Biomedical Reviews 2008; 19: 1–16.

ISSN 1310-392X

AMYGDALA AND SUBCORTICAL VISION: RECOGNITION OF THREAT AND FEAR

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The amygdala (Am) is a relatively voluminous gray substance, located in the depth of the ventromedial temporal lobe. The Am has diverse afferent and efferent connections throughout the neuraxis, and is involved in the modulation of neuroendocrine functions, visceral effector mechanisms, and in complex patterns of behavior: learning and memory, aggression and defense, pain modulation, reproduction, food intake, etc. A recently revealed important function of the Am is that it acts as the brain ' lighthouse' which constantly monitors the environment for stimuli which signal a threat to the organism. The data from patients with extensive lesions of the striate cortex indicate that unseen fearful and fear-conditioned faces elicit increased Am responses. Thus, also extrageniculostriate pathways are involved. A multisynaptic pathway from the retina to the Am via the superior colliculus and several thalamic nuclei was recently suggested. We here present data based on retrograde neuronal labeling that the parabigeminal nucleus emits a substantial bilateral projection to the Am. This small cholinergic nucleus (Ch8 group) in the midbrain tegmentum is a subcortical relay visual center that is reciprocally connected with the superior colliculus. We suggest the existence of a second extrageniculostriate multisynaptic connection to Am: retina – superior colliculus – parabigeminal nucleus – Am. This pathway might be very effective since all tracts listed above are bilateral. The function of the Am by the rapid response to the sources of threat before conscious detection is significantly altered by various neuropsychiatric diseases. ***Biomed Rev 2008; 19: 1-16.***

Key words: emotion, extrageniculostriate visual pathways, limbic system, parabigeminal nucleus, superior colliculus, tract tracing

Received 5 December 2008, accepted 18 December 2008.
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INTRODUCTION

The amygdala (Am) is a relatively voluminous gray substance, located in the depth of the ventromedial temporal lobe, ventral to the caudolateral striatum and to the pallidum. It is a very complicated structure and consists of several nuclei, divided on the basis of cytoarchitectonic, hodological, histochemical and immunohistochemical studies (1-22). The Am has diverse afferent and efferent connections throughout the neuraxis, from the cerebral cortex to the spinal cord, and is involved in the modulation of neuroendocrine functions, visceral effector mechanisms, and in complex patterns of behavior: learning and memory, aggression and defense, pain modulation, reproduction, food intake, etc. (15,18,23-46).

Recently, a new function of Am was described by two independently working teams (47-50). They found out that Am is a part of the visual system, responsible for the recognition of threat signals. Adolphs *et al* (47,48) observed a patient with a rare, autosomal recessive, genetic disease – the Urbach-Wiethe disease see 51 for exhaustive description), which has resulted in bilateral calcification of her amygdala. Young *et al* (49,50) examined a female patient with a partial bilateral amygdalotomy. Both teams provided the intriguing evidence that the bilateral Am damage compromises the recognition of fear in facial expressions while leaving intact recognition of face identity.

Amygdala and subcortical vision

Am does not receive a monosynaptic retinal input (52), e.g. the visual information should follow a polysynaptic pathway. However, several retrograde tracing studies scanned throughout the thalamus and brainstem the cells of origin of pathways to the Am but have not encountered retrogradely labeled neurons in structures that receive a monosynaptic retinal input: the lateral geniculate body, the pretectal area, the superior colliculus and the terminal nuclei of the optic tract (22,53-58).

Visual information reaches the Am from association areas rather than primary cortex (8,11,19,59,60). The observations of Adolphs *et al* (47,48) and of Young *et al* (49,50) quoted above were immediately followed by a considerable body of investigations that confirmed and extended these significant data (28,33,34,60-87). The eyes may be a particularly salient stimulus for the Am (88). Kawashima *et al* (89) reported left Am activation when subjects interpreted gaze direction, whereas the right Am was activated during eye-to-eye contact. Whalen *et al* (90) found out that the eye region was sufficient to elicit Am responses during fMRI. More specifically, the white sclera surrounding the dark pupil in fearful eyes was a necessary component of the stimulus. Consistent with these findings, a patient with bilateral damage to the Am failed to use information from the eye region when viewing faces (91). More recently, Demos *et al* (87) established that the Am is sensitive to variations in the pupil size of others. There is increased bilateral Am activity for faces with relatively large pupils, e.g. there is also a function for the Am in the detection of changes in pupil size, an index of arousal and/or interest.

Importantly, the data from healthy volunteers when masking procedures were used, and in patients with extensive lesions of the striate cortex indicate that "unseen" fearful and fear-conditioned faces elicit increased Am responses (64,66,67,78,86,90,92-95). Apparently, extrageniculate pathways are involved (64,66-68,72,78,80,90,93,94). Morris *et al* (67) suggest that the retinal inputs reach the Am via a multisynaptic pathway: superior colliculus – pulvinar – Am. This multineuronal chain was already traced in the previous studies of Benevento and Fallon (96), Jones and Burton (97) and Grieve *et al* (98). A second multineuronal chain was described by Linke *et al* (99). They traced to the lateral Am nucleus axons from the suprageniculate nucleus, the medial division of the medial geniculate nucleus, and from the posterior intralaminar thalamic nuclei. All these structures receive an afferent input from the superior colliculus. According to Zald (36), the recent observations suggest that the Am may be the lynch-pin of an organism's ability to rapidly respond to sources of threat without explicit knowledge of the presence of stimulus, i. e. before conscious detection. Data are accumulating that the Am acts as the brain's "lighthouse", which constantly monitors the environment for stimuli which signal a threat or danger to the organism (33,82).

The Am receives a noradrenergic input from locus ceruleus (10,22,100; and references therein). Recently, Liddell *et al* (82) examined the direct brainstem-Am "alarm" system for subliminal signals of fear and pointed out that locus ceruleus also plays a significant role. Previous animal experiments also provided evidence that locus ceruleus is strongly involved in facilitating the rapid neural responses to fear-related signals (101).

Following the descriptions of two multineuronal chains conveying visual information to the Am (96-99), we described a third multisynaptic pathway in which the parabigeminal nucleus plays a significant role (22,102).

Parabigeminal nucleus: structure, transmitters, connections, and participation in extrageniculostriate visual pathways

The term "corpus parabigeminum" was introduced by von Bechterew (103), according to Flechsig's suggestion to avoid confusion with nucleus lemnisci lateralis. Presently, the term "parabigeminal nucleus" (Pbg) is used. It is a small structure, located subpially along the lateral border of the mesencephalon, dorsocaudolateral to the substantia nigra (Fig. 1). It contains densely arranged, small ovoid and elongated neurons. Although with some discrepancies, Pbg was described in various mammalian species (reviewed in 105,106), while in non-mammalian species Pbg corresponds to the nucleus isthmi (107,108).

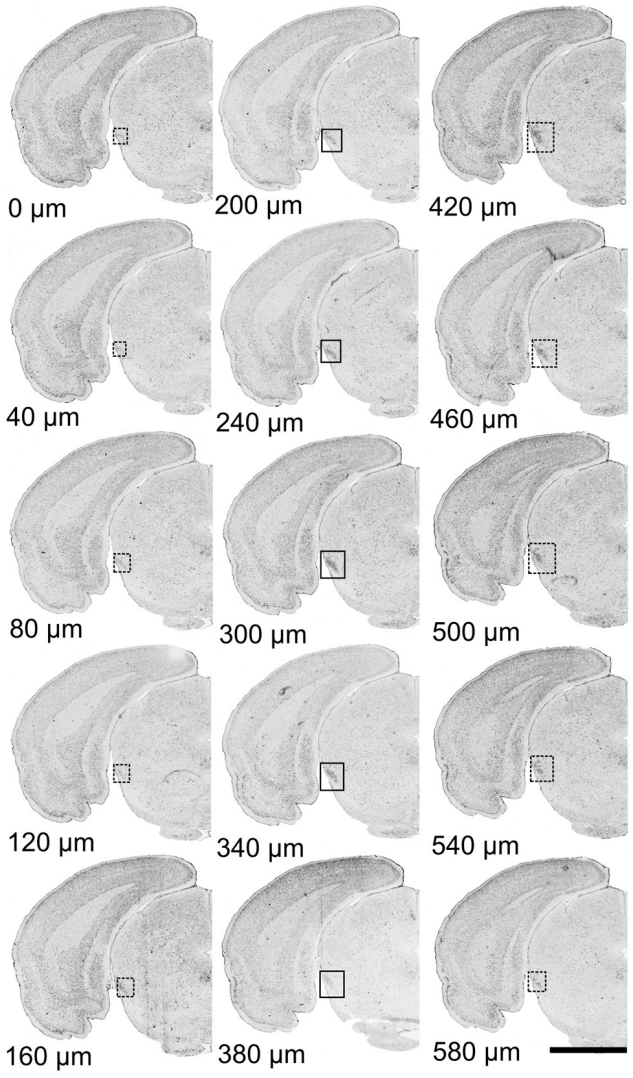

Figure 1. *The extent of the Pbg of the right hemisphere of a rat as shown by equidistant 5 µm thick sections stained with an optimized Gallyas silver stain protocol (104). The Pbg can be followed over a rostro-caudal distance of approximately 600 µm. The most rostral section containing the Pbg is signed with 0 µm, the most caudal one with 580 µm. Scale bar = 5 mm.*

Mufson *et al* (109) first convincingly described that the Pbg neurons are cholinergic and designated them as Ch8 group. This was confirmed repeatedly (110-121; see also Fig. 2). However, no cholinergic cells are present in Pbg of the monotremes (122) and of bats (123).

The classical studies (reviewed in 124) considered Pbg to be one of the nuclear groups, associated with the lateral lemniscus, but the Nauta silver impregnation studies of van Noort (124) found no connections between Pbg and the inferior colliculus. On the other hand, numerous studies in the last decades pointed out that Pbg is interconnected with several subcortical visual centers: superior colliculus, lateral geniculate body, striate-recipient zone of the pulvinar, and suprachiasmatic nucleus (96,106,108,110,113,114,117-118,124-141). In particular, the reciprocal connections between the Pbg and the superior colliculus are so strong that Graybiel (127) designated the Pbg as a "satellite system of the superior colliculus".

The hodological studies quoted above have not described interconnections between Am and Pbg. Notably, several retrograde tracing studies described various Am afferents from the

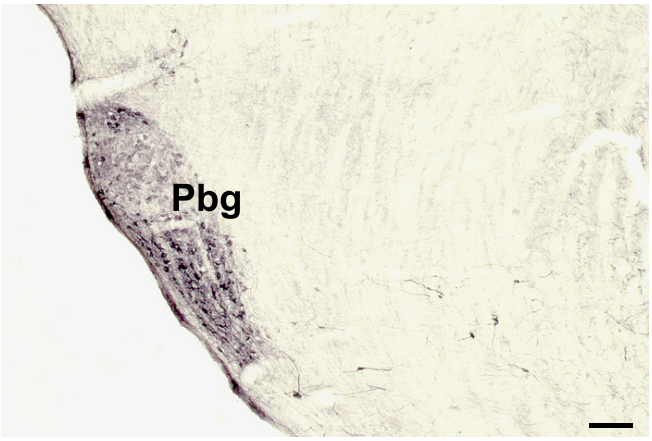

Figure 2. *Low magnification microphotograph of the caudolateral mesencephalic tegmentum. Medial is to the right. The cholinergic neurons are demonstrated with immunohistochemical staining of choline acetyltransferase. The small but sharply demarcated region containing densely arranged small cholinergic neurons is the Pbg (Ch8 group). Medial to it several scattered cholinergic neurons belong to pars dissipata of the pedunculopontine tegmental nucleus (Ch5 group). Scale bar = 250 µm.*

brainstem as well (53-58) but have not mentioned a pathway from Pbg.

While reviewing the multineuronal pain pathways that involve the Am (41) we decided to reinvestigate some connections (from spinal cord, spinal trigeminal nucleus, parabrachial nuclear complex, raphe nuclei, locus ceruleus, substantia nigra and associated dopaminergic neuronal groups) by means of retrograde transport of Fluoro-Gold, injected stereotaxically in the Am (Fig. 3). Numerous sources of afferent connections from the brainstem were described (22), and two of them, from the spinal trigeminal nucleus and from Pbg, were completely original.

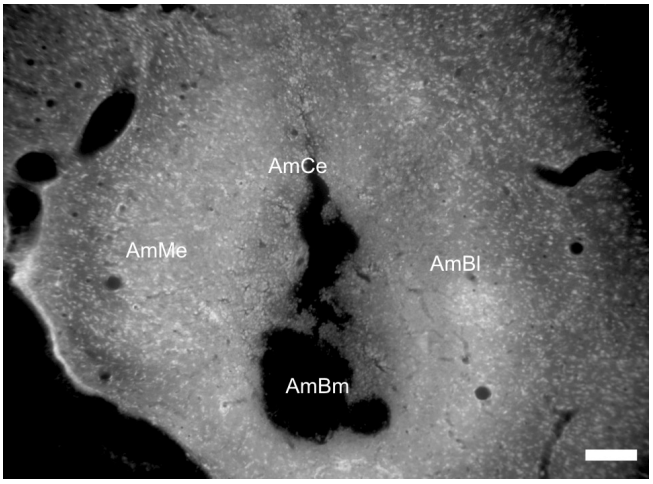

Figure 3. *Low magnification microphotograph of the injection focus involving the basomedial nucleus of the Am (AmBm) and to a lesser extent the ventral portion of the central nucleus (AmCe). AmMe – medial nucleus of Am, AmBl – basolateral nucleus of Am. Medial is to the left. Scale bar = 250 µm.*

The main target of the Pbg axons is the central nucleus of Am (Fig. 4a, b). In the cases with selective infiltration of the central nucleus with this very effective retrograde tracer, the Pbg exhibits bilaterally strong fluorescence of its neurons (Fig. 4a), whereas in cases with only a partial infiltration of the central nucleus is present, the Pbg neurons display only a light fluorescence (Fig. 4b). When followed on serial sections (Fig. 5a-d) it is evident that almost all sectors of Pbg send axons to Am and only the caudal pole of the ipsilateral Pbg remains unlabeled.

Our results strongly suggest that the newly described efferent connection from the Pbg to the Am might be a component of a third disynaptic connection from the superior colliculus to the Am, since this nucleus receives a significant input from the superior colliculus (96,106,125-128,138), and according to our results, the Pbg also projects to the Am bilaterally.

A plausible explanation, why the Pbg is constantly missing from the numerous data reviewed above, is its small size also in the human brain (115,142,143). Let us recall that even the keen eyes of Olszewski and Baxter (144) failed to recognize the Pbg as a separate entity in the human brainstem, and it was included only in the atlas of Paxinos and Huang (145) with the help of acetylcholinesterase staining.

It is remarkable that this tiny nucleus, with small neurons, emits so prominent efferent connections that in the cases of the superior colliculus and Am are bilateral. Indeed, the neurons are densely arranged, and the comparison with Nissl-stained sections suggests that at least the great majority, if not all, of the Pbg cells are projection neurons (see also 112). Nevertheless, the comparison of the number of Pbg cells with their broad and diverse innervation territories, invites the speculation that the Pbg neurons are able to innervate more than one target by means of divergent axon collaterals.

To test this hypothesis we carried out a double labeling study (102). We injected two fluorescing retrograde tracers in two targets (Fig. 6a-f, Fig. 7a, b). In the central nucleus of Am was injected Fluoro-Gold (the labeled neurons exhibit a yellow fluorescence), and in the superior colliculus multiple injections of Fluoro-Emerald were placed; by this tracer the labeled neurons exhibit a green fluorescence. These two tracers are fluorescing at different wavelength, so that each field was observed and photographed with two filters. As described above, the connection of the Pbg to central nucleus of Am is bilateral. On the ipsilateral side, the Pbg-Am neurons are concentrated in the central portion of Pbg, leaving the dorsal and ventral parts of the nucleus unlabeled (Fig. 7c). The crossed connection is more prominent. On the contralateral side the labeled neurons are located throughout the Pbg (Fig. 7d). The projection of Pbg to the superior colliculus is shown in Figs. 7e, f. This connection is also bilateral. On the ipsilateral side, two sharply delineated groups in Pbg are present – dorsal and ventral (Fig. 7e). Contralaterally projecting Pbg cells are distributed throughout the dorsoventral extent of the nucleus but are mainly concentrated in the central portion (Fig. 7f). The simultaneous tracing is demonstrated in Figs. 7g, h. It is evident that on the ipsilateral side (Fig. 7g) Pbg-Am and Pbg-superior colliculus tracts arise largely (if not exclusively) from different cell populations, as already indicated in Figs 7c, e. On the contralateral side (Fig. 7h), the cells of origin of these two pathways are mixed. There are apparently three

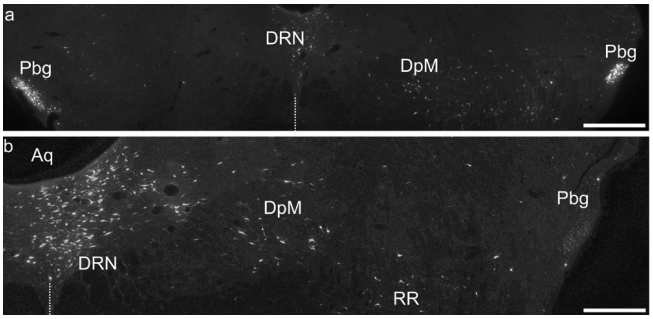

Figure 4. *(**a**) Low power microphotograph of the caudal mesencephalic tegmentum with an injection of AmCe. Strong retrograde labeling in the Pbg ipsilateral (to the right) and contralateral (to the left) to the injection side. In the midline the labeled neurons of the dorsal raphe nucleus (DRN) are seen, and on the side ipsilateral to the Am injection labeled neurons also in the deep mesencephalic nucleus (DpM) can be observed. Scale bar = 500 µm. (**b**) The caudal mesencephalic tegmentum from the case with injection focus illustrated in Fig. 3. The cells in Pbg are only lightly fluorescing when compared with the intense labeling of the DRN, DpM, and the dorsocaudal part of the retrorubral area (RR). Aq – cerebral aqueduct. Scale bar = 250 µm.*

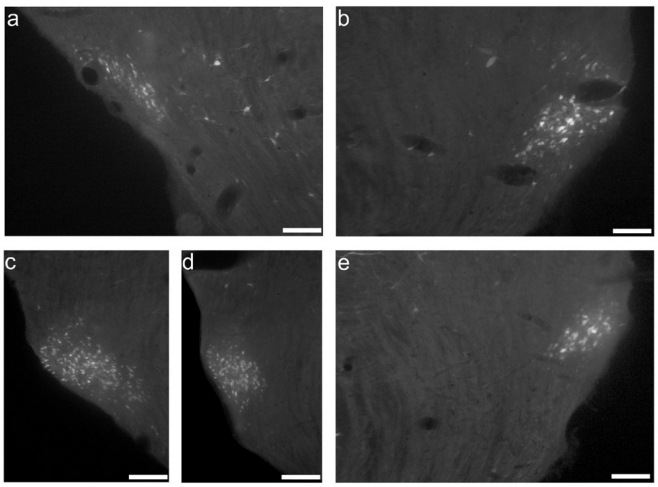

Figure 5. *Serial sections through the rostrocaudal extent of Pbg with retrogradely labeled neurons following an AmCe injection. In the rostral part of Pbg, retrogradely labeled neurons are found both contralaterally (**a**) and ipsilaterally (**b**). In the central sector of Pbg, labeled neurons are also found contralaterally (**c**) and ipsilaterally (**e**). Near the caudal pole of Pbg, retrogradely labeled neurons are only present on the contralateral part (**d**). Scale bars: a, c, d = 400 µm; b, e = 300 µm.*

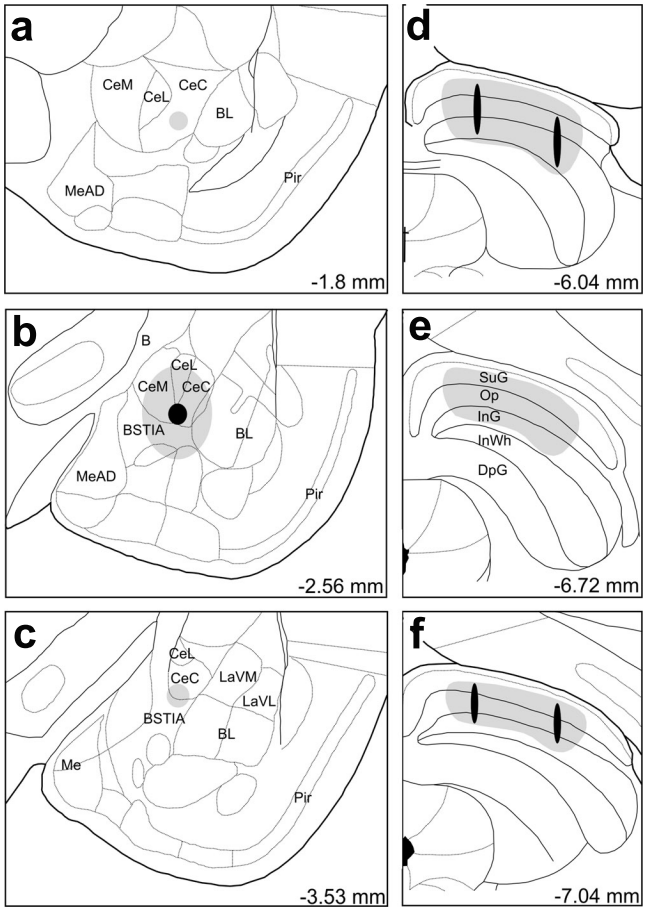

Figure 6. *Schematic diagrams showing cores (black) and halos (gray) of injections of Fluoro-Gold in the Am (**a-c**) and fluoro-emerald in the superior colliculus (**d-f**) (schematic frontal planes posterior to bregma, modified after Paxinos and Watson, 1998). B – basal nucleus of Meynert; BL – basolateral nucleus of Am; BSTIA – bed nucleus of stria terminalis, intraamygdaloid division; CeC – central nucleus of Am, capsular part; CeL – central nucleus of Am, lateral part; CeM – central nucleus of Am, medial part; DpG – deep gray layer of superior colliculus; InWh – intermediate white layer of superior colliculus; LaVL – lateral nucleus of Am, ventrolateral part; LaVM – lateral nucleus of Am, ventromedial part; Me – medial nucleus of Am; MeAD – medial nucleus of Am, anterodorsal part; Op – optic nerve layer of superior colliculus; Pir – piriform cortex; SuG – superficial gray layer of superior colliculus.*

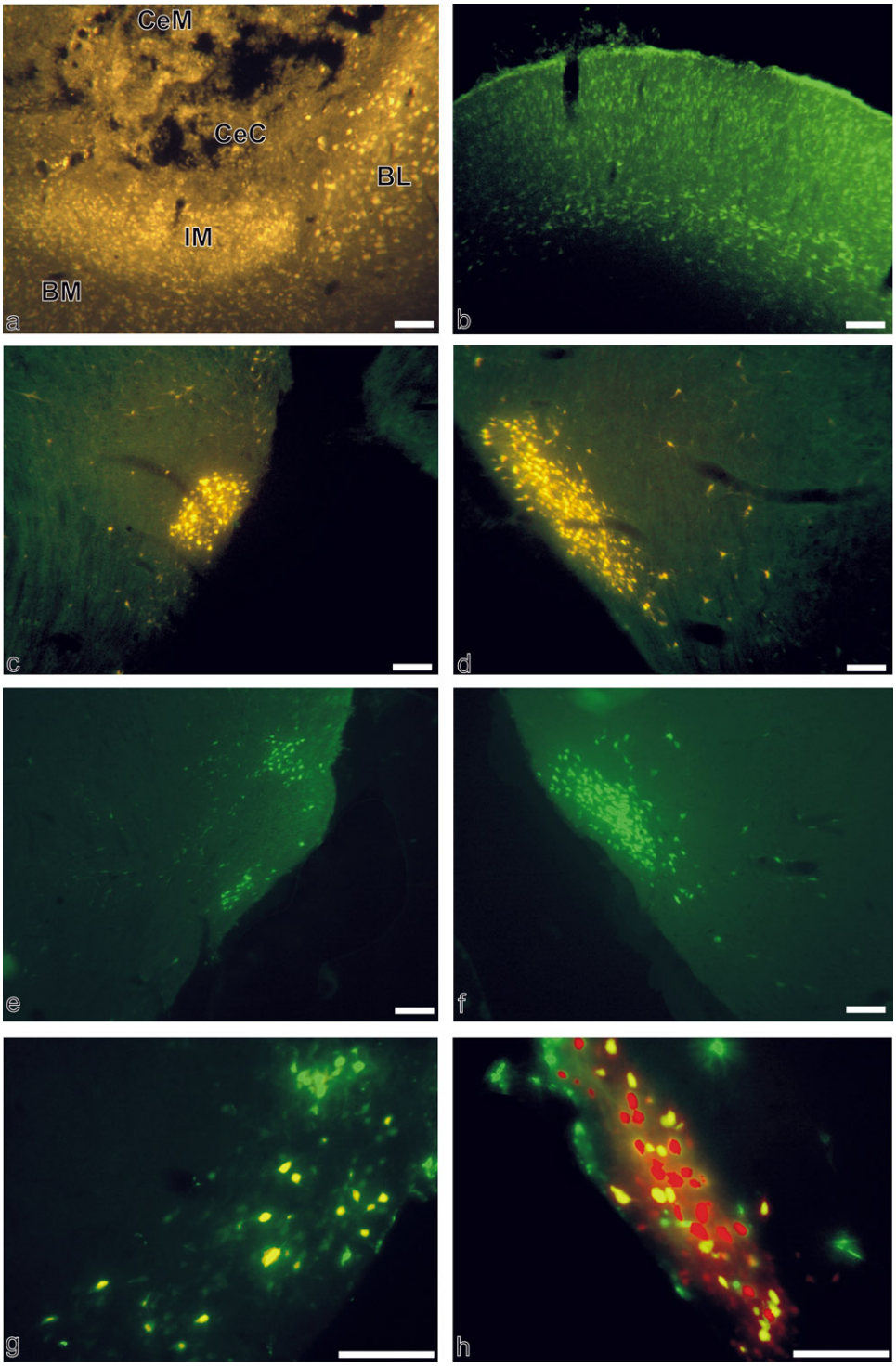

Figure 7. *(**a**) Injection of Fluoro-Gold in the Am. The central necrotic zone involves the medial (CeM) and the capsular (CeC) subnuclei of the central nucleus of Am. BL – basolateral nucleus of Am; BM – basomedial nucleus of Am; IM – intercalated cell masses of Am. Scale bar = 100 µm. (**b**) By means of four small injections of Fluoro-Emerald the superficial layers of the superior colliculus are regularly infiltrated. Scale bar = 100 µm. (**c**) Retrogradely labeled neurons in the central portion of Pbg, ipsilateral to the injection of Fluoro-Gold in the Am. Scale bar = 100 µm. (**d**) Retrogradely labeled neurons in the Pbg, contralateral to the injection of Fluoro-Gold in the Am. Scale bar = 100 µm. (**e**) Two groups (dorsal and ventral) of labeled neurons in Pbg following injection of Fluoro-Emerald in the ipsilateral superior colliculus. Scale bar = 100 µm. (**f**) Retrogradely labeled neurons in Pbg, contralateral to the injection of Fluoro-Emerald in the superior colliculus. Scale bar = 100 µm. (**g-h**) Double labeling experiment with injections of Fluoro-Gold in Am and Fluoro-Emerald in the superior colliculus. (**g**) The dorsal neuronal group of the ipsilateral Pbg exhibits green fluorescence after a superior colliculus injection. The yellow fluorescence of Fluoro-Gold marks the central Pbg neurons projecting to Am. There are no double-labeled neurons in the Pbg ipsilateral to the injection. Scale bar = 100 µm. (**h**) In the contralateral Pbg neurons projecting only to Am (yellow) can be seen, quite a few neurons project only to superior colliculus (green), and there is a substantial number of double-labeled neurons (red). Scale bar = 100 µm.*

populations: neurons that project only to the Am, a smaller number of cells that project only to the superior colliculus, and double-labeled neurons that simultaneously innervate Am and superior colliculus by means of divergent axon collaterals (indicated with red color in Fig. 7h). The crossed and uncrossed connections of Pbg to the central nucleus of Am and to the superior colliculus are summarized in Fig. 8.

The Fluoro-Emerald is not as effective as retrograde tracer as the Fluoro-Gold, yet it has a significant advantage: Fluoro-Emerald is transported also anterogradely. Axons arise from the injected superior colliculus that could be followed to the ipsilateral Pbg, where they form a very dense terminal field, in the central region, where the Pbg-Am cells are located.

Pbg emits bilateral projections to superior colliculus and Am, and also to the lateral geniculate body, which is bilateral in some species (133). The ipsilateral connection to the superior colliculus arises in the dorsal and ventral neuronal groups of Watanabe and Kawana (129) and the middle group projects to the Am. Exactly this group receives a dense terminal input from the superficial layers of the superior colliculus. Thus, there is a point-to-point multineuronal chain: superior colliculus – Pbg – Am. This characteristic labeling in Pbg was first demonstrated by Graybiel (127) in the cat (see her "band" on Fig. 6B in 127). Otherwise, the ipsilaterally projecting Pbg neurons in the cat have a broader distribution (127,130). The crossed connections are supplied by two neuronal types. Some cells project either to the Am or to the superior colliculus, and there are also neurons that simultaneously reciprocate the input from the superior colliculus, and project to the central nucleus of Am. Thus, a one and the same cell can project to visual and limbic structures.

The present results extend the previous observations that the superior colliculus conveys the retinal input to the Am via several extrageniculostriate diencephalic visual centers (Fig. 9). Despite its small size, the Pbg apparently has a strong contribution in the multineuronal subcortical pathways that transfer the retinal inputs to the Am, thus rapidly informing the "brain's lighthouse" about sources of threat before conscious detection (33,36,64,67,68,78,82).

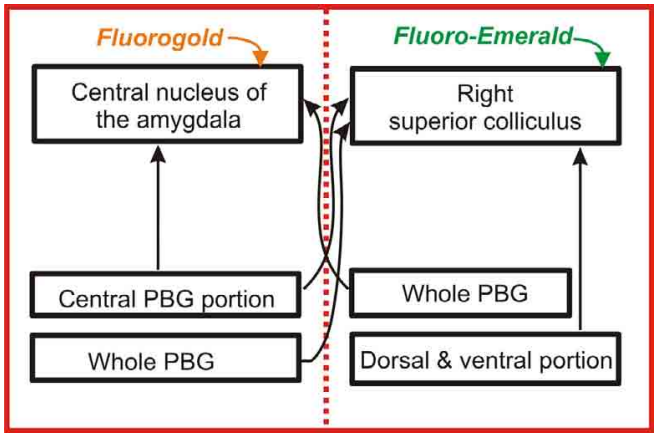

Figure 8. *Schematic representation of the crossed and uncrossed pathways from Pbg to the central nucleus of Am, and to the superior colliculus.*

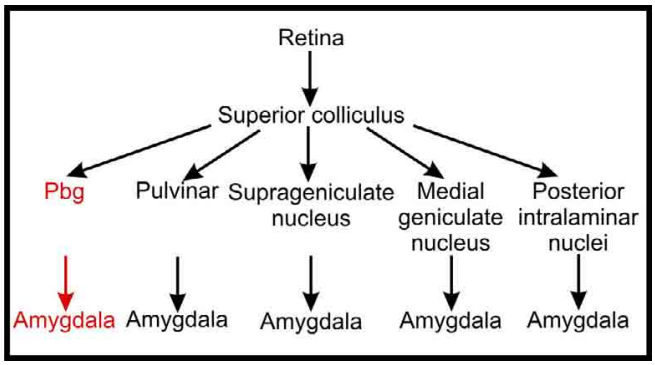

Figure 9. *The retinal input to the superior colliculus is further transmitted to the Am via five disynaptic pathways: four of them – diencephalic, and probably the most important one – from the "satellite system of the superior colliculus", the Pbg.*

Amygdala and subcortical vision in some neuropsychiatric diseases

As to be expected, the functions of the Am as a subcortical visual center are more or less altered by several neurological and psychiatric disorders. Although clinical and electrophysiological evidence indicates that the Am plays an important role in the pathogenesis of temporal lobe epilepsy, there are few detailed data on histopathological changes of Am in epilepsy patients, in contrast to numerous investigations of experimental models. Wolf *et al* (146) examined the lateral nucleus of Am in 70 surgical specimens from patients with temporal lobe epilepsy and in 10 control specimens with respect to neuronal density and gliosis. They compared the results with the neuronal loss in the hippocampal formation. In epilepsy patients the neuronal density of the lateral nucleus of Am was significantly decreased as compared to normal controls. The mean volumetric density in epilepsy patients was reduced to 59% of that in normal individuals. The neuronal loss in the Am correlated well with the presence of fibrillary gliosis.

Thus, the findings demonstrate that the Am is severely altered in most patients with temporal lobe epilepsy, and Wolf et al (146) suggest that these changes are independent of those in hippocampus. Pitkänen *et al* (147) compared the data on the Am damage in experimental and human temporal lobe epilepsy. The MRI studies of epileptic patients have shown that volume reduction of the Am ranges from 10 to 30%. In the human Am, neuronal loss and gliosis have been reported in lateral and basal nuclei. As to be expected, Pitkänen *et al* (147) encountered heavier alterations in rats with experimental status epilepticus. Recently, Daley *et al* (148) compared the Am volume in children with cryptogenic epilepsy who have complex partial seizures with that of age- and gender-matched normal children. There were no significant differences in the Am volume between epileptic and healthy children. However, within the group with complex partial seizures, the children with an affective/anxiety disorder had significantly larger left Am volumes, as well as greater Am asymmetry, compared with those with no psychopathology. Meletti *et al* (149) studied the ability of facial emotion recognition in patients with symptomatic epilepsy, evaluating whether medial temporal lobe damage is related to impairment in the recognition of specific emotions. They established that early-onset right-sided medial temporal lobe epilepsy is the key substrate determining a severe deficit in recognizing emotional facial expressions, especially fear. Yamada *et al* (150) examined the emotion recognition from facial expressions in a temporal lobe epileptic patient with ictal fear (affective aura). By this form of temporal lobe epilepsy the patients exhibit distinctly smaller Am volume (151). The patient of Yamada *et al* (150) underwent hippocampectomy which completely suppressed ictal fear. Before surgery, the patient tended to attach enhanced fear, sadness, and anger to various facial expressions. After surgery, such biases disappeared.

Schizophrenia was commonly regarded as a "functional psychosis", the implication being that the delusions, hallucinations and cognitive impairment characteristics of the disease have no organic basis. This view was due in no small way to the failure of neuropathologists to find convincing pathological changes associated with the disease in the first seven decades of the XXth century. Several studies of members of the school of Cecile and Oscar Vogt were neglected and forgotten (152,153). The first unequivocal evidences were summarized by Roberts and Bruton (152). Notably, already the first encouraging studies pointed out that the medial temporal lobe structures (parahippocampal gyrus, hippocampus and Am) are preferentially affected. These data were repeatedly confirmed (153-157; to cite only a few). According to Shenton *et al* (155) the brain abnormalities by schizophrenia are subtle and not all findings of certain teams are confirmed by other researchers. However, from 193 MRI studies, 100% of reviewed reports point out to changes in the Am. Recently, concrete and unequivocal data were presented by Kreczmanski *et al* (157). They compared several regions in brains of schizophrenics and controls and found that there is a reduced volume in the lateral nucleus of Am, and it is asymmetric: 12.1% on the left side and 17.6% on the right side. In conjunction, there is also a reduced mean total neuron number: 15.9% on the left side, and 16.2% on the right side. Already from classical clinical observations, it is generally agreed that schizophrenia patients show a markedly reduced ability to perceive and express facial emotions and they have difficulties in interpreting social information gathered from facial expression (158-160; and references therein). Several functional investigations of schizophrenic patients showed some alterations of the Am activity (80,161-167) but the results are not completely straightforward. Phillips *et al* (161) were the first to compare the responses to facial expressions in paranoid and non-paranoid patients. All patients were less accurate in identifying expressions, and showed less activation to these stimuli than normal subjects. Non-paranoids categorized disgust as either anger or fear more frequently than paranoids, and demonstrated in response to disgust expressions activation of the Am, that is associated with perception of fearful faces. Paranoids were more accurate in recognizing expressions, and demonstrated greater activation than non-paranoids to most stimuli. Paradiso *et al* (162) carried out a regional cerebral blood flow investigation by untreated schizophrenics and controls when viewing pleasant or unpleasant images. When patients evaluated the unpleasant images, they did not activate the fear-danger recognition circuit (e.g. the Am) used by healthy volunteers. Holt *et al* (163) carried out a functional MRI investigation in schizophrenic patients and healthy controls that passively viewed human faces displaying fearful, happy, and neutral emotional expressions. Relative to control subjects, the patients demonstrated significantly greater activation of the left hippocampus while observing all three facial expressions, and increased right Am activation during the initial presentation of fearful and neutral facial expressions. According to Das *et al* (80), in response to fearful facial expressions, schizophrenia patients displayed reduced Am activity, compared to controls. Williams *et al* (164) pointed out that schizophrenia patients show a disconnection

in Am-medial prefrontal cortex and autonomic arousal systems for processing fear and signals of danger. Comparing paranoid and nonparanoid patients, Williams *et al* (164) noticed that this disjunction is most apparent in patients with a profile of paranoia, coupled with poor social function and insight. Gur *et al* (166) encountered that patients showed reduced limbic activation compared with controls for the emotion discrimination task. Whereas in controls greater Am activation was associated with correct identifications of threat-related (anger and fear) expressions, patients showed the opposite effect of greater limbic activation, portending misidentifications. Furthermore, greater Am activation to the presentation of fearful faces was highly correlated with greater severity of so-called "flat effect". Finally, according to Hall *et al* (167), patients with schizophrenia showed a relative decrease in Am activation to fearful faces, compared with neutral faces. However, this difference resulted from an increase in Am activation to the neutral faces in schizophrenic patients, not from a decreased response to the fearful faces. Thus, Hall *et al* (167) think that the inappropriate activation of neural systems involved in fear to otherwise neutral stimuli may contribute to the development of psychotic symptoms in schizophrenia.

Amygdala is involved in the neuropathology of autism (168), and the time course of brain development rather the final product is most disturbed (reviewed in 169). Shumann *et al* (170) checked the increase of Am volume in normally developing children and in children with autism. Interestingly, children with autism rapidly increase the Am volume (7.5-12.5 years of age), and it is initially larger than by normally developing children that exhibit increase up to 18.5 years. Thus, there is an abnormal program of early Am development in autism. In conjunction, Munson *et al* (171) encountered that larger right Am volume was associated with more severe impairments at ages 3 and 4 years, and was predictive of poorer social and communication abilities at age of 6 years. Lack of reciprocal eye contact is an early and striking manifestation of autism (reviewed in 88), and the increased Am activity by healthy persons while observing eyes is reviewed above. FMRI studies in adults have found abnormally low activation in the Am among persons with autism relative to controls for tasks involving emotion recognition (172,173). By adults with high-functioning autism (Asperger syndrome) the function of Am is also altered (174). Aschwin *et al* (175) observed that patients with autism spectrum conditions were less accurate on the emotion recognition task compared to controls, but only for the negative basic emotions. Notably, these authors discuss their data in the light of similar findings from people with damage to the Am.

Recent data pointed out that by bipolar disorder abnormalities in prefrontal cortex, striatum and Am exist early in the course of the illness and predate illness onset (176). Am dysfunction during processing of facial expressions was encountered already in children with bipolar disorder (177). Compared with controls, patients perceived greater hostility in neutral faces and reported more fear when viewing them. Interestingly, patients had greater activation in the left Am, nucleus accumbens, putamen and ventral prefrontal cortex when rating face hostility, and greater activation in the left Am and bilateral accumbens when rating their fear of the face. Malhi *et al* (178) investigated euthymic bipolar disorder patients by emotion recognition task involving fear, disgust and neutral expressions. Patients were equally accurate in identifying facial expressions as healthy subjects but were slower to respond, especially with respect to fear and disgust. Responses to fear and disgust resulted in activation of Am and insula, respectively. Characteristically, euthymic bipolar patients responded largely to fear and healthy subjects responded more so to disgust.

Only recently it became apparent that by posttraumatic stress disorder (PTSD) the function of Am (including emotion recognition) is significantly altered (179-183). Shin *et al* (179) examined Vietnam male combat veterans and female nurse veterans with PTSD, studying the regional blood flow during the recollection of personal traumatic and neutral events. All veterans exhibited a decreased cerebral blood flow in the prefrontal cortex but only male veterans showed an increase in the left amygdala. Further, Shin *et al* (180,181) compared patients with PTSD with trauma-exposed men without this disorder. The PTSD group exhibited exaggerated Am responses and diminished medial prefrontal cortex to fearful vs. happy facial expressions. Comparable results were obtained by Bryant *et al* (183). They examined the responses to nonconscious processing of fear by PTSD patients. These patients display heightened Am activity but decreased medial prefrontal activity. However Bryant *et al* (183) established increased both Am and medial prefrontal cortex activity during nonconscious processing of fearful faces.

CONCLUSION

Until recently, it has been believed that the visual information is transferred to the Am by a multineuronal chain involving the superior colliculus and a variety of thalamic nuclei. Here we

propose the existence of a putative alternative pathway, e.g. a second extrageniculostriate multisynaptic connection to Am: retina – superior colliculus – parabigeminal nucleus – Am. This pathway might be very effective since all tracts listed above are bilateral. It seems that the function of the Am by the rapid response to the sources of threat before conscious detection is significantly altered by various neuropsychiatric diseases.

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