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Review article

Subcortical encoding of agent-relevant associative signals for adaptive social behavior in the macaque

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ABSTRACT

Primates are group-living creatures that constantly face the challenges posed by complex social demands. To date, the cortical mechanisms underlying social information processing have been the major focus of attention. However, emerging evidence suggests that subcortical regions also mediate the collection and processing of information from other agents. Here, we review the literature supporting the hypothesis that behavioral variables important for decision-making, i.e., stimulus, action, and outcome, are associated with agent information (self and other) in subcortical regions, such as the amygdala, striatum, lateral hypothalamus, and dopaminergic midbrain nuclei. Such self-relevant and other-relevant associative signals are then integrated into a social utility signal, presumably at the level of midbrain dopamine neurons. This social utility signal allows decision makers to organize their optimal behavior in accordance with social demands. Determining how self-relevant and other-relevant signals might be altered in psychiatric and neurodevelopmental disorders will be fundamental to better understand how social behaviors are dysregulated in disease conditions.

1. Introduction

Survival is the utmost priority for living organisms. Although they constantly face challenges to collect resources, the efficiency of resource collection can be increased by constructing a population (Van Schaik, 1983; Watanabe et al., 2017). In particular, humans and non-human primates are group-living species that have increased the power of populations by developing social structures, such as hierarchy and role assignment (Shultz et al., 2011; Silk, 2007; Terborgh and Janson, 1986). In the group-living context, primates actively collect many pieces of social information, including others' physical features, status, possessions, and actions, and then utilize them to better organize their own behavior (Solyst and Buffalo, 2014). This suggests that the primate brain has evolved to deal with extra cognitive load compared to living in isolation (Dunbar, 1992; González-Forero and Gardner, 2018; Whiten and Byrne, 1988).

Social cognition of primates is hypothesized to be mediated by a well-developed neocortex (Kudo and Dunbar, 2001). The development of large cortical mantles may be associated with highly sophisticated social functions, such as social learning, group formation, and cultural transmission (Pasquaretta et al., 2014). However, neuroimaging studies in macaques also point to the involvement of subcortical regions in social information processing (Sliwa and Freiwald, 2017). Moreover, the gray matter volume in various subcortical regions is either positively or negatively correlated with social status in macaques (Noonan et al., 2014; Sallet et al., 2011). In parallel with increasing attention to subcortical regions in macaques, a recent paper in humans demonstrates the contribution of subcortical regions to the default mode network (Alves et al., 2019), a set of brain regions often associated with the social brain (Mars et al., 2012). These findings suggest that the primate brain is equipped with subcortical networks that interact with cortical areas for social cognition and behavior. Subcortical structures constituting the basal ganglia, i.e., midbrain dopaminergic (DA) nuclei, dorsal and ventral striatum, external and internal segments of the globus pallidus, subthalamic nucleus, and ventral pallidum (VP), have connections with other subcortical regions including the hippocampus, hypothalamus, and amygdala, which are further connected with cortical areas, in particular, the orbital frontal cortex (OFC), medial prefrontal cortex

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(mPFC), lateral PFC, anterior cingulate cortex, and insular cortex (Haber and Knutson, 2010; Sesack and Grace, 2010). Some of these cortico-subcortical structures have been hypothesized to play a critical role in valuation and motivation, thereby linking reward information to decision making and action selection (Behrens et al., 2009). Thus, the decoding of neural signals in subcortical regions and cortico-subcortical networks during social interactions is essential for a better understanding of the primate "social brain." In doing so, macaque monkeys can serve as an ecologically valid animal model, because their social behavior and environment are similar to those of humans (Tremblay et al., 2017). Moreover, the macaque brain shares structural and functional similarities with the human brain (Mars et al., 2013; Rushworth et al., 2013; Sallet et al., 2013). From an evolutionary perspective, it has been argued that human social cognitive capabilities might have precursors in the mind of non-human primates (O'Connell and Hofmann, 2011).

The aim of the current work was to review emerging evidence for subcortical involvement in social information processing in the macaque. We show that various subcortical regions encode a mixture of key behavioral variables for decision-making, i.e., stimulus, action, and outcome, in a given context, which are further associated with agent information (self or other). Agent-relevant associative signals can vary from one region to another, but they are eventually integrated into a subjective value, or more generally, a social utility signal at the level of DA neurons. We propose that the formation of such social utility signals plays a pivotal role in adaptive social decision making and action selection, and its breakdown may lead to maladaptive social behavior in clinical conditions, such as psychiatric and neurodevelopmental disorders.

2. Agent-relevant associative signals in subcortical regions

2.1. Amygdala

The amygdala is located in the anteromedial portion of the temporal lobe (Fig. 1a). It is comprised of multiple nuclei that form connections with a variety of subcortical regions including the hippocampus, striatum, hypothalamus, and brainstem, as well as cortical regions including the mPFC and OFC (Barbas, 2000; Davis and Whalen, 2001; Ghashghaei and Barbas, 2002; Janak and Tye, 2015; Mcdonald, 1998). The amygdala has been the focus of social neuroscience research since early 80′s (Aggleton and Passingham, 1981; Brothers et al., 1990), and it is now generally accepted that the amygdala is involved in a wide range of social functions (Gangopadhyay et al., 2021). For example, lesions in the amygdala can affect social attachment (Bauman et al., 2004; Goursaud and Bachevalier, 2007). The amygdala processes facial expressions and gaze directions (Adolphs, 2010; Gothard et al., 2007; Mosher et al., 2014). The size of the amygdala is affected by social network size and hierarchy (Noonan et al., 2014; Sallet et al., 2011). Munuera et al. (2018) found shared neuronal coding between social hierarchy and reward value. In their study, monkeys fixated on images of fractal stimuli or the faces of other monkeys housed in a group cage. Fixation on the fractal images was followed by a different magnitude of reward, while fixation on the facial images was followed by the same magnitude of reward. Neurons in the amygdala encoded the hierarchical rank of individuals in the same neuronal ensembles that encoded the reward magnitude associated with nonsocial stimuli. As the hierarchical rank of individuals is related to their social value (Deaner et al., 2005), these findings demonstrate that the value of social agents is represented by the same neuronal ensembles that represent the value of nonsocial stimuli. Thus, neurons in the amygdala are likely to encode a stimulus-outcome-agent association.

Further, amygdala neurons signal object values learned through experience and social observations in a similar manner. In an observational choice task (Grabenhorst et al., 2019), two monkeys facing each other took turns at making choices between sequentially presented visual stimuli and learned stimulus-reward probabilities. The initial learning of the stimulus-reward probabilities was followed by a reward-probability reversal (to test value tracking) and then by a stimulus switch between animals (to test observational learning). A group of neurons commonly encoded the stimulus values from direct experience (self) and observational learning (other), while another group of neurons differentiated self-other agents throughout a trial. Remarkably, some neurons signaled the other's predicted choices distinctly from one's own choices. These neurons were referred to as *simulation neurons*, although it remains unknown whether they are causally responsible for simulating the partner's choice. The stimulus-value coding neurons were more prevalent in the lateral portion of the amygdala, while the simulation neurons were more frequent in the medial portion (Fig. 1a). These findings suggest that the primate amygdala represents the value signals derived from a stimulus-action-outcome-agent association (Fig. 2).

Coherent activity between the mPFC and amygdala plays a role in social value coding. In a dictator game in which an actor monkey made overt decisions to allocate a reward between self and other, neurons in the basolateral amygdala encoded the reward value for each agent (Chang et al., 2015). Such responses were absent when the outcome was passively cued, suggesting that the value signal in the basolateral amygdala is associated with active social decisions. Moreover, unilateral infusion of the neuropeptide oxytocin into the basolateral amygdala, but not the dorsolateral PFC, increased prosocial decisions. Using a similar task paradigm, the same research group showed that synchronization between the anterior cingulate cortex and basolateral amygdala was enhanced when the monkeys chose to deliver a reward to the other instead of discarding it (Dal Monte et al., 2020). In contrast, this synchronization was suppressed when the monkeys chose to deliver a reward to themselves over delivering it to both themselves and the other. These results suggest that specialized coordination between the mPFC and amygdala contributes to the expression of social decision preferences.

2.2. Lateral hypothalamus (LH)

The LH has been implicated in diverse aspects of life-supporting functions (Bonnavion et al., 2016; Mahler et al., 2014; Petrovich, 2018), including the integration of motivation and homeostatic demands (Adamantidis et al., 2007), consummatory behavior (Harris et al., 2005), stress and anxiety (Bonnavion et al., 2015; Flores et al., 2015), and learning and memory (Buckholtz et al., 2010; Cole et al., 2020; Flores et al., 2015; Sharpe et al., 2017). Anatomical studies indicate that the LH has connections with the OFC and mPFC (Kita and Oomura, 1981; Ongür et al., 1998; Reppucci and Petrovich, 2016), amygdala (Price and Amaral, 1981), ventral striatum (Haber et al., 1990), lateral habenula (LHb) (Stamatakis et al., 2016; Stamatakis and Stuber, 2012), VP (Haber et al., 1993), and septum (Carus-Cadavieco et al., 2017). It also has direct and indirect reciprocal connections with monoamine systems, including the DA (Fadel and Deutch, 2002; Matthews et al., 2016; Nieh et al., 2015; Tian et al., 2016), noradrenergic (Miyahara and Oomura, 1982; Sakurai, 2007), and serotonergic systems (Pollak Dorocic et al., 2014; Sparta and Stuber, 2014).

The role for the LH in behavioral coordination extends to social domains. Neuroimaging studies have shown that the volume of the LH and adjacent structures is larger as social hierarchy increases in macaques (Noonan et al., 2014) and is smaller in people with autism spectrum disorder compared to neurotypical individuals (Kurth et al., 2011). To clarify further how the LH processes others' behavioral information at the cellular level, Noritake et al. (2020) devised a behavioral procedure called "social Pavlovian conditioning" in which two monkeys sitting face-to-face are both conditioned with reward-predictive stimuli. Each stimulus predicted the reward outcomes for the self and partner with different probabilities. Behavioral analyses revealed that despite being objectively constant in magnitude and

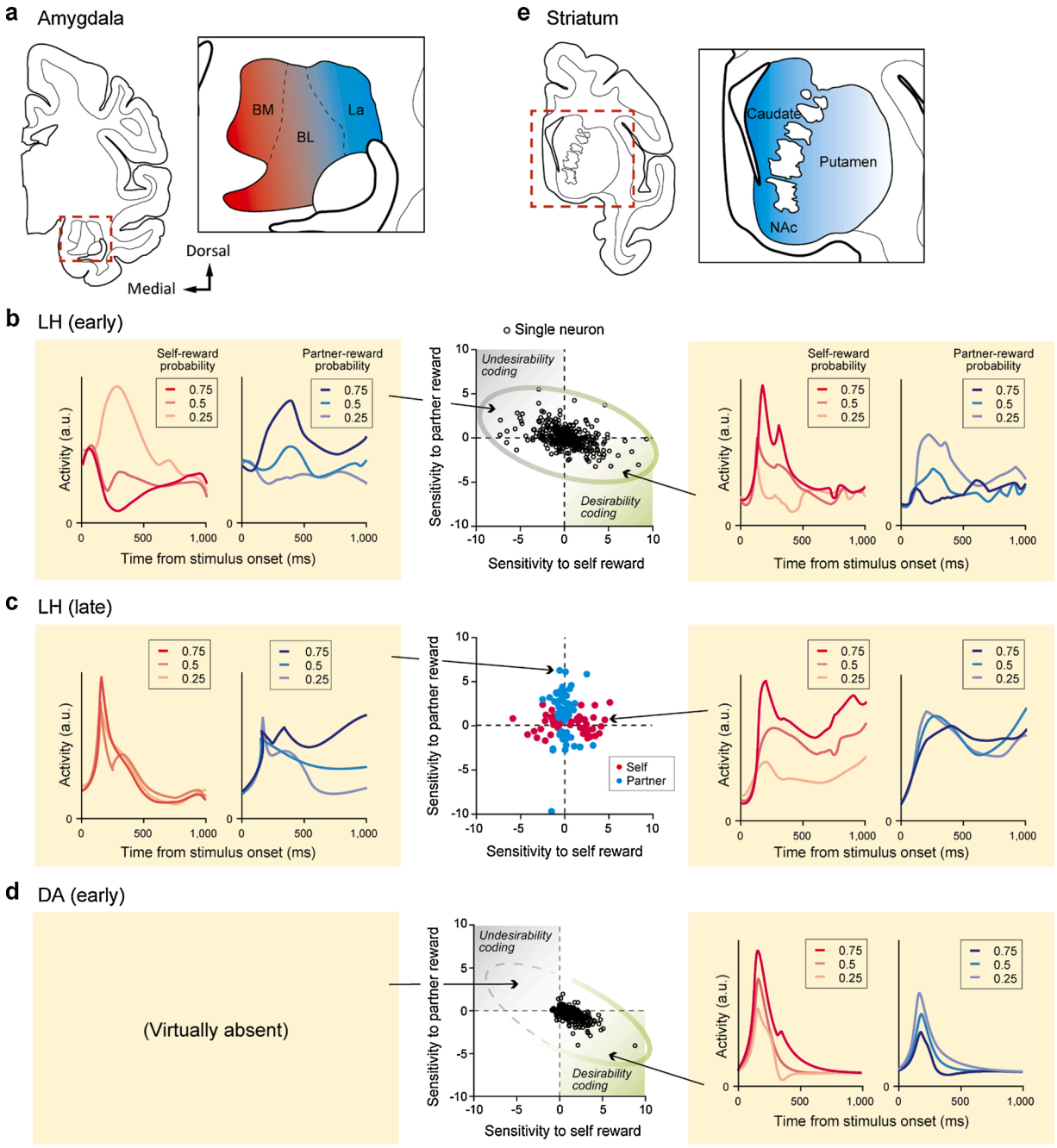

Fig. 1. (**a**) Anatomy of the amygdala. *Left*, coronal section. *Right*, enlarged view of the area indicated by the red dashed box. Stimulus value-coding neurons are prevalent in the more lateral portion (indicated by a more blueish zone). Simulation neurons are prevalent in the more medial portion (indicated by a more reddish zone). La, lateral; BL, basolateral; BM, basomedial. (**b**) Lateral hypothalamic (LH) neurons encoding the subjective value in the early stimulus epoch. Population activity for undesirability-coding neurons (left) and desirability-coding neurons (right). A scatter plot of sensitivity to self-rewards (slopes of regression between each neuron's firing rate and self-reward probability) and sensitivity to partner-rewards (slopes of regression between each neuron's firing rate and partner-reward probability) are negatively correlated across the whole population (middle). Red lines, neural activity in trial blocks in which only the self-reward probability varies ($P = 0.25$, 0.5, or 0.75), while the partner-reward probability is constant ($P = 0.2$). Blue lines, neural activity in trial blocks in which only the partner-reward probability varies ($P = 0.25$, 0.5, or 0.75), while the self-reward probability is constant ($P = 0.2$). (**c**) LH neurons encoding agent-selective reward information in the late stimulus epoch. Population activity for partner-reward-coding neurons (left) and self-reward-coding neurons (right). Blue and red dots in the scatter plot (middle) indicate partner-reward-coding neurons and self-reward-coding neurons, respectively. (**d**) Dopaminergic (DA) neurons encoding the subjective value in the early stimulus epoch. Population activity for desirability-coding neurons (right). Note that undesirability-coding neurons are virtually absent. Thus, two different sensitivities are negatively correlated across the whole population, but the data points are present mainly in the fourth quadrant. (**e**) Anatomy of the striatum. *Left*, coronal section. *Right*, enlarged view of the area indicated by the red dashed box. Neurons encoding social information are prevalent in the more medial portion (indicated by a more blueish zone). NAc, nucleus accumbens. Panels **b** and **c** were adapted and modified from Noritake et al. (2020) with permission. Panel **d** was adapted and modified from Noritake et al. (2018) with permission.

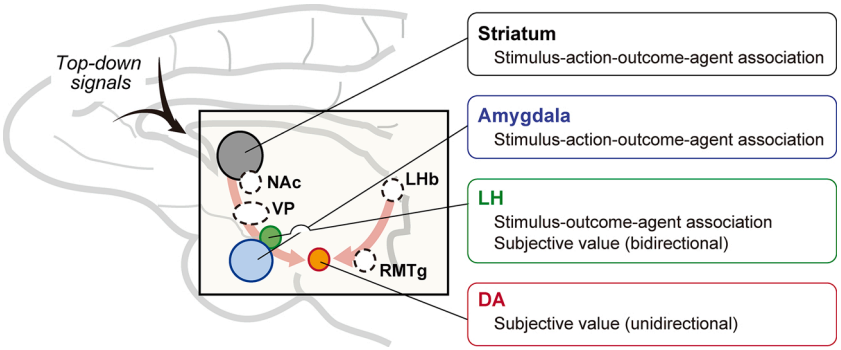

Fig. 2. Schematic illustration of social information flows in subcortical brain regions. Dashed circles depict regions in which neuronal response properties in social contexts have not been studied in non-human primates. DA, midbrain dopaminergic nuclei; LH, lateral hypothalamus; LHb, lateral habenula; NAc, nucleus accumbens; RMTg, rostromedial tegmental nucleus; VP, ventral pallidum.

probability, the subjective value of forthcoming self-rewards, as indexed by both preferences and conditioned responses, was decreased as the partner-reward probability was increased. This subjective reward value was represented by a population of LH neurons during the early stimulus presentation period (151–450 ms from stimulus onset; Fig. 1b). However, in the late stimulus period (701–1000 ms from stimulus onset), the subjective value signal disappeared. Instead, agent-specific reward signals emerged in two neuronal populations: one selectively encoding the self-reward probability (self type; Fig. 1c, right) and the other selectively encoding the partner-reward probability (partner type; Fig. 1c, left). Reversible chemical inactivation of the LH eliminated the impact of the partner's rewards on the subjective value, supporting a causal role for the LH in social value modulation. These findings indicate that LH neurons encode two types of signals in a time-dependent manner: a subjective value signal that takes others' outcomes into consideration and a stimulus-outcome-agent associative signal. These signals might be formed by using top-down signals from the mPFC (Fig. 2), where self-reward probabilities and partner-reward probabilities are represented (Noritake et al., 2020, 2018).

The subjective value in the early stimulus period is encoded in two opposing ways, i.e., desirability (or positive) coding and undesirability (or negative) coding. Specifically, a group of LH neurons exhibits a positive correlation between firing rate and degree of desirability (Fig. 1b, right). Another group of LH neurons exhibits a positive correlation between firing rate and degree of undesirability (Fig. 1b, left). This bidirectional coding has also been observed in a nonsocial context (Noritake and Nakamura, 2019). Thus, the role for the LH in processing the hedonic valence of outcomes seems versatile (Petrovich, 2018; Tye, 2018; Tyree et al., 2018). The bidirectional value coding in LH neurons stands in contrast to the unidirectional desirability coding in DA neurons (see the next section).

2.3. Midbrain DA nuclei

It is generally accepted that DA neurons in the ventral tegmental area (VTA) and substantia nigra pars compacta encode the discrepancy between an expected reward and the actually received reward, known as the reward prediction error (Schultz, 1998; Schultz et al., 1997). The reward prediction error signal has been studied and characterized in various economic contexts in which reward magnitude, probability, delay, cost, and choice options are manipulated systematically (Roesch et al., 2007; Tanaka et al., 2019; Tobler et al., 2003). Previous studies have highlighted the finding that DA neurons encode a subjective value for economically composite components in the form of formal economic utility, i.e., usefulness or satisfaction, for the actor (Stauffer et al., 2015). However, these studies have been carried out in nonsocial contexts, leaving the question open as to whether DA neurons also incorporate other-reward information into subjective value computations.

During the social Pavlovian conditioning procedure, DA neurons signal subjective value by taking other-reward information into consideration (Noritake et al., 2018). Consistent with the behavioral manifestation of the subjective value, DA neurons exhibit a greater response when others are less likely to receive a reward, but a smaller response when others are more likely to receive a reward (Fig. 1d). In these conditions, the chance and total magnitude of self-rewards are eventually the same regardless of the partner-reward probability. Unlike LH neurons, value coding in DA neurons is unidirectional, i.e., only in the positive direction (Fig. 1d), and agent-selective reward signals are virtually absent. Like LH neurons, the modulation of DA signals by partner-reward information is significantly attenuated when the partner monkey is replaced by a physical object or the partner is unable to obtain a reward (Noritake et al., 2018).

DA neurons can receive reward information from other subcortical regions including the dorsal striatum (striosomes in the caudate nucleus and putamen), ventral striatum (mainly the nucleus accumbens, NAc), amygdala, pedunculopontine tegmental nucleus, dorsal raphe nucleus, VP, LH, and LHb, and from cortical regions including the OFC, mPFC, and lateral PFC (Bernard and Veh, 2012; Frankle et al., 2006; Ghashghaei and Barbas, 2001; Joel and Weiner, 2000; Mena-Segovia et al., 2008; Morales and Margolis, 2017; Oakman et al., 1995; Ogawa et al., 2014; Volkow et al., 2017). These inputs are hypothesized to provide DA neurons with a variety of source components for producing reward prediction error signals (Tian et al., 2016). In the social Pavlovian conditioning procedure, the top-down flow of neural signals was identified from the mPFC to the midbrain (Noritake et al., 2018). This finding raises the possibility that subjective-value signals in DA neurons are formed on the basis of self-selective and other-selective reward information in the mPFC.

2.4. Striatum

How can the subjective value signal discussed above be linked to decision making and action selection in social contexts? The striatum in the basal ganglia might be the key to understanding such a link. The striatum, an input station of the basal ganglia, consists of the caudate, putamen, and ventral striatum (Fig. 1e). The striatum is in a pivotal position to integrate reward and action, with input from the subcortical reward system (see Haber and Knutson, 2010 for review), such as the substantia nigra pars compacta (Beckstead et al., 1979) and amygdala (Fudge et al., 2002; Russchen et al., 1985), and from the cerebral cortex including action-related areas (Künzle, 1975; Van Hoesen et al., 1981). The striatum also receives input from the mPFC (Calzavara et al., 2007; Selemon and Goldman-Rakic, 1985), where social and reward information processing takes place. It has been shown that in nonsocial contexts, single neurons in the striatum process self-reward information (Apicella et al., 1991; Hikosaka et al., 1989) and represent an action

value that can guide action selection under a reinforcement learning algorithm (Samejima et al., 2005). However, another line of studies has shown that striatal neurons also process others' rewards and actions.

This social aspect of striatal activity was demonstrated by recording single-neuron activity in macaques performing a social decision task (Báez-Mendoza and Schultz, 2013). In the task, two monkeys took turns at making a choice for a reward payoff indicated by cue stimuli. Four payoff conditions were used: own reward only, conspecific's reward only, reward for neither, and reward for both. Most caudate neurons responded to self-rewards. Notably, a subset of these self-reward-coding neurons were activated only when a reward was delivered according to the recorded monkey's choice, whereas a different subset was activated only when a reward was delivered according to the conspecific's choice. These findings indicate that striatal neurons can signal an action-outcome-agent association (Fig. 2a). The activity of approximately 50 % of these social actor-coding neurons was not modulated when the monkey performed the task with a nonsocial juice recipient (an empty bucket). The caudate receives input directly or indirectly from the superior temporal polysensory area (Oram and Perrett, 1996) or parietal lobe (Cavada and Goldman-Rakic, 1991), which may carry agent-specific motion information. It was further reported that striatal neurons signal errors made by the self and other (Báez-Mendoza and Schultz, 2016). Furthermore, in a reward-giving task in which the reward magnitude was asymmetric between two monkeys, some neurons preferentially responded to a disadvantageous reward inequity, while others responded to an advantageous reward inequity (Báez-Mendoza et al., 2016). These neuronal signals occurred irrespective of, or in conjunction with, self-reward coding. These data demonstrate that striatal neurons are sensitive to a difference in reward magnitude between self and others.

2.5. Other subcortical regions and circuits

The neural circuits for outcome valuation are mainly composed of limbic forebrain regions and basal ganglia. Among them, the circuitry connecting the VTA, NAc, VP, amygdala, and LH (Fig. 2, left, pink arrow) may be crucial for processing social motivation (Dölen et al., 2013) in addition to motivation and emotion in nonsocial contexts (Castro et al., 2015; Chiba et al., 2001; Fadel and Deutch, 2002; Petrovich et al., 2002). Rodent studies have demonstrated that DA projections from the VTA to the NAc can encode key features of social, but not object, interactions (Gunaydin et al., 2014), and that the functional links between the NAc, VP, and LH are important for social interactions (Bertrand et al., 1997; Coccurello, 2019). Unfortunately, the functional role of this reward circuitry in non-human primates has not been scrutinized well in social contexts, except for a study reporting the involvement of the ventral striatum in processing social information (Klein and Platt, 2013). In this study, a comparison was made between the neuronal responses to social visual information and primary fruit reward in three striatal regions, i.e., the caudate, putamen, and ventral striatum including the NAc. Distinct subpopulations of striatal neurons commonly or separately encoded social information and reward information. Social information was primarily represented in the medial striatum, largely in the ventral part including the NAc, suggesting that the processing of social visual and nonsocial reward information is weighted in the striatum (Fig. 1e). The NAc is related profoundly to addiction (Fang and Ronnekleiv, 1999; Mitrano and Smith, 2007), and the VP constitutes a final limbic common pathway (Smith et al., 2009). Dysfunction of the NAc and VP results in anhedonia, a significant lack of motivation, suggesting that they may also be essential nodes for processing hedonic and motivational signals in social contexts (Bertrand et al., 1997; Coccurello, 2019).

Another important circuit connects the internal segment of the globus pallidus, LHb, rostromedial tegmental area, and VTA (Fig. 2, right, pink arrow). These subcortical regions receive top-down input from the PFC, especially the mPFC (Freedman et al., 2000; Ongür et al., 1998). Unlike the VTA–NAc–VP/amygdala–LH circuit, the internal segment of the globus pallidus–LHb–rostromedial tegmental area–VTA circuit mainly processes negative valence information. The border zone of the internal segment of the globus pallidus provides excitatory inputs to the LHb (Hong and Hikosaka, 2008), where negative reward prediction error signals are encoded (Ji and Shepard, 2007; Matsumoto and Hikosaka, 2009, 2007; Tian and Uchida, 2015). Such signals from the LHb suppress DA neurons via inhibitory neurons in the rostromedial tegmental area (Jhou et al., 2009). The functional roles of this neural circuit in social emotion are understood poorly in non-human primates.

It has been postulated that the hippocampus constitutes the social brain (Montagrin et al., 2018). Like other subcortical regions mentioned above (Noonan et al., 2014), the size of the hippocampus is associated with social group size in macaques (Todorov et al., 2019), and learning social networks is characterized by significantly greater functional connectivity between the hippocampus and temporoparietal junction in humans (Tompson et al., 2020). The role of the hippocampus in spatial learning, navigation, and memory has been acknowledged widely (Bellmund et al., 2018; Rolls and Wirth, 2018), and this functional concept also applies to the social domain (Tavares et al., 2015). Using an observational learning task designed for rats, Danjo et al. (2018) demonstrated that the activity of CA1 pyramidal place neurons reflects the spatial location of self and conspecific, either jointly or individually. These social place neurons are also observed in the bat hippocampus in a similar observational learning task, where neural representation of a demonstrator (conspecific or object) was also identified (Omer et al., 2018). These findings suggest that place neurons play a role in associating spatial information with agent information. Such hippocampal neurons may contribute to navigation not only at the individual level but also at the group level, such as coordinated group hunting. Whether similar social place neurons exist in the primate hippocampus is currently unknown.

Finally, two other subcortical regions, the raphe nuclei and the cerebellum, are worth noting in relation to social behavior, although agent-selective behavioral signals have not been identified at the single-neuron level. The size of the raphe nucleus is greater in socially dominant macaques (Noonan et al., 2014) and pharmacological manipulation of central serotonergic function causes changes in social status in vervet monkeys (Raleigh et al., 1991). Serotonergic neurons in the rat raphe nucleus respond to rewarding events in social contexts, such as sex (Li et al., 2016). Furthermore, activity of VTA-projecting serotonergic neurons in the mouse dorsal raphe nucleus is associated with vulnerability to social stress (Zou et al., 2020). The involvement of the cerebellum in social cognition and behavior has been increasingly recognized in human neuroimaging studies, demonstrating the existence of bidirectional connectivity between the right posterior cerebellum and bilateral temporoparietal junction during mentalizing (Van Overwalle et al., 2019). People with cerebellar pathology are impaired on tasks of emotion attribution (Hoche et al., 2016). Critically, the deep cerebellar nuclei send direct excitatory projections to the VTA, and optogenetic activation of these cerebello-VTA projections modulates social preference (Carta et al., 2019). Whether the primate cerebellum also directly projects to the VTA is an important question for future work.

3. Encoding of agent-relevant associative signals and social utility signals

As reviewed here, many subcortical regions encode information about stimulus, action, and outcome, which are further associated with agent information (Fig. 2). For example, LH neurons encode a stimulus-outcome-agent association (Noritake et al., 2020), and amygdala and striatal neurons encode a stimulus-action-outcome-agent association (Grabenhorst et al., 2019; Báez-Mendoza et al., 2013; Báez-Mendoza and Schultz, 2016). These associative signals can be modulated by social contexts, such as hierarchical rank, familiarity, group size, and agency (e.g., Munuera et al., 2018). The existence of these multi-factor

associative signals is consistent with the notion of agent-specific reference frames (Chang, 2017).

In reinforcement learning theories, associative signals, such as between an action and an outcome or between a stimulus and an action, are key components for decision making and action selection (Fig. 3a, top) (Rescorla and Wagner, 1972; Sutton and Barto, 2018). These theories have been designed with a nonsocial decision maker in mind; therefore, associative signals are assumed to be directly self-relevant. However, in real life, there are many other non-self agents in a shared social environment. Although one can argue that other agents are considered merely as environmental components, they are different from nonbiological stimuli and are thus unique in at least two respects. One, other agents can be a direct competitor for finite resources. Others' choices modify what resources are available at a given point, and they also modify subjective value. Two, the self-agent (i.e., "I") can become the operation target of other agents. Thus, the use of other-relevant associative signals, be it automatic or deliberate, will be highly adaptive for social decision making. This is not surprising, because survival is a fundamental motivation for living organisms and an organism's survival depends critically on the actions of others.

Self-relevant associative signals become contingent on value and are eventually encoded in subjective terms to comply with a formal economic utility (Schultz et al., 2017; Stauffer et al., 2015). Such a utility signal would be further elaborated by incorporating other-relevant associative signals (Fig. 3a), although the degree to which these signals are considered (i.e., weighting factors) may vary between contexts and across individuals (compare Fig. 3a and b). This integration produces a social utility signal that would be more beneficial, relative to self-relevant associative signals alone, for an acting agent to make an adaptive decision and action selection in social contexts. As mentioned above, DA neurons in the midbrain are a strong candidate for the neural substrate of utility coding in nonsocial and social contexts. The conceptual framework of these arguments is in line with emerging studies in humans, where reinforcement learning theories are extended to the social domain by taking other-relevant behavioral information into consideration (Fukuda et al., 2019; Suzuki et al., 2012; Wittmann et al., 2016).

4. Concluding remarks

We have reviewed the literature supporting the contributions of subcortical regions to social information processing in non-human primates. A great deal of work now indicates that single neurons in various subcortical regions, presumably via interactions with cortical neurons, encode self-relevant and other-relevant associative signals. These signals link stimulus, action, and outcome information to particular agents, and are further integrated into a social utility signal, most likely at the level of DA neurons. We hypothesize that the social utility signal can guide one's own optimal decisions while keeping social exchanges as productive as possible. How the weighting factors for other-relevant associative signals are determined depending on social contexts and differ across individuals (Fig. 3) are important questions for future work.

Accumulating evidence suggests a structural or functional change in the above-mentioned subcortical regions in various psychiatric and neurodevelopmental disorders, such as autism spectrum disorder, schizophrenia, and social phobia (Sripada et al., 2013; Kurth et al., 2011; Mitelman et al., 2018; Sato et al., 2017), which are characterized by atypical responses to social cues. Given that these subcortical regions are areas where self-relevant and other-relevant associative signals are encoded (Fig. 2), there might be an imbalance between the two kinds of associative signals in disease conditions. For example, individuals with extremely low weighting factors for other-relevant associative signals (Fig. 3b) would have a reduced motivation to regard others during social decision-making. Such individuals may become highly egocentric owing

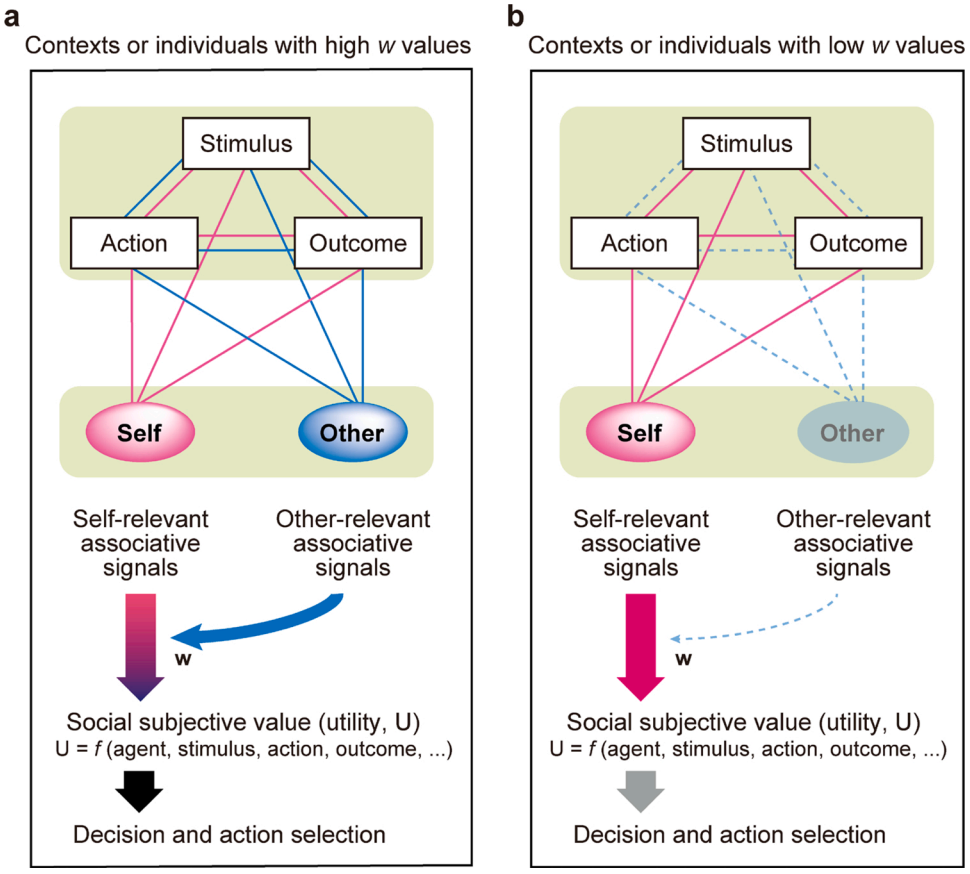

Fig. 3. Conceptual scheme showing the integration of agent-relevant associative signals into social subjective value (utility) signals. Social utility (U) is computed by the function *f*, where agent, stimulus, action, and outcome information are used as input variables. The weighting factor (*w*) can vary depending on social contexts and across individuals. (**a**) Social contexts or individuals with large *w* values. (**b**) Social contexts or individuals with small *w* values. For illustrative purposes, a small *w* value is indicated by broken blue lines.

to a pathologically enhanced priority for self-relevant associative signals. Consistent with this view, people with autism spectrum disorder are insensitive to others' facial expressions and reputation concerns during altruistic choices (Izuma et al., 2011). Moreover, in the mPFC of a macaque with a spontaneous expression of autistic phenotype, neurons selectively encoding others' actions are almost nonexistent and self-action-coding neurons are over-represented (Yoshida et al., 2016). This imbalance hypothesis is currently highly speculative and requires single-neuron recordings from subcortical regions in disease conditions. Non-human primate models of neuropsychiatric disorders, such as *SHANK3*-mutant macaques (Zhou et al., 2019) and those with maternal immune activation (Bauman et al., 2019), provide a useful platform to test the validity of the self-other imbalance hypothesis. It is also important to study which neural elements determine the weighting factors and how they are affected by different social contexts.

Mathematical theories such as a game theory and a multi-agent reinforcement learning model play a key role in the decoding of neural signals in the human brain during social interactions. For example, the reinforcement learning framework has provided important insights into the neural mechanisms by which agent-relevant associative signals develop during social learning (Fukuda et al., 2019; Suzuki et al., 2012; Wittmann et al., 2016). These studies have so far focused mainly on cerebral cortical structures, such as the mPFC, anterior cingulate cortex, and temporo-parietal junction. With refinement of the spatial resolution, this approach will also help clarify which parameters of social interactions are encoded in each subcortical region. In parallel with the development of human neuroimaging approaches at the whole brain level, electrophysiological recordings of neural activities at the single-cell level in macaques, as reviewed here, are capable of characterizing agent-relevant associative signals with fine spatiotemporal resolution. It is now technically feasible to investigate the role of less well-studied regions – the VP, NAc, rostromedial tegmental area, LHb, raphe nucleus, and cerebellum – as well as neural pathways linking these regions in encoding agent-related signals by using social task paradigms developed for macaques. In this way, human neuroimaging and macaque electrophysiology can complement each other to better understand the primate social brain at multiple scales. The two lines of approaches may also be helpful to find the similarities and differences in the organizing principle of the social brain between humans and macaques.

Declaration of Competing Interest

The authors declare no competing financial interests.

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