1: EGFR signaling in the brain is necessary for olfactory learning in Drosophila larvae

WIKIMEDIA, BOB GOLDSTEIN Early-life exposure to pathogenic bacteria can induce a lifelong imprinted olfactory memory in C. elegans through two distinct neural circuits, according to a study published today (February 11) in Cell.

Download as PowerPoint Slide Figure 7. We found that promoter activity of egfr and its activating ligands spitz, keren, and vein was most apparent in the larval MBs. In particular, no promoter activity of egfr was detected in the adult CNS. Thus, we assumed that EGFR signaling is of high physiological relevance in the differentiated larval brain and, here, is involved in the major task the MBs are known for, learning and memory. Constitutive and pan-neuronal expression of a dominant-negative form of EGFR strongly reduced olfactory learning in larvae, whereas their ability to taste and smell was not impaired, indicating that the observed learning phenotype depends on central rather than sensory defects. Moreover, using the inducible, mifepristone-dependent GeneSwitch system, we demonstrated that this learning phenotype results from impaired EGFR signaling in the functional brain and not from developmental defects caused by impaired signaling during embryogenesis. Interestingly, silencing of each of the EGFR ligand genes spitz, keren, and vein at larval stages as well as enhanced expression of secreted activated Spitz led to the same dramatic decrease of olfactory learning ability. Strikingly, reduction of EGFR signaling exclusively in the MBs revealed the same strong learning defect as was observed in larvae with pan-neuronal manipulations of the pathway. The most important result of this study is the finding that proper EGFR signaling is essential for olfactory learning in Drosophila, particularly with regard to our sparse knowledge of EGFR signaling in the developed brain. In vertebrates, EGFR signaling plays multiple roles during embryogenesis and nervous system development, but has also been linked to myelination Brinkmann et al. A link between EGFR and signaling systems associated with learning was also recently established. Notably, Hannan et al. Moreover, attenuated as well as enhanced PKA signaling has been reported to reduce learning ability in flies Drain et al. Why all three EGFR ligands are essential for proper olfactory learning is not yet understood. One possible explanation is that signaling via all ligands is necessary to maintain the proper signaling balance essential for olfactory learning. Alternatively, the system may not be organized in such a manner that different ligands can be functionally exchanged. Based on the expression patterns observed for all ligands and EGFR, different modes of signaling are possible. During Drosophila brain development, axonal structures are thought to release Spitz to activate the EGFR pathway in glial cells to promote cell survival Bergmann et al. Another EGFR ligand, Vein, is produced by pioneer neurons and is required for the survival of longitudinal glia Hidalgo et al. Our observations further suggest an alternative signaling system. Because all components of the EGFR signaling system are present in the MBs, autocrine or paracrine modes of signaling are possible. Autocrine EGFR signaling is relevant to various systems ranging from epithelial mechanotransduction Kojic et al. Thus, proper autocrine or paracrine EGFR signaling within the Kenyon cells of the MBs may be required to maintain cellular homeostasis, allowing for olfactory learning. The present findings suggest that holding a fine-tuned homeostatic balance in the cells of the MBs is critical for proper learning. In addition, signaling systems, such as the EGFR pathways that may not be directly involved in transmitting learning related content, may nevertheless be essential to enable learning.

2: Olfactory memory - Wikipedia

The olfactory nervous systems of insects and mammals exhibit many similarities, suggesting that the mechanisms for olfactory learning may be shared. Neural correlates of olfactory memory are distributed among many neurons within the olfactory nervous system.

The participants underwent a clinical evaluation, olfactory test, neuropsychological assessment, and neuroimaging assessment. Diminished olfactory identification was significantly correlated with worse cognitive performance global function, memory language, executive function, and attention and reduced grey matter volume olfactory bulb and hippocampus in the late-life depression patients. Reduced volume observed in many areas hippocampus, precuneus, etc. We found that diminished OI is correlated with poor cognitive performance particularly memory and brain atrophy olfactory bulb and hippocampus in LLD patients. Introduction Late-life depression LLD is among the most common disabling mental illnesses in older people and affects 3. LLD patients are considered at a high risk of developing dementia Kaup et al. Whether LLD is an early manifestation or a risk factor of dementia remains controversial; however, the early identification of LLD patients who are most likely to develop AD could be advantageous for timely intervention. Comprehensive assessments of cognitive function may contribute to this early screening process, and LLD patients with poor cognitive performance particularly memory deficits exhibit more structural abnormalities in AD-related regions, more functional and white matter network abnormalities, a high amyloid load with hypermetabolism, increased cognitive decline, and higher rates of conversion to AD Lee et al. However, suboptimal effort may be common in LLD patients and lead to bias in neuropsychological assessments Benitez et al. Recently, diminished olfactory identification OI has been used as a supplemental assessment for the early detection of AD and an effective biomarker of AD pathology due to its advantages of being simple, cost-effective, and noninvasive Laske et al. OI, which is the ability to identify and denominate specific odors, depends on several cognitive processes, such as semantic memory access, denomination capacities, and comprehension of instructions Rahayel et al. Therefore, OI impairment is considered to reflect the extent of cognitive impairment and brain malfunction in older individuals. In cross-sectional studies, individuals with diminished OI exhibited worse cognitive performance memory, execution function, and language Roberts et al. In a longitudinal study, OI impairment predicted a faster cognitive decline and higher rate of conversion to AD in amnestic mild cognitive impairment aMCI patients and elderly controls Roberts et al. However, whether diminished OI could contribute to identifying LLD patients at a high risk of developing AD remains unclear, because studies specifically focusing on OI in LLD patients are lacking, and previous studies investigating olfactory function in depression patients did not exclusively focus on older adults. It has been repeatedly reported that it was olfactory threshold OT rather than OI that was significantly impaired in patients with depression Naudin and Atanasova, ; Khil et al. The patterns of olfactory impairment differ between AD and depression patients, and OI deficits may be significant in AD patients but not in depression patients Naudin and Atanasova, ; thus, previous studies involving small sample sizes have successfully differentiated AD patients from depression patients using OI tests. All subjects in our study were from the Chinese Han population. All participants or their legal guardians provided written informed consent to participate in the study. The inclusion criteria for the LLD group were as follows: The following exclusion criteria were applied: Neuropsychological Assessments After the participants underwent standard clinical assessments, they were interviewed by neuropsychologists to assess their global cognitive functioning using the Mini-mental State Examination MMSE and depressive state using the item Hamilton Depression Rating Scale HAMD In addition, the participants in the NC and LLD groups underwent comprehensive neuropsychological tests to assess their performance in the following 5 cognitive domains: The raw tests scores were adjusted using normative data, summed, and scaled to compute the domain z scores Ivnik et al. The subjects completed a questionnaire surveying factors that may influence olfactory function i. All olfactory assessments were performed in a quiet, odorless, ventilated room at the Affiliated Brain Hospital of Guangzhou Medical University. All participants underwent the OT and OI tests following neuropsychological assessments. All

participants were ethnically Chinese Han and right-handed. Briefly, each T1 image was segmented into the cerebrospinal fluid, white matter, and grey matter and then normalized to the Montreal Neurological Institute template. A Gaussian kernel filter of 8x8x8 mm3 was used to smooth the modulated image. The mean left and right hippocampal grey matter volumes HVs were then extracted from the regions of interest using the anatomical automatic labelling brain atlas Tzourio-Mazoyer et al.

3: Adult neurogenesis - Scholarpedia

Olfactory memory refers to the recollection of www.enganchecubano.coms have found various characteristics of common memories of odor memory including persistence and high resistance to interference.

This type of bonding is characterized by an exclusive relationship; selective mothers will not provide maternal care to young with which they have not formed a bond. In sheep, olfaction , the sense of smell, plays a vital role in the establishment of the exclusive bond, though other senses, particularly sight and to an extent hearing, are involved as well. Additionally, domestic sheep are common worldwide, easily bred and handled, and well understood in terms of behavior and natural history, providing a solid base for more intricate study. Most animals displaying maternal instincts will care for any infant introduced to the nest. In contrast to this, selective mothers form bonds to specific individual young and will show maternal responsiveness only to these young. In sheep, young to whom the ewe is not maternally bonded will be received with aggression, generally head-butting and turning in circles away from the lamb. Natural selection is assumed to favor the evolution of mechanisms ensuring that the correct offspring receive the often costly parental investment involved in rearing. This is commonly seen in other ungulates and also in seals and primates , all species where the chance of misdirecting parental care is substantial. Responsiveness and selectivity[edit] Maternal care in sheep can be seen as composed of two components â€" selectivity and responsiveness. Maternal responsiveness can be observed broadly across species, mammalian and otherwise. This is the drive for a mother to provide care for her young. These rumbles calm and quiet the lamb, and serve as an auditory signature as the lamb ages, a cue by which lambs can identify their own mothers. Another feature of this maternally selective bond is that it is difficult to break, and very difficult to establish new bonds outside of the period immediately surrounding parturition. These licking and sniffing behaviors expose the ewe to the smell of the lamb and the amniotic fluid in which it is covered. During the period leading up to parturition, ewes will display maternal responsiveness and an attraction to amniotic fluid. After giving birth, the ewe will lick her lambs clean of fluid and membranes. Only a few minutes of this licking behavior is required for some ewes to butt away a foreign lamb, and most will show selectivity and aggression toward foreign lambs within 2 to 4 hours, but complete selectivity can take around 24 hours to develop. It is not only the natural smell of the lamb that elicits maternal response and moves forward the bonding process, but the smell of the amniotic fluid as well. In this way, amniotic fluid plays a dual function, with a role in both the development of responsiveness and selectivity. The presence of amniotic fluid is particularly important for ewes with no maternal experience. If a lamb that has been washed with water is presented to an inexperienced ewe, the ewe will not accept the lamb at her udder and will display aggressive behaviors toward the lamb. This can also occur with washed lambs and experienced dams, but the occurrence is not as reliable. It was found that depriving newly lambed ewes of access to amniotic fluid during the first 4 hours after giving birth had significant consequences on maternal selectivity as well as responsiveness. The effect of amniotic fluid deprivation appears to come from a combination of the decreased maternal attention paid to an unwashed lamb and the lessened olfactory cues to which the mother can have access through licking. A series of studies in which ewes have been rendered anosmic, or incapable of smell, provide evidence for this. However, whether the primary olfactory system , the accessory olfactory system or both are responsible for the establishment of these responsive and selective maternal behaviors remains somewhat unclear. In one study, ewes whose primary olfactory systems were incapacitated by nasal irrigation with zinc-sulfate procaine solution displayed rejection behaviors toward foreign lambs to the same degree as did control ewes. Ewes whose vomeronasal organs were rendered non-functional by electro- cauterization failed to reject alien lambs at the udder, and were noted to perform more maternal flehmens, a behavior related to vomeronasal activity. The lack of vomeronasal function was confirmed based on the formation of complete mucosal scarring over both oral and nasal openings of the nasoincisive duct. This suggests that the vomeronasal organ plays an active role in maternal identification of the lamb at the udder [9] In contrast, a study [10] examined ewes under a very similar setup, with different results. Ewes were made anosmic by irrigation of the nostrils with a zinc sulfate and procaine solution. For the

group in which vomeronasal perception was rendered inactive, the vomeronasal nerves only were severed; this was later confirmed by use of both an anterograde tracer and postmortem examination of the accessory olfactory bulb. This experiment found that vomeronasal-lesioned animals showed little difference from controls in both responsiveness and selectivity. The ewes whose primary olfactory system was disabled were impaired in responsiveness if they were inexperienced, showing a delay in maternal responsiveness, which was not seen in experienced ewes. In both inexperienced and experienced ewes, selective behavior was disrupted. It appears that this oxytocin release indirectly primes the main olfactory bulb such that this region may optimally respond to cues from the newborn lamb. It has been suggested that olfactory recognition of the lamb could be dependent on cholinergic neurons of the horizontal limb of the diagonal band of Broca projecting to olfactory targets. This does appear to be the case, as lesions of the nucleus basalis did severely impair olfactory recognition of the lamb â€" these ewes were not selective against foreign lambs, nor were they as apt at identifying their own lamb. Mother-young relationships in sheep: Journal of neuroendocrinology, 1 , p. Genetic and physiological determinants of maternal behavior and lamb survival: Journal of Animal Science, 86 14 Suppl , p. A review of the social behavior of feral and wild sheep and goats. Journal of Animal Science, 58 2 , p. Early vocal recognition of mother by lambs: Animal Behaviour, 79 5 , p. Olfactory regulation of maternal behavior in mammals. Hormones and behavior, 46 3 , p. Maternal responsiveness and maternal selectivity in domestic sheep and goats: Developmental Psychobiology, 49 1 , p. Newborn lambs and their dams: Advances in the Study of Behavior, 22, p. Amniotic fluid is important for the maintenance of maternal responsiveness and the establishment of maternal selectivity in sheep. Animal, 4 12 , p. Small Ruminant Research, 62 , p. Involvement of the main but not the accessory olfactory system in maternal behavior of primiparous and multiparous ewes. Journal of Chemical Ecology, 37 10 , p. Formation of olfactory memories mediated by nitric oxide. Nature, , p. Extensive immunolesions of basal forebrain cholinergic system impair offspring recognition in sheep. Neuroscience, 1 , p.

The olfactory system presents some rather special problems for learning because it remains in a plastic state throughout life: olfactory receptor neurons undergo continual regeneration [1]. In addition, cells from the subventricular zone of the cortex migrate rostrally to reach the olfactory bulb, where they differentiate into granule cells [2.

Odorant[edit] An odorant is a physiochemical molecule that binds to a specific receptor protein. The effects of brain injury on odor memory can be investigated through the use of these implicit memory measures leading to further overall understanding of the brain. Explicit memory[edit] Explicit, unlike implicit memory for odors, is thought by some to be a phenomenon that is exclusive to humans. There are various ways of measuring the effect of verbal labeling, which include comparison of odors and odor names, as well as the speed and accuracy with which lexical decisions are made regarding odor names. The amygdala is involved in the formation of memories of emotional experiences, particularly those associated with fear, flight, and defense. It is connected by various pathways to other parts of the brain, but most notably to the basal forebrain which contains magnocellular cells which provide extensive input into the neocortex and hippocampus. There are also direct projections to the hippocampus from the amygdala, which are involved in the integration of various sensations into memory. Neuropsychological research has suggested that this pathway is vital for the development of olfactory memories. The primary olfactory cortex and the hippocampus have extensive connections with the amygdala through both indirect and direct pathways. It is important for an animal to create memories of olfactory stimuli which threaten its survival. Without a properly functioning amygdala, olfactory memories would not be able to form which could put an animal at risk of dangerous stimuli in its environment due its lack of memory of such stimuli. The main olfactory bulb is one of the neural structures that experiences profound change when exposed to offspring odors at the time of childbirth. After birth, the smell of amniotic fluid which was previously disgusting becomes attractive for ewes. This is shown by rat pups, who avoid odors that they experienced in association with a noxious stimulus prior to birth. This causes breast odors to become more familiar and attractive, while amniotic fluid loses its positive value. These neurons have become a large part of the olfactory system throughout evolution to allow higher mammals such as primates to have a better chance for survival through more advanced methods of hunting and finding food. This allows for it to be able to detect food at long ranges without being able to see it. Communication and identification[edit] Olfactory memory has also been developed throughout evolution to help animals recognize other animals. Warning stimulus[edit] The development of a sense of smell is also thought to have arisen to function as an arousal system. Once an odor enters into conscious memory, it can signal the presence of a threat, like the smell of gas or smoke. However, odor memory can also be an implicit or unconscious process. This ability to respond automatically to a warning stimulus is much like pre-attentive processes in other sensory systems which involve the use of automatic forms of memory. These response patterns have evolved over time and involve a wide variety of motor and autonomic responses which are integrated into the behaviour pattern of reacting to a warning stimulus. A study conducted on rats showed that when a rat was exposed to cat odors, there was increased anxiety-related behaviour in the rat. The cat odor induced an inhibition of the endocannabinoid system in the amygdala which has been suggested to induce anxiety-related responses. Deficits[edit] Olfactory deficits in the brain[edit] Olfactory memory deficits can be significant indicators of brain damage and pathology. Research suggests that olfactory memory deficits can be good predictors of several mental disorders such as depression , dementia and neurodegeneration , as each disorder has its own distinct features leading to specific predictions about what type of mental disorder a person may have.

5: Olfactory learning in the rat neonate soon after birth

The first hours of a newborn rat's life entail locating and attaching to the mother's nipple not only for nutrition but also for protection and warmth. The present study sought to characterize olfactory learning in the rat neonate immediately after birth. Newborn rats were exposed to an odor at.

Neural Stem Cells Figure 2: Two criteria are typically used to define a cell as a stem cell: The evidence for multipotency of NPCs in vivo remains scant. There are two neurogenic regions in the adult brain where under physiological conditions NPCs give rise to new neurons: For those two regions several types of dividing progenitors were identified. Although they reside in the SGZ, they extend processes up into the molecular layer. Type-1 and B cells are relatively quiescent. NPCs are not limited to neurogenic regions of the brain, rather their proliferation can be observed in most CNS regions, especially after injury. However, in these other regions it appears that neurogenesis is actively repressed by the local environment - NPCs from non-neurogenic regions have been observed to give rise to neurons when transplanted into the hippocampus. Some evidence indicates that this effect is mediated by the local astrocyte populations. NPCs have historically been labeled in the brain by the addition of a proliferation marker, such as 3H-thymadine or bromodeoxyuridine BrdU; Figure 2 , bottom. Immunohistochemistry for BrdU can be combined with the detection of mature markers to identify the phenotype of the newborn cells. BrdU labeling has been used to definitively show that new neurons are incorporated into the dentate gyrus and olfactory bulb of the adult human brain Eriksson et al. Maturation of New Neurons Adult neurogenesis is unique from developmental neurogenesis because the new neurons must integrate into an established, functioning network. Much of the present knowledge about neuronal development in adult neurogenesis has been reviewed by Kempermann et al. Maturation of new neurons in the adult dentate gyrus The process of adult hippocampal neurogenesis is entirely confined to the dentate gyrus. The speed of maturation is likely experience dependent, and varies between neurons. Approximate duration of a number of distinct post-mitotic developmental phases of newborn granule cells are listed here. Figure 3 shows a scematic of the anatomical phases of granule cell growth. Less than 1 week old Immature neurons have neurite outgrowth, but often not polarized towards molecular layer. Few or no synapses, but sensitive to locally diffuse GABA, which is depolarizing. Synaptic GABA inputs can be observed, which is still excitatory. Glutamatergic inputs are not present. Immature action potentials can be observed when cells are directly stimulated. Spine formation onset and axon outgrowth: By about 16 days neurons begin to develop spines in the molecular layer. GABA transitions to inhibitory around this time. By 17 days, new axons mossy fibers can be observed forming functional connections onto downstream hilar neurons and CA3 pyramidal cells. Mossy fibers continue to mature, with boutons on CA3 neurons growing considerably by 28 days. Neurons still have unique physiological properties, including increased LTP, and different resistance, capacitance and resting potentials. Newborn neurons eventually become physiologically indistinguishable from fully mature neurons. Recent work using immediate early genes such as c-fos, Zif, and Arc as putative markers of neuronal activity have shown that water maze training Kee et al. Maturation of new neurons in the adult olfactory bulb In contrast to adult neurogenesis in the dentate gyrus, cells that were born in the SVZ migrate a long distance into their target area, the olfactory bulb. This long migration gives olfactory neurogenesis a different timescale from DG neurogenesis. After the newborn neurons reach the middle of the OB they detach from the chains and migrate radially. Newborn granule cells can be distinguished into cells with dendrites that do not extend beyond the mitral cell layer and other cells that possess non-spiny dendrites reaching into the external plexiform layer. Neuronal selection and survival One critical aspect of adult neurogenesis is the selection process. While large numbers of new neurons are born to the OB and DG, only a fraction of these cells survive. In the dentate gyrus, approximately half of the newborn neurons die within 2 weeks of birth, but this number is heavily regulated by various factors. In contrast to newborn DG neurons the selection process in the OB appears to be later in the development process, when young neurons with extended dendrites already covered with spines are susceptible to cell death. Numerous drugs and behaviors have since been shown to affect the levels of new

neurons in the brain. Modulation of neurogenesis typically occurs in one of two ways in vivo â€" either the modulator changes the levels of proliferation of NPCs, or the effect is on the survival of the new neurons. The most studied modulators have been summarized in the following tables. See Ming and Song and Abrous et al. In each of these cases, it remains unclear whether perturbed neurogenesis is a symptom of the disorder or has a causal role. Aging also has a robust effect on neurogenesis, with levels of new neurons decreasing in later stages of life. The marked decrease occurs fairly early and neurogenesis is maintained at a very low level for most of the life span. Nonetheless, because neurons are integrating into regions of relatively well described circuitry and function, several behavioral and computational ideas have been explored. These have included x-ray irradiation, anti-proliferative drugs MAM and molecular knock-downs. A range of hippocampus-dependent behaviors have been tested with mixed results see Deng et al. Trace eyeblink conditioning was shown to be affected in MAM experiments, and contextual fear conditioning was impaired following irradiation and genetic ablation of adult neurogenesis. Morris Water Maze MWM testing has shown inconsistent results in several paradigms, with some experimenters seeing deficits in short-term retention, others in long-term retention, and others no discernable differences at all. Furthermore, set of behavioral studies have demonstrated that neurogenesis may have a role in the pattern separation function of the dentate gyrus Clelland et al. Finally, a recent study has suggested that new neurons may be important in memory consolidation Kitamura et al. In addition to its presumed role in memory, the correlation of neurogenesis levels to stress has suggested a role in anxiety-related behaviors. For example, fluoxetine the active compound in Prozac is not effective as an anti-depressant in mice without adult neurogenesis due to irradiation. Olfactory bulb-dependent behavioral tasks The function of the olfactory pathway can be tested with a variety of behavioral tasks that test odor discrimination or odor learning. Using transgenic mice with reduced OB neurogenesis it could be shown that new OB neurons appear to be critically involved in odor discrimination. At the same time odor discrimination learning itself increases the survival of newborn OB neurons. The same effect on survival has been found using odor enrichment resulting in improved odor memory. Computational impact of new neurons Because the dentate gyrus is the entry structure to the hippocampus, which has a substantial history of neural network modeling, several non-exclusive computational functions have been suggested for neurogenesis. These have arisen from both theoretical and computational modeling ventures. For a more detailed review of the theoretical functions of adult neurogenesis, see Aimone, Deng, and Gage; Becker predicts that the increase in possible sparse codes due to new neurons increases the quality of memory formation in downstream hippocampal regions. Reduction of interference between new and older memories â€" Wiskott and colleagues propose that the presence of new neurons helps the dentate gyrus network respond to changing inputs. Encoding time in memories â€" Aimone et al. Olfactory bulb neurogenesis has not been as extensively studied computationally, possibly because the olfactory bulb circuit does not have the history of modeling that the hippocampus has. Adult Neurogenesis in other Species Higher levels of adult neurogenesis are observed in many non-mammalian species, many of which retain regenerative neurogenesis capabilities throughout life. Neurogenesis in the course of normal adult function has been best described in birds and fish. Birdsong system Adult neurogenesis in birds has been most heavily characterized in the higher vocal center HVC area of the birdsong system, although it has been observed in other regions, including the avian hippocampus. Bird song neurogenesis is sometimes characterized by very high levels of seasonal variation â€" with more neurons appearing in months which have higher levels of song learning. For example, in the canary brain, there is a high level of seasonal cell death of RA projecting HVC neurons in males - in low-neurogenesis, non-learning periods, the HVC is a fraction of the size of learning seasons. Many of the underlying regulators of this process have been elucidated, including seasonal variations in testosterone. The specific role of new neurons in bird song learning still unclear, but it is interesting to note that the neurogenic cells in HVC have been implicated in sparse coding, just as dentate gyrus cells in the mammalian hippocampus. Adult neurogenesis in Fish Fish have many proliferative zones throughout the brain, which are thought to be able to provide neurons to almost any region of the brain Zupanc, Consistent with other vertebrates, the olfactory bulb and dorsal telencephalon the fish equivalent of the hippocampus have robust neurogenesis, though most of the new neurons are found in the cerebellum. Because of this widespread

proliferation, the overall rate of neurogenesis appears several orders of magnitude higher in fish than in rodents â€" with an estimate over about 0. References Below we include references from classic papers, key reviews summarizing the field,and recent studies which have not been reviewed elsewhere in detail such as the computational modeling work. Altman J and Das GC - "Autoradiographic and histological evidence of postnatal hippocampal neurogenesis in rats" Journal of Comparative Neurology; 3: Scholarpedia , 2 Eugene Roberts Gamma-aminobutyric acid. Recommended reading "Adult Neurogenesis" eds.

Burrow nesting procellariiform seabirds use olfactory cues for both foraging and nest recognition. As chicks, burrow nesters develop in the dark, but are exposed to both prey-related and individual-specific scents through contact with their parents.

Chapter 15Memory and Plasticity in the Olfactory System: One of the most characteristic features of odor memory in humans is the rather unique ability of odors to vividly trigger the evocation of emotional experiences. In animals, memory for environmental odors plays a vital role because it regulates many behaviors that are crucial for survival. Moreover, conditioning procedures can be used to induce emotional olfactory learning, thus allowing an experimental approach in a laboratory environment. The aim of the present chapter is to illustrate some aspects of the neurobiology of odor emotional memory in rats, both in infancy and adulthood. We focus on fear conditioning at both developmental points, since it constitutes one of the most adapted and classical paradigms to study emotional memory in animals and has been the focus of intense investigation. We begin by reviewing the available literature describing the neural circuits involved in odor fear conditioning in adult rats, and conclude the chapter by reviewing the ontogeny of odor fear conditioning. The same experimental paradigm can be supported by overlapping but distinct neural circuits, and lead to dramatically different behavioral outcome, depending on the age at learning. This approach highlights how the fear system changes to meet the ecological demands of different life stages. Indeed, one of the most striking features of odor memory in humans resides in the amazing power of odors to vividly trigger the evocation of autobiographical experiences. Different works have shown that odor-cued memories are more emotional than memories triggered by visual or verbal cues Chu and Downes ; Herz and Cupchik ; Herz ; Herz and Schooler ; Willander and Larsson Odor-cued memories have also been described as more vivid than memories evoked by corresponding words Chu and Downes In addition, the feeling of being brought back in time to the occurrence of the event is experienced as stronger for odor-cued memories than memories evoked by words and pictures Herz and Schooler ; Willander and Larsson Interestingly, it was also shown that autobiographical memories evoked by olfactory information were older than memories associated with verbal information Chu and Downes ; Willander and Larsson This observation is in agreement with the fact that olfaction emerges very early in ontogeny and with research showing that associative odor learning begins very early in life Schaal et al. Taken together, these studies suggest that human olfaction is unique in its ability to cue the emotional aspects of autobiographical memory, including experiences formed early in life. In animals, memory for environmental odors plays a vital role because it regulates many behaviors that are crucial for their survival. For instance, and as will be developed in Section The newly learned odor becomes preferred and is approached to bring the infant in contact with the mother, although the odor also controls the complex sequencing of motor patterns to support nipple attachment in rats Cheslock et al. At adulthood, two types of powerful ethological olfactory learning have been described in the literature. The first occurs in the postpartum period, when the mother learns the odor of the newborn and is critical for the mother to accept and nurse the young. This has been eloquently described in the postpartum sheep Levy et al. The second example of ecologically significant odor learning involves chemosensory individuality Brennan and mate recognition Brennan and Keverne , which regulate reproductive behavior in mice see also Chapter 6. Thus, particularly robust and rapid odor learning occurs throughout the life span during life transitions critical for survival and reproductive success. Rapid, emotional learning is also necessary during threatening situations, to avoid that danger in the future. This type of learning is modeled by fear conditioning, where a temporal association of a neutral stimulus i. The formerly neutral stimulus acquires the ability to elicit defensive or escape responses critical in avoiding the danger and is dependent upon plasticity in the basolateral complex of the amygdala LeDoux ; Fanselow and Gale ; Davis and Whalen ; Maren ; Otto et al. This paradigm has permitted enormous progress in our understanding of emotional learning in a controlled laboratory environment. More recently, this approach has been extended to humans with remarkable convergence in the underlying neural circuitry during acquisition, expression, and extinction, suggesting some homologous control of emotional learning in

rats and humans LaBar et al. The aim of the present chapter is not to present an exhaustive review of the neurobiology of these different olfactory learning tasks, but rather to concentrate on those inducing emotional olfactory memory in rats, both at early PN ages and at adulthood. The vast majority of the existing studies on fear conditioning have been carried out using auditory or visual modalities. However, odors are at least as potent as auditory or visual cues in sustaining learned fear. Therefore, we specifically review the literature describing the neural circuit involved in odor fear conditioning in adult and infant rats, but we begin by presenting a brief review of the olfactory pathways within the brain. Neuroanatomy of the Olfactory Pathways Olfactory sensory neurons lie in the olfactory epithelium, which covers the back of the nasal cavity. The axons of the olfactory sensory neurons travel through the cribriform plate to the olfactory bulb, which is the first relay of olfactory information Figure The olfactory bulb output neurons send direct projections to the olfactory cortex, including the anterior olfactory nucleus, the olfactory tubercle, and the piriform or olfactory cortex Shipley and Ennis ; Haberly and Price ; Carmichael et al. The first unusual characteristic of the mammalian olfactory pathways is that, unlike other sensory systems, it does not need to pass through the thalamus to reach cortical areas. Indeed, there is no thalamic relay between the first relay of sensory information, namely the olfactory bulb, and the primary olfactory cortex, as is the case for other sensory modalities Figure Similarly, there is no obligatory thalamic relay for olfactory information to reach the orbitofrontal cortex. Indeed, although the piriform cortex sends sparse projections to the mediodorsal thalamus, thereby disynaptically targeting the orbitofrontal cortex, it establishes direct monosynaptic connections with the orbitofrontal cortex Datiche and Cattarelli ; Tanabe et al. These observations suggest that the thalamus might be less relevant for olfaction than for the other senses Shepherd ; Wilson and Stevenson , but see Plailly et al. Diagram illustrates the intimate link between the olfactory bulb and the limbic areas amygdala and hippocampus. Indeed, the main olfactory bulb makes dense monosynaptic contacts with nuclei of the corticomedial amygdaloid group, including the nucleus of the lateral olfactory tract, the cortical nucleus of the amygdala, and the periamygdaloid cortex Price ; McDonald These observations led Swanson and Petrovich to suggest that the corticomedial amygdala is an integral component of the olfactory system. These superficial nuclei are a major source of the projections from the amygdala to the hypothalamus Price et al. In contrast, the deeper amygdaloid nuclei, including the basolateral nuclear group, do not receive projections from the olfactory bulb and receive relatively weak projections from the olfactory piriform cortex Krettek and Price ; Luskin and Price ; Ottersen However, they receive fairly dense projections from the corticomedial nuclei within the amygdala Savander et al. Taken together, these anatomical data suggest that compared to the other sensory modalities, olfactory information has a unique direct access to the amygdala. The lateral entorhinal cortex, in turn, has been shown to project to the hippocampus via the lateral perforant path Witter and Amaral Furthermore, in addition to providing a gateway to the hippocampus, the lateral entorhinal cortex sends monosynaptic projections to the amygdala. The primary targets of the entorhinal cortex are the basolateral amygdala and the cortical nuclear complex Brothers and Finch ; McDonald and Mascagni The lateral entorhinal cortex is, therefore, in a position to transmit information from olfactory cortical areas to two major telencephalic components, the amygdala and the hippocampus, and back to olfactory areas through reciprocal connections Swanson and Kohler ; Insausti et al. Ontogenesis of the Olfactory Pathways The olfactory system is functional at birth and, as outlined in Section Amazingly, pups smell, discriminate, and process odors, yet the olfactory circuit of pups is quite immature compared to the adult rat brain. While the olfactory bulb is fairly mature at birth and functional odor maps in the glomerular layer are well defined, considerable development continues throughout the preweanling period Guthrie and Gall , For example, gamma-aminobutyric acid GABA interneurons, presumably critical for odor discrimination in adults Ennis et al. Additionally, centrifugal input from the rest of the brain begins to enter the bulb prenatally, although substantial input continues through weaning. For example, norepinephrine NE fibers from the locus coeruleus LC are present at birth, although NE released by these terminals greatly decreases as pups mature McLean and Shipley , while terminal numbers increase. While minor cholinergic ACh projection neurons arrive in the bulb as early as the first day of life to innervate the modified glomerular complex, most fibers begin to reach the bulb at PN day 6 and start to show the more typical homogenous distribution across the bulb layers McLean

and Shipley ; Le Jeune and Jourdan At birth, there is also a transient large number of neurons expressing acetylcholinesterase AChE , although this begins to decrease around PN15, and shows low adult levels by PN30 Le Jeune and Jourdan In the next relay station for olfactory information, the olfactory cortex, considerable development also occurs during the first two weeks of life and later Brunjes et al. However, the functional significance of the developing piriform on pup behavior has remained elusive, primarily due to lack of research attention. The amygdala also continues to develop during the period. The basolateral complex first emerges at E17, with most neurons produced between EPN7. Other amygdaloid nuclei lag behind the basolateral by a few days. The amygdala continues to develop until adolescence Morys et al. Olfactory information is received by the amygdala in the early neonatal period Schwob and Price and the infant amygdala responds to odors Thompson et al. However, the sequential emergence of amygdala-dependent behaviors throughout the preweanling period suggests important intra-amygdala connections continue Hunt et al. Connectivity between olfactory structures continues to become more complex. Together, the protracted development of these brain areas suggests that the neonate has a unique circuitry for odor processing that underlies developmental changes in emotional learning. A Tool for Studying Emotional Memory in Animals Among the few emotions that can be detected and quantified in animals, fear is indubitably the most common. When a rat encounters a threatening stimulus e. Among these, fear-potentiated startle and fear-induced freezing defined as complete immobility are universal fear responses seen in many animal species, including humans. These innate fear responses to a natural threat can be classically conditioned to an experimental neutral stimulus and this is referred to as fear conditioning LeDoux ; Maren ; Myers and Davis ; Maren and Quirk Fear conditioning consists of pairing an initially neutral stimulus the conditioned stimulus or CS with an aversive unconditioned stimulus US , generally a mild foot-shock. After a few trials, re-exposure to the CS alone elicits fear responses, such as freezing behavior, assumed to be part of an anticipatory response to threat and danger Rosen and Schulkin The vast majority of studies devoted to investigate the neural basis of fear conditioning have used auditory and, to a lesser extent, visual cues as conditioned stimuli. In particular, the neural pathways involved in auditory fear conditioning have been well characterized LeDoux ; Maren ; Maren and Quirk ; Myers and Davis The information carried by the auditory CS can take one of two pathways: These thalamic and cortical areas send -projections to the lateral nucleus of the amygdala, which is a site of CS-US convergence. The lateral nucleus, in turn, projects to the central amygdala, which controls the expression of fear responses by way of projections to brainstem areas. The major conclusion of these studies is that the amygdala plays a critical role in linking external stimuli to defense responses through synaptic plasticity. The amygdala would, therefore, be essential to the formation and storage of fear memories as far as auditory or visual stimuli are used for conditioning. Extinction of fear memory would involve an inhibitory action exerted by the prefrontal cortex onto the amygdala network Milad and Quirk , although disruption of memory within the amygdala has also been implicated Davis et al. In addition, the hippocampus seems to play an important role in regulating the context dependence of fear memory after extinction. Neurobiology of Olfactory Fear Conditioning in Rats Behavioral researches have shown that olfactory fear conditioning induces robust emotional responses. Moreover, in a subsequent study, Richardson et al. Thus, odors are at least as efficient as other types of sensory stimuli to induce learned fear responses. The Role of the Amygdala Concerning the neural basis of olfactory fear conditioning, there is a consensus in the existing literature that the amygdala plays a crucial role. Indeed, Cousens and Otto first showed that pre- and posttraining excitotoxic lesions of the basolateral amygdala abolished the acquisition and expression of olfactory fear conditioning in rats. In another study, Walker et al. Using an electrophysiological approach, Rosenkranz and Grace performed in vivo intracellular recordings in the lateral nucleus of the basolateral amygdala during acquisition of an odor fear conditioning under anaesthesia, in rats. Their data revealed that repeated pairing of an odor with foot-shock induced enhanced postsynaptic potential responses in neurons of the basolateral amygdala, and that this modification resulted from local changes in synaptic efficacy, and was dependant on dopamine. Another set of studies has investigated more specifically the involvement of the amygdala in the consolidation of odor fear conditioning. Specifically, Killpatrick and Cahill used reversible inactivation of the basolateral amygdala with tetrodotoxin following paired odor-shock presentation in rats. This treatment resulted in a deficit in

learning, thus suggesting that the basolateral amygdala plays a role in consolidation of odor fear conditioning. Similarly, Rattiner et al. BDNF is known to play a critical role in activity-dependent synaptic plasticity and has been implicated as mediator of hippocampal-dependent learning and memory Hall et al. The authors showed that BDNF expression was increased in the basolateral amygdala two hours after fear conditioning and that this increase occurs independently of the sensory modality of the CS.

7: 12 Tips on How to Mentally Stimulate a Dog (Based on Science)

The late-life depression with olfactory identification impairment group had worse cognitive performance (global, memory, language, and executive function) and more structural abnormalities in Alzheimer's disease-related regions than the late-life depression without olfactory identification impairment group, and global cognitive function and.

The present study sought to characterize olfactory learning in the rat neonate immediately after birth. Newborn rats were exposed to an odor at various time periods soon after birth and tested for behavioral activation and attachment to a surrogate nipple in the presence of this odor at 4–5 hours postpartum. Regardless of when pups were presented the odor 0, 1, or 2 hours after birth motor activity was greater among pups previously exposed to the odor than pups with no odor experience. Similarly, latency to attach to the nipple in the presence of the odor was lower among odor-preexposed pups, especially when odor exposure began within an hour of cesarean delivery. Odor exposure immediately after birth for just 15 minutes was sufficient to increase motor activity and to decrease latency to attach to a similarly scented surrogate nipple. These results suggest that olfactory experience very soon after birth can shape subsequent olfactory responses. The relative importance of the dearth of postnatal experience or of elevated neurochemicals immediately after birth and possible associative mechanisms underlying this learning is discussed. The widespread presence and robustness of early and diverse olfactory learning in various mammalian species is likely a consequence of its survival value during early postnatal life. Prenatal olfactory learning is critical for adaptation to the postnatal environment. As a neonate, the rat must navigate towards the nipple for its first suckling experience. It is not surprising then that many similarities exist between prenatal and neonatal olfactory learning. Nevertheless, a provocative question emerges as to what role birth might play in the continuity from fetal to postnatal life? Postnatal olfactory learning contributes to continued survival throughout early ontogeny. Results of these odor exposure studies include preferential orientation, huddling towards the odor as well as odor specific modified olfactory bulb responses. Appetitive conditioning to a novel odor, with milk as an unconditioned stimulus, has been found in the 3-hour old neonatal rat Cheslock et al. New learning immediately after birth, within minutes or a few hours after parturition, has rarely been a topic of research. Nevertheless, fetal and neonatal learning has important clinical relevance for humans Schaal et al. So why has research concerning learning in this immediate postpartum time period been largely neglected? In the past, the behavioral repertoire of the neonatal rat has been considered very limited. Nevertheless, even these procedures can sometimes be inappropriate shortly after birth. Furthermore, in human research particularly, but also with rodents, there is a desire to leave the mother-infant dyad undisturbed soon after birth. With rats, the neonate cannot see or hear, thus most work has employed gustatory and olfactory stimuli. Presenting an odorant to a newborn rat or fluid into its mouth prior to consistent independent respiration may seem to be problematic due to less sensory perception or possible asphyxiation as a consequence of the erratic breathing patterns. Most research on learning in the neonatal rat has delayed conditioning until three hours after cesarean delivery Cheslock et al. Studying the rat pup soon after delivery, however, may be quite advantageous. In view of the dramatic surge of neurochemicals e. In order to study the function these neurochemicals may have in olfactory learning just after birth, future studies will likely utilize pharmacological agents. As a first step, the following experiments describe olfactory learning soon after birth in the absence of any neurochemical manipulations. The goal of the current study was to characterize learning in the rat pup within a few minutes or hours after cesarean delivery. The effects of early postnatal odor exposure on later behavioral activation and nipple attachment in the presence of that same odor were tested as a function of how soon after birth the odor was experienced Experiment 1 and duration of that experience Experiment 2. Taking this literature into account, one might predict that odors experienced closer to the test would be recalled most effectively. Nevertheless, we predicted that odor exposure, even if short in duration, occurring immediately after birth would enhance nipple attachment behaviors and alter motor activity to those same odors more than odors experienced later and therefore closer to the test. Rats used in these experiments were maintained and treated in accordance with the guidelines for animal care and use established by the National Institutes of Health Cesarean Delivery Near

expected term E21 pups were delivered by cesarean section. Brief ether anesthesia followed by rapid cervical dislocation was administered to the dam. Next, a midline incision was made through the abdominal wall exposing the uterine horns. A small incision into the amniotic sac externalized the pup. Once the umbilical cord was ligated and cut the extraembryonic membranes were removed by a gentle rolling of the neonate on a sanitary paper towel. A timer to mark the birth time of the litter was started when the median pup was born e. Materials Heating Chamber Odor exposure procedures were at times lengthy and because the neonate is unable to thermoregulate, a heating chamber was constructed to maintain body warmth in the neonates during odor exposure. Both were encased in aluminum foil insulation. Surrogate nipple The surrogate nipple was cast from rubber latex AMACO rubber latex, Indianapolis, IN and molded into a conical form to measure 12 mm long with a rounded tip measuring 1mm in diameter and the base measuring 2. Polyethylene tubing Clay Adams, MD extended throughout the length of the nipple and attached to a syringe filled with water. The small diameter of the tubing, along with the natural viscosity of water, prevented spontaneous effusion from the tip of the nipple. Procedure Odor presentation Within the heating chamber, two pups one male and one female were placed into a hexagonal shaped shallow cup 8. This cup the pup cup was set on top of an identical cup placed upside down the base cup. This base cup added height, which enabled the pups to reach the proper temperature in the heating chamber. A cotton swab was punctured through another identical cup the odor cup , which was placed over the pup cup to present the odor. This cotton swab was never in contact with the pups. Ventilation was made possible by several holes in the pup cup created with a standard hole-puncher.

R onald Williams, 85, started learning Welsh, his native language, at the age of He grew up in south Wales, where he was raised and educated in English, and since the age of 23 has lived and.

He grew up in south Wales, where he was raised and educated in English, and since the age of 23 has lived and worked in Solihull, near Birmingham. After retiring he decided that he wanted to reconnect with his roots: Two years ago, he started learning with Say Something in Welsh , which offers a series of podcasts and runs twice-monthly classes with a teacher, where he meets and practises with other language learners. Williams is one of a cohort of older adults learning languages in later life. While the general consensus is that the younger learner has stronger powers of mimicry and retention, there is no evidence to suggest that adult learners are slower in terms of absorbing new information, according to Anil Biltoo, head of languages at SOAS, University of London. Instead, he says the key element to being a successful language learner is motivation. Learning a language and meeting people is exciting. I would hate to have to sit in a chair and rely on somebody knocking on the door to open my mouth. Christensen, a Danish year-old retiree who has lived in the UK since she was 18, has been learning Russian for 10 years. She is also interested in Russian literature and likes the sound of the language, and that it has a fairly complicated grammar. As a member of the University of the Third Age, which facilitates study groups for retired and semi-retired people, she runs two language groups. Whether it was your interest to begin with or not, you do learn something of the culture of the country. It is the first language she has learnt since studying a smattering of French at school. As a methodist minister leading an interfaith project in Bradford, where a large chunk of the population is of Pakistani heritage, she decided to learn Urdu two years ago to engage with her community and help her on visits to Pakistan. She takes group classes at Bradford College once a week. I was determined to have a go at communicating differently. Having already learnt English and German, Christen said she finds learning a language harder now because it takes more repetition before the words stick. Williams also says he finds it more difficult remembering new Welsh vocabulary than he would have 10 or 15 years ago. Although learning a new language may not always be easy for older adults, research suggests it can help slow down age-related cognitive decline. Biltoo says those coming to a language later in life have had exposure to foreign languages from travel to other countries.

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