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1 **The *foraging* gene as a modulator of division of labour in social insects**

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## 8 **The *foraging* gene as a modulator of division of labour in social insects**

### 9 **Abstract**

10 The social ants, bees, wasps, and termites include some of the most ecologically-successful  
11 groups of animal species. Their dominance in most terrestrial environments is attributed to their  
12 social lifestyle, which enable their colonies to exploit environmental resources with remarkable  
13 efficiency. One key attribute of social insect colonies is the division of labour that emerges  
14 among the sterile workers, which represent the majority of colony members. Studies of the  
15 mechanisms that drive division of labour systems across diverse social species have provided  
16 fundamental insights into the developmental, physiological, molecular, and genomic processes  
17 that regulate sociality, and the possible genetic routes that may have led to its evolution from a  
18 solitary ancestor. Here we specifically discuss the conserved role of the *foraging* gene, which  
19 encodes a cGMP-dependent protein kinase (PKG). Originally identified as a behaviourally  
20 polymorphic gene that drives alternative foraging strategies in the fruit fly *Drosophila*  
21 *melanogaster*, changes in *foraging* expression and kinase activity were later shown to play a key  
22 role in the division of labour in diverse social insect species as well. In particular, *foraging*  
23 appears to regulate worker transitions between behavioural tasks and specific behavioural traits  
24 associated with morphological castes. Although the specific neuroethological role of *foraging* in  
25 the insect brain remains mostly unknown, studies in genetically tractable insect species indicate  
26 that PKG signalling plays a conserved role in the neuronal plasticity of sensory, cognitive and  
27 motor functions, which underlie behaviours relevant to division of labour, including appetitive  
28 learning, aggression, stress response, phototaxis, and the response to pheromones.

29

30 **Keywords (5 to 6):** *foraging* gene; sociality; insects; behaviour; division of  
31 labour

32

33 **Subject classification codes:** review

## 34 **Introduction**

35           Animal social grouping is common because it increases the fitness of individuals by,  
36 for example, maximizing their access to resources and providing improved defences against  
37 predators (Wilson, 1987). Some of the most derived forms of sociality are exhibited by  
38 species of eusocial insects in the orders Hymenoptera (ants, bees, wasps) and Isoptera  
39 (termites), which together are estimated to represent more than 30% of the global animal  
40 biomass (Hölldobler & Wilson, 2009). All social insect colonies exhibit reproductive division  
41 of labour, in which majority of a colony is comprised of sterile female workers and just one or  
42 few reproductive individuals (the “queen” in social Hymenoptera and the “royal couple” in  
43 termites) (Oster & Wilson, 1978). The sterile workers, in turn, self-organize to become  
44 specialized in different tasks that are necessary for the growth and maintenance of the colony  
45 such as foraging, brood care and colony defence (Corona et al., 2016; Gordon, 2016; Leitner  
46 & Dornhaus, 2019). Although division of labour among workers is common across many  
47 different social insect taxa, different species show varying levels of individual specializations.  
48 At one extreme, workers might exhibit almost no task specialization, while at the other  
49 extreme workers might differentiate into developmentally-determined morphological castes  
50 (Oster & Wilson, 1978) (Figure 1).

51           Despite the overwhelming complexity associated with insect sociality and the  
52 regulation of division of labour, the evolutionary emergence of division of labour systems  
53 across different social insect species most likely depended on the co-option of existing  
54 sensory pathways, and associated modulatory neural circuits, to generate differential  
55 behavioural syndromes across individuals that share a common social and physical  
56 environment. Subsequently, although sensory stimuli for all tasks are simultaneously present  
57 in the colony, division of labour systems maintain differential behavioural response thresholds  
58 to task specific cues in different individuals (Figure 1). The highly-tuned network of semi-  
59 autonomous individuals provides a robust, systems-level modulation of task allocation across

60 time and space based on the overall needs of the colony (Buttstedt et al., 2016; Haydak, 1970;  
61 Krista K Ingram, 2002; Kamakura, 2011; Romain Libbrecht & Keller, 2013; Nygaard et al.,  
62 2011; Patel et al., 1960; Schwander & Keller, 2008; Schwander et al., 2010; Wheeler, 1991).  
63 Phylogenetic studies indicate that division of labour systems likely evolved multiple times  
64 across, and within, different lineages of the social hymenopterans (Gordon, 2016; Rueffler et  
65 al., 2012). Therefore, division of labour in colonies of social insects has emerged as an  
66 excellent model for understanding how animal social systems have evolved and are regulated  
67 at the physiological, molecular, and cellular levels (Kapheim et al., 2015; Robinson et al.,  
68 2005; Smith et al., 2008; Toth & Robinson, 2007; A. L. Toth et al., 2010; Whitfield et al.,  
69 2006). Transcriptomic analyses of gene expression in the brains of workers that are engaged  
70 in specific tasks, for example, have indicated that division of labour depends on broad and  
71 complex changes in many different neuronal signalling pathways across different parts of the  
72 brain and other tissues (Figure 1). This appears to occur via differential promoter activity,  
73 regulatory non-coding miRNAs, and epigenetic processes (Cash et al., 2005; Greenberg et al.,  
74 2012; K. M. Kapheim et al., 2020; Lattorff & Moritz, 2013; Simola et al., 2016; Sinha et al.,  
75 2006; Toth et al., 2007; Whitfield et al., 2006). To date, changes in the expression levels of  
76 several genes have been associated with division of labour across diverse social insect  
77 species. However, only a few have been studied in any depth. The highly conserved cGMP-  
78 dependent protein kinase gene *foraging* (*for*), in particular, has been well-studied for its role  
79 in regulating division of labour. Previous work has established a causal association between  
80 *for* and task specialization, which is conserved across multiple independently-evolved  
81 lineages. Here we review the role of *for*, first identified as a behaviourally polymorphic gene  
82 in *Drosophila* associated with larval and adult foraging decisions (J. S. de Belle et al., 1989;  
83 K. A. Osborne et al., 1997), as a conserved signalling pathway that has been co-opted for the  
84 regulation of division of labour across diverse social insect species.

## 85 **The study of sociality in the era of molecular genetics**

86 Over 50 years ago, the pioneering ethologist Niko Tinbergen published his seminal  
87 paper entitled ‘On aims and methods of ethology’ (Burkhardt, 2014; Tinbergen, 1963). With  
88 brilliant simplicity, Tinbergen argued that if biologists want to really understand “behaviour”  
89 then they need to ask the following four questions (rephrased): 1) What is the studied trait  
90 good for (its impact on fitness)? 2) How does it develop during the lifetime of an individual  
91 (development/ontogeny)? 3) How did it evolve over the history of the species (trait  
92 phylogeny)? 4) How does it work (mechanism/causation)? The emergence of modern  
93 neuroscience and neurogenetics followed in the footsteps of ethology by providing a  
94 mechanistic framework as a powerful approach to the design of behavioural studies and their  
95 interpretation in the context of brain functions (Tinbergen question #4).

96 However, modern neuroscience research is now largely framed in the context of causation and  
97 mechanism (Tinbergen question #4). Consequently, the diversity of animal species used for  
98 basic neurogenetic research has, historically, been reduced to just a few genetically tractable  
99 species that have sequenced genomes, including the roundworm *Caenorhabditis elegans*  
100 (Bargmann, 1998), the fruit fly *Drosophila melanogaster* (Bellen et al., 2010), the zebrafish  
101 *Danio rerio* (Stewart et al., 2014), and the laboratory mouse *Mus musculus* (Lehner, 2013).

102 While there is no doubt that these models have been instrumental in the phenomenal progress  
103 made in cellular and molecular neuroscience over the past three decades, the decline in model  
104 diversity is clearly an unfortunate side effect, and has negatively impacted our ability to  
105 understand behaviour in ecologically and evolutionary relevant contexts (Fitzpatrick et al.,  
106 2005; Walton et al., 2020).

107 Yet, recent advances in genetic and genomic approaches have enabled investigators to adopt  
108 modern molecular approaches for understanding the behaviour of a wider assortment of  
109 animal species in the lab and in their natural environments. Some of the first non-drosophilid

110 insects for which genomic and molecular tools for studying behaviour have made a  
111 tremendous impact are the social insects, particularly in the several independent social clades  
112 within the order Hymenoptera. One of the best established model species for sociogenomic  
113 and genetic studies is the European honey bee *Apis mellifera*. As the most dominant  
114 domesticated insect, the long tradition of beekeeping has provided investigators with a rich  
115 knowledge of its behaviour and physiology, including well-established techniques for  
116 manipulating colony demography and colony genetics via artificial inseminations (Page et al.,  
117 2002; Vanengelsdorp & Meixner, 2010). Not surprisingly, the economic importance of the  
118 honey bee has led to the development of diverse molecular and genetic resources, including a  
119 relatively well-annotated genome, high-resolution population genetics, and successful genome  
120 transformations (Ament et al., 2010; Ben-Shahar, 2014; Ben-Shahar et al., 2004; Chen et al.,  
121 2021; Foret et al., 2009; Sinha et al., 2006; Y. Wang et al., 2006; Weinstock et al., 2006;  
122 Whitfield et al., 2006; Whitfield et al., 2003). Subsequently, the progress in analysing honey  
123 bee behaviour with molecular and genetic tools has paved the way for similar breakthroughs  
124 in many additional social insect species (Karen M. Kapheim et al., 2020; Kapheim et al.,  
125 2015; R. Libbrecht et al., 2013; Sadd et al., 2015; A. L. Toth et al., 2010). Nevertheless, the  
126 genetic mechanisms by which specific genes and neuronal signalling pathways regulate the  
127 complex behaviour of social insects had remained mostly a mystery until the discovery of the  
128 gene *foraging* (*for*), a cGMP-dependent protein kinase (PKG), and its role in the regulation of  
129 behavioural plasticity in colonies of social insects (Figure 1D). Subsequent studies of this  
130 gene of in the context of division of labour have provided some important mechanistic  
131 insights into animal sociality.

### 132 **The role of *foraging* in regulating division of labour in social insect colonies**

133 The *foraging* (*for*) gene encodes a cGMP-dependent protein kinase (K. Osborne et al., 1997),  
134 a highly conserved enzyme present in all animal genomes sequenced to date (Anreiter &

135 Sokolowski, 2019; Lucas, Kornfein, et al., 2010). The *for* gene was first identified as a  
136 naturally polymorphic locus that regulates larval foraging behaviour in *Drosophila* (J.S. de  
137 Belle & Sokolowski, 1987; Sokolowski, 1980), and was later identified as a gene that encodes  
138 one of the two cGMP-dependent protein kinases (PKG) encoded by the *Drosophila* genome  
139 (K. Osborne et al., 1997). The highly conserved PKG family is broadly expressed in both  
140 neuronal and non-neuronal tissues, and has been implicated in numerous cellular and  
141 physiological functions via its kinase activity (Dason et al., 2019; Douglas et al., 2005;  
142 Francis et al., 2010; Lohmann et al., 1997; X. Wang & Robinson, 1997). In *Drosophila*, *for* is  
143 expressed in diverse tissues, including the peripheral (PNS) and central (CNS) nervous  
144 systems of both larvae and adults (Anreiter et al., 2017). Several genetic studies have revealed  
145 that the natural polymorphism in *for* contributes to diverse sensory functions, including the  
146 visual, olfaction, and gustatory pathways (Lin et al., 1992). In the CNS, *for* is expressed in the  
147 Kenyon cells of the mushroom bodies, the central complex, and the antennal lobes. It has  
148 been implicated in regulating neuronal and behavioural plasticity in diverse cognitive and  
149 motor functions such as neuronal sensitization and habituation, learning and memory, and  
150 sleep (Eddison et al., 2012; Engel et al., 2000; Scheiner et al., 2004). In addition to regulating  
151 behaviour via neuronal functions, *for* also indirectly contributes to feeding and foraging  
152 behaviours via its role in metabolic plasticity and the response to stress (Dason et al., 2020;  
153 Kaun et al., 2008; Kaun & Sokolowski, 2009; Kent et al., 2009).

154 The role of the cGMP-PKG signalling axis in regulating feeding behaviours is conserved in  
155 other animal species. For example, cGMP-signalling has been shown to regulate the response  
156 threshold of insects to pheromones (Boekhoff et al., 1993; Ziegelberger et al., 1990), and to  
157 influence olfactory communication in rats (Kroner et al., 1996; Moon et al., 1998). In the  
158 worm *Caenorhabditis elegans*, the PKG-ortholog *egl-4* plays a role in foraging, olfaction,  
159 sleep, body size and lifespan (Fujiwara et al., 2002; L'Etoile et al., 2002; Raizen et al., 2008).

160 Yet, in spite of its broad role in regulating different forms of behavioural plasticity in diverse  
161 animal species, the identities of the specific neuronal substrates modulated by *for* in the  
162 context of foraging behaviour and social insect division of labour remain mostly unknown.  
163 However, studies in genetically tractable species provide some mechanistic insights into how  
164 PKG signalling might be regulating neuronal processes associated with division labour. For  
165 example, studies in the mouse, indicate that PKG activity can have broad effects on long-term  
166 neuronal processes and behavioural plasticity via diverse downstream effectors. Neuronal  
167 PKG activity can modulate long-term potentiation (LTP) in the mammalian brain via a direct  
168 modulation of cAMP-phosphodiesterases, which regulate cAMP levels and synaptic plasticity  
169 (Bollen et al., 2014). In addition, studies of *Egl-4*, the ortholog of *for* in the worm *C. elegans*,  
170 has shown that sensory-induced neuronal plasticity within the chemosensory system depends  
171 on the transition of activated PKG to the nucleus, which leads to changes in neuronal gene  
172 expression via the modulation of heterochromatin binding proteins (Lee et al., 2010).  
173 Together, these examples illustrate the broad role *for* and related kinase genes play in  
174 regulating neuronal plasticity and organismal behaviour via diverse molecular and cellular  
175 mechanisms in the peripheral and central nervous systems of invertebrates and vertebrates.

### 176 **The *foraging* gene in social bees**

177 The realization that *for* plays a key role in regulating feeding-related behavioural  
178 plasticity in *Drosophila* suggested that the phylogenetically conserved PKG signalling pathway  
179 is also likely to be driving similar foraging-related decisions in other insect species, including  
180 in the regulation of foraging vs. brood care behaviour in social insect division of labour.  
181 Recently, *for* has also been implicated in the regulation of social networks in *Drosophila*  
182 (Alwash et al., 2021). By using transcriptomics and gene candidate approaches (Fitzpatrick et  
183 al., 2005), multiple studies have identified several key genes that play a role in regulating  
184 division of labour in honey bees including the acetylcholine esterase (*AchE*) gene (Shapira et

185 al., 2001), the *foraging* (*for*) gene (Ben-Shahar et al., 2003; Ben-Shahar et al., 2002), and the  
186 manganese transporter *malvolio* (Ben-Shahar et al., 2004). In terms of how *for* exerts its action  
187 in honey bees, follow-up studies have identified an increase in brain expression levels of *for*  
188 just prior to the initiation of foraging, which suggests that its activity may serve as a trigger for  
189 the transition from in-hive behaviours to foraging outside (Heylen et al., 2008). Furthermore,  
190 QTL analysis of foraging-related traits in honey bee populations has identified an association  
191 with QTLs in the *for* locus, suggesting that in addition to its role at the developmental and  
192 physiological timescales, *for* may play a role in shaping division of labour at the evolutionary  
193 timescale as well (Ruppell et al., 2004).

194         The discovery of *for* as a putative key regulator of division of labour in the honey bee  
195 was followed by studies investigating its role in regulating division of labour across the social  
196 hymenopteran phylogeny. It was shown that changes in *for* expression are also associated  
197 with division of labour in other species of social bees, including the Asian honey bee *A.*  
198 *cerana* (Ma et al., 2018), as well as different bumblebee species (Kodaira et al., 2009;  
199 Tobback et al., 2011). Interestingly, in contrast to the reported increased *for* expression in the  
200 brains of honey bee foragers, the expression of *for* in association with the size-dependent  
201 regulation of division of labour in bumblebees was variable, indicating higher *for* expression  
202 in *Bombus terrestris* foragers but lower in brains of *B. ignitus* foragers (Couvillon et al., 2010;  
203 Kodaira et al., 2009; Shpigler et al., 2013). Together, these studies suggest that the functional  
204 relationship between *for* activity in the brain and the behavioural states that define the  
205 probability of performing specific tasks by individual bees is complex and likely involve both  
206 central and peripheral neuronal pathways.

## 207 **The *foraging* gene in ants**

208         In ants, *for* has been shown to be involved in age-related division of labour, as in  
209 honey bees (Krista K Ingram et al., 2016; K. K. Ingram et al., 2005; Lucas et al., 2015;  
210 Manfredini et al., 2014; Oettler et al., 2015). However, in contrast to social bees, which  
211 primarily regulate division of labour on a physiological timescale, studies of *for* in ants  
212 revealed its role in regulating polyethisms in association with both age-dependent and  
213 developmentally-regulated morphological castes. For example, colonies of the ant *Pheidole*  
214 *pallidula* have two morphologically-distinct workers (Passera, 1985), each associated with  
215 specific behavioural repertoires. The majors have a large head with large mandibles and are  
216 mainly involved in the defence of the colony and processing of large food items, while the  
217 minors are smaller and are mainly involved in brood care and foraging. This morphological  
218 and behavioural division of labour was associated with changes in brain activity; minors had  
219 lower brain PKG activity than majors (Lucas & Sokolowski, 2009). In addition, although  
220 minors and majors typically perform distinct roles in the colony, when confronted with  
221 changing needs of the colony, majors may assist minors in foraging activities and minors may  
222 help with defence tasks (Aarab, 1991). Accordingly, experimental manipulations showed that  
223 majors that respond to foraging stimuli show minor-like, low brain PKG activity. Similarly,  
224 when participating in colony defence, minors showed a significant increase in brain PKG  
225 activity to major-like levels (Lucas & Sokolowski, 2009). Moreover, pharmacological  
226 treatment of minors with the PKG activator 8-Br-cGMP induced brain PKG activity, and led  
227 to an increase in defence and decrease in foraging behaviours (Lucas & Sokolowski, 2009),  
228 thus establishing a causal association between PKG activity and worker behavioural  
229 plasticity. The *foraging* gene in *P. pallidula* therefore appears to modulate both foraging  
230 behaviour and defence behaviour (Anreiter & Sokolowski, 2019; Lucas, Hughson, et al.,  
231 2010; Lucas & Sokolowski, 2009) and, under conditions that require plastic task reallocation,  
232 can drive neuronal plasticity even in species with a robust morphological division of labour

233 system (Anreiter & Sokolowski, 2019; Lucas, Hughson, et al., 2010). These findings suggest  
234 that *for* exerts at least two levels of control over worker behaviour in ants: (1) Differences in  
235 baseline brain PKG activity are associated with caste polyethism at the developmental  
236 timescale; and (2) Plasticity in PKG activity allows colony-level responses to environmental  
237 changes at the physiological timescale. This link between defence and PKG activity has also  
238 been demonstrated in a field study, where feeding the ant *Allomerus octoarticulatus* with a  
239 PKG activator, increased defence behaviour of the ant-plant *Cordia nodosa* against  
240 herbivores, suggesting a molecular basis for ant-plant mutualism (Malé et al., 2017).

241 In another ant species, *Solenopsis invicta*, *foraging* gene expression in workers was  
242 influenced by colony demography, in particular whether the colony had one queen  
243 (monogynous) or multiple queens (polygynous) (Lucas et al., 2015). Workers from  
244 monogynous colonies of *S. invicta*, which are very territorial and aggressive (Chirino et al.,  
245 2012; Tschinkel, 2006), had higher brain expression levels of *for* relative to workers from the  
246 more docile polygynous colonies (Lucas et al., 2015). Altogether, these results suggest that  
247 the *for* gene might be involved in regulating differential levels of aggression associated with  
248 territorial foraging or caste polyethisms. Recently, *for* has been shown to regulate aggression  
249 in flies as well, providing further support to the idea that the role of *for* in regulating  
250 behavioural plasticity across distant species is conserved not only for foraging behaviour but  
251 may be also for defence behaviour (S. Wang & Sokolowski, 2017).

252 Moreover in the ant *S. invicta*, *for* expression level was shown to be associated with  
253 reproductive state (future queen vs. workers) and the number of future queens (monogynous  
254 vs. polygynous) (Lucas et al., 2015), suggesting that in addition to its role in regulating  
255 behavioural plasticity in workers, *for* also contributes to reproductive division of labour in *S.*  
256 *invicta*. Interestingly, variations in colony demography (monogynous vs. polygynous) exist in

257 several ant species, and are thought to confer colony-level benefits by increasing genetic  
258 diversity, and therefore, amplifying worker behavioural differences that underlie division of  
259 labour (Cronin et al., 2013; Krista K Ingram, 2002; Manfredini et al., 2014; Pearcy et al.,  
260 2004; Ross & Keller, 1995).

## 261 **The neuroethological context of the regulation of division of labour by *for***

262         Based on theoretical and empirical studies, one of the primary models for self-  
263 organized division of labour in social insect colonies is based on the idea that animals at  
264 different behavioural states exhibit different behavioural response thresholds to task-specific  
265 stimuli (Beshers & Fewell, 2001; Duarte et al., 2012). Consequently, although workers are  
266 exposed to many or all task-stimuli in the colony, the probability that an individual worker  
267 will respond to the stimulus for a particular task varies (Bonabeau et al., 1998; Detrain et al.,  
268 1999; Duarte et al., 2012; Leitner & Dornhaus, 2019). Subsequently, molecular, genetic, and  
269 neuroethological studies have suggested that the PKG activity of *for* regulates division of  
270 labour, at least in part, via the modulation of task-specific sensory thresholds (Ben-Shahar et  
271 al., 2003; George et al., 2020; Heylen et al., 2008; Thamm & Scheiner, 2014).

272         As a kinase, *for* is likely to have numerous protein targets in the insect brain (X. Wang  
273 & Robinson, 1997). To date, the specific protein targets that mediate its role in behavioural  
274 plasticity in general, and division of labour in particular, remain mostly elusive, however,  
275 studies in various species suggest that *for* may have targets within the sensory system. Studies  
276 in *Drosophila*, for example, have indicated that *for* contributes to sucrose responsiveness in  
277 adults (Scheiner et al., 2004) and the larval nociception threshold (Dason et al., 2020). Similar  
278 effects on sensory thresholds have also been identified in *C. elegans* and rodent models,  
279 further indicating a conserved role for cGMP-dependent signalling in modulating behavioural  
280 states via sensory functions (Gangadharan et al., 2017; Jaumann et al., 2012; Levy &  
281 Bargmann, 2020). Subsequently, several studies in the honey bee have indicated that *for*

282 activity plays a role in regulating the response threshold to light, indicating that increased  
283 PKG activity drives positive phototaxis in foragers (Ben-Shahar, 2005; Ben-Shahar et al.,  
284 2003). In addition, *for* has also been implicated in honey bee sucrose responsiveness and the  
285 response threshold to queen pheromones (Fussnecker et al., 2011; Thamm & Scheiner, 2014).  
286 Together, these studies suggest that *for* is likely to regulate division of labour via multimodal  
287 modulation of sensory functions.

288         In addition to its role in regulating sensory functions, *for* has been shown to contribute  
289 to both simple forms of neuronal plasticity, such as the habituation in the giant fiber escape  
290 circuit responsiveness to sugar (Engel et al., 2000; Scheiner et al., 2004), as well as more  
291 complex processes such as visual memories (Kuntz et al., 2017; Z. Wang et al., 2008) and  
292 associative learning (Kaun et al., 2007; Mery et al., 2007) in flies. Because division of labour  
293 is often associated with differential learning and memory capacities (Ben-Shahar & Robinson,  
294 2001; Ben-Shahar et al., 2000; Roussel et al., 2009), it has been hypothesized that *for* is also  
295 likely to also modulate division of labour via its action in central neuronal circuits associated  
296 with higher level cognitive functions (Ben-Shahar, 2005; Menzel et al., 2006). Interestingly,  
297 in *Pheidole* ants, the expression pattern of *for* in the brains of majors is specific to a subregion  
298 of the mushroom bodies, while both minor and major workers share its expression in several  
299 brain regions including the lobula, which plays a role in the integration of visual cues (Lucas  
300 & Sokolowski, 2009). Although it is still unknown how the action of *for* in this specific brain  
301 region is contributing to the behaviours exhibited by minors and majors, the well-established  
302 anatomical and physiological role of the mushroom bodies in regulating division of labour in  
303 diverse social insects suggest that *for*-dependent signalling in this brain region is important for  
304 cognitive processes associated with division of labour. This is further supported by the recent  
305 findings that *for* activity is associated with interindividual differences in the dance intensity of  
306 returning foragers (George et al., 2020), and the impact of cGMP pharmacological treatment

307 on spatial learning in honey bee foragers (Tsvetkov et al., 2019).

### 308 **The *foraging* gene in other social contexts**

309       The complex role of *for* in regulating division of labour in bee and ant species  
310 indicates that this gene is highly pleiotropic, regulating not only foraging but also many other  
311 behavioural aspects of division of labour and other sociality-related traits. The study of *for* in  
312 other social species, such as wasps and termites, will yield important discoveries for  
313 understanding how *for* regulates social behaviours across diverse insect taxa. For example, a  
314 study on the comparisons of brain gene expression between the social wasp *Polistes metricus*  
315 and the honey bee *Apis mellifera* allowed to identify common molecular roots for division of  
316 labour, demonstrating the importance of *for* across lineages (Amy L Toth et al., 2010). In the  
317 termite *Reticulitermes flavipes*, a recent study showed differences in mRNA expression  
318 depending on caste, temperature and photoperiod (Merchant et al., 2019), suggesting the  
319 possibility that the differential expression of *for* may very well be important for this social  
320 insect group as well. Future comparisons between termites and social hymenopteran will  
321 likely shed even more light on how *for* regulates division of labour across phylogenetically  
322 distant social systems (Hymenoptera/Isoptera) with distinct developmental processes (e.g.,  
323 holometabolism vs. hemimetabolism).

324       Although the precise origin of insect eusociality remains mostly unknown at the  
325 molecular level, it is clear that some key neuronal signalling pathways, such as *for*, contribute  
326 to social interactions between conspecifics in non-social insects as well. For example, flies  
327 with low *for* expression are more sensitive to social context in learning paradigms than those  
328 with high expression levels (Kohn et al., 2013). In addition, *for* has been shown to be  
329 associated with population density-dependent regulation of polyphenisms in some aphid  
330 species (Tarès et al., 2013), and between solitary and gregarious forms in the locust

331 *Schistocerca gregaria* (Lucas, Kornfein, et al., 2010; Rogers et al., 2003; Tobback et al.,  
332 2013).

### 333 **Concluding remarks**

334       The association between the PKG activity of the *foraging* gene and behavioural  
335 plasticity in response to changes in the social and biotic environments, especially in the  
336 context of feeding and foraging behaviours, is conserved across a broad range of animal  
337 species, from insects to humans (Anreiter & Sokolowski, 2019; Armstrong et al., 2010;  
338 Chardonnet et al., 2014; Kohlmeier et al., 2019; Lucas, Kornfein, et al., 2010; Malé et al.,  
339 2017; Merchant et al., 2019; Robertson & Sillar, 2009; Struk et al., 2019; Tarès et al., 2013;  
340 Tobback et al., 2013). Additionally, it remains unknown whether all or only some of the  
341 alternative transcripts transcribed by *for* in at least some social insect species play a role in  
342 regulating neuronal plasticity and behaviour in social insects (Lucas & Sokolowski, 2009;  
343 Merchant et al., 2019; NCBI, 2021). Furthermore, the specific molecular targets and neuronal  
344 signalling pathways modulated by *for* activity across the evolutionary, developmental, and  
345 physiological timescales remain a mystery. Nevertheless, recent developments in transposon-  
346 mediated transgenesis and *Cas9*/CRISPR-dependent genome editing in several social insect  
347 species (Ben-Shahar, 2014; Chen et al., 2021; Kohno et al., 2016; McAfee et al., 2019;  
348 Schulte et al., 2014; Tribble et al., 2017) will likely yield new insights into the molecular and  
349 cellular pathways that underlie the role of *for*, and other important signalling pathways, in the  
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355

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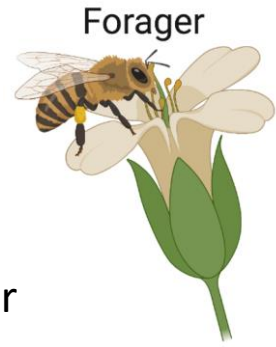
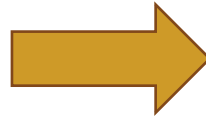
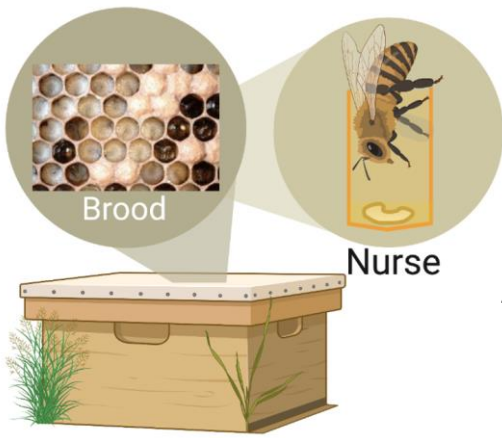
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887 **Figure 1. cGMP-dependent protein kinase is a key node in the gene network that**  
888 **regulates behavioral states associated with division of labour.** (A) Division of labour in the  
889 honey bee *Apis mellifera* is regulated solely by age-dependent processes. Young bees start  
890 their lives as nurses and typically start foraging when they are three weeks old. (B) Division  
891 of labour in the ant *Pheidole pallidula*. Tasks are regulated by developmental caste  
892 determination of “majors” and “minors”, as well by age-dependent regulation of behaviours  
893 such as nursing and foraging. Division of labour is also associated with task-specific sensory  
894 thresholds (A-B); and changes in neuronal anatomy and physiology (C). (D) Current models  
895 stipulate that *for* is a conserved regulatory node in the gene networks that regulate behavioral  
896 states across diverse social insect species. Therefore, changes in PKG activity can lead to  
897 shifts in the activity of peripheral and central neuronal populations that drive task-specific  
898 behavioral repertoires.

A



Age-dependent  
Division of labour

**Nursing state:**

1. Negative phototaxis
2. Low response threshold to brood pheromone
3. High response threshold to sugar

**Foraging state:**

1. Positive phototaxis
2. High response threshold to brood pheromone
3. Low response threshold to sugar
4. Attraction to floral odours

B



Developmental  
caste-dependent  
Division of labour

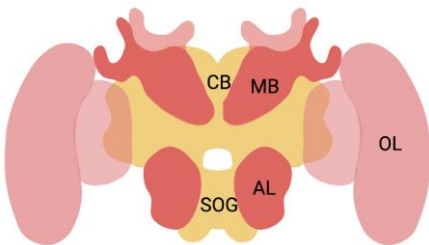
**Soldier state:**

1. Guarding
2. Low response threshold to intruders
3. High response threshold to food
4. Process large food items

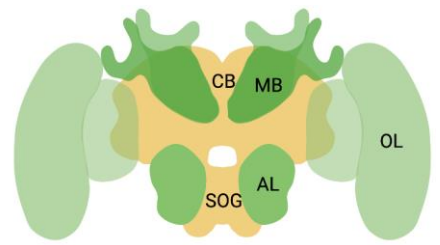
**Forager state:**

1. Food search
2. High response threshold to intruders
3. Low response threshold to food
4. Recruitment to food sources/intruders

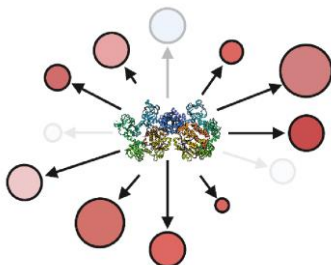
C



Brain anatomy  
and physiology



D



PKG-associated  
gene network

