (45 stimuli), expression of the eyes (27 stimuli), expression of the mouth (14 stimuli), or visibility of the eyes (for example, with glasses of different tint; 23 stimuli), all features that might conceivably contribute to the subjects' judgments. In a two-alternative forced-choice task, SM and 16 normal controls were asked to choose the face they would prefer to approach. SM performed entirely normally on this task. Logistic linear analysis, with subjects' binary choices as the dependent variable and the manipulated features as factors, showed that SM did not differ from controls in her choices with respect to any of the above features that we had manipulated. Insensitivity to particular features, in isolation, is thus unlikely to account for the impairment in judging approachability or trustworthiness in faces.

The findings suggest that the human amygdala triggers socially and emotionally relevant information in response to visual stimuli. The amygdala's role appears to be of special importance for social judgment of faces that are normally classified as unapproachable and untrustworthy, consistent with the amygdala's demonstrated role in processing threatening and aversive stimuli. An intriguing question that remains to be addressed is the amygdala's relative participation in triggering information that is innate, versus infor-
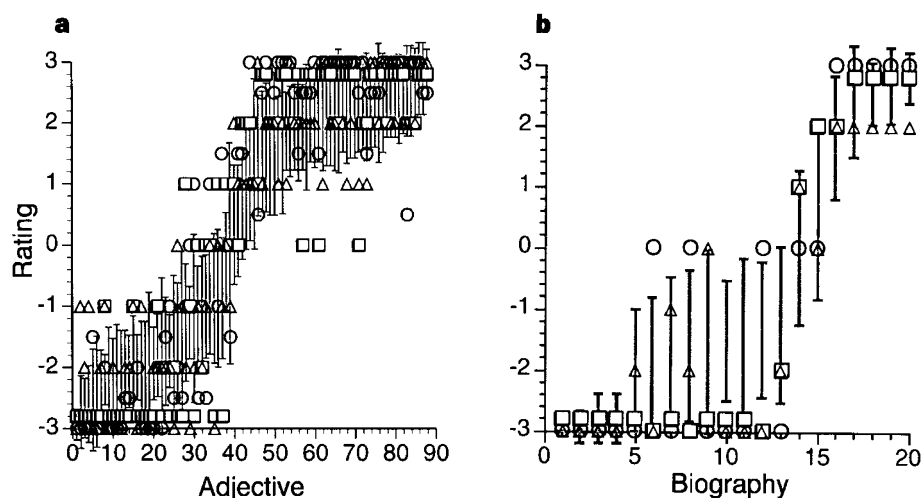

Figure 3 Disproportionate impairment in choosing the most unapproachable faces. **a**, JM's (empty squares), RH's (triangles) and normal controls' (filled squares) judgments of approachability from two-alternative forced-choice tasks. We calculated the per cent incorrect choices made for pairings involving faces at either extreme of the normal rating scale (that is, faces that were normally rated as either very approachable or very unapproachable). The x-axis shows the number of faces at either extreme of the normal rating scale over which the per cent incorrect choices was calculated. The y-axis shows the difference in the errors made (unapproachable – approachable). **b**, SM's judgments of approachability from two-alternative forced-choice tasks. The mean normal rating of approachability given to each of 5 anchor faces is shown on the x-axis, and the proportion of incorrect forced choices (out of 99) made by SM (circles) and by normal controls (grey bars show range) are shown on the y-axis. Inset, analysis of SM's data from this task for only those pairs of faces whose mean control rating differed by more than 2 rating points. Data from comparisons involving the two faces with mean control ratings of 0 were not analysed, as very few faces with ratings <−2 or >2 could be paired with them. No normal control made any incorrect choices in this analysis.

Figure 4 Likeability ratings of lexical stimuli. **a**, Ratings given by SM (2 experiments; circles), JM (squares), RH (triangles) and 20 normal controls (s.d.

shown as bars) to 88 adjectives describing personality. **b,** Ratings given by SM, JM, RH and 20 normal controls to 20 biographical descriptions of people.

Table 1 Neuropsychology background data

Subject	SM	JM	RH	Left	Right	BD Ctrl	N Ctrl
N				3	4	10	46
Age	31	67	42	29 ± 5	31 ± 5	66 ± 10	19 ± 1
PIQ	90	95	108	104 ± 24	103 ± 24	98 ± 11	–
Benton (%ile)	71st	12th	20th	32nd	50th	48th	–
Expression discrimination	70 (40)	45 (20)	59 (15)	–	–	–	–
Gender discrimination	75th	65th	65th	–	–	–	–
Gaze discrimination	64th	86th	86th	–	–	–	–

SM, JM, RH, bilateral amygdala damage; Left, Right, unilateral amygdala damage; BD Ctrl and N Ctrl, brain-damaged and normal controls. PIQ, performance IQ from the Wechsler Adult Intelligence Scale-revised. Benton, percentile score on the Benton Facial Recognition Test, a measure of ability to discriminate among unfamiliar faces[18]. Expression, gender, gaze discrimination, percentile score on two-alternative forced-choice discrimination tasks of emotional facial expressions (average and minimum (in parentheses) for the 6 basic emotions), gender, and direction of gaze. See Methods for details.

mation that is acquired through individual experience in a cultural setting[17]. ☐

Methods

Subjects. All subjects had given informed consent to participate in these studies. Brain-damaged subjects were selected from the Patient Registry of the Department of Neurology at the University of Iowa, and had been fully characterized neuropsychologically[18] and neuroanatomically[19,20].

Amygdala damage. Subject SM has complete lesions of both amygdalae, as well as minimal damage to anterior entorhinal cortex, resulting from Urbach-Wiethe disease[7,14,21,22]. Subjects RH and JM had encephalitis at ages 28 and 62, respectively, resulting in complete bilateral destruction of the amygdala and substantial damage to surrounding structures. Both patients are severely amnesic. Seven subjects with unilateral amygdala lesions (4 right, 3 left) had surgical temporal lobectomy for the treatment of epilepsy, and also had damage to hippocampus and surrounding temporal cortices.

Control subjects. We examined 10 brain-damaged controls with lesions that did not include the amygdala. Four of the subjects had bilateral lesions. Three of the subjects were amnesic consequent to anoxia and hippocampal damage. We also examined 46 normal controls (16M/30F) who were undergraduates at the University of Iowa.

Stimuli and tasks. In all tasks, stimuli within each session were presented in randomized order, and without time limit.

Approachability and trustworthiness ratings of faces. We selected from a larger set of photographs 100 final stimuli whose ratings had low variance and were evenly distributed (Fig. 2). There was no effect of subject gender on rating the faces ($P > 0.7$, ANOVA on normal data). Stimuli were black-and-white photographs of unfamiliar male ($N = 55$) and female ($N = 45$) faces in natural poses.

Subjects were asked to rate the stimuli, shown one at a time on a slide projector, on a 7-point scale (-3 to $+3$) with respect to either approachability or trustworthiness. For approachability, subjects were asked to imagine meeting the person on the street, and to indicate how much they would want to walk up to that person and strike up a conversation. For trustworthiness, subjects imagined trusting that person with all their money, or with their life. Each of the two attributes was rated in two independent sessions in counterbalanced order; there were no order effects.

Approachability and trustworthiness were chosen because (1) they are clear measures of real-life social judgment; (2) they are easy to understand; and (3) pilot data indicated that ratings of these specific attributes had lower variance than those obtained with other words, such as 'nice' or 'good'. Although approachability and trustworthiness ratings in normals were somewhat correlated (mean $r = 0.52$), there were many stimuli that received discrepant ratings on the two attributes, indicating that they were non-redundant measures of social judgment.

Forced-choice tasks. Direct pairwise comparisons of approachability were made between an anchor face, and each of the remaining 99 faces, all drawn from the same 100 face stimuli used in other tasks. We calculated the proportion of subjects' choices that differed from the choices that would be expected on the basis of the mean normal control ratings given to each of the two faces in a pair.

In one experiment (Fig. 3a), each of two anchor faces with a mean normal approachability rating of 0.0 was compared to other faces that were either very approachable or very unapproachable; data obtained with both anchor faces were very similar and were pooled. In a second experiment (Fig. 3b), each of 5 anchor faces (which included faces with a range of ratings) was compared to all other 99 faces (a total of 495 pairwise comparisons).

Lexical stimuli. We chose 88 adjectives that described personality attributes from a large standardized set[23] so as to span the range from very likeable to very dislikeable, and to exhibit maximal reliability and common usage. Twenty short biographies described people by giving information about the person's lifestyles and activities. Subjects rated how much they liked individuals described by the stimuli, on a scale of -3 to $+3$. Words were presented visually on a sheet of paper; biographical descriptions were read to subjects.

Control tasks. For each of the control tasks, we calculated thresholds at which subjects were just able to discriminate stimuli. Data were converted to percentiles compared to performances given by normal subjects ($N = 28$ for expression, 20 for gender, 28 for gaze).

Expression discrimination. Two-alternative forced-choice discriminations were made between 80 images of a neutral face, and 80 images that were linear morphs between the neutral face and facial expressions of emotion[24] (happiness, surprise, fear, anger, disgust, sadness). Subjects were asked to choose the image that showed more of a stated emotion.

Gender discrimination. Two-alternative forced-choice discriminations were made between 84 pairs of images that were morphs between an average composite of a neutral male face, and an average composite of a neutral female face, of equal age.

Gaze discrimination. Two-alternative forced-choice discriminations were made between 16 pairs of images showing the same, neutral, male face in which only direction of gaze had been varied by manipulating the digital image on a computer.

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A conditioned dendritic cell can be a temporal bridge between a CD4+ T-helper and a T-killer cell

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To generate an immune response, antigen-specific T-helper and T-killer cells must find each other and, because they cannot detect each other's presence, they are brought together by an antigen-loaded dendritic cell that displays antigens to both[1–3]. This three-cell interaction, however, seems nearly impossible because all three cell types are rare and migratory. Here we provide a potential solution to this conundrum. We found that the three cells need not meet simultaneously but that the helper cell can first engage and 'condition' the dendritic cell, which then becomes empowered to stimulate a killer cell. The first step (help) can be bypassed by modulation of the surface molecule CD40, or by viral infection of dendritic cells. These results may explain the long-standing paradoxical observation that responses to some viruses are helper-independent, and they evoke the possibility that dendritic cells may take on different functions in response to different conditioning signals.

We began our study to discriminate between two interpretations of this three-cell interaction (Fig. 1). The antigen-presenting cell (APC) has been proposed to have a rather passive relationship with the killer cell (also known as a cytotoxic T lymphocyte) and to function mainly to stimulate the helper cell to produce the interleukin (IL)-2 that the killer needs[1,2] (Fig. 1a). There is no guarantee, however, that a rare helper and an equally rare killer should find the same APC at the same time. As resting killers recognizing antigen become tolerant if there is no help[4–6], many potentially useful killers would founder while, elsewhere, some T helpers would wastefully secrete cytokines into an environment containing no killers to receive them. We therefore suggested a dynamic model (Fig. 1b) in which the T helper stimulates the APC to become able to activate the killer[6].

To discriminate between these possibilities, we studied responses to the male antigen H–Y because, first, killers that recognize H–Y are helper-dependent[6,7]; second, H–Y has no known crossreactive environmental mimics[8]; and third, primary and secondary

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responses can be easily distinguished because T cells from normal virgin female mice respond *in vitro* only if they were first primed *in vivo* with professional APCs[7,9].

Figure 2a–c shows that help is necessary for generation of killing activity against H–Y and that it can be replaced by soluble factors[1]. Female C57Bl/6 (B6) mice, immunized *in vivo* with male spleen cells, generated good *in vitro* killer-cell responses against male spleen stimulators (Fig. 2a). The responses disappeared if we removed the CD4+ cells just before the culture (Fig. 2b) and reappeared if we added soluble helper factors (concanavalin A supernatant (CAS); Fig. 2c).

In some cases where help is minimal, such as in newborns (which have very few T cells) and in B6.bm12 mice (with mutated major histocompatibility complex (MHC) class II molecules), a killer-cell response can be induced by an injection of activated male dendritic cells[10,11]. We found, however, that activated dendritic cells could not stimulate purified CD8+ killer cells unless we added helper cells, in the form of Marilyn, an H–Y-specific T-helper clone (Fig. 2e). Thus a small number of helpers may go a long way but without them dendritic cells are unable to activate killers against H–Y.

Because activated T helpers express CD40-ligand, which can stimulate CD40 to induce proliferation in B cells[12] and enhance the function of dendritic cells[13,14], we tried replacing T-cell help with antibodies against CD40. We found that overnight crosslinking with anti-CD40 antibodies turned dendritic cells into excellent stimulators (Fig. 2f). To rule out the possibility that the crosslinked dendritic cells were simply stimulating better IL-2 production from a few contaminating CD4+ cells, we tested dendritic cells from MHC-class II-knockout (MHC II KO) mice, which are deficient in MHC class II molecules because of a gene-targeted deletion. Although these dendritic cells cannot present antigen to CD4+ helpers, they became good stimulators for killers (Fig. 2h).

a Three-cell interaction
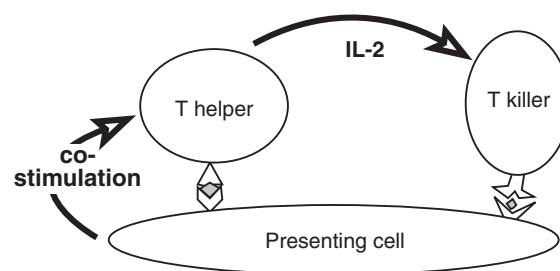
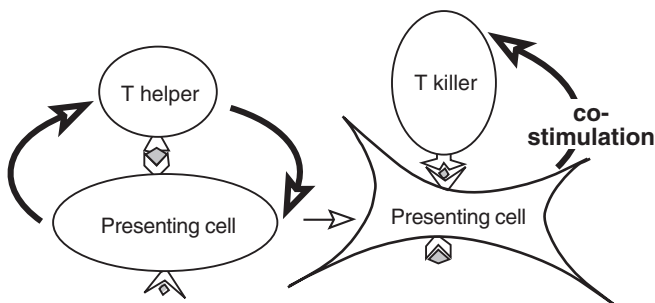**b** Sequential two-cell interactions

Figure 1 Two models of the delivery of help to CD8+ killers. **a,** The 'passive' model in which the dendritic (presenting) cell presents antigen to both the T helper and the killer but delivers co-stimulatory signals only to the helper, which is thereby stimulated to produce IL-2 for use by the nearby killer. **b,** The 'dynamic' model in which the dendritic cell offers co-stimulatory signals to both cells. It initially stimulates the T helper (left), which, in turn, stimulates and 'conditions' the dendritic cell to differentiate to a state (right) where it can now directly co-stimulate the killer.