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REVIEW

Neurogenomic mechanisms of social plasticity

Sara D. Cardoso[1,2,3], Magda C. Teles[1,2,3] and Rui F. Oliveira[1,2,3,*]

ABSTRACT

Group-living animals must adjust the expression of their social behaviour to changes in their social environment and to transitions between life-history stages, and this social plasticity can be seen as an adaptive trait that can be under positive selection when changes in the environment outpace the rate of genetic evolutionary change. Here, we propose a conceptual framework for understanding the neuromolecular mechanisms of social plasticity. According to this framework, social plasticity is achieved by rewiring or by biochemically switching nodes of a neural network underlying social behaviour in response to perceived social information. Therefore, at the molecular level, it depends on the social regulation of gene expression, so that different genomic and epigenetic states of this brain network correspond to different behavioural states, and the switches between states are orchestrated by signalling pathways that interface the social environment and the genotype. Different types of social plasticity can be recognized based on the observed patterns of inter- versus intra-individual occurrence, time scale and reversibility. It is proposed that these different types of social plasticity rely on different proximate mechanisms at the physiological, neural and genomic level.

KEY WORDS: Social behaviour, Behavioural flexibility, Neural plasticity, Behavioural states, Behavioural shifts, Epigenetics

Introduction

The ability to adapt to environmental changes is a ubiquitous characteristic of biological systems. According to classic evolutionary theory, adaptation is achieved by mechanisms that generate genetic diversity (e.g. mutation, recombination) upon which natural selection can act, such that only the organisms with higher fitness under the current environmental conditions will be likely to pass their genes on to the next generation. Thus, adaptation by natural selection depends on heritable phenotypic variation produced by genetic variation. However, in situations where the rate of environmental change outpaces the rate of genetic evolutionary change, the need for adaptive change without genetic mutation emerges. In this scenario, the evolution of phenotypic plasticity is favoured, according to which environmental cues sensed by the organism lead the same genotype to produce different phenotypes depending on environmental conditions cues (Pigliucci, 2001; West-Eberhard, 2003). Thus, despite the fact that the contribution of non-heritable phenotypic variation to evolutionary change appears to be a paradox, the evolution of mechanisms that generate it must be a common evolutionary phenomenon (Frank, 2011). Different traits show different evolutionary changes in plasticity, in terms of the time lag to respond to the environmental cue and the magnitude of the response. Among animals, behavioural traits exhibit both more rapid and stronger plasticity than morphological traits, which makes behavioural plasticity a key adaptive response to changing environmental conditions (Pigliucci, 2001).

At the proximate level, behavioural plasticity depends on the development of a central nervous system that allows for rapid and integrated organismal responses in order to maintain homeostasis (or allostasis). Many of these responses are simple reflexes and fixed action patterns elicited by a stimulus in the environment, when it determinately predicts an appropriate response. However, when environmental complexity and ambiguity increase, the capacity to adaptively modify behaviour, as a function of experience (i.e. learning) and context, is needed. One of the most ambiguous components of the environment is the social domain, as it is made of other behavioural agents with an inherent level of unpredictability of their actions, with whom the individual needs to interact. Hence, the ability of animals to regulate the expression of social behaviour, so as to adapt their behavioural output to specific situations in a complex and variable social world, is expected to depend on the evolution of plastic responses. These allow the same genotype to produce different behavioural phenotypes (social plasticity), rather than to genetically determine rules controlling fixed responses. Thus, social plasticity should be viewed as a key ecological performance trait that impacts Darwinian fitness (Oliveira, 2009; Taborsky and Oliveira, 2012).

Here we propose a conceptual framework for understanding the genomic mechanisms of social plasticity that has the following premises.

(1) Observed intraspecific variation in behaviour can be characterized by specific behavioural states (*sensu* Zayed and Robinson, 2012), which are exhibited by different behavioural phenotypes (ethotypes) characterized by the consistent expression of a behavioural profile (i.e. set of behaviours) for a given time period (see Fig. 1 for an example).

(2) These behavioural states are paralleled by specific neural states of a social decision-making network in the brain. This network is composed of two interconnected neural circuits, the social behaviour network (*sensu* Newman, 1999; see also Goodson, 2005) and the mesolimbic reward circuit, that together regulate the expression of social behaviour (O'Connell and Hofmann, 2011; O'Connell and Hofmann, 2012). Within this neural network, reciprocal connections are established between each pair of brain nuclei, such that information is encoded in a distributed and dynamic fashion. Therefore, each behavioural state is better reflected by the overall profile of activation across the network, rather than by the activity of a single node. Different combinations of activation across nodes, and variation in the strength of the connections among them, will generate an almost infinite variation in neural states that would produce equivalent behavioural states.

(3) Given that most nodes of the social decision-making network widely express receptors for neuromodulators (i.e. neuropeptides and amines) and hormones (i.e. sex steroids and glucocorticoids), the state of this network can be regulated by these molecules. This

[1]ISPA – Instituto Universitário, Rua Jardim do Tabaco 34, 1149-041 Lisbon, Portugal. [2]Instituto Gulbenkian de Ciência, Rua da Quinta Grande 6, 2780-156 Oeiras, Portugal. [3]Champalimaud Neuroscience Programme, Champalimaud Centre for the Unknown, Avenida Brasília, 1400-038 Lisbon, Portugal.

*Author for correspondence (ruiol@ispa.pt)

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List of abbreviations

AVP	arginine vasopressin protein
CREB	cAMP response element binding
DNMT	DNA methyltransferase
ERK	extracellular signal-regulated kinase
ERα	oestrogen receptor alpha protein
ERβ	oestrogen receptor beta protein
HDACi	histone deacetylase inhibitor
IEG	immediate early gene
MAPK	mitogen-activated protein kinase
MeCP2	methyl CpG-binding protein 2
miRNA	microRNA
ncRNA	non-coding RNA
NSC	neural stem cell
pCREB	phosphporylated CREB
Pol II	DNA polymerase II

sensitivity of the social decision-making network to physiological modulators allows the integration of global organismic state into social decision making and hence the coordination between relevant brain and body states (Oliveira, 2009).

(4) At the molecular level, the neurobehavioural states mentioned above correspond to specific neurogenomic states (*sensu* Zayed and Robinson, 2012) characterized by distinct patterns of gene expression across the social decision-making network in the brain, such that individuals in different behavioural states exhibit different brain transcriptomes. Differential gene expression in the relevant neural network may change the weight of each node and/or the strength of the connectivity between them, therefore contributing to the generation of multiple network states.

According to this framework, social plasticity is achieved by rewiring or by biochemically switching nodes of the neural network underlying social behaviour in response to perceived social information. Therefore, at the molecular level, it depends on the social regulation of gene expression, so that different neurogenomic states correspond to different behavioural states and the switches between states are orchestrated by signalling pathways that interface the social environment and the genotype (Aubin-Horth and Renn, 2009; Oliveira, 2012). However, social plasticity may occur at different temporal scales and vary in its degree of reversibility and within versus between individual occurrence, and this variation in the patterns of plasticity may require different proximate mechanisms.

By considering two key parameters of individual variation in behaviour, reversibility and occurrence within versus between individuals, one might identify three types of social plasticity that are expected to rely on different proximate mechanisms and to be responding to different patterns of environmental predictability (Fig. 2). When intraspecific variation in social behaviour occurs only between individuals (i.e. fixed alternative phenotypes, Fig. 2) it can be due either to a genetic polymorphism [e.g. genetically determined alternative reproductive tactics (Sinervo and Lively, 1996)], in which case it should not be viewed as a true case of social plasticity, or to developmental plasticity dependent on early social environment that is predictive of the adult environment and thus directs the individual towards alternative developmental pathways. When it occurs within the same individual, it can be irreversible with long-lasting behavioural states, such as changes in behaviour between different life-history stages (e.g. juvenile behavioural state versus adult behavioural state), or reversible usually with short-lived behavioural states within the same life-history stage (Kappeler and Kraus, 2010; Piersma and Drent, 2003; Schradin, 2013) (see Fig. 2). These three types of social plasticity potentially rely on different mechanisms at each of the levels discussed above (neural, physiological and genomic). Although classic examples of these different types of social plasticity come from different species, it should be stressed here that they are not mutually exclusive and thus may occur within the same species. For example, in an intertidal blenniid fish (peacock blenny, *Salaria pavo*) alternative tactics occur with smaller and younger males behaving as female mimics to sneak fertilizations and larger and older males being territorial and attracting females to spawn (Almada et al., 1994). When sneakers

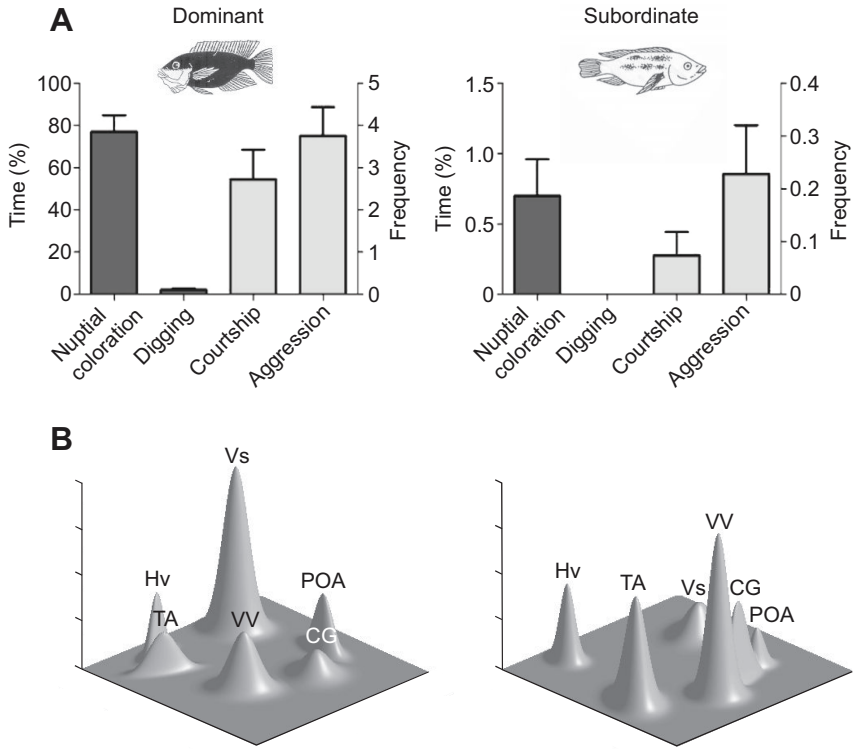

Fig. 1. Example of paralleled behavioural and neurogenomic states in dominant and subordinate males of the African cichlid fish. (A) Dominant and subordinate males express distinct status-specific behavioural states, characterized by differences in nuptial coloration, digging a bower, courting females and aggressiveness [data from Almeida et al. (Almeida et al., 2014)]. (B) These divergent behavioural states are expected to be paralleled by different patterns of activation of the social behaviour network in the brain, achieved by differential gene expression. The social behaviour network is composed of six nodes in the forebrain and midbrain areas: supracommissural part of the ventral telencephalon (Vs, teleost homologue of the extended medial amygdala in tetrapods), preoptic area (POA), central grey (CG), ventral subdivision of the ventral telencephalon (VV, homologue of the lateral septum), nucleus anterior tuberis (TA, homologue of the ventromedial hypothalamus) and ventral zone of the periventricular hypothalamus (Hv, homologue of the anterior hypothalamus).

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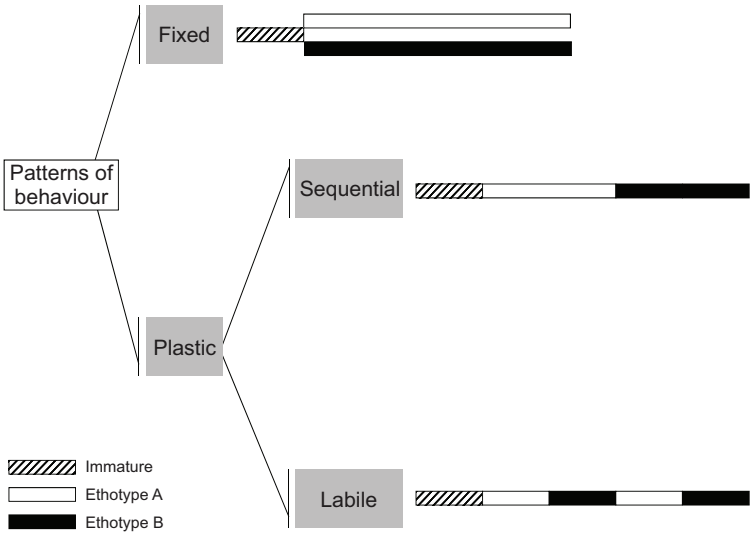

Fig. 2. Schematic representation of different behavioural plasticity mechanisms. Based on two parameters of individual variation in behaviour, reversibility and occurrence within versus between individuals, three types of social plasticity emerge. When the behaviour is fixed and occurs between individuals, for example fixed alternative phenotypes or developmental plasticity, it depends on early social environment that directs the individual towards alternative and exclusive developmental pathways. When this variation occurs within the same individual, it can be sequential, with changes in behaviour between different life stages (e.g. juvenile versus adult behavioural states), or reversible, which encompass short-lived behavioural states within the same life-history stage, and depends on an interaction between the social environment and the internal state of the individual.

grow older they become territorial nest-holder males, which corresponds to a sequential plasticity pattern (Gonçalves et al., 1996). However, not all males go through the sneaker phase; depending on their birth date, males follow different developmental routes, with some of them growing directly into nest holders (Fagundes, 2010). Thus, the two alternative developmental pathways constitute an example of fixed alternative phenotypes that co-exist with the intra-individual developmental plasticity observed in sneakers.

At the neural level, social plasticity can be achieved by two major mechanisms of neural plasticity: structural reorganization or biochemical switching of relevant neural circuits (Zupanc and Lamprecht, 2000), depending on the time scale of the plasticity. Irreversible patterns of social plasticity (i.e. fixed alternative phenotypes or sequential plasticity), which involve long-lasting changes in behavioural states, can be achieved through different forms of structural modifications that might require addition or removal of cells in these circuits (i.e. neurogenesis or apoptosis), modification of the connectivity between different components of the network (i.e. changes in the dendrite and/or axon structures) or alteration of the responsiveness of the circuit (i.e. balance of neurotransmitter and/or neuromodulator receptors) (Oliveira, 2009; Zupanc and Lamprecht, 2000). In contrast, reversible patterns of social plasticity (i.e. behavioural flexibility), which involve fast and transient changes between behavioural states, are explained more parsimoniously by biochemical switching of existing neural networks by different neuromodulatory molecules (i.e. neuropeptides, monoamines and hormones) that are released in a non-synaptic fashion and interact with receptors at multiple sites in the neural network (i.e. diffuse action), altering its functional properties by promoting either excitatory or inhibitory states (Oliveira, 2009; Zupanc and Lamprecht, 2000) (Table 1).

Similarly, at the physiological level, two types of effects of neuromodulators and hormones have been characterized and are expected to be involved in different patterns of plasticity depending on the time scale of their expression. Organizational effects occur early in development, typically within a critical or sensitive period during which the exposure to active molecules induces a long-lasting and irreversible differentiation of a behavioural state [e.g. masculinization of sexual behaviour by early exposure to androgens (Phoenix et al., 1959)]. In contrast, activational effects typically occur in fledged animals and are reversible and short-lived [e.g. triggering of sexual behaviour by administration of androgens to adult males (Moore et al., 1998; Phoenix et al., 1959)]. Thus, the integration of physiological parameters on social plasticity decisions is expected to be mediated by activational effects in the case of behavioural flexibility and by organizational or re-organizational effects in the case of fixed alternative phenotypes and sequential plasticity, respectively (Table 1).

Finally, at the genomic level, long-lasting and irreversible changes in behavioural states are expected to rely on epigenetic modifications (e.g. DNA methylation, histone modifications) of genes involved in social behaviour (e.g. oxytocin, vasopressin) or neural plasticity (e.g. the brain-derived neurotrophic factor gene *bdnf*) (Champagne and Curley, 2005; Curley et al., 2011; Szyf et al., 2008), whereas short-term and transient plasticity can be achieved by different neuronal activity-dependent mechanisms that change the neurogenomic state of the brain in response to perceived social stimuli (Aubin-Horth and Renn, 2009; Wolf and Linden, 2012) (Table 1). Therefore, irrespective of its temporal patterns, social

Table 1. Physiological, neural and genomic mechanisms underlying different patterns of social plasticity

	Fixed alternative phenotypes	Sequential (developmental) plasticity	Behavioural flexibility
Occurrence of alternative behavioural states within the same individual	No	Yes	Yes
Reversibility of alternative behavioural states	No	No	Yes
Time scale of alternative behavioural states	Long lasting	Long lasting	Short lived
Physiological mechanism	Organizational	(Re)Organizational	Activational
Neural mechanism	Structural plasticity	Structural plasticity	Biochemical switching
Genomic mechanism	Epigenetic	Epigenetic	Transient changes in gene expression

plasticity relies on both temporal and spatial changes in gene regulation in the social decision-making network in the brain.

In this paper, we will review the available literature that supports this conceptual framework, with a particular focus on the neurogenomic mechanism of social plasticity. In particular, the following specific questions will be addressed. (1) What is the evidence that specific behavioural states are paralleled by specific neurogenomic states at different time scales? (2) Can the shifts between stable behavioural states also be characterized by specific but transient neurogenomic states? (3) What are the candidate neuromolecular mechanisms that mediate socially driven shifts between behavioural states? (4) Are epigenetic mechanisms only associated with irreversible plasticity patterns or do they also contribute to transient patterns of plasticity?

Genomic correlates of behavioural states

Several studies have demonstrated that different behavioural states are associated with different profiles of gene expression in the brain. In the genomic era, advances in technology have enabled us to identify gene modules [sets of co-regulated genes or proteins (Segal et al., 2004)] that reveal a unique gene expression pattern that reflects the biological phenotype of an individual. In this section, we present representative examples of associations between behavioural and neurogenomic states for the different patterns of social plasticity identified in the previous section.

Fixed alternative phenotypes

Atlantic salmon (*Salmo salar*) have a complex life cycle composed of an initial phase of birth and growth in freshwater, followed by migration to a seawater habitat where substantial body growth is achieved, before homing to the birthplace as a large fighting male to reproduce (Aubin-Horth et al., 2009; Fleming, 1998; Verspoor et al., 2007). These large males co-exist with other smaller males, known as mature male parr, that remain during their whole development in freshwater, where they mature and reproduce using an alternative mating tactic of 'sneaking' into the nest of migrating females. The development into one or other of these two male phenotypes is plastic and depends on size achieved and energy reserves accumulated during a critical period in the spring before autumn reproduction (Aubin-Horth and Dodson, 2004; Hutchings and Myers, 1994; Thorpe et al., 1998). Thus, depending on environment and internal conditions, any male can develop into one of these two irreversible phenotypes characterized by specific behavioural states: fighting male versus sneaker male. In order to study the molecular basis of this plastic trait, Aubin-Horth and colleagues (Aubin-Horth et al., 2005b) compared males of the same age (sneaker and immature males that will eventually become large fighting males) in a genome-wide approach. The microarray analysis revealed that 15% of the genes examined vary in expression between the two male types. Many of these differentially expressed genes are involved in processes such as growth, reproduction and neural plasticity. Genes related to cognition (learning and memory) and reproduction were upregulated in sneaker males, while genes related to cellular growth were upregulated in immature males (Aubin-Horth et al., 2005a; Aubin-Horth et al., 2005b). Interestingly, even within a life history, for instance migrating males, differences were found between early and late migrants, indicating different genomic signatures at different life stages (Aubin-Horth and Renn, 2009).

Sequential (developmental) plasticity

A well-characterized example of developmental plasticity is provided by the distinct life stages and different behavioural tasks displayed by honey bees (*Apis mellifera*). During their development, bees assume different roles in their colony: (1) soon after eclosion, bees assume brood care functions (nursing); (2) after a week, they assume new roles, such as storing and processing food (e.g. turning nectar into honey); and (3) around 3 weeks of age, most bees begin foraging for pollen and nectar (Ben-Shahar, 2005; Robinson and Ben-Shahar, 2002; Whitfield et al., 2003; Whitfield et al., 2006). These different behavioural states are characterized by different profiles of gene expression in the bee brain. More than 85% of ~5500 analysed genes showed differences in expression associated with the transition from nurse to forager that are largely independent of natural age-related changes (Whitfield et al., 2006). Whitfield et al. (Whitfield et al., 2003; Whitfield et al., 2006) also showed that individual brain expression patterns are so dramatically different between life stages that they can be used to classify an individual honey bee as a nurse or as a forager with a very high accuracy rate.

Like honey bees, fire ants live in colonies with thousands of workers but instead of having a single queen, fire ant colonies can have one or more. This tendency to have either one or more queens has a genetic basis and appears to be under the control of a single gene, general protein-9 (*Gp-9*). This genetic factor determines whether workers tolerate a single fertile queen (monogyne social form, BB) or multiple queens (polygyne social form, Bb) in their colony (Wang et al., 2008). BB workers will only accept a single BB queen, and Bb workers will accept multiple Bb queens. BB workers become tolerant of multiple Bb queens when they are in colonies containing mostly Bb workers because they take on a Bb gene expression profile, showing that the BB genotype is more strongly affected by colony genotype (i.e. environment) than by their own genotype. In contrast, Bb workers do not change queen tolerance when they are in colonies containing mostly BB workers (Robinson et al., 2008). Another study on gene expression profiles between different castes of two fire ants species (*Solenopsis invicta* and *S. richteri*) revealed that genomic profiles are mostly influenced by developmental stage that exhibits a specific behavioural state than by caste membership, sex or species identity (Ometto et al., 2011). Between-species comparisons showed that workers have a considerable number of genes that are specifically upregulated or downregulated compared with males and queens. Moreover, workers also have more genes that are differentially expressed between species than do the other castes. Thus, much of the evolution of gene expression in ants may have occurred in the worker caste despite the fact that these individuals are largely or completely sterile. This can be explained by a combination of factors, including the fact that adult workers experience the most diverse environments and exhibit the broadest behavioural repertoires, and both queens and males have lost ancestral Hymenopteran feeding and self-maintenance (Ometto et al., 2011).

Behavioural flexibility

In the African cichlid fish *Astatotilapia burtoni*, males have evolved two distinct phenotypes: dominant males, which are brightly coloured, defend territories and actively court and spawn with females, and subordinate males, which have dull coloration similar to females, do not hold territories and are reproductively suppressed (Fernald and Hirata, 1977). These behavioural and phenotypic differences are reversible, and males change social status many times during their life depending on social context. Renn et al. (Renn et al., 2008) examined whole-brain gene expression in dominant and subordinate males in stable hierarchies as well as in brooding females, and identified 171 genes that were differentially expressed between the two male types. Different expression profiles

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were also found between these male morphs in the sex steroid hormone receptors, where dominant males had higher mRNA expression levels of androgen receptor alpha and beta (ARα and ARβ), and oestrogen receptor beta 1 and 2 (ERβ1 and ERβ2), but not of oestrogen receptor alpha (ERα), compared with subordinate males (Burmeister et al., 2007).

Genomic correlates of behavioural transitions

Most examples of associations between neurogenomic states and social plasticity available in the literature have measured gene expression in stable behavioural states, rather than during phases of transition between behavioural states; hence, they do not reveal whether the observed differential gene expression is the mechanism behind the phenotypic change or whether it is only a consequence of the new phenotype (Aubin-Horth and Renn, 2009). However, a few recent studies on shifts between behavioural states suggest that major changes in gene expression are also involved in these transitions.

In the three-spined stickleback, *Gasterosteus aculeatus*, shifts between aggressive and non-aggressive states can be observed. During the breeding season, males defend nesting territories, and are especially aggressive towards other intruder males (Wootton, 1976). A resident–intruder paradigm revealed differential gene expression of hundreds of genes in the brain between males that were confronted by an intruder compared with those that were not (Sanogo et al., 2012). Four areas of the brain were analysed (telencephalon, diencephalon, cerebellum and brainstem) and the greatest number of differentially expressed genes was found in the diencephalon and cerebellum, and very few genes were found in the telencephalon, an unexpected result as most of the nuclei of the social decision-making network are located in the forebrain. These differences were region specific, and each brain region presented a distinct genomic response. For example, a set of genes that was upregulated in the diencephalon was downregulated in the cerebellum and in the brainstem. A *cis*-regulatory network analysis also identified transcription factors that consistently regulate genes in all brain regions and others that can upregulate or downregulate gene expression across brain regions (Sanogo et al., 2012).

In honey bees, environmental cues also trigger shifts between behavioural states. In the colony, the queen regulates many aspects of colony organization including the reproductive state of workers. This regulation is mainly done by a pheromone produced in the mandibular gland that inhibits ovary activation (Hoover et al., 2003; Le Conte and Hefetz, 2008; Slessor et al., 2005). However, this phenotype is reversible and dependent on environmental cues. In queenless groups, worker bees develop ovaries and produce queen pheromone, but when introduced into a queenright group, there is a regression in ovary development and pheromone production (Malka et al., 2007). Genomic analysis of the mandibular gland in these two groups (queenright and queenless) identified 204 differentially expressed transcripts associated with protein catabolism and transport. These genes are likely candidates for regulating either social behaviour in queenright bees or reproductive competition behaviour in queenless workers (Malka et al., 2014).

Together, these studies illustrate that neurogenomic states are not only associated with behavioural states but also characteristic of phases of transition between states driven by social cues.

Shifting mechanisms

Following the conceptual framework presented above, transitions between behavioural states require shifts between their underlying neurogenomic states in response to relevant environmental cues perceived by the animal. At least three different neuronal activity-dependent molecular mechanisms can be proposed to translate the social information into a neurogenomic shift (Wolf and Linden, 2012) (Fig. 3).

A first mechanism consists of the activation (e.g. phosphorylation) of pre-existing proteins (e.g. phosphorylation of cAMP response element-binding protein, CREB to pCREB) that subsequently either act as transcription factors for immediate early genes (IEGs) or delayed response genes, or regulate intracellular signalling pathways [e.g. mitogen-activated protein kinase (MAPK) pathway]. An example of this activation comes from California mice (*Peromyscus californicus*). In this species, male aggressive behaviour increases in animals that are under short day photoperiods compared with

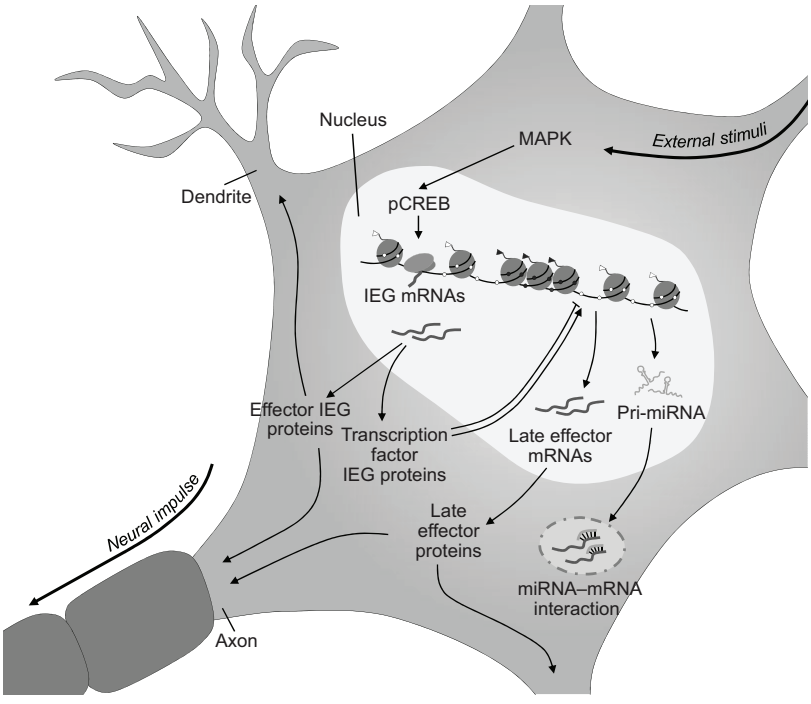

Fig. 3. Schematic representation of neurogenomic shifting mechanisms. Social information (i.e. external stimuli) can trigger a neurogenomic shift through: (i) activation of pre-existing proteins (e.g. phosphorylation of cAMP response element-binding protein, pCREB) or intracellular signalling pathways (e.g. mitogen-activated protein kinases, MAPKs); (ii) immediate early gene expression (IEG) that will act as transcription factors for other genes (i.e. late effector genes) or as direct effector proteins; and/or (iii) transcription of microRNA genes (primary-microRNA, pri-miRNA) that will be processed into single-stranded mature microRNAs (miRNAs) and regulate mRNA (mRNA) transport, translation and degradation inside the cell. Modifications introduced into the nucleosome structures and the DNA strand (i.e. methylation) together provide different states of chromatin compaction, and therefore activate or inactivate gene expression.

animals in long day photoperiods (Trainor et al., 2008). A resident intruder test revealed that a phosphorylation mechanism of ERK1 and 2 (extracellular signal-regulated kinases 1 and 2) and CREB underlies these differences. A significant increase in phosphorylated ERK (pERK) expression in several brain regions known to regulate aggressive behaviour is induced by aggression tests under short days but not under long days. However, a very different pattern is observed with pCREB immunostaining, where aggressive behaviour decreased the number of pCREB-positive cells when mice were housed under long days but not short days. Together, this data set suggests that different phosphorylation pathways are associated with the response to different environmental conditions (Trainor et al., 2010).

A second mechanism is based on neuronal activity-dependent transcription factors that mediate IEG expression inside the nucleus. Activation of IEGs corresponds to the first genomic response given within minutes of a stimulus. Recently, Saha et al. (Saha et al., 2011) were able to categorize IEGs into two groups depending on their expression time. For rapid IEGs, which are expressed within a few minutes, DNA polymerase II (Pol II) stalling was seen in the promoter region of these genes, whereas delayed IEGs, which are expressed within an hour of the stimulus, largely lacked this poised Pol II (Saha and Dudek, 2013; Saha et al., 2011). This mechanism of stalling was shown to be pertinent in regulating the timing and dynamics of gene responses, as mRNA accumulation was not affected (Saha et al., 2011). Depending on their function, IEG proteins can act themselves as transcription factors (e.g. v-fos FBJ murine osteosarcoma viral oncogene homologue gene *c-fos* and early growth response protein 1 gene *egr-1*), returning to the nucleus to regulate the expression of specific genes, or as direct effector proteins (e.g. activity-regulated cytoskeleton-associated protein gene *arc* and homer homologue 1a gene *homer1a*), regulating synaptic function (Clayton, 2000). Two examples will be presented that illustrate the role of IEGs in the neurogenomic translation of social information. In *A. burtoni*, cues from the social context are crucial for males to switch between the subordinate and the dominant phenotype. Subordinate males can be induced to become dominants by removing all competing territorial males in their tank (social ascending paradigm). Conversely, dominant males can also be induced to become subordinate by exposing them to larger dominant males (social descending paradigm) (Francis et al., 1993; White et al., 2002). At the molecular level, these behavioural shifts are paralleled by changes in the expression of the IEGs. In socially ascending males, mRNA levels of the IEGs *c-fos* and *egr-1* increased in all nuclei of the social decision-making network within the first hour of becoming dominant. Importantly, this increased expression of IEGs was not found in either stable dominant or stable subordinate males (Burmeister et al., 2005; Maruska et al., 2013a). In contrast, in socially descending males, changes in IEG expression levels were nuclei specific both for *c-fos* and for *egr-1* but never simultaneously for both (Maruska et al., 2013b). Thus, depending on the direction of the behavioural transition, different IEG activation patterns can be observed in the social decision-making network, suggesting a complex regulatory system that translates the animal's perception of the social environment into transcriptional control of late response genes necessary for adaptive phenotypic changes. A second example of the role of IEGs in neurogenomic shifts is provided by studies in songbirds. In zebra finches (*Taeniopygia guttata*), hearing a conspecific song elicits the expression of the IEG *zenk* (aka *egr-1*) in the zebra finch auditory forebrain (Cheng and Clayton, 2004). This song-induced gene expression relies on the rapid phosphorylation of ERK, which varies depending on the novelty of the song: novel songs trigger a sharp increase in ERK phosphorylation, peaking within 1–2 min of song onset, required for *zenk* expression, whereas a familiar song leads to a persistent habituation for that specific song (Cheng and Clayton, 2004; Dong and Clayton, 2009). Also dependent on the ERK/MAPK pathway is the expression of *arc*, an effector IEG that is co-localized with *zenk* and is thought to be necessary for dendritic spine outgrowth in postsynaptic signalling (Bramham et al., 2010; Velho et al., 2005). Thus, depending on the individuals' perception of the same song as either novel or familiar, IEGs can be activated with different fold changes mediating transitions between behavioural states in song learning (i.e. naive versus experienced).

A third possible mechanism consists on the transcription of microRNAs (miRNAs) that regulate mRNA transport, translation and degradation for transcription factors or synaptic proteins. An example of this mechanism is the brain-expressed miR-133, recently found to play an important role in controlling behavioural aggregation in migratory locusts (*Locusta migratoria*) (Yang et al., 2014). In this species, considered a worldwide pest, it is possible to observe two main behavioural states, the solitary phase and the gregarious phase, which are density dependent and reversible (Kang et al., 2004). When present, miR-133 suppresses the expression of two genes involved in the dopamine pathway, *henna* and *pale*, thereby regulating the dopamine synthesis important for the phase transition of locusts in response to population density stress (Yang et al., 2014). It has been shown that decreasing dopamine production through miR-133 agomir resulted in the behavioural shift from the gregarious to the solitary phase, while miR-133 inhibition promoted gregarious-like behaviour of solitary locusts. Thus, miRNA plays an important role as an activational switch in this species acting a key mediator of a transition between behavioural states.

Epigenetics of social plasticity

Accumulating evidence has shown that epigenetic marks play a key role in maintaining behavioural states by keeping different neurogenomic states in the brain. Generally, epigenetic mechanisms operate either on the DNA sequence, via DNA methylation (Miranda and Jones, 2007) and/or binding of non-coding RNA (ncRNA) (Bernstein and Allis, 2005), or on chromatin, mainly via post-translational modification of histone proteins (Borrelli et al., 2008). Within cells, these mechanisms can interact with each other to inhibit or activate gene expression not just as an on and off switch but rather in a gradient fashion, determining which proteins are transcribed in which environmental contexts. These epigenetic changes have a significant role in controlling functional and structural molecular states, therefore enabling adaptive cellular expression patterns during development and differentiation (i.e. stable modifications), or plastic changes in adult organisms (i.e. plastic modifications). In this section, we present examples where these epigenetic mechanisms were found to maintain behavioural states or to generate behavioural flexibility, not only during development but also in the adult stage.

DNA methylation

DNA methylation, which is normally associated with the inhibition of gene expression, occurs mainly at cytosine bases preceding guanines (CpG sites) that are converted to 5′-methylcystosine (5-mC) by DNA methyltransferase (DNMT) enzymes. These enzymes have two main enzymatic activities, maintenance methylation (DNMT1) necessary to preserve DNA methylation after every DNA replication cycle, and *de novo* methylation (DNMT3A/B), setting up DNA methylation patterns early in development (Bestor, 2000;

Okano et al., 1999). In honey bees, a non-reversible segregation of behaviours between queens and workers can be observed during early life (see above) and is dependent on the royal jelly diet fed during larval development. In addition to the influence of nutrition on the epigenetic status of the queen's cells (for a review, see Buttstedt et al., 2014), Kucharski and colleagues (Kucharski et al., 2008) showed that silencing the expression of *Dnmt3* in newly hatched larvae induced a royal jelly-like effect on the larval development trajectory, suggesting a role for DNA methylation in storing epigenetic information in a context-dependent manner (i.e. dependent on nutrition).

Recent findings on the mechanism behind DNA demethylation have promoted a shift in our understanding of how changes in DNA methylation are coupled to cell differentiation, development and disease. Hydroxymethylation of 5-mC to 5-hmC (hydroxymethylcytosine) by TET (ten–eleven translocation) enzymes has been proposed as the mechanism behind methyl group removal from cytosine bases followed by DNA repair machinery (Pastor et al., 2013; Tahiliani et al., 2009). Along this line, Herb and colleagues (Herb et al., 2012) were able to show that a reversible behaviour in honey bees, switching back from foragers to nurses, is also accompanied by changes in the DNA methylation pattern. These authors found that otherwise genetically identical nurse and age-matched forager bees have different methylation patterns in 155 genes found in their brain cells. However, after inducing the role reversal, the methylation patterns in 57 genes of a total of 107 differentially methylated regions (DMRs) from the former foragers changed to a nurse pattern (Herb et al., 2012). This finding suggests a subcaste-specific methylation signature that can assist in forming worker phenotypes. Also in adult male rat brains, Auger and colleagues (Auger et al., 2011) found that methylation patterns on some steroid-responsive genes were actively maintained by the presence of circulating steroid hormones (i.e. signal) that affect the expression of the socially relevant peptide vasopressin (AVP) and ERα within the bed nucleus of the stria terminalis (BNST). Castration (i.e. loss of signal) of these males dramatically reduced the expression of AVP while increasing ERα expression as a result of a shift in methylation state on the promoters of these genes, which could be prevented by testosterone replacement (i.e. signal restoration) (Auger et al., 2011). It would be interesting to see whether this mechanism is involved in seasonal reproduction in males or even in contexts of social dominance, where the social decision-making network is highly regulated by these hormones.

Histone modifications

Nucleosomes, around which DNA is wound, are structures composed of two copies of each of the core histones H2A, H2B, H3 and H4, and stabilized into high-order structures by the linker histone H1 forming the chromatin (Luger et al., 1997). The N-terminal tails of histones are exposed on the nucleosomal surface and are the target of numerous post-translational modifications (Borrelli et al., 2008; Keverne and Curley, 2008; Strahl and Allis, 2000). This provides a dynamic functional continuum between two states of chromatin compaction, which correlate primarily with active (euchromatin) and inactive (heterochromatin) states of gene expression (Berger, 2007).

Histone acetylation and phosphorylation are usually associated with active chromatin, because of the neutralization of the positive charge of the histone tail, playing an important role in integrating incoming signals (Barth and Imhof, 2010; Borrelli et al., 2008; Keverne and Curley, 2008). In prairie voles, *Microtus ochrogaster*, a socially monogamous species, pair-bond formation involves a selective affiliation of females to a partner (partner preference), which is induced by mating (Getz and Hofmann, 1986; Williams et al., 1992). Recently, the involvement of histone modifications in the regulation of pair bonding has been established (Wang et al., 2013). Female prairie voles treated with histone deacetylase inhibitors (HDACi) became bonded to their mates in the absence of a mating event. This was accompanied by a specific upregulation of oxytocin receptor (*oxtr*) and vasopressin V1a receptor (*avpr1a*) in the nucleus accumbens (NAcc), which was associated with an increase in histone acetylation at their respective promoters, similar to that observed when untreated females were mated and formed a pair bond (Wang et al., 2013). However, HDACi treatment did not promote vasopressin and oxytocin receptor expression in the NAcc of female prairie voles that were not exposed to males, indicating that other factors related to social context are required to induce pair bonds. Also, in honey bees, further investigation of the royal jelly nutrition has shown that one of its major components, the fatty acid (*E*)-10-hydroxy-2-deconic acid (10-HDA), has HDACi activity and has the capacity to reactivate the expression of epigenetically silenced genes in mammalian cells (Spannhoff et al., 2011). The examples given here on the epigenetic effects of nutrition on honey bee larvae developmental dichotomy encompass some of the mechanisms responsible for the unique brain epigenomes detected by Lyko and colleagues (Lyko et al., 2010), where over 550 genes showed methylation differences between queen and worker behavioural phenotypes.

Histone methylation does not alter the positive charge of the amino acids but can be a marker for both active (e.g. trimethylation at lysine-4 residues of histone 3, H3K4me3) and inactive regions of chromatin (Keverne and Curley, 2008). Additionally, histone methylation has a lower turnover rate, which could facilitate the stabilization of gene expression in the absence of incoming signals (Barth and Imhof, 2010; Borrelli et al., 2008). We mentioned above the key role of poised Pol II in mediating rapid IEG expression. This mechanism of stalling is itself an example of an epigenetic mechanism, because it retains permissive epigenetic marks on promoters, making the chromatin accessible to polymerases and therefore allowing a robust transcription. In addition to Pol II having its largest subunit (RPB1) phosphorylated on serine-5 residues of the C-terminus, the promoter region is enriched with histones with high levels of H3K4me3 methylation (Saha et al., 2011; Telese et al., 2013).

ncRNA

ncRNA genes produce several classes of functional RNA molecules that are highly integrated into the molecular circuitry, making them important players in the regulation of gene expression through various mechanisms, such as RNA interference and gene silencing (Bernstein and Allis, 2005; Qureshi and Mehler, 2012). One such example of ncRNAs is miRNA, small single stranded molecules of ~22 nucleotides that modify gene activity through post-transcriptional regulation of their mRNA targets. We mentioned this class of ncRNA above as a shifting mechanism in organisms, giving the example of the migratory locusts where miR-133 mediated the transition between the gregarious and solitary phases (Yang et al., 2014). They have also been recognized as having a role in the division of labour among honey bees. Greenberg and colleagues (Greenberg et al., 2012) compared the brain miRNA transcriptome of adult workers and found that miRNA expression was dependent upon social context, as several miRNAs were downregulated in honey bees that were nurses relative to foragers only when they were in colonies that contained foragers.

From integrative genomic studies elucidating the complex wiring of miRNA regulatory relationships, some preliminary conclusions can be drawn: miRNAs can act cooperatively or redundantly (Su et al., 2011), and miRNAs from one cluster tend to be involved in the same network module with a direct or indirect regulatory coordination seen in a dependent manner of miRNA cluster composition (i.e. same versus various families, respectively), suggesting distinct roles in biological processes (Wang et al., 2011). As for other transcribed RNAs, miRNA expression is itself regulated by epigenetic factors such as DNA methylation and chromatin structure (Iorio et al., 2010). An example of this interplay can be seen in the regulation of neural stem cells (NSCs) in adult neurogenesis (Shi et al., 2010; Szulwach et al., 2010). DNA methylation can also promote the biding of methyl-CpG-binding domain proteins (MBDs, e.g. MeCP2) (Hendrich and Bird, 1998) that can in turn recruit additional proteins to the locus, such as post-translational modification of histones and as well as the recruitment of Dnmt1. In rats, MeCP2 can epigenetically regulate specific miRNAs in adult NSCs such as miR-137, so that: (1) in the absence of MeCP2, miR-137 is overexpressed and promotes the proliferation of adult NSCs; and (2) in the presence of MeCP2 together with Sox2 (SRY-box containing gene 2 protein), a core transcription factor regulating stem cell self-renewal (Zappone et al., 2000), miR-137 expression is regulated, enhancing instead adult NSC differentiation (Szulwach et al., 2010). This structural reorganization (i.e. neurogenesis) is another path through which social plasticity in the neural decision-making network can be achieved.

Finally, it should be said that these three epigenetic mechanisms are expected to work together in the regulation of social plasticity, and therefore their coexistence should be observed. This can be illustrated by the transgenerational effects of maternal nurturing in rodents, which have long been the classic example of behavioural epigenetics (for review, see Curley et al., 2011). In this behavioural paradigm, female offspring of mothers that showed high levels of licking/grooming will also display high levels of licking/grooming when they become mothers later in life. High licking/grooming offspring were found to have fewer methyl groups attached to the glucocorticoid receptor promoter of exon 1_7 and histone acetylation at the lysine-9 (K9) residue of H3 (H3K9) when compared with offspring of low licking/grooming mothers, showing therefore an increased hippocampal glucocorticoid receptor expression (Weaver et al., 2004). Thus, multiple epigenetic mechanisms act together to allow the long-term maintenance of gene expression differences (e.g. epigenetic marks) depending on early social environment.

Prospects

In this review we have shown how highly responsive the brain neurogenomic states are to the environment and at storing social information, channelling in this way transient as well as long-lasting adaptations. However, to date most studies on the relationship between neurogenomic and behavioural states have either used whole-brain gene expression data or restricted their analyses to a few areas of interest in the brain. Given the distributed nature of the putative social decision-making network in the brain, a future challenge will be to characterize the neurogenomic states across this network by studying simultaneously the patterns of gene expression of the multiple network nodes. This would extend the characterization of neurogenomics to a spatial level that might be quite relevant to the understanding of the diversity of potential behavioural states produced by the relevant brain networks.

In future research at this level of genome-behaviour analysis, it will also be necessary to distinguish between neurogenomic mechanisms that lead to a specific behavioural state and those that are maintaining that same state. As discussed above, different patterns of gene expression might be associated with stable behavioural states and others with behavioural shifts, and the neuromolecular mechanisms expected to underlie states and shifts are not the same. With the development of new sequencing technologies that are becoming available to behavioural ecologists, such as RNA-Seq for transcriptome analysis, Chip-Seq for specific activity-regulated genes and Bisulfite-Seq for methylome analysis, these hypotheses are becoming testable in the short-term.

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Author contributions

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