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Review Article

The Hippocampus, Parahippocampal Gyrus and Mood Disorder in Patients with Temporal Lobe Epilepsy: A Psychosurgical Quantitative MRI Volumetric Study

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Abstract

This review reports on a study conducted in Australia in 2005 with the University of Melbourne and St Vincent's hospital, Melbourne whereby world leading brain imaging technology helped advance psychosurgical and neuropsychological research into Temporal Lobe Epilepsy (TLE). Establishing an early diagnosis of TLE improves treatment outcome and can involve assessing for subtle changes to a patient's mood, anxiety – cerebral atrophy integrity. Assessing for this integrity is often complicated by discrepancies in neuroanatomical differentiation. Quantitative volumetric Magnetic Resonance Imaging (MRI) was used to measure the volume of the parahippocampal gyrus in 20 controls and 37 patients with TLE, (16 with right medial temporal sclerosis and 21 with left medial temporal sclerosis) in order to investigate protocol that improves the early diagnosis of TLE. Patients underwent neuropsychological, neurological and interictal scalp EEG investigation for known seizure disorder, as well as volumetric MRI analysis of hippocampal and parahippocampal morphology. Patient volumetric measures were compared to the State Trait Anxiety Inventory (STAI) and Beck Depression Inventory (BDI) scores with the intention of determining the relationship between mental status and brain volume. Volumetric analysis revealed that atrophy of the right parahippocampal gyrus in patients was found to correlate to higher mood scale scores. This research demonstrated the complexities involved with defining neuroanatomical limits of cerebral regions in order to better understand mood, anxiety - cerebral atrophy relationships in patients with TLE.

Keywords: *Volumetric MRI; Hippocampus; Parahippocampal Gyrus; Mood Disorder; Temporal Lobe Epilepsy*

Prevalence of Temporal Lobe Epilepsy

It is estimated that there are approximately 65 million people affected by epilepsy worldwide [1]. Epilepsy is a chronic brain disorder characterized by recurrent seizures precipitated by aberrant electrical discharges within the brain [2]. One of the more common forms of epilepsy is Temporal Lobe Epilepsy [3]. TLE is largely associated with sclerosis of the hippocampus that can exist in either the left hippocampus, referred to as left TLE, or within the right hippocampus, referred to as right TLE.

Since TLE seizures involve the limbic lobe, they often affect limbic functions such as smell, taste, memory and emotion [4]. Mood disorder, in particular depressive symptoms, are more commonly associated with TLE than any other form of epilepsy, with clinical depression occurring in between 19 - 50% of all individuals with TLE [5]. Reasons for this are unclear, however, speculation exists as to whether cerebral atrophy (brain shrinkage) within regions of the temporal lobe relate to abnormal autonomic processes predisposing one to experience mood or anxiety disorder.

This report discusses some of the factors involved in assessing for mood, anxiety – cerebral atrophy relationships in patients with temporal lobe epilepsy with emphasis on detailed neuroanatomical differentiation. Failure to accurately define neuroanatomical regions can result in inaccurate conclusions regarding such TLE – mood and anxiety relationships. This risks complicating disease diagnosis and therefore treatment. Attention is given to the importance of determining neuroanatomical regions associated with this relationship using volumetric Magnetic Resonance Imaging (MRI). Volumetric MRI is a process that involves taking images of sections of the brain to identify the volume of each section which may indicate specific abnormalities [6].

Early Diagnosis of Temporal Lobe Epilepsy using Volumetric MRI

Epilepsy can be diagnosed in various ways with volumetric MRI providing a reliable method of assisting with diagnosis. Volumetric MRI's applications are widely reported [7,8]. Neuropsychological research has shown that people with epilepsy have problems with mood and anxiety as well as cerebral atrophy [9,10] which can be identified using volumetric MRI.

Experiment: Mood, Anxiety – Cerebral Atrophy Relationships in Temporal Lobe Epilepsy

In an attempt to learn more about mood, anxiety – cerebral atrophy relationships in temporal lobe epilepsy, the authors report on research conducted by Buttigieg and his team in Melbourne, Australia (2005). Buttigieg's team utilized an eclectic group of neuroscientists with access to world leading brain imagining technology to study a clinical sample of middle-aged patients with TLE. These neuroscientists from the University of Melbourne and St Vincent's Hospital, Melbourne applied quantitative volumetric MRI to measure the volume of the parahippocampal gyrus in 20 controls and 37 patients (mean age = 33 years old) with temporal lobe epilepsy. Patients underwent neuropsychological, neurological and interictal scalp EEG investigation for known seizure disorder, as well as volumetric MRI analysis of hippocampal and parahippocampal morphology. Patients were identified as showing either Left Medial Temporal Sclerosis (LMTS) or Right Medial Temporal Sclerosis (RMTS) – shrinkage of either their left or right limbic region (16 with right medial temporal sclerosis and 21 with left medial temporal sclerosis). Patient's mental status was assessed using the STAI [11] and BDI [12] with the intention of determining the relationship between mood states/traits to patient brain volume. The BDI and the STAI are well established measures of depression as well as state and trait anxiety respectively. The scale scores for mood status (depression, state and trait anxiety) for the patients are provided in Table 1.

	Subject Group					
	LMTS			RMTS		
Mood	M	SD	n	M	SD	n
Beck Depression Inventory	8.90	6.74	21	13.31	8.23	16
Total Score						
Spielberger STAI						
State Score	41.46	9.63		38.31	9.58	
Spielberger STAI						
Trait Score	39.27	8.76		47.69	8.01	

Table 1: *Mood Scale Scores of Depression and Anxiety for the Patient Group: Patients with LMTS and RMTS*

The results revealed that patients with LMTS, BDI scale scores showed a mean scale score representing asymptomatic values, whereas patients with RMTS revealed only mild to moderate depression [12]. However, assessment of the STAI descriptive statistics revealed more dramatic relationships to cerebral atrophy than those of the mood (depression) scale scores.

The trait anxiety scale scores reported by patients with RMTS in this study are comparable to patients who have brain damage or schizophrenia [11]. In contrast, when assessing state anxiety scale scores, both patients groups reported higher than average means for

healthy adults, however, patients with LMTS showed greater state anxiety than those with RMTS [11]. The state anxiety scale scores reported by patients with LMTS were comparable to patients with psychiatric complications [11].

Subsequent linear regression aimed to determine the nature and degree of any mood and anxiety - cerebral atrophy relationships. It was identified that cerebral atrophy of the parahippocampal gyrus was often associated with mood and anxiety disorder. It was found that in the patient sample, atrophy of the right parahippocampal gyrus was most positively correlated to mood status (R^2 = .39 p = .002). In particular, the difference of left and right parahippocampal gyrus volumes (LPhG - RPhG) was a significant predictor of depression (R2 = .39, p = .002). The effect size associated with this result (t = 3.63) is of a large magnitude and is worthy of further consideration [13]. Moreover, the sum of the left and right parahippocampal gyrus volumes (LPhG + RPhG) were significant predictors of state and trait anxiety respectively (R^2 = .23, p = .023; R^2 = .65, p = .022). The effect size associated with both findings (t = -2.47; t = 2.48) was also of a large magnitude, however, it was larger for trait anxiety. Both results are also worthy of further consideration [13]. Finally, the difference of left and right parahippocampal gyrus volumes (LPhG - RPhG) was a significant predictor of trait anxiety (R2 = .65, p < .001). Collectively, these findings from the 2005 research highlighted the role of the parahippocampal gyrus in determining mood and anxiety symptomatology in patients with TLE. The volumetric MRI analysis also revealed reduction to the volume of the right parahippocampal gyrus in patients which was correlated with higher mood scale scores.

The 2005 findings have been supported by recent research revealing parahippocampal, mood and anxiety disorder relationships [14,15]. Knutson., *et al.* [14] reported a relationship between atrophy of the left parahippocampal gyrus to anxiety. Volumetric research conducted by Wei., *et al*. [15] showed increased volumes within the parahippocampal gyrus and entorhinal cortex was linked to anxiety. Moreover, volumetric research reveals positive relationships between atrophy of the right parahippocampal gyrus to panic disorder [16] and the right parahippocampal gyrus atrophy to depression [17]. In contrast however, volumetric research conducted by Fujishima., *et al.* [18] and Mah, Binns and Steffens [19] found that volumes only within the entorhinal cortex decreased in patients presenting with depression and anxiety. Discrepancies amongst the findings are likely due to a combination of several factors including the nature and degree of psychopathology, the research sample size (e.g., Lai, 2011), genetic factors [20], including protein aggregation [21] and/or the pathological processes involving telomeric DNA [22], or seizure frequency and duration [23]. Of particular importance is the determination of the neuroanatomical limits of the structures implicated in TLE – mood and anxiety relationships. Inaccurate determination of neuroanatomical limits can also render researchers into establishing inconclusive relationships about mood and anxiety to cerebral atrophy in patients with temporal lobe epilepsy, which this report addresses.

Establishing Neuroanatomical Protocol in Patients with TLE: The 2005 Study

When determining neuroanatomical protocol, the researchers of the 2005 study ensured that MRI images were acquired pre-surgically using a high resolution 1.5-Tesla (T) Siemens Magneton MR scanner, with a coronal T1 weighted sequence, in 160 contiguous 1.4mm thick slices. Telsa is an index of an atom's alignment needed to provide a clear image for particular brain tissue in question. T1 images provided the best resolution for the coronal specimens under review. T2 and T3 images are often associated with additional heat and more noise than T1 images which can reduce image clarity. However, occasionally T2 or cadaver images provide the relevant illustration of the neuroanatomical regions implicated in this report.

The MRI scans and mood scale assessments were part of the routine presurgical evaluation. Images were then transferred to an SGI MIPS 4400 UNIX dedicated workstation for use with ANALYZE 7.5 (Mayo Foundation, Rochester, MN). The typical data set for hippocampal measures consists of 21 - 25 slices, and for the parahippocampal gyrus structures, 31 - 36 slices [24]. There were sufficient slices to achieve a high degree of accuracy, for both structures (ibid).

All images were inspected carefully to exclude other intracranial lesions by a clinic technician. Using the MRI series, the brain was extracted from the head scan by way of a three-dimensional (3D) morphometric technique. The cerebellum and brain stem scans were then disarticulated from the rest of the cerebrum. Then the internal grey structures on contiguous sagittal throughout the series were manually edited.

Experimentation proceeded once the experimenter satisfied a Pearson's inter-observer correlation co-efficient of .7, and an intra-observer reliability co-efficient ranging from 0.93 to 0.99. These values were considered appropriate for sectioning to continue [25].

Parahippocampal Gyrus and Hippocampal Volume Measurements

Rigid anatomical landmarks were used in the 2005 study to define the boundaries of the parahippocampal gyrus and the hippocampus. Volumetric measures for the hippocampus were obtained from previous analysis [24]. Volumetric protocol for both the parahippocampal gyrus and hippocampus were defined according to the cortical topographical landmarks on MRI that best approximate the cytoaritectural boundaries detailed in previous studies [26,27]. To ensure accurate protocol, the crest of the medial bank of the collateral sulcus was regarded as an easily reproducible marker for the border of the parahippocampal gyrus that helped to differentiate between the entorhinal and perirhinal cortices [24]. Anatomical guidelines for the hippocampus and parahippocampal gyrus, as well as identification of the crest as an anatomical guideline for the parahippocampal gyrus, were also assisted with reference to Duvernoy's anatomical sections [26]. Expert neurological guidance provided by psychosurgical and neurosurgical staff further guided anatomical sectioning.

Parahippocampal Gyrus

The parahippocampal gyrus is continuous with the entorhinal cortex. For uniformity, therefore, the anatomical guidelines for the parahippocampal gyrus will in part follow those of the entorhinal cortex.

Posterior limit: This is defined as the slice in which the greatest length of fornix is seen. Figure 1 provides an illustration of the posterior limit of the parahippocampal gyrus.

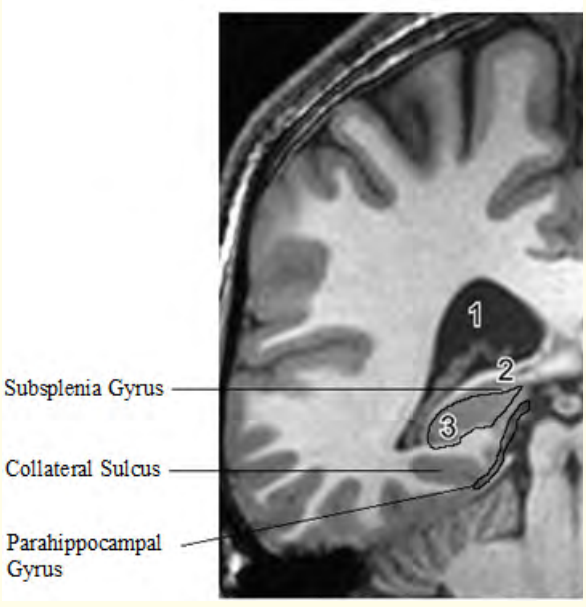

Figure 1: *Coronal image of the PhG – Posterior Limit. PhG measurements begin in this slice, showing the greatest length of the fornix. The collateral sulcus and subsplenial gyrus are also discernible at this point. 1 = atrium of the lateral ventricle, 2 = crus of the fornix, 3 = hippocampal tail. (Adapted from Konrad., et al. [29]).*

Anterior limit: This is marked by the nominated posterior limit of the entorhinal cortex, which is therefore illustrated by the emergence of the parahippocampal gyrus. That is one slice posterior to the intralimbic gyrus (refer to Duvernoy, 1991 [28] & 2012 [30]). Figure 2 provides an illustration of the anterior limit of the parahippocampal gyrus.

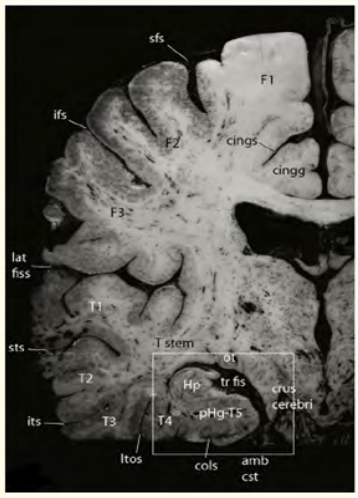

Figure 2: *Coronal section of a cadaver of the anterior limit of the parahippocampal gyrus. (Adapted from Destrieux, Bourry & Velut, 2013 [31]).*

Structure of the hippocampus body showing key landmarks for this section. A. Frontal slice of a right hemisphere after India ink injection. The temporal lobe is limited dorsally by the lateral fissure (latfiss), and medially by the ambient cistern (ambcst) and its lateral expansion, the transverse fissure (trfis). The temporal lobe is attached to the hemisphere by the temporal stem (T stem). The hippocampus (Hp) lies at the dorsal aspect of the parahippocampal gyrus (pHg-T5): cingg: cingulate gyrus; cings: cingulate sulcus; cols: collateral sulcus; F1: superior frontal gyrus; F2: middle frontal gyrus; F3: inferior frontal gyrus; ifs: inferior frontal sulcus; its: inferior temporal sulcus; ltos: lateral occipito-temporal sulcus; ot: optical tract; sfs: superior frontal sulcus; sts: superior temporal sulcus; T1: superior temporal gyrus; T2: middle temporal gyrus; T3: inferior temporal gyrus; T4: fusiform gyrus.

Throughout the structure, the caudal and rostral borders remain the same as that defined in posterior slices of the entorhinal cortex. Rostrally, a line is drawn from the lateral crest of the uncal fissure to the nearest grey-white interface. This line divides the hippocampus superiorly, and parahippocampal gyrus inferiorly. Caudally, the border is defined by a line drawn from the medial crest of the collateral sulcus to the nearest grey-white interface.

Hippocampus

Posterior limit: This part forms the intralimbic gyrus most posteriorly and anterior to this lies the band of Giacomini and gyrus uncinatus (refer to Duvernoy, 2012, [30] p. 237). Reference to Figure 1 provides an illustration of the posterior limit of the hippocampus.

In coronal images, the posterior structures are easily identified as anterior continuations of the intralimbic gyrus and the inferior border is now formed by the uncal sulcus, allowing separation of the hippocampus from the parahippocampal gyrus. Superolaterally, the amygdala comes into view, its cortical and accessory nuclei forming the lateral edge of the gyrus uncinatus. The edge is arbitrarily defined as the isthmus of this structure and is the superior border of the hippocampus.

Anterior limit: This is marked as the intralimbic gyrus, which is the most obvious feature of the hippocampus and was used to define the junction of the hippocampal head and body (refer to figure 2). This may appear as quite an isolated structure in coronal images. This is the most retro-flexed portion of the anterior part of the structure and contains the same laminae as in the remainder of the hippocampus. At this point, the posterior cerebral artery can be mistaken for the intralimbic gyrus (figure 3).

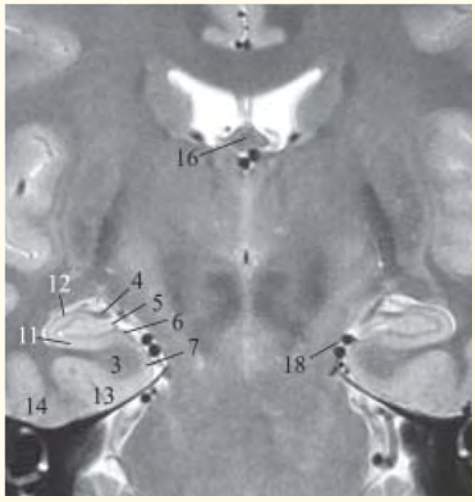

Figure 3: *Coronal T2-weighted (3.0T) MR image of normal hippocampus from anterior (a) to posterior (d) noting major neuroanatomical landmarks including vessels in: 18 ambient cistern medial to choroid fissure (basal vein superior, posterior cerebral artery inferior), 3 parahippocampal gyrus, 4 fi mbria, 5 dentate gyrus, 6 subiculum, 7 entorhinal area, 11 Cornu Ammonis, 12 alveus, 13 collateral sulcus, 14 fusiform (medial occipitotemporal sulcus), 16 fornix. The Ambient cistern and Alveus help to identify the emergence of the artery (Adapted from Thammaroj, Santosh, and Bhattacharya, 2005 [32]).*

Conclusion

Volumetric analysis in the 2005 study revealed atrophy in the patient groups. More importantly those with left medial temporal sclerosis demonstrated greater parahippocampal atrophy ipsilateral to the side of hippocampal sclerosis than those with right medial temporal sclerosis. A reduction to the volume of the right parahippocampal gyrus in patients was also found to correlate with higher mood scale scores. The findings of this research demonstrated how mood-cerebral atrophy relationships in TLE patients can be studied. The complexities involved with defining neuroanatomical limits of cerebral regions implicated in TLE and identifying mood or anxiety disorder requires careful consideration. Moreover, longitudinal research using randomized controlled designs is required to better determine cause-effect relationships of disease in people with TLE to ensure that a non-invasive, highly accurate and efficient set of diagnostic measures can be used to guide individualized treatment for patients.

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Bibliography

1. Moshé S L., *et al*. "Epilepsy: new advances". *The Lancet* 385.9971 (2015): 884-898.

2. Honig A and Van Praag HM. "Depression: Neurobiological Psychopathological and Therapeutic Advances". *John Wiley and Sons: Chichester* (1997).

3. Porter RJ and Chadwick D. "Blue Books of Practical Neurology: The Epilepsies 2". *Butterworth-Heinmeann: Boston* (1997).

4. Jackson JH. "Selected Writings of John Hughlings Jackson". In J Taylor (ed), London: Staples (1958).

5. Mendez MF., *et al*. "Depression in epilepsy: significance and phenomenology". *Archives of Neurology* 43.8 (1986): 766-770.

6. Duncan J S. "Imaging and epilepsy". *Brain* 120.2 (1997): 339-377.

7. Hogan R E., *et al*. "Hippocampal surface deformation accuracy in T1-weighted volumetric MRI sequences in subjects with epilepsy". *Journal of Neuroimaging* 25.3 (2015): 452-459.

8. Taycan S E and Taycan O. "Affective temperament profiles and clinical correlates in patients with epilepsy: a link from mood disorders". *Journal of Affective Disorders* 164 (2014): 1-4.

9. Bragatti JA., *et al*. "Is interictal EEG a biomarker for mood disorders in temporal lobe epilepsy?" *Clinical Neurophysiology* 125.10 (2014): 1952-1958.

10. Schroder J., *et al*. "Efficacy of a psychological online intervention for depression in people with epilepsy: a randomized control trial". *Epilepsia* 55.12 (2014): 2069-2076.

11. Spielberger CD. "Manual for the State-Trait Anxiety Inventory". *Palo Alto, Consulting Psychologists Press* (1983).

12. Beck AT and Steer RA. "Manual for the Beck Depression Inventory". *San Antonio, TX: The Psychological Corporation* (1987).

13. Cohen J. "Statistical Power Analysis for the Behavioural Sciences (2nd Ed.)". *Hillsdale, NJ: Lawrence Erlbaum Associates* (1988).

14. Knutson KM., *et al*. "Injured brain regions associated with anxiety in Vietnam veterans". *Neuropsychologia* 51.4 (2013): 686-694.

15. Wei D., *et al*. "Regional gray matter volume and anxiety-related traits interact to predict somatic complaints in a non-clinical sample". *Social Cognitive and Affective Neuroscience* 10.1 (2015): 122-128.

16. Lai CH. "Gray matter deficits in panic disorder: a pilot study of meta-analysis". *Journal of Clinical Psychopharmacology* 31.3 (2011): 287-293.

17. Canu E., *et al*. "Brain structural abnormalities in patients with major depression with or without generalized anxiety disorder comorbidity". *Journal of Neurology* 262.5 (2015): 1255-1265.

18. Fujishima M., *et al*. "Mild cognitive impairment, poor episodic memory, and late-life depression are associated with cerebral cortical thinning and increased white matter hyperintensities". *Frontiers in Aging Neuroscience* 6 (2014): 306.

19. Mah L., *et al*. "Anxiety symptoms in amnestic mild cognitive impairment are associated with medial temporal atrophy and predict conversion to Alzheimer disease". *The American Journal of Geriatric Psychiatry* 23.5 (2015): 466-476.

20. Hernandez C C., *et al*. "Deleterious Rare Variants Reveal Risk for Loss of GABA A Receptor Function in Patients with Genetic Epilepsy and in the General Population". *PloS one* 11.9 (2016): e0162883.

21. Buttigieg JP., *et al.* "Impact of Physics in Family Health Care: Fluorescence Spectroscopy". *Journal of Family Medicine Disease Prevention* 3:051 (2017): 1-3.

22. Epel ES., *et al.* "Dynamics of telomerase activity in response to acute psychological stress". *Brain Behaviour and Immunity*. 24(4) (2010): 531–539.

23. Morgan V L., *et al.* "Increasing structural atrophy and functional isolation of the temporal lobe with duration of disease in temporal lobe epilepsy". *Epilepsy Research* 110 (2015): 171-178.

24. O'Brien CE., *et al*. "Neuropsychological correlates of hippocampal and rhinal cortex volumes in patients with mesial temporal sclerosis". *Hippocampus* 13.8 (2003): 892-904.

25. Marchetti RL., *et al.* "Reliability of volumetric measures of mesial temporal structures". *Arquivous de Neuropsiquiatria* 60.2-B (2002): 420-428.

26. Insausti R., *et al.* "MR volumetric analysis of the human entorhinal, perirhinal and temporopolar cortices". *American Journal of Neuroradiology* 19.4 (1998): 659-671.

27. Juottonen K., *et al.* "Volumes of the entorhinal and perirhinal cortices in Alzheimer's disease". *Neurobiology of Aging* 19.1 (1998): 15-22.

28. Duvernoy H M. "The Human Brain. Surface, three-dimensional sectioning anatomy and MRI". Springer - Verlag Wien: New York (1991).

29. Konrad C., *et al.* "Defining the human hippocampus in cerebral magnetic resonance images—an overview of current segmentation protocols". *Neuroimage* 47.4 (2009): 1185-1195.

30. Duvernoy, H. "The Human Brain: Surface, Three-Dimensional Sectional Anatomy with MRI, and Blood Supply". Springer Wein: New York (2012).

31. Destrieux C., *et al.* "Surgical anatomy of the hippocampus". *Neurochirurgie* 59.4-5 (2013): 149-158.

32. Thammaroj J., *et al.* "The hippocampus: modern imaging of its anatomy and pathology". *Practical Neurology* 5.3 (2005): 150-159.

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