

Alzheimer's disease and Down's syndrome: roles of APP, trophic factors and ACh

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Recent therapeutic investigations of Alzheimer's disease (AD) have been guided by two seemingly opposed hypotheses: the amyloid cascade theory, which favors the amyloid plaques as the cause of AD; and the cholinergic theory, which favors cholinergic neuron loss as the cause. New investigations indicate that the synthesis and processing of the amyloid precursor protein (APP) is linked to the trophic actions of nerve growth factor. A pathological cascade in both AD- and Down's syndrome-related memory loss could be triggered by alterations in APP processing or ACh-mediated neuronal function, or both, which in turn trigger the overexpression of amyloid β , synaptic malfunction and trophic factor loss in target regions. This eventually leads to synaptic and dendritic loss with age.

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In Alzheimer's disease (AD)- and Down's syndrome (DS)-related dementia, the progressive nature of neurodegeneration suggests an age-dependent process that ultimately leads to degeneration of synaptic afferent systems, dendritic and neuronal damage, and the formation of abnormal protein aggregates throughout the brain. By the fourth decade of life, individuals with DS display many of the same neuropathological features (i.e. neuritic plaques, neurofibrillary tangles and degeneration of basal forebrain cholinergic neurons) as do individuals with AD, and many of these individuals develop dementia early in life [1–5]. It has been suggested that the neurodegenerative processes in AD and DS are closely related and at least partially comparable [4].

Recent findings indicate that cortical and hippocampal cholinergic synaptic systems [6,7] and trophic factors [8] can either reduce or accelerate pathogenesis and progression of AD and DS pathology by effects on amyloid precursor protein (APP) levels, metabolism and processing. The pathology of AD is determined diagnostically by several standardized clinical and pathological criteria [9–12]. Cortical plaques, neuronal tangles and degeneration of afferents to areas such as the hippocampus and neocortex are neuropathologically linked in a multifactorial progression. The exact

physiological sequence of events leading to these pathologies is unknown.

The early discovery of ACh deficiency [13] singled out the loss of this neurotransmitter as one reason for the cognitive dysfunction in AD. Recent reports have detected only slight biochemical enzyme loss in the cholinergic system in mild cognitive impairment, which is thought to be the precursor to AD [14–17], although these studies have not determined whether the function of the cholinergic system is intact. Many elegant studies support the cholinergic hypothesis [18,19], showing that a dysfunctional cholinergic system is sufficient to produce memory deficits in animal models that are analogous to Alzheimer's dementia. Nevertheless, to date, little information exists about the dynamic processes that underlie the cognitive loss and neuropathology.

The cholinergic system (and potentially other afferent systems such as the noradrenergic and serotonergic systems), APP and trophic factors are intimately linked in normal function and possibly also in pathogenesis. This article provides a synthesis of these pathophysiological interactions and new interpretations of available data and recent findings.

Transgenic, mutant and animal models

Recently, a transgenic mouse has been described that expresses a neutralizing monoclonal antibody against nerve growth factor (NGF) [8]. In these mice, brain pathology exhibits remarkable similarities to the pathology seen in progressive AD, including amyloid plaques, hyperphosphorylated tau, neurofibrillary tangles in cortical and hippocampal regions, and marked cholinergic neuron degeneration. The anti-NGF transgenic mice show more pathology resembling that found in individuals with AD than transgenic mice that express mutant APP [8]. In fact, studies using the transgenic mice with human mutations of presenilin or APP, or both, have failed to demonstrate significant alterations in the cholinergic cell body region, even though in the APP–presenilin double mutant (APPK670N, M671L and PS1M146L [20]) there is a decrease in the density of cholinergic synapses in the frontal cortex [21].

Another study (using the human APP overexpression mutant, V717F [22]) also failed to detect significant degeneration of the cholinergic neurons, even at 18 and 26 months of age, despite significant levels of amyloid plaques in the brain. These findings from transgenic mice indicate that there are factors other than faulty amyloid processing involved in the neuropathology of AD.

Consistent with the findings using anti-NGF transgenic mice [8] described above, a toxic antibody (anti-NGF) treatment paradigm in rats leads to deterioration of cholinergic CNS basal forebrain neurons and synapses, and produces a shift towards APP elevations and decreased levels of choline acetyltransferase (ChAT), which are associated with behavioral deficits in spatial orientation and memory

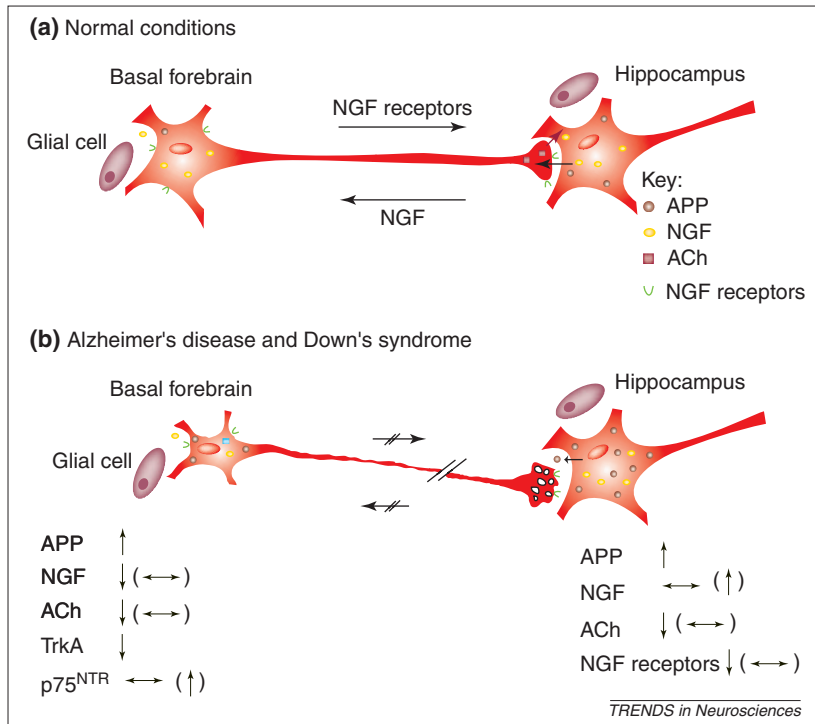


Fig. 1. Cholinergic basal forebrain neurons (a) in normal physiological conditions and (b) as postulated in individuals with AD and DS. In cholinergic neurons of the basal forebrain in individuals with AD and DS, ChAT immunoreactivity, cell size and number, and NGF and TrkA levels are decreased. In the hippocampus of individuals with AD and DS, ChAT levels and ACh-mediated signaling are reduced but NGF levels are increased or unchanged. In the hippocampus and basal forebrain of individuals with AD and DS, APP expression and A β aggregate levels are increased, whereas secreted (trophic) sAPPs are decreased. There are also degenerating terminals in the hippocampus. These altered levels indicate that NGF retrograde transport or NGF binding to trkA receptors, or both, are reduced in the individuals with AD, which results in inappropriate trophic support of the cholinergic system during degenerative disease [78]. Abbreviations: A β , amyloid β ; ACh, acetylcholine; AD, Alzheimer's disease; APP, amyloid precursor protein; ChAT, choline acetyl transferase; DS, Down's syndrome; NGF, nerve growth factor; sAPP, soluble APP; TrkA, tyrosine receptor kinase A.

tasks [6,23]. In addition, studies have been performed on mice with a segmental trisomy of chromosome 16, Ts65Dn [24,25]. The triplicated gene segment includes the gene for APP, and other genes that are present in individuals with DS [26]. These mice

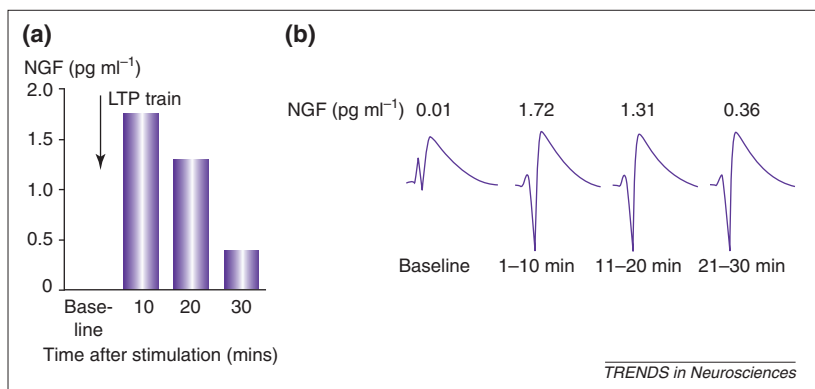


Fig. 2. Long-term potentiation (LTP)-induced nerve growth factor (NGF) release in a hippocampal slice from a young rat. (a) LTP was induced by rapid-train stimulation with an electrode, and NGF was measured by a specific NGF enzyme-linked immunosorbent assay kit in the superfusate after protein purification at different times after stimulation (10, 20 and 30 min). (b) The field potentials show the LTP induction and the NGF concentration in pg ml⁻¹. These data suggest a dynamic interaction between hippocampal activity and NGF release that could regulate synaptic terminal growth and function [67,68]. These regulatory release patterns were later also confirmed for another member of the neurotrophin family, brain-derived neurotrophic factor (BDNF) [69].

overexpress full-length APP and amyloid β , and undergo significant deterioration of the cholinergic system and basal forebrain NGF levels as young adults [24]. Ts65Dn mice exhibit reductions in basal forebrain cholinergic neuron size and number, and regressive changes in the hippocampal terminal cholinergic axonal fields, which are thought to be associated with impaired retrograde transport of NGF from hippocampus to the basal forebrain [27,28].

All of these recent animal models re-emphasize the possibility that pathological processes operating in age-related cognitive impairment, idiopathic AD and DS might be related to physiological changes in several systems, including synaptic complexes associated with cholinergic nerve terminals. Such synapses depend on the trophic action of NGF for their function [29–32]. As cholinergic degeneration in individuals with AD is closely correlated with the degree of memory impairment [13], this transmitter system and related trophic factors might also be associated with amyloid plaque formation and related trophic factors, neuronal tangles and cell degeneration (Fig. 1).

APP-related systems interact with both trophic factors and cholinergic receptors

A high percentage of basal forebrain cholinergic neurons degenerate in AD [5]. The cholinergic neurons are highly dependent upon NGF for their function [33–36], and use high-affinity tyrosine receptor kinase A (trkA) and low-affinity (p75) receptors for signaling. The trkA receptors are synthesized in cholinergic neurons and are necessary for binding and retrograde transport of the growth factor from the terminals to the cell body region, while the low-affinity receptors appear to be important for sequestering growth factor molecules to the presynaptic membrane [37–40]. However, NGF is synthesized by neurons in the target regions and is released in an activity-dependent manner [35,41,42] (Figs 1–3).

In individuals with AD, there is typically a marked loss of high-affinity trkA receptors in both cholinergic target neurons and basal forebrain neurons, which correlates with loss of cholinergic neurons [43–45]. Even though there have been some variable results regarding NGF protein levels in different brain regions of individuals with AD, most recent studies agree that there are unchanged or increased NGF levels in the hippocampus and cerebral cortex, while the levels in the basal forebrain are decreased compared with age-matched controls [46–53]. This, together with cholinergic neuron loss and dysfunction, suggests that NGF is not adequately transported retrogradely to the basal forebrain or that binding to the high-affinity receptors or release of NGF from hippocampal interneurons, or both, is deficient in the brain of individuals with AD and in animal models of aging (Figs 1,3) [49,54].

Infusion of NGF can prevent degeneration of axotomized cholinergic CNS neurons [55]. A biological basis for an interaction between APP and NGF has

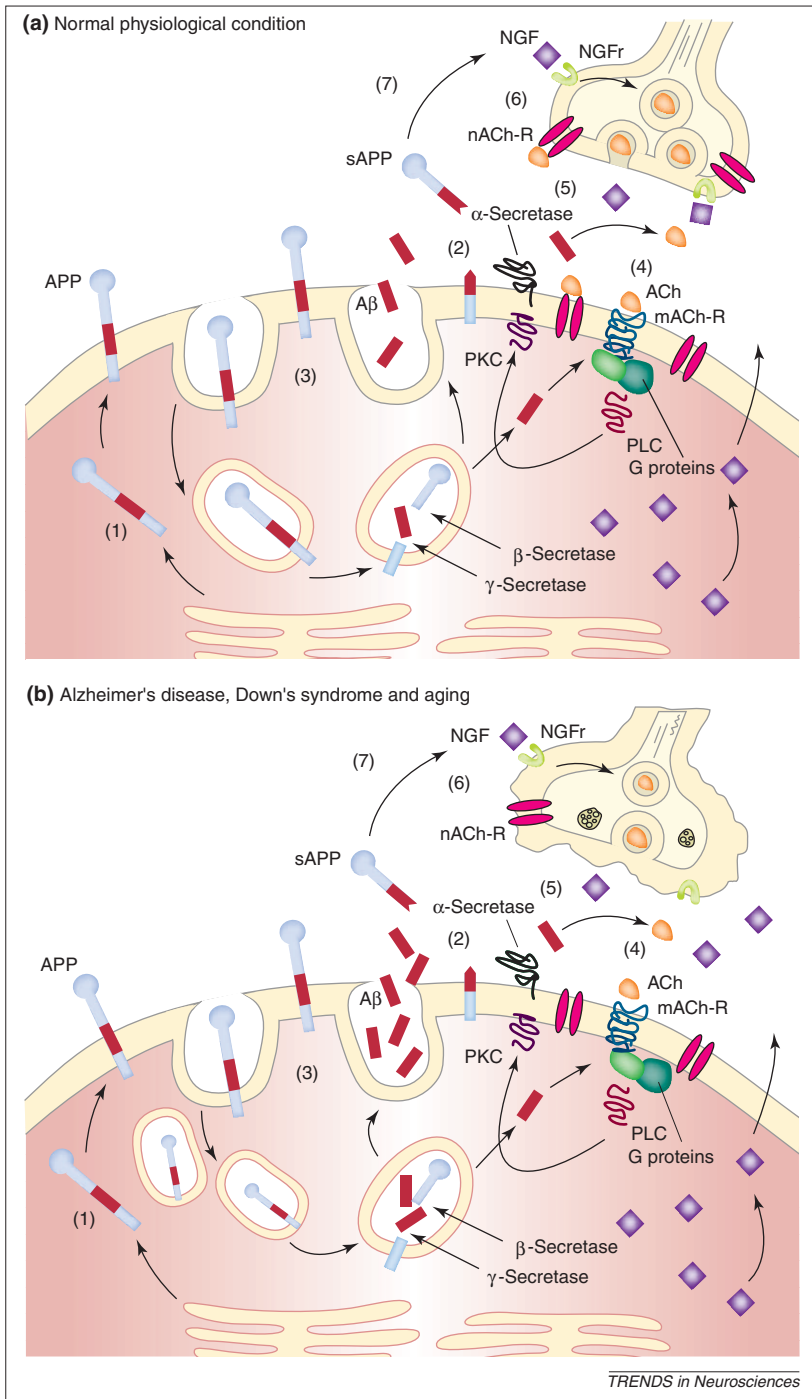


Fig. 3. Different pathways for amyloid precursor protein (APP) processing and nicotinic-receptor- and muscarinic-receptor-mediated regulation of APP metabolism (nACh-R and mACh-R, respectively). (a) (1) Newly synthesized APP is transported from the Golgi through vesicles to the cell surface (2) where it can be cleaved within the amyloid β ($A\beta$) domain by α -secretase. Mature cell-surface APP can also be reinternalized (3) into late endosomes and lysosomes, where it can be processed by β -secretase and γ -secretase to yield $A\beta$, which can be rapidly secreted into the extracellular fluid. (4) Acetylcholine (ACh) is released because of the arrival of an action potential. It binds to $\alpha 7$ nicotinic receptors ($\alpha 7$ nACh-R) presynaptically, and $\alpha 7$, M_1 and M_2 receptors postsynaptically. The $\alpha 7$ nACh-R binding results in presynaptic Ca^{2+} influx, which leads to increased ACh-mediated tone. Released ACh from presynaptic terminals also binds to G-protein-coupled muscarinic receptors and subsequent activation of phospholipase C (PLC), which hydrolyzes phosphoinositolipids to inositol-3-phosphate and diacylglycerol. Diacylglycerol activates protein kinase C (PKC), which directly or indirectly enhances α -secretase-mediated cleavage of APP. (5) $A\beta$ can interfere with cholinergic neuron function at both presynaptic and postsynaptic signaling sites (4) and (5), and increased ACh-mediated signaling leads to decreased APP levels and increased release of soluble APP (sAPP). (6) Acetylcholine release increases NGF secretion from the postsynaptic membrane, which binds to presynaptic NGF receptors (NGFr), resulting in retrograde transport of NGF to the cell body of cholinergic neurons. (7) The signaling of NGF to NGF receptors is stimulated by sAPP. (b) In Alzheimer's disease and Down's syndrome, pathological conditions and aging, there is damage to terminals and (1) increased APP expression, (2) increased $A\beta$ secretion by amyloidogenic processing, (3) internalization of mature cell-surface APP, (4) reduced ACh neurotransmission, (5) increased $A\beta$ interference of ACh signaling, and (6) reduced transport of NGF-NGFr complexes to the ACh cell body.

potentiates the effects of NGF on differentiation of catecholaminergic cell lines [60]. Soluble APP can also augment the effects of NGF, and, conversely, the expression and release of APP is temporally enhanced by NGF *in vivo* [58]. A trophic relationship between sAPP and NGF has thus been established.

The cholinergic system has been shown to have a regulatory effect on both APP and NGF-related processes. Some types of cholinergic neuron lesions can increase hippocampal NGF levels in the normal adult rodent brain [61–63]. Other findings connect muscarinic-receptor agonists and other ACh-related agents with NGF and APP. For example, recent studies have demonstrated that amyloid β_{1-42} binds to $\alpha 7$ nicotinic ACh receptors with high affinity [64]. In the same study, it was also shown that the blocking effect of amyloid β_{1-42} on the presynaptic nicotinic ACh receptors gave rise to decreased Ca^{2+} influx, and thus inactivation of the presynaptic membrane (hence, a decreased ACh-mediated tone was produced by amyloid β_{1-42} administration).

On the basis of these and other recent *in vivo* findings using ACh M_1 -receptor agonists [8,9,65], it is postulated that close relationships exist between the function of trophic factors, APP and neurotransmitters such as ACh in regulating the health of neurons (Figs 1,3). A pivotal pathological cascade in both AD- and DS-related memory loss might be triggered by alterations in APP processing or cholinergic neuronal dysfunction, or both, which triggers overexpression of amyloid β , synaptic malfunction and trophic factor loss in target regions (eventually leading to synaptic and dendritic loss in all regions involved). By this and other genetic mechanisms, abnormal levels of neurotrophic

been suggested by cell culture studies that demonstrate a dose-dependent relationship between NGF and APP messenger induction [56–58]. After exposure to NGF, primary cortical neuronal cultures showed increased levels of membrane phospholipids that might promote APP expression and secretion of the soluble form of APP (sAPP). The large membrane-spanning precursor molecule (full-length APP) can be processed into several different biologically active compounds, such as the secreted form, sAPP, which has been shown to have neurotrophic activities, and the longer aggregating forms, of which amyloid β_{1-42} is the most toxic [53,58,59] (Figs 1,3). Cell culture work also indicates that sAPP

sAPP and pathogenic levels of solubilized amyloid β might eventually cause progressive (and regressive) degeneration of cholinergic nerve terminal function in target regions (hippocampus and cerebral cortex), and thus decreased ACh-mediated tone, which leads to decreased NGF release and uptake, cholinergic neuronal cell body atrophy, and metabolic downregulation (Figs 1,3).

NGF, LTP and the cholinergic hippocampal synapse

Given that long-term potentiation (LTP) has been used as a model for synaptic plasticity and learning in the hippocampal formation, it is relevant to determine whether NGF is associated with LTP [64]. Indeed, evidence shows a significant increase in basal NGF release after LTP induction in hippocampal slice cultures (Fig. 2) [67,68]. These regulatory release patterns were later confirmed for another member of the neurotrophin family, brain-derived neurotrophic factor [69]. That hippocampal target levels of NGF are increased in aging and sometimes in AD [46], seems to contradict the degeneration and atrophy seen in cholinergic neurons, but is explained by disease and age-dependent mechanisms of reduced NGF uptake by cholinergic nerve terminals [49].

LTP induces an acute and specific release of NGF in the hippocampus, which is consistent with reports that ACh-receptor agonists have this effect [42]. However, chronic over-stimulation by ACh-receptor agonists *in vivo* in young adult mice leads to a compensatory reduction in hippocampal NGF levels, probably as a feedback signal to lower cholinergic nerve terminal function and growth (Fig. 1) [70]. Interestingly, local application of NGF to basal forebrain cholinergic neurons can give rise to a slow-onset (~20 min) but significant increase in basal firing rate, especially in cholinergic neurons in aged animals that have been shown to have decreased basal forebrain levels of NGF [68]. This increase in cholinergic neuron activity in response to locally administered NGF seen in aged animals might be an adaptive mechanism that recruits NGF to a system in need of trophic support. Thus, there is also a close relationship between NGF and this cholinergic

pathway in rapid cellular events in the basal forebrain.

It is possible that this two-way relationship is altered by events that lead to AD and DS. Enhanced LTP and afferent synaptic strength via cholinergic, serotonergic and, possibly, noradrenergic systems in the hippocampal formation has been shown to enhance memory function. Conversely, impairment of these transmitter systems reduces LTP and memory function, at least in hippocampal-dependent tasks [24,71]. As previously discussed, this is modeled by transgenic expression of an antibody against NGF [8]. Such an antibody or toxin to the trkA receptor [6,23] selectively disrupts the ACh-mediated innervation of hippocampal neurons and the functional integrity of this system. Further evidence of a close relationship between ACh-mediated transmission and APP, is the increase in the levels of sAPP found after M_1 -receptor activation. Soluble APP is considered to be a trophic substance in these systems [72–77]. Increased NGF levels seen in our studies after LTP (Fig. 2), combined with an increased release of sAPP under maximal activation of the cholinergic system would enhance NGF function. In any case, these intracellular changes and reduced metabolic functions are consistent with a dysfunction of the cholinergic system and trophic target zones in the hippocampal formation, and of other ACh-receptive regions of the cerebral cortex (Fig. 3) [65].

Comprehensive AD- and DS-like pathologies are thus produced by altered cholinergic and APP-related systems in trisomic mice that overexpress APP [27] or by *in vivo* NGF dysregulation via antibodies directly against NGF or its receptors [6,8,65]. Recent observations are consistent with the idea that there are homeostatic mechanisms regulating hippocampal NGF, APP and ACh-mediated activity. A dysregulation of one or more of these three factors would progressively lead to imbalance in neurotransmission, eventually leading to synaptic damage and neuronal cell loss relevant to memory function. Models that focus on complex interactions involved in dementias might be more realistic for achieving new drug, cellular and molecular therapies to influence both stage- and age-dependent neurodegenerative disease.

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A rationale for the structure of color space

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The colors perceived by humans in response to light stimuli are generally described in terms of four color categories (reds, greens, blues and yellows), the members of which are systematically arrayed around gray. This broadly accepted description of color sensation differs fundamentally from the light that induces it, which is neither 'circular' nor categorical. What, then, accounts for these discrepancies between the structure of color experience and the physical reality that underlies it? We suggest that these differences are based on two related requirements for successful color vision: (1) that spectra be ordered according to their physical similarities and differences; and (2) that this ordering be constrained by the four-color map problem.

The goal of any visual system is presumably to distinguish physically different objects and the conditions under which they are witnessed, thus enabling successful visually guided behavior. All visual animals achieve this end by detecting differences in the quantity of the LIGHT (see Glossary) reflected by objects or otherwise returned to the eye, which are perceived in humans as LIGHTNESS and/or BRIGHTNESS. Many animals also distinguish objects according to differences in the quality of the light they reflect (i.e. the distributions of the spectral power in the stimulus), which are perceived in humans as different COLORS.

Although descriptions of the organization of human color sensations differ in detail [1–4], they share several key features. Thus, at any given level of light intensity, color experience can be portrayed as a plane in which movements around the perimeter correspond to changes in hue and movements along its radial axis correspond to changes in saturation (i.e. changes in the relative grayness of the color) (Fig. 1). In contrast to the continuously variable spectral distributions that generate sensations of color, all colors are experienced as belonging to one of

four perceptual categories (reds, greens, blues and yellows), or combinations thereof. Thus, although the relationships between other visual sensations and the physical world that gives rise to them (e.g. sensations of shape, depth and motion) appear straightforward (i.e. the structure of physical space is roughly similar to the overall structure of the perceptual space it generates), color sensations are different: there is no obvious basis in the physical characteristics of light for either the circular ordering of colors in a plane, or their parcellation into four perceptual categories.

Why, then, is perceptual color space structured in this way, and does this structure have deeper implications for understanding the nature of vision generally? To the extent that contemporary theories of color vision have addressed these questions, the subjective structure of color experience is considered an inevitable consequence of TRICHROMACY and OPPOSITION ([5–9], but see Ref. [10]). Thus, most modern work has understandably focused on determining the cellular bases of these two physiological pillars of color sensation. As a result, the rationale for the structure of color experience is, in this view, secondary to the evolutionary value of trichromacy and opponency as such. Some of the advantages that have been suggested are: (1) optimally satisfying the constraints of information theory [11–13]; (2) promoting the perception of 'color constancy' [14–16]; and (3) helping our frugivore ancestors detect ripe fruit [17,18].

We take the opposite approach to understanding color experience. Rather than rationalizing the structure of color sensations in terms of trichromacy and opponency, we consider the structure of color space itself, asking whether color space (and thus the physiology that generates it) might represent the solution to the two fundamental problems in topology with which the evolution of color sensations must ultimately contend.

Distinguishing territories by spectral information

In examining the proposition that the structure of color experience, as such, should be a better guide to understanding color vision, a good place to start is to consider why color sensations have evolved in the first place. Many animals do not have a significant degree of color vision, and even those that do are for the most part more limited in color perception than are

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