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Asymmetric hemispheric representation of periictal heart rate modulation is individually lateralised

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ABSTRACT – Asymmetric cortical representation of cardiac function is a matter of debate and large inter-individual variability of cortical autonomic networks and different study designs may contribute to this controversy. Lateralised seizure activity in individual patients may provide valuable insights into cortical regulation of cardiac function. We report two patients with focal epilepsy who had seizures arising from both hemispheres. In Patient 1, heart rate increased over two-fold with seizures arising from the right hemisphere, whereas heart rate increased invariably less with seizures arising from the left hemisphere. In Patient 2, heart rate increased 1.3 fold or less with seizures arising from the left hemisphere, whereas a seizure with right-sided onset was followed by bradycardia and asystole. Our findings support the notion that effects on autonomic function are lateralised, although lateralisation varies from patient to patient. This may partially explain the difficulty in determining cortical representation of cardiac autonomic function.

Key words: heart rate, cortical asymmetry, autonomic function, temporal lobe epilepsy

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Cardiac function is modulated by parasympathetic and sympathetic activity, which are regulated through cortical (*e.g.* insular cortex, amygdala, and hippocampus) and subcortical (*e.g.* brain stem) networks (Napadow *et al.*, 2008). Human and animal studies have indicated that parasympathetic and sympathetic functions are, at least to some extent, asymmetrically represented in the brain. In some studies, pharmacological inactivation of the right hemisphere or electrical stimulation of the left side predominantly led to a cardiodepressive response, whereas left-sided inactivation or right-sided stimulation resulted in an increase in heart rate (HR) (Oppenheimer *et al.*, 1992; Zamrini *et al.*, 1990).

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This hemispherical lateralisation may be clinically relevant, as seizure activity involving the left temporal lobe is associated with bradyarrhythmias such as bradycardia, AV block or asystole. However, reviews of all reported cases indicate that seizures in either temporal lobe (more commonly the left temporal lobe) can be associated with bradycardia and that bilateral seizure activity is most strongly associated with bradycardia (Britton *et al*., 2006). These apparent inconsistencies in the lateralisation of autonomic function could arise from differences in patterns of seizure spread, hand dominance and nature or site of the epileptogenic lesion, as well as inter-individual variability of cortical autonomic networks. Moreover, most reports of seizure-induced HR changes compare between individuals and therefore do not provide direct evidence of autonomic lateralisation within individual patients. Here, we provide intra-individual evidence for asymmetric modulation of HR in two patients who displayed differential increase in HR when seizure onset was lateralised to the right or left hemisphere.

Case study 1

A 62-year-old, right-handed man started having occasional episodes with sudden loss of responsiveness and confusion, fifteen years after a severe head trauma (skull fracture in a rock climbing accident). These episodes predominantly occurred during the night. Cerebral MRI demonstrated white matter lesions in the left fronto-temporal region and right temporal lobe, in keeping with the prior head injury. His medical history included arterial hypertension (treated with 10 mg ramipril per day). There was no family history of any neurological disorder. Neurological examination was normal. Cardiological history was of no particular note, especially without any prior syncope or chest pain. Twelve-lead resting ECG and echocardiogram were reported to be normal.

The patient was admitted for video-EEG telemetry using scalp-EEG electrodes (10-20 system) to determine the nature of these sleep-related paroxysmal episodes. Interictal EEG revealed independent sharp waves in the left and right temporal lobe regions. Six seizures arising from either drowsiness or sleep (stage 2) were recorded. Four seizures arose from the right and two from the left temporal lobe region. Two stereotypical EEG patterns with duration of 30-48 seconds were identified: theta activity (5-7/second) in the mid- and anterior temporal region of the right hemisphere or delta-theta activity (3-5/second) in the mid- and posterior temporal region of the left hemisphere *(figure 1)*. All seizures displayed generalised EEG activity within 10-15 seconds after seizure onset and presented with similar, non-lateralising semiology consisting of oro-alimentary automatisms. Responsiveness was not tested during the seizure, but he was transiently confused after some events and had amnesia for the events he was asked to recall. Intriguingly, although both EEG patterns were associated with a transient increase in HR (as assessed by using modified lead-I ECG) from a similar resting HR of 50-60 bpm, seizures with a right-sided onset had a maximal ictal HR of 129±3.5 bpm (mean±SD, range 126-132 bpm), whereas seizures with left-sided onset only reached a maximal ictal HR of 93±4.2 bpm (range 90-96 bpm) *(figure 1C)*. After the diagnosis of post-traumatic temporal lobe epilepsy with complex partial seizures was made, treatment with lamotrigine was instituted.

Case study 2

A 57-year-old, right-handed woman started having recurrent episodes of staring, unresponsiveness and loss of consciousness without any aura, which were occasionally followed by sudden collapse two years prior to being evaluated at our epilepsy unit. Cerebral MRI was normal (and not suggestive of limbic encephalitis or other underlying epiletogenic lesions). Cardiological examinations including Holter-ECG were normal, apart from intermittent sinus bradycardia (around 48 bpm) and premature atrial complexes. With the exception of an episode of psychosis and depression (two years prior to the onset of epileptic seizures), treated with 2.5 mg olanzapine per day, there was no other relevant medical history.

Video-EEG telemetry revealed independent left and right temporal sharp waves. A total of five seizures were captured, ranging from 11-40 seconds in duration, with the ictal EEG initially lateralising to the left fronto-temporal region in four seizures and originating from the right fronto-temporal region in the other. The ictal patterns were rhythmic delta activity (3-4/second) which quickly spread to involve a wide field on the side of seizure onset with a regional maximum at the sphenoidal electrode.

The seizure on the right was associated with an initial increase of HR to about 90 bpm and followed by progressive lengthening of the RR interval to a cardiac asystole which lasted for approximately ten seconds *(figure 2)*. During this seizure, the patient became restless whilst sitting in the chair, she slumped back into the chair, her eyes rolled up and she exhibited generalised myoclonic jerks. After the seizure, she sat up again in the chair within a few seconds and had complete amnesia for the event. The seizures with left-sided onset were less clinically impressive; one seizure was associated with subtle fiddling of the hands bilaterally, whereas the others had no clear and obvious clinical correlates. HR did not change or increase to

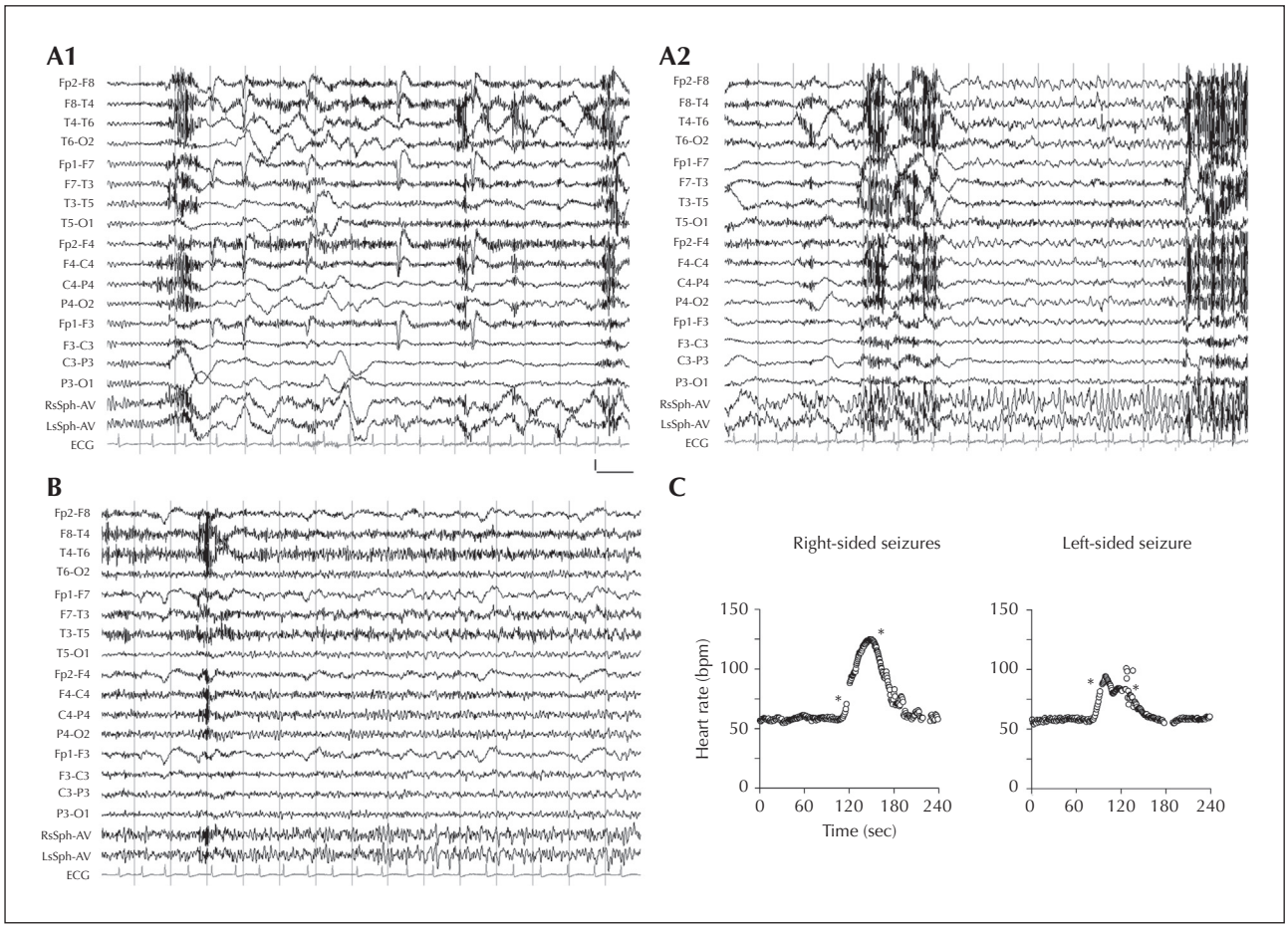

Figure 1. Original EEG/ECG traces (30 seconds) for right-sided **(A1:** prior to seizure onset; **A2**: seizure onset) and left-sided **(B)** seizure onset of *Patient 1* in a bipolar montage. Scaling 70 μV/1 s (filtered at 1 and 35 Hz). RsSph-AV: right-sided sphenoidal electrode against common average; LsSph-AV: left-sided sphenoidal electrode against common average. **(C)** Instantaneous HRs in a complex partial seizure with right-sided and left-sided seizure onset in Patient 1. Electroencephalographic seizure onset and end is indicated by asterisks.

100 bpm from a preictal HR of about 60-70 bpm during these left-sided seizures *(figure 2B)*.

The patient was diagnosed with cryptogenic bilateral fronto-temporal epilepsy with periictal bradycardia and asystole. She underwent implantation of a cardiac pacemaker, and was started on antiepileptic treatment with lamotrigine.

Discussion

The conclusions drawn from our clinical observations are limited. This was firstly due to the fact that intracranial recordings were not available and hence early contralateral spread of ictal activity to deep temporal or insular regions could not be excluded, and secondly, due to the limited number of seizures during video-EEG telemetry. Our two cases, however, exemplify the assumed asymmetry of periictal HR modulation and suggest that autonomic function is individually lateralised.

For Patient 1, we recorded four seizures with right and two seizures with left temporal seizure onset. Both seizure types had stereotypical electroclinical characteristics. Invariably, there was a greater increase in HR (2.3 fold from baseline) with seizures arising from the right hemisphere compared to the left side (1.6 fold from baseline). In Patient 2, four seizures with left and one seizure with right fronto-temporal onset were recorded. Seizures arising from the left hemisphere led to no change or an increase in HR, whereas the right-sided seizure induced bradycardia and asystole, explaining the recurrent syncope in this patient. Our findings indicated asymmetric cerebral representation of cardiac autonomic function with individually variable lateralisation. The recordings

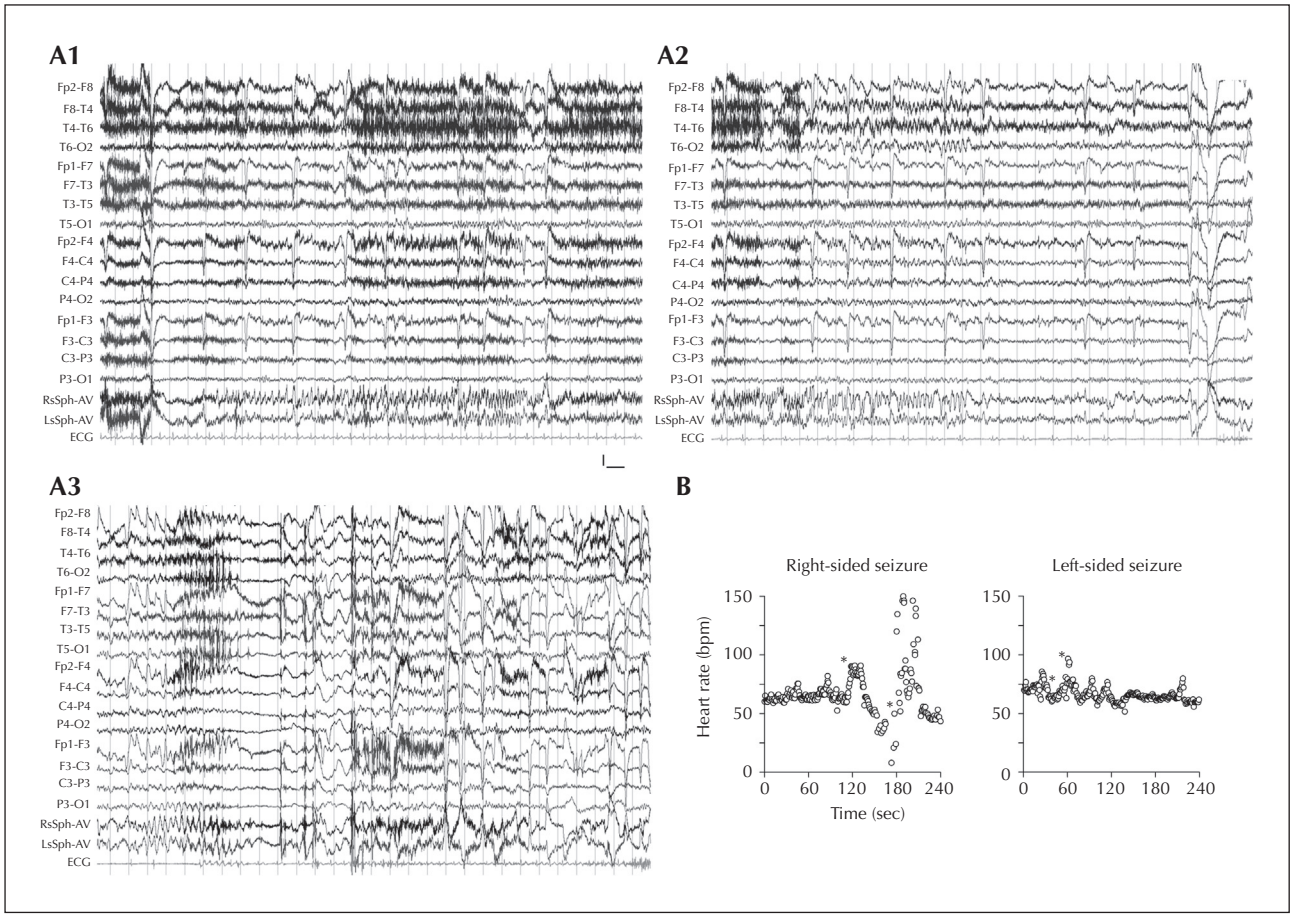

Figure 2. Original EEG/ECG traces (90 seconds) for right-sided seizure onset of *Patient 2* in a bipolar montage **(A1-A3)**. Note the increasing lengthening of RR intervals and cardiac asystole. Scaling 70 μV/1 s (filtered at 0.5 and 70 Hz). RsSph-AV: right-sided sphenoidal electrode against common average; LsSph-AV: left-sided sphenoidal electrode against common average. **(B)** Instantaneous HRs in a complex partial seizure with right-sided and left-sided seizure onset in *Patient 2*. Electroencephalographic seizure onset and end is indicated by asterisks. Note the extrasystoles/tachyarrhythmia after the asystole in **B**, left panel.

in Patient 1 suggested more prominent sympathetic activity in the right and/or more prominent parasympathetic activity in the left hemisphere, which is in keeping with some previous studies (Oppenheimer *et al*., 1992; Zamrini *et al*., 1990; Yoon *et al*., 1997; Kirchner *et al*., 2002). There are, however, conflicting studies which have reported predominant effects on parasympathetic activity based on inactivation of the right hemisphere or a lack of lateralisation of HR regulation (Ahern *et al*., 2001; Jokeit *et al*., 2000). These results could be explained by large inter-individual variability of site and strength of cortical representation of autonomic function. Furthermore, many reports have relied upon pharmacological inactivation or electrical stimulation. Therefore, analysis of intra-individual HR during spontaneous seizures gives further valuable insight into cortical lateralisation of autonomic function. Periictal bradycardia or asystole may also be associated with seizure activity either in the right or left hemisphere in individual patients, suggesting a rather stereotypical cardiodepressive response to seizure activity (Ghearing *et al*., 2007). In contrast, a previous case report described ictal bradycardia and asystole with left-sided and ictal tachycardia with right-sided seizure activity within the same patient (Kawai *et al*., 2006). In this patient, ictal EEG activity remained lateralised throughout the seizures. In our second patient, however, right-, but not left-sided, seizure onset led to ictal bradycardia and asystole, strengthening the hypothesis of asymmetric, but individual representation of cardiac function.

Cardiac arrhythmias are more frequent with increasing age and are often due to structural heart disease (Lampert and Ezekowitz, 2000). Our two patients had no particular cardiac history and cardiological examinations, including 12-lead ECG and echocardiography

in Patient 1 and 12-lead ECG, echocardiography and Holter-ECG in Patient 2, were inconspicuous. In particular, Patient 1 had no history of syncope or chest pain, and 12-lead ECG and echocardiography were reported to be normal. In Patient 2, Holter-ECG was performed, but only revealed intermittent bradycardia without any clinical symptoms or syncope. The recurrent episodes of syncope occurred after Patient 2 was treated with olanzapine. Olanzapine itself may lead to bradycardia and hypotension in both the young and the elderly (Lee *et al*., 2003; Markowitz *et al*., 2002). Furthermore, antipsychotic drugs can also favour onset of seizures. In particular, clozapine increases the risk of seizures, whereas olanzapine and risperidone are less often associated with seizures (Asenjo Lobos *et al*., 2010). In view of the very low daily dose of olanzapine, it is unlikely that the seizures were due to a side effect of antipsychotic treatment in Patient 2. Furthermore, the causal relationship between syncope and seizure onset was unequivocally established during video-EEG telemetry. Therefore, olanzapine was not discontinued, however, a cardiac pacemaker was implanted to prevent syncope and falls with subsequent trauma. After implantation, she continued having seizures, but syncope and falls were successfully prevented. To date, there are no clear-cut recommendations as to whether to implant a cardiac pacemaker in such patients. Periictal bradycardia and asystole have been shown to be self-limiting in most patients (Schuele *et al*., 2008), but may be involved in sudden unexpected death in epilepsy (Surges *et al*., 2009). We suggest that people with symptomatic periictal bradycardia and asystole should receive a cardiac pacemaker in order to prevent both syncope and injuries due to sudden falls, as well as to minimize the risk of sudden cardiac death (Strzelczyk *et al*., 2008; Surges *et al*., 2009). □

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