was sufficient to dominantly suppress Wld^S-mediated axonal protection [4]. Both studies therefore showed that expression of Nmnat or Wld^S proteins failed to protect axons after injury when Miro or Milton function was compromised, indicating that the presence of mitochondria in the axon is required for Nmnat/Wld^s-mediated axonal protection (Figure 1). However, as it is unclear whether the transport of other organelles and proteins is also disrupted with decreased Miro/Milton function, it will be critical to differentiate whether the loss of Wld^S protection is due to decreased mitochondrial numbers and function in the axon, or simply to decreased transport or expression of the Wld^S protein in the axon.

The two reports together demonstrate that Wld^S/Nmnat activity enhances mitochondrial motility and Ca^{2+} buffering and that the mitochondrion is an organelle necessary for Wld^S/Nmnat-mediated axonal protection. The processes regulating axon degeneration and the Wld^S/Nmnat enzymatic activities that are critical for axonal protection thus converge at axonal mitochondria. A clear future direction is to address whether directly enhancing these mitochondrial functions is sufficient to exert axonal protection. Moreover, identifying whether known enzymatic metabolites of the Wld^S/Nmnat proteins, such as NAD^+, interact with molecules in the mitochondria will be instrumental in understanding the full downstream mechanisms of Wld^S/Nmnat-mediated axon protection. Although there is still much to learn about the molecular processes regulating axonal degeneration and survival, these two reports have given us a boost by placing the focus squarely on the axonal mitochondria.

References

1. Deckwerth, T.L., and Johnson, E.M., Jr. (1994). Neurites can remain viable after destruction of the neuronal soma by programmed cell death (apoptosis). Dev. Biol. *165*, 63–72.
2. Wang, J.T., Medress, Z.A., and Barres, B.A. (2012). Axon degeneration: molecular mechanisms of a self-destruction pathway. J. Cell Biol. *196*, 7–18.
3. Coleman, M.P., and Freeman, M.R. (2010). Wallerian degeneration, wld(s), and nmnat. Annu. Rev. Neurosci. *33*, 245–267.
4. Avery, M.A., Rooney, T., Wishart, T.M., Pandya, J.D., Gillingwater, T.H., Geddes, J.W., Sullivan, P., and Freeman, M.R. (2012). Wld^S prevents axon degeneration through increased mitochondrial flux and enhanced mitochondrial Ca^{2+} buffering. Curr. Biol. *22*, 596–600.
5. Fang, Y., Soares, L., Teng, X., Geary, M., and Bonini, N. (2012). A novel *Drosophila* model of nerve injury reveals an essential role of Nmnat in maintaining axonal integrity. Curr. Biol. *22*, 590–595.
6. Lunn, E.R., Perry, V.H., Brown, M.C., Rosen, H., and Gordon, S. (1989). Absence of Wallerian degeneration does not hinder regeneration in peripheral nerve. Eur. J. Neurosci. *1*, 27–33.
7. Mack, T.G., Reiner, M., Beirowski, B., Mi, W., Emanuelli, M., Wagner, D., Thomson, D., Gillingwater, T., Court, F., Conforti, L., *et al*. (2001). Wallerian degeneration of injured axons and synapses is delayed by a Ube4b/Nmnat chimeric gene. Nat. Neurosci. *4*, 1199–1206.
8. Hoopfer, E.D., McLaughlin, T., Watts, R.J., Schuldiner, O., O'Leary, D.D., and Luo, L. (2006). Wlds protection distinguishes axon degeneration following injury from naturally occurring developmental pruning. Neuron *50*, 883–895.
9. MacDonald, J.M., Beach, M.G., Porpiglia, E., Sheehan, A.E., Watts, R.J., and Freeman, M.R. (2006). The Drosophila cell corpse engulfment receptor Draper mediates glial clearance of severed axons. Neuron *50*, 869–881.
10. Beirowski, B., Babetto, E., Gilley, J., Mazzola, F., Conforti, L., Janeckova, L., Magni, G., Ribchester, R.R., and Coleman, M.P. (2009). Non-nuclear Wld(S) determines its neuroprotective efficacy for axons and synapses in vivo. J. Neurosci. *29*, 653–668.
11. Sasaki, Y., Vohra, B.P., Baloh, R.H., and Milbrandt, J. (2009). Transgenic mice expressing the Nmnat1 protein manifest robust delay in axonal degeneration in vivo. J. Neurosci. *29*, 6526–6534.
12. Avery, M.A., Sheehan, A.E., Kerr, K.S., Wang, J., and Freeman, M.R. (2009). Wld S requires Nmnat1 enzymatic activity and N16-VCP interactions to suppress Wallerian degeneration. J. Cell Biol. *184*, 501–513.
13. Conforti, L., Wilbrey, A., Morreale, G., Janeckova, L., Beirowski, B., Adalbert, R., Mazzola, F., Di Stefano, M., Hartley, R., Babetto, E., *et al*. (2009). Wld S protein requires Nmnat activity and a short N-terminal sequence to protect axons in mice. J. Cell Biol. *184*, 491–500.
14. Gilley, J., and Coleman, M.P. (2010). Endogenous Nmnat2 is an essential survival factor for maintenance of healthy axons. PLoS Biol. *8*, e1000300.
15. Yahata, N., Yuasa, S., and Araki, T. (2009). Nicotinamide mononucleotide adenylyltransferase expression in mitochondrial matrix delays Wallerian degeneration. J. Neurosci. *29*, 6276–6284.
16. Wang, X., and Schwarz, T.L. (2009). The mechanism of Ca2+-dependent regulation of kinesin-mediated mitochondrial motility. Cell *136*, 163–174.
17. MacAskill, A.F., and Kittler, J.T. (2010). Control of mitochondrial transport and localization in neurons. Trends Cell Biol. *20*, 102–112.
18. Glater, E.E., Megeath, L.J., Stowers, R.S., and Schwarz, T.L. (2006). Axonal transport of mitochondria requires milton to recruit kinesin heavy chain and is light chain independent. J. Cell Biol. *173*, 545–557.
19. Stowers, R.S., Megeath, L.J., Gorska-Andrzejak, J., Meinertzhagen, I.A., and Schwarz, T.L. (2002). Axonal transport of mitochondria to synapses depends on milton, a novel Drosophila protein. Neuron *36*, 1063–1077.

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Visual Perception: Knowing What to Expect

If perception is hypothesis, where do the hypotheses come from? A new study suggests that the human visual system uses the history of past stimulation to predict its current input.

Colin W.G. Clifford

It is often said that we live in a changing world. As we go through life we adapt to those changes and build up expectations of what the future will hold. Our sensory systems face a similar challenge in dealing with different environments. There are many examples of sensory systems that are in some fashion optimised to their natural environment: consider, for example, the large eyes of the nocturnal bush baby or the acute sense of smell of the foraging honey bee. Sensory adaptation can be viewed as a process by which our sensory systems tend to remain optimized to a changing environment. Under this view, sensory systems are adaptive systems perhaps sharing principles of operation with systems as diverse as ant colonies and economies. In his classic book *Adaptation in Natural and Artificial Systems*, Holland [1] poses several fundamental questions for the study of adaptive systems. "What part of the history of its interaction with the environment does the organism retain?" is of key importance as it asks what knowledge drives the system to adapt. This question is directly addressed in the

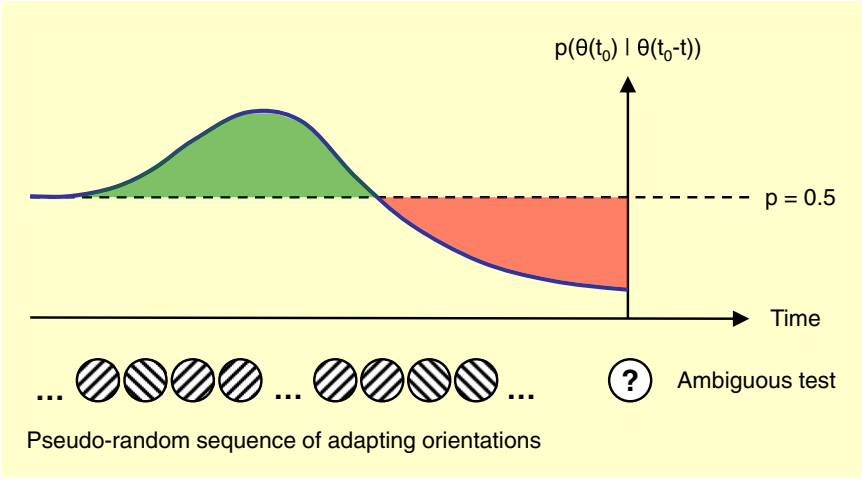

Figure 1. Dependence of perception on history of past stimulation.

The main finding of Chopin and Mamassian [2] is illustrated schematically. The perceived orientation of an ambiguous test stimulus depends in a characteristic way on the series of orientations shown in the minutes prior to the test. The test is less likely to be perceived as similar to orientations seen shortly (up to 3 minutes) before but more likely to be perceived as similar to orientations seen further into the past (5–10 minutes).

context of the human visual system by a study [2] published in this issue of *Current Biology*.

Chopin and Mamassian [2] conducted two experiments in which ambiguous test stimuli were presented at regular intervals within a series of adapting gratings varying randomly between two orientations. In the first experiment, each test stimulus consisted of a pair of gratings of these same two orientations presented one to each eye. These two orientations compete for perceptual dominance, a phenomenon known as binocular rivalry [3]. Subjects reported the dominant percept at each test presentation. Adaptation typically generates negative aftereffects, such that sensitivity to stimuli similar to the adaptor decreases and the perception of subsequent test stimuli is repelled away from the adaptor [4]. Such negative effects were observed by Chopin and Mamassian [2] at intervals of up to three minutes between adaptor and test. At longer intervals, however, the effect was reversed, such that stimuli presented 5–13 minutes previously were predictive of the perceptual interpretation of ambiguous visual information (Figure 1).

This pattern of dependence of the perceived orientation of rivalrous test stimuli on the series of preceding orientations is surprising. However, perceived test orientation might be expected to depend not only on the physical orientations of the adapting gratings, but also on the perceived orientation of prior ambiguous test stimuli [5,6]. Thus, it was important that Chopin and Mamassian [2] establish the generality of their findings beyond the binocular rivalry paradigm. Their second experiment made use of the tilt aftereffect, first reported 75 years ago [7] but still a valuable tool to vision researchers, whereby the perceived orientation of a test grating is biased by the diet of preceding orientations. Chopin and Mamassian [2] asked subjects to report to which of the two adapting orientations the test grating was closer. Unbeknownst to the subjects, the orientation of the test was in fact always midway between those of the adaptors. The results revealed that subjects were less likely to report the test orientation as being closer to the most recently presented adaptors, but more likely to report it as closer to orientations seen 2–10 minutes previously. The two experiments thus showed qualitatively similar patterns of results. In both cases, the expected negative aftereffect was observed at short adaptor-test intervals but, for longer intervals of 5–10 minutes, the effect was reversed and perceived test orientation correlated positively with the orientations presented in this earlier time window.

This finding has important implications for our understanding of adaptation. Sensory adaptation has been characterised as a process of self-calibration of the system to its environment [8–10]. Self-calibration theories of adaptation typically assume that the visual system has some internal model of the expected distribution of its response states. Deviations from this distribution drive the system to modify the stimulus-response mapping. However, where this prior expectation of the response distribution comes from is far from clear. It is usually assumed to involve a longer timescale of learning, through the developmental stage of the lifespan or even evolving across generations. So to read evidence of a timescale of 5–10 minutes is somewhat unexpected!

Within a Bayesian framework [11,12], the positive effects of adaptation suggest that the visual system is learning the prior probabilities of the stimulus distribution over a long timescale while the negative effects represent a redistribution of sensory resources in line with ideas of efficient coding [13–15]. Thus, the history of stimulation over this longer timescale is taken as predictive of future sensory input. Chopin and Mamassian [2] point out that a similar strategy leads to the gambler's fallacy in human reasoning [16]. Under the gambler's fallacy, if a coin comes up heads several times in succession the 'law of averages' suggests that it is more likely to come up tails on the next toss. By matching the recent history of coin tosses to the reference distribution built up over a longer timescale (equal frequency of heads and tails) the prediction of the gambler violates the expectation that successive coin tosses are independent.

In the context of sensory adaptation, however, the same strategy could provide a means to correct for perturbations within the system. For example, if the sensory response consistently indicates more leftwards than rightwards oriented structure in the environment, then this might be treated as an error within the system that can be corrected by turning down the gain on the mechanism detecting leftwards orientation. This would cause subsequent stimuli to be more likely to be perceived as oriented rightwards.

If the recent history really had consisted predominantly of leftwards orientation, then this would cause a physically vertical stimulus to be perceived, fallaciously, as rightwards: the tilt aftereffect. However, under more naturalistic viewing conditions such reliance on the statistical stationarity of the structure of the environment might be an intelligent means to keep the sensory system calibrated in the face of internal fluctuations in excitability.

References

1. Holland, J.H. (1992). Adaptation in Natural and Artificial Systems (Cambridge, MA: MIT Press).
2. Chopin, A., and Mamassian, P. (2012). Predictive properties of visual adaptation. Curr. Biol. *22*, 622–626.
3. Clifford, C.W.G. (2009). Binocular rivalry. Curr. Biol. *19*, R1022–R1023.
4. Clifford, C.W.G. (2010). Aftereffects. In Encyclopedia of Perception, E.B. Goldstein, ed. (Thousand Oaks, CA: Sage Publications Inc.), pp. 13–16.
5. Pearson, J., and Clifford, C.W.G. (2005). Mechanisms selectively engaged in rivalry: normal vision habituates, rivalrous vision primes. Vis. Res. *45*, 707–714.
6. Blake, R., Tadin, D., Sobel, K.V., Raissian, T.A., and Chong, S.C. (2006). Strength of visual adaptation depends on visual awareness. Proc. Natl. Acad. Sci. USA *103*, 4783–4788.
7. Gibson, J.J., and Radner, M. (1937). Adaptation, after-effect, and contrast in the perception of tilted lines. I. Quantitative studies. J. Exp. Psychol. *20*, 453–467.
8. Andrews, D.P. (1964). Error-correcting perceptual mechanisms. Quart. J. Exp. Psychol. *16*, 104–115.
9. Ullman, S., and Schechtman, G. (1982). Adaptation and gain normalization. Proc. R. Soc. Lond. B *216*, 299–313.
10. Clifford, C.W.G. (2005). Functional ideas about adaptation applied to spatial and motion vision. In Fitting the Mind to the World: Aftereffects in High-Level Vision, C.W.G. Clifford and G. Rhodes, eds. (Oxford: Oxford University Press), pp. 47–82.
11. Grzywacz, N.M., and Balboa, R.M. (2002). A Bayesian framework for sensory adaptation. Neural Comput. *14*, 543–559.
12. Stocker, A.A., and Simoncelli, E.P. (2006). Sensory adaptation within a Bayesian framework for perception. In Advances in Neural Information Processing Systems, *Vol. 18*, Y. Weiss, B. Schoelkopf, and J. Platt, eds. (London: Springer), pp. 1291–1298.
13. Barlow, H.B. (1961). The coding of sensory messages. In Current Problems in Animal Behaviour, W.H. Thorpe and O.L. Zangwill, eds. (Cambridge: Cambridge University Press), pp. 331–360.
14. van Hateren, J.H. (1993). Spatiotemporal contrast sensitivity of early vision. Vis. Res. *33*, 257–267.
15. Wainwright, M.J. (1999). Visual adaptation as optimal information transmission. Vis. Res. *39*, 3960–3974.
16. Tversky, A., and Kahneman, D. (1974). Judgment under uncertainty: heuristics and biases. Science *185*, 1124–1131.

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Fungal Morphogenesis: In Hot Pursuit

Temperature affects diverse biological processes. In fungi such as the pathogen *Candida albicans*, temperature governs a morphogenetic switch between yeast and hyphal growth. A new report connects the thermosensor Hsp90 to a CDK–cyclin–transcription factor module that controls morphogenesis.

Wenjie Xu and Aaron P. Mitchell*

Morphogenesis — the development of and transition between different growth forms — is a common theme in the fungal world. Morphogenetic pathways often respond to environmental cues. For diverse pathogenic fungi, including *Candida albicans*, *Histoplasma capsulatum*, *and Blastomyces dermatitidis*, host body temperature (37°C) is a trigger of morphological transitions. For *C. albicans*, the hyphal growth form that appears at high temperature is also prominent in infected tissue and is critical for *C. albicans* virulence [1]. Therefore, the thermal control over fungal morphogenesis is an intriguing issue from the standpoint of both cell biology and pathogenesis.

The molecular mechanism underlying temperature control of *C. albicans* morphogenesis remained elusive until 2009. At that time, Cowen and colleagues [2] reported that Hsp90, a molecular chaperone with many client proteins, had a central role in this mechanism. They found that compromising Hsp90 function by genetic or pharmacological approaches induced *C. albicans* cells to transit from the yeast form to the hyphal form, independently of temperature. It was particularly significant that Hsp90 was not simply required to complete a developmental program, as it is in many organisms, but rather that it seemed to govern hyphal formation at the developmental decision point. These findings led to the proposal that Hsp90 is a negative regulator of hyphal morphogenesis, and that high temperature may overwhelm Hsp90 with client proteins and thus relieve Hsp90-mediated inhibition [2]. Therefore, Hsp90 itself functions as a temperature sensor (Figure 1).

In a new study that recently appeared in *Current Biology*, Cowen and colleagues [3] implemented newly developed tools of *C. albicans* functional genomics to define a regulatory pathway that couples the Hsp90-dependent signal to hyphal-specific gene activation. Their previous studies had implicated the cyclic AMP-protein kinase A (cAMP–PKA) pathway in this role [2]. Surprisingly, though, the canonical transcription factor target of cAMP–PKA, Efg1, was dispensable for the response to Hsp90. Thus, the group set out to look specifically for transcription factors that govern Hsp90-responsive morphogenesis. A library of 143 homozygous deletion mutants [4] was screened for a reduced capacity to produce hyphae in response to the Hsp90 inhibitor geldanamycin. The screen paid off beautifully: a mutant lacking a previously uncharacterized transcription factor gene, *HMS1*, had a severe defect in geldanamycin-induced hyphae formation. Although the hyphal regulatory pathway is a complex meshwork of interconnected signals and transduction pathways [1], the role of Hms1 turns out to be quite specific: it is required for induction of hyphal formation by elevated temperature but not by other environmental cues, such as nutritional limitation, neutral pH, or serum. ChIP–chip and qRT–PCR analyses revealed that Hms1 is bound to DNA associated with hyphal-specific genes, such as *UME6* and *RBT5*, and regulates their transcript levels. Together these finding indicate that Hms1 plays