

# The olfactory bulb: A neuroendocrine spotlight on feeding and metabolism

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## Abstract

Olfaction is the most ancient sense and is needed for food-seeking, danger protection, mating and survival. It is often the first sensory modality to perceive changes in the external environment, before sight, taste or sound. Odour molecules activate olfactory sensory neurons that reside on the olfactory epithelium in the nasal cavity, which transmits this odour-specific information to the olfactory bulb (OB), where it is relayed to higher brain regions involved in olfactory perception and behaviour. Besides odour processing, recent studies suggest that the OB extends its function into the regulation of food intake and energy balance. Furthermore, numerous hormone receptors associated with appetite and metabolism are expressed within the OB, suggesting a neuroendocrine role outside the hypothalamus. Olfactory cues are important to promote food preparatory behaviours and consumption, such as enhancing appetite and salivation. In addition, altered metabolism or energy state (fasting, satiety and overnutrition) can change olfactory processing and perception. Similarly, various animal models and human pathologies indicate a strong link between olfactory impairment and metabolic dysfunction. Therefore, understanding the nature of this reciprocal relationship is critical to understand how olfactory or metabolic disorders arise. This present review elaborates on the connection between olfaction, feeding behaviour and metabolism and will shed light on the neuroendocrine role of the OB as an interface between the external and internal environments. Elucidating the specific mechanisms by which olfactory signals are integrated and translated into metabolic responses holds promise for the development of targeted therapeutic strategies and interventions aimed at modulating appetite and promoting metabolic health.

## KEY WORDS

appetite regulation, food intake, neural circuits, olfaction, olfactory bulb

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## 1 | INTRODUCTION: EXPLORING THE ROLE OF THE OLFACTORY BULB IN FEEDING AND METABOLISM

The escalating prevalence of obesity and eating disorders, such as anorexia, presents profound challenges to public health worldwide. Genome-wide association studies (GWAS) have revealed that many genetic variants associated with body weight, appetite and eating behaviour are highly expressed in the brain, highlighting that the brain plays an important role in controlling these aspects of metabolism.<sup>1–3</sup> For decades, attempts to understand how the brain regulates body weight have largely focused on examining the hypothalamic or brain-stem control of feeding behaviour and energy homeostasis. However, this has delivered very few therapeutic approaches to treat human obesity or eating disorders in the long term. With this in mind, an understanding of how additional brain regions and neural circuits interact to influence food intake and energy metabolism is required without delay. This review directs attention to the olfactory bulb (OB) as a metabolic sensor outside the hypothalamus<sup>4</sup> and how it integrates environmental information to guide behaviour and metabolism (Figure 1). The sense of smell, or olfaction, in terms of evolution, is the most ancient sensory modality, capable of detecting, encoding, and discriminating a myriad of environmental volatiles (odourants) crucial for identifying food and potential hazards. Beyond mere odour identification, olfaction adds emotional attributes to subjects, objects or events, influences preferences, mood and cognition, and facilitates social interactions. For most organisms smell serves as the primary sense for interacting with and interpreting the surrounding.<sup>5</sup> By elucidating the intricate relationship between olfaction and metabolism, this review endeavours to ignite novel approaches to tackle the global rise of obesity, eating disorders and related metabolic pathologies.

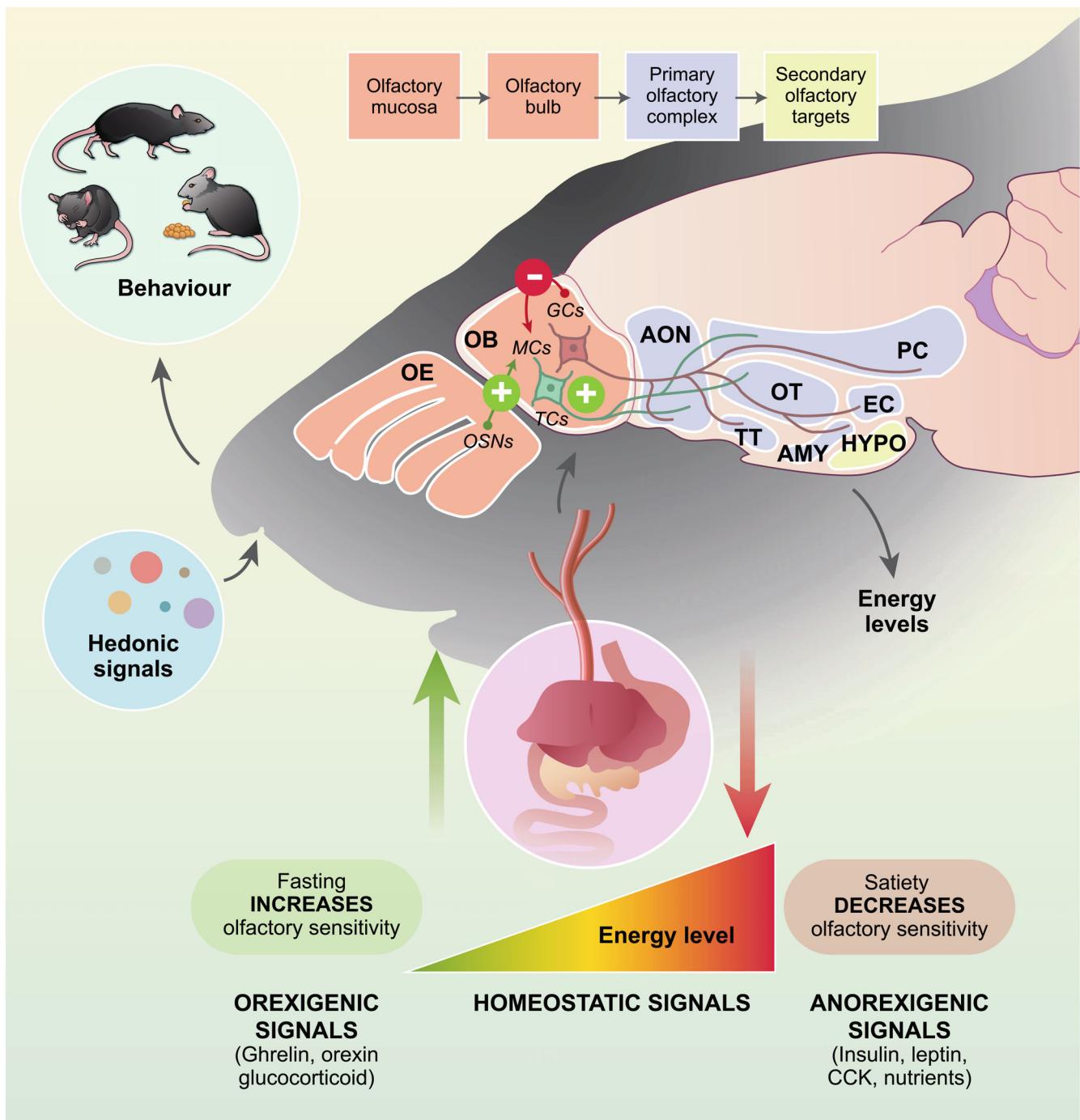
## 2 | THE OLFACTORY SYSTEM

The olfactory system consists of a sensory peripheral (olfactory epithelium) and a central part (olfactory bulb) as well as specific olfactory brain regions (primary and secondary olfactory cortex). Odourants are small airborne chemicals that can evoke sensations in the olfactory system, a result of odourant binding to specific olfactory receptors (ORs) expressed by olfactory receptor neurons (ORNs) in the epithelial tissue that lines the nasal cavities, the olfactory epithelium (OE). The OE contains millions of these specialized ORNs and notably, can regenerate throughout adulthood.<sup>6,7</sup> Olfactory receptors belong to a family of around 1000 genes encoding G-protein-coupled receptors (GPCRs), comprising the largest gene family in the vertebrate genome.<sup>8</sup> While the majority of mammals have most OR genes, humans exhibit approximately one-third of the OR genes compared with mice.<sup>9</sup> This reduction was previously thought to reflect the poor sense of smell in humans compared with other species. However, with ~400 different functional ORs,<sup>10</sup> humans can discriminate approximately more than 1 trillion odours.<sup>11</sup> Although each ORN has only one type of receptor protein, the ability to discriminate an enormously

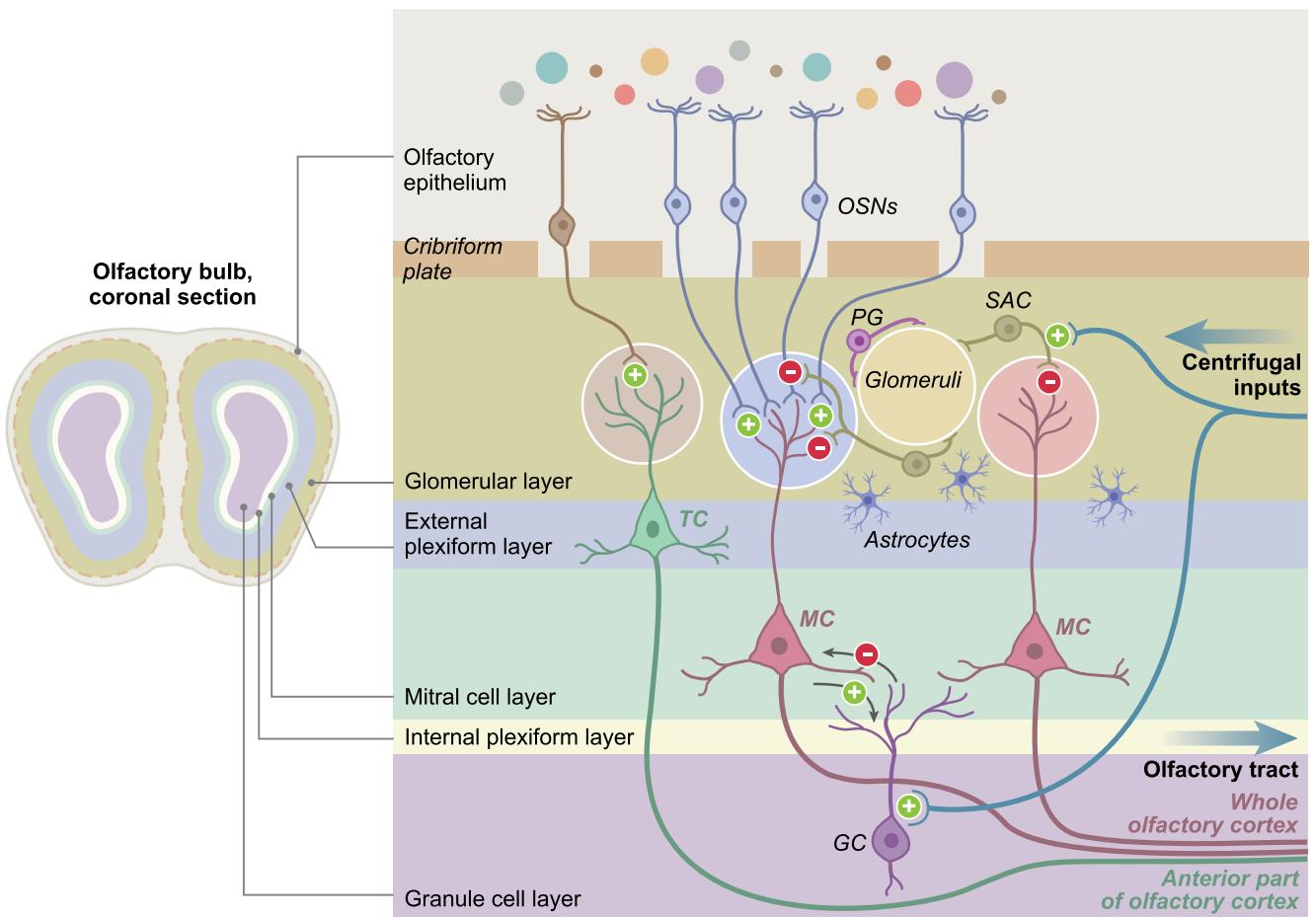
large range of odours comes from specific features of odourant molecules, which exhibit varying binding affinities to different receptors. In this way, each molecule interacts with more than one type of receptor, thereby generating a complex odour sensory signal.<sup>12</sup> Each ORN is connected to a distinct spherical neuropil structure beneath the surface of the OB, called glomerulus. Each individual glomerulus represents a single OR type and receives the inputs from multiple ORNs, so that when odourants activate ORNs a unique glomerular activity pattern is created.<sup>13</sup> Given that in nature, perceived odours are a blend of different chemicals, the mechanisms involved in the detection of various odours are complex. The OB functions as the central hub, and coordinator of olfactory transmission within the olfactory pathway, initially processing olfactory sensory information before transmitting it to the primary olfactory cortex (POC).<sup>14</sup> A distinguishing characteristic of the olfactory system is that olfactory sensory signals are directly received in the OB and transmitted to the POC, bypassing thalamic relay centers.<sup>15</sup> Consequently, the OB is often mentioned as the ‘olfactory thalamus’ as it processes sensory information before dissemination to other brain areas.<sup>16</sup> The POC engages with various cortical and limbic structures, facilitating the integration of smell with memory, emotion and taste. Thus, the olfactory system not only shapes odour perception but also influences mood and cognition due to its close association with brain areas responsible for these functions. This connection has led to olfaction being described as ‘the window to the mind and brain’.<sup>17,18</sup>

## 3 | THE OLFACTORY BULB: GATEWAY TO SCENT AND PERCEPTION

The OB is the first relay station between the external environment and the brain, receiving odour-specific inputs from ORNs, and processing this information before sending output signals to olfactory target areas. The OB is an egg-shaped onion-like concentric layered structure, and located in the anterior region of the brain, above the cribriform plate of the ethmoid bone,<sup>19,20</sup> (Figure 2). The distinct layers of the OB accommodate specific cell types. At the outermost layer, the olfactory nerve layer (ONL) contains axons of ORNs originating from the OE. These axons synapse onto the dendrites of mitral (MCs) and tufted cells (TCs) within the glomerular layer (GL), forming small round clusters, the glomeruli. Glomeruli are the primary site of odour input integration. Interneurons such as periglomerular, external tufted cells and granule cells (GC) modulate synaptic activity within the GL. Periglomerular cells surround the entire glomeruli and maintain reciprocal dendrodendritic synapses with MCs and TCs. Beneath the GL lies the external plexiform layer (EPL) and the mitral cell layer (MCL), containing the cell bodies of TCs or MCs, respectively.<sup>21</sup> MCs and TCs are the principal output neurons of the OB. Their axons form bundles that pass through the OB, merging to form the olfactory tract. Most central is the granule cell layer (GCL) containing granule cells (GC), the most abundant neurons in the OB and provide inhibitory feedback onto MCs and TCs. This intricate organization of cell types within the OB enables the integration and processing of olfactory signals, ultimately shaping odour perception.



**FIGURE 1** Representation of the olfactory bulb as an environmental sensor and integral component of the neuroendocrine system. A simplified ventrolateral schematic of the brain is shown. Hedonic odour signals are detected by specialized cells (olfactory sensory neurons, OSNs) in the olfactory epithelium (OE) that project to the olfactory bulb (OB) where mitral cells (MCs) and tufted cells (TCs) are activated. M/TCs are excitatory glutamatergic cells and are the main projecting neurons of the OB, conveying odour information to various regions in the olfactory cortex for odour recognition and processing, or further modulating secondary olfactory structures, such as the hypothalamus (HYPO). MCs project their axons dispersedly to the olfactory cortex, including the anterior olfactory nucleus (AON), piriform cortex (PC), amygdala (AMY), entorhinal cortex (EC), olfactory tubercle (OT) and tenia tecta (TT), while TCs only innervate the anterior parts of the AON, OT and PC. M/TCs also make connections with inhibitory GABAergic granule cells (GCs). Besides sensing odours, the OB is a metabolic sensor, sensing homeostatic signals (hormones, nutrients) from the periphery delivered by the stomach, intestine, pancreas, liver, and adipose. Thus, the OB integrates internal and external signals and guides behaviours and physiological responses (cognition, digestion, metabolism) by modulating olfaction performance and other brain areas.



**FIGURE 2** Neural Architecture of Olfactory Processing. Different odourants (represented by different colours) bind to specific olfactory receptors (ORs) expressed on olfactory sensory neurons (OSNs) within the olfactory epithelium. OSNs expressing the same ORs project their axons to specific spherical structures in the OB called glomeruli (shown by colour) and are the first olfactory processing station. Within the glomeruli OSNs axons reciprocally synapse with apical dendrites of glutamatergic OB output neurons (Mitral and Tufted cells, M/TCs) and various juxtaglomerular interneurons that include periglomerular (PG) neurons, external tufted cells and short axon cells (SACs). These interneurons are on the surface of glomeruli and form reciprocal synapses with OB neurons and OSNs axons, modulating olfactory information transmission: PG neurons provide GABAergic inhibition to other neurons as well as to OSNs within the glomerulus. Similarly, SACs mediate lateral inhibition among glomeruli. M/TCs are second-order olfactory neurons. Their apical dendrite establishes reciprocal synapses with OSNs and juxtaglomerular cells within the glomerulus, while their axons project to the olfactory cortex and higher cortical structures for further processing of olfactory information. MCs' lateral dendrites form reciprocal synapses with inhibitory GABAergic granule cell (GC) dendrites whose cell bodies are in the inner part of the OB and are the most numerous cells in the OB. Granule cells and SACs receive centrifugal feedback from olfactory cortices, which inhibits or disinhibits M/TCs. Due to different cell types and composition, the OB has a layered structure: glomerular layer (GL); external plexiform layer (EPL), mitral cell layer (MCL); internal plexiform layer (IPL); and granule cell layer (GCL). The EPL and IPL are neuropil layers, mainly composed of dendrites from M/TCs and GCs. Green plus signs (+) indicate excitatory synapses, while red minus signs (−) indicate inhibitory synapses.

## 4 | OLFACTION

Odourants are either inhaled during the breathing cycle into the nose (orthonasal—from outside) or from the back of the mouth while chewing (retronasal), thus contributing to flavour perception. Upon entering the nasal cavity, odourants bind ORs and depolarise ORNs.<sup>22</sup> ORNs are bipolar cells, with cell bodies located in the OE and dendrites extending to the surface of the OE, where several cilia emerge expressing ORs. Axons from ORNs travel from the OE through the cribriform plate to the OB and converge to make up the first cranial nerve, which

is responsible for transmitting olfactory information to the brain. ORNs form synaptic connections in the OB with dendrites of MCs, TCs and axon-less interneurons within the glomeruli.<sup>7</sup> After receiving synaptic information, MCs and TCs directly convey this olfactory information via the olfactory tract to the POC. While the axons of MCs project throughout the olfactory cortex, TC project their axons only to the anteromedial portion of the olfactory cortex.<sup>23</sup> The key brain regions that make up the POC, include the piriform cortex (PC), periamygdaloid cortex, entorhinal cortex (EC), anterior olfactory nucleus (AON) and the olfactory tubercle (OT) of the ventral striatum.

While the POC is part of the limbic system linking olfaction with emotions, secondary targets include the hypothalamus, hippocampus, thalamus, orbitofrontal cortex (OFC) and insular cortex, which help to integrate olfaction with metabolism, learning and memory (Figure 3).<sup>24</sup> Thus, the OB is only 1 synapse away from ORNs, which are exposed to the external world, and just a few synapses away from critical central structures regulating metabolism and cognition. While the OB processes sensory signals and coordinates their transmission, the OB also receives modulatory feedback from the cortex, and subcortical regions. The subsequent section explores the modulation of olfactory function through both intrinsic and extrinsic mechanisms.

## 5 | MODULATION OF OB FUNCTION

Olfactory processing can be modulated by intrinsic (from within the OB) and extrinsic (from outside) mechanisms.

### 5.1 | Intrinsic modulation

MCs and TCs possess an apical dendrite, which targets a single glomerulus, and several lateral dendrites. Olfactory sensory information from ORNs is received by the apical dendrites and transmitted via the lateral dendrites. Their activity is modulated by inhibitory interneurons, mainly periglomerular and granule cells (GCs), controlling the gain and strength of sensory information projected to downstream targets in a spatial and temporal manner. Interestingly, inhibitory GABAergic GCs are axon-less, instead possessing a basal and a branched apical dendrite. The basal dendrite and the unbranched initial parts of the apical dendrite receive excitatory glutamatergic inputs from M/TCs and the olfactory cortex.<sup>25,26</sup> This unique ability to modulate dendro-dendritic connections between GCs and lateral dendrites of M/TCs is called lateral inhibition.<sup>27</sup>

### 5.2 | Extrinsic modulation

Extrinsic efferent sensory inputs include those from the olfactory epithelium (centripetal) and olfactory cortex (centrifugal),<sup>28,29</sup> and extrinsic centrifugal inputs can even outweigh the sensory information from the nose.<sup>29</sup> In particular, the glomerular layer receives extrinsic centrifugal modulation, whereas some of these inputs stem from the brain, including neural fibres, neuromodulators, neuropeptides, and hormones. Centrifugal inputs come from several olfactory cortices, including the PC, AON and EC.<sup>29</sup> Of note, the OT is unique among other olfactory cortices in that it does not innervate the OB.<sup>30</sup> Earlier studies suggested the possibility of OT projection to the OB.<sup>31–34</sup> However, methodologies such as horseradish peroxidase tracing,<sup>33</sup> OT lesion approaches<sup>31,32</sup> or anterograde viral injections into the OT<sup>34</sup> are prone to off-target effects.<sup>30</sup> Subsequent studies utilizing three independent retrograde labelling approaches confirmed the absence of direct projections from the OT to the OB.<sup>30</sup> The OT may

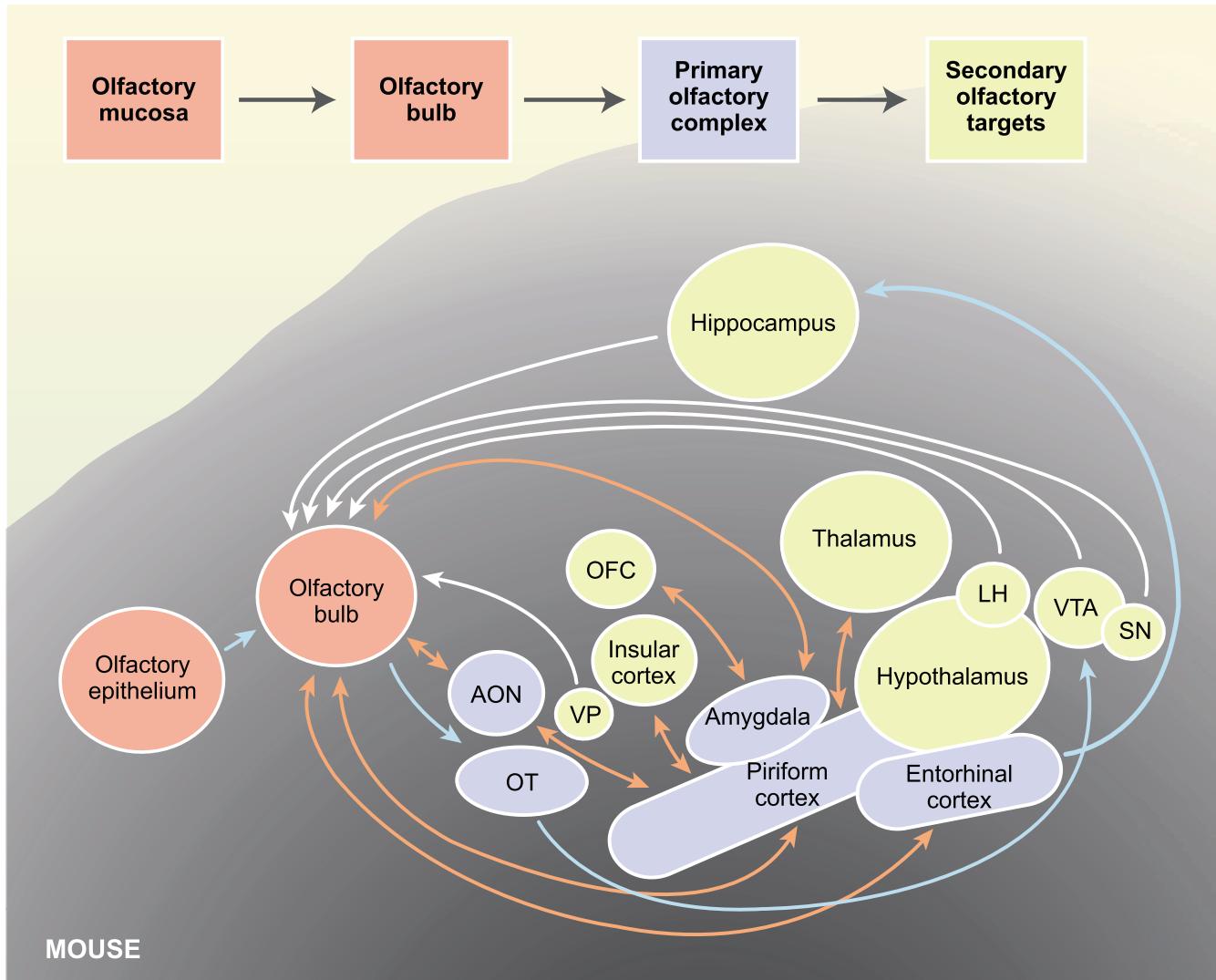
potentially play a role in modulating OB activity in a top-down, state-dependent manner.<sup>31,35</sup> If such modulation occurs, it likely involves indirect pathways, possibly through structures like the AON or PC. Future investigations employing optogenetic and electrophysiological methods could shed light on these indirect pathways and their influence on OB activity.

At least three neuromodulatory systems project centrifugal fibres to the OB: the locus coeruleus (noradrenergic), the basal forebrain (cholinergic), and the raphe nuclei (serotonergic).<sup>7,36</sup> A direct dopaminergic input to the OB from substantia nigra has also been suggested.<sup>37</sup> Centrifugal projections have been shown to be important for olfactory learning, memory, odour-reward association and feeding behaviour.<sup>28</sup>

Certain neuropeptides/-hormones are produced within the OB itself, whereas other hormones originate from the periphery and interact with receptors in the OB (centrifugal feedback)—all to modulate OB activity.<sup>29,38</sup> Specifically, vasoactive intestinal peptide (VIP),<sup>39</sup> cholecystokinin (CCK),<sup>40–43</sup> insulin,<sup>44–46</sup> ghrelin,<sup>47–49</sup> leptin<sup>46,47,50–52</sup> and orexin<sup>51,53</sup> are known to potentially influence olfactory processing. Among locally produced neuropeptides that modulate olfactory processing by acting on their respective receptors in the OB are somatostatin and glucagon-like peptide 1 (GLP-1).<sup>54</sup> Oxytocin is a hormone produced in the hypothalamus, and oxytocin receptors are found in the OB<sup>55,56</sup> and adjacent AON<sup>57</sup> suggesting oxytocin may influence social behaviour by regulating olfactory processes. Further, orexin-positive fibres, originating from cell bodies in the lateral hypothalamus (LH), have been found in the OB.<sup>53</sup> Orexin neurons are important in sleep/wakes cycles, arousal and feeding behaviour and can modulate olfactory sensitivity based on satiety levels.<sup>53</sup> Insulin, leptin and ghrelin are major metabolic hormones released into the blood from peripheral organs and circulate to the brain to act on receptors in the hypothalamus to control food intake.<sup>58–60</sup> However, several other brain areas also express these receptors, including the OB. Thus, centrifugal fibres and hormonal inputs are ways in which olfactory processing and feeding behaviour can interact (a comprehensive list of hormones and neuropeptides Tables 1 and 2).

### 5.3 | Feeding-related centrifugal projections to the OB

In regard to feeding and energy homeostasis, the olfactory system receives information from numerous brain regions involved in both homeostatic regulation and motivation/reward processing.<sup>61,62</sup> One such brain region is the hypothalamus involved in maintaining energy homeostasis and regulating food intake and metabolism.<sup>63–66</sup> The hypothalamus contains a complex neuronal network, sending out far-reaching projections to other brain areas,<sup>67</sup> including projections to the OB.<sup>30,68–71</sup> Retrograde transsynaptic tracing experiments found indirect projections (involving two to three synapses) extending toward the OB from multiple hypothalamic nuclei, including the arcuate nucleus (ARC), ventromedial hypothalamic nucleus (VMH), the paraventricular nucleus (PVN) and the dorsomedial hypothalamic



**FIGURE 3** Scheme of olfactory bulb projections discussed in this review. The olfactory nerve, formed by axons from the OSNs in the OE directly project to the olfactory bulb (OB). The neurons in the OB send their axons (forming the lateral olfactory tract) to the primary olfactory cortex (blue), important for odour discrimination and identification. Among the primary olfactory cortex are the anterior olfactory nucleus (AON), the olfactory tubercle (OT), the piriform cortex, the amygdala and the entorhinal cortex. Secondary olfactory targets (green) are brain areas receiving direct projections from the primary olfactory cortex forming intracortical connections. These include parts of the prefrontal cortex and neocortex, such as the orbitofrontal cortex (OFC), hypothalamus, thalamus, and hippocampus. Due to the OB's connections with other brain regions, it comes as no surprise that odours can regulate emotion, fear, cognition or appetite. For example, the OB directly connects via the piriform cortex to the amygdala, where emotion processing and associative learning occur. The amygdala is also involved in social behaviours. The OB also communicates via the entorhinal cortex with the hippocampus, important for odour identification, memory and learning. The orbitofrontal cortex plays a role in sensory integration, flavour perception and odour-reward associations. The olfactory cortex also connects to the hypothalamus, a brain region regulating feeding, metabolism and reproduction. The thalamus is the information relay station of all sensory modalities except smell and has a role in sleep, wakefulness, memory and learning. The ventral tegmental area (VTA) has a function in the rewarding aspects of odours. The ventral pallidum (VP) plays a role in motivated behaviours. The insula activates in response to olfactory and gustatory stimuli, especially when unpleasant, and plays a role in pain perception and emotional processing. Centrifugal efferent projections originating from olfactory cortical structures and neuromodulatory centres, such as substantia nigra (SN, dopaminergic), the locus coeruleus (noradrenergic), the horizontal limb of the diagonal band of Broca (cholinergic), and the raphe nucleus (serotonergic), do not directly impact odour discrimination, but play a crucial role in maintaining the oscillatory dynamics of the OB and mediate learning and memory processes important for odour-reward associations. This underscores that olfactory processing is strongly modulated by experience. In addition, efferent feedback may also facilitate attentional processes in olfaction, resembling the role of thalamic gating observed in other sensory modalities. Afferent projections are marked with blue arrows, reciprocal-connection are orange arrows, and efferent projections are marked with white arrows. LH, lateral hypothalamus.

nucleus (DMH).<sup>70</sup> All these nuclei play crucial roles in the regulation of appetite and energy metabolism, this study showed that the OB receives both direct and indirect projections from the lateral

hypothalamus (LH), with some direct projections originating from melanin-concentrating hormone and orexin neurons,<sup>70,72</sup> which are known to regulate body weight, appetite and arousal.<sup>53,73</sup> Similarly,

**TABLE 1** Appetite and olfactory performance regulating hormones and their receptors expressed in the olfactory bulb.

		Major source	Receptor	Expression peptide/ receptor	Olfactory bulb	Olfactory effects	References
Orexigenic	Ghrelin	Stomach	Growth hormone secretagogue receptor (GHSR)	+/+	GL, MCL, GCL, MC dendrites, mitral terminal dendritic processes	↑ olfactory sniffing behaviours, exploration and food searching	[48,49,61,62,113,114]
	Glucocorticoid	Adrenal gland	GR	?/+	GL, MCL, GCL, EPL	Acute stress is associated with improved olfactory performance	[130,132,144,248,249]
						Chronic intranasal delivery: neuronal degeneration, olfactory impairment	
	Insulin	Pancreas	IR	+/+	GL, MCL, GCL, EPL, mitral terminal dendritic processes	Neurogenesis, modulation of potassium channel Kv1.3 and MC excitability, ↓ olfactory performance depending on odour quality	[44,45,61,62,78,79,82,153]
	Anorexigenic	Leptin	Adipose	LepR	+/+	ICV insulin: ↓ odour detection, ↓ sniff frequency in response to food odour. Intranasal insulin: ↑ odour discrimination, ↓ odour sensitivity, ↓ decision making time, improved memory Chronic intranasal insulin: ↓ body weight	
	Cholecystokinin (CCK)	Intestine, brain, OB	CCK-1R, CCK-2R	+/+	GL, MCL, GCL, astrocytes, periglomerular cells	Inhibits GC and M/TCs, ↓ calcium response, ↓ odour discrimination, slows reaction time, ↓ olfactory sensitivity, ↓ food-seeking, ↓ OB coding and activation of higher centres	[46,51,52,61,62,164,166]
					CCK-1R internal granular layer CCK-2R: GL, MCL, EPL, M/TCs, MC dendrites, periglomerular cells	Excitation and suppression of MC firing, whereas CCK-1R ↑ and CCK-2R ↓ olfactory performance CCK-1R regulates neurogenesis, female sexual behaviour CCR-2R activation ↑ M/TCs inhibition, modulates olfactory recognition and memory	[41-43,61,62,171-174,250,251]
			NPY Y2R	?/+	GCL		[48,252,253]

(Continues)

TABLE 1 (Continued)

	Major source	Receptor	Expression peptide/ receptor	Olfactory bulb	Olfactory effects	References
Peptide tyrosin-tyrosin (PYY)	Gut L-endocrine cell				No effect on olfactory responsiveness	
Bombesin-homologs: Neuromedin B Gastrin-releasing peptide (GRP)	Gastrointestinal tract	NMB/Bombesin receptor 1 GRR/Bombesin receptor 2	+/- -/+		Gastrointestinal hormone release and gastrointestinal motility, involved in stress, fear and social behaviour	[254-263]
Glucose-dependent insulinotropic polypeptide (GIP)	Intestine	GIPR	?/+		Controls insulin secretion and glucose tolerance, is involved in explorative behaviour	[264-267]
Amylin	Pancreas, brain	AMY1, AMY2, AMY3	+/?		Overexpression of human amylin affects olfactory processing in <i>Caenorhabditis elegans</i>	[268-270]
Glucagon-like peptide (GLP-1)	Intestine, OB	GLP-1R	+/-	MCL, GCL, Cajal cells	Modulates microcircuits and fine-tunes olfactory information transmission, ↓ Kv1.3 activity, ↑ MCs firing frequency, ↑ olfactory sensitivity, food-seeking behaviour, ↑ odour-evoked cephalic phase insulin release	[54,170,271-273]
Vasoactive intestinal peptide (VIP)	Gastrointestinal tract, pancreas, brain	VPAC1, VPAC2 (also binds PAC1)	+/-	VPAC1: EPL VPAC2: GCL	Circadian rhythms in olfactory performance, modulates olfactory output, ↓ M/TCs activity, odour processing and olfactory behaviours	[39,274-278]
Orexigenic/ anorexigenic h	Adipose	adipoR1, adipor2	?/+	GL, MCL, GCL, periglomerular cells, neurons, astrocytes, blood vessels	Modulates OB insulin signalling	[183,184,187]

Abbreviations: -, absent; ?, unknown; +, present; EPL, external plexiform layer; GC, granule cells; GCL, granule cell layer; GL, glomerular layer; M/TCs, mitral and tufted cells; MC, mitral cells; MCL, mitral cell layer; OSN, olfactory sensory neurons.

**TABLE 2** Appetite and olfactory performance regulating neuropeptides/hormones and their receptors expressed in the olfactory bulb.

		<b>Major source</b>	<b>Receptor</b>	<b>Expression peptide/receptor</b>	<b>Olfactory bulb</b>	<b>Olfactory effects</b>	<b>References</b>
Orexigenic	Neuropeptide Y (NPY)	Brain (hypothalamus, amygdala, hippocampus, cerebral cortex) and periphery (adrenal medulla)	NPY Y2R	+/-	GL, GCL, EPL	Neuroproliferation, ↓ pre-synaptic excitatory transmission between OB neurons	[61,62,252,253,279–284]
Orexin A and B (hypocretin-1/2)	Hypothalamus	OX1, OX2	+/-	GL, MCL, GCL, periglomerular cells, MC/TC and GC dendrites and processes	Modulates MC activity ICV orexin: ↓ MCs firing and ↑ olfactory sensitivity		[51,53,61,62,67,72,73,80,81,107]
Melanin-concentrating hormone (MCH)	Hypothalamus	MCH-R	+/-	GL, MCL, GCL, cilia of interneurons in GL and GCL	Maternal behaviour, food-seeking		[61,254,285–288]
Galanin	Brain (dorsal raphe nucleus, locus ceruleus, hypothalamus, amygdala, paraventricular nucleus, and supraoptic nucleus) and periphery (gastrointestinal tract)	GALR1, GALR2	+/-	GL, GCL, external plexiform layer, tufted cells, short-axon neurons	Modulates cholinergic transmission, promotes neuronal differentiation		[61,289–293]
Endocannabinoids	Brain (hippocampus, cortex, cerebellum) and periphery	CB1R	?/-	GL, GCL, periglomerular cells	↑ odour sensitivity and processing, ↑ feeding behaviour, modulates synaptic plasticity, influences excitation state of M/TC		[61,62,294–299]
Endogenous opioids (e.g., enkephalins, endorphins, endomorphins, dynorphins, and nociception/orphanin)	Brain (hypothalamus, pituitary gland, brainstem) and periphery	Mu, delta, kappa opioid receptors	+/-		Olfactory learning, neurogenesis		[61,300–302]
Dopamine	Brain (substantia nigra, VTA, hypothalamus)	DR1, DR2	+/-	GL, MCL, GCL, EPL	Cue-reward associations, motivation, modulation of olfactory information		
					transmission, processing, and odour intensity perception	D1R and D2R ↑ cytoplasmic $\text{Ca}^{2+}$ in astrocytes	
					DR1: ↑ odour detection/discrimination, ↓ granule cells GABA/ $\text{Cl}^-$ currents and indirectly inhibits M/TCs		

(Continues)

TABLE 2 (Continued)

	Major source	Receptor	Expression peptide/receptor	Olfactory bulb	Olfactory effects	References
Anorexigenic	Corticotropin-releasing hormone (CRH)	Hypothalamus	CRHR1, CRHR2	+/-	GCL	DR2: ↓ odour detection/ dis-crimination, ↓ odour information transduction, ↓ presynaptic glutamate release, ↓ postsynaptic M/TCs excitability, ↑ GABA/Cl <sup>-</sup> currents in M/TCs
Cocaine- and amphetamine-related transcript (CART)	Brain (hypothalamus, amygdala, nucleus accumbens) and periphery	Undisclosed	+/?	?		Mice lacking CRHR1 show olfactory bulb circuit dysfunction and impaired olfactory behaviours
Oxytocin	Hypothalamus	OXTR	-/+	GL, MCL, GCL, periglomerular cells	Regulator of body weight, reward and food intake	[38,61,317]
Brain-derived neurotrophic factor (BDNF)	Brain (OB, cortex, hippocampus, hypothalamus, brainstem)	Tropomyosin receptor kinases (TrkB)	+/-	GL, MCL, GCL, periglomerular cells	↓MC excitability, ↓ GC activity, ↑ odour responses and discrimination of MC/TCs, modulates neural networks during sensory processing, ↑signal-to-noise ratio, synaptic maturation and circuit formation, ↑ social behaviour, ↑social learning	[20,55,56,176-180,318]
Vasopressin	Hypothalamus	V1aR, V1bR, OXTR	+/-	GL, MCL, GCL, EPL	BDNF ↓ Kv1.3 current, TrkB ↑ Kv1.3 channel expression, modulates appetite regulators (e.g., Insulin, leptin), olfactory learning and memory, neurogenesis	[319-322]
Neuropeptide FF	Brain (spinal cord, brainstem)	NPFFR1, NPFFR2	-/-		↓MC firing, olfactory and behavioural modulation, social odour processing	[323-325]
Melatonin	Pineal gland in the brain	MT1, MT2	+/-	GL, MCL, GCL	Pain modulation and opiate tolerance	[326,327]
Gonadotropin-releasing hormone (GrRH)	Hypothalamus, OB	GnRHR1, GnRHR3	+/-	MCL, GCL	Circadian rhythm, odour discrimination, modulation of olfactory function and depressive behaviour	[95,328-330]
	Hypothalamus and periphery		+/-	GL, MCL, GCL	Reproduction, modification of olfactory information, olfactory sensitivity to pheromones	[275,278,339-342]

TABLE 2 (Continued)

	Major source	Receptor	Expression peptide/ receptor	Olfactory bulb	Olfactory effects	References
Pituitary adenylate cyclase-activating polypeptide (PACAP)		PAC1 (binds also VPAC1, VPAC2)			Social behaviour, modulation of calcium ion activity	[61,343–350]
Orexigenic/ anorexigenic	Somatostatin	Hypothalamus, pancreas, gastrointestinal tract	SSTR1, SSTR2, +/+, SSTR3, SSTR4	SSTR2: MCL, soma and dendrites of MCs SSTR3: GCL, neuronal cilia of GC SSTR4: GL, periglomerular cells	Olfactory information processing, olfactory discrimination via SSTR2 expressed by MC SSTR4 deletion did not affect olfactory behavioural performance	[61,343–350]

Abbreviations: -, absent; ?, unknown; +, present; EPL, external plexiform layer; GC, granule cells; GCL, granule cell layer; GL, glomerular layer; M/TCs, mitral and tufted cells; MC, mitral cells; MCL, mitral cell layer; OSN, olfactory sensory neurons.

the nucleus tractus solitarius (NTS), implicated in energy homeostasis, also contributes indirect projections to the OB, as well as the rostro-ventrolateral reticular nucleus (RVLM).<sup>70</sup>

Among the reward pathways, the ventral tegmental area (VTA) and ventral pallidum (VP) send direct projections, whereas the nucleus accumbens (Acb) and lateral habenular nucleus (LHb) have indirect projections. Other authors also reported a projection from the substantia nigra to the OB.<sup>37</sup> Direct projections originating either from homeostatic or hedonic brain regions, such as VTA and LH,<sup>74</sup> suggest that these projections may act together to modify the odour value depending on the energy state (fasted/satiated).<sup>70</sup> Other food-related indirect projections were observed from the laterodorsal tegmental nucleus (LDT, reward processing) and as well as basolateral amygdaloid nucleus (BLA, positive and negative odour memory formation).<sup>70</sup> All these brain areas (Acb, LHb, LDT and BLA) have links with the VTA and thus contribute to the brain reward circuitry. Further centrifugal direct projections arise from primary olfactory regions (piriform cortex, nucleus of the lateral olfactory tract, anterior cortical amygdaloid area, dorsolateral entorhinal cortex), except for the olfactory tubercle. A direct projection to the OB was also identified from the CA1 subdivision of the ventral hippocampus and may be involved in the processing of fear- and aversive-related odours.<sup>70</sup>

## 6 | SCENTSORY INTELLIGENCE: ADAPTING OLFACTORY PERCEPTION TO METABOLIC NEEDS

The OB is a key site for hormonal and nutritional access due to the highly permeable and highly vascularized local blood-brain barrier (BBB).<sup>75,76</sup> Hormones and nutrients act on the olfactory system to adjust olfactory physiology and structure, olfactory function, odour detection and ultimately feeding behaviour. Thus, it is not surprising that the OB has high expression of numerous metabolic hormone receptors, such as insulin, leptin, GLP-1 and ghrelin.<sup>4,61,62</sup> Aligned to their appetite-regulating function, orexigenic hormones, such as ghrelin, most likely increase olfactory sensitivity, whereas anorexigenic hormones, such as leptin, may decrease olfactory sensitivity (Table 1). While current dogma indicates these key metabolic hormones regulate food intake, body weight and peripheral metabolic processing through hypothalamic circuits, the privileged access of the OB to these hormones suggests an important and unexplored influence of olfactory information to regulate feeding behaviours and feeding-related neural circuits. Indeed, hormonal uptake into the OB is faster than anywhere else in the brain making it an ideal neuroendocrine regulator of appetite and metabolism.<sup>77</sup> Moreover, modulation of feeding-related receptors in the OB indicates these hormones can indeed alter olfactory activity.<sup>45,46,78–82</sup> In addition, OB neurons also respond to nutrients, such as glucose, amino acids and fats, an essential function of energy-sensing brain regions like the hypothalamus (Table 3), which may fine-tune olfactory neuronal activity to metabolic requirements.<sup>4</sup> For example, OB neurons express hallmarks of glucose sensing cells<sup>83–87</sup> and several glucose transporters have been

**TABLE 3** Transporters involved in nutrient sensing expressed in the olfactory bulb.

Nutrient	Transporter	References
Glucose	GLUT 1, 3, 4 Sodium-Glucose Linked Transporters (SGLT1, 4); Kv1.3 mTORC1	[61,62,83-87,351-354]
Amino acids	SLC7A5/SLC3A2; SLC1A5; SLC6A15; SLC38A2, KCC2 (also SLC12A5); mTORC1; T1R1; T1R3; GPCRs type CasR (Calcium Receptor Family)	[61,355-371]
Fatty acids	SLC27A1; SLC27A4; mTORC1; GPR40 (FFA1); CD36; TRPC3,4,5; TRPC1,4; TRPM5	[61,361,365,367,372-380]

identified in the olfactory system (SGLT1,4; GLUT1,3,4; Kv1.3; mTORC1).<sup>4</sup> The abundant need for glucose processing machinery comes from the high energy demand for accurate odour processing in olfactory areas, including the OB.<sup>88</sup> However, the presence of metabolic machinery in the OB is not limited to glucose processing and includes amino acid transporters, receptors, and intracellular molecules, as well as various fatty acid solute carrier transporters.<sup>4</sup> Thus, glucose-sensing, protein sensing and lipid-sensing in the OB are all likely to play a pivotal role in controlling metabolic-related olfactory function. This represents an extension of the important roles for hypothalamic glucose-, protein- and lipid-sensing in appetite, energy homeostasis and glucose homeostasis.<sup>89-91</sup>

Metabolic disorders such as obesity are associated with impaired olfactory ability, giving further indication that olfaction is modulated by metabolic factors,<sup>61</sup> including adiposity, blood glucose and endocrine feedback.<sup>92,93</sup> In addition to metabolic factors, olfactory sensitivity follows a circadian sleep/wake cycle, similar to many physiological processes, such as feeding, locomotor activity and hormone secretion.<sup>94</sup> The OB also expresses the receptor for melatonin,<sup>95</sup> providing a potential mechanism for circadian regulation. Certainly, a post-ingestive rise in glucose, insulin or GLP-1 will impact olfactory abilities indicating how feeding state can directly affect olfactory processing. Indeed, hunger and energy deprivation increase olfactory discrimination and sensitivity,<sup>96-99</sup> whereas satiety reduces the pleasantness of food-related odours.<sup>100</sup>

## 7 | NEUROENDOCRINE CONTROL OF THE OB AND METABOLISM

Hormones can potentially modify the perception and pleasantness of specific odours as well as olfactory processing. This includes a direct interaction with receptors in the olfactory system or through indirect control mechanisms involving the interplay between olfaction, appetite regulation, memory, and motivation. The OB expresses receptors

for several metabolic hormones, associated with increased (orexigenic) or decreased (anorexigenic) feeding (Tables 1 and 2). Thus, the OB serves as a crossroads for neuroendocrine signals, where various hormones associated with appetite modulation converge. This intriguing revelation suggests that the OB acts as a pivotal node in the intricate web of neuroendocrine communication that influences our food cravings, energy balance, and overall metabolic well-being.

### 7.1 | Orexigenic hormones

Orexins (Orexin A and B or hypocretin-1 and hypocretin-2) play a role in feeding behaviours,<sup>81</sup> and central injections of orexins stimulate food intake, locomotor activity, grooming and foraging behaviours.<sup>101</sup> Additionally, orexins impact energy metabolism by stimulating metabolic rate independently of changes in food intake.<sup>102</sup> Notably, orexins enhance sympathetic tone, leading to increased blood pressure, heart rate, and other physiological responses such as gastric acid secretion or luteinizing hormone release. These effects occur at lower doses compared with those needed to induce feeding.<sup>103-106</sup>

Both orexin A and B are produced in the hypothalamus and released into the OB by centrifugal hypothalamic fibres, where they bind to two G-protein coupled receptors, OX1 and OX2.<sup>67</sup> While orexin A can bind both receptors, orexin B selectively binds to OX2 and is less potent. Hypothalamic orexin neuronal projections exhibit widespread distribution throughout the central nervous system<sup>80</sup> and olfactory sensory processing is modulated by orexigenic fibres from the hypothalamus.<sup>53,72</sup> Indeed, retrograde labelling experiments revealed that a small fraction of hypothalamic orexin A neurons directly innervate the main OB.<sup>72</sup> In the rat OB orexin-containing fibres were found in the glomerular, mitral and granular cell layer, and are originating from the lateral and posterior hypothalamus and the perifornical area.<sup>81,107</sup> The presence of orexin-containing fibres in the OB, originating from the hypothalamus, exemplifies how different brain structures influence olfactory modulation. Moreover, the responsiveness of hypothalamic orexin neurons to nutritional fluctuations,<sup>108,109</sup> such as fasting, lipid load and refeeding, underscores the metabolic impact on olfactory performance.

Postnatally, orexin receptors are expressed primarily in mitral cells, with additional expression in periglomerular, tufted, and granule cells.<sup>81</sup> Immunoreactivity was also observed in dendrites and processes of mitral/tufted and granule cells.<sup>81</sup> Orexin administration, either *in vivo* via intracerebroventricular injections or locally in OB-slices, induced a significant decrease in mitral cell spontaneous firing activity,<sup>80</sup> and either resulted in depolarisation (7%) or hyperpolarisation (30%) of mitral cells.<sup>81</sup> Further, intracerebroventricular injection of orexin enhanced olfactory sensitivity, as indicated by increased avoidance behaviour of isoamyl acetate odourised water, in comparison to saline.<sup>51</sup>

Ghrelin is produced by endocrine stomach cells and signals low body energy supplies by acting on ghrelin receptors (GHSR, Growth Hormone Secretagogue Receptor).<sup>59</sup> GHSRs are expressed throughout the CNS with significant research focusing on neuronal populations in the hypothalamus, midbrain and hindbrain.<sup>110</sup> However, there is also significant expression in the OB<sup>111,112</sup> in the glomerular, mitral

and granule cell layer.<sup>49,113–115</sup> Ghrelin is transported through the BBB and has a high uptake into the OB<sup>116,117</sup> where it is linked to increase olfactory performance and exploratory sniffing behaviour in rats and humans.<sup>49</sup> In addition, ghrelin influx across the BBB is highest during fasting and lowest in obesity.<sup>118</sup> Ghrelin administration also markedly increases OB c-fos immunoreactivity,<sup>119</sup> augments the percentage of c-fos activated OB neurons in response to the odorant 2,3-hexanedione<sup>48</sup> and activates new adult-born OB cells.<sup>115</sup> In humans, ghrelin also enhances food odour conditioning and sniffing.<sup>49</sup> Although ghrelin is known to promote food intake, reduces anxiety,<sup>120</sup> increases motivation, exploration and food-seeking,<sup>121</sup> these studies also highlight exogenous ghrelin affects olfaction. Likewise, a positive correlation between ghrelin levels and human odour intensity ratings has been demonstrated,<sup>47</sup> and postprandial changes in ghrelin affected neural responses to odours.<sup>122</sup> Low ghrelin levels were associated with decreased olfactory sensitivity and suppression of odour-evoked fMRI activity in brain regions involved in olfactory processing, including olfactory cortices. This could be driven by the effects of ghrelin on the OB. Since hunger and high levels of ghrelin increase olfactory sensitivity,<sup>49</sup> we recently examined whether ghrelin links hunger with olfaction and the implications of disrupting this feedback on food intake, metabolism and related foraging behaviours.<sup>112</sup> To investigate the behavioural and metabolic actions of GHSRs in the OB (OB<sup>GHSR</sup>), we deleted OB<sup>GHSR</sup> in adult mice and discovered OB<sup>GHSR</sup> deletion decreased olfactory sensitivity to food and non-food odours in various olfactory performance tasks. Although daily total food intake or ghrelin-induced food intake were not different, OB<sup>GHSR</sup> deletion altered feeding behaviour with mice displaying decreased number of feeding bouts in the dark phase, anhedonia, impaired food finding, and exploratory behaviour. Unexpectedly, OB<sup>GHSR</sup> deletion increased body weight, fat mass accumulation and impaired glucose tolerance. Thus, GHSR signalling in the OB is an example of how a metabolic-signalling mechanism links metabolic state to olfaction and regulates olfactory sensitivity, exploratory, feeding behaviour and peripheral energy and glucose metabolism.

Glucocorticoids are steroid hormones secreted by the adrenal glands, and play a pivotal role in maintaining basal metabolism, immunity and stress-related adaptations. Glucocorticoids have been found to boost food intake by exerting their influence either directly or indirectly on brain regions responsible for regulating appetite.<sup>123</sup> For the stress response, glucocorticoids primarily act on the stress-responsive hypothalamic-pituitary-adrenal (HPA) axis.<sup>124</sup> Glucocorticoid actions are facilitated through the intracellular glucocorticoid receptor (GR), which belongs to the nuclear transactivating superfamily, encompassing the steroid/sterol/thyroid/retinoid/orphan receptors.<sup>125</sup> Research involving whole-body knockdown studies of GR has uncovered its significance in processes like gluconeogenesis during fasting and erythropoiesis under stress conditions.<sup>126,127</sup> Additionally, studies on mice with forebrain-specific GR gene knockout have shed light on the vital role of GR in emotional and anxiety-related behaviours as well as stress-related behaviours.<sup>128,129</sup> Mice exhibited depressive symptoms, including hyperactivity and altered stress-induced locomotion with impaired HPA axis activation, underscoring the importance of GR actions in the forebrain, which also

encompasses limbic structures such as the OB. In the OB the GR was found in a few cells within the glomerular and mitral cell layer, and higher presence in the granule cell layer.<sup>130</sup> Although less established, there is some evidence suggesting an olfactory regulatory influence of glucocorticoids since stress is associated with improved olfactory performance.<sup>131</sup> A fear-inducing test involving public speaking in men elevated plasma cortisol levels and resulted in anger, while also enhancing olfactory sensitivity.<sup>132</sup> Moreover, subjects exposed to a stressful public mental arithmetic task, elevating cortisol levels, exhibited improved detection of the pungent smell of 2-mercaptoethanol.<sup>133</sup> In women, cortisol had an impact on olfactory detection through the menstrual cycle, with heightened cortisol levels correlating with enhanced odour detection capabilities.<sup>134</sup> Furthermore, higher cortisol levels in new mothers postpartum were linked to increased attraction and improved recognition of their infants' odours.<sup>135</sup> Thus, acute stress appears to enhance olfactory detection.<sup>132–135</sup> However, in mice subjected to chronic corticosterone treatment through their drinking water, the outcome is quite different. Chronic exposure resulted in the development of anxiety and depressive-like disorders, accompanied by alterations in cell survival in the OB and a decline in olfactory discrimination, acuity, and memory.<sup>136</sup> In patients with adrenal insufficiency and chronically reduced cortisol production, there was a decrease in olfactory perception threshold, indicating enhanced olfactory sensitivity. This effect was reversed by steroid supplementation.<sup>137</sup> However, studies in rat models are conflicting. After adrenalectomy, olfactory performance was either reduced<sup>138</sup> or remained unchanged.<sup>139</sup> It is important to note that individuals or animals with compromised adrenal gland function often experience more severe health problems beyond alterations in their sense of smell, suggesting the involvement of other confounding factors, such as other hormones produced in the adrenal glands, including other stress hormones with receptors identified in the OB, for example corticotropin-releasing hormone (CRH)<sup>140</sup> and adrenalin.<sup>141</sup> Intranasal glucocorticoids are widely used to relieve symptoms of nasal congestion, irritation and discomfort from allergies or hay fever. While considered safe a negative impact on paediatric growth is discussed in the literature.<sup>142,143</sup> Further, chronic intranasal corticosteroid treatment is associated with impaired olfactory function due to neuronal degeneration.<sup>144</sup>

It is worth mentioning that certain odours can lessen manifestations of the stress response, while other odours can induce stress.<sup>145</sup> For example, predator odours are known to induce a stress response in animals, leading to elevated blood pressure and increased plasma corticosterone or cortisol concentrations.<sup>146</sup> This stress response, in turn, impacts various physiological processes, including behaviours, such as freezing, protective burying, avoidance and delayed or decreased food consumption.<sup>147</sup> This neuroendocrine activation pathway serves as a compelling example of close neuroanatomical connections between olfactory and stress response pathways.

## 7.2 | Anorexigenic hormones

Insulin is secreted from the pancreas in proportion with body fat when blood sugar levels rise<sup>148</sup> and promotes glucose uptake into peripheral

tissues.<sup>149</sup> Indeed, this process is also mediated by insulin receptor (IR) signalling in the brain where insulin also acts to suppress food intake and affects energy homeostasis.<sup>58,150–152</sup> The actions of insulin in the olfactory system are probably the most well-described amongst the feeding-related hormones.<sup>62</sup> IRs are found throughout the brain, with the highest expression in the hypothalamus and the olfactory system,<sup>44</sup> including the OE, ORNs, OB, and olfactory cortices (AON, OT, entorhinal cortex, piriform cortex).<sup>44,62,82,153–155</sup> Hence, IR signalling occurs from the first step of odour detection in the OE to signal transduction and odour processing in the OB and beyond. In the OB, IRs are located in the external plexiform layer, the glomerular layer, granule cell layer and mitral cell layer. The highest expressions of IRs are found in mitral cells.<sup>44</sup> Insulin enters the olfactory system from the circulation via transport through the BBB,<sup>156</sup> and the transport rate of insulin into the OB was 2–8 times faster than into other parts of the brain,<sup>157</sup> where it has the highest insulin-binding affinities, insulin-receptor density, and IR kinase activity.<sup>44,78,157–160</sup> Moreover, insulin binding in the OB increases or decreases with feeding and prolonged starvation respectively,<sup>161</sup> suggesting metabolic state also influences the actions of insulin in the OB,<sup>44</sup> and linking olfactory capabilities with metabolic state by modifying odour processing within the OB.<sup>45</sup> Indeed, elevated blood plasma insulin levels (or reduced ghrelin levels) following a meal were linked to decreased olfactory sensitivity, perceiving odours as less intense, and accompanied by a widespread suppression of odour-evoked activity across the primary olfactory cortex and hypothalamus. These effects were observed in response to both food and non-food odours.<sup>122</sup> In line with this, administering a single intracerebroventricular bolus of insulin to fasted rats to mimic satiety, reduced odour detection in a conditioned odour aversion paradigm and sniffing frequency when exposed to a food odour compared with controls.<sup>44</sup> Insulin may influence olfactory sensitivity by exerting its effects on neurons within the OB. Patch-clamp recordings of rat OB slices showed that bath-administered insulin had divergent effects on distinct neurons within the OB network<sup>45</sup>. While in mitral cells (MCs), insulin increased the excitability by likely inhibiting two voltage-gated potassium channels, it modified the GABAergic and glutamatergic synaptic activity in interneurons that connect to MCs, generally decreasing synaptic activity. Furthermore, insulin exerted varied effects on olfactory nerve (ON)-evoked excitatory postsynaptic currents in MCs by either decreasing or increasing them depending on the initial firing rate of ON-evoked neurons. Insulin tended to reduce high firing rates and elevate low firing rates, thus decreasing inter-mitral cell response firing variability. This in turn most likely affects MCs' olfactory performance, mainly decreasing olfactory detection, depending on the quality of the odour being processed and aligning the valence of an odour with feeding signals.<sup>45</sup> Also, excitability on the level of the OE and OSNs varies depending on the nutritional status. When exposed to an odour OSNs exhibit increased excitability and firing frequency.<sup>46</sup> However, administration of insulin on the mucosa mimicked a post-prandial insulin rise and reduced the amplitude of electro-olfactogram in response to odours by 30%.<sup>82</sup> These results suggest that although insulin improves the firing rate of individual OSNs, the number of odour-activated OSNs is reduced, hence decreasing the

signal-to-noise ratio after a meal,<sup>46</sup> ultimately reducing the clarity of information sent to other brain regions. Again, this highlights the importance of the metabolic status on odour perception.

Chronic insulin exposure in obesity or diabetes is linked to impaired neural function in the olfactory system and individuals with impaired insulin sensitivity show poor olfactory performance.<sup>162</sup> Diet-induced obese mice showed altered MC action potentials and clustering, and acute insulin reduced or eliminated the response. Intranasal insulin was shown to activate IR signalling in the OB and modulate olfactory discrimination and detection.<sup>153</sup> Further, intranasal insulin caused a 5% body weight drop in rodents over 7 days.<sup>153</sup> Clinical studies also indicate that insulin via the nasal route improves cognition and memory,<sup>163</sup> however, whether IR in the OB regulate hypothalamic feeding circuits and contributes to the development of metabolic diseases (obesity, diabetes) is not known.

Leptin is predominantly secreted by white adipocytes in proportion to body fat. When leptin binds to hypothalamic leptin receptors (LepR), it suppresses food intake and thereby regulates long-term energy-balance and body weight. Although the majority of LepR are expressed in the hypothalamus, high expression is found in the OB<sup>164</sup> as well as the OSNs of the OE.<sup>165</sup> Within the OB, LepR are found in mitral cells, granule cells as well as astrocytes in the glomerular and granule cell layer.<sup>164</sup> Patch-clamp recordings of rat OSNs revealed that leptin heightens the excitability of OSNs in the absence of odours. However, it diminished the activity triggered by odours in the OE.<sup>46</sup> Similar to insulin signalling in the OB, an elevation of leptin following a meal is likely to reduce the overall signal-to-noise ratio within the OE,<sup>46</sup> as it simultaneously increases spontaneous firing frequency while decreasing odour-evoked activity. Indeed, leptin inhibited neuronal mitral/tufted cell activity in the OB by acting on voltage-dependent potassium channels and ultimately decreasing olfactory function in mice,<sup>166</sup> and ICV leptin administration decreased olfactory sensitivity in an odour-conditioned avoidance paradigm.<sup>51</sup> Obese leptin-deficient ob/ob mice perform better in a buried food paradigm<sup>167</sup> and an odour discrimination learning task, which was associated with neuronal oscillations in the OB.<sup>168</sup> Leptin replacement in ob/ob mice modified food-finding times similar to wildtypes, suggesting that impaired olfaction in obese conditions is primarily linked to high plasma leptin. Although research in rodents has demonstrated that administered leptin reduces olfactory discrimination and suppresses odour-evoked activity in OSNs,<sup>46,166</sup> the effects of meal-related increased leptin levels in humans appear to differ. Leptin levels were not found to be correlate with olfactory performance or odour-evoked fMRI brain activity.<sup>47,122</sup>

Glucagon-like peptide-1 (GLP-1) is an incretin hormone, released from the small intestine in response to a meal and promotes lowering blood glucose by promoting insulin release from the pancreas.<sup>169</sup> In addition, GLP-1 suppresses food intake via neuroendocrine actions in the brain. Interestingly, GLP-1 producing cells and GLP-1 receptors (GLP-1R) expressing cells are found on mitral cells and granular cells in the OB, suggesting the presence of an endogenous GLP-1 system in the OB. In addition, fluorescence labelled stable analogue exendin-4 was shown to arrive in the OB when given intranasally or

intraperitoneally,<sup>62,170</sup> indicating an additional neuroendocrine role in the OB. Unlike leptin, GLP-1 increases the excitability and firing frequency of mitral cells via dampening the activity of voltage-dependent potassium channels (Kv1.3).<sup>170</sup> Moreover, GLP-1 signalling in the OB boosted olfactory function in obese mice by restoring the loss of foraging behaviour and enhancing odour-induced insulin release in the cephalic phase.<sup>54</sup> The injection of GLP-1 antagonist exendin-9 in the OB of lean mice impaired food retrieval time in a buried food-finding test, whereas the agonist Exendin-4 rescued the lack of foraging behaviour of obese mice and increased olfactory sensitivity. Although the direct actions of GLP-1 signalling in the OB on food intake and metabolism were not examined, there is an interesting discordance between insulin, leptin and GLP-1 and olfaction. All three hormones are considered anorexigenic as they suppress food intake, but leptin and insulin suppress olfactory function whereas GLP-1 seems to promote olfaction, at least in a diet-induced obese model. Future studies are required to address this observation as this could be a highly relevant obesity pharmacotherapy since GLP-1R mimetics are now commonly used in the treatment of obesity or diabetes.<sup>170</sup>

*Cholecystokinin* (CCK, *pancreozymin*), a peptide hormone of the small intestine, mediates gut motility and digestion by regulating pancreatic enzymes and gallbladder contraction important for fat and protein digestion. Its sulphated octapeptide is widely distributed in the CNS.<sup>43</sup> In the OB, CCK peptide is found in the soma of tufted cells, and fibres of the external and internal plexiform layer.<sup>43</sup> CCK binds to two types of receptors: CCK-1R and CCK-2R, both of which are found in the OB,<sup>171–173</sup> whereas CCK-2R is generally the dominant form in the brain and involved in the satiety response, memory, cognition and anxiety.<sup>171,172</sup> CCK-2R occurs in the inner margins of the glomerular layer, on mitral/tufted and juxtaglomerular cells and external plexiform layer, but not on granule cell bodies.<sup>43</sup> In contrast, CCK-1R was found in the internal granular layer<sup>173</sup> as well as lateral olfactory tract.<sup>174</sup> Patch-clamp recordings showed that CCK excites mitral cells postsynaptically through CCK-1R and CCK-2R,<sup>43</sup> however, CCK-1R has stimulatory and CCK-2R inhibitory effects on olfactory performance.<sup>41</sup> CCK via CCK-2R selectively activates short axon cells by engaging with glomerular circuits to enhance the inhibition of OB output neurons. This modulation was suggested to either prevent saturation in response to high odour concentrations or increase the signal-to-noise ratio to help with the detection of low odour concentrations.<sup>42</sup> Intraperitoneal injection of CCK-1R agonists, or CCK-2R antagonists suggests that CCK enhances olfactory recognition and memory.<sup>41</sup> Chemogenetic activation of mitral cells and odour presentation suggested that stressful smells like the predator-odour Trimethylthiazoline (TMT) can increase energy expenditure, particularly in females,<sup>175</sup> and confirmed the involvement of CCK-expressing neurons in the dorsomedial hypothalamus (DMH). The findings also shed light on stress-induced thermogenesis and feeding suppression triggered by predator odour detection and underscores the enduring question of whether a particular olfactory cue possesses the ability to modulate energy metabolism.

Oxytocin is produced in the paraventricular nucleus and supraoptic nucleus of the hypothalamus and released in circulation from the posterior pituitary. In addition, these neurons send axonal projections to areas in the brain relevant for food intake regulation, including areas

also receiving inputs from the OB, for example, nucleus accumbens, amygdala, hippocampus, and anterior olfactory nucleus.<sup>20</sup> Although the OB does not receive direct oxytocinergic projections from oxytocin-producing neurons in the hypothalamus, oxytocin receptors (OXTR) are expressed in the OB, suggesting the neuroendocrine regulation of OXTR neurons in the OB.<sup>20</sup> In the OB, the OXTR is expressed in periglomerular cells and the glomerular cell layer, as well as mitral cells and the granule cell layer.<sup>55,56,176,177</sup> Oxytocin is well described to affect social behaviour and reproductive function but also has an anorexigenic effect on food intake via meal size control and meal cessation.<sup>178,179</sup> Functional MRI studies in humans indicated that oxytocin administered via the intranasal route reduced calorie intake by enhancing the activity of feeding relevant brain areas that control reward and cognition.<sup>179</sup> Of note, intranasal oxytocin did not alter olfactory function nor appetite or food choice. In mice, oxytocin infusion into the OB increased social interaction.<sup>180</sup> On a neuronal level, oxytocin enhanced odour discrimination and odour-induced mitral/tufted cell activity but reduced the spontaneous firing rate of mitral/tufted cells and odour-evoked calcium activity in granule cells.<sup>180</sup> In this manner, oxytocin increases the signal-to-noise ratio for accurate odour detection.

### 7.3 | Orexigenic/anorexigenic hormones

Adiponectin is predominantly produced in adipose tissue and plasma levels are inversely correlated to body mass.<sup>181</sup> Within the olfactory system, the adiponectin receptor (adipoR1) is expressed in OE and OE electro-olfactogram recordings suggest that it increases ORNs responsiveness to odourants as well as nearby OB.<sup>182</sup> In the OB, both receptors (adipoR1 and 2) have been identified in the periglomerular, mitral and granular cell layers.<sup>183,184</sup> In a rat model adiponectin prevented olfactory impairment induced by amyloid-beta accumulation, probably due to its described neuroprotective effects.<sup>185</sup> Interestingly, plasma adiponectin concentrations correlate with greater olfactory sensitivity in women, but not men.<sup>186</sup> Further, it has been suggested that adiponectin may modulate insulin signalling in the OB, possibly contributing to olfactory performance.<sup>184</sup> OB adiponectin injections slightly decreased IR protein content, IR phosphorylation and downstream phosphorylation of Akt. Although a role for adiponectin acting in the OB to influence metabolism is yet to be established, its ability to modulate insulin signalling and the link to nutritional status,<sup>187</sup> suggests this is a strong possibility.

The studies highlighted above collectively demonstrate a novel neuroendocrine role in olfactory function. In some cases, the direct hormonal action in the OB regulates food intake and metabolism, but in most the metabolic role has yet to be addressed. Future studies are required to address these gaps in the literature.

## 8 | OLFACTION-FEEDING INTERPLAY: THE IMPORTANCE OF SMELL FOR FEEDING AND HEDONIA

The impact of smell on appetite, food consumption and enjoyment of food is widely recognized. Indeed, one way the brain regulates food

intake behaviour is by changing the perception and pleasantness of food-related odours, a concept termed ‘alliesthesia’<sup>188</sup> and ‘sensory specific satiety’.<sup>100,189</sup> This refers to how an organism’s internal state alters the perceived pleasure or displeasure of external stimuli. For instance, food is more pleasant when hungry. And the pleasantness of food-related odours decreases when full,<sup>100</sup> or following a gastric or duodenal glucose load administered directly through a nasogastric tube. This suggests that nutrient-sensing in the digestive tract may influence the pleasantness of food-related odours.<sup>190</sup> Conversely, the ‘satiety effect’ can be induced by chewing or smelling food for a similar duration to a typical meal without the food entering the gastrointestinal system or calorie ingestion.<sup>100</sup> In addition, olfactory stimuli can evoke a food-related odour memory, and promote appetite, salivation, gastric acid secretion and food intake even when not hungry.<sup>191–193</sup> These observations have important implications for food intake control and our understanding of how the brain processes sensory-specific signals. So, what is the mechanism involved? Why does a whiff of freshly baked bread make you hungry or why does olfactory perception change when you are full?

Olfactory sensory inputs from ORs in the nasal cavity travel to the OB, the first port for sensory information to reach the brain, before touch, taste and sight.<sup>194</sup> These inputs are often decisive cues that help organisms assess whether food is available, palatable, or potentially toxic. This is an important point since feeding behaviour is not only driven by homeostatic signals but also by sensory environmental cues predicting the availability of tasty calorie-dense foods or potential external threats.<sup>195,196</sup> Further, animals exhibit different behavioural responses to the same sensory cue depending on the internal metabolic state at a given moment.<sup>197</sup> Olfaction plays a pivotal role in this intricate interplay between homeostatic and hedonic circuits, as alterations in internal conditions like hunger or satiety intricately influence the pleasurable value of odours.<sup>61</sup> Homeostasis is based on the metabolic state, wherein energy depletion and hunger amplify the motivation for food consumption. Furthermore, increased olfactory discrimination and sensitivity facilitate the detection of food cues in food-scarce environments. Contrary, olfactory sensitivity decreases during satiation and gastric distension. Besides the nutritional state, olfactory performance also depends on adiposity and is also influenced by pathologic conditions (obesity, metabolic or neurogenerative disorders).<sup>61,62,198</sup> On the other side, hedonic processes are entwined with the sensory attributes of food and the associated rewards, reflecting olfactory inputs in brain reward and motivational systems.<sup>199</sup> For example, specific food odours increase appetite and subsequent consumption of food matched to the odour.<sup>200</sup>

Sensory information from olfactory circuits uniquely bypasses the thalamus, which explains emotional imprinting, lasting memory, and evocative power of olfactory experiences.<sup>201</sup> Olfactory learning, involving dopamine-dependent strengthening,<sup>202</sup> influences motivation for food acquisition, food preferences, and meal size.<sup>189,203</sup> Olfactory cues contribute to the ‘cephalic phase’, preparing the body for an incoming meal by triggering processes such as salivation, gastric acid secretion and insulin release.<sup>189,204,205</sup> And odours paired with palatable food increase appetite in both rodents and humans.<sup>191,206</sup>

This was classically demonstrated by Pavlovian conditioning of appetitive behaviours.<sup>194,207</sup> As such, olfactory cues are crucial for forming dynamic value judgments of the surroundings and optimizing behavioural responses, such as food choice and consumption. This underscores that olfactory ability is shaped not only by internal metabolic factors but also by external olfactory cues, all impacting eating behaviour.<sup>189,208</sup> Thus, there seems to be a reciprocal relationship between olfaction and metabolism,<sup>92</sup> where olfactory information alters feeding behaviour and metabolic factors influence olfactory performance. Hence, olfaction emerges as a potent mediator of food consumption, with the potential to influence energy balance and body weight.<sup>92,175,209</sup> Consequently, the OB allows for the integration of food odours and internal metabolic-dependent signals, like hormones or nutrients, and highlights the OB’s role in regulating both sides of the energy balance equation, namely feeding and energy metabolism.

## 9 | ‘SCENT-SATIONAL HYPOTHALAMIC CONNECTIONS’: THE OLFACTORY BULB’S INFLUENCE ON APPETITE AND METABOLISM

In the hypothalamus two critical neurons are involved in hunger and satiety signalling; namely Arcuate agouti-protein related peptide (AgRP) neurons as well as Pro-opiomelanocortin (POMC) neurons. While AgRP neurons promote food intake by releasing orexigenic peptides such as AgRP, NPY or GABA, POMC neurons inhibit food intake by releasing anorectic peptides, such as alpha-melanocyte-stimulating hormone ( $\alpha$ -MSH).<sup>210</sup> Ablation of these pathways results in starvation or obesity, respectively.<sup>211,212</sup> AgRP and POMC neurons have long been believed to respond primarily to changes in energy state, with AgRP neurons increasing food intake in response to energy need and POMC suppressing food intake in response to sufficient consumption. In this feedback model, AgRP neuron activity would be expected to remain elevated until all calories required to reinstate homeostasis have been consumed. Similarly, for POMC neurons, activity should remain low until sufficient calories have been consumed. However, this is clearly not the case as studies show sensory cues of food availability inhibit and activate AgRP and POMC neurons, respectively, immediately before food intake.<sup>213</sup> Interestingly, the response magnitude of AgRP or POMC to sensory cues depends on metabolic state, food accessibility, and palatability.<sup>213</sup> Moreover, sustained changes in activity require calorie consumption since exposure to non-accessible caged food only produces short-lived changes in AgRP or POMC neuronal activity.<sup>213</sup> These studies highlight that AgRP and POMC neurons do not just react to metabolic changes but respond to sensory cues of food availability and palatability to prepare for perceived future energy demands. The model highlights the importance of sensory inputs in regulating feeding circuits and has recently been termed energy allostasis.<sup>66</sup> This new model is relevant to human behaviour since humans often eat in the absence of hunger or restrict food intake in the presence of hunger. Olfactory sensory input may be even more important due to the

potential ability to transmit both novel food-odour information and learned odour associations to hypothalamic feeding circuits. And food odours have been shown to trigger metabolic responses, such as increase of appetite, salivation and the release of digestive enzymes, thus preparing the body for the incoming meal. This interaction between energy metabolism and olfactory perception appears to work both ways, as hunger signals released during fasting (orexigenic hormones) increase olfactory function, potentially aiding in food location,<sup>97,112</sup> and AgRP activity increases preference for food odours over pheromone odours.<sup>214</sup> Recent research has unveiled that both AgRP and POMC neurons receive indirect inputs from overlapping regions within the olfactory cortex, pinpointing the origins of odour-related signals.<sup>215</sup> Furthermore, neurons of other brain areas positioned directly upstream of AgRP or POMC neurons have been identified (VMH, DMH), potentially connecting the olfactory cortex and AgRP or POMC neurons. While some AgRP and POMC neurons received olfactory inputs from both piriform cortex, medial amygdala and posteromedial cortical amygdala, there were also unique inputs to AgRP neurons from posterolateral cortical amygdaloid area and olfactory tubercle or POMC neurons from the anterior cortical amygdaloid area and lateral entorhinal cortex.

## 10 | SCENTLESS SUFFERING: OLFACTORY CHANGES AND HEALTH IMPLICATIONS

Olfaction affects appetite, hedonic aspects of food, mood and cognition,<sup>216,217</sup> and individuals who cannot smell experience depression, abnormal food perception (pleasantness/intensity), and changes in food consumption and enjoyment as well as cognition.<sup>218</sup> Anosmia, the loss of olfactory function, goes often unnoticed and is diagnosed late, leading to long-term implications on well-being and quality of life.<sup>218,219</sup> Over time these changes may compound to enhance the risk for eating disorders, obesity, cardiovascular, endocrinological or metabolic diseases as well as contribute to the progression of neurodegenerative diseases (such as Parkinson or Alzheimer).<sup>217,220–222</sup> Besides altered eating behaviours and anhedonia associated with olfactory impairments, olfactory loss also affects food preparation or the detection of spoiled foods and hazards.<sup>218,219</sup>

Common causes include sinus-nasal disease, upper respiratory infections, traumatic brain injuries, cancer, and post-viral olfactory loss, as seen in COVID-19 patients.<sup>221,223</sup> Neurodegenerative diseases and environmental toxins can also lead to olfactory impairments.<sup>224</sup> Olfactory loss is commonly associated with aging and various metabolic and neurological diseases, such as Parkinson's, Alzheimer's, diabetes, and obesity.<sup>225–227</sup> Olfactory impairments may be caused, at least in part, by the metabolic changes observed with the disease, as exposure to chronic levels of the hormone insulin (diabetes), imbalanced nutrition or increased body weight (obesity) alters olfactory structures, neuronal excitability, and axonal projections.<sup>79,228–230</sup> Also, the opposite cannot be ruled out: Olfactory dysfunction causes, or at least contributes to changes in metabolism and contributes to weight gain in obesity<sup>209</sup> or impaired glycaemic control

in diabetes.<sup>231,232</sup> Evidence for such a link that olfactory impairments affect metabolic parameters comes from various animal models (Table 4) and human pathologies (Table 5). In humans, a common biallelic gene deletion encoding olfactory receptors was found in children of obese parents, suggesting olfactory dysfunction contributes toward the development of obesity.<sup>233</sup> In addition, the ciliopathic disorder affecting the cilia of OSNs and kidneys (Bardet–Biedl syndrome) leads to obesity.<sup>234–236</sup> Collectively, these studies show that human obesity can be linked to genes affecting olfaction. Contrary, augmented olfactory sensitivity prevented diet-induced obesity in pharmacological and genetic rodent models.<sup>237–239</sup> Transgenic mice with increased olfactory sensitivity are resistant to weight gain when placed on high-fat diet (HFD),<sup>239</sup> whereas impairing olfactory sensitivity predisposes to weight gain and obesity.<sup>112,240,241</sup> One mechanistic possibility argues that an impaired sense of smell delays the immediate sensory processing of food and thus delays satiety processing, resulting in overconsumption and ultimately weight increase.<sup>209</sup> Of note, despite lower olfactory performance in obesity, obese individuals show an increased preference for odours associated with palatable energy-dense foods,<sup>242</sup> with enhanced activation of reward regions.<sup>243,244</sup> This indicates that the olfactory system is closely linked to hypothalamic circuits controlling metabolism and reward. Indeed, a recent study demonstrated that hypothalamic hunger circuits directly control dopamine release and reward processing.<sup>245</sup> Thus, the inability of olfactory information to control feeding circuits may make obese individuals more prone to external palatable food cues affecting food consumption/choices.<sup>246</sup> This idea is supported by studies showing that the ablation of hypothalamic hunger circuits promotes dopamine-driven reward eating.<sup>247</sup> Understanding the complex relationship between olfactory integration of metabolic information and hypothalamic circuits to control feeding behaviour and reward may provide new therapeutic opportunities to treat metabolism and associated diseases.

## 11 | CONCLUDING REMARKS

Here we suggest the OB should be considered as another neuroendocrine brain region, similar to the hypothalamus. It consists of cells that produce and respond to hormonal signals, which project to higher brain regions. OB neurons are regulated by feedback signals from afferents from higher brain centres, endocrine glands, and other circulating factors, including peripheral signals carried in the blood. Thus, together the OB monitors many bodily functions via these higher brain regions and circulating factors while also integrating environmental stimuli. This puts the OB in a unique position to regulate energy homeostasis and metabolism by adjusting olfactory sensitivity, guiding eating behaviour and influencing other brain regulatory systems to maintain a balanced supply of energy and nutrients.

The OB can be considered as the sensory neuroendocrine powerhouse, nestled in the brain with a window to the outside world, perceiving, recognizing, and processing odours as well as a multifaceted role in metabolic regulation, similar but not equal to the

TABLE 4 Rodent models of altered olfactory function showing the link between olfaction, behaviour and metabolism.

	Olfactory alterations	Olfactory performance	Mood	Feeding behaviour	Metabolism	References
Kv1.3 null mice	The voltage-gated potassium channel controls the excitability of major output neurons (MCs) of the OB ↓OSNs but ↑ORs expression, ↓Glomeruli size, ↑synaptic refinement	'Super-smeller': ↑olfactory discrimination/ sensitivity	↑Anxiety, 1 activity during the dark phase with ADHD-like phenotype, different activity patterns on running wheels	↑Feeding bouts but no change in caloric intake	↓Bodyweight, ↑energy expenditure, ↑glucose tolerance, resistance to diet-induced obesity (DIO)	[229,237,239,381-384]
Targeted loss of Kv1.3 of mitral/tufted projection neurons via CRISPR gene editing	↓M/T Cs excitability, ↓negative resting membrane potential, ↑action potential firing	↑Olfactory discrimination		No difference in caloric intake	Resistance to DIO, ↓body weight, ↓adipose tissue, ↑glucose tolerance, ↓plasma leptin and liver triglycerides. Unaltered energy expenditure (EE) and locomotor activity, but used more fats for metabolic substrate over that of carbohydrates	[385]
Conditional NCKX4-null mice	Potassium-dependent sodium/calcium exchanger, ↑intracellular calcium for proper activation, termination and adaptation of sensory responses		Delayed response termination without affecting odorant sensitivity, over-adapt to repeated odorant exposure by significantly ↓OSN response, ↓ability to locate buried food	↓Bodyweight		[386]
Local expression of shRNA against preproglucagon mRNA	↓GLP-1 expression in the OB	↓Olfactory foraging		↓Cephalic phase insulin response		[54]
DIO-fat enriched diet	↓OSNs, ↓neuronal excitability, ↓electro-olfactography (EOG) response	Olfactory dysfunction only for complex behavioural tasks, no deficit in buried reward finding or odour discrimination	Obesity			[99,229]

TABLE 4 (Continued)

	Olfactory alterations	Olfactory performance	Mood	Feeding behaviour	Metabolism	References
DIO-fructose enriched diet	↑OSNs, ↓OSNs apoptosis, ↓odour response, ↓electro-olfactography (EOG) response	Olfactory dysfunction, ↓odour discrimination, ↓ability to locate buried food			Obesity and T2DM	[387]
Ob/Ob mice (leptin-deficient)	↑Oscillations to facilitate learning of sensory information	↓Odour discrimination	Anxiety	Hyperphagia	Severely obese, hyperglycaemia, hyperinsulinaemia, high levels of corticosteroids, hypothyroidism, dyslipidaemia, ↓body temperature, defective thermogenesis, infertility.	[167,168]
MC4R null mice	Melanocortin 4 receptor is highly expressed in the paraventricular nucleus of the hypothalamus and plays an important role in energy homeostasis, eating behaviour, adipose tissue formation and satiety	Inability to discriminate certain odours, reward retrieval time depended on reward: no difference for chocolate but ↓reward retrieval for peanut butter, unaltered performance for fatty food odourants but inability to discriminate other odours (peppermint vs. geranyl acetate)		Improvement in mood symptoms, such as anxiety-like and depressive-like behaviours and less social avoidance	Obesity and T2DM: severe obesity, hyperinsulinaemia, hepatic insulin resistance independent of food intake, ↑fasting glucose, ↑body weight, when challenged with HFD ↓glucose clearance and insulin response, shorter life span	[99,229,388,389]
Kv1.3 null/MC4R-null mice					Kv1.3 null improved MC4R null phenotype: ↓body weight gain, ↑total energy expenditure compared with MC4R-null mice	[384]
DpTx-treated cre-OMP	Genetically engineered mice to express a diphtheria toxin receptor on OSNs to genetically ablate OSNs in mature mice			Not affected	Loss of adult OSNs protects against DIO, genetic ablation after onset of obesity abrogated further weight gain, ↓fat mass,	[390]

(Continues)

TABLE 4 (Continued)

	Olfactory alterations	Olfactory performance	Mood	Feeding behaviour	Metabolism	References
IGF1R <sup>fl/fl</sup> × OMP-Cre mice	Insulin-like growth factor 1 (IGF1) plays a role in regeneration of OSNs Ablation of the IGF1 receptor (IGF1R) was limited to mature OSNs	↑Olfactory sensitivity, ↑ability to locate buried food		Not affected	↑insulin sensitivity. Lean phenotype showed ↑energy expenditure, ↑therogenesis, ↑lipolysis (↑beta-adrenergic receptors, activated hormone-sensitive lipase)	[390]
Long-term imbalanced nutrition, favouring fat, not obese	↓OSNs, ↓olfactory sensory axonal projections	↓Odour discrimination/ perception			Pre-diabetes: ↓glucose clearance	[228]
Inducible olfactory inflammation	Chronic and local OE inflammation, ↑proinflammatory cytokines, neuroepithelial reorganization	↓Olfactory neurogenesis, ↓olfactory discrimination	↓Sociability		↓Food reward, anhedonia	[391–393]
Air pollutants exposure (2-ethyl-1-hexanol, ozone, fine particles)	Inflammatory cell infiltration into OE, ↓OSNs, ↓microglia in OB, ↓glomeruli size, ↓olfactory nerve number, ↑proinflammatory cytokines	Ability to locate buried food		↓Social recognition, ↓learning and memory, depressive-like behaviour	[394–396]	
Intranasal virus infection	Inflammatory cell infiltration into OE and OB, ↓microglia activation in OB, ↓olfactory nerve, structural changes				[397–399]	
Chronic rhinosinusitis (intranasal ovalbumin, pollen, Triton X-100, lipopolysaccharide, zinc sulphate injection)	↓OSNs, OB atrophy, ↑microglia and astrocyte activation in OB, ↑proinflammatory cytokines, disruption of functional connections from OE to OB, neurodegeneration	Olfactory dysfunction, ↓ability to locate buried food		↓Social interaction, anxiety-like behaviour	[400–404]	

TABLE 4 (Continued)

	Olfactory alterations	Olfactory performance	Mood	Feeding behaviour	Metabolism	References
Olfactory bulbectomy	Olfactory dysfunction	Depression, ↓ learning and memory, ↓ odour recognition, ↓ motivation, hyperactivity, ↑ exploration [cannibalism, altered sleep pattern, ↓ sexual activity	↓ Food-motivated behaviour	Changes in neurotransmitter turnover, altered urinary metabolic profile, ↑ body temperature, ↓ body fat, altered heart rate pattern, ↑ drinking, sodium intake and food intake, ↑ insulin response	[405–416]	
Cnga2 genetic deletion	Cyclic nucleotide gated channel 2 mutant gene (Cnga2), critical for OSNs to generate odour-evoked action potentials and important for olfactory sensory transduction, aberrant dendritic morphologies, ↓ dendritic spines and synaptic proteins	Anosmic	↓ Social behaviour, ↓ learning and memory, anxiety-/depressive-like behaviour		[417–419]	
Odorant receptor overexpression–acetophenone receptor, octanol receptor	Most OSNs express a single odourant receptor: odours acetophenone receptor (M71 or M72), and/or octanal receptor (rl7) Alteration of odour-evoked glomerular activity	Mice are able to smell, but fail odour-specific detection (acetophenone/octanal) despite activation of OSNs and glomeruli of that specific odour, ↓ discrimination and performance in associative olfactory learning	Anxiety-like behaviour	Elevated plasma corticosterone, odour-induced seizure	[420–422]	
Metabolic hormone receptor deletion in the OB-GHRS	Deletion of the ghrelin receptor (GHSR) in the OB using GHSR floxed and adenoassociated Cre-virus	↓ Olfactory sensitivity to food and non-food odours	Anxiety-/depression-like behaviour	Not affected food intake but altered feeding behaviour: ↓ feeding bouts in the dark phase, anhedonia, ↓ food finding and exploratory behaviour	↑ Body weight and fat mass, ↓ glucose tolerance	[112]

Abbreviations: DIO, diet induced obesity; M/TCs, mitral cells; MCs, mitral/tufted cells; OE, olfactory epithelium; ORs, olfactory receptors; OSNs, olfactory sensory neurons.

**TABLE 5** Human pathologies showing a link between olfaction, behaviour and metabolism.

	Olfactory performance	Mood	Feeding behaviour	Metabolism	References
Age	↓Olfactory function, ↓mature olfactory neurons, replacement of olfactory neuroepithelium by respiratory epithelium, ↓basal cell proliferation, ↓OB interneurons, ↓olfactory cortex activity under olfactory stimulation	Cognitive dysfunction, mood disorders	↓Appetite and food intake	↓Energy expenditure, olfactory dysfunction predicts 5-year mortality	[423–426]
Obesity	Severe obesity BMI >45 Obesity BMI >30 Overweight BMI >25	↓Olfactory sensitivity and odour identification ↓Olfactory function is more likely with ↑BMI and may contribute to obesity progression ↑olfactory sensitivity and attraction for energy-dense food odours (chocolate) ↑Olfactory sensitivity when hungry due to ↓postprandial suppression of ghrelin	Depression and anxiety ↑Hunger, ↑food intake, binge eating, snacking	Obesity and comorbidities	[427–429] [233,242,243,430,431] [432]
Diabetes mellitus	Uncomplicated Type 1 and Type 2 Diabetes	Normal olfactory function			[433]
	Type 1 Diabetes	Mild olfactory dysfunction with ↓odour identification	Mood swings, depression, anxiety, stress	Extreme hunger/thirst if untreated	Comorbidities, neuropathy [433,434]
	Type 2 Diabetes	↓Olfactory sensitivity and odour identification	Mood swings, depression, anxiety, stress	Extreme hunger/thirst if untreated	Comorbidities, neuropathy [232,433,435]
Anorexia nervosa	Recent onset females	↑Olfactory sensitivity			[436]
	Low body weight females	↓Olfactory sensitivity			[437]
	Very low-weight anorexics	↓Olfactory sensitivity and odour identification	Depression and anxiety	↓Food intake and hedonic value of food	[438–441]
Bulimia nervosa		Normal olfactory function			[438,439]
Bardet-Biedl syndrome	Associated with defective cilia and presents with sensory, renal and limb malformations, hypogonadism, and mental retardation	Partial/complete anosmia	Depression and anxiety, social problems	↑Food seeking activity, ↓food intake	Obesity, metabolic syndrome [236,442–445]

TABLE 5 (Continued)

		Olfactory performance	Mood	Feeding behaviour	Metabolism	References
Kallmann syndrome/isolated hypogonadotropic hypogonadism	Defective development of migration of gonadotropin-releasing hormone (GnRH) and olfactory neurons	Partial/complete anosmia	Depression and anxiety, social problems, sleep disorders	Altered appetite	Obesity, endocrine disorders, ↓fertility, delayed puberty, altered energy and bone metabolism	[234;332;446–448]
Prader–Willi syndrome	Lack of expression of inherited genes known to be located on chromosome 15, typical deletion region of PWS is in proximity of olfactory receptor genes (OR4M2, OR4N4)	Normal olfactory function but ↓activation of reward system in response to food odours	Depression and anxiety, cognitive and behavioural problems, social problems, sleep disorders	↑Appetite and food intake, food obsession, ↑food seeking, ↑satiety	Morbid obesity, endocrine disorders, delayed puberty and growth, altered energy and bone metabolism, ↓energy expenditure, diabetes mellitus	[325;449–453]
Cystic fibrosis	Thickened secretions and olfactory mucus, frequent respiratory infections	Mostly partial than complete anosmia, ↓olfactory sensitivity but normal odour identification	Depression and anxiety	Normal appetite, ↓food intake, delayed gastric emptying, ↑satiety, malnutrition	Altered energy metabolism, altered lipid and fatty acid metabolism, ↑energy expenditure, ↓glucose tolerance	[454–458]
Neurodegenerative disease	Alzheimer disease	↓Olfactory function, amyloid-beta production, tau pathology and neuroinflammation	Depression and anxiety, cognitive problems, irritability, psychosis, sleep disorders	Altered food intake and food preference	↓Body weight, ↑cortisol levels, altered brain metabolism with ↓glucose uptake	[459–466]
	Parkinson disease	↓Olfactory function, ↑dopaminergic neurons in the GL of OB, ↓cholinergic, noradrenergic and serotonergic function	Depression and anxiety	↓Appetitive motivation and food intake, ↓reward processing	↓Body weight, ↑energy expenditure	[36;467–470]
	Huntington disease	↓Olfactory function, huntingtin deposits in the OB	Depression and anxiety, irritability	↑Food intake	↓Body weight, ↑energy expenditure, ↓glucose tolerance, ↓muscle and fat mass	[471–474]
	Multiple sclerosis	↓Olfactory function, with short-term ↓olfactory sensitivity due to inflammatory activity and ↓odour identification due to neurodegeneration	Depression and anxiety	↓Appetite	↑Energy expenditure, altered lipid metabolism	[475–481]
	Amyotrophic lateral sclerosis	↓Olfactory function, altered protein expression in the OB	Emotional, behavioural and cognitive symptoms	↓Appetite	↓Body weight, altered energy metabolism, ↓glucose tolerance, ↓muscle and fat mass	[232;482–486]

(Continues)

TABLE 5 (Continued)

	Olfactory performance	Mood	Feeding behaviour	Metabolism	References
Adrenal insufficiency/Addison Disease	↑Olfactory sensitivity	Depression, irritability	↓Appetite, ↑thirst, salt craving	↓Body weight, endocrine disorders, ↓cortisol, impaired cholesterol and glucose metabolism, hypotension	[137-487]
Cushing disease	↓Olfactory function	Depression and anxiety, memory and cognitive impairments	↑Appetite, ↑thirst	↑Body weight (especially around belly), endocrine disorders, ↑cortisol, ↓glucose tolerance, ↑lipolysis and lipogenesis, peripheral insulin resistance, hypertension, skin changes	[488-490]
Hypothyroidism and pseudohypoparathyroidism	↓Olfactory function	Depression and anxiety	↓Appetite and food intake	Obesity, endocrine disorders, altered energy metabolism, ↓energy expenditure, hypotension	[491-494]
Down syndrome	↓Olfactory function and odour memory	Depression	↑Appetite, altered eating habits	↑Metabolic disorders such as obesity and diabetes, impaired glucose and lipid metabolism	[495-501]
Schizophrenia	↓Olfactory function, brain structural changes	Depressive or bipolar type, psychosis	↑Unhealthy food choice	↑Metabolic disorders, altered energy metabolism, ↓glucose uptake into the brain, ↑fatty acid catabolism	[502-507]

Abbreviations: BMI, body mass index; GL, glomerular layer; OSNs, olfactory sensory neurons.

hypothalamus. The OB interprets chemical odour cues and orchestrates information throughout the body. It communicates with the hypothalamus, the brain's master regulator of energy balance, influencing hunger, satiety, and even the way our cells burn calories. It also connects with other brain regions important for mood, memory, and learning. Understanding the OB's intricate connection to metabolism, behavioural and cognitive characteristics opens new avenues for research into obesity, diabetes, and other metabolic disorders as well as cognitive or behavioural disorders. Shedding light on how our sense of smell can impact our overall health and well-being and how we can harness the power of odours will be a significant contribution to novel treatment strategies.

## AUTHOR CONTRIBUTIONS

**Romana Stark:** Funding acquisition; investigation; project administration; writing – original draft; writing – review and editing.

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Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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## REFERENCES

1. Akbari P, Gilani A, Sosina O, et al. Sequencing of 640,000 exomes identifies GPR75 variants associated with protection from obesity. *Science*. 2021;373(6550):eabf8683. doi:[10.1126/science.abf8683](https://doi.org/10.1126/science.abf8683)
2. Locke AE, Kahali B, Berndt SI, et al. Genetic studies of body mass index yield new insights for obesity biology. *Nature*. 2015; 518(7538):U197-U401.
3. Watson HJ, Yilmaz Z, Thornton LM, et al. Genome-wide association study identifies eight risk loci and implicates metabo-psychiatric origins for anorexia nervosa. *Nat Genet*. 2019;51(8):1207-1214.
4. Julliard AK, Al Koborssy D, Fadool DA, Palouzier-Paulignan B. Nutrient sensing: another chemosensitivity of the olfactory system. *Front Physiol*. 2017;8:8468.
5. Sarafoleanu C, Mella C, Georgescu M, Perederco C. The importance of the olfactory sense in the human behavior and evolution. *J Med Life*. 2009;2(2):196-198.
6. Ming GL, Song H. Adult neurogenesis in the mammalian brain: significant answers and significant questions. *Neuron*. 2011;70(4):687-702.
7. Huart C, Rombaux P, Hummel T. Plasticity of the human olfactory system: the olfactory bulb. *Molecules*. 2013;18(9):11586-11600.
8. Gaillard I, Rouquier S, Giorgi D. Olfactory receptors. *Cell Mol Life Sci*. 2004;61(4):456-469.
9. Zhang X, Firestein S. The olfactory receptor gene superfamily of the mouse. *Nat Neurosci*. 2002;5(2):124-133.
10. Rouquier S, Blancher A, Giorgi D. The olfactory receptor gene repertoire in primates and mouse: evidence for reduction of the functional fraction in primates. *Proc Natl Acad Sci U S A*. 2000;97(6): 2870-2874.
11. Bushdid C, Magnasco MO, Vosshall LB, Keller A. Humans can discriminate more than 1 trillion olfactory stimuli. *Science*. 2014; 343(6177):1370-1372.
12. Sullivan SL, Adamson MC, Ressler KJ, Kozak CA, Buck LB. The chromosomal distribution of mouse odorant receptor genes. *Proc Natl Acad Sci U S A*. 1996;93(2):884-888.
13. Mombaerts P, Wang F, Dulac C, et al. Visualizing an olfactory sensory map. *Cell*. 1996;87(4):675-686.
14. Quintela RM, Brunert D, Rothermel M. Functional role of the anterior olfactory nucleus in sensory information processing. *Neuroforum*. 2022;28(3):169-175.
15. Courtioli E, Wilson DA. The olfactory thalamus: unanswered questions about the role of the mediodorsal thalamic nucleus in olfaction. *Front Neural Circuits*. 2015;9:49.
16. Kay LM, Sherman SM. An argument for an olfactory thalamus. *Trends Neurosci*. 2007;30(2):47-53.
17. Kivity S, Ortega-Hernandez OD, Shoenfeld Y. Olfaction—a window to the mind. *Isr Med Assoc J*. 2009;11(4):238-243.
18. Barwick AS. *Smellosophy What the Nose Tells the Mind*. Harvard University Press; 2020.
19. Nagayama S, Homma R, Imamura F. Neuronal organization of olfactory bulb circuits. *Front Neural Circuits*. 2014;8:98.
20. Oettl LL, Kelsch W. Oxytocin and olfaction. *Curr Top Behav Neurosci*. 2018;35:55-75.
21. Imamura F, Ito A, LaFever BJ. Subpopulations of projection neurons in the olfactory bulb. *Front Neural Circuits*. 2020;14:561822.
22. Pevsner J, Snyder SH. Odorant-binding protein: odorant transport function in the vertebrate nasal epithelium. *Chem Senses*. 1990; 15(2):217-222.
23. Nagayama S, Takahashi YK, Yoshihara Y, Mori K. Mitral and tufted cells differ in the decoding manner of odor maps in the rat olfactory bulb. *J Neurophysiol*. 2004;91(6):2532-2540.
24. Dade LA, Zatorre RJ, Jones-Gotman M. Olfactory learning: convergent findings from lesion and brain imaging studies in humans. *Brain*. 2002;125(1):86-101.
25. Balu R, Pressler RT, Strowbridge BW. Multiple modes of synaptic excitation of olfactory bulb granule cells. *J Neurosci*. 2007;27(21): 5621-5632.
26. Chong E, Rinberg D. Behavioral readout of spatio-temporal codes in olfaction. *Curr Opin Neurobiol*. 2018;52:18-24. doi:[10.1016/j.conb.2018.04.008](https://doi.org/10.1016/j.conb.2018.04.008)
27. Margrie TW, Sakmann B, Urban NN. Action potential propagation in mitral cell lateral dendrites is decremental and controls recurrent and lateral inhibition in the mammalian olfactory bulb. *Proc Natl Acad Sci U S A*. 2001;98(1):319-324.
28. Lazarini F, Lledo PM. Is adult neurogenesis essential for olfaction? *Trends Neurosci*. 2011;34(1):20-30.
29. Brunert D, Rothermel M. Extrinsic neuromodulation in the rodent olfactory bulb. *Cell Tissue Res*. 2021;383(1):507-524.

30. In't Zandt EE, Cansler HL, Denson HB, Wesson DW. Centrifugal innervation of the olfactory bulb: a reappraisal. *eNeuro*. 2019;6(1):ENEURO.0390-18.2019. doi:[10.1523/ENEURO.0390-18.2019](https://doi.org/10.1523/ENEURO.0390-18.2019)
31. Gervais R. Unilateral lesions of the olfactory tubercle modifying general arousal effects in the rat olfactory bulb. *Electroencephalogr Clin Neurophysiol*. 1979;46(6):665-674.
32. Shafa F, Meisami E. A horseradish peroxidase study of the origin of central projections to the rat olfaction bulb. *Brain Res*. 1977;136(2):355-359.
33. Heimer L. Synaptic distribution of centripetal and centrifugal nerve fibres in the olfactory system of the rat. An experimental anatomical study. *J Anat*. 1968;103(Pt 3):413-432.
34. Zhang Z, Zhang H, Wen P, et al. Whole-brain mapping of the inputs and outputs of the medial part of the olfactory tubercle. *Front Neural Circuits*. 2017;11:52. doi:[10.3389/fncir.2017.00052](https://doi.org/10.3389/fncir.2017.00052)
35. Wesson DW, Wilson DA. Sniffing out the contributions of the olfactory tubercle to the sense of smell: hedonics, sensory integration, and more? *Neurosci Biobehav Rev*. 2011;35(3):655-668.
36. Doty RL. Olfaction in Parkinson's disease and related disorders. *Neurobiol Dis*. 2012;46(3):527-552.
37. Hoglinger GU, Alvarez-Fischer D, Arias-Carrion O, et al. A new dopaminergic nigro-olfactory projection. *Acta Neuropathol*. 2015;130(3):333-348.
38. Nogi Y, Ahasan MM, Murata Y, et al. Expression of feeding-related neuromodulatory signalling molecules in the mouse central olfactory system. *Sci Rep*. 2020;10(1):890.
39. Wang D, Wu J, Liu P, et al. VIP interneurons regulate olfactory bulb output and contribute to odor detection and discrimination. *Cell Rep*. 2022;38(7):110383.
40. Gutierrez-Mecinas M, Crespo C, Blasco-Ibanez JM, Gracia-Llanes FJ, Marques-Mari AI, Martinez-Guijarro FJ. Characterization of somatostatin- and cholecystokinin-immunoreactive periglomerular cells in the rat olfactory bulb. *J Comp Neurol*. 2005;489(4):467-479.
41. Lemaire M, Barneoud P, Bohme GA, et al. CCK-A and CCK-B receptors enhance olfactory recognition via distinct neuronal pathways. *Learn Mem*. 1994;1(3):153-164.
42. Liu X, Liu S. Cholecystokinin selectively activates short axon cells to enhance inhibition of olfactory bulb output neurons. *J Physiol*. 2018;596(11):2185-2207.
43. Ma J, Dankulich-Nagrudny L, Lowe G. Cholecystokinin: an excitatory modulator of mitral/tufted cells in the mouse olfactory bulb. *PLoS One*. 2013;8(5):e64170.
44. Aime P, Hegoburu C, Jaillard T, et al. A physiological increase of insulin in the olfactory bulb decreases detection of a learned aversive odor and abolishes food odor-induced sniffing behavior in rats. *PloS One*. 2012;7(12):e51227.
45. Kuczewski N, Fourcaud-Trocmé N, Savignier A, et al. Insulin modulates network activity in olfactory bulb slices: impact on odour processing. *J Physiol*. 2014;592(13):2751-2769.
46. Savignier A, Duchamp-Viret P, Grosmaitre X, et al. Modulation of spontaneous and odorant-evoked activity of rat olfactory sensory neurons by two anorectic peptides, insulin and leptin. *J Neurophysiol*. 2009;101(6):2898-2906.
47. Ginieis R, Abeywickrema S, Oey I, Peng M. Testing links of food-related olfactory perception to peripheral ghrelin and leptin concentrations. *Front Nutr*. 2022;9:888608.
48. Loch D, Breer H, Strotmann J. Endocrine modulation of olfactory responsiveness: effects of the orexigenic hormone ghrelin. *Chem Senses*. 2015;40(7):469-479.
49. Tong J, Mannea E, Aimé P, et al. Ghrelin enhances olfactory sensitivity and exploratory sniffing in rodents and humans. *J Neurosci*. 2011;31(15):5841-5846.
50. Trellakis S, Tagay S, Fischer C, et al. Ghrelin, leptin and adiponectin as possible predictors of the hedonic value of odors. *Regul Pept*. 2011;167(1):112-117.
51. Julliard AK, Chaput MA, Apelbaum A, Aime P, Mahfouz M, Duchamp-Viret P. Changes in rat olfactory detection performance induced by orexin and leptin mimicking fasting and satiation. *Behav Brain Res*. 2007;183(2):123-129.
52. East BS, Wilson DA. A hunger for odour: leptin modulation of olfaction. *Acta Physiol (Oxf)*. 2019;227(2):e13363.
53. Gascuel J, Lemoine A, Rigault C, et al. Hypothalamus-olfactory system crosstalk: orexin a immunostaining in mice. *Front Neuroanat*. 2012;6:44. doi:[10.3389/fnana.2012.00044](https://doi.org/10.3389/fnana.2012.00044)
54. Montaner M, Denom J, Jiang W, Magnan C, Trapp S, Gurden H. The local GLP-1 system in the olfactory bulb is required for odor-evoked cephalic phase of insulin release in mice. *Mol Metab*. 2023;73:101738.
55. Ferguson JN, Young LJ, Hearn EF, Matzuk MM, Insel TR, Winslow JT. Social amnesia in mice lacking the oxytocin gene. *Nat Genet*. 2000;25(3):284-288.
56. Ferris CF, Yee JR, Kenkel WM, et al. Distinct BOLD activation profiles following central and peripheral oxytocin administration in awake rats. *Front Behav Neurosci*. 2015;9:245.
57. Oettl LL, Ravi N, Schneider M, et al. Oxytocin enhances social recognition by modulating cortical control of early olfactory processing. *Neuron*. 2016;90(3):609-621.
58. Agrawal R, Reno CM, Sharma S, Christensen C, Huang Y, Fisher SJ. Insulin action in the brain regulates both central and peripheral functions. *Am J Physiol Endocrinol Metab*. 2021;321(1):E156-E163.
59. Briggs DI, Andrews ZB. Metabolic status regulates ghrelin function on energy homeostasis. *Neuroendocrinology*. 2011;93(1):48-57.
60. Coppari R, Ichinose M, Lee CE, et al. The hypothalamic arcuate nucleus: a key site for mediating leptin's effects on glucose homeostasis and locomotor activity. *Cell Metab*. 2005;1(1):63-72.
61. Palouzier-Paulignan B, Lacroix MC, Aime P, et al. Olfaction under metabolic influences. *Chem Senses*. 2012;37(9):769-797.
62. Fadool DA, Kolling LJ. *Role of Olfaction for Eating Behavior*. Elsevier, Academic Press; 2020.
63. Simpson KA, Martin NM, Bloom SR. Hypothalamic regulation of appetite. *Expert Rev Endocrinol Metab*. 2008;3(5):577-592.
64. Stuber GD, Wise RA. Lateral hypothalamic circuits for feeding and reward. *Nat Neurosci*. 2016;19(2):198-205.
65. Yang DJ, Hong J, Kim KW. Hypothalamic primary cilium: a hub for metabolic homeostasis. *Exp Mol Med*. 2021;53(7):1109-1115.
66. Reed F, Lockie SH, Reichenbach A, Foldi C, Andrews Z. Appetite to learn: an allostatic role for AgRP neurons in the maintenance of energy balance. *Curr Opin Endocrinol Diabetes Obes*. 2022;24:100337.
67. Nambu T, Sakurai T, Mizukami K, Hosoya Y, Yanagisawa M, Goto K. Distribution of orexin neurons in the adult rat brain. *Brain Res*. 1999;827(1-2):243-260.
68. Broadwell RD, Jacobowitz DM. Olfactory relationships of the telencephalon and diencephalon in the rabbit. III. The ipsilateral centrifugal fibers to the olfactory bulbar and retrobulbar formations. *J Comp Neurol*. 1976;170(3):321-345.
69. de Olmos J, Hardy H, Heimer L. The afferent connections of the main and the accessory olfactory bulb formations in the rat: an experimental HRP-study. *J Comp Neurol*. 1978;181(2):213-244.
70. Schneider NY, Chauby S, Epstein AL, et al. Centrifugal projections to the main olfactory bulb revealed by transsynaptic retrograde tracing in mice. *J Comp Neurol*. 2020;528(11):1805-1819.
71. Shipley MT, Adamek GD. The connections of the mouse olfactory bulb: a study using orthograde and retrograde transport of wheat germ agglutinin conjugated to horseradish peroxidase. *Brain Res Bull*. 1984;12(6):669-688.
72. Qi M, Fadool DA, Storace DA. An anatomically distinct subpopulation of orexin neurons project from the lateral hypothalamus to the olfactory bulb. *J Comp Neurol*. 2023;531(15):1510-1524.
73. Edwards CM, Abusnana S, Sunter D, Murphy KG, Ghatei MA, Bloom SR. The effect of the orexins on food intake: comparison with

- neuropeptide Y, melanin-concentrating hormone and galanin. *J Endocrinol.* 1999;160(3):R7-R12.
74. Bernardis LL, Bellinger LL. The lateral hypothalamic area revisited: ingestive behavior. *Neurosci Biobehav Rev.* 1996;20(2):189-287.
  75. Tiret P, Chaigneau E, Lecoq J, Charpak S. Two-photon imaging of capillary blood flow in olfactory bulb glomeruli. *Methods Mol Biol.* 2009;48:981-991.
  76. Ueno M, Akiguchi I, Naiki H, et al. The persistence of high uptake of serum albumin in the olfactory bulbs of mice throughout their adult lives. *Arch Gerontol Geriatr.* 1991;13(2):201-209.
  77. Faour M, Magnan C, Gurden H, Martin C. Olfaction in the context of obesity and diabetes: insights from animal models to humans. *Neuropharmacology.* 2022;206:108923.
  78. Fadool DA, Tucker K, Phillips JJ, Simmen JA. Brain insulin receptor causes activity-dependent current suppression in the olfactory bulb through multiple phosphorylation of Kv1.3. *J Neurophysiol.* 2000;83(4):2332-2348.
  79. Fadool DA, Tucker K, Pedarzani P. Mitral cells of the olfactory bulb perform metabolic sensing and are disrupted by obesity at the level of the Kv1.3 ion channel. *PLoS One.* 2011;6(9):e24921.
  80. Apelbaum AF, Perrut A, Chaput M. Orexin a effects on the olfactory bulb spontaneous activity and odor responsiveness in freely breathing rats. *Regul Pept.* 2005;129(1-3):49-61.
  81. Hardy AB, Aioun J, Baly C, et al. Orexin a modulates mitral cell activity in the rat olfactory bulb: patch-clamp study on slices and immunocytochemical localization of orexin receptors. *Endocrinology.* 2005;146(9):4042-4053.
  82. Lacroix MC, Badonnel K, Meunier N, et al. Expression of insulin system in the olfactory epithelium: first approaches to its role and regulation. *J Neuroendocrinol.* 2008;20(10):1176-1190.
  83. Tucker K, Cavallin MA, Jean-Baptiste P, et al. The olfactory bulb: a metabolic sensor of brain insulin and glucose concentrations via a voltage-gated potassium channel. *Results Probl Cell Differ.* 2010;52:147-157.
  84. Tucker K, Cho S, Thiebaud N, Henderson MX, Fadool DA. Glucose sensitivity of mouse olfactory bulb neurons is conveyed by a voltage-gated potassium channel. *J Physiol.* 2013;591(10):2541-2561.
  85. Aime P, Palouzier-Paulignan B, Salem R, et al. Modulation of olfactory sensitivity and glucose-sensing by the feeding state in obese Zucker rats. *Front Behav Neurosci.* 2014;8:326.
  86. Al Koborssy D, Palouzier-Paulignan B, Salem R, Thevenet M, Romestaing C, Julliard AK. Cellular and molecular cues of glucose sensing in the rat olfactory bulb. *Front Neurosci.* 2014;8:333.
  87. Kovach CP, Al Koborssy D, Huang Z, Chelette BM, Fadool JM, Fadool DA. Mitochondrial ultrastructure and glucose signaling pathways attributed to the Kv1.3 ion channel. *Front Physiol.* 2016;7:178.
  88. Lecoq J, Tiret P, Najac M, Shepherd GM, Greer CA, Charpak S. Odor-evoked oxygen consumption by action potential and synaptic transmission in the olfactory bulb. *J Neurosci.* 2009;29(5):1424-1433.
  89. Magnan C, Levin BE, Luquet S. Brain lipid sensing and the neural control of energy balance. *Mol Cell Endocrinol.* 2015;418:3-8.
  90. Obici S, Rossetti L. Minireview: nutrient sensing and the regulation of insulin action and energy balance. *Endocrinology.* 2003;144(12):5172-5178.
  91. Cruciani-Guglielmacci C, Hervale A, Douared L, et al. Beta oxidation in the brain is required for the effects of non-esterified fatty acids on glucose-induced insulin secretion in rats. *Diabetologia.* 2004;47(11):2032-2038.
  92. Jovanovic P, Riera CE. Olfactory system and energy metabolism: a two-way street. *Trends Endocrinol Metab.* 2022;33(4):281-291.
  93. Zigman JM, Bouret SG, Andrews ZB. Obesity impairs the action of the neuroendocrine ghrelin system. *Trends Endocrinol Metab.* 2016;27(1):54-63.
  94. Herz RS, Van Reen E, Barker DH, Hilditch CJ, Bartz AL, Carskadon MA. The influence of circadian timing on olfactory sensitivity. *Chem Senses.* 2017;43(1):45-51.
  95. Noseda ACD, Rodrigues LS, Targa ADS, et al. MT(2) melatonin receptors expressed in the olfactory bulb modulate depressive-like behavior and olfaction in the 6-OHDA model of Parkinson's disease. *Eur J Pharmacol.* 2021;891:173722.
  96. Aime P, Duchamp-Viret P, Chaput MA, Savigner A, Mahfouz M, Julliard AK. Fasting increases and satiation decreases olfactory detection for a neutral odor in rats. *Behav Brain Res.* 2007;179(2):258-264.
  97. Cameron JD, Goldfield GS, Doucet E. Fasting for 24 h improves nasal chemosensory performance and food palatability in a related manner. *Appetite.* 2012;58(3):978-981.
  98. Hanci D, Altun H. Hunger state affects both olfactory abilities and gustatory sensitivity. *Eur Arch Otorhinolaryngol.* 2016;273(7):1637-1641.
  99. Tucker KR, Godbey SJ, Thiebaud N, Fadool DA. Olfactory ability and object memory in three mouse models of varying body weight, metabolic hormones, and adiposity. *Physiol Behav.* 2012;107(3):424-432.
  100. Rolls ET, Rolls JH. Olfactory sensory-specific satiety in humans. *Physiol Behav.* 1997;61(3):461-473.
  101. Ida T, Nakahara K, Katayama T, Murakami N, Nakazato M. Effect of lateral cerebroventricular injection of the appetite-stimulating neuropeptide, orexin and neuropeptide Y, on the various behavioral activities of rats. *Brain Res.* 1999;821(2):526-529.
  102. Lubkin M, Stricker-Krongrad A. Independent feeding and metabolic actions of orexins in mice. *Biochem Biophys Res Commun.* 1998;253(2):241-245.
  103. Chen CT, Hwang LL, Chang JK, Dun NJ. Pressor effects of orexins injected intracisternally and to rostral ventrolateral medulla of anesthetized rats. *Am J Physiol Regul Integr Comp Physiol.* 2000;278:R692-R697.
  104. Pu S, Jain MR, Kalra PS, Kalra SP. Orexins, a novel family of hypothalamic neuropeptides, modulate pituitary luteinizing hormone secretion in an ovarian steroid-dependent manner. *Regul Pept.* 1998;78(1-3):133-136.
  105. Samson WK, Gosnell B, Chang JK, Resch ZT, Murphy TC. Cardiovascular regulatory actions of the hypocretins in brain. *Brain Res.* 1999;831(1-2):248-253.
  106. Shirasaka T, Nakazato M, Matsukura S, Takasaki M, Kannan H. Sympathetic and cardiovascular actions of orexins in conscious rats. *Am J Physiol Regul Integr Comp Physiol.* 1999;277:R1780-R1785.
  107. Piantadosi PT, Holmes A, Roberts BM, Bailey AM. Orexin receptor activity in the basal forebrain alters performance on an olfactory discrimination task. *Brain Res.* 2015;1594:215-222.
  108. Cai XJ, Widdowson PS, Harrold J, et al. Hypothalamic orexin expression: modulation by blood glucose and feeding. *Diabetes.* 1999;48(11):2132-2137.
  109. Yamanaka A, Beuckmann CT, Willie JT, et al. Hypothalamic orexin neurons regulate arousal according to energy balance in mice. *Neuron.* 2003;38(5):701-713.
  110. Abizaid A, Horvath TL. Ghrelin and the central regulation of feeding and energy balance. *Indian J Endocrinol Metab.* 2012;16(Suppl 3):S617-S626.
  111. Mani BK, Osborne-Lawrence S, Mequinion M, et al. The role of ghrelin-responsive mediobasal hypothalamic neurons in mediating feeding responses to fasting. *Mol Metab.* 2017;6(8):882-896.
  112. Stark R, Dempsey H, Kleeman E, et al. Hunger signalling in the olfactory bulb primes exploration, food-seeking and peripheral metabolism. *bioRxiv.* 2023.01.26.525804; doi:10.1101/2023.01.26.525804
  113. Mani BK, Walker AK, Lopez Soto EJ, et al. Neuroanatomical characterization of a growth hormone secretagogue receptor-green

- fluorescent protein reporter mouse. *J Comp Neurol.* 2014;522(16):3644-3666.
114. Martin B, Maudsley S, White CM, Egan JM. Hormones in the naso-opharynx: endocrine modulation of taste and smell. *Trends Endocrinol Metab.* 2009;20(4):163-170.
115. Ratcliff M, Rees D, McGrady S, et al. Calorie restriction activates new adult born olfactory-bulb neurones in a ghrelin-dependent manner but acyl-ghrelin does not enhance subventricular zone neurogenesis. *J Neuroendocrinol.* 2019;31(7):e12755.
116. Diano S, Farr SA, Benoit SC, et al. Ghrelin controls hippocampal spine synapse density and memory performance. *Nat Neurosci.* 2006;9(3):381-388.
117. Rhea EM, Salameh TS, Gray S, Niu J, Banks WA, Tong J. Ghrelin transport across the blood-brain barrier can occur independently of the growth hormone secretagogue receptor. *Mol Metab.* 2018;18:88-96.
118. Banks WA, Burney BO, Robinson SM. Effects of triglycerides, obesity, and starvation on ghrelin transport across the blood-brain barrier. *Peptides.* 2008;29(11):2061-2065.
119. Shankar K, Metzger NP, Singh O, et al. LEAP2 deletion in mice enhances ghrelin's actions as an orexigen and growth hormone secretagogue. *Mol Metab.* 2021;53:101327.
120. Spencer SJ, Xu L, Clarke MA, et al. Ghrelin regulates the hypothalamic-pituitary-adrenal axis and restricts anxiety after acute stress. *Biol Psychiatry.* 2012;72(6):457-465.
121. Lockie SH, Dinan T, Lawrence AJ, Spencer SJ, Andrews ZB. Diet-induced obesity causes ghrelin resistance in reward processing tasks. *Psychoneuroendocrinology.* 2015;62:114-120.
122. Zhao Y, Bhutani S, Kahnt T. Appetite-regulating hormones modulate odor perception and odor-evoked activity in hypothalamus and olfactory cortices. *Chem Senses.* 2023;48:bjad039. <https://doi.org/10.1093/chemse/bjad039>
123. Tataranni PA, Larson DE, Snitker S, Young JB, Flatt JP, Ravussin E. Effects of glucocorticoids on energy metabolism and food intake in humans. *Am J Physiol.* 1996;271(2 Pt 1):E317-E325.
124. Chrousos GP. The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. *N Engl J Med.* 1995;332(20):1351-1362.
125. Mangelsdorf DJ, Thummel C, Beato M, et al. The nuclear receptor superfamily: the second decade. *Cell.* 1995;83(6):835-839.
126. Bauer A, Tronche F, Wessely O, et al. The glucocorticoid receptor is required for stress erythropoiesis. *Genes Dev.* 1999;13(22):2996-3002.
127. Opherk C, Tronche F, Kellendonk C, et al. Inactivation of the glucocorticoid receptor in hepatocytes leads to fasting hypoglycemia and ameliorates hyperglycemia in streptozotocin-induced diabetes mellitus. *Mol Endocrinol.* 2004;18(6):1346-1353.
128. Boyle MP, Brewer JA, Funatsu M, et al. Acquired deficit of forebrain glucocorticoid receptor produces depression-like changes in adrenal axis regulation and behavior. *Proc Natl Acad Sci U S A.* 2005;102(2):473-478.
129. Boyle MP, Kolber BJ, Vogt SK, Wozniak DF, Muglia LJ. Forebrain glucocorticoid receptors modulate anxiety-associated locomotor activation and adrenal responsiveness. *J Neurosci.* 2006;26(7):1971-1978.
130. Morimoto M, Morita N, Ozawa H, Yokoyama K, Kawata M. Distribution of glucocorticoid receptor immunoreactivity and mRNA in the rat brain: an immunohistochemical and in situ hybridization study. *Neurosci Res.* 1996;26(3):235-269.
131. Bombail V. Perception and emotions: on the relationships between stress and olfaction. *Appl Anim Behav Sci.* 2019;212:98-108.
132. Hoenen M, Wolf OT, Pause BM. The impact of stress on odor perception. *Perception.* 2017;46(3-4):366-376.
133. Pacharra M, Schaper M, Kleinbeck S, Blaszkewicz M, Wolf OT, van Thriel C. Stress lowers the detection threshold for foul-smelling 2-mercaptoethanol. *Stress.* 2016;19(1):18-27.
134. Pause BM, Sojka B, Krauel K, Fehm-Wolfsdorf G, Ferstl R. Olfactory information processing during the course of the menstrual cycle. *Biol Psychol.* 1996;44(1):31-54.
135. Fleming AS, Steiner M, Carter C. Cortisol, hedonics, and maternal responsiveness in human mothers. *Horm Behav.* 1997;32(2):85-98.
136. Siopi E, Denizet M, Gabellec MM, et al. Anxiety- and depression-like states lead to pronounced olfactory deficits and impaired adult neurogenesis in mice. *J Neurosci.* 2016;36(2):518-531.
137. Henkin RI, Bartter FC. Studies on olfactory thresholds in normal man and in patients with adrenal cortical insufficiency: the role of adrenal cortical steroids and of serum sodium concentration. *J Clin Invest.* 1966;45(10):1631-1639.
138. Sakellaris PC. Olfactory thresholds in normal and adrenalectomized rats. *Physiol Behav.* 1972;9(4):495-500.
139. Doty RL, Risser JM, Brosvic GM. Influence of adrenalectomy on the odor detection performance of rats. *Physiol Behav.* 1991;49(6):1273-1277.
140. Garcia I, Bhullar PK, Tepe B, et al. Local corticotropin releasing hormone (CRH) signals to its receptor CRHR1 during postnatal development of the mouse olfactory bulb. *Brain Struct Funct.* 2016;221(1):1-20.
141. Kawai F, Kurahashi T, Kaneko A. Adrenaline enhances odorant contrast by modulating signal encoding in olfactory receptor cells. *Nat Neurosci.* 1999;2(2):133-138.
142. Fowler J, Rotenberg BW, Sowerby LJ. The subtle nuances of intra-nasal corticosteroids. *J Otolaryngol Head Neck Surg.* 2021;50(1):18.
143. Daley-Yates PT, Larenas-Linnemann D, Bhargave C, Verma M. Intra-nasal corticosteroids: topical potency, systemic activity and therapeutic index. *J Asthma Allergy.* 2021;14:1093-1104.
144. Li P, Wang N, Kai L, Si J, Wang Z. Chronic intranasal corticosteroid treatment induces degeneration of olfactory sensory neurons in normal and allergic rhinitis mice. *Int Forum Allergy Rhinol.* 2023;13(10):1889-1905.
145. Lee EJ, Saraiva LR, Hanchate NK, et al. Odor blocking of stress hormone responses. *Sci Rep.* 2022;12(1):8773.
146. Takahashi LK. Olfactory systems and neural circuits that modulate predator odor fear. *Front Behav Neurosci.* 2014;8:72. doi:[10.3389/fnbeh.2014.00072](https://doi.org/10.3389/fnbeh.2014.00072)
147. Apfelbach R, Blanchard CD, Blanchard RJ, Hayes RA, McGregor IS. The effects of predator odors in mammalian prey species: a review of field and laboratory studies. *Neurosci Biobehav Rev.* 2005;29(8):1123-1144.
148. Henquin JC. Regulation of insulin secretion: a matter of phase control and amplitude modulation. *Diabetologia.* 2009;52(5):739-751.
149. Saltiel AR, Kahn CR. Insulin signalling and the regulation of glucose and lipid metabolism. *Nature.* 2001;414(6865):799-806.
150. Air EL, Benoit SC, Blake Smith KA, Clegg DJ, Woods SC. Acute third ventricular administration of insulin decreases food intake in two paradigms. *Pharmacol Biochem Behav.* 2002;72(1-2):423-429.
151. Bruning JC, Gautam D, Burks DJ, et al. Role of brain insulin receptor in control of body weight and reproduction. *Science.* 2000;289(5487):2122-2125.
152. Grattan DR, Andrews ZB. Insulin as a neuroendocrine hormone. *J Neuroendocrinol.* 2021;33(4):e12966.
153. Marks DR, Tucker K, Cavallin MA, Mast TG, Fadool DA. Awake intranasal insulin delivery modifies protein complexes and alters memory, anxiety, and olfactory behaviors. *J Neurosci.* 2009;29(20):6734-6751.
154. Zhao W, Chen H, Xu H, et al. Brain insulin receptors and spatial memory: correlated changes in gene expression, tyrosine phosphorylation, and signaling molecules in the hippocampus of water maze trained rats. *J Biol Chem.* 1999;274(49):34893-34902.
155. Unger JW, Livingston JN, Moss AM. Insulin receptors in the central nervous system: localization, signalling mechanisms and functional aspects. *Prog Neurobiol.* 1991;36(5):343-362.

156. Rhea EM, Salameh TS, Logsdon AF, Hanson AJ, Erickson MA, Banks WA. Blood-brain barriers in obesity. *AAPS J.* 2017;19(4): 921-930.
157. Banks WA, Kastin AJ, Pan W. Uptake and degradation of blood-borne insulin by the olfactory bulb. *Peptides.* 1999;20(3):373-378.
158. Baskin DG, Porte D, Guest K, Dorsa DM. Regional concentrations of insulin in the rat brain. *Endocrinology.* 1983;112(3):898-903.
159. Hill JM, Lesniak MA, Pert CB, Roth J. Autoradiographic localization of insulin receptors in rat brain: prominence in olfactory and limbic areas. *Neuroscience.* 1986;17(4):1127-1138.
160. Gupta G, Azam M, Baquer NZ. Modulation of rat brain insulin receptor kinase activity in diabetes. *Neurochem Int.* 1992;20(4):487-492.
161. Marks JL, Eastman CJ. Effect of starvation on insulin receptors in rat brain. *Neuroscience.* 1989;30(2):551-556.
162. Edwin Thanarajah S, Hoffstall V, Rigoux L, Hanssen R, Bruning JC, Tittgemeyer M. The role of insulin sensitivity and intranasally applied insulin on olfactory perception. *Sci Rep.* 2019;9(1):7222.
163. Keller LA, Merkel O, Popp A. Intranasal drug delivery: opportunities and toxicologic challenges during drug development. *Drug Deliv Transl Res.* 2022;12(4):735-757.
164. Prud'homme MJ, Lacroix MC, Badonnel K, et al. Nutritional status modulates behavioural and olfactory bulb Fos responses to isoamyl acetate or food odour in rats: roles of orexins and leptin. *Neuroscience.* 2009;162(4):1287-1298.
165. Baly C, Aioun J, Badonnel K, et al. Leptin and its receptors are present in the rat olfactory mucosa and modulated by the nutritional status. *Brain Res.* 2007;1129(1):130-141.
166. Sun C, Tang K, Wu J, et al. Leptin modulates olfactory discrimination and neural activity in the olfactory bulb. *Acta Physiol (Oxf).* 2019; 227(2):e13319.
167. Getchell TV, Kwong K, Saunders CP, Stromberg AJ, Getchell ML. Leptin regulates olfactory-mediated behavior in ob/ob mice. *Physiol Behav.* 2006;87(5):848-856.
168. Chelminski Y, Magnan C, Luquet SH, et al. Odor-induced neuronal rhythms in the olfactory bulb are profoundly modified in ob/ob obese mice. *Front Physiol.* 2017;8:2.
169. Seino Y, Fukushima M, Yabe D. GIP and GLP-1, the two incretin hormones: similarities and differences. *J Diabetes Investig.* 2010; 1(1-2):8-23.
170. Thiebaud N, Llewellyn-Smith IJ, Gribble F, Reimann F, Trapp S, Fadool DA. The incretin hormone glucagon-like peptide 1 increases mitral cell excitability by decreasing conductance of a voltage-dependent potassium channel. *J Physiol.* 2016;594(10):2607-2628.
171. Moran TH, Robinson PH, Goldrich MS, McHugh PR. Two brain cholecystokinin receptors: implications for behavioral actions. *Brain Res.* 1986;362(1):175-179.
172. Mercer LD, Le VQ, Nunan J, Jones NM, Beart PM. Direct visualization of cholecystokinin subtype2 receptors in rat central nervous system using anti-peptide antibodies. *Neurosci Lett.* 2000;293(3):167-170.
173. Mercer LD, Beart PM. Histochemistry in rat brain and spinal cord with an antibody directed at the cholecystokinin A receptor. *Neurosci Lett.* 1997;225(2):97-100.
174. Mercer LD, Beart PM. Immunolocalization of CCK1R in rat brain using a new anti-peptide antibody. *Neurosci Lett.* 2004;359(1-2): 109-113.
175. Jovanovic P, Pool AH, Morones N, et al. A sex-specific thermogenic neurocircuit induced by predator smell recruiting cholecystokinin neurons in the dorsomedial hypothalamus. *Nat Commun.* 2023; 14(1):4937.
176. Vaccari C, Lolait SJ, Ostrowski NL. Comparative distribution of vasopressin V1b and oxytocin receptor messenger ribonucleic acids in brain. *Endocrinology.* 1998;139(12):5015-5033.
177. Mitre M, Marlin BJ, Schiavo JK, et al. A distributed network for social cognition enriched for oxytocin receptors. *J Neurosci.* 2016; 36(8):2517-2535.
178. Liu CM, Spaulding MO, Rea JJ, Noble EE, Kanoski SE. Oxytocin and food intake control: neural, behavioral, and signaling mechanisms. *Int J Mol Sci.* 2021;22(19):10859. doi:[10.3390/ijms221910859](https://doi.org/10.3390/ijms221910859)
179. Spetter MS, Feld GB, Thienel M, Preissl H, Hege MA, Hallschmid M. Oxytocin curbs calorie intake via food-specific increases in the activity of brain areas that process reward and establish cognitive control. *Sci Rep.* 2018;8(1):2736.
180. Sun C, Yin Z, Li BZ, et al. Oxytocin modulates neural processing of mitral/tufted cells in the olfactory bulb. *Acta Physiol (Oxf).* 2021; 231(4):e13626.
181. Scherer PE, Williams S, Fogliano M, Baldini G, Lodish HF. A novel serum protein similar to C1q, produced exclusively in adipocytes. *J Biol Chem.* 1995;270(45):26746-26749.
182. Loch D, Heidel C, Breer H, Strotmann J. Adiponectin enhances the responsiveness of the olfactory system. *PLoS One.* 2013;8(10): e75716.
183. Clain J, Couret D, Planesse C, et al. Distribution of adiponectin receptors in the brain of adult mouse: effect of a single dose of the adiponectin receptor agonist, AdipoRON, on ischemic stroke. *Brain Sci.* 2022;12(5):680. doi:[10.3390/brainsci12050680](https://doi.org/10.3390/brainsci12050680)
184. Miranda-Martinez A, Mercado-Gomez OF, Arriaga-Avila V, Guevara-Guzman R. Distribution of adiponectin receptors 1 and 2 in the rat olfactory bulb and the effect of adiponectin injection on insulin receptor expression. *Int J Endocrinol.* 2017;2017:4892609.
185. Guzman-Ruiz MA, Herrera-Gonzalez A, Jimenez A, et al. Protective effects of intracerebroventricular adiponectin against olfactory impairments in an amyloid beta(1-42) rat model. *BMC Neurosci.* 2021;22(1):14.
186. Pfabigan DM, Vezzani C, Thorsby PM, Sailer U. Sex difference in human olfactory sensitivity is associated with plasma adiponectin. *Horm Behav.* 2022;145:105235.
187. Tang N, Zhang X, Chen D, Li Z. The controversial role of adiponectin in appetite regulation of animals. *Nutrients.* 2021;13(10):3387. doi: [10.3390/nu13103387](https://doi.org/10.3390/nu13103387)
188. Cabanac M, Duclaux R. Olfactory-gustatory alliesthesia and food intake in humans. *J Physiol Paris.* 1973;66(2):113-135.
189. Yeomans MR. Olfactory influences on appetite and satiety in humans. *Physiol Behav.* 2006;89(1):10-14.
190. Cabanac M, Fantino M. Origin of olfacto-gustatory alliesthesia: intestinal sensitivity to carbohydrate concentration? *Physiol Behav.* 1977;18(6):1039-1045.
191. Zoon HF, de Graaf C, Boesveldt S. Food odours direct specific appetite. *Foods.* 2016;5:1.
192. Herz RS. The role of odor-evoked memory in psychological and physiological health. *Brain Sci.* 2016;6(3):22. doi:[10.3390/brainsci6030022](https://doi.org/10.3390/brainsci6030022)
193. Mouly AM, Sullivan R. Memory and plasticity in the olfactory system: from infancy to adulthood. In: Menini A, ed. *The Neurobiology of Olfaction.* CRC Press/Taylor & Francis; 2010.
194. Fine LG, Riera CE. Sense of smell as the central driver of Pavlovian appetitive behavior in mammals. *Front Physiol.* 2019;10:1151.
195. Boswell RG, Kober H. Food cue reactivity and craving predict eating and weight gain: a meta-analytic review. *Obes Rev.* 2016;17(2):159-177.
196. Feldman M, Richardson CT. Role of thought, sight, smell, and taste of food in the cephalic phase of gastric-acid secretion in humans. *Gastroenterology.* 1986;90(2):428-433.
197. Vogt K, Zimmerman DM, Schlüting M, et al. Internal state configures olfactory behavior and early sensory processing in Drosophila larvae. *Sci Adv.* 2021;7(1):eabd6900. doi:[10.1126/sciadv.abd6900](https://doi.org/10.1126/sciadv.abd6900)
198. Apelbaum AF, Chaput MA. Rats habituated to chronic feeding restriction show a smaller increase in olfactory bulb reactivity compared to newly fasted rats. *Chem Senses.* 2003;28(5):389-395.
199. Murata K, Kanno M, Ieki N, Mori K, Yamaguchi M. Mapping of learned odor-induced motivated behaviors in the mouse olfactory tubercle. *J Neurosci.* 2015;35(29):10581-10599.

200. Ramaekers MG, Boesveldt S, Gort G, Lakemond CMM, van Boekel MAJS, Luning PA. Sensory-specific appetite is affected by actively smelled food odors and remains stable over time in normal-weight women. *J Nutr.* 2014;144(8):1314-1319.
201. Uchida N, Poo C, Haddad R. Coding and transformations in the olfactory system. *Annu Rev Neurosci.* 2014;37:363-385.
202. Li Q, Liberles SD. Aversion and attraction through olfaction. *Curr Biol.* 2015;25(3):R120-R129.
203. Morton GJ, Meek TH, Schwartz MW. Neurobiology of food intake in health and disease. *Nat Rev Neurosci.* 2014;15(6):367-378.
204. McCrickerd K, Forde CG. Sensory influences on food intake control: moving beyond palatability. *Obes Rev.* 2016;17(1):18-29.
205. Lushchak OV, Carlsson MA, Nassel DR. Food odors trigger an endocrine response that affects food ingestion and metabolism. *Cell Mol Life Sci.* 2015;72(16):3143-3155.
206. Peris-Sampedro F, Stoltenborg I, Le May MV, Sole-Navais P, Adan RAH, Dickson SL. The orexigenic force of olfactory palatable food cues in rats. *Nutrients.* 2021;13(9):3101. doi:[10.3390/nu13093101](https://doi.org/10.3390/nu13093101)
207. Sullivan RM, Wilson DA, Ravel N, Mouly AM. Olfactory memory networks: from emotional learning to social behaviors. *Front Behav Neurosci.* 2015;9:36.
208. Rolls ET. Taste, olfactory, and food texture processing in the brain, and the control of food intake. *Physiol Behav.* 2005;85(1):45-56.
209. Velluzzi F, Deledda A, Onida M, Loviselli A, Crnjac R, Sollai G. Relationship between olfactory function and BMI in normal weight healthy subjects and patients with overweight or obesity. *Nutrients.* 2022;14(6):1262. doi:[10.3390/nu1406126](https://doi.org/10.3390/nu1406126)
210. Krashes MJ, Shah BP, Koda S, Lowell BB. Rapid versus delayed stimulation of feeding by the endogenously released AgRP neuron mediators GABA, NPY, and AgRP. *Cell Metab.* 2013;18(4):588-595.
211. Luquet S, Perez FA, Hnasko TS, Palmiter RD. NPY/AgRP neurons are essential for feeding in adult mice but can be ablated in neonates. *Science.* 2005;310(5748):683-685.
212. Zhan C, Zhou J, Feng Q, et al. Acute and long-term suppression of feeding behavior by POMC neurons in the brainstem and hypothalamus, respectively. *J Neurosci.* 2013;33(8):3624-3632.
213. Chen Y, Lin YC, Kuo TW, Knight ZA. Sensory detection of food rapidly modulates arcuate feeding circuits. *Cell.* 2015;160(5):829-841.
214. Horio N, Liberles SD. Hunger enhances food-odour attraction through a neuropeptide Y spotlight. *Nature.* 2021;592(7853):262-266.
215. Kuang D, Hanchate NK, Lee CY, et al. Olfactory and neuropeptide inputs to appetite neurons in the arcuate nucleus. *bioRxiv.* 2023;1:2023.02.28.530282. doi:[10.1101/2023.02.28.530282](https://doi.org/10.1101/2023.02.28.530282).
216. Zang Y, Han P, Burghardt S, Knaapila A, Schriever V, Hummel T. Influence of olfactory dysfunction on the perception of food. *Eur Arch Otorhinolaryngol.* 2019;276(10):2811-2817.
217. Aschenbrenner K, Hummel C, Teszmer K, et al. The influence of olfactory loss on dietary behaviors. *Laryngoscope.* 2008;118(1):135-144.
218. Croy I, Nordin S, Hummel T. Olfactory disorders and quality of life—an updated review. *Chem Senses.* 2014;39(3):185-194.
219. Stevenson RJ. An initial evaluation of the functions of human olfaction. *Chem Senses.* 2010;35(1):3-20.
220. Fairburn CG, Doll HA, Welch SL, Hay PJ, Davies BA, O'Connor ME. Risk factors for binge eating disorder: a community-based, case-control study. *Arch Gen Psychiatry.* 1998;55(5):425-432.
221. Keller A, Malaspina D. Hidden consequences of olfactory dysfunction: a patient report series. *BMC Ear Nose Throat Disord.* 2013;13(1):8.
222. Van Gaal LF, Mertens IL, De Block CE. Mechanisms linking obesity with cardiovascular disease. *Nature.* 2006;444(7212):875-880.
223. Parma V, Ohla K, Veldhuizen MG, et al. More than smell-COVID-19 is associated with severe impairment of smell, taste, and chemesthesia. *Chem Senses.* 2020;45(7):609-622.
224. Whitcroft KL, Altundag A, Balungwe P, et al. Position paper on olfactory dysfunction: 2023. *Rhinology.* 2023. doi:[10.4193/Rhin22.483](https://doi.org/10.4193/Rhin22.483)
225. Morris A. OBESITY olfactory senses linked to metabolism. *Nat Rev Endocrinol.* 2017;13(9):494.
226. Peng M, Coutts D, Wang T, Cakmak YO. Systematic review of olfactory shifts related to obesity. *Obes Rev.* 2019;20(2):325-338.
227. Vega MV, Rivas AMO. Association of olfactory sensitivity with energy intake: role in development of obesity. *Nutr Hosp.* 2015;32(6):2385-2389.
228. Chelette BM, Loeven AM, Gatlin DN, et al. Consumption of dietary fat causes loss of olfactory sensory neurons and associated circuitry that is not mitigated by voluntary exercise in mice. *J Physiol.* 2022;600(6):1473-1495.
229. Thiebaud N, Johnson MC, Butler JL, et al. Hyperlipidemic diet causes loss of olfactory sensory neurons, reduces olfactory discrimination, and disrupts odor-reversal learning. *J Neurosci.* 2014;34(20):6970-6984.
230. Lietzau G, Nyström T, Wang Z, Darsalia V, Patrone C. Western diet accelerates the impairment of odor-related learning and olfactory memory in the mouse. *ACS Chem Neurosci.* 2020;11(21):3590-3602.
231. Gouveri E, Papapanas N. Olfactory dysfunction: a complication of diabetes or a factor that complicates glucose metabolism? A narrative review. *J Clin Med.* 2021;10(23):5637. doi:[10.3390/jcm10235637](https://doi.org/10.3390/jcm10235637)
232. Li J, Li M, Zhang J, Song Y. Associations between taste and smell alterations and diabetes-related comorbidities among US adults: the National Health and nutrition examination surveys 2011-2014. *Acta Diabetol.* 2022;59(3):429-433.
233. Jarick I, Vogel CIG, Scherag S, et al. Novel common copy number variation for early onset extreme obesity on chromosome 11q11 identified by a genome-wide analysis. *Hum Mol Genet.* 2011;20(4):840-852.
234. Karstensen HG, Tommerup N. Isolated and syndromic forms of congenital anosmia. *Clin Genet.* 2012;81(3):210-215.
235. Jenkins PM, McEwen DP, Martens JR. Olfactory cilia: linking sensory cilia function and human disease. *Chem Senses.* 2009;34(5):451-464.
236. Kulaga HM, Leitch CC, Eichers ER, et al. Loss of BBS proteins causes anosmia in humans and defects in olfactory cilia structure and function in the mouse. *Nat Genet.* 2004;36(9):994-998.
237. Fadool DA, Tucker K, Perkins R, et al. Kv1.3 channel gene-targeted deletion produces “super-smeller mice” with altered glomeruli, interacting scaffolding proteins, and biophysics. *Neuron.* 2004;41(3):389-404.
238. Schwartz AB, Kapur A, Huang Z, et al. Olfactory bulb-targeted quantum dot (QD) bioconjugate and Kv1.3 blocking peptide improve metabolic health in obese male mice. *J Neurochem.* 2021;157(6):1876-1896.
239. Tucker K, Overton JM, Fadool DA. Diet-induced obesity resistance of Kv1.3<sup>-/-</sup> mice is olfactory bulb dependent. *J Neuroendocrinol.* 2012;24(8):1087-1095.
240. Fernandez-Garcia JC, Alcaide J, Santiago-Fernandez C, et al. An increase in visceral fat is associated with a decrease in the taste and olfactory capacity. *PLoS One.* 2017;12(2):e0171204.
241. Lacroix MC, Caillol M, Durieux D, et al. Long-lasting metabolic imbalance related to obesity alters olfactory tissue homeostasis and impairs olfactory-driven behaviors. *Chem Senses.* 2015;40(8):537-556.
242. Stafford LD, Whittle A. Obese individuals have higher preference and sensitivity to odor of chocolate. *Chem Senses.* 2015;40(4):279-284.
243. Han P, Roitzsch C, Horstmann A, Possel M, Hummel T. Increased brain reward responsivity to food-related odors in obesity. *Obesity (Silver Spring).* 2021;29(7):1138-1145.
244. Rolls ET. Taste, olfactory and food texture reward processing in the brain and obesity. *Int J Obes (Lond).* 2011;35(4):550-561.

245. Reichenbach A, Clarke RE, Stark R, et al. Metabolic sensing in AgRP neurons integrates homeostatic state with dopamine signalling in the striatum. *Elife*. 2022;11:e72668. doi:[10.7554/elife.72668](https://doi.org/10.7554/elife.72668)
246. Boutelle KN, Knatz S, Carlson J, Bergmann K, Peterson CB. An open trial targeting food cue reactivity and satiety sensitivity in overweight and obese binge eaters. *Cogn Behav Pract*. 2017;24(3):363-373.
247. Denis RG, Joly-Amado A, Webber E, et al. Palatability can drive feeding independent of AgRP neurons. *Cell Metab*. 2015;22(4):646-657.
248. Kitraki E, Alexis MN, Papalopoulou M, Stylianopoulou F. Glucocorticoid receptor gene expression in the embryonic rat brain. *Neuroendocrinology*. 1996;63(4):305-317.
249. Sousa RJ, Tannery NH, Lafer EM. In situ hybridization mapping of glucocorticoid receptor messenger ribonucleic acid in rat brain. *Mol Endocrinol*. 1989;3(3):481-494.
250. Sui Y, Vermeulen R, Hokfelt T, Horne MK, Stanic D. Female mice lacking cholecystokinin 1 receptors have compromised neurogenesis, and fewer dopaminergic cells in the olfactory bulb. *Front Cell Neurosci*. 2013;7:13. doi:[10.3389/fncel.2013.00013](https://doi.org/10.3389/fncel.2013.00013)
251. Sun X, Liu X, Starr ER, Liu S. CCKergic tufted cells differentially drive two anatomically segregated inhibitory circuits in the mouse olfactory bulb. *J Neurosci*. 2020;40(32):6189-6206.
252. Doyle KL, Horts YJ, Herzog H, Shine J. Neuropeptide Y and peptide YY have distinct roles in adult mouse olfactory neurogenesis. *J Neurosci Res*. 2012;90(6):1126-1135.
253. Stanic D, Brumovsky P, Fetissov S, Shuster S, Herzog H, Hokfelt T. Characterization of neuropeptide Y2 receptor protein expression in the mouse brain. I. Distribution in cell bodies and nerve terminals. *J Comp Neurol*. 2006;499(3):357-390.
254. Adams AC, Domouzoglou EM, Chee MJ, Segal-Lieberman G, Pissios P, Maratos-Flier E. Ablation of the hypothalamic neuropeptide melanin concentrating hormone is associated with behavioral abnormalities that reflect impaired olfactory integration. *Behav Brain Res*. 2011;224(1):195-200.
255. Wolf SS, Moody TW, O'Donohue TL, Zarbin MA, Kuhar MJ. Autoradiographic visualization of rat brain binding sites for bombesin-like peptides. *Eur J Pharmacol*. 1983;87(1):163-164.
256. Roesler R, Schwartsmann G. Gastrin-releasing peptide receptors in the central nervous system: role in brain function and as a drug target. *Front Endocrinol*. 2012;3:159.
257. Roesler R, Kent P, Luft T, Schwartsmann G, Merali Z. Gastrin-releasing peptide receptor signaling in the integration of stress and memory. *Neurobiol Learn Mem*. 2014;112:44-52.
258. Yamada K, Wada E, Wada K. Bombesin-like peptides: studies on food intake and social behaviour with receptor knock-out mice. *Ann Med*. 2000;32(8):519-529.
259. Wada E, Way J, Lebacq-Verheyden AM, Battey JF. Neuromedin B and gastrin-releasing peptide mRNAs are differentially distributed in the rat nervous system. *J Neurosci*. 1990;10(9):2917-2930.
260. Moody TW, Merali Z. Bombesin-like peptides and associated receptors within the brain: distribution and behavioral implications. *Peptides*. 2004;25(3):511-520.
261. Ohki-Hamazaki H. Neuromedin B. *Prog Neurobiol*. 2000;62(3):297-312.
262. Gonzalez N, Moody TW, Igarashi H, Ito T, Jensen RT. Bombesin-related peptides and their receptors: recent advances in their role in physiology and disease states. *Curr Opin Endocrinol Diabetes Obes*. 2008;15(1):58-64.
263. Wada E, Way J, Shapira H, et al. cDNA cloning, characterization, and brain region-specific expression of a neuromedin-B-preferring bombesin receptor. *Neuron*. 1991;6(3):421-430.
264. Usdin TB, Mezey E, Button DC, Brownstein MJ, Bonner TI. Gastric inhibitory polypeptide receptor, a member of the secretin-vasoactive intestinal peptide receptor family, is widely distributed in peripheral organs and the brain. *Endocrinology*. 1993;133(6):2861-2870.
265. Campbell JE. Targeting the GIPR for obesity: to agonize or antagonize? Potential mechanisms. *Mol Metab*. 2021;46:101139.
266. Ding KH, Zhong Q, Xie D, et al. Effects of glucose-dependent insulinotropic peptide on behavior. *Peptides*. 2006;27(11):2750-2755.
267. Adriaenssens AE, Biggs EK, Darwish T, et al. Glucose-dependent Insulinotropic polypeptide receptor-expressing cells in the hypothalamus regulate food intake. *Cell Metab*. 2019;30(5):987-996.
268. Boccia L, Gamakaria S, Coester B, Whiting L, Lutz TA, Le Foll C. Amylin brain circuitry. *Peptides*. 2020;132:170366.
269. Yoo YM, Jung EM, Jeung EB, Jo BR, Joo SS. Amylin protein expression in the rat brain and neuro-2a cells. *Int J Mol Sci*. 2022;23(8):4348. doi:[10.3390/ijms23084348](https://doi.org/10.3390/ijms23084348)
270. Aldras Y, Singh S, Bode K, Bhowmick DC, Jeremic A, O'Halloran DM. An inducible model of human amylin overexpression reveals diverse transcriptional changes. *Neurosci Lett*. 2019;704:212-219.
271. Huang Z, Tatti R, Loeven AM, Landi Conde DR, Fadool DA. Modulation of neural microcircuits that control complex dynamics in olfactory networks. *Front Cell Neurosci*. 2021;15:662184.
272. Merchenthaler I, Lane M, Shughrue P. Distribution of pre-pro-glucagon and glucagon-like peptide-1 receptor messenger RNAs in the rat central nervous system. *J Comp Neurol*. 1999;403(2):261-280.
273. Thiebaud N, Gribble F, Reimann F, Trapp S, Fadool DA. A unique olfactory bulb microcircuit driven by neurons expressing the precursor to glucagon-like peptide 1. *Sci Rep*. 2019;9(1):15542.
274. Vu JP, Larauche M, Flores M, et al. Regulation of appetite, body composition, and metabolic hormones by vasoactive intestinal polypeptide (VIP). *J Mol Neurosci*. 2015;56(2):377-387.
275. Vu JP, Luong L, Sanford D, et al. PACAP and VIP neuropeptides' and receptors' effects on appetite, satiety and metabolism. *Biology*. 2023;12(7):1013.
276. Miller JE, Granados-Fuentes D, Wang T, Marpegan L, Holy TE, Herzog ED. Vasoactive intestinal polypeptide mediates circadian rhythms in mammalian olfactory bulb and olfaction. *J Neurosci*. 2014;34(17):6040-6046.
277. Usdin TB, Bonner TI, Mezey E. Two receptors for vasoactive intestinal polypeptide with similar specificity and complementary distributions. *Endocrinology*. 1994;135(6):2662-2680.
278. Vaudry D, Falluel-Morel A, Bourgault S, et al. Pituitary adenylate cyclase-activating polypeptide and its receptors: 20 years after the discovery. *Pharmacol Rev*. 2009;61(3):283-357.
279. Gall C, Seroogy KB, Brecha N. Distribution of VIP- and NPY-like immunoreactivities in rat main olfactory bulb. *Brain Res*. 1986;374(2):389-394.
280. Mousley A, Polese G, Marks NJ, Eisthen HL. Terminal nerve-derived neuropeptide Y modulates physiological responses in the olfactory epithelium of hungry axolotls (*Ambystoma mexicanum*). *J Neurosci*. 2006;26(29):7707-7717.
281. Negroni J, Meunier N, Monnerie R, et al. Neuropeptide Y enhances olfactory mucosa responses to odorant in hungry rats. *PloS One*. 2012;7(9):e45266.
282. Ohm TG, Braak E, Probst A, Weindl A. Neuropeptide Y-like immunoreactive neurons in the human olfactory bulb. *Brain Res*. 1988;451(1-2):295-300.
283. Blakemore LJ, Levenson CW, Trombley PQ. Neuropeptide Y modulates excitatory synaptic transmission in the olfactory bulb. *Neuroscience*. 2006;138(2):663-674.
284. Huang TW, Li ST, Chen DY, Young TH. Neuropeptide Y increases differentiation of human olfactory receptor neurons through the Y1 receptor. *Neuropeptides*. 2019;78:101964.
285. Hervieu GJ, Cluderay JE, Harrison D, et al. The distribution of the mRNA and protein products of the melanin-concentrating hormone

- (MCH) receptor gene, slc-1, in the central nervous system of the rat. *Eur J Neurosci.* 2000;12(4):1194-1216.
286. Francke F, Richter D, Bachner D. Immunohistochemical distribution of MZIP and its co-expression with the melanin-concentrating hormone receptor 1 in the adult rodent brain. *Brain Res Mol Brain Res.* 2005;139(1):31-41.
287. Alhassen L, Phan A, Alhassen W, et al. The role of olfaction in MCH-regulated spontaneous maternal responses. *Brain Res.* 2019;1719:71-76.
288. McIntyre JC, Jasson K, Ross J, Fletcher M, Reed R. The ciliary localized GPCR, MCHR1, modulates odor responses in the olfactory bulb. *FASEB J.* 2020;34(S1):1.
289. Kasa P, Farkas Z, Balaspiri L, Wolff JR. The structural localization of galanin, and its function in modulating acetylcholine release in the olfactory bulb of adult rat. *Neuroscience.* 1996;72(3):709-723.
290. Xia CY, Yuan CX, Yuan CG. Galanin inhibits the proliferation of glial olfactory ensheathing cells. *Neuropeptides.* 2005;39(5):453-459.
291. O'Donnell D, Ahmad S, Wahlestedt C, Walker P. Expression of the novel galanin receptor subtype GALR2 in the adult rat CNS: distinct distribution from GALR1. *J Comp Neurol.* 1999;409(3):469-481.
292. Cordero-Llana O, Rinaldi F, Brennan PA, Wynick D, Caldwell MA. Galanin promotes neuronal differentiation from neural progenitor cells in vitro and contributes to the generation of new olfactory neurons in the adult mouse brain. *Exp Neurol.* 2014;256:93-104.
293. Xu Z-Q, Shi T-J, Hökfelt T. Expression of galanin and a galanin receptor in several sensory systems and bone anlage of rat embryos. *Proc Natl Acad Sci.* 1996;93(25):14901-14905.
294. Soria-Gomez E, Bellocchio L, Reguero L, et al. The endocannabinoid system controls food intake via olfactory processes. *Nat Neurosci.* 2014;17(3):407-415.
295. Wang ZJ, Sun L, Heinbockel T. Cannabinoid receptor-mediated regulation of neuronal activity and signaling in glomeruli of the main olfactory bulb. *J Neurosci.* 2012;32(25):8475-8479.
296. Bhatia-Dey N, Heinbockel T. Endocannabinoid-mediated neuromodulation in the olfactory bulb: functional and therapeutic significance. *Int J Mol Sci.* 2020;21(8):2850. doi:[10.3390/ijms21082850](https://doi.org/10.3390/ijms21082850)
297. Terral G, Marsicano G, Grandes P, Soria-Gomez E. Cannabinoid control of olfactory processes: the where matters. *Genes (Basel).* 2020;11(4):431. doi:[10.3390/genes11040431](https://doi.org/10.3390/genes11040431)
298. Wang ZJ, Hu SS, Bradshaw HB, et al. Cannabinoid receptor-mediated modulation of inhibitory inputs to mitral cells in the main olfactory bulb. *J Neurophysiol.* 2019;122(2):749-759.
299. Pouille F, Schoppa NE. Cannabinoid receptors modulate excitation of an olfactory bulb local circuit by cortical feedback. *Front Cell Neurosci.* 2018;12:47.
300. Roth TL, Sullivan RM. Endogenous opioids and their role in odor preference acquisition and consolidation following odor-shock conditioning in infant rats. *Dev Psychobiol.* 2001;39(3):188-198.
301. Le Merrer J, Becker JA, Befort K, Kieffer BL. Reward processing by the opioid system in the brain. *Physiol Rev.* 2009;89(4):1379-1412.
302. Santoyo-Zedillo M, Portillo W, Paredes RG. Neurogenesis in the olfactory bulb induced by paced mating in the female rat is opioid dependent. *PLoS One.* 2017;12(11):e0186335.
303. Escanilla O, Yuhas C, Marzan D, Linster C. Dopaminergic modulation of olfactory bulb processing affects odor discrimination learning in rats. *Behav Neurosci.* 2009;123(4):828-833.
304. Korshunov KS, Blakemore LJ, Trombley PQ. Illuminating and sniffing out the Neuromodulatory roles of dopamine in the retina and olfactory bulb. *Front Cell Neurosci.* 2020;14:275.
305. Liu S. Dopaminergic modulation of glomerular circuits in the mouse olfactory bulb. *Front Cell Neurosci.* 2020;14:172.
306. Pignatelli A, Belluzzi O. Dopaminergic neurones in the main olfactory bulb: an overview from an electrophysiological perspective. *Front Neuroanat.* 2017;11:7. doi:[10.3389/fnana.2017.00007](https://doi.org/10.3389/fnana.2017.00007)
307. Casciano F, Bianchi N, Borin M, et al. Characterization by gene expression analysis of two groups of dopaminergic cells isolated from the mouse olfactory bulb. *Biology.* 2023;12(3):367.
308. Coronas V, Srivastava LK, Liang JJ, Jourdan F, Moyse E. Identification and localization of dopamine receptor subtypes in rat olfactory mucosa and bulb: a combined in situ hybridization and ligand binding radioautographic approach. *J Chem Neuroanat.* 1997;12(4):243-257.
309. van Zessen R, Flores-Dourojeanni JP, Eekel T, et al. Cue and reward evoked dopamine activity is necessary for maintaining learned Pavlovian associations. *J Neurosci.* 2021;41(23):5004-5014.
310. Tillerson JL, Caudle WM, Parent JM, Gong C, Schallert T, Miller GW. Olfactory discrimination deficits in mice lacking the dopamine transporter or the D2 dopamine receptor. *Behav Brain Res.* 2006;172(1):97-105.
311. Ennis M, Zhou FM, Ciombor KJ, et al. Dopamine D2 receptor-mediated presynaptic inhibition of olfactory nerve terminals. *J Neurophysiol.* 2001;86(6):2986-2997.
312. Vaaga CE, Yorgason JT, Williams JT, Westbrook GL. Presynaptic gain control by endogenous cotransmission of dopamine and GABA in the olfactory bulb. *J Neurophysiol.* 2017;117(3):1163-1170.
313. Berkowicz DA, Trombley PQ. Dopaminergic modulation at the olfactory nerve synapse. *Brain Res.* 2000;855(1):90-99.
314. Davila NG, Blakemore LJ, Trombley PQ. Dopamine modulates synaptic transmission between rat olfactory bulb neurons in culture. *J Neurophysiol.* 2003;90(1):395-404.
315. Davison IG, Boyd JD, Delaney KR. Dopamine inhibits mitral/tufted-granule cell synapses in the frog olfactory bulb. *J Neurosci.* 2004;24(37):8057-8067.
316. Garcia I, Quast KB, Huang L, et al. Local CRH signaling promotes synaptogenesis and circuit integration of adult-born neurons. *Dev Cell.* 2014;30(6):645-659.
317. Koju EO, Couceyro PR, Lambert PD, Ling NC, DeSouza EB, Kuhar MJ. Immunohistochemical localization of novel CART peptides in rat hypothalamus, pituitary and adrenal gland. *J Neuroendocrinol.* 1997;9(11):823-833.
318. Pekarek BT, Kochukov M, Lozzi B, et al. Oxytocin signaling is necessary for synaptic maturation of adult-born neurons. *Genes Dev.* 2022;36(21-24):1100-1118.
319. Pisani A, Paciello F, Del Vecchio V, et al. The role of BDNF as a biomarker in cognitive and sensory neurodegeneration. *J Pers Med.* 2023;13(4):652.
320. Rios M. BDNF and the central control of feeding: accidental bystander or essential player? *Trends Neurosci.* 2013;36(2):83-90.
321. Yuan TF. BDNF signaling during olfactory bulb neurogenesis. *J Neurosci.* 2008;28(20):5139-5140.
322. Colley BS, Biju KC, Visegrady A, Campbell S, Fadool DA. Neurotrophin B receptor kinase increases Kv subfamily member 1.3 (Kv1.3) ion channel half-life and surface expression. *Neuroscience.* 2007;144(2):531-546.
323. Lukas M, Suyama H, Egger V. Vasopressin cells in the rodent olfactory bulb resemble non-bursting superficial tufted cells and are primarily inhibited upon olfactory nerve stimulation. *eNeuro.* 2019;6(4):ENEURO.0431-18.2019. doi:[10.1523/ENEURO.0431-18.2019](https://doi.org/10.1523/ENEURO.0431-18.2019)
324. Ostrowski NL, Lolait SJ, Young WS. Cellular localization of vasopressin V1a receptor messenger ribonucleic acid in adult male rat brain, pineal, and brain vasculature. *Endocrinology.* 1994;135(4):1511-1528.
325. Tobin VA, Hashimoto H, Wacker DW, et al. An intrinsic vasopressin system in the olfactory bulb is involved in social recognition. *Nature.* 2010;464(7287):413-417.
326. Zhang L, Koller J, Ip CK, et al. Lack of neuropeptide FF signalling in mice leads to reduced repetitive behavior, altered drinking behavior, and fuel type selection. *FASEB J.* 2021;35(11):e21980.

327. Bonini JA, Jones KA, Adham N, et al. Identification and characterization of two G protein-coupled receptors for neuropeptide FF. *J Biol Chem.* 2000;275(50):39324-39331.
328. Corthell JT, Olcese J, Trombley PQ. Melatonin in the mammalian olfactory bulb. *Neuroscience.* 2014;261:74-84.
329. Klosen P, Lapmanee S, Schuster C, et al. MT1 and MT2 melatonin receptors are expressed in nonoverlapping neuronal populations. *J Pineal Res.* 2019;67(1):e12575.
330. Noseda ACD, Lima MMS. Olfaction and melatonin: the use of the olfactory discrimination test. *Methods Mol Biol.* 2022;2550:425-432.
331. Kawai T, Oka Y, Eisthen H. The role of the terminal nerve and GnRH in olfactory system neuromodulation. *Zoolog Sci.* 2009;26(10):669-680.
332. Taroc EZM, Prasad A, Lin JM, Forni PE. The terminal nerve plays a prominent role in GnRH-1 neuronal migration independent from proper olfactory and vomeronasal connections to the olfactory bulbs. *Biol Open.* 2017;6(10):1552-1568.
333. Jennes L, Dalati B, Conn PM. Distribution of gonadotropin releasing hormone agonist binding sites in the rat central nervous system. *Brain Res.* 1988;452(1-2):156-164.
334. Albertson AJ, Navratil A, Mignot M, Dufourny L, Cherrington B, Skinner DC. Immunoreactive GnRH type I receptors in the mouse and sheep brain. *J Chem Neuroanat.* 2008;35(4):326-333.
335. Khan MA, Ferro VA, Stimson WH. Use of a highly specific monoclonal antibody against the central variable amino acid sequence of mammalian gonadotropin releasing hormone to evaluate GnRH-I tissue distribution compared with GnRH-I binding sites in adult male rats. *Am J Reprod Immunol.* 2003;49(4):239-248.
336. Eisthen HL, Delay RJ, Wirsig-Wiechmann CR, Dionne VE. Neuromodulatory effects of gonadotropin releasing hormone on olfactory receptor neurons. *J Neurosci.* 2000;20(11):3947-3955.
337. Park D, Eisthen HL. Gonadotropin releasing hormone (GnRH) modulates odorant responses in the peripheral olfactory system of axolotls. *J Neurophysiol.* 2003;90(2):731-738.
338. Decoster L, Trova S, Zucca S, et al. An olfactory bulb GnRH neuronal population translates social relevant odors into reproductive behavior in male mice. *Res Sq.* 2023. doi:10.21203/rs.3.rs-3115610/v1
339. Hannibal J. Pituitary adenylate cyclase-activating peptide in the rat central nervous system: an immunohistochemical and in situ hybridization study. *J Comp Neurol.* 2002;453(4):389-417.
340. Jaworski DM, Proctor MD. Developmental regulation of pituitary adenylate cyclase-activating polypeptide and PAC(1) receptor mRNA expression in the rat central nervous system. *Brain Res Dev Brain Res.* 2000;120(1):27-39.
341. Nicot A, Otto T, Brabec P, Dicicco-Bloom EM. Altered social behavior in pituitary adenylate cyclase-activating polypeptide type I receptor-deficient mice. *J Neurosci.* 2004;24(40):8786-8795.
342. Irwin M, Greig A, Tvrđik P, Lucero MT. PACAP modulation of calcium ion activity in developing granule cells of the neonatal mouse olfactory bulb. *J Neurophysiol.* 2015;113(4):1234-1248.
343. Lepousez G, Csaba Z, Bernard V, et al. Somatostatin interneurons delineate the inner part of the external plexiform layer in the mouse main olfactory bulb. *J Comp Neurol.* 2010;518(11):1976-1994.
344. Scalera G, Tarozzi G. Somatostatin administration modifies food intake, body weight, and gut motility in rat. *Peptides.* 1998;19(6):991-997.
345. Nocera S, Simon A, Fiquet O, et al. Somatostatin serves a modulatory role in the mouse olfactory bulb: neuroanatomical and behavioral evidence. *Front Behav Neurosci.* 2019;13:61.
346. Lepousez G, Mouret A, Loudes C, Epelbaum J, Viollet C. Somatostatin contributes to in vivo gamma oscillation modulation and odor discrimination in the olfactory bulb. *J Neurosci.* 2010;30(3):870-875.
347. Sturgill JF, Isaacson JS. Somatostatin cells regulate sensory response fidelity via subtractive inhibition in olfactory cortex. *Nat Neurosci.* 2015;18(4):531-535.
348. Kumar U, Singh S. Role of somatostatin in the regulation of central and peripheral factors of satiety and obesity. *Int J Mol Sci.* 2020; 21(7):2568. doi:10.3390/ijms21072568
349. Saiz-Sanchez D, Ubeda-Banon I, Flores-Cuadrado A, et al. Somatostatin, olfaction, and neurodegeneration. *Front Neurosci.* 2020;14:96.
350. Stengel A, Goebel M, Wang L, et al. Activation of brain somatostatin 2 receptors stimulates feeding in mice: analysis of food intake microstructure. *Physiol Behav.* 2010;101(5):614-622.
351. Vannucci SJ, Koehler-Stec EM, Li K, Reynolds TH, Clark R, Simpson IA. GLUT4 glucose transporter expression in rodent brain: effect of diabetes. *Brain Res.* 1998;797(1):1-11.
352. Leloup C, Arluison M, Kassis N, et al. Discrete brain areas express the insulin-responsive glucose transporter GLUT4. *Brain Res Mol Brain Res.* 1996;38(1):45-53.
353. El Messari S, Leloup C, Quignon M, Brisorgueil MJ, Penicaud L, Arluison M. Immunocytochemical localization of the insulin-responsive glucose transporter 4 (Glut4) in the rat central nervous system. *J Comp Neurol.* 1998;399(4):492-512.
354. Choeiri C, Staines W, Messier C. Immunohistochemical localization and quantification of glucose transporters in the mouse brain. *Neuroscience.* 2002;111(1):19-34.
355. Anthony TG, Gietzen DW. Detection of amino acid deprivation in the central nervous system. *Curr Opin Clin Nutr Metab Care.* 2013; 16(1):96-101.
356. Drgnova J, Jacobsson JA, Han JC, et al. Involvement of the neutral amino acid transporter SLC6A15 and leucine in obesity-related phenotypes. *PLoS One.* 2013;8(9):e68245.
357. Ferry S, Traifort E, Stinnakre J, Ruat M. Developmental and adult expression of rat calcium-sensing receptor transcripts in neurons and oligodendrocytes. *Eur J Neurosci.* 2000;12(3):872-884.
358. Hagglund MG, Roshanbin S, Lofqvist E, et al. B(0)AT2 (SLC6A15) is localized to neurons and astrocytes, and is involved in mediating the effect of leucine in the brain. *PLoS One.* 2013;8(3):e58651.
359. Inoue K, Sato K, Tohyama M, Shimada S, Uhl GR. Widespread brain distribution of mRNA encoding the orphan neurotransmitter transporter v7-3. *Brain Res Mol Brain Res.* 1996;37(1-2):217-223.
360. Kageyama T, Imura T, Matsuo A, Minato N, Shimohama S. Distribution of the 4F2 light chain, LAT1, in the mouse brain. *Neuroreport.* 2000;11(17):3663-3666.
361. Lin W, Margolskee R, Donnett G, Hell SW, Restrepo D. Olfactory neurons expressing transient receptor potential channel M5 (TRPM5) are involved in sensing semiochemicals. *Proc Natl Acad Sci U S A.* 2007;104(7):2471-2476.
362. Masson J, Pohl M, Aidouni Z, Giros B, Hamon M, el Mestikawy S. The two orphan Na<sup>+</sup>/Cl<sup>-</sup>-dependent transporters Rxt1 and V-7-3-2 have an overlapping expression pattern in the rat central nervous system. *Recept Channels.* 1996;4(4):227-242.
363. Maurin AC, Jousse C, Averous J, et al. The GCN2 kinase biases feeding behavior to maintain amino acid homeostasis in omnivores. *Cell Metab.* 2005;1(4):273-277.
364. Mudo G, Trovato-Salinara A, Barresi V, Belluardo N, Condorelli DF. Identification of calcium sensing receptor (CaSR) mRNA-expressing cells in normal and injured rat brain. *Brain Res.* 2009;1298:24-36.
365. Pyrski M, Eckstein E, Schmid A, et al. Trpm5 expression in the olfactory epithelium. *Mol Cell Neurosci.* 2017;80:75-88.
366. Rogers KV, Dunn CK, Hebert SC, Brown EM. Localization of calcium receptor mRNA in the adult rat central nervous system by in situ hybridization. *Brain Res.* 1997;744(1):47-56.
367. Rolen SH, Salcedo E, Restrepo D, Finger TE. Differential localization of NT-3 and TrpM5 in glomeruli of the olfactory bulb of mice. *J Comp Neurol.* 2014;522(8):1929-1940.
368. Sundberg BE, Waag E, Jacobsson JA, et al. The evolutionary history and tissue mapping of amino acid transporters belonging to solute carrier families SLC32, SLC36, and SLC38. *J Mol Neurosci.* 2008; 35(2):179-193.

369. Voigt A, Bojahr J, Narukawa M, Hubner S, Boehm U, Meyerhof W. Transsynaptic tracing from taste receptor cells reveals local taste receptor gene expression in gustatory ganglia and brain. *J Neurosci*. 2015;35(26):9717-9729.
370. Wang C, Ohno K, Furukawa T, et al. Differential expression of KCC2 accounts for the differential GABA responses between relay and intrinsic neurons in the early postnatal rat olfactory bulb. *Eur J Neurosci*. 2005;21(5):1449-1455.
371. Yano S, Brown EM, Chattopadhyay N. Calcium-sensing receptor in the brain. *Cell Calcium*. 2004;35(3):257-264.
372. Benton R, Vannice KS, Vosshall LB. An essential role for a CD36-related receptor in pheromone detection in Drosophila. *Nature*. 2007;450(7167):289-293.
373. Dong HW, Davis JC, Ding S, Nai Q, Zhou FM, Ennis M. Expression of transient receptor potential (TRP) channel mRNAs in the mouse olfactory bulb. *Neurosci Lett*. 2012;524(1):49-54.
374. Glezer I, Bittencourt JC, Rivest S. Neuronal expression of Cd36, Cd44, and Cd83 antigen transcripts maps to distinct and specific murine brain circuits. *J Comp Neurol*. 2009;517(6):906-924.
375. Khan MZ, He L. The role of polyunsaturated fatty acids and GPR40 receptor in brain. *Neuropharmacology*. 2017;113:639-651.
376. Lee S, Eguchi A, Tsuzuki S, et al. Expression of CD36 by olfactory receptor cells and its abundance on the epithelial surface in mice. *PLoS One*. 2015;10(7):e0133412.
377. Nakamoto K, Nishinaka T, Matsumoto K, et al. Involvement of the long-chain fatty acid receptor GPR40 as a novel pain regulatory system. *Brain Res*. 2012;1432:74-83.
378. Oberland S, Ackels T, Gaab S, et al. CD36 is involved in oleic acid detection by the murine olfactory system. *Front Cell Neurosci*. 2015; 9:366.
379. Otsuka Y, Sakagami H, Owada Y, Kondo H. Differential localization of mRNAs for mammalian trps, presumptive capacitative calcium entry channels, in the adult mouse brain. *Tohoku J Exp Med*. 1998; 185(2):139-146.
380. Philipp S, Hambrecht J, Braslavski L, et al. A novel capacitative calcium entry channel expressed in excitable cells. *EMBO J*. 1998; 17(15):4274-4282.
381. Biju KC, Marks DR, Mast TG, Fadool DA. Deletion of voltage-gated channel affects glomerular refinement and odorant receptor expression in the mouse olfactory system. *J Comp Neurol*. 2008;506(2): 161-179.
382. Chelette BM, Thomas AM, Fadool DA. Long-term obesogenic diet and targeted deletion of potassium channel K(v) 1.3 have differing effects on voluntary exercise in mice. *Physiol Rep*. 2019;7(20): e14254.
383. Huang Z, Hoffman CA, Chelette BM, Thiebaud N, Fadool DA. Elevated anxiety and impaired attention in super-smeller, Kv1.3 knockout mice. *Front Behav Neurosci*. 2018;12:49.
384. Tucker K, Overton JM, Fadool DA. Kv1.3 gene-targeted deletion alters longevity and reduces adiposity by increasing locomotion and metabolism in melanocortin-4 receptor-null mice. *Int J Obes (Lond)*. 2008;32(8):1222-1232.
385. Kolling LJ, Tatti R, Lowry T, Loeven AM, Fadool JM, Fadool DA. Modulating the excitability of olfactory output neurons affects whole-body metabolism. *J Neurosci*. 2022;42(30):5966-5990.
386. Stephan AB, Tobochnik S, Dibattista M, Wall CM, Reisert J, Zhao H. The Na<sup>(+)</sup>/Ca<sup>(2+)</sup> exchanger NCKX4 governs termination and adaptation of the mammalian olfactory response. *Nat Neurosci*. 2011;15(1):131-137.
387. Riviere S, Soubeyre V, Jarriault D, et al. High fructose diet inducing diabetes rapidly impacts olfactory epithelium and behavior in mice. *Sci Rep*. 2016;6:34011.
388. Sutton GM, Trevaskis JL, Hulver MW, et al. Diet-genotype interactions in the development of the obese, insulin-resistant phenotype of C57BL/6J mice lacking melanocortin-3 or -4 receptors. *Endocrinology*. 2006;147(5):2183-2196.
389. Chuang JC, Krishnan V, Yu HG, et al. A beta3-adrenergic-leptin-melanocortin circuit regulates behavioral and metabolic changes induced by chronic stress. *Biol Psychiatry*. 2010;67(11): 1075-1082.
390. Riera CE, Tsaoisidou E, Halloran J, et al. The sense of smell impacts metabolic health and obesity. *Cell Metab*. 2017;26(1):198-211.
391. Chen M, Reed RR, Lane AP. Chronic inflammation directs an olfactory stem cell functional switch from neuroregeneration to immune defense. *Cell Stem Cell*. 2019;25(4):501-513.
392. Hasegawa Y, Namkung H, Smith A, et al. Causal impact of local inflammation in the nasal cavity on higher brain function and cognition. *Neurosci Res*. 2021;172:110-115.
393. Lane AP, Turner J, May L, Reed R. A genetic model of chronic rhinosinusitis-associated olfactory inflammation reveals reversible functional impairment and dramatic neuroepithelial reorganization. *J Neurosci*. 2010;30(6):2324-2329.
394. Miyake M, Ito Y, Sawada M, et al. Subchronic inhalation exposure to 2-ethyl-1-hexanol impairs the mouse olfactory bulb via injury and subsequent repair of the nasal olfactory epithelium. *Arch Toxicol*. 2016;90(8):1949-1958.
395. Fonken LK, Xu X, Weil ZM, et al. Air pollution impairs cognition, provokes depressive-like behaviors and alters hippocampal cytokine expression and morphology. *Mol Psychiatry*. 2011;16(10):987-995.
396. Guevara-Guzman R, Arriaga V, Kendrick KM, et al. Estradiol prevents ozone-induced increases in brain lipid peroxidation and impaired social recognition memory in female rats. *Neuroscience*. 2009;159(3):940-950.
397. Moseman EA, Blanchard AC, Nayak D, McGavern DB. T cell engagement of cross-presenting microglia protects the brain from a nasal virus infection. *Sci Immunol*. 2020;5(48):eabb1817. doi:[10.1126/sciimmunol.abb1817](https://doi.org/10.1126/sciimmunol.abb1817)
398. Schwob JE, Saha S, Youngentob SL, Jubelt B. Intranasal inoculation with the olfactory bulb line variant of mouse hepatitis virus causes extensive destruction of the olfactory bulb and accelerated turnover of neurons in the olfactory epithelium of mice. *Chem Senses*. 2001; 26(8):937-952.
399. Youngentob SL, Schwob JE, Saha S, Manglapus G, Jubelt B. Functional consequences following infection of the olfactory system by intranasal infusion of the olfactory bulb line variant (OBLV) of mouse hepatitis strain JHM. *Chem Senses*. 2001;26(8):953-963.
400. McBride K, Slotnick B, Margolis FL. Does intranasal application of zinc sulfate produce anosmia in the mouse? An olfactometric and anatomical study. *Chem Senses*. 2003;28(8):659-670.
401. Tonelli LH, Katz M, Kovacsics CE, et al. Allergic rhinitis induces anxiety-like behavior and altered social interaction in rodents. *Brain Behav Immun*. 2009;23(6):784-793.
402. Hasegawa-Ishii S, Shimada A, Imamura F. Neuroplastic changes in the olfactory bulb associated with nasal inflammation in mice. *J Allergy Clin Immunol*. 2019;143(3):978-989.
403. Hasegawa-Ishii S, Shimada A, Imamura F. Lipopolysaccharide-initiated persistent rhinitis causes gliosis and synaptic loss in the olfactory bulb. *Sci Rep*. 2017;7(1):11605.
404. Kim J, Choi Y, Ahn M, et al. Microglial and astroglial reaction in the olfactory bulb of mice after triton X-100 application. *Acta Histochem*. 2019;121(5):546-552.
405. Song C, Leonard BE. The olfactory bulbectomised rat as a model of depression. *Neurosci Biobehav Rev*. 2005;29(4-5):627-647.
406. Flores G, Ibanez-Sandoval O, Silva-Gomez AB, Camacho-Abrego I, Rodriguez-Moreno A, Morales-Medina JC. Neonatal olfactory bulbectomy enhances locomotor activity, exploratory behavior and binding of NMDA receptors in pre-pubertal rats. *Neuroscience*. 2014;259:84-93.

407. Hendriksen H, Korte SM, Olivier B, Oosting RS. The olfactory bulbectomy model in mice and rat: one story or two tails? *Eur J Pharmacol.* 2015;753:105-113.
408. Jancsar SM, Leonard BE. Changes in neurotransmitter metabolism following olfactory bulbectomy in the rat. *Prog Neuropsychopharmacol Biol Psychiatry.* 1984;8(2):263-269.
409. Zhou YF, Feng L, Liu XM, et al. Urinary metabolic disturbance in the olfactory bulbectomized rats and the modulatory effects of fluoxetine. *Life Sci.* 2019;234:116751.
410. Pieper DR, Lobocki CA, Karo KH. Olfactory bulbectomy counteracts inhibitory effect of food restriction on reproductive function. *Am J Physiol.* 1994;266(6 Pt 2):R1891-R1895.
411. Pavlova I, Drazenova E, Kratka L, et al. Laterality in functional and metabolic state of the bulbectomised rat brain detected by ASL and <sup>(1)</sup>H MRS: a pilot study. *World J Biol Psychiatry.* 2023;24(5):414-428.
412. Phillips DS, Martin GK. Effects of olfactory bulb ablation upon heart rate. *Physiol Behav.* 1971;7(4):535-537.
413. Chiaraviglio E. Effect of lesions in the septal area and olfactory bulbs on sodium chloride intake. *Physiol Behav.* 1969;4(5):693-697.
414. Perassi NI, Loyber I, Palma JA. Insulin sensitivity and glucose tolerance in rats without olfactory bulbs. *Neuroendocrinology.* 1972;9(2):83-89.
415. Brunjes PC. Lessons from lesions: the effects of olfactory bulbectomy. *Chem Senses.* 1992;17(6):729-763.
416. Primeaux SD, Barnes MJ, Bray GA. Olfactory bulbectomy increases food intake and hypothalamic neuropeptide Y in obesity-prone but not obesity-resistant rats. *Behav Brain Res.* 2007;180(2):190-196.
417. Chen Y, Liu X, Jia X, et al. Anxiety- and depressive-like behaviors in olfactory deficient Cnga2 knockout mice. *Behav Brain Res.* 2014;275:219-224.
418. Matsuo T, Hattori T, Asaba A, et al. Genetic dissection of pheromone processing reveals main olfactory system-mediated social behaviors in mice. *Proc Natl Acad Sci U S A.* 2015;112(3):E311-E320.
419. Xie AJ, Liu EJ, Huang HZ, et al. Cnga2 knockout mice display Alzheimer's-like behavior abnormalities and pathological changes. *Mol Neurobiol.* 2016;53(7):4992-4999.
420. Glinka ME, Samuels BA, Diodato A, et al. Olfactory deficits cause anxiety-like behaviors in mice. *J Neurosci.* 2012;32(19):6718-6725.
421. Nguyen MQ, Ryba NJ. A smell that causes seizure. *PLoS One.* 2012;7(7):e41899.
422. Fleischmann A, Shykind BM, Sosulski DL, et al. Mice with a "monoclonal nose": perturbations in an olfactory map impair odor discrimination. *Neuron.* 2008;60(6):1068-1081.
423. Kondo K, Kikuta S, Ueha R, Suzukawa K, Yamasoba T. Age-related olfactory dysfunction: epidemiology, pathophysiology, and clinical management. *Front Aging Neurosci.* 2020;12:208.
424. Choi JS, Jang SS, Kim J, Hur K, Ference E, Wrobel B. Association between olfactory dysfunction and mortality in US adults. *JAMA Otolaryngol Head Neck Surg.* 2021;147(1):49-55.
425. Olofsson JK, Ekstrom I, Larsson M, Nordin S. Olfaction and aging: a review of the current state of research and future directions. *i-perception.* 2021;12(3):20416695211020331. doi:[10.1177/20416695211020331](https://doi.org/10.1177/20416695211020331).
426. Pinto JM, Wroblewski KE, Kern DW, Schumm LP, McClintock MK. Olfactory dysfunction predicts 5-year mortality in older adults. *PloS One.* 2014;9(10):e107541.
427. Obrebowska A, Obrebowska-Karsznia Z, Gawlinski M. Smell and taste in children with simple obesity. *Int J Pediatr Otorhinolaryngol.* 2000;55(3):191-196.
428. Richardson BE, Vander Woude EA, Sudan R, Thompson JS, Leopold DA. Altered olfactory acuity in the morbidly obese. *Obes Surg.* 2004;14(7):967-969.
429. Koski M, Naukkarinen H. Severe obesity, emotions and eating habits: a case-control study. *BMC Obes.* 2017;4:2.
430. Patel ZM, DelGaudio JM, Wise SK. Higher body mass index is associated with subjective olfactory dysfunction. *Behav Neurol.* 2015;2015:675635.
431. Richardson BE, Vanderwoude EA, Sudan R, Leopold DA, Thompson JS. Gastric bypass does not influence olfactory function in obese patients. *Obes Surg.* 2012;22(2):283-286.
432. Sun X, Veldhuizen MG, Babbs AE, Sinha R, Small DM. Perceptual and brain response to odors is associated with body mass index and postprandial total ghrelin reactivity to a meal. *Chem Senses.* 2016;41(3):233-248.
433. Naka A, Riedl M, Luger A, Hummel T, Mueller CA. Clinical significance of smell and taste disorders in patients with diabetes mellitus. *Eur Arch Otorhinolaryngol.* 2010;267(4):547-550.
434. Duda-Sobczak A, Araszkiewicz A, Urbas M, et al. Impaired olfactory function is related to the presence of neuropathy in adults with type 1 diabetes. *Diab Vasc Dis Res.* 2017;14(2):139-143.
435. Gouveri E, Katotomichelakis M, Gouveris H, Danielides V, Maltezos E, Papanas N. Olfactory dysfunction in type 2 diabetes mellitus: an additional manifestation of microvascular disease? *Angiology.* 2014;65(10):869-876.
436. Bentz M, Guldberg J, Vangkilde S, Pedersen T, Plessen KJ, Jepsen JR. Heightened olfactory sensitivity in young females with recent-onset anorexia nervosa and recovered individuals. *PLoS One.* 2017;12(1):e0169183.
437. Fernández-Aranda F, Agüera Z, Fernández-García JC, et al. Smell-taste dysfunctions in extreme weight/eating conditions: analysis of hormonal and psychological interactions. *Endocrine.* 2016;51(2):256-267.
438. Aschenbrenner K, Scholze N, Joraschky P, Hummel T. Gustatory and olfactory sensitivity in patients with anorexia and bulimia in the course of treatment. *J Psychiatr Res.* 2008;43(2):129-137.
439. Fedoroff IC, Stoner SA, Andersen AE, Doty RL, Rolls BJ. Olfactory dysfunction in anorexia and bulimia nervosa. *Int J Eat Disord.* 1995;18(1):71-77.
440. Roessner V, Bleich S, Banaschewski T, Rothenberger A. Olfactory deficits in anorexia nervosa. *Eur Arch Psychiatry Clin Neurosci.* 2005;255(1):6-9.
441. Schreder T, Albrecht J, Kleemann AM, et al. Olfactory performance of patients with anorexia nervosa and healthy subjects in hunger and satiety. *Rhinology.* 2008;46(3):175-183.
442. Barnett S, Reilly S, Carr L, Ojo I, Beales PL, Charman T. Behavioural phenotype of Bardet-Biedl syndrome. *J Med Genet.* 2002;39(12):e76.
443. Grace C, Beales P, Summerbell C, et al. Energy metabolism in Bardet-Biedl syndrome. *Int J Obes Relat Metab Disord.* 2003;27(11):1319-1324.
444. Mujahid S, Hunt KF, Cheah YS, et al. The endocrine and metabolic characteristics of a large Bardet-Biedl syndrome clinic population. *J Clin Endocrinol Metab.* 2018;103(5):1834-1841.
445. Sherafat-Kazemzadeh R, Ivey L, Kahn SR, et al. Hyperphagia among patients with Bardet-Biedl syndrome. *Pediatr Obes.* 2013;8(5):e64-e67.
446. Kaluzna M, Kompf P, Rabijewski M, et al. Reduced quality of life and sexual satisfaction in isolated hypogonadotropic hypogonadism. *J Clin Med.* 2021;10(12):2622. doi:[10.3390/jcm10122622](https://doi.org/10.3390/jcm10122622)
447. Zaghouani H, Slim I, Zina NB, Mallat N, Tajouri H, Kraiem C. Kallmann syndrome: MRI findings. *Indian J Endocrinol Metab.* 2013;17(Suppl 1):S142-S145.
448. Bianco SD, Kaiser UB. The genetic and molecular basis of idiopathic hypogonadotropic hypogonadism. *Nat Rev Endocrinol.* 2009;5(10):569-576.
449. Bittel DC, Butler MG. Prader-Willi syndrome: clinical genetics, cytogenetics and molecular biology. *Expert Rev Mol Med.* 2005;7(14):1-20.
450. Strelnikov K, Debladis J, Salles J, et al. Amygdala hyperactivation relates to eating behaviour: a potential indicator of food addiction in Prader-Willi syndrome. *Brain Commun.* 2023;5(3):fcad138.

451. Tauber M, Diene G, Mimoun E, et al. Prader-Willi syndrome as a model of human hyperphagia. *Front Horm Res.* 2014;42:93-106.
452. Alsaif M, Elliot SA, MacKenzie ML, Prado CM, Field CJ, Haqq AM. Energy metabolism profile in individuals with Prader-Willi syndrome and implications for clinical management: a systematic review. *Adv Nutr.* 2017;8(6):905-915.
453. Bloom SE. *Assessment of Preference for Olfactory Stimuli in Individuals with Prader-Willi Syndrome*. University of Florida; 2008.
454. Guta MT, Tekalign T, Awoke N, Fite RO, Dendir G, Lenjebo TL. Global burden of anxiety and depression among cystic fibrosis patient: systematic review and meta-analysis. *Int J Chronic Dis.* 2021;2021:6708865.
455. Lindig J, Steger C, Beiersdorf N, et al. Smell in cystic fibrosis. *Eur Arch Otorhinolaryngol.* 2013;270(3):915-921.
456. O'Rawe A. Energy metabolism in cystic fibrosis. *Proc Nutr Soc.* 1992; 51(2):237-244.
457. Seegmiller AC. Abnormal unsaturated fatty acid metabolism in cystic fibrosis: biochemical mechanisms and clinical implications. *Int J Mol Sci.* 2014;15(9):16083-16099.
458. Strandvik B. Fatty acid metabolism in cystic fibrosis. *Prostaglandins Leukot Essent Fatty Acids.* 2010;83(3):121-129.
459. Csernansky JG, Dong H, Fagan AM, et al. Plasma cortisol and progression of dementia in subjects with Alzheimer-type dementia. *Am J Psychiatry.* 2006;163(12):2164-2169.
460. Heilman KM, Nadeau SE. Emotional and neuropsychiatric disorders associated with Alzheimer's disease. *Neurotherapeutics.* 2022;19(1): 99-116.
461. Murphy C. Olfactory and other sensory impairments in Alzheimer disease. *Nat Rev Neurol.* 2019;15(1):11-24.
462. Prinz PN, Vitaliano PP, Vitiello MV, et al. Sleep, EEG and mental function changes in senile dementia of the Alzheimer's type. *Neurobiol Aging.* 1982;3(4):361-370.
463. Son G, Jahanshahi A, Yoo SJ, et al. Olfactory neuropathology in Alzheimer's disease: a sign of ongoing neurodegeneration. *BMB Rep.* 2021;54(6):295-304.
464. Thomann PA, Dos Santos V, Toro P, Schonknecht P, Essig M, Schroder J. Reduced olfactory bulb and tract volume in early Alzheimer's disease—a MRI study. *Neurobiol Aging.* 2009;30(5):838-841.
465. White H, Pieper C, Schmader K, Fillenbaum G. Weight change in Alzheimer's disease. *J Am Geriatr Soc.* 1996;44(3):265-272.
466. Kumar V, Kim SH, Bishayee K. Dysfunctional glucose metabolism in Alzheimer's disease onset and potential pharmacological interventions. *Int J Mol Sci.* 2022;23(17):9540. doi:[10.3390/ijms23179540](https://doi.org/10.3390/ijms23179540)
467. Bachmann CG, Trenkwalder C. Body weight in patients with Parkinson's disease. *Mov Disord.* 2006;21(11):1824-1830.
468. Doty RL. Olfactory dysfunction in Parkinson disease. *Nat Rev Neurol.* 2012;8(6):329-339.
469. Richard IH, Justus AW, Kurlan R. Relationship between mood and motor fluctuations in Parkinson's disease. *J Neuropsychiatry Clin Neurosci.* 2001;13(1):35-41.
470. Shore DM, Rafal R, Parkinson JA. Appetitive motivational deficits in individuals with Parkinson's disease. *Mov Disord.* 2011;26(10):1887-1892.
471. Patino J, Karagas NE, Chandra S, Thakur N, Stimming EF. Olfactory dysfunction in Huntington's disease. *J Huntingtons Dis.* 2021;10(4): 413-422.
472. Pla P, Orvoen S, Saudou F, David DJ, Humbert S. Mood disorders in Huntington's disease: from behavior to cellular and molecular mechanisms. *Front Behav Neurosci.* 2014;8:135.
473. Trejo A, Tarrats RM, Alonso ME, Boll MC, Ochoa A, Velasquez L. Assessment of the nutrition status of patients with Huntington's disease. *Nutrition.* 2004;20(2):192-196.
474. van der Burg JMM, Gardiner SL, Ludolph AC, Landwehrmeyer GB, Roos RAC, Aziz NA. Body weight is a robust predictor of clinical progression in Huntington disease. *Ann Neurol.* 2017;82(3):479-483.
475. Bsteh G, Berek K, Hegen H, et al. Smelling multiple sclerosis: different qualities of olfactory function reflect either inflammatory activity or neurodegeneration. *Mult Scler.* 2020;26(1):57-68.
476. Goektas O, Schmidt F, Bohner G, et al. Olfactory bulb volume and olfactory function in patients with multiple sclerosis. *Rhinology.* 2011;49(2):221-226.
477. Mirmosayyeb O, Ebrahimi N, Barzegar M, Afshari-Safavi A, Bagherieh S, Shaygannejad V. Olfactory dysfunction in patients with multiple sclerosis; a systematic review and meta-analysis. *PLoS One.* 2022;17(4):e0266492.
478. Raimo S, Santangelo G, Trojano L. The emotional disorders associated with multiple sclerosis. *Handb Clin Neurol.* 2021;183:197-220.
479. van de Kraats C, Killestein J, Popescu V, et al. Oxysterols and cholesterol precursors correlate to magnetic resonance imaging measures of neurodegeneration in multiple sclerosis. *Mult Scler.* 2014;20(4): 412-417.
480. Weinstock-Guttman B, Zivadinov R, Horakova D, et al. Lipid profiles are associated with lesion formation over 24 months in interferon-beta treated patients following the first demyelinating event. *J Neurol Neurosurg Psychiatry.* 2013;84(11):1186-1191.
481. Manca A, Ventura L, Martinez G, et al. Energy expenditure and oxygen consumption during activities of daily living in people with multiple sclerosis and healthy subjects: an ecological approach to estimate real-life fatigue and fatigability. *Arch Phys Med Rehabil.* 2021;102(8):1482-1489.
482. Burg T, Van Den Bosch L. Abnormal energy metabolism in ALS: a key player? *Curr Opin Neurol.* 2023;36(4):338-345.
483. Lachen-Montes M, Mendizuri N, Ausin K, et al. Amyotrophic lateral sclerosis is accompanied by protein derangements in the olfactory bulb-tract axis. *Int J Mol Sci.* 2020;21(21):8311. doi:[10.3390/ijms21218311](https://doi.org/10.3390/ijms21218311)
484. Maksimovic K, Youssef M, You J, Sung HK, Park J. Evidence of metabolic dysfunction in amyotrophic lateral sclerosis (ALS) patients and animal models. *Biomolecules.* 2023;13(5):863. doi:[10.3390/biom13050863](https://doi.org/10.3390/biom13050863)
485. Merrilees J, Klapper J, Murphy J, Lomen-Hoerth C, Miller BL. Cognitive and behavioral challenges in caring for patients with frontotemporal dementia and amyotrophic lateral sclerosis. *Amyotroph Lateral Scler.* 2010;11(3):298-302.
486. Takeda T, Iijima M, Uchihara T, et al. TDP-43 pathology progression along the olfactory pathway as a possible substrate for olfactory impairment in amyotrophic lateral sclerosis. *J Neuropathol Exp Neurol.* 2015;74(6):547-556.
487. Ten S, New M, McLaren N. Clinical review 130: Addison's disease 2001. *J Clin Endocrinol Metab.* 2001;86(7):2909-2922.
488. Geer EB, Lazar Y, Couto LM, et al. A prospective study of appetite and food craving in 30 patients with Cushing's disease. *Pituitary.* 2016;19(2):117-126.
489. Heger E, Rubinstein G, Braun LT, et al. Chemosensory dysfunction in Cushing's syndrome. *Endocrine.* 2021;73(3):674-681.
490. Sharma A, Vella A. Glucose metabolism in Cushing's syndrome. *Curr Opin Endocrinol Diabetes Obes.* 2020;27(3):140-145.
491. Amin A, Dhillo WS, Murphy KG. The central effects of thyroid hormones on appetite. *J Thyroid Res.* 2011;2011:306510.
492. Deniz F, Ay SA, Salihoglu M, et al. Thyroid hormone replacement therapy improves olfaction and taste sensitivity in primary hypothyroid patients: a prospective randomised clinical trial. *Exp Clin Endocrinol Diabetes.* 2016;124(9):562-567.
493. McConnell RJ, Menendez CE, Smith FR, Henkin RI, Rivlin RS. Defects of taste and smell in patients with hypothyroidism. *Am J Med.* 1975;59(3):354-364.
494. Doty RL, Fernandez AD, Levine MA, Moses A, McKeown DA. Olfactory dysfunction in type I pseudohypoparathyroidism: dissociation from Gs alpha protein deficiency. *J Clin Endocrinol Metab.* 1997; 82(1):247-250.

495. Cecchini MP, Viviani D, Sandri M, Hahner A, Hummel T, Zancanaro C. Olfaction in people with down syndrome: a comprehensive assessment across four decades of age. *PLoS One.* 2016; 11(1):e0146486.
496. Dierssen M, Fructuoso M, Martinez de Lagran M, Perluigi M, Barone E. Down syndrome is a metabolic disease: altered insulin signaling mediates peripheral and brain dysfunctions. *Front Neurosci.* 2020;14:670.
497. Dykens EM, Shah B, Sagun J, Beck T, King BH. Maladaptive behaviour in children and adolescents with Down's syndrome. *J Intellect Disabil Res.* 2002;46(Pt 6):484-492.
498. Mazurek D, Wyka J. Down syndrome—genetic and nutritional aspects of accompanying disorders. *Rocznik Panstw Zakl Hig.* 2015; 66(3):189-194.
499. Murphy C, Jinich S. Olfactory dysfunction in Down's syndrome. *Neurobiol Aging.* 1996;17(4):631-637.
500. Ross CF, Bernhard CB, Surette V, Hasted A, Wakeling I, Smith-Simpson S. Eating behaviors in children with Down syndrome: results of a home-use test. *J Texture Stud.* 2022;53(5): 629-646.
501. Wernio E, Kłosowska A, Kuchta A, et al. Analysis of dietary habits and nutritional status of children with Down syndrome in the context of lipid and oxidative stress parameters. *Nutrients.* 2022;14(12): 2390. doi:[10.3390/nu14122390](https://doi.org/10.3390/nu14122390)
502. Dipasquale S, Pariante CM, Dazzan P, Aguglia E, McGuire P, Mondelli V. The dietary pattern of patients with schizophrenia: a systematic review. *J Psychiatr Res.* 2013;47(2):197-207.
503. Helaly AMN, Ghorab D. Schizophrenia as metabolic disease. What are the causes? *Metab Brain Dis.* 2023;38(3):795-804.
504. De Hert M, Schreurs V, Vancampfort D, Van Winkel R. Metabolic syndrome in people with schizophrenia: a review. *World Psychiatry.* 2009;8(1):15-22.
505. Moberg PJ, Agrin R, Gur RE, Gur RC, Turetsky BI, Doty RL. Olfactory dysfunction in schizophrenia: a qualitative and quantitative review. *Neuropsychopharmacology.* 1999;21(3):325-340.
506. Nguyen AD, Shenton ME, Levitt JJ. Olfactory dysfunction in schizophrenia: a review of neuroanatomy and psychophysiological measurements. *Harv Rev Psychiatry.* 2010;18(5):279-292.
507. Yang J, Chen T, Sun L, et al. Potential metabolite markers of schizophrenia. *Mol Psychiatry.* 2013;18(1):67-78.

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