SHORT REPORT

# Religiosity is associated with hippocampal but not amygdala volumes in patients with refractory epilepsy

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**Objective:** To assess the relationship between the behavioural triad of hyper-religiosity, hypergraphia and hyposexuality in epilepsy, and volumes of the mesial temporal structures.

**Method:** Magnetic resonance images were obtained from 33 patients with refractory epilepsy and mesial temporal structure volumes assessed. Amygdala and hippocampal volumes were then compared in high and low scorers on the religiosity, writing, and sexuality sub-scales of the Neurobehavioural Inventory.

**Results:** Patients with high ratings on the religiosity scale had significantly smaller right hippocampi. Religiosity scores rated by both patient and carer showed a significant negative correlation with right hippocampal volumes in this group. There were no other differences in amygdala or hippocampal volumes between these groups, or between high and low scorers on the writing and sexuality sub-scales.

**Conclusions:** These findings suggest that right hippocampal volumes are negatively correlated with religiosity in patients with refractory epilepsy.

The occurrence of ecstatic religious experiences in patients with epilepsy, although controversial, is well documented.[1] Such experiences often occur in the context of an inter-ictal behavioural syndrome characterised primarily by a triad of symptoms: (*a*) the tendency to write copiously (hypergraphia), (*b*) a sustained lack of interest in sexual matters (hyposexuality), and (*c*) an increased tendency to report spiritual and religious experiences and beliefs (hyper-religiosity).[2] The latter manifests either as a deepening of religious and mystical feelings, or as overt extravagant religious behaviour out of keeping with personal and societal norms.[3] Religious delusions are also commonly observed in the psychoses of epilepsy, occurring both between and immediately following a bout of seizures.[4]

In this study, we aimed to investigate the cerebral basis of hypergraphia, hyposexuality and hyper-religiosity components of the Geschwind system in patients with refractory epilepsy, specifically addressing the hypothesis that pathology in the amygdala and/or hippocampus is associated with the occurrence of these phenomena.[5] Accordingly, we assessed inter-ictal behaviour in a series of patients with refractory epilepsy and correlated these findings with volumetric measurements of the amygdala and hippocampus obtained through magnetic resonance imaging (MRI).

## METHOD

Thirty three residents (23 males) at the National Society for Epilepsy, Chalfont St. Peter, Buckinghamshire, UK, with refractory partial seizures were recruited via an internal review of psychiatric needs. All participants completed the patient version of the Neurobehavioral Inventory (NBI);[6] an instrument specifically developed to measure inter-ictal psychopathology in patients with epilepsy. A professional carer, who had known the subject for at least 5 years, completed the carer version of the instrument independent of the subject.

The NBI is an expanded and revised version of the scale originally developed by Bear & Fedio,[16] and consists of 100 items measuring behaviours and attitudes across 20 domains that are considered relevant to temporal lobe epilepsy. True/false responses for each of the 100 items are expected, and each sub-scale is scored by adding up all the "true" responses. Overall caseness is determined when a score of 20 is met or exceeded. The instrument has been used extensively in tertiary care, and is the only measure of TLE specific behaviour that is currently in use.

Only patients with localisation related epilepsy were included in our study. Patients with primary generalised epilepsy, severe learning disability, or a history of brain surgery (all of which have independent effects on behaviour and may confound results) were excluded.

MRI images were acquired at the Chalfont Centre for Epilepsy on a 1.5 T GE Signa scanner (GE Medical Systems, Milwaukee, Wisconsin, USA) using a T1 weighted inversion recovery prepared volume acquisition (inversion time 450 seconds; repetition time 15 seconds; echo time 4.2 seconds; flip angle 20°; 124×1.5 mm thick continuous coronal slices; matrix 256×192; field of view 24×18 cm).

Volumetric measurements were performed with the software MRreg (http://www.erg.ion.ucl.ac.uk/MRreg.html), using methods that have been described elsewhere.[7–8] Intracranial and total brain volumes were measured using the fully automatic brain segmentation software, Exbrain.[9–10] The total volumes of the amygdala and hippocampi were corrected for total brain size by division by the intracranial volume. The rater (JW) was blinded to all NBI scores. Intra-rater reliability figures were calculated from repeated measurements of a subset of 15 normal controls and produced consistent figures in the calculated intra-class correlation coefficients (right amydala 0.96; left amydala 0.94; right hippocampus 0.91; left hippocampus 0.97].

Participants were divided into three groups: (*a*) patients high and low in religiosity; (*b*) patients high and low in writing; and (*c*) patients high and low in sexuality on the relevant NBI sub-scales. For the religiosity and sexuality sub-scales, scores ⩾2 were considered to be indicative of caseness. For the writing sub-scale, scores of 1 or more were considered to be indicative of caseness, as scores on this sub-scale were generally low. The reason for the focus on these three sub-scales in hypothesis testing was because of the widespread

**Abbreviations:** MRI, magnetic resonance imaging; NBI, Neurobehavioral Inventory

recognition that this triad of behaviours is closely associated with TLE.

Separate groupings were formed for both patient and carer versions of the NBI. The groups were equivalent in terms of seizure frequency and severity as measured by the National Hospital Seizure Severity Scale.[11]

## RESULTS

Median amygdala and hippocampal volumes (expressed as per cent intracranial volumes) for the different patient defined NBI groups are presented in table 1. Descriptive and inferential statistics for the carer defined NBI groups are not presented because of the small number of participants meeting caseness criteria according to this measure.

Mann-Whitney U tests were used to compare the amygdala and hippocampal volumes in the three groups; an alpha value of $p < 0.05$ was adopted for hypothesis driven (two tailed) tests. None of the positive and negative groups was significantly different from one another in terms of amygdala and hippocampal volumes, with one exception; patients meeting criteria for hyper-religiosity had a significantly smaller right hippocampus compared with those who did not display hyper-religiosity ($U = 54.0$, $p = 0.008$, two tailed). Significant negative correlations between right hippocampal volumes and both patient ($rho = -0.402$, $p = 0.018$, two tailed) and carer ($rho = -0.401$, $p = 0.019$, two tailed) reported religiosity scores were also found (fig 1). None of the other NBI–brain volume correlations was significant.

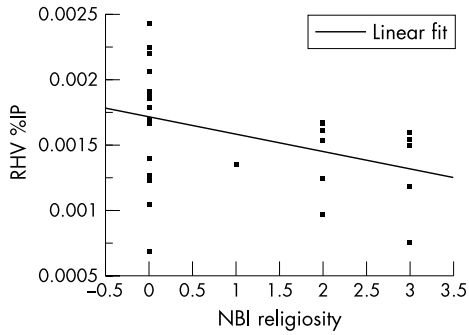


**Figure 1** Bivariate fit of right hippocampal volume (expressed as percentages of the intra-cranial volume; RHV %IP) and NBI hyper-religiosity scores.

## DISCUSSION

Patients with hyper-religiosity had a significantly smaller right hippocampus compared with those who did not display hyper-religiosity. The reliability of the observed relationship between right hippocampal volumes and religiosity is underscored by the fact that significant negative correlations were obtained with raw NBI scores provided independently by the patient and by an individual directly involved in their care. The religious and non-religious groups were not significantly different in terms of left hippocampal volumes or amygdala volumes on either side. Neither hypergraphia nor hyposexuality were associated with hippocampal or amygdala volumes.

It is noteworthy that there were no significant differences between the religiosity groups in terms of amygdala volumes. Previous studies conducted in our unit have shown changes in amygdala volumes in epilepsy in patients with co-morbid affective aggression, co-morbid affective disorder,[12–13] and psychoses of epilepsy.[14] The absence of an association between religiosity and amygdala volumes in the present sample suggests that different mesial temporal structures may be related to different aspects of inter-ictal (epilepsy specific) psychopathology.

The only other imaging study we are aware of that has shown an association between the hippocampus and aspects of Geschwind syndrome is the case of Kumagasu Minakata, a Japanese genius devoted to natural history and folklore, and famous for his immense range of works. Using MRI scans to study this man's post-mortem brain, Murai[15] found evidence of right hippocampal atrophy, which correlated with his history, which was suggestive of temporal lobe epilepsy. Many features of Geschwind syndrome (the tremendous number of articles; a tendency to write minuscule letters in compact space; lack of interest in the opposite sex; peculiar ethical concerns; proclivity to become angry on slight provocation; and notably an extraordinary interest in religious matters) were identified in a detailed study of this subject's diaries.

The instruments used in this study may be subject to some criticism. The NBI has only been validated in epilepsy based studies, and its psychometric properties have not been subject to rigorous testing. However, it has been used extensively in populations with refractory epilepsy, and is widely believed to measure behavioural features specific to the illness, which are not assessed by conventional instruments.[6]

Although inter-rater reliability for our method of MR volumetry has not been examined, the technique has consistently demonstrated good intra-rater reliability. Furthermore, the rater in this study, as in our previous experiments, was blinded to all psychopathology data. We did not correct for multiple comparisons because our study was hypothesis driven and this would have resulted in over-correction.[17] However, given that we looked for abnormalities

**Table 1** Mean hippocampal and amygdala volumes for patients with and without hyper-religiosity, hypergraphia, and hyposexuality (expressed as percentages of the intra-cranial volume)

| | Hyper-religiosity | | Hypergraphia | | Hyposexuality | |
|---|---|---|---|---|---|---|
| Brain area | Negative (n = 22) | Positive (n = 11) | Negative (n = 25) | Positive (n = 8) | Negative (n = 26) | Positive (n = 7) |
| LA | 0.1327 (0.00023) | 0.1241 (0.00025) | 0.1276 (0.00026) | 0.1367 (0.00012) | 0.1302 (0.00024) | 0.1282 (0.00023) |
| RA | 0.1426 (0.00023) | 0.1278 (0.00021) | 0.1386 (0.00025) | 0.1348 (0.00019) | 0.1383 (0.00022) | 0.1354 (0.00029) |
| LH | 0.1523 (0.00041) | 0.1551 (0.00027) | 0.1533 (0.00035) | 0.1529 (0.00043) | 0.1529 (0.00033) | 0.1543 (0.00051) |
| RH | 0.1726* (0.00041) | 0.1406* (0.00031) | 0.1690 (0.00035) | 0.1397 (0.00050) | 0.1638 (0.00041) | 0.1549 (0.00041) |

Results are given as mean (SD).
*Significant difference between positive and negative groups, $p < 0.01$.
LA, left amydala; RA, right amydala; LH, left hippocampus; RH, right hippocampus.

of two structures, hippocampus and amygdala, the significance of our main finding would survive such a Bonferroni correction.

Previous studies in this area have tended to correlate psychopathology of this nature to seizure focus, and predictions such as the "temporolimbic hyperconnection" hypothesis have been proposed.[16] Patients with both frontal and temporal seizures were included in our study, and religiosity was observed in both groups with no significant differences. Although the sample studied was too small for a meaningful interpretation of such data, and the correlation found does not necessarily imply causation, the specific and highly significant association between right hippocampal volumes and religiosity after correcting for intracranial volume is indicative of a critical role for this structure in the development of religiosity.

While a full clinical presentation of Geschwind syndrome with significant hyper-religiosity, hypergraphia, and hyposexuality is not common, individual signs and symptoms are frequently noted by neuropsychiatrists. The neurophysiology of hyper-religious behaviour, however, is still far from understood. While our results hint that hippocampal pathology might play a role, we were not able to find any other relevant publication in the literature. Thus, further studies are needed to replicate our finding and to explore the precise pathophysiology of this phenomenon. We believe therefore that our finding linking religiosity in epilepsy, which has a longstanding history in neuropsychiatry, to right hippocampal volumes is interesting and should be explored in prospective studies that involve larger patient cohorts.

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