Neuropsychiatric Symptoms of Seizure Disorders with Special Reference to the Amygdala

Michael Trimble

Abstract In this chapter, the anatomy and function of the amygdala in relationship to emotional processing are explored. It is now known that the amygdala can be activated by certain emotional stimuli, and the fearful faces paradigm has been well tested experimentally. Studies with epilepsy reveal that amygdala sclerosis often accompanies hippocampal sclerosis. Studies of patients with amygdala sclerosis show that this affects the activity to emotional stimuli of the amygdala but also the fusiform and related cortical areas distant from the amygdala. Studies of patients who have undergone temporal lobectomy show the influence of the amygdala in relation to both preoperative and postoperative affective states, especially of the nondominant hemisphere. It is concluded that further studies of the amygdala in epilepsy and other neurological disorders are valuable in studying the functions of the limbic system.

Keywords Amygdala • Psychiatry • Epilepsy • Fusiform area

Introduction

The clinical associations between epilepsy and psychiatric syndromes have now been widely accepted, and the term comorbidity is often used to express such a relationship. In the past, psychological and psychosocial explanations were widely used to explain links between such syndromes as anxiety and depression in epilepsy, although the more severe syndromes such as psychoses or the controversial personality disorders were less likely to be accounted for without considering the underlying biology of the epilepsy [1].

Part of this confusion was the result of the almost exclusive psychological approach to neuropsychiatric disorders taken by psychiatrists, and the relative neglect by neurologists of behavior problems that could be associated with

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neurological disorders. Further, in the field of epilepsy there was confusion over the distinction between seizures and epilepsy. Many people equated the two, but seizures as signs and causing symptoms are quite distinct from the underlying pathological processes of the epilepsy. The ongoing interictal electrophysiological disturbances, which presumably reflect underlying electrochemical aberrations within the brain, which are easily identifiable by various imaging techniques, may be expected to lead to continuing interictal disturbances of cerebral function, and if these occur in areas of the central nervous system that have an impact on emotion and behavior, then psychiatric disturbances may be the expected outcome for at least some people with epilepsy, depending upon the site and type of the underlying epileptic discharge.

There has been a growing literature that emphasizes not only the possible neurological underpinnings of psychiatric disorders generally, but also the psychiatric complications of neurological disorders, including epilepsy. From a purely anatomical point of view, the unravelling of the concept of the limbic system, from the earlier circuitry proposed by Papez, to the later more sophisticated elaborations of people such as MacLean, has emphasized that within the brain there were neuronal structures and circuits which have specifically to do with modulation of emotion. This was a new idea, as before the development of the limbic system concept there was no clear cerebral framework for an understanding of how the brain felt and expressed emotion. It was crucial to elaborating on the link between epilepsy and emotion to realize that two key limbic structures, the hippocampus and the amygdala, were frequently involved in the underlying pathology of epilepsy, particularly in the localization-related epilepsies, and newly developed techniques of recording from sites within the brain revealed that between seizures, interictal abnormalities were recorded from such structures. More recently, the uncovering and elaboration of the direct associations between medial temporal structures and limbic forebrain structures, and the unraveling of the neuroanatomy of the limbic forebrain by authors such as Heimer and colleagues, have given clear neurological underpinnings for an understanding of the behavioral consequences of neurological disorders, epilepsy being no exception [2].

The Amygdala

That the amygdala plays a central role in animal behaviour has been known for many years, although its precise role, and its relative importance across different species, have yet to be fully determined. Until recently several lines of evidence have pointed to the role of the amygdala in human behavior, and there is considerable evidence that this structure is closely involved with emotional responsivity in humans. Using functional magnetic resonance imaging (fMRI), it has become commonplace to image the amygdala in vivo, and there are case histories of patients who have had either damage to the amygdala or degeneration of the amygdala, revealing behavioral problems [3].

The amygdala is located at the anterior part of the temporal lobes, in front of and above the temporal horn of the lateral ventricle. It abuts the rostral part of the hippocampus and is a composite of several neuronal aggregates. There are two main components, a larger basolateral complex, which has extensive connections with the

neocortex and from which it receives polysensory information, and a central-medial division, extending medially and establishing continuity with the bed nucleus of the stria terminalis (extended amygdala; see following). The laterobasal complex is cortical, whereas the centromedial nucleus is striato-pallidal like.

The main afferent and efferent pathways traverse the stria terminalis and the ventral amygdalofugal pathway. The latter is a longitudinal association bundle linking to the ventral striatum and the medial frontal cortex. There is also a caudal part going to the lateral hypothalamus and, via the medial forebrain bundle, to the brainstem. The uncinate fasciculus that projects to the frontal cortex. The connections to the brainstem come almost exclusively from the central nucleus, the fibers ending in structures that serve autonomic and visceral functions: these include the hypothalamus, the catecholamine and serotonin brainstem nuclei, the ventral tegmental area (VTA) and the substantia nigra, the central grey matter, the dorsal motor nucleus of the vagus, and the nucleus of the solitary tract (NTS). There are also connections to the midbrain and medullary tegmentum. Those to the hypothalamus may influence the control of pituitary hormone release, especially the projections to the ventromedial nucleus, which itself projects to the arcuate nucleus. In the cortex, amygdaloid fibers are found in the orbital and medial frontal lobe, the rostral cingulate gyrus, and most of the temporal lobe [3].

It is further appreciated that the amygdala has extensive distributions to sensory cortical areas, especially the visual cortex, which presumably modify early sensory inputs [4]. The connections of the amygdala to the hippocampus are primarily via the entorhinal cortex, which is a major source of hippocampal afferents. There are direct connections to the subiculum part of the hippocampus.

Some of the widespread connections of the amygdala are shown diagrammatically in Fig. 1. Thus, the amygdala has extensive afferent and efferent connections, and when the amygdala speaks, the rest of the brain listens. The amygdala provides affective valence to sensory representations and is crucial for the emotional tone of memories. The reciprocal connections with the same cortical structures from which it receives information, including even the primary sensory cortical areas, allow for an influence of emotional tone directly on cortical sensory impressions.

Thus the structures of the limbic system, but especially the amygdala, are of great importance for the interpretation of sensory stimuli, and its efferents directly influence motor output. A reliable finding from fMRI studies is that emotional stimuli, notably emotional facial expression, enhance amygdala activity, and there is accumulating evidence that it is also associated with decision making, guiding and driving human behavior [5]. The latter may include the social appraisal of the emotional state of others and the making of value judgements in complex social situations.

The Amygdala in Epilepsy

One of the main pathologies of treatment-resistant epilepsy is mesial temporal sclerosis; this is usually linked with hippocampal lesions, of varying severity, but in some 10% of cases isolated amygdala damage can be seen, and amygdala sclerosis often accompanies hippocampal sclerosis [6]. MRI technology has now been widely

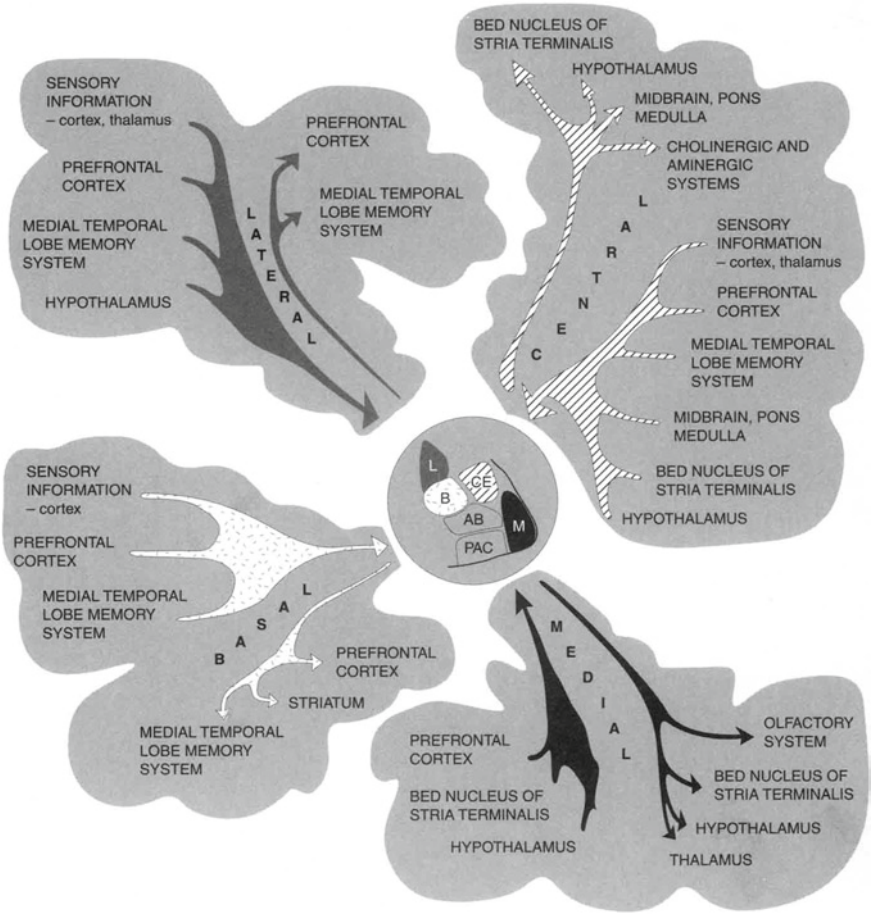

Fig. 1 The amygdala has widespread influence on cortical and subcortical structures. *L* lateral; *CE* central; *M* medial; *B* basal; *AB* accesory basal nucleus; *PAC* periamygdaloid cortex. (Reproduced with permission from Asla Pitkanen)

used to explore the brains of patients with epilepsy, and data from both structural volumetric analyses and functional data using fMRI have drawn attention to the importance of the amygdala for regulating behavior in patients with epilepsy.

Structural Changes

van Elst et al. 2000 [7, 8] carried out a series of studies examining the volume of the amydala in different groups of patients with epilepsy. In the first investigation, they examined a group of patients with intermittent explosive disorder (DSM4) associated with epilepsy, comparing their data to patients with epilepsy without such behaviors. They reported that the aggression group contained a subgroup of patients with very

small amygdala, and there was a higher prevalence of amygdala sclerosis in the aggressive patients. Twenty percent of their sample had severe amygdala atrophy in the context of a history of encephalitis. Left-sided lesions were overrepresented.

In further studies, they looked at the volumes of the amygdala in patients with epilepsy and psychosis. Two patient groups were examined: the first were patients with epilepsy and interictal psychosis ($n = 11$), and the second had post-ictal psychosis ($n = 15$). Two control groups consisted of 20 healthy volunteers and 20 randomly selected cases of temporal lobe epilepsy who had not displayed any psychopathology; these were matched for age, sex, duration of epilepsy, and anti-epileptic medication to the study group. The psychotic episodes were defined according to ICD10 criteria for the paranoid subtype of schizophrenia; the minimum requirement for the diagnosis of psychosis was the presence of delusions or hallucinations. The relationship of the psychopathology to the seizures was also determined, and the groups therefore divided into those with post-ictal and those with interictal psychoses. Further, patients with other first-axis psychiatric disorders were excluded from the study except for those with minor affective symptoms that are common in patients with temporal lobe epilepsy.

The results from the study are shown in Fig. 2. When adjusted for cerebral size (patients with psychoses of epilepsy had significantly smaller total brain volumes

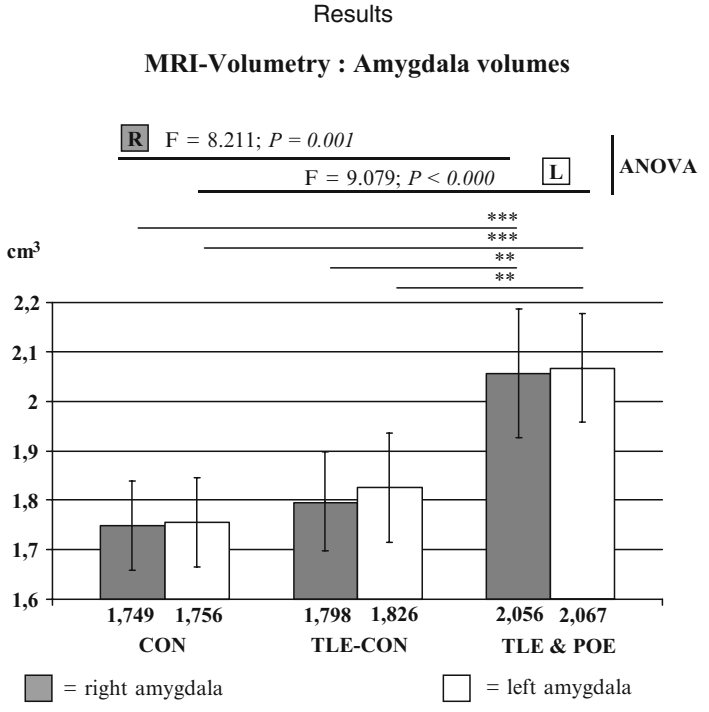

Fig. 2 Results of amygdala volumetry in epileptic psychoses. *MRI* magnetic resonance imaging; *CON* control; *TLE* temporal lobe epilepsy; *POE* psychoses of epilepsy. (From van Elst et al. [8])

compared with both healthy controls and patients without psychopathology), a highly significant (16–18%) enlargement of both the right and left amygdala volumes was found in the patients with the psychoses of epilepsy. Neither gender or age contributed to this variance, and post hoc subgroup analysis revealed that the bilateral enlargement of the psychotic patients was responsible for the overall significant findings in a factorial analysis of variance (ANOVA). When the data from the patients with post-ictal psychoses were compared with those of the interictal psychoses, no significant volumetric differences emerged. Interestingly, no significant differences in hippocampal volumes were noted.

Functional Studies

Maier et al. [9] examined patients with schizophrenia-like psychoses of epilepsy, and schizophrenia in the absence of epilepsy, using magnetic resonance spectroscopy. The hippocampus and amygdala complex were examined, and differences were noted from healthy controls. In particular, they noted a decrease of NAA in the left-sided medial temporal structures in the psychotic patients, which was maximal in the patients with psychoses and epilepsy. However, in this study the amygdala were not well defined or examined separately from the hippocampus.

More recent data have been published using fMRI. Richardson et al. [10] examined patients with epilepsy who had varying degrees of hippocampal and amygdala pathology. They gave patients a task of emotional memory encoding, comparing amygdala responses to neutral emotional stimuli. All their patients had left hippocampal sclerosis, and the responses were compared with normal controls. The extent of the medial temporal damage, in particular the severity of amygdala pathology, was reported. They showed that the encoding-related hippocampal activity for successfully remembered emotional items correlated with a degree of amygdala pathology, and the amygdala-evoked activity to remembered emotional items correlated with the degree of left hippocampal pathology. There were no correlations between measures of pathology between the examined hippocampus and amygdala. They considered that the influence of the amygdala on hippocampal encoding was expressed through effects on the hippocampus because the pathology in the left amygdala (assessed by T2 measurements) predicted reduced activity in the adjacent hippocampus for emotional stimuli, but not for neutral items.

In a subsequent investigation, the same group [11] examined the influence of viewing fearful faces on areas of cortex distant from the amygdala, again comparing patients with hippocampal as opposed to hippocampal plus amygdala pathology. Thus, seeing fearful faces not only produces a greater activation of the amygdala in healthy volunteers, but it also produces a greater activation in the face-responsive areas of the fusiform gyrus than does seeing faces with neutral expressions.

In these studies, healthy volunteers were shown to have higher bilateral activity in the fusiform and extra striate cortex in response to the fearful as opposed to the neutral faces. In the epilepsy patients, when they examined the amygdala T2 values

they found a significant relationship between the amount of sclerosis and reduced emotional activation, especially in the posterior fusiform and left occipital areas. These data reveal that the visual responsiveness of the occipital cortical areas was intact, but the enhanced emotional responses did not occur.

These data are complemented by neurophysiological studies, and also studies of patients who have had a temporal lobe removed to treat intractable epilepsy. Vuilleumier and Driver [12], using a similar experimental paradigm, reported that amygdala damage reduced or completely eliminated the enhancement of the P1 component of the visual evoked potential for fearful faces, relative to neutral faces. These findings supported the view of the distance effects of amygdala lesions on emotional processing.

Bonelli et al. [13] examined patients with anterior temporal lobe resections having assessed the preoperative amygdala activation of these patients using the fearful face paradigm. The responses of patients with refractory epilepsy were compared with healthy controls, and measures of anxiety and depression were taken preoperatively and 4 months postoperatively, being assessed with standardized anxiety and depression rating scales.

Preoperatively, the patients with left temporal lobe epilepsy had significantly reduced activation of the amygdala bilaterally, whereas patients with right temporal lobe epilepsy showed bilateral amygdala activation. Patients with right temporal lobe epilepsy revealed left and right amygdala activation that was correlated to the preoperative anxiety and depression levels, and the preoperative right amygdala activation was correlated significantly with the postoperative increases of both anxiety and depression scores. Similar correlations were not found for patients with left-sided temporal lobe epilepsy.

These data, in accordance with the other findings reported above, not only support the view that the amygdala is of considerable importance in relationship to the affective state of patients with epilepsy, but they also contributed to the studies of laterality. Thus, these data suggest that the right amygdala is of more importance in relationship to affective disorders, in keeping with the known role of the nondominant hemisphere in relationship to control of affect, and predict that resection of the right amygdala with patients who have surgery for epilepsy is more likely to lead to emotional disturbances.

Conclusions

Studies of temporal lobe epilepsy have until recently concentrated much more on the hippocampus than on the amygdala. However, particularly since the advent of modern brain imaging, with the ability to examine not only the structure, but also the function, of the amygdala, the role of the amygdala in emotional processing in a variety of settings has become clear. Further, there are studies that show that alteration of the function of the amygdala, either from structural lesions or from epilepsy, have an influence on the processing of emotional stimuli in patients with such pathologies.

In the studies reviewed in this chapter, the influence of amygdala pathology on emotional processing is revealed to be not only related to the pathology at the amygdala, but distant in its effect, influencing areas of cortex connected with the amygdala that are normally activated to a greater degree when emotional processing is required. The findings from the temporal lobe surgery studies suggest that more attention should be paid to the amygdala preoperatively in assessing patients who are more likely to develop psychiatric disturbances following surgery, postoperative depression being a particularly problematic clinical problem [14].

In contrast to the direct link shown between emotional processing and emotional responsivity in patients with epilepsy, the study with epileptic psychoses is particularly revealing. In the past there has been much discussion on the relationship between the schizophreniform psychoses of epilepsy and schizophrenia in the absence of epilepsy. In the studies of Slater and in subsequent work there has remained the suggestion that the main differences are related to the lack of the long-term deterioration of people with the schizophrenia-like psychoses of epilepsy and the maintenance of affective warmth and responsiveness. The increased size of the amygdala as reported by van Elst et al. may reflect on these phenomenological differences. Thus, outside the studies of epilepsy, an increased size of the amygdala has been noted in a number of studies of affective disorder and particularly in bipolar disorder (for review [15]). Whether the findings of increased volumes and also activity of the amygdala [with positron emission tomography (PET) studies] reflect on state or trait factors is unknown, but the findings in the psychoses of epilepsy are quite distinct from the findings in schizophrenia without epilepsy, where the consensus of studies is that the amygdala are reduced as opposed as being increased in size [15].

These studies reveal the importance of further evaluation of the amygdala in relationship not only to the psychiatric syndromes encountered outside epilepsy, but also to the importance of epilepsy as a potential model for studying links between the brain and behavior, particularly those structures intimately related to the limbic system.

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