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MINI-REVIEW

Forever young: Neoteny, neurogenesis and a critique of critical periods in olfaction

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Abstract

The critical period concept has been one of the most transcendent in science, education, and society forming the basis of our fixation on 'quality' of childhood experiences. The neural basis of this process has been revealed in developmental studies of visual, auditory and somatosensory maps and their enduring modification through manipulations of experience early in life. Olfaction, too, possesses a number of phenomena that share key characteristics with classical critical periods like sensitive temporal windows and experience dependence. In this review, we analyze the candidate critical period-like phenomena in olfaction and find them disanalogous to classical critical periods in other sensory systems in several important ways. This leads us to speculate as to why olfaction may be alone among exteroceptive systems in lacking classical critical periods and how life-long neurogenesis of olfactory sensory neurons and bulbar interneurons—a neotenic vestige– relates to the structure and function of the mammalian olfactory system.

Keywords Imprinting · Olfactory-sensory-neurons · Granule cells · Rostral-migratory-stream

Introduction

That the experiences of youth are particularly impactful on the rest of life is an ancient idea, captured in the Romantic Poet Wordsworth's idiom "The child is father of the man," and championed by such diverse personages as Sigmund Freud and the Beach Boys. Three landmark lines of investigation—studies of imprinting by Konrad Lorenz (1958), affectional responses by Henry Harlow and colleagues (Harlow and Zimmermann 1959; Seay et al. 1964), and aphasia by Penfield and colleagues (Penfield and Roberts 1959) are generally credited with bringing this phenomenon into the realm of science.

In filial imprinting, made famous in Lorenz' studies of the Greylag goose, a newborn develops a "following response" to any large object including—provocatively—the Nobel laureate himself. Harlow's studies of affectional responses established, among other findings, that macaques deprived of normal maternal bonding grow up to be seemingly neurotic individuals who are bad parents themselves (Seay et al. 1964). Penfield, drawing on his vast experience treating trauma- or disease-induced aphasia as well as the zeitgeist of linguistics, concluded "…a child's brain has a specialized capacity for learning language—a capacity that decreases with the passage of years" (Penfield and Roberts 1959).

Together, these thought paths established a unique form of learning characterized by: (1) no requirement for reinforcement; (2) strong or complete resistance to reversibility; and (3) circumscription to a specific developmental period of potentially short duration (even a few hours) with sharp temporal boundaries early in life (Lorenz 1958). Developmental phenomena that share these features bear the moniker, *critical period*. And, it is hard to think of a concept that has been more influential in neuroscience, medicine, education or society. Indeed, this is too expansive a topic for a short review. Rather, after a brief introduction describing classical examples of the physiological underpinnings of critical period in other sensory systems, attempts to find critical period phenomena in olfaction will be highlighted. Finally, we will provide a critique of the concept as applied to olfaction. In an effort to remain agnostic about candidate olfactory phenomena we will use the term, *sensitive window*, in place of critical period arguing in our discussion that this is more than a semantic

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distinction. For a more nuanced categorization of windows of plasticity in sensory systems, see Krawl (2013).

Classical sensory critical periods

Visual system

Insight into the physiological basis of critical period awaited the now celebrated studies of Hubel and Wiesel on ocular dominance plasticity in the visual cortex of kittens and macaques (reviewed in Hubel and Wiesel 1998; Hubel and Wiesel 2005). In this classic model, which remains the gold standard for studies of critical period plasticity nearly six decades after its introduction, monocular deprivation (MD) for even short periods leads to rapid changes in the physiological responses of visual cortical neurons provided it occurs during an early sensitive window in postnatal development. Following the onset of MD the open eye increases its ability to drive cortical circuits while the closed eye progressively loses this ability. Subsequent to the functional changes brought on by MD is rewiring of thalamic afferents and horizontal connections in the visual cortex (Antonini and Stryker 1993; Trachtenberg and Stryker 2001). Experience-dependent competition between thalamic afferents is a necessary condition for this process to occur, as shown by the fact that when binocular deprivation is enforced by suturing both eyelids neither eye loses its ability to drive cortex (reviewed in Hubel and Wiesel 1998). Moreover, if the eyes are experimentally (or naturally) misaligned, for example by transecting extraocular muscles, biased responses to one eye or the other are retained and sharpened while binocular responses are lost, since the sensory activity of the two eyes is decorrelated (reviewed in Hubel and Wiesel 1998). Notably, this process underlying ocular dominance plasticity is use-dependent, not merely age-dependent, a conclusion supported by experiments demonstrating that raising animals in complete darkness delays the window of plasticity even into adulthood in certain model systems (Mower 1991; Morales et al. 2002; but see Li et al. 2006, for an early sensitive period in visual cortex that is both experience- and age-dependent).

Considerable progress has been made in understanding the molecular events that underlie ocular dominance plasticity and the closing of this sensitive period. Although a detailed discussion of molecular regulation is beyond the scope of this review, it should be noted that sensory experience has been shown to alter the balance between excitation and inhibition in visual cortex driven through glutamate and GABA receptors respectively (see Hensch 2004 of review). The principal molecular mechanism that underlies synaptic plasticity at glutamatergic synapses in the visual cortex and elsewhere in the CNS relates to the activation of NMDA and AMPA receptors (Kandel et al. 2014). The voltage-dependent blockade of the open channel pores by magnesium ions makes NMDA receptors de facto "coincident detectors". This unique molecular feature of the NMDA receptor ensures that synaptic plasticity at glutamatergic synapses is modulated by the coordinated activation of pre- and post-synaptic elements (Hebbian plasticity; for a recent review, see Zenke and Gerstner 2017). Thus, presynaptic release of glutamate must be coincident with postsynaptic depolarization mediated by AMPA receptors if magnesium ions are to be expelled from the channel pores (Chater and Goda 2014). When this happens, inward current is carried by calcium (and sodium) and calcium-dependent second messenger systems mediate a host of postsynaptic effects, depending on the rate and magnitude of calcium influx (Kandel et al. 2014). Consequently, the dynamics of postsynaptic calcium influx is a key factor mediating experience-dependent competition among monocular afferent inputs in ocular dominance plasticity in the visual cortex.

However, the impacts of postsynaptic calcium dynamics are themselves subject to a host of modulators and intermediaries, including BDNF, PKA and CaMKII, which have been implicated in the downstream processes that ultimately lead to synaptic pruning, synaptic formation and neurite outgrowth or retraction instantiating structural changes in cortical circuits. Such processes account for the anatomical plasticity that favors thalamocortical afferents driven by the open eye at the expense of those monocular afferents that are driven by the closed eye (Antonini and Stryker 1993). Furthermore, BDNF may promote GABA circuit development setting the stage for plasticity by shifting the balance of excitation and inhibition and modulating the flow of experience-evoked activity in cortical circuits (Huang and Reichart 2001). This balance is germane for the opening and maintenance of the critical period for ocular dominance plasticity. However, the closing of the ocular dominance plasticity window is now thought to involve the maturation of extracellular matrix, which evidently restrains neurite growth and remodeling (Pizzorusso et al. 2002). An important implication of this work is that it would take major dissolution of the extracellular matrix surrounding mature neural circuits to reopen the sensitive period, as may be desirable in treating neurological diseases or stroke (Hensch 2004).

More recently, investigators interested in visual system development have studied cortical response properties that are thought to reflect computations performed by cortical circuits beyond the thalamic input in cortical layer IV, where ocular dominance plasticity is mediated by the differential maturation and growth of thalamocortical afferents. Thus, studies of orientation and direction selectivity in the visual cortex have yielded novel and somewhat unexpected insights into the nature of experience-dependent plasticity. Among them are unique periods of postnatal development when cortical circuits are more-or-less sensitive to the spatiotemporal structure of visual stimulation (White et al. 2001), with a sensitive period for the development of direction selectivity closing during a time when

other response properties (e.g., ocular dominance, orientation selectivity) remain malleable in an experience-dependent fashion (Li et al. 2006; White and Fitzpatrick 2007).

Recognition that distinct physiological properties of neurons and circuits in the visual system may display distinct windows of experience-dependent plasticity has prompted the concept of "plasticity hierarchy" (Hensch 2004). This concept posits that a property processed at higher levels of the visual system (e.g., in higher-order visual associational areas) has a sensitive window that opens later, lasts longer and/or may be less developmentally constrained than sensitive windows associated with physiological properties attributable to lower levels of processing. This may indeed be an accurate accounting of certain properties in visual system development associated with perceptual learning across visual associational cortex (e.g., Yang and Maunsell 2004). However, as evidenced by the early sensitive window for cortical direction sensitivity in V1, this concept may not apply in strict chronological terms for functional phenomena emerging from cortical circuitry in early visual cortex beyond the input layer where ocular dominance plasticity is first manifest.

Auditory system

Auditory cortex displays a well-characterized sensory-dependent window of plasticity corresponding, in rat, with the marked refinement of the tonotopic map between 16 and 50 days of age (Zhang et al. 2002; Chang and Merzenich 2003; de Villers-Sidani et al. 2007). Within this postnatal period, passive, chronic exposure to sound of a particular frequency range accentuates its cortical representation, interpreted as adaptive changes which persist into adulthood (Zhou et al. 2011). In contrast, similar passive sound exposure in the adult has little effect on cortical representations though rewarded or novel exposure can reinstate plasticity (Zhou et al. 2011). Interestingly, chronic exposure to uniform noise delays the sensitive window which will reopen when this milieu is removed. Closure of the sensitive window of auditory cortical plasticity is thought to involve many of the same physiological and molecular mechanisms implicated in the ocular dominance model of critical period, including GABA inhibition, NMDA-type receptor modification and local BDNF action (Zhou et al. 2011). A number of other sensitive periods have been identified that involve the auditory system including absolute-pitch development (Miyazaki and Ogawa 2006) and language acquisition (reviewed by Pinker 1994) in humans, though both assertions have been controversial. Sound localization in the barn owl is another celebrated example of critical period. In this complex task the brain's tectum must precisely align the auditory and visual maps of space to allow accurate flight and navigation to targets like rodent prey (Knudsen 1998). Placing prism goggles on owls, which creates a misalignment of the maps of visual space and intraural time difference (an auditory map), leads to compensatory remapping provided the manipulation is done early in life (Brainard and Knudsen 1998; Knudsen 1998).

Somatosensory system

Another archetypal example of critical period is found in the "barrel" field, within somatosensory cortex, which processes inputs from the specialized whisker (mystacial) pads of rodents and some other mammals. Selective sensory deprivation in rodents during a sensitive postnatal window in the first postnatal week through ablation of individual whisker follicles leads to a shrinking of corresponding barrels in cortex (Van der Loos and Woolsey 1973; Woolsey and Wann 1976). In the nearly half century that has elapsed since this discovery, a number of sensitive windows of plasticity have been discovered in the excitatory circuits of barrel cortex (reviewed in Erzurumlu and Gaspar 2012). Recent studies of the parvalbumin-inhibitory-interneuron network in barrel cortex suggest, as in ocular dominance plasticity, that maturation of inhibitory networks may be key to the timing of plasticity epochs (Lo et al. 2017).

The search for critical periods in olfaction

Olfactory sensory neurons (OSNs) and their synapses

OSNs are unique among sensory neurons in their ability to continuously regenerate throughout the life of an organism. Mature OSNs die and are replaced by immature cells, which differentiate from a progenitor cell population, eventually sending axons through the cribriform plate that make functional connections with glomeruli in the olfactory bulb (Graziadei and Graziadei 1979). The continuous turnover of OSNs raises a number of interesting questions, including how the mechanism of axon guidance is maintained throughout life, and more fundamentally, whether a critical period phenomenon—at least at the level of OSNs— would be expected in such a perpetually plastic system.

The olfactory regenerative process has been studied with the help of the olfactotoxin, methimazole, which completely but transiently ablates OSNs so their differentiation and subsequent connections to the bulb can be followed in a synchronized manner. Interestingly, this process has been shown to not only be sensory dependent but also to have a sensitive window. Methimazole treatment combined with deprivation by unilateral naris occlusion in mouse models reveals a disruption of olfactory regeneration on the occluded side of the nasal cavity in adult mice (Kikuta et al. 2015). A week of deprivation starting at the beginning of the regenerative process had no effect on the reestablishment of the olfactory epithelium. However, deprivation started during the second

week of recovery resulted in a thinner olfactory epithelium and fewer total OSNs and mature OSNs measured at four weeks-of-age. Further, when these authors labeled recovering olfactory epithelium for markers of cell proliferation and apoptosis they found the former decreased and the later increased comparing the occluded to the open sides of the nasal cavity at two-week and four-week recovery periods (Kikuta et al. 2015). Thus, immature OSNs would appear to require stimulus-driven activity during a sensitive window between approximately 7–14 days of age after cell birth lest they become susceptible to apoptosis.

In contrast to OSN turnover, which appears to have a sensitive window of activity dependence, OSN synapse formation in the bulb is continuously plastic. Cheetum and colleagues (Cheetum et al. 2016), using transgenic markers for immature and mature neurons combined with electron microscopy, in vivo time-lapse imaging, and optogenetic activation, have shown that nascent OSNs make functional but unstable synapses within the olfactory bulb. Moreover, the presynaptic terminals of both immature and mature OSNs rapidly turn over in an activity-dependent manner based on studies using naris occlusion as the method of stimulus deprivation. Interestingly, the stability of active presynaptic synapses was surprising short, even in mature OSNs, with greater than 10% turnover in 3 h; for comparison, spine turnover in adult mouse cerebral cortex is generally <1% over 6 h (Brown et al. 2007).

OSN-to-bulb map

In the mouse, each OSN typically expresses one of over a 1000 different olfactory receptor genes, and connects its axons to either of a mediolateral mirror-symmetric pair of glomeruli located in the bulb (Mombaerts et al. 1996). Evidence suggests that this OSN-to-bulb map formation has a sensitive window albeit devoid of sensory influence. Tsai and Barnea (2014) and Ma and colleagues (Ma et al. 2014) using complimentary transgenic approaches in mice to conditionally disrupt OSN axon routing, demonstrated recoverability of the normal bulbar map provided perturbations were switched on only after the perinatal period. In the Tsai and Barnea (2014) study, expression of a transgenic odorant receptor within a week of birth caused "rerouting" of axons from the cognate endogenous receptor to ectopic glomeruli, while a like manipulation switched on later had no effect. Reasoning that appropriate axon routing to the bulb may be dependent on the abundance of immature OSNs perinatally, these investigators used methimazole to induce synchronized regrowth of the olfactory epithelium in adults combined with transgenic odorant receptor expression. These manipulations, while resulting in ectopic glomeruli, failed to cause rerouting of axons from OSNs expressing the cognate endogenous receptor suggesting that mechanisms functioning perinatally, when the map is initially formed, are unavailable in adulthood (Tsai and Barnea 2014). Likewise, Ma and colleagues (Ma et al. 2014) conditionally disrupted bulbar map formation by transgenically expressing Kir2.1 channels to suppress OSN neural activity. If Kir2.1 expression was switched off near the time of birth the normal mirror symmetric pairs of glomeruli were innervated. However, if Kir2.1 expression was delayed past postnatal day 5 abnormal supernumerary glomerular innervation was observed pointing, again, to a sensitive window for map formation. That electrical activity in OSNs is only playing a permissive role in map formation was born out by additional experiments in which laminin B receptor ectopic expression, which dysregulates olfactory receptor gene expression, was associated with similarly timed map disruption (Ma et al. 2014). Taken together, these studies suggest an unconventional 'critical period' (using the authors' terminology) for OSN-to-bulb map formation that closes near the time of birth and has no role for sensory experience (Cheetham and Belluscio 2014).

The Intrabulbar map

The mirror-symmetric glomeruli that receive inputs from OSNs expressing the same olfactory receptor gene are linked by a system of intrabulbar projections made up of external tufted cells (Schoenfeld et al. 1985). In mice, these reciprocal connections are diffuse at birth but gain their maximum level of precision by the 7th postnatal week (Marks et al. 2006). Using neural tract-tracers injected into glomeruli, Marks and colleagues (Marks et al. 2006) were able to follow the maturation of the intrabulbar map. A role for experience in map refinement was established using transgenically created anosmic and naris occluded mice. Their results show that either anosmia or naris occlusion during development prevents the intrabulbar map from attaining its adult level of precision and that the latter treatment actually causes regression of map refinement compared to the normal developmental timetable. Importantly, naris occlusion performed in adult mice from either 4 to 7 or 10 to 14 postnatal weeks resulted in diffuse intrabulbar maps similar to those found in newborn mice. Thus, the intrabulbar map, like OSN synapse formation, is activity-dependent but lacking a sensitive window.

Olfactory bulb granule cells

The hippocampus and olfactory bulb are unique in the CNS of many adult mammals in that they receive a steady supply of proliferating cells from separate neurogenic niches (Lois and Alvarez-Buylla 1994; Gage 2000). In the bulb, these cells arrive along the rostral migratory stream and differentiate into inhibitory interneurons, either periglomerular cells or granule cells (Lois and Alvarez-Buylla 1994). Only a portion of granule cells, which have been the most thoroughly studied adult-born neurons in the bulb, survive and become integrated into bulbar circuitry. The survival rate of these axonless cells is experience-dependent, decreasing with odor deprivation and

increasing with odor enrichment (Lledo and Saghatelyan 2005). Yamaguchi and Mori (2005) using BrdUrd-labelling in adult mice to track granule cell survival and unilateral naris occlusion to induce deprivation have shown that there is a sensitive window in adult mice during which these interneurons are sensitive to sensory experience. Adult mice were injected with BrdUrd and then experienced naris occlusion from 0 to 14, 14–28, 28–42 or 42–56 days after injection. Only the group with naris occlusion between 14 and 28 days had statistically fewer labelled granule cells, suggesting that this two-week period after granule cell birth was a sensitive window leading to death or survival depending on sensory input. This effect could be mimicked with the application of diazepam, a positive allosteric modulator of the $GABA_A$ receptor.

Reasoning that cell death might be accelerated in the granule cell population in deprived and diazepam treated animals, the authors immunolabeled caspase-3, part of an apoptosis cascade, and other markers of cell death, after various survival durations. As predicted, both ipsilateral naris occlusion and diazepam increased apoptosis four-fold with the greatest effect occurring in 14–20 day-old granule cells (Yamaguchi and Mori, 2005). Previous investigators had shown that granule cells at this age extend dendrites into the external plexiform layer to make contact with mitral/tufted cells, the primary output neurons of the bulb (Petreanu and Alvarez-Buylla 2002). Thus, the authors (Yamaguchi and Mori, 2005) concluded that granule cell survival hinges on sensory input at the time of synapse formation with mitral/tufted cells and that this experience-dependence may allow the olfactory bulb circuits to become tailored to varying odor environments.

The timing and sensory-dependence of granule cell synapse formation in the bulb were further investigated by Kelsch and colleagues (Kelsch et al. 2009). They used transgenically labelled presynaptic and postsynaptic targets to analyze synaptogenesis under: normal levels of olfactory sensory activity, deprivation by naris occlusion, or in transgenically modified granule sells with enhanced excitability. Synapse formation was influenced by sensory deprivation during a sensitive window postnatally coinciding with that described by Yamaguci and Mori (2005). However, the effect of deprivation depended on the dendritic domain examined showing decreases in distal and basal domains and, surprisingly, increases in the proximal domain. Enhanced excitability did not affect granule cell synaptogenesis compared to controls but did rescue animals from the deprivation phenotype. These findings provide further evidence for a sensitive window in the lives of granule cells at the time of synapse formation when they are sensitive to the effects of synaptic drive or intrinsic excitability.

Olfactory cortex

Output neurons of the olfactory bulb send their axons via the lateral olfactory tract to synapse with pyramidal cells in the piriform cortex, one important division of the primary olfactory cortex that contributes to the formation of odor perceptions. Odor processing is abetted by association fibers from other pyramidal cells in the piriform and from the efferent projects of several other cortical and corticoid regions (Haberly 1998). Franks and Isaacson (2005), using patch-clamp recordings of cortical slices in rat, have found evidence for a sensory-dependent sensitive-window of synapse maturation in the piriform cortex. They show that during the first month after birth there is an increased contribution of AMPA-type glutamate receptors compared to NMDA-type glutamate receptors at lateral olfactory tract synapses, but not associational synapses on pyramidal cells. This change in relative receptor contribution is predominantly due to a loss of NMDA receptors with only a slight gain of AMPA receptors. Critically, the change in relative contribution of glutamate receptor type at lateral olfactory tract synapses was delayed in the ipsilateral piriform cortex by unilateral naris occlusion but only if the deprivation occurred during the first postnatal month. The authors go on to show that sensory experience during this sensitive window increases the long-term potentiation threshold at lateral olfactory tract but not associational synapses, a process thought to underlie the closing of the sensitive window of olfactory cortical plasticity. A follow-on study from the same laboratory, which combined patch-clamping with morphology, was able to show that the maturation of dendritic spines on sensory synapses of pyramidal cells coincided with NMDA-dependent long-term potentiation during a sensitive window postnatally (Poo and Isaacon 2007). Considered together, this work prompted the authors to concluded that the sensory-dependent window of plasticity in sensory synapses of the piriform cortex may be the basis of olfactory imprinting whereby young learn the maternal scent, a memory which becomes crystalized once this window closes.

Discussion

Critical period by any other name

As should be clear from a consideration of the claims of critical period-like phenomena in olfaction, the concept has been expropriated to include ‘all manner of sins.’ Hensch (2004), in his excellent review, laid out a set of critical period characteristics while recognizing the provisional nature of such an analysis. Among these were: (1) functional competition among inputs; (2) role of activity; (3) structural consolidation; (4) regulation by experience; (5) importance of inhibition; (6) influence of attention and motivation; (7) unique timing and duration; (8) characteristic molecular mechanisms; and (9) possibility of adult reactivation.

Though these attributes were not meant to be prescriptive, it is instructive, nevertheless, to compare them with candidate critical periods in olfaction. Consider, for example, the activity

dependence of immature OSNs discussed above (Kikuta et al. 2015). Competition, consolidation, inhibition and reactivation either do not apply or have not been demonstrated in this model. Also, the full-scale neurogenesis and apoptosis induced by the use of toxin in this model would seem to set up an artificial ordering effect, rather than a true temporal window, as ingrowing axons take up available synaptic loci in the bulb. Given these fundamental differences, is it really appropriate—in the sense of aiding understanding —to lump these observations in the same category as the processes described by Lorenz, Hubel and Wiesel and their modern day acolytes? Even more problematic is invoking critical period to describe the timing dependence of OSN-to-bulb map formation which does not even require activity and may depend more on the *ordering* of events than their developmental timing (Ma et al. 2014; Tsai and Barnea 2014). Indeed, this process shares little in common with classical models of critical period including ocular dominance, auditory map, or barrel cortex plasticity. Moreover, though it is an interesting fact that newborn neurons in the olfactory system, both olfactory sensory neurons and bulbar granule cells, require activity for their survival, describing this as a critical period process detracts from a key point: that olfaction displays a singular form of "neoteny." Present evidence argues that it is unique among sensory systems in displaying life-long neurogenesis and thus the potential for persistent circuit plasticity rather than the experience-induced functional rigidity and anatomical consolidation that characterizes classical models of critical period (Petreanu and Alvarez-Buylla 2002; Yamaguci and Mori 2005; Kikuta et al. 2015).

Conversely, it is worth considering whether the critical period concept as defined in the classical models has worn out its usefulness. If so, perhaps using the epithet promiscuously to describe any time-sensitive biological process—as it has been used in olfaction—should not be viewed as heretical. After all, we have seen in the last several decades one of the most radical paradigm shifts in the history of modern neuroscience on this topic: a revision of the dichotomy between plastic young brain and the once-presumed aplastic mature brain. Just to list a few examples, Merzenich and colleagues (Merzenich et al. 1984) have shown that digit resection or surgical digit fusion cause a reorganization of somatosensory maps in adult primates that appears to be adaptive. In mice, unlike rat, cat and primate, ocular dominance plasticity persists into adulthood albeit in a muted form (e.g. Sawtell et al. 2003). However, even in rat, prolonged sensory deprivation through dark-rearing can reopen the sensitive period for ocular dominance (He et al. 2006, 2007). In the case of the auditory system, chronic exposure of adult rats to acoustic noise reopens the critical period of auditory cortex and reverses many of the classic molecular "brakes" that are thought to underlie its termination (Zhou et al. 2011).

Even more intriguing are the various social, sensory and sensorimotor manipulations that can be implemented to increase plasticity in the adult nervous system that will be considered under the phrase "environmental enrichment." For example, housing mice in large and structurally complex cages (e.g. with toys and running wheels) will increase ocular dominance plasticity even in adults (Greifzu et al. 2014). And, extensive visual stimulation of monocularly deprived adults dramatically increases ocular dominance plasticity in 10-month-old mice (Matthies et al. 2013). Any number of other examples of enrichment-enhanced plasticity in adult animals can be found in the literature relating to other classical critical periods (see review by Hubener and Bonhoeffer 2014). To mention just one, adult barn owls allowed to hunt live prey have heightened auditory cortical plasticity compared to hand-fed controls (Bergan et al. 2005). The common theme in these and other examples of increasing plasticity through environmental enrichment is that the interventions, in most cases, would be expected to decrease inhibition and thereby change the excitatory/inhibitory balance (ibid).

Do these revisionists views of critical period, then, dilute its value as a scientific construct? We think not! While it is now widely appreciated that critical period windows are rarely absolute and can be, in any event, reopened under the right circumstances, few would doubt that the concept of heighted periods of activity-dependent and/or experience-dependent plasticity, early in life, is one of the truly transformational discoveries of the last century. We agree with Hensch (2004) that there remain compelling benefits to society yet to be fully realized that should continue to motivate and inspire critical period investigation. Among them are understanding the causal links between education and neural plasticity; development of neuroscience-based interventions for individuals recovering from brain injury; and enhancement in learning and performance among both neurotypical and neurodiverse individuals. We remain encouraged to believe that such translational outcomes are possible—even likely—with continued investigation of critical period phenomena and their neurobiological underpinnings.

However, we favor a more doctrinaire approach than has been practiced, heretofore, in the description of olfactory (see above) and other phenomena that have only superficial similarities to classical critical periods. Genetic information specifies a great deal about the building blocks necessary for the construction of neural circuits and neural systems; in addition, the assembly of those metaphorical building blocks in embryogenesis and the functional maturation of nascent circuits and systems in peri- and post-natal brain development are abetted by robust, self-organizational dynamics (Kaschube et al. 2010). By contrast, the evolutionary adaptive value of critical periods is to accomplish what would be difficult or impossible for genes or self-organization: to customize a brain/body to its ecological niche, given the complexity of a growing body, unstable environment and the survival and reproductive pressures of the natural world. Given their adaptive

value, perhaps it is not surprising, after all, that, under the right circumstances, critical periods can be reopened.

Why olfaction does not have classical critical periods

While our review of the claims of critical periods in olfaction could not be exhaustive, it does point out the increasingly liberal use of the phrase which, in our view, ultimately dilutes its meaning. An analytical evaluation of classical models of critical period reveals that the olfactory system appears to be devoid of such phenomena (Table 1). Perhaps the closest contender is the maturation of sensory synapses in the piriform cortex (see above, Franks and Isaacson 2005; Poo and Isaacon 2007) which possesses a sensitive window of activity influence. However, activity in this model only *accelerates* synapse maturation; it is not necessary for its occurrence. And, competition, inhibition, and structural consolidation, all characteristics of classical critical period, have not been established or do not apply. Indeed, in this model associational synapses, on the same pyramidal neurons with sensory synapses, maintained their plasticity into adulthood (i.e. showed no sensitive window of experience dependent change). Tangentially, olfactory imprinting, which these authors suggested might be the function of the sensitive window in piriform sensory synapse maturation, has also been localized to the olfactory bulb/locus coeruleus circuit (Moriceau and Sullivan 2005). We chose not to include an analysis of this latter model in the current review since it involves classical conditioning and thus a stimulus-reward pairing incompatible with Lorenz' definition of imprinting (classical critical periods). Thus, we concluded that while these are interesting phenomena in their own right, they lack the characteristics of classical critical period models.

Back to the central question of why olfaction may lack classical critical periods? Possible answers emerge from a consideration of the purpose of classical critical periods: to "tailor" neural circuits to each individual embedded in its particular environmental circumstance (Hensch 2004). One important kind of tailoring is developmental adjustment of internal representations of the outside world to match the changing size of a growing organism as we saw in ocular dominance plasticity and tectal map registration (Hubel and Wiesel 1998; Knudsen 1998; see discussion in Pinker 1994). By contrast, olfaction, having no spatial or temporal basis like vision or audition (e.g. sound localization), does not have to adjust to body growth, nor does it have a need for alignment with other sensory or motor maps. Indeed, one of the only hypotheses of olfaction that requires a particular spatial layout (a map) of OSN in the olfactory epithelium, the "sorption hypothesis," which posits that odors partition themselves across the mucosa according to their mucus solubility and volatility, fails when its critical assumptions are tested (Coppola et al. 2013, 2017; unpublished data).

Table 1 Critical period-like processes in the olfactory system and the characteristics they share with classical examples (Hensch 2004)

Phenomenon	Sensitive window	Role of electrical activity	Sensory experience influenced	Competition among inputs	Structural consolidation	Role of inhibition	Attention and motivation influence	Adult reactivation
OSN regeneration (Kikuta et al. 2015)	7 to 14 days after birth of neurons	Unclear	Yes	No	Unknown	No	Unknown	No
OSN to Bulb Map (Tsai and Barnea 2014; Ma et al. 2014)	< 1 week after birth	Unclear	No	No	Yes	No	Unknown	No
Intrabulbar connection map (Marks et al. 2006)	None	Yes	Yes	No	No	No	Unknown	Yes
Granule cell survival (Yamaguci and Mori 2005: Kelsch et al. 2009)	14 to 28 days after birth of neurons	Yes	Yes	No	Yes	No	Unknown	No
Olfactory cortex synapses (Franks and Isaacson 2005; Poo and Isaacon 2007	First month after birth	Unclear	Yes	No	Yes	No	Unknown	No

Another type of tailoring, as noted previously, is found in the 'instructive' role activity can have in the development of sensory maps: for example, the competitive overrepresentation in the adult rat auditory map of a frequency it was exposed to during an earlier developmental period (Chang and Merzenich 2003) or the training-induced maturation of circuits in the visual cortex for direction selectivity (Li et al. 2008; Van Hooser et al. 2012). However, in olfaction, the potential stimulus space is extremely large (though its actual magnitude is debated; see Meister 2015) given that there are over 1000 functional receptor types in the mouse participating in combinatorial mode of coding for perhaps tens-of-thousands of different stimuli (Bushdid et al. 2014). It would seem totally unworkable for each OSN type to use differential stimulus-driven activity patterns to instruct its wiring to the bulb. It is not surprising then that inhibiting sensory activity has only modest effects on the development of the OSN-to-bulb map, though intrinsic activity seems to play a permissive role (Yu et al. 2004). In fact, in an elegant series of studies, the guidance cues that ferry OSN axons to their appropriate targets have been well worked out (reviewed by Takeuchi and Sakano 2014).

There is another serious challenge to any view of plasticity in the olfactory system that would invoke the classical concept of critical period: the system's persistent neurogenesis. The conventional explanation holds that this unique feature among sensory systems allows for adaptation in novel olfactory environments throughout an organism's lifetime (e.g. Moreno et al. 2009; Kass et al. 2016; Sailor et al. 2017). Consistent with this idea, there is abundant evidence suggesting the olfactory system maintains its plasticity into adulthood, including those cases already mentioned. First, stimulus deprivation decreases the production and survival of adult-born neurons in both the epithelium and bulb (Watt et al. 2004) and also causes other anatomical and physiological changes from periphery to cortex (reviewed by Coppola 2012). In addition, enrichments studies (usually meaning the exposure to a single purified odorant at high concentrations for an extended period) abound, which have shown anatomical and physiological effects throughout olfactory pathways (reviewed in Kass et al. 2016; Liu and Urban 2017). Since odor enrichment increases the survival of adult born neurons, the nexus between odor environment, status of adult-born neurons and structure-function relationships in olfaction is well supported (Sailor et al. 2017).

Despite these associations, there are several reasons to doubt that neurogenesis persists in the adult olfactory system for the primary purpose of adapting the organism to different environments. First, in rodents, olfactory receptor expression is remarkably stable over the life time of an individual organism and over evolutionary time despite the continuous turnover of OSNs. Khan and colleagues (Khan et al. 2013) measured RNA abundance in mice using NanoString technology discovering that only ~4% of olfactory receptor transcripts were differentially expressed over the normal lifespan. And, Furudono and colleagues (Furudono et al. 2009) showed striking similarities between the groupings of odor responses in mouse OSNs measured physiologically and the quality groupings of the same odors measured psychophysically in humans suggesting considerable receptor conservation in two species occupying dramatically different niches with 75 million years since their last common ancestor. Second, manipulations like sensory deprivation or odor enrichment have had small or equivocal effects on the OSN population. For example, odor deprivation has only modest effects, increasing the abundance of some olfactory receptor transcripts and decreasing the abundance of others (Coppola and Waggener 2012), while enrichment using ligands for specific olfactory receptors increases the abundance of OSN's carrying cognate receptor in some cases but not in others (Cadiou et al. 2014).

With regard to the bulb, there have been numerous 'gain-of-function' studies implicating adult-born interneurons in a surprising range of olfactory functions including: detection and discrimination (Enwere et al. 2004; Breton-Provencher et al. 2009), perceptual learning (Moreno et al. 2009), memory (e.g. Alonso et al. 2012), and innate responses (e.g. Sakamoto et al. 2011). By contrast, 'loss-of-function' studies—in which neurogenesis is eliminated—have typically failed to show any major effects on olfactory processing (Grelat et al. 2018). Importantly, the human rostral migratory stream becomes more of a trickle than a stream beyond the embryonic period with few if any adult-born neurons reaching the bulb and yet human olfaction—though frequently maligned—is on par with that in many macrosmatic animals (Sanai et al. 2011; Laska 2017).

Finally, on logical grounds, it is unclear why olfaction—*unlike vision, audition and somatosensation*— cannot adapt to diverse and changing environments without a constant supply of new neurons. Ample evidence documents the increased structural plasticity (new synapses) that accompany the influx of perhaps a thousand new neurons per day in the bulb (e.g. Sailor et al. 2017). However, this simply begs the question of how other sensory systems manage their jobs mostly with modifications of existing (functional and silent) synapses.

One might look to the hippocampus for clues as to the function of persistent neurogenesis in olfaction, since this is the only other structure in the mammalian brain with this trait. However, currently there is no consensus on the functions of neurogenesis in this structure either, with explanations ranging from "behavioral pattern separation" (also invoked for olfaction) to forgetting (see Kempermann et al. 2018 for discussion). In the human brain, the fundamental fact of hippocampal neurogenesis in early postnatal life and across the lifespan remains in vigorous debate (Sorrells et al. 2018). Looking more broadly, neurogenesis is quite widespread across numerous adult brain regions of non-mammalian vertebrates where it promotes an amazing (from the mammalian perspective) level of regeneration and repair (Kaslin et al. 2008). Interestingly, neurogenesis is *actively suppressed* in most mammalian brain regions (*ibid*).

Collectively these considerations prompt us to offer the following speculations about the role of neurogenesis in olfaction and the relationship between this trait and the lack of classical critical periods. We aver that neurogenesis in the olfactory epithelium and bulb are not de novo adaptions allowing organisms to adjust to changing odor environments, but rather a vestigial neotenic state that has been maintained for the purposes of repair. Anyone suffering from viral rhinitis can attest to the rapidity and completeness of the temporary anosmia that can accompany this disease due to its attack on the olfactory epithelium (Dalton 2004). Clearly, OSNs lie exposed in the nasal cavity unprotected from dust, toxins, allergens and pathogens bombarding their exposed dendrites with every breath. As the only neurons with plasma membranes simultaneously in contact with both the outside-world and the brain, they form a potentially devastating portal for disease. Evidence in support of our repair perspective comes from a now classic study showing that OSNs can survive for up to a year in mice (the species' entire normal life expectancy) provided that the animals are maintained in purified air (Hinds et al. 1984), a finding that has been recently confirmed with modern transgenic cell-dating techniques (Holl 2018).

But what of the large supply of adult-born inhibitory interneurons –granule and periglomerular cells—entering the bulb each day? It is possible that the delivery of adult-born neurons from the rostral migratory stream to the bulb evolved for some separate function or functions (see above) unrelated to the olfactory epithelial neurogenesis? Applying Occam's razor to the problem renders such accounts dubious. Rather, we speculate that the constant ingrowth of newborn OSNs (excitatory input), even if partially matched by OSN death, raises the threat of creating an imbalance between excitation and inhibition that could disrupt processing in the bulbar network. In this context, an excess supply of inhibitory neurons (only about 60% survive) may be beneficial to maintaining excitation/inhibition balance and aid in the incorporation of ingrowing OSN axons to existing bulbar circuits. We remain open to the possibility that this original purpose may have subsequently been co-opted for additional uses as described above.

Conclusions

A detailed analysis was undertaken of observations in the olfactory system that have been categorized as critical period phenomena (Table 1). Results reveal that some of these processes either display experience-dependence or a temporal window or both, characters shared with classical critical periods. However, none have been shown to have all or even most of the attributes of critical periods, like those described by Lorenz and his intellectual heirs (Hensch 2004). Some scholars will undoubtedly dismiss this distinction as purely *semantic*. However, we believe that profligate use of the phrase critical period dilutes its meaning and may distract from the key point that olfaction is different from all other exteroceptive systems in lacking true critical periods. Further, we submit that the conventional analysis of why olfaction lacks critical periods has it backwards: Olfaction, we submit, does not lack critical periods because of persistent neurogenesis. Rather, olfaction was able to maintain this ancestral neotenic state because critical periods are of no particular advantage in a system lacking spatial and temporal dimensions or the usefulness of instructive environmental influences. Finally, we assert that the main advantage of neurogenesis in the olfactory epithelium and bulb are not to match an animal's chemosensory repertoire to new odor environments but to allow such a neural system so precariously situated in direct contact with a hazardous world to reconstitute itself as needed. The lack of critical periods in olfaction and the persistent neurogenesis it affords makes this one neural system that appears to remain forever young.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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