Review

Are stress responses to geomagnetic storms mediated by the cryptochrome compass system?

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A controversial body of literature demonstrates associations of geomagnetic storms (GMS) with numerous cardiovascular, psychiatric and behavioural outcomes. Various *melatonin hypotheses* of GMS have suggested that temporal variation in the geomagnetic field (GMF) may be acting as an additional *zeitgeber* (a temporal synchronizer) for circadian rhythms, with GMS somehow interfering with the hypothesized system. The cryptochrome genes are known primarily as key components of the circadian pacemaker, ultimately involved in controlling the expression of the hormone melatonin. Cryptochrome is identified as a clear candidate for mediating the effect of GMS on humans, demonstrating the prior existence of several crucial pieces of evidence. A distinct scientific literature demonstrates the widespread use of geomagnetic information for navigation across a range of taxa. One mechanism of magnetoreception is thought to involve a light-dependent retinal molecular system mediated by cryptochrome, acting in a distinct functionality to its established role as a circadian oscillator. There is evidence suggesting that such a magnetosense—or at least the vestiges of it—may exist in humans. This paper argues that cryptochrome is not acting as secondary geomagnetic zeitgeber to influence melatonin synthesis. Instead, it is hypothesized that the cryptochrome compass system is mediating stress responses more broadly across the hypothalamic–pituitary–adrenal (HPA) axis (including alterations to circadian behaviour) in response to changes in the GMF. Two conceptual models are outlined for the existence of such responses—the first as a generalized migrational/dispersal strategy, the second as a stress response to unexpected signals to the magnetosense. It is therefore proposed that GMS lead to disorientation of hormonal systems in animals and humans, thus explaining the effects of GMS on human health and behaviour.

Keywords: circadian system; geomagnetic navigation; cryptochrome; geomagnetic storms

1. INTRODUCTION

(a) *Geomagnetic navigation in animals*

The geomagnetic field (GMF) conveys orientational and positional information of substantial utility to migrating animals. Magnetoreception is thought to exist across a phylogenetically widespread array of taxa, including molluscs, insects, bony fish, amphibians, bats, rodents, artiodactylans, cetaceans, carnivorans and avian species (there are many good reviews [1–3]). Geomagnetic senses have a small overall physiological footprint and are redundantly integrated with other navigational and sensory stimuli in a complex fashion. For these reasons, they have often confounded scientific investigation, and it is only over the last few decades that their mechanisms and functionality have started to become elucidated. The majority of well-studied magnetodetection systems can be broadly divided into two categories: permanent ferromagnetic crystals normally found in the ethmoid sinuses of vertebrates, or a cryptochrome-mediated radical-pair based paramagnetic detection located in the eye. Many bird species appear to

have both systems working in tandem to produce a detailed magnetic map. These senses appear to be extremely sensitive—in order for the magnetic map to function, birds must be able to detect naturally occurring local changes in magnetic field strength that are down to perhaps 10 nT, equivalent to just a few miles or less [1]. Thresholds in the region 10–200 nT have been shown experimentally in birds and honeybees, and inferred for homing pigeons and whales [3].

(b) *Cryptochrome-based magnetodetection*

The radical-pair mechanism has been proposed as one of only a few molecular features that might plausibly be influenced by the Earth's magnetic field [4], with the yield of a biochemical reaction proceeding via a spin-correlated radical-pair-based reaction being sensitive to the orientation of an external magnetic field. A later theoretical refinement of the model proposed that the retina is well suited as an ordered structure for an array of molecules configured in various alignments with the GMF [5], with the product of the radical pair intermediate detected by the existing visual reception system. It was also hypothesized that cryptochrome was the most promising candidate molecule—it is the only

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known photoreceptor in vertebrates shown to be able to form a radical pair upon photoexcitation [5]. Mounting inferential evidence now supports a role for cryptochrome in avian magnetodetection: the hypothesized eye-localized, paramagnetic cryptochrome-based magnetodetection has a series of biophysical signatures, including (but not limited) to the following (for references and a more complete discussion, see reviews, [1–3,6]): (i) *Gene expression profile:* a high cytosolic localization of cryptochrome in avian retinal ganglion cells and co-localization with neuronal activity markers during magnetic orientation suggests a role of cryptochrome as a magnetic compass detector (beyond its established role as a circadian oscillator) [7]. (ii) *The avian compass is an inclination compass:* the radical-pair method is known to operate as an inclination compass (directional information is derived from the inclination of the field lines rather than their polarity). An inclination compass has been documented for geomagnetic navigation in every bird species tested, also revealing a corresponding insensitivity to polarity. (iii) *Geomagnetic navigation involves the eyes and is light-dependent*: the cryptochrome model proposes that magnetoreception involves photon absorption as a first step for creation of radical pairs, and therefore predicts that geomagnetic navigation will be dependent on a specific wavelength of light. It has been shown that magnetic orientation is wavelength dependent under low-intensity monochromatic light, with birds orientating well under blue wavelength, but are generally challenged under red wavelengths. (iv) *Sensitivity to oscillating magnetic fields in the low radio-frequency range*: these fields are expected to affect radical-pair reactions and compete with the effects of the GMF, but would not interfere with magnetite-based magnetodetection. Experiments with such fields have been shown to disrupt magnetic orientation behaviour of migratory birds. These results provide the strongest, albeit indirect, evidence that the biophysical mechanism underlying the magnetic compass of birds involves the radical-pair reaction, with such effects hard to reconcile with other mechanisms.

(c) *A human magnetosense?*

Somewhat surprisingly, while a human magnetosense is not widely accepted, there is accumulating evidence to suggest that such a sense—or at least the vestiges of it—may exist. It has recently been proposed that magnetoreception may be a general feature of at least mammals [4], and also that animals without a magnetosense may be the exception, rather than the rule [5]. The majority of human evolution involved migrational or nomadic lifestyles until the onset of sedentarization around 10 000 years ago [8], providing a clear functional utility for such a sense. In 1987, a meta-analysis of several studies directly testing for human geomagnetic orientation revealed a statistically significant result [9]. Recent studies with more sophisticated experimental design have confirmed these results, revealing that weak magnetic fields can trigger evoked potentials in human subjects [10]. Further human experimental studies have revealed that the visual sensitivity of man is influenced by changes to the GMF [11], interpreted as supporting evidence for the radical-pair retinal model in humans. Further publications have revealed that the fundamental

biological components for magnetoreception are present in humans. Ferromagnetic structures have been identified in human sinuses [12]. Moreover, recent experiments with *Drosophila* have revealed that the human cryptochrome CRY2 gene has functional magnetoreceptive abilities [13]. These experiments involved entraining *Drosophila* to navigate using a magnetic field, with the response shown to be blue-light dependent, thus implicating cryptochrome [14]. Moreover, cryptochrome-knockout *Drosophila* could not navigate in response to the magnetic field, providing the first direct evidence for the role of cryptochrome in magnetic navigation. In a subsequent transgenic experiment, the human cryptochrome CRY2 gene was revealed to rescue the magnetic navigation abilities of the knockout *Drosophila*, thus revealing that the human gene is functionally magnetosensitive [13].

(d) *Geomagnetic storms*

The GMF has a maximum field strength of around 70 μT at the geographical poles (where the field is near vertical) to less than 30 μT at the geomagnetic equator (where the field is parallel to the terrestrial plain). Coronal mass ejections can occasionally be directed towards the Earth. These can deliver a huge number of high-energy ions to the ionosphere, which are sufficient to cause relatively minor alterations to the strength and the direction of the magnetic field. Such events are dubbed 'geomagnetic storms' (GMS). These global disturbances can last from several hours to days, with the literature generally defining a geomagnetic storm as involving 24 h planetary average changes to the GMF of as little as around 30 nT [15–17]. Such storms occur on average once every 10 days or so, but do not occur with an even distribution. Instead, solar activity reveals a number of quasi-periodic oscillations, the most prominent of which is the approximately 11.5 year solar cycle. Furthermore, GMS tend to be more frequent at the equinoxes, and more extreme at higher latitudes [18,19].

(e) *Geomagnetic storms and human health*

A large, complex, and often controversial body of literature has linked elevated geomagnetic activity (GMA) with a range of human psychological, neurological, cardiovascular (CV), immunological and behavioural outcomes (see electronic supplementary material, table). The roots of this literature [20] lies with Russian biological science, where studies revealed a number of health associations of GMS of various strength and reproducibility, with many of these associations since investigated in the Western literature [19]. Owing to space constraints, selected evidence for the key findings is outlined below. However, the electronic supplementary material, table includes a detailed reference list.

While early Western studies on the CV system were controversial with some notable negative results [21] and a retraction [22], later studies have revealed positive associations of GMS with myocardial infarction, stroke, blood pressure, capillary blood flow and an inverse correlation with heart rate variability (HRV) [18,19,23,24]. One study observed that in years of peak GMS activity, patients admitted for myocardial infarction increased 25 per cent [25]; other studies have reported a similar relationship, accounting for a 5 per cent increase in

mortality in maximal solar years [26]. Moreover, these epidemiological studies are supported by evidence from both human [27,28] and animal [29,30] physiological studies that reveal changes to blood pressure and HRV in relation to geomagnetic disturbances.

With regard to the psychiatric literature, associations have been revealed between GMA and increased hospitalizations for depression [31] and ambulance callouts for mental disorders in general [32], with one well-cited study reporting an increase of 36 per cent in hospital admissions for males with a diagnosis of depression during periods of high GMA [31]. However, such psychiatric findings have not always been repeated and remain somewhat contentious (see electronic supplementary material, table and [18,19] for discussion).

Associations have also been demonstrated across wider health studies, correlating GMA with the total number of deaths [33]. Correlations have also been reported between solar cycles and longevity [34], although such findings remain equivocal [35]. A further series of studies have revealed associations between the solar cycle and flu pandemics [36], and a similar relationship was recently reported with papillomavirus infections [37]. Relationships have also been observed between GMA and sudden infant death syndrome [38] and epilepsy [39].

One of the few large literature reviews on GMS made the *definite* conclusion that GMA has an effect on human CV health, and the less certain conclusion that there may be an association between GMA and admissions for mental illness [18]. A review of the vast Russian magnetobiology literature concluded that 'the totality of the matter described here strongly supports the hypothesis that the GMF disturbances correlate with the general human condition' [19]. Associations of GMA with certain parameters—in particular, the CV system and melatonin suppression—are now so heavily reproduced that the associations themselves are not necessarily the subject of controversy. Rather, the fundamental question now relates to causation versus correlation. However, the obvious confounders—seasonality and latitude—are often controlled for, and the results have often been confirmed in various human and animal physiological studies both during GMS and using applied Earth-strength magnetic fields (electronic supplementary material, table). Therefore, serious consideration has been applied to a rational biological basis for these associations.

(f) The melatonin hypothesis of geomagnetic storms

A plausible mechanism of biological action of GMS has confounded biological sciences for decades—one of the primary reasons why the above findings are often treated with caution. When searching for rational explanations for the aetiology of GMS, a striking feature is their small magnitude—as little as 0.1 per cent or less of the background GMF, with typical directional changes of the field a fraction of a degree. This poses a significant problem when considering plausible biophysical mechanisms. While numerous models have been proposed (see [18,19,40] for discussion), most remain unclear and unsubstantiated by evidence. However, a series of hypotheses that argue a role for melatonin and the circadian system have gained the most widespread support [15,16,18,31,38,39,41,42].

Light is detected by the non-classical photoreceptor melanopsin in the eye, with the photic information conveyed to the suprachiasmatic nucleus (SCN), where it acts as the principal environmental synchronizer of the master mammalian circadian pacemaker, and is used to modulate coupled transcription/translation feedback loops [43–46]. This involves a molecular oscillator of several components including the Period genes (PER1, PER2 and PER3) and cryptochrome genes (CRY1 and CRY2). The SCN acts as master pacemaker that regulates many functions throughout the organism including endocrine functions (including melatonin and glucocorticoids), behavioural outputs (body temperature, sleep/wake cycles), metabolism and liver function. The pineal gland is the source of circulating melatonin, plasma concentrations of which are higher during the biological night than the day, and it is fundamentally involved in regulating the sleep–wake cycles. Retinal exposure to light at night, via the above outlined pathways, produces short-term suppression of night-time melatonin secretion in an intensity-dependent manner, which can result in the modulation of normal circadian rhythms.

The previously proposed *melatonin hypothesis* of GMS [15,16,18,31,38,39,41,42] is predicated on observations that GMA or applied magnetic fields in the geomagnetic range have been associated with lower mean nocturnal melatonin secretion (or its major metabolite 6-hydroxymelatonin-sulfate: 6-OHMS) in studies of both healthy individuals and CV patients [15,16,41, 47,48]. Such findings have been confirmed in animal experimental studies [49–54], although some negative results have been obtained [52,54] (see electronic supplementary material, table). Moreover, melatonin plays a central role in the regulation of diverse biological functions, and the other observed relationships of GMA (e.g. CV, psychiatric and immunological) all concern traits that are possibly influenced downstream by the effects of melatonin disturbance [45]. For example, there is evidence for the involvement of melatonin in various cardiopathologies [55,56]. Previous authors have therefore suggested that the influences of GMA on the CV system could be via a disruption of melatonin synthesis [47,48,57,58], with the effects transmitted to the CV system via melatonin action on the adrenal gland influencing glucocorticoid and cortisol production [59]. With the psychiatric findings, it has recently been suggested that the circadian system may be more directly involved in the aetiology of psychiatric disorders [60]. Marked changes are observed in the circadian systems of psychiatric patients [44], and circadian clock genes (including CRY2 [61]) have been associated with almost all neuropsychiatric disorders, albeit with some conflicting results [44]. Disrupted melatonin action could have further widespread deleterious effects on human health: it is an immunoenhancing modulator (thereby potentially influencing influenza and other infections) [36], is known to act as an anti-oxidant [45], is an endogenous anticonvulsant (thereby potentially influencing epilepsy) [39] and has been linked with sudden infant death syndrome [38].

While there is evidence of melatonin suppression in response to changes in the GMF, fundamental questions remain concerning the putative biophysical and molecular basis for such associations and the underlying biological *rationale* for such circadian behaviour. Below, the

evidence for the melatonin hypothesis is disinterred, reframed within the context of recent work on geomagnetic navigational magnetoreception, and extended: first, to hypothesize a specific biological candidate, and secondly, to hypothesize a novel but plausible theoretical framework.

2. CRYPTOCHROME AS THE PRIME CANDIDATE FOR THE EFFECTS OF GEOMAGNETIC STORMS ON HUMANS

Cryptochrome immediately presents itself as the prime candidate for a role linking GMS with the circadian system: of its two established functions, one is to act as a geomagnetic compass, the other is to act as a circadian oscillator. However, this is perhaps a somewhat naive appraisal of cryptochrome, as these roles are thought to be entirely distinct. During preparation and review of this manuscript, cryptochrome has, in a related manner, been suggested as a candidate gene underlying the observed relationships between the solar cycle and influenza pandemics [36] and suggested as the candidate for the controversial effects of anthropogenic sources of EMFs on human health [62,63]. These reviews are an ideal complement to this paper owing to their distinct focus (see also the electronic supplementary material for further discussion of PF-EMFs).

(a) *The evidence for cryptochrome*
(i) *Similarity of human and avian expression of cryptochrome.* Quantitative RT-PCR and immunohistochemistry of human tissue revealed a relative abundance of CRY2 transcripts localized to the inner retina and that it is also localized within the cytoplasm of some cells in the ganglion cell layer [64]. This originally led to suggestions that cryptochrome may perform a secondary retinal function of photo-entrainment of the circadian system. However, it is now known that melanopsin, rather than CRY2, primarily performs such a role [43], although some photo-entraining functionality of CRY2 cannot be excluded. Instead, it should be highlighted that this expression profile is similar to avian species, where CRY1 has also been shown to have a high cytosolic expression in ganglion cells (see electronic supplementary material, figure for visual comparison). This same expression, in avian species, has been inferred as evidence for the involvement of cryptochrome in magnetodetection [6,7]. (ii) *The human CRY2 gene is a magnetosensitive molecule.* These expression data are complemented by the above-mentioned *Drosophila* transgenic experiments, which established that the human CRY2 gene is a magnetosensitive molecule [13]. Both the location and functionality of CRY2 in humans are therefore consistent with a geomagnetic sensing role in humans. (iii) *Evidence that melatonin responses to changes in the GMF are transmitted via the eye.* A series of animal experiments provide evidence that the visual system is involved when melatonin is suppressed owing to magnetic disturbances. While applied Earth-strength magnetic stimulus significantly reduces the pineal activity and melatonin expression of rats, acutely blinded rats reveal no such response [50]. The authors concluded that this suggests a retinal magneto-sensitivity which may serve to modulate pineal function. However, a pineal magnetosensitivity cannot be excluded based on such data, as this may require a light signal as a trigger. (iv) *Evidence that melatonin response to changes in the GMF*

are light-dependent. Further animal experiments revealed that dim light is necessary to mediate the effects of the Earth-strength magnetic stimulus on pineal enzyme activity [49], with other animal studies also revealing interactions of light with the EMF [65]. However, it was revealed that the red light is sufficient to mediate the geomagnetic influence on the circadian system [49]. This finding is perhaps contrary to a role of cryptochrome in mediating these relationships—a blue-wavelength-specific response would be expected [6]. However, this could also be representative of an additional layer of complexity. Magnetoreception in nocturnal newts has been revealed to be dependent on yellow-red wavelength light, corresponding to moonlight-dependent magnetoreception [66], and some bird species appear to have multiple magnetic compass receptors operating at different wavelengths of light [6]. In humans, a series of studies have revealed a relationship between light exposure with both geomagnetic [15,16] and anthropogenic magnetic fields [67–69]. The authors argued that the reduction in 6-OHMS excretion associated with geomagnetic and electromagnetic activity may depend on low levels of ambient light. However, findings with anthropogenic EMFs remain extremely controversial, with the majority of studies producing negative results (see WHO [40] and discussion in the electronic supplementary material). (v) *Cryptochrome transgenic experiments.* Experiments with *Drosophila* revealed that applied magnetic fields influenced their circadian behaviour, and that this response was again blue-light-dependent [70]. Moreover, cryptochrome-knockout *Drosophila* did not show such a response, whereas flies overexpressing cryptochrome revealed an enhanced response. These experiments therefore provide initial direct evidence that cryptochrome is involved with transmitting magnetic field effects to the circadian system. The authors discuss the results within the context of cryptochrome acting as a secondary zeitgeber for the circadian system.

(b) *The geomagnetic field as a secondary zeitgeber?*
Several authors have previously argued that the GMF acts as a secondary zeitgeber of circadian rhythms, in addition to the primary synchronizer of the day–night-light cycle. This could operate via Schumann resonance signals [71] or the reduced variation in the magnetic field at night [42]. The electromagnetic field of 10 Hz exhibits diurnal variations [70], and it has been demonstrated that several organisms—including humans [72], mice [73] and *Musca* flies [74]—can have their circadian behaviour influenced or entrained by applied 10 Hz magnetic fields. However, there are issues with theories of the GMF as a secondary zeitgeber. There is a questionable utility of a variable secondary zeitgeber when working alongside a reliable primary synchronizer (e.g. day-light cycle). Moreover, numerous experiments have already revealed that when various species [70,72,75,76] are kept under constant lighting conditions, their circadian rhythms become free-running and decoupled from the usual 24 h cycle, i.e. they do not resort to a secondary daily geomagnetic synchronizer in the absence of the primary synchronizer. For example, the free-running circadian rhythm of humans was found to be 24.87 h in a natural geomagnetic environment (whereas under geomagnetically shielded conditions, it was demonstrated to

be a significantly longer length of 25.26 [72]). Although the experimental environment may be interfering with daily variations in the natural GMF in some of the above studies, it has been established that daily variations in the GMF across different animal facilities are essentially similar and omnipresent [77]. Thus, while the above studies confirm the influence of the GMF on the circadian system, no study has experimentally established that the natural GMF can act as a reliable zeitgeber. Instead, an alternative explanatory framework is proposed.

3. MAGNETOSENSE–HPA INTERACTIONS: TWO MODELS

(a) *A generalized model of migratory-dispersal strategies*

Migrating birds display a number of stressful physiological adaptations to long journeys with low food availability and high predation—an often nocturnal migration, reduced melatonin amplitude, increased metabolism, higher body temperature and increased energy expenditure [78]. However, just as the magnetosense is now thought to be a rather more common feature of animals than was previously considered, modern definitions of migration are much more inclusive than past interpretations [79]. The majority of species are now considered to exhibit life-history strategies that involve territoriality and home-ranges punctuated by periodic long-distant dispersals [80], which can occur for a plethora of reasons (e.g. resource availability, seasonal excursions, mating etc.) Such migrations represent a stressful phase mirrored by similar hormonal and behavioural adaptations to bird navigation, also mediated by the HPA axis [79]. While migrational life-history strategies are under complex control and poorly understood in birds and other animals, a relationship with navigational behaviour is implicated [79]. Therefore, in animals using the GMF for navigation, relationships are expected between the GMF and migrational behaviour. Given the apparent widespread existence of both long-distance dispersals and the magnetosense, hypothesized interactions between the GMF, migratory behaviour and hormonal control are possibly generalizable. In migratory birds, recent research has established that simulated GMFs influence hormonal secretion and migrational behaviour, with the elicited responses being related to specific adaptations of planned long-distant migrations such as fuelling and metabolic strategies [81,82]. In contrast to these specific strategies, unplanned dispersals in non-migratory animals might instead be expected to elicit a generalized stress reaction mediated across the HPA axis in response to unknown environments with subsequent risks such as low-resource availability and high predation. It is perhaps noteworthy that the above investigations on birds represent rare examples of animal experiments where hormonal responses to simulated MFs are as predicted by theory. Could the existing data relating changes in the GMF (either GMS or applied MFs) to hormonal behaviour in animals be appraised under a similar paradigm?

(b) *A generalized model of stress responses of sensory systems*

It has recently been suggested that in addition to simply providing compass information, the cryptochrome magnetosense provides a spherical coordinate system that serves to interface metrics of distance, direction and spatial position [83]. Magnetodetection could thereby provide a global reference system used to place local landmark arrays into a register with the local maps of other areas, to increase the accuracy of a path integration system, to define directional relationships between landmarks, and also to specify spatial locations within the landmark array. Such theories are controversial and to date there is no compelling experimental evidence (see [83] for discussion and references). However, observations with mole-rats have established that the magnetic sense is no different to the other senses, and is involved in multi-sensory integration with other inputs (e.g. vestibular, visual, etc.) [84]. Similarly, magnetically responsive activity has been identified in the nucleus of the basal optic root of birds, where the information is thought to interact with vestibular inputs [85]. Moreover, gravitational cues—derived from the vestibular system—play an essential role in cryptochrome-based magnetodetection, providing a vertical reference used to resolve the ambiguity inherent to a polarity-independent device [83]. When the vestibular system is exposed to extreme vestibular stimuli, such as hypogravity, hypergravity, horizontal or angular accelerations, there is an elicited acute stress response activated across the HPA axis [86,87], with the vestibular system being implicated in a variety of physiological and behavioural functions including modulation of circadian rhythmicity [86]. Furthermore, there is anatomical evidence for the existence of neuronal connections between the vestibular system to the SCN [87] and hypothalamic paraventricular nucleus (PVN) [86]. Thus, there exists a clear precedent for hypothesized interactions between a magnetosense and the HPA axis. Therefore, rather than stress responses of the magnetosense having evolved as a migrational strategy *per se*, as proposed above, such connections could instead be invoked as a response to extreme or unexpected signals. Such signals could degrade the proposed magnetodetective components of path integration systems [83] cause navigational disorientation, and therefore elicit a general stress response similar to those observed with the vestibular system.

Both of the above models are functionally related, involving stress responses in relation to novel, extreme or unexpected signals, and are treated as largely equivalent below. The first model appraises magnetosense–HPA interactions under classical and experimentally verified notions of the magnetosense as a primarily migrational device. However, the magnetosense is thought to have a maximum resolution of perhaps a few miles [1]. Therefore, in animals with limited dispersal ranges, it is difficult to envisage a geomagnetic component of dispersal-stress behaviour. In contrast, the second model appraises interactions of magnetosense–HPA interactions under more modern (but experimentally unverified) theoretical models [83], but as such is more widely generalizable across the animal kingdom. In fact, both models could coexist in some animals. It is therefore proposed that information from the magnetosense—known to be integrated in a hierarchical and complex fashion with the other senses [1–3]—is used in a series of related hormonal functionalities that are optimized according to the navigational, migrational or dispersal strategies of the organism.

(c) Geomagnetic storms as nature's experiment: spoofing the system?

The magnitude of GMS can dwarf the local variation in the GMF [40], and are known to cause disruptions to human navigational systems. Similarly, GMS have been suggested to cause navigational disorientation in the animal kingdom, including bees [88], birds [89] and whales [90]. In a similar manner, experimental evidence has revealed that altered magnetic field conditions can introduce significant changes in rodent directional and spatial circuits [84]. According to either of the above models, GMS would introduce signals that are incorrect—*yet coherent*—to the magnetosense and associated navigational behaviour. If the magnetosense also has the above proposed interactions with hormonal systems, then GMS would subsequently lead to disorientation of hormonal behaviour across the HPA axis. In fact, the action of GMS on humans have been previously interpreted as such a generalized stress response [47,91], with correlates largely mirroring those of a stress responses [92], involving CV pathologies, circadian disturbances, neuropsychiatric manifestations, immunological responses and apparently widespread alterations in neuroendocrine markers [47,93–95] (see electronic supplementary material, table). Therefore, the 'melatonin hypothesis' of GMS would be a somewhat limited paradigm, with GMF–melatonin interactions being just one of a set coordinated hormonal responses.

In contrast to GMS, the interactions of the magnetosense with PF-EMFs is likely to be complex, depending on factors such as field strength, frequency, timing, duration, polarization, lighting conditions, the relative changes and duration of such sources, in addition to possible temporal window effects and the age of the organism. However, as MF frequencies and strength approach the geomagnetic range and intensity, it might be expected that findings would become generally more positive, and it is interesting to speculate how the hypothesized magnetosense–HPA interactions might relate to the highly controversial literature on the influence of PF-EMFs on biological systems (see the electronic supplementary material and [62,63] for further discussion). Nonetheless, there is evidence that the compass system of at least some animals does react to PF-EMFs—overhead high-voltage power lines disrupt the normal northsouth alignment of ruminants with the GMF [96].

(d) Reappraising the existing data under the framework of magnetosense–HPA interactions

It is observed that the apparent sensitivity of melatonin suppression in response to GMS (becoming significant at around 15–80 nT [15,16,38,39,41,93,97]) mirrors the apparent sensitivity of the compass system (in the range of 10–200 nT [3]). Furthermore, many previous publications have interpreted findings with GMS under the assumption that there is some specific component of GMS that is important (e.g. Schumann resonances [71] or pc1 pulsations [24]), whereas under the current framework, it is simply the change in the usual GMF that is sufficient to elicit responses. This is supported by evidence from laboratory animal studies that it is indeed the change in applied MF that is important, rather than the main stimulus itself—removing the stimulus and

returning animals to the natural GMF also produces the observed reductions in melatonin [98].

It should be noted that the GMF is used by migrating animals in a complex, hierarchical and redundant manner, being of particularly utility in the absence of other navigational stimuli (e.g. sun, moon, stars and landmarks) [1–3]. Such hierarchical utilization of sensory input may also be reflected in the above-proposed magnetosense–HPA interactions, and the effects of GMS may therefore be particularly acute in the absence of other cues, e.g. when navigating in new or visually homogenous environments. A further related situation occurs while sleeping, owing to the absence of wakeful navigational information. Therefore, when sleeping in a geomagnetically unfamiliar environment (i.e. representing a dispersal from the home range), it would be evolutionary rational to attenuate sleep behaviour. Such speculations are consistent with apparent night-to-night temporal window effects for the influence of GMS on melatonin [16,93,98,99]. In contrast, other stress responses may be influenced more immediately by geomagnetic disturbances, as evidenced by reports of changes to CV parameters on the day of GMS [29,100], rather than such effects being purely downstream of melatonin disturbances (e.g. the day after the GMS). However, complex feedback between neuroendocrine systems [57] could, for example, compound impacts on the CV systems, involving both immediate and melatonin-mediated interactions (e.g. see discussion in Gmitrov & Gmitrova [29]).

4. SUMMARY OF EVIDENCE AND FUTURE EVALUATION

A role for cryptochrome in transmitting changes in the GMF to the circadian system is supported by several of the key correlates used to infer the role of cryptochrome in avian geomagnetic navigation. However, the evidence relies on only a handful of key papers, findings will require replicating and extending, issues need to be considered such as the role of multiple genes (CRY1 and CRY2), and other potential candidates, especially given the apparent presence of multiple receptors in other species [6]. Moreover, the hypothesis suggests the use of specific controls for cryptochrome (e.g. the use of specific wavelengths of light and oscillating magnetic fields in the low radio-frequency range) and more sophisticated experimental design (e.g. the use of shielded magnetic fields and simulated magnetic fields with specific emphasis on inclination, strength and possible temporal windows effects.) In contrast to the evidence for cryptochrome, the theoretical framework of magnetosense–HPA interactions is speculative and currently unsupported by experimental evidence. However, the existing behavioural paradigm—a secondary zeitgeber—is of questionable biological utility and contradicts experimental data. In contrast, the proposed alternative is consistent with existing notions of life-history theory and of the interactions between navigational or sensory behaviour and hormonal responses.

5. DISCUSSION AND CONSEQUENCES OF THE HYPOTHESIS

The extensive literature relating geomagnetic and solar activity to humans is often considered inexplicable and

bizarre, including correlations with crime [19], stock market returns [17], religious experience [101] and revolutions [20]. Detractors of such literature have reasonable grounds for objection—lacking a rational explanation, such findings are merely spurious associations, likely to be the result of some unexpected confounder. However, there is now evidence for a specific biophysical pathway for these findings, with existing direct and indirect experimental evidence that cryptochrome is influencing circadian behaviour in response to magnetic stimuli. A fundamental question relates to whether cryptochrome could be orientating the circadian and related hormonal system in space or time, or perhaps even a complex interaction of both. Either way, the contentious and controversial associations in the literature are—by some degree—more plausible when placed upon a reasonable biological narrative. Despite the far-fetched nature of some of the behavioural and socio-political associations, they do paint a picture that is coherent when viewed through the framework of a population-level disruption of circadian rhythms and the subsequent lost sleep and anxious, stressful days.

Finally, the implications for human health are noted for a wide variety of disorders associated with geomagnetic activity including CV disease and psychiatric disorders. Further investigations could suggest the use of novel therapeutic interventions for diseases exacerbated by GMS. In Russia—where the effect of GMS have gained much more widespread institutional acceptance [18,19,57]—a study has already trialled melatonin therapy to prevent the effects of GMS on CV patients, with positive results [58]. However, animal experimental evidence has suggested that the effects of magnetic activity on the circadian system are light-dependent. Could a simpler measure—the widespread use of sleep masks—shield at-risk patients from the negative effects of geomagnetic storms?

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