Affective blindsight: intact fear conditioning to a visual cue in a cortically blind patient

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Summary

Blindsight refers to remarkable residual visual abilities of patients with damage to the primary visual cortex (V1). Recent studies revealed that such residual abilities do not apply only to relatively simple object discriminations, but that these patients can also differentially categorize and respond to emotionally salient stimuli. The current study reports on a case of intact fear conditioning to a visual cue in a male patient with complete bilateral cortical blindness. The patient was admitted to the stroke unit of the neurological department because of complete loss of vision. Both CT and structural MRI scans confirmed lesions in both territories of the posterior cerebral artery. No visual evoked potentials could be detected confirming complete cortical blindness. During fear conditioning, a visual cue predicted the occurrence of an aversive electric shock. Acoustic startle probes were presented during and between the conditioned stimuli. Relative to the control condition, startle reflexes were substantially potentiated when elicited in the presence of the conditioned stimuli. No such potentiation was observed prior to conditioning. These data suggest that fear learning to visual cues does not require a cortical representation of the conditioned stimulus in the primary sensory cortex and that subcortical pathways are sufficient to activate the fear module in humans.

Introduction

Blindsight refers to remarkable residual visual abilities of patients suffering from damage to the striate cortex (V1). It has been demonstrated that these patients can accurately detect, discriminate and localize visual stimuli presented in their blind field, without being able to report any accompanying conscious visual experience (Weiskrantz, 1997, 2000). A number of studies showed that cortically blind patients are able to behaviourally discriminate different colours, simple shapes or movements of objects while they insist that they cannot see these stimuli (Barbur *et al.*, 1980; Stoerig and Cowey 1992; Weiskrantz, 2000). Recently, De Gelder and colleagues reported for the first time that such residual abilities do not only apply for relatively simple stimulus properties, but for emotional salience of stimuli as well (De Gelder *et al.*, 1999). In this study, De Gelder and colleagues presented short video clips of a female face pronouncing the same sentence with either a happy, angry, sad or a fearful facial expression to a patient (G.Y.) with

damage to his left occipital lobe. In various forced choice tests, patient G.Y. was able to discriminate between the different emotional expressions above chance when presented in his blind hemifield. G.Y. was not aware of the faces he responded to.

It has been suggested that this remaining but non-conscious visual capacity might be mediated by an extrageniculate parallel visual pathway to the extrastriate cortex bypassing the striate cortex (V1) and involving the superior colliculus and the posterior visual thalamus (pulvinar), which remain functional in a blindsight patient. Recent neuroimaging data by Morris and colleagues suggest that these residual abilities might also be amygdala-dependent (Morris *et al.*, 1998). In their first study with unimpaired subjects, Morris and colleagues detected stronger activation of the amygdala in PET scans in response to a conditioned stimulus (angry face) that was followed by an aversive sound. To experimentally reproduce 'blindsight' in these sighted volunteers, conscious
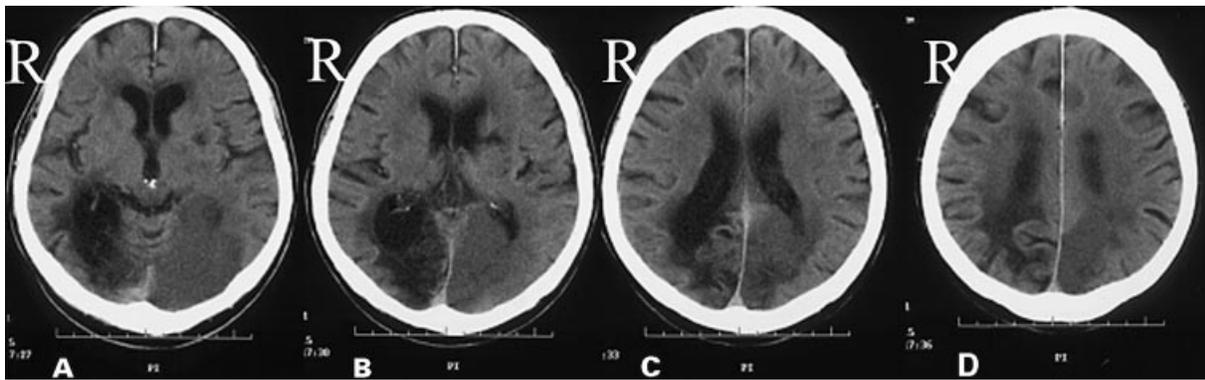
Fig. 1 (**A–D**) CT of the patient's brain at admission showing a pre-existing infarction in the right (R) PCA territory and a severe hypoattenuation in the left PCA territory indicating recent ischaemia.

perception of the conditioned stimuli was prevented using backward masking. In this masking condition, the angry faces were presented very briefly (30 ms) and then immediately followed by a second, masking stimulus. During processing of the reinforced conditioned stimulus (CS), a stronger activation of the right amygdala was observed in the masking condition, while in the non-masking condition the reinforced face elicited a stronger activation of the left amygdala. In a follow up study (Morris *et al.*, 1999), it was found that activation of the right amygdala produced by the unseen CS was reliably predicted by the activation in the superior colliculus and pulvinar. In contrast, such a relationship was not obvious when the amygdala was activated by non-masked stimuli.

Recently, Morris and colleagues reported that the same colliculo–pulvinar–amygdala pathway is also activated during processing of fearful facial expressions or fear conditioned faces when these stimuli are presented in the blind hemifield of a patient with a unilateral striate cortex damage (patient G.Y.) (Morris *et al.*, 2001). As expected, faces that were presented in the intact (left) hemifield of G.Y. elicited enhanced activation in the intact right visual cortex (compared with the blind hemifield presentations), but this activation was not modulated by the emotional expression or the conditioning history of the faces. In addition, fearful facial expressions and fear conditioned faces presented in the blind (right) hemifield did not evoke increased responses in the intact striate cortex (relative to the happy facial expressions or non-reinforced faces), but nevertheless elicited increased activation in the amygdala and in the superior colliculus. Moreover, this differential amygdala activation showed a condition-dependent covariation with the visual thalamus and superior colliculus consistent with the involvement of this pathway in processing fear-relevant stimuli.

Thus far, research on affective blindsight has revealed that a cortically blind patient can discriminate at above chance level between different emotionally salient stimuli and that the colliculo–pulvinar–amygdala pathway might mediate this residual ability. The present study examined whether a cortically blind patient can also acquire a reliable fear response to an unseen visual cue that is paired with an aversive event. Specifically, we investigated whether these subcortical pathways not only modulate implicit stimulus discrimination on a perceptual level, but can also shape simple reflexive behavioural adjustments to unseen fear-evoking stimuli. Animal data suggest that the acquisition and expression of a reliable fear response do not require a representation of the aversively conditioned stimuli in the primary sensory cortical areas (Falls and Davis, 1993; LeDoux, 1996).

We employed the startle probe methodology in our experiment to assess fear conditioning in a cortically blind patient. The startle response—a cranial to caudal spreading wave of flexor movements along the neural axis—is a primitive protective reflex that is elicited by an abruptly occurring sensory event of certain intensity (Berg and Balaban, 1999). During fear conditioning, the induced fear state of the organism facilitates this independently instigated protective reflex (for review, see Davis, 1998). The use of the startle reflex as a measure of fear conditioning has a number of advantages. First, conditioned and unconditioned anxiogenic phenomena can be measured by the modification of a simple reflex. Secondly, the reflex *per se* is not a specific component of the fear state (like freezing), but rather a response to an independent probe event that is primed (facilitated) when the fear state is present. Thirdly, the reflex can be elicited by a stimulus that can be easily controlled by the experimenter. Fourthly, the neural circuitry of the fear-induced facilitation of the acoustic startle reflex is very well described (Davis, 1998). Converging evidence indicates that the amygdala with its efferent projections represents the key structure that modulates the fear potentiated startle effect. Finally, fear conditioned startle potentiation can be reliably observed in humans and has proved to be highly replicable across laboratories (Hamm *et al.*, 1993; Hamm and Vaitl, 1996; Lipp *et al.*, 1994). Finally, in contrast to skin conductance learning, startle potentiation occurs specifically during fear conditioning, but not during non-aversive learning
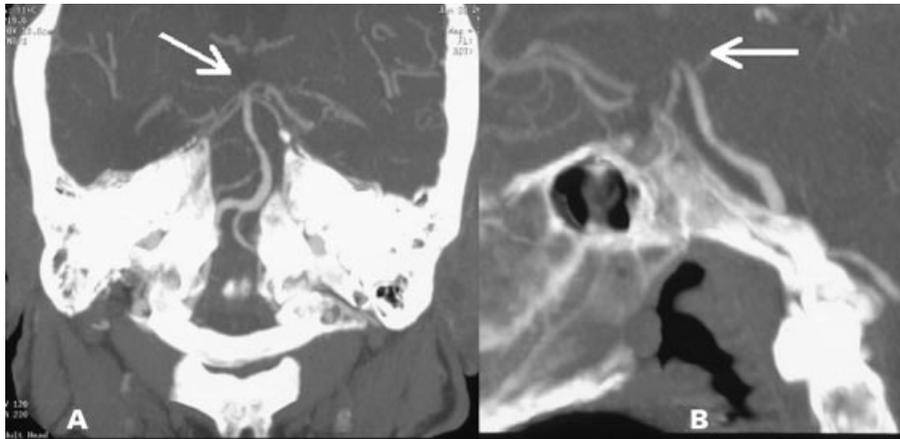
Fig. 2 CT angiography (maximum intensity projection) showing a proximal occlusion of both PCAs. (**A**) View from above and (**B**) Lateral view.

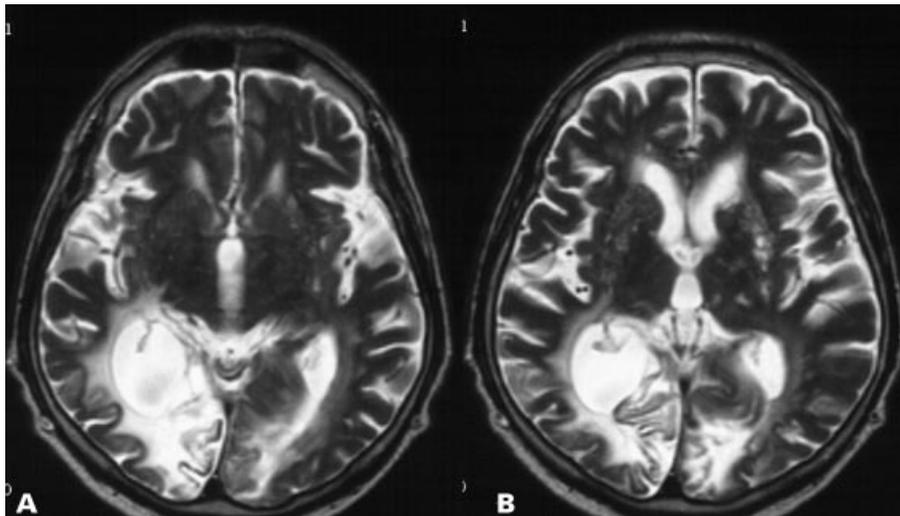**Fig. 3** T_2-weighted MRI (axial view) 3 weeks after admission confirmed that the striate cortex was bilaterally affected.

(Hamm and Vaitl, 1996; Lipp *et al*., 1994). In the current study, we used the fear conditioned startle potentiation to evaluate whether fear conditioning can be obtained to an unseen visual cue in a cortically blind patient.

Methods
Subject
K.-H. J., a 65-year-old right-handed male was admitted to the neurology clinic because of a complete loss of vision that had developed within the preceding 24 h. One year before admission, K.-H. J. had suffered a right posterior cerebral artery (PCA) infarction resulting in a left sided hemianopia following ischaemic lesions in the territory of the right PCA. At admission, the patient had suffered from a new left PCA infarction. Figure 1A–D depicts the CT scans at admission,

showing a pre-existing infarction in the right PCA territory and a less hypodense infarction in the left PCA territory indicating the recent ischaemia. CT angiography revealed a proximal occlusion of both PCAs (Fig. 2A and B). This bilateral PCA occlusion resulted in a complete loss of vision. In the MRI 3 weeks after admission, bilateral PCA infarctions could be seen (Fig. 3A and B). The current fear conditioning experiment was conducted 3 days after admission. K.-H. J was not able to recognize even bright light. He was agnostic for his blindness. The co-occurrence of cortical blindness and agnosia has been described before and is named 'Anton Syndrome'. K.-H. J. was unable to grasp objects held into his visual field and did not orient to new visual stimuli, even when asked to do so. He was also unable to describe the face of the examiner and could not recognize simple objects (e.g. pen, key). K.-H. J. did not report any feeling or awareness that

an event has occurred or that something had changed in the environment. After turning on the lights of the dark room, he did not perceive any changes in the environment. Moreover, the patient did not feel any change in the environment after leading him to a place where he could look out of a window. This complete absence of acknowledged awareness was further supported by the lack of any electrodermal and cardiac orienting responses (deceleration) to the first presentation of the visual CS. The remaining neurological status was normal with the exception of slightly exaggerated deep tendon reflexes on the left side. The patient could understand oral instructions (e.g. knock three times on the table). Writing of simple words from dictation was also possible and K.-H. J. was able to perform his signature. He gave informed consent to the present study, which was approved by the Ethics Committee of the University of Greifswald.

Visual evoked potentials

Visual evoked potentials (VEP) were examined using an electrophysiological diagnostic system (Keypoint, Medronic, Germany). Goggles were used to display the visual stimuli at a rate of 1 stimulus per second. VEPs were recorded over O_1, O_z and O_2 with F_z serving as reference electrode. Monocular VEP examination comprised three blocks of 100 stimuli alternately presented to the left and right eye. There was no detectable cortical response to the visual cues supporting the results of the clinical examination, i.e. the patient's complete bilateral cortical blindness.

Apparatus and stimulus materials

Visual stimuli were black and white slides of simple line drawings. A slide depicting a line drawing of an airplane served as the conditioned stimulus. The picture of another airplane (semantically related test stimulus) and of a semantically unrelated object (line drawing of a bed) served as test stimuli during post-conditioning. Visual stimuli were presented for 6 s using a slide projector (Kodak Ektapro 5000, Stuttgart, Germany) and a tachistoscopic shutter (G1166 Gerbrands, Arlington, MA, USA) situated in a room adjacent to the sound shielded experimental room. The slides were projected on a screen ~2 m in front of the patient. The size of the picture was 55 × 85 cm.

The unconditioned stimulus (US) was a 10 ms train of single electrical pulses (1 ms) of 500 Hz generated by a commercial stimulator (S48K, Grass Instruments, West Warwick, RI, USA). The train of pulses was isolated (SIU5) and transmitted via a constant current unit (CCU1) to a bipolar electrode (F-E10S2) at the patient's left forearm. The intensity of the electrical stimulation was increased within five warned presentations of the electrical pulse to a level that K.-H. J. described as unpleasant, but not painful. The physical intensity of the electrical stimulus was 12 mA.

The acoustic startle probe stimulus was a 50 ms burst of broadband 95 dB[A] white noise (S81-02 Coulbourn, Allentown, PA, USA) with instantaneous rise and fall times presented binaurally through headphones (MDR-CD 170 Sony, Cologne, Germany).

The eyeblink component of the startle response was measured by recording EMG activity over the right orbicularis oculi muscle beneath the eye using Ag/AgCl miniature surface electrodes (Sensormedics, Yorbahinda, CA, USA) filled with electrolyte (Marquette Hellige, Freiburg, Germany). The raw EMG-signal was amplified and filtered through a 30–1000 Hz bandpass using a Coulbourn S75-01 bioamplifier. Digital sampling with a rate of 1000 Hz started 100 ms before and lasted until 400 ms after the onset of the acoustic startle stimulus. The EMG signal was filtered offline through a 60 Hz highpass filter, was rectified and integrated with a time constant of 10 ms using a digital filter.

Skin conductance was recorded using Ag/AgCl standard electrodes (8 mm diameter, Marquette Hellige) filled with a 0.05 M sodium chloride electrolyte medium. Electrodes were placed adjacently on the hypothenar eminence of the palmar surface of the patient's right hand. A Coulbourn S71-22 skin conductance coupler provided a constant 0.5 V across electrodes and processed the signal with a resolution of 0.01 µS. The sampling rate of the signal was 10 Hz.

Lead II ECG was obtained using Ag/AgCl standard electrodes (Marquette Hellige) filled with electrolyte medium (Marquette Hellige). The signal was filtered and amplified with a Coulbourn S75-01 bioamplifier. The analogue signal was digitized with a sampling rate of 100 Hz. A peak trigger served for online registration of the R-wave within the analogue ECG signal. Data acquisition and stimulus presentations were synchronized using an IBM-compatible computer.

Experimental procedure

After arriving at the laboratory, the patient reclined in a comfortable chair and the physiological sensors were attached. The patient was instructed to orient his view straight ahead while sitting in an upright position. He was told that the acoustic stimuli being presented occasionally via headphones could be ignored.

Preconditioning

The experimental session began with six presentations of the acoustic startle stimulus without any visual foreground stimulation. The inter-trial interval (ITI) between startle probe presentations varied between 10 and 14 s. Following this habituation, 18 colour slides were presented to further ensure that the patient was cortically blind. Afterwards, the experimenter entered the room and asked the patient whether he had seen anything. K.-H. J. claimed that he did not see any visual stimulus. Then the experimenter attached the electrodes for electrical stimulation. The intensity of the electric pulse was adjusted within five warned presentations of the

pulse to a level that K.-H. J. described as unpleasant, but not painful. Then, 12 startle probe stimuli were again presented without visual foreground stimulation to ensure that the startle response magnitude reached a stable baseline level. ITIs again varied between 10 and 14 s. Then, the line drawing of an airplane (CS) was presented on the screen for 6 s and a startle probe was presented 4.5 s after slide onset. This trial served as the baseline measure of blink response magnitude during CS presentation prior to conditioning.

Conditioning

During conditioning, the line drawing of the airplane (CS) was presented on the screen for 6 s. The aversive electrical US was presented at the offset of the CS. There were 12 pairings between CS and US. On eight of these 12 CS presentations, acoustic probe stimuli were presented at 4.5 or 5 s after slide onset. Moreover, four identical acoustic probe stimuli were presented in the absence of any visual foreground stimulation and served as another control condition to assess the conditioned startle potentiation.

Post-conditioning

The conditioning phase was immediately followed by the post-conditioning trials, i.e. neither a break nor any signal indicated that no further US would be presented. During the post-conditioning phase, the reinforced CS was presented for 12 trials without the US. Moreover, the semantically related test stimulus (TS1: line drawing of another airplane) and the semantically unrelated test stimulus (TS2: line drawing of a bed) were presented for 12 trials each. During eight of these 12 presentations of each visual stimulus acoustic startle probes were administered at 4.5 or 5 s after slide onset. Furthermore, 12 startle probes were presented during the ITI. After this phase, K.-H. J. was asked whether he saw any of the pictures, whether he knew when the electrical stimulus was administered and whether he recognized anything during the experiment. The patient did not see any of the visual stimuli and was not aware of any of the contingencies in the experiment.

Data analysis

The reflex eyeblink data were scored offline using a computer program (Globisch *et al.*, 1993) that identified latency of the blink onset (in milliseconds) and peak amplitude (in microvolts). Responses starting 20–100 ms after startle probe onset and reaching peak amplitude within 150 ms from probe onset were identified as startle eyeblinks. For trials in which no response could be detected, the magnitude was scored as zero.

Skin conductance responses (SCRs) were scored as the largest increase in conductance between 0.9 and 4 s after slide onset (first interval response) (Prokasy and Kumpfer, 1973). These responses were not confounded by the presentation of the probe stimuli. The unconditioned response was scored as

the largest increase in conductance between 0.9 and 4 s after the onset of the electrical stimulus.

Interbeat intervals (R–R) were converted to heart rate in beats/minute (bpm) in 0.5 s bins (Graham, 1978). Baseline heart rate (3 s before slide or electrical stimulus onset) was subtracted from the average heart rate for every 0.5 s after stimulus onset. For each trial heart rate changes corresponding to peaks of deceleration (D1) and acceleration (A1) were identified following the rules of Gatchel and Lang (1973).

Physiological data were analysed separately for each phase of the experiment. During pre-conditioning, the blink magnitude elicited during the first presentation of the CS served as a baseline measure and was compared with the average blink magnitude elicited by the last two probes in the ITI prior to the presentation of the CS. During conditioning, startle response magnitudes to the four ITI probes were averaged to serve as control condition for the assessment of fear potentiated startle. Startle response magnitudes during the presentations of the visual CS that were accompanied by startle probes after the first CS–US pairing were averaged to assess the startle potentiation during conditioning. Accordingly, SCR magnitudes to the visual cues were averaged across all presentations of the CS following the first CS–US pairing. SCR magnitudes to the four startle probes during the ITI were averaged to serve as a baseline measure of electrodermal responding. Moreover, the mean unconditioned SCR magnitude to the 12 presentations of the US was assessed. During post-conditioning, startle response magnitudes elicited during the CS and the two test stimuli were averaged for each stimulus category and compared with each other and to the blink magnitudes evoked during the absence of any visual cue. According to the recommendations of Edgington (1995), a single subject randomization test was used to assess whether the conditioned startle potentiation was significant. The test statistic was the difference between the mean blink magnitude for the probe plus visual cue presentations and the mean blink magnitude for the probe alone presentations. Then, the data were permuted repeatedly and the test statistic was computed for each permutation. The proportion of data permutations that have a test statistic value greater than or equal to the value of the experimentally obtained results is the reported *P* value.

Results
Responses to the US

Figure 4 depicts the physiological responses to the five different intensities of the electrical stimulus. The orienting component of the heart rate response (D1) first increased for moderate intensities of the electrical stimulus and then decreased with increasing intensity of the electrical US. The accelerary component of the heart rate curve indexing a defence response to external stimulation first occurred at an intensity level of 6 mA and then increased with increasing intensity level. Moderate SCR magnitudes were observed for
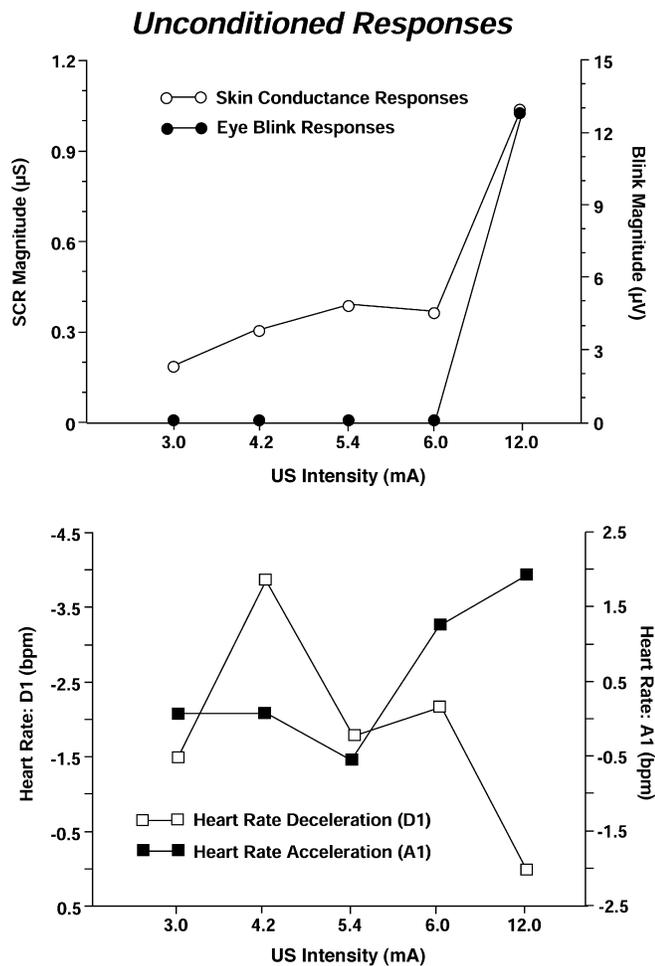
Unconditioned Responses

Fig. 4 Physiological responses to the five intensities of the unconditioned stimulus. *Top*: Skin conductance and startle response magnitudes elicited by the electrical stimulus. *Bottom*: Deceleratory (D1) and acceleratory (A1) components of the phasic heart rate responses elicited by the US.

intensities between 3 and 6 mA. SCR magnitude sharply increased when the electrical stimulus intensity was set to 12 mA. Finally, blink responses to the electrical US did not occur until an intensity of 12 mA. These data suggested that the US was actually an aversive stimulus at an intensity of 12 mA and elicited the characteristic defensive response pattern that is necessary to ensure effective fear conditioning.

Responses to the CS
Startle response magnitudes
Pre-conditioning. During the first presentation of the CS prior to US administration, the patient did not show any blink response to the acoustic probe stimulus. This was not due to a lack of general reactivity, since the same probes elicited a reliable blink response in the absence of the CS prior to conditioning (Fig 5, left upper panel).
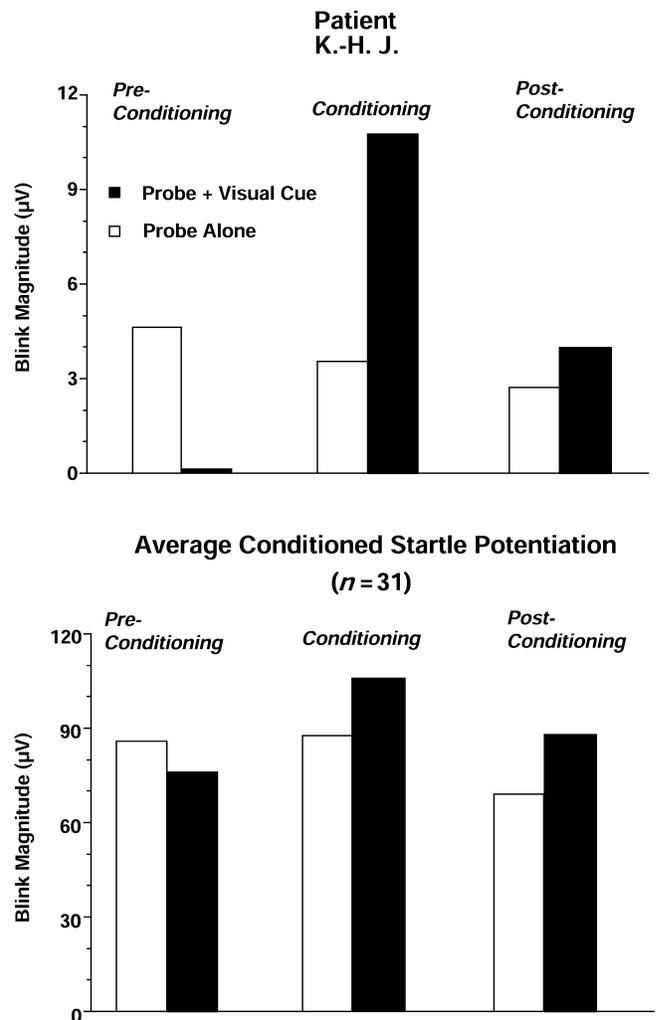

Fig. 5 Mean blink response magnitudes for startle probes presented during the visual cue and in the absence of any visual foreground stimulation during pre-conditioning, conditioning, and post-conditioning. *Top*: Response magnitudes of the cortically blind patient K.-H.J. *Bottom*: Mean response magnitudes of a sample of 31 sighted control subjects.

Conditioning. As predicted, pairing the visual cue with the aversive US resulted in a substantial potentiation of K.-H. J.'s startle responses. During conditioning, blink magnitudes to probes administered during the presentation of the visual cues increased by 162% relative to those elicited by probes presented in the absence of the conditioned stimulus. The upper panel of Fig. 5 depicts the mean blink response magnitudes for startle probes presented during the CS and in the absence of the CS (control condition). K.-H. J. showed a clear potentiation of his startle response when elicited in the presence of the unseen CS. The single-case randomization test revealed that this startle potentiation was statistically significant ($P = 0.033$). This amount of conditioned startle potentiation was even larger than that observed in a sample of normal control subjects ($n = 31$). A comparable delay conditioning experiment with the same CS and US param-

eters was also conducted with a group of 31 students (24 females, age 18–30 years) of the University of Greifswald, who gave their informed consent to participate in this study. The results of the average startle response magnitudes of this group in that study are reported as a reference to the results obtained for K.-H. J. In this sample, the amount of conditioned startle potentiation was 22% and statistically significant [$F(1,30) = 13.66$; $P < 0.01$]. The lower panel of Fig. 5 presents the blink magnitudes of the control group as a reference.

Post-conditioning In the post-conditioning phase, blink magnitudes to probes presented during the reinforced picture stimulus were larger (CS: 3.48 µV) relative to those elicited in the absence of the visual cues (ITI: 2.74 µV). This increase in blink magnitude was 45% and statistically significant as revealed by the single-case randomization test ($P < 0.002$). Again, the amount of startle potentiation was larger than that observed in a sighted control sample. For the control group, the amount of startle potentiation during post-conditioning was 28% and statistically significant [$F(1,30) = 10.6$; $P < 0.01$]. This conditioned startle potentiation, however, was not specific for the reinforced cue but rather generalized across the other visual test stimuli, irrespective of whether they were semantically related to the CS or not (CS: 3.48 µV; TS1: 4.67 µV; TS2: 3.78 µV). Thus, conditioned startle potentiation during presentation of a visual cue was maintained during post-conditioning, but was not specific to the corresponding content of the cue.

SCR magnitudes

Pre-conditioning. During its first presentation, the CS did not evoke any change in skin conductance. Thus, no initial electrodermal orienting response was observed for the visual CS.

Conditioning. During conditioning, average response magnitude to the CS only marginally increased to 0.03 µS. In contrast, the mean SCR to the electrical stimulus was 0.26 µS and to the acoustic probe stimulus during the ITIs was 0.06 µS, excluding the hypothesis that K.-H. J. might be overall non-responsive in the electrodermal response system.

Post-conditioning. Presentation of the visual cues during the post-conditioning phase did not elicit stronger SCRs than those evoked by the acoustic probe stimuli. Average response magnitudes for the visual cues were 0.02 µS for the CS, 0.07 µS for TS1 and 0.05 µS for TS2. In contrast to the blink magnitudes, these electrodermal response magnitudes during slide presentation were not larger than those elicited by the acoustic startle probes during the ITIs (0.07 µS).

Discussion

The results of the current study revealed that a patient with bilateral damage to the primary visual cortex, resulting in complete cortical blindness, is able to acquire a reliable fear response to an unseen visual cue. In contrast to the pre-conditioning phase K.-H. J's eyeblink component of the acoustic startle response was markedly potentiated during conditioning when elicited in the context of a visual cue that was paired with an aversive stimulus. When the same acoustic probe stimulus was presented in the absence of the CS, no such facilitation could be observed. Moreover, this conditioned startle potentiation was maintained during the post-conditioning phase. In contrast to previous studies on blindsight that mostly explored unilateral cases, K.-H. J. had a bilateral damage to his visual cortex. The PCA serves the entire ipsilateral striate cortex in the occipital lobe, so that an abrupt occlusion due to embolism in the proximal PCA mostly leads to a complete occipital infarction with damage to the visual cortex. Thus, bilateral proximal occlusions of the PCA, as in the case of the current patient (see Fig. 2), result in complete cortical blindness. The patient's complete loss of vision was further supported by the VEP. In all trials, the visual stimuli presented to the left and to the right eye, respectively, did not elicit any reliable cortical response. Patients with unilateral damage to the visual cortex have normal vision in the intact field and may improve their stimulus discrimination in their blind field (Kasten and Sabel, 1995; Weiskrantz, 2000), perhaps by neural plasticity in the contra-lateral visual pathways. In contrast, K.-H. J. suffered from a bilateral damage of his visual cortex, excluding the hypothesis that contralateral pathways might be responsible for the residual abilities.

Taken together, there is convincing evidence that K.-H. J. had no cortical representation of the visual stimuli. Nevertheless, the visual CS was able to activate a fear state in the patient as indexed by a reliable potentiation of the startle reflex. Using various neurosurgical, pharmacological and electrophysiological tools, it has been demonstrated in animals that the amygdala is the core structure in the acquisition and expression of conditioned fear (for review, see Davis 1992, 1997). The central nucleus serves as the main output region of the amygdala (LeDoux, 2000). Lesions of the central nucleus disrupt the expression of fear including fear conditioned startle potentiation, which seems to provide a relatively direct reflection of the activation of the central nucleus of the amygdala (see Davis, 1992, 1996). The lateral nucleus is the sensory input region of the amygdala (Romanski and LeDoux, 1993). Using neuroanatomical tracing techniques, LeDoux and colleagues demonstrated that there are two sensory pathways converging at the lateral amygdala: (i) a thalamo-cortico-amydala pathway and (ii) a direct thalamo-amygdala connection (LeDoux, 2000). In animals, it has been demonstrated that the auditory cortex is not required for the acquisition of conditioned fear to simple tone stimuli. This suggests that the sensory information about the acoustic CS can reach the amygdala via the direct connection from the medial geniculate body to the lateral amygdala (LeDoux *et al.*, 1990). Visual information is conveyed to the lateral amygdala via the ventral visual

processing stream (see Emery and Amaral, 2000). Apart from these cortical projections, visual input is also transmitted directly from the posterior thalamus to the amygdala, including projections from the medial pulvinar and the suprageniculate nucleus to the lateral amygdala (Jones and Burton, 1976; Linke *et al.*, 1999). Animal data suggest that complete removal of all primary and secondary visual cortices does not block the expression of fear potentiated startle using a visual CS (Falls and Davis, 1993). Hence, subcortical pathways are also clearly sufficient to mediate conditioned fear in animals using visual CS. The fact that K.-H. J. acquired a clear conditioned startle potentiation to a visual cue despite bilateral damage to the visual cortex supports the assumption that the human fear system can be activated by these subcortical visual pathways.

Recent findings (Morris *et al.*, 2001) further support such interpretation of the present result. In this study, patient G.Y. identified the gender of fearful and happy faces presented in his blind hemifield above chance with no differences between happy and fearful facial expressions. Moreover, a female angry face that was paired with an unpleasant tone was more often erroneously categorized as a male face, while the number of correct gender identifications of the unreinforced angry male face was around chance (43%). Probably more powerful than these behavioural data was the finding that both the fearful facial expressions and the conditioned angry face elicited enhanced blood oxygenation levels in the right and left amygdala when presented in the blind hemifield. Moreover, a positive covariation between the activation of the right amygdala and the posterior thalamus as well as the superior colliculus was found for the unseen stimuli, suggesting that these cues were processed via subcortical thalamo-amygdala connections. As a caveat it has to be noted, however, that a successful functional mapping of the human amygdala is very difficult and requires very high resolution of the images with rather small voxel sizes (see Merboldt *et al.*, 2001 for a critical comment). The current study, therefore, supports and extends the findings of Morris and colleagues in showing that a bilateral cortically blind patient shows clear evidence for fear conditioning to a visual cue that was not processed in the primary visual cortex (Morris *et al.*, 2001). Since this patient had a bilateral damage of the visual cortex, these findings cannot be explained by methodological artefacts such as the scattering of light onto intact parts of the visual field during the visual presentation. Moreover, due to the patient's bilateral damage to the visual cortex, it was not necessary to present the conditioned stimuli using a visual half-field technique. Such a procedure requires that the patient fixates a central fixation stimulus and that the visual stimuli are only flashed briefly to the right or left of the midpoint fixation, to prevent eye movements. Therefore, it is essential that the patient is able to follow the experimenter's instructions closely. Another disadvantage of the employment of such a technique is that only a trace conditioning procedure can be studied. Since the patient in the current study was a rather rare case with a bilateral damage to the

occipital cortex, a simple delay conditioning paradigm could be used. Thus, the CS could be presented centrally with a longer duration, a procedure which is more comparable to fear conditioning experiments with animals and sighted humans.

While patient K.-H. J. exhibited a pronounced potentiation of the startle response when elicited in the context of a visual cue, he did not differentiate between the specific contents of the visual test stimuli during extinction, suggesting that the subcortical route to the amygdala may process visual information only to the level of gross physical features (e.g. brightness). Such a system would serve primarily as a detection system of potential threat, while the visual cortex would be required for identification of specific meaningful contents of the different visual objects (for discussion, see Weiskrantz, 2000). Priming of protective reflexes is a very early and implicit behavioural adaptation to threat, and the threshold of the activation of this system might be very low without requiring extensive processing of specific contents of the threat cue. It has to be noted, however, that the line drawings in the current experiment were not biologically meaningful stimuli. Using biologically more relevant cues like pictures of faces or snakes might increase the stimulus specificity of the subcortical threat detection system (see Öhman and Mineka, 2001). Recent findings by De Gelder *et al.* (2002) would at least support such an interpretation. In this study, De Gelder and colleagues found that the N1 component elicited by an emotional voice was reduced if the emotional tone of the voice was incongruent to the emotional expression of a preceding face or the valence of a preceding emotional picture. This crossmodal bias effect in the N1 was obtained for both conditions if the visual cues were presented in the intact hemifields of two patients with unilateral blindsight, but was restricted to the face–voice pairings when the stimuli were presented in the blind hemifields. These data suggest that the subcortical neural circuitry is sufficient for binding face–voice pairs, but that the striate vision might be necessary to extract the semantic information from visual cues with less biological significance.

K.-H. J. showed a clear potentiation of a simple protective response when this reflex was elicited in the context of a cue that predicted the occurrence of an aversive event. It is well established from both human and animal data that the potentiation of the acoustically elicited startle reflex provides a relatively direct measure of amygdala activation. Moreover, the current findings show that cortically blind patients not only can discriminate between different emotionally salient stimuli, but that such unseen stimuli can also activate simple behavioural adjustments to threat.

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