receptors should produce an overall decrease of luminance. We suggest that this luminance decrease, which cannot itself account for reduced contrast sensitivity, causes a sudden decrease in the visual adaptation level. Indeed, recent psychophysical studies with static eyes[6] show that abrupt changes in the adaptation state produce an immediate reduction of sensitivity. This would explain why there is a peak of intra-saccadic suppression near the beginning of the saccade, that is, when acceleration is high. Most importantly, this hypothesis would account for the magno-specific loss of sensitivity. It is well known that retinal contrast gain control is a key characteristic of the magnocellular pathway, whereas it is almost absent in the parvocellular pathway. The temporal contrast created by rapid changes in the adaptation level should therefore saturate magnocellular neurons much more than parvocellular neurons. This would explain why intra-saccadic sensitivity of the magnocellular system is specifically altered and also why 'saccadic suppression' seems to act at a very early level[1].

In summary, current data seem to indicate that the so-called 'saccadic suppression' is an epiphenomenon probably occurring in the retina without any external influence. The mechanism preventing us from perceiving intra-saccadic motion is of a different nature and is still to be found.

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Response: 'Saccadic suppression' – no need for an active extra-retinal mechanism

Castet *et al.* pursue their claim that vision is not actively suppressed at the time of saccades – a claim initially made on the basis of observations showing that saccades made in the direction of moving stimuli can improve the detectability of those stimuli by reducing retinal speed[1]. This can clearly occur, and indeed the results can be well-modelled from the spatio-temporal sensitivity functions of human vision[2]. However, the fact that the suppression does not occur for saccades simulated by mirror-motion[3] suggests a central origin of the suppression. In their letter, Castet *et al.* now consider an alternative explanation, revisiting the old idea[4] that the suppression might be a by-product of mechanical shearing forces during saccades. They suggest that these forces cause the photoreceptors to bend away from the pupil on each saccadic eye movement, resulting in less-efficient wave-guiding of light (the Stiles–Crawford effect[5]), transiently changing the adaptation state of the retina and therefore lowering sensitivity.

This is undoubtedly an interesting idea, but unfortunately encounters some difficulties with much of the existing data on saccadic suppression. For example, it is well known that the Stiles–Crawford effect is unique to cones being virtually absent in rods[5]: yet strong saccadic suppression has been reported in dark-adapted conditions as low as 4×10^{-4} cd/m^2 (Refs 3,6,7). Even more problematic is the observation that in total darkness electrically produced visual phosphenes are strongly suppressed by saccades[8], which cannot be readily attributable to the optical wave-guide properties of photoreceptors.

The theory of Castet *et al.* also encounters difficulties with the specificity of saccadic suppression, which is restricted to low-frequency stimuli[7] that are modulated in luminance[9]. Changes in retinal adaptation would adversely affect all classes of neurones, and therefore affect both the luminance and chromatic response at all spatial frequencies. However, one could consider the effects of a sudden dimming of the whole visual field, an effective luminance flash that might selectively mask luminance-modulated stimuli of low spatial frequencies by acting on the contrast gain control of detectors for these stimuli. Such a flash could account for the specificity of suppression, the fact that it occurs early[9] and its dependency on saccadic size[3]. So the question becomes quantitative: can the bending of photoreceptors create a flash strong enough to produce one log-unit of masking at low spatial frequencies? Presumably the masking flash must be at least one log-unit itself (probably greater) in order to do so. The Stiles–Crawford effect is usually described by a Gaussian function, with a squared space constant (*rho*) of 0.05 (Ref. 10). One log-unit of attenuation would require the receptors to bend by a massive 12.5°, a difficult feat within their tight mosaic packing. The only available measurements of which we are aware[4] suggest that cones might bend by 2° after a 5° saccade, producing only 0.025 log-units of attenuation. Furthermore, although it is true that the maximum shear forces occur at the beginning and at the end of each saccade (when acceleration and deceleration are maximal), the viscous intra-ocular medium will dampen these effects, so the maximal tilt of the photoreceptors will not occur at saccadic onset – where suppression is maximal[3] – but some considerable time later. In short, the suppression predicted by shear forces is too little, too late.

As highlighted by Castet *et al.*, one of the more puzzling aspects of saccadic suppression is that physiological evidence for suppression has been scant and often not observed at all in early visual centres. So one has to ask why this massive luminance signal (from the Stiles–Crawford effect) does not produce a measurable change in neural activity? However, recent evidence suggests that in monkey middle temporal area (MT), the effects are complicated: some cells respond less, others more, whereas some even reverse their direction selectivity around the time of saccades[11]. Such effects are difficult to explain by misaligned photoreceptors.

Finally, a mechanism of this type would introduce a new mystery: if the bending of

photoreceptors were to cause a temporary black-out on each saccade, massive enough to produce an order-of-magnitude of masking, what would prevent awareness of these repeated black-outs? What masks the mask?

Castet *et al.* do, however, reiterate an import point: the transient and incomplete attenuation of sensitivity is not sufficient to explain why the retinal motion of saccades goes unnoticed. There are clearly other mechanisms involved. One of these could be the visual masking suggested by MacKay[12], and these effects might share the same mechanisms as the extra-retinal suppression signals (see Ref. 3). But more subtle processes might also be involved. In our early study[7] we documented qualitative changes that occur during saccades. When a large-field moving grating was jerked abruptly backwards during saccades viewers could see the jerk (though less easily than in normal viewing) but it lacked its usual attention-grabbing salience. Thus, it appears that saccades mute the neural alarm bells that normally sound when there is a sudden, large-scale change in the visual scene. The mechanism remains to be found, but might involve damping of higher neural centres involved with visual attention.

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BDNF and epilepsy – the bad could turn out to be good

In their recent review, Binder and colleagues[1] reviewed data concerning the involvement of brain-derived neurotrophic factor (BDNF) in epileptogenesis. Their main conclusion is that the upregulation of BDNF induced by seizures plays a key role in the development of hyperexcitability, in particular in the hippocampus.

However, we feel that it should be made clear that this description does not reflect the complexity of the system and, in particular, the temporal aspects of its effects. Moreover, data have revealed that BDNF not only enhances hippocampal excitability but primarily plays a role in neuronal plasticity[2]. Therefore, we support a wider concept for the properties of BDNF during epileptogenesis.

Over the past years abundant literature has shown that acute BDNF treatment in both *in vitro* and *in vivo* models induces a clear increase of neuronal excitability, suggesting that BDNF facilitates epileptogenesis. By contrast, we and others have reported that chronic intrahippocampal infusion of BDNF delays kindling development in rats. This effect is long-lasting, and outlasts the end of the infusion period by at least seven days[3–5]. Conversely, infusion of antisense oligodeoxynucleotides that reduce BDNF expression in the hippocampus, accelerates kindling progression[5]. As highlighted by Binder *et al.*, the inhibitory effects of BDNF could be secondary to the downregulation of trkB receptors. However, although chronic application of BDNF in the hippocampus does indeed reduce trkB protein levels[6], sustained phosphorylation of the receptor is observed, suggesting that the downstream transduction pathways of trkB could still be activated[7]. In agreement with this hypothesis, it has been shown that chronic BDNF infusion leads to a prolonged increase of hippocampal neuropeptide Y (NPY) (Ref. 8), the expression of which appears to be regulated by BDNF, presumably via trkB receptor activation. The sustained overexpression of NPY that is induced by BDNF follows a time course similar to that of the effects of BDNF on kindling. Because of the well-described inhibitory effects of NPY on hippocampal excitability[9], we suggest that BDNF delays hippocampal kindling, at least in part, through upregulation of NPY (Ref. 8).

These chronic inhibitory effects of BDNF are, however, compatible with its acute excitatory properties that are well described *in vitro* and *in vivo*. In order to reveal a possible immediate excitatory action of BDNF, we studied the effects of chronic BDNF infusion during 'rapid kindling'. In this paradigm, the hippocampus is electrically stimulated 12 times daily during the first four days (instead of twice daily in classical kindling), allowing for motor seizures to develop within the first three or four days of stimulation[10]. Consistent with the acute excitatory effects of BDNF, we have shown that animals infused with this neurotrophin for seven days develop clonic seizures more rapidly than control animals[5]. However, the facilitation is observed only during the first 48 hours and is followed by a strong and long-lasting suppression of kindling development.

Taken together, these observations support the hypothesis that BDNF exerts biphasic effects. First, the activity-dependent release of BDNF within the hippocampus might potentiate excitatory synaptic transmission. TrkB fusion proteins, which delay kindling development[11], probably act by preventing such mechanisms. Second and on a longer time scale, BDNF overexpression downregulates trkB receptors. However,

