Research Article

Detection of biogenic magnetic nanoparticles in ethmoid bones of migratory and non-migratory fishes

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Abstract
In this paper, the presence of biogenic magnetic nanoparticles, their localization, and quantity in the ethmoid bone and lateral ethmoid bone of Atlantic salmon, *Salmo salar*, northern pike, *Esox lucius*, and silver carp, *Hypophthalmichthys molitrix*, were studied using atomic force microscopy and magnetic force microscopy. It is shown that biogenic magnetic nanoparticles, grouped mainly in short or long chains, are contained in the ethmoid and lateral ethmoid bones of migratory (Atlantic salmon, *Salmo salar*) and non-migratory (northern pike, *Esox lucius*, and silver carp, *Hypophthalmichthys molitrix*) fishes. The number of biogenic magnetic nanoparticles in the ethmoid and lateral ethmoid bones of non-migratory fishes is of the same order of magnitude as in migratory fishes. The localization of biogenic magnetic nanoparticles in the ethmoid and lateral ethmoid bones of migratory and non-migratory fishes is similar. Thus, for the first time it was shown that the presence of biogenic magnetic nanoparticles in the ethmoid and lateral ethmoid bones of fishes is not related to their ability to navigate in the geomagnetic field.

Keywords Biogenic magnetic nanoparticles · BMN biomineralization proteins · Migratory fishes · Non-migratory fishes · Ethmoid bone · Magnetic force microscopy

1 Introduction

At the present time, biogenic magnetic nanoparticles (BMNs) have been found experimentally in algae and protists [1], worms [2], chitons [3], snails [4], ants, butterflies [5–7], honey bees [7, 8], termites [9], lobsters [10], newts [11], migratory and non-migratory fishes [12–15], sea turtles [16, 17], birds [18–21], bats [22], dolphins and whales [23], pigs [24], and humans [13, 25–29]. BMNs have been found in various human organs and tissues in normal condition [13, 25–27, 29].

The main idea of the presence of BMNs in organs and tissues of living organisms was associated with magnetotaxis and magnetoreception; therefore, organisms that move to fairly large distances in space were studied. In this connection, the question arises as to whether there is a similar localization of BMNs (the formation of chains) and how much their quantity differs in the organs and tissues of animals that hypothetically can be responsible for the magnetoreception (beak of birds, ethmoid bone of migratory fishes, brain), and other organs (heart, liver, lungs, intestines, muscles, skin, etc.), as well as in various organs of non-migratory organisms. This question is very important for understanding whether BMNs have a general function unrelated to magnetotaxis and magnetoreception. This is especially important in connection with the theoretical prediction of a common BMN biomineralization mechanism for all living organisms by bioinformatic methods [30].

That is why the purpose of this work is to determine the presence of BMNs in the ethmoid and lateral ethmoid bones of non-migratory fishes. The study of the localization and number of BMNs in non-migratory fishes and their comparison with migratory fishes have shown that

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SN Applied Sciences (2019) 1:63 | https://doi.org/10.1007/s42452-018-0072-1

Received: 26 May 2018 / Accepted: 20 November 2018 / Published online: 26 November 2018

the BMNs in the ethmoid and lateral ethmoid bones of fishes do not participate in the orientation of animals in the external magnetic field of the Earth.

2 Material and equipment

The proteome of migratory (Atlantic salmon, *Salmo salar*) and non-migratory (northern pike, *Esox lucius*, and silver carp, *Hypophthalmichthys molitrix*) fishes was aligned with the proteome of the magnetotactic bacteria (MTB) *Magnetospirillum gryphiswaldense* MSR-1, the BMN biomineralization mechanism in which has been studied in detail [31, 32], using the methods of comparative genomics. Pairwise and multiple alignment methods of the BLAST program of the National Center for Biotechnology Information were used to assess the degree of similarity between BMN biomineralization proteins of *Magnetospirillum gryphiswaldense* MSR-1 and proteins of migratory and non-migratory fishes. The generally accepted criteria were taken into account for the estimation of the degree of similarity of aligned sequences: the Ident (the number of identical amino acid residues of proteins), the E-value (the number reflecting the statistical significance of the alignment), the length (the length of the alignment), and the functions of the proteins being studied [33].

Determination of the presence of BMNs and the study of their localization in the ethmoid and lateral ethmoid bones of Atlantic salmon, *Salmo salar*, northern pike, *Esox lucius*, and silver carp, *Hypophthalmichthys molitrix*, was carried out using the «Solver PRO-M» scanning probe microscope by atomic force microscopy (AFM) and magnetic force microscopy (MFM).

The magnetic probe MFM_LM series with chip size $3.4 \times 1.6 \times 0.3$ mm, coated by CoCr, was used. This probe was used for both AFM and MFM imaging. The non-contact AFM (NC-AFM) mode was applied. The MFM scanning was carried out at a constant distance from the sample surface after AFM scanning. The probe "lift" height was 100 nm. The cantilever was calibrated using the test samples. Calibration of the probe was carried out immediately before the measurements.

The bone material of fishes was prepared before AFM and MFM scanning. Fixation of bone tissue was carried out in a 10% formalin solution. The duration of fixation was 24 h. After that, the bone tissue washed in distilled water and conducted through ethanol with increasing concentration (from 50 to 100%). Decalcification of bone tissue was carried out after complete fixation in a 10% formalin solution. A 5% nitric acid solution was used for decalcification of bone tissue, and the duration of decalcification was 24 h. After decalcification, the samples of the ethmoid and lateral ethmoid bones were rinsed for 24 h in 70% ethanol. The next stage was the impregnation of the decalcified bones with liquid paraffin at a temperature of 55 °C. After the solidification of paraffin at room temperature, a paraffin block was obtained. Slices from a paraffin block 5 µm thick were obtained using a microtome. After receiving the slices, they were placed on slides. The last stage was the release of slices from the mounting medium.

3 Results and discussion

In work [24], the presence of BMNs was theoretically shown in the overwhelming majority of organs and tissues of human using bioinformatic analysis. In turn, an analysis of the experimental data showed that BMNs are present in relevant or analogous fish organs and tissues (Table 1).

BMNs have been found experimentally in vital organs such as the brain [13, 25, 34, 35], heart [29, 36], liver [29, 36], as well as in human [37] and fish [12, 15, 38] ethmoid bone. The presence of BMNs in human lungs, intestines, muscle tissue, and skin was theoretically predicted [24],

Table 1 BMNs presence in different human and fish organs and tissues

Human organs with theoretically predicted BMN presence (+)	Experimentally confirmed BMN presence in human organs	Experimentally confirmed BMN presence in relevant or analogous fish organs
Brain (+)	Brain [13, 25, 35]	Brain [13]
Heart (+)	Heart [29]	Heart [36]
Liver (+)	Liver [29]	Liver [36]
Ethmoid bone (+)	Ethmoid bone [37]	Ethmoid bone [12, 15, 38]
Lungs (+)		Gills [36]
Intestines (+)		Intestines [36]
Muscle tissue (+)		Muscle [38, 40]
Skin (+)		Skin [38–40]
Eye (–)		Eye [36, 40]

and the presence of BMNs in relevant or analogous fish organs was experimentally confirmed [36, 38–40]. The analysis of the experimental data about the presence of BMNs in various organs and tissues of animals completely confirms the results of the bioinformatic analysis.

Most of the proteins that are involved in the BMN biomineralization in MTB are encoded in the magnetosome island (MAI) (in MamGFDC, Mms, and MamAB operons) [31] and are a manifestation of the genes of the magnetosome island [32, 41]. The MamA, MamB, MamM, MamE and MamO are proteins, without which the process of biomineralization of BMNs in MTB is impossible [42, 43]. Other proteins of the MTB MAI belong to regulatory proteins that are responsible for the control of shape, size, amount of BMNs in the cell, the formation of magnetosomal vesicles, and the formation of chains of BMNs [42]. MamK protein is a regulatory protein and is responsible for the formation of actin filaments and ensures the formation of chains of BMNs in cells of living organisms [44].

The homology of the MAI proteins of *Magnetospirillum gryphiswaldense* MSR-1 and proteins of migratory and non-migratory fishes was confirmed using generally accepted criteria. When comparing the MTB proteins and proteins of Atlantic salmon and northern pike, the Ident value is more than 18% [15], which indicates homology of MTB proteins and fish proteins [33]. Today, the recommended E-value threshold for searching for protein homologs in the NCBI database should be < 0.05, which ranges from 1e−29 to 0.023 when aligning proteins of *Magnetospirillum gryphiswaldense* MSR-1 and proteins of migratory and non-migratory fishes [15]. The length of the alignment should be > 100 amino acid residues. When comparing MTB proteins and proteins of the Atlantic salmon (*Salmo salar*), the length is 59–177 amino acid residues, and when comparing MTB proteins and northern pike (*Esox lucius*) proteins, the length is 101–174 amino acid residues [15]. A comparison of the functions of MTB proteins and proteins of Atlantic salmon and northern pike is necessary only for additional confirmation of protein homology.

The study of the MAI proteins of *Magnetospirillum gryphiswaldense* MSR-1 and proteins of migratory and non-migratory fishes showed that the corresponding homology proteins belong to the same families of proteins (Table 2).

An important step in bioinformatic analysis is the comparison of the functions of BMN biomineralization proteins of *Magnetospirillum gryphiswaldense* MSR-1 and homology proteins of Atlantic salmon and northern pike (Table 3).

Table 2 Homologs of MAI proteins of *Magnetospirillum gryphiswaldense* MSR-1 among proteins of Atlantic salmon and northern pike

Migratory and non-migratory fishes	*Magnetospirillum gryphiswaldense* MSR-1 proteins					
	MamA	MamB	MamM	MamO	MamE	MamK
	Migratory and non-migratory fish proteins					
Atlantic salmon, *Salmo salar*	TPR	Zinc transporter 4	Zinc transporter 9	Serine protease HTRA1	Serine protease HTRA1	Actin
Northern pike, *Esox lucius*	PEX5-related protein	Zinc transporter 4	Zinc transporter 9	Serine protease HTRA1	Serine protease HTRA1	Actin

Table 3 Comparison of known functions of the *Magnetospirillum gryphiswaldense* MSR-1 proteins and the Atlantic salmon and northern pike homology proteins

The name and function of the MTB MAI protein	The name and function of the homology protein of fishes
MamA—contains the TPR domain, which is involved in the function of protein–protein interactions, cell cycle, transcription, transport of proteins	TPR—is involved in protein–protein interactions, transport of proteins PEX5-related protein—is involved in the transport of proteins and alternative splicing
MamB—$Co^{2+}/Zn^{2+}/Cd^{2+}$ cation transporter	Zinc transporter 4—Zn^{2+} cation transporter [45]. It plays an important role in maintaining cellular zinc homeostasis [46]
MamM—$Co^{2+}/Zn^{2+}/Cd^{2+}$ cation transporter	Zinc transporter 9—Zn^{2+} cation transporter [46]
MamE—serine protease. The PDZ domain of the serine protease is involved in the response to heat shock, chaperone functions, apoptosis	Serine protease HTRA1—an enzyme encoded by the *HTRA1* gene. The *HTRA1* gene encodes proteins of the trypsin-like serine protease family. HTRA1 is a regulator of cell growth [47]
MamO—serine protease	

The functions of MamA, MamB, MamM, and MamE proteins are the same as the functions of migratory and non-migratory fish proteins that confirms their homology, established by bioinformatic analysis. At the same time, the presence of homologs of the MamK protein in all studied organisms suggests the possible formation of chains of BMNs by these organisms, which is confirmed by the results of MFM, which are given below. In addition, the presence of homologs of the MamK protein in all studied organisms may indicate the association of BMNs of these organisms with the cell membrane.

The multiple alignment of Mam proteins of MTB (the ability to BMN biomineralization was proved experimentally), the homologous proteins of migratory fish Atlantic salmon (the ability to BMN biomineralization was experimentally proved) and the homologous proteins of non-migratory fish northern pike was done. A search for conservative motifs that are responsible for the BMN biomineralization ability was made, and it was shown that such motifs of northern pike proteins are almost preserved compared to Atlantic salmon proteins.

Since homologs of Mam proteins were found in fishes and other multicellular organisms, and the ability to BMN biomineralization by these organisms has been experimentally proved by various methods [12, 13, 23, 28, 36, 38–40], it is unlikely that there are two analogous, but not homologous, mechanisms for the synthesis of magnetic nanoparticles in nature.

The AFM images make it possible to investigate the surface of the slices of the ethmoid and lateral ethmoid bones of the Atlantic salmon, *Salmo salar*, northern pike, *Esox lucius*, and silver carp, *Hypophthalmichthys molitrix*. In turn, the MFM images reflect the spatial distribution of BMNs, which are represented by black and white dots on the MFM images of the samples under study. The results of the study of the slices of the ethmoid bone of Atlantic salmon, *Salmo salar*, northern pike, *Esox lucius*, and silver carp, *Hypophthalmichthys molitrix*, are shown in Fig. 1, and the results of the study of lateral ethmoid bone of Atlantic salmon, *Salmo salar*, northern pike, *Esox lucius*, and silver carp, *Hypophthalmichthys molitrix*, are given in Fig. 2.

To increase the resolution of the images, an AFM and MFM study of the 15 × 15 μm section of Atlantic salmon ethmoid bone and the 10 × 10 μm section of northern pike ethmoid bone was carried out (Fig. 3).

The dark "spikes" (Figs. 1, 2) are obtained only as a result of MFM scanning and do not arise at AFM scanning of the sample surface topography. The repeating of MFM scanning several times in different (perpendicular) directions of scanning does not change the spatial distribution of "spikes." It proves that the "spikes" characterize the presence of magnetic nanoparticles. Figures 1c, f, i and 2c, f, i represent the overlapping of AFM topography image with MFM image. It means that MFM and AFM images were combined to one image with the purpose of revealing peculiarities of topography of the surface in the vicinity of BMNs.

As can be seen from Figs. 1b, e, h and 3b, d in the ethmoid bone of both migratory fish, Atlantic salmon, *Salmo salar*, and non-migratory fishes, northern pike, *Esox lucius*, and silver carp, *Hypophthalmichthys molitrix*, BMNs are mainly associated in short or long chains. It can be seen from Fig. 2b, e, h that the BMNs in the lateral ethmoid bone of the fishes under study are also mainly assembled into chains.

BMNs are found near the cavities through which nerve fibers and blood vessels pass in the human ethmoid bone [37]. So the BMNs were found mainly near the cavities through which the olfactory nerve fibers and small vessels pass from the nasal cavity of the skull in the ethmoid bone of fishes.

Table 4 gives data on the quantity of BMNs in the ethmoid and lateral ethmoid bones of migratory and non-migratory fishes.

The number of BMNs in the ethmoid and lateral ethmoid bones of non-migratory fishes (northern pike and silver carp) is of the same order of magnitude as in migratory fish (Atlantic salmon).

4 Conclusions

In this paper, it is shown that the proteins responsible for the biomineralization of BMNs in migratory (Atlantic salmon, *Salmo salar*) and non-migratory (northern pike, *Esox lucius*) fishes have the same functions confirming their homology, established by bioinformatic analysis.

The results obtained using MFM show that the ethmoid and lateral ethmoid bones of Atlantic salmon, *Salmo salar*, northern pike, *Esox lucius*, and silver carp, *Hypophthalmichthys molitrix* contain mainly short and long chains of BMNs. The localization of BMNs in the ethmoid and lateral ethmoid bones of migratory and non-migratory fish does not differ. BMNs are located mainly near the cavities through which the fibers of the olfactory nerves and small vessels pass. The number of BMNs in the ethmoid and lateral ethmoid bones of migratory and non-migratory fishes is of the same order of magnitude.

Bioinformatic analysis, as well as our experimental data and data of works of other authors, allows us to state that BMNs in the ethmoid and lateral ethmoid bones of migratory and non-migratory fishes are not related to their ability to migrate in the Earth's magnetic field. This statement contradicts the formulation of the

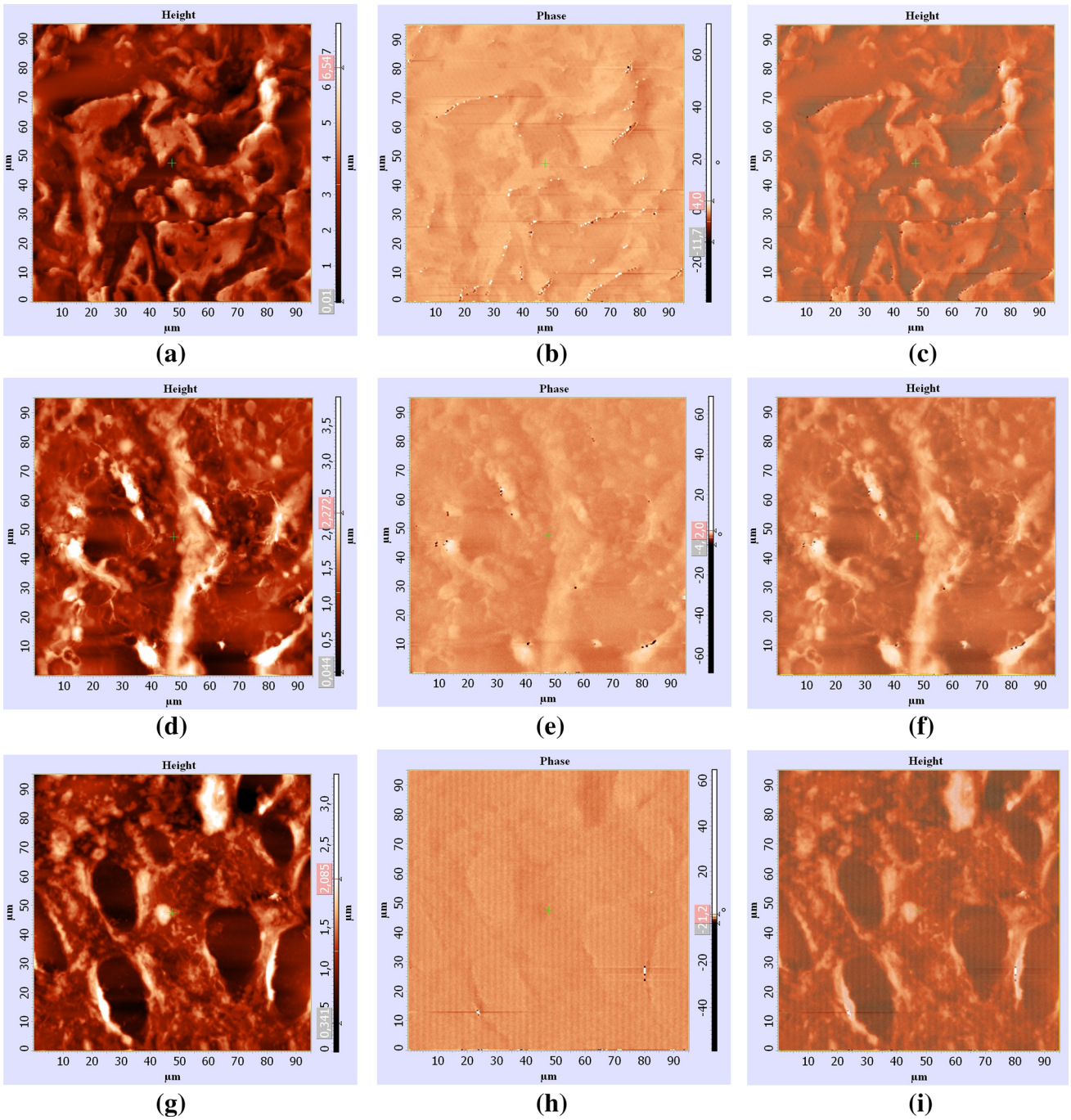

Fig. 1 Images of Atlantic salmon ethmoid bone: **a** AFM image, **b** MFM image, **c** combined AFM and MFM images; images of northern pike ethmoid bone: **d** AFM image, **e** MFM image, **f** combined AFM and MFM images; images of silver carp ethmoid bone: **g** AFM image, **h** MFM image, **i** combined AFM and MFM images

magnetite-based hypothesis for magnetoreception. However, a number of other studies are not consistent with the hypothesis that the main function of BMNs is magnetoreception, for example, detection of BMNs in human and mammalian organs, not related to migration: heart, liver, spleen [29], adrenal glands, kidneys and lungs [24], as well as the detection of BMNs in other non-migratory organisms and non-magnetotactic bacteria [48]. The work [49] showed that the destruction of the nerves connecting magnetite in the bird's beak with the brain does not affect the ability of the birds to migrate. Our study and the above studies are useful, as

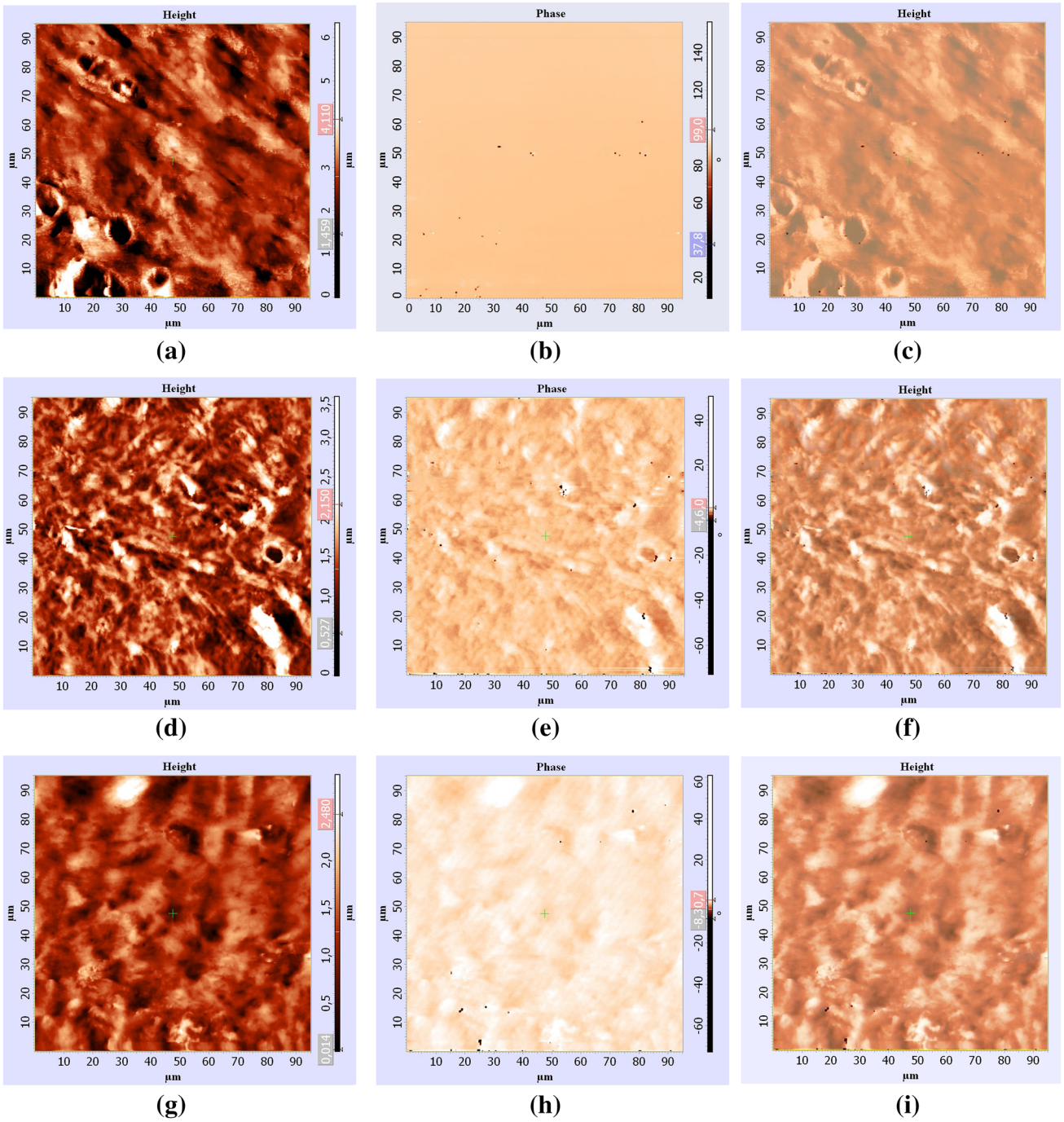

Fig. 2 Images of Atlantic salmon lateral ethmoid bone: **a** AFM image, **b** MFM image, **c** combined AFM and MFM images; images of northern pike lateral ethmoid bone: **d** AFM image, **e** MFM image, **f** combined AFM and MFM images; images of silver carp lateral ethmoid bone: **g** AFM image, **h** MFM image, **i** combined AFM and MFM images

they indicate the need to search for other functions of BMNs, not related to the magnetoreception. Therefore, this confirms the idea that BMNs have common metabolic functions not associated with magnetoreception in the overwhelming majority of organs and tissues of animals (brain, heart, liver, lungs, intestines, muscles, skin, ethmoid bone), and in particular in organs and tissues of migratory and non-migratory fishes (brain, heart, liver, gills, intestines, muscles, skin, ethmoid bone, lateral ethmoid bone).

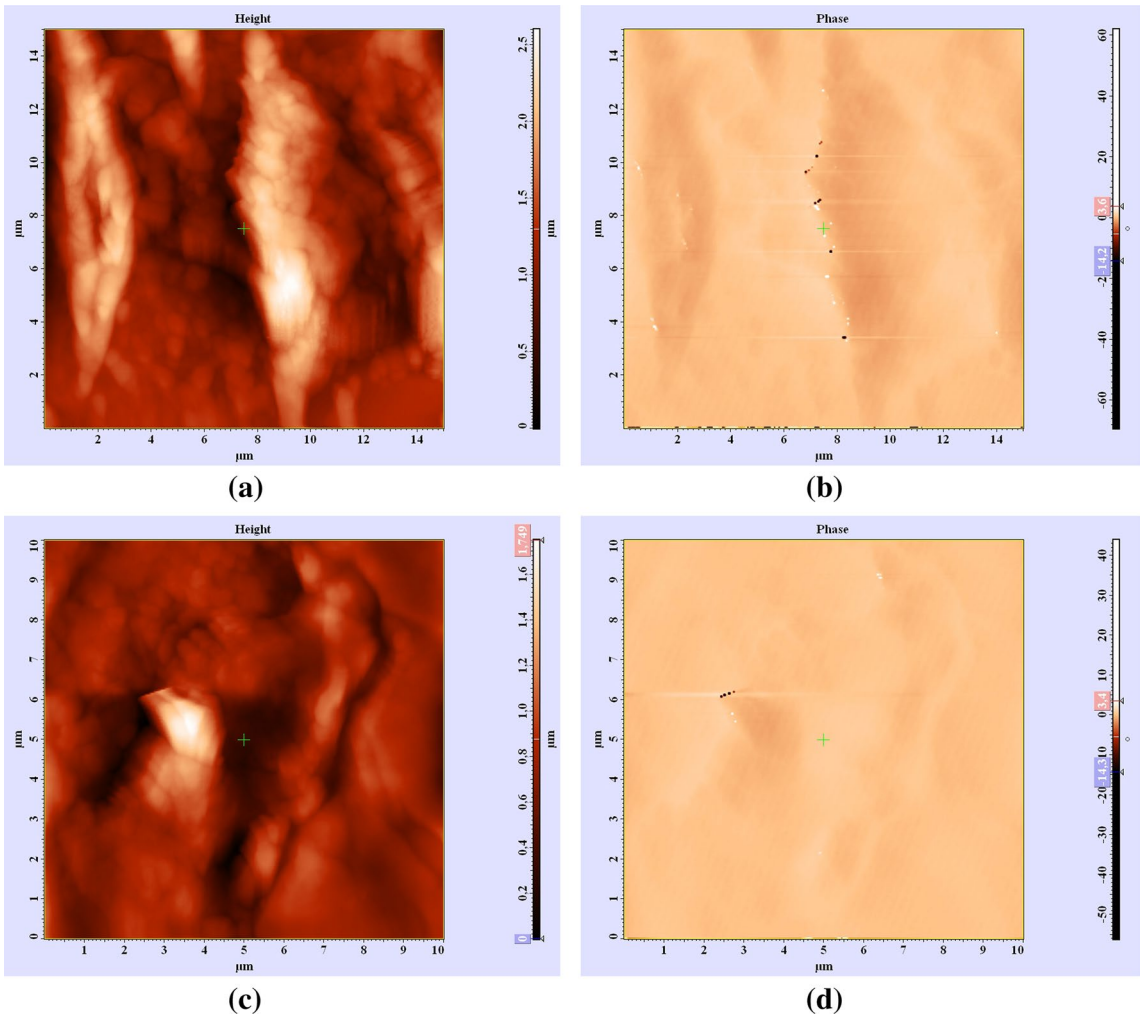

Fig. 3 Images of Atlantic salmon ethmoid bone (15 × 15 µm section): **a** AFM image, **b** MFM image; images of northern pike ethmoid bone (10 × 10 µm section): **c** AFM image, **d** MFM image

Table 4 The quantity of BMNs in the ethmoid and lateral ethmoid bones of migratory and non-migratory fishes

Migratory and non-migratory fishes	Fish organ	Number of particles (particles per 100 microns^2)
Atlantic salmon, *Salmo salar*	Ethmoid bone	150 ± 19
	Lateral ethmoid bone	99 ± 37
Northern pike, *Esox lucius*	Ethmoid bone	57 ± 3
	Lateral ethmoid bone	72 ± 17
Silver carp, *Hypophthalmichthys molitrix*	Ethmoid bone	86 ± 16
	Lateral ethmoid bone	105 ± 34

Acknowledgements This project has received funding from the European Union's Horizon 2020 research and innovation program under the Marie Skłodowska-Curie Grant Agreement No. 644348 (MagIC).

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