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Commentary

A behavioral perspective on the biophysics of the light-dependent magnetic compass: a link between directional and spatial perception?

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Summary

In terrestrial organisms, sensitivity to the Earth's magnetic field is mediated by at least two different magnetoreception mechanisms, one involving biogenic ferromagnetic crystals (magnetite/maghemite) and the second involving a photo-induced biochemical reaction that forms long-lasting, spin-coordinated, radical pair intermediates. In some vertebrate groups (amphibians and birds), both mechanisms are present; a light-dependent mechanism provides a directional sense or 'compass', and a non-light-dependent mechanism underlies a geographical-position sense or 'map'. Evidence that both magnetite- and radical pair-based mechanisms are present in the same organisms raises a number of interesting questions. Why has natural selection produced magnetic sensors utilizing two distinct biophysical mechanisms? And, in particular, why has natural selection produced a compass mechanism based on a light-dependent radical pair mechanism (RPM) when a magnetite-based receptor is well suited to perform this function? Answers to these questions depend, to a large degree, on how the properties of the RPM, viewed from a neuroethological rather than a biophysical perspective, differ from those of a magnetite-based magnetic compass. The RPM is expected to produce a light-dependent, 3-D pattern of response that is axially symmetrical and, in some groups of animals, may be perceived as a pattern of light intensity and/or color superimposed on the visual surroundings. We suggest that the light-dependent magnetic compass may serve not only as a source of directional information but also provide a spherical coordinate system that helps to interface metrics of distance, direction and spatial position.

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Key words: magnetic compass, radical pair mechanism, spatial cognition, subicular place cells.

Introduction

Nearly half a century ago, studies of migratory birds (Wiltschko and Wiltschko, 1972) and honeybees (Martin and Lindauer, 1977) provided the first clear evidence that animals can sense the geomagnetic field (for reviews, see Wiltschko and Wiltschko, 2003; Wiltschko and Wiltschko, 2005). The intervening years have provided a wealth of evidence that the magnetic sense is present in taxonomically diverse groups of animals (Wiltschko and Wiltschko, 1995). For example, among mammals there is evidence for magnetic sensitivity in mice, hamsters, rats, mole rats, bats, cows and deer (Olcese et al., 1985; Burda et al., 1990; Kimchi and Terkel, 2001; Deutschlander et al., 2003; Muheim et al., 2006a; Thalau et al., 2006; Begall et al., 2008; Holland et al., 2008). Indeed, animals that do not have a magnetic sense (humans are widely assumed to fall in this category) may be the exception, rather than the rule.

The first magnetic response to be well characterized was magnetic compass orientation by migratory songbirds (reviewed by Wiltschko and Wiltschko, 2003; Wiltschko and Wiltschko, 2005). More recent studies have investigated the functional properties of the magnetic compass in newts, sea turtles, spiny lobsters, mole rats and mealworm beetles (Phillips, 1986; Burda et al., 1990; Light et al., 1993; Lohmann and Lohmann, 1993; Lohmann et al., 1995; Marhold et al., 1997; Vacha et al., 2008a). All of these animals, except mole rats (see below) and possibly spiny lobsters (Lohmann et al., 1995) (but see Phillips, 1986), use a magnetic inclination compass that is sensitive to the axis, but not polarity, of the magnetic field (Fig. 1A). Animals with an inclination compass use the slope of the magnetic field [i.e. the direction in which the magnetic axis forms the smallest angle with the gravity vector (Wiltschko and Wiltschko, 1972)] to distinguish between the 'poleward' and 'equatorward' ends of the magnetic axis (Fig. 1C). This contrasts with a polarity or dipole compass (e.g. the pocket compass used by human navigators), which is insensitive to inclination but responds to the polarity of the field (Fig. 1B). The properties of a magnetic inclination compass in migratory birds (Wiltschko and Wiltschko, 1972) (for a review, see Wiltschko and Wiltschko, 2005) were the impetus for early models of a light-dependent magnetic compass (LDMC) involving light-driven biological reactions (Leask, 1977; Schulten, 1982; Schulten and Windemuth, 1986). Research stimulated by these models has produced behavioral and neurophysiological evidence for a LDMC mechanism in some, but not all, animals (Phillips and Deutschlander, 1997; Phillips et al., 2010). Photoreceptors in the pineal organ of newts (Deutschlander et al., 1999a; Deutschlander et al., 1999b; Phillips et al., 2001), the retina of birds (Semm et al., 1984; Semm and Demaine, 1986; Wiltschko et al., 2002) and possibly rodents (Olcese et al., 1985), and the compound eye of flies (Phillips et al., 2010) have been implicated in mediating LDMC responses. Despite the involvement of different types of

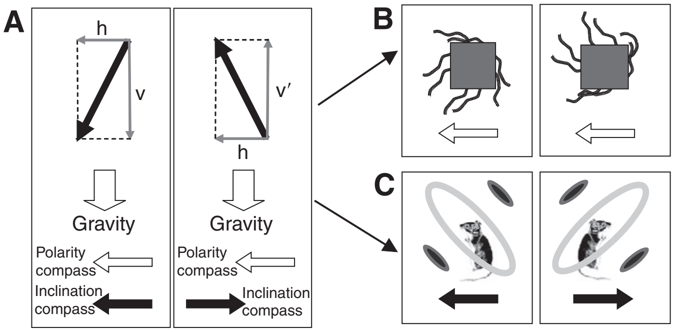

Fig. 1. Magnetic polarity *versus* inclination compasses. (A) Left diagram shows a side view of the magnetic field (black arrow sloping down to the left), with positive inclination, i.e. 'north down', found in the northern hemisphere. Gray arrows show the vertical (v) and horizontal (h) components. Open block arrow pointing downward indicates the direction of gravity. Horizontal arrows at the bottom of the diagram show the direction of orientation of an animal heading to the north in the northern hemisphere using a polarity-sensitive magnetic compass (open arrow) or an inclination magnetic compass (black arrow). Animals with an inclination compass use inclination or dip angle (e.g. the direction in which the magnetic axis forms the smallest angle with the gravity vector) (Wiltschko and Wiltschko, 1972) to distinguish between the two ends of the magnetic axis. Right diagram shows a side view of the magnetic field with negative inclination, i.e. 'north up'. Inversion of the vertical component (v′) has no effect on the direction of orientation in animals using a polarity compass (open arrows), but in animals using an inclination compass causes a reversal in the direction of orientation (black arrows). (B,C) Right and left panels – side views showing responses to magnetic field alignments in the corresponding panels of A and B. (B) Side views of sensory hairs containing chains of single-domain magnetite attached to a cellular structure (gray square). Inversion of the vertical component of the magnetic field has little effect on the response of these receptors in the horizontal plane (polarity compass). (C) Side views of response of a simple radical pair mechanism (RPM) (shown as it would appear projected on the inside of a sphere surrounding the animal); ring aligned orthogonally to the magnetic field may or may not be present depending on magnetic field intensity (Ritz et al., 2000). Inversion of the vertical component, reversing the inclination, causes the pattern to appear to be rotated 180 deg in the horizontal plane (inclination compass).

photoreceptors, the LDMC in insects (Phillips and Sayeed, 1993; Vacha et al., 2008b), amphibians (Phillips and Borland 1992a; Deutschlander et al., 1999a; Freake and Phillips, 2005) and, possibly, birds (Muheim et al., 2002; Wiltschko et al., 2010) share functional properties (i.e. light-dependent 90 deg rotations in the direction of magnetic compass orientation) that appear to result, at least in part, from an antagonistic interaction of short- and long-wavelength inputs (Phillips and Borland, 1992a; Deutschlander et al., 1999b; Phillips et al., 2010).

Subsequent studies found that the functional properties of the magnetic sense in some organisms differ depending on behavioral context and physical conditions (Phillips, 1986; Phillips and Borland, 1992a; Phillips and Borland, 1992b; Phillips and Borland, 1994; Phillips et al., 2002a; Wiltschko and Wiltschko, 2005; Stapput et al., 2008), raising the possibility that more than one magnetoreception mechanism can be present in the same organism. In addition to a LDMC, vertebrates such as birds and amphibians appear to have a non-light-dependent (i.e. magnetite and/or maghemite-based) 'map detector' used to derive geographical position from subtle gradients in the magnetic field (for reviews, see Freake et al., 2006; Winkelhofer and Kirschvink, 2010). Such magnetite-based mechanisms can provide non-compass directional information and, therefore, could have evolved to function as a compass as well. However, the majority of directional responses in which magnetite has been implicated appear to be 'alignment', rather than true compass (i.e. goal directed) responses. For example, when migratory birds are tested in total darkness, they exhibit a fixed direction of magnetic orientation that, in contrast to normal migratory (i.e. compass) orientation: (1) does not reverse seasonally, (2) is sensitive to the polarity of the magnetic field, and (3) is unaffected by low-level radio frequency (RF) fields (Ritz et al., 2004; Thalau et al., 2005; Stapput et al., 2008). In addition, (4) the fixed response of birds, but not LDMC orientation, is eliminated by anesthetization of the beak area containing the putative magnetite-based receptor (Stapput et al., 2008). In newts, a similar fixed response appears to be mediated by permanent magnetic material (presumably magnetite), and may function to position a magnetite-based map detector in a specific alignment relative to the magnetic field to obtain precise measurements of components such as intensity or inclination necessary to derive map information (Phillips and Borland, 1994; Phillips, 1986; Phillips et al., 2002a; Phillips et al., 2002b). Indeed, the only animals that may use a magnetite-based magnetic compass (as opposed to a map) are functionally blind, subterranean mole rats (Burda et al., 1990; Marhold et al., 1997; Kimchi and Terkel, 2001; Kimchi et al., 2004; Thalau et al., 2006; Némec et al., 2007). Like reduction of the visual system (Némec et al., 2007), the use of a magnetite-based magnetic compass could be an adaptation to the subterranean habitats in which mole rats live. However, a fixed alignment behavior, as opposed to a compass response, cannot be excluded in mole rats, and it remains to be determined if a magnetite-based magnetic compass exists in other mammals. Evidence from our laboratory suggests that the magnetic compass of epigeic rodents (e.g. dwarf hamsters, C57BL/6 mice) has more in common with newts and migratory birds than with mole rats (Deutschlander et al., 2003; Muheim et al., 2006a) (J.B.P. and R.M., unpublished data).

Regardless of the functional significance of the alignment responses in birds and amphibians, the fact that animals can use a magnetite-based mechanism to align themselves relative to the magnetic field adds further impetus to the question of why these animals would evolve a separate light-dependent mechanism to provide compass information. In this paper, after briefly outlining evidence that the biophysical process underlying the LDMC involves a magnetically sensitive radical pair mechanism (RPM), we discuss the possibility that the LDMC plays a previously unrecognized role in vertebrate, and in particular mammalian, spatial cognition. We suggest that the LDMC, in addition to providing a source of directional information, provides a spherical coordinate system that serves as an interface between directional and spatial perception.

The radical pair mechanism

The LDMC is proposed to involve a light-dependent biochemical reaction that forms long-lived (>1 μs), spin-correlated, radical pair (RP) intermediates (Schulten and Windemuth, 1986; Ritz et al., 2000; Cintolesi et al., 2003; Solov'yov et al., 2007; Rodgers and Hore, 2009). Maeda et al. recently demonstrated the feasibility of the RPM by showing that the alignment of an Earth-strength magnetic field can affect the lifetime of a synthetically formed RP system at low temperatures (Maeda et al., 2008). Cryptochromes, a specialized class of photopigments involved in circadian rhythms and in a variety of non-visual light responses (Sancar, 2004; Tu et al., 2004; Partch and Sancar, 2005; van Gelder, 2006), are the only animal photopigments that form persistent spin-correlated RP intermediates (Liedvogel et al., 2007; Biskup et al., 2009) and, thus, are proposed to play a central role in the LDMC.

Both cryptochromes, and the closely related photolyases that carry out blue-light-activated DNA repair, have a flavin chromophore, FAD/FADH, a highly conserved flavin-binding region, and an associated triad of tryptophan residues (Partch and Sancar, 2005; Lin and Todo, 2005). According to one reaction scheme, absorption of short-wavelength light by the fully oxidized form of the flavin results in electron transfer from the triad of tryptophans to the flavin, forming a long-lived, spin-correlated, flavin–tryptophan RP that is initially in an overall singlet state [i.e. the spins of the unpaired electrons are antiparallel (Ritz et al., 2000; Ritz et al., 2009; Cintolesi et al., 2003; Solov'yov et al., 2007) and see below]. The change in charge distribution during RP formation may result in a conformational change in the cryptochrome protein, causing it to interact with other, as yet unidentified, signaling partners. An alternative reaction scheme is one in which the resting state of the flavin chromophore is in the partially reduced, radical form ($FAD•^{-}$ or FADH•), as occurs in the photolyases, which is photoreduced to the fully reduced ($FADH•^{-}$) signaling state, and may involve a radical partner other than the tryptophan triad (Öztürk et al., 2008; Song et al., 2007; Gegear et al., 2010).

Regardless of whether formation of the RP involves an interaction of the flavin chromophore with the tryptophan triad or with some other as yet unidentified radical partner (Gegear et al., 2010), if the RPs are in an ordered array, the alignment of an Earth-strength magnetic field may influence the rate of inter-system crossing between the singlet and triplet excited states of the radical form (Rodgers and Hore, 2009). Due to conservation of spin, back transfer of an electron that returns the flavin chromophore to the fully reduced form (FAD_{ox}), which can either terminate or compete with formation of the signaling stage, can only occur when the RP is in an overall singlet state. Alignments of the magnetic field that produce greater singlet ↔ triplet mixing, reducing the singlet character of the radical pair, will decrease the rate of back transfer and increase the persistence of the radical form. Depending on which redox form of the flavin chromophore is the signaling state, the effect of the magnetic field can produce a corresponding increase or decrease in the response to light (see Phillips et al., 2010).

Several recent findings lend credence to the involvement of a cryptochrome in the LDMC. These include an effect of a strong magnetic field on RP formation in a cryptochrome (Bouly et al., 2007), and evidence for cryptochrome-mediated responses to moderately strong (6–10 times earth strength) magnetic stimuli in *Drosophila melanogaster* (Gegear et al., 2008; Gegear et al., 2010; Yoshii et al., 2009). Because cryptochromes do not function as primary visual pigments, and a cryptochrome-based RPM does not require image-forming optics, the LDMC could, in principal, be found in any tissue in the body that receives significant levels of light. However, evidence for the involvement of retinal photoreceptors in magnetoreception in birds (Semm et al., 1984; Semm and Demaine, 1986; Wiltschko et al., 2002) and, possibly, rodents (e.g. Olcese et al., 1985) points to one of the most intriguing features of the LDMC, i.e. in some animals the magnetic field may be perceived as a visual pattern superimposed on the animal's surroundings (Schulten and Windemuth, 1986; Ritz et al., 2000; Cintolesi et al., 2003; Rodgers and Hore, 2009). Given the complex 3-D pattern of response that could arise from a cryptochrome-mediated LDMC (Fig. 2), the visual system offers a number of advantages for detecting the magnetic field, including neural processing mechanisms that enhance contrast discrimination and facilitate detection of complex images against moving and non-moving backgrounds (Mouritsen and Ritz, 2005), and that integrate directional information from multiple light-dependent compass systems (Wiltschko and Wiltschko, 2003; Muheim et al., 2006b).

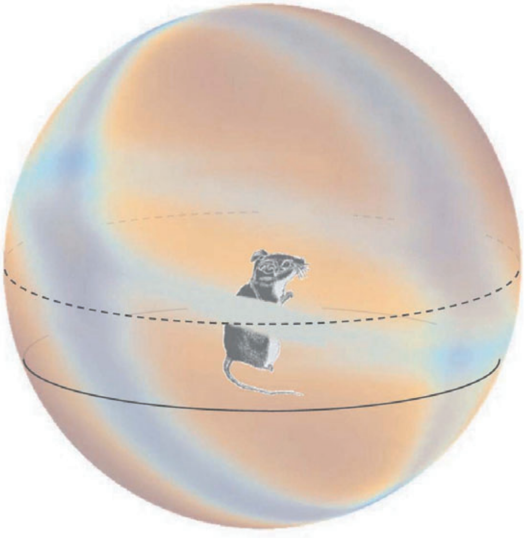

Fig. 2. Pattern generated by an earth-strength magnetic field in a model flavin–tryptophan radical pair (RP) system in which magnetic nuclei that dominate the interaction are aligned along non-parallel axes [data from Cintolesi et al. (Cintolesi et al., 2003)]. The pattern is shown as it would appear projected on the inside of a sphere surrounding the animal. If the interaction with the magnetic field occurs in retinal photoreceptors, the pattern may be perceived as a visual image superimposed on the animal's surroundings (Ritz et al., 2000; Cintolesi et al., 2003; Solov'yov et al., 2007; Rodgers and Hore, 2009). If so, the section of the 3-D pattern that the mouse would see at any one time would be limited by the size of its visual field. Red–orange regions of this figure correspond to the dark patches at either end of magnetic axis in Fig. 1C. The solid black ring indicates the level of the substrate. The dashed black ring shows the horizontal plane at the level of the retina.

Evidence for a RPM-based magnetic compass in some animals includes: (1) sensitivity to the axis, but not polarity, of the magnetic field (Fig. 1) (Wiltschko and Wiltschko, 1972; Phillips, 1986); (2) involvement of a light-dependent magnetoreception mechanism (Phillips and Borland, 1992a; Phillips and Borland, 1992b; Phillips and Sayeed, 1993; Freake and Phillips, 2005; Wiltschko and Wiltschko, 2005; Vacha et al., 2008b); (3) disruption of magnetic compass orientation outside a narrow window of static field intensities (Wiltschko and Wiltschko, 2005); (4) the absence of an effect of 'pulse remagnetization' (Beason and Semm, 1996; Munro et al., 1997a; Munro et al., 1997b); and (5) disruption by low-level alternating fields (~0.1% of the static field strength) in the low RF range (<100 MHz) that should alter the magnetic field-dependent populations of singlet and triplet energy states in a RPM (Ritz et al., 2004; Ritz et al., 2009; Henbest et al., 2004; Thalau et al., 2005; Vacha et al., 2009). In migratory birds, the effects of low-level RF fields have been shown to depend on both the intensity and relative alignment of the static magnetic field (Ritz et al., 2004; Ritz et al., 2009), providing compelling evidence for a RPM or closely related process (see Henbest et al., 2004; Rodgers and Hore, 2009); RF field intensities several times stronger than the geomagnetic field would be necessary to produce a similar effect on a magnetite-based mechanism (Henbest et al., 2004).

A simple RP system, with one electron and one nuclear spin on each radical, exhibits a 'dumbbell-shaped' pattern with symmetrical areas of higher or lower response that coincide with the two ends of the magnetic field axis, and may include one or more rings orthogonal to this axis (Fig. 1C) (Ritz et al., 2000). More realistic models taking into account multiple nuclear spins in their native alignments (e.g. Cintolesi et al., 2003; Solov'yov et al., 2007; Rodgers and Hore, 2009) suggest that the LDMC may produce a more complex 3-D pattern (Fig. 2).

Optimization of the LDMC response

The pattern of response produced by a RPM-based LDMC depends on a large number of factors, some of which may be subject to optimization by natural selection (Cintolesi et al., 2003; Solov'yov et al., 2007; Maeda et al., 2008; Rodgers and Hore, 2009). As one example, the flavin–tryptophan RP system modeled by Cintolesi et al. (Cintolesi et al., 2003) exhibits a pattern of response that is dominated by the effect of the nuclear spins of two nitrogen atoms in the flavin radical that are nearly collinear. The contributions of other nuclei, aligned along different axes can have two effects: (a) adding complexity to the pattern of response (Fig. 2), and (b) weakening the overall effect of the magnetic field and, thus, the detectability of the pattern. Cintolesi et al. (Cintolesi et al., 2003) suggest that such a RP system could be modified by natural selection to function more efficiently as a magnetic compass by changing the relative alignment of the two radicals, e.g. in a flavin–tryptophan RP the magnetic nuclei in the tryptophan radical could be aligned more collinearly with those of the two nitrogen atoms in the flavin radical. This would result in a stronger effect of the magnetic field on the response to light, and a simpler pattern that more nearly matches that of the simple RP system modeled by Ritz et al. (Ritz et al., 2000) (Fig. 1C) (see Solov'yov et al., 2007). Recent evidence suggests that formation of the RP may involve an interaction of the flavin chromophore of cryptochrome with a redox partner(s) other than the tryptophan triad. Nevertheless, the RP system modeled by Cintolesi et al. illustrates the general point, which is that changes in the relative alignment of the members of the RP can affect the complexity of the pattern produced by the magnetic field (Cintolesi et al., 2003). Rodgers and Hore have also shown that the pattern of response in a RPM-based magnetic compass would be simplified if the RP is fixed in alignment along one axis but randomly rotationally aligned around this axis (Rodgers and Hore, 2009). This would cause components of the response that do not coincide with the rotational axis to cancel out to a large degree, and leave mainly the axially symmetrical components coinciding with the rotational axis.

Importantly, however, simplifying and strengthening the pattern of response does not resolve the conundrum raised at the outset of this paper. Unless a LDMC mechanism with a simpler and more detectable pattern of response offers greater functionality than a magnetite-based magnetic compass, this would not explain why both magnetite-based and RP-based magnetoreception mechanisms have been maintained by natural selection in vertebrates as different as salamanders and songbirds.

Here we approach this question from a different point of view. We suggest that the complexity of the LDMC response (e.g. Fig. 2) should be viewed, not as an impediment to its use as a source of directional information, but rather as the key to understanding its unique functionality. In this context, it is important to emphasize two characteristics of a RPM-based LDMC perceived as a 3-D visual pattern: (1) the pattern will be more-or-less fixed in alignment with respect to a global (i.e. magnetic) reference frame (see below); and (2) the animal will remain at the center of the pattern as it moves about the environment. Given these characteristics, we hypothesize that the LDMC functions as a simple spherical coordinate system with the animal at its center, and that this coordinate system provides a reference frame for integrating directional and spatial information. If so, natural selection is unlikely to have favored a simple (i.e. 'dumbbell-shaped') pattern of response but rather a more complex 3-D pattern resulting from subpopulations of magnetic nuclei with primary axes aligned along two or three more-or-less orthogonal axes.

What role might the LDMC play in mammalian spatial perception?

In epigeic rodents, familiar landmarks exert primary control over a variety of spatial behaviors and related neural mechanisms (O'Keefe and Nadel, 1978; Taube et al., 1990; Taube and Burton, 1995; Dudchenko et al., 1997; Sharp et al., 2001; Sharp, 2002). Nevertheless, a directional sense that is not linked to visual landmarks also appears to play a central role in many aspects of rodent spatial behavior and cognition (e.g. Knierim et al., 1995; Skinner et al., 2010; van der Meer et al., 2010). Species such as rats show a remarkable ability to place neural representations of different surroundings into register. When rats are transferred to an unfamiliar laboratory enclosure, directional properties of, for example, head direction cells and subicular place cells typically retain the same absolute alignment (Sharp and Green, 1994; Knierim et al., 1995; Taube and Burton, 1995; Dudchenko et al., 1997; Sharp, 1997; Sharp, 2002; Sharp et al., 2001), suggesting that these properties are transferred to the local surroundings, rather than the other way around. The prevailing view is that different areas are linked together by a path integration system derived from self-generated, i.e. ideothetic, cues that enable the animal to keep track of its alignment as it moves, or is moved, between different locations (Knierim et al., 1995; Brown et al., 2002; Stackman et al., 2003; van der Meer et al., 2010; Skinner et al., 2010) (but see Dudchenko et al., 1997).

A magnetic compass could also play a role in linking together spatial representations of different surroundings by providing a global reference system used to place local landmark arrays into register, or by increasing the accuracy of a path integration system that enables the animal to keep track of its body alignment as it moves between local areas; accumulation of errors by a path integration system can be substantially reduced by referencing turn angles to an external compass system (Cheung et al., 2008). Within local areas, information from a magnetic compass could be used to define directional relationships between landmarks, as well as to specify spatial locations within the landmark array (Jacobs and Schenk, 2003).

Despite the potential utility of magnetic information, and the evidence for a magnetic compass in several species of rodents (e.g. Kimchi and Terkel, 2001; Kimchi et al., 2004; Deutschlander et al., 2003; Muheim et al., 2006a), to date there is no compelling evidence to suggest that the magnetic field is used by rodents as either a global reference system or as a component of the path integration system (Brown et al., 2002; Dudchenko and Davidson, 2002; Stackman et al., 2003; Sharp, 2006) (but see Kimchi et al., 2004). Indeed, several findings have been interpreted as indicating that magnetic compass cues do not play an important role in rodent spatial cognition.

The first is the primary control that visual cues exert over neural and behavioral responses, i.e. rotation of a familiar visual landmark array results in a corresponding rotation of these responses (reviewed by Sharp et al., 2001). It is important to note, however, that in migratory birds visual cues (i.e. star patterns) exert primary control over migratory orientation even though the magnetic field's role in the initial calibration of the star compass is well established (Wiltschko and Wiltschko, 2003). Therefore, the proximal control of directional responses by visual landmarks does not rule out the magnetic field playing a role in establishing the rodent responses when they are first introduced into unfamiliar surroundings.

Secondly, effects of lesions of the vestibular system on the directional properties of head direction cells in rats have been interpreted as evidence against the involvement of magnetic compass cues (Sharp et al., 2001). When rats are transferred between laboratory enclosures, individual head direction cells typically show similar preferred directions of firing in the two enclosures. Lesions of the vestibular system alter or eliminate this directional sensitivity (Knierim et al., 1995; Stackman and Taube, 1998; Stackman et al., 2002), consistent with inertial cues exerting primary control over these responses. Interpretation of these findings is complicated, however, by the vestibular system's involvement in processing gravitational information (Pleusner, 2001; Angelaki and Dickman, 2004). Gravitational cues play an essential role in the LDMC, providing a vertical reference used to resolve the ambiguity inherent in the axially symmetrical (i.e. polarity independent) pattern of response (Fig. 1C) (Wiltschko and Wiltschko, 1972; Phillips, 1986). In birds, neurophysiological responses have been recorded from the vestibular nuclei that are sensitive to both magnetic and gravitational input, suggesting that this may be a site where integration of magnetic and gravitational information occurs (Semm et al., 1984). Thus, further studies of rodents are needed to determine whether lesions of the vestibular system eliminate magnetic, as well as inertial, information.

Although a magnetic compass can be used to specify directional relationships among objects in the environment, the flexibility of the rodent spatial sense, as well as evidence for systematic coverage of large areas of space, point to an underlying process that is not simply a piecemeal assemblage of directions. Instead, there is growing evidence that spatial perception emerges from computational processes that produce regular geometrical partitioning of space (O'Keefe and Burgess, 2005; Hafting et al., 2005; McNaughton et al., 2006). Therefore, the relevant question here is how might input from a LDMC interface with internally generated map(s) of space?

As discussed previously, if an effect of the magnetic field like that shown in Fig. 2 occurs at the level of the photoreceptors or second-order neurons in the retina (e.g. in birds and mammals), it may be perceived as a visual image superimposed on the animal's surroundings (Ritz et al., 2000; Ritz et al., 2010). The result would be a compound visual image consisting of the sky and objects around the animal (the visual surroundings the animal 'moves through'), and the visual pattern generated by the magnetic field (effectively a simple, spherical coordinate system the animal 'moves with'; Fig. 2). In other words, the animal would be surrounded by a spherical coordinate system that is more-or-less fixed in direction as it moves through the environment. This may be complicated somewhat by the disparity between the alignment of photoreceptors in the retina and that of rays of light entering the eye through the lens and cornea, which determines the projection of the visual surroundings onto the retina (Fig. 3) (see Ritz et al., 2010). The effect of this disparity would be to compress the pattern generated by the magnetic field orthogonal to the line of sight, defined here as the direction viewed by photoreceptors in the center of the retina directly opposite the lens. For photoreceptors in the center of the retina, there will be little or no distortion of the pattern. The deviation of photoreceptor alignments relative to the direction of incoming light (and thus the compression of the pattern of response relative to the center of the visual image) will be progressively larger as the angle from the center of the retina increases (Fig. 3). Distortion of the pattern will be reduced or absent in vertebrate eyes in which photoreceptors involved in magnetoreception point toward the nodal point where rays of light that are not deflected by the cornea and lens intersect (Fig. 3), and would not occur in light-dependent magnetoreceptors in the compound eye of insects (Phillips et al., 2010). In the following discussion of spatial positioning, we will ignore the possible distortion of the pattern of response orthogonal to the line of sight in the vertebrate eye, because animals with retinal photo-magnetoreceptors would be able to reproduce an identical pattern at any spatial location by aligning the head in a specific direction relative to the magnetic field, e.g. to magnetic north or south as reported to occur in deer and cattle (Begall et al., 2008).

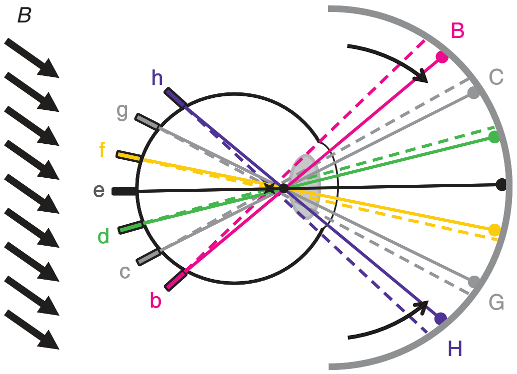

Fig. 3. Disparity between the pattern produced by the magnetic field and the visual image of the surroundings in the vertebrate eye. Cross section of the vertebrate eye showing the alignment of photoreceptors (small rectangles labeled b–h) and ray paths for light reaching the retina from the visual surroundings (solid lines connecting to the gray hemi-circle). Effects of the magnetic field (black arrows labeled '*B*') on photoreceptors in the retina will depend on the relative alignment of photoreceptors (dashed lines intersecting at the black 'X', the center of the eye's exit pupil) containing ordered arrays of light-absorbing molecules. By contrast, the projection of an image of the outside world onto the retina (solid lines connecting individual photoreceptors to corresponding locations in the visual surroundings; round symbols labeled B–H) will depend on the optics of the eye. The nodal point, i.e. the intersection of rays of light entering the eye that are not deflected by the lens and cornea, is indicated by a black dot. In this example, the discrepancy between the alignment of the photoreceptor array and the alignment of the image of the visual surroundings will cause any pattern produced by the magnetic field (shown by an arbitrary pattern of differently colored photoreceptors) to be compressed toward the line of sight (solid black line), as shown by the curved arrows. Compression of the pattern toward the line of sight will be independent of the direction the animal is facing.

The specific pattern generated by the LDMC and its appearance 'projected' onto the visual surroundings will depend not only on characteristics of the RP system (Cintolesi et al., 2003; Solov'yov et al., 1997; Rodgers and Hore, 2009), including the alignment of magnetic nuclei in the RP and the alignment of the RP array(s) in the retina, but also on the height above the substrate. In terrestrial mammals, the elevation of the eyes above the substrate may be more-or-less constant when the animal is surveying its

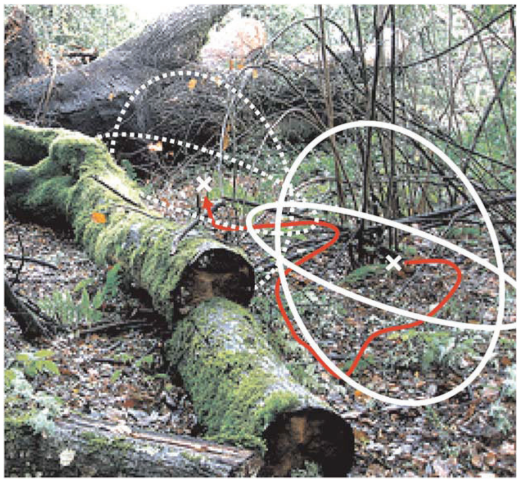

Fig. 4. Locating a previously visited site (e.g. a food cache) using the light-dependent magnetic compass (LDMC). Solid white ellipses show the hypothetical pattern generated by the LDMC at the animal's current location (white 'X'). The LDMC pattern stays in the same general relationship to the animal as it moves through the environment (as discussed previously, this may be influenced to some degree by the alignment of the animal's head). The red line indicates the animal's path of movement. A food cache hidden earlier can be located by moving within the familiar area until the current pattern generated by LDMC matches the remembered 'snapshot' of the LDMC pattern superimposed on the surroundings (dashed white ellipses). Both patterns are shown in the figure as if they were projected on the inside of a spherical surface surrounding the animal, while in the real world the pattern would appear to be projected onto the animal's visual surroundings. This mechanism would scale to the size of the animal's visual surroundings, e.g. it could help a squirrel find a buried acorn in a woodland clearing (above) or help a grazing animal to avoid a previously visited patch of endophyte-infected grasses in a large, open meadow, and could be used to define spatial relationships in three dimensions, e.g. it could help food storing birds to encode a 3-D array of cache sites or feeding stations (Krebs et al., 1996; Raby and Clayton, 2010).

surroundings (Fig. 2). If so, the distance at which some components of the 'visual' pattern are projected onto a horizontal substrate will also be relatively constant. The LDMC, therefore, could provide a metric of distance and/or be involved in integrating distance and direction, e.g. as part of a path integration system. By contrast, components of the LDMC pattern near the horizontal plane will be superimposed on the visual surroundings (objects, vegetation, terrain features, sky, etc.), irrespective of their distance from the animal. Perceptually, this would be equivalent to a visual pattern (spherical coordinate system?) that expands or contracts to fill the entire field of view.

When an animal encounters a novel environment, a compound image ('snapshot') consisting of the new surroundings with the spherical coordinate system provided by the LDMC superimposed could help to encode relationships between landmarks, as well as to place the landmark array into register with the local maps of other areas. If the animal retains a snapshot of the initial position of the LDMC's 3-D pattern on the landmark array (e.g. reflected in the subicular place cells firing fields; see below), this could be used to 'anchor' other neural representations of space to the landmark array. Matching the pattern produced by the LDMC to the retained/imprinted pattern as the animal moves could also help the animal to accurately locate a specific position within a familiar landmark array (Fig. 4), and to increase the accuracy of other (i.e. computational) maps of that space (O'Keefe and Burgess, 2005; McNaughton et al., 2006) (see Fig. S1 in supplementary material). Interestingly, Dvorkin et al., studying the exploration by mice of a featureless enclosure, found that a significant proportion of individuals established a unique location (referred to as a 'knot') near the point of release, which they returned to repeatedly over multiple days (Dvorkin et al., 2010). A knot was distinguished not by the mouse spending more time at that location (as is the case for so-called 'home bases') but rather by rapid turning that may provide an 'overview of the entire environment, allowing recalibration of the mouse's locale map and compass directions' (Dvorkin et al., 2010).

If input from the LDMC plays an important role in rodent (and, perhaps more generally, in mammalian) spatial cognition, this sensory input must reach areas of the brain involved in spatial processing. The complex 3-D pattern of response generated by a cryptochrome-based LDMC (e.g. Fig. 2) (Rodgers and Hore, 2009) could make the task of recognizing this type of sensory input quite difficult. However, individual receptors that are fixed in the surrounding tissue should remain in a more-or-less constant vertical alignment as the animal varies its heading in the horizontal plane (Fig. 5A). As a consequence, the responses of individual receptors should correspond to horizontal or conical sections through a 3-D pattern like that shown in Fig. 2. The actual responses will depend on properties of the RP system (Rodgers and Hore, 2009), the alignment of the RP array in the receptors and the inclination of the magnetic field. Nevertheless, when the LDMC response reflects the contribution of subpopulations of magnetic nuclei aligned along multiple axes (Fig. 5B), individual receptors are likely to exhibit a number of characteristic patterns similar to those shown in Fig. 5C. If the patterns of response are superimposed onto the animal's visual surroundings, they may be reflected not only in the directional properties but also in the spatial firing fields of cells that receive magnetic input, perhaps defined by the projected image of the pattern from a specific location (e.g. Dvorkin et al., 2010).

Properties compatible with LDMC input are seen in the spatial firing fields of rat subicular place cells, which are the patterns shown in Fig. 5C [data from Sharp (Sharp, 2002)]. In contrast to hippocampal place cells, the firing rate of subicular place cells depends, in part, on the animal's heading, and the firing fields retain the same spatial pattern and directional alignment when a rat is introduced to new surroundings. Furthermore, the firing fields expand or contract to encompass the area over which the animal has an unobstructed field of view (Sharp, 1997; Sharp, 1999; Sharp, 2002; Sharp, 2006). Subicular place cells with multiple firing fields are of particular interest, because they are most diagnostic of the 3-D pattern produced by a putative LDMC (Fig. 5C), and because the distinctive firing patterns suggest possible magnetic input to other spatial processing mechanisms (see Fig. S1 in supplementary material). To test whether a LMDC provides the primary input to the rat's subicular place cells, recordings could be carried out to compare the baseline pattern of firing fields in the ambient magnetic field with those obtained (a) with the magnetic field cancelled, (b) in the presence of low-level RF fields (Ritz et al., 2004; Ritz et al., 2009), or (c) under different wavelengths of monochromatic light (Fig. 5D) (Phillips and Borland, 1992a; Phillips et al., 2010) (see Appendix).

Conclusion

Given the value of the Earth's magnetic field as a source of local directional information and as a global reference system, it would be surprising if natural selection had not taken advantage of

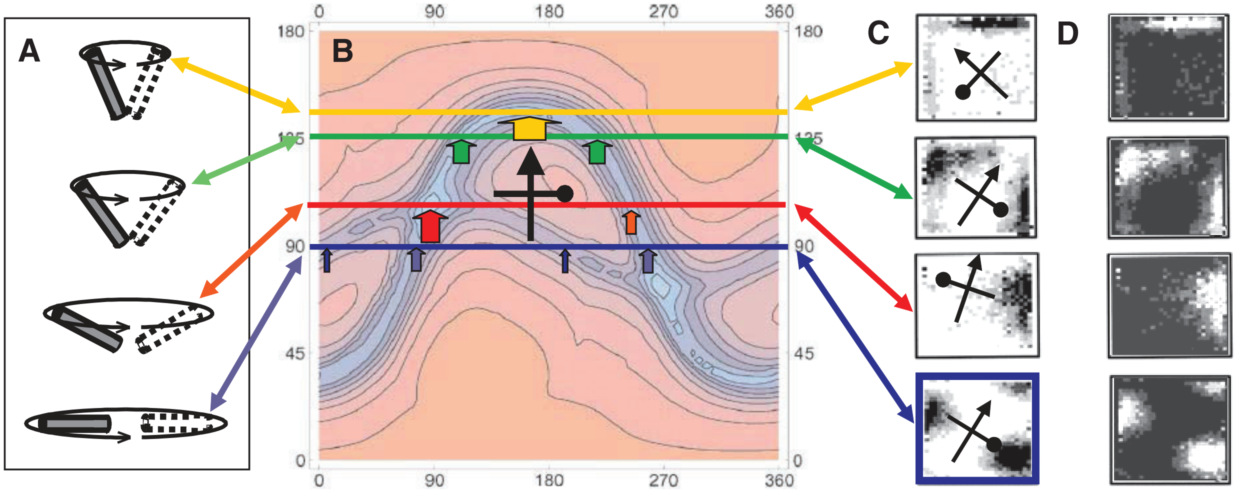

Fig. 5. Hypothesized pattern of magnetic input from individual light-dependent magnetic compass (LDMC)-based receptors [B is adapted from Cintolesi et al. (Cintolesi et al., 2003); C is adapted from Sharp (Sharp, 2002)]. (A) Changes in the alignment of hypothetical magnetic field sensors fixed in the body of an animal as it varies its heading in the horizontal plane. (B) Predicted 3-D pattern resulting from the magnetic field's effect on a model flavin–tryptophan radical pair system [adapted from Cintolesi et al. (Cintolesi et al., 2003); also plotted in three dimensions in Fig. 2]. Different colored horizontal lines superimposed on the figure approximate horizontal or conical sections through the pattern that would be sampled by single magnetic field detectors in the different vertical alignments shown in A. Arrows under each line indicate magnetic field alignments that would produce the greatest change in the response to light (see Cintolesi et al., 2003). (C) Firing fields of individual subicular place cells [adapted from Sharp (Sharp, 2002)]. Double-headed arrows connecting to horizontal lines of the same color in B show horizontal or conical sections through the hypothetical radical pair mechanism (RPM) response that would be expected to produce patterns similar to those in (C). To better see the correspondence, rotate and/or invert firing fields so black geometric shape matches the corresponding shape in the center of B; see Sharp (Sharp, 2002; Sharp, 2006) for additional recordings from subicular place cells with similar spatial firing fields. (D) Inverse or complementary patterns to those shown in C, which are predicted to occur if subicular place cells receive input from a LDMC mechanism with antagonistic spectral properties similar to those found in amphibians and insects (Phillips and Borland, 1992a; Phillips and Sayeed, 1993; Phillips et al., 2001; Phillips et al., 2010; Freake and Phillips, 2005; Vacha et al., 2008b).

magnetic input to enhance the precision and reliability of spatial processing mechanisms in rodents and other mammals. Moreover, the intrinsic properties of a RPM-based LDMC are well suited to provide not only a source of simple directional information but also a reference frame for integrating near-field and far-field directional/spatial information in three-dimensions. In some animals, this unique functionality may have tipped the balance in favor of a LDMC as the primary source of magnetic 'compass' information, allowing magnetite-based mechanisms to become specialized for other tasks such as magnetic navigation (Freake et al., 2006).

Appendix

Designing experiments to investigate the involvement of the LDMC in rodent spatial behavior

Sensitivity of the LDMC to low-level RF fields (e.g. Ritz et al., 2004; Henbest et al., 2004; Thalau et al., 2005; Ritz et al., 2009; Vacha et al., 2009) has important implications for designing experiments to investigate the role of magnetic cues in rodent spatial behavior. In a study of migratory birds exposed to a RF field tuned to the Larmor frequency (the precession frequency of the magnetic moment of an electron around an external field), Ritz et al. (Ritz et al., 2009) found that magnetic compass orientation was disrupted at an intensity of 15 nT but not 5 nT, which roughly bracketed background levels of ambient radio frequency interference (RFI); for comparison, the geomagnetic field is ~50,000 nT. Observations in our laboratory suggest that maximum sensitivity to RF in this frequency range may be as much as an order of magnitude lower (~1 nT) in an otherwise electromagnetically clean environment, and can disrupt the use of magnetic compass cues in animals as diverse as flies, salamanders and rodents (J.B.P., unpublished). Sources of RFI that may alter or eliminate the use of magnetic compass cues in laboratory environments include, e.g. thermostats, electric switches and motors, computers, as well as nearby radio transmission antennas and electric fences. Eliminating sources of RFI in typical laboratory settings can be extremely difficult because many of these sources are intermittent, and RFI may be carried by and radiated from electrical wiring far from the source, often from locations that are not under the control of investigators. Conversely, RFI-shielded rooms tend to be poorly suited for behavioral experiments with rodents, in part due to low-frequency vibrations and ultrasound produced when shielded entrance doors are opened and closed. Our experience suggests that testing facilities should be designed by behavioral scientists in collaboration with engineering colleagues who have expertise in measuring and shielding RFI. Failure to address these issues at the outset may result in years of controversy and unnecessary delays in understanding the role that magnetic compass cues play in rodent (and, more generally, mammalian) spatial cognition.

Glossary

Light-dependent magnetic compass (LDMC)

A sensory mechanism that derives directional (i.e. compass) information from the Earth's magnetic field that is altered by certain wavelengths and intensities of light, and/or abolished in total darkness.

Radical pair mechanism (RPM)

A biophysical mechanism proposed to explain the properties of the light-dependent magnetic compass in which the alignment of an Earth-strength magnetic field influences a photo-induced electron transfer (redox) reaction that forms radical intermediates ('radical pair').

Crytochromes

Light-sensitive flavoproteins that serve as photopigments in a variety of non-visual light responses in both plants and animals, affecting growth and development, entrainment of circadian rhythms and pupillary responses. Crytochromes also function as non-light-sensitive components of the mammalian circadian clock.

Photolyases

A class of flavoproteins in the same gene family as the cryptochromes that carry out light-dependent DNA repair.

Flavin adenine dinucleotide (FAD)

Cofactor that absorbs light and participates in light-dependent redox reactions in a variety of flavoproteins, including cryptochromes and photolyases.

Singlet state

A quantum state (S) in which the electron spins are antiparallel so the dipoles cancel out and the total spin moment is zero. In photo-excited electron transfer (redox) reactions, the radical pair is generally formed in an overall singlet state in which the spins of the unpaired electrons are antiparallel. When the radical pair is in an overall singlet state, an unpaired electron can back transfer to the original donor molecule, decreasing the persistence of the radical pair.

Triplet state

A set of quantum states each of which sums to S=1. In a radical pair, this occurs when the spins of the unpaired electrons are parallel and, thus, cannot occupy the same orbital, preventing back transfer of one electron to the original donor molecule, increasing the persistence of the radical pair. The triplet state is generally lower in energy than the singlet state.

Magnetite-based magnetic compass (MBMC)

A magnetoreception mechanism containing particles of the mineral magnetite that provides directional (i.e. compass) information.

Pulse remagnetization

Exposure to a brief, high-intensity magnetic pulse that can remagnetize particles of magnetite with stable magnetic moments, used to test for certain types of magnetite-based magnetoreception mechanisms. This treatment has no lasting effect on a light-dependent magnetic compass mediated by a radical pair mechanism.

Redox partner

Atom or molecule forming one member of a redox pair that undergoes an electron transfer reaction. As a consequence of electron transfer, one partner is oxidized (loses an electron) and the other is reduced (receives an electron).

Head direction cells (HDCs)

Neurons found in many parts of the brain that fire when the animal's head points in a specific direction, regardless of location. HDCs tend to be narrowly tuned, with firing rates approaching zero at approximately 45 deg on either side of the preferred direction.

Subicular place cells (SPCs)

Neurons in the subiculum of rats that fire when the animal occupies a specific spatial location or locations ('firing fields') relative to its surroundings. Properties of SPCs differ from the better known hippocampal place cells, which generally have a single firing field that changes unpredictably when the animal moves to new surroundings and is independent of the direction the animal is facing. By contrast, firing fields of SPCs show some variation in firing depending on the animal's compass heading, may consist of two or more subfields, retain the same general shape(s) and alignment(s) in different surroundings, and expand or contract to fill the animal's field of view.

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