Behavioural Brain Research, 52 (1992) 105–127

BBR 01377

Review article

The limbic system: a review of its empirical foundation

Rolf Kötter and Niels Meyer

Vogt Institute for Brain Research, University of Düsseldorf, Düsseldorf (Germany)

(Received 15 June 1992)
(Revised version received 3 August 1992)
(Accepted 11 August 1992)

Key words: Limbic system; Hippocampus; Review; MEDLINE/MEDLARS; Model in brain research; Theoretical neuroscience; Scientific concept; Heuristic method

The concept of the limbic system is highly influential in many areas of the neurosciences and in their applications to clinical medicine. The value of this concept has been questioned, denied, and defended several times in the past but a comprehensive critical evaluation has never been published. In this article we take several approaches to analyse empirical data of relevance to the limbic system. First we delineate its factual application in different areas. The limbic system has a very wide scope and divergent use. Secondly we extract criteria for its definition from research literature using the bibliographic database Medline. The limbic system has been defined variously on a number of different descriptive levels from morphology to behaviour. Thirdly we review its empirical foundations comparing evidence from different sources. The limbic system lacks an adequate empirical definition in spite of numerous efforts. Last we evaluate its construction as a scientific concept from empirical facts. The limbic system is a non-empirical explanatory concept for poorly understood brain functions. We conclude that the concept of the limbic system cannot be accepted on empirical grounds. However, it is a very attractive concept in the search for explanation of brain function. The non-empirical contents of the limbic system remains largely unexplored.

1. INTRODUCTION

The term limbic system was introduced only in 1952 by MacLean[86]. It has penetrated the neurosciences since then in so many respects that we are curious to understand the reason for its success. The investigation of the limbic system is likely to teach us important aspects of the ways in which science works.

However, the opinions on the use of the limbic system are diverse. MacLean has gone many different ways since his original paper and his current view[88] does not seem to coincide with many other interpretations of this concept. Trimble[135] for example finds the limbic system suitable in respect to the understanding of some types of epilepsy. Several authors (for example Levitt[74]) remark the lack of a general definition of the limbic system but keep on using it. Hamilton[48] regards it as a scientific hypothesis with a preliminary definition which will be reshaped continually. The most pronounced criticism comes from Brodal[19] who wants to abandon the use of the term limbic system.

While this debate has been going on for many years, the concept of the limbic system has not lost anything of its general attractiveness. Brodal[19] estimates that this concept occurs in the headings of an increasing number of articles and Nieuwenhuys et al.[105] find that the literature on the limbic system has grown overwhelmingly during the last decade.

2. WHAT IS THE IMPACT AND THE SCOPE OF THE LIMBIC SYSTEM?

This chapter is more than an introductory part or an outline of methodology. It concerns the role of the limbic system in teaching, research, and communication in the neurosciences. Here we demonstrate the factual use of this concept and point to some remarkable trends

Correspondence: R. Kötter, Department of Anatomy and Neuroscience Research Centre, University of Otago, Medical School, P.O. Box 913, Dunedin, New Zealand. Fax: (64)(3)479-0401.

which we investigate from a theoretical point in greater depth in subsequent chapters.

2.1. *The limbic system in teaching and textbooks*

The first contact with the limbic system is commonly made at the university where it has become a traditional part in the teaching of the brain. The limbic system ranks among the elementary knowledge of the brain and of brain-related behaviour. Today, no student of medicine or psychology gets away without having an idea of the limbic system and, therefore, the further spread of this concept is likely at least in the near future.

This impact can be ascertained by looking at major textbooks and reference books in the neurosciences, in psychology, and in pre-clinical and in clinical medicine as they are found for example in the reserve collections of medical libraries. Here is an arbitrary choice of such books which make use of the limbic system for describing normal or pathological brain function in their contents, main texts and/or indices:[1,12,16,17,42,43,47,59,62,63,75,104,106,108,112,117,118,120,124,139,142,145].

In these textbooks the limbic system is commonly classified as a 'cerebral structure' or a 'functional anatomical system' which is closely linked to olfaction, emotions, drives, autonomic regulation, memory, and pathologically to encephalopathy, epilepsy, psychotic symptoms, cognitive defects. It is thought to work by means of neuronal activity in reverberatory circuits which build on strong fibre connections between a number of different forebrain structures.

There are also a few textbooks which are remarkable because they deal in detail with the same subjects as the books above without referring to the limbic system a single time[7,13,73,93].

Apparently the limbic system concept is relevant to many different areas in the neurosciences and their applications. The scope ranges from anatomy and physiology to psychology and clinical medicine. However, its absence in some very detailed books makes it seem disputable or perhaps even not very well suited to describe clearly defined entities.

A closer look at one single textbook can give a rather confusing picture. For example in *Principles of Neural Science*[62] we find the following statements concerning the limbic system made by different contributors:

"The limbic lobe consists of the medial portions of the frontal, parietal, and temporal lobes that form a continuous band of cortex overlying the rostral brain stem and diencephalon. The limbic lobe is sometimes termed the limbic system because its neurons form complex circuits that collectively play an important role in learning, memory, and emotions." (p. 276).

"The limbic system has four major components that form two C-shaped structures. The hippocampus and the fornix form one C-shaped structure; the cingulate and parahippocampal gyri and their connections form the second." (p. 307).

"The mesolimbic and mesocortical systems project from the ventral tegmentum to limbic and cortical areas. The function of these projections are not known, but they are thought to participate in cognition." (p. 698).

"The limbic system consists of the limbic lobe [parahippocampal, cingulate, and subcallosal gyrus, hippocampus, dentate gyrus] and deep-lying structures [hippocampus, amygdala, mammillary body, habenula, anterior thalamic nuclei, olfactory bulb, and their connections]." (Fig. 47-1, p. 736).

"Hypothalamic and limbic structures are also important in regulating emotional behavior and reproduction." (p. 736).

"Modern anatomical studies have supported Papez's outline of the limbic system and have demonstrated extensive and direct connections between neocortical areas, the hippocampal formation, and the amygdala." (p. 737).

"Thus, our current models of the neural basis of emotional behaviour are built on ideas that James Papez proposed more than 50 years ago. We think of the hypothalamus as integrating the motor and endocrine responses that produce appropriate emotional behavior, and we think of the telencephalon suppressing emotional responses to trivial and inconsequential stimuli." ... "Current thinking has emphasized the role of the mammillary bodies and anterior thalamic nuclei in emotions; these structures appear to be more closely related to the process of memory storage. On the other hand, the amygdala, which Papez did not include in his circuit, appears to play an important role in emotions by conveying higher cognitive information to hypothalamic structures other than the mammillary bodies." (p. 747).

"Chapter 48. Hypothalamus and limbic system: Motivation" (p. 750–760). The limbic system does not appear in that chapter again.

"The D_2 dopamine receptors are expressed in neurons of the caudate and the limbic systems, specifically in the nucleus accumbens, the amygdala, the hippocampus, and parts of the cerebral cortex." (p. 860).

"The role of the mesolimbic system in emotions and memory, and the similarity between schizophrenia and certain types of psychomotor (limbic system) epilepsy in which disturbances of thought and perception are prominent, led Arvid Carlsson to propose that the positive symptoms of schizophrenia result from overactivity of the mesolimbic components of the dopaminergic system." (p. 863).

"Other areas of the limbic system are also affected [in Alzheimer's disease]. These include the olfactory bulbs, olfactory cortices, amygdala, cingulate gyrus, and hypothalamus. Limbic pathology may underlie some of the abnormal behavioral characteristics of some Alzheimer patients, such as uncontrollable violence and appetite." (p. 980).

These statements give a more detailed impression of the many different aspects of the limbic system. However, some of these aspects obviously do not fit together. Different definitions seem to exist and some are mutually exclusive. Moreover, the limbic system is broken up into subentities or taken to form part of other systems.

It may be held that textbooks and curricula cannot serve as relevant indicators of the state of the art, on the one hand because of the time lapse for concepts to appear in and disappear from relatively rarely revised books and teaching aims, and on the other hand because of the limited space and time which make it unavoidable for generalisations and imprecision to occur. In order to get a more precise idea of the impact of the limbic system we decided to look at its role in the original research literature.

2.2. *The limbic system in research literature using Medline*

How to measure the impact and the scope of a concept in neuroscience is a very controversial issue. For this purpose we decided to look at the biomedical bibliographic database Medline[122]. We describe our techniques and results to some extent since we are not aware of any other report of the specific opportunities and pitfalls of such an approach. Medline includes, among others, all references that appear in the Index Medicus and it has the advantage of being widely used and readily accessible. It stores the references (and often the abstract) of articles from an international range of scientific medical journals, adds controlled index terms (so-called subject headings) to them and provides a computer interface to retrieve the entries.

The results of retrieval depend on a number of factors: not every product of neuroscientific research is manifested in the form of a published article. However, this is a common and generally accepted way of presenting recent results to a wider scientific audience. While not every relevant journal is considered in Medline it appears that among the over 3,200 journals included the more widely spread and most generally valued journals in theoretical, experimental, and clinical neuroscience are covered. Journals again may present contributions of different kinds for example full articles, letters, editorials which may not all be drawn upon but it seems that there is a good exhaustion of the available resources. Therefore, we are confident that the choice of journal articles in Medline gives us a valid impression of the state of research.

Any piece of text can be used for searching Medline. But with the database set the results depend on the quality of the search string. There are systematic strategies provided to come to an adequate search string in the first place. A controlled thesaurus of subject headings is available to the user. Moreover, all these subject headings have been classified to form a hierarchical tree structure of subject headings which can be used to find more general or to include more specific terms. Most subject headings feature a varying number of subheadings which concern different aspects of the topic and which can be retrieved. Boolean logic is provided to combine more than one term in a search string and the search can be limited to specific fields.

The relationship between the search string and the retrieved article is straightforward with searches which relate to fields of the original article. This does not necessarily apply if thesaurus terms are searched because these are not attributed to the article by the author but by trained indexers who try to grasp the salient points of the article. On the one hand the use of controlled terms may improve the search by their accuracy, on the other hand this interposes a factor between the search string and the articles which is very difficult to evaluate. To shorten the retrieval time Medline contains a list of the indexed terms and of the number of articles they appear in. However, this tool can create confusion since not every indexed term is a controlled vocabulary term and since controlled terms may by chance occur in fields other than the index field. Medline recommends to try several search strings to ensure the retrieval of precisely the desired references.

The primary result of any search is a number of

entries which are found in the database for the search string given. This number, as we have explained above, is subject to a number of influencing factors which have to be considered. To validate the numbers of retrieved records we have looked at the actually selected entries in the database. This enables us to check for false-positive results. False-negative results have been avoided by comparison with a number of similar but more general search terms. Also, we complemented the results of Medline searches with those using another CD-ROM database, the Science Citation Index. However, using Medline has the advantage that the number of entries found in this system allows us to present at least some figures, which may well reveal significant trends. Furthermore, it is likely that the thesaurus and the classification tree which the user of Medline is offered in order to successfully retrieve the desired literature will have some effect on his notion of generally accepted scientific constructs and the logical relationship between them. The user may resort to them more often in future retrievals but also make use of them in his own articles. We also use Medline as a starting point for identifying important contributions to the limbic system concept which we regard more closely in later chapters.

The following results of retrieval relate to the covered articles published within the periods from 1974 to 1984 and 1985 to 1990 unless specified differently. The choice of these particular periods relates to the physical division of the database into time slots (1974–1984, 1985–1990, 1991).

2.2.1. *Frequency of occurrence of the limbic system*

From 1974 to 1990 we notice an almost steady increase in the overall number of articles per publishing year which are considered in Medline (Table I). In the 1985–90 slot the number for 1990 drops by one third which is related to the cut off point of the database. The 1991 edition of Medline contains additional articles published in 1990 as we show in Table I. We do not consider these additional articles (a few relate even to earlier years) of the 1991 edition in subsequent tables.

The search expression "limbic near1 system" retrieves all concurrences of the words limbic and system in one sentence with no word interposed. It will also retrieve the two terms in inversed order, but this occurs extremely seldom. The number of articles which at least once feature the term limbic system shows an increase similar to the overall number of articles with a more pronounced low around 1980 and a high around 1985.

TABLE I

Number of articles per publication year retrieved from Medline using different search strings

Ratios are calculated in % of the total number of articles retrieved for the respective year. Search strings are: Total, py = 19..; ln1s, (limbic near1 system) and py = 19..; TIorAB, ((limbic near1 system in TI) or (limbic near1 system in AB)) and py = 19..; MESH, limbic system in MESH and py = 19.. .

Year	*Total*	*ln1s*	*%.ln1s*	*TIorAB*	*%.TIorAB*	*MESH*	*%.MESH*
1974	227901	189	0.083	19	0.008	188	0.083
1975	240521	181	0.075	40	0.017	169	0.070
1976	245600	197	0.080	42	0.017	184	0.075
1977	249095	172	0.069	38	0.015	154	0.062
1978	255934	207	0.081	50	0.019	179	0.070
1979	265109	194	0.073	42	0.016	171	0.065
1980	263200	190	0.072	39	0.015	173	0.066
1981	265266	154	0.058	45	0.017	134	0.051
1982	275190	201	0.073	60	0.022	172	0.063
1983	287569	240	0.084	75	0.026	200	0.070
1984	297133	252	0.085	81	0.027	203	0.068
1985	307045	279	0.091	71	0.023	248	0.081
1986	319529	273	0.085	78	0.024	228	0.071
1987	335737	240	0.072	73	0.022	194	0.058
1988	351639	215	0.061	68	0.019	171	0.049
1989	358481	164	0.046	85	0.024	108	0.030
1990[a]	225880	115		46		81	
1990[b]	163292	114		47		82	
1990 all	389172	229	0.059	93	0.024	163	0.042
Avrg/yr:	290242	210	0.073	59	0.020	179	0.063

[a] Values from Medline 1985–90.
[b] Values from Medline 1991/1–12.

Subsequently it decreases in absolute and relative terms until it comes to a halt in 1990. The average is about 0.07% for at least any one occurrence of limbic system over the whole investigated period.

Like any arbitrary term "limbic system" can appear in the title or in the abstract field of an article. Moreover, the limbic system is found among the controlled vocabulary terms of the thesaurus. Therefore, it may be used for indexing and retrieving articles by contents even if this term has not been applied by the author originally. We differentiate between these two types of occurrences. The increase of occurrences of the limbic system but not the subsequent drop can be seen with the sum of articles featuring the limbic system in their titles or abstracts. In relation to the total number of articles we find a fairly constant appearance at about 0.02% with peak values during the mid eighties and a tendency to increase. We do not know whether the limbic system is more or less likely to appear with the continuous change of the journals considered in Medline. In any case the frequency of this term is not dropping dramatically in recent years.

Table II shows in detail that the frequency of the term limbic system in comparison with its overall appearance is low in the title (7.3%) or in the abstract (22.2%) of an article with a frequency of either or both at 27.3%. Most commonly it is used as a subject heading (85.9%). This explains why the overall occurrence of this term behaves very much like its occurrence in the index field. This difference in frequency may come about because the author and the indexer understand the limbic system in different ways. The much larger number of occurrences in the index field points to a broader definition of the limbic system as used by the indexer. He may regularly check for adequate contents and choose this term frequently from the subject headings.

TABLE II

Number of articles retrieved from Medline 1974–84 and 1985–90 respectively using different search strings

The sum is calculated and its ratio in % of the sum for limbic near1 system (ln1s).

Search string	*1974–84*	*1985–90*	*Sum*	*%*
limbic near1 system	2248	1286	3534	100.0
ln1s in TI	182	75	257	7.3
ln1s in AB	405	379	784	22.2
ln1s in MESH	1998	1030	3028	85.9
ln1s in TI or ln1s in AB	543	421	964	27.3
ln1s in TI and ai = AB	91	53	144	4.1
ln1s in TI and ln1s in AB	44	33	77	2.2
ln1s in TI and ln1s in MESH	168	73	241	6.8
ln1s in MESH and ai = AB	1074	870	1944	55.0
ln1s in AB and ln1s in MESH	165	125	290	8.2
ln1s in TI and AB and MESH[a]	41	33	74	2.1
ln1s in MJME	985	581	1566	44.3
limbic*	2785	1980	4765	134.8

[a] (ln1s in TI) and (ln1s in AB) and (ln1s in MESH).

We looked at the coincidence of the term limbic system in different fields. It is present in three fields only which are the title, abstract, and index fields. We find that more than 93% of articles featuring the limbic system in the title are also indexed with this term. In respect to the abstract field it must be noted that not all articles are stored with an abstract (as can be observed by adding "and ai = ab" to the search string). The percentage of articles with abstract varies with the particular subset of retrieved articles. The coincidences of limbic system in different fields cannot be higher than the percentage of abstracts in the subset of articles if one of the fields is the abstract field. Considering these circumstances the coincidence of articles which include an abstract and limbic system in the title (ln1s in TI and ai = AB) or index field (ln1s in MESH and ai = AB) with those that have limbic system also in their abstract field (ln1s in TI and ln1s in AB; ln1s in AB and ln1s in MESH) is very low at 53.5% and 14.9% respectively. There are no obvious synonyms of the limbic system which could be relevant to this discrepancy. The indexer seems to adhere closely to the presence of this term in the title while the author differentiates between its usage in the title and in the abstract and possibly the remainder of the article. The detailed and complex argument in the main body of articles is often difficult to cast into a salient title. In interviews with authors (see below) we found that the term limbic system serves as a short but broad heading to attract the attention of a wide range of readers. The precise definition of the contents addressed may be given later without using the term limbic system again.

We have seen that the number of articles referring to the limbic system in any of the available fields (title or abstract or index field) is larger than the number of those being indexed with limbic system. If, furthermore, we include all articles which make any use of the adjective limbic (search string "limbic*"), at all, then the number of selected articles increases considerably more. This is due to articles which are not indexed as covering aspects central to the limbic system. This increase shows that work in areas different from the limbic system quite commonly draws upon the concept of the limbic system. Since no specific definitions of the terms limbic or limbic system are given in those articles they must assume that the limbic system is generally defined. This notion, however, contrasts with all our other findings that varying and even incompatible concepts are used. Therefore, very common expressions

such as the following cannot be clearly or readily understood: limbic innervation, limbic modulation, temporal-limbic dysfunction, limbic influences, limbic signals, limbic kindling, limbic seizures, limbic epilepsy, limbic encephalopathy.

Another search string ("limbic near2 system") retrieves concurrences of the words limbic and system with a maximum of one other interposed word. It reveals such expressions as "limbic hippocampal system", "limbic olfactory system", "limbic memory system", or "limbic seizure system". These may denote subsystems of the limbic system or "limbic" subsystems of the respective systems on very different levels of description. Similarly the limbic system seems to become part of an even larger system complex as in "limbic-hypothalamic-pituitary-adrenocortical system". Again the lack of an obvious definition of the limbic system makes it difficult to see what these terms exactly refer to. Some terms are obvious redefinitions since they introduce a completely new notion, for example the computer metaphor in "limbic operating system" or the neural-network metaphor in "limbic neuronal networks"[24].

2.2.2. *The limbic system in Medline subject headings*

In the tree of subject headings the limbic system ranks on the same hierarchical level with telencephalon, diencephalon, cerebellum, brainstem, and cerebral ventricles under the common heading brain (Table III). The application of these terms is likely to be arbitrary to some extent, but the comparison demonstrates that the limbic system is not an infrequent class among them. The number of articles with this subject heading is of the same order of magnitude as those of its peers and the limbic system is more common than the classic categories of the diencephalon and telencephalon.

Obviously the limbic system is used as an anatomical term in the hierarchical tree. Anatomically, however, there are no brain structures which could make up the limbic system that are not already included in the other categories from brainstem to telencephalon. The anatomical definition of the limbic system, therefore, must be of a kind that does not fall into classical anatomical categories. But at the same time it must be sufficiently important to warrant the introduction of a completely new classification criterion.

If we follow the thesaurus tree to its branches we can see which structures are classified as constituting the limbic system. These are: amygdaloid body, gyrus cinguli, hippocampus, hypothalamus, olfactory bulb, olfactory pathways, and septum pellucidum with the further substructures septal nuclei and among the latter the nucleus accumbens. Most of these brain structures are already included under the classical anatomical headings. However, the hippocampus and the gyrus cinguli are classified under this subject heading only and not under telencephalon. This particular arrangement may indicate the importance of the hippocampus and the gyrus cinguli to the concept of the limbic system.

It can be noted that the interest in the hypothalamus has markedly decreased in recent years in favour of the hippocampus and even more the septal nuclei including the nucleus accumbens. It will be interesting to see whether this shift has an effect in respect to the concept of the limbic system.

TABLE III

Tree structure of subject headings and number of articles retrieved from Medline 1974–84 and 1985–90 respectively using single subject headings with all subheadings

The sum is calculated and its ratio in % of the sum for limbic system/all.

Hierarchical level	*1974–84*	*1985–90*	*Sum*	*%*
1 2 3 4 5 6 7				
Nervous system	3489	2914	6403	211.5
Central nervous system	5409	2927	8336	275.3
Brain	66381	44025	110406	3646.2
Brainstem	7174	4245	11419	377.1
Cerebellum	6133	3513	9646	318.6
Cerebral ventricles	3211	2188	5399	178.3
Diencephalon	1370	660	2030	67.0
Limbic system	1998	1030	3028	100.0
Amygdaloid body	2293	1233	3526	116.5
Gyrus cinguli	382	175	557	18.4
Hippocampus	6312	6193	12505	413.0
Hypothalamus	13339	4561	17900	591.2
Olfactory bulb	1535	913	2448	80.9
Olfactory pathways	538	386	924	30.5
Septum pellucidum	1103	473	1576	52.1
Septal nuclei	694	743	1437	47.5
Nucleus accumbens	600	795	1395	46.1
Telencephalon	1055	660	1715	56.6

2.2.3. *Relationship of the limbic system to its subordinate subject headings*

Articles in Medline are usually given about ten different subject headings. This property can be used to find out about coincidences of subject headings in one article. We compared the frequency with which the subject heading limbic system coincides with its subordinate subject headings i.e. articles concerning specific anatomical structures. This should give us a hint as to the impact of the limbic system concept on the notion of these structures on the one hand, and the influence

TABLE IV

Number of articles retrieved from Medline 1974–84 and 1985–90 respectively using boolean "and" to combine limbic-system/all (ls/all) and single subject headings with all subheadings

The sum is calculated and its ratios in % of the sum for the respective subject heading (SH.%) and limbic-system/all (ls.%).

Search string	*1974–84*	*1985–90*	*Sum*	*SH.%*	*ls.%*
Limbic-system/all	1998	1030	3028	100.0	100.0
ls/all and hippocampus/all	448	206	654	5.3	21.6
ls/all and hypothalamus/all	393	84	477	2.7	15.8
ls/all and amygdaloid body/all	293	117	410	11.6	13.5
ls/all and olfactory bulb/all	133	41	174	7.1	5.8
ls/all and septum pellucidum/all	123	25	148	9.4	4.9
ls/all and nucleus accumbens/all	68	72	140	10.0	4.6
ls/all and olfactory pathways/all	98	31	129	14.0	4.3
ls/all and septal nuclei/all	60	39	99	6.9	3.3
ls/all and gyrus cinguli/all	64	29	93	16.7	3.1

of these brain structures on the limbic system on the other hand. Table IV presents these subject headings in the order of decreasing coincidence in relation to the limbic system concept. Hippocampus, hypothalamus and amygdaloid body appear to be most central to the limbic system. Looking at its relevance to research on these brain structures we find quite a different order: the limbic system is more important in respect to the gyrus cinguli and the olfactory pathways than in respect to the hippocampus and the hypothalamus. The latter two brain structures, furthermore, figure in far more articles than the limbic system. Research in these areas is likely to have other interests than the limbic system while the gyrus cinguli and olfactory areas are largely implicated with the limbic system.

2.2.4. *Relationship of the limbic system to other subject headings*

Table V presents the number of articles in Medline which refer to some of the concepts of brain function which are commonly mentioned with the limbic system in textbooks. We calculated the coincidences of equivalent subject headings with the limbic system and again the percentage of coincidences in respect to the total of the number of articles on each brain function and on the limbic system respectively.

TABLE V

Number of articles retrieved from Medline 1974–84 and 1985–90 respectively

Total: using single subject headings with all subheadings; And: using boolean "and" to combine limbic system/all and single subject headings with all subheadings. The sum is calculated and its ratios in % of the sum for the respective subject heading (SH.%) and limbic system/all (ls.%).

Search string	*1974–84*		*1985–90*		*Sum*		*%*	
	Total	*And*	*Total*	*And*	*Total*	*And*	*SH.%*	*ls.%*
Limbic-system/all	1998	1998	1030	1030	3028	3028	100.0	100.0
Explode seizures[a]	7292	84	4034	57	11326	141	1.3	4.7
Schizophrenia	10651	74	5848	34	16499	108	0.7	3.6
Epilepsy	7895	56	4710	43	12605	99	0.8	3.3
Memory	5547	65	4482	30	10029	95	1.0	3.1
Emotions	4911	75	2464	15	7375	90	1.2	3.0
Autonomic nervous system	3025	25	1875	9	4900	34	0.7	1.1
Attention	4199	24	4755	9	8954	33	0.4	1.1
Cognition	4792	16	3844	7	8636	23	0.3	0.8
Anxiety disorders	1500	4	2346	9	3846	13	0.3	0.4
Affective disorders	692	1	1030	5	1722	6	0.4	0.2
Consciousness	1218	4	781	2	1999	6	0.3	0.2
Perception	1570	5	891	1	2461	6	0.2	0.2
Psychosurgery	437	22	158	5	595	27	4.5	0.9

[a] Search includes subordinate subject headings, here the subject heading convulsions.

The limbic system appears to be connected particularly with the neurological conditions of seizures, convulsions, and epilepsy. Other important implications exist with schizophrenia, memory, emotions, and to a lesser degree with the autonomic nervous system and attention. Vice versa, the limbic system seems to play a prominent role in largely the same areas. The two rank orders do not fall apart as they did above with respect to brain structures. This is perhaps the consequence of the same authors writing about both the limbic system and such brain functions, while different authors promote detailed anatomy and the limbic system concept respectively. The concept of the limbic systems seems to lend itself to broad questions rather than to detailed descriptions.

Medline does not provide the subject headings which coincide with the limbic system listed in the order of frequency. Therefore, we cannot exclude that other subject headings coincide more often than those mentioned above. We have, however, considered those which are commonly mentioned in textbooks. We have also included one important application of the limbic system concept: psychosurgery. Although its absolute frequency has markedly decreased in more recent time there is still a very strong overlap between the limbic system and psychosurgery.

2.2.5. *Retrieval of definitions of the limbic system*

The subject heading limbic system is subdivided into 24 subheadings (Table VI) which represent specific fields of focus in limbic system research. We list their relative frequencies compared to all articles indexed with the limbic system. They sum up to more than 100% since more than one subheading may be applied to one article. By far the commonest subheadings are physiology, metabolism, drug-effects, physiopathology, and anatomy-and-histology. These are the fields where we have to expect most contributions to the limbic system. If we relate this to our findings above that detailed description does poorly coincide with the limbic system then these articles may be the key to the notion of the limbic system. They may lay the foundation of this concept and thereby form the basis for further application. The aspects drug-effects and pathology are of particular interest since they point to a neurological or psychiatric interest in the limbic system. We can again note the decreasing but still present interest in limbic system surgery.

Furthermore, we want to retrieve the more general and central conceptual articles on the limbic system. Since a definition could be derived from any one of these approaches we did not allow the subheadings to be included in the retrieval (search string "limbic system/none"). Instead of the most general substantial statements in respect to the limbic system we find articles which make a particularly vague use of it. The limbic system seems to be applied as a morphological reference to the specific concern of the article which is most commonly the clinical observation of disease in patients or the experimental investigation of seizure activity.

Another approach is to look at different criteria for the application of the index term. About 50% of all articles indexed with limbic system contain it as a major subheading (Table II: "(limbic near1 system) in MJME") which should indicate that these articles make the concept of the limbic system the central concept. However, a closer look at these articles reveals no valid choice of conceptual articles. Eventually we resorted to the identification of those articles which feature the limbic system in all three fields of title, abstract and index (Table II: "(ln1s in TI) and (ln1s in AB) and (ln1s in MESH)"). These articles are derived from different

TABLE VI

Number of articles retrieved from Medline 1974–84 and 1985–90 respectively using the single subject heading limbic system with different subheadings

The sum is calculated and its ratio in % of the sum for limbic system/all.

Limbic system subheading	*1974–84*	*1985–90*	*Sum*	*%*
Limbic system/all	1998	1030	3028	100.0
Physiology	751	312	1063	35.1
Metabolism	334	236	570	18.8
Drug effects	324	217	541	17.9
Physiopathology	189	150	339	11.2
Anatomy and histology	215	85	300	9.9
Pathology	58	71	129	4.3
Enzymology	89	35	124	4.1
Cytology	63	47	110	3.6
Growth and development	34	20	54	1.8
Surgery	25	9	34	1.1
Embryology	19	12	31	1.0
Ultrastructure	21	10	31	1.0
Abnormalities	15	9	24	0.8
Injuries	14	4	18	0.6
Blood supply	6	5	11	0.4
Immunology	4	6	10	0.3
Radiography	2	4	6	0.2
Microbiology	1	3	4	0.1
Secretion	2	2	4	0.1
Radiation effects	1	1	2	0.1
Radionuclide imaging	0	2	2	0.1
Chemistry	0	0	0	0.0
Parasitology	0	0	0	0.0
Ultrasonography	0	0	0	0.0
None	69	23	92	3.0

subheadings and serve as a starting point for a general definition of the limbic system.

In summary, the picture that we derived of the limbic system from its appearance in the biomedical database Medline compared to textbooks is more detailed but shows very similar peculiarities. The limbic system is clearly a frequently used and important concept. There are strong hints at a macroscopical anatomical definition of it and the most important constituents appear to be the gyrus cinguli, the hippocampus, the hypothalamus, and the amygdala. Most structures are not exclusively important to the limbic system but also have other important roles. Although the limbic system is more commonly related to morphology there is also a substantial and even more consistent link with functional concepts. Epileptic and psychotic disorders as well as memory and emotions are strongly associated with the limbic system. The limbic system is particularly applied to broad and less well defined contexts and appears to attract a wider audience than do more complicated expressions.

2.3. *The limbic system in interviews with users*

We decided to supplement our findings with interviews with some of the authors who use the term limbic system in their publications. In this case we were not particularly interested in representative figures about the usage of the limbic system. Rather we wanted to get a better idea of the clarity of it i.e. of the definition of the limbic system, of the brain structures involved, of the important concepts related to the limbic system, and of the general feeling about the limbic system.

We worked out a written structured framework for the interview to be confident of covering most of the notions that we had come across in the literature before. At the same time we encouraged the authors to answer the questionnaire in their own words and without regard of any classificatory scheme offered. Usually, we would explain the purpose of this interview and the structure of the questionnaire. Most authors filled in the questionnaire at a later time and mailed it back to us.

The first observation is that some authors hesitated to answer right away although the questions were clear and straightforward. It appears that there are no very obvious or simple answers to most of the questions or that one has to give it a second thought. To give an example of how the questions are put:

The "limbic system" is defined by...
- macroscopy
- histology
- phylogeny/evolution
- electrophysiology
- biochemistry
- function
- on more than one level
- no strict definition/definition by context
- badly or not at all
- other suggestions:...

Very different answers are given. If there is a common line at all then there is a belief that the limbic system is anatomically defined and even more commonly it seems to be defined in a field different from that which the interviewed person is working in.

Our interviews brought to light that there is by no means a consensus about which structures should be included in the limbic system. We offered more than 60 different brain structures which were grouped by topography with synonyms pointed out. All answers are different. Most commonly mentioned are parts of the hippocampal formation/parahippocampal gyrus and of the gyrus cinguli.

Furthermore we asked what the functional relevance of the limbic system is. The answers show that the limbic system is thought to be involved in many different functions such as affects/emotions, memory, sensory processing, time perception, attention, consciousness, instincts, autonomic/vegetative control, actions/motor behaviour, and some of their disorders particularly epilepsy and schizophrenia. However, when asked about more precise functional roles then opinions are divided.

The general feeling about the usefulness of the concept of the limbic system is very diverse. It ranges from important over useful in certain respects to useless and worse.

2.4. *Conclusion*

At this point we think we can conclude that the limbic system is widely used in the teaching of neuroscience as well as in the presentation and communication of the results of scientific research. Although it must play a very important role in these respects there are some peculiarities about it. Particularly, there is the absence of an obvious or agreed definition of the limbic system. It seems to be defined by macroscopical anatomy as a collection of brain structures in different parts of the brain. However, there is neither an agreement on this nor on the exact structures which could serve for such a definition. At the same time the limbic system is regarded as a functional system with an in-

volvement in very broad and diverse brain and behavioural functions including pathological functions. However, it proved very difficult to find thoughts about more detailed theories or models. The usefulness of this concept is highly controversial. It has a role in scientific communication and it particularly links different contexts. However, it remains to be seen what constitutes its contents.

Obviously, the next step is to have a closer look at the foundation of the limbic system in the literature itself.

3. WHAT IS THE MORPHOLOGICAL CONCEPT OF THE LIMBIC SYSTEM?

In this and the next chapter we review most of the important criteria which are used to define the limbic system. The relevant literature is largely chosen from Medline where there is a correspondence of the term limbic system in the title, abstract, and index field or where appropriate subheadings are applied. Furthermore we included commonly cited references from those articles. Among the commonest are Broca[18], Papez[106], MacLean[85,86], and a few books on the limbic system such as Isaacson[53], or Doane and Livingston[32]. Although some of these references are also used in contexts different from the limbic system (for example Papez[106], emotions; Isaacson[53], hippocampus) their various coincidences are a useful criterion for retrieving very recent relevant articles from the Science Citation Index. Where applicable we supplemented this choice by more specialised references from Medline and by references given on the occasion of interviews with some of the authors. We do not pretend to cover each and every aspect which the limbic system has ever been implicated in (for example we do not go into detail about the supposed involvement in time perception, thirst, or hypertension) but we are confident that we regard all the more central aspects of it.

At this stage we concentrate first on the morphological concept because most material about the limbic system concerns this point and because it is most commonly believed that the limbic system can be defined on these grounds. Among the morphological criteria we include not just results from anatomical investigations but from all approaches which attempt to classify a system of brain structures without implying a specific functional concept of that system as a whole. This includes some results from biochemistry, pharmacology, and physiology.

3.1. *Criteria for the morphological definition of the limbic system*

When an author defines the limbic system then he may do this in a more or less explicit way. He would usually establish a particular criterion by which brain structures are included or not. If the criterion is not clearly stated then we would try to understand the argument and make it explicit. By these means we recognize a number of different criteria. Some of them are founded, for example, on different types of fibre connections between brain structures, others regard a macroscopical arrangement of certain brain structures. In this way groups of related criteria are formed which help with the delineation of equivalent, of similar, or of completely different criteria. For example some authors refer to the "limbic forebrain", others mention the term "limbic brainstem". These expressions contain among others the criterion that the brain structures involved are confined to a classical subdivision (forebrain, brainstem) of the brain. We would group this criterion with other macroscopical criteria which refer to particular positions in the brain.

Furthermore, we add opinions from other authors which take a different or contrasting view in respect to this specific criterion. This allows us to see whether there is an agreement or dispute concerning this issue. For example Nieuwenhuys et al.[105] state that the limbic system includes territories of the telencephalon, the diencephalon, and the mesencephalon. The reader may come to the conclusion that the limbic system is neither confined to the forebrain nor to the brainstem but constitutes a part of both.

Anatomical structure of the limbic system

Criterion: position at the border of the cortex. (a) The posterior gyrus cinguli forms the border of the hemispheres to the rest of the brain — possibly thought as to include both hemispheres in one (see figure in Willis[146]). (b) Broca[18] describes "le grand lobe limbique" as to separate the cerebral hemispheres from each other and from the brainstem.

Comment: Mutel[97] has a closer look and finds within Broca's limbic lobe a second concentric ring of cortex ("limbe cortical secondaire") constituting the border of the cerebral cortex. Different borders have been described in the past (see Lancisi[70], Meyer[92]). This differentiation is taken up again by Lopes da Silva et al.[80].

Criterion: only cortical or only subcortical structures (nuclei). Willis[146] and Broca[18] include superficial brain structures only. Some authors today, particularly neuroanatomists, like to view the "limbic cortex" as a useful entity (for example: ref. 80) as opposed to limbic

nuclei. As to the cortex, the contiguity of grey matter is thought to be important as opposed to (association or commissural) fibre connections. Fibre connections will be considered below and play a role in connecting different nuclei.

Criterion: specific position in the cerebral hemispheres. (a) Anatomical position between neocortex, hypothalamus/hypophysial axis and the major sensory systems[48,69]. This seems to be a functional rather than an anatomical account. (b) The limbic system constitutes the medial wall of the cerebral hemispheres (in lower vertebrates)[106,132]. This criterion seems to go back to an account of brain development by Herrick[51]. (c) Dichotomy in the organization of the anterior limbic system: a mesial septal system (relating principally to sexuality and to "preservation of the species") and a lateral amygdaloid system (relating to defence and "preservation of the individual")[37].

Criterion: macroscopical similarities of cortical structures. (a) Contiguity of grey matter uninterrupted by deeper sulci or fissures[18]. However, Broca includes to some extent white matter fibres (olfactory striae). Nieuwenhuys et al.[105] show a "lobus limbicus" of the cortex in addition to the frontal, temporal, parietal and occipital lobes. (b) Lack of gyration in gyrencephalic mammals[18].

Comment: Stephan[127] remarks that the macromorphological delimitation of the limbic cortex is insecure.

Criterion: similarity of histological features of cortical structures. (a) The cortex of the limbic lobe is comprised essentially of archicortex and paleocortex and the transitional or mesopallial cortex developing adjacent to them[86]. (b) Limbic cortex is histologically defined as archi- and periarchicortex[80]. Creutzfeldt[25] finds that the part of the gyrus cinguli which lies immediately adjacent to the corpus callosum is periarchicortex and, therefore, to be considered as part of the allocortex while the part of the convexity with areas 23 and 24 belongs to the isocortex and has thalamic inputs. Earlier Stephan[127] states that limbic cortex is predominantly archi- and periarchicortex while the delimitation in the area of the gyrus cinguli is still not clear. (c) "The mesocortex which forms the outer band makes up most of the superficial cortex of the limbic lobe and extends somewhat beyond its boundaries as perilimbic cortex."[84]. In addition to limbic cortex and perilimbic cortex further terms have been introduced for example "mesolimbic" (for example: ref. 81) or "paralimbic" cortex or system[15,147]. (d) Inner limbic ring = allocortex, outer limbic ring = transitional cortex or juxtallocortex[53].

Comment: "Parts of Broca's limbic lobe have been traditionally considered neocortex by some[85,106] and variously called allocortex, peripaleocortex, periarchicortex, proisocortex, etc. by specialists in cytoarchitectonics"[10]. We find a confusing variation of histological divisions and terms applied.

Development of the limbic system. Similarity in phylogenetical or ontogenetical development (limbic structures develop at the same time and in contrast to other brain structures)

Criterion: development at an early stage of phylogeny. The limbic system "represents an early neural development"[86]. It consists of "tissue thought to be phyletically the oldest (allocortex)"[53]. The limbic system is an old part of the brain or of the telencephalon[57].

Criterion: development at a primitive stage of phylogeny. "The paleomammalian brain, corresponding to the so-called limbic system or 'visceral brain', is an inheritance from lower mammals"[83].

Comment: Isaacson sees the development of the limbic system going back even further: "There seems to be considerable uniformity in the interconnections among the structures of the limbic system in all living vertebrates"[53].

Criterion: particular development throughout phylogeny. (a) Limbic cortical structures (paleo- and archicortex) are constant throughout phylogeny, partially regressive[18]. (b) The archipallium is atrophied in mammals[97]. (c) Archicortex is progressive in absolute terms[48,127].

Comment: several authors find no clear sequence of progression in phylogeny (for example among paleo-, archi- and neocortex[34,131]. Bayer[10] proposes a new classificatory scheme from ontogenetical data and suggests that limbic cortex has a dual phylogenetical origin from combined paleocortex and archicortex on the one hand and from neocortex on the other hand.

Criterion: similarity in ontogenetical development. (a) Stephan[127] referring to refs. 60, 82. (b) "Limbic cortex" is a distinct ontogenetic system[10].

Comment: ontogenetical development appears to be complicated: the cortical neurons are formed first in the paleocortex, then in the neocortex, and a little later in the archicortex. Differentiation occurs in the order paleo-, archi-, neocortex[25].

Fibre connections of the limbic system

Criterion: large number of fibre connections between structures[4,80,105]. "Strong connections"[53,106]; "articulates extensively"[78]; "highly interconnected"[132].

Comment: expressions like "strong connections" may as well refer to the thickness or to functional properties of fibre connections. Brodmann[20] mentions that the

criterion of myelinated (fast conducting) versus non-myelinated (slowly conducting) fibre connections could be another useful criterion for classifying cortical structures.

Criterion: closed circuits of fibre connections. (a) Cortical rings[18]; diagrams in refs. 80, 86. (b) Combined cortical and subcortical rings[5,46,71,78,86,106]; circular diagrams in refs. 5, 144.

Comment: the correctness of the Papez circuit is taken into doubt by several authors (for example ref. 96, see ref. 27). The limbic system is presented as consisting of a number of circles which are closed and linked in different ways.

Criterion: connections in the form of an open ring. "Lobus falciformis"[119]; "gyrus fornicatus"[114]; "C-shape"[91], diagram in ref. 105.

Criterion: reciprocal fibre connections. (a) Within the limbic system[69,106]. (b) Reciprocal connections of the limbic system with extralimbic cortical areas[86].

Criterion: connections, without other interposed structures, with one particular brain structure which does not have other connections. (a) To and from the hypothalamus[106]: "Primary connections"[87]; "strong interconnections", "relatively direct" with the hypothalamus[53,54]; "direct association with the hypothalamus"[56]; "direct inputs" to the hypothalamus in contrast to the neocortex[132]. The hypothalamus receives somatosensory and viscerosensory afferents which are not mediated by the cortex but only by the thalamus and/or vagal nerve. "A commonly mentioned criterion for inclusion in the limbic system is connectivity with the hypothalamus, which places in the limbic system brain areas at every level of the neuraxis, from the cerebral cortex to the spinal cord"[71]. Brodal[19] remarks that several brainstem nuclei have connections — even direct ones — with the hypothalamus (for example raphe nuclei, nucleus locus coeruleus, nucleus of the solitary tract, dorsal motor vagus nucleus, intermediolateral cell column in the spinal cord). (b) To the formatio reticularis (an uninterrupted continuum of nuclei, which extend from the septum rostrally to the midbrain caudally)[56,80]. (c) The limbic regions (here: hippocampal formation, gyrus cinguli, prefrontal and perirhinal region, septum, basomedial and central nuclei of the amygdala, nucleus accumbens, substantia innominata) form the only major route for information transfer between neocortex and hypothalamus[132].

Comment: progress in histological techniques is continually devaluating this criterion and most brain structures seem to be connected with most others. The criterion may be reformulated in the following terms: a group of structures which are more highly connected with one another than with external structures. The exact definition of high connectivity would still have to be provided since the connections are not as uniform as in the cerebral neocortex.

Criterion: chains of fibre connections. Two chains of neuronal structures which are linked to each other by the septal and preoptic areas. Each chain again has links to the hypothalamus and the formatio reticularis[100,102].

In future we expect the description of other types of regularity of fibre connections for example parallel connections between the structures as has been proposed for loops (including a "limbic" loop) involving basal ganglia, thalamus, and cortex[6].

Combinations of morphological criteria

Criterion: "The limbic system comprises the limbic cortex and structures of the brainstem with which it has primary connections"[87].

Criterion: Allo- and mesocortical areas in a seam-like arrangement having fibre connections with one another and with specific subcortical structures[132].

Criterion: Reciprocal connections of the medial wall of the hemisphere with the hypothalamus (emotions) as opposed to those of the lateral wall of the hemisphere with the nuclei of the dorsal thalamus (senses) from lower vertebrates[106], referring to ref. 51.

Criterion: The limbic system is comprised of the cortex contained in the great limbic lobe of Broca, the cortex of the insula and the temporal polar gyrus, together with subcortical nuclear structures (amygdala, septal nuclei, hypothalamus, epithalamus, anterior thalamic nucleus, and parts of the basal ganglia)[86]. This is an enumeration rather than a criterion.

Biochemical/pharmacological properties of the limbic system

Criterion: high concentration of a particular substance. (a) Zink, noradrenaline[1], benzodiazepine-receptors[28,44], (D2) dopamine-receptors[61]. (b) Peptides and their receptors[115,130]. (c) "Limbic system-associated membrane protein"[65,74]. Levitt[74] refers to a "conventional anatomic organization of the limbic system" which largely coincides with the distribution of this specific molecule.

Criterion: concurrence of different neuropeptide receptor types. Receptors for angiotensin, insulin, transferrin, and other peptides[107].

Comment: Nieuwenhuys[104] finds that "the set of 'neuromediator-rich' and 'neuromediator-dense' centres and pathways coincides largely, but not entirely, with the limbic system" unless even further brain structures are included[66].

Physiological properties of the limbic system

Criterion: spread of activity. (a) Excitatory closed circuit of fibre connections[106]. Dagi and Poletti[27] find very little evidence of activity spread within Papez's circuit but rather to the brainstem[109]. (b) Bidirectional spread of activity as recorded by strychnine neuronography[90,111]. (c) Functional anatomical connections of the hippocampus within the limbic system can be demonstrated as the pattern of activity spread with hippocampal seizures[25,26]. "Hippocampal discharges build up progressively, spread, capture the entire limbic system in sustained seizure activity, and result in a distinctive limbic pattern of neuropathological changes"[22]. (d) "It is likely that seizure activity initiated elsewhere in the limbic system will be amplified in the 'feed-forward' excitatory circuits through hippocampal synapses"[22].

Criterion: reverberatory circuits. "Neural loops where a given state of activity may be preserved for some time (typically a few hundreds of milliseconds) after a short stimulus"[80].

Comment: the concept of reverberatory circuits (more recently: oscillations) is very often mentioned in textbooks, it is rare in journal articles[49,80] and more commonly relates to the autonomic nervous system. Following Lopes da Silva et al.[80] there is very little experimental evidence for it (see Deadwyler et al.[29] who describe a trisynaptic circuit hippocampus – entorhinal cortex – dentate gyrus).

Criterion: rhythmic slow activity (theta rhythms). Rhythmic slow activity can be found in all limbic cortical areas[80]. Furthermore, manipulation of Nauta's limbic midbrain structures modulates these rhythms.

3.2. *Evaluation of the morphological definition of the limbic system*

The list above gives evidence of the extensive and still ongoing effort that is being made to come to a conclusive morphological definition of the limbic system.

The simplest type of difficulty that we encounter is the lack of a unique definition of every single brain structure which is mentioned as a constituent of the limbic system. Bayer[10] is cited above as commenting on the varying nomenclature of limbic cortex. The "hippocampus" or the "hippocampal formation" is another particularly striking example. This term may simply refer to the "hippocampus proper" (= Ammon's horn), it may also include the fascia dentata, sometimes also the subiculum, occasionally all tissue making up the "hippocampal gyrus"[53]. Moreover, the term "hippocampal gyrus" was used at least in the nineteenth century to refer to the parahippocampal gyrus (see refs. 18, 97). This ambiguous meaning of a term is sometimes difficult to interpret, particularly in some of the older literature. The recent morphological investigations tend to be more accurate in this respect and there is generally little doubt as to the exact brain structure referred to. Some great effort has been made towards classification and clarification of the terminology of the respective brain structures (for example ref. 126). This, however, is not the case where authors refer to these structures without the latest detailed knowledge of the morphology. This limitation, therefore, applies to most morphological work which was done roughly more than 10 or 20 years ago, and in particular to clinical reasoning where anatomy is still to a large extent considered on a broad macroscopical level (for example in terms such as limbic encephalitis, limbic epilepsy).

Next, the definitions of the limbic system are derived from different animal species (and occasionally humans) although we did not specifically mark this. The question of homology of brain structures is still far from being solved (see for example ref. 53). This holds true in particular in view of some of the smaller forebrain nuclei in the area of the tuberculum olfactorium in humans. Several authors have addressed this difficult issue in respect to single brain structures[133]. The consequences for the concept of the limbic system, however, have very rarely been considered[105]. It is an exception to find an outline of the limbic system limited to one species (for example the rat[48]). Usually a sufficiently homologous arrangement is tacitly supposed, which warrants general statements about the nature of the limbic system.

There are several types of definitions for example the enumeration of all members or the naming of a general criterion which separates a group of objects from others. A large number of textbook definitions of the limbic system proceed by the first method. Also, the observation of gradually distributed features such as the accumulation of a particular substance in certain brain structures (see biochemical criteria) merely leads to their enumeration as long as we do not have a clear criterion for acceptance or rejection. This enumerative approach may be taken to define a particular set of brain structures but as such it is of no value. On the one hand, without reference to a criterion it can never be falsified. On the other hand, without functional significance it cannot be applied usefully.

A revealing example of an argument is Levitt's[74] claim that the limbic system-related protein is a system-specific marker. This assumes the prior existence of a clear concept of the limbic system. A look at the diverse references given in that article (which include Papez[106] and MacLean[85] as evidence) shows that this is clearly

not the case. Confirming the concept of the limbic system by the distribution of this protein means, therefore, constructing a circular reference. It is not a criterion which can stand on its own.

If we look at the single criteria given for definition then we notice that some of them are obviously false, for example "man has the largest (relatively and absolutely) hippocampus of any animal". Others may have been satisfactory at the time of their establishment but they no more satisfy our present requirements, for example strychnine neuronography as used by MacLean and Pribram[90,111]. Broca's criteria would not be acceptable today. Nevertheless his article is very often cited probably because the overall arrangement (but not the details) of his inclusions is confirmed by the use of different techniques (for example histology[80]).

Some criteria are so vaguely phrased that the exact measure can only be guessed at. For example the term "strong connections" may refer to the number of fibres, the thickness of fibres, or to functional properties of the fibre connections. Other criteria are taken into doubt by the contrasting commentaries of other authors, for example the criterion of connections with the hypothalamus. In some cases this may simply relate to progress being made in that field of research. A controversial issue may have been investigated using better or different techniques and following this it may have been settled. This seems to be the case with the histological definition of limbic cortex as consisting of archi- and periarchicortex.

More often, however, a specific issue has been controversial or assumed for a long time and is still questionable in spite of all methodological ingenuity. The proposed existence of neuronal circuits and even more so of reverberating activity in them may serve as an example. The confirmation of these criteria is considered to be of great conceptual importance. As Smythies[123] puts it: "It should be noted here that by 'circuit' one does not mean to convey an idea of a simply connected type of relay system. The system should allow for a series of complex transformations at each succeeding stage. There is, as yet, no clear evidence". In view of this demanding scope all experimental attempts at measuring the spread of activity appear hopeless.

Some criteria seem to be incompatible with other criteria which have been found in a different context (for example: does the gyrus cinguli take part in the cortical ring, in the Papez circuit or in both?). Others fit not just the limbic system but other systems, too (for example connections with the hypothalamus, amount of dopamine). With more refined experimental observations more and more diverse links are found. Nauta[101] points out that the nervous system abounds with examples of neural structures that form part of one 'system' when viewed from one point of view and are part of quite a different one when considered in a different way. "Such ambiguities seem distressing only because of our tendency to expect a degree of separation of neural mechanisms that appears to be an exception rather than the rule in the more highly developed central nervous system." This view is correct in as far as it points out that most of the criteria rely on a strong localizationist preconception of the brain and may completely miss out the possibility of less obvious morphological arrangements. However, it is no solution in this context. If there is little or no regularity in neural mechanisms then all attempts at conceptualization should be stopped right away and be postponed until every detail about the brain will be known. If morphology is not relevant to brain function then there will be no need to study it in detail.

In any case the number of contrasting statements and reconsiderations concerning a specific issue of relevance to the limbic system has increased rather than decreased and the statements do not seem to converge towards clearly established criteria.

It is rare to find attempts at an evaluation of formerly given criteria at all. Poletti[109] is surprised that a search of the literature revealed no satisfactory experimental tests of the Papez theory. While this is our observation, too, we find a large amount of literature relating to single brain structures and their morphology without the morphological concept of the limbic system or any other concept being addressed. This may contribute to the inclusion of more and more brain structures in the limbic system as for example in the case of Nauta's[100] inclusion of mesencephalic structures. From a local point of view there may be good reasons for inclusions but at the same time the overall concept may loose coherence.

We are left with a vast accumulation of unrelated contentions concerning the morphological definition of the limbic system of which some are useless and some are clearly outdated or wrong. These should be discarded. Others are not properly evaluated or cannot be evaluated for lack of clarity or adequate methodology. At least at present there is nothing that could serve as a single adequate criterion for a morphological concept of the limbic system.

Let us assume for a moment that this lack of an adequate criterion is temporary and that eventually we will be able to delineate one or more adequate criteria for a proposed morphological definition of the limbic system. What then would this mean in respect to the other doubtful criteria put forward? Obviously they

cannot simply be discarded since they are not proved wrong. It might well be that several adequate criteria exist at the same time like Broca[18] believed that he had provided (phylogenetical constancy, morphological continuity, positional specificity). As an example we may take the histological definition of limbic cortex as archi- and periarchicortex. If this is an adequate criterion then it covers "limbic cortex" while any subcortical components are excluded. Nevertheless there might be a number of different structures which are all "directly" linked to the hypothalamus as some authors propose. Are these two definitions mutually exclusive or would they have to be combined into one as MacLean[86] does it? If several definitions can be combined then how would we have to deal with possible contradictions between them?

Without an adequate morphological definition of the limbic system and without promising candidates running up we can alternatively look for a functional definition of the limbic system.

4. WHAT IS THE FUNCTIONAL CONCEPT OF THE LIMBIC SYSTEM?

An overwhelming variety of research methods have been applied to find common functional properties of the limbic system. In order to understand the different strategies we can classify them according to their levels of functional description. It is customary to differentiate between, on the one hand, brain functions as functions which are attributed to the brain or its subdivisions and, on the other hand, behavioural functions which are described as functions of the whole organism. The latter may also include functions which are thought to be relevant at the level of social behaviour. Another distinction is made between normal functions (as far as they can be observed without interference) and pathological functions such as clinically relevant illnesses. For example Isaacson[53] found that many if not all effects of stimulation and lesion in the extrahypothalamic limbic system can be reproduced by stimulation and lesion of the hypothalamus. This statement implies that the limbic system can be functionally defined as a number of brain structures which satisfy the criterion that their manipulations show the same effects. A closer look reveals that quite diverse effects are included which range from changes in electrophysiological parameters to those in animal behaviour. In the preceding chapter we showed that Isaacson defines the limbic system also morphologically as brain structures which have direct connections with the hypothalamus. If we put these two statements together then it becomes clear that the coincidence of a morphological and several functional commonalities is taken as to define a complex functional anatomical system. This system, however, is meant to be more than a correlative construct, it gains its own life and seems to provide explanation and understanding. Here follow other opinions that we could extract from the literature:

4.1. *Criteria for the functional definition of the limbic system*

Functional significance of the limbic system on the level of brain function

Criterion: involvement in sensory information processing. (a) The limbic system has strong links to *olfactory* functions[18,143], they are "intimately related"[105]. Several textbooks consider the limbic system together with the olfactory system (for example: refs. 19, 105, 145). Comment: the particular importance of olfactory inputs has been doubted for a long time (see ref. 92) on the grounds of comparative anatomy[123,128]. (b) The limbic system is the sensory system for the *visceral* inputs[3]. ("visceral brain"[85]). Comment: many other structures are involved in the processing of visceral afferents and efferents: the hypothalamus also has different, for example somatomotor functions (ref. 53, Pribram's commentary to MacLean[86]). Swanson[131] concludes that the role in visceral processing is still an open question. (c) "Limbic structures of the temporal lobe are involved in processing *motivationally meaningful exteroceptive* information and exert a definite influence upon the secretion of anterior and posterior pituitary hormones"[41]. (d) The limbic system is *independent of sensory information* ("sinnesunabhängig")[49,127] or rather *integrating different sensory information*[85,86,131,141].

Criterion: involvement in cognitive information processing. Integration of cognitive information and passing on to the hypothalamus: perihippocampal zone (gyrus cinguli, prefrontal and perirhinal areas) corresponds to polymodal association cortex, hippocampal formation to supramodal association cortex, septo-amygdaloid complex to the gate between limbic cortical regions and hypothalamus[131].

Criterion: involvement in learning and memory. (a) This notion is more commonly mentioned in textbooks and review articles: "The limbic system plays a fundamental role in memory function"[76], there is "more than one limbic pathway involved" in memory[31], "limbic lesions have selective and specific effects on memory"[124]. (b) The "limbic operating system" controls the neocortical associative memory storage systems[24].

Comment: all experimental evidence concerning me-

mory functions is not related to the limbic system as a system but to single brain structures. It is interesting to note that the role of the limbic system has changed from the site of memory storage to the control system over (some of) the stores. The precise roles of the limbic system or any of these structures are still subject to controversy (see for example: refs. 52, 94, 148).

Criterion: involvement in emotions and sexual function. (a) The limbic system is involved in the elaboration of emotional experience and expression (ref. 86 referring to refs. 85, 106). (b) "The limbic system has been called the 'reward system'. It serves affective reactions"[8]. (c) The role of the limbic system is the integration of the internal and external worlds of the individual — thereby generation of affects; it is the system for emotional behaviour-related homeostasis[78]. (d) The limbic system is viewed as the main cerebral representative of the internal milieu, expressing its functions in the form of states of affect and motivation[99]. (e) A circuit which is involved in sexual functions: producing penile erection (in the squirrel monkey)[89], controlling reproductive functions of the ovary[64].

Criterion: involvement in motor functions. (a) "The limbic system exerts situation-dependent action on the integration of the conditioned somatomotor activity"[76]. (b) The limbic system (emotion) influences the motor system (action) via connections with the basal ganglia (nucleus accumbens as "interface")[55,95,98,103].

Criterion: involvement in the final stage of mental integration. The limbic system plays an important role in the integration of all brain functions and in the "condensation of the whole experience" as "psyche"[21].

Functional significance of the limbic system on the level of behaviour

Criterion: involvement in behaviour at a particular evolutionary level. (a) Seat of the lower faculties which predominate in the wild animals ("brute", "brutale"[18]). (b) The triune brain model[88]: (i) the paleomammalian brain or limbic brain is thought to be "nature's tentative first step toward providing self-awareness, especially awareness of the internal conditions of the body"[53,87]. (ii) "The best way to conceptualize the limbic system is as a regulator of the reptilian core brain", "it is acting to produce forgetfulness"[53].

Criterion: involvement in emotional behaviour. (a) Emotional expression can still be carried out in spite of complete removal of dorsal thalamus and cortex (ref. 106 referring to ref. 9). The cortex is necessary for emotional experience of impulses, hippocampus produces emotions, mammillary bodies (hypothalamus) and anterior thalamus are relay centres, and gyrus cinguli is the receptive field of central emotions (contact to neocortex produces emotional colouring of other psychical processes); another input is the hypothalamus for emotional colouring of sensory perception[106]. (b) "[The limbic system] has been shown to play an important role in emotional behaviour"[83,86].

Comment: Swanson[132] and Vanderwolf et al.[140] find no experimental evidence for the involvement in emotional behaviour.

Criterion: involvement in species-specific behaviour. The limbic system controls the species-specific behaviour in animals and the emotional behaviour in humans[57]. The limbic system is directly involved in the preservation of the individual and of the species[57,105].

Criterion: involvement in social behaviour. MacLean's suggestion[84] is repeated by Doane[31].

Functional significance of the limbic system in pathological brain function and behaviour

Criterion: involvement in certain types of epilepsy ("limbic epilepsy")[67,137]. (a) Epileptic fits with predominant activity in the limbic system are referred to under the heading "psychomotor epilepsy" ("psychomotorische Epilepsie")[25]. (b) Seizure activity in any structure of the limbic system can evoke temporal lobe epilepsy (amygdala)[49]. (c) The symptoms of temporal lobe epilepsy can be explained as a hyperconnection syndrome of the limbic system with sensory inputs[11]. Some effects of lesions in the lateral temporal cortex can be viewed as a disruption of the temporo-basal limbic system from neocortical control[25].

Criterion: involvement in disturbances of learning and memory. (a) Dysfunction of the limbic system leads to an amnestic syndrom in man[68]. (b) Incremental lesioning of structures of the limbic system produces increasing disturbances of learning and memory[24].

Criterion: involvement in Gilles-de-la-Tourette syndrome. The symptoms are a sequel of influences of the limbic system, more specifically of disinhibition of the limbic system, on the motor system[23,101]. "Persistent Gilles-de-la-Tourette syndrome can be successfully treated by limbic leucotomy"[116].

Criterion: involvement in neuroses. Lesions of structures in the Papez circuit are a possible cause of obsessive-compulsive disorder[33,58].

Criterion: involvement in certain types of anxiety[31]. (a) The septo-hippocampal system as a part of the limbic forebrain plays a role in anxiety and is influenced by anxiolytic drugs[45,46]. (b) The limbic system is specifically the "center for anticipatory anxiety"[44].

Criterion: involvement in disturbances of emotions. (a) Lesions and alterations of structures in the Papez circuit (for example rabies with degeneration of the hip-

pocampus) produce emotional disturbances and disturbances of consciousness[106]. The limbic system is involved in aggressive behaviour[36]. Hassler[49], however, finds such disturbances with lesions in other brain structures, too. (b) The limbic system "when skewed will lead to a disturbance of the affective-cognitive life of the individual"[135]. (c) "Recent investigations have shown that dysfunction of the limbic system of the brain underlies many disturbances of emotion and may result in some psychotic manifestations"[40].

Criterion: involvement in manic-depressive illness. (a) "This very lack of homogeneity in limbic system function, however, could provide a comprehensible mechanism for understanding the opposing aspects of manic-depressive illness"[110]. (b) Manic-depressive illness is modulated by lateralized and asymmetrical dysfunction of the anterior limbic system[37].

Criterion: involvement in schizophrenia[67]. (a) Schizophrenia is determined by lateralized and asymmetrical dysfunction of the anterior limbic system[37–39]. (b) Schizophrenia is correlated with a substance deficit in the limbic system[14,15,134]. (c) Functional disturbance of the limbic system may be the cause for childhood schizophrenia[35]. (d) The functions of the limbic system can explain the relationship between schizophrenia and epilepsy[40,67,136].

Comment: the issue of altered brain structure in schizophrenia is highly controversial (for example refs. 50, 129), the mechanism of altered brain function remains a matter of speculation.

Combined definitions of the limbic system

Criterion: involvement in all aspects of central visceral function. "There are indications that the phylogenetically old brain (classically known as the rhinencephalon and arbitrarily referred to in this paper as the 'visceral brain') is largely concerned with visceral and emotional functions"[85].

Comment: "The limbic system cannot both represent the visceral control ['visceral brain'] and integrate all internal and external perceptions ['body viscus']. The confusion which arises from an eclectic acceptance of the two alternate theories can serve no useful scientific purpose" (Pribram in ref. 86).

4.2. *Evaluation of the functional definition of the limbic system*

The functional definitions of the limbic system are not comparable with the morphological definitions above. Although they may include such concepts as "reward system"[8] or "behavioural inhibition system"[46], they usually do not address a functional concept only. The most important feature of these functional concepts is that they attempt to tie up brain structures with brain functions or behavioural functions in the sense that the morphological substrate exerts these functions. The limbic system becomes a functional anatomical system. Pathological symptoms are correspondingly signs of dysfunction of the limbic system. Therefore, we have to deal with a more complicated matter than a purely morphological system.

In the early years of the limbic system it was relatively easy to bring the morphological and functional aspects together. At the turn of the last century the limbic system (or rather its predecessors) overlapped with the olfactory system, in Papez's[106] work it became the mechanism of emotion. But all the time the unity of a morphological system was matched by the unity of a functional system. As research techniques became more sophisticated, the unity of each of the two aspects became more and more difficult to sustain. We have seen above that more and more brain structures appear to be connected with the limbic system. The morphology of the limbic system threatens to comprise the entire brain. On the other hand, it was discovered that the limbic system plays a role in more and more functional aspects of the brain. Visceral processing and sensory integration were included by MacLean[85,86]. The involvement in memory became popular with the work of Scoville and Milner[121]. The kindling phenomenon and the discovery of rhythmic activity linked the limbic system with epileptic fits and the investigation of neurotransmitters gave rise to its implication in many psychiatric illnesses. The list above indicates that the limbic system has been related to most brain functions. If we take this together then the limbic system is on its way to become a synonym for the brain and its workings as a whole[19].

Over the same time each of the functions of the limbic system began to diversify. For example memory has been split up into immediate recall, short-term to long-term memory, declarative memory, procedural memory, to name just the more common ones. A difference is made between acquisition ("learning"), storage, consolidation, recall and expression of memory. The validity of the results is limited to the specific experimental contexts. The unified concept of memory disappears behind large numbers of different operational definitions. Therefore, the limbic system seems to not just comprise more and more structures and functions of the brain, but the very contents of it breaks apart and becomes more and more difficult to ascertain. We are left with vast amounts of experimental data which cannot be accounted for by unified morphological or functional concepts. The concepts themselves are so vaguely

related that they cannot be integrated to form one limbic system.

The question is, therefore, what consequence this situation has for the concept of the limbic system. More specifically we want to investigate whether there is a way to assemble the limbic system anew from these unconnected bits and pieces. So far we looked at attempts to define all of the limbic system using one or at most a few criteria. Now we consider the literature which concerns the construction of the system. This approach presents some additional difficulties which we have to consider.

Several books concern the concept of the limbic system if we follow their titles[2,30,32,53,67,79,138] and many other articles mention to concern the limbic system (for example refs. 14, 15, 24, 41, 50, 134, 140). Most of these articles present data in particular experimental contexts, but they do little to integrate them in regard of the limbic system as a whole. In fact they could do equally well without the construct of the limbic system. The application of this term seems to be little more than lip service.

There is another type of article which makes a conceptual contribution to the limbic system. Most commonly it presents little experimental data but comments on the classical publications by Papez[106], MacLean[85–87] or Isaacson[53]. For example MacLean's concept of the triune brain is repeatedly considered. We can trace different interpretations ranging from a morphological origin to a psycho-analytical application[31]. The original articles, however, are reviews themselves and do not present many original data either. Rather than on a well-founded concept, which integrates a wide range of experimental data, we seem to impinge on the latest revision of loose ideas, which have been digested several times in succession, but whose initial empirical contents has fallen into oblivion. Since the original ideas were set up, nothing much has happened but to attach bits and pieces of recent empirical data from different sources here and there. The concept of the limbic system as a whole is not justified again on fresh grounds.

This regress explains, furthermore, why it is comparatively difficult to find original statements which take the limbic system into doubt. There is not just the general tendency of presenting positive rather than negative findings, but there is a lack of data which could be replicated in the first place. It is difficult enough to evaluate experimental data but it is even more difficult to evaluate concepts which are derived from reviewing more and more complex reviews.

Let us now consider what the general procedure is if we want to construct the limbic system from available data. We need to identify studies which correlate single brain structures with specific functional aspects. These pieces of evidence are then summed up to link one or more brain structures with one or more functions. If the resulting complex appears to have some uniformity then it will be called the limbic system (this type of strategy is taken in refs. 24, 85, 106).

We can choose from a wide range of experimental setups which correlate different observations. Some of these setups allow relatively adequate morphological control with limited behavioural relevance (for example lesion studies in behaving animals) and others at the other end of a spectrum may give detailed psychological accounts but little morphological precision (for example clinical case reports). We have to make sure that the observations and their evaluations are specific enough. It is clearly not sufficient to specify a brain structure as for example the "hippocampal area". Similarly we cannot be content with a statement that, for example, a structure is involved in "emotion". Questions to be considered are for example: what is meant by emotion? Are provisions made to differentiate between affects, emotions, motivations or to relate these to other constructs such as perception, cognition, action? Does the explanatory concept concern some or all emotions and how are these classified? Does it refer to emotional experience (introspection) or emotional behaviour (bodily change) or other aspects of emotions? Does it concern mechanisms of how emotions are developed, triggered, or controlled? The lack of specificity probably is the most common flaw of statements about the functional role of the limbic system. Psychological reasoning today has gone a long way from general and indiscriminate statements.

The next step is to assemble these diverse observations into the concept of the limbic system. Let us have a closer look at the methods which are used for this purpose. Livingston and Escobar[78] mention the criterion of "greatest coincidence of anatomical, physiological, biochemical, and clinical evidence". Isaacson[53] discusses the method of combining results in respect to the question of homology. He finds that all criteria must be taken into consideration as "soft criteria" and that it is only when all, or many, of them converge on a similar conclusion that a concept should be accepted. The flaw with this argument is that Isaacson and many others, hide the criterion for acceptance of their concepts: when do we have enough data to rely on? When is there enough convergence on a similar conclusion? How similar do these different conclusions have to be? Such criteria remain vague and subjective. If we look at it in a little more detail then the lack of knowledge becomes apparent. It is only in very broad terms of

morphology and function that all these diverse results seem to coincide in a common concept but there are few explanatory links established between them. To give some examples: how can we use our knowledge of anatomical fibre connections and neuronal excitability to explain electrical activity in the hippocampus or in the hypothalamus? How does this electrical activity relate to those in other brain areas? How are these mechanisms involved in the retrieval of memory or in the affectual toning of sensations? How do these mechanisms translate into specific experiences or expressions of emotions? What causes the clinical symptoms of psychosis? What kind of clinical treatment should be given? In order to construct adequate concepts we have to face as much detail as possible rather than to close our eyes in view of that complexity. Only then it may be possible to come to meaningful simplifications and concepts, which we need in order to apply them successfully to different contexts. Rawlins[113] concludes that "the limbic system is a title for a somewhat heterogeneous group of central nervous regions, which bear very little structural resemblance to one another and appear to have a considerable diversity of function". Accumulation or coincidence of data is insufficient to construct an explanatory concept. The limbic system founded on such coincidence is in the state of patchwork. The unifying label of the limbic system is not enough to satisfy the need for detailed unraveling of possible links.

To link observations from different experimental setups we have to evaluate logically how the results of one type of experiment relate to those of other experiments. Many assumptions have to be made, for example that the brain structures lesioned are homologous, that they play the same role in brain function or that the functional or behavioural features are equivalent. The problem of species-specificity arises (for example epileptic discharges in animal models and humans) in a similar way as we discussed it above in regard of the morphological criteria. For most of the psychiatric disorders no experimental model is available at all (for example schizophrenia) or they are highly questionable (for example in fear or anxiety: ref. 140 vs. ref. 44). The diversity increases the more different experimental setups are employed, the more different features are measured, or the more levels of functional description are involved. Thus, it is very unlikely that for example the behaviour of a cat in response to cortical ablation ("sham rage"[9]) gives a relevant prediction of the presence and site of lesion in a patient with strong aggressive behaviour or even of his conscious experience ("rage"[36]) without consideration of the underlying neuronal mechanisms. One way to deal with this problem may be to constrain the degrees of freedom of mental explanations by using biologically plausible computer simulations of the relevant neuronal structures.

How far do the explanatory links go? Wenzel[143] finds that "the information now available constitutes, at best, the olfactory-limbic-hypothalamic neurobehaviour of the rat". Our review demonstrates that even this issue remains questionable. But assuming that we will be able to construct "a remarkably coherent picture — in which anatomy, physiology, and biochemistry interlock like key pieces of a cosmic jigsaw puzzle"[77] will this be the only one possible way to fit all the bits and pieces? Experience shows that the same results may fit into several explanatory concepts. For example MacLean[86] formed the concept of the limbic system as the forebrain representation of the visceral nervous system on the one hand, and as the integrating centre of all internal and external sensory information on the other hand. Pribram criticizes these as logically exclusive definitions (Pribram's comment in ref. 86). Both of these concepts can be justified by some correlative data, but they mutually exclude each other on logical grounds. If we have several options then there must be additional factors which influence the acceptance of a particular concept. Which particular concept then should be called the limbic system? What should happen to other concepts?

5. CONCLUSION

We have seen that a large and increasing number of brain structures and functions has been implicated with the limbic system. This heterogeneous collection cannot be defined by a single criterion. To cope with it, a number of subsystems have been introduced. These, however, encounter the same problems. The limbic system has spread beyond all meaningful criteria for its definition. On the other hand, if we try to construct the limbic system from correlative data then we face a highly complex task which we have difficulty to cope with. The vast amounts of data from different experimental setups do not allow unambiguous broad statements. There is reason to believe that even further expansion of methods as such will not create much more understanding. What we need is better tools to deal with data, for example to help the comparison between different kinds of experiments, different objects of investigation, different levels of interpretation. We know very little about these difficulties and we may not have adequate heuristic tools at hand to cope with them. It should be clear that we cannot answer the question, what the correct definition of the limbic system is, as long as we make

the limbic system the purpose of our reasoning instead of trying to adhere to the available evidence. Therefore, this question should be posed in a different way. What explicit concepts of involved structures or functions of the brain can we think of? How do they perform in view of the available data? What crucial experiments should be carried out to decide between several acceptable concepts?

The limbic system is not a piece of nature given to us. It is just one out of many scientific concepts. From an empirical point of view this concept is not adequate and there is nothing to justify its continuing use in a general and indiscriminate sense.

Other and better scientific concepts have to be put forward and to be considered. The analysis of Medline shows that the limbic system does not constitute the only explanatory concept in respect to the brain structures and functions involved in the limbic system. For example the hippocampus and with it the functions of memory have to a large extent emancipated from the limbic system concept, and we may believe that we begin to understand them to some extent. The hypothalamus, some olfactory structures, and the gyrus cinguli remain more closely linked to the limbic system and with them the workings of emotions, the presumably primitive and savage functions of olfaction, and the key concepts to their surgical control. These areas seem to be far more puzzling. It is of interest to note that the limbic system represents particularly those areas in brain research which are poorly understood.

It may turn out that the limbic system becomes more and more obsolete as our knowledge increases. But so far it has a very important role to play: it meets our need and desire for explanatory concepts in the neurosciences which is reflected in the influence that the limbic system has on many areas in the neurosciences. The reasons for its explanatory power cannot be found in its empirical foundation. But there are other non-empirical features which we should be aware of and which repeatedly occur in many of the different criteria which we have listed. The concepts of the closed circuit, of the balanced functions, and of the hierarchical processing are prominent. The corresponding symbols of the circle, the balance and the ladder have served for a long time in explaining the unexplained. It is no accident that the greatest mysteries in our understanding of the brain remain with the limbic system: questions concerning the integration of all brain functions, the generation of consciousness or psyche, and finally the seat of the soul. The struggle with these questions has found an expression in the multi-faceted and controversial concept which is called the limbic system. "The term, however, is simple and enjoys universal recognition: everyone thinks he knows what is meant when he hears it"[72].

ACKNOWLEDGEMENTS

This study was supported by the Deutsche Forschungsgemeinschaft, Schwerpunktprogramm Wissenschaftsforschung (Pa 268/5-1).

REFERENCES

1 Adams, R.D. and Victor, M., *Principles of Neurology*, 3rd edn., MacGraw-Hill, New York, 1985.
2 Adey, W.R. and Tokizane, T., *Structure and Function of the Limbic System, Progress in Brain Research, Vol. 27*, Elsevier, Amsterdam, 1967.
3 Airapetyants, E.S. and Sotnichenko, T.S., The limbic cortex, its connections and visceral analyzers. In W. Adey and T. Tokizane (Eds.), *Structure and Function of the Limbic System, Progress in Brain Research, Vol. 27*, Elsevier, Amsterdam, 1967, pp. 293–304.
4 Akert, K., *Anatomie und Physiologie des limbischen Systems*, Hoffmann-La Roche & Co., Basel, 1963.
5 Akert, K., Das limbische System. In A. Benninghoff (Ed.), *Anatomie, Vol. 3*, 14th edn., Urban & Schwarzenberg, München, 1985, pp. 395–416.
6 Alexander, G.E., Crutcher, M.D. and DeLong, M.R., Basal ganglia–thalamocortical circuits: parallel substrates for motor, oculomotor, "prefrontal" and "limbic" functions. In H.B.M. Uylings, C.G. Van Eden, J.P.C. De Bruin, M.A. Corner and M.G.P. Feenstra (Eds)., *The Prefrontal Cortex: Its Structure, Function and Pathology, Progress in Brain Research, Vol. 85*, Elsevier, Amsterdam, 1990, pp. 119–146.
7 American Medical Association, *DSM-III-R*, American Medical Association, Washington, DC, 1987.
8 Arnold, M.B., Emotion, motivation and the limbic system, *Ann. N.Y. Acad. Sci.*, 159 (1969) 1041–1058.
9 Bard, P., The central representation of the sympathetic system, *Arch. Neurol. Psychiatry*, 22 (1929) 230–246.
10 Bayer, S.A., Development of the lateral and medial limbic cortices in the rat in relation to cortical phylogeny, *Exp. Neurol.*, 107 (1990) 118–131.
11 Bear, D.M., Temporal lobe epilepsy – a syndrome of sensory-limbic hyperconnection, *Cortex*, 15 (1979) 357–384.
12 Birbaumer, N. and Schmidt, R.F., *Biologische Psychologie*, Springer, Berlin, 1990.
13 Bluglass, R. and Bowden, P., *Principles and Practice of Forensic Psychiatry*, Churchill-Livingstone, Edinburgh, 1990.
14 Bogerts, B., Meertz, E. and Schönfeld-Bausch, R., Basal ganglia and limbic system pathology in schizophrenia, *Arch. Gen. Psychiatry*, 42 (1985) 784–791.
15 Bogerts, B., Wurthmann, C. and Piroth, H.D., Hirnsubstanzdefizit mit paralimbischem und limbischem Schwerpunkt im CT Schizophrener, *Nervenarzt*, 58 (1987) 97–106.
16 Bowman, W.C. and Rand, M.J., *Textbook of Pharmacology*, Blackwell, Oxford, 1980.
17 Bray, J.J., Cragg, P.A. and Macknight, A.D.C., *Lecture Notes on Human Physiology*, Blackwell, Oxford, 1990.
18 Broca, P., Anatomie comparée des circonvoluts cérébrales: le grand lobe limbique et la scissure limbique dans la série des mammifères, *Rev. Anthropol.*, 1 (1878) 385–498.

19 Brodal, A., *Neurological Anatomy*, Oxford University Press, New York, 1981.

20 Brodmann, K., *Beiträge zur histologischen Lokalisation der Grosshirnrinde*, Barth, Leipzig, 1906.

21 Ciompi, L., Affects as central organising and integrating factors: a new psychosocial/biological model of the psyche, *Br. J. Psychiatry*, 159 (1991) 97–105.

22 Collins, R.C., Lothman, E.W. and Olney, J.W., Status epilepticus in the limbic system: biochemical and pathological changes. In A.V. Delgado-Escueta, C.G. Wasterlein, D.M. Treiman and R.J. Porter (Eds.), *Status Epilepticus, Advances in Neurology, Vol. 34*, Raven, New York, 1983, pp. 277–288.

23 Comings, D.E., A controlled study of Tourette syndrome. VII. Summary: a common genetic disorder causing disinhibition of the limbic system, *Am. J. Hum. Genet.*, 41 (1987) 839–866.

24 Cramon, D. von and Hebel, N., Lern- und Gedächtnisstörungen bei fokalen zerebralen Gewebsläsionen, *Fortschr. Neurol. Psychiat.*, 57 (1989) 544–550.

25 Creutzfeldt, O.D., *Cortex cerebri*, Springer, Berlin, 1983.

26 Creutzfeldt, O.D. and Meyer-Wickeleit, R.W., Patterns of convulsive discharges of the hippocampus and their propagation, *Electroencephalograph. Clin. Neurophysiol.*, Suppl. 3 (1953) 43.

27 Dagi, T.F. and Poletti, C.E., Reformulation of the Papez circuit: absence of hippocampal influence on cingulate cortex unit activity in the primate, *Brain Res.*, 259 (1983) 229–236.

28 Dantzer, R., Benzodiazepines and the limbic system. In M.R. Trimble and E. Zarifian (Eds.), *Psychopharmacology of the Limbic System*, Oxford University Press, Oxford, 1984, pp. 148–163.

29 Deadwyler, S.A., West, J.R., Cotman, C.W. and Lynch, G., Physiological studies of the reciprocal connections between the hippocampus and entorhinal cortex, *Exp. Neurol.*, 49 (1975) 35–37.

30 DiCara, L.V., *Limbic and Autonomic Nervous Systems Research*, Plenum, New York, 1974.

31 Doane, B.K., Clinical psychiatry and the physiodynamics of the limbic system. In B.K. Doane and K.E. Livingston (Eds.), *The Limbic System: Functional Organization and Clinical Disorders*, Raven, New York, 1986, pp. 285–315.

32 Doane, B.K. and Livingston, K.E., *The Limbic System: Functional Organization and Clinical Disorders*, Raven, New York, 1986.

33 Drummond, L.M. and Matthews, H.P., Obsessive-compulsive disorder occurring as a complication in benzodiazepine withdrawal, *J. Nerv. Ment. Dis.*, 176 (1988) 688–691.

34 Ebbesson, S.O.E., The parcellation theory and its relation to interspecific variability in brain organization, evolutionary and ontogenetic development, and neuronal plasticity, *Cell Tissue Res.*, 213 (1980) 179–212.

35 Eggers, C., Die Bedeutung limbischer Funktionsstörungen für die Ätiologie kindlicher Schizophrenien, *Fortschr. Neurol. Psychiat.* 49 (1981) 101–108.

36 Eichelman, B., The limbic system and aggression in humans, *Neurosci. Behav. Res.*, 7 (1983) 391–394.

37 Flor-Henry, P., The endogenous psychoses: a reflection on lateralized dysfunctions of the anterior limbic system. In K.E. Livingston and O. Hornykiewicz (Eds.), *Limbic Mechanisms: The Continuing Evolution of the Limbic System Concept*, Plenum, New York, 1978, pp. 389–404.

38 Flor-Henry, P., Lateralized temporal-limbic dysfunction and psychopathology, *Ann. N.Y. Acad. Sci.*, 280 (1976) 777–797.

39 Flor-Henry, P., Psychiatric syndromes considered as manifestations of lateralized temporal-limbic dysfunction. In L.V. Laitinen and K.E. Livingston (Eds.), *Surgical Approaches in Psychiatry*, Medical and Technical Publishing Co., Lancaster, 1973, pp. 22–26.

40 Girgis, M., Biochemical patterns in limbic system circuitry: biochemical-electrophysiological interactions displayed by chemitrode techniques. In B.K. Doane and K.E. Livingston (Eds.), *The Limbic System: Functional Organization and Clinical Disorders*, Raven, New York, 1986, pp. 55–65.

41 Gloor, P., Physiology of the limbic system. In J.K. Penry and D.D. Daly (Eds.), *Advances in Neurology, Vol. 11*, Raven, New York, 1975, pp. 27–55.

42 Goldberg, S., *Clinical Neuroanatomy (Made Ridiculously Simple)*, MedMaster, Miami, 1986.

43 Goodman Gilman, A., Rall, T.W., Nies, A.S. and Taylor, P., *Goodman and Gilman's: The Pharmacological Basis of Therapeutics*, Pergamon, New York, 1990.

44 Gorman, J.M., Liebowitz, M.R., Fyer, A.J. and Stein, J., A neuroanatomical hypothesis for panic disorder, *Am. J. Psychiatry*, 146 (1988) 148–161.

45 Gray, J.A., Drug effects on fear and frustration: possible limbic site of action of minor tranquillizers. In L. Iversen, S. Iversen and S. Snyder (Eds.), *Handbook of Pharmacology, Vol. 8*, Plenum, New York, 1977, pp. 433–529.

46 Gray, J.A., *The Neuropsychology of Anxiety: An Enquiry into the Functions of the Septo-hippocampal System*, Clarendon, Oxford, 1982.

47 Guyton, A.C., *Textbook of Medical Physiology*, Saunders, Philadelphia, 1991.

48 Hamilton, L.W., *Basic Limbic System Anatomy of The Rat*, Plenum, New York, 1976.

49 Hassler R., Zur funktionellen Anatomie des Limbischen Systems, *Nervenarzt*, 35 (1964) 386–396.

50 Heckers, S., Heinsen, H., Heinsen, Y.C. and Beckmann, H., Limbic structures and lateral ventricle in schizophrenia. A quantitative postmortem study, *Arch. Gen. Psychiatry*, 47 (1990) 1016–1022.

51 Herrick, C.J., Morphogenesis of the brain, *J. Morphol.*, 54 (1933) 233–258.

52 Horel, J.A., The neuroanatomy of amnesia, *Brain*, 101 (1978) 403–445.

53 Isaacson, R.L., *The Limbic System*, Plenum, New York, 1974.

54 Isaacson, R.L., Memory processes and the hippocampus. In D. Deutsch and J.A. Deutsch (Eds.), *Short-term Memory*, Academic Press, New York, 1975, pp. 313–337.

55 Isaacson, R.L., Hannigan Jr., J.H., Springer, J.E., Ryan, J. and Poplawsky, A., Limbic and neurohormonal influences modulate the basal ganglia and behavior. In E. Endröczy and D. De Wied (Eds.), *Integrative Neurohumoral Mechanisms*, Elsevier, Amsterdam, 1983, pp. 23–34.

56 Iversen, S.D., Recent advances in the anatomy and chemistry of the limbic system. In M.R. Trimble and E. Zarifian (Eds.), *Psychopharmacology of the Limbic System*, Oxford University Press, Oxford, 1984, pp. 1–16.

57 Jänig, W., Limbisches System und Verhalten. In R.F. Schmidt and G. Thews (Eds.), *Physiologie des Menschen*, 21st edn., Springer, Berlin, 1983, pp. 148–157.

58 Jenike, M.A., Baer, L., Ballantine, T., Martuza, R.L., Tynes, S., Giriunas, I., Buttolph, L. and Cassem, N.H., Cingulotomy for refractory obsessive-compulsive disorder: a long term follow-up of 33 patients, *Arch. Gen. Psychiatry*, 48 (1991) 548–555.

59 Jennett, B. and Galbraith, S., *An Introduction to Neurosurgery*, Heinemann, London, 1983.

60 Kahle, W., Zur pränatalen Entwicklung der menschlichen Großhirnhemisphäre, *Habilitation*, Universität Würzburg, Würzburg, 1962.
61 Kandel, E.R., Disorders of thought: schizophrenia. In E.R. Kandel, J.H. Schwartz and T.M. Jessel (Eds.), *Principles of Neural Science*, Elsevier, New York, 1991, pp. 853–868.
62 Kandel, E.R., Schwartz, J.H. and Jessel, T.M., *Principles of Neural Science*, Elsevier, New York, 1991.
63 Kaplan, H.I. and Sadock, B.J., *Comprehensive Textbook of Psychiatry*, Williams & Wilkins, Baltimore, 1989.
64 Kawakami, M., Seto, K., Terasawa, E. and Yoshida, K., Mechanisms in the limbic system controlling reproductive functions of the ovary with special reference to the positive feedback of progestin to the hippocampus. In W.R. Adey and T. Tokizane (Eds.), *Structure and Function of the Limbic System, Progress in Brain Research, Vol. 27*, Elsevier, Amsterdam, 1967, pp. 69–102.
65 Keller, F., Rimvall, K., Barbe, M.F. and Levitt, P., A membrane glycoprotein associated with the limbic system mediates the formation of the septo-hippocampal pathway in vitro, *Neuron*, 3 (1989) 551–561.
66 Kelley, A.E. and Domesick, V.B., The distribution of the projections from the hippocampal formation to the nucleus accumbens in the rat: an anterograde- and retrograde-horseradish peroxidase study, *Neuroscience*, 7 (1982) 2321–2335.
67 Koella, W.P. and Trimble, M.R., *Temporal Lobe Epilepsy, Mania, and Schizophrenia and the Limbic System*, Karger, Basel, 1982.
68 Kornhuber, H.H., Neural control of input into long term memory: limbic system and amnestic syndrome in man. In H.P. Zippel (Ed.), *Memory and Transfer of Information*, Plenum, New York, 1973.
69 Kuhar, M.J., Neuroanatomical substrates of anxiety: a brief survey, *Trends Neurosci.*, 9 (1986) 307–311.
70 Lancisi, G.M., Dissertatio altera de sede cogitantis animae, *Opera, Vol. 2*, Geneva, 1718, pp. 302–318.
71 LeDoux, J.E., Emotion, *Handbook of Physiology, Vol. Section 1, Vol. 5, Part 1*, American Physiological Society, Washington, DC, 1987, pp. 419–459.
72 Lem, S., *Further reminiscences of Ijon Tichy. II. Memoirs of a Space Traveller*, Secker & Warburg, London, 1982.
73 Leonhardt, H., Tillmann, B., Töndury, G. and Zilles K., *Rauber/Kopsch, Anatomie des Menschen. Lehrbuch und Atlas*, Thieme, Stuttgart, 1987.
74 Levitt, P., A monoclonal antibody to limbic system neurons, *Science*, 233 (1984) 299–301.
75 Lishman, W.A., *Organic Psychiatry*, Blackwell, Oxford, 1987.
76 Lissák, K. and Endröczi, E., Involvement of limbic structures in conditioning motivation and recent memory. In W.R. Adey and T. Tokizane (Eds.), *Structure and Function of the Limbic System, Progress in Brain Research, Vol. 27*, Elsevier, Amsterdam, 1967, pp. 246–253.
77 Livingston, K.E., The experimental-clinical interface: kindling as a dynamic model of induced limbic system dysfunction. In K.E. Livingston and O. Hornykiewicz (Eds.), *Limbic Mechanisms: The Continuing Evolution of the Limbic System Concept*, Plenum, New York, 1978, pp. 521–533.
78 Livingston, K.E. and Escobar, A., Tentative limbic system models for certain patterns of psychiatric disorders. In L.V. Laitinen and K.E. Livingston (Eds.), *Surgical Approaches in Psychiatry*, University Park Press, Baltimore, 1973, pp. 245–252.
79 Livingston, K.E. and Hornykiewicz, O., *Limbic Mechanisms: The Continuing Evolution of the Limbic System Concept*, Plenum, New York, 1978.
80 Lopes da Silva, F.H., Witter, M.P., Boeijinga, P.H. and Lohman, A.H.M., Anatomic organization and physiology of the limbic cortex, *Physiol. Rev.*, 70 (1990) 453–511.
81 Lynch, M.R., Kuhn, H.G. and Carey, R.J., Chronic haloperidol–amphetamine interactions and mesolimbic dopamine, *Neuropsychobiology*, 19 (1988) 97–103.
82 Macchi, G., The ontogenetic development of the olfactory telencephalon in man, *J. Comp. Neurol.*, 95 (1951) 245–305.
83 MacLean, P.D., The brain in relation to empathy and medical education, *J. Nerv. Ment. Dis.*, 144 (1967) 374–382.
84 MacLean, P.D., Contrasting functions of limbic and neocortical systems of the brain and their relevance to psychophysiological aspects of medicine, *Am. J. Med.*, 25 (1958) 611–626.
85 MacLean, P.D., Psychosomatic disease and the "Visceral Brain": recent developments bearing on the Papez theory of emotion, *Psychosom. Med.*, 11 (1949) 338–353.
86 MacLean, P.D., Some psychiatric implications of physiological studies on frontotemporal portion of limbic system (visceral brain), *Electroencephalograph. Clin. Neurophysiol.*, 4 (1952) 407–418.
87 MacLean, P.D., The triune brain, emotion, and scientific bias. In F.O. Schmidt (Ed.), *The Neurosciences, 2nd Study Program*, Rockefeller University Press, New York, 1970, pp. 336–349.
88 MacLean, P.D., *The Triune Brain in Evolution: Role in Paleocerebral Functions*, Plenum, New York, 1990.
89 MacLean, P.D. and Ploog, D.W., Cerebral representation of penile erection, *J. Neurophysiol.*, 25 (1962) 29–55.
90 MacLean, P.D. and Pribram, K.H., Neuronographic analysis of medial and basal cerebral cortex. I. Cat, *J. Neurophysiol.*, 16 (1953) 312–323.
91 Martin, J.H. and Jessel, T.M., Development as a guide to the regional anatomy of the brain. In E.R. Kandel, J.H. Schwartz and T.M. Jessel (Eds.), *Principles of Neural Science*, Elsevier, New York, 1991, pp. 296–308.
92 Meyer, A., *Historical Aspects of Cerebral Anatomy*, Oxford University Press, London, 1971.
93 Miller, J.D., *Northfield's Surgery of the Central Nervous System*, Blackwell, Oxford, 1987.
94 Mishkin, M., Memory in monkeys severely impaired by combined but not by separate removal of amygdala and hippocampus, *Nature*, 273 (1978) 297–298.
95 Mogenson, G.J., Jones, D.J. and Yim, C.Y., From motivation to action: functional interface between the limbic system and the motor system, *Prog. Neurobiol.*, 14 (1980) 69–97.
96 Musil, S.Y. and Olson, C.R., Organization of cortical and subcortical projections to anterior cingulate cortex in the cat, *J. Comp. Neurol.*, 272 (1988) 203–218.
97 Mutel, M., *Etudes Morphologiques sur le Rhinencéphale de l'Homme et des Mammifères*, A. Humblot, Nancy, 1923.
98 Nauta, W.J.H., A simplified perspective on the basal ganglia and their relation to the limbic system. In B.K. Doane and K.E. Livingston (Eds.), *The Limbic System: Functional Organization and Clinical Disorders*, Raven, New York, 1986, pp. 67–77.
99 Nauta, W.J.H., Circuitous connections linking the cerebral cortex, limbic system, and corpus striatum. In B.K. Doane and K.E. Livingston (Eds.), *The Limbic System: Functional Organization and Clinical Disorders*, Raven, New York, 1986, pp. 43–54.
100 Nauta, W.J.H., Hippocampal projections and related neural pathways to the mid-brain in the cat, *Brain*, 81 (1958) 319–340.
101 Nauta, W.J.H., Limbic innervation of the striatum. In A.J. Friedhoff and T.N. Chase (Eds.), *Gilles de la Tourette Syndrome*, Raven, New York, 1982, pp. 41–48.
102 Nauta, W.J.H., Some neural pathways related to the limbic

system. In E.R. Ramey and D.S. O'Doherty (Eds.), *Electrical Studies on the Unanesthetized Brain*, Hoeber, New York, 1960.
103 Nauta, W.J.H. and Domesick, V.B., Crossroads of limbic and striatal circuitry: hypothalamo-nigral connections. In K.E. Livingston and O. Hornykiewicz (Eds.), *Limbic Mechanisms: The Continuing Evolution of the Limbic System Concept*, Plenum, New York, 1978, pp. 75–93.
104 Nieuwenhuys, R., *Chemoarchitecture of the Brain*, Springer, Berlin, 1985.
105 Nieuwenhuys, R., Voogd, J. and van Huijzen, C., *The Human Central Nervous System. A Synopsis and Atlas*, Springer, Berlin, 1988.
106 Papez, J.W., A proposed mechanism of emotion, *Arch. Neurol. Psychiatry*, 38 (1937) 725–743.
107 Pert, C. and Dienstfrey, H., The neuropeptide network, *Ann. N.Y. Acad. Sci.*, 521 (1988) 189–194.
108 Petersdorf, R.G., Adams, R.D., Braunwald, E., Isselbacher, K.J., Martin, J.B. and Wilson, J.D., *Harrison's Principles of Internal Medicine*, MacGraw-Hill, New York, 1983.
109 Poletti, C.E., Is the limbic system a limbic system? Studies of hippocampal efferents: their functional and clinical implications. In B.K. Doane and K.E. Livingston (Eds.), *The Limbic System: Functional Organization and Clinical Disorders*, Raven, New York, 1986, pp. 79–94.
110 Post, R.M., Does limbic system dysfunction play a role in affective illness? In B.K. Doane and K.E. Livingston (Eds.), *The Limbic System: Functional Organization and Clinical Disorders*, Raven, New York, 1986, pp. 229–249.
111 Pribram, K.H. and MacLean, P.D., Neuronographic analysis of medial and basal cerebral cortex. II. Monkey, *J. Neurophysiol.*, 16 (1953) 324–340.
112 Rang, H.P. and Dale, M.M., *Pharmacology*, Churchill-Livingstone, Edinburgh, 1987.
113 Rawlins, J.N.P., Some neurophysiological properties of the septo-hippocampal system. In M.R. Trimble and E. Zarifian (Eds.), *Psychopharmacology of the Limbic System*, Oxford University Press, Oxford, 1984, pp. 17–50.
114 Retzius, G., *Das Menschenhirn. Studien in der makroskopischen Morphologie*, P.A. Norstedt & Söner, Stockholm, 1896.
115 Roberts, G.W., Polak, J.M. and Crow, T.J., Peptide circuitry of the limbic system. In M.R. Trimble and E. Zarifian (Eds.), *Psychopharmacology of the Limbic System*, Oxford University Press, Oxford, 1984, pp. 226–243.
116 Robertson, M., Doran, M., Trimble, M. and Lees, A.J., The treatment of Gilles de la Tourette syndrome by limbic leucotomy, *J. Neurol. Neurosurg. Psychiatry*, 53 (1990) 691–694.
117 Rowland, L.P., *Merritt's Textbook of Neurology*, Lea & Febiger, Philadelphia, 1989.
118 Schmidt, R.F. and Thews, G., *Physiologie des Menschen*, Springer, Berlin, 1983.
119 Schwalbe, G., *Lehrbuch der Neurologie*, Eduard Besold, Erlangen, 1881.
120 Schwartz, S.I., Shives, G.T. and Spencer, F.C., *Principles of Surgery*, McGraw-Hill, New York, 1989.
121 Scoville, W.B. and Milner, B., Loss of recent memory after bilateral hippocampal lesion, *J. Neurol. Neurosurg. Psychiatry*, 20 (1957) 11–21.
122 Silverplatter International, *Medline Express 1974–1991*, U.S. National Library of Medicine, Boston, 1991.
123 Smythies, J.R., *Brain Mechanisms and Behaviour*, Blackwell, Oxford, 1970.
124 Squire, L.R. and Zola-Morgan, S., The medial temporal-lobe memory system, *Science*, 253 (1991) 1380–1386.
125 Stein, J.F., *An Introduction to Neurophysiology*, Blackwell, Oxford, 1982.
126 Stephan, H., *Allocortex*, Springer, Berlin, 1975.
127 Stephan, H., Die kortikalen Anteile des Limbischen Systems, *Nervenarzt*, 35 (1964) 396–401.
128 Stephan, H., Evolutionary trends in limbic structures, *Neurosci. Biobehav. Rev.*, 7 (1983) 367–374.
129 Stevens, J.R., Neuropathology of schizophrenia, *Arch. Gen Psychiatry*, 39 (1982) 1131–1139.
130 Stinus, L., Kelly, A.E. and Winnock, M., Neuropeptides and limbic system function. In M.R. Trimble and E. Zarifian (Eds.), *Psychopharmacology of the Limbic System*, Oxford University Press, Oxford, 1984, pp. 209–225.
131 Swanson, L.W., The hippocampus and the concept of the limbic system. In W. Seifert (Ed.), *Neurobiology of the Hippocampus*, Academic Press, London, 1983, pp. 3–19.
132 Swanson, L.W., Limbic system. In G. Adelman (Ed.), *Encyclopedia of Neuroscience, Vol. 1*, Birkhäuser, Boston, 1987, pp. 589–591.
133 Swanson, L.W. and Cowan, W.M., An autoradiographic study of the organization of the efferent connections of the hippocampal formation in the rat, *J. Comp. Neurol.*, 172 (1977) 49–84.
134 Torrey, E.F. and Peterson, M.R., Schizophrenia and the limbic system, *Lancet*, 2 (1974) 942–946.
135 Trimble, M.R., Disorders of the limbic system, *Integ. Psychiatry*, 2 (1984) 96–102.
136 Trimble, M.R., First rank symptoms of Schneider. A new perspective?, *Br. J. Psychiatry*, 156 (1990) 195–200.
137 Trimble, M.R, Limbic system disorders in man. In M.R. Trimble and E. Zarifian (Eds.), *Psychopharmacology of the Limbic System*, Oxford University Press, Oxford, 1984, pp. 110–124.
138 Trimble, M.R. and Zarifian, E., *Psychopharmacology of the Limbic System*, Oxford University Press, Oxford, 1984.
139 Uexküll, T. von, *Psychosomatische Medizin*, Urban & Schwarzenberg, München, 1986.
140 Vanderwolf, C.H., Kelly, M.E., Kraemer, P. and Streather, A., Are emotion and motivation localized in the limbic system and nucleus accumbens?, *Behav. Brain Res.*, 27 (1988) 45–58.
141 Vinogradova, O.S., Functional organization of the limbic system in the process of registration of information: facts and hypotheses. In R.L. Isaacson and K.H. Pribram (Eds.), *The Hippocampus, Vol. 2*, Plenum, New York, 1975, pp. 3–70.
142 Weinman, J., *An Outline of Psychiatry*, Wright, Bristol, 1987.
143 Wenzel, B.M., The olfactory system and behavior. In L.V. DiCara (Ed.), *Limbic and Autonomic Nervous Systems Research*, Plenum, New York, 1974, pp. 1–40.
144 White Jr., L.E., A morphologic concept of the limbic lobe. In C.C. Pfeiffer and J.R. Smythies (Eds.), *International Review of Neurobiology, Vol. 8*, Academic Press, New York, 1965, pp. 1–34.
145 Williams, P.L., Warwick, R., Dyson, M. and Bannister, L.H., *Gray's Anatomy*, Churchill-Livingstone, Edinburgh, 1989.
146 Willis, T., *Cerebri anatome*, Martzer & Allestry, London, 1664.
147 Yeterian, E.H. and Pandya, D.N., Corticothalamic connections of paralimbic regions in the rhesus monkey, *J. Comp. Neurol.*, 269 (1988) 130–146.
148 Zola-Morgan, S., Squire, L.R. and Amaral, D.G., Human amnesia and the medial temporal region: enduring memory impairment following a bilateral lesion limited to field CA1 of the hippocampus, *J. Neurosci.*, 6 (1986) 2950–2967.