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# On the manner in which sensory and cognitive processes contribute to epileptogenesis, and are disrupted by it

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In this paper the ideas I shall put forward will admittedly be highly speculative, but I hope not wildly so. I shall try to remain as closely tied to data as the subject matter allows.

I will begin by summarising some of the neurophysiological mechanisms whereby seizures are precipitated. These mechanisms will be deduced from a study of photosensitive epilepsy, but there is no reason in principle why they may not also apply to other forms of epilepsy as well. Although I shall use photosensitive epilepsy as a model for some of the physiological processes responsible for seizure induction, I will speculate on possible relationships between the processes of seizure induction and the processes involved in the normal neural activity that subserves thinking and particularly remembering. I will argue that there are two antagonistic physiological processes at work, one making seizures the more likely, and the other reducing the chances of their occurrence. These processes have implications for the study of epilepsy and memory. They imply not only that epilepsy can affect the process of remembering but that the reverse may also be the case: that remembering may influence the likelihood of seizures.

Patients with photosensitive epilepsy are liable to seizures induced by visual stimulation. Their sensitivity to such stimulation can be investigated using the electroencephalogram which usually exhibits a photoconvulsive response when the patient is exposed to provocative stimulation. The stimulation that will induce epileptiform activity of this kind is remarkably specific. It includes not only intermittent light but patterns. The majority of patients who are sensitive to intermittent light are sensitive also to patterns, provided the patterns have the appropriate spatial and temporal characteristics.

These characteristics strongly suggest that the epileptiform activity that the patterns evoke is induced in the visual cortex and may remain sustained within it. This is for three main reasons:

1. The nature of the pattern is critical in determining the probability of epileptiform activity; patterns of stripes are more epileptogenic than checks. It is mainly in the cortex that cells have linear receptive fields.
2. When each eye is separately exposed to a different pattern, epileptiform activity is less likely than when both eyes see the same thing. It is mainly in the cortex that binocular cells are found.
3. The topography of the epileptiform EEG activity that the patterns induce is suggestive of generators in the visual cortex. The lateralisation and vertical preponderance over the occiput change appropriately with stimulation of the left, right, upper and lower visual fields (1).

The pattern characteristics not only suggest a cortical locus for the seizure trigger, they indicate that seizure activity arises only when activation exceeds some threshold that differs from patient to patient. This inference is based on measurements of the size of patterns just sufficient to induce activity. The size of a pattern can be manipulated in a variety of ways – for example, by changing its radius and by removing sections. Regardless of the way in which the size of the pattern is altered it remains the case that seizure activity is triggered only when the area of visual cortex to which the pattern projects exceeds some limit (2).

The conclusions from these studies and others that investigate the effects of the contrast of the

pattern are closely similar: there is some critical mass of physiological activation necessary for epileptogenesis. By "mass" I refer in some admittedly ill-defined way to a combination of both the number of cells and their firing rate. It is reasonable to assume that the physiological activation responsible for inducing the discharge is normal for the simple reason that photosensitive patients usually have normal vision, at least interictally. Their visual acuity is usually normal, and they usually have normal contrast sensitivity, even for gratings which at higher contrasts would induce epileptiform activity (D Kasteleijn-Nolst Trenite, C D Binnie and A J Wilkins, unpublished observation).

To summarise the argument so far: in photosensitive epilepsy, and perhaps in other types of epilepsy as well, seizures are induced when normal physiological excitation exceeds some critical "mass". Why should this be the case? Meldrum & Wilkins (3) have reasoned that this is precisely what one might expect if there were some minimal failure of the balance between cortical excitatory and inhibitory processes. They argue that there may be low levels of inhibitory failure which have no functional consequences unless or until physiological excitation within the nerve network becomes excessive. Since neighbouring cells share inhibitory mechanisms in common, the inhibition starts to fail when the local excitation within the nerve network becomes too great.

The time over which a cell integrates its input is limited. If massive excitation occurs within a short period of time it may be more likely to cause widespread depolarisation. This is because the likelihood of the cooccurrence of two or more inputs to a cell is increased, increasing the probability of paroxysmal depolarisation. The depolarisation may result in bursting, thereby further increasing the general level of excitation within the network in a positive feedback loop. There is a limited amount of evidence that the time course of excitation is indeed important. Patterns of stripes that drift continually in one direction are very much less epileptogenic than those that repeatedly reverse their phase, or vibrate in a direction orthogonal to the stripes (4). Many cortical cells respond preferentially to contours that move across their receptive fields and often they respond selectively to one direction of motion. Patterns of stripes that vibrate or change their phase should therefore provoke excitation that has a distinct temporal sequence; large numbers of cells will tend to fire synchronously in response to each change in direction of motion. Patterns that drift in one direction should not cause rhythmic synchronisation of this kind because the pattern contours will continually drift in and out of the overlapping receptive fields of the cells.

The synchronisation that is so obvious a feature of an epileptic discharge once the discharge is underway may perhaps therefore also be important at the inception of the discharge. But this is not to say that synchronisation is strictly necessary for a discharge to be initiated. Drifting patterns may be less epileptogenic than those with other types of motion, but they are nevertheless capable of evoking electrographic epileptiform abnormalities. This suggests that synchronisation is a contributing factor rather than a necessary condition for epileptogenesis. Epileptic discharges may be evoked when normal physiological excitation exceeds a critical mass even when this excitation is not synchronised. The role of synchronisation may help to explain why photosensitive epilepsy is more common than other forms of reflex epilepsy. Sensory systems other than vision do not so readily preserve at the cortical level the low frequency temporal aspects of sensory stimulation.

So far the ideas have been developed from studies of photosensitive epilepsy. I will now try to expand these ideas, to overgeneralise them in order to see whether they might apply in other forms of epilepsy as well. The arguments will become increasingly speculative, and far more speculative than I would like, but such speculation may perhaps be excusable if at the end of it all testable predictions emerge.

I have argued that the temporal patterning of normal physiological excitation can contribute to epileptogenesis, but that synchronisation as such is not strictly necessary. Sensory stimulation that evokes a sufficiently massive excitation within the hyperexcitable region may trigger epileptic discharges even when that excitation exhibits no gross temporal patterning. If within a region of cortex (visual or perhaps also non-visual) the inhibitory mechanisms are sufficiently impaired, sensory stimulation of any kind that gives rise to massive excitation may trigger epileptic discharges. Once triggered, the discharge may remain focal or spread. Whether or not it spreads depends, I would argue, on the hyperexcitability of the tissue surrounding the site of the massive excitation. If the region of hyperexcitability is relatively focal then the discharge may not spread but remain confined within the hyperexcitable region. We have evidence that even in primary generalised epilepsy the hyperexcitability of the cortex is not uniform. The visual cortex of the two

hemispheres can show quite pronounced differences in photoconvulsive threshold. These differences can be observed as differences in the size of patterns in the left and right visual hemifields necessary to elicit epileptiform EEG activity, and as differences in the topography of the EEG response to diffuse intermittent light. Under these circumstances the inhibitory failure would appear to be localised, or at least lateralised to one hemisphere. It is as if the visual cortex of one cerebral hemisphere is more hyperexcitable than that of the other (1,5).

Whether or not a discharge spreads may depend not only on the hyperexcitability of surrounding tissue but on the activity within that tissue. Hughlings Jackson was the first to draw attention to the fact that when an epileptic seizure spreads slowly according to the "march" that now bears his name, the spread can be prevented by sensory stimulation of regions of the body bordering on those affected by the seizure. Presumably the normal activity of neurons in the vicinity of the epileptic activity prevents the recruitment of these neurons into the seizure discharge. What is the basis of this competitive recruitment? I suspect it may have something to do with the effects of synchronisation I mentioned earlier. When neurons are going about their "lawful business" the temporal patterning of their activity will differ from the rhythmic activity characteristic of an epileptic discharge. The refractory period of individual neurons subsequent to firing may mean that when a nerve network is active, and there is little overall temporal coherence, the network is less likely to be recruited into synchronised abnormal activity than when it is relatively quiescent.

In principle, there is no reason why the excitation responsible for the discharges need arise only from sensation. Discharges might arise from the excitation associated with processes that are exclusively cognitive in nature. However, it is only rarely that an association between seizures and thinking will be observed. If the inhibitory failure is widespread and extreme the relationship between normal physiological processes and seizures will not be apparent. There will be too great a diversity of brain activity capable of triggering epileptic discharges. If, however, the inhibitory failure is localised, then only activity within a localised region of cortex will be associated with seizures. It will then become apparent that seizures are associated only with certain types of activity, those that demand the functions for which the hyperexcitable region of cortex is specialised.

Wilkins and co-workers (6) described a patient who suffered seizures induced by a particular type of thought. On investigation, mental activity that involved the spatial manipulation of information in the mind's eye was associated with an increased probability of epileptiform EEG activity. In general the type of thinking that precipitated such activity was that impaired after lesions of the parietal lobes. The patient gave no evidence that parietal function was impaired, but it was as though excessive excitation within this region provoked seizure discharges. Possibly some region of parietal cortex was hyperexcitable, and any excitation within this region that exceeded some critical mass led to a spread of abnormal firing. One important aspect of this patient's problem was not simply the nature of the mental activity, but the effort expended on it. It was when the visuo-spatial thought processes were effortful that seizures discharges were likely.

The effort that cognitive activity involves is extremely hard to quantify, but several operational definitions have been used including (a) pupil diameter, (b) the reaction time to respond to signals that are peripheral to the main task and (c) the efficiency at performing two tasks at once. The latter techniques have also been used to reflect the so-called "working memory system" (7). This system manipulates information and stores the results of intermediate computation. It is thought to be involved in tasks such as reading, reasoning and arithmetic calculation. If a task makes extensive use of working memory it will generally be more effortful than a task that does not, and it is this sense of effort that I would like to consider further. Perhaps there is a neurological correlate of working memory to be found in the extent of physiological excitation that a task involves. This point of view receives a limited support from studies of the cerebral blood flow associated with tasks of different kinds. It may be the tasks that involve the retention of partially processed information that are associated with a global increase in cerebral blood flow: Lassen and co-workers (8) report that such increases in flow tend to be associated with effortful mental activity.

Binnie and co-workers (9,10) have investigated the effects on short-term memory of subclinical EEG discharges. In the course of their investigation they noted that the incidence of discharges was affected by the memory task. The effect of the task varied from one person to another, although discharges were generally more likely to occur when the stimulus material was being presented than at other phases of the task, such as response production. Perhaps the involvement of working

memory was greatest during stimulus presentation. If so, stimulus presentation may have been associated with the greatest physiological excitation. Such an interpretation would be in line with Baddeley's findings on the role of working memory in the learning and recall of material. Baddeley and co-workers (11) have interfered with working memory by giving people subsidiary tasks to perform whilst they attempted to memorise material and subsequently recall it. The subsidiary tasks had their greatest effect during stimulus presentation, suggesting that it was during stimulus presentation that working memory was maximally in use. In this respect it is interesting that it was during stimulus presentation that EEG discharges were most likely to impair performance (9). The impairment was most likely to be observable when the length of the stimulus series was difficult enough to result in about 30 per cent errors. The incidence of discharges was therefore greatest when the resulting cognitive impairment was greatest. Assuming that this is not simply a reflection of the sensitivity of the experimental technique, this result is of some theoretical interest. Perhaps it was only when the physiological excitation was extensive that it was likely to induce a discharge, and it was only when the cognitive activity involved many brain regions that there was a reasonable chance of a localised discharge interfering with the neural substrate of this cognitive activity.

Aarts and co-workers (9) reported that lateralised subclinical discharges had a selective effect on verbal or non-verbal short-term memory as appropriate to the hemisphere involved in the discharge. It would obviously be of interest to know whether the increase in discharge incidence was also selective, and dependent on the hemisphere involved in the discharge. For example, it is conceivable that in patients with a left-temporal focus, the discharges within the left temporal region might be increased in incidence during the presentation of verbal information, and decreased during the presentation of non-verbal information. The argument runs as follows. If the region of hyperexcitable tissue is confined to the left temporal lobe, verbal rather than non-verbal information processing is likely to increase the chances of a critical mass of excitation within that region. The spread of a discharge is likely to be reduced by activation of areas that are not hyperexcitable, such as the right temporal region. Unfortunately, all we know at present is that certain tasks have been associated in some patients with an increased discharge rate, and in others with a decreased discharge rate.

There are implications for the prevention of seizures. The avoidance of precipitating factors is one obvious ploy but there are doubtless many other less obvious techniques that take advantage of competitive recruitment. If a patient suffers seizures that begin with a focal discharge which is accompanied by symptoms that the patient is able to recognise, there may be cognitive strategies that prevent the discharge spreading. Patients could in principle be taught to perform some task that involved excitation within areas of the brain that were not hyperexcitable, although it is perhaps only in a few cases that such tasks could be selected on anything other than a trial-and-error basis. Techniques of this kind have been classified by Mostofsky & Balaschak (12) as "interruption procedures", and although the literature is very sparse, there is limited evidence that these procedures have their place in clinical management (13,14).

I have argued that "massive" firing within the nerve net is an important contributor to epileptogenesis if the region within which the activation is concentrated is hyperexcitable, and that, if the hyperexcitability is not diffuse, activation in non-hyperexcitable areas may prevent the spread of a discharge. With the new imaging techniques that are now available our knowledge of the structural basis for information processing within the brain may improve sufficiently to put these ideas to the test.

This paper is full of speculation, far more so than I would like. If the speculation is to be justified it should lead to predictions that are testable, if not now, then when appropriate techniques become available. I will finish by listing explicitly one of the predictions that can most readily be made and most readily tested:

In patients who exhibit consistently localised focal epileptiform EEG activity, the incidence of these abnormalities should be increased by cognitive activity that involves regions of the brain involved in the focus (e.g. cognitive activity that is, in other patients, impaired after lesions in the region of the focus). The incidence of EEG abnormalities should be decreased by cognitive activity that involves other brain regions.

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