of *Current Biology*, Vardi *et al.* [13] now show that expression of the gene PtNOA1 (nitric oxide-associated protein), which encodes a GTP-binding protein belonging to the highly conserved YqeH subfamily, is increased in response to challenge with DD. By genetically manipulating *Phaeodactylum* cells to overexpress PtNOA1, Vardi *et al.* [13] have revealed a number of critical downstream responses in what appears to be a complex signalling pathway. Interestingly, PtNOA1 was shown to localise to the chloroplast. Overexpression of PtNOA1 led to increased production of NO and suppression of a plastid-localised superoxide dismutase (MnSOD) that had been shown to be an essential component of oxidative-stress responses in diatoms [14]. Other physiological effects of PtNOA1 overexpression included reduced photosynthetic efficiency, reduced growth, increased metacaspase expression and increased caspase activity. Adhesion of *Phaeodactylum* to its substrate was also compromised by the overexpression of PtNOA1. The authors propose that PtNOA1 acts as a switch in regulating threshold responses to environmental stress. While it is not yet known whether PtNOA1 is essential in this signalling pathway, since the gene has yet to be experimentally knocked down, this work indicates that PtNOA1 has a significant role in integrating external chemical cues with growth responses and, ultimately, cell death.

While there are many examples of cell–cell communication in the marine environment, including quorum sensing by marine bacteria [15,16], the role of PtNOA1 reveals one of the first examples of cell-death signals potentially acting both to reduce grazing pressure directly and to induce cell death in the grazed population. This new study by Vardi *et al.* [13] provides compelling evidence that chemical signals released by diatoms in a population may be perceived by others, potentially amplifying and spreading a message throughout the population. It is becoming more widely appreciated that PCD may have benefits for population growth and turnover of unicellular organisms (for example, see [3]). While the detailed ecological implications of PCD in phytoplankton populations are still far from clear, it is very likely that the occurrence of PCD confers a selective advantage. In some cases this advantage may be obvious. For example, in certain dinoflagellates, activation of PCD pathways in response to oxidative stress under limited CO_2 availability has been shown to lead to spore formation and, potentially, dispersal of the population to a more favourable growth environment [17]. In diatoms, there is no evidence that PCD gives rise to any such dispersal mechanisms; however, there appears to be significant selective advantages associated with the removal of damaged or compromised cells from the population by allowing resource recycling to actively growing cells [3]. It is also possible that this may be part of a complex mechanism that reduces the numbers of cells available in regions of high grazer density, providing a secondary control of grazer population growth.

References

1. Ianora, A., Boersma, M., Casotti, R., Fontana, A., Harder, J., Hoffman, F., Pavia, H., Potin, P., Poulet, S.A., and Toth, G. (2006). New trends in marine chemical ecology. Estuaries Coasts *29*, 531–551.
2. Berges, J.A., and Falkowski, P.G. (1998). Physiological stress and cell death in marine phytoplankton: induction of proteases in response to nitrogen or light limitation. Limnol. Oceanogr. *43*, 129–135.
3. Bidle, K.D., and Falkowski, P.G. (2004). Cell death in planktonic, photosynthetic microorganisms. Nat. Rev. Microbiol. *8*, 643–655.
4. Berman-Frank, I., Bidle, K.D., Haramaty, L., and Falkowski, P.G. (2004). The demise of the marine cyanobacterium, *Trichodesmium* spp., via and autocatalysed cell death pathway. Limnol. Oceanogr. *49*, 997–1005.
5. Kolodkin-Gal, I., Hazan, R., Gaathon, A., Carmeli, S., and Engelberg-Kulka, H. (2007). A linear pentapeptide is a quorum-sensing factor required for mazEF-mediated cell death in *Escherichia coli*. Science *318*, 652–654.
6. Schroeder, D.C., Oke, J., Malin, G., and Wilson, W.H. (2002). Coccolithovirus (Phycodnaviridiae): Characterisation of a new large dsDNA algal virus that infects *Emiliania huxleyi*. Arch. Virol. *147*, 1685–1698.
7. Jacquet, S., Heldal, M., Iglesias-Rodriquez, D., Larsen, A., Wilson, W.H., and Bratbak, G. (2002). Flow cytometric analysis of an *Emiliania huxleyi* bloom terminated by viral infection Aquat. Microb. Ecol. *27*, 111–124.
8. Suttle, C.A. (1994). The significance of viruses to mortality in aquatic microbial communities. Microb. Ecol. *28*, 237–243.
9. Bidle, K.D., Haramaty, L., Barcelos, E., Ramos, J., and Falkowski, P. (2007). Viral activation and recruitment of metacaspases in the unicellular coccolithophore, *Emiliania huxleyi*. Proc. Natl. Acad. Sci. USA *104*, 6049–6054.
10. Ianora, A., Miralto, A., Poulet, S.A., Carotenuto, Y., Buttino, I., Romano, G., Casotti, R., Pohnert, G., Wichard, T., Colocci-D'Amato, L., *et al*. (2004). Aldehyde suppression of copepod recruitment in blooms of a ubiquitous planktonic diatom. Nature *429*, 403–407.
11. Ribalet, F., Wichard, T., Pohnert, G., Ianora, A., Miralto, A., and Casotti, R. (2007). Age and nutrient limitation enhance polyunsaturated aldehyde production in marine diatoms. Phytochemistry *68*, 2059–2067.
12. Vardi, A., Formiggini, F., Casotti, R., De Martino, A., Ribalet, F., Miralto, A., and Bowler, C. (2006). A stress surveillance system based on calcium and nitric oxide in marine diatoms. PLoS Biol. *4*, e60.
13. Vardi, A., Bidle, K., Kwityn, C., Thompson, S.M., Callow, J.A., Callow, M.E., Falkowski, P., and Bowler, C. (2008). A diatom gene regulating nitric-oxide signaling and susceptibility to diatom-derived aldehydes. Curr. Biol. *18*, 895–899.
14. Wolfe-Simon, F., Starovoytov, V., Reinfelder, J.R., Schofield, O., and Falkowski, P.G. (2006). Localization and role of manganese superoxide dismutase in a marine diatom. Plant Physiol. *142*, 1701–1709.
15. Joint, I., Downie, A., and Williams, P. (2007). Bacterial conversations: talking listening and evesdropping. Philos. Trans. Roy. Soc. *362*, 1115–1117.
16. Joint, I.R., Tait, K., Callow, M.E., Callow, J.A., Milton, D., Williams, P., and Camara, M. (2002). Cell-to-cell communication across the prokaryote-eukaryote boundary. Science *298*, 1207.
17. Vardi, A., Berman-Frank, I., Rozenberg, T., Hadas, O., Kaplan, A., and Levine, A. (1999). Programmed cell death of the dinoflagellate *Peridinium gatunense* is mediated by CO2 limitation and oxidative stress. Curr. Biol. *9*, 1061–1064.
18. Falciatore, A., Formiggini, F., and Bowler, C. (2001). Perception of environmental signals by a marine diatom. Science *288*, 2363–2366.

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Multisensory Integration: A Late Bloomer

Under many circumstances, human adults integrate information from different sensory modalities, such as vision and hearing, in a statistically optimal fashion. New results suggest that optimal multisensory integration only develops in middle childhood.

Marc O. Ernst

Some environmental properties, such as the positions, sizes, and orientations of objects, can be estimated via multiple senses, including vision and touch. Multisensory signals can therefore carry redundant information.

Several recent studies have shown that human adults use the redundant sensory information in a statistically optimal fashion (for example [1–3]). The individual information sources to be integrated are weighted according to their reliabilities and the resulting combined estimates are more reliable than any information source by itself. An interesting and important question is whether the optimal use of multisensory information is present early in childhood or develops only later. Two recent papers in *Current Biology* [4,5] report evidence that the ability develops only in middle childhood.

Gori *et al.* [4] have shown that the integration of visual and haptic (feel) cues to size and orientation does not become optimal until relatively late in development: sometime between 8 and 10 years of age. In their carefully conducted study, they first measured discrimination performance for the individual cues in order to make predictions for optimal integration. Presenting both cues simultaneously, they then showed that children less than 8 years of age do not optimally integrate the information from the two modalities; instead, they rely on one or the other sense for their perceptual judgments. Interestingly, they do not rely predominantly on the more reliable of the two senses — rather they rely on haptic information when judging size and on vision when judging orientation.

This conclusion is supported by the results of Nardini *et al.* [5], who assessed the ability of subjects of various ages to navigate under visual guidance, and found no sign of optimal multisensory integration in children younger than eight years of age. The experimental procedure used in this case did not allow the authors to test for optimal integration, but the results still show that adults make efficient use of the available multisensory information, whereas children below eight years of age do not.

Taken together, these two studies [4,5] make a compelling case that optimal multisensory integration only occurs in children older than eight years. The consistency of the results is remarkable and raises a set of interesting questions, the foremost being: why does optimal integration occur so late?

During development, the human body undergoes dramatic changes. Not only does it grow, but some of the sense organs, such as the ear and eye, also show a remarkable reorganization [6,7]. For example, the photoreceptors of the human retina are still developing well after birth and migrate toward the fovea in a complex way [6]. To continue to make sense of the sensory signals, receptor outputs have to be constantly reinterpreted to take account of the changes associated with development. Furthermore, different sense organs may develop at different rates. In order to know which signals belong together for integration, the sensory systems also have to be recalibrated continuously. And to recalibrate, the intersensory discrepancy has to be detected. For this, the system needs access to the individual multisensory signals so that it can compare them. Gori *et al.* [4] argue that this need is the reason why optimal intergration is not possible in early childhood — the benefits of integration are traded for extra plasticity.

However, adults constantly adapt and recalibrate their perceptual and sensori-motor systems (for example [8,9]), while they continue to integrate the multisensory signals optimally. For example, if the range of the arm is artificially enlarged during tool use, or if glasses distort the geometry of the visual image, the perceptual system needs to take these changes into account by recalibrating the discrepant sensory maps and thereby bring them back into correspondence [10]. In fact, the multisensory systems in adults are quite plastic on a relatively short timescale (often an hour or two) of experiencing new statistical regularities [11–13]. Thus, it is questionable that plasticity during development is the reason that optimal multisensory integration takes more than eight years to develop.

Could there be other reasons for the late development of optimal multisensory integration as well? In order to analyse whether performance is optimal or not, the entire perceptual process from stimulation to decision must be considered. For multisensory integration, this includes establishing the correspondence between the different sensory signals, the actual integration process, and the perceptual decision mechanism. Development in any of these subprocesses could be the cause of the failure to integrate optimally.

Establishing the correspondence between signals — that is, knowing which signals belong together — can be very difficult. Furthermore, without knowing the correspondence, signals can neither be integrated nor recalibrated. Adults seem to be flexible and able to use prior knowledge when inferring correspondence. For example, multisensory integration is known to break down when there is a spatial separation between the sensory signals that indicates that the two signals might come from different sources [14]. But if there is a visible cause for the spatial separation, such as when looking at an object via a mirror, integration still occurs and can even be optimal [3,15]. In the study by Gori *et al.* [4], participants were looking at an object mounted on the front surface of a metal plate, while they were touching an object mounted on its back. They were told they are seeing and touching the same object. For integration to occur, correspondence between these two objects has to be established. Adults behaved optimally under these conditions [4] (see also [3]), so they are apparently able to establish correspondence between the visual and haptic signals. Perhaps young children are unable to establish the correspondence.

Adults are very able to adjust the perceptual decision process according to task demands. This flexibility is a necessity in order to behave optimally under varying circumstances. For example, when the task is to estimate the size of an object, Gori *et al.* [4] and many others have shown that adults integrate both sensory signals — the visual and the haptic size signals — in an optimally weighted fashion (for example [1,4]). In a slightly different task, however, in which participants are instructed to report on either one of the two information sources available — the visual or the haptic size — they behave differently [16]. What constitutes optimality for this estimation task depends on the relationship between the two sources of information and the knowledge that the system has about this relationship. When the subject is instructed to report only one source, it is optimal to *use* the second source for the perceptual estimate as well, if the system knows that it carries redundant information (mandatory fusion) [17]. By using the second source of information, the perceptual

estimate becomes more reliable. But it is optimal to *not use* the second source — or at least to weight it differently — if the system knows that there is a chance that the modality signals may be biased relative to one another, which might occur during body growth or tool use. In this case, there is a potential cost in using the second source of information because the combined estimate would be biased [16,18]. Adults seem to be able to use the available sensory information differently depending on the task demands and to adjust their perceptual estimates in order to minimize the cost or to maximize the benefit [19]. Perhaps children take longer to learn that.

In summary, the empirical evidence that optimal integration occurs relatively late in a child's development is strong. But why integration emerges so late and which stage in the integration process is suboptimal are still open questions.

References

1. Ernst, M.O., and Banks, M.S. (2002). Humans integrate visual and haptic information in a statistically optimal fashion. Nature *415*, 429–433.
2. Alais, D., and Burr, D. (2004). The ventriloquist effect results from near-optimal bimodal integration. Curr. Biol. *14*, 257–262.
3. Helbig, H.B., and Ernst, M.O. (2007). Optimal integration of shape information from vision and touch. Exp. Brain Res. *179*(4), 595–606.
4. Gori, M., Del Viva, M., Sandini, G., and Burr, D.C. (2008). Young children do not integrate visual and haptic information. Curr. Biol. *18*, 694–698.
5. Nardini, M., Jones, P., Bedford, R., and Braddick, O. (2008). Development of cue integration in human navigation. Curr. Biol. *18*, 689–693.
6. Rubel, E.W., and Ryals, M.B. (1983). Development of the place principle: Acoustic trauma. Science *219*, 512–514.
7. Banks, M.S. (1988). Visual recalibration and the development of contrast and optical flow perception. In Perceptual Development in Infancy. The Minnesota Symposium on Child Psychology, *Volume 20*, A. Yonas, ed. (Hillsdale: Erlbaum), pp. 145–196.
8. Adams, W.J., Banks, M.S., and van Ee, R. (2001). Adaptation to three-dimensional distortions in human vision. Nat. Neurosci. *4*(11), 1063–1064.
9. Burge, J., Ernst, M.O., and Banks, M.S. (2008). The statistical determinants of adaptation rate in human reaching. J. Vis. *8*, 1–19, Article 20.
10. Knudsen, E.I., and Knudsen, P.F. (1985). Vision guides the adjustment of auditory localization in young barn owls. Science *230*, 545–548.
11. Atkins, J.E., Fiser, J., and Jacobs, R.A. (2001). Experience-dependent visual cue integration based on consistencies between visual and haptic percepts. Vis. Res. *41*, 449–461.
12. Ernst, M.O. (2007). Learning to integrate arbitrary signals from vision and touch. J. Vis. *7*, 1–14.
13. Knill, D.C. (2007). Learning Bayesian priors for depth perception. J. Vis. *7*, 1–20.
14. Gepshtein, S., Burge, J., Ernst, M.O., and Banks, M.S. (2005). The combination of vision and touch depends on spatial proximity. J. Vis. *5*, 1013–1023.
15. Helbig, H.B., and Ernst, M.O. (2007). Knowledge about a common source can promote visual-haptic integration. Perception *36*, 1523–1533.
16. Ernst, M.O. (2005). A Bayesian view on multimodal cue integration. In Human Body Perception from the Inside Out, Günther Knoblich, *et al*., eds. (New York: Oxford University Press), pp. 105–131.
17. Hillis, J.M., Ernst, M.O., Banks, M.S., and Landy, M.S. (2002). Combining sensory information: mandatory fusion within, but not between, senses. Science *298*, 1627–1630.
18. Bresciani, J.-P., Dammeier, F., and Ernst, M.O. (2006). Vision and touch are automatically integrated for the perception of sequences of events. J. Vis. *6*, 554–564.
19. Trommershäuser, J., Maloney, L.T., and Landy, M.S. (2003). Statistical decision theory and the selection of rapid, goal-directed movements. J. Opt. Soc. Am. A *20*, 1419–1433.

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Phagocytic Signaling: You Can Touch, but You Can't Eat

The ability of phagocytes to discriminate between viable/healthy and apoptotic/foreign/abnormal cells is of fundamental importance; a recent study provides new molecular insights into the function of CD47–SIRPα signaling in this discrimination.

Jason M. Kinchen and Kodi S. Ravichandran

On a daily basis, the human body turns over 100–200 billion cells, including unwanted cells that do not have the right developmental fitness (for example, during hematopoiesis), superfluous cells (such as excess lymphocytes that remain after a pathogenic challenge has been removed), and damaged or aged cells (such as aged erythrocytes) that need to be removed as part of the cellular homeostasis in the body. The turnover of these cells begins with the induction of an apoptotic program or other cellular changes that mark them for removal, and continues with the subsequent recognition of altered features by phagocytes, leading to a highly efficient and immunologically silent removal of these unwanted/dying cells [1]. The phagocytes that carry out this clean-up exercise include macrophages, dendritic cells, Kupffer cells of the liver (e.g. for removal of aged erythrocytes) as well as many neighboring cells, although the relative contribution of each type of phagocyte is unknown. Inherent in this clean-up process is the need to specifically and selectively remove unwanted cells whilst sparing neighboring healthy cells that are found within the same tissue milieu.

The discrimination of the healthy from the unwanted/aged/dying cells appears to be achieved at two levels. First, the cells intended for removal display markers or ligands called 'eat-me' signals, i.e. 'altered self', which can in turn be recognized by receptors on the phagocytes. Second, healthy cells appear to have markers called 'don't-eat-me' signals that actively inhibit phagocytosis [1–4]; these signals are either downregulated in the dying cells or present in an altered conformation. While significant strides in recent years have been made towards our understanding of eat-me signals and their recognition (see [1,5], for review), progress in our understanding of how don't-eat-me signals function has been slower. The cell-surface protein CD47 on healthy cells and its engagement of a phagocyte receptor, SIRPα, appears to constitute a key don't-eat-me signal. A recent study [6] now sheds light on the molecular events that are negatively affected by CD47–SIRPα signaling with larger implications for our understanding of the phagocytic process (Figure 1).

Phagocytes use a broad variety of receptors to recognize the altered-self state. Typically, the steps in phagocytosis involve the recognition