Sights Unseen

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Yuqian Ma, Jin Bao, Yuanwei Zhang, Zhanjun Li, Xiangyu Zhou, Changlin Wan, Ling Huang, Yang Zhao, Gang Han, and Tian Xue, "Mammalian Near-Infrared Image Vision through Injectable and Self-Powered Retinal Nanoantennae," *Cell* 177, no. 2 (2019), doi:10.1016/j.cell.2019.01.038..

The recent emergence of nano-optics and nanophotonics, as well as numerous associated nanomaterials, has made it possible to manipulate interactions between light and matter on a nanometric scale. This new branch of optics has much to offer physicists, chemists, and biologists. Indeed, a new means to harness and exploit the properties of light will likely form the basis for any number of novel and innovative applications.[1] The work of Yuqian Ma et al. is a case in point. In the 1990s, researchers developed nanomaterials capable of rendering objects seemingly invisible—albeit in electromagnetic rather than optical terms.[2] In their own work with nano-objects, Ma et al. are seeking to achieve the opposite effect. Their goal is to reveal the invisible.

The nano-objects at the center of this study are nanocrystals (NCs). Their physical properties have been well known since the 1960s and differ markedly from those of nonlinear crystals, such as potassium niobate and materials exhibiting second harmonic generation. For the purposes of Ma et al., it is the property of upconversion that plays a crucial role. Substances with this capability are able to emit light with a wavelength that is shorter than that of the excitation wavelength. This is an invaluable property when seeking to transform infrared (IR) into visible light that is capable of exciting the photoreceptors of the retina and thus generating an electrical signal the brain can process. NCs with similar properties have been synthesized and employed in biomedical applications for many years.[3]

The approach outlined by Ma et al. is striking. As part of their study, NCs were injected into the eyes of mice and anchored to the surface of the retina using chemical functionalization. In principle, an IR image would be formed on the retina and partially transformed into a visible image by the anchored NCs. Although these experiments may seem unusual at first glance, this is a serious study based on established protocols.

Numerous tests conducted by Ma et al. demonstrated unambiguously that the injected mice exhibited sensitivity to a wavelength of 980 nanometers (nm), well above the upper limit of 700 nm that is normally visible to mammals. The mice were not only sensitive to light, and could recognize shapes at this wavelength, but also maintained their normal vision in the visible spectrum. From a technical point of view, the research described in this paper is innovative and even impressive. A few points, though, bear further discussion.

In their paper, Ma et al. refer to the upconversion nanoparticles as nanoantennae. Over the past decade, optical nanoantennae have been the subject of numerous studies. Taking their cues from conventional electromagnetic antennae operating in the microwave and terahertz range, researchers have sought to harness the optical properties of nano-objects to achieve similar functionality.[4] As is the case with electromagnetic antennae, this process involves optimizing the coupling between distant external radiation and the excitation of charge density oscillations on the surface of receptors, as well as local currents within them.

The nano-objects used as receptors in nanoantennae are generally developed from noble metals such as gold and silver. These substances exhibit electrical resonances in visible and near-IR ranges that can be coupled with light, specifically plasmon resonances, to amplify electromagnetic effects and compensate for absorption. In a 2011 study, Lukas Novotny and Niek van Hulst succinctly defined optical antennae as nano-optical systems used "to convert the energy of free propagating radiation to localized energy, and vice versa."[5] In their study, Ma et al. used nonlinear nano receiving-antennae to convert IR radiation into visible light.

Energy transfer processes at different scales are an interesting topic in relation to this research. Radiation with a wavelength of 980 nm emanating from an LED is capable of illuminating nonlinear NCs. The result is visible radiation with spectral components capable of exciting photosensitive cells in the retina. NCs used for such purposes are typically 20 nm in size and comparatively small compared to the wavelengths involved. The field radiated by the NCs consists of evanescent waves, for the most part, along with radiative waves. Each spectral component emitted is also associated with charge density oscillations possessing distinct resonant frequencies, confined to the surface of the NCs.

In the experiments by Ma et al., the precise distance between the NCs and the photoreceptor cones and rods to which they were anchored is hard to gauge. Judging by the diagrams they provide,[6] it seems that the NCs were in direct contact with the photoreceptors, positioned at a distance of only a few nanometers. Due to their proximity, energy transfer between the NCs and the photoreceptors could be partially nonradiative, implying a transfer of charge or dipole rather than a transfer of visible photons absorbed by the photoreceptors. Such exchanges are known as Dexter energy transfers or Förster resonance energy transfers. In the case of radiative transfers, it is the radiative or evanescent electromagnetic field that is absorbed by the photoreceptors. Although not addressed directly in the paper, it would be interesting to examine the relative contributions of these radiative and nonradiative, or evanescent and propagating, transfers in more detail. In the case of nonradiative transfers, considering the subwavelength size of the nanoantennae, the suitability and adaptation of the photoreceptors for handling such transfers over longer periods is a topic that requires further investigation.

Any examination of the NCs employed in the study by Ma et al. should also include an assessment of their performance as nanoantennae. An effective receiving antenna design is one in which the operating parameters have been optimized for a particular application and can efficiently detect and convert a radiative wave into exploitable confined energy. Optical nanoantennae are characterized by a range of precisely defined parameters such as impedance and dissipation, directivity, amplification, local density of the electromagnetic state, absorption cross section, and so on. Some of these parameters have important implications. The dissipative capabilities of the nanoantennae employed by Ma et al., for example, can be used to quantify heat emissions that could damage the retina in the long term. None of these parameters is discussed as part of their study. For this reason, it is debatable whether their designation of nanoantennae is entirely merited. NCs may be functional optical nanoantennae, but their true effectiveness and suitability remains unclear.

Ma et al. express optimism concerning any risk of biotoxicity associated with their approach. On this point, their views are reinforced not only by their own research, but also by that of other groups. The latter studies found no evidence of harmful health effects over periods of several weeks, as measured by an absence of inflammation and cell death.

The upconversion nanoparticles contain, among other things, fluorine and the rare earth elements ytterbium, yttrium, and erbium. Even if the approach outlined in this paper is developed further in the years ahead, the required quantities of these substances will in all likelihood remain low. Questions about sustainable development in relation to the supply, life cycle, and environmental impact of rare earth elements are not an immediate concern.

Despite the studies undertaken and the sunny outlook of the authors, it is nonetheless difficult to believe that this type of intervention would not cause some degree of adverse health effects in the long term.[7] On this point, the optimism expressed in the paper seems premature.

The mammalian eye is a complex organ optimized for imaging in the visible light spectrum. As part of these experiments, IR images were formed on the retina of an organ that is not naturally sensitive to this wavelength. Although the experiments by Ma et al. have yielded impressive results, their approach has some important limitations. At least two phenomena may occur that have the potential to drastically limit the effectiveness of such an approach.

The eye is mainly comprised of aqueous and vitreous components that are semitransparent to visible wavelengths. For wavelengths above 900 nm, tissue absorption increases sharply.[8] Eyes repeatedly exposed to IR risk overheating and tissue damage that may eventually lead to a degradation in function.

The spatial resolution of an optical imaging system is governed by the wavelength of the light being observed and the physics of diffraction. In these experiments, a decrease in the maximum detectable spatial frequency of a patterned sample was observed in the near infrared range in comparison to the visible range. This was likely not a coincidence. The decrease by a factor of approximately two between the two ranges corresponds roughly to the ratio of the two wavelengths.

A dioptric imaging system will invariably exhibit some degree of geometric and chromatic aberrations. In the case of the latter, even if the mammalian eye is able to focus precisely on the IR image, it is unclear whether the IR image will be in the same plane as the visible image. From a simple Cauchy dispersion model, it seems that the IR image is likely formed behind the visible image. The result would be two images on different planes: a visible image and an IR image that can be transformed into a visible image by the NCs anchored to the retina. The mammal would then be faced with an unconscious choice between seeing the visible image clearly and a blurry IR image, or vice versa. It would be interesting to examine this focusing process in more detail. In the case of IR imaging, a longer wavelength, such as a thermal IR wavelength of 10 micrometers, would greatly amplify some of the effects already described.

It is difficult to imagine potential uses for a similar or analogous approach in humans. IR cameras and detectors that work along the spectrum from near-IR to long-wavelength thermal IR are both efficient and widely available. Such devices offer high-quality imaging and, in some cases, are able to capture spectral information and even temporal resolution. These capabilities mean that it is now possible to analyze phenomena that occur at ultrafast speeds.[9] Prototype IR devices have been demonstrated that use nanocrystals for the purposes of upconversion, as is the case in this study.[10]

Compared to these other systems, the approach taken by Ma et al., which involves a potentially hazardous modification of the retina, does not appear to offer any particular advantages. Assisting nonhuman mammals to acquire IR vision also appears to have little practical value. Indeed, the significance of this work will likely become apparent elsewhere in the field. As the authors suggest, it may be in the treatment of eye diseases and wider vision research that the real benefits from their research are realized.

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1. See, for example, a recent work dealing with nanophotonics and its applications: Sergey Gaponenko and Hilmi Volkan Demir, *Applied Nanophotonics* (Cambridge, UK: Cambridge University Press, 2010).
2. Wenshan Cai et al., "Optical Cloaking with Metamaterials," *Nature Photonics* 1, no. 4 (2007): 224–27, doi:10.1038/nphoton.2007.28.
3. Chengchen Duan et al., "Recent Progress in Upconversion Luminescence Nanomaterials for Biomedical Applications," *Journal of Material Chemistry* B 6, no. 2 (2018): 192–209, doi:10.1039/c7tb02527k.
4. Constantine Balanis, *Antenna Theory: Analysis and Design* (New York: Harper & Row, 1982).
5. Lukas Novotny and Niek van Hulst, "Antennas for Light," *Nature Photonics* 5, no. 2 (2011): 83–90, doi:10.1038/nphoton.2010.237.
6. In particular, illustration 1F and the photos labeled 1L. See Yuqian Ma et al., "Mammalian Near-Infrared Image Vision through Injectable and Self-Powered Retinal Nanoantennae," *Cell* 177, no. 2 (2019), doi:10.1016/j.cell.2019.01.038.
7. Giovanni Pagano et al., "Health Effects and Toxicity Mechanisms of Rare Earth Elements—Knowledge Gaps and Research Prospects," *Ecotoxicology and Environmental Safety* 115 (2015): 40–48, doi:10.1016/j.ecoenv.2015.01.030.
8. Thomas van den Berg and Henk Spekreijse, "Near-Infrared Light Absorption in the Human Eye," *Vision Research* 37, no. 2 (1997): 249–53, doi:10.1016/s0042-6989(96)00120-4.
9. G. Romano et al., "An Ultrafast IR Thermography System for Transient Temperature Detection on Electronic Devices," *2014 Semiconductor Thermal Measurement and Management Symposium (SEMI-THERM), San Jose, CA, 2014*, 80–84, doi:10.1109/semi-therm.2014.6892219.
10. Marcus Strom, "Night-Vision Glasses: Nanocrystals Developed at ANU Allow Direct Vision into the Infrared," *Sydney Morning Herald*, December 7, 2016.

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