Hippocampal signal complexity in mesial temporal lobe epilepsy: a noisy brain is a healthy brain

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A B S T R A C T

Patients with mesial temporal lobe epilepsy (mTLE) show structural and functional abnormalities in hippocampus and surrounding mesial temporal structures. Brain signal complexity appears to be a marker of functional integrity or capacity. We examined complexity in 8 patients with intracranial hippocampal electrodes during performance of memory tasks (scene encoding and recognition) known to be sensitive to mesial temporal integrity. Our patients were shown to have right mesial temporal seizure onsets, permitting us to evaluate both epileptogenic (right) and healthy (left) hippocampi. Using multiscale entropy (MSE) as a measure of complexity, we found that iEEG from the epileptogenic hippocampus showed less complexity than iEEG from the healthy hippocampus. This difference was reliable for encoding but not for recognition. Our results indicate that both functional integrity and cognitive demands influence hippocampal signal complexity.

Key words
Mancano

Introduction

Recent computational modelling suggests that variability or 'noise' in physiological signals may be an important parameter reflecting both the processing capacity and the functional integrity of biological systems (for example, see Jirsa et al., in press). The temporal behaviour of signals in these systems has both stochastic and deterministic properties and thus is neither completely predictable nor entirely random. This structural richness should be thought of as *complex* rather than simply variable (Costa et al., 2005). Costa and colleagues devised a metric to evaluate signal complexity, called multiscale entropy (MSE), which emphasizes the way signals behave over a range of temporal scales from fine (e.g., over milliseconds) to coarse (over minutes) (Costa et al., 2002, 2005). This feature of MSE is important because it differentiates between signals whose variability is purely random (such as white noise) and those comprised of both random and deterministic components (such as 1/f or coloured noise). That is, signals that are purely random show a rapid decline in the MSE curve with increasing scale whereas those with temporal interdependencies will have a more gradual shift in the MSE curve. In applying this framework to cardiac signals, Costa and colleagues found that the complexity of inter-beat intervals demonstrated a progressive reduction from healthy young adults to healthy elderly adults

to patients with congestive heart failure (Costa et al., 2005). Thus, in the heart, there is reason to believe that loss of complexity may be a biomarker of pathological dynamics.

While MSE has not been applied to brain signals in patient populations, there has been some exploration of signal variability in several cohorts. These studies suggest an inverted U-shaped function relating system variability and system integrity or capacity, such that neurologically compromised cohorts can show either more or less variability than their respective controls. Several recent studies using EEG or MEG have reported that changes in variability in patients with depression, schizophrenia or mild Alzheimer's disease were correlated with emotional or cognitive deficits (Winterer et al., 2000; Linkenkaer-Hansen et al., 2005; Montez et al., 2009). Nenadovic and colleagues observed that temporal variability in EEG coherence was a positive predictor of recovery from pediatric traumatic brain injury (Nenadovic et al., 2008). Finally, with epilepsy patients undergoing intracranial electroencephalography (iEEG), researchers have shown reduced variability (as demonstrated by increased temporal autocorrelations) in epileptogenic tissue (Parish et al., 2004; Monto et al., 2007). Thus, in the healthy brain, neurocognitive and neurophysiological operations may depend on an optimal amount of internal variability (Frank et al., 1999).

Here, we examined complexity as a potential marker of functional integrity of the hippocampus in patients with mesial temporal lobe epilepsy (mTLE). Similar to Parish and colleagues (Parish et al., 2004), we studied patients with depth electrodes in both hippocampi, a situation that affords a unique opportunity for high-fidelity recording of field potentials. As all patients in our study were eventually determined to have seizures originating from the right hippocampus, we could directly compare signals from focal epileptogenic regions to contralateral mesial temporal regions not involved in seizure generation. Importantly, the preceding clinical studies of brain variability examined signal dynamics while participants were resting or freely behaving. In contrast, we assessed signal dynamics in the context of memory tasks known to engage mesial temporal regions. We chose this tactic because complexity is suggested to reflect not only 'baseline' integrity but also the adaptability or functional capacity of a system (see McIntosh et al., in press). For example, Costa and colleagues reported that the typical differentiation of cardiac dynamics between awake and sleep states was reduced in patients with severe cardiac pathology (Costa et al., 2005). In brain, McIntosh and colleagues demonstrated that maturational increases in complexity in children aged 8-15 were related to more stable behavioural outcomes on a memory task (McIntosh et al., 2008). Thus, we hypothesized that cognitive challenge might be important in understanding complexity differences between healthy and epileptogenic hippocampi.

We recorded iEEG from hippocampi while participants performed memory tasks of scene encoding and recognition. To measure signal complexity, we used MSE (Costa et al., 2002, 2005), which has an advantage over other measures of complexity in that it can be applied to shorter time series. This is particularly helpful in our case, as our time series were defined in the context of behavioral tasks with brief episodic timescales (i.e., not resting state). In line with the previous papers on signal variability in epilepsy, we expected lower MSE values for the epilpetogenic hippocampus.

Methods

Participants

Eight patients (four male) with mTLE participated in this study. Although scalp recordings had been insufficient to determine the side of epileptogenicity with the precision required for surgical planning, intracranial recording eventually revealed the right mesial temporal lobe to be the epileptogenic zone in all eight patients. Five patients had radiological evidence of right mesial temporal sclerosis (MTS), two additional patients had structural abnormalities (MTS, developmental dysplasia) of the right hippocampus confirmed at pathology, and one had no obvious mesial temporal pathology. Demographic characteristics, performance on the scene recognition task, and selected measures from baseline neuropsychological evaluation are presented in Table I. Of note, the neuropsychological data clearly demonstrate a significant impairment in visual memory, typically subserved by the right temporal lobe, relative to intact verbal memory, associated with left temporal functioning, in our cohort (p < 0.05 for contrast of composite scores).

Table I. - Patient demographics, performance on the scene recognition task during iEEG, and measures of verbal and visual memory from pre-operative neuropsychological assessment.

Patient	Age	Age of Onset	Full- Scale IQ[a]	Scene Recognition % correct[b]	Verbal Memory Composite[c]	Visual Memory Composite[d]
1	33	14	100	92	-0.93	-2.09
2	41	25	118	73	-1.12	-0.35
3	30	8	100	87	0.61	-2.08
4	60	48	107	78	0.30	0.49
5	30	17	113	78	0.17	-0.82
6	26	11	108	77	0.64	-1.42
7	59	38	103	95	0.27	-1.21
8	35	15	96	82	0.32	-1.24

[a] from Wechsler Abbreviated Scale of Intelligence; [b] Accuracy is based on hits + correct rejections; [c] age-corrected z-scores for combination of total learning from Rey Auditory Verbal Learning Test and number correct from Warrington Recognition Memory Test for Words; [d] age-corrected z-scores for combination of total learning from Rey Visual Design Learning Test and number correct from Warrington Recognition Memory Test for Faces.

Task

During iEEG recording, patients completed two memory tasks. For scene encoding, there were 60 trials with 3500 ms presentations of a scene and a 500 ms interstimulus interval. A novel scene was presented on 30 trials; for the remaining 30 trials, 2 scenes were presented repeatedly (15 presentations of each). The use of both novel and repeated scenes is an adaptation of fMRI memory protocols that show greater mesial temporal response for novel scenes (Stern et al., 1996; Yamaguchi et al., 2004; Daselaar et al., 2006; Westmacott et al., 2008). Patients were instructed to look at each scene and to try to memorize the novel ones for a subsequent memory test; they were told that the repeating scenes would not be tested. Order of presentation was randomized for each subject and no overt response was required during encoding. The recognition test occurred after a five-minute interval of task instruction. The 30 once-presented scenes from the encoding task were intermixed with 30 new scenes and presentation order was randomized for each subject. Patients were instructed to press one mouse key to signify recognition of 'old' items (from the encoding task) and another to signify 'new' items. Stimulus presentation terminated at the response and there was a 1000 ms interstimulus interval.

iEEG recording and data preprocessing

Digitized signals were recorded referenced to a subgaleal ground electrode, acquired at a sampling rate of 5 kHz (24 bit analog-digital conversion; low pass filtered at 1 kHz) and stored for offline analysis (Synamp2, Compumedics). For all analyses the signals were band pass-filtered (0.1 Hz-250 Hz) and decimated to 500 Hz. Within the mesial temporal lobe, we used the depth electrode contact that was identified to be within the hippocampus from post-implantation imaging (either MRI or post-operative CT fused to the pre-operative MRI). Data for analyses comprised all encoding and recognition trials irrespective of recall status. Epochs were 800 ms, with 200 ms pre-stimulus onset and 600 ms post-stimulus onset. None of the recognition trials included responses as the shortest RT was 617 ms and all epochs in which epileptiform activity was noted were discarded. Fig. 1 shows electrode placement and representative tracings form the right and left hippocampi.

MSE estimation of temporal signal complexity

We used MSE to estimate entropy at different time scales. For a detailed description of the MSE measure and its relevance for the analysis of signal complexity, see Costa and colleagues (Costa et al., 2002, 2005). The algorithm calculates sample entropy as a measure of predictability in the signal at different temporal scales. The calculation of MSE involves two steps. First, the data are resampled to create several different temporal scales. For each scale, data points within non-overlapping windows are averaged (e.g., scale 1 is the raw time series, scale 2 averages over 2 time points, etc.). This procedure can be viewed as a smoother version of decimation. Second, sample entropy is calculated for each time
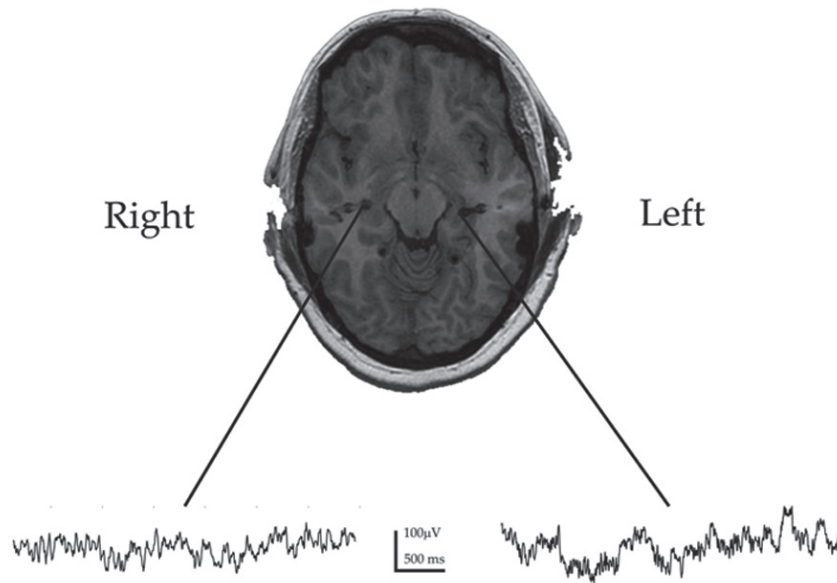
Fig. 1. - Axial scan from a representative mTLE patient with iEEG recordings. Depth electrodes were placed orthogonally to the long axis of the hippocampus, with the deepest contact in the hippocampus. The brain is displayed according to radiolological convention (R = L). The tracings indicate 3000 ms epochs recorded during encoding from the depth electrode within hippocampus for each side.

series, measuring predictability by evaluating the appearance of repetitive patterns. We calculated MSE for each trial using the algorithm available at www.physionet.org/physiotools/mse/ with parameter values m (pattern length) = 2 and r (tolerance) = 0.5. The length of the time series was 400 data points, corresponding to 800 ms epochs at sampling rate of 500 Hz. For each subject, electrode- and condition-specific MSE estimates were obtained as a mean across within-trial entropy measures for scales 1-8. We did not calculate MSE measures for scales greater than 8 because the corresponding time series were too short for reliable sample entropy estimation (i.e., we had less than 50 time points for scales greater than 8).

PLS

Statistical assessment of MSE differences between electrodes and conditions was performed using partial least squares analysis (PLS) (Lobaugh et al., 2001; McIntosh et al., 2008). PLS is a multivariate technique similar to canonical correlation, except that is maximizes the covariance between two data sets rather than the correlation. PLS is performed on data matrices consisting of subject MSE estimates. The rows of the matrix contain condition blocks, and each subject has a row of data within condition blocks. The columns of the data matrix contain the MSE measures. PLS data matrices are averaged within condition and grand mean centered by column across all conditions. The mean-centered matrices are then decomposed with singular value decomposition to identify the latent variables (LVs) that show similarities or differences between experimental conditions. For each LV, the decomposition creates three new matrices: (1) weights or saliences for the rows, which indicate a contrast that characterizes the similarities or differences between conditions, (2) weights or saliences for the columns, which indicate the linear combination of MSE scale that maximally relates to the contrast, and (3) the singular value, which was the covariance between the contrast and the MSE weights.

Statistical significance of the latent variables identified by PLS was assessed using permutation tests. The permutation test assesses whether the effect represented in a given LV, captured by the singular value, is sufficiently strong to be different from random noise. The test involves random reassignment of subjects to conditions and then the re-computation of PLS with permuted data. A probability value is derived from the number of times out of 1000

that the singular value from each permuted data set is greater than or equal to that of the original data. The reliability of MSE weights was determined with bootstrap estimation of confidence intervals, using 500 bootstrap samples. The singular vector weights for each MSE coefficient are divided by the bootstrap estimated standard error, giving a bootstrap ratio. The bootstrap ratio is similar to a z-score if the distribution of singular vector weights is Gaussian (McIntosh and Lobaugh, 2004).

Results

Patients found the scene memory task relatively easy and recognition performance was well above chance. Mean accuracy (hits + correct rejections) was 83% (range 73-95%).

Our initial PLS analysis included all four conditions (i.e., epileptogenic right hippocampus in encoding, non-epileptogenic left hippocampus in encoding, epileptogenic right hippocampus in recognition, non-epileptogenic left hippocampus in recognition) as we had no specific hypotheses regarding possible difference between tasks. This PLS revealed one significant latent variable ($p < 0.0001$) which differentiated left hippocampal signal during encoding from right hippocampal signal during encoding and recognition, with stable differences at temporal scales 2 through 6 (see Fig. 2). Given that the contribution from left hippocampus during recognition was unstable (i.e., the 95% confidence interval includes zero), we suspected that there may be some differentiation between tasks. Therefore we examined encoding and recognition tasks in separate analyses. During encoding, there was a significant difference ($p = 0.01$) between hippocampi, with the left side showing higher entropy at temporal scales 2 through 8 (see Fig. 3). A similar, but not statistically reliable ($p = 0.08$) pattern was identified for recognition (see Fig. 4). To explore the task-related effect further, we focused on the healthy (left) hippocampus only. Here, there was a significant difference ($p = 0.02$) between conditions, with higher entropy at multiple temporal scales for encoding relative to recognition (see Fig. 5). This should, however, be considered a post-hoc analysis as we did not have a priori predictions regarding task effects, unlike the clear predictions regarding healthy vs. affected side.
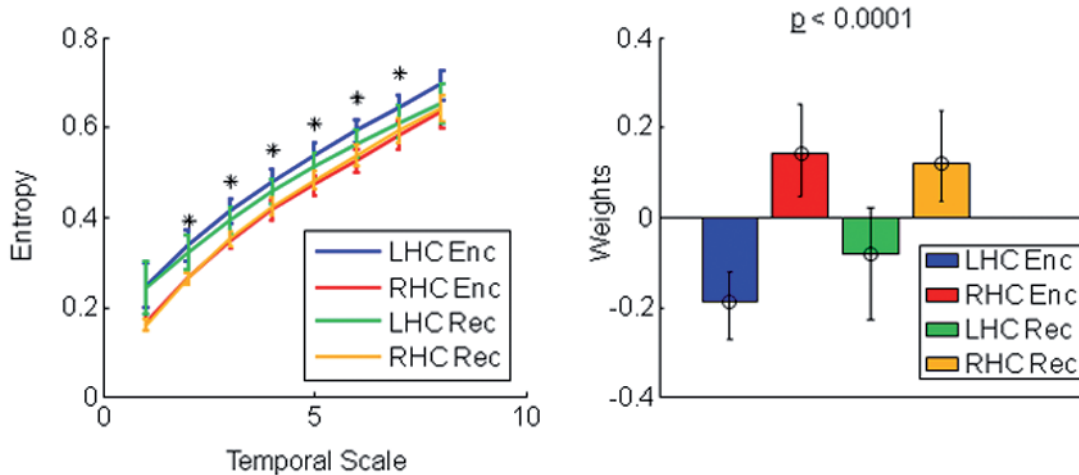

Fig. 2. - Differences in multiscale entropy estimated across all four conditions (i.e., epileptogenic right hippocampus in encoding, non-epileptogenic left hippocampus in encoding, epileptogenic right hippocampus in recognition, non-epileptogenic left hippocampus in recognition). Left panel shows group mean entropy with error bars representing standard errors. Stars indicate temporal scales at which the contrast shown in the right panel is stably expressed. Right panel shows PLS contrast differentiating entropy in non-epileptogenic left hippocampal signal during encoding from epileptogenic right hippocampal signal during encoding and recognition. The error bars indicate the 95% confidence intervals derived from bootstrap estimation.
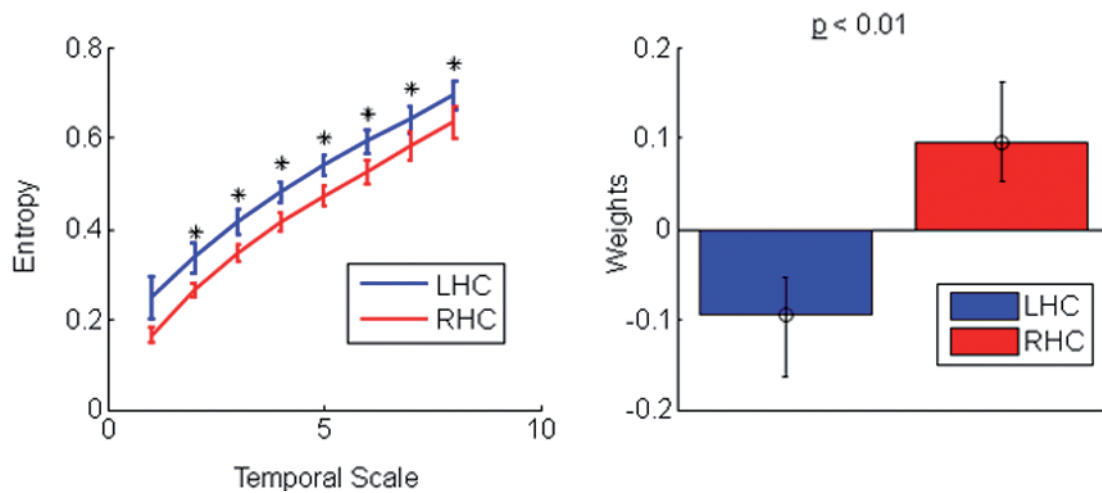
Fig. 3. - Differences in multiscale entropy estimated across epileptogenic right hippocampus and non-epileptogenic left hippocampus in encoding. Left panel shows group mean entropy with error bars representing standard errors. Stars indicate temporal scales at which the contrast shown in the right panel is stably expressed. Right panel shows PLS contrast differentiating entropy in non-epileptogenic left hippocampal signal during encoding from epileptogenic right hippocampal signal during encoding and recognition. The error bars indicate the 95% confidence intervals derived from bootstrap estimation.
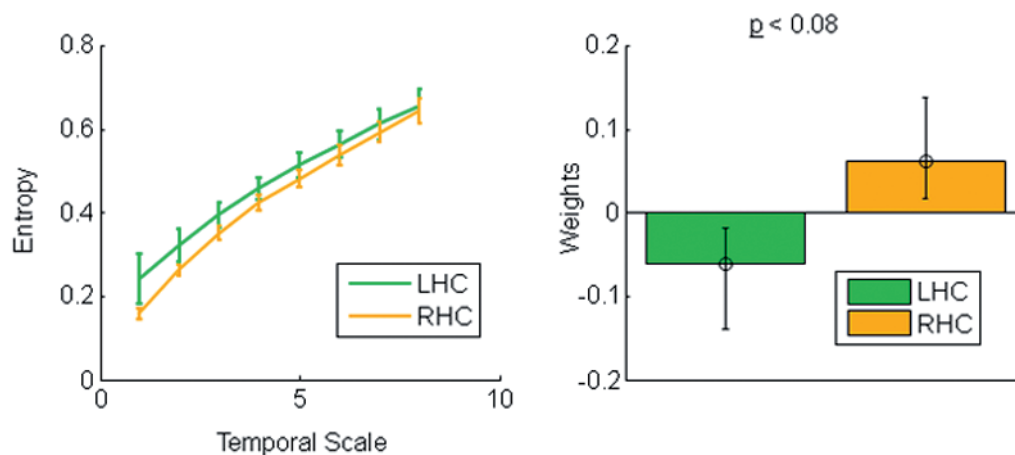

Fig. 4. - Differences in multiscale entropy estimated across epileptogenic right hippocampus and non-epileptogenic left hippocampus in recognition (note this pattern is not reliable, as p = 0.08). Left panel shows group mean entropy with error bars representing standard errors. There are no temporal scales at which the contrast shown in the right panel is stably expressed. Right panel shows PLS contrast differentiating entropy in non-epileptogenic left hippocampal signal during encoding from epileptogenic right hippocampal signal during encoding and recognition. The error bars indicate the 95% confidence intervals derived from bootstrap estimation.

Discussion

In accord with our hypothesis, we found reduced signal complexity in epileptogenic (right) hippocampus as compared to 'healthy' (we should note that while the right hippocampus was identified as the epileptogenic focus for all patients, there was interictal activity recorded from the left hippocampus over the course of the clinical recording in some cases) (left) hippocampus for encoding. While the findings were not reliable for recognition, there was a trend in the same direction. These results replicate and extend previous reports of reduced variability (as measured by increased long-range temporal cor-
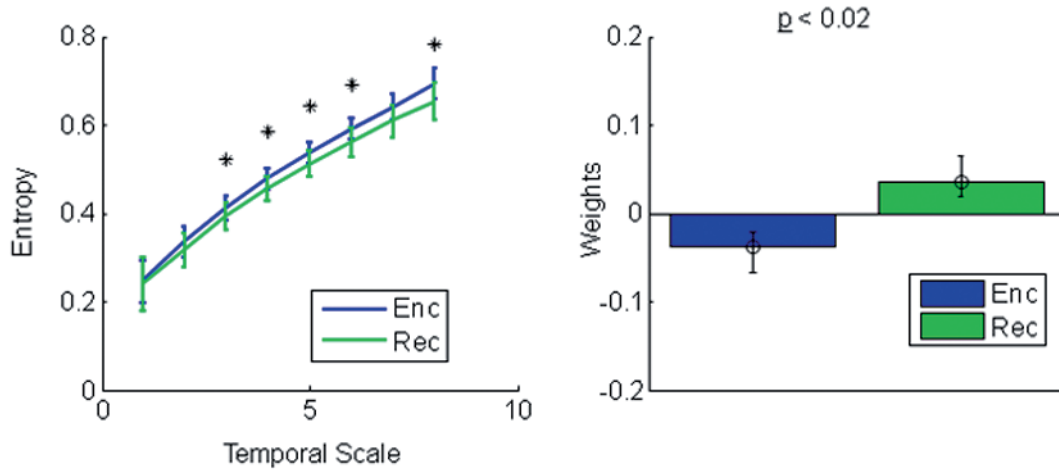
Fig. 5. - Differences in multiscale entropy estimated across encoding and recognition conditions for the non-epileptogenic left hippocampus in recognition. Left panel shows task mean entropy with error bars representing standard errors. Stars indicate temporal scales at which the contrast shown in the right panel is stably expressed. Right panel shows PLS contrast differentiating entropy in encoding from recognition for the left hippocampal signal. The error bars indicate the 95% confidence intervals derived from bootstrap estimation.

relation) in epileptogenic tissue (Parish et al., 2004; Montez et al., 2009). The previous studies examined task-independent signal over a lengthy time period (approx. 20 minutes) whereas we examined signal recorded during a relevant behavioral challenge over a much shorter time period (800 ms). The similarity of findings, despite these methodological differences and the small sample sizes in these studies, suggests that brain signal variability is a robust biomarker of neuronal system integrity in patients with epilepsy. We used memory tasks known to engage mesial temporal regions because we thought they might enhance our ability to detect variations in signal complexity. We did not anticipate that the difference between healthy and epileptogenic tissue would vary between encoding and recognition tasks. Despite similar MSE profiles, there was a clear difference in the fidelity with which these memory operations discriminated between healthy and epileptogenic hippocampi. This may reflect a greater engagement of the hippocampus in scene encoding versus subsequent recognition, making encoding a better behavioral challenge for the hippocampus (Kohler et al., 2002; Spaniol et al., 2009) or it may reflect broader differences in cognitive set or attention. Alternately, our tasks may place difference demands on the *adaptive capacity* of the hippocampus. The encoding task included both once-presented stimuli and items that repeated

multiple times, whereas the recognition task included no repeating stimuli. Based on numerous functional neuroimaging studies, memory theorists have suggested that the hippocampus, particularly the anterior region from which we recorded, acts as a 'novelty detector' (Tulving et al., 1996; Parkin, 1997; Martin, 1999; Nyberg, 2005; Kumaran and Maguire, 2007). That is, hippocampal activity decreases dramatically with multiple repetitions of particular stimuli, indicating habituation (Strange et al., 1999, 2005b; Fischer et al., 2000, 2003). A similar decrease in firing has recently been reported for population recording of neurons from the hippocampus (Pedreira et al., 2010). One could argue that during our encoding task, rapid novelty detection to unique items and habituation to repeated items creates a binary state; 'on' for novel stimuli and 'off' for habituated ones. During recognition, old items have been seen only once before at encoding, thus no stimuli have undergone habituation and there is a singular 'on' state in the hippocampus. Put another way, there is greater entropy, a measure of that reflects the expected uncertainty of events in a particular context, in the encoding event stream and the hippocampus appears to be sensitive to such probabilistic contexts (Strange et al., 2005a). Thus, if complexity is a metric that reflects adaptation to environmental change or task-relevant contingencies, the structure of the encoding

task may have made it a more sensitive indicator of system complexity. We do have some preliminary evidence in support of this conjecture as MSE was significantly greater for encoding than recognition in the non-epileptogenic hippocampus.

Greater complexity in a biological system is hypothesized to reflect (1) a high capacity to adapt to changes in environmental contingencies or demands; and (2) relative freedom from pathology or other factors (e.g., aging) that degrade information carried by output variables (Costa et al., 2005). Thus, the observed degradation in hippocampal complexity during memory operations may be strongly modulated by task parameters. This speculation can only be confirmed with additional experiments that vary parameters relevant to complexity independent of the nature of the task or instructional set (e.g., proportion of repetitions during encoding, target-foil similarity at recognition). Although we not aware of relevant cognitive studies, there are parallel findings assessing biological noise during a gross manipulation of state: sleep versus wakefulness. These studies show that the difference in signal variability for healthy versus unhealthy tissue in both brain and heart is attenuated in sleep (Costa et al., 2005; Parish et al., 2004).

There are some limitations to this study. First, we have data from only two electrodes in eight patients; therefore power is low and this may have contributed to negative findings for recognition. Nonetheless, the effect size is clearly sufficiently robust for encoding and for discriminating the two memory conditions in the non-epileptogenic hippocampus. Second, we did not distinguish between correct and incorrect trials in the analyses as there were not enough trials available. Third, although we proposed that complexity is a parameter linked to functional integrity, the current design does not allow us to directly evaluate correlations with behavior. Specifically, we do not have separate performance measures for epileptogenic and healthy hippocampi. In the future, we could incorporate cognitive probes that are differentially sensitive to left and right hippocampal function during recording. Finally, all participants in the current study had right mTLE. Although we anticipate that these results would generalize to patients with left mTLE, this remains to be validated. Nonetheless, our results provide new insight into signal complexity as it is affected by both functional integrity and cognitive state.

References

Costa M., Goldberger A.L., Peng C.K. Multiscale entropy analysis of complex physiologic time series. *Phys. Rev. Lett.*, **89**: 068102, 2002.

Costa M., Goldberger A.L., Peng C.K. Multiscale entropy analysis of biological signals. *Phys. Rev. E.*, **71**: 021906, 2005.

Daselaar S.M., Fleck M.S., Cabeza R. Triple dissociation in the medial temporal lobes: recollection, familiarity, and novelty. *J. Neurophysiol.*, **96**: 1902-1911, 2006.

Fischer H., Furmark T., Wik G., Fredrikson M. Brain representation of habituation to repeated complex visual stimulation studied with PET. *Neuroreport*, **11**: 123-126, 2000.

Fischer H., Wright C.I., Whalen P.J., McInerney S.C., Shin L.M., Rauch S L. Brain habituation during repeated exposure to fearful and neutral faces: a functional MRI study. *Brain Res. Bull.*, **59**: 387-392, 2003.

Frank T.D., Daffertshofer A., Beek P.J., Haken, H. Impacts of noise on a field theoretical model of the human brain. *Physica D*, **127**: 233-249, 1999.

Jirsa V.K., Sporns O., Breakspear M., Deco G., McIntosh A.R. Towards the virtual brain: network modeling of the intact and the damaged brain. *Archives Italiennes de Biologie*, **in press**.

Kohler S., Crane J., Milner B. Differential contributions of the parahippocampal place area and the anterior hippocampus to human memory for scenes. *Hippocampus*, **12**: 718-723, 2002.

Kumaran D. and Maguire E.A. Match mismatch processes underlie human hippocampal responses to associative novelty. *J. Neurosci.*, **27**: 8517-8524, 2007.

Linkenkaer-Hansen K., Monto S., Rytsala H., Suominen K., Isometsa E., Kahkonen S. Breakdown of long-range temporal correlations in theta oscillations in patients with major depressive disorder. *J. Neurosci.*, **25**: 10131-10137, 2005.

Lobaugh N.J., West R., McIntosh A.R. Spatiotemporal analysis of experimental differences in event-related potential data with partial least squares. *Psychophysiology*, **38**: 517-530, 2001.

Martin A. Automatic activation of the medial temporal lobe during encoding: lateralized influences of meaning and novelty. *Hippocampus*, 9: 62-70, 1999.

McIntosh A.R. and Lobaugh N.J. Partial least squares analysis of neuroimaging data: applications and advances. *Neuroimage*, 23 Suppl 1: S250-263, 2004.

McIntosh A.R., Kovacevic N., Itier R.J. Increased brain signal variability accompanies lower behavioral variability in development. *PLoS Comput. Biol.*, 4: e1000106, 2008.

McIntosh A.R., Kovacevic N., Lippe S., Garrett D., Grady C., Jirsa V.K. The development of a noisy brain. *Archives Italiennes de Biologie*, **in press**.

Montez T., Poil S.S., Jones B.F., Manshanden I., Verbunt J.P., van Dijk B.W., Brussaard A.B., van Ooyen A., Stam C.J., Schelten P., Linkenkaer-Hansen K. Altered temporal correlations in parietal alpha and prefrontal theta oscillations in early-stage Alzheimer disease. *Proc. Natl. Acad. Sci. USA*, 106: 1614-1619, 2009.

Monto S., Vanhatalo S., Holmes M.D., Palva J.M. Epileptogenic neocortical networks are revealed by abnormal temporal dynamics in seizure-free subdural EEG. *Cereb. Cortex*, 17: 1386-1393, 2007.

Nenadovic V., Hutchison J.S., Dominguez L.G., Otsubo H., Gray M.P., Sharma R., Belkas J., Perez Velazquez J.L. Fluctuations in cortical synchronization in pediatric traumatic brain injury. *J. Neurotrauma*, 25: 615-627, 2008.

Nyberg L. Any novelty in hippocampal formation and memory? *Curr. Opin. Neurol.*, 18: 424-428, 2005.

Parish L.M., Worrell G.A., Cranstoun S.D., Stead S.M., Pennell P., Litt B. Long-range temporal correlations in epileptogenic and non-epileptogenic human hippocampus. *Neuroscience*, 125: 1069-1076, 2004.

Parkin A.J. Human memory: novelty, association and the brain. *Curr. Biol.*, 7: R768-769, 1997.

Pedreira C., Mormann F., Kraskov A., Cerf M., Fried I., Koch C., Quian Quiroga R. Responses of human medial temporal lobe neurons are modulated by stimulus repetition. *J. Neurophysiol.*, 103: 97-107, 2010.

Spaniol J., Davidson P.S., Kim A.S., Han H., Moscovitch M., Grady C.L. Event-related fMRI studies of episodic encoding and retrieval: meta-analyses using activation likelihood estimation. *Neuropsychologia*, 47: 1765-1779, 2009.

Stern C.E., Corkin S., Gonzalez R.G., Guimaraes A.R., Baker J.R., Jennings P.J., Carr C.A., Sugiura R.M., Vedanthan V., Rosen B.R. The hippocampal formation participates in novel picture encoding: evidence from functional magnetic resonance imaging. *Proc. Natl. Acad. Sci. USA*, 93: 8660-8665, 1996.

Strange B.A., Fletcher P.C., Henson R.N., Friston K.J., Dolan R.J. Segregating the functions of human hippocampus. *Proc. Natl. Acad. Sci. USA*, 96: 4034-4039, 1999.

Strange B.A., Duggins A., Penny W., Dolan R.J., Friston K.J. Information theory, novelty and hippocampal responses: unpredicted or unpredictable? *Neural. Netw.*, 18: 225-230, 2005a.

Strange B.A., Hurlemann R., Duggins A., Heinze H.J., Dolan R.J. Dissociating intentional learning from relative novelty responses in the medial temporal lobe. *Neuroimage*, 25: 51-62, 2005b.

Tulving E., Markowitsch H.J., Craik F.E., Habib R., Houle S. Novelty and familiarity activations in PET studies of memory encoding and retrieval. *Cereb. Cortex*, 6: 71-79, 1996.

Westmacott R., Silver F.L., McAndrews M.P. Understanding medial temporal activation in memory tasks: evidence from fMRI of encoding and recognition in a case of transient global amnesia. *Hippocampus*, 18: 317-325, 2008.

Winterer G., Ziller M., Dorn H., Frick K., Mulert C., Wuebben Y., Herrmann W.M., Coppola R. Schizophrenia: reduced signal-to-noise ratio and impaired phase-locking during information processing. *Clin. Neurophysiol.*, 111: 837-849, 2000.

Yamaguchi S., Hale L.A., D'Esposito M., Knight R.T. Rapid prefrontal-hippocampal habituation to novel events. *J. Neurosci.*, 24: 5356-5363, 2004.