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Influence of the microbiota-gut-brain axis on behavior and welfare in farm animals: A review

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Abstract

There is increasing evidence of a pivotal role of the gut microbiota (GUT-M) in key physiological functions in vertebrates. Many studies discuss functional implications of the GUT-M not only on immunity, growth, metabolism, but also on brain development and behavior. However, while the influence of the microbiota-gut-brain axis (MGBA) on behavior is documented in rodents and humans, data on farm animals are scarce. This review will first report the well-known influence of the MGBA on behavior in rodent and human and then describe its influence on emotion, memory, social and feeding behaviors in farm animals. This corpus of experiments suggests that a better understanding of the effects of the MGBA on behavior could have large implications in various fields of animal production. Specifically, animal welfare and health could be improved by selection, nutrition and management processes that take into account the role of the GUT-M in behavior.

32 **Key words:** Microbiota, microbiota-gut-brain axis, behavior, welfare, emotion, livestock

33

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58 **Introduction**

59

60 The gut microbiota (GUT-M) has received increased interest for several years because it is involved in
61 many functions in humans and animals. The GUT-M is composed of bacteria, archaea, viruses and
62 eukaryotes (including protozoa and fungi). The GUT-M has been demonstrated to influence immune
63 function for years and to have wide impacts on health. Moreover, impairments of gut health can lead
64 to many intestinal diseases and to dysbiosis, an unbalance in GUT-M, which facilitates many
65 pathological states involving infections with pathogens or metabolic disorders [1-4]. The GUT-M has
66 also a pivotal role in many extra-intestinal tissues and in various developmental processes and
67 metabolism in host organs such as the liver, adipose tissue, bone, *etc* [5]. The brain is also a major
68 target of the GUT-M because the microbiota produces metabolites and neurochemicals. At the same
69 time, neurotransmitters like epinephrine and norepinephrine from the host influence the growth and
70 virulence of bacteria [6]. The relationship between the GUT-M and the brain, so called microbiota-
71 gut-brain axis (MGBA) includes influences upon brain development, neural processes (such as
72 myelination or neurogenesis), pain processes, the hypothalamo-pituitary axis (HPA) and behavior [7].
73 The MGBA is also called microbiome-gut-brain axis by some authors, since the microbiome consists
74 of not only the microbiota, but also microbiota genomes and products [8]. Although some methods
75 used to investigate the MGBA have been recently criticized [9], there are more and more studies
76 describing the influence of the GUT-M on the central nervous system (CNS) and the mechanisms
77 involved in this interaction. The influence of the GUT-M on behavior is increasingly reported in
78 rodents using germ-free animals (living in the absence of detectable living microorganisms) or in
79 rodents and humans following the use of special diets affecting GUT-M composition, or microbiota
80 transfer [10-16] using antibiotics or probiotics (live strains of strictly selected microorganisms which,
81 when administered in adequate amounts, confer a health benefit on the host (see [17] for
82 definitions). These studies demonstrate that there is increasing evidence that changes in the GUT-M

83 affect physiological and behavioral processes that are directly relevant to welfare such as stress,
84 anxiety, changes in social behavior and memory. Whilst demonstrations of the influence of the GUT-
85 M on behavior in farm animals remain scarce, manipulation of the microbiota in farm animals by
86 supplying probiotics is common to improve production. Therefore, a critical examination of the
87 influence of the GUT-M on behavior would be especially interesting from an animal welfare
88 perspective.

89 This review aims at summarizing the influence of the MGBA on behavior in rodents and humans and
90 to point out what has been observed in farm animals. Moreover, because the GUT-M varies
91 according to host genetics and many external factors (Figure 1), we suggest that the GUT-M could be
92 used to improve behavior and welfare on the farm.

93

94 **I – The gut microbiota and its impact on brain development and behavior in rodent and** 95 **human models**

96

97 There is increasing evidence that the microbiota can influence host behavior. Most of the
98 investigations on behavior have focused on the GUT-M in vertebrates where various routes of
99 interaction between the GUT-M and the brain have been identified, including the immune and the
100 enteroendocrine pathways, the enteric nervous system and the vagus nerve (Figure 2). Products of
101 bacterial metabolism and structural components of bacterial cell walls influence a wide range of
102 processes including host immune responses (e.g. cytokines) and activation of enteroendocrine cells
103 which can affect the nervous system locally and systemically. The enteric nervous system is a major
104 interface between the GUT-M and the host and it forms the most complex of intrinsic nerve circuits
105 outside the CNS [18]. Through its neuronal networks and numerous neurotransmitters, it mirrors
106 many aspects of the CNS and intimately interfaces with it *via* the autonomic nervous system.
107 Although seldom recognized, the number of neurons in the enteric nervous system is comparable to

108 the number of neurons in the spinal cord, leading some authorities to refer to the enteric nervous
109 system as the “second brain” or the “little brain” [18]. Moreover, research has demonstrated that 80
110 percent of the vagus nerve fibres carry information from the gut to the brain, rather than the other
111 way round [19]. Thus, the vagus nerve is a major pathway of the MGBA as demonstrated by surgical
112 sections that abolish the effect of the GUT-M on the brain and on behavior in mice [20-23].
113 Conversely, the brain modulates the physiology of the gut, the enteric immune system and the
114 composition of the GUT-M. This influence can impair gut activity especially during host stress [24-26].
115 The GUT-M can additionally influence the behavior of host’s conspecifics through sensory cues even
116 if they are not considered usually as constitutive of the MGBA [27]. These cues are mainly olfactory
117 [28] but the GUT-M could even be related with visual cues in some cases: in pigeons for example
118 [29], GUT-M composition is related to feather microbiota composition and the bacterial load on the
119 plumage has been shown to influence the iridescent color of the feathers which is a fitness cue for
120 the congeners.

121

122 *1- Effects on anxiety-like behavior and stress responses*

123 The question of the role of the GUT-M in anxiety-like behavior was raised following the pioneering
124 study of Sudo et al. [30] which showed hyperactivity of the HPA axis under stress conditions in germ-
125 free mice (without any microbiota) compared to specific pathogen-free mice. Other teams have
126 subsequently confirmed the influence of the GUT-M on the development and regulation of the stress
127 response system [13,14,16,31]. In addition, patients with gastro intestinal disorders such as irritable
128 bowel syndrome (IBS) also have a deregulation of HPA axis activity [32,33]. Consequently, a link
129 between the MGBA and anxiety-like behavior is not surprising and a significant modification of
130 anxiety-like behavior has been observed in germ-free rodents compared with specific pathogen-free
131 rodents in various tests [34-39]. These studies reveal the importance of the genetic background in
132 the influence of the GUT-M on behavior. Indeed, the absence of GUT-M leads to increased anxiety-

133 like behavior in rodent strains genetically prone to exacerbate emotionality (F344 rats and BALB/c
134 mice) [11,12] and provoked a reduction of anxiety-like behavior in moderately emotive strains (NMRI
135 and Swiss mice) [37,38]. The germ-free rodent studies represent a large part of the literature on the
136 MGBA concept. Nevertheless, the germ-free animal presents several important physiological
137 alterations compared to a colonized one such as a reduction of the growth, alterations of the
138 digestive functions or immune system impairments ([40] for review), thus it is not easy to
139 demonstrate that the behavioral modifications observed in these animals are a direct consequence
140 of the absence of GUT-M rather than of physiological changes. However, some authors have tried to
141 reinforce the role of the presence of GUT-M in their studies by re-introducing standard microbiota
142 into these germ-free animals and have observed a reversal of behavioral responses following
143 bacterial colonization [37,39]. When it is not completely abolished, the GUT-M can be modified by
144 the use of antibiotics. BALB/c mice treated with a mixture of nonabsorbable antimicrobials
145 (bacitracin, neomycin and pimaricin) for seven days showed reduced anxiety-like behavior compared
146 to controls in a light-dark box test [20]. Similarly, the low doses of penicillin in late pregnancy and
147 early postnatal life induced long-term changes of microbiota composition and behavior. The
148 antibiotic-treated mice exhibited impaired anxiety-like and social behaviors, and displayed a
149 higher level of aggression in several tests, while concurrent *Lactobacillus rhamnosus* JB-1 probiotic
150 supplementation prevented some of those alterations [41]. However, these results must be
151 interpreted cautiously because antibiotic treatments are known to have neuroactive and neurotoxic
152 potential. Regardless or in addition to their microbicidal effects, the antibiotics themselves may also
153 influence enteric, peripheral and central nervous system functions [10].

154 Probiotics are live naturally occurring microorganisms which can improve health directly or indirectly
155 by inhibiting growth and attachment of pathogens and favor the development of the intestinal
156 epithelium and the immune responses. A probiotic can be used alone or in combination with other
157 probiotics, a cocktail of microorganisms that may have different or common properties [42]. The
158 exact mechanisms through which probiotics provide benefits are being studied and may differ

159 depending on the specific formulation. These mechanisms include modifications of the pH of the
160 gastrointestinal tract, the provision of nutrients to the host, the production of antimicrobial or
161 signaling molecules, competition with pathogens for ecological niches and available nutrients,
162 promotion of the intestinal cell differentiation and turnover, increased mucus production and
163 maturation of the immune system. Many studies in the literature suggest an anxiolytic effect of some
164 probiotics. Mice treated with the probiotic *Lactobacillus rhamnosus* expressed reduced anxiety
165 compared to control mice during the elevated plus maze [33] and a chronic administration of
166 *Lactobacillus plantarum* leads to lower anxiety-like behavior in the open-field and elevated plus maze
167 tests [43]. More demonstrative yet, Bercik et al. [44] showed that a daily gavage with the probiotic
168 *Bifidobacterium longum* can normalize anxiety-like behavior in mice with infectious colitis in the step-
169 down test and a supplementation with the probiotic *Lactobacillus helveticus* has led to a reduction
170 of chronic stress-induced anxiety and depression in rats [45]. Messaoudi et al. [46] investigated the
171 effect of a mixture of two probiotics (*Lactobacillus helveticus* and *Bifidobacterium longum*) on
172 rodents and human volunteers. In both cases, a decrease in anxiety was revealed. Infection with
173 pathogenic bacteria is another way to modify the composition of the GUT-M, which often leads to
174 increased anxiety-like behavior in rodents. An infection of mice with *Campylobacter jejuni* or
175 *Citrobacter rodentium* exacerbated anxiety-like behavior compared to control mice in different
176 situations such as the elevated plus maze or the hole-board open field test [19,47,48]. Furthermore,
177 the anxiogenic effects of these infections were not the result of an immunological response but
178 appeared to be a direct action of bacteria on neural activation pathways [19,47]. However, one of
179 the most striking experiment on the influence of the GUT-M on anxiety-like behavior is the study of
180 Bercik et al. [20] who carried out a GUT-M transfer between a low (NIH Swiss) and a high (BALB/C)
181 anxiety-like mouse strains presenting different microbial profiles based on denaturing gradient gel
182 electrophoresis (DGGE). The germ-free BALB/c mice that received the GUT-M from the opposite
183 mouse strain were less anxious than the controls BALB/c mice during the step-down test. In contrast,
184 germ-free NIH Swiss mice responded more anxiously than controls during the same test. Therefore,

185 this experiment suggests that the GUT-M would be involved in the anxiety-like phenotype of these
186 mice. Taken together, these findings suggest a significant influence of the MGBA on anxiety-like
187 behavior.

188

189 *2- Effects on memory*

190 It is now increasingly recognized that the GUT-M communicates with the brain and acts on several
191 brain structures such as the amygdala, the cortex and the hippocampus that all have a key role in
192 memory processes [12,37,40]. Moreover, the relationship between anxiety and memory and learning
193 has been widely demonstrated, suggesting an effect of the GUT-M on cognitive abilities [30,49,50].
194 This idea is supported by results obtained when comparing germ-free mice and specific pathogen-
195 free mice in the novel object test and the T-maze test [15]. In both tests, the germ-free mice
196 displayed memory deficits. Consistent with these findings, treatment with an antibiotic formulation
197 resulted in a cecal composition shift with reduction of Firmicutes and Bacteroidetes and increase of
198 Proteobacteria and Cyanobacteria and a decrease in memory capacities in mice subjected to novel
199 object recognition test and social transmission of food preference test [51]. The influence of an
200 antibiotic treatment on memory may nevertheless depend on the number of antibiotic products
201 used and the sensitivity of the bacteria to this antibiotic. For example, in the Morris water maze the
202 vancomycin antibiotic had no significant effect on murine memory despite a significant alteration of
203 fecal microbiota [2]. The gut microbiota may also have different effects depending on the type of
204 memory assessed. In a recent study, a treatment with an antibiotic mixture strongly disrupted
205 microbial composition of mice and impaired novel object recognition but not spatial memory in the
206 Barnes maze test [52]. Studies on probiotics supplementation agree that there are beneficial effects
207 on memory performance in rodents [33,45,53-55]. Works conducted on pathogenic infections (with
208 *E. coli* or *C. rodentium*) reported deleterious effects on memory in the mouse [15,56] and, in both
209 cases, a treatment with probiotics attenuated these memory impairments. However, it is important

210 to emphasize that only the study of Smith et al. [54] performed a GUT-M composition analysis
211 following probiotic administration and reported significant changes in the fecal microbiota of the
212 mice. In humans also, improvement of emotional memory after probiotic administration has been
213 associated with changes in GUT-M community composition [57].

214 An alternative strategy for modifying the microbiota is to use dietary prebiotics. Prebiotics are
215 fermentable oligosaccharides or polysaccharides that induce the growth of some gut bacteria that
216 increase gut health. Unabsorbed or undigested carbohydrates are fermented by the gut microbiota
217 in the large bowel, producing different end products like short-chain fatty acids (SCFAs) and lactic
218 acid, which may have multiple effects. For example, it has been described that oral administration of
219 fructo-oligosaccharides (FOS) and galacto-oligosaccharides (GOS) affects behavior and specifically
220 anxiety, depression-like behavior, cognition, and social behavior. These modifications are related to
221 specific gene expression in the hippocampus and hypothalamus, gut microbiota composition, several
222 SCFAs produced, and elevations in corticosterone and pro-inflammatory cytokine levels [6].

223 Modifications of the GUT-M through changes in raw materials of the diet appear also to influence
224 cognitive abilities. An enrichment of beef in the diet of mice increases the microbial diversity in the
225 colon and their memory scores in the hole-board apparatus [58]. A diet characterized by a high-fat
226 composition also leads to differences in GUT-M composition and to memory impairments in the
227 mouse and the rat [29,59,60].

228 However, studies are still needed to strengthen a causal relationship between GUT-M changes and
229 memory abilities in these nutrition experiments.

230

231 *3- Effects on social behavior*

232 The MGBA seems to be also involved in other highly emotional behaviors such as social behavior.
233 This behavior is impaired in germ-free rats in a test which consists of measuring behavior during an
234 encounter with an unknown partner [36]. During the 2 minutes of the test, compared to specific

235 pathogen-free rats, the germ-free rats spend less time sniffing an unknown. These results are
236 consistent with what Desbonnet et al. [24] found in a mouse model tested in the 3-chambered
237 sociability test. The germ-free mice displayed social preference deficits by spending less time
238 exploring a chamber containing a mouse than an empty chamber. In addition, when the germ-free
239 mice are post-weaning colonized, their behavioral responses are reversed in the same test. However,
240 this result could not be replicated in a subsequent study using the same mouse strain and the same
241 3-chambered test in which the authors observed opposite results [35]. Indeed, germ-free mice
242 expressed greater social preference than specific pathogen-free mice. The authors assumed that the
243 difference in the age of the germ-free mice between the two studies could be the explanation for the
244 contradictory findings. They also mentioned the hyperactive behavioral responses of the mice in the
245 Arentsen *et al.* work [35] and the differences in living conditions of the specific pathogen-free mice
246 (isolators rearing in a study and not in the other). More recently, social behavior impairments and
247 dysbiosis in the gut have also been reported in mouse offspring from mothers fed with a high-fat diet
248 [61]. Interestingly, a probiotic (*Lactobacillus reuteri*) supplementation in the drinking water during 4
249 weeks led to the normalization of social behavior and this reversal of the social deficits involved the
250 vagal pathway. In conclusion, all these data indicate that the GUT-M is required for a normal
251 expression of social behavior in rodents. Moreover, differences of GUT-M composition have been
252 revealed between autistic and control patients in an expanding volume of studies [42,62-64].
253 Similarly, altered GUT-M composition and social deficits have also been noted in a murine model of
254 ASD [65,66]. These mice are characterized by disturbed anxiety-like and stereotyped behavior similar
255 to those observed with germ-free mice [38]. An administration of probiotic *Bacteroides fragilis* has
256 improved many of these behaviors including anxiety-like behavior (open-field exploration),
257 communication deficits (ultrasonic vocalizations) and stereotyped behavior [65]. More interestingly,
258 Sandler et al. [67] tested the effect of an antibiotic on 11 children with regressive-onset autism.
259 Significant behavioral improvements were noticed during the treatment period and the behavioral
260 improvements disappeared after the treatment. It has also been recently demonstrated that

261 *Lactobacillus reuteri* rescues social deficits in various mouse models for ASD based on genetic,
262 environmental and idiopathic alterations [68].

263

264 4- *Influence on feeding behavior*

265 Fetissov [69] suggested that the bacteria-host communication influences the appetite-satiety balance
266 in humans and rodents. First, bacterial components and metabolites have been shown to stimulate
267 satiety pathways in the host in the short term through the stimulation of endocrine cells involved
268 and the production of peptides related to feed intake [70,71]. Secondly, bacterial peptides use
269 systemic routes and might act directly in the hypothalamus and so play a role in the long-term
270 regulation of appetite. Moreover, the GUT-M appears to be involved in the expression of taste
271 receptors in rodents [72,73].

272 It is now recognized that the MGBA is involved in many behavioral responses in humans and rodents
273 and interventions with probiotics reinforce the theory of the influence of the GUT-M on behavior and
274 the cognitive abilities. However, it is also important to note that the causal mechanisms by which the
275 GUT-M and the brain communicate are not well described or understood and further investigations
276 are needed to shed light on this microbiota-gut-brain axis communication.

277

278 **II- The gut microbiota of farm animals**

279

280 There is an increasing knowledge about the composition of GUT-M of farm animals (ruminants,
281 horse, pig, rabbit, chicken, turkey, etc). Indeed, it is very important to characterize the GUT-M in farm
282 animals so that it is possible to detect normal and abnormal changes. This knowledge should help to
283 define and identify dysbiosis and to restore a healthy GUT-M. It should also help to predict
284 susceptibility to infection and prevent welfare and health problems since GUT-M composition is

285 involved in the control of pathogen colonization [74,75]. However, understanding GUT-M
286 composition is a complex issue since it varies along the digestive tract and there are also differences
287 between lumen and mucosa, and even between the tip of the villi and the crypt. Moreover, GUT-M
288 variations are induced by many factors related to the host and to the host environment.

289

290 1- Investigation of the *GUT-M in farm animals*

291 While the GUT-M is composed of bacteria, but also viruses, archea and eukaryotes and while
292 bacteriophages have been shown to have an important role in bacteria composition, most studies
293 only take into account the bacterial composition of the GUT-M. This is in line with methods available
294 to measure this composition since there are more libraries of bacteria available for 16S rRNA gene
295 sequencing than for viruses, archea and eukaryotes. Several methods are used to characterize the
296 the GUT-M. The 16S rRNA gene sequencing directed by PCR, is commonly used to quantify GUT-M
297 diversity and is effective in demonstrating the major phyla, families or genres, but sometimes gives
298 limited resolution. The table provides the characteristics of GUT-M bacteria in the main farm species
299 (cow, sheep, horse, pig, rabbit, chicken, quail, duck) established by 16S rRNA gene sequencing. This
300 table gives the composition at phylum level and sheds light on the large variation found within host
301 species. Though not the main focus of this review, it is clear that accurate descriptions of the
302 composition (at the genus or the species level) of the bacteria in different parts of the digestive tract
303 greatly help us to understand the effects of host and external factors of modulation on the GUT-M
304 ([71] in cow for example). Quantitative metagenomic shotgun sequencing also aims at investigating
305 diversity directly from samples but can be technically challenging and is less frequently used. Other
306 approaches look for GUT-M functionality by metatranscriptomics (RNA sequencing), metaproteomics
307 (Mass spectrometry) or metabolomics (High resolution spectroscopy).

308 Each gut compartment hosts a microbiota with a particular composition and many studies
309 investigated GUT-M composition along the digestive tract ([76] in pigs; [77] in horses; [78] in quail).

310 In horses for example, the composition of the GUT-M collected in the lumen is very different in
311 caecum and colon compared to the upper compartments (stomach, jejunum and ileum) and is
312 different from the GUT-M from mucosa [77]. In this example, data suggest that analysis from feces
313 would be related to colonic segments only, but would not be related to upper compartments.
314 Numerous studies use fecal samples to avoid animal sacrifice, which could be misleading.

315 Gut microbiota of the small intestine, caecum and colon in healthy adults is dominated by bacterial
316 species belonging to two main phyla, Gram positive Firmicutes and Gram negative Bacteroidetes
317 (Table). The small intestine is usually dominated by Firmicutes with major families including
318 *Lactobacillaceae*, *Peptostreptococcaceae* or *Enterococcaceae*. Microbial complexity considerably
319 increases in distal parts of intestinal tract, i.e. in the caecum and colon. It is important to remember,
320 however, that the descriptions of the gut microbiota leave out many important factors such as host
321 genetics, age or feed regime (see below) that may give rise to much greater variation. These factors
322 may affect microbiota development and composition in the youngest animals and the differential
323 development in early days of life.

324

325 2- *Variations in the GUT-M linked to the host*

326 The host genetics affects the GUT-M in numerous ways and this impact is related to inter and intra
327 species differences in the GUT-M [79]. Domestication has also induced changes in GUT-M
328 composition. For example, a metagenomic approach followed by a quantitative PCR showed that the
329 GUT-M in wild Suidae (wild boars and Red river hogs) was characterized by a high abundance in
330 *Bifidobacterium* which was not the case in domesticated Suidae characterized by abundance in
331 *Lactobacillus* and *Enterobacteriaceae* as the major family [80]. It is important to note that diet was
332 not controlled and thus confounded with genetics in this study. However, it has been demonstrated
333 in domesticated pigs from the Pietrain strain that pig genome influences the GUT-M in the mid-colon
334 and that the heritability of the load of some bacteria can even reach high values such as 0.32 to 0.57

335 [81]. Differences in the GUT-M related to host genetics have also been established between lines of
336 the same species. With chicken lines selected on body weight, Zhao et al. [82] demonstrated that the
337 host genotype and gender affected 68 out of 190 GUT-M species and that among them 15 belonged
338 to *Lactobacillus*. Genetic selection on *Salmonella* carriage in chickens enabled the detection of
339 Quantitative Trait Loci (QTLs) for both resistance to carrier state and resistance to *Salmonella*
340 colonization [83,84]. Some bacterial families can be affected particularly by host genotype: in Pekin
341 and Muscovy ducks for example, genotype affects *Lachnospiraceae*, *Bacteroidaceae* and
342 *Desulfovibrionaceae* in the cecum, while overfeeding affects other families such as *Clostridiaceae*,
343 *Lactobacillaceae*, *Streptococcaceae* and *Enterococcaceae* [85]. A divergent genetic selection on
344 increased digestive efficiency in chickens was linked to changes in the GUT-M and has enabled the
345 detection of QTLs related to the presence of some GUT-M bacteria [86]. In chickens, QTL for the
346 presence of bacteria such as *Lactobacillus* and *L. crispatus* co-localize with QTLs for feeding behavior
347 [87]. Host genetics would then influence both the behavioral phenotype and GUT-M composition. It
348 is highly probable that behavior and the GUT-M influence each other as it has been demonstrated in
349 stress processes where the brain influences gut peristalsis and GUT-M composition while the GUT-M
350 interacts with CNS and the HPA axis [13].

351 The age of the host is also a major factor and the ontogeny of the GUT-M has been studied in many
352 farm animals. The changes during early life have been described in several farm animals (chick: [88];
353 calf: [89,90]; piglet: [91]; foal: [92]). Microbial colonization is a complex process influenced by the
354 host and many external factors, including maternal microbiota, birth process, early diet, perinatal
355 stress and antibiotics use.

356

357

358 3- Variations of the GUT-M linked to the environment

359 The environment dramatically influences the newborn's GUT-M. In mammals, the contact of the
360 newborn animal with its mother is physiologically indispensable and during parturition, the offspring
361 is naturally inoculated with microbiota from the mother. However, in case of avian farm species, the
362 young birds are industrially hatched, which means that eggs are disinfected and chicks reared
363 without any contact with their mother or any older conspecific and the source of microbiota is thus
364 limited to the environment. This way of husbandry is in sharp conflict with the natural conditions,
365 where the mother bird represents the principal source of the GUT-M. Experimentally, young chicks
366 reared in a sanitized environment with no contact with older conspecifics had profoundly different
367 microbiota compared with chicks which were kept for 24 hours with the adult hen [93].

368 Other external factors such as infections can give rise to unbalance in the GUT-M. For example, early
369 exposure to pathogenic bacteria can shape the overall microbiota composition in chicks infected with
370 *Salmonella* Enteritidis inducing an expansion in the *Enterobacteriaceae* [94] and exposures to
371 *Campylobacter jejuni* revealed that the shift of the GUT-M varies upon the age at which the chickens
372 become colonized by this bacteria [95]. Parasitism can also influence GUT-M composition and the
373 interplay between helminths and the bacterial populations is being elucidated. The various ways
374 both populations influence each other are complex [96] and suggest that a better knowledge of the
375 gut microbiota of nematodes themselves could lead to a better prevention of parasitic diseases [97].

376 Throughout life, housing conditions influence cecal microbiota in rabbits [98] and pigs [99] showing
377 that environmental bacterial load influence the GUT-M. Breeding in different rearing systems can
378 also influence GUT-M composition at the phylum level. For example, Bacteroidetes and
379 Proteobacteria were more prevalent in chickens reared under free-range conditions than in cages,
380 but this difference was manifested only in one of both lines [100]. Stocking density can influence
381 crop and cecal microbiota composition in chickens [101]. Rearing conditions inducing stress can also
382 influence the GUT-M. In horses for example, weaning and transport are stressful events and both can
383 affect the GUT-M composition [102,103]. In Mach's experiment, foals' microbiota was modified
384 during the first week after weaning until a relatively stable gut community was established at day 7

385 post-weaning. This modification can be partly explained by the nutritional change, however GUT-M
386 composition after weaning was slightly modulated by the weaning method suggesting that the stress
387 induced by the abrupt method has impacted the microbiota modification. An experiment in pigs has
388 shown that even mild handling stressor such as single daily weighing is able to alter the GUT-M [104].
389 Another very important external modulation of the GUT-M is given by the feed which may drastically
390 influence GUT-M composition and activity. Such influences are being increasingly studied since diets,
391 or the water bacterial load, may induce unbalance in the GUT-M and lead to pathological states. Such
392 unbalance can lead to dysbiosis and then enteritis, or to other diseases targeting some other organs
393 such as lungs, since unbalance gives rise to inflammation of the gut wall and facilitate bacteria
394 leakage across the epithelial wall. This modulation by the diet has mainly been investigated in farm
395 animals and reviewed in many animal species [105] for review in horses; [106] in chicken; [107] in
396 piglets, [85,108] in ducks, *etc*). Most of these studies compare diets based on high fiber with diets
397 containing raw materials providing high energy levels. Other nutritional means used to modify the
398 GUT-M are the provision of prebiotics or probiotics. Prebiotics are fermentable oligosaccharides or
399 polysaccharides that induce the growth of some gut bacteria that increase gut health while, as
400 previously mentioned, probiotics are microorganisms which improve animal health directly or
401 indirectly by producing substrates that stimulate growth of commensals, inhibit growth of
402 pathogens, favor the development of the intestinal epithelium and the immune responses. Probiotics
403 are largely used in animal nutrition to improve gut health, increase feed efficiency and milk quality
404 [42,109] and it has been demonstrated in piglets that they can influence serotonin and dopamine
405 concentrations in the hypothalamus [110]. They are also use to prevent the effects of stressful events
406 such as transportation in horses for example [111] but this improvement is not always related to a
407 change in the GUT-M as mentioned by a meta-analysis carried out in calves [109]. Lactic acid bacteria
408 are commonly used as probiotics, and their impact on gut health, immunity and the prevention of
409 the establishment of pathogenic bacteria has been increasingly studied.

410 Farm animal GUT-M can thus vary with a wide range of factors each of which have many different
411 consequences but the results on behavior are weakly documented and rarely taken into account.
412 Furthermore, only few studies have used GUT-M manipulations to disentangle effects of nutritional
413 or environmental factors and GUT-M effects.

414

415 **III- Effect of the microbiota-gut-brain axis on behavior in farm animals**

416

417 There is emerging evidence that the GUT-M is able to influence behavior in farm animals as has been
418 shown in rodents and humans. Colonization of farm animals with a pathogen was known to induce
419 sickness behavior for a long time, but recent studies demonstrate that the influence of the MGBA is
420 not limited to the area of disease and can also occur in healthy animals. Studies based on germ-free
421 animals, provisions of probiotics or prebiotics, diet modifications, demonstrated that changes in the
422 GUT-M are related with changes in many behavioral patterns. Because of the size of farm animals,
423 this influence of the MGBA has been established mainly with studies using probiotics while very few
424 studies on germ-free animals are available since these animals must be kept in isolators.

425

426 *1- Effects on emotional reactivity and anxiety-like behavior*

427 A recent experiment with germ-free birds demonstrated that the absence of GUT-M reduces
428 emotional reactivity in Japanese quail in fear and social perturbation situations without major
429 influence on growth [112]. The authors used germ-free quail chicks that were kept germ-free or
430 inoculated with a dilution of GUT-M from adults of the same line. Quail chicks were reared and
431 tested in isolators in order to avoid contamination. Germ-free quails spent less time in tonic
432 immobility, were less reactive during the social separation test and were less neophobic in a novel
433 object test than inoculated quail chicks. The use of a GUT-M transfer has also demonstrated the

434 influence of microbiota on emotional reactivity in this species [113]. The authors used genetic lines of
435 quails that have been selected for either a high fearfulness (E+) or a low fearfulness (E-). Germ-free
436 quail chicks from the E+ line were inoculated with feces from either a E+ quail or from a E- quail and
437 were reared in different isolators. Quails that received feces from the E- line expressed a lower
438 emotional reactivity during the second week of age than the quails colonized by feces from the E+
439 line. This result was reversed two weeks later. These behavioral differences can be related to GUT-M
440 differences and modifications over time and they could be the consequence of the resilience of the
441 GUT-M to recover its equilibrium present in the E+ host, which is in part driven by the host genotype.
442 Abdel-Azeem et al. [114] showed that the administration of the probiotic *Bacillus amyloliquefaciens*
443 helped to reduce distress calls in turkeys and the supplementation of the diet with a probiotic
444 (*Pediococcus acidilactici*) reduced emotional reactivity in quails [115].

445 In horses, the relationship between the GUT-M and behavior has been suggested by correlations
446 obtained in fistulated horses submitted to behavioral tests before and after a nutritional change
447 [116]. The modification of the diet from a fibrous diet with 100% hay to a diet with increased energy
448 (57% hay and 43% barley) induced significant increases of colonic total anaerobic bacteria, lactate-
449 utilizing bacteria and amyolytic bacteria concentrations. After this transition, the horses were
450 submitted to a sociability test where behavior was analyzed when an unfamiliar horse was
451 introduced into the adjacent stall and to a neophobia test assessed from the reaction to the presence
452 of a novel object placed near a feeder in a test arena. The time spent in vigilance during the
453 sociability test tended to positively correlate with cecal and colonic amyolytic bacteria
454 concentrations while the time spent in vigilance during novel object test was correlated with caecal
455 lactate-utilizing and colonic amyolytic bacteria concentrations.

456

457 2- *Effects on memory*

458 As in rodents, probiotics have been shown to enhance memory in quail: supplemented birds made
459 fewer errors in a test where they had to remember the cup they had previously visited among eight
460 rewarded cups [115]. In Yucatan pigs, differences in the maternal diet during gestation and lactation
461 have been used to modify microbiota activity in the sows and their offspring [117]. Sows were either
462 fed a standard diet or a Western diet enriched in energy, sugar and fat. SCFAs used to measure
463 microbiota activity were decreased in sows fed the Western diet and in their piglets. Piglets from
464 sows fed the Western diet, i.e with reduced GUT-M activity, had higher working memory in a hole
465 board test where they had to learn where were the bowls that contained chocolate-coated peanuts
466 among unrewarded bowls.

467

468 3- *Effects on social behavior*

469 Using probiotics, it has been shown that spores of *Bacillus amyloquefaciens* decrease aggression in
470 turkeys [114]. However, the most promising information was obtained for feather pecking behavior
471 in hens. Gentle feather pecking is considered as a normal social exploratory behavior and consists in
472 a soft pecking while severe feather pecking is an intense pecking and pulling out feathers which can
473 induce pain in the victim. This injurious behavior considered as an abnormal behavior have been
474 recently supposed to be associated with the MGBA. Indeed, it has been shown that divergently
475 selected lines of hens for severe feather pecking also differ in hens' GUT-M [118] and in immunity
476 [119]. Nevertheless, it is still not possible to decide conclusively whether differences in feather
477 pecking induced difference in the GUT-M or whether differences in the GUT-M induced difference in
478 behavior via the MGBA [120]. The latter explanation agrees with data about GUT-M metabolites such
479 as total SCFAs and biogenic amines since both were also different between these lines [121] and
480 SCFAs have been shown to be involved in the MGBA and influence social behavior. Differences in the
481 gene expression of two genes (ABCB1 and TNSF15) involved in inflammatory bowel disease (IBD) are
482 also been reported between birds expressing feather pecking or not [122]. Moreover, the serotonin

483 whose synthesis depends on various bacterial families in the GUT-M [49,50,123,124] is also involved
484 in feather pecking behavior in hens [120]. Ingestion of feathers could lead to an increase of gut wall
485 stimulation and therefore an impaired serotonin signalling [125]. These data would then be in
486 agreement with an influence of GUT-M activity on the development of feather pecking through the
487 MGBA. Brunberg et al. [125] proposed to investigate if the differences in GUT-M composition are
488 already present in the young chick before the development of feather pecking behavior in order to
489 characterize the main direction of the microbiota-gut-brain interactions in this model.

490

491 4- *Effects on feeding behavior*

492 Gut pathogens may induce illnesses states that are commonly accompanied by reduction in feed
493 intake but some other influences of the GUT-M on feeding behavior can be found in farm animals.
494 In turkeys, spores of *Bacillus amyloquefaciens* have been shown to increase feeding frequency and
495 duration [114]. The genetic lines of chickens divergently selected on feed efficiency we previously
496 mentioned differ in feeding behavior and a QTL for feeding behavior co-localizes with QTLs for some
497 bacteria from the GUT-M [87]. This co-localization suggests an influence of these bacteria on eating
498 behavior but this influence still need to be strengthened by experiments using GUT-M manipulation.
499 Changes in feeding behavior induced by the MGBA are suspected in ruminants when they are
500 affected by acidosis which occurs with high-energy low-fiber diets. Eating behavior can be modified
501 with rumen liquor transplantation when cows are affected by acidosis [126] and even if pain
502 alleviation or inflammation reduction can also explain the effect on eating behavior, this veterinary
503 practice suggests that rumen microbiota influences appetite in such pathological state. In cows
504 affected by subacute acidosis, ruminal GUT-M is modified [127] and feeding behavior is affected with
505 a reduced feed intake and a reduced duration of rumination. *Saccharomyces cerevisiae*, a probiotic
506 commonly used in ruminants, has a protective effect on physiological changes induced by acidosis
507 such as reduction of the ruminal pH, changes in volatile fatty acids [42,128] and it has been shown to

508 induce also behavioral changes such as reduction of the minimum interval between meals and
509 tendency for longer time spent ruminating [129].

510 This limited information about the influence of the MGBA on behavior in farm animals suggests that
511 it can have large influences that have not been properly appreciated. These influences of the GUT-M
512 on behavior can be added to its influence on health *via* its role in the immune response and tends to
513 put the GUT-M as a pivotal actor for welfare state achievement [130].

514

515 **IV- Prospective of the microbiota-gut-brain axis concept in the welfare of farm animals**

516

517 The concept of the MGBA leads us to reconsider many factors that can influence behavior and health
518 in farm animals. The influence of the MGBA will have to be taken into account in future and that
519 may drastically change genetic selection, infection detection, nutrition and management processes.
520 Furthermore, the improvement of gastrointestinal functionality is of the utmost importance because
521 it positively influences health and welfare of animals, but also performance by preventing loss in feed
522 efficiency and the use of antibiotics.

523

524 *1 Selecting the host GUT-M*

525 Even if a recent article demonstrated that the human GUT-M is shaped more by environmental
526 factors than by human genome [131], we should not underestimate the influence of the host
527 genetics on the colonization of the gut by the microbiota. Several studies have demonstrated that
528 the host genome influences the composition of the GUT-M. For example, a study from twins has
529 identified many microbial taxa whose abundances were influenced by host genetics [132] and
530 associations between host single nucleotide polymorphisms and bacterial taxa have been described
531 [133]. The host gut is able to select the microbiota it encounters and only part of the bacteria present

532 in the gut are able to develop in it. This explains why different genetic lines reared in similar
533 conditions and fed the same diets have different GUT-M compositions. Selection for different
534 genotypes could then lead to differences in GUT-M and consequently in behavior, immunity and feed
535 efficiency [134]. As previously mentioned, selection for increased feed efficiency has led to
536 differences in GUT-M in chickens and several QTLs are related to these differences in GUT-M
537 composition and co-localize with loci involved in feeding behavior [87]. Moreover, these lines
538 divergently selected for feed efficiency also differ in emotional reactivity. It appears then that these
539 differences in behavior may have been driven by the effect of selection on the host genes involved in
540 behavior, but also on the genes involved in GUT-M carriage.

541 A better understanding of the relationship between the host genome, the GUT-M and deleterious
542 behaviors would be of great interest for animal welfare. A comprehensive link between the GUT-M
543 and feather pecking could lead to alternative strategies for selection against this damaging behavior.
544 As previously indicated, many rearing situations can induce stress and are related with changes in the
545 GUT-M. It appears then that when stressful situations cannot be avoided, selection for resilient GUT-
546 M would help reducing anxiety-like and depressive-like behaviors.

547

548 *2 Improving behavior via nutrition and the GUT-M*

549 The MGBA concept should have large consequences in livestock nutrition. Diet composition (use of
550 prebiotics or probiotics or raw materials) is already carefully checked to favor a good GUT-M and gut
551 health. However, it appears with the MGBA that diet composition will also have to be designed for
552 desired behaviors or to ensure a “good” neurobiological development when more data are available.
553 Supplementation with pre- or probiotics would be useful before or during stressful events such as
554 manipulation or transport, to avoid the activation of the HPA axis and anxiety-like behaviors. The
555 provision of various amino acids modifies GUT-M composition but the consequences on behavior are
556 poorly documented. In chickens, provision of tryptophan has been shown to modify the GUT-M [135]

557 and to reduce serum corticosterone, serotonin and heat shock protein 70. These results can be
558 related with other studies demonstrating that tryptophan metabolism into serotonin is involved in
559 feather pecking behavior [136] and that its supplementation can reduce gentle feather pecking
560 behavior in this species [137]. Moreover, a better understanding of the roles of GUT-M in feeding
561 behavior, especially in modulation of appetite and satiety, could have large consequences on animal
562 nutrition. Animal nutrition is presently based on our knowledge of needs and the ability of various
563 diets to fulfil these needs but if it is considered that the GUT-M also modulates appetite and satiety
564 as shown in rodents and humans, this could have large consequences on feed preferences and intake
565 if it is established in farm animal. In future, nutritional rules for farm animals could be improved by
566 increased knowledge about the way bacterial growth modulates the digestive cues related to satiety
567 and taste, and about peptides produced by bacteria that could be involved in the hypothalamic
568 regulation of appetite. A better understanding of appetite regulation would help managing feed
569 intake, feed frustration and anorexia related to disease states.

570 From a practical point of view, provision of pre- or probiotics in addition to the diet is the easiest way
571 to influence the GUT-M *via* nutrition. Prebiotics and probiotics can have complementary effects,
572 however there are expensive contrary to the modifications of the feed composition. For poultry,
573 probiotics could be fed at the hatchery in order to improve gut colonization. *In ovo* injection of
574 prebiotics or a combination of pre-and probiotic at the 12th day of the embryonic development has
575 been shown to influence host transcription and appears to stimulate the proliferation of the
576 embryonic GUT-M [138,139]. We need more studies to quantify the long-term effect on health and
577 behavior of such provision of pre- or probiotics at the hatchery. An exciting new perspective on GUT-
578 M - host symbiosis comes from the finding that pioneer colonizers, the first bacteria to reach the
579 neonatal gut, will impact the future health since they can directly influence the development of the
580 intestine and the nutrient matrix it provides for sequential implantation of future microorganisms
581 [140].

582 In mammals, the GUT-M can even be orientated before birth since the maternal diet can influence
583 GUT-M composition in the offspring. As previously mentioned in rodents [141], the maternal diet can
584 influence GUT-M activity in the offspring and this modulation can influence social behavior. In
585 piglets, GUT-M activity (measured by quantitative analysis of SCFAs) is reduced and responses to
586 reward are modified when sows are fed with a high-sugar and fat diet during pregnancy [117]. Such
587 demonstrations suggest that nutrition of breeders may be able to modulate behavior in the offspring
588 and that this has to be investigated in farm animals.

589

590 *3- Improving management practices through the GUT-M*

591 Many husbandry situations can give rise to stress states during animal rearing and this state may
592 modify GUT-M composition which can reinforce the negative effects of stress. Based on these
593 interactions described among the MGBA, it appears that protecting a balanced GUT-M would help in
594 the management of stress [13,142] and this would help preventing infection [24]. We saw that most
595 of studies focusing on behavior used probiotics that were able to decrease stress cues [114,115] and
596 to modify behavior and prevent various diseases such as acidosis in ruminants [128,143]. Nutritional
597 transition focusing specific GUT-M changes could also help reducing stress since we saw in horses
598 that these GUT-M changes due to increased diet energy are related to behavioral stress response
599 related to particular bacteria [116].

600 A better knowledge about the MGBA of the farm animal would also help to detect silent infections
601 and then modify the management of many diseases. Changes in behavior are commonly used to
602 detect illness. Inflammatory states are commonly associated with changes in a reduction of comfort
603 and feeding behavior and in motivation for social interactions. However, some pathogens do not
604 induce illness cues at animal level and this asymptomatic carrier state prevents the detection of such
605 infections. The existence of the MGBA suggests that changes in behavior could happen, even if the
606 host does not express classical sickness behavior commonly associated with disease. This would

607 explain why the presence of *Campylobacter*, a bacterium that is involved in a foodborne toxico-
608 infection in human, can be detected by automated behavioral analysis of poultry flocks [144] while
609 no clinical cue can be detected in chickens carrying this bacterium. Another example is given with
610 chickens that have been infected by *Salmonella* Enteritidis and that are also considered as
611 asymptomatic carriers. While no clinical cue can be detected in each infected chick, changes in
612 behavior occur during the weeks and sometimes the days following infection: reduction in feeding
613 [145], in inter-individual distances and in running bouts [146].

614

615 4- Needs for improved tools to use the MGBA

616 This enhanced understanding requires improved methods. The use of germ-free animals (mainly
617 rodents but also chicks) has been critical to our understanding of how the GUT-M can influence
618 health, disease, and behavior especially when coupled with mono-association (inoculation with a
619 single bacterial strain), defined microbiota, or humanized microbiota strategies. To circumvent some
620 of the physiological disadvantages of germ-free and mono-associated mice (poor barrier effect,
621 maturation of immune response and intestine development) while still maintaining a controlled
622 microbiota, mice reconstituted with defined microbiota were established. Schaedler initiated these
623 studies by defining key cultivable bacteria, which were experimentally inoculated to germ-free mice
624 in various “cocktails” of aerobes and anaerobes [147,148]. The cocktail was refined and standardized
625 resulting in “altered Schaedler's flora” (ASF) that is now most commonly used in gnotobiotic research
626 and companies [149]. The ASF community offers significant advantages to study homeostatic as well
627 as disease-related interactions by taking advantage of a well-defined, limited community of
628 microorganisms. Now, it would be interesting to develop such cocktails of bacteria for each farm
629 animal species to go further in the MGBA studies.

630 Additionally, moving forward, we face a number of challenges in each animal model. For example,
631 the vast majority of intestinal microorganisms remain uncultivable. Can novel culture methods or

632 creative strategies to eliminate selectively targeted agents be developed? How to include other GUT-
633 M members like viruses, protozoa and fungi in the MGBA analyzes? How do we avoid microbiota drift
634 to optimize reproducibility among studies? Can microbiota be banked adequately for future studies?
635 Facing these issues is a great challenge to improve our knowledge about the MGBA in farm animals.

636

637 **Conclusion**

638

639 Thanks to the many ways of manipulating the GUT-M (germ-free, antibiotics, probiotics, diet,
640 microbiota transfer), it is increasingly recognized that the microorganisms colonizing the host's
641 digestive tract can directly or indirectly act on the nervous system and influence host behavior. The
642 majority of studies on the subject have used rodent or human models and it seems that the GUT-M
643 can influence emotional behavior, memory capacities, social and feeding behavior also in poultry,
644 pig, horse and ruminants. However, germ-free animals reared and kept in isolators are poor models
645 for farm animals and it will be a big step to apply results to the farm environment. Many studies are
646 correlational and the presence of specific microorganisms is not controlled experimentally while
647 investigations with microbiota reconstitutions that reverse behavioral changes and investigate
648 mechanisms are still lacking. Many methodological issues have to be faced to get a better knowledge
649 about the variations of the GUT-M, the role it can play in the MGBA of the farm animal and how it
650 could help reducing certain deleterious behaviors and increasing behavioral adaptation *via* genetic
651 selection, nutrition, stress management and detection of silent infections. In summary, it is
652 necessary to take this MGBA concept into account in an applied interest to farming conditions since
653 it can have large consequences in animal welfare.

654

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659

660

661 Table and figure captions

662 Table: Taxonomic profiles of major gut bacterial communities at the phylum level in farm animals
663 using 16 rRNA gene pyrosequencing (Percentage of sequences assigned), based on [89], [150], [77],
664 [151], [98], [95], [78], [85].

665 Figure 1: Gut microbiota as a key actor for animal welfare

666 Figure 2: Influence of the microbiota-gut-brain axis on behavior

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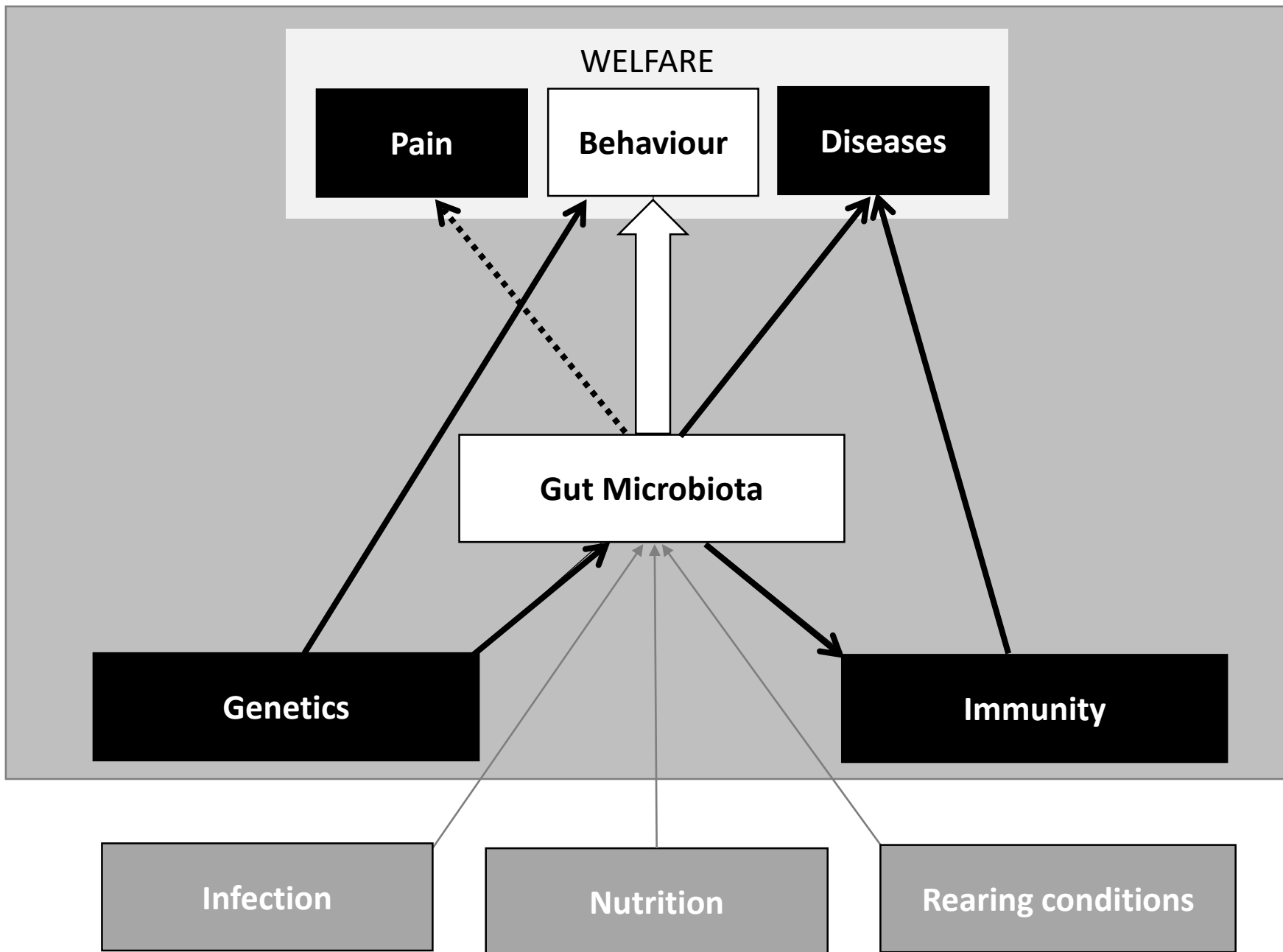
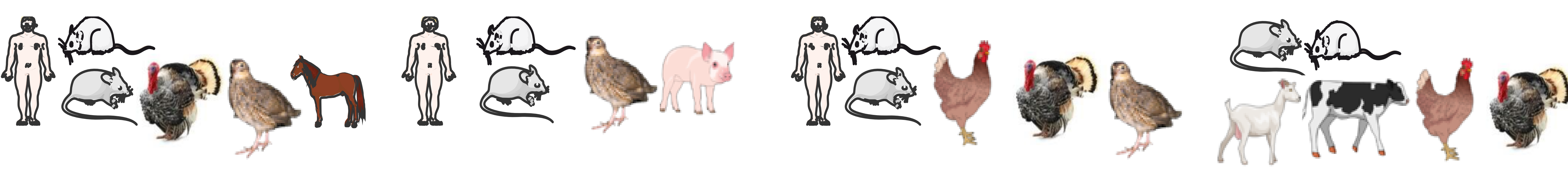
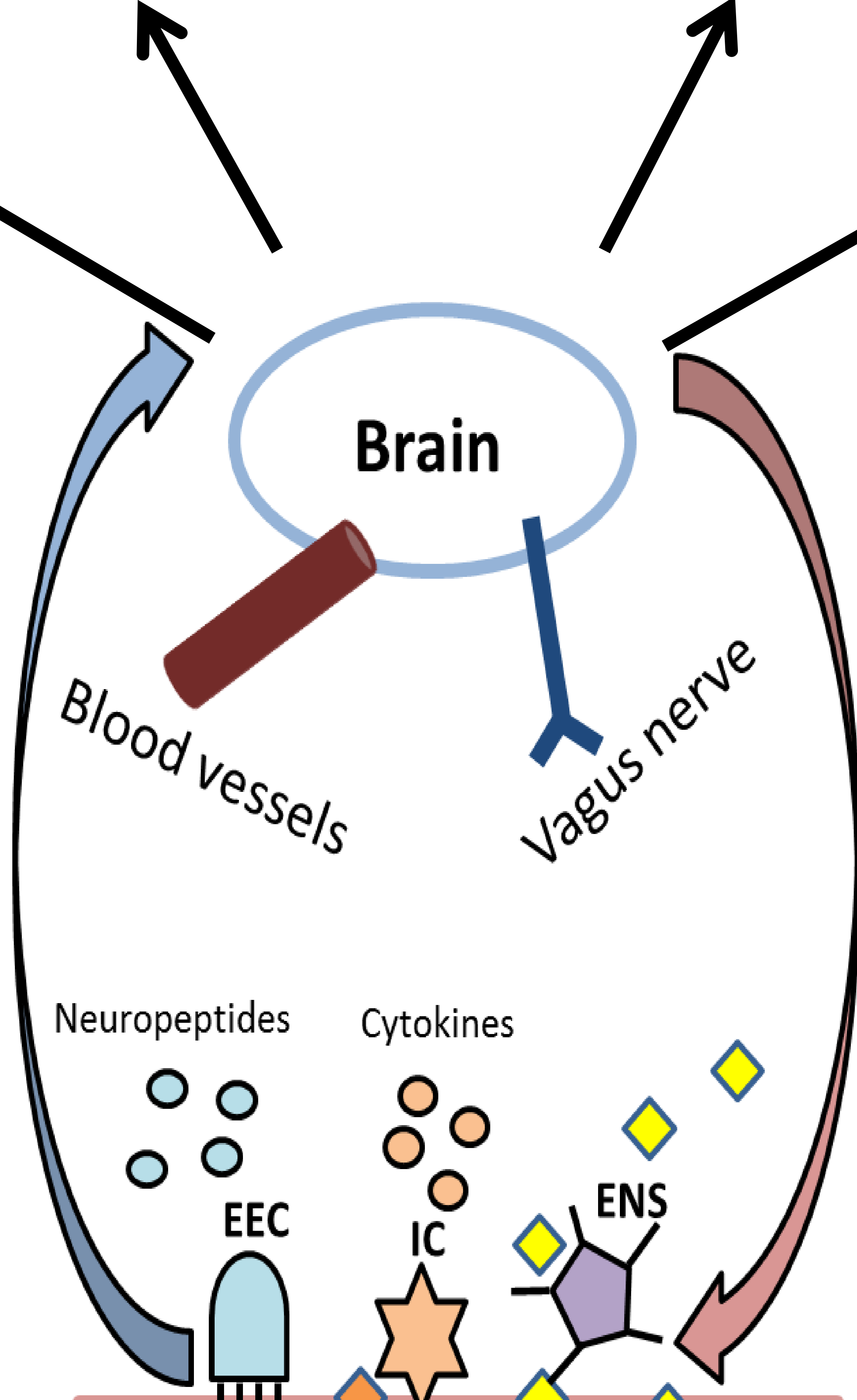


Figure 1: Gut microbiota as a key actor for animal welfare



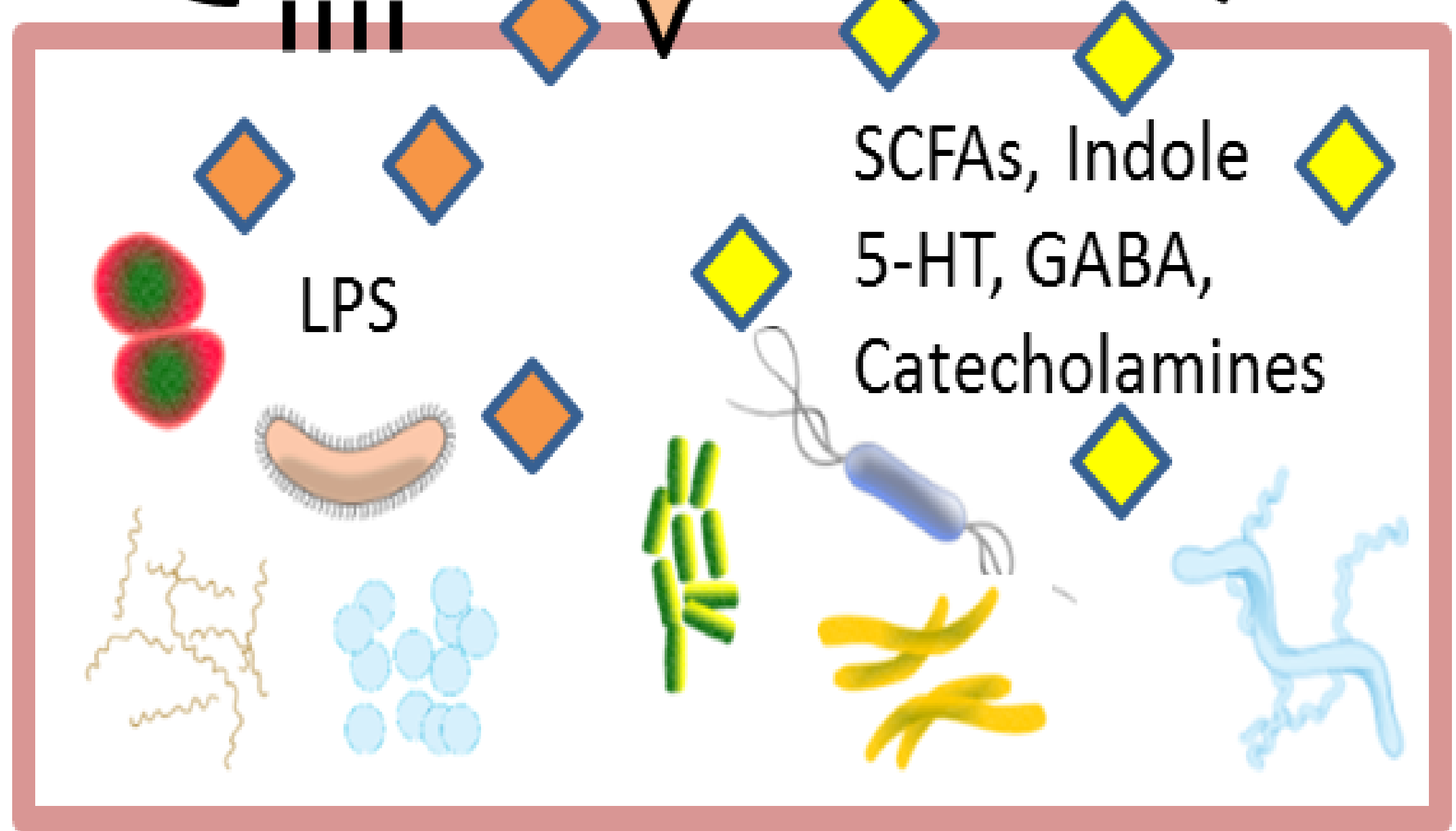
Anxiety-like behavior **Memory capacities** **Social behavior** **Feeding behavior**

✘ - + ▲ ■ ✘ - + ▲ ● ✘ + ● - + ▲ ●



Influence on the brain:
Brain development
Myelination
Neurogenesis
HPA axis

Influence on the gut:
Gut physiology and motility
Microbiota composition



Gut microbiota

Germ-free ✘ **Antibiotics -** **Probiotics +** **Infection ▲** **Microbiota transfer ■** **Diet modification ●**

Figure 2: Influence of the MGBA on behavior.

Different strategies can be used to modify the gut microbiota composition (indicated at the bottom of the figure: germ-free animals, antibiotic, probiotic, pathogen infection, microbiota transfer, dietary modification). The gut microbiota composed of viruses, archaea and bacteria can act directly or indirectly on the brain via cell structural components (lipo-polysaccharides = LPS) or with the release of microbial metabolites (short-chain fatty acids = SCFAs, neurotransmitters, catecholamines, indole ...), that can be absorbed by the intestinal epithelium, then released into the bloodstream and cross the blood-brain barrier; use the immune pathway and the production of pro-inflammatory cytokines by immune cells (IC); stimulate the enteric nervous system (ENS) and its sensory neurons or induce the secretion of neuropeptides by entero-endocrine cells (EEC). All these molecules can reach the brain via the blood circulation or the activation of vagal afferent fibers. In addition to the effects on brain development, myelination, neurogenesis or HPA axis activity, the consequences of the MGBA have been investigated on the anxiety-like behavior in human, rodent, turkey, quail and horse; on memory capacities in human, rodent, quail and pig; on social behavior in human, rodent, chicken, turkey and quail; on feeding behavior in rodent, goat, cow, chicken and turkey. The bi-directional communication of this MGBA also involve effects of the nervous system on gut microbiota motility, physiology and composition.

Table: Taxonomic profiles of major gut bacterial communities at the phylum level in farm animals using 16 rRNA gene pyrosequencing (Percentage of sequences assigned)

Host	Gut segment	References	Phylum				
			Firmicutes	Bacteroidetes	Actinobacteria	Proteobacteria	Verrucomicrobia
Cow	Rumen	[89]	25-58%	38-75%	<1%	0-5%	-
Sheep	Rumen	[150]	49%	47%	<1%	<1%	<1%
Horse	Cecum	[77]	30-50%	30-50%	-	5%	<7%
Pig	Hindgut	[151]	35-95%	<2%	<1%	3-40%	-
Rabbit	Cecum	[98]	83%	6%	<1%	<1%	-
Chicken	Cecum	[95]	85%	-	6%	6%	-
Quail	Cecum	[78]	56-70%	25-35%	-	-	-
Duck	Cecum	[85]	34%	57%	-	7%	-