

# 1 **Genetics and developmental biology of cooperation**

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## 24 **Abstract**

25 Despite essential progress towards understanding the evolution of cooperative behaviour, we  
26 still lack detailed knowledge about its underlying molecular mechanisms, genetic basis,  
27 evolutionary dynamics and ontogeny. An international workshop 'Genetics and Development of  
28 Cooperation', organized by the University of Bern (Switzerland), aimed at discussing the current  
29 progress in this research field and suggesting avenues for future research. Here, we synthesize  
30 the concepts of genetic and non-genetic inheritance of cooperation, and we review a quantitative  
31 genetic framework that allows for the inclusion of indirect genetic effects. Furthermore, we argue  
32 that including non-genetic inheritance, such as trans-generational epigenetic effects, parental  
33 effects, ecological and cultural inheritance, provides a more nuanced view of the evolution of  
34 cooperation. We summarize those genes and molecular pathways in a range of species that seem  
35 promising candidates for mechanisms underlying cooperative behaviours. Concerning the  
36 neurobiological substrate of cooperation, we suggest three cognitive skills necessary for the  
37 ability to cooperate, 1) event memory, 2) synchrony with others and 3) responsiveness to others.  
38 Taking a closer look at the developmental trajectories that lead to the expression of cooperative  
39 behaviours, we discuss the dichotomy between early morphological specialization in social  
40 insects and more flexible behavioural specialization in cooperatively breeding vertebrates.  
41 Finally, we provide recommendations for which biological systems and species may be  
42 particularly suitable, which specific traits and parameters should be measured, what type of  
43 approaches should be followed, and which methods should be employed in studies of  
44 cooperation in order to better understand how cooperation evolves and manifests in nature.

45

## 46 **Introduction**

47 The question of how cooperation evolves has been a major conceptual puzzle for biologists for  
48 centuries. Despite significant inroads in our understanding of the evolution of cooperation over  
49 the past 60 years, it remains one of the major challenges in biology to date. While most research  
50 into cooperation has been devoted to the functional significance of cooperation, an increasing  
51 number of scientists argue that a more holistic approach incorporating functional and  
52 mechanistic aspects of phenotypic traits is necessary to provide a complete picture (Soares *et al.*

53 2010; Weitekamp & Hofmann 2014; Bshary & Oliveira 2015; Taborsky & Taborsky 2015). First, by  
54 only focussing on the functional significance, one implicitly assumes that cooperation is not  
55 constrained by their underlying physiological, neural, molecular and developmental mechanisms.  
56 However, behaviours such as cooperation can only evolve by changes in those underlying  
57 mechanisms (Fawcett *et al.* 2013). Second, an integrative approach allows us to address  
58 questions of convergent molecular evolution (Aubin-Horth 2015) which is of particular  
59 importance for cooperation since it is thought to have evolved multiple times independently  
60 (Maynard-Smith & Szathmary 1997). Finally, theoretical and empirical research can be mutually  
61 informative. Detailed knowledge of the mechanisms underlying cooperation and evolutionary  
62 constraints on cooperative traits could lead to the development of models that better reflect the  
63 actual environmental complexity (McNamara & Houston 2009; Soares *et al.* 2010).

64

65 Our goal in the workshop 'Genetics and Development of Cooperation' organized by the University  
66 of Bern, held in Bern, Switzerland in February of 2016, was to explore new horizons in the fields  
67 of genetics and developmental mechanisms of cooperation. A list of the guest speakers and the  
68 titles of talks, as well as the names of the workshop participants, is provided in the supporting  
69 information. In the workshop, we focused on cooperative strategies such as reciprocity,  
70 mutualism, and coercion between family groups and non-kin for feeding, protection and raising  
71 young. We also discussed cooperative parental care, parent-offspring and sibling conflict, and  
72 communal nesting. Plenary talks were used as a launching pad for discussion sessions and poster  
73 sessions showcased individual participants' research. In the following sections we relate the  
74 content and questions raised by the workshop sessions. Moreover, we provide an outlook and  
75 further avenues for research in an effort to synthesize the various key points raised by the  
76 workshop.

77

### 78 **Modes of inheritance of cooperation**

79 Defining cooperation is notoriously difficult because of the complex interplay of fitness costs and  
80 benefits that accrue over different time periods and the varieties of situations under which it  
81 occurs (Sachs *et al.* 2004). For the purpose of the workshop, we followed the definition given in

82 Taborsky & Taborsky (2015) stating that "cooperation refers to the simultaneous or consecutive  
83 acting together of two or more individuals by same or different behaviours". Cooperative acts  
84 are typically costly for the individuals involved, but their net result is a fitness benefit.  
85 Cooperation can evolve if it yields immediate or delayed fitness benefits for all partners.  
86 Alternatively, if one partner can coerce the other into cooperation, only the receiver gains fitness  
87 benefits. Cooperative acts that yield direct fitness benefits for all partners are, for instance,  
88 improved prey capture when hunting in small groups in wolves (MacNulty *et al.* 2012), lowered  
89 predation risk through flocking behaviour in birds (Beauchamp 2003), reduced heat loss in  
90 huddling penguins (Ancel *et al.* 1997) and increased energetic benefit during V-formation flight  
91 in migrating birds (Voelkl *et al.* 2015; Voelkl & Fritz 2017). Altruistic behaviours, however, impose  
92 costs on actors without yielding direct benefits and result in a net decrease of the actor's direct  
93 fitness while increasing the recipient's fitness (Lehmann & Keller 2006). Examples of altruism  
94 include sterile castes of social insects that raise a queen's offspring (reviewed in (Ratnieks &  
95 Wenseleers 2008), but also the willingness to share food, engage in collective warfare, or to bear  
96 costs to punish non-cooperators in encounters with unrelated and even unknown individuals in  
97 humans (Fehr & Fischbacher 2003).

98  
99 An explanation of how such costly altruistic behaviours may evolve is predicated in the  
100 theoretical work by Hamilton who suggested that altruistic genes evolve under the scenario of  
101 inclusive fitness (Hamilton 1964a; b). In his seminal paper (Hamilton 1964b), he stipulates under  
102 which conditions altruism should evolve by deriving the famous Hamilton's rule,  $rB > C$ . Under  
103 this scenario, costs to the focal individual (C) are outweighed by the benefits to the receiver (B),  
104 weighted by the genetic relatedness (r) between the two individuals. If the costs and benefits are  
105 similar, cooperation should arise based on genetic relatedness, which is also known as kin  
106 selection. Despite this illuminating theoretical foundation, definite evidence for specific drivers  
107 for the evolution of cooperation remains difficult to identify for many species that display  
108 cooperative behaviours. For example, the evidence for kin selection as a driver of cooperation is  
109 mixed (Riehl 2013; Taborsky *et al.* 2016) and costs and benefits can be difficult to assess and  
110 compare objectively within and between species (Hatchwell & Komdeur 2000; Sachs *et al.* 2004).

111 Knowledge of the genetic, molecular and physiological mechanisms that underlie cooperative  
112 behaviours can greatly improve our understanding of the evolution of cooperation. For instance,  
113 genetic variation in cooperative behaviours reflects their evolutionary potential, i.e. how those  
114 traits can respond to natural selection. Evolutionary theory predicts that cooperative behaviour,  
115 like other phenotypic traits, should have a heritable basis if they are the product of adaptive  
116 evolution (Tinbergen 1963; Komdeur 2006; Hofmann *et al.* 2014). In fact, there is some empirical  
117 support for heritable differences in cooperative behaviours (e.g. in western bluebirds *Sialia*  
118 *mexicana* (Charmantier *et al.* 2007), and in humans (Cesarini *et al.* 2008). However, an individual's  
119 cooperative tendency is likely to be influenced additionally by social and non-social  
120 environmental conditions to allow for plasticity during development or to fine-tune payoffs in its  
121 current situation (Fischer *et al.*, *in revision*; Kasper *et al.*, *in revision*; Koenig *et al.* 1992; Stiver *et*  
122 *al.* 2004; Sanderson *et al.* 2015b). Moreover, non-genetic inheritance of cooperation through  
123 social interactions and cultural transmission may add additional layers to the complexity of the  
124 evolution of cooperation (Uller & Helanterä; Avital & Jablonka 2000; Danchin *et al.* 2011), but  
125 this field is thus far underdeveloped for cooperation.

126

### 127 *Genetic inheritance and indirect genetic effects*

128 For a cooperative – or any other – trait to be subject to selection, it needs to vary among  
129 individuals. This variation should result in differential fitness and should be heritable (Lewontin  
130 1970). Quantitative genetic models allow researchers to explore the extent to which genetic  
131 variation influences phenotypic variation by estimating the proportional contributions of  
132 heritable genetic variation and environmental variation to the total phenotypic variation. By  
133 combining these estimates with estimates of the fitness consequences of this variation, we can  
134 predict how a trait will respond to selection (Lande & Arnold 1983).

135

136 Accounting for the social environment of individuals adds a further dimension to cooperative  
137 behaviour because it involves interactions with other individuals, making the behaviour of an  
138 individual contingent upon the behaviour and genotype of its social partners. Therefore, the  
139 cooperative phenotypes should be considered as being partly influenced by interactions with

140 social partners and the genes they carry: i.e., their 'interacting phenotype' (Moore *et al.* 1997).  
141 This influence of the social environment sets those traits apart from traits that are solely  
142 influenced by heritable genetic and non-social environmental components, and therefore  
143 requires additional theoretical considerations (Bleakley *et al.* 2010). Especially for cooperative  
144 traits, we can expect that the genotypes of interaction partners affect the fitness of an individual  
145 in a similar way as the individual's own genes (McGlothlin *et al.* 2014). For instance, in species  
146 that provide biparental care, parents can negotiate the amount of care each provides which  
147 equally affects both parents' fitness in terms of offspring survival (McNamara & Houston 2005).  
148 Another example where social environment may play a key role is cooperative breeding, where  
149 helpers might adjust their helping effort based on the contributions of other group members  
150 (Adams *et al.* 2015). Parents can reduce their level of care when helpers are present (Taborsky *et al.*  
151 *et al.* 2007; Johnstone 2011), or where subordinates are coerced into helping (Clutton-Brock &  
152 Parker 1995; Fischer *et al.* 2014).

153

154 In his talk, 'A social effects perspective on kin selection', Jason Wolf outlined the quantitative  
155 genetic version of Hamilton's rule that takes into account the impact of the focal individual's own  
156 phenotype on its fitness ('non-social selection gradient',  $\beta_N$ ), but also the phenotype of the  
157 individual with whom it interacts ('social selection gradient',  $\beta_S$ , Fig. 1, (McGlothlin *et al.* 2014).  
158 This model demonstrates that selection will favour altruism when the benefits ( $\beta_S$ ), weighted by  
159 the phenotypic similarity of the partners, are greater than the costs ( $-\beta_N$ ). In cases where  
160 phenotypic similarity solely arises due to genetic relatedness, it is equivalent to Hamilton's  
161 relatedness term (Queller 1992; McGlothlin *et al.* 2014). However, genetically unrelated  
162 individuals can be phenotypically similar. Covariances between the partners can arise due to the  
163 influence of genes expressed in another individual, providing an 'alternative pathway from  
164 genotype to fitness' via indirect genetic effects (IGEs, McGlothlin *et al.* 2014). Unlike a direct  
165 genetic effect (DGE) where an individual's genotype directly affects its phenotype, IGEs are the  
166 expression of one individual's genotype influencing the expression of another individual's  
167 phenotype. Thus, IGEs need to be scaled by a parameter that reflects the genetic influence of an  
168 interaction on the trait expressed in the focal individual. Here, the interaction effect coefficient

169 ( $\psi$ ) illustrates this relationship and ranges from -1 to 1 (Fig. 1). In the absence of genetic  
170 relatedness, cooperation should only evolve if benefits scaled by the interaction effect coefficient  
171 ( $\psi\beta_S$ ) outweigh costs ( $-\beta_N$ ). This framework provides an extension of the quantitative genetics  
172 approach to Hamilton's rule to interactions between unrelated individuals. Mutually beneficial  
173 behaviours can evolve even in the absence of relatedness between the interaction partners,  
174 because both partners gain direct net fitness benefits immediately or with some delay, and hence  
175 no conflict of interest occurs (Lehmann & Keller 2006). Many examples of cooperation in birds  
176 (Riehl 2013), fish (Wong & Balshine 2011), vampire bats (Wilkinson *et al.* 2016), humans (Jaeggi  
177 & Gurven 2013) and insects (Field & Leadbeater 2016; Gadagkar 2016) demonstrate that  
178 interaction partners are indeed often unrelated. Therefore, kin selection may not be the primary  
179 evolutionary force driving cooperation in these systems (Taborsky *et al.* 2016), and alternative  
180 hypotheses focusing on the IGEs should be considered.

181

### 182 *Non-genetic inheritance*

183 Heritability is not limited to the transference of genetic information from parent to offspring.  
184 Non-genetic information can potentially contribute to the evolution of a cooperative trait if it is  
185 transmitted from one generation to the next (Uller & Helanterä, in press). Distinguishing between  
186 different forms of heritability is crucial, because the form of transmission determines who  
187 inherits from whom and also how reliable the transmitted information is. In his talk 'Nongenetic  
188 inheritance, maternal effects, epigenetics, and cultural transmission: where are we now?',  
189 Etienne Danchin discussed the concept of inclusive inheritance, which allows not only for the  
190 transference of information via genes, but also through mechanisms of non-genetic inheritance  
191 (Danchin *et al.* 2014). Non-genetic inheritance is defined as the transmission of factors other than  
192 the DNA sequence from ancestors to offspring that affect the offspring's phenotype  
193 (Bonduriansky & Day 2009). Some of these mechanisms include heritable epigenetic effects,  
194 parental effects, ecological (or habitat) inheritance, and cultural (or social) inheritance (Danchin  
195 *et al.* 2011).

196

197 Narrow sense epigenetic inheritance occurs when phenotypic variation arises from heritable  
198 changes in gene expression, rather than differences in the DNA sequence itself. This variation can  
199 occur as a result of structural changes to the genome. For example, the modification of histone  
200 proteins or the methylation of cytosine bases in DNA can upregulate, downregulate, or silence  
201 gene expression (Jenuwein & Allis 2001; Suzuki & Bird 2008; Lee *et al.* 2010). These epigenetic  
202 modifications can be inherited from one generation to the next (Jablonka & Raz 2009; Danchin  
203 *et al.* 2011). For example, mice that are conditioned to fear an odour for its associated negative  
204 stimulus pass on the fear of this odour to their descendants. Hypomethylation of an odour  
205 receptor gene (*Olf151*) is transferred via the gametes, resulting in naïve mice having an innate  
206 fear of the odour (Dias & Ressler 2014). If and how epigenetic inheritance influences cooperative  
207 traits and learned social behaviours warrants further investigation.

208

209 Parental effects—effects that parents have on the phenotype of their offspring, but not via the  
210 inherited genome—can also act as mechanisms for non-genetic inheritance (Mousseau & Fox  
211 1998). The relevance of parental effects is now widely accepted and considered an additional  
212 source of heritability that contributes to parent-offspring resemblance with important  
213 evolutionary implications. Parental effects can be genetic, when parental genetic variation is the  
214 cause of the environmental component affecting offspring development (Danchin *et al.* 2011).  
215 However, parental effects can also be non-genetic (Danchin *et al.* 2011). For instance, helping  
216 tendencies in cooperative breeders have been shown to be influenced by maternal identity  
217 (Kasper *et al.*, *in revision*). To date, the exact mechanism of transmission is unclear, but candidate  
218 mechanisms are maternal allocation of resources towards egg size or composition (Russell *et al.*  
219 2007; Taborsky *et al.* 2007; Robinson *et al.* 2008), or parental care quality (Fischer *et al.*, *in*  
220 *revision*; Goodson *et al.* 2005), which may have subsequent bearing on offspring phenotypes.  
221 Parental effects can be accounted for in quantitative genetics models by including them as IGEs  
222 (see 'Genetic inheritance of cooperation').

223

224 Individuals may modify their environments through a process known as 'niche construction' that  
225 might alter the selective forces they experience (Laland *et al.* 2016). These modified



226 environments can be passed down to offspring through ecological inheritance, which contributes  
227 to inclusive heritability (Danchin *et al.* 2011). For example, termite mounds are cooperative  
228 efforts to modify temperature and humidity and are inherited both within and across generations  
229 (Odling-Smee *et al.* 2003). Within the quantitative genetic framework we developed earlier this  
230 means that phenotypes of others (the 'partners' in Fig. 1) modify the environment, which changes  
231 the selection gradients affecting the fitness of the focal individual ( $\beta_N$  and possibly  $\beta_S$  in Fig. 1)  
232 and these environments can be inherited.

233

234 Finally, cooperative behaviours can also be transmitted via cultural inheritance (Avital & Jablonka  
235 2000; Danchin *et al.* 2011). For cultural information to be conveyed, a trait must be (i) socially  
236 learned, (ii) transmitted across generations or from older to younger individuals, (iii) expressed  
237 sufficiently long to be picked-up by younger individuals and (iv) individuals must be able to  
238 generalize the social information to use it in new contexts (Danchin & Wagner 2010). For  
239 example, in cooperatively breeding long-tailed tits *Aegithalos caudatus*, individuals preferentially  
240 help at the nests of related birds. Kin recognition and inclination to help are determined through  
241 the similarity of vocalizations, which are learned in early development (Hatchwell *et al.* 2001;  
242 Sharp *et al.* 2005). If kin recognition operates only via those vocalizations and individuals are able  
243 to recognize kin they have never encountered before based on their dialect, kin recognition  
244 depends on culturally inherited differences in song.

245

246 An important consideration for all non-genetic inheritance mechanisms is their significance  
247 relative to genetic inheritance mechanisms. The contributions of non-genetic inheritance are  
248 likely to be highly variable depending on the trait and species in question, and their effect on the  
249 pace, and direction of evolution and maintenance of traits can be highly significant (Kirkpatrick  
250 & Lande 1989). For instance, non-genetic inheritance could explain the missing heritability — a  
251 lack of genetic markers explaining parent-offspring resemblance — in certain traits. Non-genetic  
252 inheritance could also play a role in the spread of novel alleles, maladaptive behaviours, and  
253 major organisational transitions (Danchin *et al.* 2011). An interesting way to investigate the  
254 relative importance of non-genetic inheritance is by incorporating it in quantitative genetic

255 models through the introduction of a double pedigree: one for genetic and one for non-genetic  
256 correlations (Helanterä & Uller 2010; Day & Bonduriansky 2011).

257  
258 Prior to any empirical efforts, it is vital to consider under which conditions non-genetic  
259 inheritance is expected to be adaptive. In a group discussion on “Non-genetic inheritance and  
260 the evolution of social/cooperative traits” led by Reinder Radersma, we explored such conditions  
261 for adaptive non-genetic inheritance. First, the transference of information across generations is  
262 beneficial in cases where the environment varies in a repeatable and predictable way over time.  
263 Generation time should be shorter than the period of environmental change, leading to a  
264 correlation between the parental phenotype and the environment the offspring will encounter.  
265 Second, changes in the environment should happen at a rate faster than the genome is able to  
266 accommodate (English *et al.* 2015b; Leimar & McNamara 2015; Fig 2). Third, within-generation  
267 phenotypic plasticity should be too costly, or individuals are physically, developmentally, or  
268 behaviourally constrained to adequately respond to the changing environment (Uller 2008).  
269 Finally, the benefits of non-genetic inheritance of a trait must outweigh the costs of the  
270 inheritance mechanism (Uller 2008). The reliability and quality of the information offspring or  
271 parents are able to gather about the environment is a critical component of the costs and greatly  
272 affects the adaptiveness of different inheritance mechanisms (Leimar & McNamara 2015).  
273 Further theoretical development, in tandem with empirical studies, should help to elucidate and  
274 quantify non-genetic inheritance of cooperative traits and behaviours in the future.

275  
276 *Relevance of IGEs and non-genetic inheritance to understanding the evolution of cooperation*

277 The IGE framework has the potential to improve our understanding of the evolution of  
278 cooperation by modelling how social interactions with conspecifics shape the fitness of  
279 cooperating individuals. Specifically, IGEs can be thought of as epistatic interactions between the  
280 focal trait and genes expressed in conspecifics and are thus part of the genetic architecture of a  
281 trait (Meffert *et al.* 2002). By providing the possibility of more realistic models of the non-additive  
282 selective pressures posed by the social environment on cooperative traits, different conclusions  
283 about the rate and even the direction of evolution might be drawn than from frameworks that

284 do not explicitly model IGEs. For instance, for social interactions that involve feedback loops  
285 between the same or different traits expressed in interacting individuals, the rate of evolution is  
286 expected to be 5 to 9 times faster than in the absence of IGEs, given that  $\psi$  is rather high (Fig. 1B  
287 and C, Moore *et al.* 1997). Furthermore, by changing the resemblance of relatives, the presence  
288 of IGEs could mask or exaggerate heritable genetic variance (Bijma & Wade 2008).

289  
290 The inclusive inheritance framework provides a more nuanced view of the evolution of  
291 cooperation by treating inheritance as a multidimensional phenomenon. For instance, failing to  
292 incorporate cultural inheritance into models of evolution of human behaviour is demonstrated  
293 to lead to substantive discrepancies between predicted and observed evolutionary outcomes  
294 (Richerson & Boyd 1978). Moreover, the phenotype with maximum fitness can differ depending  
295 on the mode of inheritance—for example between genetic and cultural inheritance—and thus  
296 conflict between these systems can arise. This means that maladaptive behaviours like costly acts  
297 of altruism towards unrelated individuals could spread in a population in cases where variance in  
298 cultural transmission is higher than variance in genetic transmission. Consequently, positive  
299 cultural selection could override negative selection in the genetic domain (Aguilar & Akçay 2016).

300

### 301 **Genetic and molecular pathways underlying cooperation**

302 A cursory review of genetic mechanisms in various systems demonstrates that there are  
303 numerous molecular pathways leading to the evolution of cooperative traits (Table S1 in the  
304 supporting information). Although a variety of molecular mechanisms have been identified, the  
305 overwhelming majority of studies indicate that hormonal regulatory pathways seem to hold the  
306 key to the evolution of cooperation in many of the examples found in social insects and  
307 vertebrates (Table S1).

308

309 The changes in how reproductive hormonal signalling systems work can have significant  
310 consequences for the emergence of helping behaviour which is often associated with suppressed  
311 reproduction. The insulin signalling – juvenile hormone (JH) – vitellogenin (Vg) regulatory  
312 pathway is a fundamental component involved in the evolution of cooperation in insects. Here

313 both JH and Vg are related to reproduction with JH being a gonadotropin and Vg being a yolk  
314 protein (Corona *et al.* 2007). In many insect species, JH and Vg are synergistically regulated  
315 (Handler & Postlethwait 1978; Comas *et al.* 1999; Sheng *et al.* 2011). In contrast, the regulation  
316 of JH and Vg in eusocial honeybees, *Apis mellifera*, is antagonistic (Corona *et al.* 2007) and  
317 regulates caste differentiation and division of labour in honeybees. The same regulatory pattern  
318 in the JH-Vg pathway was recently discovered in two sub-social species, the European earwig  
319 *Forficula auricularia* and the burying beetle *Nicrophorus vespilloides* (Engel *et al.* 2016, Wu *et al.*,  
320 *unpublished*). These findings suggest that this pathway may be co-opted in post-hatching  
321 parental care behaviours and in social evolution (Corona *et al.* 2007).

322  
323 In vertebrates, oxytocin (OXT), vasopressin (AVP), their non-mammalian homologs mesotocin,  
324 isotocin (IT) and vasotocin, and dopamine and serotonin are key endocrine players in cooperative  
325 behaviour (Soares *et al.* 2010; Ebstein *et al.* 2010; Madden & Clutton-Brock 2011; Anacker &  
326 Beery 2013). These hormones affect social affiliation (Reddon *et al.* 2015), social recognition and  
327 approach (Thompson & Walton 2004), reward estimates (Messias *et al.* 2016a), social learning  
328 (Messias *et al.* 2016b; Soares *et al.* 2016) and pair bonding (Insel & Shapiro 1992). For example,  
329 in humans, OXT is suggested to favour trust and parochial cooperation (De Dreu 2012), whereas  
330 AVP increased cooperative tendencies in reciprocal interactions (Rilling *et al.* 2012). Cooperation  
331 can also be enhanced or decreased by social stress and its underlying hormones (glucocorticoids,  
332 GCs). For example, in many social species, reproductive suppression of subordinate individuals is  
333 regulated by behaviours of dominant individuals that elicit higher levels of GCs in subordinates  
334 (Creel *et al.* 1996; Sanderson *et al.* 2015a).

335  
336 The neuroendocrine pathways regulated by hormones appear critical for the evolution of  
337 cooperative behaviours in vertebrates (Goodson 2005, 2013; Donaldson & Young 2008; Soares  
338 *et al.* 2010; O'Connell & Hofmann 2011a; c), but the strength and direction of their regulatory  
339 effects depend on species, social context, and sex. A recent comparison of brain gene expression  
340 of IT and AVT and their receptors between different social and non-social species pairs of cichlids  
341 revealed contrasting patterns (O'Connor *et al.* 2015). Furthermore, experimentally increased OXT

342 (or its homolog IT) increased helping behaviours and decreased aggression in cooperatively  
343 breeding meerkats, *Suricata suricatta* (Madden & Clutton-Brock 2011), and the sensitivity to  
344 social information in *N. pulcher* (Reddon *et al.* 2012), but it decreased sociability in this species  
345 (Reddon *et al.* 2014). However, the direction of the effect of IT treatment depended on the pre-  
346 treatment sociability in gold fish (Thompson & Walton 2004), and OXT had no effect in house  
347 mice, *Mus musculus domesticus* (Harrison *et al.* 2016). In humans, experimentally administered  
348 OXT increased cooperation within groups, but also enhanced competition between groups (De  
349 Dreu 2012). Interestingly, these effects of OXT on social behaviour in humans have been  
350 demonstrated to differ between women and men (Gao *et al.* 2016).

351  
352 The evolution of sociality from solitary ancestry and the evolution of cooperative from non-  
353 cooperative behaviours requires the emergence of novel social traits (Taborsky & Taborsky 2015).  
354 Genes present in solitary species could be co-opted towards social evolution. For example, *Vg*  
355 encodes the precursor of yolk protein (Corona *et al.* 2007); in sub-social European earwigs and  
356 burying beetles its expression is associated with parental care (Roy-Zokan *et al.* 2015; Wu *et al.*  
357 unpublished); in eusocial honey bee it regulates division of labour and caste differentiation  
358 (Amdam *et al.* 2003, 2004). Another example is the *PebIII* gene which had a direct genetic effect  
359 on the metamorphosis of the solitary insect *Drosophila melanogaster* (Sabatier *et al.* 2003). In  
360 the sub-social European earwigs, this gene is co-regulated and co-adapted between parent and  
361 offspring. RNAi knock-down of this gene showed an indirect genetic effect on offspring  
362 development and a direct genetic effect on maternal future reproduction in the earwigs (Wu *et al.*  
363 unpublished). Potential neo-functionalization or sub-functionalization of this gene was found  
364 in the eusocial termite *Reticulitermes flavipes*, with differential expression of two transcripts of  
365 *PebIII* between reproductive castes (Steller *et al.* 2010).

366

### 367 **Neurobiological mechanisms of cooperation**

368 Group-living animals often cooperate, as well as compete, with the same individuals multiple  
369 times over their lifespan. To assess the costs and benefits of social interactions, individuals need  
370 to continuously process social stimuli and keep track of past interactions. Responding to the

371 multitude of daily social challenges encountered by social species requires behavioural flexibility  
372 and social competence (sensu Taborsky & Oliveira 2012; Bshary & Oliveira 2015). These complex  
373 social decisions require highly developed neuronal networks, which integrate many brain areas  
374 and populations of neurons (Platt *et al.* 2016). For example, group size and the corresponding  
375 availability of social partners predict structural changes of the thickness of grey matter in multiple  
376 brain regions (Sallet *et al.* 2011). Group size also leads to functional change in terms of different  
377 co-activation of two brain regions, the superior temporal sulcus and the rostral prefrontal cortex  
378 (Sallet *et al.* 2011). To understand how individuals make flexible social decisions while engaged  
379 in cooperative or competitive interactions, researchers often focused on species with more  
380 complex cognitive abilities such as humans or primates. However, recent work has highlighted  
381 that many physiological and neurological mechanisms are conserved across taxonomic groups  
382 (O'Connell & Hofmann 2011c). Further, seemingly cognitively demanding abilities, such as  
383 individual recognition or keeping track of past interactions, might be the result of learning  
384 processes involving operant-conditioning rather than sophisticated cognitive mechanisms  
385 (Bshary *et al.* 2016). Hormones and ontogeny can also affect the cognitive skills necessary for the  
386 ability to cooperate. We suggest these consist of three aspects: 1) event memory, 2) synchrony  
387 with others and 3) responsiveness to others. For example, zebra finches were prevented from  
388 cooperating in a prisoner's dilemma task when their stress hormone levels were experimentally  
389 raised. These hormones reduce memory capacity required for reciprocity and remove incentive  
390 for cooperation (Larose & Dubois 2011). In addition, humans and many animals cooperate better  
391 when more receptive to social stimuli through synchronization in terms of personality,  
392 experience, or hormonal physiology. For example, shared excitement synchronizes brain activity  
393 in humans to enable better cooperation in times of need (Nummenmaa *et al.* 2012).

394  
395 It is now well established that two evolutionarily conserved neural circuits are fundamental in  
396 regulating social decision-making in vertebrates and are commonly referred to as the Social  
397 Decision Making Network (SDMN) (O'Connell & Hofmann 2011b). The SDMN is comprised of two  
398 neural circuits: the mesolimbic reward system, which evaluates the salience of external stimuli  
399 to generate an adaptive response, and the social behaviour network, which evaluates external

400 stimuli (Goodson 2005). Only the interconnected activity of both systems enables animals to  
401 regulate and implement adaptive behavioural outputs in response to environmental challenges  
402 and opportunities. Many hormones that influence key aspects of cooperative behaviour, such as  
403 OXT, AVP, dopamine or serotonin, are part of the SDMN. However, even though the SDMN is  
404 doubtless an important player in social behaviour, it remains an open question whether  
405 cooperative behaviour itself is regulated by the SDMN.

406

#### 407 **Developmental regulation of sociality/cooperative behaviour**

408 Modes of development can have a huge impact on the evolution of early phenotypic  
409 specialization versus extended phenotypic plasticity (English *et al.* 2015a). Invertebrates, and in  
410 particular eusocial insects, are more prone to early developmental specialization because they  
411 have to commit to the development of a certain phenotype before metamorphosis (Wilson  
412 1971). Most social insects show a strict behavioural and morphological caste differentiation  
413 determined by different developmental trajectories, which leads to a division of labour in insect  
414 colonies (Wilson 1971). Arguably, the most famous example is the development of queens in  
415 honeybees induced by the ingestion of royal jelly (Kaftanoglu *et al.* 2011). Early caste  
416 determination is a common phenomenon in most eusocial insects where nutrition and inhibitory  
417 pheromones play an important role (Schwander *et al.* 2010). There are, however, a number of  
418 social insect species that are cooperative breeders without morphological specializations, which  
419 can switch between the role of subordinates and dominants within a lifetime (Field & Leadbeater  
420 2016; Gadagkar 2016).

421

422 In contrast to many social insects, most social vertebrates remain morphologically and  
423 behaviourally flexible throughout their life. For example, dominant breeders and subordinate  
424 group members in cooperatively breeding vertebrates maintain their full reproductive capacity  
425 (Bruitjes *et al.* 2011; Bell *et al.* 2012), but can adapt their social roles and behaviours contingent  
426 on the social context and environmental conditions (Bruitjes & Taborsky 2011). Therefore, most  
427 social vertebrates do not develop morphological specialisations based on their social rank or role  
428 (Carter *et al.* 2014; Huchard *et al.* 2014; Sanderson *et al.* 2015b; Taborsky *et al.* 2015; Zöttl *et al.*

429 2016, but see Jarvis 1981; Fischer *et al.* 2015). Nevertheless, early behavioural specialization  
430 might be beneficial, for instance, when deciding if and when to disperse (Fischer *et al.*, *in revision*;  
431 Zöttl *et al.* 2013), if and when to challenge the dominant individual in the home territory (Sharp  
432 & Clutton-Brock 2011), and whether to rear offspring communally or solitarily (Jo Manning *et al.*  
433 1995). All of these decisions require specific behavioural repertoires. Bolder, more risk-prone  
434 phenotypes are more successful dispersers (Chapman *et al.* 2011) while larger individuals with  
435 superior fighting abilities are better able to challenge dominants for territory take-overs (Huchard  
436 *et al.* 2016). A communal nest requires individuals to express prosocial behaviours towards  
437 breeding partners and foreign young (Weidt *et al.* 2008, 2014; Dugdale *et al.* 2010). Social  
438 behaviour can be costly (Grantner & Taborsky 1998; Cram *et al.* 2015) and misdirected  
439 behaviours may have high fitness costs and can lead to evictions from the group (Bell *et al.* 2012),  
440 infanticide (Schmidt *et al.* 2015) and even to fatal conflicts (Enquist & Leimar 1990). Thus,  
441 environmentally induced developmental programming of behavioural strategies, e.g. via  
442 parental effects or own early experience, might be also important in cooperatively breeding  
443 vertebrates.

444  
445 The cues responsible for early phenotypic specialization are diverse and can induce phenotypic  
446 specializations between and within social groups. For example, intragroup caste specialization is  
447 dependent on group size (Ferguson-Gow *et al.* 2014) or the level of competition between nests  
448 (Passera *et al.* 1996) in ant species. In cooperatively breeding vertebrates, group size can  
449 influence maternal investment in eggs. Smaller eggs are produced when more helpers are  
450 available to compensate for the reduced maternal investment in individual eggs (Russell *et al.*  
451 2007; Taborsky *et al.* 2007). In turn, offspring developing in larger groups may express different  
452 behavioural phenotypes than offspring from small groups as a result of developmental plasticity  
453 (Fischer *et al.* 2015). Within-group factors such as the provision of more or better food to  
454 particular group members can lead to divergent behavioural phenotypes such as the  
455 development of different caste phenotypes in social insect societies (Schwander *et al.* 2010) or  
456 different degrees of competitiveness in some vertebrates (Buston 2003; Heg *et al.* 2004a;  
457 Huchard *et al.* 2016).



458  
459 A second important role of developmental plasticity for social organisation is the regulation of  
460 conflict within groups. The level of conflict in cooperative societies is particularly high when  
461 subordinates are fertile and therefore have a vested interest their own breeding opportunities.  
462 Subordinates queuing for a dominant position may compete with other subordinate group  
463 members about the position in the social hierarchy (Huchard *et al.* 2016). If access to  
464 reproductive opportunities is strongly skewed towards a few dominant individuals, conflicts over  
465 reproduction can also arise between dominant breeders and maturing subordinates (Heg *et al.*  
466 2004b). As social rank is often size-dependent, developmental plasticity of growth strategies may  
467 play a key role in either reducing or enhancing conflict. In response to social cues obtained from  
468 other group members, growth may be strategically enhanced to outcompete rivals or reduced to  
469 lower potential conflict with dominant group members. In her talk 'Measuring cooperation and  
470 associated phenotypes in the field: developmental trajectories and genetic basis', Elise Huchard  
471 showed that in cooperatively breeding meerkats, growth rates remain flexible throughout the  
472 entire ontogeny (Huchard *et al.* 2014). In this species, rank position depends on size and age, and  
473 subordinate females queue for the position of the dominant female, which is usually the oldest  
474 and heaviest female of the group. When Huchard and colleagues (Huchard *et al.* 2016)  
475 experimentally increased the growth rate of a subordinate by supplemental feeding, same-sex  
476 rivals responded by accelerating their own growth and food uptake. Conversely, subordinates of  
477 the cooperatively breeding cichlid fish, *N. pulcher*, inhibit their growth if their size difference to  
478 the same-sex dominant breeder becomes too small, as subordinates reaching body sizes too  
479 close to that of dominants risk expulsion from the group (Heg *et al.* 2004b).

480  
481 Finally, developmental processes may mediate conflict between dominant breeders and their  
482 offspring and future helpers or workers. In cooperative societies, not only are offspring  
483 dependent on care, but become carers themselves later in ontogeny. The optimal contribution  
484 to alloparental care required by dominant breeders versus the optimal contribution subordinate  
485 helpers are willing to give may diverge and depend on the options for dispersal and independent  
486 breeding by subordinates (Russell & Lummaa 2009). For instance, in his talk 'Hormonal signals,

487 epigenetic regulation, maternal effects, and their consequences for cooperation and conflict',  
488 Nikolaus von Engelhardt suggested that breeding females endow eggs with hormones or RNA  
489 transcripts, which might influence growth and behavioural propensities of offspring in a way that  
490 optimizes maternal fitness. These maternal effects may then influence the offspring's future  
491 willingness to contribute to alloparental care of younger broods. At the prenatal stage offspring  
492 depend on parental cues to adjust their development, since they do not directly experience their  
493 environment. However, offspring may use cues obtained postnatally to "disagree" with the  
494 maternal program and reverse their behavioural tendencies (Fischer *et al.* 2015).

495  
496 Because of the important role of developmental plasticity for the regulation of cooperative  
497 behaviours it is conceivable that in the course of the evolution of cooperation, environmentally  
498 induced phenotypic plasticity precedes, or even facilitates, genetic adaptation known as the  
499 'plasticity-first hypothesis' (West-Eberhard 2003; see Levis & Pfennig 2016 for a review). In a first  
500 step plasticity enables a rapid adaptive response to changing environments through phenotypic  
501 accommodation. In a second step, genetic accommodation allows for the relatively slow  
502 refinement of genotypes by accumulating beneficial genetic mutations. This, together with the  
503 co-option of genes as discussed in previous sections, could provide an answer to the longstanding  
504 question how novel cooperative traits emerge when cooperative species evolve from non-  
505 cooperative ancestors. Since the underlying genetic architecture of cooperative behaviour is  
506 arguably complex and polygenic, genetic adaptation alone is unlikely to account for these  
507 relatively fast transitions. Thus, phenotypic plasticity that precedes genetic adaptation as  
508 described above might offer another explanation for the fast emergence of cooperative traits.

509

## 510 **Outlook**

511 In previous sections we discussed ways in which cooperative behaviour can be transmitted from  
512 one generation to the next, either genetically, through heritable epigenetic changes, or through  
513 social learning and culture. We also outlined reasons why the evolutionary dynamics of  
514 cooperative traits might be less straightforward than generally assumed. Following Anna

515 Lindholm's talk and the ensuing discussion, here we focus on practical considerations and we  
516 provide promising avenues for future research in the genetics and development of cooperation.  
517

518 **Which systems are suitable?** The suitability of a system will ultimately depend on the exact  
519 question under investigation. In general, information on individuals is required for quantitative  
520 genetic approaches and desirable for molecular genetic approaches. Some taxa show a naturally  
521 occurring array of closely related species with a range of cooperative social behaviours. For  
522 example, Hymenoptera display a wide cooperative continuum from solitary to subsocial to  
523 eusocial species (Wilson 1971), and species of the teleost family Cichlidae represent a wide range  
524 of social systems from non-social to highly social (Taborsky 1994; Heg & Bachar 2006). The  
525 parasitoid bethylid wasps presented by Ian Hardy at the workshop provides an excellent example  
526 of a tractable social study system. In one of these species, *Sclerodermus harmandi*, multiple  
527 unrelated foundresses cooperatively rear each other's offspring on a single host resource  
528 (Kapranas *et al.* 2016). There is a broad scope for experimental manipulation of resource size,  
529 relatedness, foundress number, and offspring survival in bethylid wasps (e.g. Sreenivas & Hardy  
530 2016). The quasisocial nature of this species makes it a particularly suitable candidate for the  
531 study of cooperative behaviours in insects at the threshold of the evolution of complex sociality.

532  
533 Comparisons between the genomes and transcriptomes of species along the continuum of  
534 sociality can indicate likely genes and pathways for further investigation (Robinson *et al.* 2005;  
535 Rehan & Toth 2015; Kapheim 2016; Trapp *et al.* 2016; Toth & Rehan 2017). Comparisons within  
536 species are also useful to examine possible molecular causes of phenotypic variance. Systems in  
537 which individuals differ in their tendency to cooperate or cheat in social situations (Santorelli *et al.*  
538 2008), or in the amount of alloparental care to provide (Fischer *et al.*, *in revision*; Kasper *et al.*,  
539 *in revision*), are particularly well suited to studies of the underlying genetic architecture or gene  
540 expression patterns at the basis of cooperative phenotypes. Furthermore, the evolution of  
541 cooperative behaviours might not only depend on interactions within, but also between species  
542 (West *et al.* 2007) or between different organizational levels of sociality (West & Gardner 2013).  
543 We provide an example for multilevel cooperation, namely between microbiota and their host,

544 in the supporting information.

545

546 **Which specific traits and parameters should be measured?** It is of paramount importance to  
547 understand the biology of a system well enough in order to be able to accurately quantify fitness,  
548 and to decide which traits to measure. It is especially important to carefully consider if the  
549 phenotype measured is indeed a target of selection. In some instances, it might be better to  
550 measure the underlying mechanism, for instance an individual's physiology or cognitive ability,  
551 instead of the behavioural phenotype (behavioural gambit, Fawcett *et al.* 2013). Moreover, the  
552 interaction coefficient  $\psi$  could itself be considered a trait that varies genetically between  
553 individuals and is thus subject to selection (Bleakley & Brodie IV 2009) and of particular  
554 importance for the evolution of cooperative traits. For instance,  $\psi$  can be estimated empirically  
555 as the partial regression coefficient of a phenotype on its partner's phenotype while keeping the  
556 direct genetic influence constant. However, this requires isogenic lines or large-scale breeding  
557 designs with repeated measures of the same genotype with different social partners. Measuring  
558 individual-level phenotypic proxies could provide a more feasible approach for vertebrates,  
559 assuming a close phenotype-genotype resemblance (Edenbrow *et al.* 2017). Those proxies could  
560 be estimates of the extent to which traits covary between interaction partners, for example,  
561 spatial proximity.

562

563 **What type of approach should be followed?** Ideally, questions about the genetic basis of  
564 cooperative traits should combine both field observations and controlled laboratory studies.  
565 Moreover, insights gained from theoretical modelling of mechanisms underlying cooperation  
566 (see Supporting Information) and quantitative genetic modelling, for instance indirect genetic  
567 effects, should be considered. While the study of wild populations provides a more realistic  
568 picture of selective pressures in nature, a laboratory setting allows for easier control of  
569 confounding non-genetic effects (e.g. parental or other transgenerational effects) that  
570 potentially distort estimates of heritability (Kasper *et al.*, *in revision*). Ideally, field studies should  
571 use cross-fostering techniques to account for and estimate those effects (Hadfield *et al.* 2013).  
572 Likewise, laboratory experiments should use offspring of wild-caught individuals to preserve

573 natural patterns and breadth of genetic variation within the population and avoid artefacts due  
574 to genetic drift or lab-specific selection. Furthermore, studying individuals in highly artificial test  
575 settings that do not properly reflect the actual biology of a species could lead to ecologically or  
576 evolutionarily meaningless results. This caveat is corroborated by recent studies that found an  
577 effect of laboratory rearing on gene expression, physiology, behaviour and social dynamics in  
578 paper wasps *Polistes fuscatus* (Jandt *et al.* 2015) and an effect of the laboratory environment on  
579 prosocial behaviour of chimpanzees (Tennie *et al.* 2016).

580

581 **Which methods should be employed?** As with selection of study species, approach, trait, and  
582 setting, the most appropriate experimental method depends on the questions being asked.  
583 Quantitative genetic methods provide insight on the relative proportions of heritable and several  
584 types of environmental variance of cooperative traits and their covariance with other traits, and  
585 thus on the inheritance and genetic architecture of a cooperative trait. Combined with selection  
586 experiments, they can be used to predict how traits respond to selection. This could be followed  
587 up by quantitative trait locus or genome-wide association study approaches to search for  
588 candidate genetic polymorphisms that are responsible for phenotypic differences in cooperative  
589 tendency. Recent association studies in humans have shown that particular genotypes for the  
590 oxytocin receptor (OXTR) gene were highly associated with Asperger Syndrome, a type of autism  
591 (Di Napoli, Warrier *et al.* 2014). Particular genotypes may also be associated with OXTR and social  
592 empathy as measured through cooperative games (Thompson, Hurd *et al.* 2013). Several new  
593 technologies are available for the manipulation of gene expression at the transcriptomic level  
594 (e.g. RNA interference, Castel & Martienssen 2013), or by altering genes at the DNA level (e.g.  
595 gene editing via CRISPR-Cas, Hsu *et al.* 2014). These approaches could be employed to verify and  
596 validate candidate genes once identified by the above approaches. Future studies should  
597 incorporate new technologies for detecting genetic and epigenetic signatures of cooperation. For  
598 example, comparing genomes between closely related species exhibiting a continuum from  
599 solitary life style to advanced sociality may provide insights into the genomic structure underlying  
600 cooperation and the evolution of sociality along phylogenetic trees (Fischman *et al.* 2011;  
601 Kapheim *et al.* 2015). Furthermore, exploring correlations of epigenetic marks with phenotypic

602 variation in cooperativeness may provide insight in how gene expression is regulated in response  
603 to environmental factors (Jensen 2015; Li-Byarlay 2016). Investigating the stability of those  
604 epigenetic marks over time can shed light on the molecular pathways connecting previous social  
605 experience to future cooperative behaviour (Cardoso *et al.* 2015; Shpigler *et al.* 2017). Thus, in  
606 conclusion, we advocate a holistic approach that integrates complementary methods to unravel  
607 the proximate and ultimate causation of cooperation and social evolution, including comparative  
608 phenotypic and genomic approaches to tackle questions of adaptation and convergent evolution,  
609 the study of norms of reaction and shifts in gene regulatory networks to appreciate the role of  
610 phenotypic plasticity, and the study of interactions between individuals and their social and  
611 physical environment to unravel the role of natural selection.

612

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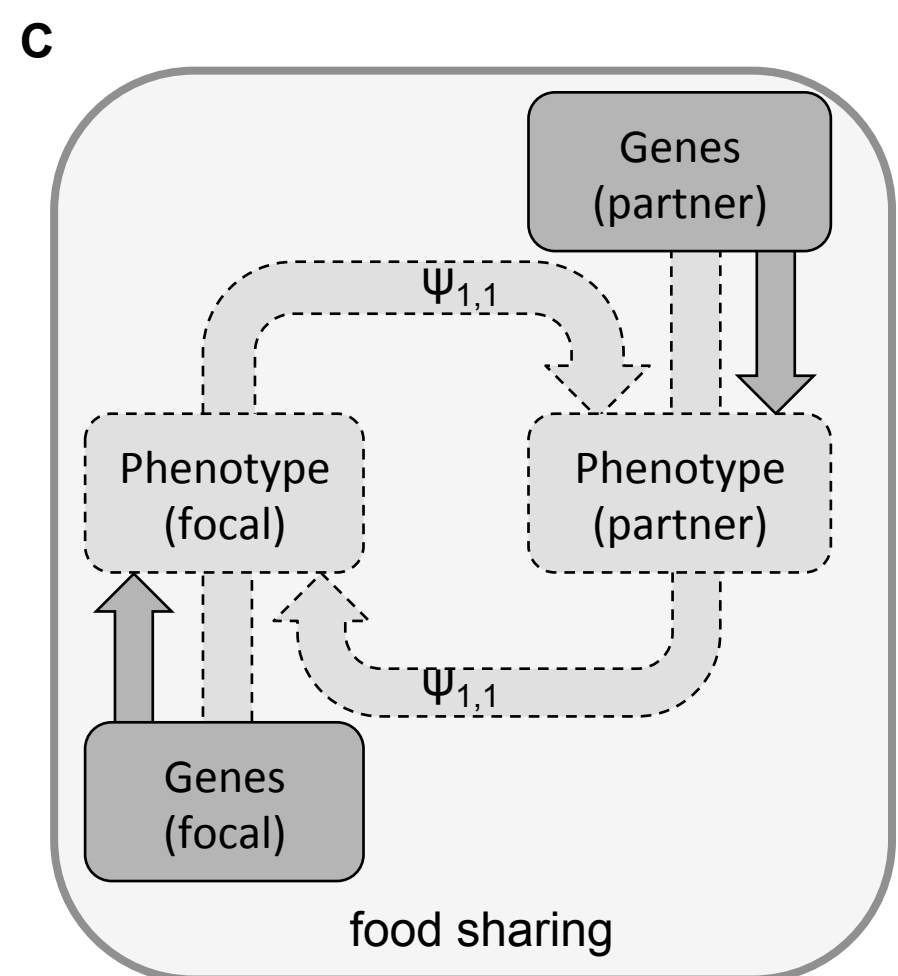
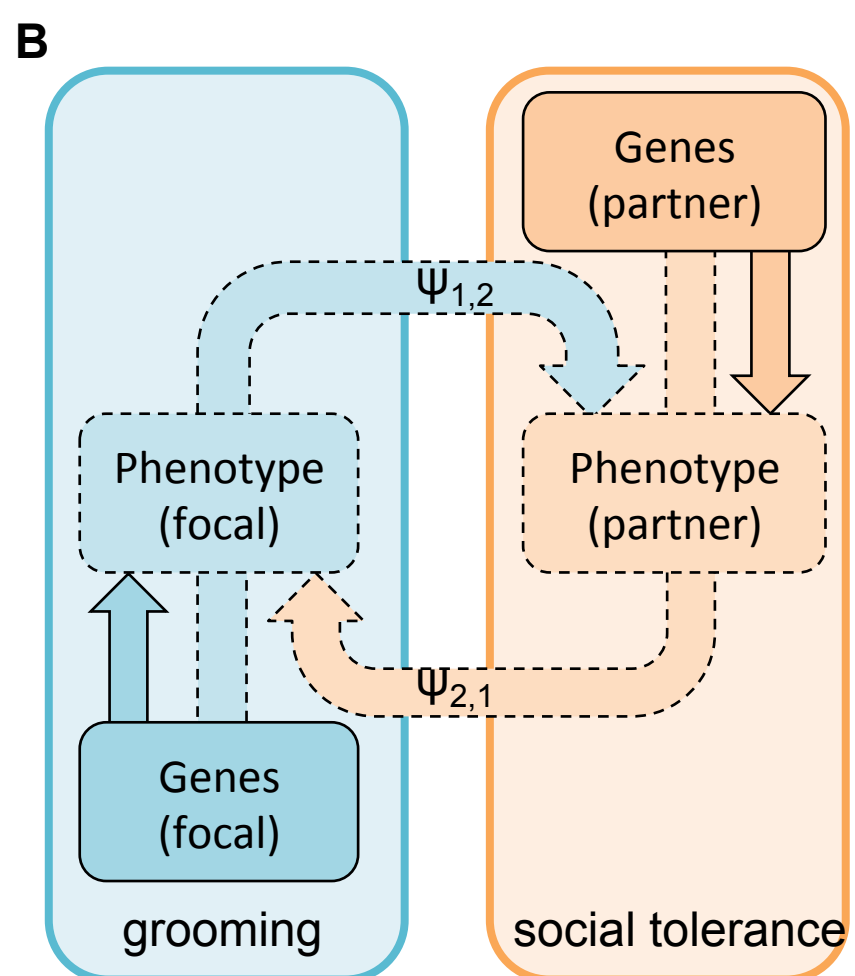
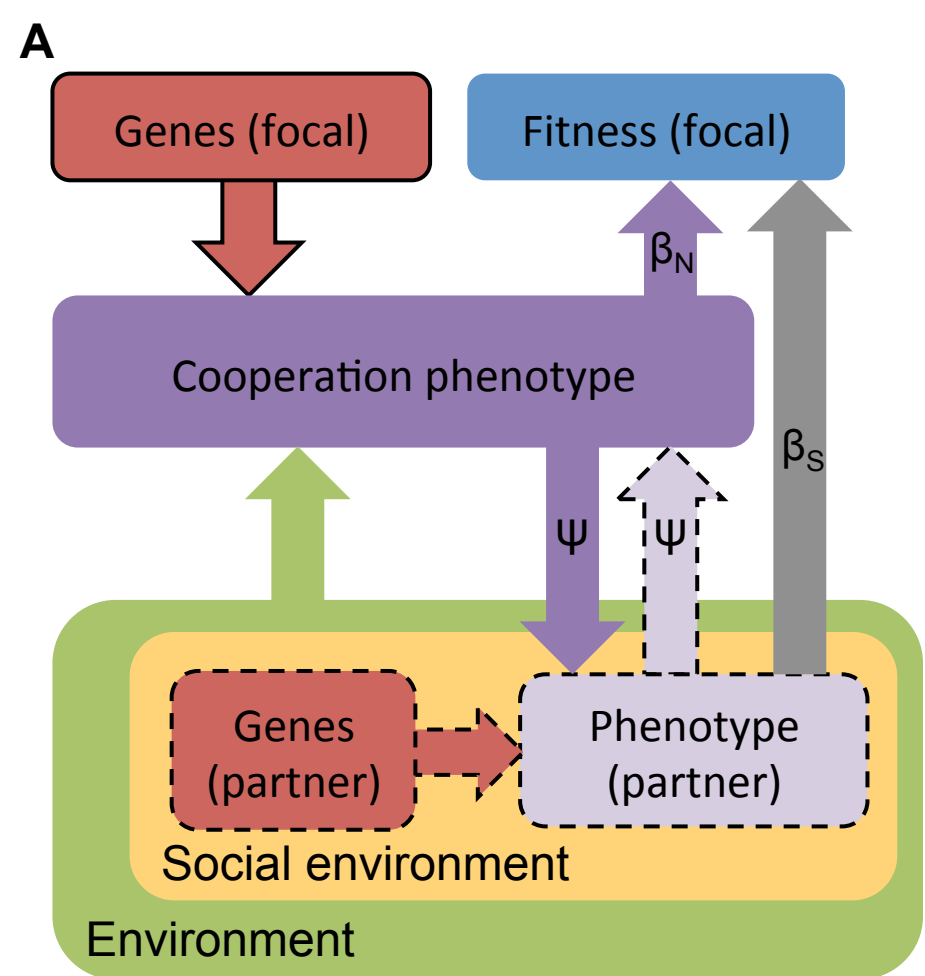
1016 **Figure Legends**

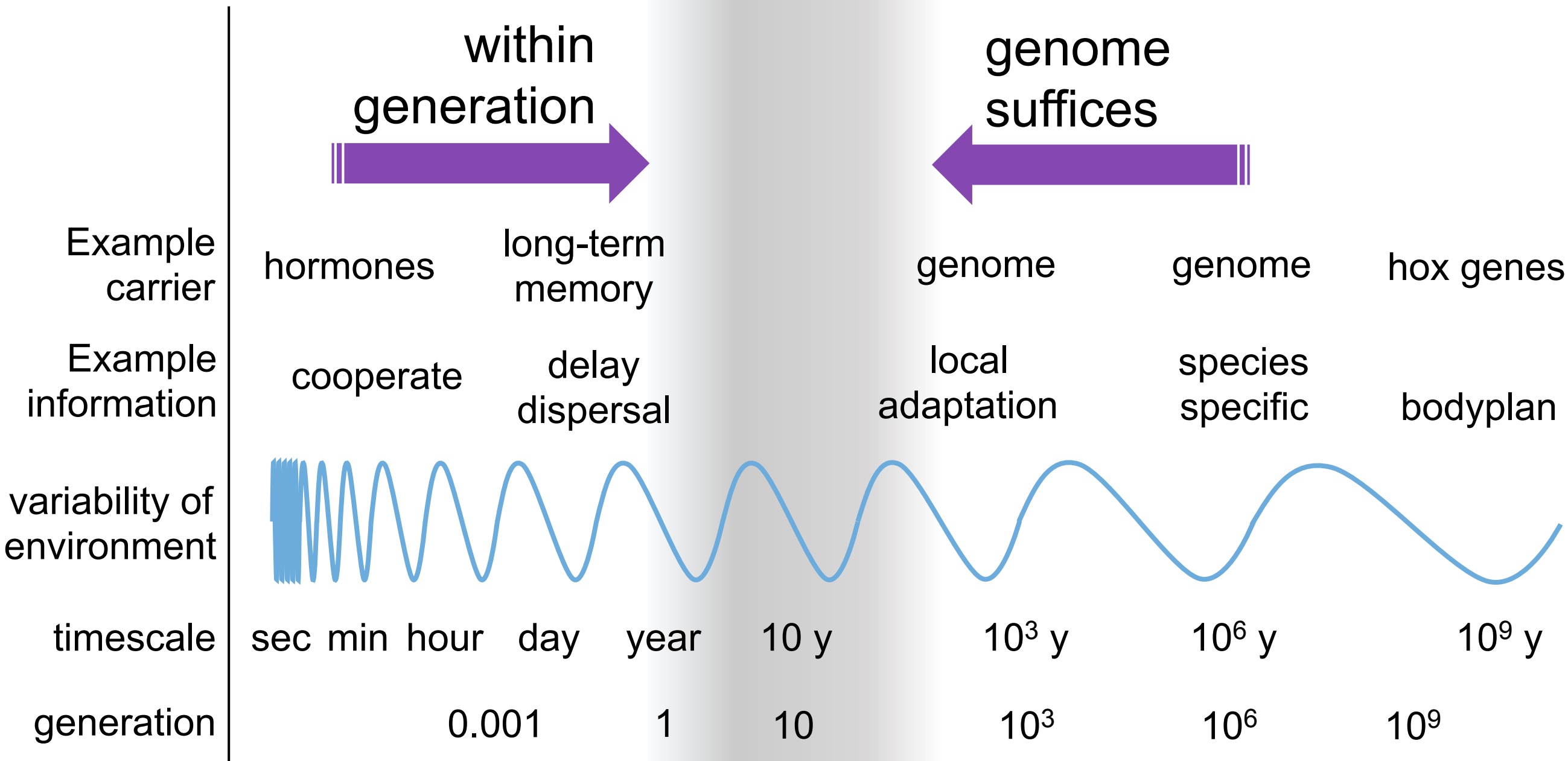
1017 Figure 1. Indirect genetic effects on cooperation. An individual's own genes and its environment  
 1018 jointly influence its cooperation phenotype (direct genetic effect, solid black line), which  
 1019 influences the focal's fitness ('non-social selection gradient',  $\beta_N$ ). Cooperative behaviours are  
 1020 expressed in a social setting that constitutes a component of the environment. **A** Non-reciprocal  
 1021 indirect genetic effect: A cooperation partner's genes influence the focal's phenotype indirectly  
 1022 via the partner's phenotype (indirect genetic effect, dashed black line). The strength of the  
 1023 influence of the genes in the social environment on the focal's phenotype is reflected by the  
 1024 interaction effect coefficient,  $\psi$ , and thus the focal's fitness is affected by genes expressed in  
 1025 other individuals ('social selection gradient',  $\beta_S$ ). **B** Two different traits expressed in two  
 1026 individuals influence each other reciprocally. For instance, the focal individual grooms its partner,  
 1027 which leads to an increased tolerance towards the focal ( $\psi_{1,2}$ ), which, in turn, results in more  
 1028 grooming by the focal ( $\psi_{2,1}$ ). **C** The same trait expressed in two different individuals influences  
 1029 itself reciprocally. For instance, the focal's propensity to share food with its partner could  
 1030 increase the partner's propensity to share food and vice versa ( $\psi_{1,1}$ ). Assuming a  $\psi$  of 0.75, the  
 1031 feed-back loops depicted in B and C lead to a 5 and 9-fold increase in the evolutionary rate  
 1032 compared to models without IGEs (Moore *et al.* 1997).

1033  
 1034 Figure 2. Non-genetic inheritance indicated on the information retention axis (in grey). The  
 1035 information retention axis symbolises the time scale at which information needs to be retained  
 1036 in a biological system to be adaptive. This adaptiveness depends on the variability of the selective  
 1037 environment. There is scope for non-genetic inheritance when information needs to be  
 1038 transferred over generations (arrow pointing to the right) and the environment is too variable  
 1039 for genes to adapt (arrow to the left). The number of generations, the time scale and the  
 1040 variability of the environment are conceptual examples - roughly at scale - and are study system  
 1041 specific. The types of information and the information carriers are hypothetical examples.

1042

1043





# ***Molecular Ecology***

Supporting Information

## **Genetics and developmental biology of cooperation**

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## Workshop speakers and participants

Jason Wolf (University of Bath, UK) spoke about the need to incorporate the social environment as a part of the genetic architecture of cooperative traits into quantitative genetics models. Ian Hardy (University of Nottingham) provided a detailed case study of cooperative brood care and resource conflict within bathyloid wasps. Elise Huchard (CNRS Montpellier, France) presented her work on the interplay of genes and environment in shaping growth trajectories of cooperatively breeding meerkats. Anna Lindholm (University of Zurich, Switzerland) led a discussion session on how to select suitable systems, which molecular methods should be applied, in which cases controlled laboratory studies should be preferred to field observations, and which parameters should be measured. Etienne Danchin (CNRS Toulouse, France) detailed various empirical studies demonstrating modes of non-genetic inheritance, social information, and their evolutionary implications. The broader theoretical implications of non-genetic inheritance to sociobiology and evolution of cooperative behaviour were discussed in a session led by Reinder Radersma (University of Lund, Sweden), while Nikolaus von Engelhardt (Plymouth University, UK) led a discussion session about physiological mechanisms and their role in cooperation.

The workshop was organized by Claudia Kasper and Maddalena Vierbuchen from the University of Bern, Switzerland, and attended by the following persons (given in alphabetical order): Laurie Belcher (University of Bath, UK), Rhiannon Bolton (University of Liverpool, UK), Christelle Couchoux (University of Sussex, UK), Filipa Cunha-Saraiva (KLIVV, University of Veterinary Medicine, Vienna, Austria), Jeremy Field (University of Sussex, UK), Stefan Fischer (University of Liverpool, UK), Janaina Lima de Oliveira (University of Bath, UK), Kenyon Mobley (University of Lausanne, Switzerland), Philip Madgwick (University of Bath, UK), Aura Raulo (University of Helsinki, Finland), Maria Reyes (University of Bern, Switzerland), Eva Schultner (University of Helsinki, Finland), Sakshi Sharda, Barbara Taborsky and Michael Taborsky (University of Bern, Switzerland), Bernhard Völkl (Vetsuisse Bern, Switzerland), Mukta Watve and Cecilia Wikström (University of Bern, Switzerland), Min Wu (University of Basel, Switzerland).

## Genetic and physiological mechanisms of cooperative behaviours across taxa

**Table S1.** Examples of genetic and physiological mechanisms for cooperation across taxonomic groups indicating whether a genetic polymorphism (GP) has been identified, or whether differential gene expression in hormones and their receptors are responsible for phenotypic differences (DGE). We also present studies that identified differences in hormone levels (HL) or distribution of hormone receptors (RD) as the mechanism underlying cooperative phenotypes.

	System	Type of cooperative behaviour	Mechanism	GP	DGE	HL	RD	Citations
Proteo-bacteria	<i>Vibrio fischeri</i>	Quorum sensing/bioluminescence	<i>Ain</i> and <i>lux</i> proteins	X				(Lupp & Ruby 2005)
	<i>Myxococcus xanthus</i>	Fruiting bodies to survive starvation	PX mutation	X				(Fiegna <i>et al.</i> 2006)
Amoebozoa	Slime molds ( <i>Dictyostelium discoideum</i> )	Colony formation	<i>dimA</i>	X				(Foster <i>et al.</i> 2004)
Plants	<i>Volvox carteri</i>	Reproductive altruism	<i>RegA/SAND-like domain</i>	X	X			(Kirk <i>et al.</i> 1999; Nedelcu & Michod 2006)
Fungi	Budding yeast ( <i>Saccharomyces cerevisiae</i> )	Biofilm-like cooperation	<i>FLO-1</i>	X				(Smukalla <i>et al.</i> 2008)
Animals	<i>Caenorhabditis elegans</i>	Social vs. solitary feeding behaviour	<i>Npr-1</i>			X	X	(Macosko <i>et al.</i> 2009)
Insects	Honeybee ( <i>Apis mellifera</i> )	Division of reproductive castes and labour	Insulin-juvenile hormone-vitellogenin pathway, vitellogenin receptor, <i>Anarchy</i>		X	X		(Amdam <i>et al.</i> 2003; Corona <i>et al.</i> 2016; Ronai <i>et al.</i> 2016a; b)
	Termites ( <i>Cryptotermes secundus</i> )	Reproductive division of labour	<i>Neofem2</i>		X			(Korb <i>et al.</i> 2009)
	Ants ( <i>Solenopsis invicta</i> )	Monogynous/polygynous colony (supergene/'social chromosome')	Gp-9	X				(Keller & Ross 1998; Wang <i>et al.</i> 2013)
	Ants ( <i>Polyrhachis moesta</i> )	Queens cooperate (have nest together)	Octopamine			X		(Koyama <i>et al.</i> 2015)
	Earwigs ( <i>Forficula auricularia</i> )	Parent-offspring co-adaptation, maternal care	PebIII, Th, juvenile hormone-vitellogenin pathway and vitellogenin receptor		X			Wu <i>et al.</i> , unpublished
	Burying beetles ( <i>Nicrophorus vespilloides</i> )	Parental care	juvenile hormone-vitellogenin pathway and vitellogenin receptor		X			(Roy-Zokan <i>et al.</i> 2015; Engel <i>et al.</i> 2016)
Teleosts	Gold fish ( <i>Carassius auratus</i> )	Social approach behaviour, vasotocine inhibits social approach, isotocine stimulates it	arginine vasotocin/isotocin			X		(Thompson & Walton 2004)
	Lamprologine cichlids	Social behaviour expression	arginine vasotocin/arginine vasotocin receptor isotocin, isotocin receptor 1, isotocin receptor 2		X	X		(O'Connor <i>et al.</i> 2015; Reddon <i>et al.</i> 2015)
Birds	Ruff ( <i>Philomachus pugnax</i> )	Cooperative male-male relationships (different mating phenotypes) in leks	Androsteroid homeostasis (HSD17B2)	X				(Küpper <i>et al.</i> 2015; Lamichhaney <i>et al.</i> 2015)
	Great tits and blue tits ( <i>Parus major</i> , <i>Cyanistes caeruleus</i> )	Parental care and corticosterone levels covary	corticosterone, testosterone			X		studies cited in (Hau & Goymann 2015)
	White-throated sparrows ( <i>Zonotrichia albicollis</i> )	Parental care; monogamy, aggression differences between white and tan morph (morph is det. by supergene)	Steroid metabolism; serotonin	X				(Tuttle <i>et al.</i> 2016)

Mammals	Meerkats ( <i>Suricata suricatta</i> )	'Cooperative syndrome' (increased digging, guarding, pup-feeding and associating with pups; decreased aggression)	oxytocin			X		(Madden & Clutton-Brock 2011)
	Domestic dog ( <i>Canis lupus</i> )	Social bonds	oxytocin			X		(Romero <i>et al.</i> 2014)
	Rodents general	Species differences in alloparental care	oxytocin receptor				X	(Olazábal & Young 2006)
	Mice ( <i>Mus musculus</i> )	Communal nesting & lactation	oxytocin			X		(Harrison <i>et al.</i> 2016)
	Rats ( <i>Rattus norvegicus</i> )	Maternal care; epigenetic (cytosine methylation)	Estrogen receptor ER- $\alpha$		X			(Champagne <i>et al.</i> 2006)
	Rats ( <i>Rattus norvegicus</i> )	coordination during cooperative task	Norepinephrine, serotonin, dopamine			X		(Tsory <i>et al.</i> 2012)
	<i>Peromyscus californicus</i> , <i>P. maniculatus</i> (monogamous vs polygamous species)	Pair bond as a proxy for group living	V1aR/ oxytocin receptor				X	(Young <i>et al.</i> 2001; Hammock & Young 2005; Anacker & Beery 2013)
	Prairie voles ( <i>Microtus ochrogaster</i> )	Reduced alloparental effort in males when treated with antagonist	oxytocin			X		(Bales & Carter 2003)
	Tuco-tucos ( <i>Ctenomys sociabilis</i> & <i>C. haigi</i> )	Communal nesting	oxytocin receptor				X	(Anacker & Beery 2013)
	Naked mole rats ( <i>Heterocephalus glaber</i> )	Cooperative breeding/eusociality	oxytocin receptor				X	(Anacker & Beery 2013)
	New World primates general	Social behaviour	oxytocin / oxytocin receptor and arginine vasopressin /Va1 receptor	X				(Bergey <i>et al.</i> 2016; French 2016)
	Vervet monkeys ( <i>Chlorocebus aethiops</i> , <i>C. pygerythrus</i> )	Parental care/parent-offspring interaction	dopamine receptor D4	X				(Kaitz <i>et al.</i> 2010; Fairbanks <i>et al.</i> 2012)
	Chimpanzees ( <i>Pan troglodytes</i> )	Building cooperative relationships; oxytocin levels elevated after grooming	oxytocin			X		(Crockford <i>et al.</i> 2013)
	Chimpanzees ( <i>Pan troglodytes</i> )	Kin and non-kin bonds, food sharing	oxytocin			X		(Wittig <i>et al.</i> 2014)
	Humans ( <i>Homo sapiens</i> )	Pro-social behaviour (dictator game)	arginine vasopressin receptor 1a; receptor S 3 repeat	X				(Knafo <i>et al.</i> 2008; Avinun <i>et al.</i> 2011)
		Pro-social behaviour (dictator game; social value orientation task), Autism	oxytocin receptor	X				(Israel <i>et al.</i> 2009; di Napoli <i>et al.</i> 2014)
	Social behaviour/ parental care/parent-offspring interaction, Self-reported social behaviour	dopamine receptor D4, dopamine receptor D5, IGF2	X				(Bakermans-Kranenburg & Ijzendoorn 2006; Sheese <i>et al.</i> 2007)	
	Donation behaviour	COMT Val158Met (rs4680)	X				(Reuter <i>et al.</i> 2011), but see (Anacker & Beery 2013) (no effect)	
	Self-reported social behaviour	GABRB2 (rs187269)	X				(Tsang <i>et al.</i> 2013)	

## **Multilevel cooperation - case study 'Cooperation and microbiota'**

An important future avenue to understand the complexity of cooperation lies in the study of 'multilevel' cooperation. Recent evidence highlights that individual behaviours are not only influenced by the properties of the cooperation partners and the group (Carpenter 2004; West *et al.* 2007), but also by the properties of higher organizational levels of sociality (West & Gardner 2013). For example, the presence or absence of conflict between groups is predicted to influence within-group social behaviours and may ultimately determine the amount of cooperation (Radford *et al.* 2016). Specifically, we believe that the field of microbiome science will highlight a unique 'multilevel' perspective on cooperation. While cooperative systems have been studied in various scales from genes to cell organelles, single-celled organisms like bacteria (Rakoff-Nahoum *et al.* 2016), to multi-cellular organisms (Maynard-Smith & Szathmary 1997; Bourke 2011), a simultaneous, "multi-level" perspective on the cooperation of bacteria with their host species is still lacking. Microbiota, the mutualistic bacteria living in and on their host vertebrates, form a functionally essential part of their host phenotype through complex interactions that can be seen as a form of multilevel-multispecies cooperation: the bacteria cooperating within, but also with their host. Furthermore, several authors suggested mutualistic microbes as a factor driving the evolution of social behaviour or the initial sociality (Troyer 1984; Lombardo 2008; Ezenwa *et al.* 2012; Montiel-Castro *et al.* 2013), a pre-requisite of host cooperative behaviour. This is because transmission of microbes through social contact has the potential to both enhance host immunity (Troyer 1984; Lombardo 2008; Archie & Theis 2011; Gilbert *et al.* 2015) and directly affect host social behaviour (Bravo *et al.* 2011; Ezenwa *et al.* 2012; Montiel-Castro *et al.* 2013). In this way immunological factors, mainly microbiota, can create a positive feedback loop in the evolution of sociality (Fig. 3). The consequence of a more synchronized, diverse and resilient microbiota within a host social group can be seen by itself as a form of multi-level immunological cooperation, analogous to behavioural cooperative defence mechanisms.

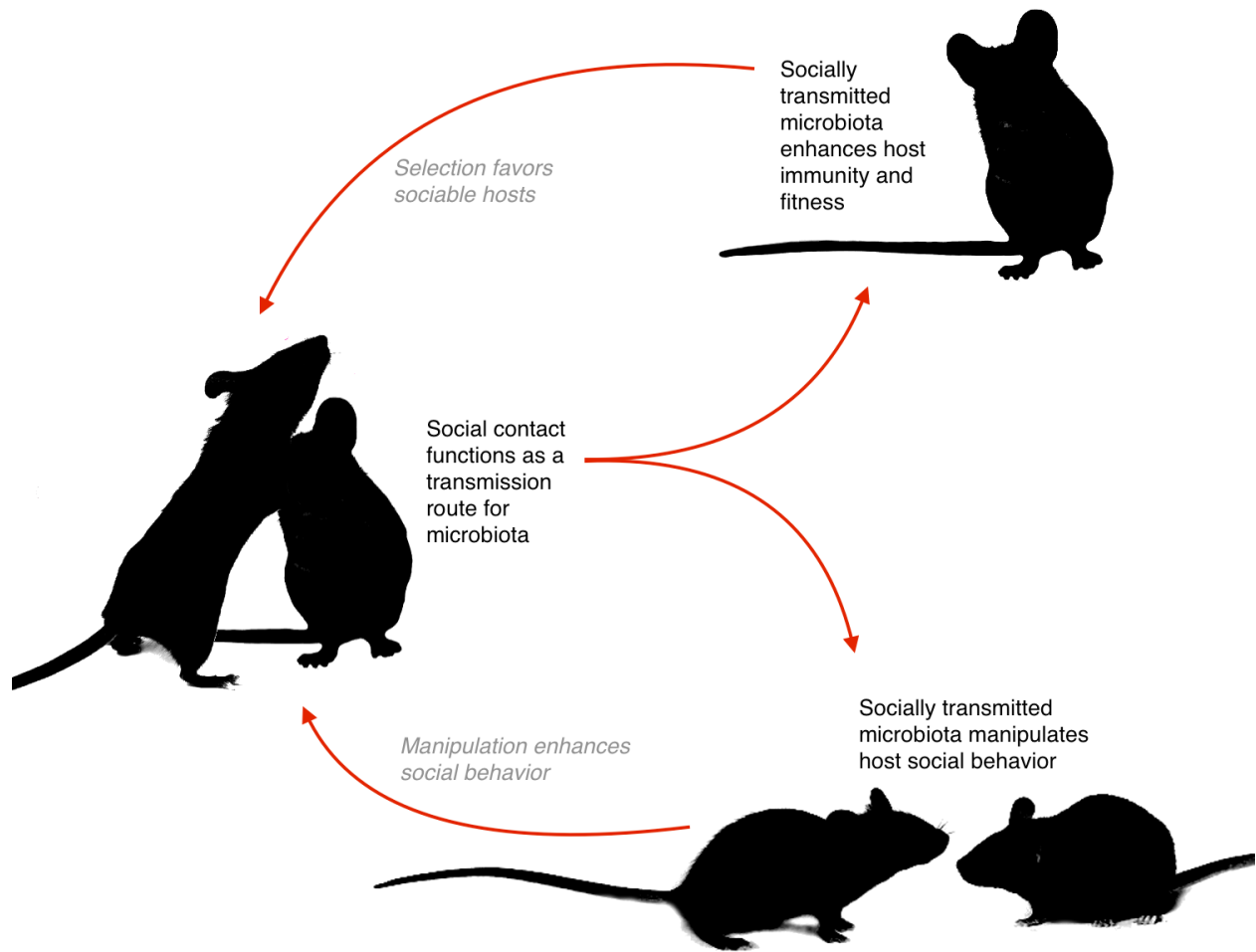


Figure 3. Evolutionary framework for positive feedback loop of host social behavior and social transmission of microbiota. Socially transmittable microbiota has the potential to manipulate host behaviour as well as enhance host immunity and subsequent fitness.

## Future avenues of modelling the evolution of cooperation

Cooperation is a flexible and complex trait. It is now apparent that adaptive cooperative behaviour is not shaped solely by genes, but also by non-genetic environmental factors. So far, satisfactory explanations for the evolution of decision rules of animal cooperation and the evolution of the genetic architecture and cognitive mechanisms underpinning these rules are largely lacking. Although this field is still in its infancy, promising first theoretical results demonstrating that the particular mechanisms clearly play a role in determining evolutionary outcome (Akçay & Van Cleve 2012; Berg & Weissing 2015; Quiñones *et al.* 2016). For instance, (Berg & Weissing 2015) showed that different behavioural architectures (1:1 genotype-phenotype mapping vs. a neural network) or different mutation regimes greatly influence decisions in cooperative games and consequently the dynamics and outcome of social evolution. These findings challenge the standard optimality theory often used to model cooperation. Theory thus may need a paradigm shift towards considering underlying mechanisms, rather than behavioural outcomes, as target of selection (Fawcett *et al.* 2013).

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