

# The Relationship between the Magnetic Compass and Vision in Birds: In Search of Receptor Cells

L. A. Astakhova,<sup>1</sup> A. Yu. Rotov,<sup>1,2</sup> and N. S. Chernetsov<sup>1,3,4</sup>

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The existence of a magnetic compass system was first demonstrated in birds. Since then, extensive data have been accumulated on the operation of the magnetic compass in birds and its relationship with visual reception. The currently dominant concept is that the receptor supporting operation of the magnetic compass in birds is located in the retina. The most popular hypothesis for how magnetic field receptors work is the radical pair hypothesis, in which cryptochrome, more specifically, the cryptochrome 4a isoform, is the candidate for the role of the primary magnetoreceptor molecule. Recent research has yielded data on the interaction of cryptochrome with various proteins involved in the phototransduction cascade, along with promising data from electrophysiological studies combining visual (light) and magnetic stimulation. In addition, a number of morphological studies of the avian retina are also helping to narrow the range of possible cells for the role of magnetoreceptor, with double cones being currently the most likely candidate. In this review, we discuss the latest research in this area.

**Keywords:** birds, magnetic compass, retina, cryptochrome, cone.

**Introduction.** During their lives, many animals perform long-distance movements, go beyond their home range and cross novel and often inhospitable areas. During such movements, they need to select and maintain a certain compass direction. This ability is termed orientation, and the set of behavioral adaptations that provide them with this ability is called the compass system [Chernetsov, 2016; Mouritsen, 2018]. Moreover, during local journeys within the familiar home range, if the animal is faced with the task of moving in a straight line for any prolonged period of time, it must have a compass system based on global cues, not just on local landmarks (Finkelstein et al., 2016).

For many animals, the global compass and positioning cue is the Earth's magnetic field. The fact that many ani-

mals from different taxa, both vertebrates and a variety of invertebrates, have a magnetoreception as a distinct sensory modality, in addition to the well-known photo-, chemo-, mechano-, and electroreceptive senses, has been confirmed experimentally. The existence of a magnetic compass system, which provides the ability to select and maintain the direction of migratory movements, was initially demonstrated in birds [Wiltschko, 1968; Wiltschko and Wiltschko, 1972]. Evidence for the magnetic compass has been reported for rodents [Deutschlander et al., 2003; Diego-Rasilla et al., 2013; Malewski et al., 2018], bats [Holland et al., 2006], anurans [Diego-Rasilla et al., 2013; Shakhparonov and Ogurtsov, 2017], bony fishes [Quinn, 1980; Bottesch et al., 2016], crustaceans [Lohmann et al., 1995], and insects [Guerra et al., 2014; Dreyer et al., 2018; Gegear et al., 2008; Fleischmann et al., 2018]. It is not impossible that humans, who despite numerous attempts have never been found to have magnetoreception [Chernetsov et al., 2021], are rather an exception among animals. It must however be emphasized that the available evidence for the use of a magnetic compass is most reliable in the case of birds, where it has been repeatedly demonstrated by a number of independent

<sup>1</sup> Sechenov Institute of Evolutionary Physiology and Biochemistry, Russian Academy of Sciences, St. Petersburg, Russia; e-mail: lubkins@yandex.ru.

<sup>2</sup> Orbeli Institute of Physiology, National Academy of Sciences of the Republic of Armenia, Yerevan, Armenia.

<sup>3</sup> St. Petersburg State University, St. Petersburg, Russia.

<sup>4</sup> Zoological Institute, Russian Academy of Sciences, St. Petersburg, Russia.

research groups. Migrating birds provide a model group of organisms for research on magnetoreception as a sensory modality, despite the fact that these are wild animals which do not breed in laboratory conditions (i.e., they have to be taken from the wild).

According to the current view, the magnetic compass system of birds is closely linked to photoreception [Astakhova et al., 2020a]. One of the most convincing arguments supporting this view (but not the only one) is the fact that the correct operation of the compass system requires light with particular spectral characteristics. That the functionality of magnetic compasses depends on the available light spectrum has been demonstrated in various behavioral experiments both on wild migratory birds [Wiltschko, 1978; Wiltschko et al., Munro et al., 1997; Rappl et al., 2000; Muheim et al., 2002; Stapput et al., 2008] and on laboratory species – the domestic chicken *Gallus gallus*, the homing pigeon *Columba livia*, and the zebra finch *Taeniopygia guttata* [Wiltschko and Wiltschko, 1998; Wiltschko et al., 2007; Pinzon-Rodriguez and Muheim, 2017]. Taken together, these studies show that birds can use their magnetic compass successfully under short-wavelength light (near ultraviolet, violet, blue, green) and that when a certain threshold in the yellow-green region of the spectrum (wavelength approximately 550–570 nm) is crossed, they become disoriented. These results make a strong case for a link between the structures supporting the operation of the magnetic compass and light-sensitive neural tissue, the retina.

This review addresses the search for the primary magnetoreceptor cell in the retina, which currently remains unknown. The review will highlight various approaches to answering this question and, on the basis of the latest experimental data, the most likely candidate for this role is suggested; in addition, the prospects for further research in this direction are outlined.

**Search for a Magnetoreceptor Cell by Localization of Magnetosensitive Molecules. Biophysical model of compass magnetoreception.** The most detailed concept of the biophysical mechanism of the sensory system underlying the magnetic compass sense in birds is the radical pair model, which suggests a chemical magnetoreceptor based on reversible biradical reactions [Hore and Mouritsen, 2016]. Two important properties of the magnetic compass of birds known from behavioral experiments, its inclination and light dependence, point to this possibility [Wiltschko and Wiltschko, 1972, 1995, 1999, 2001]. A major point for an adequate model of magnetoreception is identifying the receptor molecule and the type(s) of magnetosensitive cells involved in signal formation. The most obvious candidate receptor molecules are cryptochrome proteins, which have the ability to form radical pairs.

The hypothesis that magnetosensitive receptors may be based on chemical reactions was put forward in the late 1970s–1980s [Schulten et al., 1978; Schulten, 1982; Schulten and Windemuth, 1986]. Until the beginning of the

21st century, this hypothesis did not attract the attention of biologists as it was very abstract and did not offer physiologically plausible mechanisms for the perception and transduction of magnetic signal in living organisms. In 2000, these ideas led to formulation of the radical pair model [Ritz et al., 2000], which proceeds from the concept that birds can use photosensitive cryptochrome molecules as magnetoreceptors. It has been hypothesized that cryptochromes are located in cells in the avian retina and that they undergo photooxidation as a result of absorbing photons with a particular energy. The radical pair model explains the behavioral results outlined above as follows: only photons with a particular energy (i.e., light of a particular wavelength) can induce electron transfer from a cryptochrome molecule to a receptor (which is most likely the cryptochrome cofactor flavin adenine dinucleotide, FAD). This results in formation of a pair of molecules with unpaired electrons, consisting of a cryptochrome donor and its partner operating as acceptor. This radical pair exists for periods ranging from a few nanoseconds to a few milliseconds, eventually either recombining or decaying into more energetically stable reaction products. The relative probabilities of decay and recombination of a radical pair are determined by the ratio of its lifetime to the rate of the reversible reaction interconverting the products, which depends on the intensity of the external magnetic field and its orientation with respect to the magnetic axis of the pair. As a result, the proportions of the different products of such a reaction vary depending on the magnitude and direction of the external magnetic field.

The authors of the radical pair model suggested that cryptochrome molecules should be arranged to ensure that the movement of radical pairs is limited, for example, by being attached to elements of the cytoskeleton or cell membranes [Ritz et al., 2000]. The retina of the eye is well suited to the role of a tissue where these processes take place, as the membrane disks of photoreceptors have an ordered orientation. How could birds perceive a magnetic field via radical pairs? It has been suggested that different biradical reaction products can modulate photoreceptor sensitivity in different ways, operating through a biochemical cascade [Ritz et al., 2000]. It can be suggested that radical pair products of one type would lead to the inhibition of visual information, while those of another will lead to enhancement (or vice versa). The result of this modulation of the neuronal signal in different parts of the retina is that photoreceptor sensitivity will differ depending on the orientation (and, thus, position in the retina) of the cryptochrome-containing photoreceptor to the magnetic field vector. As a result, the bird can literally “see” the magnetic field, i.e., perceive it as a visual image (for example, a darkened or, conversely, a whitish transparent spot) superimposed on the standard visual picture of the world.

It should be noted that the radical pair model does not explain all the known experimental facts. For instance, the operation of the magnetic compass of birds has reliably

been shown to be disturbed by very weak alternating magnetic fields in the megahertz range. The effect of alternating magnetic fields has been reported for frequencies of 0.4–85 MHz [Ritz et al., 2004; Thalau et al., 2005; Ritz et al., 2009; Engels et al., 2014; Pakhomov et al., 2017; Kobylkov et al., 2019; Leberecht et al., 2022] and oscillation amplitudes more than three orders of magnitude smaller than the intensity of the static geomagnetic field, in the nanotesla to tens of nanoteslas range. This effect is explained qualitatively within the framework of the radical pair model as resulting from the spin resonance of the electrons forming the radical pair [Hiscock et al., 2017]. However, a satisfactory quantitative explanation of this phenomenon remains to be obtained: experimentally, magnetic compass orientation in birds is disturbed by alternating magnetic fields with amplitudes two orders of magnitude smaller than the theoretical model suggests [Kavokin, 2009]. Some signal amplification mechanism might produce this effect [Hiscock et al., 2017], but no model of such an internal amplifier has as yet been proposed [Kavokin, 2009].

**Cryptochromes as magnetoreceptor molecules in the retina.** Cryptochromes constitute a large family of flavoproteins which absorb light predominantly in the blue region of the spectrum, contain flavin as a cofactor, and have a mass of 50–70 kDa. The ability to absorb light is determined by the presence of flavin (in the form of FAD) and pterin. Cryptochromes were proposed as magnetically sensitive molecules [Ritz et al., 2000], as these proteins represent the only known class of molecules in vertebrates capable of forming radical pairs after absorbing photons. However, it should be noted that sensitivity to the geomagnetic field requires radical pairs to have quite long lifetimes, at least 10  $\mu$ sec, while in vitro experiments on cryptochromes of migratory birds have demonstrated lifetimes not exceeding hundreds of nanoseconds [Xu et al., 2021]. On the other hand, this can be explained by the absence of the specific conditions in which cryptochromes exist inside magnetoreceptor cells.

Cryptochromes are found in higher plant and animal cells and different classes of cryptochromes perform different biological functions [Chaves et al., 2011]. *Drosophila*-type cryptochromes (type I), found in animals, are photopigments involved in synchronizing circadian rhythms directly with ambient illumination; mammalian-like cryptochromes (type II) are able to synchronize circadian rhythms indirectly and perform a number of other functions [Michael et al., 2017]; cryptochrome type IV was well recently discovered in birds, amphibians, fish, and reptiles [Zoltowski et al., 2019]. Of these types, six different cryptochrome isoforms (Cry1a, Cry1b, Cry2a, Cry2b, Cry4a, and Cry4b) are currently known to be expressed in the avian retina. Several studies in recent years have addressed the location of these cryptochrome isoforms in specific retinal cell types and even in individual cell compartments, along with the relationship between their expression profile and seasonal and circadian cycles. Depending on the results obtained, different groups

of researchers were inclined to favor participation of one or another type of cryptochrome in the mechanism of the magnetic compass in birds.

It should be noted that reliable immunohistochemical determination of the selective expression of different types and isoforms of cryptochromes in the avian retina is challenging. Research groups working in this field approached the task by sequencing various isoforms and producing selective antibodies to each [Günther et al., 2018]. The profiles and patterns of expression of some types and isoforms of cryptochromes in avian retina make them unlikely candidates for the role of the key molecule in the mechanism of the magnetic compass. Thus, Cry2 in the retina of the European robin *Erithacus rubecula*, homing pigeons, and chickens is found in the inner segments of photoreceptors and in ganglion cells in the outer and inner nuclear layers; in terms of subcellular localization, it is present in the cytoplasm and nuclei of the cells forming these layers [Einwich et al., 2022]. The authors of this study noted that expression in nuclei supports the involvement of Cry2 in the regulation of circadian rhythms in birds rather than involvement in the process of magnetoreception. Studies of the interaction of Cry2 in the pigeon retina support this hypothesis, as the main partners for interaction with Cry2 were proteins involved in regulating circadian rhythms (PER2, CLOCK and ARNTL) [Balay et al., 2021].

Until recently, the Cry1a isoform was regarded as a promising candidate for the role of magnetoreceptor molecule. This cryptochrome was found in ultraviolet (UV)-sensitive cones in the chicken and European robin retina [Nießner et al., 2011]. This group argued that the distribution pattern of this cryptochrome in cones indicates light-induced conformational changes – it is found in the retina of birds illuminated with whole-spectrum light or light in the range 373–590 nm (i.e., from UV to green) before preparations were made; Cry1a and the specific opsin were colocalized in UV-sensitive cones; Cry1a was not detected in the same compartments in birds exposed to red light or kept in the dark [Nießner et al., 2011, 2014]. However, other researchers failed to reproduce this result in the retinas of chickens, homing pigeons, European robins [Bolte et al., 2021], or zebra finches [Pinzon-Rodriguez and Muheim, 2021].

Some authors consider Cry4a a more likely candidate for the role of magnetoreceptor molecule [Günther et al., 2018; Görtemaker et al., 2022]. In European robins, which are a classic object for magnetoreception studies [Wiltschko and Wiltschko, 1972] and where the existence of a magnetic compass system has been repeatedly confirmed independently in behavioral experiments, Cry4 was colocalized with a red-sensitive visual pigment, indicating its expression in the outer segments of double cones and possibly red-sensitive single cones [Günther et al., 2018]. The Cry4a isoform found in European robins is known to show a significantly stronger response to changes in the magnetic field than Cry4 in chickens and homing pigeons [Xu et al., 2021].

***Interaction of cryptochromes with proteins of the phototransduction cascade.*** A major point in considering how the magnetoreceptor sensory system in the avian retina might work is to find signaling pathways through which the primary sensing molecule (cryptochrome or other candidate) could signal a change in the magnetic field. The last few years have seen a sequence of reports of research by a team led by Koch and Mouritsen [Wu et al., 2020, Görtemaker et al., 2022] demonstrating the possibility of Cry4 interaction with proteins directly involved in the phototransduction cascade in avian photoreceptors.

The phototransduction cascade underlying visual perception provides the conversion of photon energy into an electrical signal. This is a multistage cascade of reactions, the main components in which are the visual pigment excited by a photon, the G-protein transducin, which transmits the signal from the visual pigment to the effector enzyme, phosphodiesterase (PDE), which decreases the intracellular concentration of cyclic guanosine monophosphate (cGMP), leading to closure of ion channels in the photoreceptor plasma membrane [Pugh and Lamb, 2000; Arshavsky and Burns, 2014].

The first of the two studies cited [Wu et al., 2020] developed a yeast-two-hybrid system to identify potential molecular interaction partners for European robin Cry4. A wide range of candidates was identified in the first screening phase, this being narrowed down to the six most promising candidates in the second phase: red-sensitive cone opsin (LWS); the  $\alpha$ -subunit of the G-protein transducin-2 (GNAT2); guanine nucleotide-binding protein subunit  $\gamma$  10 (GNG10); potassium voltage-gated channel subfamily V member 2 (KCNV2); retinol-binding protein 1 (RBP1), and retinal G-protein-coupled receptor (RGR). Based on these six interaction targets, the authors proposed hypothetical pathways for incorporating the Cry4 signal into the visual transduction pathway. Their view was that in the case of the interaction of Cry4 with red-sensitive cone opsin, the phototransduction cascade in a given photoreceptor type could be triggered in response to a magnetic stimulus, starting at its first stage. Alternatively, the interaction of Cry4 with the G-protein  $\alpha$ -subunit could involve activation of the phototransduction cascade from its second stage, while the interaction of Cry4 with potassium voltage-gated channels would allow it to change the membrane potential of the photoreceptor directly.

As GNAT2 and GNG10, identified as Cry4 interaction partners as reported in [Wu et al., 2020], are cone-specific orthologs of subunits of the heterotrimeric G-protein transducin, which mediates phototransduction in vertebrate photoreceptors, the second study performed by the same group [Görtemaker et al., 2022] described a more detailed investigation of the potential interaction of Cry4a with European robin GNAT2 at the molecular level. Biosensors based on surface plasmon resonance were used to analyze the process of protein-protein interaction and its kinetic parameters; in

addition, the occurrence of such an interaction in vitro was confirmed in an affinity precipitation study. Furthermore, the same study demonstrated an interaction between European robin Cry4a and transducin-2 G-protein  $\alpha$ -subunit in avian neuroretinal cell cultures using the fluorescence resonance energy transfer (FRET) method. Although the possibility of such an interaction occurring directly within avian cones has not yet been verified, these findings seem very promising for elucidating the signaling pathway underlying the avian magnetic compass.

**Search for a Magnetoreceptor Cell Using the Electrophysiological and Morphological Features of the Retina. *Structural features of avian retina.*** Birds have the most highly developed visual system among the vertebrates and their retina has a number of significant differences from the retina of mammals. First, the avian retina is avascular – it has no vascular system penetrating the inner neuron layers [Willis and Wilkie, 1999]. Trophic function is provided by the pigment epithelium and the pecten, a pleated structure originating from the optic nerve area (the blind spot) and extending to the periphery of the retina [Wingstrand and Munk, 1965; Jasiński, 1973]. Neural cells in the avian retina (bipolar, horizontal, amacrine, and ganglion cells) also have a number of adaptations to the lack of direct contact with the vascular system, such as specific processes that connect them to Müller glial cells [Quesada and Genis Galvez, 1985]. As in other vertebrates, these neurons form a layered structure, though the cell density and the extent of branching of their processes, especially in the inner layers responsible for preliminary processing of the visual signal, is very high, indicating the complexity of the task they perform [Seifert et al., 2020].

Light-sensitive cells in avian retinas, i.e., photoreceptors, as in other vertebrates, are divided into rods and cones. The retinas of most bird species have five types of cone: ultraviolet-, blue-, green-, and red-sensitive cones differ due to the expression of different visual pigments, and cones of the additional type, the double cones, that contain a red-sensitive pigment and constitute two receptor cells electrically connected to each other [Hart, 2001]. Thus, birds have tetrachromatic color vision, distinguishing many more shades (and over a wider spectral range) than most other vertebrates. Moreover, bird cones contain specific structures, the oil droplets, which are colorless or colored spherical formations containing carotenoid molecules dissolved in drops of lipid [Toomey and Corbo, 2017]. Colorless droplets have been shown to act mainly as light-focusing structures, collecting incident light onto a small light-sensitive cone outer segment, while colored droplets act as selective light filters, reducing the degree of overlap of the sensitivity spectra of different types of cones [Wilby and Roberts, 2017]. Oil droplets are also found in other vertebrates, but they achieve the greatest diversity in birds, where they form a set of highly selective light detectors covering the visible and near ultraviolet parts of the spectrum [Kelber, 2019; Baden and Osorio, 2019].

Some researchers have suggested that avian photoreceptors are also capable of distinguishing the polarization of incident light, though their specific morphology makes it difficult to imagine how this could occur. The dipole moments of visual pigment molecules are distributed randomly, diffusing in the plane of cell membranes, but always perpendicular to the cell axis and the direction of naturally incident light, which theoretically excludes sensitivity to the polarization of light [Roberts et al., 2011]. Despite the existence of studies demonstrating behavioral responses to changes in the polarization of light in birds [Muheim, 2011; Åkesson, 2014], the correctness of the experimental protocols used is currently under question. In particular, Melgar et al. [2015] conducted a study whose results indicated that perception of light polarization as a separate stimulus cannot be detected in birds; this report also expressed doubts about the correctness of the interpretation of experimental results obtained previously. It should be noted that the task of experimentally separating responses to a change in the polarization of light from the response to a change in illumination intensity is very difficult. Existing positive results may well be explained in terms of responses to changes in light intensity.

It should be noted that some animals, including birds, have another type of photoreceptor located in the pineal organ of the brain, i.e., pinealocytes, which may also be candidate magnetoreceptor cells [Collin and Oksche, 1981; Bailey and Cassone, 2005]. However, surgical removal of the pineal organ in pied flycatchers (*Ficedula hypoleuca*) while maintaining circadian rhythms with daily injections of melatonin has been shown not to cause impairments in orientational behavior [Schneider et al., 1994]. Moreover, birds have a functional region presumptively responsible for processing magnetoreceptor signals in part of the visual hyperpallium (the analog of the visual cortex of mammals), the so-called cluster N [Mouritsen et al., 2005; Heyers et al., 2007]. Cluster N receives signals from the retina via the thalamofugal visual pathway through the lateral geniculate body of the thalamus. Chemical lesioning of cluster N (by introducing cholera toxin) led to the loss of the ability to orientate in the magnetic field in robins [Zapka et al., 2009]. It should be emphasized that cluster N is not an anatomically distinct structure, but a functional area of the avian visual hyperpallium [Heyers et al., 2022]. These data also indicate that the most likely location of the magnetoreceptor function in birds is the retina.

**Electrophysiological studies seeking the magnetic compass mechanism in the retina.** Although the idea of using an electrophysiological approach to solve ongoing challenges in studies of the light-sensitive magnetic compass in birds has been suggested in recent years, the only published work in this area describes a series of electrophysiological studies of the structures of the visual pathways in the brain by Semm, Beason, and Demaine in the 1980s. This group showed that a significant proportion (70%) of the

neurons in the optic tectum (the analog of the mammalian superior colliculus) of the homing pigeon [Semm and Demaine, 1986] and branches of the trigeminal nerve of the bobolink *Dolichonyx oryzivorus* [Beason and Semm 1987; Semm and Beason, 1990] are sensitive to the direction of the external magnetic field, some responses depending on the illumination wavelength. However, a later study using similar experiments on a large sample of birds failed to reproduce these results [Ramirez et al., 2014], which casts doubt on their relevance.

To the best of our knowledge, the first published work on the electrophysiology of magnetoreception in the avian retina was performed by our group. In a series of studies, we tested whether a change in the direction of the magnetic field could affect the photoresponses of avian retina. Our study method consisted of electroretinographic recording from avian isolated retinas, with changes in the direction of the magnetic field combined with blue or red flashes of light to elicit photoresponses. In the first two reports in this series [Rotov et al., 2018, 2020], this experimental protocol was applied to the retina of pigeons, which, although not migratory birds, still presumably use a magnetic compass when homing [Walcott and Green, 1974]. The results showed that the amplitude of the total response of the pigeon retina to flashes of blue, but not red light, depended on whether the magnetic field vector was parallel or perpendicular to the plane of the retina at the time at which the response was recorded; the effect was small but statistically significant. A more detailed investigation of the influence of the magnetic field direction on the isolated photoreceptor response of the pigeon retina showed that this electroretinogram component of the response to blue flashes was independent the direction of the magnetic field. This result could be explained in terms of the fact that the photoreceptor response in this study consisted mainly of the rod component. Our further studies [Astakhova et al., 2020b; Rotov et al., 2022] used the same approach to address the effects of magnetic fields on the photoresponses of the European robin retina, a nocturnal migrant, and a classical model in behavioral studies of the magnetic compass in birds. Retinas in these two studies were divided into four parts, as is customary in histological studies – the nasal, ventral, temporal, and dorsal quadrants. This division makes sense, as these areas may perform slightly different functions (due to differences in the images falling on these areas) in visual processes in real life, and it was suggested that such areas might also have a different relationship with magnetoreception. This suggestion was confirmed, and magnetic field direction was found to affect the amplitude of ERG responses only to blue flashes and only in the nasal quadrant of the retina in European robins. In addition, the magnetic field effect was detected only on presentation of moderately intense blue flashes, but not when a certain stimulus intensity was exceeded.

In general, the results from these electrophysiological studies are in good agreement with results from a large pool

of behavioral studies on the light dependence of the magnetic compass of birds: behavioral experiments showed that different bird species were disoriented in long-wavelength light (red, yellow), but retained the ability to orient themselves in a magnetic field under short-wavelength illumination (green, blue, violet, and UV) [Munro et al., 1997; Rappl et al., 2000]; in addition, they lost the ability to navigate in light of shorter wavelength but higher intensity [Muheim et al., 2002; Johnsen et al., 2007].

**Morphological studies of the avian retina in relation to the search for possible magnetoreceptor cells.** Research groups studying the mechanism of the magnetic compass of birds have also made notable efforts in recent years to studying the morphological features of the retina in different species, as this might shed light on which cells or structures could be the morphological basis of magnetoreception [Seth et al., 2021]. The morphological studies of potential magnetoreceptor cells published to date have paid most attention to double cones and their signal transduction pathways in the retinas of birds, as these have been suggested not to be involved in color vision but to perform other functions [Kirschfeld, 1998]. One such study was reported by Günther et al. [2021] and addressed the interactions between different types of cones, primarily double cones, and second order retinal neurons, i.e., bipolar cells, in chickens using multibeam scanning electron microscopy of serial sections. This group showed that double cones have close and numerous contacts with neighboring double cones; in addition, 15 types of bipolar cell were identified, 13 of which form contacts with at least one of the members of double cones. A detailed reconstruction of individual double cones showed that their principal and accessory members are connected by a structure resembling a tight gap junction. The authors took the view that tight gap junctions of this type could close in conditions in which the magnetoreceptor stimulus becomes more significant than the visual signal, i.e., the members of the double cone can operate relatively independently during perception of a magnetic stimulus.

Another study by the same group [Chetverikova et al., 2022] asked the question whether double cones form a regular pattern in the retina of migratory birds (European robins), as this is an important prerequisite for this type of cone to perform a magnetoreceptor function. Double cones were visualized in this study using an immunohistochemical method (with an antibody that binds to calbindin, a reliable selective marker for double cones), with analysis of the resulting whole-retina images for the regularity of the locations of adjacent pairs of double cones. The results indicated that the array of double cones is highly regular and that the angle between adjacent double cones in the central regions of the retina approaches  $90^\circ$ – $90^\circ$ , with angles of  $180^\circ/0^\circ$  in the peripheral areas. The authors came to the conclusion that if the alignment of Cry4 in both members of double cones (principal and accessory) is regular and identical, then the regular mosaic of neighboring double cones

seen at the periphery of the retina in European robins and domestic chickens should contribute to the performance of the magnetoreceptor function by this area.

Another noteworthy morphological observation in the retina of the European robin was made by our group [Rotov et al., 2022]. We found that only the nasal quadrant of the European robin retina showed an effect due to changes in the direction of the magnetic field in the electrophysiological part of the study and asked how it might differ from other quadrants in its morphology. An unexpected finding was that pale yellow double cone oil droplets in the nasal quadrant (and the adjacent ventral quadrant) appeared to be more intensely colored than oil droplets of the same type in other areas of the retina. This phenomenon was demonstrated using light microscopy supplemented by microspectrophotometry (allowing the spectra of individual subcellular structures to be recorded), which revealed a statistically significant shift in the absorption of oil droplets of double cones in the nasal quadrant to the longer-wavelength region. Microscopic images also showed that the accessory member in at least some double cones in European robins, unlike the principal member, does not contain an oil droplet. An intensely colored yellowish droplet would block the passage of short-wave light to the outer segment of the principal member of the double cone, while the outer segment of the accessory member would receive the full light spectrum and could act as a magnetoreceptor. In this case, adequate implementation of magnetosensitivity would require two accessory members of double cones located in a specific orientation relative to each other, which is consistent with the data on the regular arrangement of double cones at the periphery of the retina in the European robin [Chetverikova et al., 2022].

**Main Candidates for the Role of Magnetoreceptor Cells in the Retina of Migrating Birds.** Based on aforementioned experimental data and the hypotheses arising from them, double cones appear to be the cell type most likely performing the magnetoreceptor function in the retina (Fig. 1).

Overall, this is the most common cone type in the avian retina, accounting for about 50% of all cones. At the same time, their contribution to color vision is not obvious. This suggests that double cones in the avian retina could have other important functions. The most popular molecular candidate for the role of the primary magnetic field sensing molecule, Cry4, has been shown to be expressed in the outer segments of the principal member of double cones, its expression level increases during the migration season [Günther et al., 2018], and it has been shown to be able to interact specifically with the red-sensitive opsin typical of this photoreceptor type [Wu et al., 2020]. Furthermore, the retinas of migratory birds show a regular mosaic formed by adjacent double cones, with the angle between cones being close to  $180^\circ/0^\circ$  at the periphery, which is required to separate changes in stimulus caused by polarization of light and the magnetic field [Chetverikova et al., 2022]. The ques-

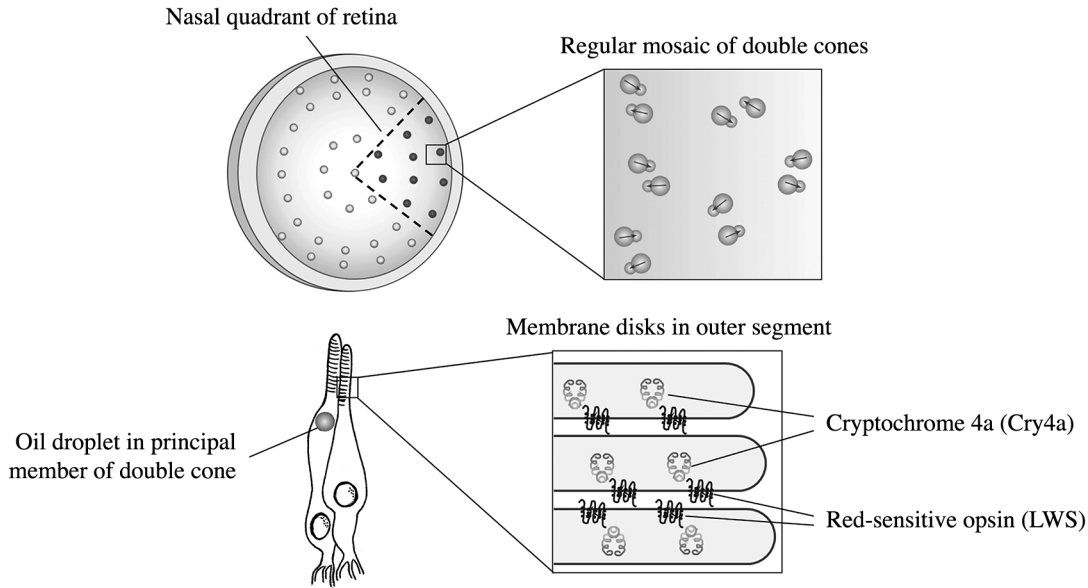


Fig. 1. Double cone of the retina in birds as a magnetoreceptor based on current experimental data. *a*) Magnetically sensitive cells are located in the nasal quadrant of the retina, while double cones at the periphery form a regular mosaic (the angle between neighboring cells is  $180^\circ/0^\circ$ ). *b*) A brightly colored oil droplet, typical of the nasal quadrant, blocks access of short-wavelength light to the outer segment of the principal member of the double cone. Cryptochrome isoform type 4a is expressed in the outer segment of the accessory member of the double cone and the ordered structure of the membrane discs provides a specific spatial orientation for the magnetosensitive molecules. Cryptochrome 4a is colocalized with the red-sensitive opsin of double cones and the cone transducin isoform and is able to interact specifically with them, probably modulating the activity of the phototransduction cascade.

tion of how a magnetosensitive cone should separate the perceived information concerning light and magnetic field seems to be extremely important when searching among retinal cells for a possible candidate for the role of magnetoreceptor cell, and current views hold that it is the mutual orientation at an angle of  $180^\circ$  that favors the possible perception of the direction of the external magnetic field vector [Worster et al., 2017].

Additionally, our data show a more intense coloration and spectral shift of the oil droplet in the principal member of double cones in the nasal quadrant of avian retina and suggest that these cells have a role in magnetoreception, with no similar changes having been found for other cone types [Rotov et al., 2022]. The presence of such a droplet in the principal member of the double cone has the result that the part of the spectrum required for cryptochrome activation will not reach its outer segment, such that only the accessory member can receive information about the magnetic field. Thus, only a small population of double cones, located in the nasal quadrant of the retina, are candidates to be magnetoreceptors. Some authors cite the presence of tight contacts between the main and accessory members, leading to electrical mixing of signals from the two members, as an argument against the leading role of double cones in magnetoreception [Wiltshko et al., 2021]. However, as noted above, other authors suggest that such tight contacts may be blocked in those lighting conditions in which the magnetoreceptor signal becomes the more significant stimulus [Günther et al., 2021].

UV-sensitive cones might be another candidate for the role of magnetoreceptor cell. Cry1a expression was detect-

ed in the outer and inner segments of these cells and their oil droplets freely transmit light in the visible range, including short-wavelength light, as required for cryptochrome activation [Bischof et al., 2011]. Nonetheless, a regular pattern has not been demonstrated in the case of UV-sensitive cones, although the potential presence of such a mosaic was examined by Chetverikova et al. [2022]. In addition, UV-sensitive cones appear to play an important role in color vision [Smith et al., 2002], which seems to be their primary function in the avian retina.

**Conclusions. Prospects for further search for a magnetoreceptor cell.** Specific magnetic field receptor cells remain to be reliably identified in the avian retina, though various experimental data point to double or UV-sensitive cones. The role of these cells in magnetoreception undoubtedly requires direct experimental verification. An obvious solution to this problem is to conduct experiments on birds with knockout of cryptochrome genes, which have been suggested to play the role of primary molecular magnetic field sensors: Cry4 to test the role of double cones and Cry1a for UV-sensitive cones. However, genetic manipulation in birds is difficult because of the inaccessibility and complex structure of the zygote, though there are currently approaches to solving these problems [Woodcock et al., 2017]. Another important problem is the fact that migratory passerine birds, for which the presence of magnetic sensitivity has been reliably established, do not breed in the laboratory conditions, and the results of behavioral experiments on species available in the laboratory (chickens, homing pigeons and zebra finches) should be treated with caution.

Another important approach consists of recording the responses of individual retinal cells to seek a population responding to magnetic stimulation. Although recording the electrical responses of individual ganglion cells using multi-electrode arrays at first sight seems to be an attractive method, artifacts caused by rapid changes in the magnetic stimulus have been found to mimic the shape of neuron spikes, thereby complicating data analysis [Ahlers et al., 2022]. However, this study also showed that these induction artifacts can in fact be clearly separated from neural responses on the basis of their spatiotemporal characteristics, which gives hope for new electrophysiological data to be obtained soon. An alternative to direct recording of the electrical responses of cells is provided by calcium imaging, a technique that allows activity to be recorded in terms of changes in the intracellular  $\text{Ca}^{2+}$  ion concentration. Fluorescence intensity – which is not subject to induction artifacts from alternating magnetic fields – is recorded in this methodology. Although imaging of the retina, which is itself a light-sensitive tissue, seems to be a difficult task, protocols have now been developed that allow such experiments to be carried out on the retina of mammals [Briggman and Euler, 2011; Euler et al., 2019], such that this technique is very promising. As ganglion cells are probably not the primary sensors of the magnetic field, data on their activity in a changing magnetic field will only narrow the scope of the search for a magnetoreceptor among neurons in the outer layers of the retina in the near future. The problem of unambiguous identification of the primary receptor cell will evidently require employment of fundamentally new methodological approaches and its solution may take several years.

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