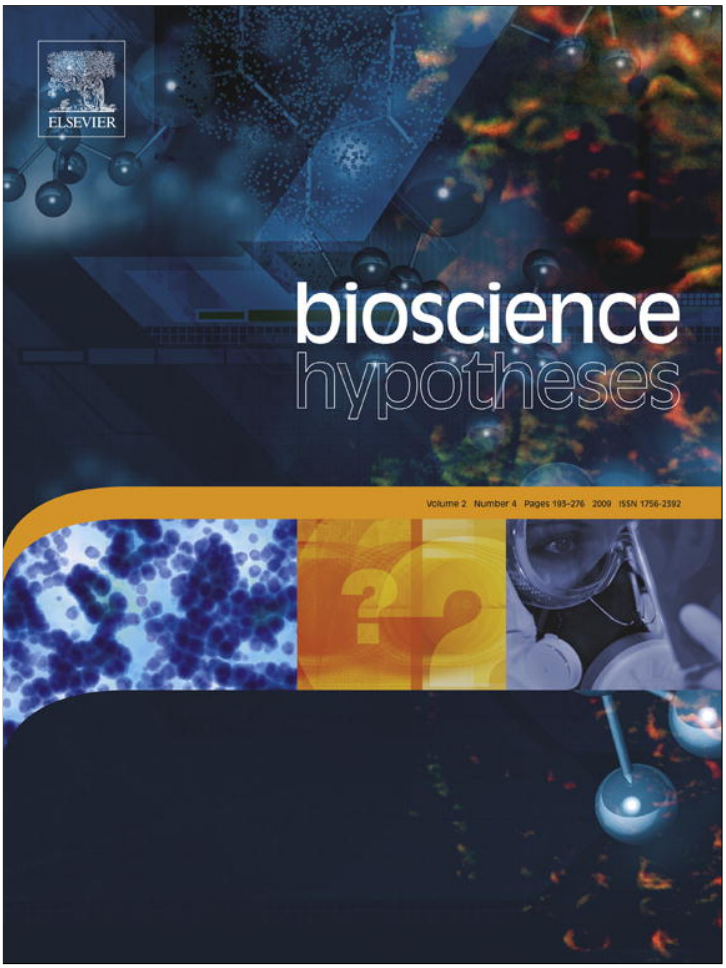

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Emergence and transmission of visual awareness through optical coding in the brain: A redox molecular hypothesis on visual mental imagery

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Abstract Does the primary visual cortex mediate consciousness for higher-level stages of information processing by providing an outlet for mental imagery? Evidence based on neural electrical activity is inconclusive as reflected in the ''imagery debate'' in cognitive science. Neural information and activity, however, also depend on regulated biophoton (optical) signaling. During encoding and retrieval of visual information, regulated electrical (redox) signals of neurons are converted into synchronized biophoton signals by bioluminescent radical processes. That is, visual information may be represented by regulated biophotons of mitochondrial networks in retinotopically organized cytochrome oxidase-rich neural networks within early visual areas. Therefore, we hypothesize that regulated biophotons can generate intrinsic optical representations in the primary visual cortex and then propagate variably degraded versions along cytochrome oxidase pathways during both perception and imagery. Testing this hypothesis requires to establish a methodology for measurement of in vivo and/or in vitro increases of biophoton emission in humans' brain during phosphene inductions by *transcranial magnetic stimulation* and to compare the decrease in phosphene thresholds during transcranial magnetic stimulation and imagery. Our hypothesis provides a molecular mechanism for the visual buffer and for imagery as the prevalent communication mode (through optical signaling) within the brain. If confirmed empirically, this hypothesis could resolve the imagery debate and the underlying issue of continuity between perception and abstract thought.

Introduction

Increasing evidence shows that visual perception and visual mental imagery share common neural substrates in the brain. In particular, there is evidence that both perception

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and imagery induce activation in retinotopically organized (RTO) striate and extrastriate cortex [1].

In cognitive science, the long-standing *imagery debate* involves two rival theories: Kosslyn's *pictorial theory* versus Pylyshyn's *tacit knowledge* explanation. Kosslyn's pictorial theory claims that visual mental imagery exploits the top-down neural pathways (deployed in normal vision to direct visual search and to enhance object recognition) in order to generate visual representations in striate and extrastriate cortex, which are then processed by the visual system, just as if they were visual percepts. Kosslyn has proposed two different kinds of representation, i.e., surface representation or ''depictive representation'', which is an image that we experience as if we perceived a picture, and a ''deep representation'', which is the underlying latent information stored in long-term memory [2] from which depictive representations are generated. Kosslyn uses the term *visual buffer* to indicate the ensemble of RTO areas in the occipital lobe. This buffer is a transient depository of information through which the shape of an object is made explicit and accessible for further processing (visualization or identification), supporting both visual perception and imagery.

According to Pylyshyn, however, activation of early visual areas during visual mental imagery is epiphenomenal [3]. Furthermore, mental imagery is explained away by language-like representations and can be reduced to tacit knowledge used in general thinking. In other words, we represent objects much more abstractly in a symbolic/propositional format, rather than analogic or depictive format as posited by pictorial theory. When having the experience of seeing ''mental pictures'' in our mind's eye, we are just thinking of having such representations. What we really do is to use our implicit knowledge of how things usually appear to us, to simulate what would be like to have mental images and use them in several circumstances resembling our experience during actual perception.

A related, current debate in cognitive neuroscience is whether early areas within the human primate and visual systems, especially V1 (striate cortex), are linked to the content of visual consciousness as hypothesized by pictorial theory. While V1 seems to be activated by mental visual imagery and other cognitive activities involving awareness, these findings are inconsistent and do not explain why or how the involvement of V1 should be necessary to determine visual awareness in other, higher-level areas of the brain [4]. To explain how a putative mechanism may mediate awareness of visual content in the rest of the brain, a number of equally possible *reverse hierarchy models* have been proposed [4] but no specific explanatory mechanism.

The hypothesis

The imagery debate is still unresolved, and there is no credible biophysical candidate that meets the constraints and the available evidence on reverse hierarchies as applied to imagery and visual cognition. Here, we propose a hypothesis that could fill these gaps in knowledge. We hypothesize that objects in the visual field are directly represented in the visual cortex by congruent patterns of biophotons — 'pictures of light' — generated by bioluminescent radical processes in retinotopically organized mitochondrial cytochrome oxidase-rich (RTO CO-rich) neural networks of V1.

Detailed description of the hypothesis

Our hypothesis is represented schematically in Fig. 1; next, we describe in detail the key components of the chain of processes shown in the figure.

Phosphenes as biophotons

One of us has proposed that the brain can operate by means of holograms during informational processes by biophotons, and phosphene phenomenon is due to the intrinsic perception of induced or spontaneous increased biophoton emission of cells in various parts of the visual system [5—7]. Cortical phosphene lights may be nothing but biophotons originated from retinotopic mitochondrial CO-rich visual areas. Phosphenes lights may be nothing but biophotons originated from retinotopic mitochondrial CO-rich visual areas. If it can be proved that perception of phosphene lights is due to biophotons, intrinsic regulated biophotons in the brain can serve as a natural biophysical (redox molecular) substrate of visual perception and imagery.

Retinotopic organization, cytochrome oxidases, and columnar structure in visual areas

In primates, LGN, the striate cortex (V1) and many extrastriate visual cortical areas including V2, V3, and V4, are organized in a retinotopic manner, respecting the topological distribution of stimuli on the retina [8]. One of the most persuasive examples of columnar structure is provided by the distribution of mitochondrial CO in the primary visual cortex. The V1 (CO-dense blobs) and V2 (CO-dense stripes) comprise regions of various CO activities, which can subserve different functions [9]. CO blobs of the visual cortex are associated with the modular organization of the visual cortex and the streaming of visual information into parallel processing pathways. Neurons tuned to different stimulus features but the same retinal positions are grouped into retinotopic arrays of hypercolumns. Hypercolumns contain three subsystems: 1) the ocular-dominance columns, which segregates inputs from the right and the left eye; 2) iso-orientation columns, which segregate neurons that respond best to a given stimulus orientation; 3) columns sensitive to objects attribute of the visual stimulus such as color and spatial frequency, these cells are located in the mitochondrial CO-rich blobs [10].

Reactive species as second messengers in cells and the brain

Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are generated most notably by cyclo-oxygenases, lipoxygenases, cytochrome P450 oxidases, xanthine oxidases, nitric oxide synthases, the mitochondrial respiratory chain, and NADPH oxidases [11]. ROS and RNS are traditionally viewed as dangerous byproducts of

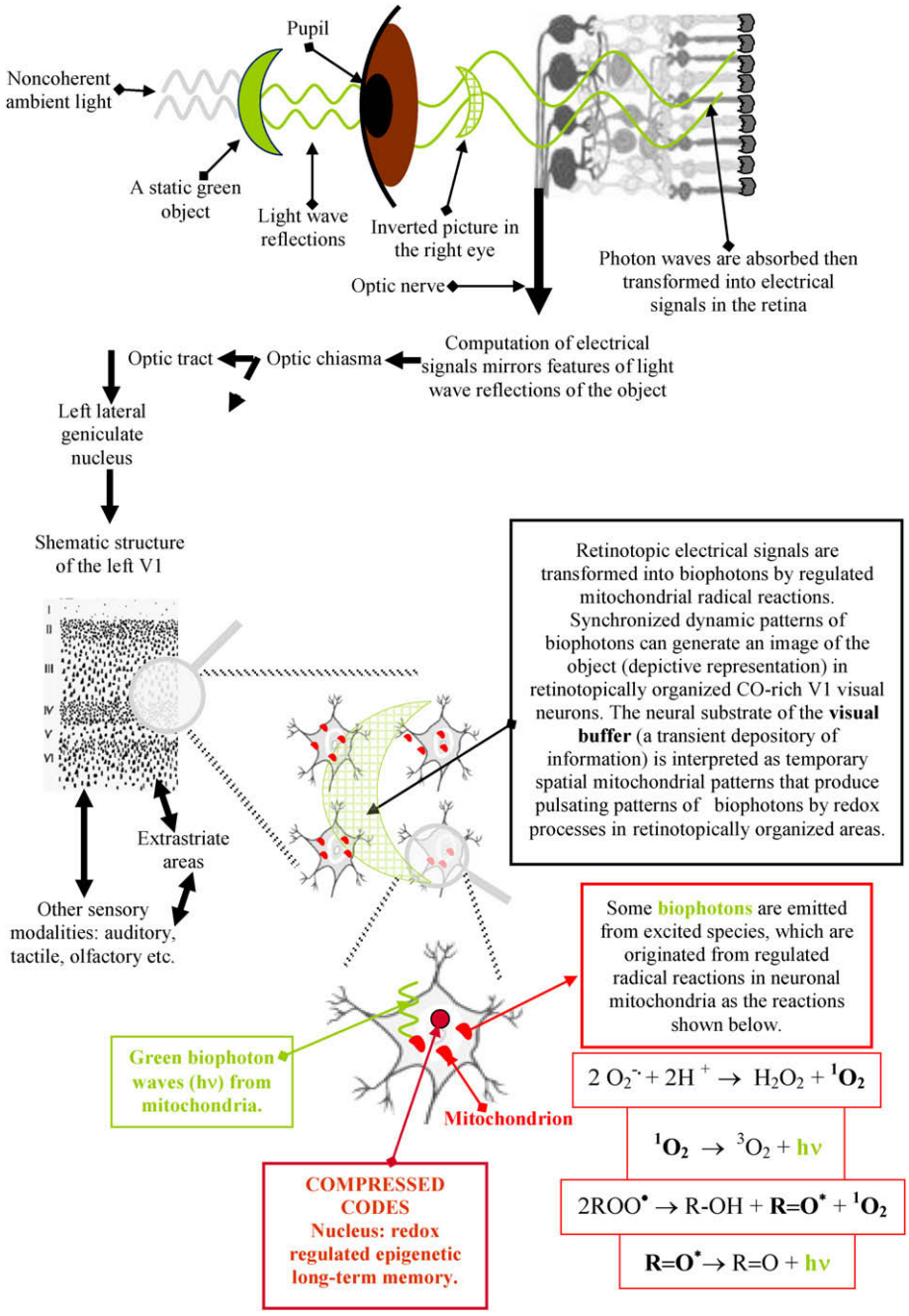

Figure 1 Depictive representation of a static and coloured object by biophotons in RTO CO-rich V1 areas. Light wave reflections from object are transformed into electrical signals in the retina. Retinotopical electrical signals are conveyed to V1 then are transformed into biophotons in neurons by mitochondrial radical/redox processes. Computation by several neurons represents a small point of retina. V1 neurons work as pixels by regulated biophotons. Therefore, we can get a depictive representation about object by biophotons within retinotopical V1. This model is restricted to a static and coloured object. Under real circumstances, computation of different kinds of visual information (motion, contrast, size, orientation, spatial frequency, etc.) by biophotons is a more complex process. This figure also shows some known radical reactions from which excited species (for example: singlet oxygen $^1O_2$ or excited carbonyl group $R = O*$) are originated. These excited state species quickly emit regulated biophotons while they return to the stable ground state.

cellular metabolism. The oxidative stress can be defined as an imbalance between oxidant production and the antioxidant capacity of the cell to prevent oxidative injury. However, recent findings have provided evidence of fundamental roles of ROS and RNS in intracellular signaling and intercellular communication processes. ROS and RNS can regulate gene expression, apoptosis, cell growth, cell adhesion, chemotaxis, protein—protein interactions and enzymatic functions, Ca^{2+} and redox homeostasis, and numerous other processes in cells [11—13]. Oxidative modifications of amino acids in proteins can serve to regulate enzyme activity [14].

ROS and RNS are also essential for normal brain functions and synaptic processes. Free radicals and their derivates act as signaling molecules in cerebral circulation and are necessary in molecular signal processes such as synaptic plasticity, neurotransmitters release, hippocampal long-term potentiation, memory formation, etc. under physiological circumstances in the brain [15—19]. Hence, productions of ROS and RNS are precise mechanisms used in signaling pathways during normal cellular processes in the brain.

Controlled biophoton emission in cells and the brain

Biophotons (ultraweak bioluminescence, ultraweak photon emission) are continuously emitted by all living cells without any excitation [20—26]. The source of biophotons is due to the different biochemical reactions, especially bioluminescent radical and nonradical reactions of ROS and RNS, and the simple cessation of excited states. For examples: non-enzymatic and enzymatic lipid peroxidation, mitochondrial respiration chain and peroxisomal reactions, oxidation of catecholamines, oxidation of tyrosine and tryptophan residues in proteins, etc. [27—29]. The main source of biophotons derives from oxidative metabolism of mitochondria [30].

Neural cells also emit continuously biophotons during their natural metabolism. In vivo intensity of biophoton emission from a rat's brain correlates with cerebral energy metabolism, EEG activity, cerebral blood flow, and oxidative stress [31]. Spontaneous biophoton emission from neural tissue depends on the neuronal membrane depolarization and Ca^{2+} entry into the cells [32]. Indeed, the neural activity-dependent ultraweak biophoton emission has been measured from hippocampal slices of rat brain [25,31,32].

If the generation of ROS and RNS is not a haphazard process, but rather a strict mechanism used in signaling pathways under various physiological conditions, biophoton emission may not be a byproduct of biochemical processes but it could be linked to precise signaling pathways of ROS and RNS. Namely, during natural oxidative metabolism, regulated generation of ROS and RNS can also generate regulated ultraweak biophoton emission in cells and the brain. This means that regulated electrical (redox) signals of neurons can be converted into biophoton signals by bioluminescent reactions. Consequently, information appears not only as electrical signal but also as regulated biophoton (optical) signal in the brain.

We should consider that the real biophoton intensity within cells and neurons can be considerably higher than one would expect from the measurements on ultraweak bioluminescence, which are generally measured macroscopically several centimeters in distance from the tissue or cell cultures!! Namely, the most significant fraction of natural biophoton intensity cannot be measurable because it is absorbed during cellular processes.

Biophoton communication with natural photosensitive biomolecules

Biophoton communication (as weak optical communication) can be performed by natural photosensitive biomolecules of cells and neurons. Biophotons can be absorbed in the visible range by natural chromophores such as porphyrin rings, flavinic, pyridinic rings, lipid chromophores, aromatic amino acids, etc. [33—35]. Mitochondrial electron transport chains contain several chromophores among them cytochrome oxidase enzyme [33]. Photosensitive biomolecules can transfer the absorbed biophoton energy to nearby biomolecules by resonance energy transfer, which can induce conformation changes and trigger/regulate complex signal processes in cells.

Long-term memory as redox controlled epigenetic memory

Several authors have suggested that the long-term memory can be performed at the level of modified DNA molecules (transcription-dependent long-term memory formation) [36—39]. In particular, visual recognition of an object seems to be the result of interactions between epigenetic influences and basic neural plasticity mechanisms. Direct evidence has been found for the involvement of mtDNA in cognitive function [40]. Mitochondria have central role in maintaining genomic stability and in controlling essential nuclear processes [41]. The function of mitochondria is controlled by interactions between nuclear and mitochondrial genes [40]. Oscillations of the mitochondrial energy states occur as a consequence of the interplay between mitochondrial ROS production and ROS scavenging systems in cells [42]. Regulated production of mitochondrial free radicals can modulate gene expression processes and rewrite nuclear epigenetic information. Therefore, long-term visual memories can be interpreted as a long-term epigenetic formation. This nuclear epigenetic information can be rewritten or retrieved by mitochondrial free radicals and cellular redox processes [43].

Depictive representations generated by biophotons in RTO CO-rich visual areas during visual perception and imagery

Information can be represented by energetic processes of CO activity of mitochondrial networks in RTO CO-rich visual areas during visual perception and visual imagery. We have seen that mitochondria are the main source of biophotons generated by reactive species. Besides, mitochondrial CO activity is considered an endogenous marker of neuronal oxidative metabolism, which is regulated by neuronal activity.

Under various physiological conditions, ROS and RNS work as secondary messengers, and are associated with biophotons emission of cells. Consequently, biophotons emission can also be a regulated process. During visual perception, the topological distribution of photon stimuli on the retina is transformed into electrical signals and carried to the striate cortex by the optic nerve. Then retinotopic electrical signals are converted into regulated biophotons by synchronized free radical processes of mitochondrial networks in RTO CO-rich visual areas. Therefore, during visual perception, synchronized activation of neuronal cells can produce intrinsic ''depictive representations'' by activity-dependent biophotons of mitochondrial network in RTO CO-rich visual areas.

During visual imagery, top-down processes activate and regulate the encoded epigenetic long-term visual information. The latter type of information can be retrieved by redox and radical processes. Subsequently, mitochondrial networks can generate dynamic patterns of bioluminescent photons by regulated redox (radical) processes. Finally, synchronized dynamic patterns of bioluminescent photons can generate depictive representations in RTO CO-rich visual areas.

Visual buffer

The Visual buffer would be used ''bottom-up'' to display visual percepts and ''top-down'' to display internally generated images [2]. The proposed neural substrate for this buffer would be the striate and extrastriate visual areas. Recently, Tong suggested that the temporal and spatial dynamic patterns of mitochondrial distribution can compose a transient ''mitochondrial memory code'' that dictates the potentiation of specific synapses and the plasticity of the neuronal network [44]. In our hypothesis the neural substrate of the visual buffer (a transient depository of information) is interpreted as temporary spatial redox and mitochondrial radical patterns that produce pulsating patterns of bioluminescent biophotons by regulated redox processes in RTO areas. These pulsating patterns of bioluminescent photons generate intrinsic images in RTO visual areas. Since calcium is essential for production of ROS and an increase in intracellular calcium concentration can be stimulated by ROS, the implication is that there is a crosstalk between calcium and reactive oxygen species [13]. Consequently, the visual buffer can be achieved by temporary distribution and activity patterns of mitochondrial networks' calcium and reactive oxygen species, and the latter can produce pulsating spatio-temporal patterns of biophotons within neurons.

Testing the hypothesis

If it can be proved that conscious retinotopic phosphene lights are biophotons, then intrinsic regulated biophotons can serve as a natural biophysical (redox molecular) substrate of visual perception and visual imagery. However, it is very difficult to directly test the present hypothesis, since the real biophoton intensity within cells can be considerably higher than one would expect from the measurements on ultraweak bioluminescence, which is generally measured macroscopically several centimeters in distance from the tissue or cell cultures. Namely, the most significant fraction of natural biophoton emission cannot be measured because it is absorbed during cellular processes.

Testing the proposed hypothesis will then require a converging methods approach. First of all, a methodology needs to be established to measure in vivo and/or in vitro increases of biophoton emission in humans' and animals' brain during phosphene inductions by TMS. In vitro increases of biophoton emission should be measured in animals' brain slices induced by similar parameters as those used in phosphene inductions by TMS. Experimental paradigms using TMS in humans should be coupled with fMRI and EEG/ERP. In particular, it is known that hallucinogenic drugs produce phosphenes. Therefore, in vitro increases of biophoton emission should be measured in animals' brain slices produced by hallucinogenic drugs because they induce over expression of free radicals and excited species, which are the main sources of biophotons. In vivo increases of biophoton emission should be measured in animals' brain produced by hallucinogenic drugs. Both hallucinogenic drugs and visual mental imagery can decrease the phosphene threshold (PT) compared to control subjects. Consequently, procedures should be devised to test the TMS effect on PT during visual mental imagery in hallucinogenic drug users and in vivo measure of the phosphene threshold by TMS in animals' brain during administration of high dose antioxidants. Mitochondrial CO activity, which is a marker of neural activity, depends on external low frequency and low intensity magnetic fields. Thus, further investigations should test whether human subjects experience coloured phosphenes induced by repeated TMS and whether changing the frequency of repeated TMS could shift/change the experienced color of phosphenes to another kind of color. In addition, tests should be conducted to establish whether TMS-induced phosphene thresholds depend on visualized monochrome colors, namely, while subjects generate full visual mental images of the different kinds of monochrome colors. Finally, a series of other tests should be conducted to track down CO pathways and detect mitochondrial flavoprotein or NADH autofluorescence by testing in vivo animals at the same cortical points of phosphene induction from both TMS and imagery.

Implications of the hypothesis

Compatible with current evidence about V1, our hypothesis provides a redox molecular mechanism for the visual buffer and for imagery as the prevalent communication mode (through weak optical signal) within most areas of the brain. Our hypothesis is based on the natural redox, energetic and bioluminescent processes of neuronal cells. Ultraweak photons originate from controlled generation of ROS and RNS. Regulated electrical (redox) signals of neurons can be converted into biophoton signals. Therefore, information in the brain appears not only as electrical (chemical) signal but also as a controlled biophoton (optical) signal. Biophoton (weak optical) communication can be performed by various photosensitive biomolecules of neuronal cells.

Mitochondrial networks are structural and energetic networks. Therefore, information processes can be represented by energetic processes of temporal and spatial dynamic patterns of mitochondrial distribution in neurons. The main source of biophotons originates from mitochondria. Temporal and spatial energetic processes of mitochondrial distribution (as energetic/redox/visual buffer) can produce temporal and spatial dynamic patterns biophotons in neurons. Accordingly, during synchronized activation of neuronal cells in RTO CO-rich visual areas, activity-dependent biophotons from coordinated energetic processes of mitochondrial network in space and time can create intrinsic pictures in the visual system. This means that the retinal visual information can be represented by regulated biophotons of mitochondrial networks in RTO CO-rich visual areas.

During visual perception, the visual buffer (as mitochondrial energetic, redox, and bioluminescent buffer) can use bottom-up and top-down processes to display visual percepts, and makes possible visualization and identification of objects. Visual perception works as an iterative process between the bottom-up processes (from retinal map) and the top-down (long-term information) processes as long as the perceived image and deep representations have the same picture convergence. During visual imagery, top-down processes activate and regulate the encoded epigenetic long-term visual information. The latter type of information can be retrieved by redox and radical processes. Then mitochondrial networks generate dynamic patterns of bioluminescent photons by regulated redox (radical) processes. Finally, synchronized dynamic patterns of bioluminescent photons can generate depictive representations in RTO CO-rich visual areas.

This hypothesis is consistent with claims that long-term visual memories are stored as compressed (epigenetic) redox codes. We can identify objects because the same compression process is used every time we see an object, and thus what is stored in memory will match what it is produced when we see the object again. The important implication is that there is no homunculus in our head but the image representation is processed so that signals are sent to other parts of the brain in which they undergo dynamic ''binding'' with other forms of representations such as linguistic and conceptual representations. This binding corresponds to higher levels of cognitive interpretations connected with thinking and reasoning [45]. Indeed, these higher-level cognitive processes may need to become progressively more abstract or schematic because the visual contents of the representations generated from regulated biophotons become progressively degraded during the transmission along pathways from V1 (and other early visual areas) to higher-level associative areas with decreasing CO-based processes.

If confirmed empirically, our hypothesis resolves the imagery debate as it shows that (pace Pylyshyn) pictures could literally reside in the brain in both perception and imagery and these representations may be distinctively different from other forms of representations (i.e., propositional descriptions) up to a point (at least at the level of V1 and extrastriate areas) in the stream of information processing. In spite of representational dualism, the redox hypothesis suggests that binding between analogic-perceptual and propositional-abstract formats may emerge as a natural consequence of the dynamic ''crosstalk'' between the visual system and the rest of the brain.

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