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Doubling down on dual systems: A cerebellum–amygdala route towards action- and outcome-based social and affective behavior

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ABSTRACT

The amygdala and cerebellum are both evolutionary preserved brain structures containing cortical as well as subcortical properties. For decades, the amygdala has been considered the fear-center of the brain, but recent advances have shown that the amygdala acts as a critical hub between cortical and subcortical systems and shapes social and affective behaviors beyond fear. Likewise, the cerebellum is a dedicated control unit that fine-tunes motor behavior to fit contextual requirements. There is however increasing evidence that the cerebellum strongly influences subcortical as well as cortical processes beyond the motor domain. These insights broadened the view on the cerebellum's functions to also include social and affective behavior. Here we explore how the amygdala and cerebellum might interact in shaping social and affective behaviors based on their roles in threat reactivity and reinforcement learning. A novel mechanistic neural framework of cerebellum–amygdala interactions will be presented which provides testable hypotheses for future social and affective neuroscientific research in humans.

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1. Introduction

Recent accounts of how the amygdala orchestrates social and affective behavior propose a dual-systems model (Balleine & Killcross, 2006; Corbit & Balleine, 2005; van Honk et al., 2022). According to this model, the central-medial amygdala (CMA) governs reactive, model-free behavior, whereas the basolateral amygdala (BLA) subserves goal-directed, model-based

behavior (Balleine & Killcross, 2006; Drummond & Niv, 2020; Olsson et al., 2020; Phillips et al., 2003). These notions are neurobiologically rooted in the observation that these ventral and dorsal subregions of the amygdala contain distinct cell-types and evolutionary trajectories (Janak & Tye, 2015). Elaborate links to the model-based and model-free dual-systems theory have been provided by amygdala-manipulation studies in animals and experimental work in humans with focal BLA damage (Balleine & Killcross, 2006; Corbit & Balleine, 2005;

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Rosenberger et al., 2019; Terburg et al., 2018; van Honk et al., 2022).

The cerebellum demonstrates an analogous evolutionary-driven organization with parallel projections towards the CMA and BLA. The cerebellum is known for its involvement in motor-related function, but there is increasing evidence for the cerebellum to play a much broader role in, among others, threat processing, reinforcement learning, and the model-based modulation of social and affective behaviors (Adamaszek et al., 2017; Kruithof et al., 2022; Van Overwalle et al., 2020).

In the groundbreaking work of Jordan Grafman interdisciplinary methodologies are pivotal for progress in psychology, psychiatry, and neuroscience. An interdisciplinary approach is also required for understanding how the amygdala and cerebellum interact. Therefore, we will apply Grafman's method to the case of the amygdala and cerebellum. We will combine cognitive and affective approaches, insights from clinical and healthy populations, and evidence from animal and human neuroscience to underscore the importance of amygdala–cerebellum interactions for social and affective behavior. Using this interdisciplinary approach, we will formulate a novel framework that describes how the cerebellum interacts with the amygdala on the behavioral level.

This framework will be centered around threat-reactivity and reinforcement learning. Not only because the amygdala as well as the cerebellum have profound importance for these processes as discussed below, but also because they lie at the basis of many, if not all, social and affective behaviors. More specifically, threat reactivity forms and maintains automatic approach/avoidance motivations, while reinforcement learning forms and maintains goal-directed approach/avoidance motivations. Together, these shape more complex affective and social behaviors (Carver & Harmon-Jones, 2009; Terburg & van Honk, 2013).

We will furthermore approach threat reactivity and reinforcement learning from the viewpoint of the model-free/model-based framework. In this framework punishment and reward processing underlie the value-based learning of actions and consequences, which subsequently shapes (social) behavior (Cushman, 2013; Drummond & Niv, 2020). Model-free learning involves trial and error processing, which shapes the value of actions and the subsequent motivation to act. Model-based learning involves the formation of forward prediction models that shape the value of action-outcomes and the motivation to act (Crockett, 2013; Drummond & Niv, 2020). As such, we distinguish the learning process from the resulting motivated behavior. In threat reactivity we view, for instance, (implicit) conditioning as a form of model-free learning and learning about specific action-escape associations as model-based learning. These learning processes subsequently inform the model-free motivation to fight, flight or freeze in case of threat and the model-based motivation to perform goal-directed escape actions. Likewise, in reinforcement learning we describe trial and error processing in terms of model-free learning (e.g., general Pavlovian to instrumental transfer), and predictive learning of action-outcome associations as model-based learning (e.g., specific Pavlovian to instrumental transfer). These learning processes subsequently shape model-free motivations related to the

emotional value of an action, and model-based motivations related to the instrumental value of the action-outcome. Together we consider these the building-blocks that underlie more complex affective and social behaviors. By combining them we aim to generate testable hypotheses for broadening our understanding of human social and affective behavior in terms of the interplay between the amygdala and cerebellum.

2. Amygdala

The traditional account of the human amygdala as center of fear was born from the holistic view that damage to the amygdala results in reductions of fear responsivity, experience and recognition (Adolphs et al., 1994, 1995; Feinstein et al., 2011). Driven by animal research and more focal amygdala damage studies in humans, the amygdala is now seen as a heterogenous structure of which the subregions have different, sometimes even opposing, functions (van Honk et al., 2016). Indeed, the amygdala consists of many subnuclei with functions not limited to fear processing. In humans, where imaging techniques lack spatial resolution compared to animal studies, three main subdivisions can be distinguished of which two can be consistently linked to social and affective behavior. These are the central-medial amygdala (CMA) which includes the central (CeA) and medial nuclei (MeA) and the basolateral amygdala (BLA) including the lateral, basolateral, basomedial and basoventral nuclei (Amunts et al., 2005; Bzdok et al., 2013). Interestingly, these subregions mirror the cortical expansion across evolution seen when comparing reptilian, mammalian, and primate brains. The CMA consists mainly of striatal-type tissue whereas the BLA consists of more cortical-type tissue, and indeed we see across evolution a relative growth of the BLA compared to CMA (Janak & Tye, 2015). Consequently, the human BLA is larger in size compared to the CMA, but combined they are in prime position to function as a hub between subcortex, striatum and cerebral cortex.

With respect to threat processing and reinforcement learning, two main networks can be distinguished. First a serial-processing network supporting threat reactivity in which sensory information arrives from the thalamus, sensory systems and hippocampus in the BLA which in turn coordinates the CMA's output towards the subcortical threat system (i.e., hypothalamus, periaqueductal gray, locus coeruleus and other brainstem nuclei) (LeDoux & Daw, 2018). Second, a parallel-processing network supporting reinforcement learning in which the BLA and CMA act on the nucleus accumbens (NAc) in parallel fashion (Balleine & Killcross, 2006). Interestingly, in both these models the CMA and BLA hold a balance in support of shaping social and affective behavior in an either reactive or context-dependent manner.

In a recent line of studies, we (authors JvH and DT) investigated a group of individuals with Urbach Wiethe disease (UWD), a recessive function mutation within the extracellular matrix protein 1 gene (Hamada et al., 2002). In the South African UWD population that we studied the disease typically results in focal and bilateral calcifications within the BLA, while the CMA remains functional (Terburg et al., 2012; van Honk et al., 2016). These focal BLA calcifications turn UWD

therefore into a unique amygdala-lesion model for human behavior, which we used to investigate how these amygdala subregions contribute to social and affective behavior. For this we focused on threat behaviors using the serial-processing model on the one hand and how reinforcement learning shapes social decision-making using the parallel-processing model on the other hand.

2.1. Threat reactivity

Threat reactivity is largely driven by the interplay of midbrain structures and the autonomous nervous system, which together promote rapid responding to (potential) threat (LeDoux & Daw, 2018). Strongly hormone driven, the hypothalamus can adjust activity in the locus coeruleus (LC) and periaqueductal gray (PAG) which orchestrate autonomous arousal and reactive threat behaviors such as fight, flight and freeze. The amygdala influences this system via the serial-processing amygdala network (Barbas et al., 2003). In this network (highly) processed sensory information arrives in the BLA which in turn projects to the CMA which connects to the threat system at the level of the hypothalamus as well as midbrain areas such as the PAG and the LC located in the pons of the brainstem (LeDoux & Daw, 2018). In this process the BLA is typically seen as responsible for threat conditioning and learning and the CMA for executing the associated threat reactivity. In the South African UWD sample we indeed found that BLA damage was associated with reduced threat conditioning (Klumpers et al., 2015). We however also repeatedly observed that interference of threat-related imagery on executive functioning was amplified in these individuals (De Gelder et al., 2014; Hortensius et al., 2016, 2017; Terburg et al., 2012). These experiments typically followed a design in which an already acquired threat response (e.g., automatic processing of faces, body-poses and scenes with threat-related content) conflicted and interfered with goal-directed behavior (e.g., color-naming, perceiving and judging other stimulus characteristics). In these tasks, individuals with BLA damage typically show a slow-down in color-naming (Terburg et al., 2012), reductions and slow-down in perceptual judgment performance (de Gelder et al., 2014) and increased threat-related reactivity in cortical areas associated with action preparations (Hortensius et al., 2016, 2017). Together, this gave rise to the hypothesis that the BLA might be crucial for regulating and reducing threat reactivity in favor of goal-directed behavior.

To investigate this further we performed a cross-species translational study to examine if and how the interplay of BLA and CMA can adjust threat-reactivity to the context at hand (Terburg et al., 2018). We compared humans with and without BLA damage to find the causal effect of BLA damage and used chemogenetic manipulation of BLA and CeA to investigate the associated pathways in rats. Humans as well as rats were placed in a situation where a threat-of-shock could be avoided by performing a goal-directed action. As measures of threat reactivity we used escape performance, behavioral freezing and startle-potentiation in the rat-studies, and startle-potentiation and functional magnetic resonance imaging (fMRI) in humans. Results showed that, particularly in situations where rapid goal-directed action is required to

escape the threat, the BLA is crucial for down-regulation of reflexive passive threat behaviors (i.e., freezing and startle potentiation). Mechanistic insights based on chemogenetic manipulation and fMRI showed that the BLA performs this role via activating an oxytocin-mediated behavioral switch in the CeA which reduces threat reactivity at the level of the brainstem. In sum, the BLA can provide context-dependent modulation of threat reactivity to facilitate goal-directed behavior even during threatening situations (Terburg et al., 2018).

2.2. Reinforcement learning and social decision-making

Experimental work on the parallel-processing network of the amygdala was triggered by a study in which participants with and without BLA-damage performed in several single-shot trust games in which they had to decide to invest an amount of money in an unknown trustee (van Honk et al., 2013). The invested money was tripled by the experimenter and the trustee decided to return (part of) the money to the participant. We found that the participants with BLA damage invested nearly double the amount of money. Importantly, we excluded that this was due to increased risk-taking. Furthermore, the BLA-damaged participants did not expect higher returns, nor did they judge the trustees as more trustworthy. Based on these results we concluded that the participants with BLA damage invested more money out of generosity and explained this from the perspective of the parallel-processing network (van Honk et al., 2013).

In the parallel-processing network the BLA and CMA both project to the NAc which is the most prominent structure for reinforcement learning and goal-directed behavior (Balleine & Killcross, 2006; Corbit et al., 2013). The BLA does so directly and the CMA indirectly via the bed nucleus of the stria terminalis (Hulsman et al., 2021). Rodent neuroscience has linked these projections to specific forms of reinforcement learning and associated decision-making (Balleine & Killcross, 2006; Cartoni et al., 2016; Corbit et al., 2013). Reinforcement learning typically takes the form of Pavlovian-to-instrumental transfer where predictive cues can shape, through trial-and-error, the learning of goal-directed behavior. Such predictive cues activate general motivation or specific actions to obtain a goal or reward, which respectively depend on the CMA and BLA (Cartoni et al., 2016). This process shapes behavior such that the CMA is crucial for executing intuitive and habitual actions, whereas the BLA is crucial for learning and executing instrumental action (Bray et al., 2008; Corbit & Balleine, 2005). Following evidence that when people are forced to rely on intuitive and habitual decision-making they become more generous (Rand et al., 2012), we assumed that due to BLA damage the parallel-processing network is biased towards CMA processing resulting in more generous behavior (van Honk et al., 2013). In a follow-up study, where we used a repeated trust game design, we could confirm that differences in reinforcement learning was an underlying mechanism. In the repeated trust game, the participants play the trust game repeatedly with the same person which ensures that they can learn from the other's behavior and update their own responses. Using such a design we demonstrated that people with BLA-damage did not learn to update their behavior in the face of repeated trust-violations (Rosenberger et al., 2019).

Arguably due to the BLA damage, the individuals with UWD lack the ability to learn the instrumental behaviors that reduce generosity and favor monetary outcome for themselves. In short, in these BLA damaged subjects the CMA-driven generosity prevails over BLA-driven personal reward maximization. Computational neuroscience operationalizes these processes in terms of whether behavior, and the associated value-based decision making, is driven by a context-specific model of action and outcome (Olsson et al., 2020). In this framework, punishment and reward processing underlie learning of the value of actions and outcomes (Drummond & Niv, 2020). When making value-based decisions, action and outcome may compete when their value is not aligned to each other. Typically, the value of an action is driven by the acute punishment/reward driven emotion associated with that action, which underlies habit-related model-free learning. The value of an outcome is driven by a causal model of the changing environment in interaction with reward optimization (Crockett, 2013; Drummond & Niv, 2020). As such, this results in instrumental model-based learning favoring optimal outcomes. Thus, model-free decisions underlie habitual and intuitive actions that prefer the emotion related to the action over potential outcome. Model-based decisions on the other hand underlie instrumental-calculative actions that focus on optimizing outcome. Importantly, the latter focuses on the value of the context-specific outcome of the action, whereas the former emphasizes the value of the action itself (Crockett, 2013; Drummond & Niv, 2020). Following this framework and our previous trust game results, the BLA should thus be crucial for making outcome-based decisions. This hypothesis was tested in the context of moral decision-making using moral dilemmas, which are typical examples of decision-making scenarios where the value of actions and outcomes do not align, resulting in a conflict between model-free (action value) and model-based (outcome value) motivations.

In a typical moral dilemma, one makes the decision to sacrifice someone to save multiple others. The action to sacrifice is a highly emotional one that we intuitively avoid, whereas the outcome of that action, that is less fatalities, is generally preferred (Bleske-Rechek et al., 2010; Conway & Gawronski, 2013; Greene, 2013; Navarrete et al., 2012; Nichols & Mallon, 2006). Such moral decisions are thus a typical dual-process which encompasses a conflict between action-based or model-free motivation, and outcome-based or model-based motivation (Cushman, 2013; Greene et al., 2001). Typically, the ventromedial prefrontal cortex (vmPFC) is described as the structure where these streams come together fed by both the BLA and the NAc (Shenhav & Greene, 2010, 2014). Following the parallel processing model BLA damage would thus result in more action-based motivation which is exactly what we observed in our moral dilemma study. Indeed, people with BLA damage consistently chose to not sacrifice someone in order to save multiple others (van Honk et al., 2022).

2.3. The dual-process view on the amygdala

When the observations from above are combined we see that both in the serial-processing model of threat-reactivity and parallel-model of reinforcement learning the BLA subserves

instrumental goal-directed behavior, and the CMA intuitive, impulsive, and reactive behavior. This dual-process organization mimics their respective evolutionary development as the BLA consists of more cortical-type and the CMA consists of more striatal-type tissue and projections. Furthermore, the relative increase in size of the BLA compared to CMA across evolution further emphasizes this distinction.

3. Cerebellum

The cerebellum is located in the posterior fossa and despite its modest size contains more than half of the total neurons present in the brain (Azevedo et al., 2009). The flocculonodular lobe is phylogenetically the oldest part of the cerebellum and implicated in oculomotor control, muscle tone, body posture and balance. The cerebellum can be further divided into two hemispheres and a midline region called the vermis. Each hemisphere consists of an anterior and a phylogenetically younger posterior lobe separated by the primary fissure (O'Hearn & Molliver, 2001). The deep cerebellar nuclei (DCN) constitute the output structures of the cerebellum and are composed of the fastigial nucleus, interposed nuclei, and dentate nucleus. These relay information to the extracerebellar regions via the superior cerebellar peduncle with a midline to lateral organization such that the fastigial nucleus mainly receives input from the vermis and the dentate nucleus from the posterior lobe (O'Hearn & Molliver, 2001). The middle cerebellar peduncle contains afferent fibers stemming from pontine nuclei, while the inferior cerebellar peduncle contains both efferent and afferent fibers (O'Hearn & Molliver, 2001).

Comparative analyses indicate that the cerebello-cortical system in mammals, originating mostly from lateral parts of the posterior lobes, shows the highest rate of brain evolution within the cerebellum (Smaers & Vanier, 2019). In fact, methods to examine evolutionary rate changes in mammals indicate that the increase in cerebellar volumes even outpaced the cerebral cortex resulting in larger cerebella relative to neocortex size compared to other anthropoid primates (Barton & Venditti, 2014). In conjunction with the established involvement of the anterior cerebellum in sensory-motor processing and (skill) learning, the phylogenetic developmental trajectory of the cerebellum suggests that the closed-loop interconnections between the lateral posterior cerebellar hemispheres and cerebral cortical association areas play a key role in cognitive functions (Barton & Venditti, 2014; Magielse et al., 2022). This assumption is further supported by comparative data showing that the progressive development of the dentate nucleus in humans results from the ventral region which connects to the cerebral cortical association areas and not the dorsal region which connects to the motor regions of the cerebral cortex (Matano, 2001). Together with the medial posterior vermis and its cortico-nuclear projections to the emotion-dedicated subcortical regions of the brain, the cerebellum is well suited to contribute to complex social and affective behavior (Adamaszek et al., 2022; Schutter, 2020; Schutter & van Honk, 2005; Van Overwalle et al., 2020).

3.1. Threat reactivity

There is ample evidence for the cerebellum playing a significant role in threat reactivity. The cerebellar vermis is suggested to integrate bodily (interoceptive) and external sensory signals necessary to process threat-related stimuli in order to facilitate the transition from perception to action. In line, inactivation of the vermis, or its main output region the fastigial nucleus, leads to impairments in threat-reactivity and defensive behavior in cats and rodents (for an overview of studies, see Lawrenson et al., 2022).

In humans, a coordinate-based meta-analysis of studies demonstrated bilateral activity of the amygdala and vermal lobule VI as part of the core network of fear processing (Tao et al., 2021). This part of the human vermis has also been shown to react to conditioned threat stimuli (Lithari et al., 2015), which is remarkably similar to the involvement of this region in the consolidation phase of threat conditioning in rats (Sacchetti et al., 2004). This is further highlighted by the observation that the vermis has inhibitory effective connectivity with the amygdala when processing non-emotional bodily motion and the insula inhibits the vermis when processing emotional bodily motion (Sokolov et al., 2020). Sokolov et al. (2020) argued that this connectivity pattern indicates that the vermis uses input from the insula to adapt affective processing at the level of the amygdala. This form of emotion regulation might thus be the pathway through which the vermis can affect the threat reactivity and consolidation of conditioned fear observed by Sacchetti et al. (2004). Moreover, a recent review of a large body of anatomical, physiological, behavioral, and functional neuroimaging results showed that the cerebellum plays a role in the extinction of conditioned (defensive) responses in rodents and humans (Doublié et al., 2023). The cerebellum thus seems to play a role in all stages of threat conditioning.

Interestingly, these findings support the proposed theoretical link between model-free learning (in this case threat conditioning) and medial, or vermal, areas of the cerebellum. Moreover, this link might extend to the expression of threat behaviors as vermal lobule VI is also important in the coupling of sensory- (e.g., pain), autonomic- (e.g., sympathetic activity), affective- (e.g., fear) and motor-related signals (e.g., action readiness) (Habas, 2021), which together serve a sensory-motor integration function and subsequent behavioral expression.

An important form of behavioral expression of threat reactivity is aggression, in which a growing number of studies find a role for the cerebellum. Results from a coordinate-based activation likelihood estimation meta-analysis in humans suggest the cerebellum can provide for a balance between model-based threat assessment and emotion regulation on the one hand and model-free expression of reactive aggression on the other (Klaus & Schutter, 2021). In particular, the right posterior cerebellar hemisphere (that is, Crus I–II) regulates cognition-driven threat assessment and medial-anterior cerebellar regions, e.g. the vermis, are involved in the expression of aggression (Klaus & Schutter, 2021). This concurs with evidence that medial-anterior cerebellum, and the vermis in particular, connects through the fastigial

nucleus to the PAG and hypothalamus, which are main nodes of the reactive threat network (Haines & Dietrichs, 1984; da Silva et al., 2023). In mice, this pathway is indeed associated with the expression of rage (Zanchetti & Zoccolini, 1954) as well as aggression towards intruders (Jackman et al., 2020).

Together this evidence shows that the vermis is involved in the modulation and regulation of affective behavior at the level of the amygdala and in all stages of threat conditioning. In case of acute social threat projections to the PAG support defensive reactivity underlying model-free behaviors such as rage and (reactive) aggression, and posterior cerebellar regions might drive the model-based regulation of emotion and aggressive tendencies.

3.2. Reinforcement learning and social decision-making

As discussed earlier, in model-free reinforcement learning rodents and humans typically start with random actions and develop over time, based on trial and error, a preference for actions that lead to the highest reward. Lesion work indicates a distinct role for the striatum in model-free reinforcement learning, which was confirmed in computational studies indicating striatal involvement in model-free reward prediction errors (O'Doherty et al., 2004; Yin et al., 2004). Based upon its functions and intricate connections with the NAc, amygdala and cerebral cortical association areas, the cerebellum is able to monitor, compare, and especially time patterns of events using prediction and reward-based error feedback. Indeed, predictive timing is associated with signal activity in the vermis in conjunction with the brain's reward system (Lošák et al., 2016). As such, the cerebellum is described as a neural correlate of an internal timing system which encodes temporal intervals on the (sub)millisecond time scale (Koch et al., 2007). This system is critical when it comes to dealing with the complexity of signals subserving associative reinforcement learning.

Due to the relative homogenous architecture of the cerebellar cortex, synaptic plasticity at the parallel fiber-Purkinje cell junction provides one of the several cellular bases for supervised and reinforcement learning in the cerebellum (Ito, 2006). This enables the cerebellum to learn without the need for explicit instructions as in the case of reinforcement learning which is driven by feedback-related reward/error signals in response to behavior (Yamazaki & Lennon, 2019). Error-based (model-free) reinforcement learning thus aims to maximize anticipated reward (error free) based on trial and error. Such model-free reinforcement learning with respect to the cerebellum is furthermore associated with habit formation and stereotypical behavior as shown by abolishment of devaluation insensitivity following cerebellar damage in overtrained rats (Callu et al., 2007).

This type of learning is also considered to be the first step in model-based reinforcement learning as it can calibrate forward prediction models (Sokolov et al., 2017). Indeed, observations of predictive, non-sensorimotor encoding properties of granule cells receiving input from mossy fibers, point towards the ability of the cerebellum to process signals subserving the forward predictions of perceptual and mental states (Wagner et al., 2017; Wolpert et al., 2003). Such model-based systems are guided by internal forward models of the

environment which are subsequently updated based on prediction errors. This model-based approach enables simulation of future states reached by actions and evaluations of outcome probabilities. For example, reward-based motor learning in animals has established the role of the cerebellum together with the basal ganglia in the formation of internal models of its state, allowing the animal to make predictions on how future actions will impact that particular state (Kruithof et al., 2023; Pierce & Péron, 2022). Furthermore, computational modeling approaches indicate a role for the prefrontal cortex in state prediction errors (Gläscher et al., 2010). Indeed, empirical findings of a recent functional neuroimaging study confirm involvement of the prefrontal cortex in theory-based reinforcement learning, which is considered a strong form of model-based reinforcement learning (Tomov et al., 2023). Interestingly, this study also showed that model-based reinforcement learning recruits the posterolateral cerebellum (Crus I) (Tomov et al., 2023). These studies thus illustrate that along with areas of the prefrontal cortex (PFC) and basal ganglia, the posterolateral cerebellum is part of a neural network implicated in model-based action-outcome planning.

Interestingly, model-based action-outcome predictions can be considered an underlying mechanism for mental simulation (Dreher & Grafman, 2002; Fermin et al., 2016). Mental simulation, or Theory of mind (ToM), refers to one's ability to infer mental states of others such as emotions, beliefs and intentions, and enables a person to predict the behavior of others to guide social decision-making. Importantly, reinforcement learning, and the formation of internal prediction models, are processes underlying this interaction of ToM and social decision-making (Brown & Brüne, 2012). The modular selection and identification for control (MOSAIC) model for sensorimotor control attempts to provide a computational framework for explaining this interaction of social processing and decision-making (Wolpert et al., 2003). Analogous to sensorimotor integration, the MOSAIC model considers social interactions and decision making as the result of interactive loops between self-generated and observed communicative actions (Wolpert et al., 2003). These interactive loops contribute to model-based behavior through the formation of internal prediction models which are argued to be encoded in the cerebellum (Wolpert et al., 1998). Such internal prediction models of social behavior are, for instance, supported by the perception of biological motion (e.g., face and body movements). Interestingly, the superior temporal sulcus (STS), the area most prominently linked to biological motion perception, has shown structural as well as functional connectivity with the cerebellar Crus I (Sokolov et al., 2011, 2014, 2018), which could be one of the pathways by which the cerebellum supports the process of forming internal prediction models of social behavior.

Combined, this supports the notion that the cerebellum can play an essential role in ToM and social decision making through its role in the formation of internal prediction models. Indeed, recent evidence shows that Crus II of the posterolateral cerebellar hemisphere is also among the key regions involved in ToM (Van Overwalle et al., 2020). For example, implicit action sequence learning of an agent's true-false belief orientation, a process related to ToM, recruits Crus

II (Pu et al., 2023) along with bidirectional connectivity with the temporo-parietal junction (TPJ) and medial prefrontal cortex (mPFC). Moreover, posterior cerebellar Crus I and II also react to violations of an anticipated social behavioral outcome (Pu et al., 2023), an observation that not only underscores their respective involvement in processing intention in biological motion and action sequences, but also their combined importance for ToM.

Evidence for cerebellar involvement in social decision-making comes from a meta-analysis of eleven fMRI studies which examined the neural correlates of fairness using the Ultimatum Game (Gabay et al., 2014). The Ultimatum Game is a widely used social decision-making task to examine individual responses to unfairness and decisions to accept or reject a monetary offer made by another person at a cost for oneself. Activation of the anterior insula, anterior cingulate cortex, supplementary motor area and posterolateral cerebellar Crus I were observed in response to unfair offers. These activations are in agreement with activity in brain regions associated with norm violation and motivational conflict (Gabay et al., 2014). Furthermore, bilateral activity in lobule VI of the posterior cerebellum as part of activation of a complex network which includes the amygdala has been found to positively correlate with compassion in response to viewing visual scenes depicting suffering (Mercadillo et al., 2015). Compassion is a moral emotion that promotes social cooperation and prosocial decision-making which relies heavily on ToM. Similarly, indignation is another moral emotion that drives social decision-making in which Crus II detects violations of social norms and generates prediction error signals as described by the MOSAIC model (Moll et al., 2005; Wolpert et al., 2003).

In sum, the cerebellar vermis can, via its role in model-free learning and influence on striatal areas form and maintain habitual and reactive reward behaviors. Posterolateral areas such as Crus I and II drive model-based learning and behavioral expressions. Through this, they influence complex social behaviors such as ToM and social decision-making. These functions subsequently affect cortical processing on several levels, among which vmPFC mechanisms associated with social decision-making and insula, STS and TPJ mechanisms associated with ToM.

3.3. The dual-process view on the cerebellum

Taking these behaviors together, the cerebellar organization of distinct vermis and posterior lobe contributions to social and affective behavior is evident. The vermis, via the fastigial nucleus, supports reactive threat behaviors and habit formation through model-free reinforcement learning, whereas posterolateral areas, via the dentate nucleus, are suggested to support more complex threat assessment, model-based action planning and higher-order emotional functions such as ToM (Kruithof et al., 2022). This dual-process organization is strikingly similar to how the amygdala's subregions, CMA and BLA, promote similar behaviors. Below we will attempt to integrate these separate dual-process systems with the goal to provide a framework on how they interact and complement one another based on the existing functional and structural neuroanatomical evidence.

4. The cerebello-amygdala connection

Evidence for direct anatomical connections between the cerebellum and temporal lobes dates back to animal research performed in the late 1950s and mid-1970s. Electrical stimulation of the vermis in dogs elicited neural response in several limbic regions including the amygdala (Anand et al., 1959). This observation was confined to the posterior vermis as neither electrical stimulation of the anterior vermis nor neocerebellar lateral hemispheres evoked any response. Since the vermis primarily connects to the fastigial nucleus of the DCN via inhibitory projections from Purkinje cells, numerous studies have addressed the role of the fastigial nucleus in the cerebello-limbic pathways. It was for instance shown that rectangular electrical pulses, delivered between the leads of an electrode located in the fastigial nucleus, resulted in electrical potentials in both the hippocampus and amygdala in rhesus monkeys (Heath & Harper, 1974). These findings were corroborated by results from a histological study in cats and monkeys where it was shown that ablation of the fastigial nucleus caused degeneration of fibers which entered the hippocampus and BLA (Heath & Harper, 1974). In addition, the short response latency to fastigial stimulation as well as the histological findings suggested monosynaptic connections between the fastigial nucleus and medial temporal lobe regions. Moreover, the termination points of these cerebellar projections to the hippocampus were diffuse, while for the amygdala the termination points were confined to the basolateral nucleus.

Injection of a biotinylated dextran amine tracer into the dentate nucleus of the cerebellum of rats revealed bilateral monosynaptic projections running through the superior cerebellar peduncle between the dentate nucleus and the central as well as basal nuclei of the amygdala (Çavdar et al., 2022). Ipsilateral monosynaptic projections between the dentate nucleus and the lateral nuclei of the amygdala were also observed. These connections were confirmed in humans with high resolution 3 T tractography data, where also additional fastigial nucleus-amygdala connections were identified (Çavdar et al., 2022). Another recent study that combined tracing techniques with neuroimaging and optophysiology failed to find monosynaptic connections between the cerebellum and amygdala in the mouse brain (Jung et al., 2022). However, disynaptic connections between the DCN and BLA via the centromedial and parafascicular nuclei of the thalamus were found. In addition, thalamic neurons receiving input from the DCN were observed to project to the nucleus accumbens and anterior cingulate cortex (Jung et al., 2022).

In sum, the vermis is in the position to directly influence the hippocampus as well as the BLA via the fastigial nucleus. Posterior parts of the cerebellum, via the dentate nucleus, project to both subregions of the amygdala (i.e., CMA and BLA) as well as the nucleus accumbens, either directly and/or via the thalamus.

As noted earlier, a considerable amount of experimental animal literature illustrates the importance of the vermis in threat-related and defensive behaviors. Its connections to the BLA and hippocampus have predominantly been linked to emotion regulation (Sokolov et al., 2020) and consolidation of conditioned fear (Sacchetti et al., 2004). An interesting observation in this regard is that during acquisition and retention of

conditioned fear (eye-blink startle), pharmacological inactivation of the CeA with muscimol also lowers neural activity in the cerebellar interposed nuclei which are important for finetuning motor responses (Farley et al., 2016). This suggests that the CeA updates cerebellar threat related motor-learning during acute as well as already acquired fear responses. Threat conditioning in all its aspects seems thus to be supported by a feedback-loop encompassing vermis, BLA, CeA and cerebellar nuclei in the DCN.

As noted earlier, the vermis has also extensive projections to the PAG and hypothalamus, via the fastigial nucleus (Da Silva et al., 2023; Haines & Dietrichs, 1984), which are particularly important for the expression of threat-related behaviors. Interestingly, these pathways seem to operate in parallel to the CMA, stimulating similar behaviors. Firstly, lesion studies in rats demonstrated that the posterior cerebellar vermis is critical for conditioned and unconditioned freezing behavior through projections to the PAG (Frontera et al., 2020). Furthermore, in line with prior research showing changes in emotional behavior of rats following cerebellar lesions, selective damage of the vermis caused a remarkable reduction of fear-related behaviors. Vermis-lesioned rats as compared to sham-operated rats, for example, showed fewer defensive responses such as freezing and avoidance in the presence of a cat, and more exploratory behavior in an open-field (Supple et al., 1987). Interestingly, these behaviors seen in vermis-lesioned rats are remarkable similar to the reduced freezing responses governed by the ventrolateral PAG and increased exploratory behavior seen in amygdala-lesioned rats (Blanchard & Blanchard, 1972; Sarter & Markowitsch, 1985). Moreover, ablation of the amygdala has classically been reported to have a “taming” effect and damage to the anterior vermis causes notable decreases in aggression as well (Berman, Berman, & Prescott, 1974). In agreement, lesions of the fastigial nucleus markedly reduce “irritability” caused by septal damage in rats (Berntson & Torello, 1982; King & Meyer, 1958). Finally, similar to amygdaloid lesions (Jonason et al., 1973), destruction of the fastigial nuclei, but not lateral nuclear lesions such as the dentate nucleus, caused notable reductions in open-field exploratory behavior and conspecific social interactions (Berntson & Schumacher, 1980).

In humans a recent study showed that the vermis expresses inhibitory effective connectivity with the amygdala when processing non-emotional bodily motion and that the insula inhibits the vermis when processing emotional bodily motion (Sokolov et al., 2020). As noted before, Sokolov et al. (2020) argue this connectivity pattern indicates that the vermis uses input from the insula to adapt affective processing at the level of the amygdala. Unfortunately, focused studies on the medial cerebellar nuclei in humans are lacking (Doubliez et al., 2023), thus strong conclusions about cerebellar-amygdala connectivity can as of yet not be drawn.

In sum, when combining the connectivity patterns of the cerebellum in relation to social and affective behaviors we again see a distinction between vermis supported behaviors and posterior lobe supported behaviors. The vermis-fastigial nucleus system supports reactive threat behaviors and habit formation through projections towards the PAG, BLA and NAc, whereas the posterior lobe-dentate nucleus system seems to support more complex threat assessment, model-based

action planning and higher-order emotional functions via projections to the CMA and BLA as well as other limbic structures and cortical areas.

5. Towards a cerebellum-amygdala framework of social and affective behavior

Multiple parallels draw attention when comparing the amygdala and cerebellum. Both can be described as dual-process systems that, when comparing their anatomy, exist of two distinct subsystems with separate phylogenetic trajectories. When comparing their behavioral functions, we see that these dual-process systems support, on the one hand, reactive, conditioned, and model-free behavior and, on the other hand, goal-directed, planned and model-based behaviors. Interestingly, this distinction in behaviors can be applied to a broad spectrum of social and affective behaviors. In threat behaviors they represent (conditioned) fight-flight-freeze reflexes and reactive aggression on the one hand and threat assessment, emotion regulation and goal-directed escape on the other. In reward behaviors they represent (conditioned) habitual actions on the one hand and outcome-based behavior on the other. In social behaviors they represent action-based decision making on the one hand and outcome-based decision making and ToM on the other. When looking at the connections between the cerebellum and amygdala a neural model emerges that reflects how they potentially work together to support this range of functions (see Fig. 1).

The vermis projects via the fastigial nucleus to the threat system (hypothalamus and PAG) supporting the full range of reactive threat behaviors in parallel with the CMA, but also links (via the thalamus) to the BLA and hippocampus, subserving the regulation and conditioning of such behaviors. The posterior cerebellum projects, via the dentate nucleus, to both amygdala subregions as well as NAc and limbic, prefrontal and temporal cortical regions. This organization provides the posterior cerebellum with the ability to promote the model-based functions at the level of the BLA as well as cortical areas.

This model shifts the focus from a more established role of the vermis in model-free reactive and conditioned

behaviors, to more hypothetical roles of posterior cerebellum in the adjustment of these, and higher-order social, behaviors in a model-based fashion. The posterior cerebellum can potentially do so via its projections to cortical areas as well as its (mostly indirect) connections to limbic areas, most particularly the BLA. Following this model, neuroimaging studies should be able to evaluate specific hypotheses regarding the vermis/posterior distinction in relation to model-based and model-free social and affective behaviors, and evaluate the associated functional and effective connectivity patterns, most notably between posterior cerebellum and the limbic and cortical systems. Neurostimulation studies could causally assess these predictions by targeting lateral and/or medial cerebellum thereby modifying the balance between model-based and model-free behaviors (Klaus & Schutter, 2022).

In terms of the repercussions of this model for cortical processing there are two targets that warrant first attention. As discussed earlier we consider threat reactivity and reinforcement learning as building blocks for social decision making and ToM. The cortical areas typically linked to these complex social behaviors are the vmPFC (Gangopadhyay et al., 2021), STS and TPJ (Henry et al., 2015; Alcalá-López et al., 2019). As described above these areas are targets for cerebellum-amygdala interactions, both in terms of model-based and model-free processing (see also Fig. 1). Indeed, amygdalar connections to the vmPFC are central to our model representing how a balance of model-free and model-based input resulting from cerebellum-amygdala interactions can inform social decision-making. Connections towards ToM related areas in the temporal cortex, particularly the TPJ, are less straightforward to describe, but the evidence above discussing how the cerebellum is involved in social mentalization yields several testable hypotheses. More specifically, one could expect that upregulation of the model-based cerebellar stream increases control over impulsive behaviors and augments instrumental motivations in social decision making (vmPFC) as well as increasing the ability to relate to, and take the perspective of, others (STS and TPJ). Likewise, upregulation of the model-free stream should result in opposite effects.

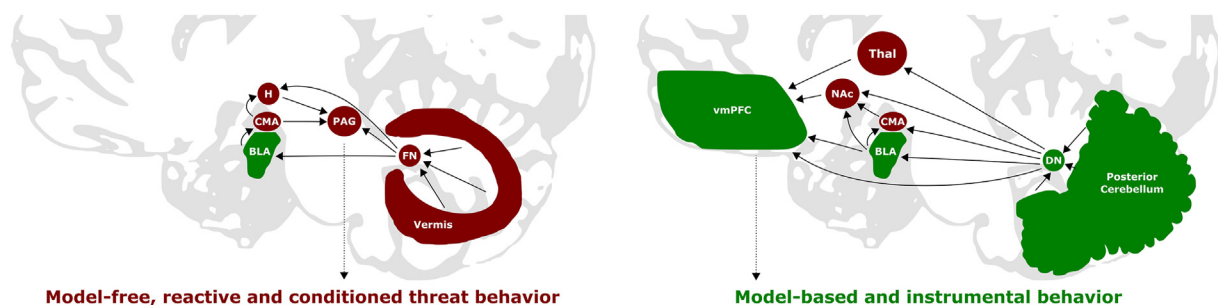


Fig. 1 – Schematic illustration of how the cerebellum and amygdala interact to support social and affective behavior. **Left panel:** The vermis, via the fastigial nucleus (FN), modulates the reactive threat system directly, via the PAG and hypothalamus, in support of reflexive threat reactivity and model-free behavior. Direct and indirect (via the thalamus, not shown here) projections to the BLA (and hippocampus) support emotion regulation and threat conditioning. **Right panel:** Posterior cerebellum modulates goal-directed behavior by connecting to both amygdala subregions as well as NAc and extensive limbic and prefrontal and temporal cortical connections (here represented by, but not limited to, the vmPFC via the thalamus). These projections potentially push the system towards model-based instead of model-free behavior, which supports ToM (via the STS and TPJ) and outcome-based decision-making (via the vmPFC).

Finally, the balance of model-free and model-based processes that underlie social decision-making and ToM at the cortical level has relevance for social and affective disorders. For example, behaviors associated with aggression-related disorders can be categorized as either reactive or instrumental. The first being a result of exaggerated threat reactivity or lack of control thereof, and the second linked to lack of affective empathy and decision-making towards personal outcome optimisation without considering the consequences for others (Blair, 2013; Henry et al., 2015; Terburg et al., 2009). In line with the above one could thus hypothesize that stimulation of the model-free cerebellar pathways will increase reactive aggression. Moreover, given that in our model cerebellar activity is also linked to ToM, a cognitive component of empathy, stimulation of the model-based pathways may result in increased instrumental aggression. Herein, the effects on the vmPFC might promote model-based decisions in favor of the self and the effects on the temporal areas may help to understand others' intentions and motivations. Together these could underlie the manipulative behaviors associated with instrumental aggression and psychopathy.

6. Conclusion

In this paper we have argued that the amygdala and cerebellum influence similar social and affective behaviors from the observation that they share phylogenetical, anatomical, and behavioral characteristics. We have combined these lines of evidence into a novel framework that describes how the cerebellum interacts with the amygdala on the behavioral level. This theoretical framework is applicable to many forms of social and affective behaviors, ranging from threat-reactivity to social decision making and theory of mind, which guides the formulation of novel testable hypotheses and scientific research. As such, we hope that this paper provides new directions to study the interplay of the amygdala and cerebellum in the coordination of human social and affective behavior.

CRedit authorship contribution statement

David Terburg: Writing – original draft, Writing – review & editing. Jack van Honk: Writing – review & editing. Dennis J.L.G. Schutter: Writing – original draft, Writing – review & editing.

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