effective delivery of a miRNA-targeted agent to tumor cells *in vivo*. Moreover, it would most likely be necessary to identify, prior to treatment with such an agent, those tumors demonstrating a strict dependency on miR-21. Despite the relatively broad overexpression of miR-21 in various cancers [11], it seems unlikely that all, or even most, tumors that overexpress miR-21 would demonstrate significant regression following miR-21 inactivation. Therefore, a more extensive analysis of miR-21 addiction in a large panel of cancer cell lines and mouse tumor models would be of considerable value in initially assessing the scope of miR-21 dependency across the cancer landscape. Such an analysis should also provide some perspective on the therapeutic index one would anticipate in the context of therapeutic targeting of miR-21. In this regard, it will also be of interest to determine the potential consequences of miR-21 disruption in normal tissues, which has not been reported thus far.

In light of the technical challenges associated with the direct targeting of miR-21, it may also be useful to identify the critical gene target(s) of miR-21 that mediate its oncogenic function, as one or more of these may constitute more pharmacologically tractable targets. Given that miR-21 has been shown to have multiple putative gene targets [10,15,16], functional validation studies will be required to address this potentially complex issue. However, since miRNAs generally promote the repression of gene expression, and it is therefore not surprising to find that many of the established targets of oncomiRs are in fact tumor suppressor genes [15,19,20], it may prove difficult to identify 'druggable' oncomiR-regulated targets.

In sum, these new findings by Medina *et al.* [7] add yet another dimension to the oncogene addiction phenomenon. The possibility of targeting specific miRNAs required to maintain tumor cell survival as a therapeutic strategy is provocative, but is certainly a challenging prospect from a drug development and delivery standpoint. Future efforts will undoubtedly be required to establish the broader significance of oncomiR addiction, to identify the most relevant miRNAs in specific tumor indications, to establish the mechanisms by which miRNA overepression contributes to the maintenance of tumor cell viability, and to develop therapeutic strategies to inactivate specific miRNAs. And these are just the little things…

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Visual Perception: Ambiguity Involving Parietal Cortex

Our brain is constantly interpreting ambiguous sensory input to deliver a stable perceptual representation of the environment. Two new studies suggest that superior parietal cortex plays a causal role in resolving perceptual ambiguity. Ironically, their results are somewhat ambiguous as to what that role might be.

Colin W.G. Clifford

It is easy to underestimate the complexity of the visual processing required to make sense of the world around us. It was arguably only when the pioneers of artificial intelligence started trying to program computers to see that the true magnitude of the task of vision became widely

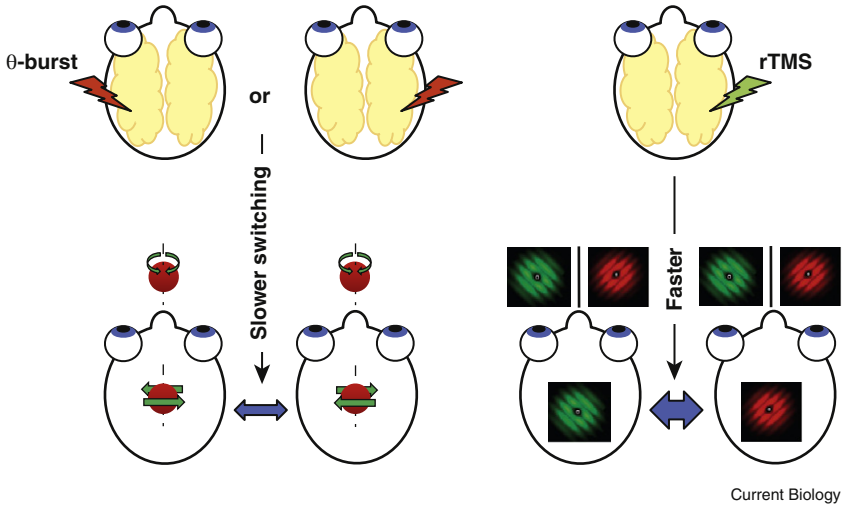

Figure 1. Effects of TMS on the perception of bistable stimuli.

Theta-burst stimulation for 40 seconds over either the left or right superior parietal lobe slowed the rate of alternation between perceived directions of ambiguous structure-from-motion [3]. In contrast, 30 minutes of rTMS over the right superior parietal lobe speeded switching in binocular rivalry [4].

appreciated [1]. Rather than passively processing the retinal image, our brain actively generates and tests predictions about the source of its sensory input [2]. Two studies published in this issue of *Current Biology* [3,4] implicate a particular part of the brain's parietal lobe as playing a causal role in resolving ambiguous visual information.

To study how our brain goes about organizing our visual input it would be useful to keep the stimulus constant and monitor the effects of the organizational processes in isolation. Fortunately, there are certain bistable visual stimuli that allow us to do just that. For example, we perceive only one of two dissimilar images presented one to each eye; the other is initially suppressed from awareness but, as we continue viewing, our perception alternates between the images. This phenomenon is termed binocular rivalry [5,6]. A second example is ambiguous structure-from-motion, whereby a set of dots each oscillating in position about a common axis gives rise to the perception of a three-dimensional shape rotating in depth [7]: the ambiguity is in the direction of rotation, which is perceived to alternate over time. The dynamics of perceptual alternations are qualitatively similar between individuals and across different types of stimulus [8], apparently characteristic of endogenous neural processes continually trying to resolve conflicting sensory input. Quantitatively, however, the rate of perceptual switching varies markedly from person to person [9].

Kanai and colleagues [3] exploited this inter-individual variability to localize the neural mechanisms underlying perceptual alternation in ambiguous structure-from-motion. The researchers measured the perceptual alternation rate in a cohort of 52 subjects for whom they had detailed neuroanatomical data. In this way they were able to identify parts of the brain whose structural variation correlated with the behavioural data. Three structural measures — grey matter thickness, grey matter density and white matter integrity — consistently implicated the superior parietal lobe (SPL) as a region involved in perceptual switching. Specifically, the rate of a subject's perceptual switching correlated positively with the thickness and density of the grey matter and the integrity of the white matter in the SPL of his or her brain. To validate these findings, the researchers then conducted an experiment in which they used transcranial magnetic stimulation (TMS) to disrupt the function of the SPL in eight new subjects. They found that 40 seconds of theta-burst stimulation over the SPL of either hemisphere was sufficient to induce significant slowing in the rate of perceptual alternation.

The other new study also reports an effect of TMS to the SPL on the rate of switching between bistable percepts: Carmel and colleagues [4] found that 30 minutes of repetitive TMS (rTMS) over the right SPL significantly increased the rate of subsequent perceptual alternation. No significant effect of stimulating left SPL was observed. Although both papers report significant effects of TMS to right SPL on the subsequent perception of bistable stimuli, the effects are in opposite directions: Kanai *et al.* [3] found that TMS slows perceptual switching, whereas Carmel *et al.* [4] report that the alternations are more frequent (Figure 1).

It is possible that the key difference between the studies lies in the brain stimulation protocols. Theta-burst TMS and rTMS have both been shown to depress cortical function [10,11], but further research is required to understand their effects more fully. The procedures for localising the SPL also differed somewhat, but there is no clear evidence that they were stimulating anatomically distinct sites. And it seems unlikely that the difference could be due to the use of ambiguous structure-from-motion *versus* binocular rivalry. Previous studies have suggested that patterns of neural activation in the early visual areas may be more reliable in predicting perceptual state during binocular rivalry than for ambiguous structure-from-motion [12,13]. However, both are susceptible to effects of attention and voluntary control [14] — functions commonly associated with parietal cortex [15].

The results of the two studies [3,4] might thus appear hard to reconcile. However, dynamical models of bistable perception are invariably non-linear, involving a balance of excitatory and inhibitory interactions between competing neural representations [16], so perhaps we should not be surprised if even subtle differences in the way that neural interactions are perturbed can produce qualitatively distinct perceptual outcomes. That stimulation of the SPL can affect the rate of subsequent perceptual alternations — albeit in either direction — marks it as a promising site to target in future investigations.

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