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Review

Brain–immune interactions and the neural basis of disease-avoidant ingestive behaviour

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Neuro–immune interactions are widely manifested in animal physiology. Since immunity competes for energy with other physiological functions, it is subject to a circadian trade-off between other energy-demanding processes, such as neural activity, locomotion and thermoregulation. When immunity is challenged, this trade-off is tilted to an adaptive energy protecting and reallocation strategy that is identified as '*sickness behaviour*'. We review diverse disease-avoidant behaviours in the context of ingestion, indicating that several adaptive advantages have been acquired by animals (including humans) during phylogenetic evolution and by ontogenetic experiences: (i) preventing waste of energy by reducing appetite and consequently foraging/hunting (illness anorexia), (ii) avoiding unnecessary danger by promoting safe environments (preventing disease encounter by olfactory cues and illness potentiation neophobia), (iii) help fighting against pathogenic threats (hyperthermia/somnolence), and (iv) by associative learning evading specific foods or environments signalling danger (conditioned taste avoidance/aversion) and/or at the same time preparing the body to counteract by anticipatory immune responses (conditioning immunomodulation). The neurobiology behind disease-avoidant ingestive behaviours is reviewed with special emphasis on the body energy balance (intake versus expenditure) and an evolutionary psychology perspective.

Keywords: cytokines; ecological neuro-immunology; disgust; behavioural immune system

1. AN OVERVIEW

For decades, it was believed that the immune system was autonomous from neural activity. However, empirical and experimental evidence accumulated showing a strong relationship between the central nervous system (CNS), behaviour and the immune system, boosting the emergence of a new interdisciplinary area at the beginning of the 1980s specifically studying such interactions: PsychoNeuroImmunology [1]. However, a fundamental question is still so far unsolved: what are the adaptive advantages of developing neuro–immune interactions? Focusing on different models of food intake behaviour, such as neophobia, illness anorexia, as well as in postprandial associative learning models, we propose that disease-avoidant ingestive behaviours are one of several other physiological responses (e.g. thermoregulation, energy storage mobilization, immunity, sleep patterns) orchestrated to achieve a better adaptation of the organism to a constantly threatening environment. In particular, we consider such avoidant behaviours in the context of the individual energy economy, intake versus expenditure (see §4).

The adaptive value of neuro–immune interactions is highlighted by their remarkably widespread manifestation in animal biology, including the phyla *Chordata*, *Mollusca* and *Arthropoda* to date [2–7]. As reviewed below, immune responses (table 1) involve a substantial investment of energy [8–11]; therefore immunity is subject to a trade-off between other highly energy-demanding processes, such as reproduction, lactation, foraging/hunting, social interaction and learning. This trade-off results ultimately in an adaptive energy-protecting strategy identified as '*sickness behaviour*' [12]. In contrast, food selection and intake are two essential behaviours for every animal to maintain an appropriate energy balance. Thus, the sensory capacity to detect relevant immune-generated molecules may lead to the evolutionary advantage of gathering appropriate information for the brain to integrate with other exteroceptive stimuli and/or previous experiences, and to respond aptly; for instance, by allocating stored fuel to energy-demanding cells; as well as to learn and anticipate environmental threats and prepare the body for counteraction by associative learning processes [13]. This view is in agreement with the recent concept of a so-called '*behavioural–immune system*'—a system

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One contribution of 11 to a Theme Issue 'Disease avoidance: from animals to culture'.

Table 1. Summary of innate and adaptive immune responses.

	innate immune responses	adaptive immune responses
receptors	germline-encoded	antigen receptors are products of site-specific somatic recombination
distribution	subset-specific but non-clonal	antigen receptors are clonally distributed
repertoire	limited selected in groups of individuals within a given species	immense selected in each individual within a given species
immune memory	no	yes
cellular component	phagocytic cells (e.g. neutrophils, macrophages, monocytes), also NK cells, eosinophils, dendritic cells.	lymphocytes (e.g. T- and B-cells, NK cells)
humoral component	complement, certain cytokines (e.g. IFN, TNFα), enzymes (e.g. lysozyme), nitric oxide	immunoglobulins, certain cytokines (e.g. IL-2) primary / secondary naive B cells / memory B cells [IgM] > [IgG] / [IgM] < [IgG] slow, weak and unspecific / fast, robust and specific
speed of the response	immediate maximal response	a lag time between exposure and maximal response

designated not to fight pathogens post-infection, but rather to avoid infection in the first place [14,15]. Interestingly, recent data coming from this evolutionary psychology perspective indicate that threat-management systems (self-protection and disease-avoidant systems) in ancestral human populations might shape critical features of our current '*precautionary psyche*' with the ultimate goal of minimizing threats to reproductive fitness [16]. In particular, it has been proposed that the disease-avoidant system is characterized by the emotion of '*disgust*' that in humans might include, but not be limited to, ingestive behaviours, thus potentially affecting current human social and political spheres [17,18]. Furthermore, the disease-avoidant system seems somehow to dictate our partner selection and correct time of procreation by disgust signals such as adolescent acne [19], interestingly disappearing at time when prefrontal cortex functions are fully developed, assuring that in addition to being sexually mature, the selected partner will be emotionally, intellectually and physically fit to be a parent.

As reviewed in detail in §§2 and 3, appetitive and consummatory eating behaviours are significantly affected by the immune-derived molecules elicited by peripheral challenges (e.g. viruses, bacteria or tumour cells resulting in innate and learned disease-avoidant ingestive behaviours, figure 1). In the most simple case, it has been shown that cytokines elicited by bacterial components increase innate avoidant behaviour (neophobia) to novel gustative stimuli and also to novel environments. Recently, a novel family of olfactory receptors has been described, with a function associated with the identification of pathogens or of pathogenic states, indicating that some avoidant behaviours are elicited upon detection of such odorant molecules of ill individuals or toxic food. In addition to illness-anorexia, when relevant gustatory/olfactory stimuli precede immune activation, strong associative learning processes occur, even after a single pairing trial. Moreover, the postprandial categorization of new food as '*safe*' or '*dangerous*' significantly affects individual food selection long after the association phase, i.e. results in conditioned taste avoidance/aversion (CTA), which is considered to be an adaptive food selection strategy. More importantly, anticipatory immune responses in humans and animals can be the result of Pavlovian conditioning (e.g. pairing of a neutral taste with an immunomodulating agent) [20–22]. It would also be convenient to clarify that many of the conditioned responses, in particular those that fall in the visceral associative learning are considered as non-declarative memories or implicit memories [23].

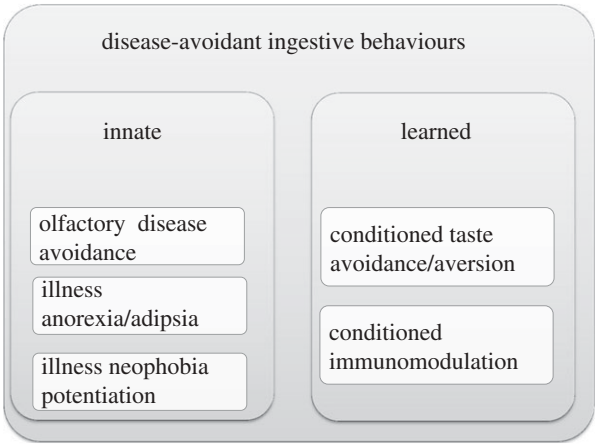

Figure 1. Appetitive and consummatory behaviours are significantly affected by the immune-derived molecules elicited by peripheral immune challenge resulting in innate and learned disease-avoidant ingestive behaviours. Such avoidant behaviours are the result of phylogenetic evolution and ontogenetic experiences with the ultimate goals of: (i) preventing waste of energy, (ii) avoiding unnecessary danger by promoting safe environments, (iii) helping to fight against pathogenic threats, and (iv) by associative learning it may also be possible to evade specific foods or environments signalling danger and/or at the same time prepare the body to counteract by anticipatory immune responses.

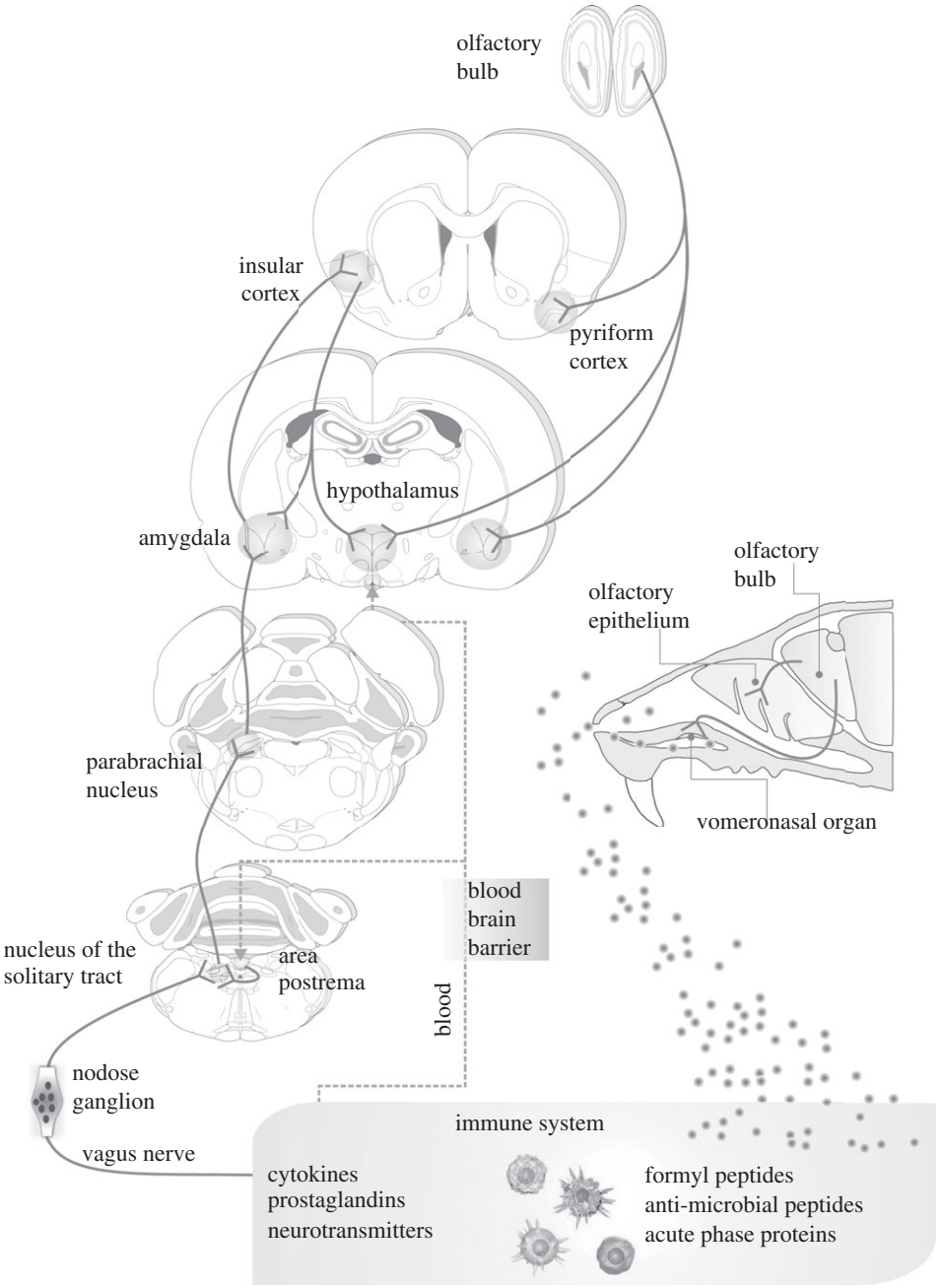

Figure 2. Neurobiology of disease-avoidant ingestive behaviours. The vagus nerve provides the major neural pathway identified to date. From bottom to top, the initial chemosensory transduction events occur in immune cells that respond to specific chemical components expressed by dangerous micro-organisms. Afterwards in a paracrine-like manner, a close interaction of lymphocytes with sensory neurons bearing appropriate immune-transmitter receptors (e.g. cytokines, prostaglandins, neurotransmitters) leads to viscera–sensory afferent neural signalling [24,30]. This neural pathway is complemented by a humoral afferent pathway (dotted line) involving access of immune-generated molecules throughout circumventricular organs and/or being transduced within the brain perivascular space (see figure 3). In general, the hypothalamus and the nucleus of the solitary tract are constantly involved in processing visceral–immune signalling, being two key neural integrators of energy homeostasis (e.g. appetite, thermoregulation, sleep; reproduction [31]). Besides these structures, two cortico-limbic structures are of relevance within neuro–immune interactions; the insular cortex and the amygdala, being neural nuclei responsible for: (i) stimuli hedonic categorization, (ii) emotionality, and (iii) associative learning, in animals as well as in humans [32–36]. Another important sensory route used to avoid sick individuals or contaminated food is the olfactory system. Specific vomeronasal receptors are capable of detecting volatile molecules derived from activated leucocytes and also from pathogens [37]. From top to bottom, this sensory activation would modulate behaviour through canonical olfactory relays in the olfactory bulb, pyriniform cortex and hypothalamus.

Thus, the immune-conditioned responses that we shall review in this paper would mainly fall under this category.

To induce any behavioural change, the brain needs to receive appropriate interoceptive and/or exteroceptive signals. Peripheral immunological challenges signal the CNS via different afferent pathways, which have been extensively reviewed elsewhere [24–29]. Mainly based on animal models, a discrete neural network composed of hindbrain, hypothalamic and cortico-limbic structures has been identified that processes peripheral immune signalling. In figures 2 and 3, we summarize the current knowledge on the afferent crosstalk of the immune system and the

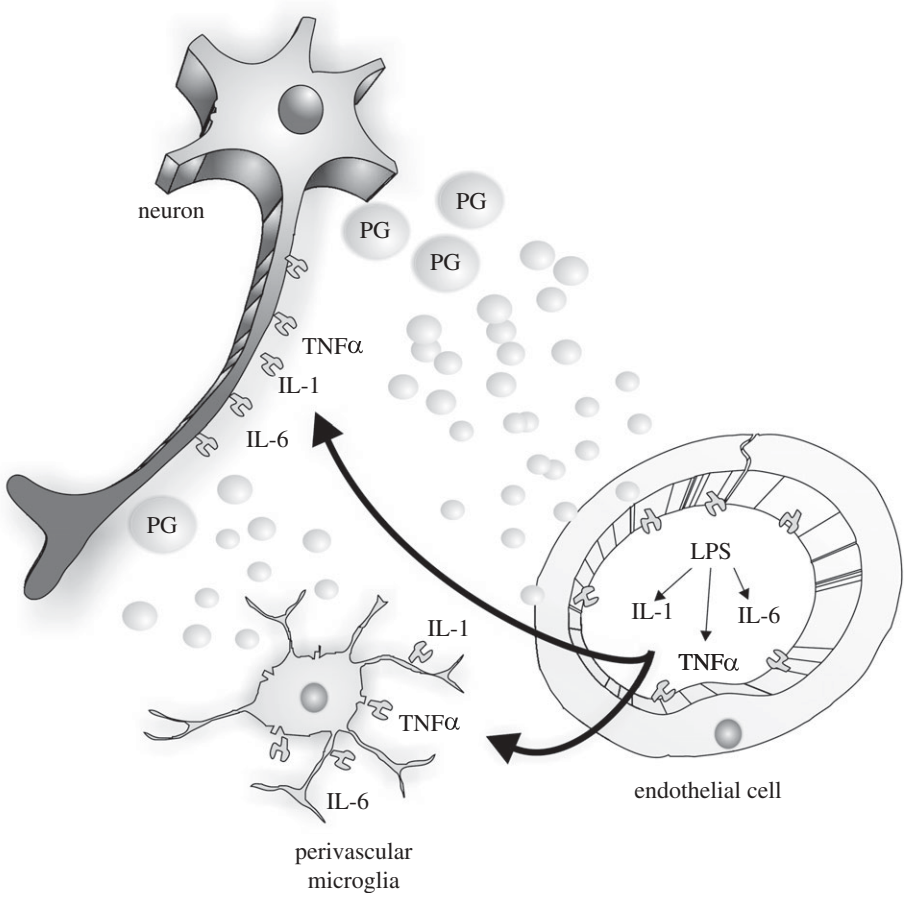

Figure 3. Pericerebral neuro–immune interactions. Immune-transmitters can cross the blood–brain barrier or originate a second wave of diffusible messengers within the brain parenchyma [26,38,39]. Cytokines or prostaglandin locally produced by endothelial cells or perivascular microglia can activate neurons that project to specific brain areas or diffuse into the brain parenchyma to reach their targets. Thus, activation of neurons can be direct or indirect and potentially occurs in the whole brain. However, receptors relevant for neuro–immune communication in the brain are preferentially located in the vicinity of circumventricular organs, from which the signal is relayed to other brain regions through neuron-to-neuron comunication. IL, interleukin; LPS, lipopolysaccharide; PG, prostaglandins; TNF, tumour necrosis factor.

brain, particularly relating to ingestive avoidant behaviours.

2. INNATE DISEASE-AVOIDANT INGESTIVE BEHAVIOURS

(a) *Olfactory avoidance of disease*

Mammals rely on olfaction to interact adequately with each other and with their environment [40]. Olfactory receptors are used to identify odorants and pheromones. In this regard, the expression of formyl peptide receptors by vomeronasal sensory neurons in multiple mammalian species has recently been reported [37]. Importantly, the same receptors are expressed by immune cells such as granulocytes, monocytes or macrophages, and recognize multiple agonists. These molecules are associated with inflammation or disease; examples include formyl peptides which are released by Gram-negative bacteria, virus-derived peptides, some antimicrobial peptides and acute phase proteins [41–43]. *In vitro* expression of olfactory mouse formyl peptide receptors showed sensitivity to disease/inflammation-related ligands [37]. Using an *in situ* approach the same authors reported neuronal responses to the same kind of molecules, shedding light on a novel class of vomeronasal agonists. Importantly, these compounds are not part of a group defined by chemical composition or structure, but rather by a link to pathogens, or to inflammation, which may result from an immune response to germs, suggesting that through olfaction mammals can specifically detect contaminated compounds such as spoiled food, or alternatively, enable the identification of unhealthy conspecifics via the evaluation of secretions, supporting innate disease-avoidant behaviours (figure 2). Interestingly though, the long-standing tradition of physicians assisting anamnesis based on olfaction of the patient's '*humours*' has been almost extinguished in modern allopathic tradition [44]. In this regard, the diagnostic power of odours has recently been revalorized using an '*electronic nose*' tuned to specifically detect volatile pathogen metabolites [45].

(b) *Illness anorexia*

Lipopolysaccharide (LPS), a component of Gram-negative bacteria, administration has been used as a model of acute infection with concomitant anorexic and adipsic effects [46–49]. Proinflammatory cytokines released in response to LPS seem to act synergistically on the CNS to elicit anorexia and

adipsia [50,51], employing a discrete neural network (figure 2). Notably, the administration of LPS reduces the frequency of meals, while interleukin (IL)-1β reduces both meal frequency and size [52]. Similarly as in animals, in humans low-dose LPS reduced food intake in the first 4 h without causing nausea [53], and reductions in food intake correlated with plasma levels of tumour necrosis factor (TNF) and IL-6 [54]. Illness anorexia is acknowledged to help maintain bodily integrity in the face of infections and physical injuries [46,55]. It is conceptualized as part of an energy allocation process involving reducing activities such as hunting/foraging and digestion, which would otherwise consume the energy required to heal wounds or reduce bacterial load, or correct microbiota imbalances. Some evidence indicates that food deprivation may limit supply of micronutrients needed by particular bacteria, e.g. *Listeria monocytogenes*, to proliferate [56,57]. Also, several rodent models of cancer frequently show anorexia [58–62], which could be attributed to the microenvironment surrounding tumour cells, as well as tumour cells themselves that produce pro-inflammatory cytokines which in turn trigger inflammation [63].

To date, efficient therapies to treat patients suffering from illness anorexia are few [28,64,65]. Interestingly, however, repeated administration of LPS, at short time intervals, results in a tolerance status characterized by reduced cytokine production and secretion from immune cells [66,67]. Several physiological responses to LPS are affected in LPS-tolerant animals [68–71]. In line with this, anorexia is also reduced after repeated and frequent encounters with LPS [48,72].

Using functional imaging technique it is now possible to disentangle the neural origins of the human '*sickness*' feeling [32–34]. In this series of experiments, where typhoid vaccine was used as a peripheral inflammation model, the authors found that in addition to significant increase in fatigue, confusion and impaired concentration (appetite was not assessed), peripheral inflammation (in particular circulating IL-6) activated human brain interoceptive (encoding representation of internal bodily states) regions such as the insular cortex and amygdala (figure 2), as well as the anterior cingulate cortex, medial prefrontal cortex, nucleus accumbens and superior temporal sulcus. All together, these data strengthen the idea of a common pathophysiological neural basis for major depressive disorder and sickness-associated mood changes.

(c) *Illness potentiates food neophobia*

Staphylococcus aureus, a Gram-positive bacterium, is a major cause of food poisoning in humans, eliciting a stereotypical vomiting response [73]. Thus the test of choice for assessing its biological activity is a monkey feeding test [74]. *Staphylococcus aureus* enterotoxins induce massive T lymphocyte activation via the T cell receptor, and are thus named superantigens [75,76]. Challenging animals with staphylococcal superantigens results in enhanced circulating levels of cytokines such as IL-2, interferon (IFN) and TNF [77,78]. Furthermore, brain activity is modulated shortly after peripheral superantigen challenge [35,38,79–81]. Specifically, it has been proposed that emotionality may be enhanced in this context by central corticotrophin-releasing hormone alterations [80]. For instance, inoculations with low doses of staphylococcal enterotoxin B augmented food neophobia, but only when it was also associated with a specific context [82]. However, neither mobility nor subsequent 24 h body weight loss were affected, which stands in contrast to generalized illness anorexia [83,84]. In comparison to a naive condition, after exposure to a certain food, superantigen inoculation did not modify intake of that particular and now familiar food [82–84]. These data suggested that the massive T-lymphocyte response to superantigens potentiates food neophobia. Interestingly, however, superantigen-enhanced neophobia was also evident towards inanimate, non-gustatory objects, reflecting increased anxiety and/or generalized neophobic behaviour [82]. Recently, in freely behaving rats we have documented that within the first 100 min after superantigen inoculation, electrical activity of cortico-limbic structures, such as the amygdala and the insular cortex, is strongly activated [35], thus substantiating the behavioural modifications elicited during this immune activation.

In summary, peripheral immunological processes seem to enhance emotionality [85], thus potentiating innate avoidant behaviours. We hypothesize that such avoidant behaviours would have the adaptive advantage of reducing unnecessary danger when body energy resources might be demanded by leucocytes to mount effective defence against pathogenic threats (see §4).

3. ASSOCIATIVE LEARNING AS AN EVOLUTIONARY STRATEGY TO AVOID DANGER

CTA is a special kind of associative learning in which subjects acquire aversion to a taste cue (conditioned stimulus: CS) when it is followed by malaise (unconditioned stimulus: US); thus taste is readily associated with malaise or sickness [86]. Taste–sickness associative learning is based on the naturalistic relation of food ingestion with its possible postprandial immunotoxicological consequences [87]. In a broader perspective, classical conditioning can be understood as learning about the temporal or causal relationships between external and internal stimuli to allow for the appropriate preparatory set of responses before biologically significant events occur [88]. In this regard, the capacity to associate a certain immune response or status (e.g. allergens, toxins, antigens) with a specific extereoceptive stimulus (e.g. context or flavours) is of high adaptive value. We have hypothesized that this capacity was acquired during evolution as an adaptive strategy in order to protect the organism and/or prepare it for danger [87,89]. For instance, a sensitized individual exposed to a specific antigen (and its categorization as an allergen) might associate this with a specific environment or food. An adaptive response is then elicited, consisting first of behavioural modifications, in order to avoid the place or food associated with the antigen [90–92]. If this is not possible, then the individual will try to reduce the contact with the allergen, e.g. by coughing, sneezing [93],

or vomiting [94]; at the same time their immune system may prepare the body for interaction with the antigen, for instance, by mast cell degranulation [95–98] or antibody production [21,99–101]. Although under experimental conditions such an association could be extinguished, it is probable that it will last for a long time, since in natural circumstances the individual may try to avoid contact with any environmental cues that signal the CS. In this regard, postprandial taste categorization as '*safe*' or '*dangerous*' is of vital relevance in modifying predator selection in the natural habitat [102–104], and probably also food choice in human markets [105]. In general, avoidant behaviour is just part of a coherent set of physiological responses orchestrated to first escape danger and/or prepare for its counteraction employing body defence systems (or the so-called behavioural–immune system [14,15]). In §§3*a* and 3*b* the development of the concept of behavioural conditioning immunomodulation and its neurophysiology will be reviewed; §3*c* is dedicated exclusively to documenting human studies in this context.

(a) *Conditioned immunosuppression*

In the 1970s a remarkable finding by Ader and Cohen was published [106]; these investigators were studying CTA extinction when they accidentally found that animals were dying by evoking CTA induced by cyclophosphamide (US). They had conducted such experiments with different US, and none of the animals had ever died. Besides the induction of gastric malaise, cyclophosphamide was already well known for its cytotoxic immunosuppressive properties [20]. Later by using immunological assessments, they discovered that conditioned animals showed in addition to CTA a strong conditioned immunosuppression elicited by the mere presentation of the taste (CS), explaining the deaths of the animals.

Several laboratories have investigated the neural pathways involved in CTA (for reviews see [86,107,108]). One of the advantages of using CTA to study neural control over the immune system is that some of those pathways are also involved in the interaction between the immune system and the CNS (figure 2). Taste fibres carry information about the meal flavour to the nucleus of the solitary tract in the brainstem. Visceral fibres carrying the feedback from food ingestion converge to the same brainstem and midbrain areas in which receptors for cytokines have been described [109,110]. Receptors for cytokines [111] and neurons responding to both gustatory and visceral stimuli are found in the pontine taste area of the parabrachial nucleus (second gustatory relay). From the parabrachial nucleus, one major projection of fibres passes to ventral forebrain structures, including the amygdala, lateral hypothalamus and the substantia innominata, and a second projection passes to the posterior ventromedial and ventromedial nuclei of the thalamus. The thalamic taste area projects to the insular cortex, a region 1 mm wide by 3 mm long located along the rhinal sulcus in the rat. The insular cortex (Krieg's areas 13 and 14) has been referred to as the gustatory or visceral cortex because it receives taste and visceral information from the thalamus [112,113]. These anatomical connections suggest that the insular cortex plays an integral role in the mediation of visceral reactions, and potentially also emotions. The insular cortex has been involved in mediating the associations between taste and illness, since the insular cortex ablation disrupts the acquisition and recall of CTA. However, it should be pointed out that the insular cortex is not involved in the hedonic responses to taste; thus like normal rats, insular cortex-lesioned animals prefer sucrose as well as low concentrations of sodium chloride over water and reject quinine and acid solutions. Also, taste responsiveness remained intact even in decerebrated or anaesthetized rats [107,108]. Interestingly, recent human data combining functional magnetic resonance imaging and multiorgan physiological recordings found the insular cortex to be responsive to the magnitude of subjectively experienced visually induced disgust [34], in agreement with data showing that human insular activity is also affected by disgusting odours [114], arguing in favour of a somatotopically organized representation of bodily physiological state within the insula, providing valuable support to revitalize the old somatic theories of emotions [115].

As explained, the insular cortex is essential for the acquisition and retention of CTA learning. Taking advantage of the CTA-based model of conditioned immunosuppression, in a series of experiments conducted in our laboratories, we have demonstrated that excitotoxic lesions aimed at the insular cortex disrupt the acquisition of conditioned immune responses and CTA [116]. The results showed that animals receiving lesions into the insular cortex but not in the parietal cortex showed disrupted acquisition of both conditioned immunosuppression and CTA, since the insular cortex lesioned animals showed similar antibody production as the group to which CS was not presented. Furthermore, insular cortex lesions do not affect either the normal humoral immune response or the immunosuppressive effects of cyclophosphamide; thus, the insular cortex could be involved in the modulation of associative mechanisms of immunosuppressive conditioning, as has been suggested for CTA [116]. Interestingly, data from lesion studies in humans suggest that perception of disgust, regardless of sensory modality, may depend on the structural integrity of the antero-ventral insular region [117].

In line with these observations, we have also identified the neural substrates involved in conditioned immunosuppression using cyclosporine A, a calcineurin inhibitor specifically blunting T-lymphocyte reactivity [36]. The conditioned effect in the immune response (i.e. lymphocyte proliferation and cytokine production) was differentially affected by insular cortex lesions. This study corroborates evidence that the insular cortex is essential for both acquisition and evocation of immune-conditioned response. In contrast, the amygdala appears only to mediate the input of visceral information necessary during acquisition, whereas the ventromedial hypothalamic nucleus appears to participate only in the output pathway to the immune system, which may produce the conditioned immunosuppresive response. Taken together,

these data show that across different conditioning models and substances used as unconditioned stimuli, the insular cortex and the amygdala are essential brain areas for immune learning to take place (figure 2).

(b) *Conditioned immunoactivation*

Although several researchers have been working on conditioned immune responses, the conditioned enhancement of antibody production is still poorly investigated (for review see [118]). However, we have been able to show enhancement of serum antibody production to a defined antigen [21]. By pairing the novel taste of saccharin with an antigen protein (hen egg-white lysozyme) and afterwards re-exposing the subject to the conditioned taste, we demonstrated a reliable increase in antibody production. The conditioned production of antibodies of classes IgG and IgM was in a pattern similar in both magnitude and temporal course to that found after re-injection of the same doses of the antigen, resembling a normal secondary immune response [116]; see table 1. One of the advantages of using antigens as opposed to immunosuppressants is the absence of side or undesirable effects. These experiments have been replicated by us and other laboratories [99,101,119]. Furthermore, in agreement with the brain areas that were involved with conditioned immunosuppression, Chen *et al.* [101] were able to demonstrate that conditioned immunoactivation significantly increased c-Fos activation of the insular cortex.

Analogous avoidant conditioned behaviours have been elicited after pairing gustatory stimulation and subsequent peripheral proinflammatory cytokine administration [120–123]. However, not all cytokines are able to induce a similar degree of association; taste-TNFα requires a much higher dose and more association trials than IL-1β [124], and pairing taste with IFN-α may not induce a stable association to taste memory traces [125].

It should be mentioned that this kind of associative learning would strongly depend on the individual immune history. For instance, we have documented that during LPS tolerance status, rats categorize saccharin taste as *'familiar-safe'*, although its consumption was followed by the administration of a high dose of LPS [72]. In contrast, for LPS-naive animals, saccharin's hedonic value was reduced after its trace memory was followed by the same LPS stimulus. For these animals, the taste–LPS engram was solid and stable. Such behavioural data are in agreement with previous reports in which oral tolerance development against ovalbumin was sufficient to block the aversion of egg-diet in allergic animals [92,126] that otherwise develop a strong food-avoidant behaviour [127]. In this regard, food allergic animals displayed an increased c-Fos expression in the hypothalamus and amygdala following intra-oral antigenic challenge, which is completely abolished by previous repeated intake of lower doses of the same antigen resulting in an oral tolerance phenomenon [92,126]. Also it was reported that LPS-induced c-Fos expression in the central nucleus of the amygdala is reduced after development of LPS tolerance [128]. Using implanted wireless deep-brain electrodes technique, we have recorded *in vivo* neural electrical activity in freely behaving rats during LPS challenges under naive and tolerance states [35]. We observed a paradoxical response; although circulating cytokine levels were blunted after five daily LPS inoculations, the insular cortex and amygdala electrical responses were faster and stronger than those observed in the same animal when LPS was administered in the naive immune condition. Although further investigation is necessary to clarify these particular results, the fact is that messengers other than cytokines may be involved in the afferent immune-to-brain communication; for instance, prostaglandins (figure 3) released by endothelial and/or perivascular cells as a response to circulating LPS [38] yield a plausible explanation. Alternatively, the animals might be conditioned (e.g. injection as CS, and LPS as US) and such '*paradoxical*' neural recording may actually reflect the neural correlate of a conditioned response.

In general, peripheral cytokine release occurring while taste trace memory is under categorization seems to be responsible for the strength of the taste–immune engrams resulting in avoidant behaviours. In this regard, a dose–response relationship has been demonstrated between the amount of a given immune stimulus, employed as US associated with a taste, and the resulting conditioned behavioural response: the stronger the immune stimulation, the more pronounced the CTA behaviour [72,129,130]. Furthermore, it has been reported that a low-dose antigenic challenge does not induce significant immune or behavioural responses in naive animals; however, after an immune sensitization procedure, the same challenge also worked as a US, inducing a strong behaviourally conditioned avoidance response [131]. Overall, these results suggest that the same areas involved in conditioned immunosuppression could also be involved in conditioned immunoactivation (figure 2).

But how does the CNS modulate changes in the peripheral immune system? There are three main efferent neuro–immune pathways (reviewed elsewhere [25,132–134]): the hypothalamic–pituitary–adrenal (HPA) axis (humoral), the sympathetic–adrenal–medullary axis and the parasympathetic nervous system including the vagus nerve. Briefly, descending projections to hindbrain affect vagal output, affecting many autonomic functions, including direct innervations to primary and secondary immune organs. Activation of the HPA axis results in the production of glucocorticoid hormones and catecholamines [135] regulating cytokine balance [136] and vice versa. The sympathetic nervous system regulates immunity by innervation of lymphoid organs and the release of noradrenaline, and a hormonal component that regulates immunity systemically through the release of adrenaline from the medulla of the adrenal glands [137]. Coupling of the sympathetic nervous system and the HPA axis leads in the spleen to stronger effects through activation of β-adrenoceptors and glucocorticoid receptors [138]. Finally, parasympathetic activity, via acetylcholine receptor activation in immune cells, has been revealed as an important modulator of inflammatory responses; the '*anti-inflammatory cholinergic reflex*' [139]. In summary, the brain

and immune system intensively and extensively interact, sharing pathways, messengers and receptors, explaining a substantial part of the neurobiology behind disease-avoidant ingestive behaviours.

(c) *Conditioned immunomodulation in humans*

So far, few attempts have been undertaken to specifically investigate conditioned effects which directly modulate peripheral immune functions in humans. Since the nineteenth century, anecdotal case studies have reported the occurrence of allergic-like symptoms in the absence of allergens, provoked simply by visual cues (a picture of a hay field or an artificial rose = CS [140]). Conditioned dermatitis was elicited in adolescent male subjects as a result of evoking a specific association [141]. In another case report, asthmatic patients suffering from skin sensitivities to house-dust extract and grass pollen were exposed to these allergens by inhalation [142]. After a series of conditioning trials, they experienced allergic attacks after inhalation of the neutral solvent used to deliver the allergens. This work showed not only fast conditioning of the asthmatic attack, but also tenacious retention and a lack of extinction. More recently, this view was further supported by experimental data from patients with allergic rhinitis; after the association phase, elevated mast cell tryptase in mucosa was observed when an intranasal saline application was given simultaneously with the CS [143]. Another type of allergic reaction, the delayed-type hypersensitivity response, was tested in healthy volunteers who received five monthly tuberculin skin tests [144]. In this conditioning protocol both tuberculin and saline were injected; while the latter was taken from a green vial, tuberculin was drawn from a red vial. On the test day, the colour labelling of the substances was reversed. Although the saline injections did not induce a skin reaction (erythema and induration), the severity of the symptoms was significantly blunted in all the subjects tested when the tuberculin was drawn from the green vial (i.e. conditioned effect). However, a similar protocol using various allergens (e.g. mite dust or fur) taken from coloured vials did not result in conditioned modulation of skin reactions [145].

Associative learning has been consistently reported in the context of cancer treatment, particularly chemotherapy [146]. As mentioned before, chemotherapy agents (e.g. cyclophosphamide) generally have immunosuppressive effects. These agents are typically administered in cycles, with each outpatient treatment infusion followed by a period of recovery prior to the next infusion. From a conditioning perspective, clinic treatment visits can be viewed as '*association trials*' in which the distinctive salient features of the clinic environment are contingently paired with the infusion of immunosuppressants. For instance, the immune function was assessed in cancer patients in hospital prior to chemotherapy and compared with assessments conducted at home. Proliferative responses to T-cell mitogens were lower for cells isolated from blood samples taken in the hospital (i.e. after evocation) than for home samples [147]. These results were replicated in female [148] and paediatric patients receiving chemotherapy [149]. In addition, chemotherapy patients often develop conditioned-nausea [147,150–152], -anxiety [153,154] and -fatigue responses [155] to reminders of chemotherapy, which can also be elicited by thoughts and images of chemotherapy [156,157], raising the possibility that conditioned effects may affect patients for years after treatment.

Only a few human studies have so far documented immune parameters at the cellular level being affected by behavioural conditioning procedures. Conditionability of natural killer cell numbers and their lytic activity in healthy volunteers were reported after evoking a taste–adrenaline association [158]; however, these effects could not be replicated [159]. The efficacy of conditioning was also tested in multiple sclerosis patients, for whom four monthly cyclophosphamide infusions were contingently paired with the taste of aniseed-flavoured syrup [160]. Long-term treatment with cyclophosphamide decreases blood leucocyte numbers and often leads to leukopenia. Interestingly, after six months of administering the placebo infusion paired with the drink (i.e. evoking taste–cyclosphosphamide engram), eight out of ten patients showed a conditioned reduction in peripheral leucocyte numbers. In addition, by pairing IFN-γ injections with a distinctively flavoured drink, it was possible to induce an elevation of neopterin and quinolinic acid serum levels after evoking such an association in healthy volunteers [161]. However, it has been hypothesized that more than a single associative learning trial pairing a distinctive taste with IFN-β injections is necessary in order to produce immune conditioned effects [162]. This view is supported by experimental data for healthy male volunteers where the immunosuppressive drug cyclosporine A was paired four times with a distinctively flavoured/coloured solution [22]. After association, the mere re-exposure to the drink induced conditioned inhibition of *ex vivo* cytokine (IL-2 and IFN-γ) mRNA expression and cytokine release, as well as of the proliferative responsiveness of human peripheral blood lymphocytes, similar to the drug effect.

Finally, it should be mentioned that recently both basic and clinical research have focused on elucidating the neurobiology behind the placebo effects [163,164]. In this regard, experimental data indicate that conscious expectation and unconscious behavioural conditioning processes appear to be the major neurobiological mechanisms capable of releasing endogenous neurotransmitters and/or neuro-hormones that mimic the expected or conditioned pharmacological effects. To date, research on placebo responses affecting immune-related diseases is still scarce, but there are consistent indications that skin and mucosal inflammatory diseases, in particular, are strongly modulated by placebo treatments (for a review, see [165]). In summary, the brain's capability to modulate peripheral immune reactivity has been impressively demonstrated by paradigms of behavioural conditioning in animal experiments as well as in human studies.

4. ENERGY BALANCE DURING SICKNESS

The regulation of energy homeostasis and the immune response are crucial for an organism's survival.

Metabolism and immunity have been linked throughout Metazoan evolution to ensure the storage of energy for times of deprivation and defence against pathogens in case of infection. In fact, the structural units of the metabolic and the immune system are derived from common precursors [166]. Thus, the insect fat body consists of the mammalian homologues of liver, adipose, blood and immune cells. Mammalian adipose and liver tissues contain both metabolic and immune cells, and are in close proximity to blood vessels for fast communication with other sites in the body; common signalling pathways and regulatory molecules are involved in immune and metabolic processes. More specifically, adipocytes and macrophages both secrete cytokines and can be activated by pathogen components, for example, by LPS [166]. Interestingly, pre-adipocytes are still able to differentiate into macrophages, and both are genetically related. Inflammatory genes that are expressed by both macrophages and adipocytes are also adipocyte-specific metabolic genes [167–169].

Now the dependency between the energetically '*expensive*' immune processes and metabolism becomes clear: the immune response '*competes*', for example, with thermoregulation, growth, reproduction or lactation for energy [170]. Accordingly, those processes can be downregulated in cases of severe or chronic inflammation, or malnutrition. However, an energy surplus (i.e. obesity) can also impair immune responses and induce chronic inflammation or the so-called '*metaflammation*' [166].

(a) *The cost of immunity*

Usually a human adult (male/30 years/70 kg/1.7 m) needs 7000 kJ = 1671 kcal per day to cover basal metabolic activities [171], and with a moderate workload, about 10 850 kJ = 2590 kcal per day are needed [172]. Although the human brain constitutes only 2 per cent of the body weight, it accounts for 25 per cent of the energy expenditure (2000 kJ = 478 kcal per day [173]), and is thus the privileged energy '*consumer*' in the body. Neurons and glia cells oxidize mainly glucose to maintain resting membrane potentials, but primarily energy is employed for neurotransmission (ca. 87%) [174,175]. It has been calculated that the overall cost of synaptic transmission plus action potential propagation for a pyramidal glutamatergic neuron firing at 4 Hz would be 2.8×10^9 ATP neuron^{-1} s^{-1} [176]. The basal energy consumption for maintenance of the resting potential is 3.4×10^8 ATP neuron^{-1} s^{-1} and 1.0×10^8 ATP glia cell $^{-1}$ s^{-1}; thus considering a 1 : 1 neuron : glia ratio it is calculated as a combined consumption of 3.4×10^9 ATP cell^{-1} s^{-1} [174,175]. These calculations are in remarkable agreement with estimates made *in vivo* using magnetic resonance scanning [177]. In contrast, immune cells (including lymphocytes, granulocytes and macrophages) consume approximately 1600 kJ = 382 kcal per day when they are not activated (i.e. in the basal metabolic state) [10,178]. However, effector immune responses depend on three energy expensive features: (i) cellular movement, (ii) clonal expansion, and (iii) globulin production [179]. For instance, the mitogenic stimulation of thymocytes or naive T-cells induces about a 20-fold increase in glucose uptake within 1 h [180]. Thus, in an activated state leucocytes can raise their energy demands to 1750–2080 kJ = 478–497 kcal per day [10]. For instance, mice immunized with an innocuous and non-proliferating antigen display approximately 20–30% increases in oxygen consumption and metabolic heat production compared with pre-immunization baseline values [181]. Further calculations indicate that an increase in metabolic rate of approximately 9–30% is usual: it is known that activation of leucocytes occurs with minor surgery, which increases heat production by more than 10 per cent of the metabolic rate. The metabolic rate is also increased with multiple bone fractures by 15–30%, sepsis leads to an increase of 50 per cent and extensive burns cause a large increase of 100 per cent or more [10,11]. In this regard, fever is associated with a 7–13% increase in caloric energy consumption per 1°C increase in body temperature [178], the rough energy investment of a 70 kg person for walking 45 km [182]. It should be mentioned, that leucocytes use all types of fuels, but approximately 70 per cent is from glucose and glutamine [179,183,184]. But, how can energy-rich fuels be provided to the immune system when energy is limited?

(b) *Circadian energy allocation*

Because brain and muscles need much energy-rich fuel during the day, the major activities of the immune system occur during sleep [10]. Fuel allocation to the immune system is time-dependent (figure 4). In a fasting subject, fuel provision to the body starts by activation of the HPA axis and sympathetic nervous system in the morning. Sympathetic and HPA axis hormones support fuel provision mainly for the brain and muscle by stimulating triglyceride lipolysis, β-oxidation of fatty acids, glycogenolysis, gluconeogenesis and some protein breakdown. In addition, these hormones inhibit many aspects of the immune system, but not secretion of natural polyclonal antibodies or leucocyte traffic in the blood [185–188]. Leucocyte traffic in the blood is needed for immune surveillance of the body, and this occurs during the daytime. Hormone levels start to decrease in the afternoon and reach a minimum at midnight; this prevents energy-rich fuel provision to brain and muscles. In parallel, hormonal inhibition of the immune system is largely decreased. In contrast, during the night, energy-rich fuels are mainly allocated to the immune system. Shortly after sleep onset, growth hormone, which stimulates gluconeogenesis, promotes glucose allocation to the immune system. Since leucocytes use mainly glucose, growth hormone-associated provision of glucose is important during this time [179,189]. In addition, serum levels of ketone bodies, free fatty acids and glycerol rise from late afternoon until midnight by threefold to sevenfold [190], which represents another important fuel source for immune cells. It is noteworthy that infections lead to sickness behaviour, which increases sleep time and time in bed [12,55], thus also promoting allocation of energy-rich fuels to the activated immune system [191]. In this regard, it has been hypothesized that the circadian

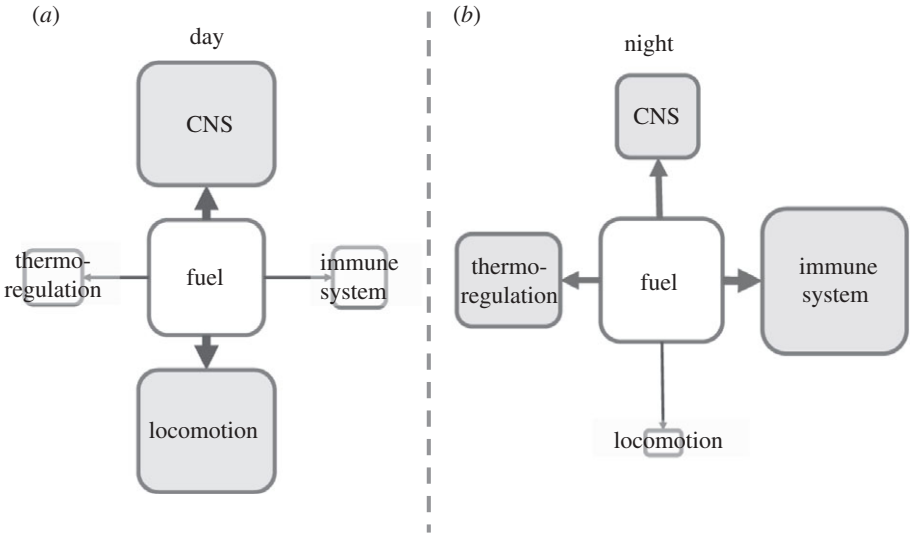

Figure 4. Circadian fuel allocation. During the day (*a*) many aspects of immune function are inhibited due to the immunosuppressive effects of cortisol and noradrenaline. In contrast at midnight (*b*), the level of these hormones is low, but growth hormone, prolactin and melatonin are secreted shortly after sleep onset, which activates the immune cells [10]. A tight circadian allocation of fuel is accomplished to cover energy demands optimally. However, when immunity is compromised an '*energy demand reaction*' is elicited by leucocytes mobilizing fuel stocks and supressing demand from other organs/systems, with the overall purpose of preferentially allocating fuels to activated immune cells. Concomitant behavioural changes prevent waste of energy, avoid unnecessary danger and promote safe environments, but at the same time help fight against pathogenic threats; if they survived, the individual would probably form associative memories to anticipate similar threats and/or to counteract inevitable future encounters.

rhythms of the neuroendocrine and immune systems belong to an important programme necessary for provision of energy-rich fuels to daytime and night-time *'consumers'* [10].

During activation of the immune system, degraded muscle proteins are used for gluconeogenesis in the liver. In the presence of an elevated sympathetic activity and slightly increased activity of the HPA axis, gluconeogenesis results in higher glycaemia [10] and hyperlipidaemia [192–194]. Free fatty acids induce insulin resistance in many tissues [195] and, in parallel, pro-inflammatory cytokines such as TNFα can disturb insulin receptor and insulin-like growth factor-1 receptor signalling [196,197]. Importantly, however, not all cell types become insulin insensitive during inflammation. Remarkably, leucocytes maintain insulin sensitivity during such conditions; immune cells incorporate glucose via glucose transporters that are activated by specific stimuli, such as LPS, anti-CD3 antibodies, cytokines and hormones such as leptin and insulin [184,198]. In conclusion, an '*energy demand reaction*' is elicited by the immune system during infection/inflammation, mobilizing fuel stocks (lipolysis/glucogenolysis) and inducing insulin resistance in liver, adipose tissue and muscle, with the overall purpose of allocating energy-rich fuels to activated immune cells [10]. Concomitant changes in behaviour prevent waste of energy (reproduction, social interaction, foraging/hunting), avoid unnecessary danger (neophobia/hyperalgesia) and promote safe environments (lethargy/anhedonia), but at the same time stimulate specific strategies to help fight against pathogenic threats, activating and promoting innate and adaptive immunity by costly hyperthermia [199,200] and somnolence [201]; finally through associative learning, it may also be possible to avoid certain foods or environments signalling danger and/or at the same time prepare the body to counteract by anticipatory immune responses (conditioning).

5. CONCLUSION AND PERSPECTIVES

The interplay of the brain and the immune system provides several adaptive advantages to animals facing different environments with constant threats. During pathogenic insults, an orchestrated leucocytic reaction fights against them, but at the same time appeals for energy to restore immunity. Through behavioural changes, including several avoidant behaviours, an energy-protecting strategy is promoted, with the overall goal of restoring the body to health. Furthermore, an adaptive strategy based on associative learning as well as on genetic transmission seems to have evolved to avoid disease, the so-called '*behavioural–immune system*' [15]. Recently, it has been reported that an aggressive immune response (IL-6 production after *ex vivo* LPS challenge of peripheral blood cells) can be induced by the mere visual perception of other people's disease symptoms [202]. In this line of thinking, another recent report shows an increased immune reactivity of mouth mucosa (increased salivary TNF-α) to disgusting pictorial stimuli [203]. Interestingly, it has been found that at least some of the patterns of disgust follow a parent-to-child transmission (learned), but other so-called '*core disgust elicitors*' are present in early childhood (innate) [204], indicating that both onto- and phylogenetic developments are behind our disgust elicitor patterns, and might be the basis of our common morality and ethical judgements [205,206], as well as ethnic idiosyncrasy.

Although at a first glance contradictory, kin altruism has also been hypothesized to be driven by

immune–pathogen interactions based on major histocompatibility complex (MHC) polymorphism [207]. This hypothesis suggests that pathogen and parasite avoidance act as a driving force for kin selection, and preferential association with relatives decreases the probability of infection with unfamiliar pathogens; thus altruistic behaviour towards kin will further decrease the danger of infection by increasing the representation of relatives in a group. The fact that olfaction and the MHC have been strongly linked [208] provides further support to this perspective. Actually, in the 1970s Lewis Thomas proposed that functions of the MHC in recognition of '*self*' and '*non-self*' might have evolved from earlier needs of organisms to differentiate conspecifics from members of other species (i.e. maintain phylogenetic identity) by chemical recognition [209]. Thomas was the first to speculate that such an evolutionary origin of MHC might still be reflected in chemical sensory signalling of individuality in advanced taxa.

As a conclusion, an understanding of the complexity behind the neuro–immune crosstalk and its energetics sheds light on disease-avoidant behaviour as an ancient driver of the necessity both to maintain identity and to avoid threats. All in all, it is expected that such transdisciplinary perspective will help to provide treatments for some human diseases (e.g. obesity, depression, anxiety, allergies), as well as an understanding of some parts of the most remote and antique corners of our psyche.

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