OCCURRENCE OF BAND 3 DELETION AMONG CHILDREN IN THE MADANG AREA OF PAPUA NEW GUINEA

	Cerebral malaria (CM) $n=35$		Uncomplicated malaria (UM) $n=57$		Healthy individuals (HI) $n=103$
Demographics and parasitology					
Mean age in years (s.d.)	4.2 (2.7)	<0.001*	3.5 (1.9)	<0.001†	5.8 (2.1)
Range	1–10		0.8–11		2–11
Area: North (%)	19 (54) in 12 villages	0.20*	35 (61) in 22 villages	0.02†	43 (42) in 11 villages
South (%)	16 (46) in 13 villages		22 (39) in 15 villages		60 (58) in 10 villages
Mean $\log_{10}$ (*P. falciparum* +1) (parasites per μl (s.d.))	4.05 (1.25)	<0.001*	4.09 (0.68)	<0.001†	2.04 (1.71)
Gene frequency and morbidity association					
Band 3 deletion prevalence rate and CI	0% 0–10%		8.8% 3–19%		14.6% 8–23%
Odds ratio, CI and *P* value					
Unadjusted	0 0–0.75	0.01*	0.56 0.15–1.76	0.33	1
Adjusted for age and geographical area	0 0–0.21	<0.001*	0.26 0.06–0.94	0.04	1

Only children living in villages are included. Those living in towns or in suburban areas have different ethnic origins, with known differences in prevalence of the deletion. CM, patients recruited at the Madang General Hospital, defined according to published criteria[10], with a slight modification of the Blantyre coma score[11]. UM, children who attended health facilities in the same areas with a recent history of fever, no other major symptoms or signs, and with a confirmed *P. falciparum* asexual blood stage parasitaemia. HI, children who had not complained of symptoms during the previous week. They were included irrespective of their parasitological status. Deletion in the erythrocyte band 3 gene was determined using polymerase chain reaction (see, for example, ref. 12). The strength of association between the band 3 deletion and disease severity was assessed by comparing the prevalence rate of the red-cell variant gene in CM cases and in HI using Fisher's exact test (two-tailed), and by the exact 95% confidence interval (CI) for the odds ratio. UM and HI were also compared. Adjustment for age and area was made by logistic regression. A quadratic effect of age was fitted because of a significant departure from linearity. Likelihood-based confidence intervals were calculated. * *P* value for CM against HI; † *P* value for UM against HI.

in South-East Asian ovalocytosis is speculative. It is known that ovalocytes are relatively resistant to invasion[5,6] and that they provide some protection against parasitaemia[3]. It seems likely from this study that ovalocytosis might protect against uncomplicated morbidity from malaria to about the same extent as it protects against parasitaemia. Cerebral malaria is a potentially fatal disease, so the frequency of the band 3 deletion in these patients can be taken as an indicator of its selective advantage. We could find no heterozygous individuals among the cerebral malaria cases; ovalocytosis would thus seem to protect from death by malaria.

The view that ovalocytosis is maintained in the population by an advantageous effect operating solely against parasite invasion is questionable. Experimental observations suggest that band 3 deletion plays a specific role in the pathogenesis of cerebral malaria through decreased cytoadherence of infected red cells to cerebral microvessels. This process follows a modification of the band 3 protein in infected red cells and cytoadherence can be blocked in mice with polyclonal antiserum against a polypeptide corresponding to the human band 3 residues 546–553 (ref. 7). Unlike the case of thalassaemic and HbS-containing red cells, previous studies, including samples from the Madang area, have not supported a modifying role of ovalocytic cells on the rosetting ability of red cells[8]. It seems unlikely, therefore, that the protection against cerebral malaria conferred by ovalocytosis in Papua New Guinea operates through the rosetting mechanism.

In screens of around 2,000 subjects (including heterozygous matings) (C.S.M. *et al*, unpublished observations), we have found no individuals homozygous for band 3 deletion. It is thus likely that homozygosity is lethal *in utero*. Ovalocytosis in Papua New Guinea may not be a balanced polymorphism. However, if we assume an equilibrium and that all homozygotes for the band 3 deletion die *in utero*, a prevalence of 15% heterozygosity in the general population, as we have in this study, would imply that 9% of all homozygotes without the gene variant die of malaria before reproduction[9].

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Extrapolation or attention shift?

SIR — Interceptive actions, such as hitting a moving target or catching a ball, need to be adequately timed in order to be successful. Because there is a significant time delay in the transmission of information along the visual pathways, there could be a critical difference between the perceptual and actual position of a moving object. Nijhawan[1] proposed that a moving object is seen closer to its actual physical location, extrapolated from features of the motion, partially compensating for the delay in visual processing.

Most observers report a perceptual misalignment between two sets of aligned dots when one set is in motion (*a* in the figure). Two outer pairs of dots, diametrically opposed to each other, are momentarily flashed in perfect alignment with an inner pair of continuously rotating dots. The moving dots, which are generally seen ahead of the flashing dots, would have their position, according to Nijhawan[1], perceptually extrapolated by about 80 ms.

We interpret this effect as resulting from a longer time delay involved in the visual processing of the flashing dots, rather than an extrapolation of the moving dots. In a series of experiments to investigate attentional mechanisms, we found a clear dependence of this effect on the location of the flashing dots. The magnitude of the perceived misalignment increased as the flashing dots were moved away from the fixation point (*b* in the figure).

In further, but still preliminary, experiments with two other observers, using a similar set-up, we also examined the case in which the positions of the flashing and moving dots were switched, as well as the the original experiment. In all situations, the moving dots were perceived as located ahead of the flashing dots. However, in the switched version of the experiment, the mean angle of perceived misalignment showed a much smaller, or no, dependence on the location of the moving (outer) dots. Furthermore, its magnitude was comparable to those obtained when the flashing (outer) dots were closer to the

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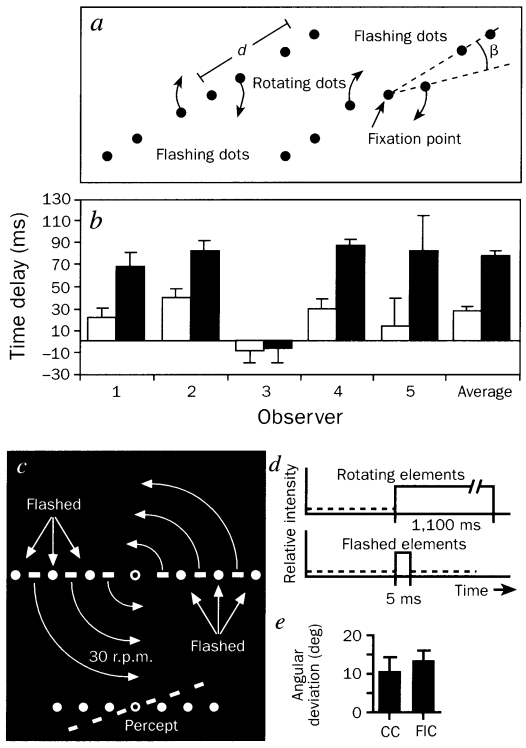

Experimental design and results of: *a, b*, Baldo and Klein, and *c–e*, Khurana and Nijhawan. *a, Left*, the stimulus, a pair of dots 1.3° apart in the visual field, rotating at 25 r.p.m. about a central dot (fixation point). Two pairs of dots were flashed in perfect alignment with the central and rotating dots. Distances, *d*, from the central dot to the midpoint between each pair of flashing dots, used in our tests, were 1.45° and 4.74°. *Right*, The situation as reported by most observers: the rotating dots are seen ahead of the flashing dots. The perceived misalignment, β, was assessed by letting the observer adjust the flashing dots until they appeared in alignment. *b*, The misalignment as a time delay and the mean time delay from five naive observers measured at two different distances (data averaged over all observers and weighted by inverse variance). Two other observers, under a similar experimental set-up, offered similar results concerning the original experiment (average time delays: 33 ± 9 ms and 83 ± 7 ms for closer and farther flashing (outer) dots, respectively). A switched version of the experiment was also used where the outer dots moved and the inner dots flashed. The perceptual effect was qualitatively the same, but the strong dependence on the location of the outer (moving) dots was not observed (average misalignment: 24 ±14 ms and 19 ± 9 ms for the closer and farther locations, respectively). These values are comparable to those found in the original experiment, when the flashing (outer) dots were closer to the fixation point. ❑, 1.45°; ■, 4.74°. *c*, The observer fixated the central dot while attentively tracking[6] a line (length = 6.9°) composed of 6 rectangles rotating at 30 r.p.m. A horizontal line (length = 7.8°), composed of 6 circles interleaving the rotating line, was flashed for 5 ms. Observers reported the perceived relative positions of the two lines by varying the angle between two adjustable lines. A strong flash-lag effect was reported (percept). *d*, The intensity profiles of the rotating and flashed elements as a function of time in the FIC condition. *e*, Of 10 observers, 5 viewed the FIC condition first and the complete cycle (CC) second; the order was reversed for the remaining five. A paired *t*-test showed no significant difference between the angle means for the CC and FIC conditions; mean FIC − mean CC = 2.8, $t(9) = 1.70$, $P > 0.10$. The average ($n = 10$) angular deviations for the CC and FIC conditions yield time delays of 58.61 and 74.17 ms, respectively.

fixation point in the original experiment (see figure legend).

These findings support the idea that the perceptual effect is mainly involved in the location of the flashing dots in the visual field. We hypothesize that some amount of time, dependent on eccentricity, is required to bring the flashing dots to a sufficiently high level of sensory awareness for a 'snapshot' of the moving dots to be taken. Such a time delay would be related to the abrupt onset of the flashing dots and might involve attentional mechanisms, either in capturing attention[2] or in shifting the focus of attention from one place to another across the visual field[3,4].

Purely sensorial mechanisms, operating preattentively and depending on eccentricity, cannot yet be discarded. More experiments are needed to distinguish between these possibilities, but we believe that an attentional hypothesis should be examined further.

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KHURANA AND NIJHAWAN REPLY — Baldo and Klein's hypothesis involves the 'shift' or 'capture' of attention from moving elements to flashed elements of abrupt onset. We used two experimental manipulations to distinguish between this and the hypothesis that the lag of predictably moving objects is 'corrected' by the visual system through extrapolation[1], or through some form of neural facilitation applied along the inferred trajectory of moving objects. Neural responses for inferred motion, where an explicit motion signal from the retina is absent, have been observed[5]. Flashed objects, on the other hand, are unpredictable and subject to expected neural delays, which cause their apparent lag.

We addressed the 'attention shift' hypothesis by spatially interleaving the moving and flashed elements. In this condition, observers attentively tracked[6] a rotating line composed of six rectangles. A horizontal line composed of six circles was flashed for 5 ms (*c* in the figure). As the flashed elements occupy the spaces between the attended rotating elements, attention shifts should be negligible and the flash-lag effect should not be observed. However, this display produced a strong effect (*e* in the figure).

Delays due to 'attention capture' were tested by the abrupt onset of both the moving and flashed elements. The display was modified such that the flashed and rotating elements came on simultaneously for 5 and 1,100 ms, respectively. In this 'flash-initiated' cycle (FIC), the rotating and flashed elements have an equally abrupt onset (*d* in the figure), and thus both capture attention equivalently. If delays due to attention capture cause the effect, then none should be observed in this condition. The effect we found, however, did not significantly differ in strength from that observed in the 'complete' cycle (*e* in the figure). When flashed and moving objects are equated in terms of the shift-time or capture-time of attention, observers continue to report the flash-lag effect.

We explain the FIC results on the basis of parallel processing in the visual system[7,8]. The neural processing of both the rotating and the flashed lines begins simultaneously, but the observer does not perceive either stimulus for approximately 100 ms (ref. 9). During this time, the retinal image of the line rotating at 30 r.p.m. has moved through 18°, triggering a motion signal in the magnocellular stream. We suggest that lag-correction, which probably occurs in the fast magnocellular stream, is implemented within that period. The correction process is complete within the time window required for neural signals to yield visual awareness, and before the onset of attentional processing[10].

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