caused by fork collisions can be dealt with by the traditional DNA damage checkpoint. In summary, the data provide compelling evidence that cells attenuate DNA replication during periods of heightened transcription to avoid genomic catastrophes.

Mrc1 is not only required for replication fork progression but also for amplification of checkpoint signaling during replicative stress, for example when deoxyribonucleotides are depleted by hydroxyurea (HU) [9,13]. Specifically, Mrc1 serves to amplify checkpoint signaling by the Rad53 kinase, which involves Mrc1 phosphorylation by Rad53. Importantly, the Rad53 and Hog1 phosphorylation sites in Mrc1 are distinct, and the *mrc1*^{3A} allele supports normal checkpoint signaling and cell survival during replication stress. Thus, Mrc1 participates in distinct osmostress and replication stress pathways, governed by Hog1 and Rad53, respectively.

The study raises numerous interesting questions. One concerns the mechanism of how Mrc1 phosphorylation prevents replication initiation. Previous results suggest that assembly of the Cdc45, Mcm2-7, GINS (CMG) replicative helicase complex is required for recruitment of Mrc1 and Pol ε to the replisome [14,15], whereas Mrc1 is not normally required for recruitment of Cdc45 [16]. In this light, it is surprising that Hog1-phosphorylated Mrc1 binds origins and delays loading of Cdc45 and Pol ε [2]. The data imply that osmostress converts Mrc1 into a dominant negative inhibitor that binds pre-RCs and prevents loading of Cdc45 and Pol ε. A possible precedent for Mrc1 functioning as an inhibitor is seen in fission yeast, where deletion of Mrc1 enhances replication initiation efficiency at some origins and where Mrc1 can bind origins independently of Cdc45 [17]. In the future, it will be interesting to explore the mechanistic basis of how Mrc1 inhibits origin firing under different conditions. An interesting point is that slowing down replication forks should increase rather than decrease the probability that an RNA polymerase encounters a replication fork. Perhaps Mrc1 phosphorylation not only slows, but also stabilizes the fork in the event of collision with RNA polymerase.

Another pressing question is whether the conclusions of this study apply to metazoans. In support of this notion, high osmolarity and other stresses promote phosphorylation of the MCM2-7 loading factor Cdt1 by the mammalian SAPKs p38 and JNK, thereby inhibiting origin licensing [18,19]. Whether post-licensing events of origin firing and fork progression are also inhibited, and whether this avoids clashes with transcription, remains to be tested. Based on the findings by Duch *et al.*, it seems likely that cells will use many creative strategies to manage the conflict between replication and transcription.

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Causality: Perceiving the Causes of Visual Events

Adapting to visual collisions increases the tendency to see the colliding objects as sliding over one another, rather than as one 'launching' another, but only in the adapted retinal location. This demonstrates a low-level perceptual component to the interpretation of the causes of visual events.

Alan Johnston

Imagine a billiard ball rolling directly towards another: it makes contact, stops and then the other ball rolls forwards. Naturally, we see a collision and have the impression that the first ball caused the second to move.

The philosopher David Hume [1,2], however, proposed that we could not deduce the action of the second ball from only knowing about the first. Many alternative scenarios are possible. Hume reasoned that our impression that the one ball caused the action of the other must come from induction. By induction we conclude all swans are white because all swans we have ever seen are white. Hume thought seeing many examples of one ball hitting another allowed us to relate cause to the effect. As they reported recently in *Current Biology*, however, Rolfs *et al.* [3] have found that adaptation to collisions can actually reduce the impression of one object 'launching' another, and that this only occurs for the adapted region of the visual field, providing evidence for a perceptual component to the interpretation of launching as a causal interaction.

Michotte [4] took Hume's scenario and studied it by varying the spatiotemporal parameters of 'launching', while asking subjects to report their impressions of whether one ball caused the action of the other. Because he found that the detailed spatiotemporal properties of the display had a systematic effect on the perception of launching, he viewed the causal impression as perceptual rather than consciously inferred [5]. However, Michotte relied on subjective reports.

In their new work, Rolfs *et al.* [3] exploited a modification to Michotte's launch display which provides for a gradual transition between causal and non-causal percepts. If the first ball in the launching paradigm continues after first contact, covering the second ball before it moves off, then it appears to pass over rather than launch the second ball. Rolfs *et al.* [3] varied the amount of coverage from trial to trial and recorded the percentage of trials on which subjects reported the passing percept. Passing increased systematically with overlap. After viewing multiple instances of collisions, however, the tendency to see passing for any particular degree of overlap increased. Therefore, viewing collisions reduced the tendency of subjects to see a collision in a partly ambiguous display. A crucial observation was that the effect of adaptation only occurred when the test stimuli were presented in the same retinal location as the adaptor; no change in responding occurred for test events located at another retinal location. If the adaptation altered expectations in a more cognitive non-spatial system used for inferring causal relations, then there would be no reason for the adaptation to be space-specific.

Rolfs *et al.* [3] went further. The adaption may be localised to the same position relative to the point of fixation (a retinotopic frame of reference) or in the same spatial location on the screen (a spatiotopic frame of reference). The authors separated these alternatives by shifting the point of fixation between adaptation and test. They found the adaption effect was completely retinotopic, allowing them to conclude that the adaptation must be occurring somewhere within the retinotopically mapped peripheral or cortical visual system. This is strong evidence that the effect is perceptual, rather than the result of conscious inference or anchoring [6]. In the case of anchoring, the observers might simply be reporting how different the test stimulus appeared in comparison to the just previously seen adaptor.

Rolfs *et al.*'s [3] results take us away from the simple cataloguing of conditions for perceived causality, because now perceptual causality can be manipulated by altering the adaptive state of the visual system. We do, however, need to consider what is being adapted. Clearly the localised spatial region is not being desensitised to causality in the most general sense, as there is no evidence that any other causal attribution at that spatial location would be affected by collision adaptation.

Timing is an important determiner of causal relationships. We know that perceived duration [7] and timing [8] can be altered at specific retinotopic locations after motion adaptation and that adaptation to temporal offsets can alter audiovisual timing [9]. If adaptation altered the spatiotemporal characteristic of the collision, this could have a knock on effect on the tendency to see launching or passing over. Many low-level properties of the stimulus giving rise to the pass percept are similar to those inducing the collision percept, and Rolfs *et al.* [3] found no effect of adapting to passing over, suggesting low-level adaptation is not a key factor, but we should note the passing over adaptor and the collision adaptor are necessarily physically different. In a supplemental experiment, Rolfs *et al.* [3] measured the proportion of launching as a function of the temporal delay between the first stimulus stopping and the second moving: there was no clear temporal shift in the function after adaptation, although there was a reduction in launching, suggesting that timing is not affected in this paradigm.

Hume pointed out that temporal coincidence was not enough to relate two events, we also require a necessary connection, which means the cause has the power to deliver the effect. One aspect of necessary connection is the notion of contingency. Contingency can be reduced if events sometimes occur without the cause and sometimes the cause does not generate the effect. This was studied by Schlottman and Shanks [10], who showed that the experience of colour changes in the second stimulus which reliably indicated whether it moved or not did not appear to alter the quality of the launch percept, supporting the view that launching was perceptual rather than a consequence of cognitive inference. Interestingly, adapting to passing over, in which the cause did not deliver the effect, had little influence.

Adaptation may alter some perceived property of the objects involved rather than acting on the perception of causality directly. In a very general sense, perception refers to the processes by which we encode the causes of the dynamic visual images impinging on our retinae. When looking at a statue we effortlessly become aware of the three-dimensional shape of the form, the colour of the material, the direction of the illumination and where we are in relationship to the object. We do this even though each of those physical causes combine to determine the brightness of the image at any given point. Much of what is often referred to as mid-level vision is concerned with studying how we unravel the causes of the image — the inverse problem [11].

The behaviour of objects can also allow us to perceive aspects of their physical nature. Uniform motion implies rigidity. The wobble of jelly implies compliance. The gloop of honey implies viscosity. The relative speeds before and after a collision can influence the perception of relative mass [12]. Rolfs *et al.* [3] consider adaptation changes the tendency to

infer transfer of motion from one object to another — a transfer of the object property of momentum. This implies adaptation of a perceptual relationship rather than an adaptation of an object property *per se*. But if that inference is derived from experience (induction), even at a perceptual level as advocated by Helmholtz and Southall [13], it is not clear why repeated evidence of collisions should undermine it. Furthermore, object properties, and presumably their relations, are properly tied to objects rather than spatial locations. A full explanation of causal adaptation will need to outline what type of retinotopically specified representation is altered in the neural pathway between the stimulus and the ensuing percept. Nevertheless, this new paradigm offers a way to study the perception of causality through adaptation, opening up many new avenues of investigation.

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Neural Odometry: The Discrete Charm of the Entorhinal Cortex

A recent study finds that the grid reference system in entorhinal cortex, used for computing distances during self-localization, has a discretized and modular organization. This has implications both for how the system develops and also for how it functions.

Kathryn J. Jeffery

In order for a map to work it needs a metric grid reference (Figure 1A): this has turned out to be just as true for the brain as for a mariner's chart. The brain's map grid reference is located in the entorhinal cortex, in which it was recently discovered that neurons are tuned to a combination of distances and directions [1]. The result of this tuning is one of the most striking patterns observed in neurobiology: the hexagonal polka-dot pattern formed from patches of activity (or 'firing fields') laid down by the cells as the animal moves around the environment (Figure 1B,C). This pattern has led to the name 'grid cells' for these neurons, and they are thought to serve as a distance-measuring device (like a car's odometer) for the navigation system.

Grid cells are hard to find and record, and so initial studies were only able to sample a few at a time. These early studies observed that the scale of grids (the distance between the firing fields; Figure 2A green bars) increases steadily from the dorsal-most to ventral-most regions of entorhinal cortex [1,2], providing capacity for the brain to represent spaces of different sizes. These studies also seemed to find that the orientation of the grids was coherent across the whole population for a given animal in a given environment, leading to the conclusion that the system acts as an integrated whole. Now, Stensola *et al.* [3] have used an improved method of neuronal recording that allows the sampling of many neurons at once (186 in their best ensemble), and found that, rather than acting as a single integrated unit, the cells appear to be organized in a modular fashion, with the modules behaving quasi-independently. This surprising result constrains not only our models of how the system wires up in the first place, but also of how it operates in adulthood.

This modularity finds expression in a number of ways. First, the increase in the scale of the grids from dorsal to ventral entorhinal cortex is not continuous but, surprisingly, discrete. A hint of this was first reported by Barry *et al.* [4] after recording small numbers of grid cells at a time, and Stensola *et al.* [3] have confirmed this with their large data set. Although absolute grid scale was evenly distributed across animals, the ratio between the scale of one set of grid cells (one module) and the next appears similar across scales and also across animals, at around 1.42, though there is considerable variation. Although these discretized scales increase from dorsal to ventral entorhinal cortex, there is overlap, such that a given dorso-ventral level contains cells expressing grids of more than one scale. All in all, there seem to be four or five of these scale modules in a given animal, although more may be revealed with further study of the most ventral regions (not sampled in this experiment).

A second kind of modularity was observed in the orientations of the grids, which are evidently not coherent, as first thought, but which also appear to vary discretely. Since orientation is thought to be conveyed by a class of compass-like neurons known as head direction cells [5], this suggests that the connection between a given grid cell and the head direction system is partly informed by the local network architecture and is not entirely random.