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Perception: Transient Disruptions to Neural Space–Time

How vision operates efficiently in the face of continuous shifts of gaze remains poorly understood. Recent studies show that saccades cause dramatic, but transient, changes in the spatial and also temporal tuning of cells in many visual areas, which may underly the perceptual compression of space and time, and serve to counteract the effects of the saccades and maintain visual stability.

David Burr[1] and Concetta Morrone[2]

It has long been known that saccades, the fast ballistic eye-movements that periodically reposition gaze on items of interest, present hefty challenges to the visual system. It somehow manages to annul these brisk movements from the retinal images in order to perceive a stable world [1]. Psychophysical studies show that spatial vision is grossly distorted at the time of saccades, resulting in a severe but transient compression of the spatial metric [2]: visual stimuli are seen to be much closer to each other than they actually are. Perhaps even more mysterious is the recent observation that time is also compressed around the time of saccades [3], so pairs of brief stimuli separated by 100 milliseconds are seen to be separated by only 50 milliseconds. The timecourse for temporal and spatial compression is very similar, suggesting that they are both manifestations of the same phenomena.

Ibbotson and colleagues [4,5] have recently reported that in cortical areas MT and MST of the macaque monkey, cells respond to visual motion generated by saccades sweeping over stationary texture with considerably shorter latency than they do to texture moving at comparable speeds during fixation: on average 30 milliseconds for saccade-elicited motion compared with 67 milliseconds during fixation (Figure 1). Interestingly, the shortening of latencies follows a different pattern in the two areas: in MST latencies halve during saccades, while in MT they seem to be all flattened to about 30 milliseconds, irrespective of the latency in normal viewing. In this issue of *Current Biology*, Ibbotson *et al.* [6] suggest that these changes in latency could underlie the psychophysically observed temporal compression. This idea is not unreasonable, as previous studies in macaque [7] have shown that areas MT and MST are strongly implicated in encoding of spatial position, and that their spatial code 'collapses' around the time of saccades, making these areas likely neural substrates for spatial compression.

It is clear that a reduction in latency could cause compression of time during some intervals. If the first stimulus were presented before the saccade, it would arrive in MT cells some 67 milliseconds later; but if the second bar, presented 100 ms after the first, were to occur near the saccade, it should have a shorter latency and arrive only 30 milliseconds later, 130 milliseconds after the presentation of the first bar: a difference of 63 rather than 100 milliseconds. The changes in latencies may also explain a particularly uncanny aspect of data our group has reported [3], the apparent inversion of temporal order at some specific conditions: if the second stimulus were subjected to shorter latencies than the first, it could well overtake it and be seen to arrive first. Indeed this would make good sense, as the psychophysically observed temporal inversion occurred only for stimuli presented within a very specific time window (60–80 milliseconds before saccadic onset), a tight range where it is feasible that the second but not the first may be subjected to peri-saccadic acceleration.

Ibbotson *et al.*'s [6] data are also consistent with another counterintuitive finding: that the precision for judging duration is better during saccades than during fixation. As Figure 1 shows, average response latencies of MT neurons are not only shorter during saccades than fixation, but the spread of latencies is considerably less, particularly for MT cells (reflected by the standard deviations, and by inspection of the scattergram). If these signals were used to judge duration, the decreased variability in the population should lead to the increased precision observed psychophysically.

Although the reduced latencies provide a good qualitative description for the effects of saccades on time perception, they fail quantitatively. While the temporal inversion occurred only at very specific times relative to saccade onset, strong (two-fold) compression of time occurred for a period of over 300 milliseconds, extending well before saccadic onset to well after its completion. As the stimulus pairs were separated by only

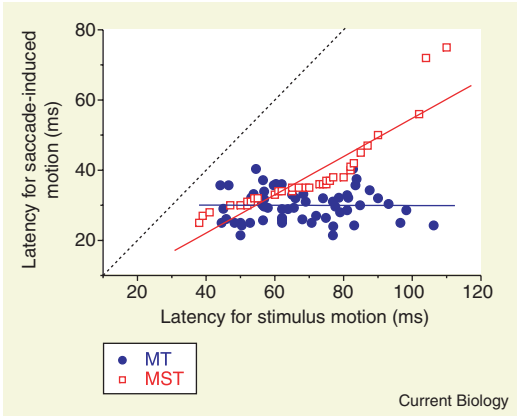

Figure 1. Response latencies of MT and MST cells to motion elicited by a monkey making a saccade across a textured field, against the response latency to the same motion played back while the monkey fixated.

All latencies are greatly reduced during saccade viewing, without a single cell showing a longer latency during saccades than fixation. The green and red lines show the regressions for the two types of cell: for MT the latencies were completely uncorrelated; for MST they were well correlated (r = 0.9), with a slope of 0.5, suggesting a halving of latencies during saccades. Not only were the latencies reduced on average, the spread was far less during saccades, particularly for MT. For MT cells the standard deviation in saccade condition was 4.5 ms, compared with 15 ms during fixation. For MST the standard deviations were, respectively, 11 and 18 ms.

100 milliseconds, it is not conceivable that over all this period the second of the pairs had a saccade-induced reduced latency, while the first did not. Furthermore, as Ibbotson *et al.* [6] observe, the same latency argument should lead to an expansion of time for stimuli presented towards the end of the saccade, of the same magnitude and duration: the first becomes accelerated with respect to the second, so the gap increases. Although the psychophysical data do show the slightest hint of expansion for late stimuli, this is nowhere near as great as the compression.

Thus, while the reduced latencies may well represent a partial explanation for compression of time during saccades, they are far from the whole story. Perhaps this is not surprising, as neural latencies have not in the past proven particularly successful in explaining temporal phenomena, neither the flash-lag effect [8] nor perceived temporal asynchrony of different attributes [9] (see, for example, [10,11]). Indeed, time perception in general is not well understood. Do we sense the passage of time directly, or is it derived from sensing events that occur over time? Is there a central clock, or do we rely on local and potentially asynchronous mechanisms? One fact that is beginning to emerge is that for short, subsecond intervals, time and space are not completely independent for the brain, but are tightly linked [12].

The neurophysiological effects of saccades on the spatial properties of receptive fields have been extensively studied. In many extrastriate areas, including LIP (known to be important in judging duration [13]), V3A and FEF, receptive fields are dramatically modified before and during saccades [14,15]. They shift in anticipation of the saccade, and in doing so, may expand transiently during the period that neurons respond to both the pre-saccadic and post-saccadic location [15]. The expansion of the receptive fields is an obvious candidate for the neural substrate of transient spatial compression, as all stimuli flashed within the expanded field will be seen in the same position. Changes in the temporal properties of the receptive fields at the time of saccades have not been studied extensively.

However, the fact that the latencies of neurones in areas such as MT and MST become shorter [4,5] implies that saccades cause changes in temporal dynamics. Indeed, in all cells in areas V3A and FEF that remap their receptive fields at the time of saccades, their remapped response is faster than that during fixation [15]. These changes in latency may be symptomatic of far more complex changes in the cells spatio-temporal tuning. For example, they may become transiently oriented in space-time, consistent with evidence that MT motion direction tuning can invert during saccades [16]. By analogy to the mechanisms that perceive objects veridically while they are in motion [17], this transient spatio-temporal tuning may serve to effectively annul the effects of the saccade, maintaining stability. In doing so, these cells may transiently generate the bizarre spatial and temporal phenomena at the moment of saccades, normally not perceived in continuous viewing.

Coping with saccades is not easy for the visual system. Retinal information must be continually updated with the new eye coordinates on-line, within 100 milliseconds at most. This updating is achieved by drastic remapping of receptive fields of neurones in various cortical areas, with exquisite efficiency. Given that there exists a limit for the speed of transmission of neural information, it is feasible that this rapid rearrangement introduces dramatic transient deformations in spatio-temporal receptive field organisation, similar to those that occur in physical systems approaching the maximum speed of information transmission [18].

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Transcription: Adjusting to Adversity by Regulating RNA Polymerase

Under growth-limiting conditions, budding yeast shut down transcription of genes of the translation apparatus. Recent studies have shown that this response is signaled, in part, by multiple pathways that converge on Maf1, leading to a change of this protein's phosphorylation state and its relocation to the nucleus, where it represses RNA polymerase III.

E. Peter Geiduschek and George A. Kassavetis

Actively dividing cells dedicate about three-quarters of their nuclear transcription to producing the RNAs of the translation machinery. RNA polymerase (pol) III, which makes 5S ribosomal RNA, precursor tRNAs and a handful of other small RNAs, is responsible for about 10–15% of the nucleoside triphosphate consumption by nuclear transcription. The high (free) energy cost of this activity provides a powerful selective advantage to being able to coordinate pol III (and pol I) activity with cell growth. For free-living microorganisms this means that pol III activity must respond to changes in the environment that are signaled through diverse pathways [1].

In 2002, Ian Willis and colleagues [2] showed that, in the budding yeast *Saccharomyces cerevisiae*, multiple signaling pathways converge on a single protein, Maf1, the key negative regulator of pol III transcription. Maf1 proteins are ubiquitous in the eukaryotes; they have three relatively conserved segments that have not been found in any other proteins. No structure has yet been determined for a Maf1 protein; *S. cerevisiae* Maf1, with 395 amino acids, is somewhat larger than others. Three recent papers [3–5] greatly advance our understanding of the mode of action of Maf1 and put the key puzzles about its mechanism of action into sharp focus.

The *MAF1* gene was originally identified in a yeast screen for mutations affecting the efficiency of action of a nonsense suppressor tRNA: a nonsense mutation truncating Maf1 greatly diminished suppression and was shown also to confer temperature sensitivity for growth on glycerol as the sole carbon source. (Both phenotypes are handy for genetic analysis but their physiological and mechanistic relation to what follows remains obscure.) Overexpression of a fragment of the largest pol III subunit, Rpc160, suppressed these phenotypes, indicative of a *genetic* interaction between Maf1 and pol III [6].

The new research connecting Maf1 with the regulation of pol III transcription started with a four-laboratory collaboration which showed that certain *RPC160* mutations also suppress the above-mentioned *maf1* mutant phenotypes, and obtained evidence for a *physical* Maf1–pol III interaction. Cells with tagged *RPC160* and *MAF1* genes yielded extracts in which modest fractions of Rpc160 and Maf1 were found to co-immunoprecipitate. Deleting *MAF1* was also found to elevate cellular levels of mature tRNAs considerably, and crude extracts from these cells were found to be more active for all pol III transcription than the corresponding wild-type cells [7].

Shortly thereafter, it was shown that cells lacking Maf1 do not repress pol III transcription in response to genotoxic stress, treatment with chlorpromazine (generating membrane stress, as would secretory defects) or rapamycin (mimicking nutrient limitation), or after undergoing the transition to stationary phase. It was concluded that the separate signaling pathways communicating these stresses to the pol III transcription machinery converge on Maf1 [2].

Fast forward to 2006 and the most recent work that is the principal motivation for this dispatch. This work has clarified a number of important points about Maf1. It is a phosphoprotein with six consensus protein kinase A (PKA) phosphorylation sites and two nuclear localization signals, one of which overlaps two PKA sites. Maf1 is predominantly cytoplasmic in actively growing cells [3,4] but further analysis [5] has shown that there is also considerable nuclear accumulation under these conditions. When cells are shifted to conditions that lead to repression of pol III