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The Emotional Cerebellum

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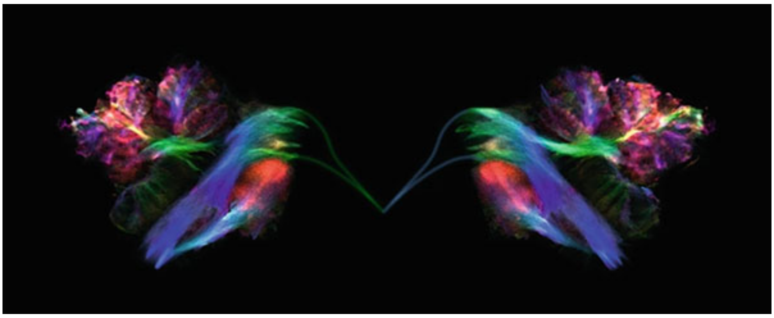

Hummingbirds. Colour-coded tract-density images generated from 0.8 mm diffusion-weighted MRI in a single healthy participant. Sagittal slices include depictions of fibres in the brainstem (coloured blue, running infer/superior), pons (red, medial/lateral), and cerebellum—with the superior cerebellar peduncle in green traversing from the cerebellum into the brainstem. 2021, Christopher J. Steele, Concordia University, Montreal, Quebec, Canada

Foreword

Homo sapiens

Cerebellum research is at a point where the close ties between the social-emotional cerebellum and the evolutionary rise of *Homo sapiens* can begin to be revealed. This idea is strongly supported by the detailed and verifiable paleontological analysis of the progression of socially, emotionally intense stone-tool making and the resultant capacities of the social-emotional cerebellum. These capacities drive uniquely human cumulative culture, the accumulated elaborations of culture we all share. The relatively new discipline of neuroanthropology (the study of the relationships between the brain and cumulative culture) proposes that the progressive evolution of stone-tool making was largely behind the evolution of *Homo sapiens*. This paleontological story can suggest that it is the social and emotional prediction capacity of the cerebellum that is to a very great extent behind the sapience we see in the astounding mental and technological elaborations of cumulative culture.

Linnaeus (1758) with limited knowledge of the brain in his time could only roughly refer to our species, with its great accumulation of culture, as *Homo sapiens*. However, the collective significance of the chapters of this book provides evidence that strongly supports the idea that the emotional, cognitive, and social functions of the *cerebellum* can be said to be the fundamental key behind our unique human ability to constantly move toward an optimized cumulative culture. With the tremendous advances in just how the cerebellum contributes to the rise of our cumulative culture consisting of everything from art, music, language, and mathematics to technology that mimics the mind (computers), perhaps it is time to embrace the massive contributions of the cerebellum as Linnaeus might have if he had known what cerebellum research and the authors of this book have provided—might he have understood that the cerebellum plays many key roles in our understanding of the meaning of the “sapience” of *Homo sapiens*?

To stress the important, undeniable relevance of neuroanthropology to the chapters in this book, an example of how learning stone-tool making critically involved social and emotional prediction and control by cerebellar internal models for approximately 2. 6 million years (1.7 million years for advanced stone tools) of adaptive selection is presented. Neuroanthropologists Stout and Hecht’s (2017) careful and detailed study of the extended repetitive practice necessary to stone-tool making is quoted at length so as to make its processes clear to a broad audience of both old and new to cerebellum research. Stout and Hecht refer to stone-tool making as "high fidelity" (imitative) social learning. As an example of this high fidelity social learning they describe how it takes place during the interaction between the learner and the teacher—that is, as we now know, how this interaction is modeled in the cerebellum:

> Knapping is a "reductive" technology involving the sequential detachment of flakes from a stone core using precise ballistic strikes with a handheld hammer (typically stone, bone, or antler) to initiate controlled and predictable fracture. This means that small errors in strike execution can have catastrophic, unreversible effects [*Thus (1) requiring intense-precise elaboration of theory of mind (ToM) which the learner must apply to the likely mental processes of the teacher, and (2) shaping emotional-motivational states in the learner's autobiographical knowledge base—i.e., knowledge of past and future action/interaction sequences related to the self*[1]]. Experiments by Bril and colleagues have shown that fracture prediction and control is a demanding perceptual-motor skill reliably expressed only in expert knappers. Building on this work, Stout and colleagues found that even 22 mo ($\bar{x}$= 167 h) of knapping training produced relatively little evidence of perceptual-motor improvement, in contrast to clear gains in conceptual understanding. (Stout and Hecht, 2017, Vandervelt L., 2019)

> The key bottleneck in the social reproduction of knapping is thus the *extended practice* [italics added] required to achieve perceptual-motor competence. This requires mastery of relationships, for example between the force and location of the strike and the morphology, positioning, and support of the core, that are not perceptually available to naïve observers and cannot be directly communicated as semantic knowledge. Attempts to implement semantic knowledge of knapping strategies before perceptual-motor skill development are ineffective at best, and such knowledge decays rapidly along knapping transmission chains when practice time is limited, even if explicit verbal teaching is allowed. *For observational learning, the challenge is to translate visual and auditory information of another's actions to appropriate motor commands for one's own body. This may be accomplished by linking the observed behavior with preexisting internal models* [Stout and Hecht are referring here to internal models in the cerebral cortex and not in the cerebellum] *of one's own body and actions through associative learning and stimulus generalization* [italics added]. Novel behaviors are copied by breaking them down into familiar action elements (e.g., lift, turn, twist), matching these, and reassembling. (pp. 7862-63). (Stout and Hecht, 2017, Vandervelt L., 2019)

We now know that what Stout and Hecht referred to as associative learning and stimulus generalization in the italicized portion immediately above are more correctly understood as the learning of internal models in the cerebellum. While Stout and Hecht did not mention the cerebellum in their research, the implications of this 2.6/1.7 million years of socially driven adaptive focus of thousands of generations of learners on the detailed bodily movement and facial expressions of the teacher for the evolution of the social cerebellum are obvious.

At the beginning of their above quote, Stout and Hecht (2017) pointed out that learning highly repetitive stone-tool knapping is a situation where "small

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[1] In keeping with the stone-tool evolution view of the evolution of autobiographical knowledge, it is important to point out that autobiographical knowledge consists of components which span (somewhat in the order of increasing optimization of forward control) the evolution of *Homo sapiens*, namely, spatial-visual, semantic episodic, and semantic conceptual. See Martinelli P, Sperduti M, & Piolino P. (2013). Neural substrates of the self-memory system: new insights from a meta-analysis. *Human Brain Mapping,* 34: 1515–1529. DOI: 10.1002/hbm.22008 for a discussion of these components of autobiographical knowledge.

errors in strike execution can have catastrophic, unreversible effects." For the learner, anticipation of such catastrophic effects would be quite emotionally stressful, and even for accomplished stone knappers this anticipation and emotional stress would be present, but controlled by elements of autobiographical knowledge (e.g., semantic knowledge of autobiographical knowledge manipulated in self-talk) containing the likelihood of predictive precision. Thus, cerebellar control of emotion during both this stressful social observation and solitary practice would have been selected in the evolving cerebellum.

Astonishing Parallels from Cerebellum Research

Although arrived at through a completely different disciplinary perspective, this idea and the italicized portions of the above quote fit astonishingly well with Van Overwalle, Manto, Leggio, and Delgado-Garcia's (2019) description of the social cerebellum's prediction of social-emotional states of others through the learning of theory of mind (ToM) and its relationship to the likewise cerebellar construction of an autobiographical self. ToM refers to one's mental simulative capacity to make inferences about the mental states of others. Van Overwalle, Manto, Leggio, and Delgado-Garcia argued that the cerebellum plays the following roles in the construction and manipulation of ToM and autobiographical knowledge:

> We hypothesize that the cerebellum acts as a "forward controller" of social, self-action and interaction sequences. We hypothesize that the cerebellum predicts how actions by the self and other people will be executed, what our most likely responses are to these actions, and what the typical sequence of these actions is. *This function of forward controller allows people to anticipate, predict and understand actions by the self or other persons and their consequences for the self, to automatize these inferences for intuitive and rapid execution, and to instantly detect disruptions in action sequences*.... The cerebellum would be a "forward controller" that not only constructs and predicts motor sequences, but also takes part in the construction of internal models that support social and self-cognition. In this respect, the cerebellum crucially adds to the fluent understanding of planned and observed social interactions and contributes to sequencing mechanisms that organize autobiographical knowledge. Because the fundamental organization of the cerebellar circuitry is identical in many species adopting social behaviors, our hypothesis can also be valid throughout the animal kingdom. (p. 35) (Van Overwalle F, Manto M, Leggio M, Delgado-García, 2019, Vandervelt L., 2019)

Elsewhere in their 2017 earlier quoted article Stout and Hecht argued that the learning of stone-tool making required a good share of both observational learning of sequences of action (as described directly above) and *solitary* practice to refine the details necessary to those sequences; they suggested deliberate practice. In deliberate practice as described by Ericsson, Roring, and Nandagopal (2007), the learner focuses attention on self-perceived weak aspects of their performance that are related to the attainment of the teacher's level of performance. It is my view that autobiographical knowledge is what was adaptively selected in the evolution of this powerful and necessary solitary practice, because it resulted in learners that were both motivated and able to institute self-driven practice toward the level of precision and goal attainment they had observed in the teacher. As a footnote here, it is important to note that Van Overwalle et al.'s above final sentence concerning organization of cerebellar circuitry throughout the animal kingdom would of course apply to any species of early Homo that originated stone-tool making 2.6/1.7 million years ago (i.e., any pre-Homo *sapiens* species).

These overall connections place the evolution of stone-tool making as a verifiable framework through which to further understand why the cerebellum would be importantly involved in emotional aspects of theory of mind and autobiographical knowledge and therein to possibilities of disorders as described by Schmahmann's "cerebellar cognitive affective disorder" (CCAS). The importance of these points, while providing important evolutionary background for cerebellum researchers, is that it can alert whole new audiences of readers to the chapters of this book and to their significance in understanding the roles of the cerebellum in the evolution of cumulative culture. It does this specifically because it reveals where and how advances in ToM and linked autobiographical knowledge that are essential to the motivation for solitary practice (and resultant skill optimization) took place in the cerebellum among *Homo sapiens*. Since these cerebellar capacities can reasonably be seen as the marks of our species' evolution of progressive cumulative culture, this suggests that in actuality we are to a great extent *Homo sapiens* due to the evolution of the social/emotional contributions of the cerebellum. This newer understanding of *Homo sapiens* can focus study on new aspects of the prehistory, history, and future development of our species. The chapters of this book represent important steps in that direction and should be of strong interest to a broad audience of readers including those in anthropology, cognitive neuroscience, neuroanthropology, psychology, and a variety of studies of deliberate practice in the field of education.

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Part I

Basic Principles of Cerebellar Function in Emotion

1

Introduction into the Role of the Cerebellum in Emotion

Michael Adamaszek, Mario Manto, and Dennis J. L. G. Schutter

Abstract

The cerebellum is well known for its contribution to motor performance, but less for its involvement to cognitive and affective processing. The growing interest of clinical and neuroscientific research has resulted in a fascinating focus on the cerebellar mechanisms of emotion. Advances in functional neuroimaging and noninvasive stimulation protocols have successively delineated circumscribed cerebellar areas with its functional and topographic connections to the conventionally predominating cerebral cortex in basic as well as high order emotion processing. This encompasses all information processing stages which include perception and attention, and the evaluation and integration of emotion cues to the trajectories in motor, cognitive, and affective behavior. Not surprisingly, research has identified the cerebellum being part of the brain's network associated with art, morality, and social cognition. This book will provide an overview of the details of these intriguing issues, supporting a contemporary understanding of the fundamental as well as specific features of cerebellar functions within emotion processes.

Keywords

Behavior · Cerebellum · Emotion · Neuroscience · Psychology

The cerebellum with its role in mental functions gains considerable attention in the rapidly expanding field of fundamental and clinical neuroscience. The previously predominant understanding of the cerebellum was in the context of motor-related behavior and considered to be the sole cerebellar function in clinical neurology. However, this traditional view is now increasingly challenged and the cerebellum is now receiving increasing attention by the scientific community as a brain region that contributes to a broad spectrum of non-motor areas as well. The idea that the cerebellum plays a role beyond being a hub within the complex neural networks of the primary and supplementary motor cortex is to a significant extent due to modern experimentation, such as functional magnetic resonance imaging, which has revealed cerebellar involvement in neural processes of related non-motor behaviors. These discoveries have led to a critical review and reappraisal of the classical view of the cerebellum

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as entirely a motor-dedicated region in the last three decades. The view that the cerebellum is a brain structure primarily devoted to motor functions is no longer attainable.

The idea that the cerebellum is also involved in the perception and processing of emotions is not new and can already be traced back to early observations in the 1940s, potentially representing a first step toward a systematic neuroscientific evaluation on this idea. For example, Moruzzi (1941, 1947) and also Zanchetti and Zoccolini (1954) reported autonomic hypothalamic outburst and rage-like behavior in response to electric stimulation of the cerebellum. These findings concur with a subsequent outlining of Anand et al. (1959) that the cerebellum has connections to the limbic system, providing a neuroanatomical basis for a role in the emotion-dedicated subcortical circuits. Just a few years later, Prescott (1970) hypothesized that the cerebellum is involved in virtually all aspects of emotion, acting as a “master integrator of regulatory systems for sensory-emotional and motor processes.” This concept reflects the growing systematic investigation within neuroscience, provided by the following research line of Heath and his findings on cerebellar implementation in affective behavior (Heath et al. 1978; Heath et al. 1980). Furthermore, Leiner et al. (1986 and 1989) in the 1980s outlined the observations that in parallel with the cerebral cortex the cerebellar hemispheres and dentate nuclei underwent huge volumetric expansions in the course of human evolution. These observations provide a possible phylogenetic account for the involvement of the cerebellum in cognition and emotion. Leiner et al. hypothesized that these cerebellar regions project to prefrontal and other association cortices in humans and higher primates, forming closed cerebello-cortical loops (Fiez 1996). It was suggested that cerebellar damage could compromise the integrity of the cerebello-cortical system and as a net result leads to cognitive impairments (dysmetria of thought). This possibility was further elaborated by the pioneering work of Schmahmann that started back in the 1990s and has continued to the present day (Schmahmann and Sherman 1997, 1998; Schmahmann 2010; Schmahmann et al. 2019). In line with the fast development of experimental human brain research from the 1990s onward, empirical studies confirmed that the cerebellum contributes to high-level cognitive and affective domains. Indeed, the large body of available scientific data indicates that the cerebellum is part of the distributed cortico-limbic networks involved in perception, attention, language, appraisal, feelings, and cognitive control and regulation processes as part of the brain’s executive functions (Habas et al. 2009; Buckner 2013; Schmahmann et al. 2019). In terms of the evolutionary trajectory of the human brain, there is some evidence that both the parietal cortex and the cerebellum have undergone the comparatively largest growth rate in terms of developmental history (Neubauer et al. 2018), which is unlikely a coincidence. At the same time, the strong forward and feedforward connections between the prefrontal cortex and the cerebellum were highlighted in various works (e.g., Middleton and Strick 2001). Indeed, research in primates has successively outlined that the posterior and particularly the lateral parts of the cerebellum have expanded disproportionately in the human brain, and are interconnected with the cerebral cortex covering a wide range of attention and control-related functions of the fronto-parietal networks (Strick et al. 2009; Marek et al. 2018). Involvement of the cerebellum in development of visuospatial processing, working memory, executive functions, theory of mind, and the conscious experience of emotions and feelings is suggested to stem from an increase in social interactions and communication when humans transitioned from living in solitary to living with fellow members and form groups (Neubauer et al. 2018; Marek et al. 2018).

The cerebellum or little brain is a neural structure located in the posterior fossa of the skull beneath the tentorium and the occipital lobe of the cerebral hemisphere (O’Hearn and Molliver 2001). The adult human cerebellum accounts for approximately ten percent of total brain volumes. Despite its modest size, the cerebellum contains more than half of the total neurons present in the human brain (Azevedo et al. 2009).

Phylogenetically, the posterolateral parts of the cerebellum have, in concert with the cerebral cortex, undergone a rigorous volumetric expansion (Balsters et al. 2010; Weaver 2005). Interestingly, a recent successful attempt to unfold the complex and intricated cerebellar cortex revealed that its surface is almost 80 percent of the total surface of the cerebral cortex (Sereno et al. 2020). In addition to the three-layered cortex, the cerebellum consists of deep cerebellar nuclei (DCN) and white matter (O'Hearn and Molliver 2001). The DCN consists of four paired deep gray matter nuclei called (1) the fastigial nuclei, (2) the globose nuclei, (3) the emboliform nuclei, and (4) the dentate nucleus. Together they form the sole output regions of the cerebellum. The relatively homogenous cellular composition of the cerebellar cortex comprises an outer molecular layer made up of axons and dendrites of cerebellar neurons and interneurons consisting of basket and stellate cells, a Purkinje cell layer, and a granular layer made up of granule cells and Golgi interneurons. In terms of its evolution, the cerebellum can be divided into three more or less distinct regions: the archicerebellum (flocculonodular lobe), paleocerebellum (anterior part of the cerebellum and vermis), and neocerebellum (posterolateral hemispheres) (O'Hearn and Molliver 2001). The archicerebellum, the phylogenetically oldest part of the cerebellum, is connected to the vestibular system and reticular formation in the brainstem. The paleocerebellum has connections to the spinal cord, brainstem, as well as subcortical structures (Schutter 2013). The neocerebellum as the phylogenetically youngest part of the cerebellum is evolved in concert with the cerebral cortical association areas to form closed cerebello-thalamo-cortical loops (O'Hearn and Molliver 2001). While there exist several taxonomies, the cerebellum is most commonly divided into a series of lobes and lobules. The anterior lobe consists of lobules I–V and is anatomically separated from the posterior lobe by the primairy fissure, whereas the posterior lobe consists of lobules VI, Crus I and II, VIIB, VIII–IX, and the flocculonodular lobe has been labeled lobule X, respectively (O'Hearn and Molliver 2001).

The trafficking of incoming and outgoing signals occurs along three white matter bundles known as the cerebellar peduncles. The inferior cerebellar peduncle (restiform body) is a cordlike bundle of afferent and efferent white matter fibers that connects the medulla oblongata with the cerebellum. The middle cerebellar peduncle (brachium pontis) connects the cerebellum to the pons and is composed entirely of afferent (input) fibers. Finally, the superior cerebellar peduncle (brachium conjunctivum) consists of efferent fibers and constitutes the output channel of extracerebellar areas. Figure 1.1 shows the main anatomical components of the cerebellum.

The notion of cerebellar contributions to human emotions was decisively established by the seminal neuropsychological study by Schmahmann and Sherman (1998). The authors assessed in detail the clinical findings of cognitive impairments as well as changes in affective behavior following cerebellar lesions. The so-called cerebellar cognitive-affective syndrome (CCAS) or Schmahmann's syndrome has been validated by a multitude of clinical and imaging studies. The corresponding affective components of Schmahmann's syndrome include personality changes, behavioral disinhibition, inappropriate behavior, altered mood regulation, anger, blunting of affect, pathological crying and laughter, obsessive-compulsive tendencies, and psychotic thinking (Schmahmann 2004). The emotional disturbances were mainly observed in relation to damage to the vermis, which predominantly projects to autonomic, reticular, and limbic brain regions. The number of neuroimaging studies on the individual topographic and temporal connections of certain domains of emotion processing has led to a rethinking of the neural mechanisms underlying the recognition, experience, and regulation of emotions (Schutter, 2019). In the meantime, the significance of the prefrontal cortex (PFC), notably the dorsolateral prefrontal cortex (DLPFC), orbitofrontal (OFC) and ventromedial (vMPFC), and the anterior cingulate cortex (ACC) in the attention, motivation, and emotion-related processes, has been established. Furthermore temporally and spatially bound activities of subcortical areas such as the amygdala and sections of the basal ganglia have

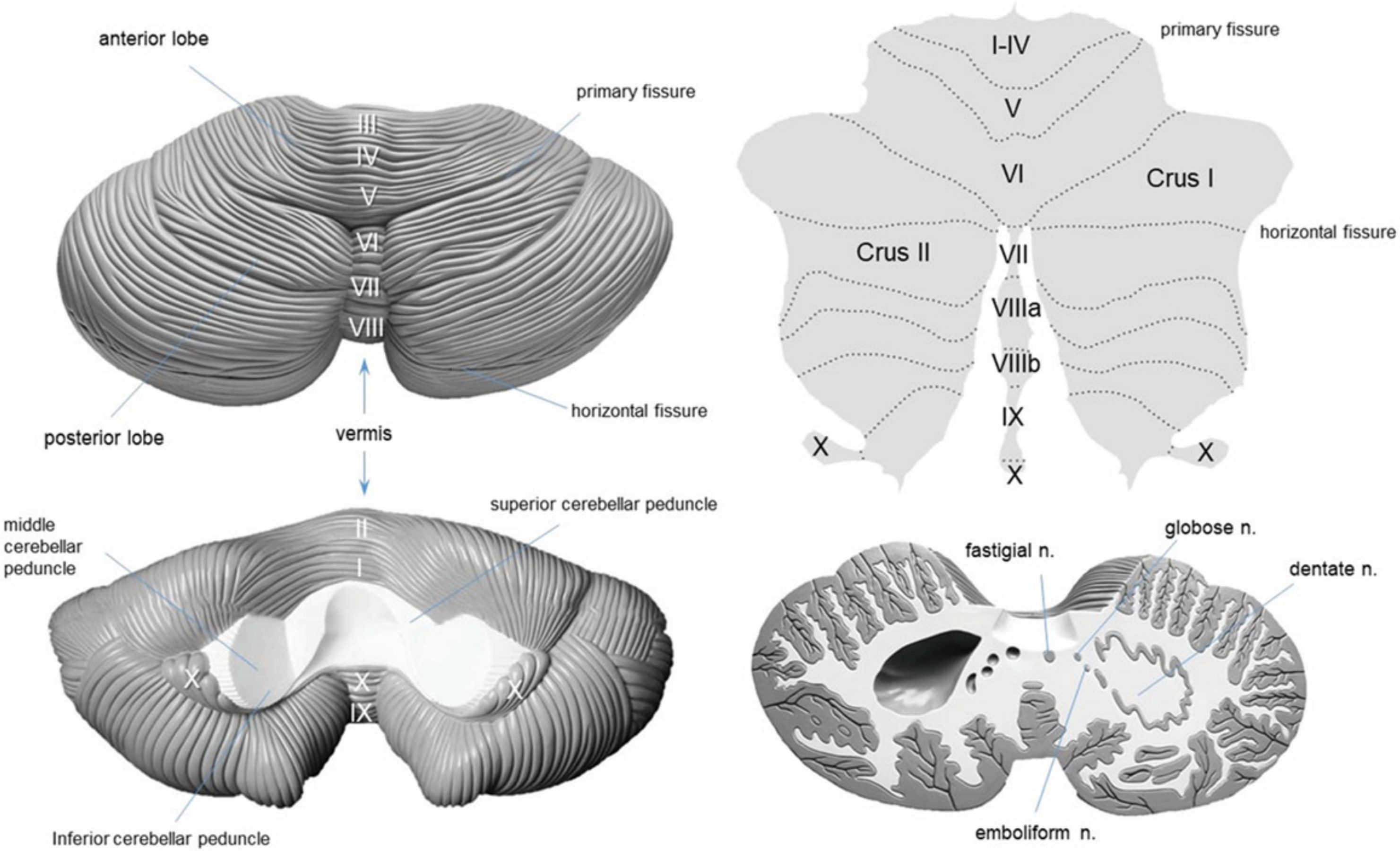

Fig. 1.1 Gross neuroanatomy cerebellum

been highlighted (LeDoux 2000; Pessoa 2013). Along the growing awareness to functionally integrate the various subcortical and cortical networks to better understand the neurological basis of emotion, the cerebellum is increasingly recognized as playing a significant role in this functional integration process (Stoodley and Schmahmann 2009; Buckner 2013; Adamaszek et al. 2017). It can now be readily assumed that distinct areas of the cerebellum are part of distinct cerebello-cortico-limbic circuits, integrated in larger, broadly extending networks with a focus within cerebral fronto-parietal, fronto-temporal, and parieto-temporal axis systems of the brain. These axes arguably represent higher-order associative connections as the neural basis of the individual functional performances of specific cognitive and affective domains (Schmahmann 2010; Adamaszek et al. 2017; Argyropoulos et al. 2020; Schmahmann et al. 2019).

Based on the work of Schmahmann as well as the systematic investigations of other groups worldwide, the existence of discrete functional areas of the cerebellum has paved the way for new insights into cognition- and emotion-based higher order mental phenomena that include empathy, theory of mind, moral judgment, and action. Indeed, several individual posterior cerebellar sections, including lobule VI, Crus I and II of lobule VII, and also parts of lobule VIII, have been shown to be embedded in a complex system consisting of a wide array of neural circuits that operate as functional modules in a decentralized, highly parallel fashion selectively engaged by environmental demands to produce adaptive behavior (Ito 2008; Schmahmann et al. 2019). The importance of the cerebellum in emotion and social cognition is further illustrated by the growing number of empirical studies (Van Overwalle et al. 2020). For example, a large number of available scientific studies have established the significance of the cerebellum as part of distinct neural networks in the recognition and processing of emotional facial expressions (Kilts et al. 2003; Fusar-Poli et al. 2009; Schutter et al. 2009; D'Agata et al. 2011; Ferrucci et al. 2012; Adamaszek et al. 2014, 2015). Yet, other studies have examined the contributions of the lateral hemispheric regions of the cerebellum for attending to emotionally laden salient cues (Adamaszek et al. 2013; Turner et al. 2007; Styliadis et al. 2015). Results showed that predominantly posterior parts of the cerebellum, including vermal area of lobule VII with its Crus I and II, contribute to the discrimination of salient cues as well as facial and acoustic expressions of emotions across different valence and arousal levels. Even though the contributions of the vermis and fastigial area of the deep cerebellar nuclei were not considered, the relationship between the neocerebellum and the predominantly prefrontal and parietal components of emotion recognition in particular to its inclusion of affective ingredients in object perception and evaluation further underlines the functional significance of the cerebellum in emotions.

A turning point in the transition from the motor-centered view toward a modern understanding of the cerebellum as a distinct part of the neural circuits dedicated to higher-order processes may have been the work by Parsons and Bower during the end of the nineties of the last century and the first decade of this century. Their observations and reflections on cerebellar activities and sensory process pathways introduced a new way of thinking with a greater focus on sensory-receptive and integrative functions of the cerebellum (Parsons et al. 2009). This novel approach is in agreement with the idea that the posterior cerebellar hemispheres and their functional connections to the parietal and prefrontal regions play an active role in the regulation of task-related activity of the specialized cerebral networks. Moreover, the integration and control of cognitive and affective contextual factors of a perceived sensory event are of further importance for selecting the optimal behavioral response. To this end, the responsible cerebral fronto-parietal networks arguably include reciprocal pathways to specific locations in the vermis and posterolateral hemispheres of the cerebellum (Leiner et al. 1986; Ivry and Fiez 2000; Demirtas-Tatlidede and Schmahmann, 2013; Argyropoulos et al. 2020). In support of the latter notion, the posterior parts, especially lobule VII with Crus I and II, in cognitive and affective tasks, but also vermis and its connections to the limbic networks, are assumed to be involved in the processing of visceral, autonomic, and other emotion-relevant information (Habas et al. 2009 and Adamaszek et al. 2017; Stoodley and Schmahmann 2009; Koziol et al. 2014). Considering the putative role of the cerebellum within the presumed cerebello-cortical integration of functions, the cerebellum deems to support the brain's operative and predictive functions. In addition, the cerebellum is considered to be part of an internal model in which specific cerebellar units guide the precise representation of sequential and temporal information of exteroceptive and interoceptive signals in response to task-related cognitive and affective processes (Ito 2008). According to Ito (2008), the cerebellum with its evolutionary developed access to specific neural network provides a synchronized tracking and controlling of the interrelated activities between the perception of an object and its subsequent processing stages. This particular neural tracking is supposed to be in dependency of different manipulations of mental representations within specialized cerebellar areas in favor to gain an optimal behavioral response based on the integration of sensory, affective, and cognitive signals. This might even represent a fascinating and animating hypothesis that would fit the idea of specific cerebellar contributions to executive networks in face of increasing function complexity (D'Angelo and Casali 2013; Adamaszek et al. 2017), regulating the speed, smoothness, and finally the appropriateness and accuracy of the processes in the cerebral cortex, providing for a skillful execution including its related affective constituents during the early and late processing stages (Leiner et al. 1986; Schmahmann 2010). Accordingly, the assumption of a central cerebellar executive, that is the active process of adapting ongoing behavior to subsequent and forthcoming sequelae, points to a generic property of a predictive interface in task-dependent neural networks to anticipatory adjustments at the level of the cerebral cortex to maximize current and future task performance (Ivry and Fiez 2000; Ito 2008). Moreover, this proposal is strengthened by empirical observations showing that cerebellum topographically maps to the central executive control networks (ECN), the default network (DMN) (Habas et al. 2009; Krienen et al. 2009; Brady et al. 2019), and attention networks (Allen et al. 1997; Akshoomoff and Courchesne 1994; Breska and Ivry 2020) (for an overview, see Table 1.1).

In keeping with the growing body of knowledge about the role of the cerebellum in high order mental functions of the brain, the "emotional" cerebellum might operate at several specific and non-specific levels along the responsible large-scaled networks along the lateral and medial prefrontal as well as parietal areas. Besides the structural and functional neuroanatomic descriptions with a focus on the vermis and paravermal areas, lobules VI–VIII including Crus I and II, and the deep cerebellar nuclei, the mechanisms of action, including its sequential and time-dependent operation modes, are of particular interest in decoding the cerebellar activation patterns associated with the generation, experience, and regulation of emotions. This volume offers novel and unique insights into the hitherto available positions of the contributions and responsibilities of the cerebellum in affective processing by covering the basic and advanced facts and notes in contemporary neuroscience. In this volume, we would like to take the reader on a journey that goes beyond the conventional cortico-limbic oriented theories of emotion. The structural and functional neuroanatomic foundation of the cerebellum in emotion is first discussed by Marine Thomasson and Julie Péron in Chap. 2. In Chap. 3, Oliver Baumann and Jason Mattingley provide an account of the cerebellum in emotion processing by separately evaluating its impact for components of emotion processing. These components include physiological responses, emotional expressions, and the cognitive appraisal processes that influence the generation, experience, and regulation of emotions. Federico D'Agata and Laura Orsi discuss the cerebellar correlates of emotion recognition in Chap. 4. Emotional learning and memory is the main topic of Chap. 5 covered by Melanie Mark, Johanna Pakusch, Thomas Ernst, and Dagmar

Table 1.1 Brain regions and associated (not exhaustive) main functional correlates discussed within the context of the cerebellum and emotion

	Structure	Associated functional correlate(s)
1	Amygdala	Relevance detector; emotional learning; emotion perception
2	Anterior cingulate cortex	Outcome anticipation; performance monitoring; vigilance
3	Striatum	Habit; learning; reward; action selection
4	Pallidum	Regulation of voluntary movement
5	Subthalamic nucleus	Suppression of unwanted movements
6	Substantia nigra	Dopamine production site; initiating movements; learning
7	Hippocampus	Learning; memory
8	Hypothalamus	Regulation of metabolic and endocrine processes; circadian rhythms
9	Insula	Disgust; taste; interoception; bodily homeostasis
10	Nucleus accumbens (ventral striatum)	Reward reinforcement; liking
11	Parietal cortex	Sensory integration; visuospatial attention
12	Pons	Regulation and control of vital bodily functions
13	Prefrontal cortex	Executive and regulatory functions
14	Reticular formation	Arousal
15	Septum pellucidum	Pleasure; reward; reinforcement learning; prosocial behavior
16	Temporal cortex	Language; object recognition
17	Thalamus	Relay station
18	Ventral tegmental area	Reward; sex; motivational salience; positive emotions; associative learning

Timmann who provide a comprehensive overview of the basic cerebellar mechanisms. The neurotopographical and neurophysiological aspects of the cerebellum will be covered in chapters 6–8. Christophe Habas will provide an overview of the complex neural topography of individual fiber bundles and their connections to the cerebral cortical networks within the context of emotion recognition, emotion processing, and behavior. Michael Adamaszek and Ken Kirkby focus on electrophysiological signatures of emotion recognition and processing to reveal their temporal dynamics in which the cerebellum plays an important role. Corresponding to the more spatial aspects as outlined by Christophe Habas, and the more temporal aspects of cerebellar involvement in the specific network activities in emotion processing as explained by Michael Adamaszek and Ken Kirkby, Jana Klaus, and Dennis Schutter elaborate on the now respectable knowledge of noninvasive brain stimulation approaches to the cerebellum in the modulation of emotion functions and the possible future therapeutic aspects of the treatment of emotion processing disorders. The third section of the book is devoted to the involvement of cerebello-cortical networks in higher-level domains of emotion processing. In Chap. 9, Jordan Pierce and Julie Péron discuss the role of the cerebellum in habit formation by way of monitoring and modulating precisely timed sequences of events using prediction and reward-based error feedback signals. In Chap. 10, Chiara Ferrari, Andrea Ciricugno, and Zaira Cattaneo provide an account of the cerebellum contribution to the processes underlying the complex details of body language perception and emotion. Chapter 11 authored by James Houston, Jahangir Maleki, Frank Loth, Petra Klinge, and Philip Allen in Chap. 11 addresses the growing insights of the cerebellum in various aspects of pain processing. In Chap. 12, Hyemin Han follows up by discussing what cerebellar aspects are known for the neural mechanisms of morality, and what the possible implications may be for ongoing and outstanding research. Specific functions of the cerebellum with regard to the brain's sensory processing pathways that, in addition to cognitive ones, have a high emotional component and separately characterize social development, which are highlighted in chapters 13 and 14. Stefan Evers and Bernadette Tölgyesi in Chap. 13 summarize the cerebellar features in neural networks of music perception, whereas Chap. 14 of Michael Adamaszek, Zaira Cattaneo, Andrea Ciricugno, and Anjan Chatterjee captures the hitherto little-known cerebellar functional components in the perception and processing of visual art and creativity. Silvia Clausi, Michaela Lupo, Giusy Olivito, and Maria Leggio summarize the complex body of empirical work on the cerebellum and social behavior, and offer explanations for cerebellar-based impairments in the social-affective domain related to neurological and psychopathological conditions. In Chap. 16, Daniela Laricchiuta, Eleonora Picerni, Debora Cutuli, and Laura Petrosini review their comprehensive work on cerebellar aspects of higher-order emotion processes and address how the embodiment approach may represent a unifying perspective for examining the cerebellar role in emotional behavior and psychological traits.

The fourth and final section of this volume deals in two separate chapters with aspects of the cerebellum that are particularly relevant for the clinical fields of neurology, psychiatry, and clinical psychology, and which therapeutic options currently might be feasible. Dennis Schutter presents in detail the clinical and imaging knowledge to date on the characteristics and peculiarities of emotion disorders, which are of significant importance especially with regard to clinical assessment and possible therapeutic applications. Kim van Dum, Mario Manto, and Raf Meesen conclude in their chapter on these clinical aspects of disorders of emotion recognition and emotion processing with a focus on the rehabilitative application possibilities, which have not been attempted in this form so far. In many respects, this chapter covers the often lamented discrepancy between the functional disorders described in clinical and neuroscientific work in the case of circumscribed or diffuse damage within the cerebellum and the necessary treatment possibilities of function restoration or compensation.

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2 Principles of Brain and Emotion: Beyond the Cortico-Centric Bias

Marine Thomasson and Julie Péron

Abstract

Affective neurosciences have largely contributed to the elaboration of theoretical and neuroanatomical models through research conducted in non-primate animals and human beings. However, for methodological and historical reasons, knowledge has developed by focusing mainly on the cerebral cortex, resulting in a lack of investigations of the functional aspects of subcortical structures such as the cerebellum and the basal ganglia. The close anatomical connections revealed between these two structures, as well as their reciprocal connections with the cerebral cortex, lead to a vertically organized model of the brain. Both the cerebellum and the basal ganglia are involved in the different components required during an emotional episode. Their respective specificity in the analysis of temporal patterns contributes to the optimal processing of emotional signals such as those that can be conveyed by the voice (emotional prosody). Internal temporally structured event representation, built from the salient modulation extractions performed by the cerebellum, is used by the basal ganglia to recruit and synchronize the activity of the cortical and subcortical structures required for the relevant processes.

Keywords

Basal ganglia · Cerebellum · Emotional prosody · Cortico-centric · Synchronization

2.1 Introduction

During the last century, affective neuroscience highlighted the complexity of affective processing from a conceptual and neuroanatomical point of view. Current studies have emphasized the involvement of large-scale brain networks in emotional processes, including the limbic system consisting of the thalamus, hypothalamus, hippocampus, amygdala, septum, and cingulate cortex, parts of the basal ganglia (e.g., striatum, internal and external segments of the pallidum), substantia nigra (pars reticulata and compacta), and subthalamic nucleus (Percheron et al. 2012), and finally the cerebellum (Bostan and Strick 2010; Anand et al. 1959). The role of the cerebellum and basal ganglia during emotional processes has been neglected until recently in favor of their motor contribution. The field of human affective neuroscience was indeed largely affected by historical and methodological barriers, discussed later in this chapter, which restricted the exploration of subcortical structures other than the amygdala, a phenomenon called

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the cortico-centric bias. However, in recent years, these obstacles have been overcome, mainly as a result of clinical neuropsychological observations in humans that have allowed researchers to develop theoretical propositions regarding the functional specialization and integration of brain networks beyond the cerebrum, including the basal ganglia and cerebellum, in the synchronization of emotion components. Indeed, componential approaches suggest that emotional processes are elicited and dynamically patterned by involving synchronized changes in distinct functional subsystems including those involved in motivation and motor expression.

In this chapter, we first present the appraisal theory of emotion and one particular model, the component process model (CPM), which is arguably well suited to model and study neural network-inspired approaches. CPM has shown to be particularly heuristic in the development of theoretical models of the functional role of subcortical structures during an emotional episode. In the second section, we show why the basal ganglia and the cerebellum have been neglected in affective neuroscience until recently. Finally, in the third section, we propose an original model, using the example of vocal emotion decoding (i.e., emotional prosody), in light of the different roles fulfilled by what has been called the "vertically organized brain" (Koziol and Budding 2009), which includes the cerebrum, the basal ganglia, and the cerebellum.

2.2 The Neuropsychology of Emotions: Insights from the Component Process Model Framework

Emotions play a central and special role within the cognitive system because most of the psychological mechanisms are either necessary for emotions, influenced by emotions, or involved in the modulation of emotions (Davidson et al. 2004). The models of emotions recently proposed are derived from theories of cognitive evaluation (appraisal) of emotion that suggest that cognitive processing was involved in the origin of emotions (Grandjean et al. 2008). From that perspective, many studies conducted in psychology have contributed to the conceptualization of emotion as a multicomponent phenomenon (Sander and Scherer 2014).

2.2.1 Emotion as a Synchronous Modification of Several Components

According to the CPM (Scherer 1984), emotions can be defined as episodes of synchronized changes occurring in an organism's components that include physiological arousal, cognitive appraisal of the situation, subjective feelings, motor expression, and action tendencies (Grandjean and Scherer 2008). These dynamic processes are produced in response to environmental events, either internal (e.g., thoughts, sensations, or memories) or external (e.g., other people's behavior or changes in situation), which are of significance to that organism (Scherer 2001; Sander and Scherer 2014). For example (see Fig. 2.1), after an individual hears a gunshot, changes will occur at the *physiological level* (e.g., blood pressure and heart rate increase, stress hormones such as cortisol and adrenaline are released); a *cognitive evaluation* of the event will occur (perceptual processing such as the distance from the gunshot, an understanding of the causes and consequences of the event, a link to the well-being and goals of the individual); and an expression of fear can appear on the individual's face, with brow raising and jaw dropping at the *motor level*. In parallel, in this situation, particular *action tendencies* will be prioritized (e.g., avoidant behavior or search for outside help). In addition, a *subjective feeling* will emerge ("I'm afraid") on the basis of the coupling between these components or of dimensions such as valence (i.e., pleasant vs. unpleasant) and arousal (intensity). Thus, when the components of emotion unfold in relative synchrony (or synchronization), a subjective feeling can emerge within an emotional episode and be perceived by the person at the conscious level (i.e., experience of a feeling at time t) (Glauser 2014).

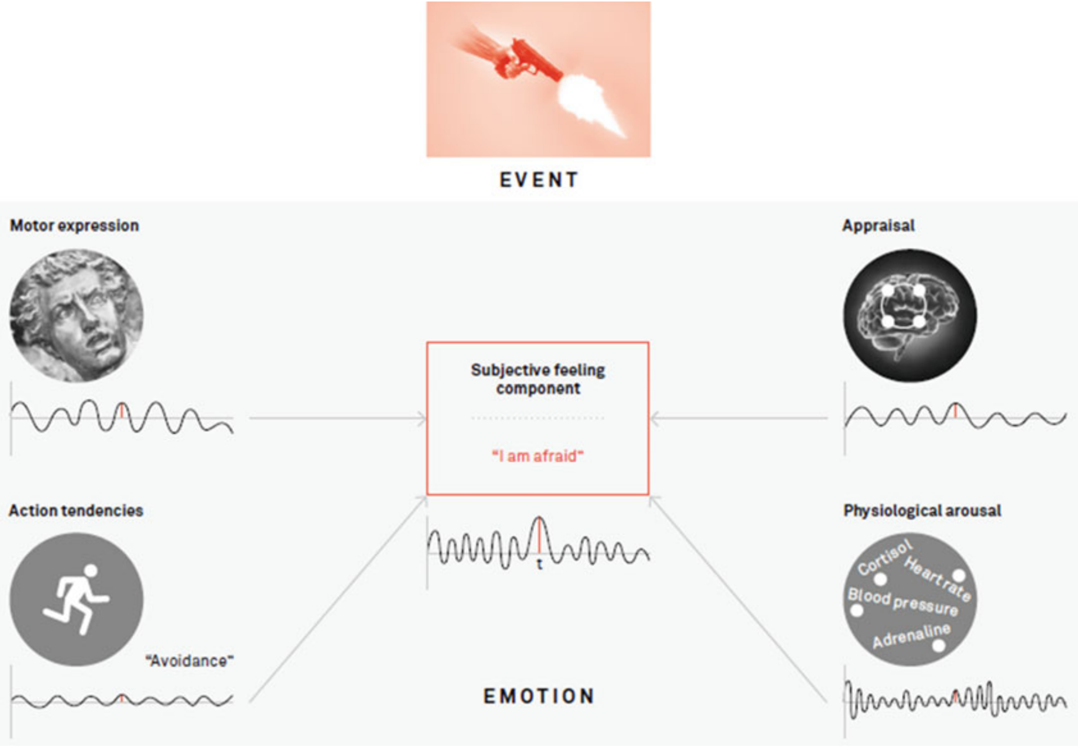

Fig. 2.1 Illustration of emotional component synchronization during the emergence of a subjective feeling following a specific event according to the component process model (Scherer 2001). The synchronization of the components of motor expression, arousal, appraisal, and action tendencies, at time t, allows the production of a conscious subjective feeling

This model therefore suggests processes of synchronization and integration between the different components, as well as parallel and sequential processing of information according to different evaluation criteria on different levels (for further details concerning the CPM, see Sander et al. 2005). Figure 2.1 provides a synthetic view of the theoretical psychological proposition of the CPM. This model invited affective neuroscience to identify the neuronal substrates involved in these different stages and components of emotion processing and to explore possible dissociations in clinical populations. It offered a heuristic model in the sense that the notion of synchronization proved to be particularly relevant in understanding the role of the basal ganglia (Péron et al. 2013) and the cerebellum (Pierce and Péron 2020).

2.2.2 Neural Basis of Emotion

Although the well-known circuit-level theory of emotion, proposed by Papez (1937) and completed by MacLean (1955), implicated some subcortical structures, it emphasized the cortical structures in the processing of emotions. The anterior nuclei of the thalamus, hypothalamus, septum, hippocampus, and amygdala were named on the subcortical side, and the cingulate cortex and prefrontal cortex were named on the cortical side. The role of cortical regions has been widely studied. For example, the ventromedial prefrontal cortex is involved in integration of diverse cognitive and emotional processes, as it has close connections with the anterior insular cortex and the amygdala (Gainotti 2020; Dixon et al. 2017). The anterior insula is reported to be involved in pain processing and empathy, as it is suggested to be an important region for integrating external and internal emotional information to form a “global emotional moment” (e.g., Craig 2009). In addition, the cingulate cortex was highlighted as a leading actor in emotional regulation in monitoring conflict between the functional state of the organism and any new information that has potential affective or motivational consequences (e.g., Bush et al. 2000). Nevertheless, the centrality of these structures in affective processes has been strongly criticized in view of the mainly cognitive and not exclusively emotional role that they could play (LeDoux 1998; Roxo et al. 2011). For example, the rostral anterior cingulate and anterior insula participate extensively in cognitive processes that are likely unrelated to emotion (Wager et al. 2008). Concerning the subcortical structures, the studies describing their role in affective processing are less numerous in the literature, with the exception of those concerning the amygdala. Indeed, the amygdala was considered one of the most important brain regions for emotion-related processes, with a key role in the processing of social signals of emotion (particularly those involving fear) (LeDoux 2003), in emotional conditioning, and in the consolidation of emotional memories (Phelps and LeDoux 2005). Moreover, the amygdala is a “relevance detector,” being involved in the appraisal and labeling of significant stimuli in the context of individual such as needs, goals, desires, and values that contribute to the elicitation of an emotion (for a review, see Sander et al. 2003).

Overall, most models advocate an overrepresentation of the cortex in emotional processes, with the exception of some subcortical structures such as the amygdala or the anterior nucleus of the thalamus. Indeed, as will be discussed in the next section, for both historical and methodological reasons, subcortical regions, currently recognized as being involved in human emotions, have been marginalized for a very long time.

2.3 The Cortico-Centric Bias in the Field of Neuropsychology of Emotions

The cortico-centric bias describes the tendency to see emotion as a production of the neocortex (Berridge 2009). This view was mainly adopted by theorists who studied emotions in human beings and primates, whereas scientists who studied emotional and motivational behavior in non-primate animals more strongly emphasized the role of subcortical structures in emotional processing (Berridge 2009). Thus, the differences generated by these two fields of research, both conceptually and methodologically, could explain the difference in emphasis between cortical and subcortical regions for emotion processes.

2.3.1 On the Origins of the Cortico-Centric Bias of Emotions

According to Berridge (2009), a *first* argument in favor of this cortico-centric view is that the emotional tasks used in human affective neurosciences most of the time require high-level cognitive judgment (e.g., recognize and label the expressed emotion), whereas most of the tasks in animal studies use more “primary” stimuli such as conditioned stimuli. This argument implies that correlational studies conducted in humans are more driven by the involvement of cognitive processes, as humans are more likely to use cortical regions, whereas studies in animals are more likely to be driven by subcortical regions. *Second*, technical constraints of imaging studies are also a reason for this cortico-centric vision. For example, magnetic resonance imaging (MRI) or positron emission tomography techniques are designed to detect changes in blood flow/metabolism in specific regions that are spatially organized. We could thus think that cortical regions, being more spatially segregated, are more likely to be detected as activated during an MRI task.

2.3.2 Updating the Cortico-Centric Vision

Related to Berridge's first argument, inferences made based on human research, and more specifically neuropsychological testing, have often led to the belief that cognitive impairment is the result of a cortical brain lesion or dysfunction. However, strong evidence is now observed in the literature concerning the role of subcortical structures in a range of highly specialized behavioral functions, including those related to cognition (e.g., Koziol and Budding 2009). Both the basal ganglia and the cerebellum are involved in memory and executive and attentional functions (e.g., Graybiel and Mink 2009; Grahn et al. 2009; Schmahmann 2019; Silveri and Misciagna 2000). Moreover, it has even been shown that during associative learning tasks performed by monkeys in which simultaneous recordings were made in the prefrontal cortex and the caudate nucleus, the activity of the caudate nucleus adapted quickly to contingencies, even before the prefrontal cortex and before a significant improvement in performance occurred (Pasupathy and Miller 2005). This observation suggests that subcortical structures such as the caudate nucleus are likely to be mobilized even before other cortical structures, such as the prefrontal cortex, are mobilized for specific processing and even for high-order controlled cognitive processes. Second, regarding the notion of spatial segregation versus integration, it has been shown that the striatum and cerebellum are also parcellated into functional subdivisions underlying motor, cognitive, and emotional processes (Alexander et al. 1990; Stoodley and Schmahmann 2009). This bias toward cortical activations during emotional tasks performed with brain imaging protocols is more due to the size of the structures, as signal detection does not work in structures whose neurons are too densely packed. In other words, the neurons in subcortical structures, like, for example, in the subthalamic nucleus and hypothalamus, are too closely packed to allow subpopulations to be visualized based on vascular blood flow.

Following this reasoning, we understand why structures that do not belong to the cortex, such as the cerebellum and the basal ganglia, are likely to be involved in the processing of emotions on a sensory as well as a cognitive level. The localizationist vision, used in models to describe brain architecture that supports human emotions, helps conceptualize how an emotional response is generated but does not reflect the complexity of the process, because brain circuits are interconnected at multiple levels and mutually influence each other. Further evidence from neuroimaging and clinical studies suggests a brain network for affective processing—organized in multiple input and output loops that, in addition to the cerebral cortex, include the basal ganglia and cerebellum, in which the three structures are considered "equal functional partners."

2.4 Beyond the Cortico-Centric Bias: The Cerebellum and the Basal Ganglia in the Brain Network Underlying Emotion

Anatomical studies in animals, particularly in studies that use neural tracing techniques, have revealed neuronal connections between the associative areas of the cortex and the basal ganglia, as well as circuits between these same areas of the neocortex and the cerebellum (Bostan and Strick 2010, 2018). Moreover, the structures of the limbic network (e.g., amygdala, cingulate cortex) are connected to the basal ganglia and the cerebellum, which, in addition to the direct connection between these two regions, argues in favor of modulatory and reciprocal influences on affective processing throughout the brain (Habas et al. 2009).

2.4.1 Basal Ganglia Involvement in the Synchronization of Human Emotion Components

Functional MRI studies (Péron et al. 2016), electrophysiological data (Péron et al. 2014; Bénis et al., 2020), and deep brain stimulation (DBS) of the basal ganglia (Péron et al. 2013) have provided direct evidence for a specific role of the basal ganglia in human emotions. Interestingly, researchers have reported deficits in several emotional components following subthalamic nucleus (STN) DBS in patients with Parkinson's disease, allowing a better understanding of the functional roles of the dopaminergic pathways and basal ganglia in these processes. For example, modifications of subjective feeling and arousal have been observed following this surgery (Serranová et al. 2011; Vicente et al. 2009), as well as impairments in both facial (Péron et al. 2010a; Dujardin et al. 2004) and vocal (Péron et al. 2010b, 2015) emotion recognition. Cognitive and action tendency components are also affected, as deficits in inhibition processing (Parsons et al. 2006; Aron and Poldrack 2006) and modulations in motivational processes (Lardeux et al. 2009) were revealed following STN DBS. These results strongly point to the involvement of the STN in all components of emotional processing, leading to a proposal concerning the nature of its role. According to Péron et al. (2013), the STN, together with the basal ganglia, may play a central role in emotional processing by *coordinating the activity* of the cortical and subcortical brain structures needed to process emotions. More specifically, the basal ganglia may retrieve data from different parts of the cortex and subcortex, as well as from the brain stem (Coizet et al. 2009) and the cerebellum (Bostan and Strick 2010), and on this basis, *recruit and synchronize* the activity of the cortical and subcortical structures required for the relevant process. Moreover, the basal ganglia may be critically involved in *constructing performance units of sequence representations*, also called chunks. These packages are composed of specific items of information (e.g., emotional information) previously selected to allow more automatic processing. These chunked patterns occur for sequential, repetitive motor, cognitive, and emotional behaviors (or a combination thereof) induced by a triggered stimulus (internal or external). As result, once started, these behaviors may come to an end without conscious control (Graybiel 2008). Overall, the basal ganglia would play a "meta-role" in emotional processing by selecting and coordinating cortical and subcortical response patterns. The close connections between the basal ganglia and the cerebellum (Bostan and Strick 2018) lead to the question of the intervention of the cerebellum in this hypothesized role of the basal ganglia, as well as the nature of the specific role (if any) that the cerebellum may play in emotional processing.

2.4.2 Cerebellar Involvement in the Synchronization of Human Emotion Components

The hypothesis of cerebellar involvement in emotional processes has been reinforced only in recent years (Adamaszek et al. 2017). Clinical manifestations, such as pathological laughter and crying, or the blunting affect observed in patients with atrophy or cerebellar degeneration or stroke, have prompted researchers to question the role of the cerebellum in human emotions (Kish et al. 1988; Levisohn et al. 2000). Several studies in the literature seem to indicate cerebellar involvement in components of emotional processing.

Subjective Feeling and Arousal Using emotional pictures to induce emotional states, researchers have shown a decrease in pleasant experience in response to happiness-evoking stimuli in patients with cerebellar lesions (Turner et al. 2007) and demonstrated cerebellar activations following the presentation of aversive pictures (Bermpohl et al. 2006). Interestingly, the functional segregation of primary emotions in the cerebellum has been suggested, with spatially distinct patterns of activity in the posterior lobe of the cerebellum, as well as common sites of activation underlying the existence of shared neural networks (Baumann and Mattingley 2012). Moreover, temporal hierarchical processing of arousal and valence has been demonstrated in the cerebellum, with arousal processing first (occurring in both vermal (VI and VIIIa) and hemispheric (left Crus II) lobules) followed by valence processing and its interaction with arousal (occurring in left V and VI lobules and Crus I) (Styliadis et al. 2015).

Recognition of Emotion Studies have highlighted that patients with cerebellar stroke exhibit impairment of facial emotion attribution (Adamaszek et al. 2014), in particular for negative emotions (Moulton et al. 2011; Schutter and van Honk 2009). This disturbance seems not to be specific to the visual modality but is present when emotions are conveyed by the human voice, as there is evidence to support deficits in recognizing emotional prosody (Thomasson et al. 2019; Adamaszek et al. 2014). According to a previous study (Thomasson et al. 2019), fine-grained deficits were observed, with patients giving erroneous ratings on the Surprise scale when they listened to fear stimuli. It seems that the patients identified the target emotion well but, at the same time, made misattributions regarding non-target emotions. Interestingly, these disturbances could be linked with the cerebellar contribution to timing and sensory acquisition (Baumann et al. 2015). Increased cerebellar activity has been reported during pitch discrimination tasks (Petacchi et al. 2011), and in the right cerebellar vermis ($xyz = 2, -64, -34$) which is thought to be related to modulation of fundamental frequency in emotional speech production (Pichon and Kell 2013). Moreover, cerebellar patients have difficulties in comparing the durations of two successive time intervals (Ivry and Keele 1989). More specifically, Gooch et al. (2010) found that patients with damage to the middle-to-superior lobules or the left hemisphere showed more significant impairments in accuracy on several timing tasks, suggesting the specific involvement of these regions in time perception. This therefore suggests early (sensory) but also later (cognitive) cerebellar participation in the processing of emotions, which seems consistent, given the involvement of the cerebellum in cognitive processes.

Appraisal Processes Impairments in executive functions (e.g., set shifting, abstract reasoning, verbal fluency, planning, working memory), often with perseveration, distractibility, or inattention, have been found in patients with cerebellar cognitive affective syndrome (Schmahmann and Sherman 1998). These processes are crucial to emotional processing and their alteration is manifested by disinhibition and poor affect regulation. In addition, recent models include the cerebellum in the decision-making process (Roldan Gerschcovich et al. 2011; Wang et al. 2020), a cognitive function that is largely modulated during the course of an emotional response (Brosch and Sander 2014).

Action Tendencies and Motivational Processes Symptoms such as lack of initiation or apathy could be observed in patients with cerebellar impairment (Schmahmann et al. 2007). Intriguingly, cerebellar dysfunction was found in autism spectrum disorders and schizophrenia (Villanueva 2012), and a disruption in the reward system was shown in patients with these neurodevelopmental diseases (Simon et al. 2015; Dichter et al. 2012). Interestingly, a recent study conducted in mice demonstrated direct excitatory projections from the cerebellum to the ventral tegmental area, which is one of the brain regions that processes and encodes reward. Accordingly, Carta et al. (2019) have suggested that both the cerebellum and the basal ganglia could coordinate dopamine functions and thus regulate the motivation and reward process.

Taken together, this evidence suggests that the cerebellum has a role in all components of emotion. Similar observations have been previously established concerning the STN, it being conceptualized as a structure that would produce temporally organized neural co-activation patterns at the cortical and subcortical levels that are essential for generating emotions and related feelings (Péron et al. 2013). This observation leads to the hypothesis of a meta-cognitive role of the cerebellum during emotion processes. From the evidence regarding its role in detecting and minimizing prediction error based on differences in the current state and the intended goal state (Pierce and Péron 2020), we speculate that it could play a specific role in the very fine adjustment of emotional responses through its Purkinje cell output. Accordingly, the following integrated model of emotional processing could be suggested. For pedagogical purposes, the example of emotional prosody is used, but the computational role proposed below for each part of the vertically organized brain can be transposed for each emotional component, as well as for each domain and subdomain of motor and cognitive processes.

2.4.2.1 Toward an Integrated Cerebello-Basal Ganglia-Cortical View of Emotion

In the framework of the CPM and studies investigating cerebellar involvement in emotion, one proposition is that in each component of the organism, the cerebellum could detect and then adjust the encoded temporal pattern for a given response in order to get as close as possible to the expected response, this expected response being conceptualized as an internal model in reference to the research conducted on cerebellar motor activity (Ito 2008). This ability to adjust and correct responses very finely (whether motor, cognitive, or emotional) is possible in particular because of the ability of the cerebellum to analyze irregular temporal patterns (Breska and Ivry 2018). This work is done in coordination with the basal ganglia, which select and strengthen appropriate cortical responses by using reward feedback (Bostan and Strick 2018). One means of fulfilling this function might be through the ability of the basal ganglia to process regular temporal patterns (Breska and Ivry 2018).

Accordingly, taking the example of emotional prosody processing, the cerebellum would participate, along with the basal ganglia, in the organization of sound processing and temporal predictions (Grandjean 2021). The right cerebellar hemisphere would be specifically involved in extraction of the salient modulations in the speech envelope, such as fluctuations in amplitude, whereas the left would be involved in tracking salient modulations in fine-grained speech structures, such as frequency transitions (Stockert et al. 2021; Callan et al. 2007). From these extractions, an internal temporally structured event representation would be built, which would allow, via reciprocal interaction between the cerebellum and temporal cortex, fitting of the cortical representation of the auditory information in a relevant point in time. These processes would lead to optimal processing of the salient acoustic parameters (Stockert et al. 2021). The basal ganglia could use the internal representation of the temporal structure of sound sequences to recruit and synchronize activity of the cortical and subcortical structures required for the relevant process, as well as to strengthen and refine units of previously established sequence representations (chunks), or to build new units. Interestingly, clinical studies can tell us about the specific, but not the mutually exclusive, effects that disturbances in either the cerebellum or basal ganglia can have.

Taking the example of the recognition of emotional prosody assessed with a task that uses continuous analog scales, a disturbance of the basal ganglia, as in the case of Parkinson's disease, could lead to a deficit in attribution of the correct emotion (Stirnimann et al. 2018). The basal ganglia would not succeed in increasing the activity in the neuronal representations corresponding to previous experiences, which would have allowed the correct identification of the target emotion. On the other hand, cerebellar impairment will mainly lead to misattributions (Thomasson et al. 2019). Patients can correctly identify the target emotion but also tend to make wrong attributions. A first selection of responses, among which the correct one is found, could be made by the basal ganglia, but the cerebellum fails to extract the salient variations from the acoustic features of the stimuli and consequently

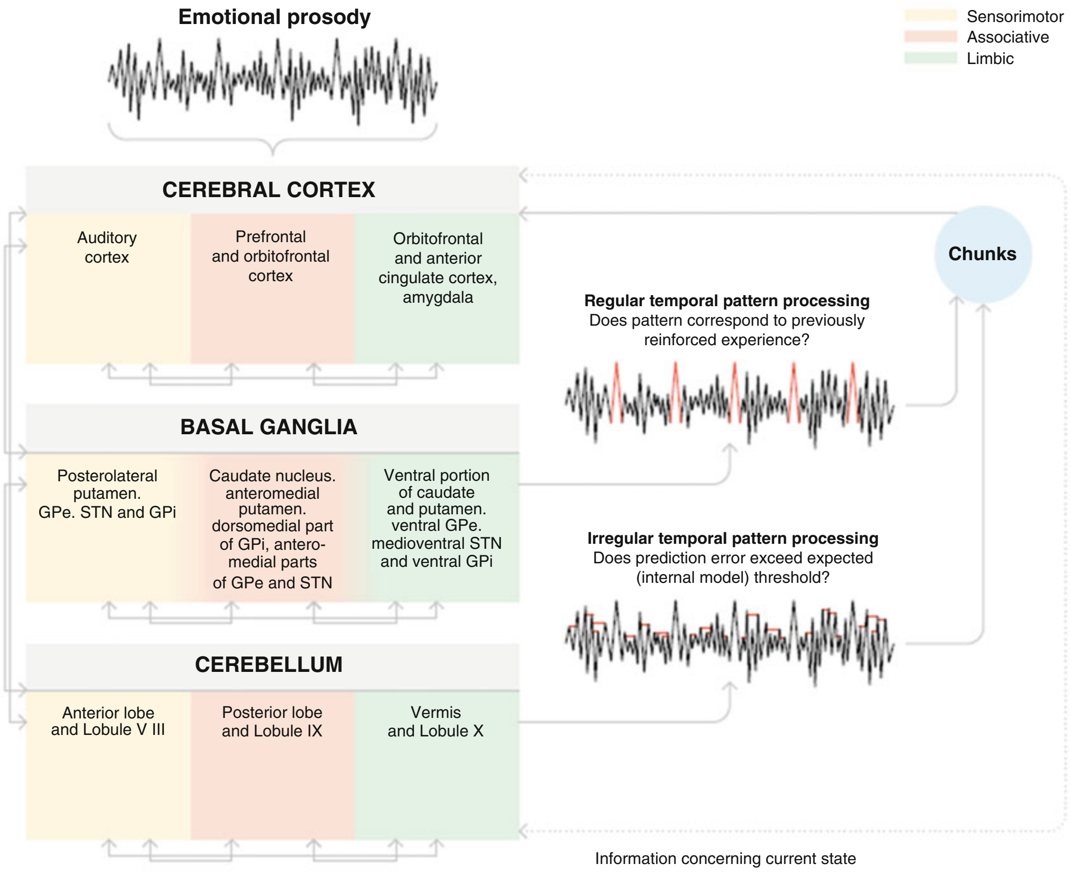

Fig. 2.2 Integrated model of emotional prosody processing. An emotional prosodic stimulus is processed by the cortex, the basal ganglia, and the cerebellum. Each sensorimotor (yellow), associative (orange), and limbic (green) region of each structure takes part in this processing. The functional gradient present for the basal ganglia is represented by the overlapping colors. The basal ganglia and the cerebellum are involved in different temporal pattern processing. The basal ganglia process regular temporal patterns in order to detect global similarity with previous responses to what was previously rewarded. The cerebellum processes irregular temporal patterns to detect the fine variations that possibly deviate from what is tolerated in terms of a response in relation to the individual's current state. The chunking process is elaborated by the basal ganglia if emotional sequences are recurrent, as induced by a triggered stimulus (internal or external), and, once started, it may come to an end without conscious control. Chunks are also refined by the cerebellum to gain precision so that the basal ganglia can activate downstream regions more quickly to generate a response. Abbreviations: *GPe* external globus pallidus, *GPi* internal globus pallidus, *STN* subthalamic nucleus

fails to build an optimal temporally structured event representation, leading to difficulties in refining the cortical and basal ganglia response. More studies are needed to investigate how the various subprocesses involved in vocal emotional processing—drawing on sensorimotor activity, emotion, and cognition—are differentially represented in the cerebellum and possibly connected to different basal ganglia. Figure 2.2 provides a synopsis view of how the theoretical proposition and meta-vision concerning collateral effects caused by disturbances in emotion processing in more general functions, such as habit formation, could be proposed, which is discussed in Chap. 9.

2.5 Conclusion

The functional role of the cerebellum in cognitive and emotional processes has been neglected for many years. However, like the basal ganglia, the cerebellum seems to be involved in all components of human emotions. From a vertically organized brain perspective, the cerebellum would participate in the optimal processing of each feature that modulates the emotional event through its ability to encode and detect fine variations in temporal processing patterns. By generating temporally structured event representations, the cerebellum would allow optimal processing of the salient parameters necessary for the proper processing of an emotional event. The basal ganglia would also contribute to the smooth running of this emotional processing by using the cerebellar internal model to recruit and synchronize the activity of the cortical and subcortical structures required for the relevant process. This would also contribute to the strengthening and refining of units of sequence representations previously established (chunks) or to the building of new units. Overall, in view of the crucial role that the cerebellum plays in both emotional and cognitive functions, more attention should be paid to the clinical assessment of patients with cerebellar deficits. Indeed, the symptoms caused by cerebellar dysfunction are often discrete. For example, as we highlighted in this chapter, emotional prosody recognition deficits observed in patients with cerebellar stroke consisted of misattributions but the correct identification of the target emotion. In this context, neurorehabilitation for these patients takes on its full meaning with, for example, training for the decoding of low-level sensory processes to improve emotional prosody processing.

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Cerebellum and Emotion Processing

3

Oliver Baumann and Jason B. Mattingley

Abstract

Clinical examinations and neuroimaging investigations have dramatically changed the prevailing view of human cerebellar function and suggest contributions beyond movement control. Of these new views, perhaps the most intriguing proposal is that the cerebellum plays a key role in regulating emotion. According to the *dysmetria of thought* theory, the cerebellum provides accuracy, consistency and appropriateness to cognitive and affective functions, as it does for movement-related operations. Despite the value of a universal theory on cerebellar function, it is also essential to consider its unique contributions to specific functional domains. This chapter aims to provide an accentuated account of the cerebellar role in emotion processing by separately evaluating its impact for sub-components of emotion processing. These include physiological responses that contribute to the subjective or "feeling" component of emotion, emotional expressions that serve essential social-communicative functions, and the cognitive appraisal process that determines the emotional significance of events and therefore affects the generation and modulation of emotions.

Keywords

Cerebellum · Emotion processing · Feeling · Physiological arousal · Emotional expressions · Cognitive appraisal

3.1 Cerebellum and Emotion Processing

The cerebellum has an important and well-known role in the control and coordination of movements. In 1824, Pierre Flourens, one of the founders of modern neuroscience, removed the entire cerebellum of a pig to investigate its functional role in behaviour. After the procedure, the pig was unable to stand or walk. He repeated the process with similar results in pigeons and dogs, and concluded that the cerebellum is responsible for movement control (Flourens 1824). Flourens' assertion matched the predominant clinical picture of cerebellar disease, which was long understood to result in imprecise movement control (Holmes 1917, 1939). These and related explanations of the role of the cerebellum seem to have satisfied most scholars and clinicians, and effectively ended debate on the topic for the next 150 years.

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More recently, careful clinical examinations and neuroimaging investigations have dramatically changed the prevailing view of human cerebellar function and suggested instead contributions beyond movement control (Baumann et al. 2015; Koziol et al. 2014; Mariën et al. 2014; Van Overwalle et al. 2020). Of these views, perhaps the most intriguing proposal is that the cerebellum plays a key role in regulating emotion (Adamaszek et al. 2017). In a longitudinal follow-up study of 20 patients with cerebellar lesions, Schmahmann and Sherman observed significant behavioural and affective changes, now commonly known as the "cerebellar-cognitive–affective syndrome" (Schmahmann 2004). Following this work, a spectrum of emotional and behavioural deficits has been described in patients with both acquired and congenital cerebellar damage, ranging from apathy and indifference to aggressive behaviour (Hoche et al. 2018).

In addition, human neuroimaging studies have provided evidence for a cerebellar role in emotion processing in non-clinical samples (Adamaszek et al. 2017; see also Chap. 6: "Topography of Emotion in Cerebellum"). For instance, we used functional magnetic resonance imaging (fMRI) to identify neural activity patterns within the cerebellum in 30 healthy human volunteers as they categorised images that elicited each of the five primary emotions: joy, anger, disgust, fear and sadness (Baumann and Mattingley 2012). We found that stimuli within each category resulted in distinct patterns of cerebellar activity. However, we also found localised regions of overlap in the activation patterns across pairs of emotions, implying shared neural networks. For instance, there was partial overlap in activations associated with fear and anger (paravermal lobules VI and Crus I), anger and disgust (vermal lobule IX), and joy and sadness (vermal lobule VIIIA). Our study was the first to show that the cerebellum represents the five primary emotions in functionally distinct subregions, mirroring to some extent the segregation of emotion processing seen in the neocortex (e.g. Phan et al. 2002). In addition, our study showed that all five emotions evoked activity in the cerebellar vermis and the intermediate parts of the cerebellar hemispheres (i.e. the paravermis), thus highlighting a critical role for the medial cerebellum in emotional processing. In line with our results, several clinical studies have reported that the affective component of the cerebellar cognitive–affective syndrome is most notable when lesions involve the vermis and paravermis (Schmahmann and Sherman 1998; Schmahmann et al. 2007).

Further support for a cerebellar role in emotional processes comes from anatomical and electrophysiological studies in cats and non-human primates, showing cerebellar projections to emotion-related areas of the brain, including the hypothalamus, amygdala, and basal ganglia as well as the neocortex and brainstem nuclei (Anand et al. 1959; Blatt et al. 2013; Middleton and Strick 2001; Schmahmann 2001; Schutter and van Honk 2005; Snider and Maiti 1976).

Given the evidence for cerebellar involvement in emotion processing, it is natural to ask what specific role it plays. According to the *dysmetria of thought* theory (Schmahmann 1991), the cerebellum provides accuracy, consistency and appropriateness to cognitive and affective functions, as it does for movement-related operations. Building on this idea, Schmahmann (1996) coined the term "universal cerebellar transform", to capture the idea of a singular functional principle. This hypothesis is underpinned by the observation that, in contrast to the neocortex, cerebellar anatomical organisation and computational principles are relatively uniform. Its macrostructural uniformity, characterised by repeating corticonuclear micro-complexes[1] (Schmahmann 2019), is contrasted by a rich heterogeneity of topographically arranged connections with the rest of the brain (Buckner et al. 2011; Habas et al. 2009; O'Reilly et al. 2010). The deficits that emerge following cerebellar lesions are therefore largely determined by the function of the cortical areas to which the damaged cerebellar region is connected. In terms of its uniform computational principles, the cerebellum

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[1] See De Zeeuw (2021) for a review on the subtleties and subclassifications of microzones and microcomplexes at the cellular level.

provides fast and parallel processing of its diverse inputs, but produces minimal outputs (Ito 2006). More specifically, each input received by the cerebellum is processed by around 10,000 granule cells, the outputs of which converge on a much smaller number of Purkinje cells (around 200,000 granule cells are connected with just one Purkinje cell). The Purkinje cells send their outputs to a small group of deep nuclear cells, which project their signals back to the cortex and other subcortical areas via the thalamus (Linas et al. 2004). Information processing in the cerebellum is swift, and signals are typically processed within a couple of milliseconds (Snider and Stowell 1944). The cerebellum is therefore considered essential for all sensory and motoric tasks that require high (i.e. millisecond range) temporal precision (Baumann et al. 2015; Ivry and Keele 1989).[2] These functional and structural features have led to the hypothesis that the cerebellum is ideally suited for the rapid detection of internal and external stimulus patterns, and can rapidly generate outputs that provide predictive state estimates (i.e. internal models; Ito 2008). Importantly, while neocortical brain areas are also known to be involved in the formation of mental models of the world, the cerebellum plays a unique role due to its ability to rapidly process internal and external signals and to therefore provide feedforward models, in contrast to feedback models, which are naturally slower (Adamaszek et al. 2017; Baumann et al. 2015; Koziol et al. 2014; Nixon 2003).

Cerebellar feedforward models allow for the generation of corrective signals that help to maintain optimal performance in highly time-critical responses (Adamaszek et al. 2017; Baumann et al. 2015; Koziol et al. 2014; Nixon 2003), akin to an oscillation dampener optimising performance (Schmahmann 2019). On this view, the cerebellum is regarded as a support structure that does not control, but rather fine-tunes cognitive and affective responses, akin to its role in motor behaviour.

Despite the value of a universal theory on cerebellar function, it is also essential to consider its unique contributions to specific functional domains. This chapter aims to provide an accentuated account of the cerebellar role in emotion processing by separately evaluating its impact for sub-components of emotion processing. Emotion can be regarded as a multifactorial concept that includes *physiological* components (and subjective experience thereof), *expressive* components and *cognitive* components (Izard 2010). In the following, we will discuss the cerebellar contributions to each of these components before providing an integrative discussion and an outlook for research and practice.

3.2 Cerebellar Contribution to the Physiological Component of Emotion

Physiological arousal has long been recognised as a key component of emotion (Lange 1885; James 1894; Schachter and Singer 1962), and the cerebellum maintains projections to brain areas underpinning control of physiological arousal. Briefly, the autonomic nervous system, which is divided into sympathetic and parasympathetic branches, controls emotional arousal. The sympathetic branch is related to increased arousal and the functional role of preparing the body for action (“fight or flight”). In contrast, the parasympathetic system is related to decreased arousal and restorative body functions, such as sleep and digestion. Relative dominance of sympathetic vs. parasympathetic activation is associated with elevated responses in prominent markers of physiological arousal, such as heart rate, respiration and sweating response. In addition, there are some more subtle signals, such as changes in temperature, muscle tension and gastric activity (Levenson et al. 1990; Vianna and Tranel 2006). The complex neural systems that underpin arousal are located in the brainstem, thalamus, hypothalamus and basal forebrain (Jones 2003). These receive inputs from cortical

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[2] The timing hypothesis suggests that the cerebellum provides a near-infinite set of interval type timers, which allow for task-specific timing-functions (Ivry 1997; Bareš et al. 2019).

and subcortical emotion processing areas including the amygdala, insula, basal ganglia and neocortex. The hypothalamus, in particular its paraventricular nucleus, plays a vital role in the modulation of arousal via its regulation of the pituitary gland and the secretion of hormones (Engelmann et al. 2004). Stimulation of the posterior hypothalamus has been found to modulate sympathetic arousal responses, such as pupillary dilation, respiratory rate, heart rate and blood pressure (Hess 1957).

Anatomical and electrophysiological studies in cats and non-human primates have shown direct cerebellar projections to crucial brain areas underpinning physiological arousal, including the hypothalamus (Blatt et al. 2013). More specifically, the vermis, fastigial nucleus and interpositus nucleus maintain projections with key regions underlying the autonomous control of arousal (Strata 2015). There is also direct functional evidence that implicates the cerebellum in modulating autonomic responses. Studies in cat have revealed that bilateral lesions of the rostral fastigial nucleus affect mean arterial pressure and reflexive heart rate responses, and lead to overall decreased resting heart rate (Chen et al. 1994). Similarly, a more recent study showed that microinjection of acetylcholine, and muscarinic acetylcholine receptor activation in the cerebellar cortex led to decreases in arterial pressure and heart rate (Zhang et al. 2016). These outcomes suggest that the cerebellum augments sympathetic cardiovascular responses and inhibits parasympathetically mediated responses.

In humans, evidence for a cerebellar influence on autonomic arousal processes comes mainly from brain imaging studies. Styliadis et al. (2015) used magnetoencephalography to record the spatial and temporal profile of brain activity in response to emotion-evoking images. Importantly, Styliadis et al. (2015) investigated the distinct neural response to varying degrees of arousal and valence (i.e. the extent to which an emotion is positive vs. negative), using images from the International Affective Picture System (IAPS; Lang et al. 1999). The IAPS comes with normative ratings for stimuli along the orthogonal dimensions of arousal and valence. Overall, Styliadis et al. (2015) observed cerebellar responses ~160 ms after stimulus onset. Using the arousal and valence ratings as regressors, they identified distinct areas of the cerebellum involved in the processing of those two affective dimensions. Specifically, whereas valence was related only to one hemispheric area of the cerebellum (left lobule VI), arousal was associated with activity in several vermal (lobule VI and VIIIA) and hemispheric areas (left Crus II). The indication of a vermal role in modulating arousal is consistent with its anatomical connectivity profile, since it maintains direct bi-directional connections with the hypothalamus (Haines et al. 1984), as well as brainstem reticular nuclei (Brodal 1975; Dietrichs and Walberg 1979). These findings also align with our own fMRI data showing that the high-arousal emotions of fear and anger elicit activity in vermal lobule VI (Baumann and Mattingley 2012). Apart from identifying this spatial pattern of emotional arousal vs. valence in the cerebellum, the study by Styliadis et al. (2015) also revealed new insights into the temporal domain of cerebellar processing. While valence-related activity appeared relatively late and was short-lived (420–530 ms), arousal-related activity could be detected early and was sustained (160–980 ms). These findings further support the notion that the cerebellum independently contributes to a physiological arousal component of emotion, as well as a cognitive component of emotion related to the appraisal of valence.

Physiological arousal is essential for bringing the body into a situation-appropriate state (i.e. fight/flight vs. restoration; Thayer 1989). In addition, it is the conscious awareness of those bodily states, known as interoception, that leads to the subjective (“felt”) component of emotions (Critchley and Garfinkel 2017). Nummenmaa et al. (2014) asked several hundred participants, using a topographical self-report tool, about the distinct bodily sensations they associate with specific emotions. The authors found that different emotional states (e.g. anger, sadness, joy) were associated with distinct, but culturally universal topographic somatotopic maps (i.e. the maps were consistent across Western European and

Asian participants). For instance, whereas both anger and happiness were associated with perceived elevated activity in the upper chest (likely a reflection heart rate and respiration-related changes), happiness, but not anger, also included sensations related to the gastric system. These observations are corroborated by human brain imaging studies showing somatosensory activity correlated with emotion-related somatic experiences (Nummenmaa et al. 2012).

Given the diverse range of interoceptive channels and crosstalk between them, the neural systems underpinning such bodily sensations are complex. However, several lines of evidence indicate that the anterior insula is the central hub at which interoceptive signals converge, and the central structure underpinning subjective feelings (Craig 2009; Strigo and Craig 2016). Functional and structural MRI data have suggested that the size and activation of the anterior insula are related to individuals' ability and precision in detecting heartbeats (Critchley et al. 2004), and positron emission tomography data have shown that activity in the insula is related to gastric distensions (Barrett et al. 2004). Together these studies suggest that the insula underpins our ability to perceive internal bodily sensations and is crucial for the subjective feeling-related aspect of emotion. Importantly, human imaging studies have revealed functional connections between the insula and the cerebellum (Allen et al. 2005; Habas et al. 2009), suggesting a role of the cerebellum in interoceptive processing of arousal. In an fMRI study conducted by Gray et al. (2007), participants were presented with auditory signals that were either aligned or misaligned with their heartbeats. The condition that involved time-shifted auditory feedback led to increased activity in the insula and the cerebellar vermis (lobule VI), suggesting that both areas are involved in perceiving one's own heartbeat, that is, interoception.

Finally, neuropsychological case studies of patients with isolated cerebellar lesions have provided compelling examples of dysregulated physiological arousal. For instance, Annoni et al. (2003) reported on a patient with left cerebellar stroke involving the fastigial nucleus who presented with undifferentiated skin conductivity responses to positive and negative outcomes in a reinforcement learning task. These physiological abnormalities were further accompanied by blunted affect, highlighting the role of arousal in the modulation of emotion.

Taken together, the studies reviewed above provide compelling evidence that the cerebellum plays a central role in the modulation of autonomic physiological responses. As discussed, situation-appropriate states of arousal are not only important for bodily attitudes of action readiness, but also for consciously experienced feelings.

3.3 Cerebellar Contribution to the Expressive Component of Emotion

While emotions help us, at the individual level, to avoid physical threats to our well-being, they also serve essential social-communicative functions (Keltner et al. 2006). For most people in stable, developed countries, threats to well-being are more likely to originate in the social rather than the physical environment. Emotions help us navigate social interactions and solve social problems by providing a communicative signal to those we interact with. Humans and other animals have potent non-verbal means to communicate emotional messages, including facial expressions, movement and posture signals, and vocal signals (Skinner 2013). The display of emotional expressions can lead to specific, immediate behavioural responses, highlighting the need for precise signalling to avoid miscommunication. In the facial expression of emotions, the movement of just a single muscle can significantly impact the perceived social message (Matsumoto and Hwang 2014). For example, nuances in the expression of a smile might deflect or exacerbate hostile behaviour. Correspondingly, humans can recognise posed emotions with a high degree of certainty (McLellan et al. 2010). Moreover, the importance of precision in expressing emotions is highlighted by the problems experienced by individuals with dysregulated emotional functions.

Dysregulation of emotional expression can present in the form of exaggerated or blunted emotional expression. Interestingly, pathological expressions of emotion are often dissociated from the feeling component, e.g. exaggerated expressions of emotion are not necessarily linked to correspondingly exaggerated feelings (Poeck 1985; see also Chap. 17: "Cerebellum and Emotion Disorders"). As a post-stroke syndrome, dysregulation of emotion expression is most often seen after lesions involving the anterior cortex-internal capsule/basal ganglia-ventral brainstem circuitry (Kim and Choi-Kwon 2000). The classic explanation for dysregulation of emotional expression is that it is caused by a lack of inhibition of subcortical nuclei that are in direct control of facial and respiratory function (Wilson 1924). However, this loss-of-inhibition hypothesis is too simplistic to account for the clinical picture, because the dysregulation involves both increased and decreased intensity of emotional expressions, in addition to contextually inappropriate displays of emotion (Bharathi and Lee 2006; Choi et al. 2013).

Cerebellar dysfunction has been proposed to explain the complex patterns of dysregulated expressions of emotions. Schmahmann and Sherman (1998) observed major behavioural and affective changes in patients with cerebellar damage, ranging from apathy to pathological crying and laughing. Further support for a cerebellar role in modulating emotional expressions comes from a case study by Parvizi et al. (2001), who reported on a patient who exhibited pathological crying and laughter post-stroke. This case is unique since the lesions were relatively small (in the millimetre range) and were confined to the white matter of the brainstem and cerebellum. These lesions were situated along white matter pathways connecting the cerebrum, brainstem and cerebellum. Thus, the patient's symptoms were interpreted as being due to partial deafferentation of the cerebellum from descending cerebral inputs. The characteristics of the functional deficits, in combination with the specific pattern of neural damage, support the hypothesis that the cerebellum has a crucial role in maintaining emotional responses that are optimised in terms of intensity and timing (Adamaszek et al. 2017; Schmahmann 2019). The importance of temporal precision in facial expressions of emotion is well recognised, and evidenced by the fact that mental connotations can change within milliseconds (Ekman and Friesen 1978; Haggard and Isaacs 1966). The cerebellum exerts modulatory control over facial muscles via projections that originate in its dentate and interposed nuclei, and that connect to the facial nuclei and brainstem via the red nucleus (Delgado-García and Gruart 2005; Gibson et al. 1987; Hoover and Strick 1999; Van Kan et al. 1993).

Likewise for vocal expressions of emotion, temporal precision is inherently important since carefully timed variations express the valence and intensity of an individual's emotions (Banziger and Scherer 2005). Several reports have shown that the cerebellum plays an important regulatory role in vocal utterances (Mariën et al. 2014). The most well-known cause of vocal deficits after cerebellar damage is dysarthria, in which dysregulated control of the tongue and voice box leads to slurred speech. Dysarthria after cerebellar lesions is also associated with disordered phonation, which refers to inappropriate pitch or loudness of the sounds produced (Mariën et al. 2014). Neuroimaging studies have shown that speech production engages the representation of articulatory muscles in the sensorimotor cerebellum, specifically medial lobule VI bilaterally and the dentate nucleus (Thürling et al. 2011). In addition, data from human lesion studies suggest that the vermal and paravermal aspects of lobules V–VI and VII–VIII are involved in the production of vocal utterances (Mariën et al. 2014).

While emotional expressions can be consciously elicited and modulated, significant aspects of emotional expression and their detection are regulated automatically and thus apparently not under conscious control (de Gelder and Hadjikhani 2006). The automatic and precise adjustment of emotional expressions based on incoming information requires the ability to predict state trajectories. There is a consensus that the cerebellum uses forward models to generate precise predictions of perceptual, sensorimotor and cognitive states (Adamaszek et al. 2017; Baumann et al. 2015; Koziol et al. 2014), which not only aid the generation of facial expressions but also their decoding by the perceiver. Emotion recognition deficits associated with transient disruption (via brain stimulation) or permanent cerebellar lesions have been reported for the visual (Ferrucci et al. 2012; Turner et al. 2007) as well as the auditory domain (Thomasson et al. 2019). Further evidence for a cerebellar role in implicit emotion processing comes from a repetitive transcranial magnetic stimulation (rTMS) study that showed that cerebellar stimulation, but not visual cortex stimulation, resulted in faster reaction times to subconsciously perceived (masked) images of happy faces (Schutter et al. 2009).

3.4 Cerebellar Contribution to the Cognitive Component of Emotion

While there are many definitions of cognition, in considering cognition as an integral component of emotion, it is useful to limit the definition to mental processes that depend on acquired representations (Izard 1993; Izard and Malatesta 1987). Those acquired mental representations of the physical and social environment are thought to allow for a dynamic appraisal process that can trigger and shape emotional states (Scherer 1993). The cognitive appraisal process determines the emotional significance of events and therefore affects the generation and modulation of emotions. The appraisal process can be further compartmentalised into several separate dimensions, such as the appraisal of goal-relevance, intentionality, and consistency with social norms (Ochsner and Gross 2014; Scherer 2001). In any given situation, multiple appraisals may coexist, resulting in multifaceted affective experiences and underlining the complexity of this process. The appraisal-related cognitive component of emotion is thought to exist on a continuum that ranges from simple and automatic discrimination to complex and deliberate appraisal processes (Izard 1993; Izard and Malatesta 1987). This conceptual continuum can be mapped onto a continuum of emotion-related brain systems, ranging from subcortical structures including the amygdala and striatum, to higher-level cortical systems such as the insula, orbitofrontal and ventromedial cortex (Damasio et al. 2000).

The prefrontal cortex is generally regarded as the prime cortical structure for regulating the more basic emotional processes originating in subcortical structures (Bechara and Damasio 2005; Ochsner and Gross 2014). The critical role of the prefrontal cortex in emotion regulation is evidenced by its involvement in almost all affective disorders (Dixon et al. 2017). According to the appraisal-by-content model, evaluation of the emotional significance of events serves as a unifying principle for the role of the prefrontal cortex in emotion processing (Dixon et al. 2017). Moreover, distinct subregions of the prefrontal cortex are specialised for supporting appraisals for different contexts and contents. The prefrontal-mediated cognitive appraisal process is therefore thought to lead to the generation of contextually appropriate emotions and action tendencies.

As for the other two components of emotion discussed above (i.e. physiology and expression), the cerebellum also plays a crucial role in the modulation of cognitive processes, resulting in improved and context-appropriate performance (Koziol et al. 2014). The fact that the cerebellum is reciprocally connected with a range of limbic structures and prefrontal cortical areas provides a robust neuroanatomical argument in favour of cerebellar involvement in the cognitive component of emotion (Blatt et al. 2013; Middleton and Strick 2001). Furthermore, behavioural evidence corroborates the idea of a cerebellar contribution to appraisal-related aspects of the generation and modulation of emotion. Van den Berg et al. (2020) compared the risk-taking attitudes of 134 patients with cerebellar lesions following stroke (involving the posterior lobes of the cerebellum, particularly in lobules VI, VIII and Crus I) relative to a control group. Participants' risk-taking behaviour was assessed using the Action

Selection Test (Vlakveld 2011), which consists of driving scenarios and requires participants to indicate what they would do in a specific situation (“do nothing”, “release accelerator”, or “brake”). The main finding was that, compared with the control group, the cerebellar patients took significantly more risks. In addition, the same group of patients was impaired in recognising fearful expressions in the Ekman 60 Faces Test of the Facial Expressions of Emotions Battery (Young et al. 2002), which suggests that the impaired decision-making behaviour is underpinned by deficits in emotion processing. While studies based on stroke-induced lesions lack the degree of anatomical precision desired, this study is nevertheless a compelling example of the impact of cerebellar damage on the cognitive appraisal-related component of emotion processing. In contrast, Clausi et al. (2015) assessed cerebellar patients and found that their risk-taking behaviour was not impaired, but did observe a reduction in patients’ conscious experience of regret. Interestingly, autonomous physiological measures were unimpaired, suggesting a dissociation between cerebellar contributions to the arousal component of emotion and the cognitive appraisal-related component (Shuman et al. 2013). The cerebellum’s contribution to cognitive aspects of emotion processing also extends to high-level social-emotional tasks that require complex cognitive reasoning (see Chap. 15: “Cerebellum and Emotion in Social Behavior”). For instance, several imaging studies have revealed involvement of the posterior cerebellar hemispheres in concert with several cerebral association areas, in social mirroring and mentalising tasks (Buckner et al. 2011; Van Overwalle et al. 2014). Moreover, neuropsychological reports of patients with cerebellar degenerative atrophy revealed behavioural profiles characterised by impairments in social perspective-taking, which were further accompanied by reduced functional connectivity between posterior cerebellar lobules and cortical regions involved in social-emotional reasoning (Clausi et al. 2019).[3]

Several subtheories have aimed to explain the cerebellar contribution to specific cognitive processes, such as aiding the detection of sequences (Molinari et al. 2008) or supporting the learning of associative relationships (Ernst et al. 2019; Timmann et al. 2010). As mentioned earlier, however, most of those proposals can be incorporated into the overarching idea that the cerebellum is crucial for the formation of internal models of the world for the prediction of future events (Ito 2008; Miall and King 2008). Applied to cognitive appraisal processes, this implies that the cerebellum supports the swift and accurate classification and recognition of emotional valence. Ferrari et al. (2018) provided support for this suggestion using a non-invasive brain stimulation approach (see Tomlinson et al. 2013 for an overview on cerebellar brain stimulation). More specifically, they found that transient virtual lesions of the cerebellum, via transcranial magnetic stimulation, led to reduced accuracy in explicit and implicit measures of emotion recognition. Their task required 36 participants to judge the emotional expressions and the gender of male and female faces. In comparison to an occipital control site, stimulation of the cerebellum significantly impaired appraisals of facial expressions. Interestingly, cerebellar stimulation also affected implicit appraisal processes, since gender judgements for emotionally expressive faces, but not neutral faces, were also impaired. This finding suggests that if cerebellar support for emotional appraisal is disrupted, other emotion-related brain areas (such as the prefrontal cortex) must compensate, affecting accuracy for other cognitive operations. Complementary evidence for a cerebellar contribution to swift emotional appraisal processes comes from another brain stimulation study, which applied a weak, tonic direct current to the cerebellum (Ferrucci et al. 2012). Relative to a sham (i.e. no stimulation control) condition, cerebellar direct current stimulation led to a significant reduction in response time for the identification of facial expressions of emotions. Interestingly, this effect was only observed for

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[3] For a review on the role of the cerebellum in perspective taking and embodied emotional-cognitive processes see Chap. 17:” Cerebellum, Embodied Emotions, and Psychological Traits”.

negative but not positive facial expressions, which could be explained by the fact that negative stimuli generally evoke more robust physiological and behavioural responses than neutral or positive events (Fox et al. 2000). Moreover, from a perspective of survival optimisation, fear and anger are expected to be more directly related to fast behavioural actions than positive emotions, i.e. the former are highly time-critical responses (Mobbs et al. 2015).

Taken together, several lines of evidence suggest that the cerebellum is involved in the cognitive component of emotion, leading to a faster and more accurate appraisal of emotional stimuli and situations. Cognitive-emotional processes are predominantly underpinned by the posterior cerebellar hemispheres, in contrast to the arousal-related aspects of emotion which are associated with the vermal regions (Adamaszek et al. 2017; Leggio and Olivito 2018).

3.5 Discussion

The preceding sections presented evidence to suggest that the cerebellum contributes to distinct components of emotion processing. These include physiological responses that contribute to the subjective or "feeling" component of emotion, emotional expressions that serve essential social-communicative functions, and the cognitive appraisal process that determines whether stimuli and context elicit emotions and, if so, what type. Moreover, the evidence is in line with the universal hypothesis of cerebellar functioning, which suggests that the cerebellum optimises functioning by providing accuracy, consistency, and appropriateness to cognitive and affective functions, as it does for movement-related operations (Adamaszek et al. 2017; Baumann et al. 2015; Koziol et al. 2014; Nixon 2003; Schmahmann 2019).

While the idea of a cerebellar role in the regulation of emotion was originally spurred by patients with neurodegenerative disease (e.g. ataxia) and stroke (Schmahmann 2004), it is important to note that more recent neuroimaging studies have shown cerebellar abnormalities in several neurological and psychiatric conditions, including depression, bipolar disorder, anxiety disorder, schizophrenia and autism (Baldaçara et al. 2008; Konarski et al. 2005; Moberget and Ivry 2019; Stoodley and Schmahmann 2010). The link with autism appears to be particularly strong. Wang et al. (2014) reviewed several lines of evidence showing that damage to the cerebellum in early human development is related to an increased risk of developing autism spectrum disorder later in life. The resulting deficits, such as hypersensitivity to sensory stimuli, have been interpreted as due to a deficit in cerebellar internal models that predict external events, such as the sensory consequences of behaviour (Sinha et al. 2014). In the absence of temporally precise forward models, neocortical learning and control processes are reliant on slower feedback control mechanisms (Parrell et al. 2017). Moreover, neuroimaging data suggest that even in the normal population, macro- and micro-structural variations in cerebellar areas are linked to variations in personality and mood. For instance, Laricchiuta et al. (2014) used MRI to investigate links between volumetric differences in the cerebellum and personality factors. They found that increased cerebellar volume was linked to higher novelty-seeking tendencies (i.e. increased risk-taking behaviour and sensitivity to rewards), whereas decreased cerebellar volume was associated with higher harm avoidance tendencies (i.e. excessive worrying and pessimism). Considering the universal theory of cerebellar function, these findings suggest that the cerebellum provides internal models of social-cognitive contexts and behaviours that become increasingly accurate and eventually allow behavioural responses to become faster, more precise, and independent of cortical control. The findings are also in line with the continuum hypothesis of mental disorders, namely, that personality traits can range from healthy interindividual variability to abnormal and harmful behavioural profiles (Sommer 2010). Previous studies have shown that individual differences in one's disposition to experience negative emotions can be partially explained by differences in white-matter fibre connections in emotion-related brain networks. For example, trait anxiety in healthy populations has been found to correlate with white-matter microstructure in amygdala-ventromedial prefrontal pathways (Kim & Kim and Whalen 2009). An important goal for future research is to investigate whether individual differences in structural connectivity of the cerebellum are related to variations in the disposition to experience negative emotions and the ability to regulate them.

Human neuroimaging has provided valuable insights into the functional anatomy and connectivity of the human cerebellum (Baumann and Mattingley 2012; Guell et al., 2018; Habas et al. 2009; Habas 2010; Habas 2021; Habas and Manto 2018; Stoodley and Schmahmann 2018). Nevertheless, neuroimaging techniques lack the spatial and temporal precision of invasive axonal tracing and single-cell recording techniques. Therefore, some uncertainty remains regarding the precise functional and structural connectivity of the human cerebellum. Uncovering the functional map and connection parameters of the cerebellum in healthy humans will enhance diagnostic classification and treatment response predictions in individual patients, which will allow clinicians to identify subgroups of patients with distinct pathophysiological causes of emotional dysregulation.

3.6 Conclusion

The cerebellum makes an essential contribution to emotion processing, by facilitating accurate and context-sensitive emotional responses. Our chapter has reviewed various lines of evidence indicating cerebellar contributions to all sub-components of emotion processing, including physiological responses that contribute to the subjective or “feeling” component of emotion, emotional expressions that serve essential social-communicative functions, and the cognitive appraisal process that determines the emotional significance of events and therefore affects the generation and modulation of emotions. Future research aimed at unravelling the functional neural architecture of emotion processing is needed to refine theories posited to explain deficits in emotion regulation in neuropsychiatric disorders associated with cerebellar abnormalities (Konarski et al. 2005). Broader recognition of a cerebellar role in emotional processes will help to identify emotional deficits that at present may go undiagnosed in clinical groups, and will ultimately aid the development of targeted interventions.

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Cerebellum and Emotion Recognition

4

Federico D'Agata and Laura Orsi

Abstract

In this chapter, after having clarified which definition of emotion we followed, starting from Darwin and evolutionary psychology, we tried to examine the main mechanisms of emotional recognition from a behavioral and cerebral point of view: emotional contagion and cognitive empathy. The link between these skills and social cognition has been discussed. We tried to understand through the description of comparative studies on animals, studies on populations with cerebellar lesions in animals and humans, neurostimulation studies, and studies on neuropsychiatric pathologies with alterations to the cerebellar networks the possible involvement of the cerebellum in these mechanisms, also investigating its possible causal role. The evidence, even if mainly of a correlational type, is numerous and robust enough to be able to affirm the existence of significant involvement of the cerebellum in social cognition and in the recognition of negative emotions, especially fear.

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Keywords

Cerebellum · Social cognition · Emotion recognition · Cerebellar stroke

4.1 Some Definition about Emotion and Emotion Recognition

It is important, talking about the cerebellum and emotions, to give some definitions, but it is not easy as there does not exist a consensual definition of what emotions are, either in philosophy or in affective science (Scarantino and de Sousa 2021). It is more common, in exemplificative or prototypical descriptions, to consider emotions as intentional (directed toward something), motivating (fueling action), valenced (positive vs. negative), conscious, short-lived, preverbal, recalcitrant to reason, universal (transcultural and transspecies), associated with typical expressions, embodied, indicators intertwined with arousal and physiological functions (Aristotle et al. 2014; Aristotle and Lanza 1987; Damasio 1994; Descartes 2011; Descartes and Obinu 2010; Hume 1987; Lucretius Carus and Fellin 2013; Sartre and Pirillo 2004; de Spinoza et al. 2017). But their heterogeneity is huge; we can easily think counterexamples (Barrett et al. 2019) of the previous attributes: e.g., long-lived grief, unconscious fear of failing in life, without prototypical facial expression like regret,

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depending on culture like respect, exclusively human-like schadenfreude, and opportunistic signals of admiration or happiness.

Following the *Stanford Encyclopedia of Philosophy* (Scarantino and de Sousa 2021), it could be useful to try to describe an emotion by 5 components: evaluative (e.g., danger detection), physiological (e.g., increased heartbeat), phenomenological (e.g., uneasiness), expressive (e.g., frown), behavioral (e.g., flee), and cognitive (e.g., focus attention). We of course will be more interested in the expressive component that needs to be perceived and processed for emotion recognition, but that, in general, can be absent, hidden, or difficult to detect.

We need to answer the questions of how emotions are expressed, what is the mechanism that humans use to detect and recognize these expressions, why is it useful to identify them, and is the cerebellum necessary, important, or helpful for this task?

We can investigate the role of the cerebellum in the recognition of emotions using tools that try to map neural circuits and areas involved with invasive (e.g., microelectrode array recordings) and noninvasive techniques (e.g., magnetic resonance). Lesions or alterations in the development of cerebellar structures in both humans and animals can also help. Finally, with the comparative study between animal species, we can juxtapose cerebellar and behavioral differences.

The limitations of these tools derive from the fact that they rarely constitute causal evidence but often only correlations. Surely the most robust evidence derives from lesion studies on animal models, but they have other limitations: the communication and understanding of emotions in animals are reduced and they are often studies linked to conditioning paradigms and fear that is the emotion most simple to study and control in an experimental setting.

4.2 Emotion Recognition Mechanisms and Social Cognition

Ekman (2009) commenting on Darwin's pioneering work on emotions (Darwin and Ekman 2009) describes the 5 main contributions that he took up in his theorization: emotions are discrete, are expressed mainly through the face, are universal, are present in other species (among these Darwin mentioned horses, dogs, cats, bees, and roosters), and are "serviceable habit." This last concept is interesting, a "serviceable habit" is not a characteristic that is selected with a precise purpose, but it is simply an association between a helpful behavior and its typical expression. For example, if it can be useful in exploring space to open our eyes when we do it because we feel fear, we will begin to associate this motor reflex with the state of fear. This position has been taken up in a reinforced version by evolutionary psychologists which believe that the expression of emotions may be an adaptive behavior present in different animal species. A growing number of studies suggest that many aspects of higher-order social functions, including emotion recognition, may be present in species ranging from primates to rodents, indicating a conserved role in social animals (Ferretti and Papaleo 2019). An indicator of aggression, for example, can make the encounter between two animals less dangerous, or a signal of joy and optimism can discourage a predator. Where the social aspects become more important and complex, the ability to decipher the expressions of the conspecifics becomes essential. For example, to a group of animals in which the fear felt by one that detects a danger can alert and scare the whole group to safety (Ferretti and Papaleo 2019). In humans, it is even more complex as the emotional expression can be associated with its awareness and the understanding of other mental states, so humans can modulate, control, or simulate emotion expression, at least partially (e.g., acting), without considering the cultural and language aspects that can influence emotion expression and detection.

Two possible, non-mutually exclusive mechanisms underlying emotion recognition have been proposed: emotional contagion and cognitive empathy (Nieuwburg et al. 2021).

Emotional contagion is a rather low-level bottom-up mechanism in which the state of the observed is automatically synchronized with that of the observer by copying the expressions of others and allowing for emotional convergence. To explain the contagion, theories of simulation and imagination have sometimes been proposed (Keysers and Gazzola 2007); the cerebellum could be involved having been observed to have a role in many tasks of this type (Koziol et al. 2014). Some theories propose the mirroring or automatic copying of observed motor behaviors and physiological states (Errante and Fogassi 2020); also in this case the cerebellum could play a role by being involved in learning by association and in many simple and complex reflexes (Bracha et al. 2000).

The second mechanism, the cognitive empathy, requires the ability to recognize emotion in the observed without necessarily experiencing it (Cuff et al. 2016). The most accredited hypothesis is that it is due to a mechanism linked to the representation of the emotions of others or their mental states and that social cognition skills developed subsequently in evolution (Nieuwburg et al. 2021). Primate studies, especially on great apes and Old-World monkeys, have led to results that are difficult to interpret. On the one hand, it seems clear that both mechanisms are present in some species, but it is not possible to decipher a clear pattern to understand if the two mechanisms have evolved from each other and which was the first (Nieuwburg et al. 2021). From the data, it can be assumed, but much more information is needed, that the mechanisms also depend on the sociality of the studied species, on their habitat, and on the type of studied signal (visual or auditory) and that therefore a certain answer cannot be given; we could hypothesize by observing cases of autonomous and parallel evolution of these capacities (Nieuwburg et al. 2021). However, we can certainly say that many non-human species belonging to the order of primates possess these skills in more or less sophisticated forms and that they all share a brain organized in a very similar way, with comparable scale laws, with a very dense neuron packed cerebellum connected to many different brain cortex areas capable of supporting new complex visual-motor and social behaviors (Nieuwburg et al. 2021).

A lot of studies (Ferretti and Papaleo 2019) have shown that many social mammals (dogs, horses, primates, sheep) possess skills related to the recognition of emotions (emotional contagion, contagious yawning, scratching, mimicry, consolation behavior, adaptive behavioral responses to signal like eyes opening, ears moving, lip-smacking, facial expressions) and that these abilities can be extended to recognize emotions also between different species (interspecies interactions). Attempts are being made to expand this type of study to other animals, such as invertebrates (Perry and Baciadonna 2017). There remain many difficulties in approaching the study of emotions in this kind of creatures; above all the Aplysia, the Drosophila, and the bees have been studied (the latter with complex collective and social behaviors). There have been observed variations related to ingeniously crafted stimuli that can be linked to fear and with optimistic and pessimistic behaviors (Perry and Baciadonna 2017). Also, if even in brains as simple as those of the invertebrates described above, phenomena that can be compared to emotional processing can be recognized, it is practically impossible to compare them to the behaviors and abilities observed in social mammals. This observation would be very interesting given the absence of a structure like the cerebellum in these invertebrates under study. However, it is interesting to note that in more complex invertebrates such as the octopus which, from the point of view of ethological observation, demonstrate very complex and behaviors suggestive of emotional processing (Crook 2021), the cerebellum is not present as in the social mammals described above. Even more interesting, however, is the comparative study of the brain structures of cephalopods which identified brain structures with a cellular organization like that of the cerebellum (Shigeno et al. 2018). We generally speak of convergent evolution. Whether this structure can also be involved in the production and recognition of emotions is certainly not possible to say now, but it is an interesting idea that would deserve to be explored.

4.3 Evidence of Cerebellum Involvement in Social Cognition

In 100 milliseconds, humans can decode many social cues that inform about the emotional state of others guiding their behavior. This skill is part of social cognition, the capacity used by humans to understand and interact with other people in a social environment (Frith and Frith 2012). The ability to recognize emotive facial expressions is one of its most important features. The perception of others as subjects endowed with goals, beliefs, thoughts, and emotions, as well as the use of these talents to establish interactions between two or more individuals, will be included in the basic competencies of social cognition (e.g., attachment, teamwork, obedience, imitation, respect of social norms). Children can respond to social stimuli (e.g., facial expressions, joint attention) at a very early stage in their development (Richards 1974; Striano and Reid 2006), and developing these abilities is critical. However, there are numerous unanswered problems, the most important of which is whether social cognition is a distinct type of cognition or if it is based on a general mechanism adapted from emotion and cognitive processing. It is important to note that the cerebellum is engaged in many cognitive and affective skills that are required for good social cognition functioning, but its specificity is more debatable. Two main topics in social cognition recall the two main mechanisms of emotion recognition: the mirroring field, and the theory of mind (ToM) field, which studies the role of midline structures in mentalizing about the states of others (Keysers and Gazzola 2007). The study of important brain areas for social cognition has revealed that it requires a large, distributed network that connects many different areas specialized in different tasks, such as goal selection, action planning, appraisal, and evaluation, rather than a single specialized area with a small number of neurons (Adolphs 2009). An important specialized area, for humans, is the fusiform gyrus and, in general, the lower ventral areas of the temporal lobe that are important for semantic decoding of shapes and the visual processing of faces (Fonville et al. 2014; Harry et al. 2013). However, it has been shown that other areas are involved when expressions become dynamic and are not simple static images; in this case, the inferior occipital gyrus and the superior temporal sulcus play a decisive role working together (Ishai 2008). Premotor areas, in particular the ventral area F5 which contains mirror neurons in monkeys, were observed to be active in the perception of expressions (Likowski et al. 2012). Another key area for the recognition of emotions is the amygdala (Adolphs 2010). Many have hypothesized that there are two different processing paths, a fast and phylogenetically older one aimed above all at the recognition of fear that includes the amygdala and a slower one capable of greater detail and precision in the classification (Dolan and Vuilleumier 2003). It is not clear whether the fast path is somehow independent of consciousness or if there are simply parallel channels involving multiple areas including, among others, the amygdala, the orbitofrontal cortex, the anterior insula, and the anterior cingulate cortex (Pessoa et al. 2002). Furthermore, the idea that the amygdala can only be involved in the recognition of fear, or general negative emotions related to avoidance behaviors, has recently been challenged. Currently, the opinion is that the amygdala can rapidly discriminate the emotional value and therefore also process positive emotions (Britton et al. 2006). It is very interesting to note that the cerebellum plays a significant role in this network by working together with many of the aforementioned areas. Depending on the brain area, there are specific connections to the cerebellum that can work together with integration and automation functions. It is therefore certain that the cerebellum relates to this network, less certain its role. In particular, the posterior lateral cerebellum (Crux I and II) works together with the prefrontal cortices, while the posterior cerebellar vermis works together with the amygdala and the ventral orbitofrontal medial areas (Adamaszek et al. 2017).

Some studies, especially in the rat, have tried to clarify which areas are responsible for emotion-based behaviors and have found some overlap between the different species. The amygdala, the insula, and the anterior cingulate cortex were found as significant areas (Ferretti and Papaleo 2019). However, the precise role that these areas play in emotional recognition in animals remains to be clarified.

However, also if we can describe the network related to social cognition, it remains to be demonstrated if social cognition is hard-wired into the brain or not (Baetens et al. 2014; Balsters et al. 2013). There is convincing evidence derived from data obtained in healthy subjects and patients with cerebellar damage of the involvement of the cerebellum in many basic social cognition skills. Healthy subjects showed posterior cerebellar activations during joint attention (Gordon et al. 2013), during anticipation of social group success (Aue 2014), during observation and imitation of facial emotions (especially negative emotions), during goal-directed actions (Gazzola and Keysers 2009; Schraa-Tam et al. 2012), and during mother–infant interaction (Rocchetti et al. 2014). In a meta-analysis (Van Overwalle et al. 2014), partial involvement of the cerebellum was found in event or person mentalizing or mirroring tasks. In addition, a critical contribution to higher abstraction mentalizing was found as well. Several important findings correlate connections of the cerebellum to brain areas, in particular, the amygdala and the frontal cortex, with the size of the social group or social status, both in humans (Kanai et al. 2012; Zink et al. 2008) and in monkeys (Noonan et al. 2014; Sallet et al. 2011).

Cerebellar stroke patients showed impairment in the ability to recognize emotions (Adamaszek et al. 2014, 2015). In the first study, Tübingen Affect Battery (TAB) was used to assess recognition of emotional facial expression and emotional prosody in 15 patients with a cerebellar infarction and 10 age-matched controls. The patient group revealed only slight to moderate ataxia or dysarthria, and no disturbances of ocular movement or evidence of mood disorder. There was no significant difference between groups in simple discrimination subtests, but the patient group had lower performance than controls in emotional subtests. The amount of impairment was greater for more demanding tasks such as cognitive and cross-modal subtests, as evidenced by large effect sizes. This pattern of impairment was observed for both facial and prosody stimuli. In patients, fear was significantly associated with more errors; the larger the volume of the lesion the greater the deficit on more emotional and complex tasks. The great majority of the patient sample had lesions of the posterior lobes of the cerebellum (see Fig. 1, first row). The second study comprised eight patients with discrete ischemic cerebellar lesions and eight control patients without any cerebrovascular stroke using event-related potential (ERP) to measure responses to faces from the Karolinska Directed Emotional Faces Database. Analyzing the late ERP responses, the N170 amplitude, indexing early perception of faces, was pronounced in all participants for faces compared to non-face neutral images indicating preserved recognition of faces in comparison to non-facial stimuli for both samples. Also, the late positive potential (LPP) showed clear augmentation to faces compared to non-facial neutral stimuli in both groups, but late ERP in parietal areas responses to emotional vs. neutral face expressions, however, was only significantly increased for faces with an emotional expression compared to neutral faces in the control group. Analyzing each facial emotional expression, the cerebellar lesion group showed diminished LPP for anger and particularly for fear (the other emotions showed only a trend), a negative correlation between the volume of cerebellar infarction and LPP for fear at both parietal sensors, and a strong negative correlation between some TAB subtests and diminished LPP for fear. Correlation analysis indicated that lesions of cerebellar area Crus I contribute to ERP deviations (see Fig. 1, third row, for the localization of the lesions).

Similar results have been found in patients with cerebellum degeneration (spinocerebellar

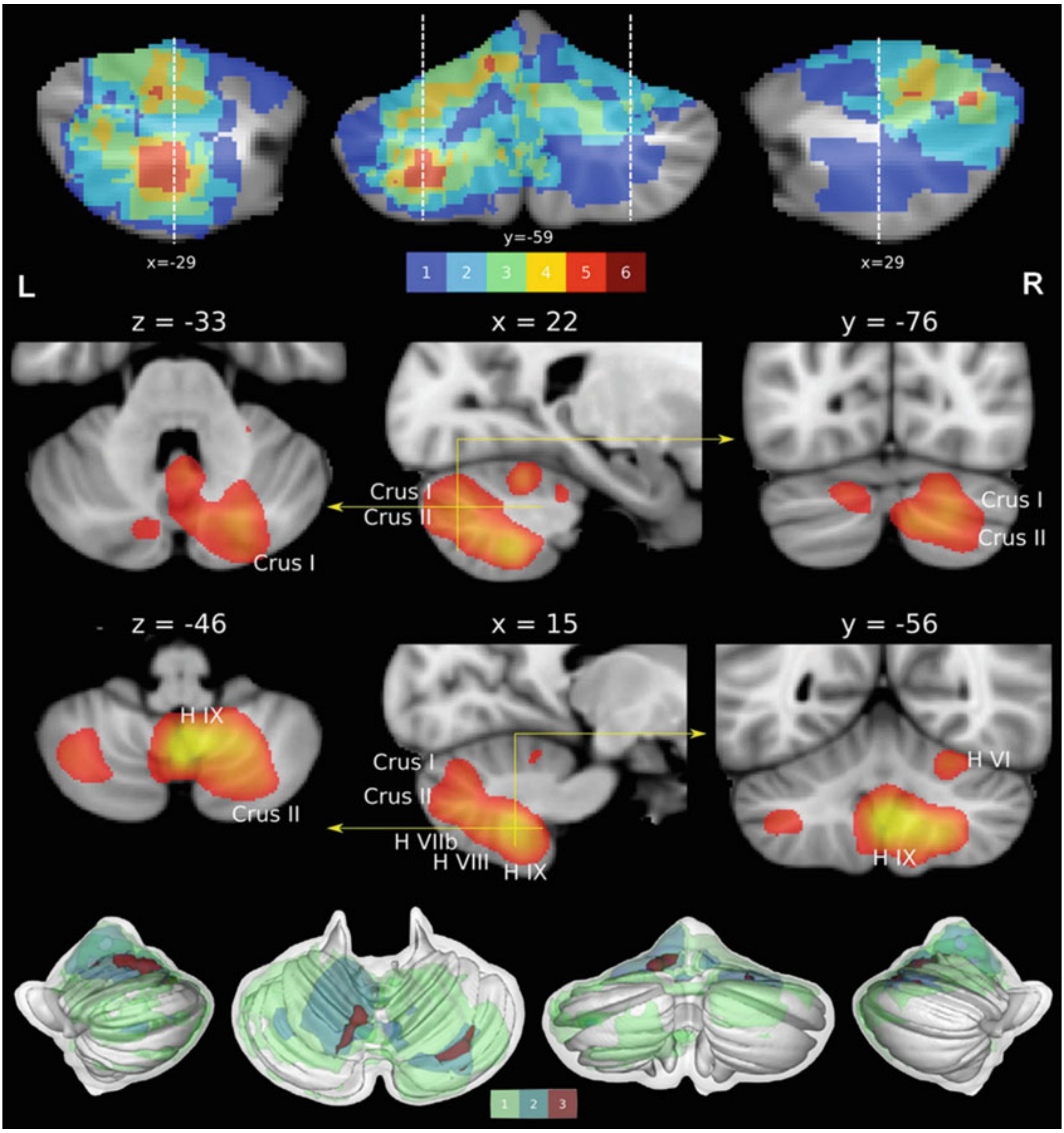

Fig. 1 Lesion mapping correlations for stroke and deficits in emotion recognition. *L* left, *R* right, *H* cerebellar hemisphere, MNI coordinates in mm. Composite image of cerebellar lesions of patient sample superimposed on axial, coronal, and sagittal projections of the cerebellum. First row 15, second row 22, and third row 8 stroke patients. The overlapping is color coded (second row red = 1 patient, yellow = 3 patients). Adapted by Adamaszek et al. (2014, 2015, 2019) with permission

ataxia); they had deficits in ToM and recognition of face emotional expressions, especially of social emotions like guilt, with a gradient related to the complexity of the stimulus (Clausi et al. 2018; D'Agata et al. 2011; Sokolovsky et al. 2010). The specificity of these findings can be questioned; cerebellar degeneration could be large nonfocal and associated with psychological and neuropsychological dysfunctions (Orsi et al. 2011). Also, cerebellar strokes could be associated with a wide spectrum of psychological, behavioral, and cognitive alterations (Adamaszek et al. 2017).

Two studies strengthened the link between cerebellum and emotion recognition beyond a simple correlation. In the first (Adamaszek et al. 2019) the controls to compare the 22 cerebellar strokes (CI) were 22 Parkinson's disease patients (PD) and 16 supratentorial strokes. In the study also age, cognition, and mood were controlled to mitigate the confounding factors. There were no differences for age, sex, education, or handedness between the 3 groups; low BARS scores indicated motor disabilities below the moderate level; thus, patients predominately had slight to moderate ataxia or dysarthria, section III UPDRS scores indicated moderate motor impairment for PD, and supratentorial stroke subjects had only slight motor disability with a low NIHSS score. On post hoc testing, CI was significantly lower, attributable to the TAB emotional subtests, but not the perception subtests. In CI fear errors were significantly greater. Examining topographic descriptors, the most common lesions were in the posterior cerebellum (crus 1, crus 2, or both) and the 3 patients without involvement of these regions had normal TAB scores (see Fig. 1, second row). The neuropsychological assessment did not reveal significant differences between the groups.

In the second (Ferrucci et al. 2012) 22 right-handed volunteers participated in the study; reaction times (RTs) and accuracy (number of incorrect responses) were collected during an emotion recognition task. Anodal and cathodal cerebellar tDCS (20 minutes) both significantly enhanced sensory processing in response to negative facial expressions but left positive emotion and neutral facial expressions unchanged. Sham tDCS and over the right prefrontal cortex did not have any effect.

Patients with schizophrenia have changes in fronto-temporal-thalamo-cerebellar networks, decreased cerebellum volume, and cerebellar neurotransmitter dysfunctions in clinical groups (Yeganeh-Doost et al. 2011). Affective bluntness, emotion detection deficiencies, and social difficulties are all hallmarks of schizophrenia, and they may be linked to cerebellar-derived changes in emotion, leading to conflicting findings for ToM (Mothersill et al. 2016).

Research on autism spectrum disorder provides some of the most convincing evidence (ASD). The deletion of Tsc1 (tuberous sclerosis 1) produces morphological changes in Purkinje cells as well as aberrant behavior, including disrupted social interactions, in genetically engineered mice, implying a direct relationship between cell function and ASD deficits (Tsai et al. 2012). Patterns of ASD gene coexpression are specifically expressed in the cerebellum throughout the early postnatal years; also, early disturbance of the cerebellar circuitry is strongly connected with ASD, with a risk ratio as high as 40 (Wang et al. 2014).

Developmental diaschisis is a fundamental concept that has emerged: cerebellar dysfunction during critical sensitive periods may disrupt the maturation of distant neocortical circuits (Wang et al. 2014); ASD deficits resulting from early-life lesions are, with the exception of the cerebellum, to a large extent recoverable over time (Fig. 2).

Many ASD symptoms (motor, emotional, and social) can be grouped into a framework that shows the illness as a prediction deficit (Sinha et al. 2014) caused by a loss of frontal cortex-cerebellum connectivity throughout development.

This fronto-cerebellar network may play a role in both ontogeny and phylogeny. It has been discovered that the posterior cerebellar lobes, frontal cortices, and pontine connections coevolved in parallel in monkeys and humans (Balsters et al. 2010; Ramnani et al. 2006). These cerebello-thalamo-cortical networks are important in human evolution (Barton 2012), but whether the use of tools or the size and complexity of the social group was the key determinant of evolutionary pressure is still debated (Dunbar and Shultz 2007). Some researchers used phylogenetic comparative analysis to show that the cerebellum and frontal structures not only co-evolved but were also related to tool development and the size of the social group (Barton 2012). This means that if we think of the cerebellum as part of a single system, both in terms of phylogeny and ontogeny, we can see how vital it is in the development of many critical social cognitive skills.

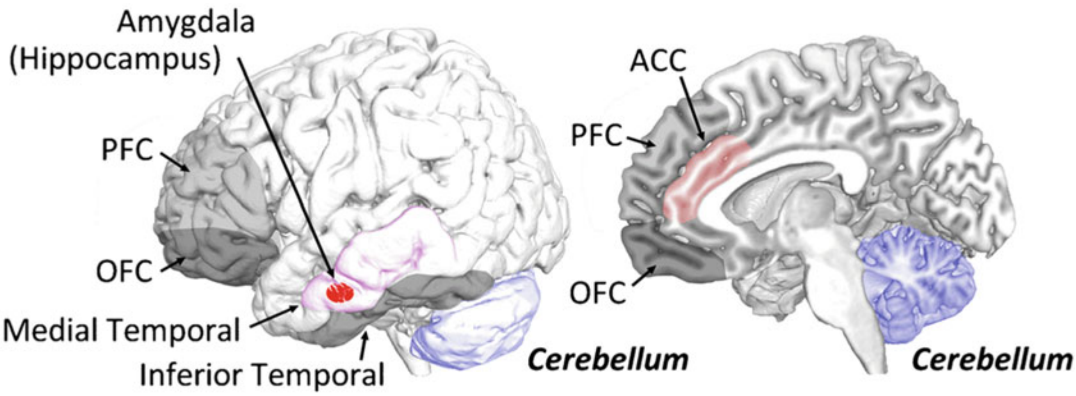

Fig. 2 Lesion mapping for early and late injuries resulting in autism social deficits. Brain areas result in lasting autism spectrum disorders and social deficits when injured neonatally (blue), in adulthood (red), or that can be fully or partially compensated after an injury regardless of age (light or dark gray). Medial temporal area is depicted in violet to indicate that both neonatal and adult injuries can cause social deficits, but only if the whole medial structures are damaged; for neonatal lesions, deficits are not compensable. Data about ACC neonatal lesion are nowadays lacking. *PFC* prefrontal cortex, *ACC* anterior cingulate cortex, *OFC* orbitofrontal cortex. Brain renders were realized with Mango (http://ric.uthscsa.edu/mango) from the MRIcron canonical ch2better.nii template (http://www.mccauslandcenter.sc.edu/mricro/mricron). Adapted by (Wang et al. 2014). Copyright 2014 by Cell Press. Adapted with permission

4.4 Conclusions and Future Research

In conclusion, we can summarize the chapter.

First, in the future, it is necessary to improve the definition of emotion to make the experimental results more comparable. However, since this is a problematic and complex operation, researchers should, at least, start by clearly signaling their position, making explicit the operational definition of the measures used and the theoretical framework adopted.

Second, we can affirm, with some confidence, that there is evidence of the involvement of the cerebellar system in emotion. Similarly, we can consider as probable the role of the cerebellum in social cognition in understanding the emotional state of other humans, especially when they express negative emotions such as fear. However, doubts remain about the specificity and the moment in which this role is played. It is therefore essential to investigate with causal studies and no longer just correlational ones. A family of techniques that appears very promising in this sense is that of noninvasive brain neurostimulation (NIBS). For such studies to be valid they must be properly constructed. A suggestion could be to start from the coordinates extracted from meta-analyses of neuroimaging studies to hypothesize the cerebellar areas most likely involved and to use these as neurostimulation targets. A paradigm of interference during emotional recognition tasks seems to be the first choice, ideally repeating the interference at different times, guided by an accurate timing that can distinguish the various stages of processing during emotional recognition, perhaps using EEG monitoring, compatible with the stimulation for triggering. Furthermore, an adequate number of multiple control conditions must be considered to reinforce the conclusions. It should be verified that stimulations of the frontal cortex do not lead to the same type of interference and that stimulations on the back of the head, close to the scalp coordinates of cerebellar stimulation but affecting the visual occipital cortex, do not have a similar effect. Finally, cognitive and attentional tasks should also be evaluated during stimulation of the same cerebellar and control sites of stimulation to verify the cerebellum specificity during emotional processing.

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Cerebellum and Emotion Memory

5

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Abstract

Fear is an important emotion for survival, and the cerebellum has been found to contribute not only to innate affective and defensive behavior, but also to learned fear responses. Acquisition and retention of fear conditioned bradycardia and freezing have been shown to depend on the integrity of the cerebellar vermis in rodents. There is a considerable number of brain imaging studies, which observe activation of the human cerebellum in fear conditioning paradigms. Different to what one may expect based on the initial cerebellar lesion studies, activations related to the learned prediction of threat go well beyond the vermis, and are most prominent in the lateral cerebellum. Different parts of the cerebellum likely contribute to learning of autonomic, motor, emotional and cognitive responses involved in classical fear conditioning. The neural operation which is performed in the various parts of the cerebellum is frequently assumed to be the same. One hypothesis is that the cerebellum acts as, or is part of, a predictive device. More recent findings will be discussed that the cerebellum may not only be involved in the processing of sensory prediction errors, but also in the processing of reward and reward prediction errors, which may play a central role in emotions and emotional learning. Current knowledge about the intrinsic learning mechanisms underlying fear memory in the cerebellum, and its connections with subcortical and cortical fear circuitry will be presented. The chapter will conclude with a discussion on how disordered cerebellar fear learning may contribute to affective disorders.

Keywords

Fear · Conditioning · Aversive · Survival · Eyeblink · Freezing · Skin conductance response

5.1 Introduction

The cerebellum is well known for its contribution to motor learning, and disorders in motor learning have been related to motor performance deficits in patients with cerebellar disease (Miall et al. 1993; Bastian 2006). The cerebellum is likely also involved in learning and memory processes in the cognitive and emotional domains (Timmann et al. 2010; Apps and Strata 2015), but this has been studied in much less detail. In the emotional domain, most studies have examined the

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contribution of the cerebellum to learning and memory of fear, an important emotion for survival. In this chapter, we will focus on human and animal findings on classical fear conditioning.

5.2 Fear Conditioning, a Behavioral Paradigm to Study Emotion Memory in Animals and Humans

The conservation and evolution of the cerebellum from ancient fish to man implicate its necessity for survival. It most likely plays an important role in coordinating an animal's defense system (e.g., flee, freeze, attack, startle response) in response to threats and dangerous situations, so they can respond in a timely and appropriate manner. The fight or flight response equally occurs in humans in response to harmful events or threat. Fear can not only be triggered by adverse stimuli but also by a previously neutral stimulus or cue in the environment which was coupled to an adverse stimulus. This conditioning process where an unconditioned stimulus (US), for example a predator, is coupled to a conditioned stimulus (CS) such as rustling leaves to elicit a freezing response. So, the next time the animal hears the rustling of leaves it associates this auditory cue with the predator and freezes regardless if the predator is present due to fear memory. Fear conditioning also happens in humans. For example, if a certain song plays on the radio at the time one gets involved in a serious car accident, hearing the same song will elicit fear, at least for some time in the future. The ability to extinguish a no longer threatening fear memory, a process called extinction is equally important for survival. For example, an animal would waste its resources on seeking food in a place further away from home when the threat no longer exists. To better understand the mechanisms underlying these processes, scientists developed the classical Pavlovian fear conditioning paradigm based on the findings of Ivan P. Pavlov on conditioned reflexes which is widely used in animal and human research. Many of the basic principles defining the terminology that Pavlov coined such as conditioning, conditioned versus unconditioned stimuli, extinction and delay are still being used today (Pavlov 1927, see Pavlov 2010 for translation). In delay conditioning, the conditioned stimulus (CS) is presented prior to the onset of the unconditioned stimulus (US), and the CS and US end simultaneously. The majority of fear conditioning experiments in rodents use an established cue dependent fear conditioning paradigm where an electrical foot shock (US) is coupled to a tone (CS) and results in freezing or other fear conditioned responses (CR; Fig. 5.1) (Wotjak 2019). In humans, the most commonly differential fear conditioning protocols used include the presentation of a CS+, e.g., a visual cue, which is followed by an aversive unconditioned stimulus (US), e.g., an electrical shock, and a CS- which is never followed by an aversive US (Fig. 5.2) (Lonsdorf et al. 2017). A CS- is presented to control for non-associative processes like orienting responses, sensitization and habituation. In humans, skin conductance responses (SCR) and questionnaires (e.g., valence and arousal ratings) are common measures to assess conditioned responses (CR). Retrieval of fear CRs requires time to consolidate (consolidation) the fear memories. Although only implicit fear memories caused by an automatic reflexive fear response can be measured in animals, they may have various memory systems as in humans, but we currently have inadequate paradigms to identify these memory storage systems. Retrieval of these CRs can be cue dependent (i.e., tone exposure alone in a new context) and/or context dependent. A cue dependent retrieval response (e.g., freezing in rodents) relies on mainly exposure to the CS alone (tone) in a completely novel context. Whereas context dependent fear retrieval relies on subjection of the animal to the identical context (environment) in the absence of the CS or US. In human fear conditioning protocols, acquisition and retrieval of conditioned responses are often tested in the same context, and cue- and context-related fear associations are not clearly separated. Repetitive exposure to the CS alone in a novel context or the same context without the CS or US eventually leads to the extinguishing of the CR, a process called

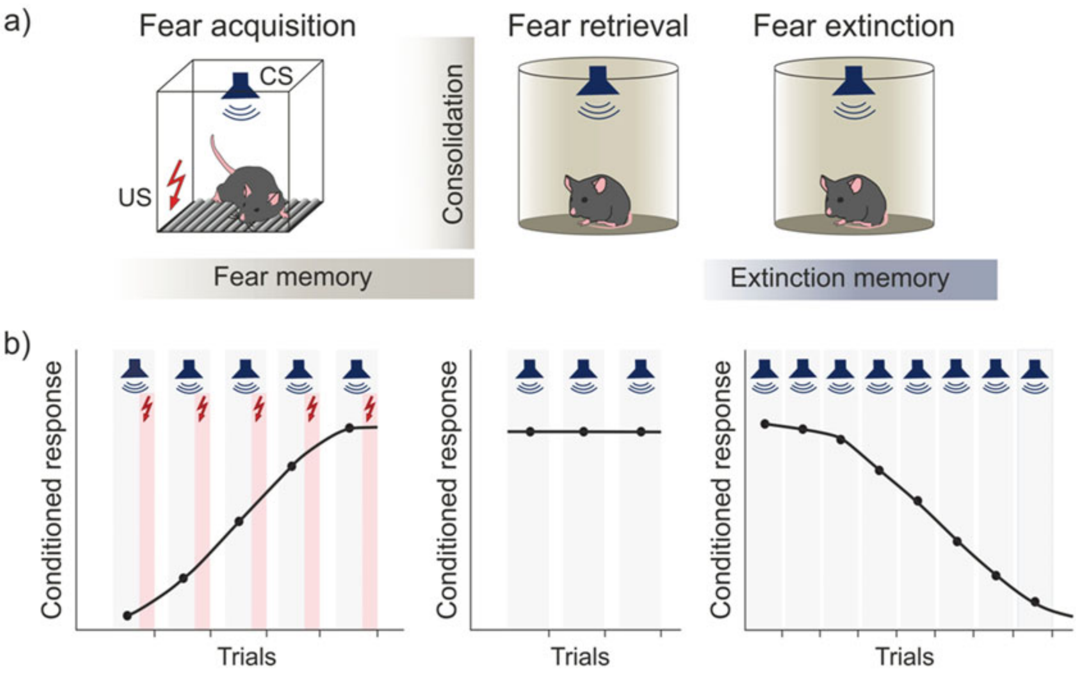


Fig. 5.1 Cue dependent fear conditioning paradigm in rodents. (**a**) Schematic diagrams depicting the different conditions in which rodents learn the fear association. Coupling of a former neutral tone, the conditioned stimulus (CS) to an aversive foot shock, the unconditioned stimulus (US) results in a fearful conditioned response (i.e., freezing) to the tone (CS). After a 24 h fear memory consolidation period, the fear memory is tested in the retrieval session by exposure to the conditioned stimulus (CS) in a new unfamiliar context. Fear extinction is the result of a decrease in the conditioned response through the formation of an extinction memory which counteracts the persistent fear memory. Erasure of the initial associative memory also plays a role. (**b**) A schematic drawing of the conditioned response to the CS. At the beginning of fear acquisition, the fear response to the tone is absent. After a few repetitions of CS/US pairings, the animal associates the tone with the shock, and the conditioned response evolves and increases. Fear retrieval shows a high conditioned response to the tone alone which indicates that the rodent learned the association. Fear extinction leads to a decrease of the conditioned response by repeated exposure to the CS alone until the animal is no longer reacting with a conditioned response to the CS

extinction. Extinction of fear memories is equally important as formation of fear memories for the survival and conservation of resources. In contrast the over exaggeration of these emotions can lead to anxiety disorders, post-traumatic stress and phobias in humans. The role of the cerebellum and its circuitry in the acquisition and extinguishing of fear memories is incompletely understood (Hu et al. 2015). However, new insights from animal and human studies provide us with a better mechanistic understanding of fear memories from a cerebellar perspective which will be reviewed in this book chapter.

5.3 Cerebellum Contribution to Fear Memory: *Findings in Animals*

The first indications that the cerebellum is involved in defensive behaviors began with cerebellar electrical stimulations to cerebellar vermis and fastigial nuclei regions in cats. These stimulations produced a hypersensitivity to sound and touch, and escape behaviors such as struggling, lashing of the tail and rage (Clark 1939; Chambers 1947; Moruzzi 1956). In contrast, cerebellar vermis or fastigial nuclei ablations led to docile behaviors and lethargy in

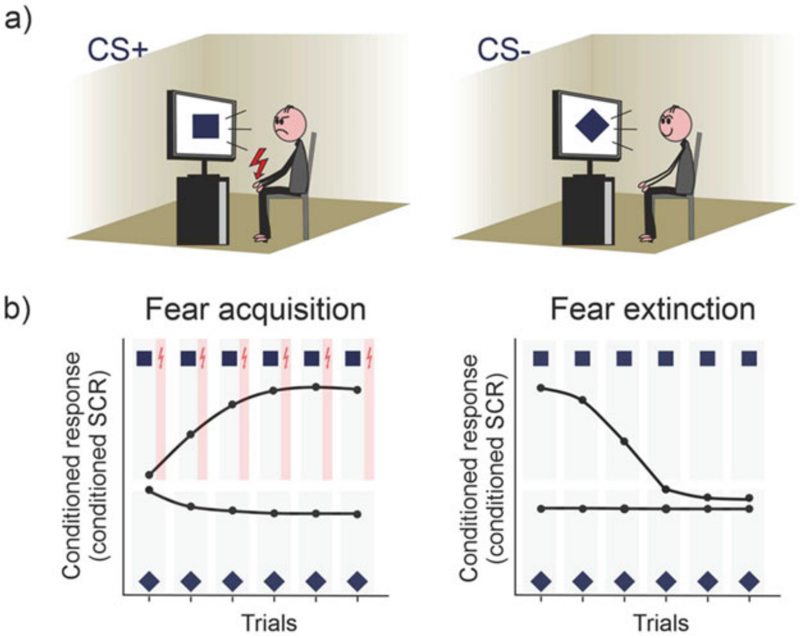


Fig. 5.2 Differential fear conditioning paradigm in humans. In the fear acquisition phase, one conditioned stimulus (the CS+, here: a square shown on the screen) is coupled with the aversive US (here: an electric shock applied to the hand), whereas another conditioned stimulus (the CS-, here: a rhombus shown on the screen) is never coupled with the unconditioned stimulus (US). Participants learn that the appearance of the CS+, but not the CS- predicts the occurrence of the US. As a consequence, the presentation of the CS+, but not the CS-, elicits conditioned fear responses, e.g., an increase of skin conductance responses. In the extinction phase, neither the CS- nor the CS+ are followed by the US. In initial CS+ extinction trials, the learned fear is retrieved. During extinction training participants learn that the CS+ is no longer followed by the US, and fear responses no longer occur. Note that in human fear conditioning studies, acquisition and extinction learning is frequently done in the same context

cats and monkeys (Chambers and Sprague 1955; Sprague and Chambers 1959; Peters and Monjan 1971; Berman et al. 1974). Furthermore, lesion studies in rat cerebellar vermis elicited active nearing to a cat, substantial reduction in freezing and less defecation. Whereas non-lesioned controls showed the complete opposite in all categories, actively tried to avoid the cat and showed increased freezing and defecation. Under fearful conditions rats will show less general activity to novel, brightly lit open areas and thigmotaxis (wall-hugging behavior). Lesioned rats showed more general activity, less thigmotaxis and decreased latency to center compared to their controls in a brightly and dimly lit open field. Similarly, vermal lesioned rats recovered much faster from neophobia (a fear of new) to new drinking water than controls (Supple et al. 1987). Lesions of the ventromedial hypothalamus (VMH) provoke over exaggerated defense behaviors in different mammalian species (Albert and Walsh 1982, 1984) which are reduced by cerebellar vermal lesions in rats. These included an attenuation of hyper-defensiveness, spontaneous mouse killing and freezing in otherwise aggressive VMH lesioned rats (Supple et al. 1988).

The cerebellum has been found to contribute not only to innate affective and defensive behavior, but also to learned fear responses. Acquisition and retention of fear conditioned bradycardia have been shown to depend on the integrity of the anterior cerebellar vermis in rats (Supple and Leaton 1990; Supple and Kapp 1993). Likewise,

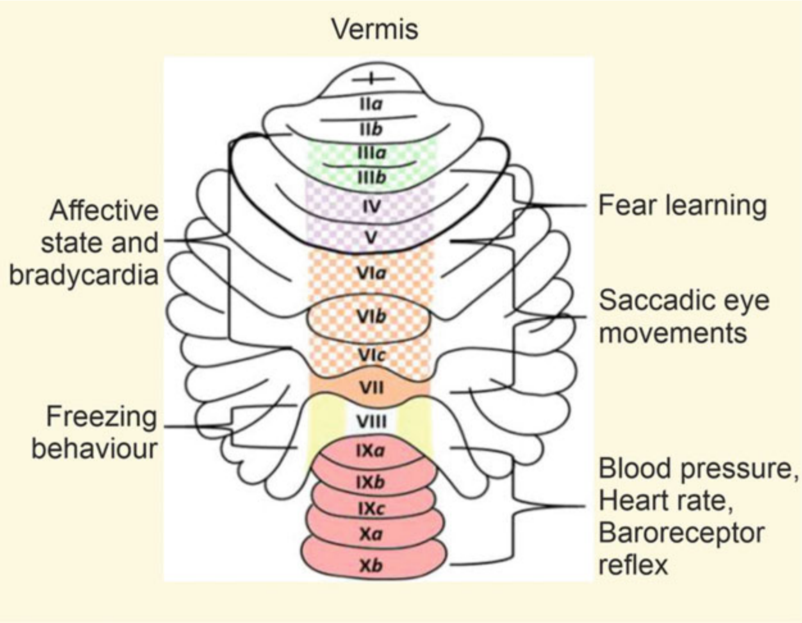


Fig. 5.3 Regions of the cerebellar vermis associated with different functions related to defensive behaviors. Shown localization of functions are predominantly based on studies in rodents. Reproduction of Fig. 5.8 published in the section "The Cerebellar A Module and Emotional Behavior" by Lawrenson, Lumb and Apps (published in Apps et al. 2018; Creative Commons Attribution license)

inactivation of the cerebellar cortex by irreversible ablation and reversible localized lidocaine administration impaired the acquisition of conditioned cardiac responses in a classical fear conditioning paradigm where a visual light (CS) was coupled to an electric shock (US), and bradycardia was measured as the CR in goldfish (Yoshida et al. 2004; Yoshida and Hirano 2010). In these studies, unconditioned heart rate responses remained unchanged. The cerebellum has also been shown to contribute to fear conditioned freezing (Sacchetti et al. 2002; Watson et al. 2013; Koutsikou et al. 2014). More specifically, vermal lobule VIII is involved in innate and learned freezing behavior (Fig. 5.3; Watson et al. 2013; Koutsikou et al. 2014; Apps et al. 2018). The contribution of the cerebellum to fear conditioned freezing appears to go beyond the medial cerebellum. Sacchetti and colleagues (Sacchetti et al. 2002, 2007) found that irreversible inactivation of the cerebellar vermis and interposed nuclei during consolidation drastically diminished retrieval of freezing to acoustic and contextual fear tests. More recently, disordered fear conditioning has also been shown in mouse models of cerebellar degeneration. For example, a complete knock in and Purkinje cell (PC) specific transgenic mouse model for spinocerebellar ataxia type 1 (SCA1) showed deficits in fear conditioning (Asher et al. 2020). Together these data implicate a cerebellar role not only in the acquisition but also the consolidation of fear memories.

5.4 Cerebellum Contribution to Fear Memory: *Findings in Humans*

As outlined above, lesion data in rodents show that fear conditioned bradycardia is severely attenuated following lesions of the vermis, whereas fear conditioned bradycardia remains intact following lesions of the intermediate cerebellum (Lavond et al. 1984; Supple and Leaton 1990). Lesions of the intermediate cerebellum, in particular of lobule VI and the interposed nuclei, however, are well known to abolish acquisition, recall and relearning of conditioned nictitating membrane/eyelid responses in rodents (Lavond et al. 1984; Christian and Thompson 2003; Freeman and Steinmetz 2011). Although comparatively few studies have investigated fear conditioning in patients with cerebellar disease, findings are in good accordance with the rodent lesion data: Fear conditioned potentiation of the startle response was reduced in patients with lesions of the cerebellar midline, but remained intact in patients with lesions of the lateral cerebellar hemisphere (Maschke et al. 2000). Likewise, patients with lesions of the medial cerebellum showed attenuated fear conditioned bradycardia (Maschke et al. 2002). Lesions of the cerebellar hemisphere, in particular lobule VI, on the other hand, impede the acquisition and storage of conditioned eyeblink responses in humans (Topka et al. 1993; Gerwig et al. 2003; Thieme et al. 2013).

The observation that different parts of the cerebellum appear to be involved in fear conditioning and in eyeblink conditioning has been interpreted within the framework of the two-stage or two-factor theory of aversive conditioning (Thompson et al. 1987; Lindquist 2020). According to this theory, conditioned fear responses are acquired in a first and fast stage of learning. Conditioned fear responses are nonspecific CRs, that is they occur in response to any kind of aversive US (Winters et al. 2002). Specific CRs are learned in a second and slower stage. Specific CRs are discrete skeletal motor conditioned responses, e.g., conditioned eyeblink responses. Learned fear is thought to be a necessary prerequisite to acquire specific aversive reactions. In fact, a third stage of learning has been proposed, in which the initially acquired fear responses are extinguished because they are no longer needed (Magal and Mintz 2014; Lindquist 2020). The first stage of aversive conditioning is usually associated with the amygdala and the second stage with the cerebellum. In the suggested third stage of learning, fear-related memory has been proposed to be extinguished in the amygdala via output of the cerebellar nuclei (Magal and Mintz 2014). The observation that stimulation of the cerebellar nuclei inhibited responses of the amygdala to aversive periorbital stimulation appears to support this hypothesis (Magal and Mintz 2014). The two- (or three)-stage theory of aversive conditioning has recently been challenged. Acquisition of conditioned eyeblink responses is likely facilitated by preceding fear conditioning because of a change in salience of the unconditioned and conditioned stimuli gated via the amygdala, but does not require learning in the amygdala (Farley et al. 2016; Steinmetz et al. 2017). Recent findings in humans support the so-called sensory gating hypothesis of the amygdala (Inoue et al. 2020). Concomitant fear extinction impeded extinction of eyeblink CRs, which was accompanied by increased autonomic responses. Fear extinction, however, was not significantly altered by concomitant eyeblink extinction. Findings are difficult to explain with the two-stage theory of aversive conditioning, which predicts the suppression of conditioned fear once conditioned eyeblinks are acquired. Thus, conditioning of autonomic fear responses and specific aversive motor reactions appear to be two largely autonomous forms of associative learning, and as outlined above, different areas of the cerebellum are involved. In fear conditioning paradigms, on the other hand, learned associations go beyond the association of autonomic responses.

There is a considerable and still growing number of brain imaging studies, which observe activation of the human cerebellum in fear conditioning paradigms. Different to what one may expect based on the initial cerebellar lesion studies focusing on fear conditioned bradycardia, activations related to the learned prediction of threat go well beyond the vermis. In fact, in most human brain imaging studies, activations in the lateral cerebellum are most prominent. In a seminal functional magnetic resonance imaging (fMRI) study, Ploghaus et al. (1999) reported that the experience of pain activated the anterior cerebellum including the vermis, whereas the anticipation of pain activated the posterior cerebellar hemispheres. Although this dissociation could not be replicated in later studies (Michelle Welman et al. 2018; Ernst et al. 2019), many studies found fear learning-related activations in the posterolateral cerebellar hemispheres. For example, Fischer et al. (2000) reported fear learning-related increases of regional cerebellar blood flow (rCBF) in the left cerebellar hemisphere using positron emission tomography (PET). In another PET study examining fear conditioned

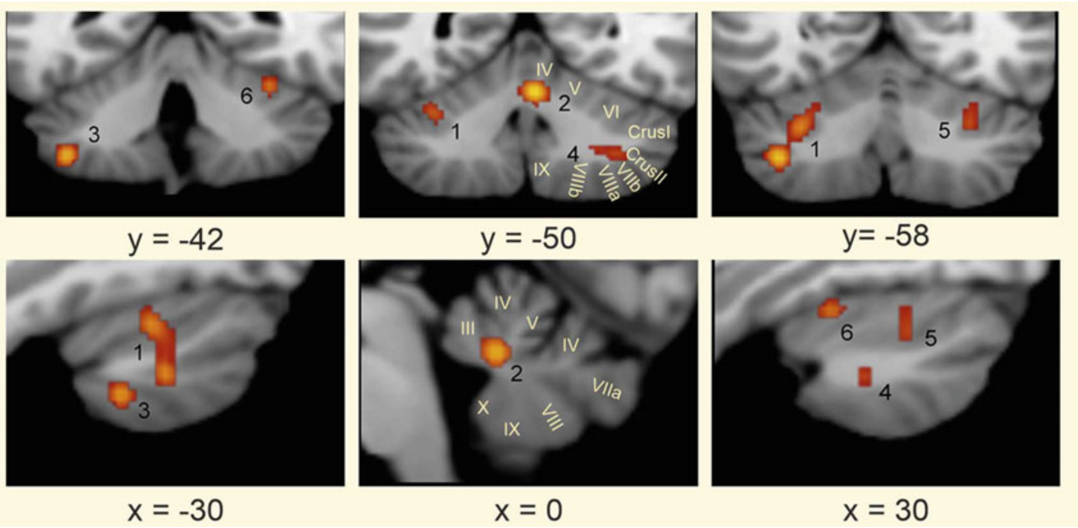


Fig. 5.4 Regions of the cerebellar cortex associated with fear acquisition learning based on a meta-analysis of functional magnetic resonance (fMRI) data in humans. Adapted from Fig. 5.2 in Lange et al. (2015; with permission, Elsevier licence number 5046410366972). Numbers indicate six clusters of significant activation-likelihood in the cerebellum associated with fear learning. Labelling of cerebellar lobules has been added according to MRI atlas of the cerebellum published by Schmahmann et al. (1999). *x*, *y* = Talairach coordinates

potentiation of the startle response, increased rCBF was found in the medial cerebellum, but within the left cerebellar hemisphere related to the initial conditioning of fear (Frings et al. 2002). In subsequent years, many fMRI studies observed cerebellar activations related to the acquisition of learned fear, as long as the cerebellum was included in the field of view. Lange et al. (2015) performed a meta-analysis of 21 fear conditioning fMRI studies which reported cerebellar activations. They found cerebellar activations in six cerebellar clusters (Fig. 5.4). One cluster was localized in the culmen (that is vermal lobules IV and V) which is in good accordance with the early animal and human lesion studies (Fig. 5.3; Apps et al. 2018). The other clusters were found in both cerebellar hemispheres. Anatomical labelling included lobules IV, V, VI and IX. Later studies also reported activations in Crus I in addition to lobule VI bilaterally (Michelle Welman et al. 2018; Ernst et al. 2019). These areas in the cerebellar hemispheres overlap with areas known to contribute to motor, emotional and cognitive processes (Guell et al. 2018; King et al. 2019). This suggests that the cerebellum contributes to a multitude of responses which are learned in fear conditioning paradigms.

Firstly, lobule V and part of lobule VI are part of the motor area in the anterior cerebellum, more specifically the hand representation is localized in lobule V (Manni and Petrosini 2004). Seymour and colleagues (Zhang et al. 2016) performed electromyography (EMG) to detect muscle activity of the arm in a fear conditioning fMRI study. Muscle activity recorded in the CS-US time window showed a significant correlation with fMRI signals at the border of lobules V and VI within the ipsilateral cerebellar hemisphere. Thus, activation of cerebellar motor areas is likely related to (subliminal) conditioned limb withdrawal responses in fear conditioning paradigms. Zhang et al. also recorded EMG from facial muscles and skin conductance responses (SCRs). Aversive facial expressions and the autonomic SCRs are unspecific responses to threat, and learned responses correlated with fMRI activation in amygdala-striatal regions. One may also have expected activations of the cerebellar vermis. Indeed, vermal activation was observed in the meta-analysis performed by Lange et al. (2015), but is frequently missing in individual fear conditioning fMRI studies (e.g., Ploghaus et al. 1999; Ernst et al. 2019).

Anatomical and functional brain imaging data provide supportive evidence that motor functions are represented in lobules I-VI and VIII within the cerebellar cortex, and non-motor functions in lobules VI, VII and likely IX/X (Stoodley and Schmahmann 2018; Guell et al. 2018). fMRI activations in the posterolateral hemispheres reported in the fear conditioning literature overlap with cerebellar areas related to emotional and cognitive tasks. Emotional tasks have been shown to result in activations of the vermis (the so-called limbic cerebellum; Guell et al. 2018) but also the more medial parts of the posterolateral hemispheres and lobule IX/X (Guell et al. 2018; King et al. 2019), whereas the more lateral parts of the posterolateral hemispheres contribute to cognitive functions. Lateral activations may reflect the more cognitive aspects of fear conditioning, that is learning a cognitive association. Likewise, activation of the posterolateral cerebellum (Crus I and II) has been described in a predictive language task (Moberget et al. 2014). Participants showed marked cerebellar activation when the final word of a five-word sentence was different from what they expected based on the initial four words (e.g., two plus two is *apple*). Contingency awareness may also play a role (Dawson and Furedy 1976; Lonsdorf et al. 2017), and is likely linked to working memory processes (Dawson and Furedy 1976). In fact, learned fear-related cerebellar activations in lobules VI and Crus I overlap with areas in the cerebellum which have been shown to contribute to working memory processes (e.g., Guell et al. 2018; King et al. 2019).

In summary, different parts of the cerebellum likely contribute to learning of autonomic, motor, emotional and cognitive responses involved in classical fear conditioning. These areas are located within the vermis, the motor and the non-motor compartments of the cerebellar hemisphere, respectively. The neural operation which is performed in the various parts of the cerebellum is frequently assumed to be the same because the microscopic structure of the cerebellum is highly homogeneous (Caligiore et al. 2017; Sokolov et al. 2017). One hypothesis is that the cerebellum acts as, or is part of, a predictive device (Popa and Ebner 2019). This has been studied in greatest detail in the motor domain. Given that prediction errors are thought to be the main drivers of associative fear learning (Holland and Schiffino 2016; Rescorla and Wagner 1972), the cerebellum may also act as a predictive device in the emotional domain. Sensory prediction errors are thought to drive cerebellar motor learning (Miall et al. 1993; Bastian 2006). The cerebellum is assumed to function as a forward model, which, based on motor commands and contextual information, predicts sensory consequences of movement (Miall et al. 1993). The model is updated by sensory prediction errors, i.e., the difference between predicted and experienced sensory consequences. More recent findings suggest that the cerebellum is also involved in the processing of reward and reward prediction errors, which may play a central role in cerebellar non-motor functions and learning (Carta et al. 2019; D'Angelo 2019; Medina 2019). Reward-based or reinforcement learning information about success or failure is used to guide learning. In contrast to sensory prediction errors, this error signal does not carry information about the direction of change that will improve performance. The contribution of the cerebellum to reward-based learning will be discussed in more detail below.

5.5 The Specialized Architecture of the Cerebellum Embraces Diverse Plasticity Mechanisms

The cerebellum has a highly repetitive, intricate circuitry which is spatially divided into ten different lobules I-X, including the vestibulocerebellar flocculonodular lobe (lobule X) and the deep cerebellar nuclei (DCN). Within these lobules is a complex interconnected microcircuitry between the different neurons located in distinct layers of the cerebellar cortex. The major cell types include large Purkinje cells (PC) lined together in the Purkinje cell layer, tiny abundant granule and sparse Golgi cells (GoC) residing in the granular cell (GC) layer and interneurons (IN), e.g., basket and stellate cells in the molecular layer. Purkinje cells are the sole output of the cerebellar cortex receiving excitatory inputs from mossy fibers (MF) via the GC-parallel fiber (PF) and the inferior olive (IO) via climbing fiber (CF) (De Zeeuw et al. 2021). Moreover, they display a unique spike activity consisting of simple and complex spikes, making PC easily identifiable during electrophysiological recording (Fig. 5.7b). Excitatory inputs from the MF control the PC simple spike activity whereas climbing fiber inputs modulate PC complex spike activity. Basket and stellate cells receive excitatory input from GC to disynaptically inhibit PC while being excited by GC. GoC cells receive excitatory input from MF and GC to cause feedback inhibition on GC. Moreover, bilateral inhibition of identical neurons occurs between PC, molecular layer IN and GoC. In specialized areas of the cerebellum PC inhibit GC. Excitatory outputs from the DCN amplify the cerebellar cortex circuitry during associative learning (Gao et al. 2016) and inhibitory, GABAergic outputs from the DCN feedback on the IO to inhibit climbing fibers and PC complex spike activity (Kim et al. 2020). Besides the diversity of cell types, the cerebellar cortex is divided into sagittal zones based on the molecular expression of zebrin (aldolase C) positive or negative PC. Zebrin positive and negative PC have different resting rates, intrinsic firing properties, protein expression patterns and DCN connections (Cerminara et al. 2015; De Zeeuw et al. 2011, 2021). For instance, zebrin positive zones have the tendency toward learned rises in simple spike activity rather than reductions like zebrin negative zones.

Originally the cerebellum was proposed to be involved in motor learning via a process called long-term depression (LTD) at PF-PC synapses known as the Marr-Albus-Ito theory (Marr 1969; Albus 1971; Ito 2001) based on error driven supervised learning. Since then, we have expanded our knowledge and understanding of cerebellar learning and realize that it is a complex, synergistic coordination of long-term synaptic and intrinsic plasticity changes at various synaptic sites within the cerebellar cortex and nuclei, and include not only implicit sensory error-based learning, but also reward-based (or reinforcement) learning which has primarily been associated with the basal ganglia (Doya 1999). The majority of cerebellar synapses express different forms of plasticity mechanisms such as LTD, long-term potentiation (LTP) or short-term plasticity events at the pre- and post-synaptic terminals using specific molecular cascades to implement their actions. These cerebellar synapses have extended well beyond the PF-PC synapse to synapses between PC and MLI (molecular layer interneurons), CF and GoC via CF to GC and GoC, MF and MLI via PF. Additionally, MLI and GoC form synapses within themselves (Fig. 5.5). Details concerning the various cerebellar synapses and their plasticity mechanisms will not be discussed further in this chapter (Gao et al. 2012; De Zeeuw et al. 2021). Given the diversity of plasticity mechanisms at multiple synaptic sites in the cerebellar cortex concedes to a wide range of learning, patterns of learning by PC and a tighter temporal and spatial regulation of plasticity at PF-PC synapses. Many of these observations have been made in eyeblink conditioning. Whether the same principles apply in fear conditioning has only rarely been studied. To date electrical recordings at specific synapses in cerebellar regions during the acquisition, retrieval and extinction of learned fear have only rarely been performed. The current challenge is to determine which region, synaptic sites and combination of plasticity events are involved in the acquisition and storage of specific fear memories in the cerebellar cortex. Current knowledge of intrinsic learning mechanisms underlying fear memory in the cerebellum is summarized in the next section.

5.6 Intrinsic Learning Mechanisms Underlying Fear Memory in the Cerebellum

A key to understanding how the cerebellum contributes to fear memory is unraveling the mechanisms of plasticity at the pertinent synaptic

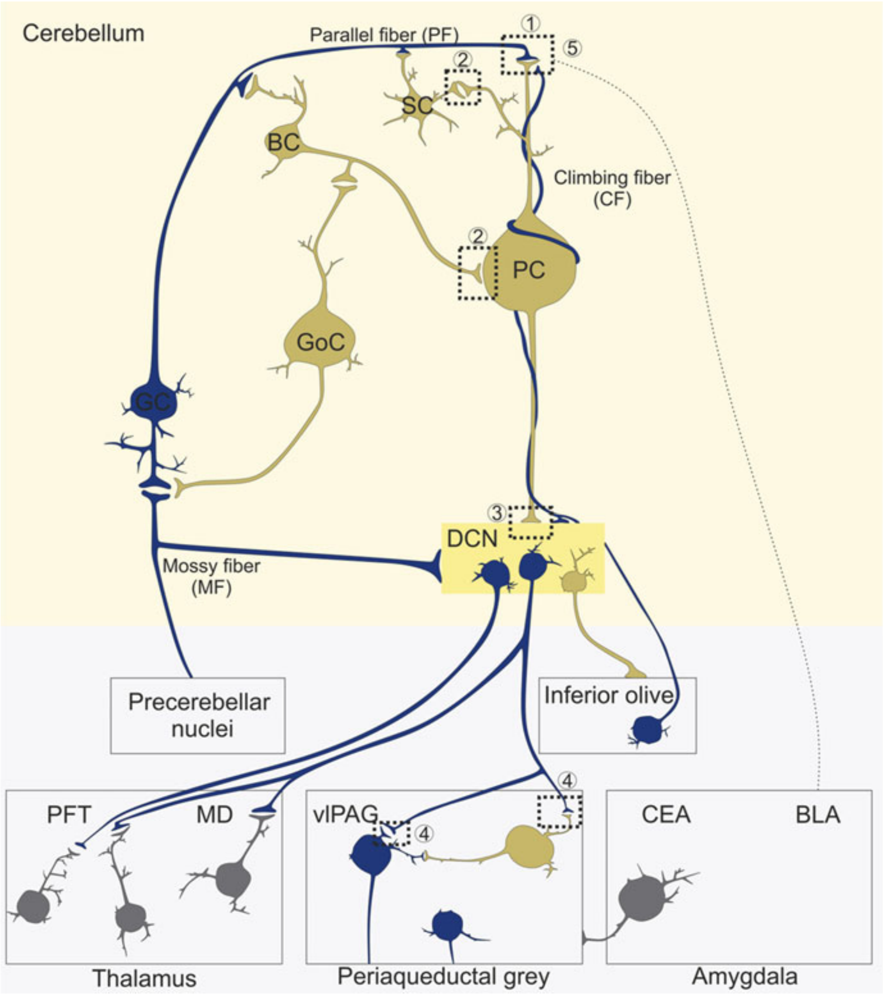


Fig. 5.5 Cerebellar circuitry modulating fear conditioning. Key connections within the cerebellum and to other brain regions from the cerebellum. Dashed rectangles accentuate synapses involved in fear conditioning. (**1**) PF-PC synapses display long-term potentiation (LTP) after acquisition of learned fear responses (Sacchetti et al. 2004; Zhu et al. 2007) and are important for fear acquisition and retrieval (Han et al. 2021; Otsuka et al. 2016). (**2**) After fear acquisition GABA activity is increased at molecular layer interneurons (MLI)-PC synapses (Scelfo et al. 2008). However, its role in fear conditioning is controversial (Marshall-Phelps et al. 2020). The role of additional synaptic connections in fear conditioning for example at BC-PC and SC-PC need to be determined. (**3**) Chemogenic activation of the G-protein / Gq-pathway in PC impaired fear memory consolidation (Dubois et al. 2020). (**4**) Chemogenic and optogenetic control of fear extinction could be bidirectionally modulated via the G-protein/Gq or Gi pathway DCN-vlPAG pathways (Frontera et al. 2020). (**5**) Inactivation of the BLA inhibited fear learning and the formation of LTP at the PF-PC synapse (Zhu et al. 2011). The pathway of this interaction is unknown and therefore depicted as a dashed line between the amygdala and the PF-PC synapse. Inhibitory neurons are depicted in yellow, excitatory neurons in blue and unknown neurons in gray. *BC* basket cell, *BLA* basolateral amygdala, *CEA* central amygdala, *CF* climbing fiber, *DCN* deep cerebellar nuclei, *GoC* Golgi cell, *GC* granule cell, *MD* mediodorsal thalamus, *MF* mossy fiber, *PC* Purkinje cell, *PF* parallel fiber, *PFT* parafascicular thalamus, *SC* stellate cell, *vlPAG* ventrolateral periaqueductal gray

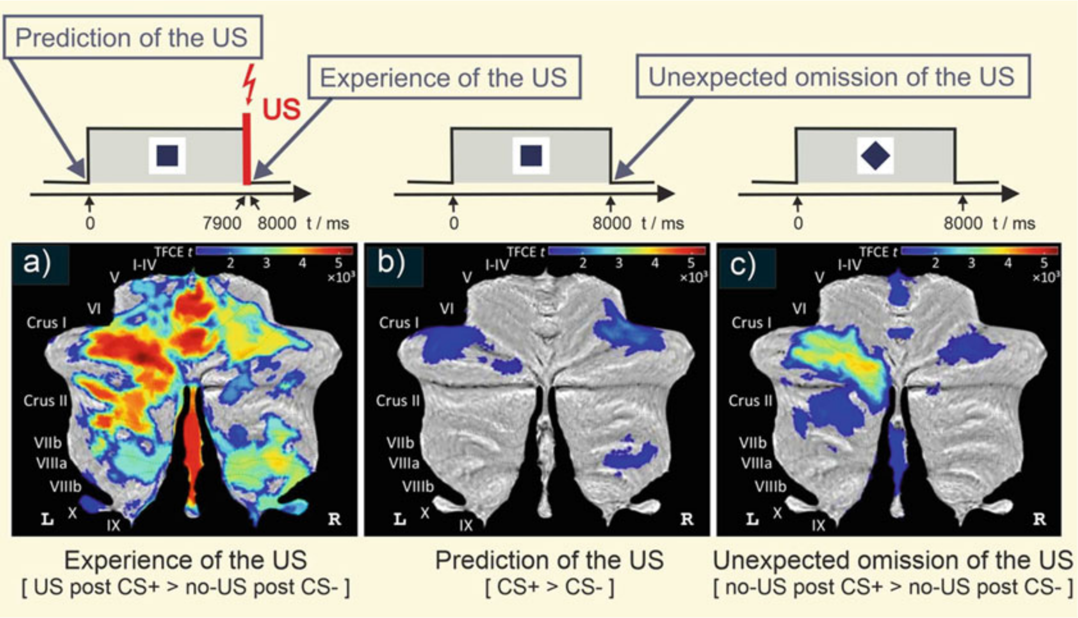
sites during a fear learning task. Past studies in the last 20 years are slowly making breakthroughs on the different intrinsic learning mechanisms the cerebellum is employing to regulate fear memories. One of these initial studies showed increases in PC firing in vermal lobules III-V during a Pavlovian fear conditioning paradigm in rabbits (Supple et al. 1993). Later Sacchetti and others were able to identify the synaptic sites (PF-PC, MLI-PC) and plasticity mechanisms used for fear conditioning consolidation (Fig. 5.5; Sacchetti et al. 2004; Zhu et al. 2007; Scelfo et al. 2008). They found long-lasting increases in spontaneous and miniature GABAergic events at MLI-PC synapses and in LTP at PF-PC synapses in cerebellar lobules V and VI but not in IX and X from fear conditioned animals 10 min (short-term fear memory) and 24 hr (long-term fear memory) following a classical fear conditioning paradigm where a tone was coupled to a foot shock. Contrary to these results, it was recently shown that cerebellar MLI inhibition of PC was not necessary for the acquisition or short- and long-term memory retrieval of cued and contextual fear memories in adult mice using a genetic mouse line lacking the GABA$_A$-γ2 subunit which ablates MLI synaptic inhibition onto PC (Marshall-Phelps et al. 2020). Furthermore, *hotfoot 4 J* mice with synaptic plasticity impairments at their PF-PC synapses (Yuzaki 2003), showed short- (10 min after fear conditioning) and long-term (24 h after fear conditioning) deficits in cue dependent fear retrieval (Sacchetti et al. 2004) suggesting the involvement of PF-PC synaptic plasticity in fear memory formation. *Hotfoot 4 J* mice displayed no differences in cue or context dependent fear conditioning freezing responses compared to controls indicating that *hotfoot* mutant mice do not have any sensory or motor abnormalities which could inhibit their fear memory acquisition. LTP at the PF-PC synapse can be either a cAMP-dependent, presynaptic response or nitric oxide (NO) dependent, postsynaptic event. Since AMPAR agonists, an upstream effector of NO, enhanced and AMPAR antagonist attenuated postsynaptic currents in conditioned mice, fear conditioned induced LTP responses appear to be postsynaptic and AMPAR dependent. In contrast, inducible LTP responses at PF-PC synapses were not detectable in unpaired administration of US and CS where no fear CR were elicited and in naïve controls or at CF-PC synapses (Sacchetti et al. 2004). Similarly, no fear-related behavior changes in LTD or intrinsic membrane properties of PC firing (e.g., input resistance, inward rectification, maximal firing frequency, first inter-spike interval, post-burst afterhyperpolarization, action potential threshold, amplitude and afterhyperpolarization) were observed in fear conditioned mice, suggesting that LTP may play a role in the consolidation of fear memory (Zhu et al. 2006, 2007). Additional fear conditioning studies in goldfish where a light (CS) was coupled with an electric shock (US) demonstrated that PC simple spike firing was reduced after CS presentation (Yoshida and Kondo 2012). Together these cerebellar fear behavior recordings from rodents and goldfish suggest that short- and long-term fear memories are coupled with enhanced and diminished PC activities and plasticity changes in LTP.

Current studies have revealed cellular and molecular mechanisms involved in controlling fear memories. For example, ablation of the signal transducer and activator of transcription 3 gene from specifically PC in the cerebellum (STAT3^{PKO}) elevated AMPAR expression and impaired LTP at PF-PC synapses in mice. In fact, STAT3^{PKO} mice showed enhanced LTD instead of LTP after fear conditioning and increased short- and long-term retrieval of fear memories (Han et al. 2021). Moreover, endogenous endocannabinoids such as 2-arachidonoylglycerol (2-AG) activate endocannabinoid receptor 1 (CB1R) leading to suppression of neurotransmitter release and intrinsic excitability via MLI (Castillo et al. 2011; Kano et al. 2009; Dubois et al. 2020). Fear conditioning and memory consolidation are controlled by the GABAergic-induced degradation of 2-AG in the cerebellum of rodents (Shonesy et al. 2014; Dubois et al. 2020). Fear learning increases GABA release which leads to elevated 2-AG degrading enzyme, monoacylglycerol lipase, decreases in 2-AG and MLI excitability in vermal lobules V/VI and augmented fear conditioning and memory consolidation. In contrast elevating endocannabinoid pathway via a G_q DREADD (Designer Receptor Exclusively Activated by Designer Drugs) in PC diminished cue dependent fear memory retention which can be reversed with administration of a CB1R antagonist (Fig. 5.5; Dubois et al. 2020). The rate limiting enzyme tyrosine hydroxylase (Th) for synthesizing catecholamines (e.g., dopamine, epinephrine and norepinephrine) is localized in zones of cerebellar PC which colocalize with zebrin II positive cells in the vermal lobules VI-X and Crus I and II and constitutes only 18% of the cerebellar PC (Locke et al. 2020). A 50% reduction of Th in this small population of Th positive PC and the lateral cerebellar nucleus but not in the locus coeruleus resulted in a slower rate of fear extinction with no change in Pavlovian fear conditioning and social recognition and working memory deficits which could not be attributed to sensorimotor, anxiety or gross motor deficits (Locke et al. 2020).

5.7 Cerebellum as a Predictive Device

The presentation of the aversive unconditioned stimulus in initial paired CS-US trials is unexpected, and is considered to be the error signal which drives associative fear learning (Holland and Schiffino 2016; Rescorla and Wagner 1972). Likewise, the omission of the US in initial extinction trials is unexpected, and can be considered as an error signal which drives extinction learning (Kalisch et al. 2019). A recent fMRI fear conditioning study found that the cerebellar cortex showed significant activation related to the learned expectation of the aversive stimulus confirming previous results (Ernst et al. 2019). Cerebellar activation, however, was most prominent in unreinforced CS+ trials at the time the aversive US was expected but did not occur (Fig. 5.6). Because the unexpected omission of the aversive US has been considered rewarding (Kalisch et al. 2019), cerebellar activation may be related to reward prediction error.

In fact, recent, elegant state of the art investigations in rodents using reward-based motor association paradigms provide strong evidence for the role of the cerebellum in predicting reward (Hull 2020). Rodents were trained to perform a certain movement to receive a reward. Findings in these reward-based studies may extend to punishment-based paradigms, since removal of a reward can be perceived as punishment and vice versa removal of a punishment can be perceived as a reward (Felsenberg et al. 2018). Two compelling studies by Heffley and coworkers demonstrated that calcium activity in PC undergoing a reward-based associative learning task accurately reflect climbing fiber induced PC complex spike activity (Fig. 5.7b) and signal reward predictions from lateral areas of the cerebellum (Heffley et al. 2018; Heffley and Hull 2019). Not surprisingly, PC calcium signals shifted earlier in association to a learned cue in response to predicting a reward in lateral areas of the cerebellum, however shifted back when the reward was given unexpectedly (Fig. 5.7a). Unexpected reward admission also ignited greater PC complex spike activity in lobule VI and Crus II whereas unexpected reward omission generated increased PC complex spike activity in lobule VI but not Crus I and II (Heffley and Hull 2019). These calcium imaging studies provide convincing evidence that PC activity, receiving inputs from the inferior olive afferents, are contributing to predicting errors in reward-based associative learning tasks (Hull 2020). In addition to confirming these studies, Michael Häusser's lab identified populations of PC in lobule VI segregated into reward activating microzones which displayed increased complex spike activity at reward delivery and reward suppressing microzones which exhibited inhibition (Kostadinov et al. 2019). The higher expectation of a reward (increased reward predictability) triggered lower PC driven calcium activities compared to unexpected admission or omission of rewards. Together these data strongly suggest that climbing fiber induced PC complex spike activity predicts errors in learned reward reinforced association tasks and that distinct regions of the lateral cerebellum may have



Experience of the US [US post CS+ > no-US post CS-]

Prediction of the US [CS+ > CS-]

Unexpected omission of the US [no-US post CS+ > no-US post CS-]

Fig. 5.6 Differential cerebellar activations related to the experience, prediction and unexpected omission of an aversive stimulus. *Top row*: Fear conditioning paradigm performed in healthy human participants during 7 T fMRI imaging. 10 paired CS+/US trials, six CS+ only trials, and 16 CS- only trials were presented in pseudorandomized order. The long CS-US interval (CS duration: 8 s, US duration: 100 ms; CS+ and US coterminated) allowed separation of cerebellar fMRI activation related to the US (i.e., experience of the aversive stimulus; indicated by second arrow), the CS+ (i.e., prediction of the aversive stimulus; first arrow) and the (unexpected) omission of the US (third arrow). *Bottom row*: (**a**) Cerebellar activation related to presentation (i.e., the experience) of the aversive stimulus [fMRI contrast 'US post CS+ > no US post CS-']; (**b**) Cerebellar activation related to the prediction of the aversive stimulus [contrast 'CS+ > CS-']; (**c**) Cerebellar activation related to the (unexpected) omission of the aversive stimulus [contrast 'no-US post CS+ > no US post CS-']. Cerebellar activations are shown projected on a cerebellar flatmap (Diedrichsen and Zotow 2015). All contrasts calculated using TFCE and familywise error correction ($p < 0.05$). *CS* conditioned stimulus, *L* left, *R* right, *TFCE* threshold-free cluster enhancement, *US* unconditioned stimulus. Adapted from Figs. 5.1 and 5.3 in Ernst et al. (2019; Creative Commons Attribution license)

diverse functions during a reward-based learning tasks. In these studies, climbing fiber activity increased both to unexpected rewards and unexpected omission of rewards, consistent with unsigned prediction error (or surprise). Medina and colleagues investigating eyeblink conditioning also found evidence that climbing fiber activity followed learning rules more consistent with reinforcement than supervised error-based learning theory (Ohmae and Medina 2015). They found, however, that climbing fiber activity was signed, that is increased to the unexpected presentation of an aversive (US, an air puff delivered to the eye) and decreased to the unexpected omission of the US in extinction trials (Ohmae and Medina 2015; Kim et al. 2020).

To date it is unknown whether reward signals are distributed throughout the cerebellum, or only to specific areas. The majority of the animal studies cited above, recorded in posterolateral cerebellar areas which support non-motor function. Whether reward signals also play a role in cerebellar-dependent fear learning processes has never been studied in detail. Sensory prediction errors, i.e., the difference between predicted and experienced sensory consequences, may also play a role, e.g., in the performance of accompanying limb withdrawal reflexes.

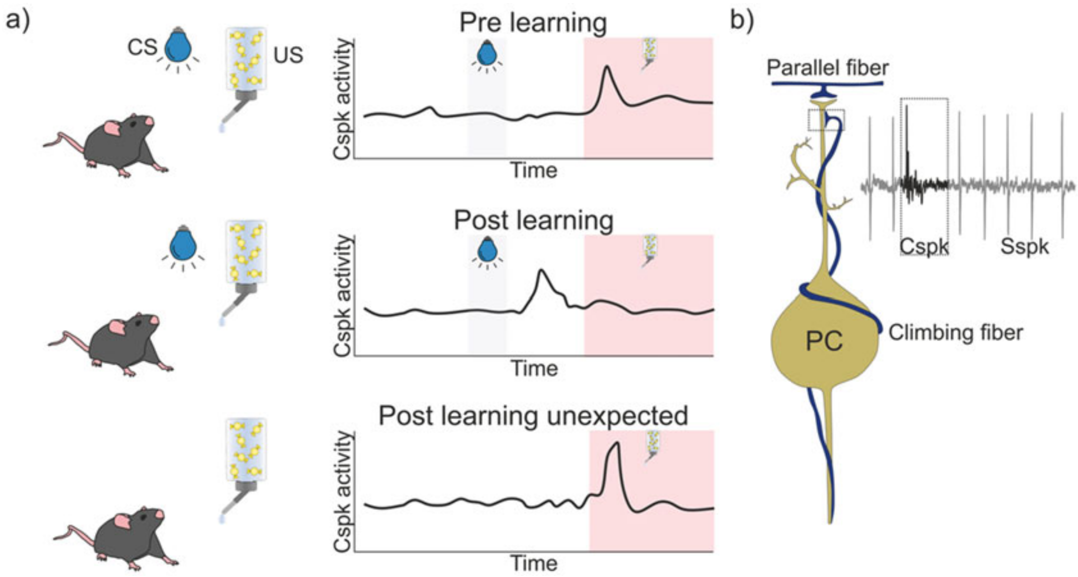


Fig. 5.7 Contribution of the cerebellum to reward predictions. (**a**) Schematic drawing of complex spike (Cspk) activity as reward predictors in the lateral cerebellum (Heffley and Hull 2019). Complex spike activity was increased when the sugar water reward (US) was given during pre-learning and shifted before the US and after the light (CS) during post-learning. Unexpected US resulted in an even higher Cspk when the US was given. (**b**) Inhibitory Purkinje cells (PC) receive excitatory input through parallel fibers and climbing fibers. Purkinje cells can develop two different spiking patterns, simple (Sspk) and complex (Cspk) spikes. Cspks are driven by climbing fiber innervation, and Sspks are spontaneously active or are driven by parallel fiber input. The dotted rectangle represents the CF-PC synapse and on the bottom the pattern of the corresponding PC activity

The spatial and temporal discrimination of associative learning tasks in the cerebellum is proposed to be executed via the physiological diversity and abundance of MF-GC synapses in mice. Individual GC can receive and integrate multiple sensory stimuli from MF. For example, vermal lobules V and VI, known to contribute to fear associations in rodents (Sacchetti et al. 2002), receive acoustic and nociceptive MF projections (Snider and Stowell 1944; Huang et al. 1982; Saab and Willis 2003). Upon coactivation by several sensory inputs, single GC relay the temporal coding information through the activation specific synaptic pathways. This mechanism refines the diversity of sensory representation while at the same time enhancing pattern separation to improve temporal coding strategies (Chabrol et al. 2015). This model presumes that diverse populations of GC encode multiple sensorimotor information from MF into a sparse and high-dimensional representation both spatially and temporally for PC. Furthermore, in agreement and extending this sparse code model Wagner and colleagues (Wagner et al. 2017) found that GC encode reward signals during appetitive operant (forelimb) and classical conditioning tasks. Small populations of sparse GC from lobule VI responded to reward, reward anticipation or reward omission. Their responses were increased and temporally shifted (latencies to the reward became shorter) in anticipation of the reward with learning. Learned tasks or anticipated rewards produced lower GC responses and more synchronized GC activity with increased learning compared to unexpected admission or omission of rewards. Although GC sensorimotor representations were low dimensional, anatomically clustered (not sparse) and non-temporally patterned in behaving zebrafish larvae (Knogler et al. 2017), further experiments in the future will hopefully clarify the model used by GC to spatially and temporally relay information to PC. Sendhilnathan and colleagues found that PC simple spike firing originating from GC in the mid-lateral cerebellum represented a reinforcement error signal which approaches zero as the monkeys learn to associate arbitrary symbols to each hand task for a sweet, liquid reward (Sendhilnathan et al. 2020). These PC simple spike firing patterns are distinct from motor or sensory events. The information from the previous trial is stored as either a success or failure throughout the subsequent trials and declines over the trials until the monkey learns the association. These data provide a sparse code mechanism on how cerebellar GC may encode and relay higher order cognitive and emotional functions such as fear memories to PC in an enriched, multidimensional context.

5.8 Fear Circuitry Beyond the Cerebellum

Functional connectivity MRI studies in humans show that the cerebellum is connected with higher cerebral areas via the cortico-ponto-cerebellar and cerebello-thalamo-cortical loops (Apps and Strata 2015; Bohne et al. 2019). Moreover, past tracing studies in mice and monkeys demonstrate that the cerebellum is either directly or indirectly connected to key circuitry involved in emotional memory processes including the hippocampus, prefrontal cortex (PFC), periaqueductal gray area (PAG), ventral tegmental area (VTA), basal ganglia (BG) and basolateral amygdala (BLA) (Fig. 5.8; Sacchetti et al. 2009; Strick et al. 2009; Apps and Strata 2015; Tovote et al. 2015; Bohne et al. 2019). To date there are only a few studies directly showing a contribution of the cerebellum to emotional memories by influencing extracerebellar regions which we will discuss in this section. Inactivation of the basolateral amygdala with the protein synthesis blocker, anisomysin, inhibited fear learning induced LTP in cerebellar lobules V and VI and fear memory consolidation 5 min but not 6 h after fear conditioning (Fig. 5.5; Zhu et al. 2011), indicating that fear learning induced LTP in the cerebellum may be modulating memory consolidation via the BLA within the first 6 h after fear acquisition. The VTA is known to modulate reward behaviors and recently aversive learning via their dopaminergic neurons (Waddell 2013; Felsenberg et al. 2018; Kalisch et al. 2019). Optogenetic inhibition of the VTA by cerebellar DCN axons expressing ArchT (Archaerhodopsin) elicited an avoidance behavior in a test for social preference where VTA optogenetic stimulation by cerebellar DCN axons expressing ChR2 (Channelrhodopsin-2) lured mice to a preferential area or object (Carta et al. 2019), suggesting a cerebellar contribution

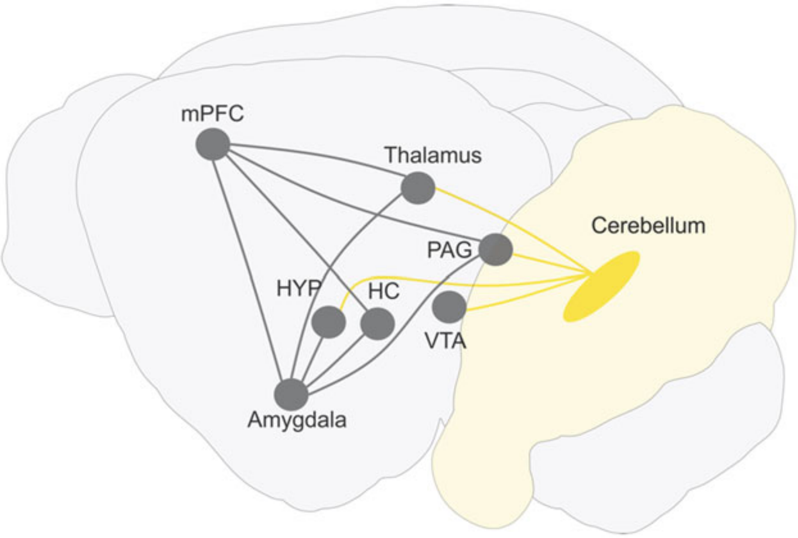


Fig. 5.8 Long-range projections from the cerebellum to brain areas of the fear network. Direct connections from the cerebellum to other brains regions are depicted in yellow and indirect connections in gray. *HC* hippocampus, *HYP* hypothalamus, *mPFC* medial prefrontal cortex, *PAG* periaqueductal gray, *VTA* ventral tegmental area

to aversive and appetitive behaviors via the VTA-cerebellar circuitry. Another important circuitry, vlPAG (ventrolateral PAG) to the magnocellular medulla mediates innate and learned freezing behavior due to fear (Tovote et al. 2015, 2016). Cerebellar glutamatergic projections originating from the fastigial nucleus (FN) of the DCN to glutamatergic and GABAergic neurons in the vlPAG bidirectionally modulate the strength of fear memories (Fig. 5.5; Frontera et al. 2020). FN terminals preferentially excite dopaminergic neurons (≈70%) and to a lesser extent excitatory, transcription factor Chx10 and inhibitory glutamate decarboxylase 2 positive neurons (≈20%) (Vaaga et al. 2020). Optogenetic stimulation of FN terminals in vlPAG evoked EPSCs in dopaminergic neurons and both EPSCs and IPSCs in Chx10 positive neurons. Furthermore, optogenetic stimulation of Chx10 positive neurons elicits freezing in mice. Based on these results, most likely the glutamatergic FN projections are exciting dopaminergic inhibitory neurons which are suppressing glutamatergic, Chx10 positive neurons leading to a diminished freezing response or enhanced fear extinction. Another investigation verified the temporal control of fear conditioning and also the rate of fear extinction during acquisition through the cerebellar FN-vPAG circuitry in rats. Additionally, inhibition of FN activity within the vPAG reduces temporal precision of vPAG offset during consolidation, fear induced ultrasonic vocalizations during acquisition and the rate of fear extinction during retrieval and increases rearing behavior during early extinction (Lawrenson et al. 2021). Altogether these results provide evidence that the cerebellum contributes to the temporal precision of vPAG ability to encode fear memories in a timely manner including the survival behaviors freezing, ultrasonic vocalizations and rearing.

In conclusion, the cerebellum is part of an extended fear memory circuitry which includes many subcortical and cortical areas such as the amygdala, PAG, VTA, PFC, basal ganglia and hippocampus. The cerebellum may play a key role in receiving information from and sending refined information to various subcortical and cortical areas to fine-tune our fear memory.

5.9 Cerebellar Contribution to Disordered Fear Learning May Contribute to Affective Disorders

In this chapter we have reviewed evidence that the cerebellum contributes to fear conditioning. Abnormalities in the acquisition and extinction of fear learning are known to contribute to the pathophysiology of fear and anxiety-related disorders (Milad et al. 2014; Fullana et al. 2020), and it has been proposed that cerebellar dysfunction may play a role (Moreno-Rius 2018; Hilber et al. 2019). On the other hand, changes in affect have been described in patients with cerebellar disease, and are part of the so-called Cerebellar Cognitive Affective Syndrome (CCAS) initially described by Schmahmann and Sherman (1998). So far, large systematic studies of the incidence of anxiety and other emotional disorders such as depression in well-defined cerebellar patient populations are lacking. Generating solid numbers is also made difficult because many cerebellar diseases have significant extracerebellar involvement, and the burden of a chronic, often hereditary disease may also result in anxiety and depression. Notwithstanding, cerebellar patients presenting with CCAS can display emotional and affective dysregulation of their emotions leading to overemotional behaviors and personality changes which is covered in detail in other chapters of this book. For example, past studies from patients with mutations in the P/Q type calcium channel (e.g., episodic ataxia type 2, EA2, and spinocerebellar ataxia type 6, SCA6) reported a neuropsychiatric phenotype. In general, EA2 patients display personality, attention, figural memory, verbal memory, but also anxiety disorders, which are mild in SCA6 individuals (Klinke et al. 2010; Almeida-Silva et al. 2013; Indelicato et al. 2019). Patients suffering from autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) characteristically show superior cerebellar vermis atrophy and can present psychiatric symptoms including panic disorders (Mignarri et al. 2014). Collectively these patient studies strengthen our hypothesis that the cerebellum may be involved in the processing of emotions such as fear and that cerebellar dysfunctions may be contributing to psychiatric disorders. Future studies in larger patient populations with diseases confined to the cerebellum and using cerebellar specific neurodegenerative mouse models such as EA2 and SCA6 for investigating deficits in fear learning and memories will hopefully provide mechanistic insights and open new therapeutic options to rescue these emotional impairments.

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Conflict of Interest

All authors declare no conflicts of interest.

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Part II

Cells and Molecules of Emotions in the Cerebellum

6 Topography of Emotions in Cerebellum as Appraised by Functional Imaging

Christophe Habas

Abstract

Emotions induce complex patterns of cerebellar activity likely reflecting specific cerebellar modulation and multidimensional integration of the emotional experience, based on context-specific dynamic recruitment of limbic, cognitive, mnesic, and sensorimotor cortico-cerebellar loops. Meta-analyses have reported constant recruitment of lobules VI–VII during basic emotions. Activation of rostral lobules II–VI and lobule VIII may be preferentially in relation to motor responses, whereas rostral and caudal vermal activation may be linked to autonomic regulation and associative learning in conjunction with amygdala. Cognitive integration of emotion may rely, at least, on activation of limbic salience network (automatic bottom-up detection of salient stimulus), default-mode network (memory- and knowledge-based categorization), and central executive network (response selection and emotion regulation). As lobules VI–VII straddle all these intrinsically networks, it could be hypothesized that this part of the neocerebellum constitutes an integrator/modulator hub of the emotion-related limbic and cognitive system.

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Keywords

Topographic cerebellar mapping · General emotion network · Intrinsic connected networks · Cerebellar modulation

6.1 Introduction

Human emotions consist of a multidimensional experience including subjective feelings associated with autonomic/hormonal (bodily adaptation and homeostasis), motivational (appetitive versus aversive stimulation), motor (outward expression and goal-directed behavior such as freezing, fight, or flight), and cognitive (conceptualization, emotion regulation) responses. Six fundamental (discrete) emotions have been described: fear, anger, disgust, sadness, surprise, and happiness, which can vary, at least, in terms of hedonic valence (pleasant versus unpleasant), intensity (arousal), and duration, and which can be identified by facial and bodily expressions. Emotional experience also includes pain and social emotions, and depends on many factors such as psychological or cultural characteristics. Emotions can be triggered by genetically determined or learned (stimulus pairing during conditioning) stimuli (Anderson and Adolphs 2014). Despite the description of this universal basic emotions, it turns out that they are not underlaid by distinct dedicated neural networks, but rather resulted from combination of several intrinsically

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connected networks (Touroutoglou et al. 2015), which transiently defines a "general emotion network" (GEN) common to different emotions (Lindquist et al. 2012; Jastorff et al. 2015). GEN is composed by a limbic affect core (amygdala, hypothalamus, ventral striatum, and brainstem structures such as periaqueductal gray matter), and limbic and cognitive cortices. From a phylogenetic viewpoint, GEN may have first encompassed during evolution survival subcortical circuits centered the limbic core (innate automatic visceral/somatic responses, conditioning, arousal) and ventral striatum (motivation) (LeDoux 2012a, 2012b). Motivation constitutes a vital internal drive ascribing appetitive or aversive value to a stimulus or state, whereas emotion corresponds to the readout of the said drive that triggers an innate or learned proper behavior (Schutter and van Honk 2005). In a second time, these inherited survival circuits might have been modulated by and integrated in more phylogenetically recent cognitive networks in charge, for instance, of awareness, attention, language, memory, or volitional control (LeDoux and Brown 2017). It is noteworthy, for instance, that amygdala is activated by all facial emotions and that each emotion engages a distinct widespread neural network although partially congruent with other rested emotions (Diano et al. 2017). In summary and in a "constructionist" way, an emotion can be regarded as a higher-order, multidimensional conscious cognitive experience rooted in the recruitment of limbic core and intrinsic networks functionally embedding survival circuits.

It is now firmly established that the cerebellum is not only connected with emotion-related circuits but is also involved in emotion recognition, evaluation, and learning, and in emotion-driven motor responses, even if the exact cerebellar computational contribution to emotion remains still matter of debate (Schutter and van Honk 2005; Schmahmann and Caplan 2006; Adamaszek et al. 2017). Since the cerebellum acts as a general modulator and integrator calculating internal models, it may intervene in adjusting and optimizing autonomic/motor and cognitive aspects of emotion, through its vermis and lobule VIIa, respectively. From a neuroimaging standpoint, structural and functional data have substantiated interconnections between cerebellum and limbic system as well as all intrinsic networks. Stimulation fMRI has allowed to define a cerebellar topographic mapping of emotions using fundamental or complex emotion recognition (such as decoding facial expression or gestures)/regulation/conditioning, emotional valence estimation, empathy, and painful stimulation.

6.2 Cerebellar Topographic Mapping

Functional imaging has allowed to establish a precise anatomo-functional parcellation of the human cerebellum whose specific territories belong to well-delineated, parallel cortico-cerebellar close-loops. The cerebellum encompasses five main, more or less spatially segregated, zones: (1) a sensorimotor region (lobule IV-VI rostral and VIIIb), (2) a visual retinotopically organized region (oculomotor vermis, lobules VIIb-VIIIb), (3) an auditory region (lobules V and crus 1–2), (4) a cognitive region (lobules VI caudal-IX, and especially crus 1–2 within the lobule VIIa), and (5) an affective region (lobules VI-VII including the vermis in (Stoodley and Schmahmann 2009), and/or right lobules IV-V-VI-IX and bilateral lobules VIII and crus 1 in: Keren-Happuch et al. 2014). Moreover, resting-state functional connectivity showed that most of these cerebellar regions partake in intrinsically connected circuits: (1) the sensorimotor networks (lobule V-VI and VIII), (2) the default-mode network (lobules VIIa and IX), (3) the right and left central executive network (lobule VIIa), (4) the dorsal attentional network (lobules VIIb/VIIIa), and (5) the (limbic) salience network (lobules VI-VII) (Habas et al. 2009; Brissenden et al. 2018). Moreover, seed-based resting-state connectivity detected cerebello-limbic functional coupling between lobules I-V and VIII-IX and amygdala/hippocampus (Sang et al. 2012), between lobules VI and VIII and amygdala (Habas 2018), between crus 1 and hypothalamus

(Kullmann et al. 2014), between lobule IV and ventral tegmental area (Murty et al. 2014), and between cerebellum and insula (Cauda et al. 2011). Tractography studies confirmed anatomical interconnection between cerebellum and: basal ganglia, hypothalamus, hippocampus, amygdala (reviewed in: Habas and Manto 2018), antero-medial and mediodorsal thalamus, and habenula (Grodd et al. 2020).

Therefore, the cerebellum can participate in emotional processing either directly through its affective region and the salience network, or indirectly through the other cortico-cerebellar loops potentially recruitable for attentional, executive, or motor processes accompanying emotion-driven behavioral response.

6.3 Stimulation Functional Imaging

More precisely, fMRI detected more widespread cerebellar activation during emotion processing. Vermal (v) and paravermal (p) cerebellar activations were observed during categorization of fundamental emotions such as anger (lobules vpVI-vpVIIa-vIX), sadness (lobules vpVI-vVIIa-vVIIIa), disgust (lobules vV-vpVI-vVIIIa-vIX), fear (vpVI-vpVIIa-vVIIb), and happiness (vpVIIIa) (Baumann and Mattingley 2012). In this same study, no gender differences were detected in the pattern of cerebellar activations, and partial spatial overlaps were noted between activation patterns for specific emotion within the associative neocerebellum. However, females compared to males exhibited greater vermal activation for visually-induced negative emotions (Hofer et al. 2006) although no sex difference was reported regarding valence and arousal ratings (Domes et al. 2010), and greater left cerebellar activation for positive emotion. During an observation and imitation task, negative emotions (anger and disgust) compared to positive emotions (happiness and surprise) induced more intense and widespread cerebellar activation in hemispheres of lobules VI-VIIa and vermis of lobules VIII-IX, and crus 2, respectively (Schraa-Tam et al. 2012). Listening to other's spoken emotional narratives induced correlation between right cerebellar activation (lobules VI and IX) and negative valence of emotion, and between anterior and posterior vermis and arousal (Nummenmaa et al. 2014). This preferential cerebellar activation for negative emotion and valence could resort to vital motor preparation for aversive or defensive behavior ("fight or flight"). Using an independent component analysis, recognizing facial expression of fear (Romero-Rebollar et al. 2016) was shown to modulate the functional connectivity positively between the vermis and hemispheres of left and right lobules V-VI and the medial prefrontal cortex, and negatively between the left crus 1 and the parahippocampus. Positive valence of each emotion elicited bilateral greater activity of lobule VI compared to negative valence, and right lobule vVI was preferentially engaged by happy positivity (An et al. 2018). Dynamic facial expression of anger specifically recruited the right lobule V (Kilts et al. 2003). Processing angry facial expression is enhanced in the right lobule V in the context of jealousy traits (Zheng et al. 2019). Functional coherence between specific zones of the right crus 1, left amygdala, and right dorsolateral prefrontal cortex, involved in emotional face processing, appeared to be strong and highly reproducible across fMRI sessions as estimated by test-retest reliable procedure (McDermott et al. 2020). Unpleasurable rating of mixed martial arts is associated with high functional connectivity between the left lobule VI and the accumbens nucleus (Porges and Decety 2013). Moulton et al. demonstrated that pleasant images specifically activated the right lobules VI-crus 1, whereas unpleasant images activated bilateral right lobules VI-VIIIb, vermis of lobule IX, and left crus 1. Right lobules VIIb, VIII, and IX also contribute to analyze emotional prosody (Thomasson et al. 2019). As the cerebellum is involved in temporal processing, it could compute or decode temporal cues of the vocal rhythm in relation with emotion expression. Transcranial magnetic stimulation applied over the left posterior cerebellum disturbs anger recognition based on body and gesture emotional expression

(Ferrari et al. 2019) and transcranial electric stimulation of the cerebellum, mainly lobule VII, enhanced recognition of facial anger and sadness (Ferrucci et al. 2012). Listening to music during script-driven mental imagery of emotional scenes increased activity in the anterior cerebellum (Li et al. 2019) and listening to sad music recruits left lobule V (Mitterschiffthaler et al. 2007). It is noteworthy that patients suffering from cerebellar diseases fail to correctly recognize and discriminate facial and vocal cues of emotions (Adamaszek et al. 2019).

Both positively and negatively valenced emotional words activated the right anterior cerebellum (Hofer et al. 2007), which may belong to the emotion- and/or the language-related part of the cerebellum (Keren-Happuch et al. 2014).

Dispersed activations were observed in the vermis, fastigial nucleus, and archicerebellum in relation with vegetative and affective aspects of thirst (Parsons et al. 2000). In particular, (1) activation of lobule vIII was positively correlated with thirst score, (2) uvula (lobule X), lobule VI, and crus 1 were recruited during maximum thirst, and finally, (3) left lobule VI displayed the strongest activation after drinking to satiation.

Noxious thermal stimuli provoke activation of anterior vermis, lobule VI, and deep cerebellar nuclei, whose amplitude was modulated by pain intensity (Helmchen et al. 2003). Left lobules VI-crus 1-VIIb seems especially recruited by emotional content linked to noxious thermal stimulation (Moulton et al. 2011). Pain empathy also causes bilateral activation of lobule VI-VII (crus 1) (Jackson et al. 2005). Thus, pain mental imagery and pain feeling recruit the same cerebellar areas. Leg withdrawal reflex due to (electrical) painful stimulation evokes bilateral activation lobules vp III-IV and VIII in relation with motor component of the reflex, as well as lobule vVI and lobules VI-crus 1 putatively ascribed to fear or startle-like reactions (Dimitrova et al. 2003)

Fear conditioning involved vermis of lobule IV-V (culmen) and lobules IV-VI and IX (Lange et al. 2015), Culmen could subserve fear-related bradycardia (Maschke et al. 2002). Fear-conditioned potentiation of the acoustic startle response is accompanied by increased activity in the left cerebellar hemisphere (Frings et al. 2002), whereas the vermis and hemispheres of lobules V-VI intervene in habituation of the acoustic startle response (Timmann et al. 1998).

Reward prediction is accompanied by activation or deactivation of the vermis (culmen) and the right posterior lobe (Wilson et al. 2018). For instance, unexpected (monetary) reward caused activation of the non-motor neocerebellum: crus 2 (Ramnani et al. 2004). It remains to be determined whether cerebellar activation resulted from emotion, motivation, error prediction, or reward expectation. This neuroimaging results are in agreement with recent neuroanatomical data identifying, in animal, interconnections between cerebellum and the nucleus accumbens via the ventral tegmental area (reviewed in: Wagner), as well as between thalamus and basal ganglia through dentato-thalamo-striatal and subthalamo-ponto-cerebellar (crus 2 and lobule VIIb) pathways (Bostan and Strick 2010). Tractography has confirmed strong interconnections between cerebellar cortex/dentate nucleus and basal ganglia (internal globus pallidus, substantia nigra, subthalamic nucleus) (Milardi et al. 2016). Cerebellum may interact with basal ganglia in associative reward-based learning (Bostan et al. 2013) all the more that nucleus accumbens is in resting-state functional coherence with the lobules VII and IX (Cauda et al. 2011). In patients affected by gambling disorder, Piccoli et al. (2020) described stronger functional connectivity between cerebellum (right lobules V-VI-VIIb and crus 2, and left lobules VIIIab-IX) and nucleus accumbens, correlated with severity of the associated disorder (anxiety, impulsivity, depression, cognitive distortions, and sensitivity to stress).

Orgasm elicited strong activity in the cerebellum: left lobule V and right lobule III in women as well as lobules vVI-VI-VII during the post-orgasm recovery (Wise et al. 2017), and right lobules vV and VIII, left lobule vVII and left lobule VI, and bilateral crus 1 in man during ejaculation (Holstege and Huynh 2011). Such cerebellar activations are difficult to interpret as orgasm implies pleasure feeling, imagination/memory, autonomic and sensorimotor activities.

Premenstrual dysphoric disorder occurring during luteal phase is accompanied by increased activation of the cerebellum (vermis and hemisphere of lobule VI-VIIa) (Rapkin et al. 2011; Berman et al. 2013) pointing out a potential endocrine modulation of the emotional cerebellar activity.

Cerebellar activation was also observed during emotional regulation using neurofeedback. For instance, Paret et al. (2016) found recruitment of crus 1 during down-regulation of amygdala response to aversive pictures. Strong and inverse correlation was measured between the amygdala-cerebellar (right lobule V and left crus 1) functional connectivity and anxiety in adolescents suffering from generalized anxiety disorder (Liu et al. 2015).

In summary, it turns out that: (1) emotion feeling, imitation, decoding, rating, empathy, and regulation evoke cerebellar activation, (2) at least, basic emotions (anger, fear, surprise, sadness, happiness, disgust, thirst, pain) and especially "negative" emotions induce cerebellar recruitment preferentially of lobules V to IX with a predominance of lobule VI-VII, and with some spatial overlaps, (3) all these basics emotion activated the cerebellar vermis (and fastigial nucleus) likely in charge of postural and autonomic adjustments, and (4) emotion-driven patterns of cerebellar activation are context-dependent (psychological traits, environmental conditions) and anatomically dispersed, sometimes overlapping, in several sublobules. For instance, fear or pain might also involve cerebellar regions in relation with attention to autonomic adjustment, salient stimuli, prediction of potential threat, motor preparation for withdrawal or escape, estimation, and selection of the best behavioral response. Furthermore, Brooks et al. (2019) found that recognition of facial emotion relies on individual's cultural and idiosyncratic conceptual knowledge, using multivoxel pattern-analysis approach applied to the activity of the right fusiform face area. These data imply strong participation of executive and mnesic functions in emotion categorization. In this vein, it is worth emphasizing that lobules V-IX recruited by emotions also belong, as we already mentioned above, to intrinsically connected networks (ICNs) in charge of motor, limbic, and executive processing.

6.4 Intrinsic Networks

At the network level, as aforementioned, the cerebellum partakes in parallel cortico-cerebello-cortical closed loops. At least, three of these loops dynamically interact in GEN: SN, DMN, and CEN, in collaboration with the core affect (amygdala), VN, and language network (Touroutoglou et al. 2015; Pessoa and McMenamin 2017a). More precisely, the GEN comprises: prefrontal, cingulate, (para-)hippocampal, temporal, temporo-parieto-junctional, and occipital cortices, basal ganglia and cerebellum (vermis of lobule VI, crus 1 and 2, lobule VIII). First, the connectivity pattern of GEN does not permit accurate emotion discrimination by machine learning, pointing toward to a general cognitive, semantic, motor, and executive processing common to all emotions. Second, several peculiar interconnections between GEN nodes and other brain areas appeared to reflect however specific emotion. Third, SN is activated for all tested basic emotions (Touroutoglou et al. 2015). SN, in relation with the anterior cingulate cortex (ACC), exerts a general function of bottom-up detection, filtering and integration of internal or external salient cues (Seeley et al.) of context- and stimulus-dependent switching between DMN and CEN activity (Menon and Uddin 2010) for reallocation of attentional and executive resources to salient stimuli (working memory, emotion categorization and evaluation, prediction, motor response adaptation and selection, associative learning) (Marek and Dosenbach 2018). SN can also compete or collaborate with the motivational system (Pessoa 2009). Participation of SN nodes, especially ACC, insula, and prefrontal cortex, in emotion processing was reported, for example, in: emotion-induced recall/imagery or cognitive-demanding emotional tasks (Phan et al. 2002), appraisal and expression of negative emotion as well as motion regulation (Etkin et al. 2011), feeling of sadness, emotional scene processing (Sabatinelli et al. 2011), participants' rating of their own emotional (in relation with left crus 2) and autonomic experience (Straube and Miltner 2011; Zaki et al. 2012), emotional stimulus encoding in memory (Barnacle et al. 2016), and pain processing. Luo et al. (2014) revealed a competition between dorsal insular and anterior cingulate cortices (SN), on the one hand, and amygdala and occipital cortex, on the other hand, during a N-back task with fearful compared to neutral faces. Higher activation of amygdala and occipital cortex was correlated with lower activation of the SN core, and with higher working memory-load condition (2-back versus 0-back). In this latter condition, activation of the left lobule VI was correlated with memory load. Therefore, decreased activity of SN was associated with increased activity in the affect core, and was correlated with increased memory and emotional processing load.

Conversely, DMN deactivation was observed during discrimination of emotional faces especially for negative emotions (Sreenivas et al. 2012) but Diano et al. (2017) found enhanced functional coupling between amygdala and two nodes belonging to DMN (precuneus and posterior cingulate cortex) during perception of angry. However, some specific nodes of DMN could be recruited during subjective happiness feeling (in relation to the right precuneus and amygdala: Sato et al. 2015, 2019), emotional autobiographical recall (Bado et al. 2014), (intense) esthetic experience (Vessel et al. 2012), prior-knowledge-based and context-based abstract representation of discrete emotions (Satpute and Lindquist 2019), socially-induced cognitive emotion regulation (Xie et al. 2016), and negative valence of emotion (Nummenmaa et al. 2014). DMN and SN displayed enhanced functional connectivity in relation with emotional awareness demonstrating collaboration between these two circuits for conscious interoceptive and conceptual integration of emotion (Smith et al. 2017).

Finally, observation of action performed in different emotion contexts modulates activity of the right lobule connected via the ventro-lateral thalamus to the supplementary motor area (Mazzola et al. 2013), indicating emotion-driven recruitment of the sensorimotor network.

In summary, it can be postulated that emotion-related complex pattern of cerebellar activation can include functionally linked cortical (and deep nuclear) loci belonging to SN (salient stimulus detection, arousal, bottom-up attentional reallocation, autonomic and cognitive integration, ICNs switching, emotion awareness and categorization) tightly connected with the affect core, CEN (executive control such as working memory and response selection, cognitive flexibility), sensorimotor network (motor planning and execution such as startle, withdrawal and avoidance reflexes, bodily expression, vocalization), and DMN (happiness feeling, memory recall, abstract representation of emotions, conceptualization, future envisioning). More precisely, what has been called the "emotional" cerebellum combined, in a context-specific and emotion-specific manner: (1) a core limbic zone (vermis and fastigial nucleus) in relation to amygdala, (2) ventral striatum and motor cortex, a sensorimotor zone (lobule IV-VI and VIIIb), and a cognitive zone in relation with nodes of CEN (lobule VIIa), DMN (lobules VII and IX), SN (lobules VI-VII), and DAN (lobules VII-VIII; when top-down attention is oriented toward external emotional/incentive stimulus). It is obvious that vermis and hemispheres of lobule VII, which is interconnected with associative prefrontal, parietal, temporal, and cingulate cortices (Krienen and Buckner 2009; O'Reilly et al. 2010), as well as with amygdala (Roy et al. 2009), straddle the core network and the main intrinsic networks, and have consequently been identified as an "emotional" part of the cerebellum. It would be interesting to determine, using machine learning, whether the specific emotion-driven cerebellar activation patterns, reflecting the overlying distributed cortical and subcortical network, can distinguish the causal emotion and its constitutive components.

6.5 Conclusion

The cerebellum is involved in emotion processing and exhibits a complex functional topography of basic emotions. This complexity roots in the cerebellar integration of the affective, autonomic, cognitive, semantic, incentive, mnesic, and motor dimensions of the emotional experience. This multidimensional aspect is subserved by context-specific and dynamic recruitment of specific intrinsically connected networks (Raz et al. 2016), including, as a core circuit, the salience network and the cerebellar lobules VI-VII. Consequently, in a "constructionist" view (Lindquist and Barrett 2012) or "conceptual act theory," the cerebellum could be regarded as an active integrator bridging circuits contributing to elaborate emotions. It remains notwithstanding to determine, besides this integrator role, whether the cerebellum specifically shapes certain aspects of emotions as a general modulator or internal model processor. Simplistically, however, it can be assumed that the cerebellar anterior lobe has first been incorporated in emotion-related survival circuits for rapid and stimulus-specific motor response execution (aversive or defensive behaviors, reflex potentiation or inhibition, which explains the cerebellar preferential recruitment by negative emotions, bodily expression of emotion for social interaction), and associated autonomic adjustments (pain resistance, metabolism, and arousal adaptation), and for detection of salient stimuli (salience network). In a second time, the neocerebellum in relation with top-down and goal-directed attentional, language (semantic categorization), and executive networks (working memory, emotion regulation, context- and knowledge-dependent response selection) might have been integrated in the affective system exerting a volitional control and adaptation of more complex emotion-driven behavior. Processing internal models could have enabled the cerebellum to anticipate consequences of emotion-triggered responses so that the executive network and the basal ganglia (Pierce and Péron 2020) can select or adapt the most appropriate behavioral response among a wider range of (learned) responses beyond the innate ones.

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The Neurophysiology of the Cerebellum in Emotion

7

Michael Adamaszek and Kenneth C. Kirkby

Abstract

Neuroscientific investigation of the detailed neurophysiology of emotion processing is a rapidly progressing field, which has opened discussion on key findings regarding the timing characteristics of the neuronal networks involved. Study designs incorporating quantitative electroencephalography (EEG) and event-related potentials (ERP) have mapped neuronal representations at various stages of emotion processing, identifying early and late stages corresponding to cerebral activity in attention and in appraisal of emotion. Interestingly, in addition to confirming aspects of cerebral cortex involvement, these investigations have also implicated the cerebellum in emotion processing. This has led to research aimed at distinguishing the contributions of cerebellar and cerebral networks and how these may interrelate. With respect to underlying neurophysiological mechanisms, ERP studies confirm that the cerebellum is involved in both early and late stages of processing of salient emotion cues, and also in capturing emotions in facial expressions. Topological analyses indicate direct connections between the vermis, Crus I, and Crus II areas of the cerebellum and the cerebral area of lateral prefrontal cortex. This suggests a broad evolutionary development of large-scale cerebral networks in emotion. In this chapter, we highlight findings to date of neurophysiological activity related to cerebellar participation in emotion processing. The neurophysiological findings, which by inference represent underlying neural activity, emphasize an integrative role of the cerebellum in emotion.

Keywords

Cerebellum · Emotion processing · Neurophysiology · Prefrontal cortex

7.1 Background

The cerebellum has been increasingly recognized for its contribution to the regulation of affect and affective behavior, leading to growing interest in the fundamental neuroanatomical and neurophysiological characteristics of emotion. Neuroanatomical research has identified connections between the cerebellum and circumscribed cerebral areas. These include a number of distinct areas of the cerebellum that subserve emotion processing, in particular the vermis lobules, the hemispheric areas of lobules VI and VIIB, and the

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predominantly midline areas Crus I and Crus II (Stoodley and Schmahmann 2009; Argyropoulos et al. 2019). These topographical observations have been facilitated by the extensive utilizing of neuroimaging in clinical neuroscience, especially functional magnetic resonance imaging (fMRI) and positron emission tomography (PET). By comparison, there has been limited research into the temporal characteristics of neural activity linking the cerebellum with cerebral cortical areas involved in higher-order cognitive and particularly emotional processing.

An important agenda for research into the neurophysiology of the cerebellum, with respect to emotion and associated domains of affective behavior, lies in the ascertainment of the full extent of underlying neural transmission including widely dispersed pathways connecting with and forming large-scale neuronal networks across the brain. The precise neurophysiological contributions of the cerebellum to these cerebral networks, as formulated in the timing and sequencing hypotheses, remain a matter of some debate (Leggio et al. 2011; Styliadis et al. 2015). Another key concept of interest is that of a universal cerebellar transform (UCT) whereby the layered neuronal structuring of the cerebellum governs in a consistent manner the transformation of information inputs into outputs to cerebral cortex (Schmahmann 2010). Accordingly, the favored internal model of Ito (2008) is a further conceptualized processing scheme emphasizing the specific cerebellar connections to the prefrontal cortex (PFC) in particular to cognitive and affective domains, stimulating neuroscientific research aimed at disentangling the peculiarities of cerebellar involvement in large-scaled networks. Focused techniques such as electroencephalography (EEG), in particular event-related potentials (ERP) as the stimulus-driven extracts of EEG, which is predominately considered to study specific cortical patterns in emotion, have an obvious role to play in investigating the basic neurophysiological mechanisms attributable to the cerebellum in emotion. However, the current evidence base in support of these well-reasoned conceptualizations is limited, with the neuronal circuits and their electrophysiological profile having been examined in only a few sufficiently powered studies. This is especially the case when it comes to studies that elucidate the influence of the cerebellum on higher-order cerebral networks. This has proven to be the case in studies examining electrophysiological patterns in identified tracts within the cerebellum which respond to emotion processing tasks. However, few studies have addressed the relationship between activation of these neuronal circuits in the cerebellum and their impact on the activity of higher-order networks in the cerebrum. More advanced paradigms for evoking ERP, as have been informative in ascertaining cerebral components of emotion processing, may be used or adapted to focus on cerebellar components and connections. Such studies yield characteristic patterns of neural activation in response to experimental paradigms employing tasks involving salient emotional contents of differing valence and arousal, as well as the emotional contents of differing valence of facial expressions, irrespective of the herein following outcome in terms of subjective feeling or influences of cognitive, affective, and motor behavior. A key conceptual issue is whether the cerebellum operates as part of specific segregated networks in conjunction with hubs in subcortical areas such as the thalamus, amygdala, and basal ganglia. Such networks may integrate hierarchical elements of emotion processing through their reciprocal connections to associative regions in the prefrontal and temporoparietal lobes (Dolcos et al. 2020).

In this chapter we summarize current understanding and issues pertaining to the neurophysiology of the cerebellum in emotion. Our focus is on the set of temporal and spatiotemporal electrophysiological features identified in research to date and critical to our understanding of the complex neurophysiological signal that represents cerebellar neuron assemblies engaged in emotion processing. The other major avenue of our understanding of cerebellar neurophysiology in emotion, the spatial distribution of incoming and outgoing information processing, has been derived from extensive research using structural and functional neuroimaging, as outlined by

Christophe Habas in his fascinating chapter in this volume.

7.2 Neurophysiology of Emotion in the Human Brain: Electrophysiological Insights

There is an extensive body of literature about the neural processing of emotions in the human brain. The majority of findings have accrued from study designs based on functional MRI, delineating the neurotopographical features of underlying neural pathways. Most of these studies examine specific emotion processing using block designs, producing detailed brain maps showing the precise neuroanatomic localizations of cerebral blood flow alterations, indicating increased neural tissue activity (Damasio et al. 2000; Kotz and Paulmann 2006). Some studies also applied event-related cue designs in order to contrast the cues of interest against a larger number of control cues (for an overview, see Olofsson et al. 2008). Alongside these mainly topographic aspects of emotion, a comparable effort has been made in electrophysiological approaches for studying the temporal and spatiotemporal issues of emotion processing. In contrast to the MRI domain, recording of the neural signals as derived by EEG and to a major extent ERP has resulted in fascinating insights into timing characteristics of activity in neuronal networks that guide emotional attention, perception, recognition, and expression, observed during tasks eliciting cognitive and affective behavior (Aftanas et al. 2004; Carretié et al. 2001; Junghöfer et al. 2006; Olofsson et al. 2008; Oknina et al. 2012). Technical capabilities have advanced to permit the concurrent analysis of surface and deep brain recorded neural signals, under precise affective conditions (Hauk et al. 2002). This means that in addition to the time line, the spatiotemporal characteristics of discrete electrophysiological signals can be extracted, adding to the reference set of composite signals of brain function.

Neurophysiological patterns of principal emotion processing are captured by specific electrophysiological techniques of interest in studying basic as well as higher-order brain activity in emotion processing. Basic brain activity has been identified as specific responses of autonomic nerve connections guiding the perception of affective cues with reactions of several internal systems such as cardiovascular, pulmonary, and gastrointestinal, as well as specific cue-dependent skin responses (Gray et al. 2012; Jerath and Crawford 2015). Moreover, the startle response or the blink reflex are examples of rapid brain activities specifically at the subcortical level, with neural connections in the brainstem, representing early reaction features of emotions below the threshold of consciousness (Larson et al. 2000). At the other end of the spectrum to these phylogenetically early neural responses, high-order affective processing associated with conscious awareness has been a growing domain of affective neuroscience in humans, with the topographic and functional organization of the responsible neuronal networks in particular of the cerebral cortex a matter of vigorous scientific investigation (e.g., research on the human connectome and affectome) (Becker et al. 2019; Dolcos et al. 2020).

A substantial area of research is directed to elucidating both structural and temporal aspects of specific topics of emotions such as visual or auditory attention, perception, and recognition, as well as the expression of emotion at the individual level and particularly social behavior (Damasio 2002; Davidson et al. 2003; Vuilleumier and Brosch 2009). A hallmark finding is that visual attention to stimuli containing salient affective cues results in early and late ERP over the temporo-occipital and centro-parietal regions, which are assumed to be intrinsic and robust features of the brain in emotion processing in healthy humans (Carretié et al. 2001; Junghöfer et al. 2006; Olofsson et al. 2008). Thus paradigms using affectively laden cues with different valence and arousal characteristics, e.g., as systematically catalogued by the International

Affective Picture System (IAPS), have been repeatedly shown to elicit an early ERP like the early posterior negativity (EPN) at 200–300 ms poststimulus over temporo-occipital surface locations of the surface. This is assumed to indicate early facilitated sensory processing of affective cues of the extended visual system, independent of top-down control (Schupp et al. 2014). Furthermore, such paradigms elicit augmented late positive potentials (LPP) over parietal areas, indicating an intrinsically higher relevance accorded to affective cues, which persists through subsequent stages of processing of affective cues (Sabatinelli et al. 2013). Notwithstanding, the validity of functional neurophysiological paradigms using cue sets derived from the IAPS to study certain emotion processing stages has been the subject of debate, recommending a cautious stratification in terms of some possible bias mechanism for uncontrolled selection of picture subsets (Lang et al. 1999). For example, a study by Delplanque et al. (2007) found some confounding effects between the arousal dimension of the investigated pictures of IAPS and the energy in low frequencies. However, a majority of the studies using the affective cues of IAPS considered additional test items such as the Self-Assessment Manikin (SAM) (like the mentioned work of Schupp), or even evaluated different picture sizes (Sanchez-Navarro et al. 2006), which were able to approve the significance of each emotion content to their study results.

The perception and evaluation of emotions in facial expressions is another fascinating domain of emotion processing in humans, where again the time distribution of the early and subsequent neural signals has been a subject of particular interest. Thus far, several studies of ERP in healthy subjects have indicated that perception of faces per se occurs early, manifested in an augmented N170. The later processing of specific details of the face such as emotional expression usually displays augmented LPP, indicating that higher-order neocortical pathways are tasked with analyzing the details of facial cues and selection of adaptive behavioral responses (Eimer and Holmes 2002, 2007). More specifically, the N170 is assumed to be the early surface EEG signal over occipital areas in relation to the perception of faces and reflecting the pre-categorical perceptual encoding of faces in face-specific visual areas, among others the fusiform face area (FFA) and the superior temporal sulcus (STS) (Kanwisher et al. 1997; Krolak-Salmon et al. 2004). The LPP in the range of 550–900 ms over occipito-temporal, frontal and right temporal areas reflect the analysis of categorical aspects of facial expressions at higher-order stages (Bentin et al. 1996; Eimer and Holmes 2002, 2007). Indeed, lesions of the PFC were accompanied by disrupted ERP after 200 ms, emphasizing the PFC and its attentional resources as crucial to the recognition of emotional facial expression at late processing stages (Suwazono et al. 2000; Yago and Knight 2000). Therefore, LPP are considered as neural correlates of this later neocortical stage, i.e., processing emotional facial expression for the purpose of generating intentional control of behavior in a strategic and task-dependent fashion (Eimer and Holmes 2007; Wong et al. 2009).

The investigation of the cerebral responses to certain emotion cues has been predominately focused on the visual pathways, which might be feasible in terms of the high impact of visual attention to the surrounding space of salient cues in real world conditions. Nevertheless, there are also some intriguing research reports on the less recognized auditory attention to affective cues, which interestingly found comparable features as in visual paradigms. For example, the work of Grass et al. (2016) found a similar early negativity potential shift at posterior sites in an ERP paradigm of vocal cues with emotion versus neutral contents, and also an augmentation of emotion-ladened vocal cues in the late phase of stimulus processing at the anterior sites. These findings resemble the mentioned observations of early and late ERP in visual cues with specific emotion content, thus indicating a comparable order of the assumed large-scaled networks in emotion processing with a first step of encoding the emotion information at the temporo-occipital, and the following higher-order processing at the parieto-prefrontal cortices (Schachter and Sommer 2009).

7.3 Neurophysiology of Emotion in the Cerebellum

7.3.1 Basic Pathways of Emotion in the Cerebellum

The impact of the cerebellum on neurophysiological patterns of emotion processing has been studied along a broad scale from evolutionary basic autonomic responses up to activity of higher-order neural circuitries. A commonly reported influence of the cerebellum on affective behavior is a disproportionate response to aversive stimuli (Schutter and van Honk 2009; Baumann and Mattingley 2012; Ferrucci et al. 2012; Adamaszek et al. 2017). The notion that the cerebellum promotes recognition and discrimination of negative basic emotions at a neurophysiological level was noted in some early brain stimulation experiments (Ploghaus et al. 1999; Sacchetti et al. 2007; Koutsikou et al. 2014). These experiments also provided some information regarding connections to proximate and more widespread neuronal networks (see also the animating review of Sacchetti et al. 2009). While cerebellar input to autonomic pathways to specific areas of the brainstem, but also subcortical regions of the hypothalamus, seems to track along with a closed neuronal loop in several milliseconds, in higher-order emotional processing ERP data characterize the cerebellum as an active interface with important functions in large-scale cerebral networks in particular to the prefrontal, parietal, and temporal associations cortices (Habas et al. 2009; Buckner 2013). Cerebellar input to autonomic pathways is indicated by reports of impaired responsiveness of arterial blood flow to aversive stimuli (Nisimaru 2004) and reduction of the decrease in heart rate normally associated with fear conditioning in subjects with vermal lesions (Maschke et al. 2002). These findings emphasize cerebellar participation in autonomic pathways such as regulating the cardiovascular system in emotional contexts (Blood et al. 2015). Additional observations include an impaired skin conduction response to negative stimuli attributed to a left cerebellar lesion (Annoni et al. 2003), an impaired startle response after vermal lesions (Lopiano et al. 1990), and an impaired blink reflex to fear stimuli in medial cerebellar lesions (Maschke et al. 2000). These point to specific neurophysiological mechanisms of the cerebellum that are involved in unconscious responses mediated by autonomic neural pathways during emotional processing and associated behavioral routines.

The substantial association of the cerebellum with aversive emotions such as fear is suggestive of a likely role of the cerebellum in emotional memory. Indeed, an increasing number of studies have pointed out that the cerebellum, with particular emphasis on the cerebellar vermis, plays a role in memory formation of emotionally laden stimuli and therefore in the associative processes that form emotional memory traces (see the fine overview of Sacchetti et al. 2009). Amnesia is reported in rats after reversible inactivation of the cerebellar vermis, as shown for paired sensory stimuli to unconditioned aversive stimulation (Sacchetti et al. 2002), confirmed by several additional studies (Ruediger et al. 2011; Koutsikou et al. 2014; Gianlorenço et al. 2015). A recent study found that blockade of the basolateral amygdala, a key site for fear learning, prevents the formation of learning-related plasticity in the vermis (Zhu et al. 2011). Considering this finding with the observation that vermal and fastigial stimulation induce electrophysiological responses in the basolateral amygdala (Snider and Maiti 1976) suggests a bidirectional interaction of the vermis with the amygdala during emotional associative processes. Very early case studies in humans reported involvement of the cerebellum in eliciting negative feelings in a patient after electrical stimulation of the dentate nucleus and superior peduncle (Nashold and Slaughter 1969). Comparable early studies in treating patients suffering from psychiatric disturbances such as depression reported improvement of emotional symptoms, such as aggression, anxiety, and depression, after chronic stimulation of the cerebellum (Heath et al. 1978; Turner et al. 2007). In more recent times, the increasing application of non-invasive cerebellar stimulation such as transcranial direct current stimulation (tDCS) has been observed for alterations of several cerebellar skills in humans including motor control, learning, and emotion processing (Schutter et al. 2003; Schutter and van Honk 2006; Ferrucci et al. 2012; Ferrucci and Priori 2014; Schutter in Adamaszek et al. 2017). Indeed, early findings by Heath indicated specific cerebellar involvement in affective regulation, as electrical stimulation of the cerebellum, was associated with clinical improvements of mood and personality variables in psychiatric disorders, in particular in depressive states (Heath 1977; Heath et al. 1981). These findings are also of particular note for the presumption of cerebellar involvement not only in basal or autonomic sensory, but also in higher-order emotion processing, which might occur in parallel neural pathways providing a high degree of affective regulation in unconscious as well as conscious brain state (Damasio et al. 2000; Parsons et al. 2001; Evans et al. 2002).

7.3.2 Early and Late Emotion Processing

As noted, there are few but intriguing studies considering the electrophysiological features delineating the neurophysiology of the cerebellum in linking to the cerebral networks carrying higher-order cognitive and emotion functions. This presumably reflects the long history of cerebellar research concentrating on its role in motor coordination, and similarly the concentration on the cerebral cortex in neuroimaging studies of cognition and emotion. Nevertheless, the literature regarding electrophysiology of the cerebellum and higher-order cognition and emotion processing is worthy of discussion.

A frequently investigated electrophysiological signal in cognitive neurophysiology is represented by the P300, an ERP with two components, the P3a emerging at target stimuli within a series of frequent and less important stimuli and the P3b for unexpected novel stimuli, around the fronto-parietal and prefrontal cortical surface, reflecting cognitive information processing to salient or quite new information event within a series of frequently occurring standard stimuli (Polich 2007). Research on this ERP has primarily been directed to cerebral networks in cognition but has subsequently been extended to include the role of the cerebellum. Thus delayed P300 latencies and reduced P300 amplitudes have been reported in several studies of cerebellar damage (Tachibana et al. 1999; Paulus et al. 2014; Adamaszek et al. 2013; Rusiniak et al. 2013; Mannarelli et al. 2015). In a further study applying tDCS in healthy subjects, the cathodal stimulation over the left cerebellar hemisphere reduced the P300 amplitude for both the orienting and discrimination phases of attentional processing (Mannarelli et al. 2016). A study of electrophysiological signals related to cognitive-behavioral processing in degenerative cerebellar disease found abnormal frontal P3a and abnormal reorientation negativity (RON), both indicating disturbed attention and set-shifting in association with impaired error-awareness (Tunc et al. 2019). A similar effect of impaired cognitive processing on divided attention tasks is seen in a psychophysiological study, depicting a prolonged latency of mismatch negativity as a correlate of impaired automatic attentive discrimination in cerebellar degeneration (Moberget et al. 2008). Whereas these fascinating findings of specific ERP were in relation to primarily cognitive tasks, they might be of interest for capturing electrophysiological patterns of emotion in view of the coupling of cognitive-affective processing as part of a complex set of top-down and bottom-up information flows, resulting in an adaptive behavior response (Bentin et al. 1996; Eimer and Holmes 2002 and 2007).

7.3.3 Emotion and Attention

The neurophysiological mechanisms by which the cerebellum contributes to emotion attention as a principle mode of regulation of affect and behavior can be studied with electrophysiological tools such as the EEG or in particular by ERP. However, EEG investigations on this topic are very rare, which may reflect the limited impact of the cerebellum on background activity in the EEG. In this regard, Schutter performed some interesting investigations studying the impact of transcranial stimulation of the cerebellum on emotion processing. In an early study (Schutter et al. 2003), a high frequency repetitive transcranial stimulation (rTMS) to medial cerebellar regions resulted in a shift of frontal gamma activity in EEG, which was associated with an elevated mood and alertness. A second study applied single-pulse TMS over the vermis again in healthy subjects, which resulted in increased theta activity in EEG (Schutter and van Honk 2006). Finally, a study of rTMS inhibition by applying 20 mins of cerebellar, occipital or sham 1 Hz rTMS, were performed on 3 separate days in 12 healthy subjects (Schutter et al. 2009). In this study, negative mood was noted on an emotion regulation task following cerebellar rTMS, but this was not associated with any change in the EEG. This emphasizes the necessity of customized technical procedures in studying the electrophysiological background of the cerebellum, in particular for the detection of feedforwarded neural signals to the cerebral networks which are critically located near the surface derivations.

According to the basic processing of emotions, that is the underlying processes of emotion regulation and reactivity (Del Piero and Margolin 2016), the hypothesis of cerebellar involvement in early and late stages of attention to affective cues might be achievable by using the specific technical approach of ERP. Specific paradigms of salient stimuli with differing levels of emotion valence and arousal are used to simulate an ecological surrounding such that inputs from the cerebellum engage bottom-up and top-down-control mechanisms in processing affective stimuli within the brain networks involved. There are some studies (Adamaszek et al. 2013 and 2015; Styliadis et al. 2015) using pictorial affective cues taken from the IAPS and confirmed to evoke certain early and late event-related potentials to cues of different emotion valence and different emotion arousal. An initial case study (Adamaszek et al. 2013) of a patient with a stroke of the posterior cerebellar lobe was conducted, focusing on two ERP components, that is the EPN as a marker of early attention to affective cues (Schupp et al. 2014) and LPP as a marker of the forwarding of affective cues for further evaluation within the responsible cerebral networks (Junghöfer et al. 2001; Olofsson et al. 2008). This case report, as a preliminary study of neurophysiological patterns of emotion processing, revealed a shift of the topographical distribution of the early response, assumed due to a high attentional load, depicted as an augmentation of the EPN over temporoparietal instead of the typical temporo-occipital areas when the subject viewed high arousing affective images coupled with a distracting visual line-counting task. In addition, there was a shift of the topographical distribution of the LPP to high affective arousing images over frontal instead of the typical centroparietal areas (see Fig. 7.1). Interestingly, at a follow-up recording after two years, these ERP were associated with a shift of the EPN to temporo-occipital, and of the LPP to centroparietal areas of the surface, also corresponding with improvement in the patient's ataxia and behavior. These ERP data were intriguing for capturing specific brain potentials in emotion in a case of cerebellar dysfunction, pointing to a critical impact of the cerebellum on prefrontal areas, in particular around the orbitofrontal cortex, known for its importance in processing emotional cues. The results suggested a recruiting of neural pathways of the responsible networks of the prefrontal cortex as a major hub of top-down control of incoming affective information, thus compensating for the reduction or loss of inputs from the cerebellum along the ventral attentional system. As a second and nevertheless further interesting finding, the results of this case study could be considered as a crucial example of a positive neural reorganization of the affected cerebral network in the form of a circumscribed component, here parts of the dorsal cerebellum with compensatory neural adaptations of the cerebellum and related networks, encoding salient affective cues at early and forwarding at late stages. Notwithstanding, an additional crossover investigation of these paradigms in a sample of eight patients suffering predominately from

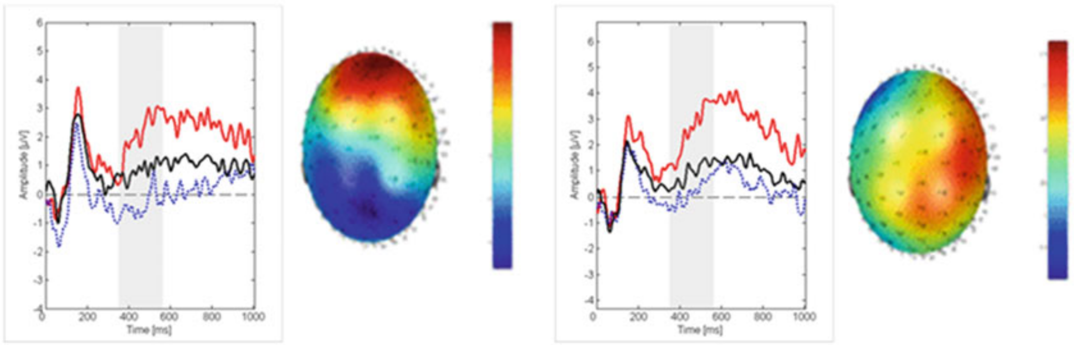

Fig. 7.1 ERP of emotion of different valence and arousal to salient visual events. The ERP curves of the early (EPN) and late (LPP) phases of the emotion (neutral = dotted blue line; positive valence = red lines; negative valence = black lines) perception in patient (left area) and control healthy subjects (right area) are displayed. The corresponding power maps of the LPP are added closely to the ERP, indicating a prefrontal maximum in patient versus the centro-parietal maximum in control subjects

ischemic lesion of the posterior cerebellum replicated these findings of impaired encoding of visual affective cues, suggesting a dependency of the predominant prefrontal cortex to cerebellar inputs in guiding the top-down control of incoming affective information along bottom-up stages of primary and visual associative cortex areas in encoding and forwarding emotion processing in responsible networks of the human brain (Adamaszek et al. 2015, 2017).

The above described electrophysiological findings proposing cerebellar involvement in the coding of affective cues with different valence and arousal as drawn from the IAPS are supported by a comparable study design in healthy subjects (Styliadis et al. 2015), emphasizing the timing of cerebellar responses to affective stimuli according to the presumed parallel processing and therefore the progression of visual information details of the perceived affective cues. This magnetoencephalography (MEG) study outlined differential spatiotemporal processing of valence and arousal across distinct cerebellar lobules with different time phases. The earliest activity related to high arousal in left Crus II and Vermal lobule VI, followed by unpleasant valence in left Crus I. After this activation in left Crus I, an interaction effect between pleasant valence and high arousal was seen in left VI and Crus I. As the authors concluded, these observations suggest an integrative process of the cerebellum between attentional and emotional signals, fulfilling the presumption of cerebellar actions along separate time lines in supporting the active large-scale neuronal networks in encoding and forwarding affective cues to the responsible hubs such as the thalamus, the temporal, and parietal and then finally to the prefrontal cortex, resulting in integrative emotion processing.

7.3.4 Emotion Recognition

A further issue of interest in the cerebellar neurophysiology of emotion is participation in perception and recognition of emotions in face expressions. Several reports indicated a role of the cerebellum in recognizing and discriminating emotional facial expressions, in particular for negative emotions (Turner et al. 2007; Fusar-Poli et al. 2009; Ferrucci et al. 2012; Adamaszek et al. 2014). This encouraged studying the details of the pathways of the cerebellum and its contribution to integration of emotional responses in social behavior. Initially, neuroimaging observations outlined topographical aspects of cerebellar contributions to emotional face recognition (Fusar-Poli et al. 2009). Prompted by this knowledge, the less defined temporal characteristics were addressed in further studies investigating the neural signatures of the cerebellum associated with recognizing the emotion value in human face expressions. Following the presumption of specific neurophysiological patterns of the cerebellum in emotion recognition, a study by Ferrucci pointed to this by an enhanced perception of negative emotions in facial expressions after tDCS of the cerebellum, whereas the perception of positive and neutral facial expressions remained unchanged (Ferrucci et al. 2012). This study confirmed and strengthened knowledge of this role of the cerebellum. The authors of this chapter then investigated the specific time course of the underlying neural activity (Adamaszek et al. 2015). In this study, a strong N170 over temporo-occipital and diminished LPP over centro-parietal cortex areas were found in a sample of patients suffering a circumscribed ischemic cerebellar lesion, in response to faces drawn from the Karolinska catalogue (KDEF) with expressions of different basic emotions (i.e., sadness, joy, anger, or fear). These findings suggested preserved encoding in early recognition, but impaired forwarding of emotions in facial expressions to later higher-order processing stages. Interestingly, the diminished LPP amplitudes were observed in particular to the two basic emotions fear and anger, emphasizing the notion hitherto of specific cerebellar involvement in emotions of negative valence and high arousal. Moreover, dipole source estimations identified increased activation of the PFC for the LPP with a stronger representation of fear and anger at the left than the right PFC, whereas control subjects showed a stronger activation of the right PFC to these emotions. Finally, reduced LPP for fear and anger were significantly correlated to lesions of the left Crus I, suggesting a specific input from Crus I to higher-order processing of socially relevant emotions (see Fig. 7.2). Moreover, the contralateral distribution of the LPP dipole, assumed to represent compensatory neural activities in cerebellar damage, might be of interest in terms of the successively identified connections of the cerebellum, in particular for the dorsal parts of the neocerebellum, to areas of the PFC in emotion processing for behavioral evaluation and response preparation (Habas 2009; Stoodley and Schmahmann 2009). Nevertheless, the participants in the Adamaszek et al. (2015) study were predominately afflicted by a lesion of the left cerebellar hemisphere, so a possible bias of the findings of impaired forwarding of facially expressed emotions might be a matter of debate. In fact, there is still no consensus about a distinct lateralization of the cerebellum to specific emotion processing domains (Adamaszek et al. 2017), in particular for different valence or arousal, so this restriction of the study sample of Adamaszek should be considered in further studies onto this peculiar request.

Findings of altered LPP to facial emotion expressions in circumscribed cerebellar lesions were reported in a recent study by Houston et al. (2018), investigating the cerebellar inputs to emotion perception by a specific paradigm of a dual-task emotion perception task in patients suffering a cerebellar malformation (Arnold Chiari Malformation Type I). In this study, subjects were presented different auditory stimuli (i.e., a pure tone or white noise of 22 Hz, 8 bits) and, in parallel, faces with different emotional expressions (neutral, happy, angry), both with different stimulus onset asynchrony (100, 300, or 900 ms). A crucial finding of their study was a preserved divided attention as assessed by P300 amplitude and latency, but a frontalization of ERP amplitudes for facial expressions in patients. This pattern of effects is in accordance with the observations in Adamaszek et al.'s (2015) study with a shift of the LPP for facial expressed basic emotions, indicating a compensatory recruitment of the responsible cerebral network in its approach for guiding the emotion information at the prefrontal cortex as sequelae of lacking cerebellar feedback (Cappell et al. 2010; Reuter-Lorenz and Cappell 2008). Interestingly, the study by Houston et al. (2018) detected a significant effect for emotion in which happy faces were identified the fastest, followed by neutral faces and then by angry faces, suggesting that the recognition of negative, that is angry faces, was in particular impaired in patients with cerebellar malformation. As a conclusion, the results of the study evidenced that emotional deficits in

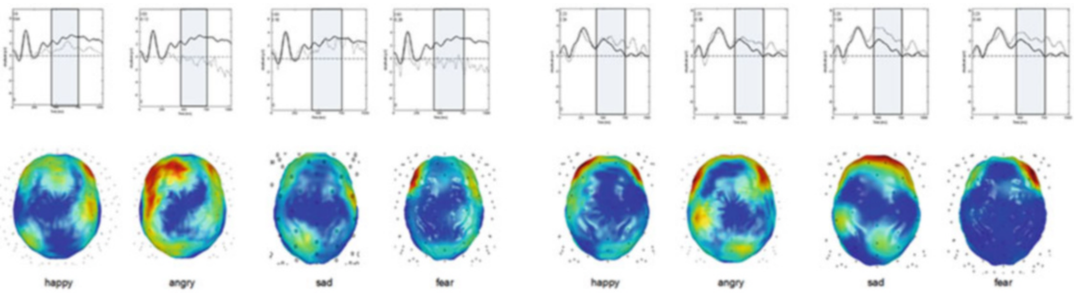

Fig. 7.2 ERP curves (upper panel) and their corresponding dipole source maps (lower panel) to each emotion (happy, angry, sad, fear) in face expressions are displayed, respectively. The maximum of late positive potentials (LPP) over parietal areas is centered around 600 ms. Adapted from Brain Research, Volume 1613, Pages 1–12, Adamaszek et al., © Elsevier 2015

cerebellar disorder have been assumed as originating from conscious, controlled processes rather than from preconscious object perception (Houston et al. 2018). However, as the results of a study by Schutter and colleagues pointed to a cerebellar impact also on preconscious processing of basic emotions (Schutter et al. 2009), further studies might provide more insights into the cerebellar mechanisms in preconscious and conscious processes of emotion.

7.4 Theoretical Considerations of Neurophysiological Inputs of the Cerebellum in Emotion

In regard to the outlined descriptions and the current assumptions of the underlying neurophysiological principles, emotion processing is considered as a part of complex distributions of attending or perceiving external and internal cues with a different significance and dimension, among other the valence and arousal, which are forwarded along large-scale cerebral networks in temporal, parietal, and prefrontal cortices, the amygdala, and the hypothalamus (Davidson et al. 2003; Pessoa 2013; Dolcos et al. 2020). According to the presumption of the distribution of external stimuli across the brain with a high degree of interactivity between cortical and subcortical brain regions including the cerebellum, a high degree of local connectivity is mixed with long-range connections that allow all regions of the brain to be linked by very short paths (Pessoa 2013). Indeed, these networks are communicating through extensive reciprocal connections between the primary and associative sensory, temporal, visual, and auditory regions, the parietal regions as part of the dorsal attention network, and subareas including the insula and the cingulate cortex of the PFC (Bowers et al. 1991; LeDoux 2000; Adolphs 2004; Pessoa 2008). The PFC, in particular the neuroanatomically separated DLPFC and ventromedial prefrontal cortex (VMPFC), plays an important role in attending to and comprehending external emotional cues like facial expressions or salient events, especially in response to negative aversive, like sad, fearful, or angry facial expressions (Sprengelmeyer et al. 1998), preparatory to mounting an appropriate emotional response. Moreover, the third major area of the PFC, the orbitofrontal and related medial regions have been found to be associated with the control of affective and motivational functions (Happaney et al. 2004). The amygdala (LeDoux 2000) and insula (Pessoa 2005) are also involved in the appraisal of emotional significance. In addition, areas of the temporal lobes, in particular the medial temporal lobe (MTL), with its memory-based mechanisms, are assumed to be substantially involved in arousal-dependent effects (Kensinger and Schachter 2006). The cerebellum, in particular parts of the vermis, and lateral hemispheric lobules VIIB and Crus I/II, are connected to these cerebral regions, in particular to the above-mentioned regions of PFC, in topographically mapped reciprocal circuits (Middleton and Strick 2000). This network enables the neural processing of cognitive and affective items along even widespread and fine-graded neural circuits constituted by these well-established cerebral domains (Habas et al. 2009; Stoodley and Schmahmann 2009; Buckner et al. 2011; Baumann and Mattingley 2012; Argyropoulos et al. 2019). Notwithstanding, there is still no clear spatial segregation of evolutionary new regions of the cerebellum in terms of functional connectivity with limbic versus association cortices, so this particular issue remains to be clarified (Argyropoulos et al. 2019).

With reference to the growing literature on this topic, the cerebellum emerged to interact within phylogenetically conservative, but also more complex cerebral network assemblies along cortical, subcortical, and brainstem regions in order to mediate facilitatory processes in emotion (Timmann et al. 2009). A crucial issue concerning the cerebellum is its input to the complex segregated circuits in emotion processing is the bias toward negative valence and high arousal (Colibazzi et al. 2010; Moulton et al. 2011), which might indicate a strong relevance for determining the meaning of incoming stimuli and the prediction of the needed neural response in guiding the motor and/or cognitive as well as affective components in human behavior, thus integrating basal and higher-order processing avenues (Sacchetti 2009; Schmahmann 2010; Adamaszek et al. 2013, 2015 and 2017; Argyropoulos et al. 2019). This function is presumably one of the key functions of the cerebellum, that is the identification in cue control, using internal models to match changes in sensory input that accompany behavioral actions such as motor movements or cognitive and affective responses for adjusting accordingly (Krakauer and Shadmehr 2007). Applying this conceptualization to emotional processing, the cerebellum might use internal models to identify and shape appropriate emotional, motor, and cognitive-behavioral reactions to a given sensory state, with the basal ganglia computing the cost-benefit and the optimal resource allocation, and the prefrontal cortex as converging the information for guiding the behavior outcome (Ito 2008). Interestingly, the role of the basal ganglia in comparison to the cerebellum in emotion processing has arisen some specific interest in the underlying mechanisms in recent years, so both are representative for the two main subcortical areas of the assumed large-scaled neural networks in decoding emotion issues of salient cues or even in social relevant communication such as facial or vocal expressed emotions (Adolphs 2004; Péron et al. 2012; Adamaszek et al. 2019). Both subcortical regions share some principal modes of feedforwarding emotion information to the responsible cortical areas, whereby the basal ganglia have been identified to act along the synchronization of the cortical areas and the different cerebellar regions rather along the error-based mode, but both, in particular the substantia nigra (SN) and the deep cerebellar nuclei (DCN), deem to serve for the integration of multiple cortical inputs within or across domains irrespective of the valence or arousal (Pierce and Péron 2020). In fact, the exact subcortical interplay of the basal ganglia and the cerebellum to emotion between themselves and to the different cortical areas with their task-dependency remains subject of further neurophysiologic investigations, even to clarify the details of the impact of the cerebellum and the basal ganglia onto emotion attention and recognition (Adamaszek et al. 2019).

From a functional point of view, the cerebellum is proposed to act as an interface amongst the different neural signal processing of emotions, which are feedforwarded along dynamic main and side paths between bottom-up stages of signals received (such as delivered by faces, voices, and bodily cues) and top-down factors (stereotypes and prior knowledge) that lead to unified perceptions and reactions to emotional triggers (Freeman Freeman and Ambady 2011; Dolcos et al. 2020). These dynamic interactive paths are implemented in particular attentional and executive domains including emotional working memory to a varying degree (Dolcos et al. 2020), subsuming the broad spectrum of neurophysiological research findings of cerebellar inputs to different neural networks as described in this chapter. A crucial issue is that the identification of cerebellar areas as active in receiving and feedforwarding neural signals carrying emotion information has arisen from the observation that efferents from the central nuclei of the cerebellum project to multiple divisions of the ventrolateral thalamus, from where they are forwarded onto multiple associative cortical areas (Habas et al. 2009; Strick et al. 2009; Moulton et al. 2011). This conceptualization is in keeping with the findings of the MEG study by Styliadis et al. (2015) suggesting different timing characteristics in cerebellar processing stages of dimensional emotion ingredients, including valence and arousal. A heuristic and therefore exhaustive concept clearly differentiating arousal from the valence of affective cues is still a matter of debate (Lindquist et al. 2016). The observations of topographically spread cerebellar activity in analyzing subtle emotion information present in a single salient event, for example, a striking landscape engendering positive affect versus a scene of a criminal couple engendering negative affect, as displayed in the IAPS catalogue, might point to a methodological approach to disentangling the parallel and therefore integrative processing of complex stimuli at cerebellar computational stages.

Given that the thalamus strategically allocates cerebellar output to cerebral areas, the observed impaired activities within these circuits may result in altered affective network processing of such discrete information regarding emotional ingredients, like salient visual or auditory cues with a different valence and/or arousal of the environment such as facial or vocal expression from the visual and auditory cortices passing through the thalamus and onto other substantial hubs in the amygdala, the parietal and ventrolateral, ventromedial and orbitofrontal regions of the PFC (LeDoux 2000; Pessoa 2008). Thus the cerebellum is assigned a key role in the rapid synchronization of motor and sensory information processing (Aso et al. 2010). This may include the recognizing of and responding to emotional cues in particular through Crus I and Crus II (Styliadis et al. 2015), forwarding information along the dentate nuclei and the thalamus to the connected associative cortices, in particular the PFC and its subterritories (Ramnani 2006; Habas et al. 2009; Krienen and Buckner 2009; Strick et al. 2009). Thus, the cerebellum seems to take part in serial as well as parallel computations at intracerebellar and cerebello-cerebral networks that handle stimulus perception (Snow et al. 2014; Ivry 2015), feeding into neuronal pathway loops that facilitate forwarding functions which anticipate the results and therefore predict the intended pattern of motor or sensory activity (Keele and Ivry 1990; Leggio and Molinari 2015). Moreover, the presumption of cerebellar activity in early and forwarding stages of affective stimulus evaluation, and therefore different temporal patterns in correspondence to serial and parallel cerebellar processing of affective cues, might be corroborated by the observation of compromised cerebellar response to salient affective cues with impaired early and late ERP and otherwise the compromised cerebellar response only to the late but not the early ERP to basic emotions in facial expressions (Adamaszek et al. 2013 and 2015; Houston et al. 2018). Nevertheless, these ERP findings on cerebellar contributions of emotion processing are limited to paradigms of visual stimuli, i.e., although clinical and neuroimaging investigations demonstrated cerebellar involvement in the recognition and processing of emotion at the auditory or vocal level (Adamaszek et al. 2019; Ceravolo et al. 2021), there is still no feasible research work on specific electrophysiologic characteristics. The compelling electrophysiological findings are in line with the topographical delineation of a strong cerebellar connection to the subterritories of the PFC and the assumed diaschisis concept of cerebellar lesions to the cognitive-affective disturbances as typically addressed to the PFC, subsuming the arguments of compensatory activities of homologous including mirror neurons besides the PFC regions in face of the connectivity loss in the default cerebellar-cerebral loop to the lateralized PFC (Leiner et al. 1989; Turner et al. 2007; Schmahmann 2010; Buckner et al. 2011; Kircher et al. 2013; Adamaszek et al. 2015). The more detailed consideration of the cerebellar-prefrontal connections according to a specific lateralization of the left PFC handling approach-related positive cues, and the right PFC in behavioral inhibition to negative cues (Davidson et al. 2003), as the Adamaszek et al. (2015) study observed with an augmented activation of the left PFC in cerebellar lesions, might correspond to the presumption of involvement of the left ventrolateral prefrontal gyrus (vlPFC) as part of the inferior frontal gyrus (IFG) in cognitive processing of negative affect and relevant to emotional empathy (Shamay-Tsoory et al. 2009; Kircher et al. 2013), but also social norm recognition, social inhibition, and prosocial behavior (Krautheim et al. 2020). Independent of the current unknowns in possible specific lateralization details of parts of the IFG to discrete information processing of affective and cognitive values, for example, concerning asymmetries along primarily affective valence and/or other subsiding aspects such as arousal and motivational ones, the left IFG has been already detected as significantly active in processing negative (i.e., anger and fear) emotion valences of face expressions in a meta-analysis of functional neuroimaging data (Fusar-Poli et al. 2009). The IFG is part of several hubs such as the dorsolateral (DLPFC), medial (mPFC), and orbitofrontal (OFC) locations of the PFC. The PFC modulates different response patterns in emotional control, integrating the emotional information and corresponding cognitive components for the purposes of stimulus appraisal and comparison as well as decision-making for preparing appropriate behavioral responses (Jiang et al. 2014; Becker et al. 2019). These prefrontal hubs might be encountered by several feedforwarding cerebellar-prefrontal connections along subdivisions of the thalamus with fine-graded detailed information for domain-specific integration, whereby the lateral prefrontal areas including the IFG may rather account for the control of affective processing, and the medial and orbitofrontal regions rather for the affective appraisal and motivation as part of the reward processing (Ito 2008).

Considering all the recognized connections to the cerebellum and its impact on emotion processing, the vermis, but also the lobules VI, VII, and VIII, may function as a specific interface between sensory stimuli, the emotional state of the subject, including visceral components, and motor and behavioral responses, whereby the hemispheric lobule VII including Crus I and Crus II and the lobule VIII are of particular interest in terms of the evolutionary younger stages of emotion control at the prefrontal cortex (Krienen and Buckner 2009; E et al. 2014). Thus, learning-related plasticity at this site with its long-term potentiation (LTP) and long-term depression (LTD) of neural activity may be necessary to relay emotional, cognitive, and motor behaviors appropriate to given sensory stimuli and maintain this information for a long time period (Sacchetti in Adamaszek et al. 2017). Indeed, the vermis has been assumed to be involved in all of the putative phases of the emotional memory process, i.e., acquisition (Ploghaus et al. 1999; Maschke et al. 2002), consolidation (Sacchetti et al. 2002; Gianlorenço et al. 2015), storage/retrieval and reconsolidation (Sacchetti et al. 2007), and extinction (Utz et al. 2015) of emotional memories. These several domains of emotion memory again suggest cerebellar parallel processing of discrete affective information or otherwise patterns of a given set of a salient stimulus such as a threatening scene or fearful face expression for generating appropriate patterns of emotional and cognitive behavioral responses, whereby the variously observed activities of lobule VI, lobule VIIB, Crus I, Crus II, and possibly IX (Stoodley and Schmahmann 2009; Hoche et al. 2018) in functional neuroimaging and electrophysiology might elucidate the subtle processing of multimodal associative memory traces with its significance for a distributed response along sensory, motor, cognitive, and affective lines of the human brain. Interestingly, Doya et al. (2002) postulated three learning algorithms proposed in computational neuroscience, i.e., unsupervised statistical learning, reinforcement learning, and supervised learning, which could be considered as the main functions of the cerebral cortex, the basal ganglia, and the cerebellum, respectively. Thus, the cerebellum basically possesses a learning capability to acquire internal models if climbing-fiber inputs provide appropriate error signals, which might be subsumed as a "feedback-error-learning" scheme (Kawato et al. 2020).

As already introduced by Styliadis et al. (2015), considering the reported studies of cerebellar actions in different emotion paradigms with respect to emotional theories of anatomical segregation and specialization of cortical and subcortical structures for distinct categorial emotions (Wicker et al. 2003; Adolphs 2004) or different dimensions of emotions (Anders et al. 2004; Dolcos et al. 2004), the cerebellum is feasible to take part to specific temporal activity profiles (Esslen et al. 2004; Hot and Sequeira 2013), maybe for the dimensional (i.e., arousal and valence) as well as the categorial representation of affective cues. Notwithstanding the fact that a deeper knowledge about the differentiation of the responsible cerebellar areas to dimensional versus categorial issues of emotion processing, that is the processing of emotions along independent dimensions such as valence and arousal, and/or along distinct universal emotions with discriminative signatures, needs further clarification (see Lindquist et al. 2016), Styliadis et al. pointed out, the cerebellar lobules are engaged in swift evaluations to highly arousing as well as unpleasant stimuli, with slower evaluations to pleasant and highly arousing stimuli, therefore disentangling a specific spatiotemporal profile of the intertwined cerebellar processing, particularly in Crus I and lobule V for adapting the valenced information of the stimuli (pleasant/unpleasant) and influencing the forthcoming evaluations either strongly (and possibly faster) or less strongly (and possibly slower) (Styliadis et al. 2015). This assumption is in line with the findings of temporal aspects of emotion processing, considering a two-stage model of emotion-attention interaction (Schupp et al. 2007). Here, a first stage predominates a perceptual processing of emotionally significant information (as reflected by an EPN and N2) and novel stimuli (reflected by the N2), whereas a second stage involves elaborate and sustained attentional processing modulating the emotional significance and attention history synergistically (as reflected by an LPP) (Chen et al. 2018). However, as emotion processing depends on several integrative activities such as the thalamus, the cingulate cortex, and the prefrontal areas of DLPFC and mediolateral prefrontal cortex (MLPFC), a multiple waves model as proposed by Pessoa (2013) emphasizes a broad cortical and subcortical network architecture in coordinating and regulating the flow of multimodal information, which is accomplished via a series of thalamo-cortical loops. In regard to the striking findings of specific temporal and structural activities, the described cerebellar lobules VII, Crus I, and Crus II might provide specific signal wave tuning.

The assumption of specific cerebellar actions to otherwise cerebral network signal flows is in line with the proposed role of the cerebellum as a general coordinator of neuronal loops in its reciprocal cerebral connections, regulating the activation and inhibition levels of addressed cortical areas, thus controlling the speed, timing, and appropriateness of cognitive processes (Baillieux et al. 2008; Mannarelli et al. 2019). More specifically, the role of the cerebellum is likely to exploit conflicting signals to improve future predictions and/or produce online changes of behavior in response to the error in evaluating temporal patterns (Mannarelli et al. 2019), which might cover the emerging reports outlining the cerebellar role in perception and related attention domains to cognitive as well as affective functioning, which emphasizes the presumption of a perceptual organization (Tunc et al. 2019). Indeed, already some early studies reported impairments of spatial manipulation and spatial attention (Wallesch and Horn 1990; Levisohn et al. 2000), and recently deficits of attention and set shifting (Ivry 2015; Kansal et al. 2017) in cerebellar disease. Of additional note, the repeatedly reported cerebellar activations in oculomotoric, in particular the well-known saccadic, movement might indicate a further providing in emotion experience. There are some intriguing findings of activations of the paraflocculus (Zeki et al. 2014) and the lobule VI (King et al. 2019) in functional neuroimagings, which were associated with more in-depth evaluation of emotional stimuli, like the associated ocular or eye-gaze movements during the scanning of characteristic details of a cue like the sequence and the proportion, or just the color and brightness of a scene with emotion features, all which might be sensitive for deficits in timing the underlying neuronal signals. These observations further illustrate the assumption that different parts of the cerebellum, that is lobules VII–VIII and IX primarily for emotion, and other regions such as the paraflocculus and the lobule VI for additional cue details, might be active along parallel neural processing lines in evaluating and feedforwarding the distinct information of complex cues to the responsible neural networks involving the prefrontal, parietal, and temporal association cortices.

In regard to the forwarding neural pathways along the dentate nucleus of the cerebellum, non-motor subregions of the cerebellar dentate nucleus are engaged in pre-attentive encoding and forwarding of event-based temporal sensory information to the parietal, frontal, and temporal cortex via the thalamus, forming complex neuronal circuits engaged in early and late processing stages of incoming signals, all with a timing control at the millisecond level to enable effective coordination (Timmann et al. 2009; Aso et al. 2010; Kotz and Schwartze 2010; Leggio et al. 2011; Styliadis et al. 2015). According to the proposed pre-attentive detection of emotional information of the inner and outer environment (Palermo and Rhodes 2007), the cerebellum may integrate event-based temporal information along a pattern recognition (Albus 1971; Kawato et al. 2020), derived from attending to emotional cues through fine-graded feedforward computation to the active large-scale cerebral processing systems, guiding the demanded or otherwise suitable sensomotoric, cognitive, and affective response patterns (Stoodley and Schmahmann 2009; Strick 2009; Kotz and Schwartze 2010; Leggio et al. 2011; Ivry 2015). This functional approach might even be feasible in understanding the observed affective impairments in cerebellar lesions as a result in lacking of temporal coordination of appropriate sequences and decreased recall of established internal representations of emotional, in particular cues of a negative valence, resulting in critical delays of cerebral processing stages (Adamaszek et al. 2013; Adamaszek et al. 2015). This assumption is in line with the recent discussion of Cabaraux that an acute dysfunction of the cerebellar circuitry is subject to an acute inability to implement the forward model, caused by deficits in timing and/or impediments in synergy, resulting in impaired predictive computation of the intended human behavior (Cabaraux et al. 2020).

A specific matter of ambiguity concerns the understanding of the modular organization and functionality of the cerebellum in receiving, operating, and feedforwarding affective cues within the associative cerebral cortices. Considering the functional cerebellar organization of computing neural signals at microzones, which are hierarchical/heterarchically organized, the cerebellum is deemed to act with inert multiple modules, internal modules, and hierarchy/heterarchy (Kawato et al. 2020). The microzones are arranged along specific time and synergy axes of an internal forward model processed within cerebellar microzones, which in turn result in converging inputs to the Purkinje neurons, providing a unique property of a perceptron in the brain (Cabaraux et al. 2020). Nevertheless, there are currently several debates in the cerebellar literature, among others, as to whether the cerebellum performs the same single computational function across domains such as a Universal Cerebellar Transform (UCT) or performs multiple functions consisting of functionally distinct computations (Guell et al. 2018; Diedrichsen et al. 2019). Various hypotheses have been put forth that might form the basis of the UCT theory, which has been linked to stereotyped cerebellar computations such as error-based learning, error monitoring, forward control, prediction, timing, or sequencing (Argyropoulos et al. 2019). The concept of a single computation mode as explained by the UCT concept might be of interest, if considering the cerebellar functions as generally characterized at an algorithmic level, including prediction (Miall 1998), internal models (Ito 2008), timing (Ivry 2015), and automatization (Balsters and Ramnani 2011; but see also Chap. 10 on emotional habits in this volume). In addition, the UCT might be feasible for the related conceptualization of a principle cerebellar function of a predictive forward model for state estimation (Ito 2008) and supporting the generation of contextual semantic expectancy (Lesage et al. 2012). This assumption concurs with the idea of Ito, who favored the hemispheres of the cerebellum to provide internal models (which can be forward or inverse) of the tasks processed within the responsible networks along the areas of prefrontal cortex (Ito 2008). Of note, neural circuits of the cerebellar cortex have been identified as much more uniform, regardless of different regions and zones (Tsutsumi et al. 2019), than those of the cerebral cortex, supporting the assumption of a uniform computation theory for the cerebellum (Apps and Hawkes 2009). However, as some researchers argued, if it turns out that each cerebellar region integrates information from a combination of cortical regions, then theoretical accounts would need to consider how the cerebellum modulates or gates communication between these regions (Diedrichsen et al. 2019). In addition, different regions of the cerebellum receive mossy-fiber and climbing-fiber inputs from many different areas of the brain and the rest of the nervous system (Kawato et al. 2020). Therefore, studying the cerebellar activity to cognitive domains of cerebral networks still should consider the context of the activity patterns in the cerebral cortex, which might be applicable not only for motor but also for non-motor domains of cognition and emotion (Diedrichsen et al. 2019).

7.5 Conclusions

There is growing consensus regarding the role of the cerebellum in emotion processing. The cerebellum has been extensively probed in both neuroimaging and electrophysiological testing paradigms. Neuroimaging studies have yielded information regarding the topography of afferent and efferent pathways connecting cerebellar nuclei and prefrontal cortex, in the millimeter range. The electrophysiological studies discussed in this chapter have provided insights into the fine-grained temporo-spatial aspects of emotion processing, in the millisecond range. Taken together, these lines of research are mutually informative, producing a composite picture of topographic and functional peculiarities, indicating where and how parts of the cerebellum are engaged in discrete domains of emotion such as attention, recognition, and discrimination of affective cues. Decisive findings in this chapter go beyond the association of structures with functions, toward an understanding of how emotion processing unfolds in the cerebellum and is passed on to large-scale neuronal networks in the cerebral cortex responsible for the further contextualization of emotional information and implementation of behavioral responses. Of particular note are the findings of cerebellar involvement at early and late stages of emotion processing involvement to the temporal distributed integration and fine-grading of emotion processing along large-scale inter-connected networks responsible for processes of attending to and evaluating affective cues in its behavioral significance. The electrophysiological findings summarized in this chapter emphasize neurophysiological mechanisms involving large-scale neuronal networks, with dependency on serial and parallel contributions from distinct parts of the cerebellum, supporting the processing of emotions in early attention and following deeper evaluation.

The findings of research to date into the neurophysiology of emotional processing by the cerebellum form a suitable vantage point to comment on emerging trends in neuroscience research. Electrophysiological research protocols such as the study of ERP offer the most sensitive characterization of time characteristics of neurophysiological pathways. Further, ERP studies can identify specific contributions of the cerebellum to cerebral networks in domains of interest such as emotional attention, emotional recognition, emotional empathy, and emotional behavior. Electrophysiological procedures show promise in bridging the gaps in topographic descriptions of cerebello-cerebral pathways, since they distinguish the neurophysiological characteristics of these pathways in the sub-second range (Ivry 2015). Therefore, the significance of the electrophysiological measurements with regard to the original activities of the cerebellum must be understood with appropriate caution, that is distinction between the cerebellar and the cerebral parts (including the basal ganglia) will hardly be possible without additional information such as above all the task-bound examination characteristics, so the electrophysiological patterns derived from the surface EEG as well as the obtained distinct ERP represent the specific actions of the large-scaled cerebral networks as capable at the brain surface, which are influenced by task-specific cerebellar contributions. Nevertheless, a recent investigation of capable EEG features in association to cerebellar activations is intriguing, so intermittent theta-burst TMS has been observed to increase the temporal complexity of the cerebral network EEG signals as measured by multiscale entropy, and furthermore influenced the impact to different band broad oscillations according to the site (hemispheric, vermal) of stimulation of the cerebellum (Farzan et al. 2016). Thus, more specific technical applications such as MEG or combined fMRI-EEG recordings might solve the demand of displaying temporal and structural features of the cerebellum to a specific task of emotion processing to a sophisticating level.

The rigorous study designs that have increased our understanding of the cerebellar neurophysiology of emotion, as reviewed in this chapter, and the increasing breadth and depth of neuroscientific research, offer perspectives into possible treatment options in several neurological and psychiatric sequelae of cerebellar dysfunction. Thus, the same electrophysiological methods used to discern temporal responses in emotion processing in discrete cerebellar areas can also ascertain the neuroplasticity of compromised domains of emotion processing due to cerebellar disorders. A combination of neuroimaging and electrophysiological techniques may increase the resolution of both timing and topographic parameters, distinguishing the internal cerebellar contributions to mediating finely tuned processing of distinct emotional cues. Research along these lines might indicate the stimulating or inhibiting properties of transcranial cerebellar stimulation needed for subserving the cerebral networks to produce or fail in optimal emotional behavior. Further research may also clarify which domains of the cerebellum serve general and which specific roles in the processing of emotion (e.g., specific contributions to different emotional valences in face and body expressions, autonomic functions of pain). In addition, the identification of core computations may result in finer-grained behavioral paradigms in evaluating and therefore promoting the challenging requests in disentangling the neurophysiology of the cerebellum in emotion.

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8

Non-invasive Brain Stimulation of the Cerebellum in Emotion

Jana Klaus and Dennis J. L. G. Schutter

Abstract

Transcranial magnetic and direct current stimulation are non-invasive brain stimulation techniques that are used to investigate cerebellar functions in healthy and clinical populations. These approaches allow transient modulation of neural excitability of the human cerebellar cortex to directly examine phenomenological, behavioral, and physiological aspects of motivation and emotion. While cerebellar neurostimulation in the field of social and affective neuroscience is still in its initial phase, empirical evidence confirms the direct involvement of the cerebellum in motivation and emotion. Non-invasive stimulation of the cerebellum provides a unique experimental approach to study the relation between the cerebellum and emotions in humans.

Keywords

Cerebellum · Emotion · Transcranial direct current stimulation · Transcranial magnetic stimulation

8.1 Introduction

Stimulation of the cerebellum has a long history that dates back to the eighteenth century. Luigi Rolando (1773–1831) was among the first to pioneer the use of electric currents to study cerebellar functions and observed that galvanic currents applied to the cerebellum of animals can elicit convulsions (Ponce et al. 2021). The administration of electric currents to examine cerebellar neurophysiology of motor functions in healthy and neurological populations was further pioneered in the subsequent centuries. The Italian scientist Giuseppe Moruzzi (1910–1986) used electric currents to show that the cerebellum is involved in emotions by providing evidence that autonomic activity associated with hypothalamic-induced sham rage in cats could be modulated by electrically stimulating the cerebellum (Zanchetti and Zoccolini 1954). The introduction of non-invasive brain stimulation techniques including transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS) provided a novel safe and minimally invasive means to study the relationship between the cerebellum and emotions in humans (Cattaneo et al. 2021). While early research with weak electric currents was abandoned during the 1960s, partly due to the lack of systematicity of findings, empirical proof that tDCS can modulate neural excitability in a polarity-dependent fashion back in 2000 (Nitsche and Paulus 2000) triggered a renewed interest in this technique by researchers

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and clinicians. The resurgence of tDCS in the last decades is actually due to TMS, a technique introduced in 1985, which was used to activate the corticospinal tract in order to show changes in motor-evoked potentials of the hand muscles following tDCS (Nitsche and Paulus 2000). In addition to targeting the cerebral cortical areas of the brain, the fact that the cerebellar cortex faces the cranium has led to an increasing number of non-invasive brain stimulation studies in basic and clinical neurosciences that explore the functional contributions of the cerebellum in motor, cognition, and, more recently, emotions. In this chapter technical and methodological aspects of cerebellar TMS and cerebellar tDCS in studying the cerebellar correlates of human emotions will be discussed and a brief overview of the scientific literature will be provided.

8.2 Cerebellar Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation technique that was developed at the Royal Hallamshire Hospital in Sheffield (England) (Barker et al. 1985). The technique is based on Faraday's law of electromagnetic induction which dictates that when a conductor is placed inside a rapidly varying magnetic field, an electric current will be created in the conductor. Therefore, whenever high amounts of stored energy in capacitors connected to a coil are released via an electronic switch, an electric current will start to flow through the coil. In keeping with Ørsted's law, the electric current will create a brief magnetic field that, unattenuated through the scalp and skull, causes a secondary electric current in the underlying conducting nerve tissue. When the electromagnetic pulse is strong enough, the secondary current will give rise to a transmembrane potential which depolarizes neurons and produces action potentials.

The first human study in which the cerebellum was targeted showed that single-pulse TMS induces brain responses located over anterior scalp regions as recorded with conventional electrodes (Amassian et al. 1992). These distal brain responses were explained by transsynaptic activation of the dentato-thalamo-cortical pathway through local activation of the cerebellar cortex. Subsequent studies demonstrated that high-intensity single-pulse TMS applied to the midpoint between the inion and the mastoid could elicits cerebellar inhibitory effects on the contralateral primary motor cortex (M1) (Ugawa et al. 1995). This cerebellar inhibitory effect is suggested to stem from TMS-induced activation of the inhibitory GABA-driven Purkinje cells that dampen the excitatory output of the deep cerebellar nuclei to M1 via ventral thalamic projections (Daskalakis et al. 2004).When 5–8 ms after a cerebellar TMS (conditioning) pulse, a single TMS (test) pulse is applied to M1, the motor-evoked potential (MEP) recorded from the hand muscles will be markedly smaller as compared to single-pulse TMS to M1 without the preceding cerebellar TMS pulse. The 5–8 ms latency concurs with the onset of anterior electroencephalographic (EEG) responses to contralateral cerebellar stimulation found earlier by Amassian et al. (1992). In addition, anterior EEG responses in the theta frequency range (4–7 Hz) were registered in response to single-pulse TMS administered over the cerebellar midline as compared to sham and occipital single-pulse TMS in healthy human volunteers (Schutter and van Honk 2006). In a more recent study, neuro-navigated single-pulse cerebellar TMS was interleaved with EEG recordings to examine associations between electrocortical responses and levels of (inhibitory) GABA and (excitatory) glutamate in the prefrontal cortex as measured with magnetic resonance spectroscopy (Du et al. 2018). Single-pulse cerebellar TMS over the midline induced bilateral anterior broadband synchronization in the theta-gamma frequency range (4–45 Hz) that was inversely associated with GABA concentrations in the medial frontal lobe. Subsequent analyses indicated that the higher EEG frequency range (9–45 Hz) contributed the most to this association. It has been proposed that increased availability of GABA facilitates local processing effects in the cerebral cortex that reduces phase locking of large neural populations, consequently causing less EEG synchronization on the macroscopic level (Du et al. 2018). These studies among many others illustrate that magnetic stimulation is capable of inducing both local as well as distal neurophysiological effects, thereby establishing TMS as a viable probe to study cerebellar functions. While the effects of single-pulse TMS are short-lived, when applied in a repetitive (rTMS) or patterned fashion, like theta burst stimulation (TBS), neurophysiological effects typically outlast the stimulation period and can be used to transiently modulate neural excitability levels of the tissue that is being targeted. For example, 900 pulses delivered at 1 Hz over the right cerebellar cortex resulted in a significant reduction of cerebellar capacity to inhibit M1 output for at least 30 minutes after rTMS (Popa et al. 2010). In the same study, continuous TBS (cTBS), which consists of three-pulse bursts at 50 Hz repeated every 200 milliseconds for 40 seconds (600 pulses), also yielded significant reductions in cerebellar inhibition of M1 for at least 30 minutes. By contrast, the administration of three-pulse bursts at 50 Hz repeated every 200 milliseconds for 2 seconds separated by 8 seconds of no stimulation (a protocol known as intermittent TBS; iTBS) can enhance the inhibitory function of Purkinje cells for 30 minutes (Koch et al. 2008). The observation of changes in frontal resting-state EEG activity following fast-frequency rTMS applied to the cerebellum further suggests the efficacy of cerebellar TMS to modify local and distal neural activity (Garg et al. 2013; Schutter et al. 2003). While the precise mechanisms are still under investigation, the modulation of cerebellar excitability is suggested to involve complex local synaptic processes at the level of Purkinje cells associated with, on the one hand, long-term depression (LTD) from slow-frequency rTMS and cTBS, and, on the other hand, long-term potentiation (LTP) from fast-frequency rTMS and iTBS. Furthermore, selective facilitatory and inhibitory effects on excitatory granule cells and GABA-ergic interneurons with lower excitability thresholds have also been suggested to contribute to the mechanisms by which TMS modulates cerebellar physiology (Koch 2010).

Following the earlier intracranial electric stimulation studies in animals and humans that provided evidence for cerebellar involvement in the brain’s emotion and motivation circuits (Berman et al. 1974; Heath et al. 1978, 1980; Zanchetti and Zoccolini 1954), the introduction of TMS and the possibility to effectively target the little brain offered a unique non-invasive and safe alternative to further explore the relation between the cerebellum and emotions in humans. Among the first attempts was a pilot study that investigated the effect of high-frequency repetitive transcranial magnetic (rTMS) stimulation over the medial cerebellum (Schutter et al. 2003). In a sham-controlled crossover design, healthy volunteers received a 20- minute stimulation regimen consisting of 80 trains of 10 seconds of 25 Hz rTMS followed by 5 seconds of no stimulation for a total of 20 minutes. On separate days and in varying order, participants received real rTMS over the midline cerebellum, lateral cerebellum, and occiput or sham rTMS over the medial cerebellum using an iron core coil (Epstein and Davey 2002). Figure 8.1a shows results of a computer simulation performed with SimNIBS software (Thielscher et al. 2015) of the electric field produced by the iron core coil over the medial cerebellum in a realistic head model.

Results showed that midline cerebellar rTMS as compared to placebo induced a significant shift in anterior asymmetry, from left to right dominance in the fast (30–50 Hz) EEG spectrum, whereas no effects were observed to occipital and lateral cerebellar rTMS. Interestingly, spontaneous reports of increased alertness and positive mood state were recorded exclusively after midline cerebellar rTMS.

In keeping with the early intracranial electrical stimulation studies in animals that demonstrated cerebellar connectivity to brain structures involved in cognitive and emotive functions, a subsequent sham-controlled crossover study in healthy volunteers was performed in which EEG responses to sixty single pulses of TMS over the medial cerebellum were recorded in healthy human volunteers (Schutter and van Honk

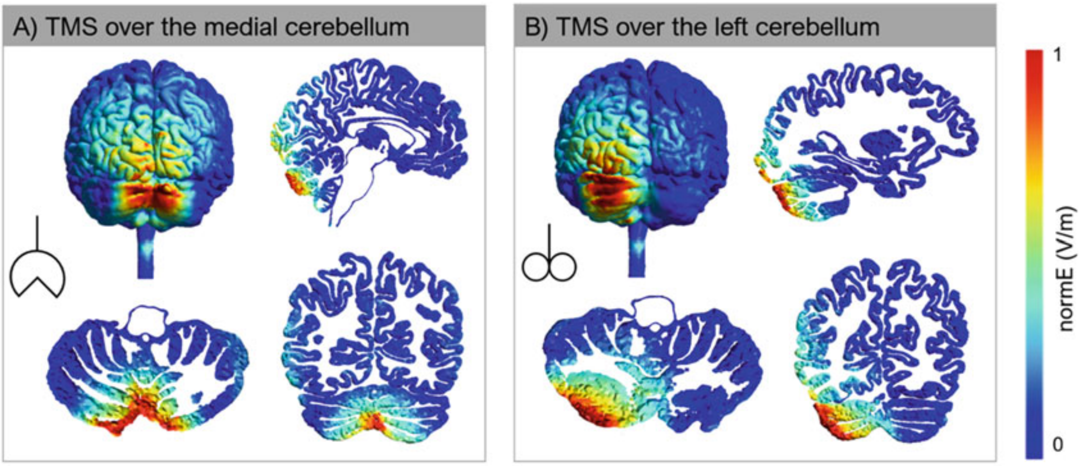

Fig. 8.1 Distribution of the electric field induced by TMS (dI/dt = 1.00 × 1.0e6 A/s) over the medial cerebellum to target the vermis with an iron core coil (**a**) and the left posterior cerebellum with a conventional double winding 70 mm figure of eight-shaped coil on a realistic head model (**b**)

2006). Analyses showed a significant and frequency-specific increase of theta (4–7 Hz) activity to single-pulse medial cerebellar TMS as compared to sham and occipital TMS. Since animal and human research relates theta activity with the septo-hippocampal complex and anterior cingulate cortex, which are important limbic brain structures involved in cognition and emotion, it was speculated that, in addition to the cerebello-cortical connections found by previous studies, the cerebellum is part of the core neural limbic circuitry involved in emotions. The findings of both studies are in line with more recent research that has found evidence that cerebellar stimulation can entrain local field potentials in the frontal cortex and drive synchronization of cerebello-cortical and cortico-cortical networks (Tremblay et al. 2019). Results reported in this study do not only further substantiate the contributions of the medial cerebellum to large-scale synchronization in non-motor-related brain areas, but also provide indirect and incremental support for cerebellar involvement in the experience and regulation of emotions. The latter assumption is supported by a study that directly investigated the effects of cerebellar rTMS on emotion regulation in healthy volunteers (Schutter and van Honk 2009). In a randomized, counterbalanced within-subjects design spanning across three experimental sessions, twelve healthy, young, right-handed volunteers received 20 minutes of continuous real 1 Hz rTMS over the midline cerebellum and occiput, and sham rTMS to the medial cerebellum. Mood state inventories were acquired prior to and immediately after rTMS and following an emotion regulation task (ERT). In the ERT, participants were instructed to either look at aversive and neutral scenes, or to suppress the negative feelings experienced while watching aversive scenes. No changes in baseline-corrected mood were observed immediately after rTMS. However, significant increases in baseline-corrected negative mood following the ERT were reported only after active cerebellar rTMS. This suggests that, arguably due to rTMS-related interference of cerebellar functioning, participants were less able to effectively regulate the emotional content associated with the aversive scenes causing an increase of negative mood. The findings concur with the existing evidence of emotion dysregulation in cerebellar patients and cerebellar abnormalities found in psychiatric patients with impaired emotion regulation (for a discussion see Chap. 17).

In another randomized, cross-over sham-controlled study, effects of 15 minutes of 20 Hz (i.e., 90 trains of 5 seconds on and 5 seconds off) rTMS over the medial cerebellum on implicit processing of emotional faces were examined in healthy volunteers (Schutter et al. 2009). Implicit face processing was measured with the masked emotional faces response task which consists of 14 millisecond presentations of an emotional or neutral face directly followed by the presentation of a masking stimulus. The face and mask are presented in different colors and the participant is instructed to name the color of the ink in which the mask is printed. Performance in terms of slower or faster color naming of the emotional as compared to the neutral faces trials varies as a function of the participant's motivational state. For example, masked fearful faces more readily capture automated attention in anxious individuals which results in slower color naming of the mask in comparison to masked neutral faces. In other words, the motivational state of the individual is presumed to drive the implicit (pre-attentive) reactions to the emotional facial expressions and influence the color naming of the subsequent presentation of the mask. As compared to occipital or sham rTMS, high-frequency rTMS over the cerebellum was associated with significant increases in response times to masked happy, but not fearful or neutral facial expressions. The selectivity of the findings implied that the response to happy facial expressions could not be explained by a general effect of rTMS on motor responsivity. In addition, an objective awareness check confirmed that participants were not able to consciously identify the expression of the faces. No evidence for changes in self-reported mood was found. The slower color naming of the masking stimulus following happy facial expressions can be interpreted as indicative of an increased pre-attentive bias to positive stimuli as a result of increased appetitive motivation following high-frequency rTMS over the medial cerebellum.

To understand the complex changes in emotion regulation capacity and attentional processing following rTMS to the medial cerebellum, a role may be reserved for the processing and regulation of the sympathetic and parasympathetic nervous system. The link between the medial cerebellum and the autonomic nervous system (ANS) was explored by applying neuronavigated iTBS on three consecutive days to the vermis and left and right cerebellar hemispheres in healthy volunteers (Demirtas-Tatlidede et al. 2011). Results showed a significant increase in thirst and a trend toward increased appetite following vermal stimulation, signaling elevated approach- and reward-related motivation. These findings concur with the reports of increased responsivity to happy facial expressions after 20 Hz rTMS over the medial cerebellum (Schutter et al. 2009). Furthermore, iTBS to the posterior vermis induced a significant decrease in heart rate which indicates a cerebellar-mediated increase of parasympathetic input over the sympathetic branch of the ANS. In addition to the vermis, short bursts of high-frequency rTMS (20 Hz) to perturb left posterolateral cerebellar activity were found to impair the perception of emotional facial expressions during an incidental cognitive task in which participants were instructed to classify the faces as either male or female (Ferrari et al. 2018). Crucially, a control experiment showed no effects when participants were instructed to identify the sex of neutral faces exclusively. In addition to the cerebellar role in implicit emotion processing, interrupting cerebellar activity with TMS also reduced the sensitivity to correctly recognize the emotional expression of faces (Ferrari et al. 2018). These findings are in agreement with the idea that the posterolateral regions of the cerebellum play a role in perception and even imitation of emotional expressions (Schraa-Tam et al. 2012). Further evidence for the involvement of the cerebellum in emotion processing comes from a recent sham-controlled study in healthy volunteers that tested the effects of 15 minutes of 1 Hz cerebellar rTMS on corticospinal excitability in response to viewing fearful and neutral facial expressions (Ferrari et al. 2021). In another study the interfering effects of tripe-pulse TMS (20 Hz) with a 70-mm figure of eight-shaped coil over the prefrontal cortex (PFC) and right cerebellum on social attitudes were investigated in healthy volunteers (Gamond et al. 2017). The targeted regions were localized by means of stereotaxic navigation on individual estimated magnetic resonance images (MRI) using a warping procedure aligning a high-resolution MRI template with the volunteer's scalp model and craniometric points. The targeted cerebellar site corresponded to cerebellar right Crus I. In two separate behavioral experiments, evidence was found that TMS administered to the PFC and right Crus I abolished the positive attentional bias to in-group members as evaluated with an attitude priming task. These findings indicate that, next to the PFC, the cerebellum is involved in mediating implicit socio-emotional attitudes and may be differentially involved across varying social contexts (Gamond et al. 2017). Figure 8.1b illustrates an estimation of the electric field induced by a figure-of-eight coil on a realistic head model. Corticospinal excitability was assessed by measuring the MEP from the left and right first dorsal interosseous muscle to a single pulse of TMS applied to the motor cortices. Results showed that real as compared to sham 1 Hz rTMS over the left posterolateral cerebellum lowered the MEP amplitude evoked by single-pulse TMS to right M1 during the presentation of fearful, but not neutral faces. In addition, the MEP amplitude evoked by single-pulse TMS to ipsilateral M1 was not affected after left-sided 1 Hz rTMS to the posterolateral cerebellum. Interestingly, the data cannot be explained by an inhibitory effect of 1-Hz rTMS on Purkinje cells, as this would have increased the excitability along the dentato-thalamo-cortical pathway, causing a net facilitatory effect on the fear-mediated MEP. Perhaps disruption of the cerebellum may have led to reductions in the processing of salient threat-related stimuli which normally would increase corticospinal excitability in preparation for action (Schutter et al. 2008). The latter explanation adds to the idea that the cerebellum interfaces with the limbic and motor areas of the brain in the perception and coordination of appropriate behavioral responses.

In addition to faces, body postures are another non-verbal source involved in emotional expressions (de Gelder et al. 2015). Research has demonstrated that body expressions signaling threat recruit brain areas dedicated to emotion, action observation, and preparation as shown by increases of corticospinal excitability to single-pulse TMS (Hortensius et al. 2016). To explore the contribution of the cerebellum to these processes, online disruptive rTMS was administered over the left posterior cerebellar region of healthy volunteers who were instructed to discriminate between pairs of body postures expressing positive and negative emotions presented on a computer screen (Ferrari et al. 2019). TMS administered to the cerebellum as compared to the visual cortex and vertex as control sites interfered with the ability to discriminate between pairs of body postures when one of the postures displayed threat. The findings show that the cerebellum is sensitive to different features of information that carries biologically relevant (e.g., threat) signals. It is therefore plausible to assume that the cerebellum is also involved in the processing of sounds and odors that signal threat-related information (Billot et al. 2017; Indovina et al. 2014). The latter idea fits the universal cerebellar transform (UCT) theory which posits that the cerebellum is able to perform computations and integrate signals from different modalities (Schmahmann et al. 2019).

8.3 Cerebellar Transcranial Direct Current Stimulation

Transcranial direct current stimulation (tDCS) is another commonly used technique to non-invasively modulate neuronal activity by administering a continuous weak electric current (1–2 mA) applied with two or more electrodes placed on the scalp. Unlike TMS, tDCS does not induce action potentials, but modulates resting state membrane potentials of neurons through polarization. Polarization changes the spontaneous firing of neurons and affects neural excitability as a function of the direction of the current flow in the underlying tissue (Priori 2003; Woods et al. 2016). For cerebellar tDCS, specifically, the induced electric field is suggested to polarize the superficial cortical layer that includes the large Purkinje cells (Grimaldi et al.

2016). In addition, tDCS will most likely also affect other neural elements in the cerebellar cortex, including granule and inhibitory cells, as well as climbing and mossy (axonal) fibers. The changes in the cerebellar cortex are complemented by transsynaptic modulation of the deep cerebellar nuclei, mainly through the inhibitory output of the Purkinje cells (Grimaldi et al. 2016). For motor cortex stimulation, tDCS-induced modulation of cortical excitability has been shown to differ as a function of the polarity of the electrodes. The positively charged anode causes neuronal depolarization in the underlying tissue and increases spontaneous neural firing and cortical excitability as measured by MEPs, while the negatively charged cathode causes neuronal hyperpolarization and reduces spontaneous neural firing and cortical excitability (Nitsche et al. 2008; Nitsche and Paulus 2000). While this polarity-dependent effect is often considered a generic mechanism by which tDCS establishes its effects in the cerebral cortex, marked differences in cytoarchitecture and morphology of the cortical regions outside the motor cortex illustrate that this polarity-dependent effect on neural tissue is not straightforward. As will be illustrated below, this mechanism is even less unequivocal for cerebellar tDCS (Ferrucci et al. 2015; Grimaldi et al. 2014; Oldrati and Schutter 2018; van Dun et al. 2016).

Neurophysiological effects of cerebellar tDCS can, for instance, be quantified by examining cerebellar brain inhibition (CBI), which arguably serves as an index of inhibitory connections between the cerebellar cortex and the dentate nucleus. As mentioned earlier in this chapter, applying a single conditioning TMS pulse over the cerebellum 5–8 seconds before applying a test pulse over the contralateral motor cortex reduces the observed MEP (Ugawa et al. 1995). In a series of experiments, Galea et al. (2009) measured the effects of 25 minutes of anodal, cathodal, or sham tDCS over the right cerebellum on CBI. In this study, the active electrode was placed over the right cerebellar cortex (3 cm lateral to the inion), while the return electrode was placed over the ipsilateral buccinator muscle. Across eight participants, cathodal tDCS significantly decreased CBI relative to baseline (i.e., prior to stimulation) and relative to post-anodal and -sham tDCS, respectively. Further, this effect lasted up to 30 minutes post-stimulation, as demonstrated in a separate sample of six individuals. By contrast, the authors reported stimulation intensity-independent increase of CBI to anodal tDCS in another sample of eight participants. Overall, these findings were taken as evidence for a polarity-dependent effects of tDCS on cerebellar (and by proxy motor cortex) excitability. That is, cathodal tDCS decreases Purkinje cell excitability, resulting in a reduction of the inhibitory effect the conditioning TMS pulse exerts on the connection between the dentate nucleus and the motor cortex, whereas anodal tDCS increases Purkinje cell excitability and enhances the inhibitory connection. Importantly, however, a follow-up study which combined plasticity-inducing paired associative stimulation (PAS) with anodal, cathodal, or sham tDCS did not find evidence for polarity-specific effects (Hamada et al. 2012). Using similar tDCS parameters, the authors found the expected PAS-related increase in MEPs following sham tDCS, but no such effect was observed following anodal or cathodal tDCS. Overall, this suggests that while cerebellar tDCS is able to modulate cerebello-cortical pathways, the direction of the physiological effect is difficult to anticipate. To further address this issue, magnetic resonance spectroscopy (MRS) has been used to investigate the effects of tDCS on neurotransmitter concentrations in the cerebellum (Jalali et al. 2018; Moussa-Tooks et al. 2020). Jalali et al. (2018) found no evidence for changes in (excitatory) glutamate and (inhibitory) GABA concentrations in the right cerebellar hemisphere following 25 minutes of anodal tDCS at an intensity of 2 mA over the right cerebellum. Also, a study by Moussa-Tooks et al. (2020) did not yield consistent effects on neurotransmitter concentrations to 1.5 mA anodal or sham tDCS over the left cerebellar hemisphere for 20 minutes.

While our understanding of the mechanisms of tDCS and in particularly how transcranially applied electric current interacts with brain tissue is still in its infancy, cerebellar tDCS does reliably induce behavioral and physiological modulation as evidenced by numerous controlled studies. However, the effects are typically small and results show large interindividual variability. It is therefore not surprising that the outcome of cerebellar tDCS is hard to predict. A meta-analysis examining the efficacy of cerebellar tDCS to modulate behavior in motor and cognitive tasks found significant absolute effects (i.e., not assuming a particular direction of the effect for anodal or cathodal tDCS) of cerebellar tDCS, with overall larger effect sizes for studies in the motor in comparison to the cognitive domain (Oldrati and Schutter 2018). Importantly, however, there was no evidence for polarity-*specific* effects for either anodal or cathodal tDCS.

Empirical studies employing cerebellar tDCS that specifically address affective processes in healthy volunteers are still limited. Ferrucci et al. (2012) were the first to demonstrate an effect of cerebellar tDCS on emotion recognition. In their study, healthy volunteers received anodal, cathodal, or sham tDCS (2 mA, 20 min) through two 6 × 7 cm electrodes placed over the medial cerebellum and the right deltoid muscle. Before and after stimulation, participants were presented with angry, sad, happy, and neutral faces and asked to indicate the depicted emotion. Following anodal and cathodal tDCS, reaction times in response to negative facial expressions were reduced compared to baseline, while performance on neutral or positive faces was not affected. Sham tDCS did not modulate performance, and no effects of active tDCS on self-reported mood and anxiety were found. These results were taken as evidence that the cerebellum is primarily involved in the processing of negative emotional content, in line with its reciprocal connections to the amygdala.

A recent study investigated the effect of both anodal and cathodal cerebellar tDCS on predicting social action sequences (Oldrati et al. 2021). In particular, participants were asked to decide whether short videos of people performing a given action would end in an individual action (e.g., a child eating an apple) or an interpersonal action (e.g., a child handing an apple to another child). During the familiarization phase, implicit predictions were cued by random color combinations present in the videos, and it was subsequently investigated in a testing phase whether the processing of highly as opposed to lowly predictable social actions were modulated by cerebellar tDCS. For this, anodal, cathodal, and sham tDCS (2 mA, 20 min) were applied through two 5 × 5 cm electrodes placed over the right cerebellar hemisphere and ipsilateral buccinator muscle while participants performed the task. Results showed that anodal tDCS significantly improved task accuracy for low-expectancy trials, while cathodal tDCS decreased accuracy for high-expectancy trials. Crucially, these stimulation-specific effects were only observed during the actual testing phase, in which implicit predictions had already been established. Furthermore, confirming the domain-specific contribution of the cerebellum to the processing of social action scenes, no effects of tDCS on a control task using shapes as stimuli were observed. Overall, this supports the concept of a "social cerebellum" (Van Overwalle et al. 2020), in which the prediction of social events involves the (right) cerebellum.

In light of the cerebellum's reciprocal monosynaptic connections to the hypothalamic-pituitary-adrenal axis (Schutter 2012), another recent study investigated whether cerebellar tDCS can modulate self-reported mood and cortisol levels (Gheorghe et al. 2021). In forty-five volunteers, individual cortisol levels were measured before, immediately after, and 10 and 30 minutes after cerebellar tDCS. Additionally, subjective mood ratings were assessed before and after stimulation. The healthy participant sample was divided into three groups receiving either 2 mA anodal, cathodal, or sham tDCS for 15 min over the cerebellum, with the two 5 × 7 cm electrodes placed over the midline and the right deltoid muscle. None of the tDCS conditions affected cortisol levels at any of the time points. However, both anodal and cathodal tDCS resulted in improved self-reported mood relative to baseline, providing some tentative evidence about potential mood-regulating effects of cerebellar tDCS. In a similar vein, Newstead et al.

(2018) reported improved subject mood ratings in participants receiving a single or three consecutive 12-min sessions of active frontocerebellar tDCS at 2 mA relative to sham tDCS. In this study, two 5 × 5 cm electrodes were placed over the right cerebellum and the left dorsolateral prefrontal cortex (10–20 electrode position F3). Again no polarity-specific effects were observed, further adding to the notion that the cerebellum is not sensitive to polarity-dependent neuronal modulation. Interestingly, the mood improvement demonstrated an additive effect, with steadily increasing effects following each of the three stimulation sessions. In sum, the small number of available studies do provide preliminary evidence for the potential of cerebellar tDCS to modulate emotion processing (Ferrucci et al. 2012), social processing (Oldrati et al. 2021), and mood (Gheorghe et al. 2021; Newstead et al. 2018). Further research into the neurophysiological mechanisms of these effects is warranted.

To get a better understanding of the physiological mechanisms related to cerebellar tDCS, it is important to consider the unique cerebellar cell morphology. Early work in the turtle cerebellum showed that electrical stimulation affects different kinds of cerebellar cells depending on how their cell bodies are oriented relative to the applied electric field (Chan et al. 1988). Furthermore, the delicate folding of the cerebellar cortex likely causes large differences in polarization, which is determined by the angle between the electric field elicited by the injected current, and the somatodendritic axis of the targeted cells (Rahman et al. 2014). Additionally, inconsistent findings may partly be caused by the large number of methodological degrees of freedom inherent to the application of cerebellar tDCS. Factors like stimulation intensity and duration as well as electrode positioning and size are not standardized for cerebellar tDCS. Computational field modeling studies have attempted to shed some light on the question of how strongly and focally the cerebellum can be targeted by tDCS (Gomez-Tames et al. 2019; Parazzini et al. 2014; Rezaee and Dutta 2019). While these studies have documented the potential of cerebellar tDCS to target predominantly posterior regions of the cerebellum with sufficiently high field strengths, the focality of these elicited fields remained an open question. In a recent study, we therefore simulated electric fields induced by the commonly used montage, in which the return electrode is placed over the ipsilateral buccinator muscle in 20 individual brains (Klaus & Schutter 2021, Sci Rep). As demonstrated in Fig. 8.2a in one exemplary brain, this montage using 5 × 5 cm electrodes is successful in reaching the targeted cerebellar region, but crucially suffers from low focality, as indexed by significant current spread in extracerebellar regions. In an attempt to minimize this unwanted effect, we further simulated electric fields from six alternative montages in which smaller electrodes (3 × 3 cm) were placed in gradually higher vicinity to each other. Maximum focality was obtained by placing the electrodes approximately 2 cm below EEG positions I2 and P10 (Fig. 8.2b). Overall, this suggests that previous studies using the buccinator montage likely did not target the cerebellum in a focal way, precluding definitive conclusions about its isolated involvement in the function investigated. Future work will need to verify the behavioral and neurophysiological effect of the proposed alternative montage. Furthermore, acknowledging the special anatomical location of the cerebellum, individual differences in skull thickness and cerebrospinal fluid are likely to be important factors in determining efficacy within and across individuals.

Finally, an exciting avenue for cerebellar stimulation research is transcranial alternating current stimulation (tACS), in which applying alternating currents to the targeted area can entrain brain oscillations to a desired frequency. Recent work has shown the potential of cerebellar tACS to modulate CBI (Naro et al. 2016; Spampinato et al. 2021). Future studies will need to establish whether this technique is suitable for modulating emotional and affective processing as well.

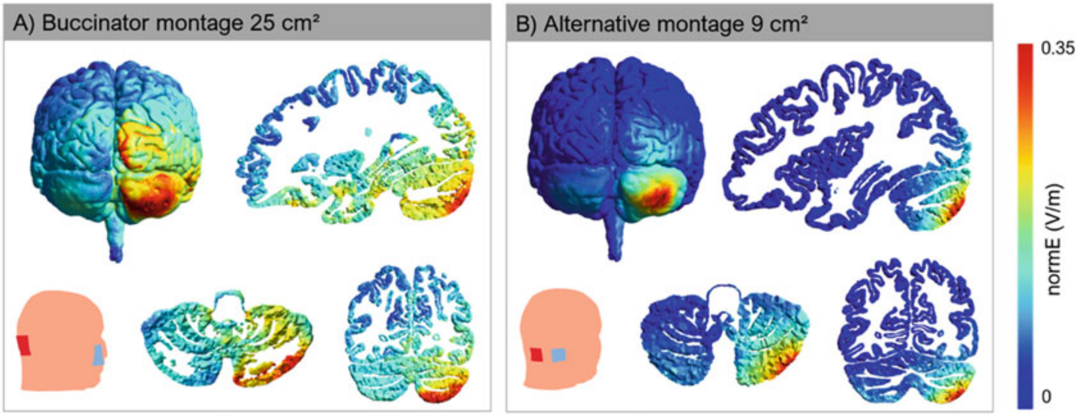

Fig. 8.2 Distribution of the electric field induced by tDCS targeting the right posterior cerebellum placing two 5 × 5 cm electrodes over the right cerebellum and the right buccinator muscle (**a**) or placing two 3 × 3 cm electrodes 2 cm below electrode positions I2 and P10 (**b**). Simulations were performed with SimNIBS software (Thielscher et al. 2015)

8.4 Conclusion

Through its ability to transcranially manipulate superficial neural tissue with exogenous electromagnetic pulses and weak electric currents, non-invasive brain stimulation techniques provide a direct means to examine the involvement of the human cerebellum in emotions. The currently available empirical studies confirm that manipulating the cerebellum has a direct impact on the elicitation, experience, and regulation of emotions. These studies show that non-invasive brain stimulation techniques offer a unique and valuable approach in cerebellar neuroscientific research and potentially provide new directions in biologically oriented non-invasive treatments of psychological disorders (see Chap. 17).

The fact that the word emotion is derived from *emovere,* which is Latin for “move through” and “move out”, illustrates the intimate conceptual link between perception, emotion, and action. The cerebellum may well lie at the heart of connecting these different facets which ultimately constitute emotional experience and drive human behavior. However, cerebellar non-invasive brain stimulation still faces several methodological and technical issues, particularly related to its physiological working mechanisms and spatial resolution/focality. These issues warrant further research to improve the applicability of TMS and tDCS in the cerebellar neurosciences of emotion.

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Conflict of Interest The authors have no competing interests to declare.

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Part III

Cerebellum and Emotion in High Order Domains

9 Reward-Based Learning and Emotional Habit Formation in the Cerebellum

Jordan E. Pierce and Julie A. Péron

Abstract

There is growing evidence of the cerebellum's contribution to emotion processing from neuroimaging studies of healthy function and clinical studies of cerebellar patients. As demonstrated initially in the motor domain, one of the cerebellum's functions is to construct internal models of an individual's state and make predictions about how future behaviors will impact that state. By utilizing widespread connections with neocortex and subcortical regions such as the basal ganglia, the cerebellum can monitor and modulate precisely timed patterns of events using prediction and reward-based error feedback in a diverse range of tasks including auditory emotion prosody recognition. In coordination with a broader affective network, the cerebellum helps to select and refine emotional responses that are the most rewarded in a particular context, strengthening neural activity in relevant regions to form a representational chunk. This chunked set of affective stimuli, cognitive evaluations, and physiological responses subsequently can be enacted as a unitary response (i.e., an emotional habit) more quickly and with less attentional control than for a novel stimulus or goal-oriented action. Such emotional habits can allow for efficient, automatic, stimulus-triggered responses while maintaining the flexibility to adapt output when prediction errors signal a renewed need for cerebellar modification of cortical activity, or, conversely, may lead to behavioral or mood disorders when habitual responses persist despite negative consequences.

Keywords

Cerebellum · Basal ganglia · Reward · Habit · Emotional prosody

9.1 Introduction

The cerebellum's contribution to motor control has been studied for many decades, yet its role in a broader set of cognitive and affective functions has been emphasized only in the last 20 years (Bostan and Strick 2018; Buckner 2013; Schmahmann 2019). Specifically, as introduced in the earlier chapters of this volume, one area in which the cerebellum exerts its modulatory influence is emotion recognition and expression. Extant findings have demonstrated that as an individual interacts with the environment, the cerebellum constructs an internal model of the current sensorimotor state and predicts how future thoughts or actions will change this state (Ito 2008; Popa and Ebner 2019; Wolpert et al.

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1998). Accordingly, the cerebellum monitors performance via feedback errors, learns rewarded and punished behavioral patterns, and adjusts its functional outputs to optimize neocortical responses. This modulation occurs via reciprocal connections with neocortex and subcortical nuclei that respond to salient, novel, and rewarding stimuli in the environment (Buckner et al. 2011; Clausi et al. 2017; Habas 2018; Hoshi et al. 2005; Pierce and Péron 2020) and allows the cerebellum to contribute to a broad array of tasks.

In order to form an accurate predictive model for such tasks, it has been proposed that the cerebellum participates in sequence learning. This function was first recognized in the motor domain, but now encompasses learning of a diverse set of sequences/patterns based on social cues, verbal or spatial scripts, speech, or emotional stimuli, among others (Ackermann 2008; Bostan and Strick 2018; Heleven et al. 2019; Kotz et al. 2013; Leggio and Molinari 2015; Leggio et al. 2008; Peterburs et al. 2019; Van Overwalle et al. 2020). By recognizing timing patterns within stimulus sets, the cerebellum, in coordination with the basal ganglia, can predict the subsequent event in a series, biasing reciprocally connected neocortical regions to anticipate and attend to salient or novel features in the environment and prepare motor and cognitive responses (Grandjean 2020; Péron et al. 2013; Pierce and Péron 2020; Popa and Ebner 2019). Over time, predictable sequences or distributed neural patterns are coalesced into mnemonic chunks that can be accessed more readily from memory and executed with minimal top-down control (Graybiel 2008). The cerebellum thus contributes to habit formation by fine-tuning performance not only in the domain of motor control, but also in the emotional/affective domain (Pierce and Péron 2020). Habits consist of repetitive motor, cognitive, or emotional behaviors or thoughts elicited by specific stimuli or situations that are learned over time, performed largely automatically without conscious supervision, and are resistant to competing task interference (Graybiel 2008; Ramnani 2014); here, we define *emotional* habits as such learned responses that occur in reaction to or via recognition of affective, emotional, or social stimuli and/or involve the performance of repetitive emotional expressions and behaviors. Ideally, emotional habits allow humans to interact effectively with their social peers, moderate their own mental state, adaptively avoid threats, and pursue positive outcomes (Clausi et al. 2017; Grandjean 2020; Van Overwalle et al. 2020), yet they can also contribute to affective disorders when the habitual behavior is insensitive to contextual cues or negative outcomes. The following sections will provide evidence for the cerebellum's involvement in motor learning and habit formation, describe emotional habit formation using the example of auditory processing of emotional prosody, and finally provide clinical evidence of disrupted affective habit formation and expression in patients with cerebellar damage.

9.2 Motor Learning and Rewards in the Cerebellum

Before describing how the cerebellum may support emotional habit formation, it is useful to consider first how the cerebellum supports habit formation and learning in the well-studied motor domain. Indeed, the uniform architecture of the cerebellar hemispheres (but see Apps 2016) has led researchers to propose that a single computation (or a small set of computations; see Diedrichsen et al. 2019) accounts for the function of the cerebellum across domains (Schmahmann 2000). Therefore, the cerebellum is able to participate in a wide range of tasks using a relatively limited set of computations by utilizing topographically organized reciprocal connections with most of the neocortex and a number of subcortical regions (Buckner et al. 2011; Marek et al. 2018; Stoodley and Schmahmann 2018). The mechanisms underlying learning, rewards, and habit formation have been investigated most thoroughly in the cerebellum with respect to motor function, particularly using animal models that allow for direct and detailed analyses of cerebellar circuitry (Callu et al. 2007; Kostadinov et al. 2019; Mauk et al. 2014). Utilizing these invasive techniques, researchers have characterized the anatomical inputs and outputs of the cerebellum and many of the functional capabilities of its neural circuits, while others have applied these findings to the study of human cerebellar motor function.

9.2.1 Cellular Pathways for Motor Learning

Studies from the animal literature have demonstrated that the cerebellum receives inputs from mossy fibers from the pons and climbing fibers from the inferior olive (Fig. 9.1), which convey different types of information about the individual's current condition. Mossy fibers transmit signals from the neocortex that correspond to the present sensorimotor and internal state of the individual (Wagner and Luo 2020). Conversely, climbing fibers convey a teaching signal that is derived from a sensorimotor or reward-based prediction error signal arising from differences between the current and expected state. Manipulation and observation of different cerebellar pathways using the eye blink conditioning paradigm (Freeman 2015; Hansel et al. 2001; Mauk et al. 2014) highlighted that the critical contribution of the cerebellum to learning a conditioned response (i.e., a blink after a tone that was initially paired with an air puff) depends upon mossy fiber and climbing fiber signals consistently occurring with optimal temporal proximity (Mauk et al. 2014).

Importantly, the climbing fiber signal shapes how the Purkinje cells, which are the main computational neurons in the cerebellar hemispheres, respond to the numerous granule cell inputs they receive (Hull 2020; Wagner and Luo 2020). These teaching signals lead to long-term depression of granule cell inputs (parallel fibers) on the inhibitory Purkinje cells, a process which constitutes an important cerebellar learning mechanism (Freeman 2015; Jörntell and Hansel 2006), although several complementary mechanisms likely exist across the different neuronal populations of the cerebellum and deep cerebellar nuclei (Hansel et al. 2001; Hull 2020). Through these synaptic changes, the Purkinje cells learn which granule cells are transmitting pertinent information relative to other contextual signals, thus allowing the cerebellum to improve its computational power, form associative memories, and support adaptive motor control (Ito 2006). Specifically, cerebellar learning may inform the construction of an internal model of motor movements that represents the current state and expected outcome state, which is shaped iteratively following error feedback and influences the cerebral cortex to optimize behavior as needed (Caligiore et al. 2019; Ito 2008).

9.2.2 Rewards and Motor Learning in Animals

In addition to the behavioral conditioning paradigms that informed the aforementioned cellular learning mechanisms, learning within the cerebellum also has been demonstrated for reward-based motor paradigms. The reward signals for this type of cerebellar learning may originate from connections with the basal ganglia, including the ventral striatum, and the ventral tegmental area, where dopamine release tracks the positive (reward) or negative (punishment) outcome of a behavior (Bostan et al. 2010; Carta et al. 2019; Hoshi et al. 2005; Hosp et al. 2019; Pelzer et al. 2013). Within the cerebellum, granule cells have been shown to respond to reward delivery and anticipation, as well as to when an unexpected reward is given or an expected reward is withheld (Wagner et al. 2017; Wagner and Luo 2020). Similarly, climbing fiber input has been shown to convey reward signals in mice performing a visuomotor task, with the strength of the response to predictable rewards decreasing over the course of learning (Kostadinov et al. 2019). This type of diminishing response also was reported in monkeys during reinforcement learning, with the reward-based error signal in Purkinje cells weakening as the animal learned the correct visuomotor association (Sendhilnathan et al. 2020). These findings demonstrated that the cerebellum does not calculate a simple motor difference error for specific movements, but that it can account for and

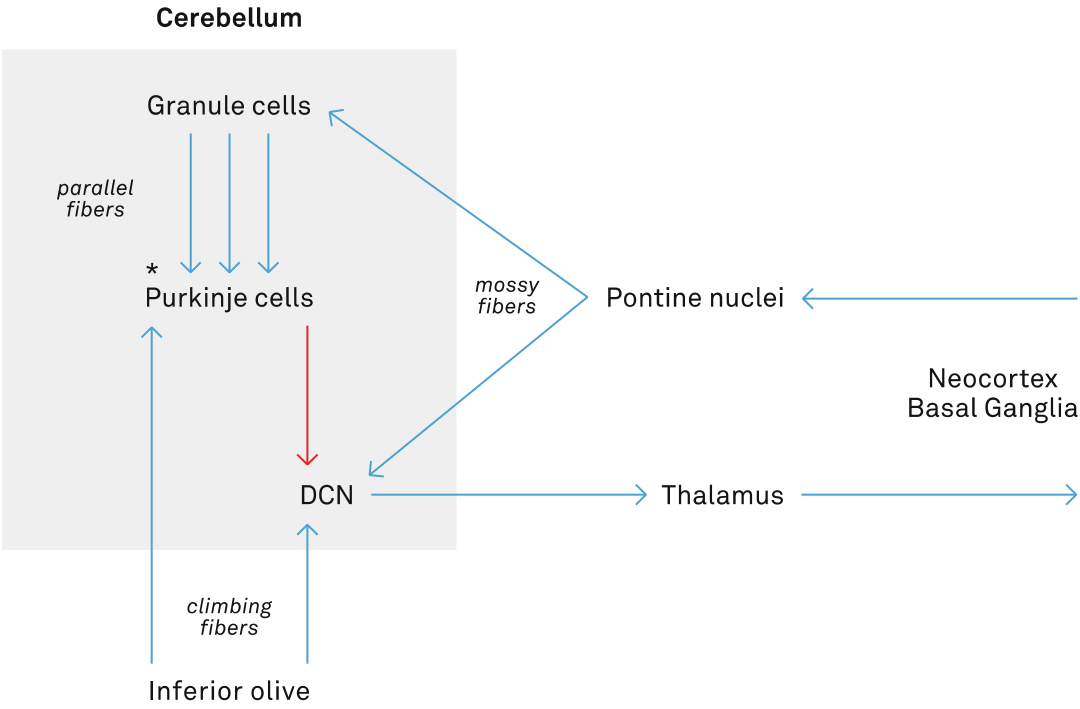

Fig. 9.1 Diagram of the organization of the cerebellum. The figure illustrates the major input/output pathways of the cerebellum and connections within the cerebellum that contribute to prediction error-based learning. Blue arrows denote excitatory connections and the red arrow denotes the inhibitory output from the Purkinje cells. * indicates one site of cellular learning through long-term depression. *DCN* deep cerebellar nuclei

receive feedback on reward contingencies and formulate predictions for contextually defined goals.

9.2.3 Human Studies of Motor and Reward-Based Learning

Extending these findings from animal studies, human neuroimaging studies have shown comparable motor learning activity in the cerebellum. An early functional magnetic resonance imaging (fMRI) study demonstrated cerebellum activation during learning of a sequence of finger movements (Doyon et al. 2002). Participants exhibited cerebellum activation early in the learning process, but this signal diminished after extended task practice and activity shifted to the basal ganglia and neocortex. More recently, Liljeholm and colleagues conducted an fMRI study on habit formation and expression using a novel task designed to distinguish between goal-directed actions and habits (Liljeholm et al. 2015). They reported cerebellar and caudate activation primarily for habit learning and response automatization rather than for the implementation of a previously established motor routine. Finally, a study on motor reinforcement learning probed three stages of task performance: exploratory behavior (trial and error), model-based performance, and motor memory-driven responses (Fermin et al. 2016). Along with areas of the prefrontal cortex (PFC) and basal ganglia, the posterior cerebellum was activated for internal model-based learning of response sequences, while the anterior cerebellum was part of a motor network that ultimately stored the memory and implemented the habitual response (see also Penhune and Steele 2012). Together these studies illustrate that portions of the cerebellum (and basal ganglia) are critical for motor learning as part of a dynamic process of habit formation that shifts from effortful, attention-demanding action exploration to automatic performance of a familiar motor sequence (Ramnani 2014).

Furthermore, human studies of reward-based learning also have suggested a role for the cerebellum. For example, Ramnani and colleagues conducted an fMRI study in which participants were presented with expected or unexpected rewards and non-rewards, and reported activation in the cerebellar vermis following unexpected rewards (Ramnani et al. 2004). Another fMRI study reported left lateral cerebellum activation on trials where participants chose a large, delayed reward over a smaller, immediate reward (Tanaka et al. 2004). These neuroimaging results were followed up by behavioral studies of reinforcement learning that showed faster learning when punishment was administered and better memory when rewards were given (Galea et al. 2015; Song and Smiley-Oyen 2017). The authors therefore proposed that these feedback methods have different effects on cerebellar error sensitivity, with reward requiring more trials to acquire learning but leading to more lasting effects. Finally, a study of cerebellar patients (Thoma et al. 2008) demonstrated that although patients could learn initial stimulus associations successfully, they exhibited deficient reward-based reversal learning. Taken together, these studies suggest that the human cerebellum is involved in reward processing, yet the specific features of the reinforcement learning process to which it uniquely contributes are not fully understood.

9.3 Emotional Habit Formation

Based on the findings from motor learning tasks described above and evidence of the cerebellum's contribution to emotion recognition and expression (Adamaszek et al. 2017; Baumann and Mattingley 2012; Schmahmann and Sherman 1998; Strata 2015; Thomasson et al. 2019; Van Overwalle et al. 2020), it is proposed that the cerebellum performs a similar prediction error-based learning function within the emotion domain and supports the acquisition of emotional habits. When the brain perceives a stimulus and identifies it as biologically relevant (i.e., likely to impact the individual's homeostatic needs and affective state; Barrett et al. 2007), multiple nodes of emotion, sensorimotor, and cognitive networks are engaged, including the amygdala, basal ganglia, PFC, and cerebellum (Fig. 9.2). The stimulus may consist, for example, of a human voice speaking in a tone and cadence that convey the individual's emotional state (e.g., a slow, low-pitched voice of a speaker who is sad). This emotional prosody allows individuals to perceive affect from a vocal utterance based on its non-linguistic acoustic properties such as the fundamental frequency (i.e., pitch), energy envelope (i.e., loudness), and timing (Grandjean 2020; Scherer 1995). As the brain recognizes the auditory stimulus as a salient event, it begins to form an internal representation constructed from the stimulus' features, its context, prior experience with similar stimuli, possible responses, and likely outcomes (reward or punishment) by strengthening associations between neurons that respond near the time the stimulus occurs, especially when the response yields a positive reward. Over time, a goal-directed behavior for such a stimulus (e.g., approaching someone who is speaking sadly to offer comfort) may shift into a habitual, automatic emotional response (Graybiel 2008; Liljeholm et al. 2015). The following sections will describe how this emotional representation is constructed and how the cerebellum strengthens and modifies this representation during the habit formation process.

9.3.1 Acquiring Emotional "Chunks"

Following the initial perception of the stimulus, learning commences as associations form between the acoustic features of the stimulus, visual cues that accompany the voice, the semantic content of the words, and other incidental aspects of the environment (Brosch et al. 2010). A physiological response (e.g., increased heart rate) is paired with preparation for action (e.g.,

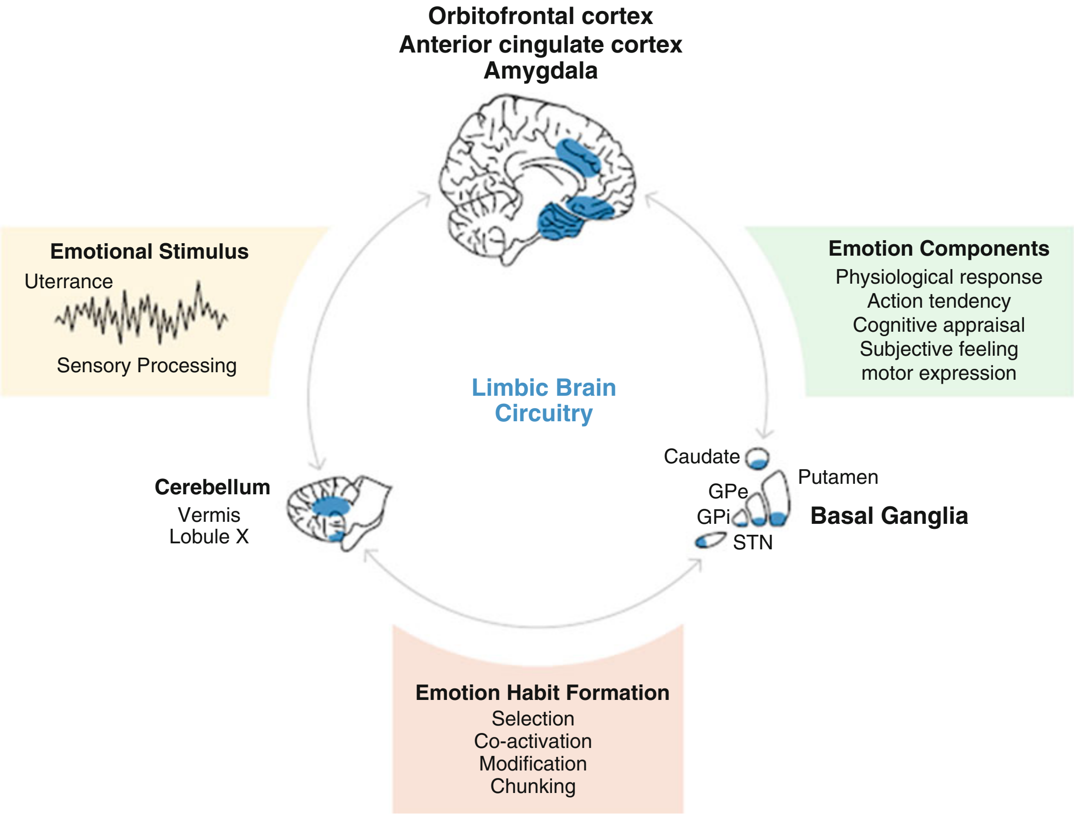

Fig. 9.2 The cerebellum functions as part of a limbic/affective brain network that also includes medial prefrontal/orbitofrontal cortex, the amygdala, and the basal ganglia. Reciprocal anatomical and functional connections between such regions allow the cerebellum to contribute to emotional habit formation by monitoring the internal affective state and fine-tuning output according to prediction and reward-based error feedback signals. In the case of emotional prosody, affective circuitry processes a vocal utterance to extract emotional content and generates components of an emotion experience such as a physiological response, cognitive appraisal, and motor expression. With repeated occurrences of the stimulus, the network iteratively builds toward an emotional habit as selection and co-activation of particular components strengthen their association, forming a "chunk" that can be performed later with minimal attentional control. *STN* subthalamic nucleus, *GPi* globus pallidus internal segment, *GPe* globus pallidus external segment

fleeing) and may be tied to a subjective feeling (e.g., fear), which collectively can activate areas including the brainstem, hypothalamus, amygdala, and motor cortex (Aue et al. 2007; Critchley and Harrison 2013; Sander et al. 2018; Scherer 2009). These different aspects of the emotional response then are integrated into a cohesive episode via synchronized long-range neural oscillations that facilitate the transmission of information among sensory, limbic, and cognitive brain regions and allow the emotional experience to reach the level of consciousness (Grandjean et al. 2008; Fries 2005; Péron et al. 2013; Scherer 2009). Consequently, vocal expressions can be classified as having positive/negative valence, high/low arousal, and/or belonging to a discrete emotion category (Laukka 2005). The entire experience of the emotional stimulus then is grouped together as a unit or "chunk" that is strengthened through repeated exposure when coupled with positive rewards or the avoidance of punishment. The associated neural pattern of activity can be reactivated automatically during a subsequent encounter to produce the appropriate behavior (Graybiel 2008; Mauss et al. 2007). For example, chunks formed among prosodic sensory cues in superior temporal cortex may be more quickly identified by the PFC as belonging to an angry voice, leading to faster recognition of the social implications of that anger and a better chance of habitually enacting the desired defensive posture or verbal rebuttal (Grandjean 2020; Pierce and Péron 2020).

9.3.2 The Role of the Cerebellum

As other areas of the brain such as auditory temporal cortex, the amygdala, and orbitofrontal cortex begin to analyze the sensory features, salience, and social context of the emotional stimulus, respectively (Grandjean 2020), the cerebellum monitors the fitness of each element of the response with respect to the current state and goal state, modifying the parameters of the implementation as needed to minimize its prediction error (Leggio and Molinari 2015; Pierce and Péron 2020; Schultz and Dickinson 2000). Additionally, the relative timing of the stimulus components is registered by the cerebellum to build an internal model of the emotional event and its reward (or the lack thereof). As with the motor learning paradigms described above, in the emotional domain, prediction errors conveyed by the climbing fiber signal could shape the sensitivity of Purkinje cells to certain parallel fiber inputs (Wagner and Luo 2020), strengthening or weakening output signals back to limbic cortical and subcortical regions, such as the orbitofrontal cortex, insula, and amygdala (Buckner et al. 2011; Habas 2018). If similar stimuli are perceived again at a later moment, the lasting changes in cerebellar synapse sensitivity allow learned neocortical associations to be re-activated more readily and the emotional chunk to be strengthened further when feedback supports the existing model. Over time, this emotional chunk (i.e., pattern of activity in emotion-sensitive regions), or multiple chunks, will be more quickly and automatically selected to generate a habitual response, thereby reducing the need for supervisory posterior cerebellar (and PFC) involvement in habit execution (Doyon et al. 2002; Fermin et al. 2016).

On the other hand, if an unexpected outcome occurs (e.g., mistaking a surprised voice for a fearful voice) that results in a large prediction error from the model (Ito 2008; Popa and Ebner 2019), the cerebellum must intervene and instruct downstream neocortical regions to adjust their responses (e.g., firing rates or synaptic weights; Schultz and Dickinson 2000). In this manner, the cerebellum refines the emotional chunk that was formed in neocortex to better match the emotional stimulus with an appropriate thought or action (e.g., learning that a friend's surprised (not fearful) voice does not signal a dangerous situation) and minimize the prediction error of its internal model in future encounters. Importantly, learning associations and acquiring habits are dynamic processes in which the cerebellum continually monitors input and output and adjusts the degree of its intervention according to the current context and feedback signals (Caligiore et al. 2019; Peterburs and Desmond 2016).

In contrast to the posterior cerebellum's involvement in learning emotional habits, the cerebellar vermis may be especially critical for regulating unconscious autonomic responses to emotional stimuli (Clausi et al. 2017). Indeed, this region often has been identified as a central part of the "limbic cerebellum" in neuroimaging tasks and clinical studies (Baumann and Mattingley 2012; Colibazzi et al. 2010; Schienle and Scharmuller 2013; Schmahmann et al. 2007). The coordination of learning in the associative posterior lateral cerebellum and the automatic physiological response in the cerebellar vermis allows the cerebellum to monitor emotional events and refine behaviors and thoughts to create an optimized habitual emotional response.

9.3.3 Coordination with the Basal Ganglia

Much of the learning of new habits by the cerebellum occurs with the close cooperation of the basal ganglia (Caligiore et al. 2019; Bostan and Strick 2018). The basal ganglia work to gate cortical responses to a new stimulus or cognitive state, allowing relevant actions and thoughts to be initiated and inhibiting competing actions/thoughts (Mink 1996; Nambu et al. 2002). Interestingly, most, if not all, of the nuclei of the basal ganglia contain functional subdivisions that correspond to sensorimotor, associative, and limbic domains, based on their pattern of connectivity with other brain networks (Arsalidou et al. 2013; Krack et al. 2010; Péron et al. 2013; Pierce and Péron 2020). These subdivisions are not fully distinct, however, but partially overlap and similar computations may be performed for each functional domain. The dorsal striatum, for example, has been associated with motor habit formation and performance (Packard and Knowlton 2002). On the other hand, ventral portions of the striatum (including the nucleus accumbens) and the subthalamic nucleus have close connections with limbic regions such as the substantia nigra, amygdala, and orbitofrontal cortex and contribute strongly to reward processing and other affective functions such as emotional prosody recognition (Alheid 2003; Denys et al. 2010; Grandjean 2020; Graybiel 2008; Péron et al. 2016). During the formation of emotional habits, processing within the basal ganglia may shift from primarily activating the ventral striatum toward the dorsolateral sensorimotor caudate as behaviors become automated (Yin and Knowlton 2006). The affective functions of the striatum, thus, influence habit formation in the basal ganglia broadly by signaling which actions yield rewards or punishments in order to strengthen or weaken behaviors associated with a specific stimulus or context (Grahn et al. 2008; Graybiel 2008; Yin and Knowlton 2006).

The contribution of the basal ganglia to emotion processing is evident from studies of patients undergoing deep brain stimulation of the subthalamic nucleus to treat motor symptoms in Parkinson's disease, which have demonstrated subtle deficits for both positively and negatively valenced stimuli in both the auditory and visual modality (Drapier et al. 2008; Mallet et al. 2007; Mirdamadi 2016; Péron et al. 2013; Péron et al. 2010; Péron et al. 2017; Vicente et al. 2009; Voruz et al. 2020). Damage to the basal ganglia, therefore, may disrupt the execution of previously established emotional habits by failing to select the appropriate response and sufficiently inhibit competing responses. As a result, this will have a negative impact on patients' affective functioning without completely eliminating their emotion recognition abilities that rely on other regions such as the amygdala and sensory cortices (Péron et al. 2013).

During healthy emotion processing, the basal ganglia synchronize relevant cortical oscillations by allowing only the correct response to be enacted while inhibiting interference from competing or incidental response activity (Mink 1996; Péron et al. 2013). This synchronization strengthens a set of events following a given stimulus (i.e., an emotional chunk), building toward a unified representation of the new habitual response (Graybiel 2008). Once the habit is acquired, less input is required from PFC about current goals or from dopaminergic centers about rewards before a decision threshold is reached and the response can be performed as a complete unit with minimal attentional control. Furthermore, via direct subcortical connections with the cerebellum, the basal ganglia can transmit information regarding the appropriate response, the timing of the response, and reward contingencies of the response to ensure that the cerebellum can update its internal model predictions efficiently (Bostan and Strick 2018; Buhusi and Meck 2005; Hoshi et al. 2005; Péron et al. 2017; Pierce and Péron 2020). As the basal ganglia select the desired response set, the cerebellum monitors feedback regarding its predictions and continually adjusts activity within the selected (e.g., limbic) regions to improve performance.

9.3.4 Habits and Emotional Prosody

In the case of emotional prosody, a core cortical network consisting of primary auditory cortex in the temporal lobe, voice sensitive areas in the superior temporal gyrus, and motivation-based evaluative modules in the inferior frontal lobe responds to the auditory stimulus and extracts relevant affective features. Simultaneously, an extended limbic network that includes the medial frontal lobe, insula, basal ganglia, amygdala, and the cerebellum modulates the typical response pattern to the stimulus via numerous functional interconnections (Frühholz et al. 2012, 2016; Grandjean 2020; Kotz et al. 2013; Schirmer and Kotz 2006; Witteman et al. 2012). The role of the cerebellum (and basal ganglia) in emotional prosody was investigated in a recent fMRI study of healthy adults that utilized pseudosentences spoken by angry, happy, or neutral voices (Ceravolo et al. 2021). Portions of cerebellar Crus I and II, lobules VI-VIII, the vermis, and the dentate nucleus were more activated when judging angry or happy voices compared to neutral voices and showed heightened functional connectivity with the basal ganglia during the task. These findings indicate that the cerebellum is indeed sensitive to emotional prosody and, more generally, may aid in analyzing non-rhythmic sounds in conjunction with rhythmic sound processing in the dorsal basal ganglia (Breska and Ivry 2016; Frühholz et al. 2016; Kotz et al. 2014). Further work is needed to better clarify how the role of the cerebellum in general emotional prosody processing specifically extends to habit formation.

Speculatively, the cerebellum's sensitivity to emotional prosody and temporal patterns may contribute to the emergence of an emotional habit as it builds a prediction for the individual's future sensorimotor and affective state following an emotional auditory stimulus within a certain context (Cheron et al. 2016; Ivry and Spencer 2004). With repeated presentations of this stimulus type, the cerebellum (and other brain regions) begins to learn optimal associations between the inputs and appropriate outputs to create a more structured, automatized response (i.e., a habit) within the cortical regions that process emotional prosody (Grandjean 2020). Therefore, it is proposed that the cerebellum's demonstrated involvement in emotional prosody processing (Adamaszek et al. 2014; Ceravolo et al. 2021) allows it to construct an emotional habit structure that biases how an individual responds to the next instance of emotional prosody, potentially dampening unproductive physiological responses or elaborating socially meaningful facial cues automatically to communicate most effectively with the speaker.

9.4 Clinical Implications

The previous section proposed how emotional habits form in healthy individuals, yet much of the insight into the affective function of the cerebellum originated in clinical studies of patients with cerebellar damage and from anatomical investigations of patients with psychiatric disorders. The disruption of cerebellar function via injury or disease can lead to a myriad of symptoms including affective personality changes and cognitive deficits, in addition to the well-recognized motor dysfunctions (Leggio et al. 2008; Olivito et al. 2018; Schmahmann 2019; Schmahmann and Sherman 1998; Turner et al. 2007). These affective changes may arise from improper cerebellar feedback due to inaccurate internal models of emotional contexts that, in turn, disrupt the formation or execution of habitual responses to the emotional stimuli. Differences in cerebellar anatomy and function have been associated with psychiatric conditions such as autism spectrum disorders (ASD), attention deficit/hyperactivity disorder (ADHD), schizophrenia, bipolar disorder, depression, and obsessive-compulsive disorder (OCD; Adamaszek et al. 2017; Anticevic et al. 2014; Bruchhage et al. 2018; Chen et al. 2013; Clausi et al. 2019; Depping et al. 2016; Fatemi et al. 2012; Gill and Sillitoe 2019; Schmahmann et al. 2007), where inappropriate emotional responses may occur or habitual behaviors may persist despite negative affective feedback or punishment. Although each of these conditions involves diverse clinical symptoms and affects numerous brain regions, evidence is accumulating for a specific impact of or on the cerebellum that may alter emotional habit formation and performance.

For example, in OCD and ADHD, problems with impulsive and compulsive behaviors may be due to a difficulty inhibiting motor sequences or interrupting habit performance, processes that normally are supported in part by the cerebellum

(Miquel et al. 2019). If the cerebellum cannot accurately construct an internal model, then faulty cerebellar output to PFC or basal ganglia (which may be impaired themselves) can contribute to a failure to select and strengthen the correct response amid competing neural noise, preventing inappropriate or habitual responses from being inhibited and new responses from being learned (Bostan and Strick 2018; Fermin et al. 2016; Gillan et al. 2011, 2014; Sander et al. 2018). An inability to incorporate negative feedback for this behavior into a new cerebellar model (perhaps due to disrupted connections with reward systems in the striatum or ventral tegmental area; Bostan et al. 2010; Kostadinov et al. 2019) may perpetuate the undesirable behavior, leading to clinical symptoms. Furthermore, different disorders may reflect disruptions to particular functional loops between the cerebellum, basal ganglia, and neocortex. For example, the persistence of maladaptive habits in OCD may arise from dysfunction within the limbic loop that prevents cerebellar modification to existing habits based on feedback (Miquel et al. 2019), whereas motor (and perhaps affective) symptoms in Parkinson's disease may arise from deficits in the sensorimotor loop that prevents automatic performance of habits and thus requires increased cerebellar activity to support slow, conscious, executive supervision of actions (Drapier et al. 2008; Péron et al. 2013; Wu and Hallett 2013).

Furthermore, ASD has been associated with early cerebellar abnormalities, particularly a reduced number of hemispheric (and possibly vermal) Purkinje cells, that may be linked to the development of impaired social/emotional habits in addition to motor and language deficits (Bruchhage et al. 2018; Fatemi et al. 2012). For example, difficulties with social skills may arise in part due to affective cues (e.g., an emotional facial expression) that cannot be properly incorporated as feedback signals into an internal model to build predictions and guide the formation of appropriate habitual social responses. Additionally, the repetitive behaviors and preference for routines observed in ASD may reflect altered reward circuitry (Fatemi et al. 2012; Gotham et al. 2013; Subramanian et al. 2017), from which the cerebellum receives input for learning and adjusting behaviors. Nonetheless, the array of ASD symptoms involves numerous mental processes governed by multiple brain regions (such as the basal ganglia) and the precise contribution of the cerebellum has yet to be determined.

More generally, the cerebellum's connections with limbic regions or the default mode network may explain its association with mood disorders and affective symptoms such as neuroticism, blunted affect, or rumination (Clausi et al. 2019; Depping et al. 2016; Lupo et al. 2015; Schmahmann et al. 2007; Schutter et al. 2012). Again, the inability to construct accurate models of the current (emotional) state of the individual, their environment and how ongoing (negative) thoughts will impact their mood could lead to inappropriate, or inadequate modification of limbic network activity, poor mood awareness (Adamaszek et al. 2017; Clausi et al. 2019), and the persistence of unwanted affective/reward-seeking habits or thought patterns (which may also contribute to drug addiction; Miquel et al. 2020; Moulton et al. 2014).

When considering patients with lesions to the cerebellum, one clinical study (Adamaszek et al. 2019) found a higher proportion of errors for emotion recognition (especially fear) for vocal and facial expressions in cerebellar patients with lesions encompassing Crus I and II, as compared to two other patient groups. Their results identified the cerebellum as an important lesion site underlying emotion recognition impairment (see also Thomasson et al. 2019), while patients with dysfunction of the basal ganglia due to Parkinson's disease and patients with general cortical lesions did not show similar deficits, extending their previous findings of emotional impairment in cerebellar patients compared to healthy controls (Adamaszek et al. 2014). These emotion recognition difficulties may have arisen because of the cerebellum's inability to incorporate incoming sensory information (e.g., the emotional prosody of a voice) into its internal model. Thus, when other brain regions such as the PFC and amygdala respond to an emotional stimulus, they may rely upon missing, slow, or faulty cerebellar feedback to adjust the initial prediction for interpreting the perceived emotion, biasing the response toward familiar, habitual emotional reactions with poor specificity to the current context. Despite the current evidence from these various clinical conditions and assessment techniques, the precise causal links between cerebellar anatomy/function and clinical disorders/ emotion deficits remain to be clarified fully.

9.5 Conclusion

There is increasing recognition across clinical (Adamaszek et al. 2015; Clausi et al. 2019; Leroi et al. 2002; Lupo et al. 2015; Schmahmann and Sherman 1998; Thomasson et al. 2019; van den Berg et al. 2020; Van Overwalle et al. 2020) and neuroimaging studies (An et al. 2018; Baumann and Mattingley 2012; Bermpohl et al. 2006; Ferrari et al. 2018; Lee et al. 2004; Schutter and van Honk 2009) of the cerebellum's contribution to non-motor functions, notably in the affective domain. This chapter described findings related to the cerebellum and emotional habit formation, using the example of auditory processing of emotional prosody. The cerebellum builds an internal model of the current state and forms predictions about future states based on the context and one's previous experience with emotional stimuli. Over time, the cerebellum learns associations among stimuli and between stimuli and rewarded responses, and optimizes behavior through outputs to the neocortex and basal ganglia, thus strengthening a repeatedly rewarded response. Once the habit is established, cerebellum involvement is reduced to monitoring for prediction errors while the routine thought or action is completed seemingly automatically. If, however, emotion circuits in the cerebellum are damaged by disease or injury, an individual may present with a mood disorder or dysfunctional reward-seeking behavior, potentially driven in part by the uncorrected implementation of maladaptive emotional habits. In conclusion, although the cerebellum contributes to emotion processing within the context of large, dynamic brain networks, growing evidence indicates that the cerebellum also plays a unique role in processing of prediction errors, rewards, and learning of new habits within the emotional domain.

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10 Cerebellar Contribution to Emotional Body Language Perception

Chiara Ferrari, Andrea Ciricugno, and Zaira Cattaneo

Abstract

Body language is a powerful form of non-verbal communication providing important information about the emotions and intentions of others. The ability to infer other's emotions from their bodily movements and postures recruits an extended network in the brain that encompasses both cortical and subcortical regions. In this chapter, we review recent evidence suggesting that the cerebellum is a critical node of this network. Specifically, we present convergent findings from patients', neuroimaging and non-invasive brain stimulation studies that have shown that the cerebellum is involved in both biological motion perception and in discrimination of bodily emotional expressions. We discuss the potential underlying mechanisms that drive the recruitment of the sensorimotor (anterior) and cognitive (posterior) cerebellum in inferring others' emotions through their bodily movements and postures and how the cerebellum may exert these functions within different cortico-cerebellar and limbic-cerebellar networks dedicated to body language perception.

Keywords

Body language · Emotions · Biological motion · Cerebellum · Prediction · TMS

10.1 Introduction

Since the postulation of the Cerebellar Cognitive Affective Syndrome (Schmahmann and Sherman 1998; see also Argyropoulos et al. 2020), growing evidence has supported the view that the cerebellum contributes to affective and social functions (e.g., Adamaszek et al. 2017; Van Overwalle et al. 2020a), as well as to other high-order processes, beyond its well-known role as motor controller (e.g., Guell et al. 2018a; King et al. 2019). In the social domain, the cerebellum seems to mediate the regulation of our own emotions and the understanding of others' emotional and mental states, such as intentions, goals, and predispositions (Adamaszek et al. 2017; Van Overwalle et al. 2020a). However, the functional mechanisms and the specific broader brain circuits through which the cerebellum contributes to emotional processing remain to be clarified.

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This chapter aims to shed light on the role of the cerebellum in understanding others' emotions focusing on emotional signals conveyed by bodily postures and gestures. Indeed, if on one hand prior research has mostly employed faces as stimuli, considering them the most effective cues for non-verbal emotional communication, on the other hand, growing evidence suggests that body language is a rich source of information that can reveal people's goals, intentions, and emotions (De Gelder et al. 2010; for a review see De Gelder et al. 2015). In the next paragraphs, we provide a brief overview of the available evidence on the neurocognitive systems mediating the processing of body expressions. We then specifically consider empirical findings supporting the role of the cerebellum in inferring emotions from bodily cues. We propose potential underlying mechanisms driving the involvement of the cerebellum in inferring others' emotions through their bodily movements and postures and we discuss how the cerebellum may exert these functions within different cortico-cerebellar and limbic-cerebellar networks dedicated to body language perception. In the concluding part, we consider some open questions that still need to be addressed, which will pave the way for future research.

10.2 The Importance of Body Signals in Conveying Emotional States

As humans, we heavily rely on our bodies to express our emotions. Accordingly, we are typically quite proficient in inferring emotions, as well as goals, intentions, and dispositions, through the observation of others' body postures and gestures (e.g., Atkinson et al. 2004; Proverbio et al. 2010, 2014; Tipper et al. 2015; Tracy and Matsumoto 2008), a capacity that emerges early in the development (Fox and McDaniel 1982; Pavlova et al. 2001; Zieber et al. 2014).

Psychological and neuroscience researchers have long neglected the importance of the body in conveying emotional information. Indeed, the dominant view was that only facial expressions could be considered reliable indicators of one's emotional state (e.g., Darwin 1872/2005), whereas the contribution of the body in emotional communication was regarded as quite marginal and limited to the signaling of gross affect or emotion intensity (Ekman and Friesen 1967). Nevertheless, in the last twenty years, consistent findings have shown that bodily movements and postures are able to convey specific information about a person's emotional state (for a recent review see, Witkower and Tracy 2019). Indeed, the expressive repertoire of emotional body postures, movements, and gestures is extremely diverse, encompassing primary emotions and self-conscious emotions, such as embarrassment, shame, and pride (Dael et al. 2012). Moreover, body expressions may even be more effective than facial expressions in conveying one's emotions in particular situations, for instance when the interacting agents are distant and facial expressions cannot be properly processed (Martinez et al. 2016; for reviews see De Gelder 2009, 2016; Yovel and O'Toole 2016) or when the expresser does not face the viewer (Coulson 2004; Sogon and Masutani 1989). Also, certain emotions—such as anger—are better recognized when expressed by a body posture than by a facial expression (De Gelder 2009), and there are cases—as when an emotion is particularly intense—in which body signals are fundamental to disambiguate emotional facial expressions (Aviezer et al. 2008).

According to the model proposed by de Gelder and collaborators (2015, see Fig. 10.1), viewing emotional bodies first engages ventral stream regions selectively dedicated to (neutral) body processing (paralleling face-processing dedicated circuits), that is the extrastriate body area and the fusiform body area, responsible for featural and configural processing of body stimuli (van de Riet et al. 2009). This low-level information enters then a *visuomotor* circuit that involves the posterior superior temporal sulcus (pSTS), the inferior parietal sulcus, and the premotor cortex. The *visuomotor* circuit, connected with the amygdala, mediates the conscious analysis of bodily movements (i.e., biological motion) and the implementation of adaptive behaviors in response

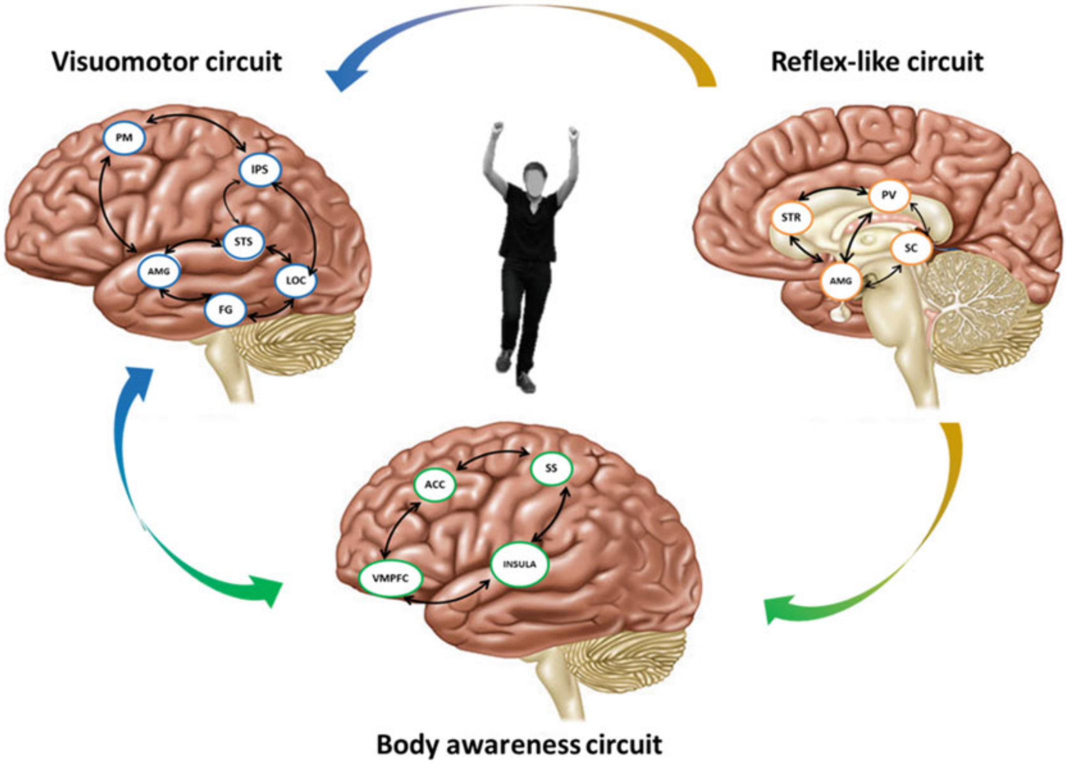

Fig. 10.1 Schematic representation of the three interrelated brain networks involved in emotional body language, according to De Gelder and collaborators (image modified from De Gelder 2006; De Gelder et al. 2015). The visuomotor circuit (blue, upper left) involves the lateral occipital complex (LOC), superior temporal sulcus (STS), intraparietal sulcus (IPS), fusiform gyrus (FG), amygdala (AMG), and premotor cortex (PM). The reflex-like circuit (orange) involves the superior colliculus (SC), pulvinar (PV), striatum (STR), and amygdala (AMG). The body awareness circuit (green) involves the insula, somatosensory cortex (SS), anterior cingulate cortex (ACC), and ventromedial prefrontal cortex (VMPFC)

to the specific emotion shown by the perceived body. Critically, the posterior STS is not only involved in processing biological motion but also represents a core area of the social brain that integrates and coordinates information from the action-observation, the mirror, and the mentalizing networks (Deen et al. 2015; Yang et al. 2015; Yovel and O'Toole 2016). If the processing of emotional faces also activates this region (e.g., Ferrari et al. 2018a; Pitcher 2014; for a review see, Pitcher 2019), perception of emotional body expressions seems to activate specific motor-related structures that are not triggered by emotional faces (van de Riet et al. 2009), suggesting that processing of emotional bodies is specifically related to the possible implementations of actions in response to the observed agent. In parallel, the emotional content conveyed by body stimuli triggers response in a set of subcortical regions (e.g., the amygdala, the superior colliculus, pulvinar and striatum) that enable rapid automatic reflex-like reactions (*reflex-like* circuit). Hence, the amygdala functions as an interface between the cortical and sub-cortical circuits involved in processing emotional bodies. Moreover, both circuits are closely connected with structures that support bodily sensations and bodily awareness (i.e., insula, somatosensory, anterior cingulate, and ventromedial prefrontal cortices) that contribute to the detection and recognition of others' bodily expressions by integrating visceral, attentional, and emotional information (i.e., interface circuit) (De Gelder et al. 2015).

Recent neuroimaging and neurostimulation findings suggest that the cerebellum may be a critical—so far neglected—node of the circuits involved in emotional bodies processing, and, in particular, a node of the *visuomotor* circuit. Indeed, the cerebellum does not only reciprocally communicate with pSTS during the perception of human body movements (e.g., Sokolov et al. 2014, 2018), but it is also a node of the cerebello-amygdaloid resting-state network that is likely in charge of sensorimotor, emotional, and motivational integration of somesthesic stimuli (Habas 2018).

10.3 Overview of Current Evidence on the Role of the Cerebellum in Reading Others' Body Language

At first glance, one may argue that the cerebellum is involved in processing emotions expressed by bodies by virtue of low-level motor-related mechanisms activated by viewing other's gestures. This would be in line with the renowned role of the cerebellum in planning and controlling movements (for a review see, Koziol et al. 2014). However, this hypothesis does not fit with the finding that viewing of emotional bodies consistently activates posterior sectors of the cerebellum that are not directly involved in motor control (e.g., Ferrari et al. 2021a; Lindenberg et al. 2012). Indeed, the cerebellum shows a clear functional segregation along the anterior-posterior axis, with a preferential activation of the anterior cerebellum (the *sensorimotor* cerebellum that includes lobule I-V and adjacent parts of lobule VI and lobule VIII in the posterior cerebellum) during motion-related and movement mirroring tasks and a preferential activation of the posterior cerebellum (the *cognitive* cerebellum, lobule VI-X) during non-motor-related tasks (Schmahmann 2019). The posterior cerebellum has been found to support a wide range of high-level functions, ranging from social and emotional inferential processes to semantic processing and memory mechanisms (e.g., Ferrari et al. 2018b; King et al. 2019). Functional connectivity evidence converges in indicating greater (reciprocal) functional communication between the anterior cerebellum and somatosensory and sensorimotor cerebral regions and between the posterior cerebellum and high-order cerebral regions (Buckner et al. 2011; Schmahmann 2019). Although the cerebellum is characterized by a much more complex topography (King et al. 2019) in which lobular boundaries do not necessary define functional subdivisions and that might be better represented in terms of continuous gradients of functional differentiation (Guell et al. 2018a), the distinction between anterior-sensorimotor and posterior-cognitive seems to be well established (Schmahmann 2019).

Available evidence suggests that the anterior cerebellum is recruited when perceiving emotional bodily expressions (Kana and Travers 2012; Peelen et al. 2007), possibly due to motor resonance mechanisms (for a review, see Agnew et al. 2007). Motor resonance is defined as the internal activation of an observer's motor system, specifically attuned to the perceived movement, and is thought to result from the activity of neurons homologous to the mirror neurons described in the monkey ventral premotor cortex (Gallese et al. 1996). Activation in the anterior cerebellum may thus be particularly sensitive to the amount of implied motion of the selected bodily stimuli. In turn, there is large consensus that the posterior cerebellum is a critical component of the neural system dedicated to the processing of emotional body language (Ferrari et al. 2021a; Jastorff et al. 2015; Lindenberg et al. 2012; Prochnow et al. 2013). The study of the mechanisms implemented by the posterior cerebellum when analyzing the emotional content of bodily expressions is an issue that reflects the broader debate on the functions of the cerebellum across the motor and the cognitive domain. Indeed, a key question when studying cerebellar high-level functions is whether these can be reconciled with a common mechanism. Schmahmann (1996) proposed the Universal Cerebellar Transform (UTC) theory, according to which the cerebellum would contribute in a similar way to the motor, cognitive, and emotional domain by implementing the same function that is by acting as an *oscillation dampener*, rapidly and automatically optimizing the performance according to the context. This theory has been developed upon the neurophysiological observation that the cerebellar cortex cytoarchitecture is essentially constant throughout its structure and upon neuropsychological data that show that cognitive and affective impairments in patients with cerebellar injuries follow the logic of motor symptoms (Guell et al. 2018b). It has also been suggested that the common mechanism underlying cerebellar involvement in the sensorimotor and cognitive domain is the implementation of forward models that allow prediction based on prior experience (Miall et al. 1993; Siman-Tov et al. 2019; Tanaka et al. 2019). Nevertheless, Diedrichsen and colleagues (Diedrichsen et al. 2019) have recently challenged the idea of a uniform contribution of the cerebellum across domains, proposing the concept of the *cerebellar multiple functionality* that suggests that the same underlying circuit may implement functionally distinct computations.

10.3.1 The Cerebellum in Biological Motion Perception

Perceiving biological motion is essential for inferring emotions expressed by others' movements and gestures. Reading others' mind relying on their bodily postures and gestures is a process composed of different (sub)components. These include first-order processing (implicit detection of biological motion), direct processing (explicit discrimination between features of the biological motion stimuli, e.g., rightward vs. leftward walker), and instrumental processing of biological motion. The latter implicates that the observer takes advantage of the processing of a biological motion stimulus for a secondary purpose, i.e., to disclose distinct and potentially more complex information, such as inferring about other's intentionality, emotional states, or actions (Federici et al. 2020; see also Casile and Giese 2005; Troje and Westhoff 2006, for similar models). Biological motion perception has been traditionally investigated using point-light animations that consist of displays created by attaching lights to major joints while people are in motion. This paradigm has the main advantage to help to minimize availability of structural cues and thereby to separate information revealed by motion from other sources (e.g., shape, color, Pavlova 2012). Accordingly, since its development (Johansson 1973) this methodology has been employed in a large number of behavioral and neuroscience investigations (for a review see, Yovel and O'Toole 2016).

A series of neuroimaging and neuropsychological studies by Sokolov and collaborators have consistently demonstrated that the cerebellum is critically involved in processing biological motion. Specifically, using fMRI Sokolov et al. (2012) observed increased activity in response to point-light upright walker animations compared to scrambled-walker animations selectively in the left posterior cerebellar hemisphere, in Crus I and lobule VIIB (see also Jack et al. 2017; Vaina et al. 2001, for similar results). Accordingly, Sokolov et al. (2010) showed that patients with (left) posterolateral but not anteromedial cerebellar lesions showed impaired visual sensitivity to the presence of a walker in point-light displays, supporting neuroimaging evidence in pointing to a role of the posterior cerebellum in mediating biological motion perception. These findings are further corroborated by anatomical and functional connectivity analyses showing that some sectors of the posterior cerebellum, and in particular left lobule VI and left Crus I/II, are functionally connected to the right posterior STS (e.g., Jack et al. 2011, 2017; Sokolov et al. 2012, 2014, 2018).

Further support for a critical role of the posterior cerebellum in processing biological motion comes from recent studies using non-invasive brain stimulation. By transiently interfering with ongoing neural activity in the targeted area, non-invasive brain stimulation sheds light on brain-behavior *causal* relationships (Parkin et al. 2015; Pascual-Leone et al. 2000). In a recent study, Ferrari et al. (2021b) targeted different sectors of the posterior cerebellum using transcranial magnetic stimulation (TMS) while participants were engaged in a biological motion perception task. Healthy adult volunteers had to discriminate point-light animations depicting a biological figure in motion (performing various activities such as walking, kicking, or throwing) from non-biological motion animations (scrambled versions of the original stimuli, in which dot positions were randomly modified while preserving their kinematics). TMS was delivered during the task over a medial site (vermal lobule VI) and over a more lateral site (left lobule VI/Crus I) of the posterior cerebellar lobe. Vertex was also stimulated as control site. The authors also manipulated the timing of the cerebellar stimulation, by delivery magnetic pulses either at the onset of the animations or after 300 ms from the display of the biological motion stimulus, so that cerebellar TMS preceded (onset) or followed (300 ms) the activation of the right STS (e.g., Hirai et al. 2003; Sokolov et al. 2018). Indeed, prior MEG and ERP studies estimated that right STS activates during biological motion tasks between 170 and 350 ms after the animation onset (Hirai et al. 2003, 2005; Jokisch et al. 2005; Krakowski et al. 2011; Pavlova et al. 2005). Ferrari et al. (2021b) reported that TMS delivered at the onset of the animations selectively interfered with the task when given over the medial cerebellum, possibly reflecting interference with early movement identification. In turn, when stimulation was delivered at the later time point, likely following STS response to biological motion, participants performed worse when TMS was delivered over the left cerebellar hemisphere, suggesting specific interference with higher-level cortical processing. These TMS data complement the neuroimaging and patients' findings of Sokolov and collaborators, providing evidence for a causal role of the left lateral posterior cerebellar hemisphere in mediating biological motion processing. Whether the right cerebellar hemisphere is also involved in processing biological motion has not been tested. Although the issue of a possible lateralization of cerebro-cerebellar circuits involved in biological motion perception has never been systematically explored, previous studies have suggested that cognitive networks (such as the language network) that are strongly lateralized within the cerebrum may also be lateralized within the cerebellum (Wang et al. 2013). However, findings from the social domain overall point to a bilateral pattern of activation in the posterior cerebellum during tasks related to affective and social cognition (e.g., Guell et al. 2018c; Keren-Happuch et al. 2014; Stoodley and Schmahmann 2009; Van Overwalle et al. 2020a, 2020b). Future investigations should shed light on possible patterns of task-related lateralization in the posterior cerebellum in the social and affective domain.

Another line of research that has provided a compelling case for the involvement of the cerebellum in processing bodily expressions is that on autistic spectrum disorder, a syndrome characterized by impairments in several social abilities (Lai et al. 2014). Consistent evidence suggests that individuals affected by autism may show impairments in biological motion processing (for recent reviews, Federici et al. 2020; Todorova et al. 2019). Critically, autistic spectrum disorder has been recently associated with anatomical and functional abnormalities in the cerebellum (e.g., D'Mello et al. 2015; Yu et al. 2011; for a meta-analysis see Stoodley 2014). Indeed, autistic individuals show a reduced cerebellar volume in the anterior (inferior cerebellar vermis, lobule IX), and posterior cerebellum (left lobule VIIIB, and right Crus I) compared with neurotypical cohorts (Yu et al. 2011), with higher symptomatology being associated with lower gray matter volumes in right Crus I/II (D'Mello et al. 2015). Importantly, atypical effective connectivity between right posterior STS and bilateral lobules VI and right Crus I/II has been found to be specifically linked to (impaired) processing of biological motion in autistic individuals, with the extent of this abnormal connectivity correlating with the social impairment showed by the autistic participants (Jack et al. 2017). Federici et al. (2020) have conducted a meta-analysis in which they specifically investigated alterations in biological motion perception in autism and found that the most consistent and severe impairment showed by patients with autism occurs when tasks require instrumental recognition (vs. first order and direct processing) of the biological motion, which is the use of the biological motion stimuli to make more complex social and emotional inferences about the agent (see Todorova et al. 2019 for similar evidence). The results of Federici et al. (2020) might be interpreted as suggesting that the function of the posterior cerebellum in processing bodily stimuli is not concerned with low-level visual processing but rather with the extraction and use of more complex bodily information relative to affective and social meaning.

As mentioned above, it has been hypothesized that the function that the cerebellum exerts in cognitive processes (in analogy with the motor domain) is to generate predictions based on previous experience (Miall et al. 1993; Tanaka et al. 2019). Previous studies on biological motion have showed that the ability to create predictions based on the representation of already known movements (created upon past experience) is essential for the detection and identification of other individuals' movements (Kawai et al. 2017; Thornton et al. 2002). Being able to anticipate (or predict) others' movements seems to facilitate inferences about the intentions and goals of others' actions, favoring the development of appropriate re-actions and thus smoothing social interactions. As recently proposed by Sokolov et al. (2018), during biological motion tasks, prediction about others' movements might be generated in the prefrontal cortex and, through pSTS, sent to the posterior cerebellum that would be in charge of fine-tuning these predictions and send them back to STS. In this view, one possibility is that mechanisms related to motor control and prediction of sensory consequence of one's own movements implemented by the sensorimotor (anterior) cerebellum may have expanded to the posterior cerebellum allowing these predictions to be used to identify others' movements (Oldrati et al. 2021; Sokolov et al. 2017). In line with this, both lesions to the anterior and the posterior cerebellum (lobule VII) have been found to impact on action-perception coupling, that is the facilitation that self-generated movements have upon the detection of others' (similar) actions (Christensen et al. 2014).

10.3.2 Emotional Body Language Perception

Most of what we know about a cerebellar role in the domain of emotional body language perception comes from studies not specifically focusing on the cerebellum. An instance of this is the fMRI study of Lindenberg et al. (2012) who investigated the neural correlates of imagined execution and perception of valenced emblematic gestures (gestures widely used for conveying socially and emotionally relevant information, such as "thumbs up"). The authors found that the paravermal region of the posterior cerebellum (Lobule VI/Crus I) selectively responded to emblematic (emotional) gestures vs. control gestures. Further evidence for a role of the posterior cerebellum, and, in particular, of its paravermal sectors, in processing emotional information conveyed by bodies comes from a TMS study in which healthy participants had to discriminate between static angry and happy body postures, while receiving TMS over the left paravermal sectors of the posterior cerebellum. Interfering with the posterior paravermal cerebellum affected participants' ability to discriminate between body emotional expressions of happiness and anger compared to the stimulation of the control sites, indicating that this region is causally involved in perceiving others' emotional states when conveyed by body postures (Ferrari et al. 2021a). Also, in this case the authors only targeted the left cerebellum, it remains thus to be addressed whether interfering with the corresponding paravermal right cerebellar sector also affects emotion discrimination.

Overall, cerebellar activity in response to bodily stimuli seems to show an organization on the medial-to-lateral axis. Prior evidence has already outlined the existence of a medial-to-lateral functional gradient in the posterior cerebellum with sensorimotor processes being more medially located, and cognitive functions being primarily distributed in the lateral portion of the posterior cerebellum (Guell et al. 2018a; Klein et al. 2016; Timmann et al. 2010). Initial evidence seems to suggest that such similar gradient applies to affective function involving body language. Indeed, regions dedicated to the understanding of action's intentions and goals (in more cognitive or metalizing tasks) seem to be located in lateral sectors of the (left) cerebellum (Sokolov et al. 2012, 2014, 2018; Ferrari et al. 2021b; Vaina et al. 2001, for a review of cerebellar activations during social tasks see Van Overwalle et al. 2020b). In turn, regions recruited during the processing of emotional content of body movements are located medially (in vermal and paravermal areas, Ferrari et al. 2021a; Lindenberg et al. 2012), observation consistent with the renowned role of the vermis in emotion regulation (e.g., Schmahmann 2010), and in the etiology of affective disorders (Schutter 2016).

However, the distinction between lateral/medial cerebellar sectors for tasks that involved emotional processing may be conceived more along a continuum rather than a binary subdivision, possibly depending also on the specific paradigm used. For instance, Jastorff et al. (2015) correlated the pattern of brain activation with the subject's perceptual sensitivity for emotionally expressive gait (e.g., subject' ability to discriminate emotional vs. neutral gait) and found that subjects more sensitive to the emotional gait exhibited stronger activation of the posterior lateral cerebellum for emotional bodily stimuli compared to neutral ones. In line with this, Prochnow et al. (2013) found that the discrimination of both emotional facial expressions and gestures was related to enhanced activity in the same cerebellar region that is the lateral (left) cerebellum (lobule VI). If on one hand these studies suggest an involvement of the posterior lateral cerebellum in emotional tasks, on the other hand the identified cerebellar peaks of activation in these studies are still overall more medial that those reported in social tasks (e.g., Sokolov et al. 2012). All this considered, the hypothesis of the existence of a medial-to-lateral functional gradient in the posterior cerebellum related to affective and social functions deserves further investigation, for instance employing tasks that require increasingly less emotional and increasingly more social/mentalizing processes.

An open question is whether the cerebellar recruitment during emotion processing depends on the valence of the expressed emotion. Indeed, consistent evidence suggests that the cerebellum may be particularly (if not exclusively) recruited in case of negative emotions that are known to trigger in the perceiver robust "fight or flight" response (e.g., De Gelder et al. 2004). A recent TMS study (Ferrari et al. 2021a) showed that cerebellar TMS had a detrimental effect on the ability to discriminate emotional bodies only when the bodies expressed negative emotions (like anger or sadness), while cerebellar TMS did not affect discrimination of positive body expressions (i.e., happiness and surprise, see Ferrucci et al. 2012 for similar results using faces as stimuli). The selective role of the posterior cerebellum in processing negative bodies may thus reflect fast preparation mechanisms to respond to a potential threat, again based on prediction mechanisms by which an agent expressing a negative emotion may signal a potential danger to the perceiver. Accordingly, a recent TMS study has shown that changes in motor cortical excitability (measured by motor evoked potentials, MEP) in response to fearful (vs. neutral) facial expressions are modulated by the posterior cerebellum (Ferrari et al. 2021c). This effect might be even stronger when considering emotional cues conveyed by body postures that are tightly linked to action-related mechanisms (De Gelder et al. 2010; Ramsey 2018). Accordingly, we may speculate that the cerebellum participates in emotional understanding of others' body postures and movements only in particularly (evolutionary) salient contexts, that is when the stimuli trigger immediate (defensive) response in the perceiver.

10.4 Conclusions

Current evidence shows that the posterior sector of the cerebellum is a critical region both for discrimination of biological motion and for the understanding of intentions, goals, and emotions conveyed by bodily expressions (Ferrari et al. 2021a, b; Lindenberg et al. 2012; Jastorff et al. 2015; Prochnow et al. 2013). This finding fits well with the recently recognized role of this phylogenetically newer cerebellar region (posterior cerebellum) in social cognition (for a review, see Van Overwalle et al. 2020a) and with its nowadays well-established function in cognitive processing (for reviews see, Koziol et al. 2014; Schmahmann 2019). Body postures and gestures also trigger motor-related responses in the anterior (sensorimotor) cerebellum (Kana and Travers 2012; Peelen et al. 2007), but these responses seem to reflect low-level processing of the stimuli. The cerebellar contribution to the reading of emotional body language is a complex phenomenon that follows different pathways within an extended cerebro-cerebellar-subcortical network. Within the framework of network neuroscience that views the brain as a connectome of interacting nodes that synchronize activity to support adaptive behavior (Bassett and Sporns 2017; Palesi et al. 2020), the study of cerebro-cerebellar functional connectivity represents a valuable approach to shed light on the underlying cerebellar mechanisms mediating social and emotional functions. Accordingly, the analysis of the temporal dynamics of the interactions between the cerebellum, the visuomotor, the reflex-like and the body awareness systems (see De Gelder et al. 2015) might increase the understanding of the neurofunctional mechanisms that characterize the perception of body language and the specific role of the cerebellum. Despite it is difficult to apply to the cerebellum traditional approaches of signal recording with techniques typically employed to investigate temporal aspects of brain processing (i.e., EEG and MEG) (but see Andersen et al. 2020), some TMS protocols appear feasible and promising to investigate the cerebro-cerebellar connectivity.

To date, available evidence indicates that the contribution of the cerebellum is not selective for processing emotions from bodies. Indeed, several studies reported cerebellar activations (left Crus II and left lobule VI, as well as Crus II vermis) in response to emotional faces (e.g., Adamaszek et al. 2015; Ferrari et al. 2018c; Ferrucci et al. 2012; Schraa-Tam et al. 2012; for a review of neuroimaging studies Fusar-Poli et al. 2009; see also Prochnow et al. 2013). Nonetheless, it would be interesting to assess whether the same cerebellar sectors process emotional information conveyed by different stimuli, for instances whether emotional faces and bodies trigger activation in the same or in different cerebellar region, or whether there is a valence-dependent (possibly lateralized) functional gradient. Indeed, many theories have suggested that different valenced emotions (e.g., positive vs. negative emotions) may recruit the two cortical hemispheres to a different extent (e.g., Adolphs et al. 2001; but see Ferrari et al. 2017; Lindquist et al. 2016). Accordingly, a similar lateralization may be observed in the cerebellum (Wang et al. 2013). Another point that remains to be clarified is whether the functional organization of the posterior cerebellum is characterized by a medial-to-lateral gradient, with medial regions more involved in emotional processing and lateral regions in mentalizing (see Guell et al. 2018a; Van Overwalle et al. 2020a).

Research along these lines would not only critically contribute to clarify the role of the cerebellum in emotional processing but they would also shed light on whether the role of the cerebellum in social and affective processes may be explained by a unique mechanism (i.e., prediction) or in turn whether this region exerts different functions depending on the specific task/situation and on the specific stimuli features.

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Influence of Pain on Cognitive Dysfunction and Emotion Dysregulation in Chiari Malformation Type I

11

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Abstract

It has been well demonstrated that the cerebellum is associated with cognitive and affective processing as well as the traditionally conceptualized motor function. In the present chapter, we explore the behavioral and neurobiological implications of a common congenital cerebellar condition, Chiari malformation Type I, on cognitive and affective processing. We also emphasize the associations between Chiari-related chronic pain, cognitive dysfunction, and emotion dysregulation. Based on our review of the literature, we argue that chronic pain can account for a substantial amount of the cognitive dysfunction and emotion dysregulation in Chiari malformation Type I. Yet, there also exists aspects of Chiari-related cognitive dysfunction and emotion dysregulation that appear to be at least partially independent of chronic pain and more directly associated with abnormalities in cerebrospinal fluid flow dynamics and cerebro-cerebellar communication pathways.

Keywords

Chiari malformation · Cognitive control · Attention · Emotion regulation · Chronic pain

11.1 Introduction

Chiari malformation Type I (CMI) is a radiologically defined congenital condition qualified by a descent of the cerebellar tonsils below the foramen magnum, leading to both an anatomical obstruction of the cerebrospinal fluid cisterns at the base of the skull and an anatomical distortion of the cerebellar structure (Fig. 11.1) (Milhorat et al. 1999). Symptom presentation is often unique, but pain in the form of acute pressure, chronic occipital headache, and neck/shoulder pain is the most relevant element in the clinical presentation and social impact. CMI patients frequently self-report pain levels akin to those experiencing chronic pain syndromes such as fibromyalgia, low back pain, and diabetic

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peripheral neuropathy (Dworkin et al. 2009; Houston et al. 2019a; Garcia et al. 2019). Chronic pain in CMI has also been associated with greater pain sensitivity and disruption of top-down pain modulation, further leading to deleterious biological and psychological outcomes (Garcia et al. 2019; Allen et al. 2018; Bushnell et al. 2013).

The pathophysiology of pain in CMI is purely based on mechanical assumptions. Given that patients often present with Valsalva-induced head and neck pain (Mueller and Oro' 2004), it is assumed that the pain is triggered by the anatomical obstruction of cerebrospinal fluid (CSF) flow at the base of the skull and the impaired regulation and equilibration of CSF pressure between the cranial and the spinal compartments (Alperin et al. 2015; Ibrahimy et al. 2021; Shaffer et al. 2014). This may also result in an irritation of pain receptors of the dura mater and small blood vessels at the base of the skull initiating neuropathic pain pathways and causing chronic headaches (Fontaine et al. 2018). One pathological hallmark of CMI is a reduced posterior fossa volume that may be associated with reduced venous drainage through the jugular veins (Houston et al. 2018a), furthering the altered pressure regulation at the base of the skull (Alperin et al. 2015). Mechanical intradural irritation of the C1 and C2 vertebrae nerve roots from the altered CSF dynamics at the base of the skull has also been proposed as a generator of the occipital-based headaches (Noseda et al. 2019). Animal models also support this concept. For example, nociceptors in the posterior dural area over the cerebellum are linked with neurons in the C2-C4 region of the spinal cord in rats (Noseda et al. 2019).

Critical to the present discussion, chronic pain has been proposed to account for the observed cognitive dysfunction among CMI patients, often being described as “brain fog” and concentration difficulties. Work from multiple independent groups have established an understanding that CMI is associated with cognitive deficits including, but not limited to, attentional control (Houston et al. 2019a; Allen et al. 2014; González and Campa-Santamarina 2018; Kumar et al. 2011), executive function (Allen et al. 2014; García et al. 2020a; García et al. 2020b; Klein et al. 2014), and episodic memory (Houston et al. 2019a; Allen et al. 2018; González and Campa-Santamarina 2018; García et al. 2020a). Rogers et al. (2018) provided the most comprehensive review at the time of publication of cognitive deficits in CMI. The authors reviewed both the adult and pediatric literatures and came to several important conclusions. First, attention and working memory deficits are evident in adult CMI. Second, there is also preliminary evidence of a processing speed deficit in adult CMI, though additional research using larger samples and utilizing matched controls is necessary. Third, language deficits have not been consistently identified in adult or pediatric CMI. Fourth, evidence of visuospatial deficits in adult CMI is largely lacking and evidence of developmental disruptions in visuospatial abilities is mostly confounded by intellectual disability. In concluding their review, the authors also highlighted the limited empirical research investigating the cognitive profile of CMI and encouraged the careful consideration of chronic symptoms, namely chronic pain and neuropsychiatric symptoms, that may at least partially explain the cognitive deficits exhibited by CMI patients. Since the time of publication, works from multiple independent groups have replicated the results from reviewed studies in the work of Rogers and colleagues and further established connections between domain-specific cognitive dysfunction in CMI, chronic pain, and anxious-depressive symptomatology.

Beyond its direct impact on cognitive function, chronic pain also affects person-environment (PE) interactions and informs the emotional landscape and health-related decision-making in CMI patients. For example, those who experience chronic pain are less likely to engage in physical activity, achieve success in the workplace, and enjoy leisure activities with social contacts (Duenas et al. 2016). Chronic pain in CMI has also been associated with greater pain sensitivity

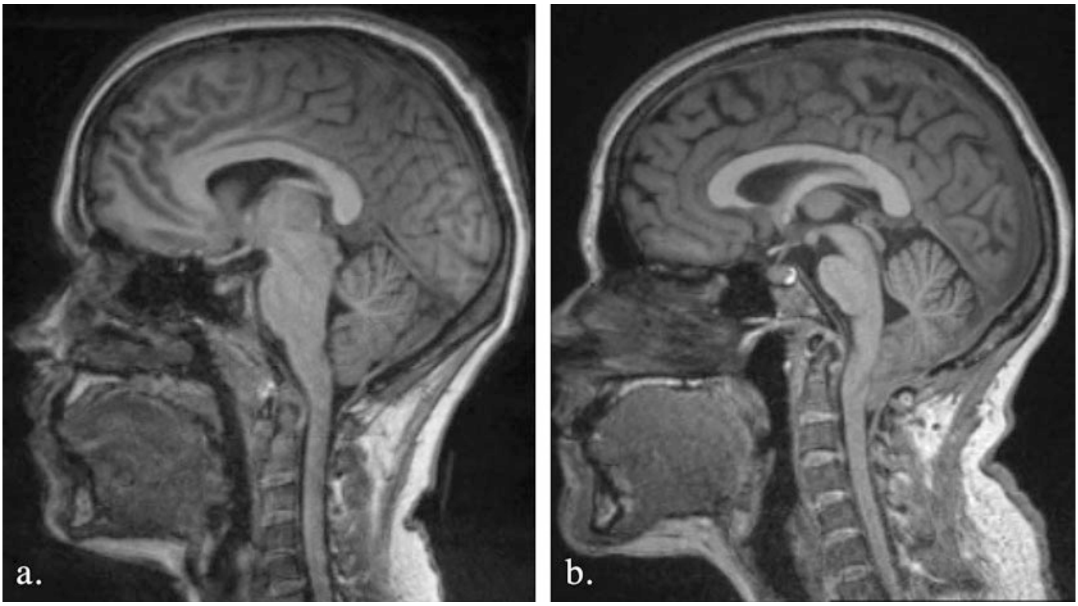

Fig. 11.1 Midsagittal radiological presentation of (**a**) a healthy control and (**b**) a patient diagnosed with Chiari malformation Type I. Image adapted from Houston et al. (2018b)

and disruption of top-down pain modulation, further leading to deleterious biological and psychological outcomes (Garcia et al. 2019; Allen et al. 2018; Bushnell et al. 2013). Duenas and colleagues (2016) provide an excellent review of the multifaceted effects that chronic pain can have on patients' lives and emphasize the need to take a biopsychosocial approach to understand the experience of individuals who experience chronic pain (see Fig. 11.2).

As such, the nature of the relationship between CMI and disruptions to cognitive and emotion function is now understood to be quite complex (Ibrahimy et al. 2021; García et al. 2021). This complexity has also been elucidated in part by recent investigations of brain microstructure and functional connectivity abnormalities in CMI. For example, in our work (Allen et al. 2018; Houston et al. 2018b, 2020, 2021), we have established a conceptual model to account for cognitive dysfunction and affective dysregulation in CMI by assuming that pain serves as a prepotent stimulus that draws limited attentional capacity. These studies have also implicated chronic pain effects on some, but not all, aspects of cerebro-cerebellar communication abnormalities (Houston et al. 2020, 2021). Thus, it remains an open question as to whether cognitive deficits are directly associated with CMI pathophysiology or whether they are secondary to developmental pain or neuropsychiatric symptom effects.

The present chapter reviews the current empirical understanding of chronic pain effects on cognitive and emotion function in CMI. Particular attention will be placed on studies focusing on controlled cognitive and emotion processing that utilized inferential statistics and representative sampling techniques. In other words, while we acknowledge the importance of clinical case reviews and scientific letters, this chapter will emphasize generalizable findings from peer-reviewed articles. Additionally, research on implicit and autonomic cognitive processing will be de-emphasized, though future investigations in this area are encouraged. We conclude the chapter with clinical care considerations and suggestions for future study.

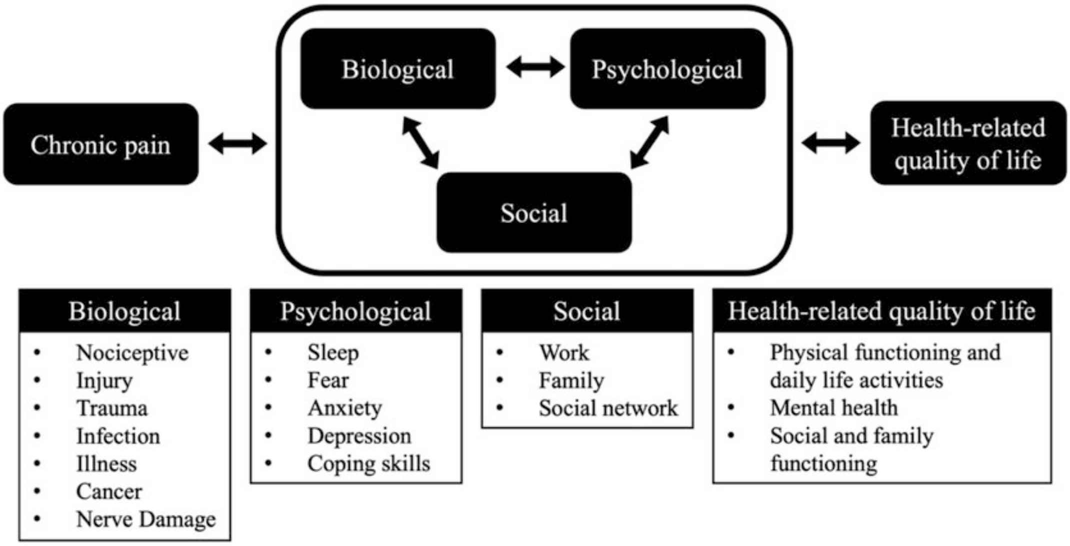

Fig. 11.2 Conceptual biopsychosocial model of pain and consequence on the quality of life. Chronic pain has reciprocal relationships with biological, psychological, and social functions, which have evocative interactions with each other and on health-related quality of life. Figure inspired by Duenas et al. (2016)

11.2 Behavioral Evidence of Pain Effects on Attention and Executive Dysfunction

Kumar and colleagues (2011) and Allen and colleagues (2014) provided two early landmark studies that demonstrated pervasive cognitive deficits in CMI patients relative to matched healthy controls. Each study had strengths but was also understandably limited given the limited research body at the time of publication. From these early studies, several considerations for future study became apparent regarding methods of assessment, treatment status of CMI patients, sample size requirements, and covariate considerations including the impact of chronic pain.

Kumar et al. (2011) utilized standardized neuropsychological tests (Trail Making Test, Figure Connection Test, and performance subset of the Wechsler Adult Intelligence Scale (WAIS) modified for the Indian population) in a sample of 10 CMI patients (presumably pre-surgical candidates) and 10 age- and sex-matched controls. Results indicated deficits in processing speed, response inhibition, and working memory. Despite the small sample size, Kumar and colleagues' work was instrumental in validating CMI patients' complaints of cognitive dysfunction and demonstrated that CMI-related cognitive deficits could be identified using comprehensive neuropsychological assessment. There were also notable limitations of the study including a small sample size, limited statistical control of false discovery, and the absence of symptom variables including chronic pain and anxious-depressive symptomatology.

Allen et al. (2014) both replicated several of the findings from Kumar et al. (2011) and rectified several of the design limitations of the earlier study. The authors examined CMI-related differences in processing speed, response inhibition, and working memory utilizing a series of laboratory tasks (computerized Digit-Symbol Coding, Stroop, and Operation Span tasks). Allen and colleagues used a considerably larger sample of 24 CMI patients and 24 age- and education-matched controls. However, unlike Kumar et al., the CMI patients had all undergone posterior fossa decompression surgery, a common surgical procedure with the purpose of reducing compression of the cerebellar tonsils and brainstem and alleviated symptoms such as headache and chronic pain. CMI patients exhibited performance deficits on all cognitive tasks. Additionally, self-reported pain and anxious-depressive symptomatology were correlated with processing speed and working memory measures. Given these correlations, the authors re-analyzed their cognitive task data after controlling for self-report measures via analysis of covariance (ANCOVA). Results indicated that self-reported pain and anxious-depressive symptomatology could fully account for case-control differences in processing speed and working memory, though response inhibition deficits could not be accounted for by these variables.

Taken in tandem, the results from Allen et al. (2014) and Kumar et al. (2011) largely established the generalizability-focused (i.e., relying upon representative sampling and population-level inference) empirical literature on cognitive deficits in CMI. The results from these two studies also corresponded well to earlier case studies (Novegno et al. 2008; Furuya et al. 1998; Pearce et al. 2006; Riva et al. 2011) and the experiences of several physicians who frequently treated CMI patients. The two studies demonstrated case-control differences in pre- and post-surgery CMI patients, respectively. They also demonstrated that CMI-related cognitive deficits could be identified via neuropsychological testing and more targeted laboratory testing and that symptom variables could at least partially explain the cognitive dysfunction experienced by CMI patients.

Yet, several questions remained. The impact of Chiari decompression surgery on CMI-related cognitive dysfunction remained an open question. There were also several aspects of cognitive function that were not explored in these two studies, namely language, episodic memory, aspects of executive function, and social cognition. Another major lingering issue regarded the neurobiological associations of cognitive deficits in CMI. At the time of publication of these early studies, much of the research interest in CMI derived from neuroradiological research groups and focused primarily on macro-level brain structure. To our knowledge, Kumar et al. (2011) were the first to also include neuroimaging data and conduct correlational analyses between neuroimaging data (via diffusion tensor imaging-DTI) and cognitive performance. Many of these questions would be approached in the subsequent cohort of published research that would take place between the publication of Allen et al. (2014) and the present.

Expanding upon their earlier work, Allen and colleagues (2018) aimed to directly assess the relationship between chronic pain and memory in CMI patients. Further, they sought to explore the relationship between individual differences in the cognitive-affective personality process of rumination, the tendency to focus on oneself repeatedly to evaluate (often negatively) one’s past actions, and reflection, the tendency to focus on oneself repeatedly to maintain a general awareness of one’s feelings and mental processes (Harrington and Loffredo 2010). The researchers used the international Chiari 1000 registry project, an online database which includes demographic characteristics, symptomatology, cognitive performance measures derived from web-adapted neuropsychological assessments, and any imaging data volunteered from CMI patients. Notably, the database includes an updated self-reported pain measure similar to the measure from the researchers’ earlier study (Dworkin et al. 2009). The results indicated that CMI patients with low levels of self-reported pain exhibited cognitive benefits (i.e., improved verbal memory on a modified Rey Auditory Verbal Learning Task (Schmidt 2009)) from engaging in self-focused reflection. Conversely, those with high levels of self-reported pain did not benefit from similar behaviors. Results were interpreted as suggesting that distraction due to pain can partially, but not fully, explain memory deficits in CMI.

In an effort to replicate and expand earlier neuropsychological assessment results, García and colleagues published a trio of studies that collectively comprise the most comprehensive neuropsychological testing data in the literature (García et al. 2018a, b, 2020a). Importantly, each of these studies incorporated self-report measures of chronic pain and anxious-depressive symptomatology. García et al. (2018b) required a group of 39 CMI patients who had not undergone Chiari decompression surgery and 39 sex- and education-matched controls to complete a comprehensive neuropsychological assessment battery that targeted aspects of executive function, verbal fluency, visuospatial function, verbal memory, and processing speed. Relative to the controls, CMI patients exhibited poorer scores on all measured aspects of cognitive function. Moreover, case-control composite scores in each of the measured cognitive domains remained significant after controlling for chronic pain and symptomatology variables, suggesting that pain could not account for the observed cognitive deficits. Though, it should be noted that the effect magnitude of the case-control differences did attenuate to varying degrees, suggesting that pain and symptomatology characteristics could partially account for some of the CMI-related cognitive deficits.

García et al. (2018a) built upon the results of this study by including a sample of CMI patients who had previously undergone Chiari decompression surgery. In the study, decompressed CMI patients, non-decompressed CMI patients, and healthy controls matched for sex and education completed a highly similar neuropsychological assessment battery to that of the author's previous study. Results largely replicated the previous findings with the notable addition that case-control differences were found to be nearly identical across decompressed and non-decompressed CMI patients. That is, similar patterns of statistically significant differences and effect sizes[1] were observed between decompressed CMI patients and healthy controls and non-decompressed CMI patients and healthy controls. Moreover, the authors conducted additional analyses comparing the cognitive profiles of the CMI patients by decompression surgery status. These additional analyses yielded no significant differences between the two groups. Importantly, all the group differences observed in the study were re-tested and found to remain significant, though again somewhat attenuated in effect magnitude, after controlling for chronic pain and anxious-depressive symptomatology.

García et al. (2020a) took a more targeted approach to explore cognitive deficits in CMI. In this study, a mixed sample of 26 decompressed and non-decompressed CMI patients and 26 sex- and education-matched controls completed a battery of assessments that targeted visuospatial function, with the use of the Block Design and Visual Puzzles subtests of the WAIS IV (Drozdick et al. 2018), Benton Judgment of Line Orientation (BJLO) test (Benton et al. 1994), and the Rey-Osterrieth Complex Figure (ROCF) test (Rey 1941). CMI patients exhibited deficits on all tasks except the ROCF. Interestingly, self-reported chronic pain could account for group differences in Block Design, but not Visual Puzzles or BJLO differences. The authors interpreted this pattern of findings as suggesting that chronic pain may affect executive visuospatial capacities that are emphasized in the Visual Puzzles and BJLO tasks to a lesser degree than visuospatial attention capacities that are emphasized to a greater degree by the Block Design subtest.

In addition to working with the Chiari 1000 registry data, Allen and colleagues simultaneously collected prospective data from an independent group of 20 CMI patients and 20 age-, sex-, and education-matched controls who were recruited while undergoing decompression surgery consultation. This prospective sample completed a series of self-report measures, completed a brief neuropsychological assessment, completed a functional neurophysiological assessment in which participant engaged in a facial expression identification task while being recorded by an electroencephalogram (EEG), and submitted to a neuroimaging sequence that included structural MRI, DTI, and resting-state functional MRI (fMRI) (see Fig. 11.3).

Two of these studies, Houston et al. (2019a, 2018b), were particularly important in demonstrating the effect of pain on different aspects of cognitive dysfunction in CMI. Houston et al. (2019a) utilized a routine clinical

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[1] Effect sizes estimated using mean difference and standard deviation data provided in the article.

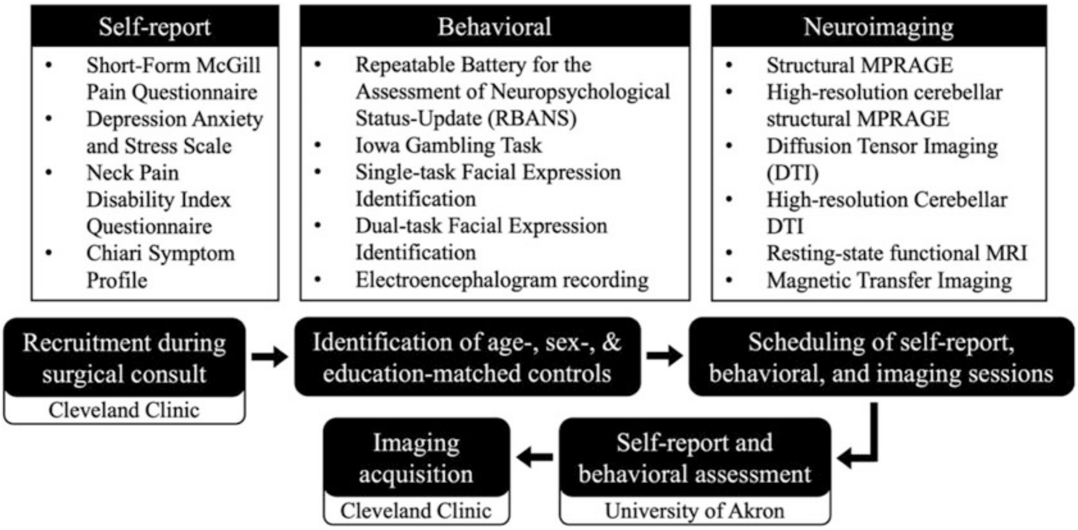

Fig. 11.3 Study protocol for the research that resulted in the publications of Houston et al. (2018b, 2019a, 2020, 2021). For more information on the self-report and behavioral measures, please see the following references: Short-Form McGill Pain Questionnaire (Melzack 1987); Depression Anxiety and Stress Scale (Henry and Crawford 2005), Neck Pain Disability Index Questionnaire (Fairbank et al. 1980), Chiari Symptom Profile (Mueller and Oro' 2013), Repeatable Battery for the Assessment of Neuropsychological Statue-Update (RBANS) (Randolph 2012), Iowa Gambling Task (Bechara et al. 1994), and Facial Expression Identification tasks and electroencephalogram recording (Pollock et al. 2012)

assessment in the form of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Randolph 2012). The assessment consists of 12 subtests assessing five cognitive domains—attention, language function, visuospatial skills, and immediate and delayed memory—and was chosen for its brevity and ease by which it could be included in a standard clinical protocol. CMI patients exhibited clinically meaningful deficits in the attention, immediate memory, and delayed memory subscales. After controlling for group differences in self-reported pain, only the case-control difference in performance on the attention subscale remained significant. Of note, the RBANS attention subscale consists of coding and span tasks that reflect aspects of selective and focused sub-domains of attention. The authors concluded that the chronic pain experienced by CMI patients could account for much, but not all, CMI-related cognitive dysfunction. More specifically, given that attention deficits persisted after controlling for chronic pain in both the Houston et al. (2019a) and the earlier Allen et al. (2014) studies, the authors interpreted this as indication that attention dysfunction may be a central feature of the cognitive profile of CMI.

Houston and colleagues (2018b) took a unique approach by examining the divided attention capacities of CMI patients using behavioral indices and event-related neurophysiological recordings from an EEG. While EEG methods lack the spatial resolution of functional MRI methods, EEG is capable of sub-millisecond temporal precision and is able to identify component neurophysiological processes using non-invasive, scalp-based electrodes. The researchers utilized a specific type of EEG analysis in which neurophysiological activity is linked to external stimulus presentation. The resultant time-locked EEG waveforms are referred to as event-related potentials (ERPs) and can be compared across conditions and groups. The underlying physiological processes that establish ERPs have been well established based on temporal and spatial waveforms characteristics. The researchers targeted two specific waveforms, the early P1 waveform (70–170 mm post-stimulus onset) and later P3 waveform (400–600 mm post-stimulus onset). In the context of their study, the P1 waveform represents integrative visual processing and threat orienting (Dehaene and Changeux 2011; Eason et al. 1969), whereas the P3 reflects effortful cognitive control and motivational processes (Houston et al. 2018c; Krolak-Salmon et al. 2001; Rellecke et al. 2011, 2012).

In the study, participants completed two facial expression identification tasks. The first task served as a baseline and required participants to rapidly identify emotional facial expressions derived from the standardized NimStim database (Tottenham et al. 2009). The second task variant incorporated a similar facial expression identification component, but also included a preceding tone discrimination task that required a response prior to identifying the presented facial expression. The lag between the two tasks was manipulated using the psychological refractory period (PRP) paradigm, a method of assessing divided attention that is frequently used in cognitive psychology research (Pashler 1984, 1994). The PRP paradigm allows for the isolation of central processing resources, and it is generally found that response times to the second task are dependent upon the proximity of the preceding task, referred to as a lag or PRP effect (see Fig. 11.4). In individuals with deficient divided attention capabilities, the magnitude of lag effects is greater. Thus, the authors hypothesized that they would observe relatively greater lag effects in CMI patients.

Results indicated that CMI patients were slower in identifying the facial expressions compared to the matched controls in both single and dual-task conditions (i.e., a processing speed deficit). However, the magnitude of the lag effect in the dual-task variant was not different between CMI patients and controls. That is, despite slower processing speed, CMI patients did not exhibit a deficit in allocating attentional resources to identify the emotional expressions. To further explore the processing speed deficit, the authors re-analyzed their data after controlling pain and anxious-depressive symptomatology. These variables accounted for the response time difference in the dual-task variant but could not account for the processing speed deficit observed in the single-task variant. Moreover, the neurophysiological ERP analysis of the P1 and P3 ERP waveforms yielded no differences between CMI patients and controls on divided attention parameters. The second focus of Houston et al. (2018b) was to ascertain whether CMI patients also exhibited an emotion processing deficit, which is the focus of the ensuing section.

Prior to discussing evidence of pain effects on emotion dysregulation in CMI, we note one additional study provided by Lázaro and colleagues (2018) that sought to appraise verbal fluency impairments in CMI patients. The authors used a case-control design with 51 CMI patients and a control group that was approximately equivalent in age, sex, and education level. Approximately half (53%) of the CMI patients had undergone surgical intervention related to their CMI diagnosis. All participants completed the FAS Word Fluency task from the Controlled Oral Word Association Test (Ruff et al. 1996) and the Hospital Anxiety and Depression Scale, a self-report measure of anxious-depressive symptomatology (Zigmond and Snaith 1983). While the authors did not directly collect data on chronic pain symptomatology, they did include anxious-depressive symptomatology as a covariate. CMI patients exhibited deficits in both semantic and phonetic verbal fluency that could not be accounted for by anxious-depressive symptomatology. Moreover, case-control differences in the fluency measures could not be accounted for by decompression surgery status. Together, this provides indirect evidence that chronic pain, which itself is associated with both anxious-depressive symptomatology and the likelihood of undergoing Chiari decompression surgery, could not account for deficits in verbal fluency.

In sum, the data accumulated from the rigorous case-control studies to date suggest that chronic pain plays a major causal factor in the cognitive dysfunction observed by CMI patients. In particular, chronic pain appears to at least partially account for episodic memory, working memory, and processing speed deficits. However,

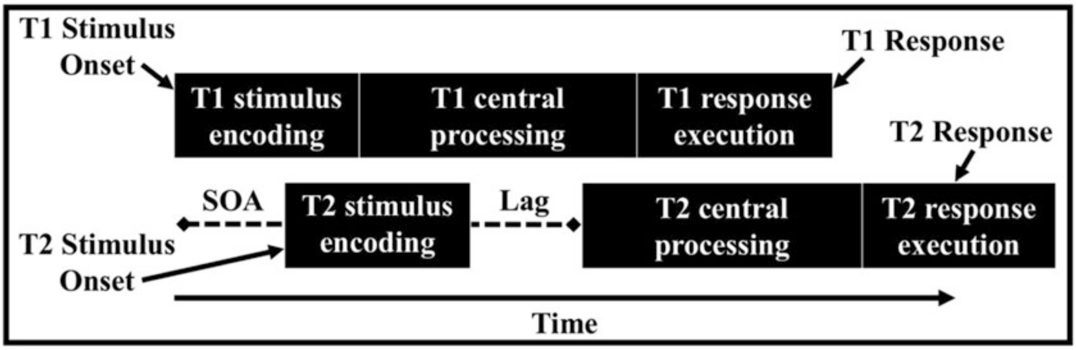

Fig. 11.4 Depiction of a single trial of the PRP paradigm as used in Houston et al. (2018b). Participant responses to the second task are generally longer when there is a shorter lag between the two tasks. T1-Task 1; T2-Task 2; SOA-stimulus onset asynchrony between the two tasks. Figure adapted from Houston et al. (2018b)

current evidence suggests that attention and executive function deficits cannot be as easily clarified by chronic pain or related anxious-depressive symptomatology. It is also unclear whether language deficits contribute to the cognitive profile of CMI. While Lázaro et al. (2018) identified fluency deficits that could not be accounted for by anxious-depressive symptomatology and García et al. (2018b) identified deficits that could not be accounted for by chronic pain or symptomatology variables, Houston et al. (2019a) failed to identify language deficits regardless of whether additional symptomatology variables were included in the analysis.

11.3 Behavioral Evidence of Pain Effects on Emotion Dysregulation

Relative to our understanding of the dynamics between pain and cognitive dysfunction in CMI, less is known regarding the relationship between the chronic pain experience of CMI patients and emotion dysregulation. For the purpose of the present review, we will reference two categories of emotion processing: (1) emotion perception/recognition and (2) emotional attributions including theory of mind/mentalizing and social cognition. Emotion recognition is generally considered to be a lower-level process and includes aspects of threat detection and other processes that are at least somewhat automatic/reflexive. By comparison, emotional attributions require the decoding of others' mental states based on observable information and comprise three overlapping abilities: the identification of emotionally relevant information in one's environment, the generation of subjective emotional experiences and one's response to the generated experiences, and the regulation of subjective emotional experiences and responses (Hoche et al. 2016; Coricelli 2005; Clausi et al. 2019; Overwalle et al. 2014). Importantly, both behavioral and neurobiological research have established these two sets of functions as distinct from one another (Oakley et al. 2016; Barbato et al. 2015; Fitzpatrick et al. 2018).

To our knowledge, there are currently four case-control studies that have investigated pain effects on emotion dysregulation in CMI, three of which also included cognitive assessments that have been previously described (Houston et al. 2018b; García et al. 2018a, b). In addition to these three, García and colleagues (2020b) contributed an additional work that specifically targeted emotion recognition and attribution capacities of CMI patients. Like their previous work, the authors relied upon a comprehensive neuropsychological assessment battery in their investigation. In a sample of 26 CMI patients and 26 sex-, age-, and education-matched controls, emotion recognition was assessed using the Facially Expressed Emotion Labelling (FEEL) Test (Kessler et al.

2002). Emotional attribution was tested using the Faux Pas test (Stone et al. 1998), Happé's Strange Stories (HSS) test (Happé 1994), and Ice-Cream Van task (Perner and Wimmer 1985). Results indicated that CMI patients performed more poorly on all measures but were particularly challenged by the three tasks requiring emotional attributions. Moreover, after controlling for self-reported anxious-depressive symptomatology, group differences in emotion recognition on the FEEL test were no longer significant. By comparison, neither self-reported chronic pain nor anxious-depressive symptomatology could account for the group differences in emotional attribution measures. The authors interpreted their findings as suggesting that CMI was associated with disruptions to the mentalizing network, while CMI-related emotion recognition deficits could be better accounted for by symptomatology variables.

As previously mentioned, the remaining studies were not primarily focused on CMI-related differences in emotion dysregulation. However, each complements the comprehensive analysis of García et al. (2020b). The most direct replications of these findings also derive from García and colleagues (2018a, b). These two studies arrived at very similar conclusions to their earlier study. CMI-related deficits in emotional attributions were identified using the HSS test in both studies and effect magnitudes were similar across decompressed and non-decompressed patients. Self-reported chronic pain and depressive symptomatology could not account for the observed deficits. In contrast, findings of CMI-related deficits in emotion recognition were less consistent. While García et al. (2018b) identified CMI-related deficits using the FEEL test and Benton Facial Recognition test (Benton et al. 1994), the effect magnitudes were approximately half the size of the emotional attribution deficits exhibited by CMI patients. Moreover, these differences could be fully accounted for by CMI-related differences in chronic pain and anxious-depressive symptomatology. Also relying upon the FEEL test, García et al. (2018a) identified small CMI-related deficits in emotion recognition for CMI patients who had undergone decompression surgery, but not those who had not undergone surgery. Once again, chronic pain and symptomatology variables could fully account for the observed differences.

Returning to the Houston et al. (2018b) EEG study, the authors had planned[2] to provide an initial investigation into potential emotion processing deficits in CMI by requiring participants to complete an emotion recognition task within the previously discussed PRP paradigm (Fig. 11.4) as well as a baseline emotion recognition task. While CMI patients did not exhibit the expected attention deficit, the authors did identify CMI-related differences in emotion recognition in the single-task, but not the PRP task variant in which happy emotional expressions elicited faster responses in controls, but not CMI patients. More importantly, distinct patterns of neurophysiological activity were identified across the groups. While CMI patients and matched controls exhibited consistency in their early perceptual responses as measured by the P1 waveform, case-control differences were identified for the P3 waveform that is believed to represent effortful control and motivational processes (see Fig. 11.5). Whereas control participants exhibited greater neurophysiological activity in response to angry emotional expressions relative to happy or neutral expressions (i.e., an expected response for normally functioning individuals (Houston et al. 2018c)), CMI patients did not exhibit distinct patterns of neurophysiological activity across angry, happy, or neutral expressions.

While not tested at the time of publication, we performed a re-analysis of this P3 data for the present chapter in which we controlled for self-reported chronic pain using ANCOVA. The re-analysis results suggest that the abnormal neurophysiological response observed in CMI patients could be fully explained by the chronic pain experiences of CMI patients. Thus, when taken in conjunction with the conclusion drawn from Houston et al. (2018b), these results suggest

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[2] Project planning for the Houston et al. (2019a, 2018b) studies began in 2014 upon the completion of Allen and colleagues' initial publication.

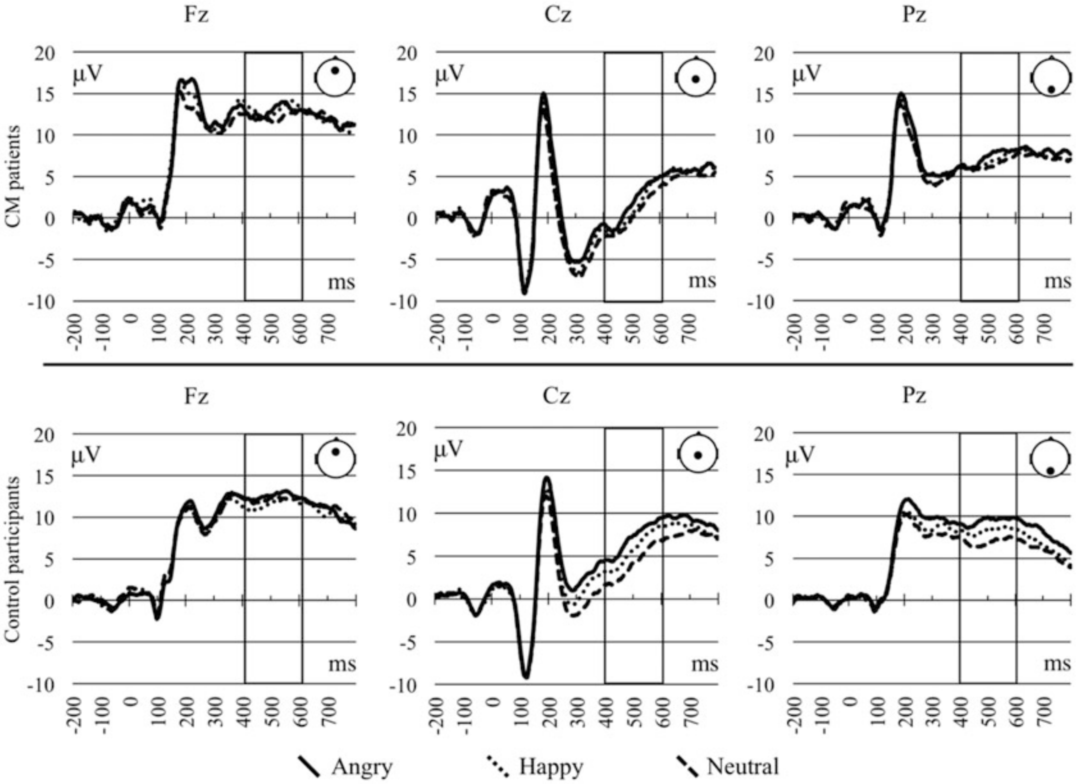


Fig. 11.5 Electroencephalogram-based P3 event-related potentials by emotion across measured channel locations for CMI and control participants in Houston et al. (2018b). Facial expression stimulus onset is represented by 0 on the x-axis. Lines represent the three emotional expression conditions derived from the NimStim database. Differences in neurophysiological responses were apparent across emotion condition in controls at both midline central (Cz) and midline parietal (Pz) channels. CMI patients did not exhibit distinct patterns of neurophysiological activity in response to the different emotional expressions at any measured channel site. μV-microvolts; ms-milliseconds. Figure adapted from Houston et al. (2018b)

that emotion recognition deficits observed in the CMI patients are due to controlled motivational processes (i.e., measurable in the P3 window), which in turn likely results from downstream effects of chronic pain.

In summarizing the evidence for CMI-related emotion dysregulation, several patterns have emerged from the nascent literature. First, there is evidence of both emotion recognition and emotional attribution deficits in CMI. Second, CMI-related emotional attribution deficits have been more reliably identified and case-control differences in emotional attribution capabilities appear to be substantially greater than emotion recognition deficits when considering effect magnitudes. Third, CMI-related emotion recognition deficits, but not emotional attribution deficits, can be best accounted for by chronic pain and anxious-depressive symptomatology. Hence, the evidence to date suggests that processes associated with forming emotional attributions, including theory of mind/mentalizing and social cognition, are part of the profile of CMI and cannot be accounted for by comorbid chronic pain and related symptomatology. These findings also indirectly speak to disruptions in the neural architecture that underlie controlled cognitive and emotion function. In the ensuing section, we review neuroscientific literature on the dynamic relationship between chronic pain and the networks underlying cognitive dysfunction and emotion dysregulation in CMI.

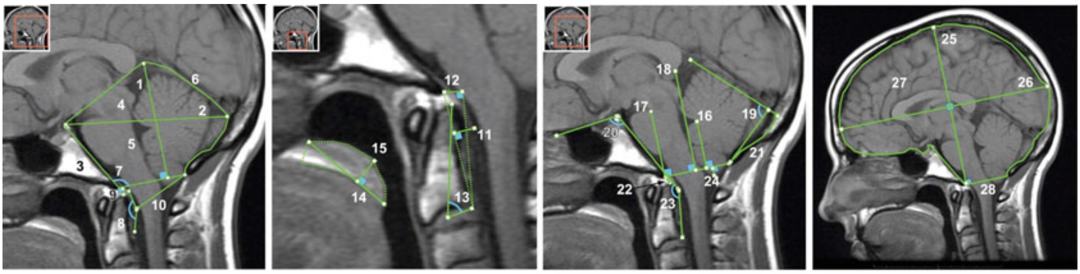
11.4 Neurobiological Foundation of Pain Effects on Cognitive Dysfunction and Emotion Dysregulation

Classically, the study of Chiari malformations can be traced to the fields of histology and, later, neuroradiology (Tubbs and Oakes 2013a, b). Largely, this work focused on establishing an understanding of the causes and the consequences of the hallmark cerebellar malformation on structures proximal to the Posterior Cranial Fossa (PCF). Through this work, it was generally assumed that the observed structural malformations to the cerebellum, along with associated disruptions to the development of midbrain and hindbrain structures, could account for the functional disturbances exhibited by patients (i.e., headache, chronic pain, motoric disturbances, numbness, brain fog, etc.), though the mechanisms were generally not empirically evaluated. This work has been influential in studying CMI specifically, with at least two dozen studies evaluating the macro-level brain morphology characteristics of the condition (Houston et al. 2018a; Sahuquillo et al. 1994; Heiss et al. 2012; Karagöz et al. 2002; Smith et al. 2013; Eppelheimer et al. 2018; Eppelheimer et al. 2019; Biswas et al. 2019; Khalsa et al. 2018). Houston et al. (2018a) summarized the findings from the structural imaging literature in indicating that CMI: (1) is associated with a reduced height of PCF structures in relation to the foramen magnum; (2) is characterized by the sharper angulation of the clivus in relation to the odontoid process; and (3) is distinguished by the retroflection of the odontoid process. Notably, in the literature, there have been few attempts to empirically identify associations between these structural abnormalities and symptom variables. For example, though unpublished in the final version of the manuscript, Houston et al. (2018a) also conducted correlational analyses between self-reported chronic pain and 29 morphometric measures on a comparatively large sample of 162 adult female CMI patients and 140 age-, sex-, and BMI-matched controls (see Fig. 11.6). There was not a single significant correlation between morphometric measures and self-reported pain in CMI patients, a finding that was later replicated in a smaller group of male CMI patients using a similar methodology (Houston et al. 2019b).

Thus, there was a long-standing gap in the CMI literature that has only recently begun to be filled by studies that are more focused on patient experience variables and symptomatology. These studies have either more explicitly analyzed the relationship between brain macrostructure and measures of patient function and symptomatology (García et al. 2020b) or utilized contemporary structural and functional imaging methods that show promise as being correlated with CMI symptomatology variables (Ibrahimy et al. 2021). Below, we review the burgeoning neuroscientific literature, emphasizing studies that sought to empirically identify the brain-based biological mechanisms that might explain the interplay between chronic pain, cognitive dysfunction, and emotional dysregulation experienced by CMI patients.

As previously mentioned, numerous studies have identified behavioral evidence of cognitive dysfunction and emotion dysregulation in CMI. Of these, several also included measures of macro-level brain morphology. For example, García et al. (2020b) measured tonsillar position in their participants in conjunction with their measures of social cognition and pain. In a secondary analysis, the authors reported on correlations between tonsillar position, headache pain, cervical spine pain, and lumbar spine pain. The authors found no significant correlations between these measures, suggesting that chronic pain was not associated with tonsillar position. Similarly, García et al. (2018b) did not identify correlations between tonsillar position, physical pain, or anxious-depressive symptomatology in a supplementary analysis of their data.

The most elaborative study that incorporated structural imaging measures comes from Houston et al. (2019a). This study, which investigated



1. Height of the posterior cranial fossa - the perpendicular distance from the most anterior portion of the tentorium to the McRae´s line.
2. Posterior cranial fossa anteroposterior diameter - a line from the top of the clivus to the internal occipital protuberance.
3. Clivus length - the distance between the dorsum sellae and the most inferior point of the clivus (basion).
4. Posterior cranial fossa area - delimited by the tentorium, the occipital bone, McRae line, and clivus.
5. Posterior cranial fossa osseous area - delimited by the occipital bone, McRae line, and the clivus.
6. Tentorium length - the distance from the most posterior aspect of the corpus callosum to the internal occipital protuberance along the dural fold.
7. Boogard angle - constituted by the clivus length and the McRae line.
8. Dural angle - the angulation of the dural reflection over the clivus, and the visualized portion overlying the dorsal aspect of the odontoid.
9. Basilar impression - the perpendicular distance from the tip of the odontoid process to McRae line.
10. Anteroposterior dura-opisthion diameter - the distance between the vertex of the dural angle and the opisthion.
11. Grabb-Oakes - measurement was defined as the perpendicular distance from a line formed by the basion to the maximum posterior-superior convexity of the odontoid to the posterior-inferior edge of the C2 vertebrae.
12. Basion to posterior axial line - the perpendicular distance from the basion to a tangential line drawn along the posterior aspect of the odontoid process.
13. Odontoid angle - formed by the top of the odontoid process, with the vertex as the midpoint between the anterior-inferior and the posterior-inferior corticated portion of the odontoid, and the posterior-inferior base of the odontoid process.
14. Soft palate length - the distance from the posterior margin of the hard palate to the tip of the uvula.
15. Soft palate thickness - the maximum thickness of the soft palate drawn perpendicular to the soft palate length.
16. Fastigium height - a perpendicular line from the fastigium of the fourth ventricle to McRae line
17. Pons height - a perpendicular line from the cephalad aspect of the pons at the mid-brain junction to McRae line.
18. Corpus callosum height - a perpendicular line from the inferior most aspect of the splenium of the corpus callosum to the McRae line.
19. Tentorium angle - formed by the tentorium and the internal occipital protuberance to the opisthion.
20. Basal angle - a line extending across the anterior cranial fossa to the tip of the dorsum sellae, and the line drawn along the posterior margin of the clivus.
21. Occipital bone length - the distance from opisthion to the internal protuberance of the occipital bone.
22. Basion-dens interval - the minimum distance from the basion to the tip of the odontoid process.
23. Wackenheim angle - formed by a line along the clivus and a line tangent to the posterior aspect of the odontoid process until the base of the C2 vertebrae.
24. Tonsillar position - the perpendicular distance between the tip of the cerebellar tonsil and the McRae line
25. Intracranial height - the maximum length of the skull perpendicular to the plane of foramen magnum.
26. Intracranial diameter - the maximum length of the skull parallel to the plane of foramen magnum.
27. Intracranial area - delimited by the outer portion of the cerebrum, the occipital portion of the occipital bone, McRae line, and the clivus connected at the dorsum sellae (excluding the sella turcica).
28. McRae line - the distance calculated from basion to opisthion.

Fig. 11.6 Common morphometric measures in the Chiari malformation literature. Figure adapted from Houston et al. (2018a), which showed no significant relationship of these measures to self-reported chronic pain

case-control differences in performance on a neuropsychological assessment battery while controlling for self-reported pain, also included 27 morphometric measures similar to those used in Houston et al. (2018a). Of the 27 included measures, only one, tonsillar position, was correlated with self-reported pain (i.e., greater pain was associated with greater tonsillar descent). The other 26 measures were not correlated with pain. The authors concluded that despite identifying a small number of significant correlations involving morphometric measures, macro-level brain structure alone is unlikely to be a source of etiological understanding of functional outcome measures such as cognitive function and chronic pain.

A recent pair of studies by García and colleagues (2021) and Ibrahimy and colleagues (2021) also stress the relationship between brain structure and self-reported chronic pain, though in a manner unique to other structural imaging studies. Utilizing data from the Chiari 1000 registry, García et al. (2021) recorded 13 midsagittal morphometric measurements within the PCF compartment, including 4 measures of CSF space anterior and posterior to the spinal cord. The authors recorded these measurements in an effort to understand the crowding of these areas that stem from CMI-related midbrain and hindbrain abnormalities and the relationship between CSF space crowding and chronological age. The authors also included self-reported chronic pain as a covariate in their analyses and discovered that not only did narrower anterior CSF space anterior to the cerebellum in the cistern area correlate with greater self-reported pain, but it also accounted for the relationship between developmental increases in self-reported pain with age. These results were particularly interesting given that a morphometric measure of CSF space had shown to be correlated with a symptom variable, whereas direct measures of cerebellar structure were not correlated with chronic pain or other symptomatology variables. Ibrahimy and colleagues (2021) expanded upon these morphometric findings through the use of patient-specific computational fluid dynamic analysis. In their study, the authors analyzed two groups of CMI patients: those that did and did not experience cough-associated headaches. CSF motion was simulated for both groups and results indicated that a measure of CSF flow restriction, integrated longitudinal impedance, better predicted cough-associated headache than tonsillar position. Thus, when considering the results from these two studies in concert with the earlier García et al. (2018b, 2020b) and Houston et al. (2019a) studies, it appears at this time that the relationship between chronic pain and macro-level brain structure can be primarily attributed to anterior CSF space dynamics. Yet, it is still unclear as to what mechanisms are driving this relationship given the limited ability of macro-level brain analyses to draw inference on neural pathway integrity and regional communication. To approach these issues, specialized imaging techniques are required. Fortunately, there have been some initial efforts, using DTI and resting-state fMRI, to further explore some of the underlying mechanisms behind CMI and associated symptoms.

Beginning in 2011 with the work of Kumar and colleagues, there has been an interest in examining how the microstructure of communication pathways between the cerebellum and cerebrum is affected by the presence of CMI (Kumar et al. 2011; Houston et al. 2020; Kurtcan et al. 2018; Krishna et al. 2016). The majority of these studies have sought to measure structural integrity of brain white matter through the use of DTI. These studies have relied upon standard measures that capitalize on the diffusion of water along axon bundles. Healthy white matter tracts consist of a coherent organization of bundled axons of similar orientation, which results in parallel diffusion of water along the axon bundles. However, in cases of axonal degeneration and/or demyelination, there is a disruption of coherent diffusion (Peters 2002). Typical microstructure parameters used to index tissue integrity are fractional anisotropy, mean diffusivity, axial diffusivity, and radial diffusivity, which have demonstrated associations with pathology and functional deficits (Beaulieu 2002; Bihan et al. 2001; Inglese and Bester 2010; Mori and Zhang 2006; Song et al. 2005). Of these studies, Houston et al. (2020) was the only one to include a measure of pain in their imaging analysis. The authors identified higher fractional anisotropy values in their sample of 18 CMI patients and 18 age-, sex-, and education-matched controls, a finding which replicated the earlier results of

Krishna et al. (2016) and Kurtcan et al. (2018), albeit in different brain regions (though see Kumar et al. 2011). Moreover, supplementary analyses in Appendices A and B of Houston et al. (2020) indicated several DTI parameters that were correlated with self-reported pain. Of note, fractional anisotropy in both left and right anterior corona radiata, right superior longitudinal fasciculus, and genu were correlated with self-reported pain (see Fig. 11.7). Similarly, measures of diffusivity in the right sagittal stratum, left superior longitudinal fasciculus, left and right anterior corona radiata, and genu were correlated with self-reported pain.

The authors interpreted their DTI findings as potentially reflecting an increase in inflammatory compression, a hypothesis previously stated by Krishna et al. (2016). However, the authors also considered a series of additional mechanisms that could have accounted for their DTI results. These mechanisms included decreases in axonal diameter, reductions in cortical volume, microscopic deficits of axonal structures, and reactive astrogliosis. Houston and colleagues (2020) noted that their findings of CMI-related neural microstructure abnormalities both proximal and distal to the cerebellum and PCF compartment suggest that CMI is a whole-brain phenomenon and not restricted to structures that are directly affected by cervico-medullary compression (Houston et al. 2020). The authors also conceded that their DTI-based analysis could only indirectly speak to CMI-related functional connectivity abnormalities between brain regions, which to directly evaluate would require measures of coherent activation between brain regions using functional MRI.

To our knowledge, there is only one published functional MRI study on CMI patients that includes measures of cognitive function, pain, and symptomatology. Houston and colleagues (2021) examined case-control differences in cerebro-cerebellar functional connectivity using resting-state fMRI (see Fig. 11.3). As with their previous studies, Houston et al. (2021) also examined the relationship between these case-control differences and measures of chronic pain and cognitive performance. The authors identified both CMI-related functional hyper connectivity and hypoconnectivity between cerebellar seed regions and cerebral destinations that were associated with both chronic pain and attention deficits exhibited by CMI patients (see Figs. 11.8 and 11.9).

Chronic pain could account for the relative hypoconnectivity exhibited by CMI patients between left cerebellar lobule III and the left inferior frontal gyrus/right Crus II as well as between the cerebellar vermis I/II and the left superior frontal gyrus. However, functional hypoconnectivity in CMI patients between the posterior cerebellar pathway and right supramarginal gyrus, as well as cerebellar vermis VII and right lingual gyrus, was not associated with chronic pain. Patterns of CMI-related functional hyperconnectivity were also associated with pain. Relative hyperconnectivity between the posterior cingulate and left parahippocampal gyrus, as well as between Crus I and the left superior frontal gyrus, were attributed to CMI-related chronic pain. By comparison, CMI-related functional hyperconnectivity between the posterior cingulate and left globus pallidus, left cerebellar lobule VIII and left postcentral gyrus, and vermis IX and precuneus was found to be independent of chronic pain.

Patterns of relative hypo- and hyperconnectivity in CMI patients were interpreted as being the result of pain drawing upon attentional resources, likely resulting in downstream deficits in cognition. Pathways of relative hypoconnectivity were also identified that were independent of pain and attention, which were posited to be the result of functional alteration of the pathway due to prolonged pain sensation. Moreover, both cortico-ponto-cerebellar and cerebello-thalamo-cortical pathways were implicated in the results interpretation. While not addressed in the study, there remains the possibility that CMI-related functional connectivity abnormalities could also reflect disruptions in the development of structures underlying the central modulation of pain during development and resulting in hyperalgesia and associated cognitive deficits (Ossipov et al. 2010; Moulton et al. 2010). However, there is some evidence to suggest against this notion. Initial evidence from our

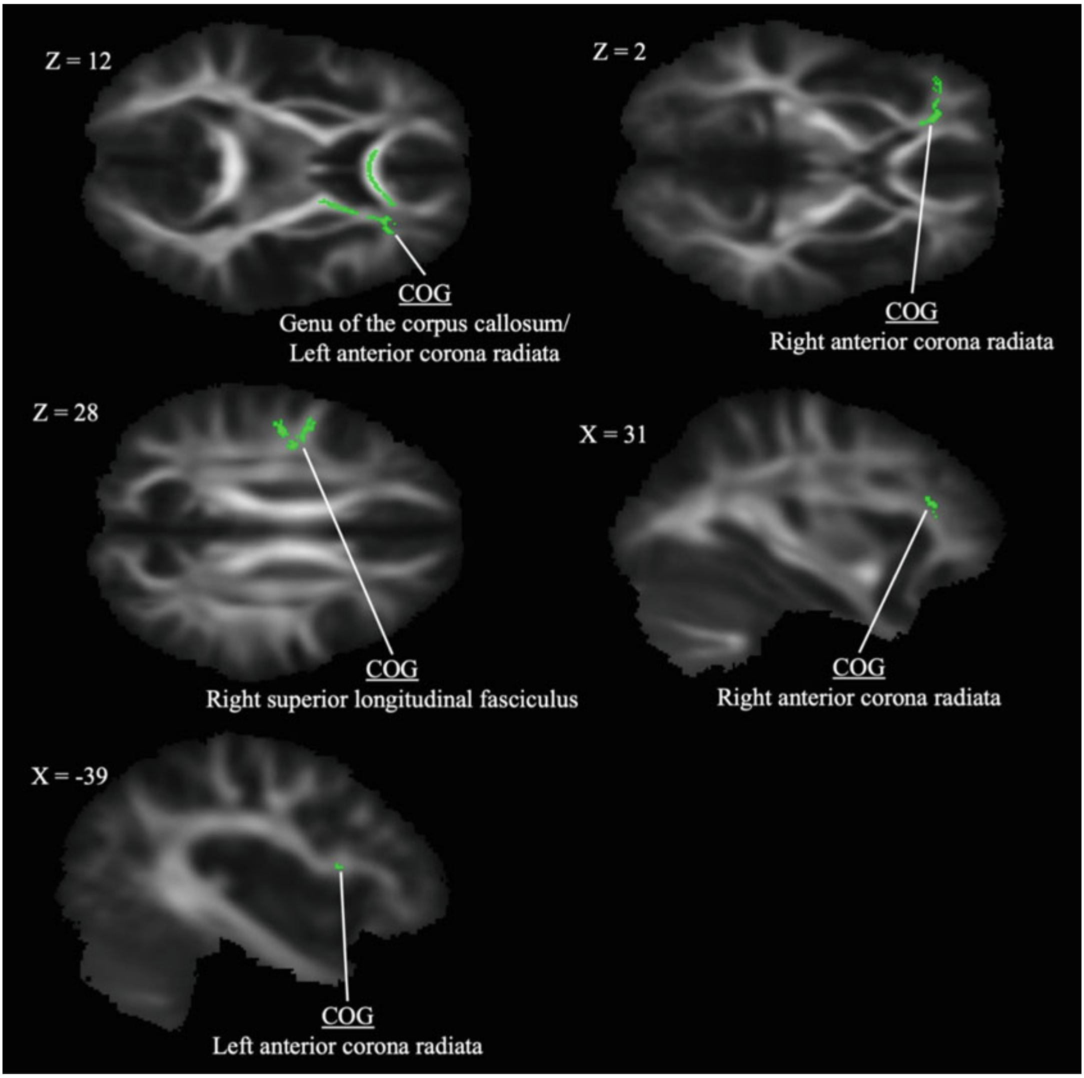


Fig. 11.7 Clusters of significant positive correlation between fractional anisotropy and self-reported pain in a sample of CMI patients and age-, sex-, and education-matched controls. Figure adapted from Houston et al. (2020)

ongoing research suggests that chronic pain is not as common a symptom in pediatric Chiari cases relative to adult-onset CMI. We also feel that the replicated finding of greater fractional anisotropy (i.e., rather than lower FA) in DTI studies better indicates reactive mechanisms akin to those observed in cerebellar lesion studies (Ruscheweyh et al. 2014).

Compared to the behavioral literature, the neuroscience literature on the dynamics between chronic pain and CMI-related cognitive dysfunction and emotion dysregulation is still in early stages. Initial findings implicate anterior CSF space compression, as well as a series of brain microstructure abnormalities and functional connectivity irregularities involving afferent and efferent pathways between the cerebellum and cerebrum, with CMI-related chronic pain. Early results also suggest that brain microstructure analyses may be the most promising sources for

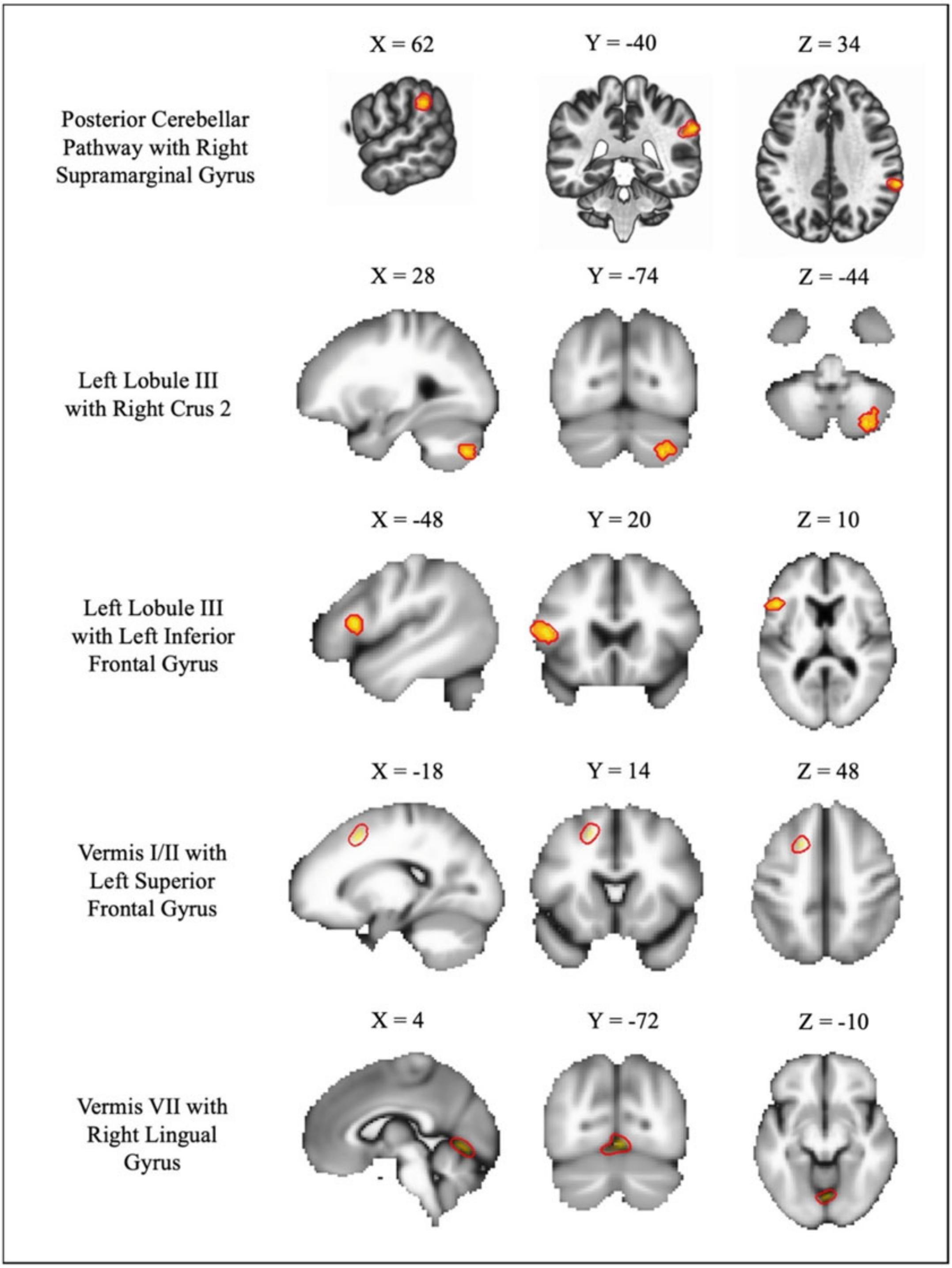


Fig. 11.8 Regions of CMI-related relative hypoconnectivity between cerebellar seeds and areas of connectivity. Figure adapted from Houston et al. (2021) and originally published under CC BY 4.0

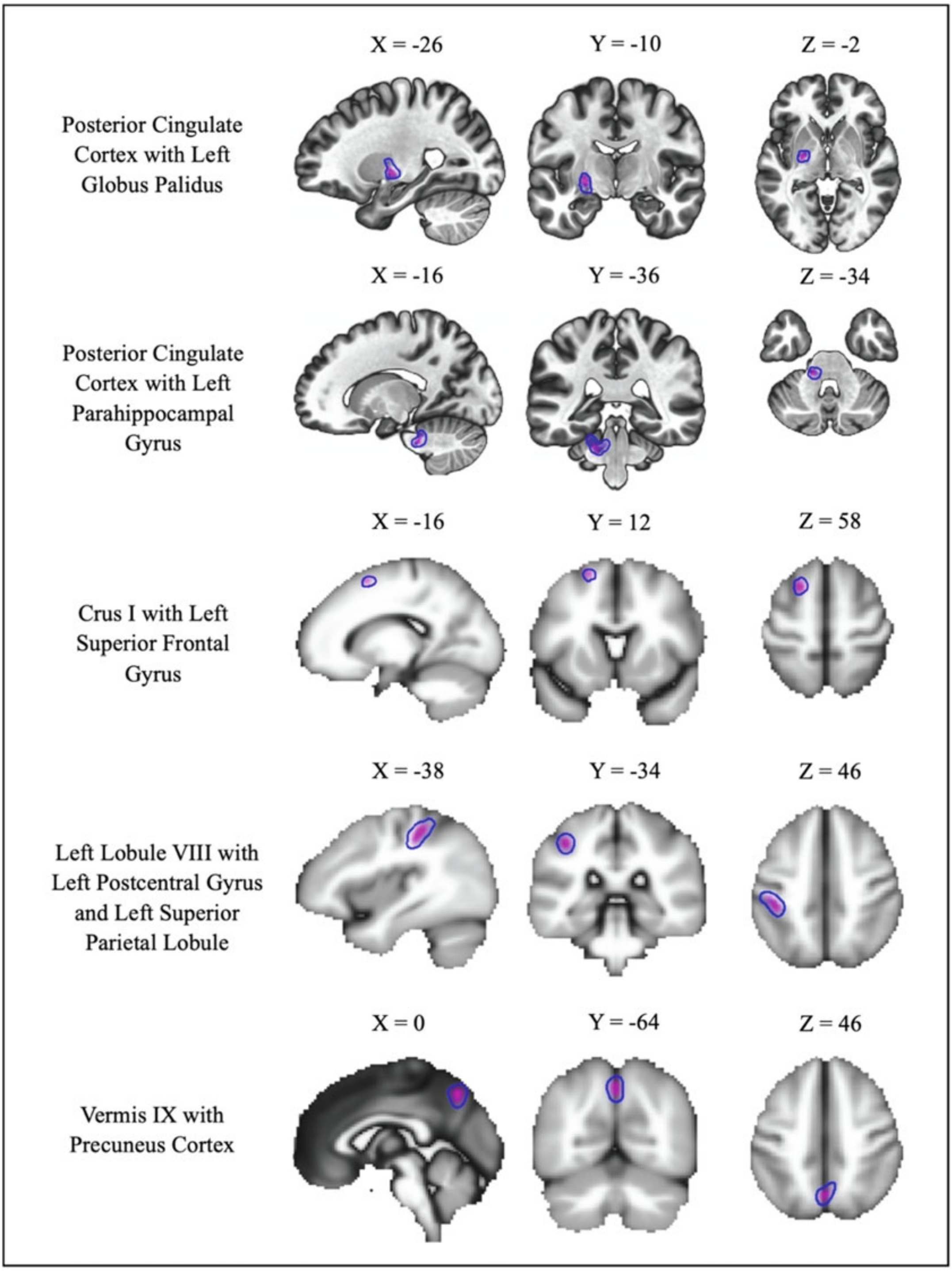


Fig. 11.9 Regions of CMI-related relative hyperconnectivity between cerebellar seeds and areas of connectivity. Figure adapted from Houston et al. (2021) and originally published under CC BY 4.0

elucidating the mechanisms behind CMI cognitive and emotion processing deficits as well as the relationship between these deficits and chronic pain. However, much of this early work is based upon few and generally small datasets of CMI patients, and replication studies are critically needed to better inform clinical care.

11.5 Clinical Considerations

Irrespective of the condition being considered, pain is a difficult construct to evaluate because of its subjective nature. That is, pain has been exceptionally difficult to objectively study because radiological evidence of structural abnormalities or damage is often not distinguishing of the patient pain experience. For example, it is not uncommon for two CMI patients presenting with similar posterior cranial fossa or cervical spine abnormalities to report meaningfully different pain severity. This has led to the use of self-report measures such as the numerical rating pain scale and the visual analog scale that link either words or graphical pictures describing pain intensity (Haefeli and Elfering 2006), as well as the revised short form of the McGill Pain Questionnaire (Dworkin et al. 2009) that includes a series of 22 describing words for pain symptoms rated on an 11-point scale. All three of these types of self-report pain scales have shown clinical utility, and the McGill Pain Questionnaire has been particularly valuable as it includes separate subscales for continuous, intermittent, neuropathic, and affective pain.

CMI patients' scores on these types of assessments along with qualitative pain reports during clinical interviews often provide a major consideration for treatment approach. Yet, it is important to remember that these static measures of pain only provide a small, fuzzy snapshot of the pain experience. As indicated by the biopsychosocial model of pain introduced earlier, many of a patient's person-environment interactions can be affected by their pain experience. When considering the longevity of the typical chronic headache and neck pain symptomatology in CMI, this likely includes thousands of patient's person-environment interactions. From deciding not to attend a child's sporting event because of the pain elicited by sitting on gymnasium stands to resigning from employment because of the physical demands they cannot meet, day-to-day decision-making processes are consistently affected across many contexts. These contexts include decision-making tied to physical and mental health, interpersonal relationship dynamics, and the capacity to work (see Fig. 11.1). It is important to remember the continuous nature of the person-environment interactions. As discussed, patients engage in reflective and ruminative processes tied to previous decisions related to their health and quality of life. Allen and colleagues (2018) provided an empirical example of these processes when they suggested that Chiari patients who have undergone decompression surgery are disappointed when they continue to experience chronic headaches and experience negative consequences to cognitive function as a result.[3] Given these considerable complexities, we encourage clinicians to take a holistic view of the pain exhibited by their CMI patients when suggesting treatment options.

There is also a potential positive aspect to the pervasiveness of chronic pain on CMI symptomatology when discussing the symptom maintenance and improvement. Given that a considerable degree of CMI-related cognitive dysfunction and emotion dysregulation can be attributed to the pain experienced by CMI patients, there leaves open the potential for interventions targeting the alleviation of pain, attenuation of pain, or pain acceptance to have a meaningful impact on the capacities of CMI patients. While the empirical work on this topic is largely lacking, there have been initial efforts to address whether pain alleviation could improve cognitive and emotion function in CMI. For example, Holmes et al. (2019) reported a case study on the use of group Acceptance and Commitment Therapy (ACT) in six middle-aged CMI

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[3] The authors speculated that this was because neuropathic pain networks underlying the central sensitization of pain are not directly targeted by decompression surgery.

patients. This treatment approach, based on relational frame theory and emphasizing mindfulness, focuses on functional contextualism. For example, a patient experiencing chronic pain might be led to better understand how their personal pain experience might negatively impact their beliefs associated with being able to live a meaningful life. The patient may then be led to learn methods to orient themselves to here-and-now experiences and prioritize aspects of their lives that they find meaningful. CMI patients participating in the case study showed self-rated improvements in pain, coping, and daily functioning based on descriptive data. Much more work is needed in this area, particularly work that empirically evaluates the relationship between psychotherapy outcomes, chronic pain, and behavioral and the neurobiological irregularities discussed previously.

Focusing specifically on the pain assessment of CMI patients, self-reports of chronic pain in CMI, particularly headache pain, can also confound CMI diagnosis. CMI patients with whom we have interacted in our lab have commonly expressed their frustrations of being previously diagnosed with conditions such as chronic migraine, fibromyalgia, or other neurologic conditions. While it is noteworthy that in many of these cases, the patients also met the diagnosis standards for these comorbid conditions (i.e., CMI with fibromyalgia, Raynaud's syndrome, etc.), it was nevertheless frustrating to the patients that the Chiari "puzzle piece" was missing from their diagnosis. In particular, patients felt disheartened that their ultimate treatment intervention, typically Chiari decompression surgery, was delayed, often for years, as a result of the missed diagnosis. Chiari awareness campaigns seek to lessen the likelihood of these patient experiences. CMI diagnosis sensitivity will also likely benefit from increased academic research interest in the cerebellum and increased clinical research interest in cerebellar conditions, though to what degree it remains to be seen.

Going beyond the challenges and potential boons presented by patient self-reports, the budding neurobiological literature that emphasizes cerebellum and posterior cranial fossa tissue strain and cerebro-cerebellar connectivity also presents the potential for more objective, or at least more predictive, measures of chronic pain. In other words, where patient self-reports of pain are highly dependent on cognitive, affective, and personality variables, neurobiological markers of pain may better predict patient pain symptomatology and treatment trajectories. In particular, we feel that imaging studies of brain microstructure and functional connectivity may provide a foundation on which to build an understanding of neurobiological markers of CMI-related pain (Houston et al. 2020, 2021). If the research in these areas were to be better clarified, one could imagine the benefits of providing individualized treatment suggestions based on a patient's specific neurobiological profile.

One final clinical consideration for which there is largely a void of evidence is how the cognitive dysfunction and emotion dysregulation in CMI is associated with other cerebellar conditions, namely Cerebellar Cognitive Affective Syndrome (CCAS), also known as Schmahmann's Syndrome (Schmahmann and Sherman 1998; Manto and Mariën 2015; Hoche et al. 2018). For example, many of the disruptions in cognitive and emotion function identified in the CMI literature would be consistent with CCAS. Similarly, both cortico-ponto-cerebellar and cerebello-thalamo-cortical pathways have been indicated in each condition. Future CMI studies would benefit from the inclusion of the relatively new CCAS scale (Hoche et al. 2018) and ideally include a comparison CCAS sample without CMI. Studies incorporating this design could not only better clarify the underlying etiology behind CMI-related deficits through the much more expansively studied CCAS framework but also provide additional understanding of the influence of pain on the neurobiological networks underlying the deficits in both conditions.

11.6 Conclusion

It is clear that CMI is characterized by the disruption of cognitive function and emotion regulation. Current evidence implicates deficits in attention and executive function, along with deficits in forming emotional attributions as being central to CMI presentation. Moreover, CMI-related chronic pain has been demonstrated to divert resources away from effortful cognitive and affective processes, leading to disruptions in episodic memory, working memory, processing speed, and emotion recognition. Initial evidence attributes these deficits to disruptions in CSF flow dynamics in the anterior-posterior cranial fossa and abnormalities in the afferent and efferent pathways associated with cerebro-cerebellar communication. Advancements in pain assessment and treatment will be critical to improving patient outcomes and understanding the underlying etiology behind CMI-related disruption in cognitive and emotion function due to pain.

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Cerebellum and Emotion in Morality

12

Hyemin Han

Abstract

In this chapter, I examined the relationship between the cerebellum, emotion, and morality with evidence from large-scale neuroimaging data analysis. Although the aforementioned relationship has not been well studied in neuroscience, recent studies have shown that the cerebellum is closely associated with emotional and social processes at the neural level. Also, debates in the field of moral philosophy, psychology, and neuroscience have supported the importance of emotion in moral functioning. Thus, I explored the potentially important but less-studied topic with NeuroSynth, a tool for large-scale brain image analysis, while addressing issues associated with reverse inference. The result from analysis demonstrated that brain regions in the cerebellum, the right Crus I and Crus II in particular, were specifically associated with morality in general. I discussed the potential implications of the finding based on clinical and functional neuroimaging studies of the cerebellum, emotional functioning, and neural networks for diverse psychological processes.

Keywords

Morality · Emotion · fMRI · Reverse inference · Bayesian inference · Meta-analysis · NeuroSynth · Cerebellum · Default mode network · Executive network

In this chapter, I intend to examine the association between the cerebellum and moral functioning, particularly emotional aspects in morality, that has not been well studied in the fields. So far, findings from studies in neuroscience have provided scholars with additional evidence regarding how human morality is functioning at the neural level (Han et al. 2019). However, the majority of them have paid attention to regions in the cerebrum instead of those in the cerebellum (Demirtas-Tatlidede and Schmahmann 2013). Given emotion plays important roles in human morality (Prinz 2006; Han 2014) and recent works in neuroscience support the close association between the cerebellum and emotion (Adamaszek et al. 2017), the relationship between the cerebellum, emotion, and morality is worth careful consideration.

Hence, to address the aforementioned gap in the literature, in this chapter, I will briefly overview the historical and theoretical backgrounds related to neuroscience of morality and explore the association between cerebellum and emotion in morality based on large-scale neuroimaging data analysis. First, I will start with overviewing the history of debates regarding the roles of

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reasoning and emotion in morality to provide background information about why studying emotion is important in moral psychology (Rest et al. 1999; Prinz 2006; Han 2014). Second, recent research on the role of the cerebellum in emotional and social processes (Adamaszek et al. 2017) will be reviewed to elaborate the point why exploring the relationship between the cerebellum, emotion, and morality will be able to provide useful insights to better understand human moral functioning. Third, large-scale brain image analysis, NeuroSynth (Yarkoni 2011; Yarkoni et al. 2011), will be introduced as a way to explore the neural correlates of morality in the cerebellum. To examine its methodological strengths in neuroimaging data exploration, I will also briefly discuss limitations associated with reverse inference in the current functional neuroimaging methods (Glymour and Hanson 2016) as well. Finally, I will discuss the potential implications of the finding from the large-scale analysis and directions for future research on morality.

12.1 Historical Backgrounds about Debates on Reasoning, Emotion, and Moral Functioning

There have been continuous debates on which psychological functionality (e.g., moral reasoning or moral emotion) constitutes the basis of morality (Kauppinen 2013; Birondo 2017). Such debates have been across different fields that are interested in morality, including but not limited to moral philosophy, psychology, and neuroscience (Prinz 2006; Han 2014), since the ancient era (Parry and Thorsrud 2021). In the modern era, moral psychology concerning about the mechanism of human moral functioning has attempted to answer the aforementioned question based on empirical evidence (Doris et al. 2020). When the cognitive revolution, which significantly contributed to forming the basis of modern psychology and neuroscience (Miller 2003), occurred, the majority of psychologists interested in morality focused on cognitive aspects of morality, particularly those associated with moral reasoning. For instance, Jean Piaget, who proposed the model of moral development among children and was one of psychologists who inspired the cognitive revolution, delved into how moral reasoning, particularly reasoning about rules and authorities, develops among children (Piaget 1948). Moreover, Kohlberg (1981) examined more sophisticated forms of moral reasoning and deliberation. He underscored the role of reasoning in moral functioning and proposed the developmental model of moral reasoning based on large-scale interview data (Kohlberg 1984). According to his model, people make moral judgment based on reasoning, particularly reasoning about why a behavioral decision that they make is deemed to be morally appropriate (Kohlberg 1975). Researchers who were inspired by these theoretical models have examined the relationship between moral reasoning and behavior, which is considered as the ultimate outcome of moral functioning (Kohlberg and Hersh 1977; Ketefian 1981).

However, there have been criticisms on the models of moral functioning focusing on the role of moral reasoning (Han 2014). The most fundamental critique is that the result of moral reasoning per se does not necessarily result in moral motivation, and finally, actual moral behavior (Hoffman 1979; Blasi 1980). The gappiness issue (Darnell et al. 2019) regarding the gap between moral reasoning and behavior has motivated scholars to seriously reconsider psychological processes other than reasoning, emotional processes in particular, to better explain the mechanism of moral behavior. Even Neo-Kohlbergians (Rest et al. 1999), who updated the classical Kohlbergian model, have acknowledged the necessity of additional psychological processes in their conceptual model of moral functioning. To address the gappiness issue, they added moral sensitivity, motivation, and character, which are based on affective and motivational processes, to their four components model (Bebeau 2002; Walker 2002). The Neo-Kohlbergians acknowledged the importance of emotional aspects of morality (e.g., empathy) although the classical Kohlbergian model was mainly based on moral reasoning.

As briefly overviewed, the majority of scholars who were interested in morality have eventually endorsed the importance and value of emotional processes in moral functioning. Even moral psychologists who initially underscored the roles of reasoning in morality now attempt to embrace psychological components that are not within the realm of reasoning, emotional components, in explaining moral functioning as shown in the case of Neo-Kohlbergians. To better understand the context regarding how the scholars ended up with acknowledging the necessity of emotion in morality, in the following section, I will review philosophical, psychological, and neuroscientific works that support the viewpoint.

12.2 Philosophical, Psychological, and Neuroscience Works Supporting the Roles of Emotion in Morality

Recent works in the fields of philosophy, psychology, and neuroscience of morality may suggest that it would be impossible to completely reject the role of emotion (or sentiment) in moral functioning in general (Haidt 2003; Moll et al. 2003; Prinz 2006). For instance, philosophers who support moral sentimentalism, particularly those who propose a strong form of sentimentalism, argue that emotion plays fundamental roles in moral functioning, including moral judgment, which has been regarded within the realm of deliberation and reasoning (Prinz 2006). Furthermore, motivational externalists, who argue that either reasoning or emotion per se is not sufficient to generate motivation, such as a group of virtue ethicists, also acknowledge the importance of emotion in moral functioning, particularly production of moral motivation and action (Shafer-Landau 2000; Kristjánsson 2012). Although some moderate motivational externalists do not endorse the strong form of sentimentalism that asserts that moral emotion is a sufficient requirement for moral judgment (Kristjánsson 2012), they acknowledge the point that psychological components other than reasoning, particularly emotions relevant to morality, are required for moral motivation and behavior (Han 2016). These philosophical accounts by moral sentimentalists and motivational externalists propose that emotion should be considered as a necessary component in moral functioning (Kristjánsson 2007, 2012; Han 2014).

Findings from studies in psychology and neuroscience also support the aforementioned philosophical viewpoint. We may start with briefly overviewing the classical case of Phineas Gage (Damasio 2006). When Gage got an injury in his ventromedial prefrontal cortex, his general cognitive abilities, such as arithmetic calculation, were not impacted by the injury. However, his emotional abilities started malfunctioning. Although he was able to make formal judgments within social and moral contexts properly, he became antimoral and antisocial in terms of his behavior. More recent studies that examined patients with brain lesions in the prefrontal areas reported findings that were consistent with the classical case. Saver and Damasio (1991) reported that patients who had lesions in their prefrontal regions showed problems in social and moral behavior even if their abilities of moral judgment and reasoning were not significantly different compared with ordinary people in many instances. In fact, neuroimaging studies have demonstrated that these regions, including the ventromedial prefrontal cortex and orbitofrontal cortex, play fundamental roles in emotional generation and regulation (Moll et al. 2001, 2002). Hence, as proposed by motivational externalists, these classical and recent studies that examined patients with prefrontal lesions may support that emotional processes are inseparable from moral functioning, particularly generation of moral motivation and behavior at the neural level.

The aforementioned accounts and findings in the fields of moral philosophy, psychology, and neuroscience may unequivocally support the point that emotion is essential in moral functioning even if it could not be considered as a sufficient component and the argument made by philosophers who supported the strong form of moral sentimentalism is not the case (Prinz 2006; Kristjánsson 2007; Han 2014). The lack of abilities to generate and regulate emotions is found to cause motivational and behavioral issues in the domain of morality even if they do not necessarily be associated with problems in moral reasoning as shown in the previous studies (Saver and Damasio 1991; Damasio 1994). Based on these empirical works supporting the necessity of emotion in morality, in the next section, I will overview the relationship between the cerebellum, emotion, and moral functioning that has been relatively less studied in previous research in neuroscience (Demirtas-Tatlidede and Schmahmann 2013).

12.3 Association between the Cerebellum and Moral Functioning in Previous Studies

One point to note in a relation with research on the cerebellum, which is the main topic of this edited volume, is that until recently, only few neuroscientists have seriously considered and examined the association between morality and the cerebellum (Demirtas-Tatlidede and Schmahmann 2013). So far, in the majority of the previous studies related to the aforementioned topics, researchers have paid attention to regions in the cerebrum (Adamaszek et al. 2017). Even if Greene et al.'s (2001, 2004) foundational studies have significantly impacted the field by demonstrating the importance of both cognitive and affective processes in moral functioning, they were mainly concerned about activity in cerebral regions, particularly the prefrontal cortex and inferior parietal lobule. Similarly, almost all of the philosophical, psychological, and neuroscientific works introduced above to substantiate the necessity of emotion in moral functioning have also examined lesions and activity in cerebral regions.

However, recent works examining activity in cerebellar regions associated with emotional, social, and moral psychological processes suggest that we need to pay attention to the cerebellum (Demirtas-Tatlidede and Schmahmann 2013). Neuroscientific studies focusing on the cerebellum, particularly those examined patients with localized lesions in cerebellar regions presented evidence supporting the importance of the cerebellum in emotional, social, and moral functioning (Adamaszek et al. 2017). Related to emotion, social, and moral functioning, which are our main interest, for instance, one clinical study demonstrated that lesions in the cerebellum were significantly associated with the decreased intensity of experienced pleasure in response to happiness-evoking stimulations (Turner et al. 2007). Furthermore, lesions in cerebellar regions caused problems in emotional regulation and social behavior across different clinical cases (Schmahmann et al. 2007).

Also, recent functional neuroimaging studies have also reported significant activity in regions in the cerebellum in task conditions related to emotion, social, and moral functioning. For example, several previous studies demonstrated the connectivity between the cerebellum and other brain regions in the default mode network, such as the precuneus and medial prefrontal cortex (Habas et al. 2009; Tang et al. 2013); this brain circuitry has been found to be closely correlated with various social and moral functioning (Sevinc and Spreng 2014; Boccia et al. 2016; Garrigan et al. 2016; Han 2017; Eres et al. 2017). Although Han et al. (2016) did not specifically focus on activity in the cerebellum in their fMRI study, they found significant interactions between cerebellar regions and regions in the medial prefrontal cortex and posterior cingulate cortex in moral dilemma resolution.

Several meta-analyses of related previous fMRI studies also support the aforementioned point. In general, Keren-Happuch et al.'s (2014) meta-analysis demonstrated that across different fMRI studies, diverse cerebellar regions showed common activity in different domains of psychological processes, i.e., emotion, executive functioning, language, music, timing, and working memory. Furthermore, in the cases of psychological processes related to higher order social cognition, Van Overwalle et al.'s (2014) meta-analysis reported that mirroring and mentalizing, which are required for perspective taking and moral cognition (Harenski et al.

2012a), are significantly associated with activity in wide range of regions in the cerebellum. Given the results from the meta-analyses, it is obvious that activity in the cerebellum is significantly associated with diverse cognitive and affective processes, including those that are inseparable from moral functioning (Demirtas-Tatlidede and Schmahmann 2013; Adamaszek et al. 2017), such as emotion, executive functioning, and mentalizing (Harenski et al. 2012b; Han 2014; Barrasso-Catanzaro and Eslinger 2016), and such associations are well supported by accumulated neuroimaging evidence.

These previous works focusing on the associations between emotion, social and moral functioning, and the cerebellum, including clinical studies, neuroimaging studies, and meta-analyses, suggest that we need to acknowledge the roles of the cerebellum in the aforementioned domains. Although previous philosophical, psychological, and neuroscientific works about morality have primarily focused on the cerebrum, it would be time to start looking at the relatively less examined realm, the cerebellum, to better understand moral functioning, which requires the cooperation between emotion and reasoning.

12.4 How to Examine the Association between Moral Functioning and the Cerebellum in the Current Chapter

Although previous neuroimaging studies have provided evidence supporting the association between the cerebellum and psychological processes related to emotion and social and moral functioning, we need to consider methodological issues associated with reverse inference in the previous studies (Poldrack 2008, 2011). Researchers have been concerned about the issues related to reverse inference while associating a specific functionality of interest and activity in a brain region of interest. According to concerns regarding naïve reverse inference, because multiple, not one, psychological and behavioral functions are associated with one brain region, finding significant activity in a certain brain region in a certain task condition could not be a sufficient condition to map the brain region to the task condition (Ramsey et al. 2010; Glymour and Hanson 2016). This can also be problematic in our endeavor to examine the role of the cerebellum in moral functioning. Even if previous neuroimaging studies have found significant activity in the cerebellum in moral task conditions, such results do not necessarily mean that the cerebellar regions that showed significant activity specifically play roles in moral functioning.

Thus, to better examine cerebellar regions that are specifically associated with morality, we need to consider how to address the issues associated with reverse inference. As a possible solution, I intend to examine the neural correlates of moral functioning, particularly those in the cerebellum, with large-scale brain image analysis (Yarkoni et al. 2011). To consider why large-scale brain image data analysis can be a possible way to address problems associated with reverse inference, first, I will briefly discuss what are the problems and why the problems make difficult to interpret findings from neuroimaging studies (Poldrack 2008; Ramsey et al. 2010; Glymour and Hanson 2016). Then, I will examine why large-scale analysis can be a potential solution and describe how to perform the analysis (Yarkoni et al. 2011; Poldrack 2011). Based on the aforementioned conceptual and methodological discussions, I intend to demonstrate regions in the cerebellum that are specifically associated with moral functioning with large-scale analysis and discuss the implications of the result. Finally, I plan to suggest several ideas for future research on the relationship between the cerebellum and morality.

12.5 Reverse Inference in Neuroimaging Studies: Issues and Potential Solutions

Neuroscientists have primarily been interested in identifying brain regions or circuitries associated with a psychological or behavioral functionality of interest in their neuroimaging studies. For instance, in the case of fMRI studies focusing on morality, scholars attempt to examine which brain regions or circuitries are significantly associated with the task conditions, moral functioning task conditions (Moll et al. 2003; Han 2016). In the most cases, they compare neural activity in the moral task conditions and that in the control or resting condition to identify which regions show relatively greater activity in the moral task conditions (Friston et al. 1998). Even if several regions are identified to show greater activity through these procedures, it is not possible to argue that the regions are specifically associated with morality without any reservation due to the issue associated with reverse inference (Glymour and Hanson 2016). Because one brain region is associated with multiple functionalities, it is impossible to exactly map a specific functionality of interest to a specific brain region even if the region showed significant activity in a task condition of interest (Poldrack 2008).

Why naïve reverse inference could be problematic in interpreting results from neuroimaging studies, particularly matching identified neural activity to a specific psychological or behavioral functionality of interest, can be explained from Bayesian perspective (Poldrack 2011; Han and Park 2018). As I mentioned, scholars are primarily interested in $P(H|D)$, the likelihood that a specific functionality of interest is associated with a specific region (H) given observed neural activity in the region (D) (Han and Park 2018). However, what we can actually learn from a neuroimaging study is $P(D|H)$, the likelihood to discover a certain pattern of neural activity in a region (D) when a functionality of interest that is tested (H) (Glymour and Hanson 2016). This is the case because in most neuroimaging studies, scholars acquire data about neural activity while participants are engaging in one or a limited number of specific psychological or behavioral tasks. Thus, if we try mapping functionalities of interest to brain regions solely based on observed neural activity patterns from a neuroimaging study, we conflate $P(D|H)$, which can actually be estimated from the study, with $P(H|D)$, our primary interest (Han and Park 2018; Han et al. 2018). Without any further data, only with observed experimental outcomes, $P(D|H)$, we cannot properly examine the specific neural correlates of the functionality of interest, $P(H|D)$. In other words, a naïve trial to reversely infer $P(H|D)$ from $P(D|H)$ with limited data is highly likely to commit a fallacy.

A possible way to address this issue and properly estimate $P(H|D)$ that we are primarily interested in is analyzing large-scale neuroimaging data (Yarkoni et al. 2011). From Bayes Theorem, we can learn about why this can be a potential solution of the issue. According to Bayes Theorem, $P(H|D)$ is estimated as follows (Wagenmakers et al. 2018):

$$\begin{aligned} P(H|D) &= \frac{P(D|H)P(H)}{P(D)} \\ &= \frac{P(D|H)P(H)}{P(D|H)P(H) + P\left(D|\overline{H}\right)P\left(\overline{H}\right)} \end{aligned}$$

In the case of neuroimaging studies, as I described, $P(D|H)$ is the pattern of neural activity (D) in a presented task condition (H) that can be actually acquired from the studies. Now, from the equation, we can see additional terms are introduced. $P(H)$ indicates the prior probability of whether a functionality is the case that we assume before observing neural activity. $P(D)$ indicates the baseline of neural activity in general, which is observed across all different functionalities or task conditions. As expanded above, $P(D)$ can be estimated with $P(D|H)P(H)$ and $P\left(D|\overline{H}\right)P\left(\overline{H}\right)$. Although $P(D|H)$ is estimable from one or a limited number of neuroimaging studies, we cannot easily estimate $P\left(D|\overline{H}\right)$ because $P\left(D|\overline{H}\right)$ means the likelihood to observe neural activity in a specific region (D) when functionalities other than the functionality of our interest to be tested in our neuroimaging study $\left(\overline{H}\right)$ are tested. To acquire the information, neural activity associated with all psychological and behavioral functionalities should be examined (Poldrack 2008).

As an effort to address the difficulty, Poldrack (2011) explored a possible way to implement the aforementioned mechanism to estimate $P(H|D)$. In his study, he intended to examine the neural correlates of linguistic functioning.

Unfortunately, one practical difficulty that should be addressed during the process was that acquiring the complete information about $P\left(D|\overline{H}\right)$ is practically impossible, because doing so requires examining neural activity associated with all functionalities and task conditions. Thus, as a way to approximate $P\left(D|\overline{H}\right)$, Poldrack (2011) estimated the baseline neural activity in previous fMRI studies by exploring BrainMap database (Fox and Lancaster 2002; Fox et al. 2005; Laird et al. 2005). With the acquired baseline information, he estimated $P(D|H)$, neural activity specifically associated with linguistic functioning. Although their estimation was based on information acquired from a limited number of previous studies via BrainMap, there is one major takeaway from their study that can inform scholars who intend to examine $P(H|D)$: utilization of large-scale neuroimaging database can provide a practical solution to estimate baseline neural activity, which is essential in addressing issues related to reverse inference.

At this point, NeuroSynth can be considered as a practical solution to implement the aforementioned technical idea and gather information about the ontology of a functionality of interest (Yarkoni 2011). When Poldrack (2011) conducted the reverse inference study, he had to gather neuroimaging data by manually exploring BrainMap. However, NeuroSynth automatically crawls activation information from published articles and associates the activity information with corresponding task condition information (Yarkoni et al. 2011). As a result, as of February 28, 2021, NeuroSynth database includes 507,891 activation foci reported in 14,371 studies, and 1335 task condition keywords associated with activity information. Based on the large-scale database, NeuroSynth can automatically generate a brain map presenting $P(H|D)$, once a user specifies the keyword of a functionality of interest to be analyzed. The resultant $P(H|D)$ map demonstrates voxels reporting significant activity associated with a functionality of interest when the baseline activity across all task conditions stored in the database is controlled. Hence, given the size of its neuroimaging database and user-friendly interface for analysis map generation, NeuroSynth would be a viable solution to infer $P(H|D)$. Due to the aforementioned benefits, I also employed NeuroSynth to examine the neural correlates of morality in examination of their association with the cerebellum.

12.6 Result of NeuroSynth Analysis

I generated a $P(H|D)$ map with a keyword, “moral,” with NeuroSynth to examine the neural correlates of morality. Overall, the map generation procedures were identical to what Han (2020) did in their examination of the neural circuitry of moral functioning. To generate the map, I selected a keyword “moral,” which was pre-registered in NeuroSynth (see https://neurosynth.org/analyses/terms/moral/ for further details). Once the keyword was selected, NeuroSynth extracted activation information from 87 studies associated with the keyword, “moral.” A total of 2806 activation foci were extracted. Then, NeuroSynth estimated $P(H|D)$ of “moral” with the extracted activation information and the baseline activity information with the whole database. The estimated $P(H|D)$ map was thresholded at $p < 0.01$ (false discovery rate corrected). Figure 12.1 shows the resultant thresholded $P(H|D)$ map of “moral.” Not surprisingly, the result demonstrates that cerebral regions in the medial prefrontal cortex, orbitofrontal cortex, anterior and cingulate cortex, precuneus, and temporoparietal junction showed significant activity in moral-related task conditions after controlling for the baseline activity. This result is consistent with findings from previous fMRI studies that focused on various moral functionalities and reported significant activity in the default mode network and cortical midline structures (see Bzdok et al. 2012; Sevinc and Spreng 2014; Boccia et al. 2016; Garrigan et al. 2016; Han 2017; Eres et al. 2017 for meta-analyses).

Interestingly, I was able to find a cluster of significant voxels in the cerebellum from the resultant $P(H|D)$ map, which was produced after

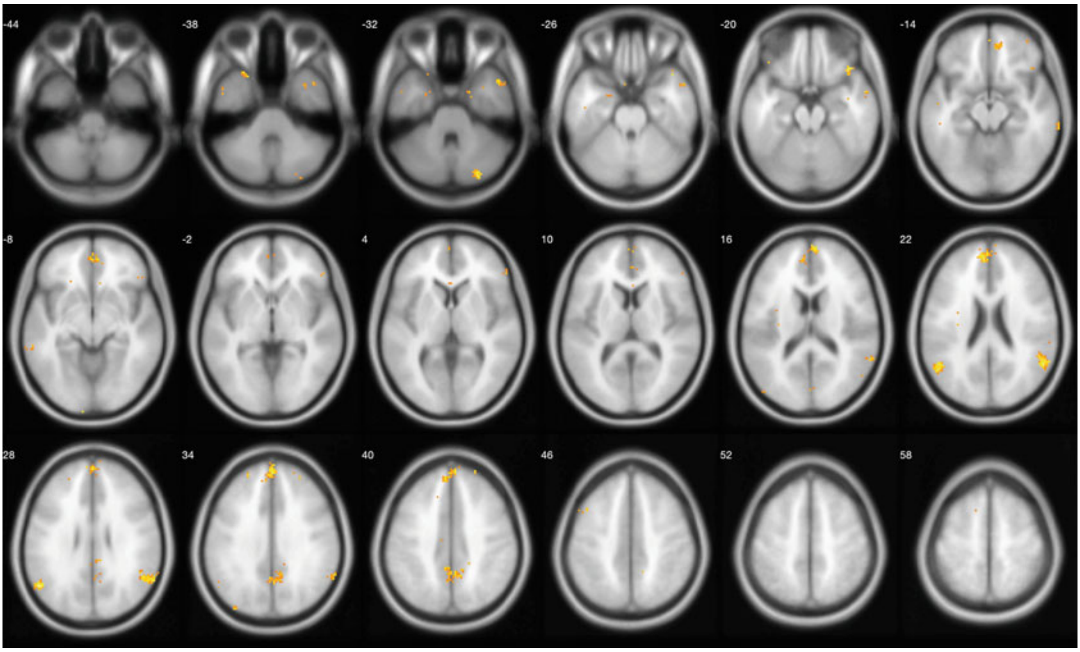

Fig. 12.1 Brain regions reported significant activity when a keyword, "moral," was selected on NeuroSynth. Note: All significant voxels were thresholded at $p < 0.01$ (false discovery rate corrected). The slice view was generated with XjView (Cui et al. 2015)

controlling for the baseline neural activity (see Fig. 12.2). There were 56 voxels (56 voxels × 8 mm^3/voxel = 448 mm^3) that showed significant activity in "moral" in the right Crus I and Crus II. This cluster was the only cluster that showed significant activity in the whole cerebellar region.

12.7 Considering the Relationship between Moral Functioning and the Cerebellum with Neuroscientific Evidence

In my NeuroSynth analysis, I found that the cerebellar regions in the right Crus I and Crus II reported significant activity in moral task conditions. One point that is worth consideration is that both the right Crus I and Crus II reported significant association with emotional functioning in previous studies focusing on the cerebellum, and social and emotional neuroscience. We may start with revisiting the meta-analyses of fMRI studies that introduced previously to have more ideas about the association between the right Crus I and Crus II and emotional processes. According to Keren-Happuch et al. (2014), the right Crus I reported significant activity in emotion-related task conditions across different studies. A consensus paper based on a wide literature review also presented that the right Crus I and Crus II were significantly associated with the perception of emotion as well as emotional evaluation and regulation based on evidence from clinical and functional neuroimaging studies (Adamaszek et al. 2017). Given these, the Crus I and Crus II seem to be cerebellar regions that are particularly associated with diverse emotional processes. Hence, the findings from my NeuroSynth analysis and the aforementioned previous studies of the cerebellum and emotion may support the arguments made by a group of moral philosophers, psychologists, and neuroscientists that emotion should be

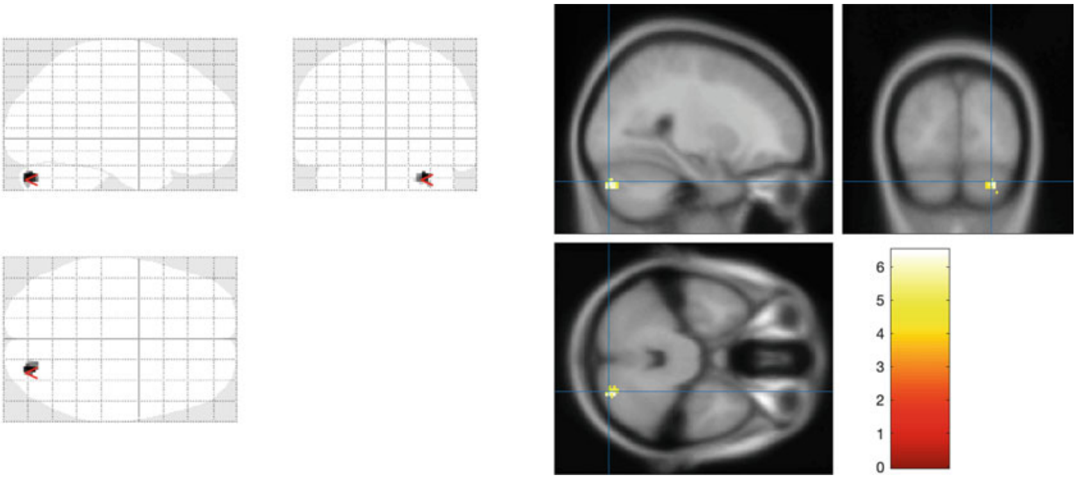

Fig. 12.2 A cluster in the cerebellum showed significant activity when a keyword, "moral," was selected on NeuroSynth. Note: Peak MNI coordinate: (26 -84 -32). All significant voxels were thresholded at $p < 0.01$ (false discovery rate corrected). The image was generated with XjView (Cui et al. 2015)

considered as a fundamental part of morality (Damasio 1994; Prinz 2006; Moll and de Oliveira-Souza 2007).

One interesting point regarding the aforementioned activity in the Crus areas is the laterality of the activity. My NeuroSynth result regarding the neural correlates of morality revealed that only the right Crus, not the left Crus, reported significant common activity. However, bilateral Crus activity was reported in the previous meta-analyses (Keren-Happuch et al. 2014; Adamaszek et al. 2017). One possible explanation about the difference regarding the laterality of activity is that the functionalities of interest that were examined were different across different meta-analyses. In the case of my NeuroSynth meta-analysis, I particularly focused on "morality." On the other hand, the previous meta-analyses were primarily interested in "emotion" in general. Thus, my analysis perhaps reported more focused unilateral activity in the right Crus due to the specificity of its functionality of interest. The unilateral activity in the right Crus associated with morality can also be supported by a recent ROI-based meta-analysis. Van Overwalle et al. (2020) reported that only the ROI in the right Crus, not the left Crus, partially predicted activity associated with moral functioning. Future studies may need to examine the laterality of the Crus activity in moral functioning to clarify this point with additional evidence.

However, even if that is the case, it is obvious that brain regions other than Crus I and Crus II, e.g., the amygdala, insula, ventromedial prefrontal and orbitofrontal cortices, and other regions in the cerebrum, are also found to be associated with moral emotion (Moll et al. 2002; Decety et al. 2012; Raine 2019; Han 2020). In addition, there was a previous study that demonstrated the significant interaction between the cerebellar and cerebral regions in moral task conditions (Han et al. 2016). These points suggest that exclusively associating moral emotion with the cerebellum could not be convincing. Hence, it would be necessary to examine how the cerebrum and cerebellum are connected and interacting with each other instead of exclusively focusing on the cerebellar regions in understanding the big picture of emotional processes and morality at the neural level.

Several neuroimaging studies have reported that the Crus I and Crus II are functionally connected with other brain circuitries associated with moral functioning (Habas et al. 2009; Tang et al. 2013; Van Overwalle et al. 2014), particularly the default mode network and executive network (Chiong et al. 2013; Han et al. 2016; Han 2017). As previously introduced, Han et al. (2016) reported the significant interaction between the cerebellar regions including the right Crus I and Crus II and the default mode network regions, the medial prefrontal cortex and posterior cingulate cortex in particular, in moral dilemma conditions. The aforementioned right cerebellar regions showed the stronger interaction when emotionally provocative dilemmas were presented versus when less provocative dilemmas were presented (Greene et al. 2001, 2004). These default mode network regions, the medial prefrontal cortex and posterior cingulate cortex, have been found to be significantly associated with morality in pervious meta-analyses (Sevinc and Spreng 2014; Boccia et al. 2016; Garrigan et al. 2016; Han 2017; Eres et al. 2017). Also, the regions significantly overlap with regions associated with self-related psychological processes, such as self-referencing and autobiographical memory processing (Levine et al. 2004; Mitchell et al. 2005; Immordino-Yang et al. 2009; Lou et al. 2010; Han 2017). Given self-related processes constitute the basis of moral functioning in the reality, the integration of moral judgment, emotion, and motivation within oneself in particular (Damon 1984; Colby and Damon 1992), the significant functional connectivity between the cerebellar regions and default mode network regions is worth noting. The result may suggest that the cerebellar regions, the Crus I and Crus II in particular, shall be considered as one of hubs in the brain network that organizes interactions between affective and cognitive processes in moral functioning.

Furthermore, Habas et al. (2009) reported a significant connectivity between the right Crus I and II and the executive network including regions in the lateral prefrontal cortex, dorsomedial prefrontal cortex, lateral parietal cortex, and insula (Seeley et al. 2007). According to research in developmental psychology, executive functioning associated with the executive network at the neural level includes abilities required for cognitive control and emotional regulation, such as planning, inhibit control, attentional control, and working memory (Hinnant et al. 2013). These abilities constituting executive function have been known to be needed for sophisticated moral judgment and moral functioning. For instance, the abilities for cognitive and emotional regulations are required for empathizing with others in difficulties and understanding their perspectives; making a sound moral judgment and implementing moral behavior based on the judgment could not be done without the aforementioned abilities (Lahat et al. 2012; Lahat 2015). Given these, the significant connectivity between the right Crus I and Crus II and the executive functioning can be understood as evidence suggesting that the cerebellar regions are in a brain circuitry that connect emotional processes and regulatory processes. Because moral judgment as well as moral functioning in general rely on the interaction and cooperation between cognitive and affective processes (Moll et al. 2003; Han et al. 2016), the cerebellar regions, the Crus I and Crus II, are deemed to play significant roles in the aforementioned interaction and cooperation.

Findings from clinical neuroscience can provide additional evidence to the aforementioned points related to the connectivity between the cerebellar regions and the default mode and executive networks. Tang et al. (2013) compared the functional connectivity between regions in the cerebellum and the default mode network and executive network between participants with versus without antisocial personality disorder. They demonstrated that presence of antisocial personality disorder was associated with the decoupling between activity in the right Crus I and that in the aforementioned two networks. Given both networks play fundamental roles in morality, including moral judgment (Chiong et al. 2013; Lahat 2015; Han et al. 2016; Han 2017), the disrupted connectivity between the networks and Crus I is worth further consideration. The Crus I is a part of the brain network of emotional processes (Adamaszek et al. 2017), so the aforementioned decoupling might be associated with the deficit in emotional processes required for moral functioning (Saver and Damasio 1991; Damasio 1994; Moll and de Oliveira-Souza 2007), and finally, antisocial traits (Tang et al. 2013).

Aspects related to mentalizing are also interesting. Van Overwalle et al. (2014) reported that the right Crus I was connected to the mentalizing network dealing with person and abstract mentalizing. Since mentalizing is about inferring others' beliefs or intentions, this ability is required to make appropriate moral judgment (Harenski et al. 2012b). Particularly, to be able to properly infer others' emotional statuses within problematic situations, feel empathic concern with them, and implement appropriate moral behavior in such situations, the mentalizing abilities are required (Hooker et al. 2008; Harenski et al. 2012b). The evidence may support the point that the right Crus I constitutes a part of the neural circuitry of mentalizing that plays fundamental roles in emotional and motivational aspects of morality.

The cerebellar regions found to be specifically associated with morality, the right Crus I and Crus II, can be regarded as a part of hubs in brain networks constituting the neural basis of morality as discussed so far. Previous meta-analyses and clinical studies have reported that these regions are particularly associated with diverse emotional processes, including emotional perception and regulation (Schutter and van Honk 2005; Schmahmann et al. 2007; Keren-Happuch et al. 2014; Adamaszek et al. 2017), which are required for moral functioning (Moll et al. 2003; Han et al. 2016). Furthermore, neuroimaging studies have shown that the cerebellar regions are closely connected with brain circuitries associated with psychological processes that constitute the basis of moral functioning, the default mode network, executive network, and mentalizing network (Habas et al. 2009; Tang et al. 2013; Van Overwalle et al. 2014; Han et al. 2016).

Finally, neuroscientific studies that employed investigation methods other than fMRI, such as the structural neuroimaging, Electroencephalography (EEG), and transcranial magnetic stimulation (TMS), also support the involvement of the Crus regions in the socio-emotional-moral functioning network. First, structural neuroimaging studies have revealed the connectivity between the Crus and cerebral regions particularly within the context of affective processing, including affective regulation and empathy, at the anatomical level (Stoodley and Schmahmann 2010; Picerni et al. 2021). Second, Farzan et al. (2016) demonstrated the alternation of neural activity in the default mode network in the cerebellar regions, which is closely associated with moral functioning (Moll et al. 2007; Immordino-Yang et al. 2012), when they stimulated the Crus region with the TMS. Third, Li et al. (2021) reported in their EEG study that sensitivity to disgust, which plays a fundamental role in emotional processes in moral functioning (Moll et al. 2005), was significantly associated with neural activity in the network including the Crus and superior frontal cortex. These results from the previous studies employing diverse investigation methods may support the point that the cerebellum, particularly the Crus, could not be separable from the neural network associated with moral functioning that includes cerebral regions with additional evidence.

The evidence overviewed so far supports the point that the cerebellar regions, the right Crus I and Crus II in particular, are parts of the hubs in a brain that functionally connect different psychological processes, including emotional processes, for moral functioning. Because morality could not be exclusively explained in terms of either reasoning or emotion, but should be understood based on the interaction and cooperation between reasoning and emotion (Moll et al. 2003; Kristjánsson 2012; Han 2016), the cerebellar regions, which have not been sufficiently studied within the context of morality (Demirtas-Tatlidede and Schmahmann 2013), should be further investigated to improve our knowledge of moral functioning.

12.8 Concluding Remarks and Future Directions

In this chapter, I examined the association between the cerebellum, emotion, and morality, which has not been well studied in neuroscience. Debates in the fields of moral philosophy, psychology, and neuroscience support the point that emotion is an essential component constituting human morality (Han 2014). Given both clinical and functional neuroscience studies have shown the relationship between activity in the cerebellum and emotion and social functioning (Adamaszek et al. 2017), it would be worth considering how the cerebellum is related to morality. As a way to explore the association, I employed NeuroSynth, a tool for large-scale fMRI data analysis to address the issues associated with reverse inference (Yarkoni et al. 2011; Poldrack 2011) and found that the right Crus I and Crus II showed significant activity in moral task conditions. Based on this finding, the position of the cerebellar regions as parts of a hub in neural networks for emotional as well as cognitive processes that are required for optimal moral functioning was discussed.

Of course, I do not intend to argue that this chapter can disclose every single aspect of the cerebellum related to emotional and moral functioning. Instead, it would generate novel research questions for and ask neuroscientists to pay attention to the cerebellum, which has been relatively less studied but is deemed to play fundamental roles in morality, in future studies. One point that shall be considered is that the majority of the previous neuroimaging studies that have addressed the cerebellum and emotion have not directly targeted morality as their primary research focus (Demirtas-Tatlidede and Schmahmann 2013; Adamaszek et al. 2017). Rather, they have focused on emotional and social processes in general while not employing morality-related task conditions. Although Han et al. (2016) reported the significant interaction between the cerebellum and default mode network in moral dilemma solving, they started with examining the cerebral regions in the network; the association of the cerebellar regions was found from the while-brain analysis instead of the region of interest (ROI)-based analysis. Hence, based on examinations and discussion in this chapter, future studies may need to employ moral task conditions while setting the cerebellar regions as ROIs in their neuroimaging analysis for better topic-specific analysis with improved statistical power (Cremers et al. 2017).

Moreover, ideas proposed in this chapter will also be able to inspire additional experimental studies. First, researchers may consider applying the TMS or transcranial direct current stimulation (TDCS) on the Crus regions to examine the causal relationship between activity in the regions and moral functioning. For example, previous studies have applied the TMS and TDCS to cortical regions, such as the temporoparietal junction, and reported significant changes in moral functioning (Young et al. 2010; Ruff et al. 2013). Similarly, future studies will also be able to examine the causal relationship by altering neural activity in the Crus regions. Furthermore, researchers may also consider developing and testing psychological interventions targeting moral psychological mechanisms associated with the Crus regions. For example, a previous moral psychological intervention was invented based on the findings from neuroimaging studies that illuminated the core psychological process associated with moral motivation (Han et al. 2016, 2017, 2019; Han 2017). Given the prior case, the findings about the activity in and psychological processes associated with the Crus regions, which are closely related to emotion and motivation, might be able to inform future moral psychological studies, particularly those focusing on psychological interventions.

Another point related to methodological concerns may also need to be considered in future studies. Although the concerns related to reverse inference were able to be at least partially addressed by employing NeuroSynth, it would not be a perfect solution in research on the cerebellum and morality. Given NeuroSynth conducts analysis based on information of the coordinates of activation foci reported in published articles, it does not analyze full brain images containing statistical information in each voxel (Yarkoni et al. 2011; Eickhoff et al. 2011). Given the relationship between the cerebellum and morality has not been well studied and supported by evidence so far, it would be more informative if large-scale analysis focusing on this topic is performed with full statistical images that can provide more accurate structural information about neural activity in the cerebellum (Salimi-Khorshidi et al. 2009; Han and Park 2019). Although it would be practically difficult to gather full image data instead of coordinates information data, by utilizing technologies to share statistical images (e.g., NeuroVault (Gorgolewski et al. 2015)), the aforementioned aim will be able to be achieved in the long run. Hence, for better large-scale analysis to get accurate information about the functional association between the cerebellum, emotion, and morality, I suggest researchers share image data from their research projects, and finally, conduct topic- and ROI-focused studies based on the shared data.

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Music and the Cerebellum

13

Stefan Evers and Bernadette Tölgyesi

Abstract

The cerebellum is involved in almost all cognitive functions related to music perception and music production. This has been shown by functional imaging and by similar techniques. In addition, lesion studies (i.e. examining patients with cerebellar infarction or tumour) also give evidence of this involvement. Different parts of the cerebellum have been identified for different aspects of these processing tasks and their individual connections to the cerebral cortex as well as to the basal ganglia. It has been shown for example that cerebellar disorders impair music perception in particular in melody comparison and metrum tasks. First research approaches are trying to use the current knowledge on the role of the cerebellum in music perception for therapeutic processes in degenerative disorders such as Alzheimer's disease.

Keywords

Music perception · Music production · Cerebellum · Cerebellar disorders · Functional brain imaging

13.1 Introduction

Besides its involvement in motor control, the cerebellum plays a role in cognitive processing including music processing. Adults show deficits in various cognitive and affective domains, in particular to executive, attentional, memory and behaviour functions after damage to the cerebellum, which subsequently has been subsumed for a syndrome called "cerebellar cognitive affective syndrome (CCAS)." In terms of the impairments in emotion, CCAS may involve deficiencies in emotion identification as well as in emotion regulation (see an overview in Adamaszek et al. 2017). Therefore, music is also a topic for research on the cerebellum in concern to these noted cognitive and affective issues. In particular, the role of the cerebellum in relation to emotions in music is a hitherto little considered but nevertheless exciting area in neuroscience on specific higher order functions of the cerebellum, which raises some specific enquiries to clarify the underlying mechanisms. In this chapter, we aim to review the different links between music perception or music production and the cerebellum.

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13.2 Music Perception Network and the Cerebellum

Music perception always involves a network of different brain structures depending on the type of music and the circumstances of perception. Among these brain structures, the cerebellum has been frequently identified to be included within the responsible networks, whereby details of the underlying mechanisms remain unclear. According to the data available so far, the cerebellum has a separate function in the temporal dimension of signal processing of sensory perception, which in turn influences the respective motor execution as well as the associative cognitive and affective perception. Given that time information processing is essential for motor control as well as for music perception (Molinari et al. 2003), the investigation of musical skills in people with cerebellar damage seems not only sensible but also promising, and such investigations are also quite practicable in musically untrained patients, since non-musicians have basic musical skills.

Nevertheless, experimental approaches in brain research on music are difficult to carry out because music is a complex cognitive task, and its perception also depends on pedagogical and cultural aspects. Therefore, the different aspects of music processing have been examined as separate parameters and with different methods. We follow this approach in this narrative review and summarise the findings on the link between the cerebellum and music perception for the different parameters of music.

13.2.1 Rhythm

In neuroimaging studies, Parsons described distinct neural structures as activated when musicians had to detect specific melodic, harmonic, or rhythmic errors (Parsons 2001). In this study, among other brain regions, the cerebellum showed activation during all three exercises, but in the rhythm task cerebellar activation was about twice as high as compared to the harmony and the melody task. In particular, when musicians and non-musicians were asked to discriminate pairs of rhythm, non-musicians showed higher cerebellar activity in the meter, tempo and pattern discrimination. However, musicians displayed a stronger activation of the cerebellum for the duration discrimination. This finding presumably reflects differences in strategy, skill and cognitive representation of musicians and non-musicians, which in turn might indicate a dependency of brain function on specific skill acquisition at cerebral and cerebellar sites.

A further interesting study was published by Molinari et al. (2003), who studied a group of patients with cerebellar atrophy and another with focal cerebellar damage in comparison to healthy control subjects. In this study, participants had to detect changes of rhythm frequency. As a result, the subjects of cerebellar atrophy showed significant inferior results, suggesting that cerebellar pathologies may differentially influence the ability to appreciate rhythm changes. In addition, cerebellar damage seems to affect the variability and thus the stability of motor response as both groups were tested in their ability to tap synchronously following an auditory stimulus. Interestingly, an involvement of the anterior and posterior lobes of the cerebellum in the memory for rhythm has been confirmed by a study applying a specific functional magnetic resonance imaging (fMRI) protocol (Sakai et al. 1999).

The cerebellum has been shown to be involved in the perception and synchronisation of musical beat. In an MRI study by Paquette and collaborators, the researchers used voxel-based morphometry to correlate inter-individual differences in the performance of the Harvard Beat Assessment Test (H-BAT) with local inter-individual variations in grey matter volumes across the entire brain in 60 individuals (Paquette et al. 2017). The analysis of the obtained data identified significant co-variations between performances on two perceptual tasks of the H-BAT in association with the beat interval change discrimination (faster, slower) and grey matter volume variations in the cerebellum. The threshold for discrimination in the Beat Finding Interval Test (quarter note beat) was positively associated with grey matter volume variation in cerebellum lobule IX in the left hemisphere and crus I in both hemispheres. Moreover, the discrimination threshold for the Beat Interval Test (simple series of tones) showed a positive association with grey matter volume variations in left cerebellar crus I/II. Summarising these results, the cerebellum was shown to take part in beat interval discrimination tasks, whereby the cerebellar grey matter and overall cerebellar integrity are presumably important for temporal discrimination abilities.

Rhythm as the basic time structure of music is composed of distinct temporal components such as meter, pattern and tempo. Each component requires different computational processes, i.e. meter involves repeating cycles of strong and weak beats, whereas pattern relies on intervals at each local time point, which vary in length across segments and are linked hierarchically. Finally, tempo is subject to frequency rates of underlying pulse structures. A positron emission tomography (PET) of Thaut et al. (2014) assessed the neural patterns of brain activity to rhythmic elements in adult musicians and non-musicians. In this study, crucial interests were put on the covert same-different discriminations of (a) pairs of rhythmic, monotonic tone sequences representing changes in pattern, tempo and meter, and (b) pairs of isochronous melodies. In their peculiar neuroimaging study, pattern, meter and tempo tasks were associated with focal activities in right, or bilateral, areas of frontal, cingulate, parietal, prefrontal, temporal and cerebellar cortices. In more detail, meter processing alone activated areas in right prefrontal and inferior frontal cortex, which were associated with more cognitive and abstract representations. Moreover, pattern processing alone recruited right cortical areas involved in different kinds of auditory processing. Tempo processing alone engaged mechanisms of somatosensory and premotor information (e.g. posterior insula, postcentral gyrus). Finally, melody resulted in activity different from the rhythm conditions (e.g. right anterior insula and various cerebellar areas). These findings suggest the outlines of some distinct neural components underlying the components of rhythmic structure (Thaut et al. 2014).

13.2.2 Timing Aspects

Several studies examined the timing aspect of the cerebellum. It was reported that cerebellar patients are impaired in discriminating time intervals (Nichelli et al. 1996). In addition, it was demonstrated that the cerebellum contributes to the production of a timed motor response, especially when it is complex and/or novel (Ivry et al. 1988; Jueptner et al. 1995; Penhune et al. 1998).

A precise movement control such as for tapping, in addition to certain time keeping functions, is required to perform tasks of rhythm and metrum. In particular, metrum tasks are impaired in patients with cerebellar lesions (Ivry and Keele 1989). Although the rhythm determines the metrum, the retention of a stable metrum demands a targeted motor timing as well as a precise motor control. As shown in previous research, patients with cerebellum damage may develop impairments of these properties. Moreover, as a meta-analysis on tasks related to music and timing outlined (Keren-Happuch et al. 2014), the two aspects of the field are inherently similar, where it is a matter of knowing the chronological sequence, tasks in these two domains recruit separate activations. Based on the theory that parts of the cerebellum process via an internal timing mode, and again considering the evidence suggesting that timing is associated with knowledge of temporal order, it was expected that among the responsible cerebellar activations for timing, there would be subsets of activations for the rhythmic aspects of music processing. However, results in this meta-analysis revealed recruitment of distinct regions, with music-related tasks consistently demonstrating significant activation in right lobule IV/V, bilateral lobules VI and VIII, whereas timing uniquely showed an activation of the right lobule VI (Keren-Happuch et al. 2014).

13.2.3 Pitch and Timbre

Besides rhythm, metrum and timing, pitch and timbre are the other important basic parameters of music processing, in which cerebellar structures are presumably involved. For example, a study of Parsons found that patients with cerebellar degeneration were strongly impaired in a pitch discrimination task, whereby the degree of impairment correlated with the severity of their ataxia disorder (Parsons 2001). Another study of Parsons et al. assessed the performance of patients with cerebellar degeneration in an ordinary pitch discrimination task (Parsons et al. 2009) and revealed strongly impaired discrimination abilities. Interestingly, the amount of this impaired discrimination correlated with the degree of cerebellar atrophy.

With regard to the underlying structural aspects, Gaab et al. (2003) stated that the supramarginal gyrus of the parietal lobe may function as a storage site of short-term pitch information. Moreover, the authors suggested an important role of the cerebellum for performing a pitch memory task. High cognitive processes like auditory information retention might depend on a mechanism separate from that of comparing two successive tones. According to a study by Zatorre et al. (1994) by applying a positron emission tomography (PET), changes of cerebral blood flow revealed a wider cortical and subcortical range being involved if, in contrast to the absence of memory load, the pitch retention was required. Therefore, as a summary of the present literature, the cerebellum is undoubtedly involved in tasks that require sensory data acquisition such as pitch via multiple connections to cortical and subcortical areas.

The putative function of the cerebellum for sound processing was also studied in two auditory tasks by Lega et al. using a pitch discrimination and a timbre discrimination task (Lega et al. 2016). In their study, healthy subjects performed a pitch and a timbre discrimination task prior and after receiving offline low-frequency transcranial magnetic stimulation (TMS) over the right cerebellum. As a result, when activity within the right side of the cerebellum was suppressed by inhibitory 1 Hz TMS, the participants' ability to discriminate pitches, but not timbres, was impaired. These findings point at least in some aspects to a causal role of the cerebellum of sound processing, which might be important for understanding the impact of cerebellar lesions on sensory functions in particular at a clinical perspective.

Congenital amusia is a lifelong neurodevelopmental disorder of music-related pitch processing. A study research of Zhang using a specific fMRI protocol focused on the neuronal network in patients with congenital amusia speaking a tonal language (Cantonese) (Zhang et al. 2017). The rationale for this study was that previous studies of speakers of non-tonal languages had suggested neural deficits of innate amusia in the music-selective neural circuitry in the right inferior frontal gyrus (IFG). After all, it had remained unclear whether this finding could be generalised to congenital amusics in tonal languages. To address this question, the research group investigated the neural circuits that underlie the processing of relative pitch intervals in pitch-matched Cantonese level tones and musical stimuli in Cantonese speakers with congenital amusia and musically healthy controls. As a result, Cantonese-speaking amusic subjects depicted abnormal brain activities in a largely distributed neuronal network during the processing of lexical tone and musical stimuli. Furthermore, while control subjects showed significant activation in the right superior temporal gyrus (STG) and cerebellum independent of the lexical tones and music, amusic subjects showed no activation in these regions at all. According to the authors, their observation rather reflects a functional deviation of the neural mechanism of relative pitch processing in the amusic subjects. Interestingly, the authors found no significant group difference in the right IFG. Taken together, the findings of Zhang et al. (2017) imply that the neuronal deficits in tonal language speakers might differ from those in non-tonal language speakers, and overlap partly with the neuronal circuitries of lexical tone and musical stimuli processing (e.g. right STG).

In summary, evidence from activation studies, lesional studies and congenital musia suggest that the cerebellum is involved in pitch, but not in timbre, processing in a clinically pertinent way.

13.2.4 Music Identification

The cerebellum is also involved in higher cognitive functions such as identifying and categorising sounds as music. The most effective cues for music identification, i.e. rhythm or melody, were studied in three experiments of Hébert and Peretz (1997). In their study, the combination of pitch and duration, i.e. also cerebellar functions, was most relevant for retrieving data from long-term memory for music (Hébert and Peretz 1997). Accordingly, data of several neuroimaging studies demonstrated separate activations of specific brain regions while accessing stored pieces of music (Platel et al. 1997; Rauschecker 2005; Satoh et al. 2006). Satoh et al. (2006) suggested an implementation of brain regions responsible for retrieval from long-term memory as well as verbal and emotional processing (i.e. bilateral anterior parts of the temporal lobe, superior temporal regions and parahippocampal gyri) when evaluating the familiarity of a composition. In fact, the process of recognising familiar melodies deems to proceed in several steps. After sensory auditory information acquisition, a melody image is formed. In subsequent steps, melodies stored in long-term memory are retrieved and compared with this melody image. Satoh et al. also point out that during the recognition of familiar melodies, brain areas involved in the formation of a melodic image are active, as are those areas involved in the retrieval of melodies from long-term memory (Satoh et al. 2006).

Nevertheless, the involvement of the cerebellum in these pathways of music recognition remained uncertain after the first studies. In several PET series, a contralateral coactivation of auditory temporal cortex and lateral cerebellum suggests that they form a distributed circuit of auditory processing (Parsons 2001). According to neuroimaging (Habas et al. 2009) and anatomical (Strick et al. 2009) findings, there is a clear evidence of cerebro-cerebellar connectivity as representative for cerebellar involvement in this cognition (Petacchi et al. 2011). The PET study of Petacchi et al. detected a particular activity of the cerebellum for passive listening in healthy subjects. This activity was even elevated during pitch discrimination, and furthermore associated with the difficulty of the task (Petacchi et al. 2011).

Of separate interest in the study of cerebral mechanisms in music processing is also the identification of those areas in the cerebral cortex in which the internal processes of the encoding of musical elements are controlled. In a study by Rauschecker, the brain areas involved in the encoding and retrieval of melodies were investigated via a functional MRI examination (Rauschecker 2005). In this experimental study, the brain activation of healthy subjects was investigated during the silent anticipation of familiar music, since it could be assumed that with the first sequence of a familiar melody, the following part can be anticipated. In the study, the respective regional activations during the silent anticipation of a melody on the one hand, and those activations during simple listening to music on the other hand, were recorded and compared with each other. In this interesting paradigm, in addition to the activations of different cerebral areas, namely the anterior part of the right superior temporal cortex, the right inferior frontal cortex and anterior insula, the left anterior prefrontal cortex, and the anterior cingulate, a significant bilateral activation of the posterior lateral cerebellum was observed during the anticipation task. With these results, it was shown which brain areas are involved in the perception of music via bottom-up and again top-down control pathways, with the lateral cerebellar areas being involved in the anticipation of musical sequences and thus the construction of melodic strands.

The importance of a melodic image for the recognition of melodies has already been explained in an earlier section. As a work group around Herholz found, this generation of musical images is accompanied by integrated activations within distinct networks of predominantly cerebral, but also proportionally cerebellar brain structures (Herholz et al. 2012). In this indicative work of Herholz et al. about the neural underpinnings of the processes that characterise the generation of a melodic image, participants were presented with the titles and lyrics of well-known songs, which stimulated them to mentally vocalise. In this functional MRI study, the main results were even expected, i.e. during the imagination of the vocalisation, co-activations of motor and premotor areas were detected. Interestingly, the area in the cerebellum that represents the tongue and lip movements was activated too. With these active brain areas revealed during the imagination, the importance of an auditory motor loop was conclusively emphasised. In addition, the importance of the cerebellum for mental vocalisation during musical imagination was also elaborated.

With regard to the mechanisms of emotional and memory levels functioning in music, imaging studies on the neural brain structures responsible for this are of separate interest. Here, imaging procedures can provide information, as Altenmüller's research group recently attempted to clarify in a special paradigm (Altenmüller et al. 2014). In their study, subjects were presented with short excerpts of film music with emotional features during an fMRI recording. A particular question here was which brain structures were activated in the sequences of the film music excerpts successfully retrieved from episodic long-term memory (Altenmüller et al. 2014). As a result, sequences of musical stimuli in contrast to sequences of silence activated parts of the left anterior cerebellum in addition to various cerebral cortical regions. Interestingly, old music pieces vs. new music pieces led to activations within the left medial dorsal thalamus and that of the left midbrain. Another finding was that regions within the right inferior frontal gyrus and left cerebellar hemisphere triggered to specific activation for recognised vs. unrecognised old pieces. For the stimuli with pleasant pieces of music, there was again activation prefrontally within the left medial frontal gyrus as well as the right superior frontal gyrus, to that of the left precuneus, but also the left posterior cingulate (PCC), the middle temporal gyri bilaterally and the left thalamus, compared to less pleasant pieces. This very elegant fMRI study thus identified specific brain networks that highlighted interrelated network activities for the retrieval of musical memories and the emotional processing of symphonic film music. With these results, the importance of the valence of a piece of music for the memory performance and its thus also extremely rapid recognition were worked out in a fascinating fashion.

Another functional imaging study by Demorest et al. (2010) had as its object the investigation of cultural factors that influence the shaping of music perception and music memory. In this fMRI study, the hypothesis was formulated that listeners show different activation patterns related to music processing when encoding and retrieving culturally familiar and unfamiliar stimuli. Here, it was hypothesised that people would elicit broader neural activation when presented with culturally unfamiliar or even unfamiliar musical sequences, which in turn would map onto more complex memory tasks (Demorest et al. 2010). In their study, US and Turkish subjects were presented with novel music examples from their own and a foreign culture for identification, which were a series of short excerpts taken from the longer examples. Using this separate paradigm, it was shown that subjects in both groups were more successful in remembering music from their own culture. In the analysis of the fMRI data, stronger activation when listening to culturally unfamiliar music was indeed found within the left cerebellar hemisphere, the right angular gyrus, the posterior precuneus and the right middle to inferior frontal areas. Stronger activations were again recorded in the cingulate gyrus and the right lingual gyrus, provided the subjects remembered culturally unknown music.

Another study demonstrating cerebellar involvement in the networks for the separate perception and processing of musical information has already been undertaken by Griffiths (2000). This PET study involved six subjects with musical hallucinations following acquired deafness. According to the results of this specific PET examination, the brain areas were to be identified in particular, which highlight their functional significance via an increase in activity depending on the severity of the hallucination. A group analysis could not identify any effects for the primary auditory cortex. Instead, cluster-correlated activities were detected in the posterior temporal lobe, the right basal ganglia, the cerebellum and the inferior frontal cortices. Interestingly, these cluster activities captured functional networks that bear quite striking resemblance to those in the normal perception and imagination of segmented sound patterns presented earlier in paradigms. These results are therefore consistent with the proposed neuropsychological and neural mechanisms of music perception.

An interesting question in the investigation of cerebellar mechanism in music perception is to what extent the known process involvement of the cerebellum in spatial domains (Argyropoulos et al. 2020) should be taken into account here. A paper by Picazio et al. (2013) provides an exciting insight here, which addressed this question using non-invasive transcranial magnetic stimulation. In this work, the activity of the cerebellum of subjects was investigated in the connection of spatial and musical domains, which could be presented in the context of tasks of embodied (EMR) or abstract (AMR) mental rotation during listening to Mozart's sonata KV 448. The Mozart sonata was chosen because it is known to increase spatiotemporal reasoning (one of the so-called "Mozart" effects), which was observed independently of continuous theta burst stimulation (cTBS) of the left cerebellar hemisphere (Picazio et al. 2013). This effect was indeed observed even in the absence of cerebellar cTBS, i.e. listening to music did not influence either of the two mental rotation tasks here either, which means that a specific "Mozart effect" could be judged to be refuted. On the contrary, cerebellar theta-burst stimulation before listening to music caused the subjects to perform the EMR task faster and less accurately, but not the AMR task. Inhibition of the cerebellum by cTBS thus unmasked the effect of music listening on motor imagination. These results thus provided quite vivid evidence for a coupling of cerebellar networks between music listening and a specific sensory-motor integration for the realisation of embodied representations.

In summary, the studies described above suggest an important role of the cerebellum in the recognition of music and song. The cerebellar areas, mainly of the posterior lobes, seem to play an important role in pitch discrimination. Interestingly, the function of the cerebellum in specific music perception has also been demonstrated in musical hallucinations. According to the literature reviewed here, the left anterior parts of the cerebellum in particular can be ascribed a significant activity for the processes of music recognition.

13.2.5 Emotion Processing

According to previous findings, the cerebellum is active at various levels of emotion processing, in addition to the well-studied brain structures of the prefrontal cortex and the insula, furthermore the amygdala and the hippocampus (Baumgartner et al. 2006). These mechanisms of the cerebellum in emotion processing, which are increasingly understood in detail in the literature, naturally point to a special importance for music perception. An early and indeed pioneering study on the cerebellar parts of emotion processing was published by Schmahmann and Sherman (1998). In this study of patients with acquired or congenital cerebellar damage, which is still exciting today, behavioural changes were recorded that affected areas of executive functions, spatial perception, language, but also personality (Schmahmann and Sherman 1998). In addition to these predominantly cognitive domains, disturbances of affect regulation were also observed, so that the term cerebellar cognitive-affective syndrome was formulated by the authors. In view of the lack of evidence of additional cerebral brain injuries for which these clinical functional changes would be plausible, Schmahmann and Sherman justified the recorded cognitive-affective disorders as causal on the basis of neuronal connectivity of the cerebellum to the cerebral regions. Their assessment of specific cerebellar mechanisms within affective domains was based on earlier identifications of the cerebellum within limbic circuits, as elaborated in the work of Anand et al. (1959) or Snider and Maiti (1976).

Given the growing evidence for specific cerebellar inputs within neural networks of emotion recognition and processing, further work has emerged examining individual details such as features of emotional valence. An investigation by Hopyan et al. (2010) of the emotion processing of children with a treated benign (e.g. astrocytoma) or malignant (e.g. medulloblastoma) cerebellar tumour did not show any significant impairment compared to healthy control subjects in tasks in which immediate recognition of the basic emotions of joy and sadness in pieces of music was required. In the detailed analysis, however, a weakness in the recognition of sad musical moods was found in the children with medulloblastoma. However, another observation in the study by Hopyan et al. that is well documented in the literature was that cross-modal perception and processing of specific emotions depend on an intact cerebellar-cerebral connection. In the aforementioned study, deficits were found in the children with a cerebellar tumour in two control tasks in which the children were asked to compare the emotions of joy and sadness in music and, in contrast, in poetry (Hopyan et al. 2010). The results in the above-mentioned work correspond well with comparable work (for an overview, see Adamaszek et al. 2017) that, on the one hand, the cerebellum takes a larger share in the perception and processing of negative basic emotions, and on the other hand, the cerebello-prefrontal axis exerts a differently pronounced function in the cross-modal allocation of emotions. The special preference of the cerebellum for negative emotions has also been well elaborated in detail in various animal models of emotional learning, in which cerebellar lesions showed deficits especially for negative emotions such as anger or fear (Sacchetti et al. 2009).

In addition to an early study by Reiman et al. (1997), in which the cerebellum was shown to be involved in emotional reactions to exteroceptive sensory stimuli, a similarly early study by Imaizumi and colleagues was also able to show a cerebellar function for different negative and positive valences in their sample (Imaizumi et al. 1997). The authors examined in a PET those brain regions that function significantly in spoken words for the identification of emotions associated with surprise, disgust, pleasure and also fear. In this exciting approach, significant activation was recorded within the cerebellum, but also in parts of the frontal lobe, revealing the strong functional relationship between these brain regions reported elsewhere for these tasks as well. Another neuroimaging study investigated the cerebellar connections to neural networks during the processing of emotional image perception tasks (Bermpohl et al. 2006; Styliadis et al. 2015). Specific cerebellar contributions to the recognition of emotional speech recognition, i.e. especially the affective prosody of spoken sentences, could be characterised quite respectably in the work of Wildgruber et al. (2005) and Adamaszek et al. (2017), among others.

The findings to date on specific cerebellar functional features within the networks that process the experience of emotions are diverse, and yet still leave some questions open with regard to individual aspects such as that of emotional learning (Sacchetti et al. 2009) or emotional valence discrimination (Styliadis et al. 2015). With regard to the particular human capacity of emotional valence discrimination, cerebellar patients tend to have deficits in the recognition of the basic emotions such as joy or anger, and thus pleasant and unpleasant emotions, which they do not reliably grasp (Adamaszek et al. 2017). In relation to this dichotomy of pleasant and unpleasant emotions, research has shown that the neural systems contributing to these categories are closely linked (Lane et al. 1997). With regard to cerebellar characteristics in this categorical distinction of basic emotions, Turner et al. (2007), for example, found significantly increased cortical activity in the left medial temporal lobe as well as in the occipito-temporal cortex, and increased activity in the cerebellum when viewing unpleasant images compared to neutral or pleasant images. In line with the findings of this work, it was assumed that the brain structures usually responsible for processing unpleasant emotions were impaired as a result of the cerebellar lesions (Turner et al. 2007). Similar to the work of Adamaszek et al. (2015), in which emotion processing occurs increasingly in the prefrontal cortex in the case of cerebellar lesions, the formation of alternative neuronal circuits was also discussed for Turner's findings in order to maintain the preservation of fear experiences, which is important from an evolutionary perspective, even in the case of cerebellar damage. In line with neuroscientific considerations of neuronal plasticity, the above-mentioned findings and the discussions triggered by them vividly underline that the cerebellum contains structures of dynamic networks, the majority of which are still the subject of lively research (Turner et al. 2007).

13.3 Music Production and the Cerebellum

It is obvious that the cerebellum is an important part of the network regulating music production. Which specific mechanisms have been detected to date to better understand the role of the cerebellum in music production?

13.3.1 Physiology

To further understand the physiological features of cerebellar processes within music perception and processing, techniques that highlight the haemodynamic changes during cerebellar activations in specific paradigms may be considered. Previous work by Koeneke et al. (2004) investigated precisely these cerebellar haemodynamic responses in highly skilled keyboard players and control subjects during complex tasks requiring one- and two-manual finger movements. Using this specific fMRI study, which employed a classical box-car design with alternating rest and activation blocks of 20 s each, strong haemodynamic responses were recorded in motor and supplementary motor areas, but also in the cerebellar hemispheres (anterior and intermediate zones) in both groups during the task conditions. However, non-musicians generally showed stronger haemodynamic responses in both cerebellar hemispheres, while skilled keyboard players activated essentially the right cerebellar hemisphere (Koeneke et al. 2004). From these striking differences in cerebellar activations, it was concluded that a different cortical activation pattern is triggered in keyboard players due to many years of motor practice. In accordance with a neural plasticity of motor learning, it can rather be assumed from the present study results that fewer neurons are recruited for trained keyboard playing movements. Morphologically, the different motor performance of such differently trained individuals would understand the observed different volume of activated cortical areas, reflecting the different demands of motor effort in the two groups. Interestingly, the work of Koeneke et al. also recorded activation of the vermis, which is thought to represent emotional or even motor aspects of eye movements when playing the keyboard (Koeneke et al. 2004).

Neural plasticity within motor systems of the central nervous system as a function of motor learning has been well demonstrated many times. Indeed, several studies have shown that training motor skills over long periods of time leads to a reorganisation of neural networks, which is reflected in changes in brain morphology (Sato et al. 2015; Vaquero et al. 2016). These processes of neural reorganisation are complicated and many details are still poorly understood, especially for changes in the vocal system, within which largely intrinsic reflex mechanisms determine these changes. An interesting paper by Kleber et al. (2010) investigated these processes in highly gifted opera singers, but also conservatoire-level voice students, and finally, as a control, in amateurs during the singing of an Italian aria using neuroimaging techniques (Kleber et al. 2010). In this striking fMRI study, increased functional activation of the bilateral primary somatosensory cortex representing the articulators and larynx was identified for vocal skill training. In addition to these cortical activations, experienced singers also showed increased activations in the basal ganglia, thalamus and cerebellum. Interestingly, a precise regression analysis demonstrated a correlation between functional activation and increased singing practice, inferring increased activity of a cortical network along with increased involvement of implicit motor memory areas at the subcortical and cerebellar levels for training singing skills (Kleber et al. 2010).

Sung and spoken language, notwithstanding their differences in certain vocal and prosodic aspects, share many similarities in terms of their physiology of articulation and perception, but also in terms of the phonology, phonotactics, syntax and semantics of the underlying language. In addition to the numerous cerebral sections, cerebellar involvements are also of increasing interest for song and speech, as they were investigated in more detail in a nice paper by Callan et al. (2007). In this work, the authors were able to highlight considerable overlap in the lateral aspect of lobe VI of the posterior cerebellum in the literature on the perception and production of song and speech. This region is plausible because of its somatotopic representation of the lips and tongue; in the context of speech, this region may use internal models of vowel tract articulation that simulate well-learned phonological and/or segmental articulatory-auditory and oral sensory mappings that are used in both speech and singing (Callan et al. 2007). In addition, recent studies have shown a specialisation of the left cerebellar hemisphere in the processing of song, and again a special function of the right cerebellar hemisphere in the processing of speech, although for both hemispheres in lobule VI this seems to be less true than in the representation of speech and song (Callan et al. 2007). Provided one takes into account the observation of crossed patterns of anatomical connectivity between the cerebellum and the cerebral cortex, these results can be applied to the hypothesis that the right cerebellum differentially processes high-pass filtered information (segmental properties) and the left cerebellum differentially processes low-pass filtered information (prosodic, melodic properties) (Callan et al. 2007).

With regard to specific haemodynamic effects of cortical and subcortical areas in music perception and processing, another recently published study by Gonzalez's research group should be mentioned here (González et al. 2020). In this neuroimaging study, functional magnetic resonance images of cortical regions of 13 professional cellists were acquired in an MRI scanner during their interpretation of excerpts of baroque and contemporary music (González et al. 2020). For both styles of interpretation, common cortical motor and sensory regions were identified in the maps of cortical activations and connectivity, but these showed different hemispheric intensity levels. Interestingly, only certain auditory and motor regions, i.e. the gyri Heschl, the superior frontal gyrus, the planum temporale and the caudatum were activated during the interpretation of baroque music. In contrast, during the interpretation of contemporary music, increased activations occurred in the vermis, the insular cortex and the parietal operculum. These discrepancies in the interpretation of baroque and contemporary music were presumably attributed to the different cognitive, sensory and motor requirements of the individual styles underlying musical interpretation (González et al. 2020).

Using functional MRI, the research group of Segado et al. (2018) investigated which brain activations are responsible for coherent auditory-motor music perception and processing. This study examined comparisons of functional brain activations during singing and again during cello playing in the same individuals, where similar voluntary auditory-motor associations during cello playing were also assumed for singing (Segado et al. 2018). The background to this study was that playing an instrument as well as singing require highly specific associations between sounds and movements, and according to the literature for the production of musical sounds, strikingly similar neural networks are assumed in both cases. This study approach again took into account that singing is an evolutionarily relatively old human trait whose auditory-motor associations are also used in speech and non-linguistic vocalisations. In turn, the pitch range of the cello shows parallels to the human voice, although cello playing is ultimately completely independent of the vocal apparatus and can therefore be used to separate the responsible auditory-vocal network from the auditory-motor network, even if musicians tend to produce a vocalisation when playing an instrument (Segado et al. 2018). Finally, as a result of the study by Segado et al. in their specific fMRI paradigm, brain activity during cello playing was found to overlap in many areas with those of the auditory-vocal network during singing, for the primary motor cortex, the dorsal premotor cortex, the supplementary motor cortex and also the primary and periprimal auditory cortex in the superior temporal gyrus including the Heschl's gyrus. Further overlap of neural networks between these two levels was identified in the anterior insula, anterior cingulate cortex, intraparietal sulcus and also cerebellum, but not the periaqueductal grey and basal ganglia (Segado et al. 2018).

Taken together, the cerebellum thus also has an intriguingly significant role in music perception and processing in these studies, which are closely related to the neural networks of the cerebral cortex. The neural plasticity of the cerebellum also seems to have a special physiological condition for training individual patterns in certain skills. Instrumental training in particular leads to specific activations of certain regions in the cerebellum depending on the type and intensity of the training and the musical experience, which will be the subject of further research.

13.3.2 Cerebellum Morphological Plasticity

With regard to the morphological aspects of the brain to music, numerous cross-sectional and longitudinal studies have been able to show correlations between expertise to music and areas of responsible regional brain anatomy, in which the cerebellum also plays an important part. For this separate aspect, for example, a discordant monozygotic (identical) twin design was used to investigate the expertise-dependent effects on neuroanatomy using music training as a model behaviour, mainly to test genetic factors and the shared environment of upbringing (de Manzano and Ullén 2018). In this study, for identical twins with high discordance in relation to piano playing, a greater cortical thickness in the auditory-motor network of the left hemisphere, furthermore a better developed white matter microstructure in relevant pathways in both hemispheres and in the corpus callosum was revealed for the musically active twin. In addition, a larger volume of grey matter in the left cerebellar region with lobuli I-IV and V was found in the piano players. This finding was considered a clear evidence that a significant part of the differences in brain anatomy between experts and non-experts was due to causal effects of training.

A similar observation was made by Hutchinson's research group in their examination of high-resolution T1-weighted MR images from a large, prospectively collected database, which described larger cerebellar volumes for professional keyboard players than for non-musicians (Hutchinson et al. 2003). Interestingly, this increase in volume in male musicians was proportionate for both absolute and relative cerebellar volume, but not for the whole brain. In the further detailed analysis, a correlation was again calculated between the lifelong intensity of music practice and the relative cerebellum volume in the group of male musicians. In the separate analysis of the morphological characteristics of female musicians and non-musicians, no significant differences in cerebellar volumes were found. Based on these exciting results, a structural adaptation in the cerebellum to long-term motor and cognitive functional demands was assumed, which would explain the significantly larger cerebellar volume in male musicians and the positive correlation between relative cerebellar volume and lifelong exercise intensity. The noticeable gender effect remained uncertain, with a higher plasticity of the brain to influences of testosterone being discussed for this phenomenon of male musicians.

The observation that early music training and timing also exert an effect on the cerebellum was investigated in further study with a focus also on regional differences in structural volumes (Baer et al. 2015). In this study, cerebellar grey and white matter volumes were evaluated using a novel automatic multi-atlas segmentation pipeline in adult musicians and non-musicians during completion of a standard finger-tapping task. Data analysis revealed lower volumes of bilateral cerebellar white matter and right lobulus IV, V and VI for early trained musicians compared to late trained musicians. An interesting finding was a smaller volume of cerebellum for those musicians who had better timing performance, greater musical experience and an earlier age at onset of musical training, with better timing performance particularly associated with smaller volumes of right lobule VI. From these imaging results, it could in turn be concluded that not only does the age of onset of musical training influence the functional volume increase of the cerebellum, but also that lobule VI plays a role in timing. Finally, the observation of smaller cerebellar volume associated with music training and timing performance is likely to reflect more efficient implementation of low-level timing and sensorimotor processes (Baer et al. 2015).

The hypothesis of a connection of the cerebellum to musical learning was investigated in a study by Bruchhage et al. which examined the volumes of individual areas of the cerebellum in a specific training of drumming (Bruchhage et al. 2020). More precisely, this study compared the volumes of cerebellar lobules and white matter microstructure as well as cortical thickness of healthy non-musicians before and after a demanding multimodal motor training to learn drumming with age-matched control participants. Significant volume changes were identified for 8 weeks of drumming training, with increases in left VIIIa grey matter, relative decreases in VIIIb and vermis crus I volume, and white matter microstructure in the inferior cerebellar peduncle. In addition to these plastic changes in the cerebellum, an increase in the cortical thickness of the left paracentral, right precuneus and frontal portions of the right (but not left) superior frontal gyrus was seen, inferring an interplay of cerebellar learning with cortical structures via specific cerebello-prefrontal pathways.

In summary, this substantial work has shown that musical training induces morphological changes in the cerebellum independent of the type of musical performance.

13.4 Cerebellar Disorders and Music Perception: An Experiment

13.4.1 Setting

A separate study (Tölgyesi and Evers 2014) on cerebellar characteristics influencing music perception should be considered here in detail, in order to give an impression of the clinical research on the role of the cerebellum in music perception. The results of this study, which are still quite recent, make it possible to understand the specific effects of cerebellar disorders on music perception, especially with regard to individual characteristics such as rhythm, metre and melody structure, but also emotional aspects. The study used specific clinical tests of musical ability in patients with ischaemic (focal infarction; $n = 11$) or genetic (Machado-Joseph disease; $n = 4$) cerebellar disease, and compared them with 30 healthy controls (Tölgyesi and Evers 2014).

In the experimental study, Tölgyesi and Evers applied a clinical test of musical ability, which has been formerly used in patients with cerebral infarctions (Lorenz 2000), and is divided into five parts:

1. *Rhythm and metre*: Participants had to reproduce short rhythmic sequences by tapping a pencil on a table. Correctness of rhythm and metre were scored separately, so that a maximum of 16 points could be achieved for rhythm and 16 points for metre.
2. *Comparison of melodies*: Of two consecutive melodic sequences, the subject was asked to decide whether the two melodies were the same or different, with a total of 16 points achievable for correct comparison.

3. *Emotions*: This subtest consisted of 12 short improvised pieces of three to four bars in duration. Each piece represented a certain emotion, which the respondent had to name correctly. A total of 12 points were attainable in this subtest.
4. *Pitch discrimination*: 12 different pairs of notes were played on a piano and the participant had to determine whether the second note was higher or lower than the first. This specific subtest of correct pitch discrimination was to be completed with a maximum of 12 points.
5. *Melody recognition*: The subjects listened to 14 short pieces from the beginning of a familiar song (10×) or an unfamiliar improvisation (4×), whose melody was to be correctly identified as familiar (familiar) or unfamiliar. This last subtest was again to be completed with a maximum score of 14 points.

Taken together, the sum of the individual subtests required a total score of 86 points. In the subtests, most tasks are very easy to complete, which also means that quite high ceiling effects have to be kept in mind, i.e. abnormal results are expected in clearly and severely affected persons.

13.4.2 Results

The test results of the examination of the patients with an average age of 56 years are shown in Table 13.1. Significant differences between the patients and the control subjects were obtained in the three subtests on metre, melody comparison and emotion, but there was also a significant difference for the total score of the test. In three subtests, rhythm and pitch, the patients also achieved lower correct scores, only this finding did not remain statistically significant. Taking the mean total score of the control subjects (i.e. 69.7 points) as the average normal score, the lower limit of a normal test result is 52 points (i.e. minus two standard deviations). According to this calculation, seven patients (47%) but no control person showed abnormal results in this test. A differentiated consideration of the patients with regard to the aetiology of the cerebellar disease showed individual differences in the respective subtests. In the relatively small subgroup of patients with Machado-Joseph disease, we found significant differences in two subtests, i.e. patients with cerebellar infarction performed significantly better in the melody comparison task (11.3 ± 2.4 vs. 9.3 ± 2.2; $p < 0.05$) and in the melody recognition task (12.8 ± 0.9 vs. 10.8 ± 2.1; $p = 0.007$) than did patients with Machado-Joseph disease as the cause of cerebellar dysfunction.

With these results, it was found that patients with a structural cerebellar disorder were impaired in the perception of musical parameters in the subtests of metre, emotion and melody comparison. Where a musical rhythm can be understood as a movement with regular and irregular impulses, it is obvious that keeping time is an indispensable prerequisite for a successful performance. According to the results of this study, in cerebellar dysfunction, the regular and tightly focused movements required to maintain the exact metre in time may be impaired. The present results vividly reveal the complexity of relationships and interactions in the recognition of melodies. In the study, the strategic features of individual subjects' task performance when presented with the opening melody of a familiar or improvised composition, such as internal anticipation of the upcoming melodic pattern, were not affected. Interestingly, these impairments were found essentially in the subgroup of patients with Machado-Joseph disease, and thus a chronic degenerative, rather than in those with an ischaemic, cause of cerebellar dysfunction. Here, further studies are promising to characterise more precisely the neurotopographic relationships of the cerebellum to the cerebral networks responsible for perception or active memory of familiar melodies.

In humans, music is associated with emotions in a variety of aspects, such as the tempo (e.g. the number of beats per minute) and the mode (e.g. major/minor) of the music (Dalla Bella et al. 2001). The improvisation tracks in the emotion identification subtest evoked a clearly defined emotion according to their design. In the present study, patients with a cerebellar disorder

Table 13.1 Results of testing musical ability in the patients and the control subjects. Data are presented as arithmetic mean and standard deviation. Statistical comparison by Mann-Whitney-U-test (ns denotes not significant)

	Patients ($n = 15$)	Control subjects ($n = 30$)	Significance
Rhythm	7.9 ± 3.9	9.4 ± 2.9	ns ($p = 0.378$)
Metrum	8.6 ± 3.3	15.5 ± 1.2	$p < 0.001$
Melody comparison	10.7 ± 2.5	14.3 ± 0.7	$p < 0.05$
Emotion	8.1 ± 2.1	8.8 ± 0.7	$p < 0.05$
Pitch	9.1 ± 2.2	10.0 ± 1.6	ns ($p = 0.104$)
Melody recognition	12.3 ± 1.6	12.4 ± 1.4	ns ($p = 0.638$)
Total score	56.7 ± 9.3	69.7 ± 9.0	$p < 0.01$

were less successful in this emotion subtest compared to healthy control subjects. Of four patients (three with an ischaemic, one with a chronic-degenerative genesis), the emotion anger was conspicuously often not recognised, which corresponds well with the observations of a special importance of the cerebellum in negative basic emotions. What was striking in the study was the patients' lack of awareness of the errors in the musical performances tested. Since severely disabled patients did not participate in the study, the clinical relevance of the results was difficult to classify anyway. Regardless of this, the test protocol used can certainly be included as an additional instrument for recognising specific musical limitations of the affected patients with brain dysfunction, even within the cerebellum. It is certainly important to distinguish the aetiology of cerebellar dysfunction, which had not been done in this way in the present work. In fact, the study results cannot be resolved with certainty in detail, especially since other parts of the cerebellum may also be affected in genetically determined, chronic degenerative cerebellar diseases such as Machado-Joseph disease, which might also influence the test results of musical abilities.

13.5 Therapeutic Implications

Despite the large number of pioneering and plausible studies on the neural background of music perception and the neurotopographical aspects of the processing of music in the brain, i.e. the cerebral cortex, the basal ganglia as well as the cerebellum, only a few studies have so far worked out the role of the cerebellum in more detail. In view of the also well-studied therapeutic effects of music in neurorehabilitation (see Chatterjee et al. 2021), this circumstance is surprising, where the therapeutic effects of music also suggest promising approaches for diseases within the cerebellum. In accordance with the aspects of cerebellar involvement in music perception elaborated here, a targeted activation of the cerebellum, for example, via the use of music in neurorehabilitative settings of supporting therapeutic processes with the aim of neural reorganisation within the cerebellum or the affected cerebello-cerebral connections could indeed be important. The causal basis for this assumption is grounded in the fact that music is typically used to facilitate or support motor movements, and moreover, is increasingly used in movement rehabilitation (Devlin et al. 2019). In addition, there is some evidence that music imagery, which has been reported to lead to similar brain signatures as music perception, may also support movement (Haire et al. 2021). It remains unclear whether and what influence the imaginal or musical cues have on the activation of individual motor systems of the human brain during simple movements. Here, again, a paper by Schaefer et al. (2014) is of interest, in which the neuronal activity during wrist flexions to heard or imagined music was compared with self-control of the same movement without stimuli in an fMRI study (Schaefer et al. 2014). In this work, the image data analyses focused predominantly on the motor networks of the brain, applying a mask of BA4, BA6, the basal ganglia, the motor nuclei of the thalamus and the whole cerebellum. As a result, movement to music, compared to self-directed movement, resulted in significantly increased activation in the left cerebellar lobulus VI. Movement to imagined music, compared to self-directed movement, in turn, significantly more activated the pre-supplementary motor area (pre-SMA) and the right globus pallidus. Significantly higher activity in lobulus VII of the cerebellum as well as the right hemisphere and the vermal lobulus IX was recorded in a direct comparison of the music and imagination conditions for the movements in the music condition, whereas significantly higher activity in the pre-SMA was shown for the imagination condition. Based on these results, the stimulation of movement by actual or imagined music appears to affect different network regions, including cerebellar regions, during movement, suggesting subtle differential modulation of heard and imagined cues to movement.

Notwithstanding the as yet unclear neurophysiological mechanisms, personalised music programmes have been proposed as a complementary therapy in cognitive rehabilitation and particularly for patients with Alzheimer's disease, as clinical studies have demonstrated improvements through music perception in agitation, anxiety and behavioural symptoms (Garrido et al. 2017). This recommendation is also well highlighted in an fMRI paper by King et al. which found specific effects on brain connectivity for individuals with clinically diagnosed Alzheimer's disease following a period of training with a personalised music listening programme (King et al. 2019). In this recently published work, patients with AD demonstrated specific activation of the SMA, a region associated with memory for familiar music and typically spared in early AD, when listening to a music they preferred. Interestingly, imaging data analysis for the condition of preferred musical stimuli revealed an increase in functional connectivity not only in cortical but also in cortico-cerebellar networks. With these separate results, again the complexity of brain connectivity in music perception and processing becomes clear, where the cerebellum also takes its part in the benefit of a therapeutic music training programme in patients with Alzheimer's disease (King et al. 2019).

A particular challenge in the study of elements of music therapy effectiveness is the interaction and therapeutic relationship between the patient and the therapist. A pilot study by Steinhoff et al. (2015) highlights this issue, where this work observed a reduction in specific pattern changes in the brains of four individuals with Unresponsive Wakefulness Syndrome during music therapy (Steinhoff et al. 2015). In this imaging study, three PET scans were performed in each patient: (1) at rest, (2) during the first music therapy exposure and (3) during the last music therapy exposure. To compare treatment effects, two patients in the music therapy group received music therapy for 5 weeks between the second and third PET examinations, and two other patients in the control group received no music therapy in the interim. According to the tracer uptake with a focus on the frontal, hippocampal and cerebellar regions, it was found that with some differences in these three observed brain regions, the tracer uptake was higher (34%) in the music therapy group than in the control group after 5 weeks. These preliminary results, with concordant activation of the cerebellum as well, provide fascinating evidence of cerebellar involvement in a specific music therapy treatment setting, which should inform further research. In summary, it is stated that in the few but promising studies, the separate involvement of the cerebellum in the therapeutic application of music in the use of passive or active music therapy is to be emphasised, so that further clinical and neurofunctional studies for the detailed investigation of the specific characteristics of the cerebellum, in particular the detailed analysis of the individual cerebellar regions and their connections above all to the (pre)frontal, the parietal and also the temporal cortex in connection with specific music therapy settings may be awaited with excitement.

13.6 Perspectives

With the work presented here and the considerations associated with it, we conclude that the traditional assumption of learning and maintaining essential components of culture (here: music) is not only the responsibility of the cerebral cortex alone, but also of the cerebellum in part. This specific performance of individual cerebellar structures, still to be clarified in detail, is learned through the repeated improvement of predictions, but also the control by internal models in the cerebellum and made available to the cerebral networks responsible for this (Ito 2008). According to Vandervert (2016), the following new explanations for music learning can be discussed:

- how the recent evolutionary expansion of the cerebellum was involved in the co-evolution of earliest stone tools and language leading to the cerebellum-driven origin of culture;
- how cerebellar internal models are blended to produce the creative, forward advances in culture;
- how the blending of cerebellar internal models led to human, multi-component, infinitely partitionable and communicable working memory.

In summary, according to previous research, the cerebellum is clearly found to be involved in both the hearing of music and the production of music, and thus in music processing. In clinical and neuroimaging research, different parts of the cerebellum have been identified for different aspects of these processing tasks and their connections to individual connections to the cerebral cortex as well as the basal ganglia have been elaborated. In this still rather young field of research, relatively little is known about the effects of disorders or damage to the cerebellum on music processing, and in turn the therapeutic influence of functional modulation of individual cerebellar target areas on music processing. This last aspect in particular will certainly play an important role in future neuroscientific research on music therapy.

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The Cerebellum and Beauty: The Impact of the Cerebellum in Art Experience and Creativity

14

Michael Adamaszek, Zaira Cattaneo, Andrea Ciricugno, and Anjan Chatterjee

Abstract

There is growing interest in the cerebellum's contributions to higher order functions of the human brain. When considering specific activities of the human cerebellum related to art, we differentiate two broad areas. Neural activity within different locations of the cerebellum is involved in art perception and in artistic creativity. The cerebellum plays an underappreciated role in neuroaesthetics, including the perception and evaluation of art objects, their appreciation and affective aesthetic experience. Certain areas of the cerebellum presumably are of particular relevance, incorporating cognitive and affective issues within large-scaled neural networks in perceiving and appraising artworks. For art creativity, many investigations report cerebellar implementations. Important areas in these domains are evolutionary younger parts of the cerebellar hemispheres, in particular the lobule VII with its Crus I and II, influencing crucial networks such as the Default Mode Network in optimizing creativity. These structures help guide pattern recognition and in art appreciation as they may play a role in predicting ongoing neural network activities through a crucial frontoparietal axis. In this chapter, we consider how our current neuroscientific understanding of cerebellar functions point to a likely role of the cerebellum in art appreciation and creativity.

Keywords

Cerebellum · Art creativity · Art experience · Multiple sensory integration · Internal models

14.1 Introduction

One of the most striking species-specific features of *Homo sapiens sapiens* is the ability to create novel ideas and solutions. Creativity is expressed in art, where artists use alternative and innovative ways to depict objects and scenes to convey specific semantic messages through different styles and media. Research on the neural basis of creativity, which has flourished in recent years, attempts to understand the brain mechanisms associated with creative thought (Benedek 2018; Chen et al. 2020). In a similar vein, researchers

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have tried to understand neural processes underlying the perception and appreciation of such artistic creations. In this regard, neuroaesthetics is a growing research field that investigates the neural underpinnings of aesthetic experiences (for reviews: Chatterjee and Vartanian 2014; Nadal and Skov 2015, Pelowski et al. 2017).

Aesthetic experiences are likely to be mediated by a flexible interplay between three main neural systems: the *sensory-motor*, the *emotion-valuation*, and the *meaning-knowledge* systems, the so-called “aesthetic triad” (coined by Chatterjee and Vartanian 2014) (see Fig. 14.1). Accordingly, widely distributed networks of brain regions involved in both low- and high-level processes, spanning from the occipital to frontal lobes are associated with aesthetic judgments about visual stimuli (for a meta-analysis, see Boccia et al. 2016; Chuan-Peng et al. 2020). Creative thinking also relies on dynamic interactions of large-scale brain systems cooperating to support the complex cognitive processes during creative cognition and artistic performance, such as goal-directed memory retrieval, response inhibition, and internally focused attention (Beaty et al. 2016, 2019).

Although cerebellar activity is sometimes observed in neuroimaging studies on creativity (Chamberlain et al. 2014; Saggar et al. 2015; Sunavsky and Poppenk 2020; for reviews, see Beaty et al. 2016; Chen et al. 2020) and aesthetic experience (Ishizu and Zeki 2013, 2014, 2017; Kirk et al. 2009a; Lacey et al. 2011; Vartanian and Goel 2004; for a meta-analysis see Boccia et al. 2016), its role is rarely discussed. More often, the cerebellum is excluded from analysis. Such a gap in our knowledge is surprising given that certain areas of the cerebellum (particularly its posterior lobe) serve as a critical hub of extended brain networks that mediate high-order cognitive, affective, and social processes (Adamaszek et al. 2017; Schmahmann 2019; Van Overwalle et al. 2020) through bidirectional connections with cortical and subcortical structures in the cerebrum (Buckner et al. 2011; Habas 2018; Habas et al. 2009). In this chapter, we provide an overview of the neurocognitive and emotional mechanisms subtending creativity and aesthetic appreciation. We then review empirical findings reporting cerebellar involvement in aesthetic perception and evaluation of artistic visual stimuli and the creative processes involved in art production. Finally, we propose potential mechanisms accounting for the involvement of the cerebellum in the aesthetic experience and how the cerebellum might implement these mechanisms through cortico-cerebellar and limbic-cerebellar networks.

14.2 The Cerebellum and Creativity

Most available studies on creativity in the visual arts are based on general views of creativity, which are typically contextualized as the production of both novel and useful forms (Pelowski et al. 2017). Cognitive models of visual creativity propose that creative ideation involves retrieval of semantic associations and their conceptual combination, executive functions including visual imagery, and an evaluation of responses, including inhibition of those that are irrelevant (Abraham 2014; Benedek and Neubauer 2013; Benedek et al. 2014; Sowden et al. 2015). Accordingly, neuroimaging studies on visual creativity report significant recruitment of right prefrontal regions (i.e. inferior and middle frontal gyri), thalamus and fusiform gyrus (for meta-analyses, see Boccia et al. 2015; Gonen-Yaacovi et al. 2013; Pidgeon et al. 2016). Furthermore, as shown by a study conducted on visual artists (Ellamil et al. 2012), the default mode network (DMN)—which is implicated in self-referential processing and is typically suppressed when a person engages with the external environment (Raichle et al. 2001)—contributes to the generation of novel ideas, possibly extracting useful information from memory. Additionally, the executive control network, comprising the dorsolateral prefrontal cortex (dlPFC), inferior frontal gyrus (IFG), and inferior parietal areas, evaluates the efficacy of candidate ideas and modifies them to meet the constraints of the goals of the task at hand. Both networks are connected with subcortical structures such as the striatum. The striatum releases dopamine in computing rewards and integrates information about action plans,

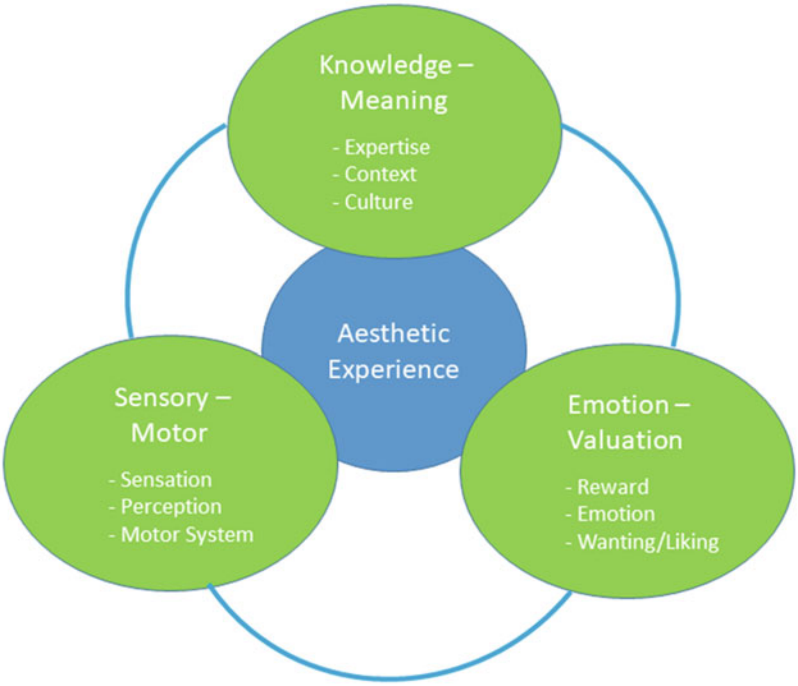

Fig. 14.1 The aesthetic triad, according to Chatterjee and Vartanian 2014, suggesting a model of three large-scale systems, i.e. the sensorimotor, knowledge-meaning and emotion-valuation, generating aesthetic experiences

motivation, strategy shifts and inhibitory control (Bostan et al. 2018). The balance in the dopaminergic release in these neural networks and the interplay of prefrontal-striatal circuits affect human creativity by increasing cognitive flexibility (Nijstad et al. 2010; Zabelina et al. 2016).

For art creativity, many investigations report cerebellar involvement (Chamberlain et al. 2014; Cogdell-Brooke et al. 2020; Fornazzari et al. 2020; Gao et al. 2017, 2020; Makuuchi et al. 2003; Miall et al. 2009; Ogawa et al. 2018; Saggar et al. 2015; Schlegel et al. 2015; Sunavsky and Poppenk 2020). Most of these studies report an increased involvement of circumscribed locations within the cerebellum accompany specific tasks like the development of drawing skills. Studying morphological features of the brain in art creativity, Chamberlain et al. 2014) reported greater white and gray matter density in the left anterior cerebellum, as well as the supplementary motor area (SMA) was associated with increased skill in drawing. Nevertheless, similar findings of cerebellar involvement were already reported in the early works of Makuuchi et al. (2003) as well as Miall et al. (2009). Makuuchi noted not only a structural, but also a functional increase in neural activity within bilateral posterior cerebellar hemispheres and anterior vermis (Makuuchi et al. 2003). The specific cerebellar findings in these studies were assumed to reflect growing perceptual proficiency following continuous training in drawing. This proficiency might be associated with developments in capturing procedural meaning and enhanced visual perception through the deconstruction and reconstruction of visual scenes as worked out when drawing (Kozbelt and Seeley 2007; Chamberlain et al. 2014), i.e. the integration of external visual cues, internal memory traces, and motor actions. So an artist shows superior skills in visual perception, and fine motor skills (Kozbelt and Seeley 2007), the specific training refines their perception of object details such as size, volume, and bodily space with procedural knowlegde (Rode et al. 2018). They also observed increased functional activities, associated with a structural expansion of the gray matter volume (GMV) in associative cerebral cortex areas such as the SMA and the prefrontal and parietal lobes. This expansion might be the result of increased task activity when subjects train in art creativity. As a result, this increased activitiy is accompanied by perceptual enhancement through specific visuo-motor and visuo-spatial mechanisms. Beyond these primary visual avenues, the observed increased activities of prefrontal-parietal and associated motor cortices might point to involvement of cognitive and affective aspects of visuo-creative perception and thinking, such as elaboration, flexibility, fluency, and originality, guiding spontaneous improvisation and figural creativity along several domains of a large-scaled sketchpad including the central executive and (visual and visuo-spatial) working memory of the drawing person (Baddeley 2003; Saggar et al. 2015). Interestingly, Chamberlain et al. (2014) found more creative thinking in participants after a drawing training course, suggesting that neural plasticity in the cerebellum integrates visual perception and creative action.

Sunavsky and Poppenk (2020), in an exploratory meta-analysis of neuroimaging studies about cognitive and neuroimaging predictors of individual differences in creativity, found multimodal contributions of the cerebellar anterior lobe, as well as less spatially and directionally consistent contributions from lobules VI–VIII, to multiple measures of creativity. Moreover, the anterior cerebellum and the parahippocampal gyrus were reliable predictors of creativity, suggesting two crucial brain sites have specific roles in working and long-term memory relevant to problem solving and imagination. Although cerebellar activations in art creativity had been observed in the right or even bilateral hemispheres, the left cerebellum with its strong connections to the right cerebral areas including the SMA (Schwartze et al. 2012) and posterior parietal cortex (Striemer et al. 2019) is of particular interest because of its possible association to visuo-spatial attention. Additionally, the cerebellum may participate in art creativity through its role in controlling eye movements guiding drawing in art production. Cohen (2005) observed a positive relationship between the frequency of eye fixation switches and the accuracy during the drawing actions of artists, which might indicate an unburdening of working memory. Markey et al. (2019) supported this assumption of a relationship of eye fixation to art perception, finding longer fixations in visual perception tasks for inconsistent objects as indicating an attempt to resolve the inconsistency into the expectations regarding the underlying schematic structure (e.g. the glass is *under* the bar) and/or meaning (e.g. a scene portrays a woman and a dolphin sitting in a car) (Markey et al. 2019). Schlegel et al. (2015) observed that increasing activity in the right anterior cerebellum was associated with motor control, proprioceptive feedback, and coordination between eye and hand movements (Buckner 2013; Floyer-Lea and Matthews 2004; Miall et al. 2001) in relation to subsequent drawing lessons. This activity might account for the dorsal (or vision for action) stream role in spatial awareness and guidance of movements such as the brush stroke. Thus, the cerebellar contribution to multisensory visuo-spatial analysis in creative production and perception might be subserved not only by the connections between the posterior cerebellar lobe and the parietal (in particular the posterior parts) cortex, but also by the supporting eye movements affected by the flocculus–paraflocculus and posterior vermis (Miall et al. 2000; Thier and Ilg 2005; Thier and Markanday 2019; Zeki et al. 2014). Notwithstanding, the specificity of these different cerebellar connections might depend on the task and therefore be involved in high-order domains of creativity, i.e. parallel connections to supplementary motor areas might engage with other sensorimotor learning tasks.

Besides the sensorimotor aspects of the cerebellum in art production, its role in higher order domains of art creativity is more intriguing. Functional neuroimaging studies showed that activations of the dorsolateral prefrontal cortex (DLPFC) and the posterior cerebellum covary with the number of solutions in creative processes (Goel and Vartanian 2005), indicating cerebellar involvement within distributed neural network in creativity. Creativity follows a three-level model with each specific neural activation modes, as suggested by Kaufman et al., a claim derived from observations in non-human primates (Kaufman et al. 2011). On this model, one level recognizing novelty relies on hippocampal functions with links to dopamine systems (Kumaran and Maguire 2009). A second level addresses observational learning, which among other structures, involves the cerebellum (Torriero et al. 2011). Finally, a third level processing innovative behavior is mainly instantiated by the prefrontal cortex with a balance between functions of the right and left hemisphere (Aupperle Robin and Martin 2010). For instance, the findings described by Chamberlain et al. (2014) of increased creative thinking associated with structural increase of the left cerebellum and SMA points to the assumption that the cerebellum is subsequently involved in these behavioral levels linking cognitive and affective processing at each level (Petrosini et al. 2015).

Hence creative thinking and action require different solutions: a role for the cerebellum is feasible when considering the cerebellar connections to the lateral and medial prefrontal cortices, parietal cortex, inferior temporal gyrus, and basal ganglia. As Ogawa et al. (2018) assumed, higher creative insight is achieved not only through creative common networks, including the DMN, but also through insight-specific connections such as semantic and cerebral-cerebellar networks (Jung-Beeman et al. 2004; Saggar et al. 2015). Whereas parts of the PFC (OFC, insula with its anterior, dorsal and posterior regions, and the anterior cingulate cortex) involve specific functions of cognitive control, decision making, emotion, autonomic interoception, somatosensory perception, and apprehension of salience which all constitute a comprehensive map of parallel processes in creativity (Liu et al. 2017), i.e. the details of a creative action assembles a broad spectrum of neural information, which is guided by parts of the PFC to gain the appropriate and meaningful synthesis in creative action. The impact of the cerebellum in particular with its crus I, processing the computation of visual information, including inverse kinematic mapping (Taig et al. 2012), is of particular relevance in disentangling mechanisms and their neural connections to crucial areas of the PFC to different degrees in creative process. According to Buckner and colleagues (Buckner et al. 2011), the Crus I and II are major regions coupled to the DMN, emphasizing the need to clarify the role of the Crus I and II in creativity and related cognitive and affective aspects. Since the DMN might initiate insight processing, the associated cerebral-cerebellar networks might be guiding insight-specific information, which modulates insightful problem solving as part of creative thinking.

The cerebellar contribution in creative processing at each level might be relevant to timing, sequencing and modeling of visual and auditory informations of an object that provides rapid and flexible manipulation of motor, cognitive, and affective demands (Vandervert 2017; Bostan and Strick 2010; Koziol et al. 2010; Saggar et al. 2015). This contribution of implicit brain processes might occur through specific parts of the anterior (in particular lobule V) and posterior (in particular lobule VI, VII including Crus I and I, and VIII) cerebellum (Habas et al. 2009; Krienen and Buckner 2009; Buckner 2013; Saggar et al. 2015; Ogawa et al. 2018). In fact, the cerebellum's role in mediating between environmental information and relevant motor, cognitive and affective actions likely apply to the implementation of novel strategies. According to internal models and mechanisms of error-based learning, the cerebellum adapts cerebral cortical activity to the individual context (Ito 2008; Schmahmann 2010). In particular, such influence on associative cortices, specifically at prefrontal sites, might modulate the outcome of ongoing creative processing traces (Petrosini et al. 2015). Therefore, reciprocal connections between the cerebellum and the lateral (DLPFC, IFG) and medial (vmPFC) areas of the PFC could serve as an interactive connection to formulate specific, in some instances new creative outcomes (Pochon et al. 2001; Bellebaum and Daum 2007; Koziol and Lutz 2013), comprising the implicit and explicit processes to problem solving (Ito 2008). These cerebellar contributions to attention and art creativity might interact with several neural networks, including the visual working memory, but also the ventral and dorsal attentional streams in task control with its adaptation and goal-direction mechanisms. Furthermore, cerebellar connections to prefrontal regions, specifically the DLPFC, could identify and clarify novel aspects for systematic storage and retrieval of mental models and representations, which might be relevant to implicit and explicit processes of an ongoing creative acts (Saggar et al. 2015). Implicit processing relies on cerebral-cerebellar interactions along inverse and forward models to facilitate and increase the efficiency of repetitive actions on mental representation (Ito 2008). Indeed, the Aha! effect characterizes the stage of a successive application of implicit processing (via inverse and forward modeling of the sensory informations along the responsible parallel cerebellar-cerebral networks) with an emerging conscious awareness of a solution to the creative task (Ito 2008; Petrosini et al. 2015; Saggar et al. 2015; Argyropoulos et al. 2020). This means, that the cerebellum feeds an internal model directly to a target neural assembly in the cortex, and/or along a parallel cerebellar-cerebral pathway as an inverse signal response. The Aha! effect therefore might represent the summation of a complete neural process within the responsible network, substantially within the PFC. The interactive processing of the highly distributed neural networks between different cerebellar sites and associative cortex areas thus support and therefore guarantee precise, fast and task-dependent execution and control of ongoing creative processing in the human brain. In terms of a more comprehensive view considering the application of internal models, the cerebellum presumably provides several different internal models to solve the demands of motor, cognitive and affective processing traces of the responsible neural networks in specific multimodal task processes, which could be feasible also for processes in creativity. According to several reports of cognitive and emotion impairments in cerebellar damage, the frequent afflicted attentional and executive domains are subject to worsening in quality (Parsons and Fox 1997; Ivry and Fiez 2000; Koziol et al. 2014), which might be relevant to creativity.

14.3 The Cerebellum and Art Perception

Aesthetic appreciation is the result of a dynamic interaction between different cortical and subcortical neural networks (for review, see Boccia et al. 2016; Chatterjee and Vartanian 2014). The extent to which a visual stimulus is preferred modulates neural responses at the level of low- and mid-visual processing of stimuli in regions in the ventral and dorsal visual pathways (Calvo-Merino et al. 2008; Chatterjee et al. 2009; Lacey et al. 2011; Vartanian and Goel 2004), likely reflecting the influence of bottom-up factors related to the salience of stimuli's perceptual features and top-down processes related to voluntary attention. Similarly, activation in cortical and subcortical motor-related regions is influenced by preferences (Calvo-Merino et al. 2008, 2010; Cazzato et al. 2016; Ishizu and Zeki 2013), possibly associated with implicit responses to the stimulus. These responses contributing to aesthetic evaluation may underpin a perceiver's empathic response toward visual art (Leder et al. 2012; see also Ticini et al. 2014, 2015). Moreover, implicit mechanisms related to motor preparation may also be at play, such as approach/avoidance behavior elicited by the perceived beauty or ugliness in the stimulus (Faust et al. 2019; Kawabata and Zeki 2004; see also Di Dio et al. 2007). Critically, aesthetic judgments are tightly linked to affective processes as demonstrated by the activations in both subcortical (i.e. striatum, amygdala, putamen) and prefrontal limbic and reward-related regions when viewing beautiful stimuli (e.g. Cupchik et al. 2009; Ishizu and Zeki 2013; Vessel et al. 2012). Furthermore, recent evidence suggests that the DMN might also be critically engaged when one finds an artwork especially moving (Belfi et al. 2019; Vessel et al. 2019). Indeed, activity patterns from the DMN can predict aesthetic appeal across visual stimuli, such as artworks, landscapes, or architecture (Vessel et al. 2019), possibly by monitoring the observer's internal state during continued engagement with aesthetically pleasing experiences, as well when disengaging from non-pleasing stimuli (Belfi et al. 2019).

Art perception and appreciation is the counterpart of the cerebellar contribution to creativity and may share similar mechanisms through reciprocal connections between associative cortices and certain parts of the cerebellum (Saggar et al. 2015; Ogawa et al. 2018). Nevertheless, the cerebellar involvement in art perception and appreciation is tied to the lateral hemispheres of the cerebellum, perhaps reflecting less motor and more cognitive and affective domains in art experience.

In contrast to neuroimaging and electrophysiological evidence for a cerebellar role in perception and processing of visual art, there are no relevant clinical data. Notwithstanding, previous clinical investigations of cerebellar involvement in emotion processing as reported by Schmahmann and Sherman (1998) and Adamaszek et al. (2013, 2014), might be relevant to cerebellar-cerebral involvement, especially feedforward connections to prefrontal, temporal, and parietal cortex and subcortical areas, in cognitive and affective cue perception and recognition. These findings may elucidate the cerebellar role in domains of emotion processing as applied to art perception and appreciation. A first approach arises from the close relationship between the aforementioned cerebral areas of emotion recognition of salient stimuli, such as the perception and discrimination of emotional facial expressions, for which cerebellar involvement is clear from clinical and neurophysiological observations (Adamaszek et al. 2013, 2015; Schutter and van Honk 2009; Ferrucci et al. 2012; Ferrari et al. 2018a). Indeed, the cerebellum appears to be a crucial hub in regulating one's emotional states (Adamaszek et al. 2017) and is a fundamental component of mentalizing network by which people read another individuals' mind (intentions, goals, emotions, thoughts, beliefs) (Van Overwalle et al. 2020). The posterior cerebellum has bidirectional anatomical and functional connections with cortical and subcortical regions involved in emotional processing (Buckner et al. 2011; Habas et al. 2009; Habas 2018; Sang et al. 2012). Based on the cerebellar role in recognizing emotions in facial expressions, the question arises whether the cerebellum also assigns aesthetic value through recognition and discrimination of emotions in art images. In an ongoing study, Adamaszek et al. (2021) postulate such a function for the cerebellum based on interim data analysis. In the study, similar to Melcher and Bacci (2013), patients with circumscribed injury to the cerebellum, predominantly in the posterior lobe, as well as healthy subjects of comparable age, were presented with art images with varying levels of valence and arousal. Participants assessed pictures from different art periods (fifteenth to twentieth centuries) with different emotions depicted (joyful, fearful, sad, angry, disgusted, neutral). The interim evaluation suggests that patients categorized the emotional valence of fewer pictures correctly. A separate test of affect discrimination of art pictures, i.e. the assignment of one presented art picture with a predominant basic emotion (i.e. joyful, fearful, sad, or angry) to a matching emotion of a disctinct art picture among a separate selection of four presented art pictures with different predominating basic emotion, remained without statistically significant effect. These provisional results suggest a cerebellar function of emotion recognition of visual stimuli that extends to art image representations (see also Ferrari et al. 2018b).

Despite these reasonable considerations of cerebellar functions in art perception, few studies have pursued this line of inquiry. Several neuroimaging studies report cerebellar activations in aesthetic perception, although most of these studies do not properly consider these activations. Indeed, many neuroimaging studies in cognitive and affective neuroscience are cortico-centric, and omit or do not include the entire cerebellum. Furthermore, disadvantages in MRI quality result in low cerebellar signal-to-noise ratio, and different cellular functions of the cerebellum without aerobic glycolysis (Vaishnavi et al. 2010) contribute to weak or even absent cerebellar activations when assessed by blood oxygenation levels (Marek et al. 2018). Finally, the cerebellum, in contrast to the cerebral cortex, has high individual variability, which further complicates its measurement in aesthetic paradigms. Therefore, it seems appropriate to study the neural underpinnings of aesthetic engagement by analysing resting state functional connectivity (RSFC). Williams et al. (2018) found the cerebellum involved with the right striatum and the ventral attention network, suggesting a cerebellar role in attention and processing of sensory information including engagement with the DMN. Further neuroimaging findings of the cerebellum in visual perception and analysis of aesthetic objects are reported by Ishizu and Zeki, who found expected activity in medial parts of the OFC, different parts of the cingulate cortex, the basal ganglia, and also in the cerebellar lobule VII with its Crus I and II (Zeki et al. 2014; Ishizu and Zeki 2014, 2017). The cerebellar findings are of particular interest, as the circumscribed activations of the lobule VII for different visually perceived aesthetic stimuli, i.e. for displayed mathematical formulas, images of beauty and ugly scene expressions, and images of different emotion valence such as joyful and sorrowful. Moreover, the activations of the Crus I and II differed in part according to emotion category of the stimuli, i.e. the Crus I was more responsive to negative, and Crus II more responsive to positive valence, which might be due to specific role of the activated parts of the lobule VII for the domain of emotion expressions in visual perception (Ishizu and Zeki 2017). The different patterns of functional connectivity of the cerebral areas such as the mOFC might be relevant to two specialized systems, i.e. a reward-related and an empathy-related system. These systems could relate to differently engaged nodes of the large-scaled networks associated with positive or negative emotional valence in visual perception and analysis also in art, as the mOFC (in particular A1) involvement for the experience of beauty is positive, rewarding, and pleasurable (Ishizu and Zeki 2017). Indeed, the cerebellum may act as a bridge between emotion and cognition, becoming activated by various tasks involving emotion judgments, empathy, and information updating relative to reward (Melcher and Bacci 2013).

The consideration of different specialized systems in relation to reward and empathy as two domains of multiple processing pathways of aesthetic experience in human brain leads to the request of disentangling the cerebellum and its subdivided regions in cognitive and affective aspects of aesthetic experience. Indeed, the processing emotional cues in art is likely to be complex, involving cortical areas such as the ACC, OFC, the insula, and the IFG, but apparently involving also certain areas of the cerebellum (Wang et al. 2014; Hoche et al. 2016), which are in turn connected with aforementioned cortical areas of the PFC. These regions can be viewed as a bridge between emotion and cognition, becoming activated in various tasks involving emotion judgments, empathy, and information updating relative to reward (Melcher and Bacci 2013). Moreover, the cerebellar involvement in various emotions, e.g. subjective emotion of plesantness and unpleasantness (Kühn and Gallinat 2012; Pujol et al. 2018), facial expressions Ferrucci et al. 2012; Schutter and van Honk 2009; Adamaszek et al. 2015; Ferrari et al. 2018a), voices (Adamaszek et al. 2014; Thomasson et al. 2019) and language (Keulen et al. 2017), and in various cognitive domain, e.g. executive functions (in particular set-shifting, abstract reasoning, working memory, visuo-spatial organization) (Schmahmann and Sherman 1998; Ito 2008; Marek et al. 2018), should be candidates for cerebellar contributions to the cerebral processing pathways of aesthetic perception and evaluation. Whereas the phylogenetically older parts of the cerebellum, in particular the vermal structures, are thought to be involved in basic affective response mechanisms with little or no access to conciousness (in particular for short-looped circuits processing rapid responses for threating or strong unpleasant emotions), the relatively younger parts within the expanded lateral hemispheres are frequently tied to more elaborated processing of emotions, which are coupled to processings of associated cognitive domains (Buckner 2013). In this view, the cerebellar lobule VII with its Crus I and II may function as a central hub in diverse large-scaled neural networks of aesthetic processing and across different stimulus categories (e.g. faces, paintings, music, architectures, moral judgments, mathematical equations (e.g. Kühn and Gallinat 2012; Vartanian et al. 2013; Zeki et al. 2014).

Aesthetic experiences can be subdivided into processing stages from the early perception of an object, followed by late stages involving cognitive top-down mechanisms (Pelowski et al. 2017). According to a recent proposed model of Pelowski et al. (2017), which closely follows previous developed models of art experience such as those proposed by Chatterjee (2004) with a focus on visual interactions in art experience and Leder and Nadal (2014) with a emphasis of cognitive aspects, perceptual analysis, implicit memory integration and explicit classification represent earlier art processing, while cognitive mastery including the check of self-relevance and schema congruence and stages guiding art evaluation are tied to later stages. Affective processing occurs in parallel with cognitive processing, e.g. the evaluation of emotional valence when processings both content and form.

The principle observation that object perception and evaluation have early, intermediate, and late stages of are typical in cognitive neurophysiology. In fact, early signals elicited by emotion-laden task are reflected in bottom-up processes, whereas subsequent top-down processes are predominately reflected by ongoing intermediate and late stages of affective stimulus evaluation (Sabatinelli et al. 2013). While these observations are typically ascribed to cortical networks, the involvement of the cerebellum in modality-specific perception and processing across different stages is also evident from neurophysiological studies. Adamaszek et al. (2013, 2015) and Styliadis et al. (2015) reported that cerebellar structures are involved in early, intermediate, and late recognition and processing of salient stimuli as demonstrated using affectively loaded images of the IAPS. More precisely, both studies applying event-related potentials (ERP) paradigms with emotion-ladened IAPS images showed that the cerebellum, in particular the Crus I and II of the cerebellar hemispheres, were associated with the early and late stages of the responsible cerebral networks along the temporo-occipital as well as the frontoparietal networks of emotion processing. Moreover, a different time course of early and late reflecting temporal delineations were found for valence (positive and negative) and arousal (high low), indicating segregated involvement of the cerebellum to different affective ingredients of emotion processing. Accordingly, these studies emphasize not only the functional feedforward connections between the cerebellum and parietal and prefrontal cortex, but also its temporal attributes, which might apply to timing in art perception (Jacobsen 2013; Markey et al. 2019). In fact, such neurophysiological patterns of early and late ERP reflecting specific encoding of emotion and cognitive cues have been described in two electrophysiological studies by Jacobsen and Höfel (2001, 2003). In these studies, an aesthetic judgment elicted a fronto-central located negative deflection (around 300 and 400 ms) after stimulus onset, reflecting impression formation in the brain, and a late positive potential (LPP), reflecting evaluative categorization of the perceived aesthetic stimuli (Cacioppo et al. 1994). Sustained analysis of symmetry, in contrast, resulted in a longer lasting, late-onset ERP deflection with a posterior distribution. In another electrophysiological investigation of aesthetic evaluation in paintings (Markey et al. 2019), the authors used digital reproductions of surrealistic paintings, containing semantic or syntactic inconsistencies. The obtained ERP associated with the semantic and syntactic aesthetic discrimination showed different time courses, i. e. an early phase around 400 ms poststimulus predominated by a neural signal evolution for semantic, followed by a late phase around 600 ms for syntactic aspects in aesthetic discrimination. The latter observations are of interest since Adamaszek et al. (2013) identified cerebellar contributions to syntax processing in a linguistic paradigm. The cerebellum also contributes to semantic processing (Jacob et al. 2019), perhaps through a principal cerebellar connection to frontoparietal networks that guiding internal models of semantic and syntactic order and meaning in paintings and lyrics.

Studies comparing brain circuits involved in the aesthetic evaluation of visual artworks and non-artistic stimuli (e.g. photographs or altered versions of original paintings) report specific activations for the artworks in occipital regions (Di Dio et al. 2007; Lutz et al. 2013; Mizokami et al. 2014), as well as limbic and reward-related structures, such as the insula, ventral striatum and caudate nucleus (Di Dio et al. 2007, 2011; Lacey et al. 2011; Vartanian and Goel 2004). A few of these studies also report cerebellar activations in the right lobule VI and bilateral lobule VIIb, for the aesthetic evaluation of artworks, but not with the same judgment for non-artistic stimuli (Di Dio et al. 2011; Mizokami et al. 2014; Vartanian and Goel 2004; but see Di Dio et al. 2007; Lutz et al. 2013). These findings suggest that the cerebellar contribution might be modulated by the artistic status of stimuli, thus suggesting that artworks, representing more salient (emotional) stimuli, may trigger greater cerebellar activations (Moreno-Rius 2018; Pierce and Péron 2020).

14.4 Functional Aspects of the Cerebellum in Art Experience

A critical and comprehensive understanding of the cerebellum in neuroaesthetics faces the challenge of mapping the growing neuroscientific knowledge about art perception and processing to an increasingly differentiated understanding of cerebellar involvement in higher order functions of the brain. The cerebellum is essential for cognitive and emotional processings that are pertinent to empathy, theory of mind, moral judgment and action, and in all likelihood aesthetic evaluation. These psychological functions are embedded in complex systems consisting of neural circuits that operate as modules in a decentralized, highly parallel fashion selectively engaged by environmental demands to produce adaptive behavior. The cerebellum is suited to regulate these distributed systems to modulate behavior automatically and optimize states around a homeostatic baseline adapting to the relevant context (Leiner et al. 1986; Ivry and Fiez 2000; Demirtas-Tatlidede and Schmahmann 2013; Argyropoulos et al. 2020).

Neuroscientific research into the cerebellum has mapped the cerebellar connections to association networks of the cerebral cortex, including central executive control networks (in particular DLPFC) and the DMN (Parsons and Fox 1997; Habas et al. 2009; Krienen and Buckner 2009; Brady et al. 2019). The underlying neural organization of the cerebellar-cerebral connections constituting large-scale feedforward pathways is a focus of contemporary research into cerebellar contributions to high-order neural networks (Benagiano et al. 2018; Guell and Schmahmann 2020; Sereno et al. 2020). The intracerebellar neural organization of functional modules and the cerebello-thalamo-cerebro-cortical circuits (CTCC) might be considered main structural elements (see also Fig. 14.2), whereby the CTCCs of the posterior cerebellar hemispheres, i.e. lobule VI up to VIII, are segregated and progressively interconnected associative cognitive brain areas such as the prefrontal and parietal lobes, the amygdala, hippocampus, temporal lobe, hypothalamus, septal nuclei, basal ganglia including the nucleus accumbens (Heath and Harper 1974; Haines et al. 1997; D'Angelo and Casali 2013; Palesi et al. 2020). Lobules VII through X, as non-motor areas of the cerebellum, are linked to the dentate nuclei in cognitive, and to the midline fastigial nucleus in limbic functions (Schmahmann 2010). Interestingly, the sensorimotor functions are linked to the anterior cerebellum, but also in part to lobule VIII (and parts of lobule VI), whereas the cerebral associations areas are heavily linked to lobule VII (Crus I and II), with spread to lobule VI (Krienen and Buckner 2009; O'Reilly et al. 2010). The crus I and II is a special hub, as suggested in a meta-analysis by Keren-Happuch et al. (2014), which outlined a topographically organized cerebellar parcellation with the crus I and II for executive functions, emotion, language, and working memory. This topography underpins the observations of the cerebellar role in cognitive domains of executive and default mode networks such as abstract reasoning, problem solving, and self-reference (Schmahmann 2010; Vandervert 2017; Steward et al. 2019; Argyropoulos et al. 2020).

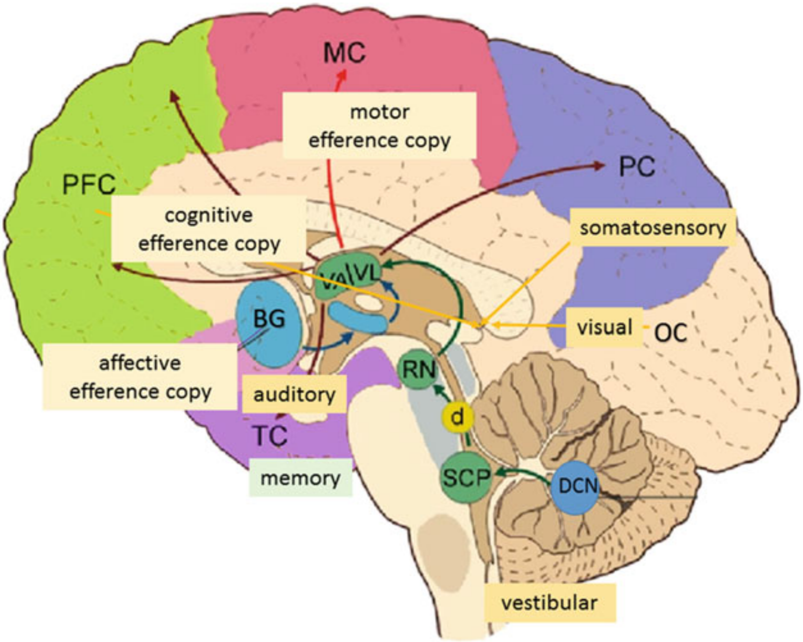

Fig. 14.2 Overview of cerebellar-cerebral connections of eloquent sensory or associative cortex areas. According to the main connection lines, cerebral information enters the appropriate areas within the cerebellum via the pons, whereas outgoing signals go along the superior peduncle to the thalamus via the deep cerebellar nuclei and the dentate nucleus and further to the responsible areas, mainly of the prefrontal cortex. Abbreviations: *PFC* prefrontal cortex, *MC* motor cortex, *PC* parietal cortex, *TC* temporal cortex, *OC* occipital cortex, *BG* basal ganglia, *VA/VL* ventroanterior/ventrolateral thalamus, *RN* ruber nuclei, *SCP* superior cerebellar peduncle, *DCN* deep cerebellar nucleus. Under permission of Palesi et al., Brain Funct Struct (2014)

Similarly, the cerebellum may prioritize, process, and coordinate emotional experience along bottom-up- and top-down pathways (D'Angelo and Casali 2013). In a recent brief overview by Habas (2017), the "emotional" cerebellum might include several specific and non-specific areas, whereby these topographically divided areas occur in two main clusters. More precisely, one cluster, substatiated by vermal and paravermal areas in association to deep cerebellar nuclei (especially the fastigial nuclei) with a prominent role of lobules VI-VII, may take part in primary emotion processing of salient cues. This "medial limbic" part of the cerebellum may belong to the salience network, including the insula, frontal operculum, anterior cingulate and medial prefrontal cortices, but maybe also include the amygdala and hippocampus (Habas 2017). The other cluster involves the laterally located lobules VI–VIII, especially crus I and II, as parts of the executive cerebellum with its connections to the dentate nucleus, and regions of the prefrontal cortex including cingulate cortex, but also the hypothalamus, may be recruited by cognitive aspects of emotion processing (working memory, attention allocation, emotion evaluation, response selection) or associative learning, constituting a phylogenetically more recent "limbic" area within the cerebellum. Both clusters (medial and lateral "limbic" cerebellum) seems to be not only involved in experience of emotion, but also in the control and coordination of autonomic, cognitive, and appropriate behavioral responses along salience and executive networks (Habas 2017). These topographical distinctions point to specific contributions of cerebellar areas with its feedforward actions to the large-scaled networks, supporting the control, organization, and comprehension of complex sequences involved in different technical and social intelligence (Barton

2013) including language and visual displays such as facial expressions, gestures, and presumably arts. These functions subserved by the cerebellum in attentional, but also executive and default mode networks of the prefrontal cortex (PFC) and the posterior parietal cortex (PPC) along a precise timing of sensory predictions, including visuo-spatial integration (Ivry and Fiez 2000; Schmahmann 2010; Buckner 2013), and a specific cerebellar involvement in probalistic reasoning of external events (Vandervert 2018), which are integrated in fast and unconscious automatic processing.

The neuroanatomical and neurofunctional connections of cerebellar areas to cerebral networks of high-order domains strengthen the hypothesis that the cerebellum interfaces with information sequencing and the temporal characteristics of cognitive and affective cues. One crucial mode of providing such high-order processes is represented by the specific cerebellar actions in sensory encoding as it has been emphasized to attention (Allen et al. 1997; Courchesne et al. 1994; Breska and Ivry 2020). The specific impact of distinct cerebellar areas on these sensory attention modes is to guide incoming information from the environment, thus manipulate objects and forward this detailed information for further integration, facilitating the efficiency of sensory systems with its connections to motor and non-motor areas, including autonomic neural systems (Gao et al. 1996; Parsons and Fox 1997; Ivry and Fiez 2000). The cerebellum provides feedback to cerebral activity in ongoing behavior, including adaptation to subsequent or even future sequelae, pointing to a predictive interface in task-dependent neural networks in error-based corrective mechanisms. This means that the cerebellum compares the signals of stimulus-activated neural networks for a predictive match, forming anticipatory adjustments to signals from the cerebral cortex and therefore supporting optimal outcomes (Courchesne and Allen 1997; Paulin 1997; Ivry and Fiez 2000; Ito 2008; Schmahmann 2010). These predictive functions of the cerebellum are presumably related to the internal model of Ito (2008), which explain feedforward cerebellar-cerebral modes in guiding sequential and temporal information of ongoing visual or acoustic task-related cognitive and affective processing most effectively (Ivry and Keele 1989; Moberget and Ivry 2016; Bares et al. 2019). Accordingly, the cerebellum function as a versatile supervised learning machine of spatiotemporal information that constructs or generates internal models for the control and adaptation of behavior across contexts (Koziol et al. 2014). This role outlines the cerebellar relevance to executive networks in face of increasing situational complexity (D’Angelo and Casali 2013). This assumption fits observed clinical findings of disturbed motor and non-motor functions in cerebellar disorders, indicating a blurring of time-dependent fine-graded signal of motor and non-motor coordination (Ivry and Keele 1989; Ito 2008; Schmahmann 2010; Argyropoulos et al. 2020) as has been found in a variety of perceptual tasks across different sensory modalities such as audition (Ivry and Keele 1989; Mangels et al. 1998), vision (Ivry and Diener 1991; Nawrot and Rizzo 1995), somatosensation (Grill et al. 1994), and speech (Ackermann et al. 1999). A principal feature of an internal model is the harmonious tracking and control of interrelated activities between a perceived object (including sensory and attentional domains) and following stages of object processing (Ito 2008) that involves manipulation of mental representation and behavioral decision such as the analysis and computation of specific sensory modalities to suitable motor, cognitive, and affective behavior outcome (O’Halloran et al. 2016). This specific cerebellar mode in generating internal models may be particularly critical for art perception and evaluation. The context under which stimuli are viewed influences aesthetic appreciation by modulating the individuals’ predictions regarding the sensory and emotional reactions within art engagement (Chatterjee and Vartanian 2014) and the associated neural activity in the OFC and medial prefrontal cortex (Kirk et al. 2009b), which suggests that activity within emotional and reward neural circuitry is biased by subjects’ prior expectations about the likely hedonic value of stimuli according to their source.

An interesting model directly relates the aesthetic experience within a predictive coding framework (Kesner 2014; Van de Cruys and Wagemans 2011; Wagemans 2017; see also Wolf 2020). According to this model, a temporary state of unpredictability (i.e. prediction error) is important for the emergence of perceptual pleasure when encountering a work of art. Within this framework, to engage with a work of art, viewers must adapt their prediction mechanisms to recognize art as a specific class of objects whose nature is ambiguous. Moreover, viewers sustain a flow of predictions, from low-level sensory predictions required for object recognition, to more abstract semantic, conceptual, and affective inferences aimed at grasping the meaning of the artwork (Kesner 2014). Aesthetic pleasure is experienced when the perceiver succeeds in solving the prediction error and moves from an initial state of high uncertainty that captures attention (higher prediction errors), to a final state of the models' refinement (higher predictability and a reduction of the prior prediction errors). Critically, the process of minimizing prediction errors is further, and perhaps decisively, affected by the viewer's access to external facts, extra-pictorial information, such as artwork captions or titles, that cannot be gathered from the visible configuration of the image itself. Still, the observer's mindset, like personality traits, affective style, art expertise, as well as the momentary psychosomatic state, determines which top-down expectations and predictions are generated, and form priors that operate in the perception of art (Kesner 2014). The cerebellum may play a role in these predictive mechanisms.

Accordingly, as Thach (1998, 2007) and also Schmahmann (2010) outlined, the cerebellum is linked to cognitive activities, presumably by regulating the speed, smootheness, capacity, consistency, and appropriateness or otherwise accuracy of the underlying processes in cerebral cortex and therefore as a skillfull execution of mental acts including embodied affective constituents (Leiner et al. 1986; Thach 1998; Ito 2008; Schmahmann 2010). In regard to the requested mode of the cerebellum in visual art, the findings in several clinical and neuroimaging trials for supporting neural networks in imagery tasks are quite intriguing in approaching a comprehensive view of the cerebellum in visual perception and analysis of art objects (Decety et al. 1990; Parsons et al. 1997; Sergent et al. 1992). Different domains of the working memory are active for many aspects of art creativity and perception by retrieving and monitoring specific informations including the anticipation of sequences along executive, spatial, and tonal function levels, as it has been also proposed for music practice (Chen et al. 2008; Schulze and Koelsch 2012). The cerebellar efficacy to specific art training, whether in painting or music performance, is probably due to a discrete neuroplasticity and the resulting cerebro-cerebellar improvement of the central executive functions of working memory. Moreover, as it has been argued for music training (Lee and Noppeney 2011), cerebellar-premotor circuitries deem to work on a forward model mapping integrating, i.e. blending or binding visual, auditory, and tactile information. According to Ito (1997) and Vandervert (2015), the improvement of the crucial working memory here can be understood as the result of the learning of error-driven cerebellar internal models, whereby these error-driven adaptive cerebellar internal models progressively increase the speed, consistency, and appropriateness of the central executive (and other components) of working memory in different, among others, visuo-spatial domains (Thürling et al. 2012). The cerebellum provides moment-to-moment, unconscious, very short time-scale, anticipatory information (Akshoomoff et al. 1997) for cognitive, emotional, and motor integration, and, thereby, for voluntary control also of art creation and perception. Interestingly, Yomogida et al. (2004) suggested a critical involvement of the cerebellum in mental visual synthesis, assuming that this visual synthesis consists of taking part of various personal conceptions and combining them to give new forms and images more selective (Vandervert 2015). This consideration might be of particular interest when applying the approach of the development of creativity in modern art to new forms and gestures, such as Picasso elaborating his artistic virtuosity in the paintings of the middle creative periods (see example in Fig. 14.3), which might be also a result of blending of internal models within old and new visuo-spatial contexts as provided by responsible areas of the prefrontal and parietal, but also the cerebellum (Lee and Noppeney 2011). In fact, as Picasso was driven by a cognitive-emotional intent concerning his concept of the purpose of art, this cognitive-emotional intent and conception arising in the cerebral cortex drives the blending of cerebellar internal models (Imamizu et al. 2007) learned during acquisition of his skills of art composition and during his real-time professional renderings. Accordingly, these cerebellar internal models are sent to and blended in the cerebral cortex before and during the rendering of his art, with each painting feeding back in a positive feedback loop to his ongoing artist development. As this ongoing development takes place in this positive feedback loop the art would become increasingly “abstract” (Vandervert 2022).

Nevertheless, the cerebellum in association with the parietal, in particular PPC, and the strong connections to lateral (dorsolateral) and medial (ventromedial and orbitofrontal) areas of PFC, are likely to be involved in feedforward control (Ito 2008; Schmahmann 2010; Buckner et al. 2011), which is emphasized by the elaborated growth of these brain regions in human evolution (Ito 2008; Schmahmann 2010; Buckner 2013; Neubauer et al. 2018; Marek et al. 2018). The evolution of cerebello-cerebral connections to these prefrontal, parietal, and temporal areas underpins the presumed cerebellar involvement to the frontoparietal networks with its broad processing in high-order domains such as creativity and art experiences (Zaidel 2013). As Marek et al. (2018) suggested, the lateral and posterior parts of the cerebellum are disproportionately expanded in the human brain, co-activating with the cortex across a vast array of control-related functions supported by the frontoparietal network (Marek and Dosenbach 2018), including error processing (Dosenbach et al. 2006; Fiez 1996), task switching (Monsell 2003), and language (Mariën and Borgatti 2018). The functional development of the parietal cortex to orientation, attention, cue perception, sensomotoric processing and visuo-spatial integration, fits cerebellar developments in visuo-spatial processing, working memory, social cognition and also affective processing. A prominent growth of these brain parts is therefore fairly representative for the increasing need for human communication to meet the demands of adapting between the internal conditions to specific external conditions of the environment (Neubauer et al. 2018; Marek et al. 2018). In addition to cerebellar coding of motor and sensory patterns, cognitive and affective-behavioral patterns come into question here in order to map external events as well as artistically designed mapping of experiences and assumptions, reality and imagination in the respective contexts in the best possible way and to derive decisions or plans of action (Ivry and Fiez 2000; Zaidel 2013). The cerebellum is indeed active, i.e. its posterior parts, especially lobule VII with crus I and II, in cognitive and affective tasks, but also vermis with its phylogenetically older parts in connection with limbic networks, in the acquisition of emotional information (Koziol et al. 2014). Since these areas are also active in simple as well as complex action decisions, cerebral-cerebellar connections are assumed to process incoming sensory signals within visual neuronal process pathways in the form of art representations in detail and assign multimodally to the cognitive and affective as well as motor and autonomic reaction or action levels.

14.5 Conclusion

Since the proposal of the Cerebellar Cognitive Affective Syndrome or otherwise Schmahmann’s syndrome (Schmahmann and Sherman 1998) that described executive functioning, language, visuo-spatial deficits and anomalous affective behaviors following cerebellar dysfunction, a growing number of studies focused their investigations on the cerebellar role in high-order domains of our behavior. This new research led to a more comprehensive appreciation of the cerebellum as a critical node of extended networks allocated to

Fig. 14.3 Woman in a fish hat, Picasso 1942. Under permission of http://freepicture24.blogspot.com

high-level and more abstract cognitive and affective processing, through anatomical and functional connections with both cortical and subcortical structures in the cerebrum (Buckner et al. 2011; Habas 2018; Habas et al. 2009; Sang et al. 2012).

Notwithstanding the advance of our knowledge about high-level cerebellar functions, the contribution of the cerebellum to art experiences, and in particular to art creativity and art appreciation, has been almost completely neglected. The findings reviewed in the present chapter suggest that posterior cerebellar regions, predominantly in lobule VII with its Crus I and I as well as the vermis comprising cortico-cerebellar and limbic-cerebellar networks, should be considered of particular interest in diverse large-scale neural networks of aesthetic processing, including art perception and appreciation as well as creative thinking. Considering the cerebellar role in context-based predictions and the involvement of predictive mechanisms in driving aesthetic pleasure as well as improvisation and creativity, the cerebellar functional significance in neuroaesthetics may rely on its ability to implicitly implement and coordinate both low-level sensorimotor predictive mechanisms and higher-level inferences requiring the appraisal of the cognitive and affective salience of stimuli. Future research is needed to disentangle the specific role of the cerebro-cerebellar networks in different facets of aesthetic experiences.

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Cerebellum and Emotion in Social Behavior

15

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Abstract

Accumulating evidence suggests that the cerebellum plays a crucial role not only in the motor and cognitive domains but also in emotions and social behavior. In the present chapter, after a general introduction on the significance of the emotional components of social behavior, we describe recent efforts to understand the contributions of the cerebellum in social cognition focusing on the emotional and affective aspects. Specifically, starting from the description of the cerebello-cortical networks subtending the social-affective domains, we illustrate the most recent findings on the social cerebellum and the possible functional mechanisms by which the cerebellum modulate social-affective behavior. Finally, we discuss the possible consequences of cerebellar dysfunction in the social-affective domain, focusing on those neurological and psychopathological conditions in which emotional and social behavior difficulties have been described as being associated with cerebellar structural or functional alterations.

Keywords

Cerebellar sequencing · Social interactions · Prediction · Cerebro-cerebellar circuits · Social-affective alterations

15.1 General: Emotions in Social Behavior

Emotional processing includes immediate physiological responses and both automatic and intentional behavioral reactions to life events, proving critical to individuals' survival and adaptive social relationships (Lerner et al. 2015). Humans are intrinsically predisposed to perceive and understand their own and others' emotions and are constantly engaged in social interactions (Zaki and Ochsner 2011). One of the most primitive and key processes for successful social interactions is the ability to infer others' emotions from visual and acoustic features, such as facial expressions and vocalizations (Schaller and Rauh 2017). While this ability reflects automatic aspects of emotion recognition, the ability to integrate contextual information with emotional states and to make detailed appraisals based on the interplay between present and past conditions is a reflection of more conceptual aspects of emotion recognition (Siciliano and Clausi 2020). Emotion recognition represents one of the two core components of social cognition, a composite human function defined by Brothers (Brothers and Ring 1990) as

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"the processing of any information which culminates in the accurate perception of the dispositions and intentions of other individuals." The other component of this complex function is termed mentalizing or theory of mind (ToM), which consists of the advanced capacity to recognize and attribute mental states, such as emotions, intentions, and beliefs, to others (Premack and Woodruff 1978). This human ability allows us to make abstract social inferences in terms of past, future, or hypothetical events to adaptively predict social-affective behaviors (Van Hoeck et al. 2013). Emotion recognition and ToM are two closely linked processes since the recognition of others' emotional state and related relevant cues culminate in the recognition of intentions (Brothers and Ring 1990). In this framework, social cognition processes could be viewed along a continuum, ranging from more automatic emotional processing to the recognition of complex emotional and mental states. Along this continuum, the ability to recognize the emotional state of others, based on specific situations and contexts, coincides with the capacity to empathize with them and has been defined as the affective component of ToM (Abu-Akel and Shamay-Tsoory 2011). Whereas affective ToM is thought to involve emotional contagion and empathetic appreciation of others' emotional states, cognitive ToM is believed to require the understanding that others may have beliefs and intentions that differ from ours (Shamay-Tsoory 2011). Although these two components are separate aspects of ToM, their cooperation is needed to guarantee effective social interactions (Shamay-Tsoory et al. 2009). This model is in line with the one proposed by Coricelli (2005), which described a two-mind reading process: an unconscious/automatic process that allows the decoding of others' intentions by the recognition of action and emotional contagion and a conscious/voluntary process that is linked to the ability to take the perspective of others and to use anticipatory and comparative mechanisms to make assumptions regarding their mental state (Coricelli 2005).

The multifaceted nature of these functions is supported by extended and dynamic neural networks composed of limbic areas, including the amygdala, hippocampus and insula (Phillips et al. 2003; Kipps et al. 2007; Gu et al. 2012), and cortical and associative areas, such as the anterior cingulate cortex, superior temporal sulcus (STS), temporo-parietal junction (TPJ), medial precuneus, and medial and lateral prefrontal cortex (Kennedy and Adolphs 2012; Van Overwalle et al. 2014). Despite the high specialization of these structures, constant interactions between them are needed to accomplish such complex functions, and overlaps can be found between emotional and social brain (Fossati 2012).

Nevertheless, the large-scale network sustaining all the functions covered under the umbrella term social cognition has yet to be well defined, and the role of the cerebellum is becoming increasingly emphasized (Van Overwalle et al. 2020a). The demonstrated influence of the cerebellar vermis, termed the "limbic cerebellum," in emotional processing represents a crucial starting point for broadening its role in related affective and social fields (Adamaszek et al. 2015; Leggio and Olivito 2018). Indeed, recent MRI studies have shown cerebellar involvement in different aspects of social-affective behavior (Van Overwalle and Mariën 2016; Van Overwalle et al. 2020b). In particular, it has been highlighted that specific and phylogenetically more recent regions of the cerebellum are activated during complex social cognition tasks and are coupled with brain areas belonging to the mentalizing network (Van Overwalle et al. 2014; Van Overwalle and Mariën 2016). This interesting issue will be described in depth in the following sections.

15.2 The Role of Cerebro-Cerebellar Circuits in Social-Affective Behavior

Consensus is growing on the starring role of the cerebellum in social-affective behavior. Indeed, although this very interesting field is still at its early stages, many research findings point to a better understanding of the involvement of the cerebellum in social-affective domains. Substantial data come from structural and functional neuroimaging studies, which provide a useful characterization of the cerebellar functional topography for emotional (Stoodley and Schmahmann 2010) and social processing (Van Overwalle et al. 2014, 2015).

The cerebellar vermis has been indicated as the principal target of limbic connections, supporting the modulation of more "primitive" emotions (Schmahmann 1991; Schmahmann 2000) and the processing of stimuli that are critical for the emotional/affective experience (Schmahmann and Sherman 1998). In contrast, more complex emotional processing, such as social mentalizing, recruits specific regions in the posterior cerebellum (Van Overwalle et al. 2014, 2015). Accordingly, in a recent meta-analysis, Van Overwalle et al. (2020b) investigated which areas of the posterior cerebellum are specialized for social mentalizing and found that the Crus II was shown, in approximately 75% of the studies, to support domain-specific social cognition tasks related not only to social mentalizing but also to self-related emotional experience. Interestingly, among the mentalizing tasks, the highest percentages were found in subcategories examining attribution of others' emotions (27%) and emotional self-experiences (17%). Notably, predominant activity during mentalizing tasks has also been found in the lobule IX of the cerebellum.

Considering that social cognition is a sophisticate mental processes, neuroimaging studies on brain functional connectivity (FC) have proven very useful in characterizing the complex brain networks involved in this function. In this field, the findings accumulated within the past decade have proven the presence of segregated cerebellar functional organization that allows the cerebellum to play a crucial role in emotional and social processing through its functional interactions with specific emotional and social brain cerebral regions (Leggio and Olivito 2018). Specifically, a study investigating the pattern of resting-state FC among vermal, paravermal, and hemispheric regions of the cerebellum (Sang et al. 2012) suggested that the cerebellum has a third functional subdivision, beyond the motor and cognitive subdivisions, that is devoted to emotional processing. Functional coherence was found between the cerebellum and brain limbic structures typically implicated in emotional regulation, such as the hippocampus and the amygdala (Sacchetti et al. 2009; Milner et al. 1998; Phelps and Le Doux 2005). In particular, the vermal I–VI, Crus II–X, hemispheric I–VI, and Crus II and IX regions are functionally connected to the hippocampus, while the vermal I–V, VIIb, VIIIa,b, and IX and hemispheric I–VI and VIIb regions are more functionally connected to the amygdala (Fig. 15.1a).

Further studies investigating cerebellar contributions to cerebral intrinsic connectivity networks reported patterns of functional coherence between the vermal and hemispheric parts of the lobule VI, the adjacent Crus I, and the dentate nuclei with the salience network (Habas et al. 2009). This network includes the dorsal anterior cingulate cortex and the fronto-insular cortex and is involved in interoception, autonomic regulation, and emotional regulation (Seeley et al. 2007). Lateral hemispheric regions of the posterior cerebellum (especially the Crus I/II), which are part of the "executive cerebellum," also show connectivity with the salience network (Habas et al. 2009; Stoodley and Schmahmann 2010) and are likely to be recruited when more cognitive aspects of emotional processing are in demand.

Several resting-state fMRI studies also proved the participation of the posterior portions of the cerebellum (Crus I/II) in intrinsic connectivity networks related to social mentalizing (Habas et al. 2009; Buckner et al. 2011). In particular, while motion-related mirroring movement tasks have been shown to recruit "somatomotor" networks in the anterior cerebellum (Buckner et al. 2011), nonmotion-related mentalizing tasks have been shown to recruit the "default/mentalizing" network in the posterior cerebellum (Crus II), specifically when a high level of abstraction is required (Van Overwalle and Mariën 2016).

Connectivity fMRI studies have reported participation of the cerebellum in the default mode network (DMN) (Habas et al. 2009; Buckner et al. 2011), highlighting a crucial role of the cerebellar

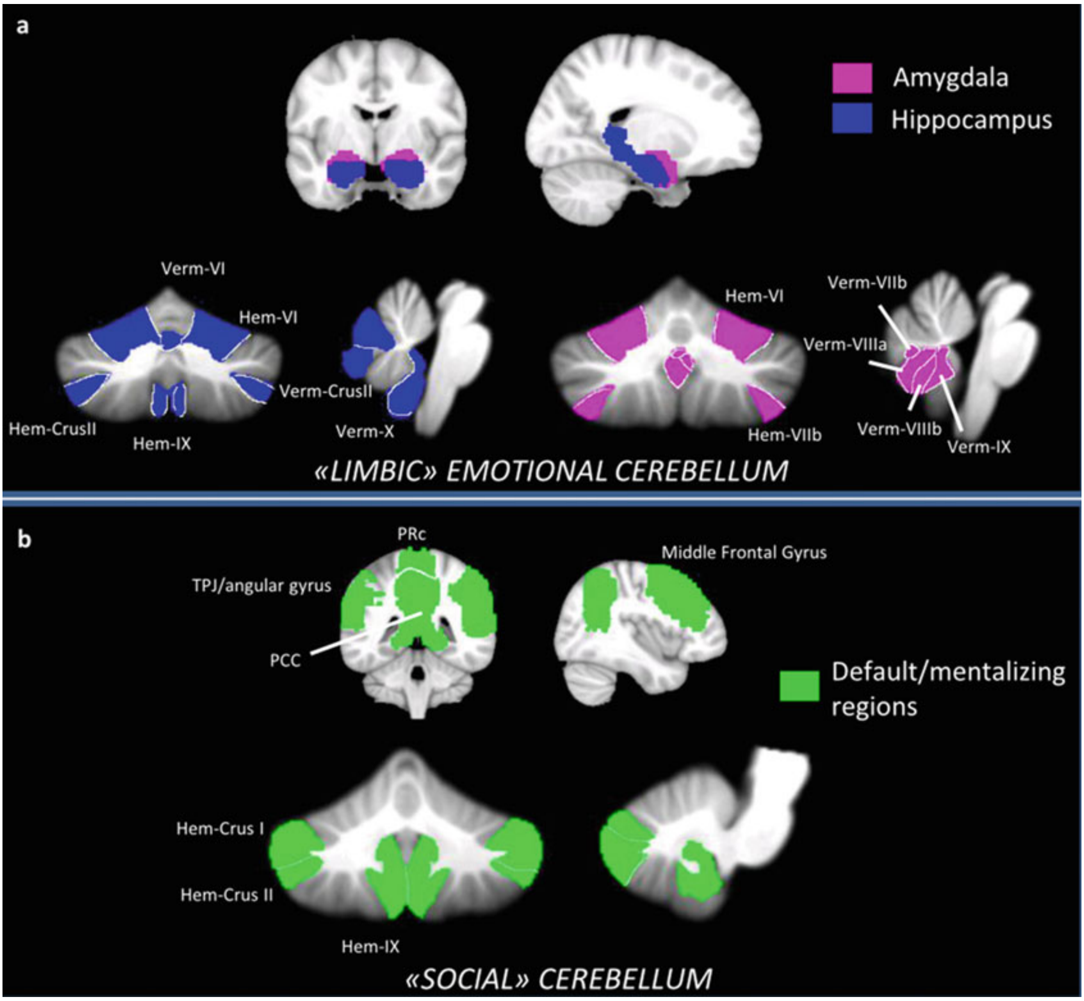

Fig. 15.1 Cerebellar functional topography for affective/emotional and social domains. Cerebellar lobules are segregated by affective/emotional and social mentalizing functions and superimposed on the Spatial Unbiased Infratentorial Template. (**a**) Cerebellar lobules of the limbic/emotional cerebellum having connectivity with limbic brain regions: amygdala (in violet) and hippocampus (in blue); (**b**) cerebellar lobules of the social cerebellum having connectivity with default/mentalizing brain regions (in green). *Verm* vermal, *Hem* hemispheric, *TPJ* temporoparietal junction, *PRc* precuneus, *PCC* posterior cingulate cortex

Crus I/II. The DMN is of particular interest in the context of mentalizing functions since it includes a set of cerebral regions that are particularly relevant for the social understanding of others, such as the TPJ, posterior cingulate cortex, precuneus, lateral parietal/angular gyrus, medial prefrontal cortex, and superior frontal gyrus (Schilbach et al. 2008). The cerebellar Crus I/II has been shown to be functionally coupled to default mode regions, while the anterior Crus I is functionally associated with the cerebral frontoparietal network (Bernard et al. 2012).

Consistent with these data, altered cerebello-cerebral functional connectivity has been reported in adults with autism spectrum disorder (Olivito et al. 2017a, 2018), a neurodevelopmental disorder typically characterized by an impairment in social mentalizing (Baron-Cohen 1995; Hill and Frith 2003). In particular, altered FC was found between the cerebellar Crus II and cortical

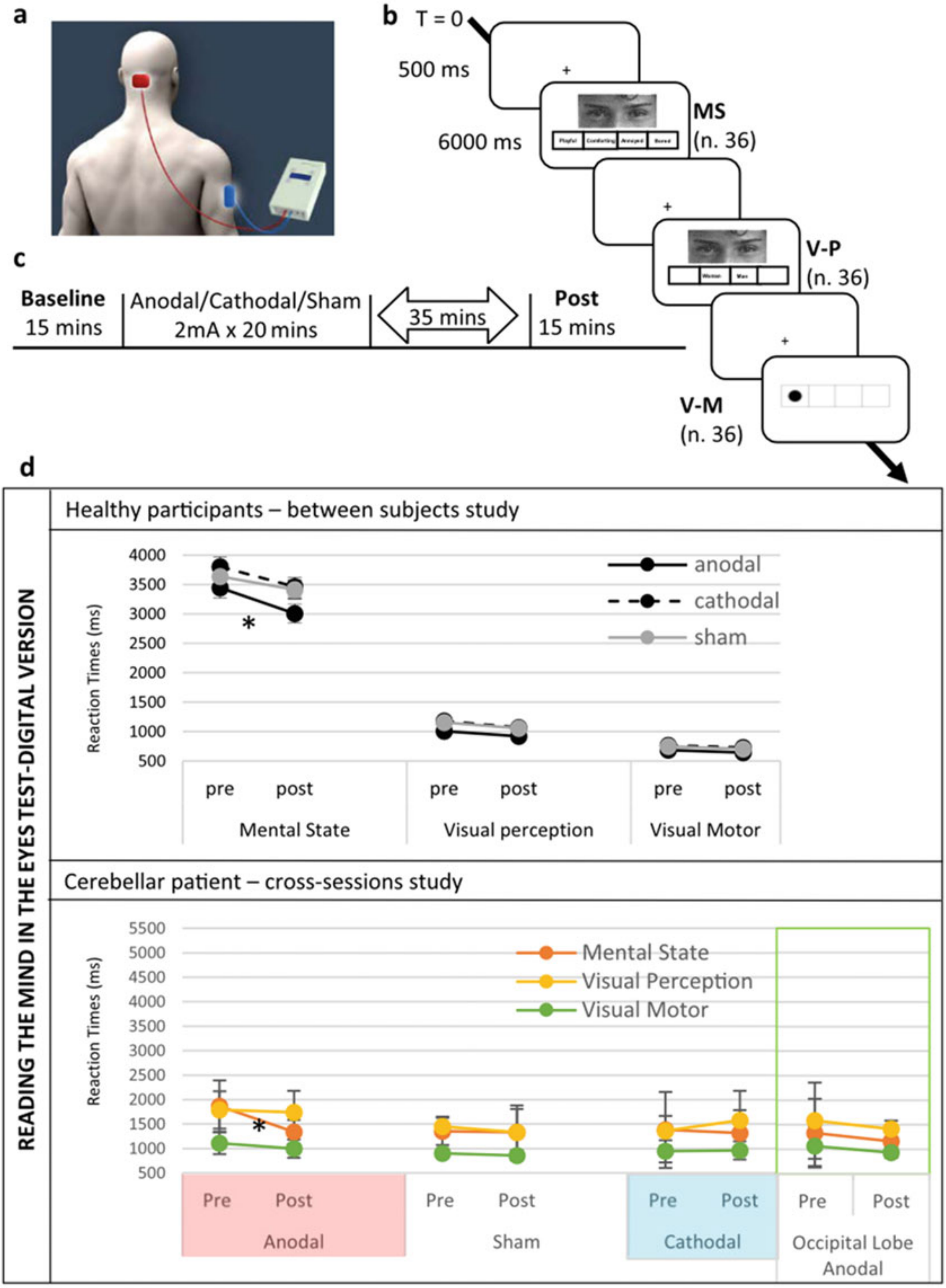

Fig. 15.2 tDCS montage, experimental protocol, stimuli examples and behavioral results. (**a**) Extra-cephalic montage: the active electrode was placed on the cerebellar vermis and the reference electrode was placed on the right deltoid; (**b**) tDCS protocol; (**c**) Stimuli examples of the digital Reading the Mind in the Eyes Test: mental state (M-S) visual perception (V-P) and visual motor (V-M) stimuli are showed; (**d**) Study results in healthy

regions belonging to the DMN (Olivito et al. 2018). Interestingly, a meta-analysis of connectivity studies has identified a cerebello-cerebral mentalizing network that is particularly involved when a high level of abstraction is required, such as inferring group stereotypes, a person's traits, or a person's past (Van Overwalle and Mariën 2016). This network included the right posterior cerebellar region corresponding to the Crus II and bilateral mentalizing regions in the cerebrum, such as the bilateral TPJ, precuneus, and medial prefrontal cortex (Fig. 15.1b). A recent study using dynamic causal modeling showed that bidirectional connectivity exists within this network and that cerebral and cerebellar mentalizing areas are effectively connected via closed loops. In particular, the bidirectional (closed-loop) connectivity between the Crus II and bilateral TPJ has been specifically related to high-level social understanding (Van Overwalle et al. 2019a).

Taken together, these data confirm the existence of cerebellar functional segregation for emotional and social processing and suggest that the cerebellum significantly contributes to emotional processing both in the early stages of emotional perception and recognition and in the modulation of more complex social-affective behaviors.

15.3 The Role of the Cerebellum in Emotional Component of Social Cognition

15.3.1 From Emotion Regulation to Mentalizing Abilities: The Advent of the Social Cerebellum

In recent years, different research groups have paid great attention to the contribution of the cerebellum in emotional processing and social-affective behavior, going beyond its well-known role in the motor and cognitive domains. Early research reports regarded cerebellar involvement in *emotion regulation* and *affective disorders*, such that impaired modulation of affective behavior has been recognized as a part of "cerebellar cognitive affective syndrome" (CCAS) (Schmahmann and Sherman 1998). Subsequent clinical studies in individuals with cerebellar focal or degenerative damage showed symptomatology that ranged from inappropriate affective reactions to external events, such as pathological laughter and crying (Parvizi et al. 2001, 2007), agitation, impulsivity and irritability, to difficulties in processing negative emotions (fear and anger), mood fluctuations or affective flattening and depressive disorders (Richter et al. 2005; Tavano et al. 2007).

Moreover, clinical evidence has reported that the cerebellum also participates in the ability to consciously define our own affective state. Indeed, patients with cerebellar damage presented with difficulties in feeling conscious emotions of regret subsequent to disadvantageous choices in a gambling task (Clausi et al. 2015) and in explicitly recognizing their bad mood in the presence of clinically relevant depressive disorder (Clausi et al. 2019a).

Most of these alterations have been associated with damage to the vermis, which is part of the limbic cerebellum and is well known for its involvement in emotional processing and regulation (Parvizi et al. 2001; Richter et al. 2005; Schmahmann 2001; Stoodley and Schmahmann 2009). Interestingly, animal studies have shown that potentiation of excitatory and inhibitory synapses, which impinge on Purkinje cells at the level of the vermis, correlated with associative learning of fear, an emotion that is endowed with high adaptive value, and has long-lasting

Fig. 15.2 (continued) participants and in one patients affected by cerebellar atrophy. In the healthy participant's study, each subject was assigned to one of three groups in which anodal, cathodal, or sham stimulations was delivered. Instead, in the cerebellar patient, the anodal, cathodal, and sham stimulations were delivered over the cerebellum in three double-blind sessions (with 1-week interval). Moreover, one occipital lobe stimulation session was performed as further control condition. $*p < 0.005$

effects (Sacchetti et al. 2009; Zhu et al. 2007; Scelfo et al. 2008). These data allow us to hypothesize that learning-related plasticity at the level of the vermis might be crucial for relaying appropriate emotional and motor behaviors in response to external stimuli and maintaining this information for long periods. Thus, through its connections with the limbic system, the vermis may act as the interface between sensory stimuli, emotional state, and behavioral responses.

Since emotion regulation and affective state awareness are crucial abilities in social interaction and in the adaptation to new social contexts, the cerebellum implication in these functions paved the way to further investigation about the social-affective cerebellum.

Studies have primarily focused on the cerebellar contribution in emotional processing from facial expressions (Adamaszek et al. 2015; Schutter et al. 2009; Ferrucci et al. 2012). Facial expressions are crucial for non-verbal social interactions and are markers of internal states and intentions (Phillips and David 1995; Schupp et al. 2004). Recognizing facial expressions is vital in a complex social world, as it permits one to detect the emotional state of another person and provides cues on how to respond in social situations (Frank and Stennett 2001; Grossmann and Johnson 2007).

The contribution of the cerebellum in this domain is supported by studies using non-invasive neuro-stimulation techniques targeting the human cerebellum, such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) (van Dun et al. 2017). Specifically, Schutter et al. (2009) found that repetitive TMS (20 Hz) over the cerebellar vermis increased emotional responsiveness to happy facial expressions with no changes in consciously experienced mood. In the same way, tDCS delivered over the cerebellar vermis significantly reduced the time needed to identify negative facial expressions, such as anger and sadness (Ferrucci et al. 2012). More recently, facilitative effects of tDCS over the cerebellar vermis on the ability to recognize mental states of others through the eyes expression was found in both healthy subjects and patients with cerebellar ataxia (personal observations) (Fig. 15.2). These studies used the digital version of Reading the Mind in the Eyes (RME) test, an advanced ToM task that involves more implicit emotional processing and requires recognizing complex facial emotions and mental states from photographs of the eye region (Baron-Cohen et al. 2001).

These preliminary findings are in line with clinical observations in patients affected by neurodegenerative cerebellar pathologies in whom low performance on the RME test, difficulties in attributing negative emotion, and impaired performance on advanced mentalization tasks have been reported (D'Agata et al. 2011; Sokolovsky et al. 2010; Clausi et al. 2019b, 2021). Impairments in visual emotional attention and emotional face recognition have also been reported in subjects affected by cerebellar hemisphere damage (Adamaszek et al. 2013, 2015). In this context, the cerebellum has been characterized as an active interface with large-scale cerebral pathways that are involved in emotionally conscious processes. In line with this, fMRI studies have shown that the cerebellum, in addition to the amygdala and prefrontal cortex, is activated during conscious processing of emotional faces (Fusar-Poli et al. 2009). In fact, specific portions of the cerebellum are part of brain networks, including the amygdala–medial prefrontal circuitry, which contribute to determining the meaning of external stimuli and coherently reacting to them (Ghashghaei et al. 2007). Specifically, the medial prefrontal cortex plays a key role in complex aspects of emotional processing, such as social interactions (Rudebeck et al. 2008). Amygdala activation has also been associated with the perception of emotion (Adolphs 2002) and emotional arousing effects (Le Doux 2007; Wallentin et al. 2011).

The cerebellar involvement in emotions and social-affective behavior is strongly supported by neuroimaging meta-analyses in healthy subjects, which show that different areas of the cerebellum can be linked to specific social-cognitive processes, such as mirroring and mentalizing (Van Overwalle et al. 2014, 2015). In fact, as detailed in Sect. 15.2, although the vermis seems to participate in autonomic and implicit processing of emotions, the posterior portions of the cerebellum (i.e., the Crus I and II) have been proposed to mediate emotional content at higher cognitive levels (Timmann et al. 2010) and social cognition processing (Van Overwalle et al. 2014, 2015). In line with this suggestion, posterior regions of the cerebellum were shown to be activated during conscious feelings and empathy of pain (Singer et al. 2004) and are connected with the temporal, parietal, and prefrontal cortices (Ramnani 2006), which are involved in cognitive elaboration of emotional content (Lane 2008).

Accordingly, the causal role of the posterolateral region of the cerebellum in inferring others' mental states from observation of their body language has also been demonstrated in neurostimulation studies. For example, Ferrari et al. (2018, 2019) showed that TMS over the left posterior cerebellar hemisphere affects the discrimination of emotional facial and body expressions in static pictures of real-life individuals. Overall, the abovementioned data from studies employing non-invasive brain stimulation and neuroimaging techniques converge to the view that the cerebellum acts not only in automatic perceptual processing but also in conscious processing of emotional and mental state information required for adequate social functioning. However, one question remains open: how does the cerebellum participate in processes related to the social-affective domain?

Currently, the most widely accepted hypothesis is that the modulatory actions that the cerebellum exerts on projection areas in the cerebral cortex are crucial not only for motor adaptation to sudden environmental changes but also for the optimization of social interactions and adaptation to the social context in accordance with internal and external emotional changes. This idea has been substantiated by the existence of anatomo-functional circuits (see Sect. 15.2) that allows the cerebellum to exert its function as part of the social-affective brain.

15.3.2 Cerebellar Modulation of Social-Affective Behavior: Theoretical Hypotheses

As illustrated above, the involvement of the cerebellum in social-affective behavior is becoming an accepted notion in the scientific community (Van Overwalle et al. 2020a). In parallel with the interest in defining the emotional and behavioral aspects by which the cerebellum plays a role and with the need to characterize the cerebello-cortical networks involved in the control of these functions, several groups of researchers in recent years have tried to elaborate specific theoretical hypotheses about the way in which this particular brain area influence the social-affective functioning.

15.3.2.1 Universal Cerebellar Transform and Dysmetria of Thought Theories in Social Behavior

One of the theories that has been posited to explain cerebellar functioning in emotional processing and social-affective behavior is the "uniform cerebellar transform" (UCT) hypothesis (Schmahmann 1991, 1998, 2000). It states that the cerebellum contributes to different domains by a singular neurological computation due to the repeating cytoarchitecture of its cortex and to the topographical organization of the extensive reciprocal anatomical connections between specific regions in the cerebellum and the sensory-motor and associative cortices (Schmahmann 2001; Schmahmann and Pandya 1997). Although the cerebellar cortex has an essentially uniform, monotonously repetitive architecture, immunohistochemistry has shown that it contains anatomically identifiable parasagittal bands (Hawkes et al. 1993) that appear to have connectional and physiological specificity (Hallem et al. 1999). Thus, the functional specificity of each cerebellar module is determined by the cortical brain region to which it is connected. Indeed, there is anatomical specificity linking each cerebral cortical area with unique patterns of termination in the basilar pons, which in turn is linked with specific regions of the cerebellar cortex. The cerebellar cortico-nuclear projections are then transmitted to specific areas of the thalamus before returning to those cerebral areas from which the projection originated (Kelly and Strick 2003). Based on its characteristic anatomical organization, the authors suggested that the cerebellum performs a universal cerebellar transform on the information to which it has access (Schmahmann 1991, 1998, 2000).

Following this idea, the uniform structure of the cerebellar cortex enables a unique computation that modulates the processing of multiple streams of information not only in sensorimotor and cognitive domains but also in emotional and social-affective domains. The cerebellum may serve as an oscillation damper, smoothing out performance in all domains and modulating behavior (Schmahmann 1998). Specifically, with respect to social-affective behavior, it has been hypothesized that the cerebellum acts to compare the consequences of actions with the intended outcomes, that is, to match reality with perceived reality. This is possible through existing cerebellar anatomical links with systems that control these functions, such that the vermis, fastigial nucleus and flocculo-nodular lobe are linked with the limbic system, whereas the cerebellar posterior areas are linked with paralimbic areas and association cortices concerned with the integration of emotional experiences into the repertoire of perceptions and behaviors required for social interactions (see Sect. 15.2 for further details).

The UCT theory is supported not only by neuroimaging findings on cerebro-cerebellar circuits but also by evidence on the significant relationships between social behavior and other motor and non-motor domains (Schmahmann 2000; Schmahmann and Sherman 1998; Schmahmann et al. 2019). Indeed, a new line of inquiry has examined general organizational principles that are shared between social and other motor and non-motor domains and has provided evidence that cerebellar social neuroanatomy can be contextualized within a larger triple representation principle that is common across numerous non-motor domains in the cerebellar cortex. Specifically, similar to the well-established descriptions of a double motor representation in lobules I–VI and VIII (Snider and Eldred 1952), it has been demonstrated that all non-motor processes in the cerebellar cortex might simultaneously engage some aspects of lobules VI/Crus I (first non-motor representation), lobules Crus II/VIIB (second non-motor representation), and lobules IX/X (third non-motor representation) (Buckner et al. 2011; Guell et al. 2018). In the same way, social processing exhibited a first and contiguous second representation in lobules Crus I/II and a third representation in lobule IX (Guell et al. 2018). This organization allows the parallel processing of complex information such as that required in social-affective behavior.

As a corollary of the UCT hypothesis, the same authors defined the ‘dysmetria of thought’ theory according to which the symptoms consequent to cerebellar damage can reflect universal cerebellar impairment, namely, dysmetria. In line with this, cerebellar malfunctioning can also lead to dysmetria in the cognitive and affective domains, which refers to the concept of dysmetria of the movement typical of patients with ataxia (Schmahmann 1991; Schmahmann and Sherman 1998). Indeed, in the motor domain, it is well known that a cerebellar lesion results in impairments of coordination, precision, and fluidity of motor control; in the same way, in the cognitive and affective domains, a cerebellar lesion leads to impaired coordination, precision, and fluidity of thought and emotion, including social processing (Schmahmann 2000; Schmahmann and Pandya 1997; Schmahmann et al. 2019). Impaired modulation of affect and mismatches between reality and perception of reality are central and defining features of psychoses, including schizophrenia and related disorders, bipolar affective disorders and related illnesses. Therefore, the role of the cerebellum in the pathophysiology of these conditions becomes plausible in the context of the dysmetria of thought hypothesis.

15.3.2.2 Cerebellar Sequencing and Prediction in Social Interactions

Increasing evidence on the functional diversity of structurally similar cerebellar modules has also enlarged the perspectives for hypothesizing other possible functional processes underpinning cerebellar influence in social-affective behavior. Within this framework, another theory was recently applied to explain the mechanisms by which the cerebellum is involved in non-motor processes, including social-affective domains, and is referred to as the "sequence detection theory" (Van Overwalle et al. 2020a; Leggio et al. 2008, 2011; Leggio and Molinari 2015). Sequencing is defined as the ability to perceive, represent, and execute spatio-temporal relations among events that follow a particular order. It can be considered a supra-modal function encompassing all human activities and crucial to the predictive processing of the brain (Savalia et al. 2016).

The "sequence detection theory" posits that the cerebellum plays a central role in sequencing (Leggio et al. 2008, 2011; Braitenberg et al. 1997). The cerebellum receives patterns of sequential temporal or spatial events via the pontine nuclei and compares them with information conveyed by climbing fibers. This interaction provides data regarding previously encountered sequences and consequently generates internal models useful in making predictions. Because of these mechanisms, the cerebellum can recognize sequential events and identify possible errors in the expected sequence, thereby acting as a feedforward controller that guarantees anticipatory actions (Molinari et al. 2009; Sokolov et al. 2017).

In the traditional view, the cerebellum has been related to motor processes, where internal models are considered to be responsible for the construction, detection, and application of motor sequences (Ito 2008). Through feedback and feedforward control, individuals become capable of predicting and adjusting movements in accordance with sudden environmental changes. More recently, Leggio et al. (2008) and Van Overwalle et al. (2019b) proposed that during human evolution, the cerebellum advanced and began engaging in similar processes for purely mental sequences. The authors argued that the cerebellum is also involved in the construction of internal models of mental processes during social interactions, in which the prediction of sequential events plays a central role (Clausi et al. 2019b; Van Overwalle et al. 2019b). Specifically, in the social-affective domain, as in the sensorimotor domain, the cerebellum may act by matching external information (social inputs) with the internal model of a specific social event linked to previous experiences, contributing to the formation of judgements on the mental state of others and predicting the consequences of social actions based on an individual's beliefs and the social norms (Koster-Hale and Saxe 2013). Thus, to accomplish these functions in a fluid and automated manner, the cerebellum might modulate higher-order cortical areas by detecting socially predictable sequences (e.g., internal model of a social action) and promoting optimized feedforward control over activity (Sokolov et al. 2017; Van Overwalle et al. 2019b; Middleton and Strick 2000). This allows us to anticipate and understand the consequences of others' actions and to recognize deviations in the predicted outcomes of social interactions to modify future social expectations. When cerebellar damage occurs, fast and continuous information comparisons between external stimuli and internal model results are affected; thus, subjects fail to recognize deviations/errors in social interactions and to adjust their response according to social expectations, as recently observed in patients with cerebellar neurodegenerative diseases (Clausi et al. 2021; Van Overwalle et al. 2019c).

Strong support for these theoretical hypotheses also comes from recent fMRI studies in healthy subjects (Heleven et al. 2019), in which activation of regions in the posterior cerebellum was observed during the construction of sequences of social actions that required understanding of the mental state of the protagonist (e.g., involving false or true beliefs) or when social predictions were violated (e.g., violations of social norms) (Berthoz et al. 2002).

Overall, the role of the cerebellum in predictive coding and adaptive control could be crucial in the social cognition domain because anticipation, adaptation, and learning are indispensable for successful social interactions and adaptive social behavior. This brain area could assist in learning and understanding social action sequences, supporting optimal predictions about imminent or future social interactions. In line with this theory, impaired sequencing and prediction mechanisms could be considered possible functional substrates of emotional and social-affective alterations in pathologies characterized by cerebello-cerebral dysfunctions.

15.4 Social-Affective Behavior in the Presence of Cerebellar Structural and Functional Alterations

The characterization of cerebellar involvement in specific aspects of emotional processing and social cognition and deeper knowledge of the mechanisms by which the cerebellum participates in social-affective domains assume strong significance in those pathological conditions that present both maladaptive social-affective behavior, and cerebellar structural and functional alterations. In the present section, we will focus on specific neurodegenerative diseases and psychiatric and neurodevelopmental conditions.

15.4.1 Social-Affective Behavioral Alterations in Patient with Cerebellar Pathologies

Evidence in the clinical field has shown that difficulties in recognizing basic emotions and difficulties with social behaviors are present in patients with focal and degenerative cerebellar pathologies (Adamaszek et al. 2014, 2015; Sokolovsky et al. 2010). Indeed, since the identification of emotional and affective changes found in patients with focal lesions of the cerebellum leading to the description of the CCAS (Schmahmann and Sherman 1998), the number of studies assessing emotional and social competences in cerebellar patients has exponentially grown. Indeed, difficulties in empathizing and mentalizing abilities have been described in a patient with cerebellar stroke involving the vermis and the posterior regions of the cerebellar hemispheres (Gerschovich et al. 2011). Moreover, clinical studies have evidenced specific patterns of social-affective alterations in patients with different types of cerebellar degenerative pathologies. For example, difficulties in the recognition of emotions were found in individuals with complex cerebello-cerebral degeneration and patients with isolated cerebellar degeneration (Sokolovsky et al. 2010; Hoche et al. 2016), while patients with spinocerebellar ataxia type 1 showed selective difficulties in the attribution of mental states (Sokolovsky et al. 2010).

Interesting findings have come from a recent behavioral and neuroimaging study with patients affected by various forms of cerebellar ataxia (Clausi et al. 2019b). In this study, patients presented with difficulties in basic aspects of social behavior, such as emotional contagion and recognition of the emotions of others, and in its more complex aspects, such as the ability to simulate, anticipate, and predict mental states of others. Intriguingly, cerebellar patients also have gray matter reductions localized in specific portions of the cerebellum (vermis and bilateral Crus I/II), which showed decreased functional connectivity with cerebral areas involved in mirroring and mentalizing processes (Abu-Akel and Shamay-Tsoory 2011; Clausi et al. 2019b).

In a more recent anatomo-functional study in a homogeneous cohort of SCA2 patients (Clausi et al. 2021), alterations in social cognition were found to be associated with structural damage to specific cerebellar lobules and microstructural alterations in the cerebellar peduncles, which are involved in different aspects of social-affective processing. Specifically, the correlational analyses evidenced that impairments in anger attribution were mainly related to the degree of gray matter atrophy in right lobules VIIIB and IX. This finding is consistent with increasing evidence that vermal and paravermal cerebellar areas are involved in the processing of ‘primitive’ emotions (Bauman and Mattingley 2012), such as fear of dangerous stimuli and anger towards aggressors (Schmahmann 1991), and participate in detecting, integrating, and filtering emotional information as a part of a cerebello-cortical-limbic network (Habas et al. 2009). In contrast, patients’ impairments in more complex components of social cognition were associated with atrophy in specific posterior cerebellar regions (right Crus II). As reported above, this cerebellar area is associated with complex brain networks involved in mentalizing abilities (Van Overwalle et al. 2014; Habas et al. 2009; Sokolov et al. 2017).

Moreover, the scores of the patients on the Reading the Mind in the Eyes test were related to the cerebellar peduncle microstructural damage reported in an SCA2 cohort (Olivito et al. 2017b). These data have been explained with consideration of the well-known function of the cerebellum as a predictor (Sokolov et al. 2017; Ito 2008). Indeed, since the abovementioned task requires determination of the meaning of the expression in the eyes and an automatic and rapid inference of another person’s mental state (Baron-Cohen et al. 2001), the cerebellum might act by matching the external information (i.e., expression of the eyes) with the individual’s internal model of eye region expression linked to previous experiences, thus contributing to an immediate judgment about the other’s mental state. Notably, the middle and posterior peduncles are the feedback and feedforward limbs of the cerebello-cortical system, respectively, through which the cerebellum receives information and sends information back to cerebral regions (Ramnani 2006). Therefore, it is reasonable to assume that fiber degeneration within the cerebellar peduncles could interfere with the communication between the cerebellum and the cortical projection areas involved in the more automatic mentalizing processes.

Considering the complexity of information processing in the social cognition domain and the cerebellar interplay with the brain networks involved in these processes, it is reasonable to infer that neuroanatomical damage that occurs in cerebellar patients may account for their behavioral impairments and also alter cerebello-cortical interactions. Accordingly, in a recent study, altered inter-nodal connectivity between the right Crus II and cerebral areas involved in more complex aspects of mentalization, such as the dorsomedial prefrontal cortex and the TPJ, was found in SCA2 patients (Olivito et al. 2020).

In summary, the findings reported above offer a new point of view regarding specific symptomatology in patients with cerebellar ataxia, where the importance of links between social behavior difficulties and cerebellar damage has often been underestimated or neglected, with direct consequences on clinical practice.

15.4.2 Cerebellar and Social-Affective Alterations in Neurodegenerative Disorders and Psychiatric and Neurodevelopmental Conditions

Several studies have described impairments in social functioning and mentalizing processes not only in patients affected by cerebellar pathology (D’Agata et al. 2011; Sokolovsky et al. 2010; Clausi et al. 2019b) but also in individuals affected by neurodegenerative disorders (Poletti et al. 2012), such as Alzheimer’s and Parkinson’s diseases (Wu and Hallett 2013; Jacobs et al. 2018) and behavioral variants of frontotemporal dementia (Van den Stock et al. 2019), that have often been associated with cerebellar alterations.

A recent study suggested that the impaired cerebellar modulation described in sporadic Alzheimer’s disease may be predictive of the onset of cognitive and neuropsychiatric deficits (Jacobs et al. 2018). With this disease, cerebellar gray matter reductions have been found to progressively evolve, beginning with early involvement in the vermis and the posterior cerebellar lobe and extending to the anterior cerebellar lobe in more advanced stages (Jacobs et al. 2018; Toniolo et al. 2018). As both structural and functional cerebellar modifications progress in parallel with pathological changes in the cerebral cortex, social-affective behavioral alterations evolve as well. Moreover, in people with Parkinson's disease, cognitive, behavioral, and mentalizing impairments arise after the onset of motor symptoms; this progression of disease parallels the degree of structural and functional changes occurring in both the cerebellum and cortical areas involved in higher-order functions (Wu and Hallett 2013; Camicioli et al. 2009; Nishio et al. 2010). Difficulties in the mentalizing domain have often been reported in patients affected by behavioral variants of frontotemporal dementia (Pardini et al. 2013; Desmarais et al. 2018), who show correlations between task performances and atrophy in posterior regions of the cerebellum (Crus I and II) (Van den Stock et al. 2019; Synn et al. 2018).

A specific role for the cerebellum has been hypothesized in the onset of emotional and mentalizing difficulties described in some psychiatric and neurodevelopmental disorders (Corcoran et al. 1995; Fatemi et al. 2012; Bora et al. 2016; Bora and Berk 2016). Indeed, a number of neuroimaging studies in individuals affected by schizophrenia, depressive and bipolar disorders, and ASD have shown structural and functional alterations in regions of the "social cerebellum" and in cerebello-cerebral mentalizing networks (Adler et al. 2007; Becker and Stoodley 2013; Kim et al. 2014). Specifically, microstructural disruptions in cerebro-cerebellar pathways (Kanaan et al. 2009) and intracerebellar white matter (Kim et al. 2014) were found in schizophrenic individuals, who often present with difficulties in the automatic process of mentalizing and fail to select the appropriate behavioral representation for understanding the actions and intentions of others (Das et al. 2012; Martinez et al. 2019). In these patients, alterations in cerebellar forward modeling have been considered to be the cause of hallucinations because of the inability to distinguish between internal states and external events (Frith et al. 2000; Ford and Mathalon 2012).

Moreover, altered functional connectivity between the posterior cerebellum and mentalizing regions, such as the TPJ, medial prefrontal cortex, and posterior cingulate, has been reported in individuals with a diagnosis of bipolar disorder (Liu et al. 2012; Wang et al. 2015) and in those with depressive states. In particular, reduced volumes and decreased activity in the vermis and posterior cerebellar lobes (Adler et al. 2007; Mills et al. 2005; Narita et al. 2011; Kim et al. 2013; Sani et al. 2016) and reduced functional connectivity between the posterior cerebellum and the amygdala, inferior frontal gyrus (orbital), and striatum have been described in patients with bipolar disorder (Shaffer et al. 2018; Wang et al. 2016; Li et al. 2015). Likewise, decreased functional connectivity between the cerebellum and temporal and parietal regions has been shown in individuals with major depressive disorder (Guo et al. 2013).

In these clinical populations, including individuals in both manic and depressive states (Bora et al. 2016; Bora and Berk 2016) and remitted patients with bipolar disorder (Bora et al. 2005; Bora and Pantelis 2016), alterations in mentalizing are thought to affect social behavior. Accordingly, preliminary studies in patients affected by type 1 or type 2 bipolar disorder (in a euthymic state) showed specific mentalizing problems characterized by difficulties understanding another person's mental state and considering their beliefs and intentions (personal observations). In a recent single case study, Lupo and colleagues (Lupo et al. 2018) added new insight into the role of the cerebellum in socio-affective processing in the context of specific psychiatric conditions and demonstrated not only that there was an association between the onset of a manic state and the presence of a focal cerebellar lesion but also that the pattern of impaired functional connectivity in the patient overlapped with cerebello-cerebral mentalizing networks.

Finally, the cerebellum seems to be implicated in ASD (Fatemi et al. 2012), a neurodevelopmental condition mainly characterized by difficulties in ToM abilities (Baron-Cohen et al. 2001). Cerebellar dysfunction has recently gained attention as a potential biomarker of this condition (Fatemi et al. 2012). Indeed, early developmental damage in the cerebellum is considered one of the major risk factors for ASD (Wang et al.

2014) and has been associated with deficits in affective and internalizing behaviors and with social withdrawal (Limperopoulos et al. 2007), thus suggesting that atypical cerebellar development as well as dysfunctional cerebello-cerebellar networks could contribute to ASD-related behaviors (Stoodley and Limperopoulos 2016).

Further support for this idea has been derived from resting-state functional connectivity studies in individuals with ASD that reported reduced functional connectivity between specific regions in the posterior cerebellum and regions in the "social brain" relevant for social interaction. Indeed, low resting-state functional connectivity between the Crus II and the TPJ adjacent to the STS (Igelström et al. 2017) and altered functional connectivity between the dentate nucleus and the cortical regions involved in social cognition were reported in adults with ASD (Olivito et al. 2017a, 2018). Accordingly, a recent study in ASD showed that more severe scores on the Autism Diagnostic Observation Schedule were associated with the degree of hypo-connectivity between Crus I/II and lobule IX and brain areas involved in language, emotional and social domains, including the bilateral STS, inferior frontal gyrus, amygdala and specific nodes in the default mode network (Arnold Anteraper et al. 2019).

Taken together, these observations suggest that the study of cerebellar functioning in these pathologies could be crucial for a better comprehension of the neurobiological bases of social behavior impairments in neurodegenerative and psychiatric disorders, holding great promise for a better understanding and treatment of a variety of social impairments.

15.5 Conclusions and Future Directions

In the present chapter, we have described converging evidence from clinical studies in patients with cerebellar alterations and fMRI and neurostimulation studies in healthy individuals that point to recognizing the involvement of the cerebellum in specific aspects in the social-affective domain. The emotional and affective components of social skills are crucial for adaptation to the surrounding environment, especially in the presence of pathological conditions. A better comprehension of the mechanisms by which the cerebellum influences the neural substrates of social-affective behavior could have important clinical implications not only in the presence of a cerebellar pathology but also in specific psychiatric and neurodevelopmental disorders.

Knowledge of these aspects is essential in clinical practice because, on the one hand, behavioral alterations can have an impact on quality of life and compliance with pharmacological and rehabilitative treatments of individuals; on the other hand, knowing the neural basis of these alterations can facilitate the development of rehabilitation protocols to modulate cerebellar excitability, allowing clinicians to influence/improve symptomatology in individuals suffering from social-affective alterations. Among these innovative treatments, non-invasive neuro-stimulation techniques should be mentioned as a useful method for investigating the causal and potential clinical role of the cerebellum in social functioning (van Dun et al. 2017).

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Cerebellum, Embodied Emotions, and Psychological Traits

16

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Abstract

This chapter addresses how the embodiment approach may represent a unifying perspective for examining the cerebellar role in emotional behavior and psychological traits. It is not intended to be exhaustive, but rather it can be a good starting point for advancing the cerebellar neural mechanism underlying embodiment. Our goal is to provide illustrative examples of embodied emotions and psychological traits in the emerging field of emotional and cognitive cerebellum. We illustrate how the cerebellum could be an important hub in the embodiment processes, associated with empathic abilities, impaired emotional identification and expression (as occurring for example in the presence of alexithymia), and specific psychological constructs (i.e., hypnotizability).

Keywords

Embodiment · Empathy · Alexithymia · Hypnotizability · Crus 1 · Crus 2 · Cerebellar lobule VI · Cerebellar lobule IV/V

16.1 The Embodied Foundations of Emotions

Influential theories suggest that bodily factors are constitutive of cognition in the sense that any human cognition is embodied and passes through bodily experiences.

Embodiment theory posits that cognitive and emotional processes are shaped and rooted in our biological constitution (Critchley and Garfinkel 2017). The general ideas that the mind is grounded in the whole body, rather than being a piece of "software" installed only in the "hardware" of the brain and that emotional states arise from physiological changes from within the whole body allowed to bridge the Cartesian dichotomies between mind and body, cognition and emotion, culture and nature, rationality and irrationality (Damasio and Carvalho 2013). This point of view had novel implications for understanding the content of the conceptual system for emotion and the *implied structures* (Damasio and Carvalho 2013; Niedenthal et al. 2005). Crucially, embodiment involves the central processing of bottom-up afferent signals from the body along with top-down regulatory directives in a bidirectional relationship. The physiological signals may be represented as subjective feelings and thus may lead to behaviors adjusting the current state.

According to embodiment theory, processing of information about concrete facts (i.e., songs, emotional faces, personality characteristics) or

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abstract concepts (i.e., social, emotional, or psychological constructs) is triggered, influenced, updated, associated with, and even dependent on perceptual, somatosensory, motor, neuroendocrine, and autonomic nervous system activities (Niedenthal et al., 2005). Importantly, the embodied emotion is formulated through bodily sensations and usually expressed through action. Notably, long before scientists came to demonstrate how our emotions affect our bodies, William James in the essay titled "What is an Emotion?" (1884) asserts that "*the bodily changes follow directly the perception of the exciting fact, and that our feeling of the same changes as they occur is the emotion*" and subsequently in the volume "The Principles of Psychology" (1890/1907) he writes "*the world experienced comes at all times with our body as its center, center of vision, center of action, center of interest. Where the body is 'here'; when the body acts is 'now'; what the body touches is 'this'; all other things are 'there' and 'then' and 'that'*." Challenging common presuppositions about the ordering of an emotional episode, James argued that it is not an emotion causing the bodily changes, but the corporeal reverberations are actually the raw material of the emotion itself. Note that for more recent emotion theories and researches (such as Izard 2009), a common complaint against James' theory is that it fails to assign a cognitive role to emotions, identifying them with feelings of bodily changes.

Embodiment involves the brain capturing modality-specific states and then re-instantiates parts of the same states to process the emotion-related information. The somatosensory ability allows feeling what is occurring inside the body, still discriminating between physiological and emotion-related bodily states (Khalsa et al. 2018). Note that interoception encompasses proprioceptive and visceral signaling, and it is related to all physiological organs that relay signals to the brain about the current physiological status of the body. Mapping onto the brain, this information allows for a nuanced representation of the body physiological state, important for maintaining homeostatic conditions and critical for emotion processing and self-awareness recognition. Distinct emotions have been associated with distinct patterns of bodily sensations and actions that have a certain universality as to how emotions are organized and represented in the body (Nummenmaa et al. 2014). For example, in all cultures most basic emotions are associated with sensations of elevated activity in the upper chest area, likely corresponding to changes in breathing and heart rate, the sensations in the upper limbs are prominent in approach-oriented emotions, anger, and happiness, whereas the sensations of decreased limb activity are a defining feature of sadness, and finally, the sensations in the digestive system and around the throat region are mainly related to disgust. Whether negative or positive, emotions are experienced in the body, facilitating our ability to identify, respond to, and interact with our internal and external environment.

16.2 Empathy as Embodied Emotional-Cognitive Process and Its Relation with the Cerebellum

After being a longstanding center of philosophical debate, the concept of empathy has crossed the borders of the philosophical domain and has been addressed by social, developmental, clinical, and dynamic psychology and subsequently even by neuroscience. Contributions from this rich variety of fields resulted in an overabundance of operational definitions. As Husserl suggested (1931), any intersubjective experience should be conceived as an empathic experience in which we consciously ascribe intentional acts and feelings to another subject. Such an experience is made possible because of physical, sensorial, and perceptual similarities with the "other" seen as *Leib* (notably, Husserl distinguishes between *Leib*, the component that is experientially based in our living body, and *Körper*, the physical structure).

The premise to understand the empathic process is that self-awareness and sensitivity of our own emotional states are prerequisites to accurately comprehend the other's states. At a phenomenological level, the empathy construct can be conceived as a primary interaction between individuals, with one experiencing and sharing the feelings of the other. In fact, the empathic capacity allows sharing the affective states of others, exerting cognitive control, predicting, and understanding others' feelings, motivations and actions, without losing sight of whose feelings belong to whom, and behaving accordingly (de Waal and Preston 2017). The self/other distinction is one of the basic characteristics distinguishing empathy from other forms of "feeling with the other": empathy presupposes *alterity*. Empathy promotes prosocial and cooperative behaviors (de Waal and Preston 2017; Leblanc and Ramirez 2020; Preston and de Waal 2002) and enables people to navigate the social world they live in. Without the capacity to empathize, we would be lost in our complex world, requiring ever-increasing flexibility to adapt to fast-changing social relationships and mutual understanding (Luyten et al. 2020).

Empathy is regulated by both affective and cognitive components that produce emotional understanding (Shamay-Tsoory et al. 2009a). Affective empathy refers to the ability to share the state of other persons through observation or imagination of their experience, and as a consequence of other's state usually leads to an appropriate isomorphic emotional response. Cognitive empathy refers to the abilities of Perspective Taking and Theory of Mind (ToM) that allow predicting and understanding other's mental state by using cognitive processes. Combined, these processes enable to understand beliefs, desires, and emotions of others in real-life or imaginary situations. The idea that empathic capacities are associated with somatosensory, interoceptive, and autonomic processes that tend to simulate those of another person closely fits with the notion of embodiment. In the context of embodied empathy, it is critical to consider that we use our own bodies to simulate information originating from others' body and face to share and understand their emotions, since empathically experiencing other's emotional states comes from "re-creating" other's feelings in ourselves. It has been proposed that the individuals have an understanding of the mind and emotions of others through "mirroring" or "resonance" mechanisms responsive to the other's bodily states (Gallese and Goldman 1998).

The affective and cognitive components (emotional regulation, affective representations, self-awareness, cognitive flexibility, perspective-taking, and mentalizing) of empathy are mediated by specific and interacting neuronal systems, as indicated by the possibility of distinct impairments of the affective or cognitive empathy in specific clinical disorders. For example, schizophrenia, depersonalization, and narcissistic personality disorder are characterized by deficits in affective empathy (Ritter et al. 2011; Shamay-Tsoory et al. 2007), while bipolar disorder and borderline personality traits are associated with impairment in the cognitive empathy (Harari et al. 2010; Shamay-Tsoory et al. 2009a, b). Even within non-clinical populations, the balance between the capacities of affective and cognitive empathy varies from one individual to another, uniquely defining the empathic experience for each person (Moore et al. 2015).

At the neurobiological level, most research has assessed empathy as a state rather than a trait and has mainly focused on the neocortical activation associated with empathy-eliciting situations (Lamm et al. 2007). Neuroimaging studies (Bilevicius et al. 2018; Fan et al. 2011) have reported consistent activation of brain structures specifically associated with each component of empathy. Namely, the anterior cingulate cortex (ACC) and anterior insula (AI) are mostly recruited in affective empathy, whereas the medial cingulate cortex (MCC) and adjacent dorsomedial prefrontal cortex (DMPFC) in cognitive empathy.

As in the prefrontal cortex, the two empathic processes appear topographically distinct even in the cerebellum, with the posterior vermis being activated mainly in affective processing of empathy, and the posterior lateral cerebellum, and particularly Crus 1 and Crus 2 regions, being activated in cognitive components. fMRI studies (Gu et al. 2012; Moriguchi et al. 2007; Singer et al. 2004) reported that empathy for other's pain is associated with cerebellar activation. Bilateral lesions to the cerebellar posterior vermis and hemispheres provoke deficits of empathy and ToM (Clausi et al. 2019; Roldan Gerschcovich et al. 2011), and patients with various types of cerebellar damage are impaired in ToM tasks (Sokolov 2018). Furthermore, a distinct mentalizing network directly connected to the cerebral mentalizing network has been identified in Crus 1 and 2 (Buckner et al. 2011).

The cerebellar involvement mainly in cognitive empathy fits with the significant covariation in activity of the right lateral cerebellum with self-rated individual differences in empathy for pain described by Singer et al. (2004), with the repeatedly reported cerebellar involvement in social cognition (Van Overwalle et al. 2014, 2020) and with the activation throughout right Crus 1 and 2 associated with ToM tasks (King et al. 2019). In a pediatric brain-injured sample, the individual differences in cerebellar volumes predicted ToM outcomes, and the volumetric reductions in the Cerebro-Cerebellar Mentalizing Network predicted poor ToM performances (Ryan et al. 2017). In children affected by autism spectrum disorders, voxel-based morphometry analyses revealed reduced volumes in right Crus 1 and 2, and the degree of cerebellar volumetric reductions correlated with the severity of symptoms in social interaction, communication, and repetitive behavior (D'Mello et al. 2015). More specifically, it has been reported that the size of the empathic imbalance between cognitive and emotional components positively correlates with autism traits in a neurotypical population (Shalev and Uzefovsky 2020). Interestingly, when predominant on affective empathy, cognitive empathy is related to stronger connectivity in interoception, autonomic monitoring, mentalizing and socio-cognitive networks that include the cerebellum (Cox et al. 2012). Furthermore, the cerebellum contributes to the empathic aspects linked to cognitive flexibility that allows adopting the subjective perspective of the other and to executive and regulatory processes that modulate the subjective feelings associated with emotions.

In contrast to these numerous findings, few investigations have specifically addressed the structural underpinning of empathy as a trait in healthy subjects, and the vast majority of research has so far mainly focused on the cerebrum, neglecting cerebellar regions. Recently, Picerni et al. (2021) analyzed the associations between macro- and micro-structural cerebellar measures and levels of affective and cognitive trait empathy (measured by the self-report Interpersonal Reactivity Index, IRI) in a large sample of healthy subjects of both sexes. The scores of Fantasy IRI-subscale that assesses one's ability to imaginatively transpose themselves into feelings and actions of fictitious characters in books, movies, and plays were positively associated with the volumes in right cerebellar Crus 2 and pars triangularis of inferior frontal gyrus (Fig. 16.1, upper part). Furthermore, the increased volumes in Crus 2 were accompanied by diminished values of Mean Diffusivity in the same area, indicating an increased functional capacity. Reading a book or watching a movie are non-innate brain activities, which may occupy a very significant part in the daily life of many people, presumably because of their considerable adaptive value. During such activities, it often opens a window into characters' thoughts and feelings, so that people respond in thought and feeling to fictive situations as if they actually occur. Ultimately, these activities help subjects to optimize decisions and actions, learn about existing or fictive worlds, and stimulate motivation and imagination, functioning thus as a sort of "emotional gym," in which empathic capacities may be exerted. In watching a movie or reading a book, subjects may be so emotionally moved to get lost in the fictive happenings of the stories as if these were real, and imaginatively perceive themselves as transposed into the character's thoughts and feelings, experiencing the character's happenings from the character's perspective, and merging with or "being" that character. Thus, empathy abilities are involved in emotional information processing not only "on-line," when we respond to real emotional objects, but also "off-line," when we represent emotional symbols (Niedenthal et al. 2005). Notably, the empathic responses are embodied either when we tend to mimic the behavior of others actually present and when we process bodily signals originating from information about others stored

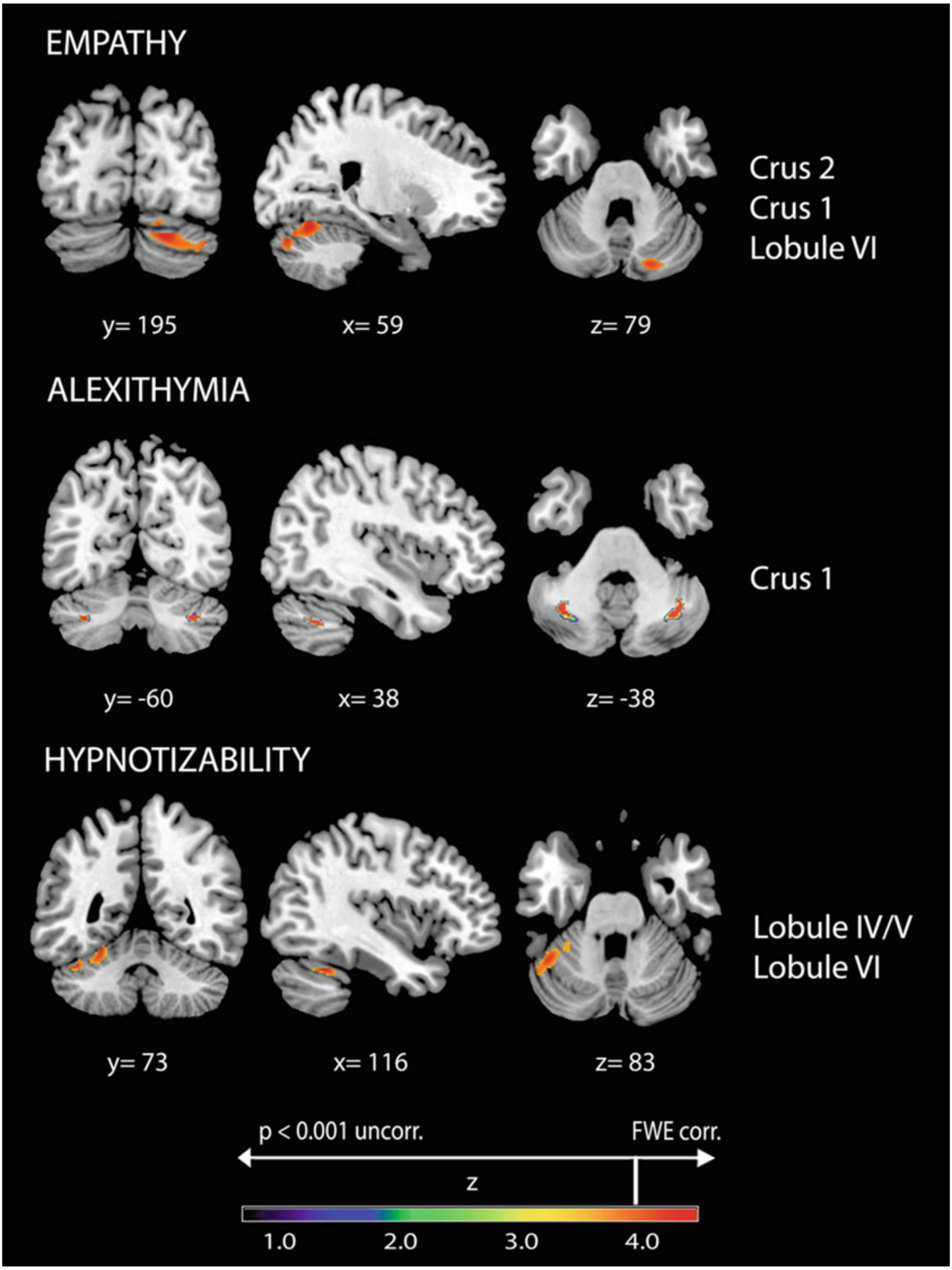

Fig. 16.1 Association between cerebellar gray matter volumes and embodiment-related psychological constructs. In the upper part, the volumes in right Crus 1, Crus 2, Lobule VI were associated with Empathy scores (specifically, with the scores of Fantasy subscale of Interpersonal Reactivity Index). In the middle part, the volumes in bilateral Crus 1 were associated with Alexithymia scores (evaluated by 20-item Toronto Alexithymia Scale). In the lower part, the volumes in left Lobules IV/V and VI were associated with Hypnotizability scores (evaluated by Stanford Hypnotic Susceptibility Scale, Form A). The reported significant differences survived to familywise error correction (FWE) for multiple comparisons. *z* above colorbar indicates normalized *t*-values. In figure left is left and coordinates are in Montreal Neurological Institute space

in long-term memory, even in the case the others are fictional characters.

In line with its contributions to the motor and affective domain, one of the main mechanisms underlying cerebellar functionality involves the generation of internal models (Ito 2008). The internal models are neural representations that encode the context-specific dynamics of concrete or abstract representations to facilitate predictive control of the system. The internal models directly compute the final outputs that produce the desired affective outcomes (inverse models) or encode the transition from actual sensory states to future (predicted) sensory consequences through an efference copy of the last command (forward model) (Ito 2008; Ramnani 2006). Furthermore, inputs to the cerebellum regarding the salience and motivational value of emotional stimuli guide internal models to determine how an emotional response could benefit individuals in their current state and, thus, shape how the output from the cerebellum modifies the emotional response. Therefore, the cerebellum checks whether an individual's state deviates from the expected state during emotion processing, and if the prediction error exceeds a given threshold defined by the context, the cerebellum refines the cortical response and recalibrates the internal model. And yet, since the predictions are based on information from the cortex to the cerebellum (efferent copies), and error signals are sent from the cerebellum to the cortex, the co-activation of the cerebellum and neocortical areas appears to be needed to successfully manage any mismatch (Ito 2008; Ramnani 2006). Similarly, to what happens in the sensorimotor system, even within the emotional/social realm the cerebellar function is characterized by the associated processes of forward modeling and error sensitivity that allow anticipating the other's behavior or one's own reactions (Sokolov et al. 2017; van Overwalle et al. 2020). We are now proposing that the concepts of prediction and error processing may be advanced to understand the cerebellar contribution to empathic abilities toward real people or even fictional characters. When the subject empathizes with other people, the cerebellar forward model potentially generates representations and predictions regarding other's feelings. Internal models are developed by using past perceptual, motor, and socio-emotional experiences of the empathizer, and are framed by the intentions, beliefs, and feelings of the other. The degree of matching between the subject and the other relies on such representations, but the subject can efficiently match with the state of the other to the degree that s/he has already existing representations for that state, pointing out the experience-dependence of such a process, in analogy to what previously described for the motor domain (Calvo-Merino et al. 2006).

Interestingly, in Picerni et al. (2021), in addition to volumes of right Crus 2 the Fantasy IRI-subscale scores were associated with volumes of right pars triangularis of the inferior frontal gyrus. As known, the cerebellum has vast connections with the prefrontal cortex, whose functions are related to the ability to live sociably and communicate with others, being key nodes of the mirror neuron system (MNS) (Cattaneo and Rizzolatti 2009; Molenberghs et al. 2012). Given its observation-execution matching properties, MNS provides the appropriate mechanism for empathy and imitation (Iacoboni 2009) and allows identifying goals and intentions of others by their resemblance to stored representations for the same states (experience-dependence). MNS may facilitate thus the simulation of behavior—even emotional—of the other (Kaplan and Iacoboni 2006).

It has been postulated that the prefrontal areas are activated when two or more emotional states—such as one's own and that of the other (in real life or imaginary situations)—are simultaneously processed and integrated to form a higher-order empathic state (Shamay-Tsoory et al. 2009a, b). It has been reported the peculiar engagement of the right inferior frontal cortex when comparing conditions in which the subject attributes a mental state to a character in a story in which the subject is featured and one in which s/he is absent (Vogeley et al. 2001). Further evidence for the critical role of the right inferior frontal cortex in the inhibition of self-perspective, comes from a case report of a subject with a lesion of this area who was impaired in ToM tasks that required the suppression of his own perspective but performed well if *it* did not (Samson et al. 2005). Thinking of or viewing a person who experiences a powerful emotion stimulates mirroring mechanisms and, through the implementation of the internal models provided by the cerebellum, might form embodied representations of that emotion grounded in perceptual, sensorimotor, and visceral control loops. These embodiment circuitries act as a boost for subsequent socio-emotional processes, allowing the remapping of other's states into the corresponding subject's perceptual, sensorimotor, and visceral brain areas making the subject experience the same emotion as the other (Preston and de Waal 2002; Niedenthal 2007; Preston 2007). The more similar the other's state is to something the subject has already experienced, the more his/her representations will match the other's state (Preston and de Waal 2002). Specifically, embodied models of empathy suggest that the capacity to detect own internal bodily signals should allow for a simulation of others' states on own body, leading thus to a fine-tuning to others' emotional and affective states (Bernhardt and Singer 2012). Consistently with these considerations, in the conceptual framework of social cognition, the concepts of empathy and embodiment are closely intertwined (Niedenthal 2007). However, embodied models struggle to explain why projecting other's affective states on own body does not cause confusion between which responses belong to ourselves and which to someone else. It has been hypothesized that the aforementioned mechanisms of affective simulation and embodiment should be matched with compensatory processes that help to distinguish self-generated stimuli from other's stimuli, forming and maintaining a clear distinction between self and other. These compensatory processes could be the efference copy signal provided by the cerebellum and the sensory and interoceptive signal processing at cortical and cerebellar levels. To differentiate between self and other, the brain needs to predict the sensory consequences of self-produced actions. According to the efference copy theory, the brain suppresses perception of self-produced sensory stimuli just by developing efference copies. A dysfunction of the efference copy at the forward comparator might weaken the sense of self-agency ("*I am the initiator of my own emotions and actions*"), such that self-induced sensory changes lose their 'self' tag and the individual no longer feels that he or she controls himself or herself. Furthermore, even the processing of sensory and interoceptive signals might serve to differentiate between self and other, by strengthening the representation of the subject's real body properties, at the expense of vicarious simulations of those from others (Palmer and Tsakiris 2018). In fact, the embodied self is likely established through processing of afferent tactile, proprioceptive and interoceptive information. Recently, deactivations have been demonstrated during self-touch and activations during touch by others in areas involved in somatosensory processing, social cognition, and salience. Interestingly, among those activated areas was the cerebellum (Boehme et al. 2019).

In summary, depending on how empathy is triggered, the affective and cognitive components of empathy are differentially involved. Thus, either the automatic tendency to mimic the other's expressions (bottom-up processing) and the capacity for imaginatively transposing ourselves into the feeling and thinking of the other (top-down processing) may be engaged. This co-recruitment of top-down and bottom-up components suggests that empathizing with the other's states relies upon the use of affective processing, cognitive representations related to the other's mental state, embodiment, and reactivation of information from one's own past experiences. The bidirectional traffic in the cerebellum fits well with its processing of somatic, cognitive, and emotional signals, suggesting it as critical hub in the networks implicated in mind–brain–body interactions, highlighting the involvement of the cerebellum in socio-cognitive processes and supporting the view of a "social cerebellum," and more specifically of an "empathic cerebellum."

16.3 Alexithymia as Embodied Emotional-Psychological Process and Its Relation with the Cerebellum

Alexithymia is a construct of personality characterized by impairment in cognitive, emotional, and affective processing. It describes people with deficiencies in identifying, processing, or describing subjective feelings or emotional aspects of social interaction, difficulty in distinguishing between feelings and bodily sensations of emotional arousal, and limited affect-related fantasy and imagery. In the mid-1960s, the psychiatrist John C. Nemiah and his colleague Peter E. Sifneos undertook systematic studies of the cognitive style of individuals that found it extremely difficult to describe their subjective feelings. This was what in 1972 led Sifneos to coin the term "alexithymia," which is formed by the roots of several Greek words, and literally means "lack of words for emotion." People with alexithymic traits have a tendency to focus on facts without affective involvement rather than inner experiences (Sifneos 1972; Taylor and Bagby 2004). Internal experiences are believed to be minimized, and attention is focused externally, an effect that some Authors have attributed to altered interoception (Dobrushina et al. 2020). Although alexithymia is not a psychological disorder in itself, it is associated with enhanced risk of psychological impairment and is present in a broad spectrum of psychiatric and psychosomatic disorders, as chronic pain, somatoform disorders, addictive disorders, anxiety, and depression (Taylor and Bagby 2004). The presence of high alexithymic traits results in impairment in empathy, and the inverse relationship of these two constructs characterizes the broad psychiatric and psychosomatic spectrum (Moriguchi et al. 2007).

Neuroimaging studies in subjects with high alexithymic traits have shown less activation in brain areas associated with emotional awareness, such as the ACC, fusiform gyrus, amygdala, parahippocampal gyrus and insula (Kano et al. 2003; Pouga et al. 2010; Reker et al. 2010). As for volumetric variations, negative correlations between alexithymia scores and amygdala and insula volumes were described (Laricchiuta et al. 2015), supporting the view that in alexithymia altered processing of emotional stimuli is associated with a reduction of reactivity and volume in limbic structures. Furthermore, negative correlations between alexithymia scores and ACC volumes were reported (Laricchiuta et al. 2015).

More connected with the cerebellar lens through which we are viewing the alexithymic brain, there are alterations in the cerebellar activity (Kano et al. 2003; Moriguchi et al. 2007; Kh et al. 2012) or volumes (Laricchiuta et al. 2015) reported in the presence of alexithymia. Positive associations have been found between alexithymia scores (obtained in the 20-item Toronto Alexithymia Scale), and gray matter (GM) volumes in bilateral cerebellar Crus 1 (Fig. 16.1, middle part), without significant alterations of micro-structural (density, surface, and orientation of cells) parameters (Laricchiuta et al. 2015). The enlarged volumes in Crus 1 described in subjects with high alexithymic traits corroborate the notion of cerebellar involvement in cognitive, emotional, and affective processes and fit with the consistent activation unique to emotional processing described in bilateral Crus 1 (Kh et al. 2012; Stoodley and Schmahmann 2010). How the brain structure—specifically, the volume—relates to function is a debated issue. In fact, on the assumption that larger populations of neurons can produce larger outputs, and can therefore be more influential than smaller populations of neurons, a greater-than-average volume may signify greater-than-average power to carry out specific functions. However, a greater-than-average volume may signify even a smaller-than-average power, considering that for example a deficient pruning might render the area suboptimal in terms of a less fine-tuned and functionally optimized structure. At the same time, even a smaller-than-average volume may be related to increased and more tuned efficiency. Human and experimental evidence tends to favor the "larger-is-more-powerful" position. In fact, training on particular tasks or experiencing complex environments does increase the volume of the functionally related brain structures (Boyke et al. 2008; Di Paola et al. 2012), supporting that volume tends to positively covary with function. Thus, it is possible to suggest that the increased volumes of Crus 1 could result in an enhanced inhibitory output of Purkinje cells, the only efferent fibers of the cerebellar cortex, on the deep cerebellar nuclei, modulating thus their excitatory output.

Neuroanatomical (Bostan et al. 2013) and fMRI (Habas et al. 2009) studies indicate that Crus 1 and lobule VI constitute a node in the cortico-limbic network centered on the dorsal ACC and fronto-insular cortex, and involved in detecting, integrating and filtering emotional information. Even the act of identifying emotional intonation (affective prosody) produces activation in Crus 1 and lobule VI, VII (Wildgruber et al. 2005). Furthermore, it has been reported that negative emotional faces evoke prominent activation in Crus 1 and 2 as well as in lobules VI and IX (Schraa-Tam et al. 2012). Aversive stimuli in the form of noxious heat and unpleasant images produce increased activation in Crus 1 and lobule VI negatively correlated with the activation of limbic and para-limbic areas, as para-hippocampal gyrus, ACC, and hypothalamus (Moulton et al. 2011).

The link between alexithymia levels and cerebellum (positive relation) and limbic system (negative relation) suggests a specific functional role for the cerebellar involvement in emotional processing in general and in alexithymia in particular (Fusar-Poli et al. 2009). Cerebellar nuclei project to extra-cerebellar targets, including the limbic system (Bostan et al. 2013). The inhibited nuclear activity could result in a reduced excitatory input to limbic and para-limbic structures that, in turn, could undergo a volumetric reduction because of the diminished activation level. Such a mechanism, however hypothetical, is in line with classical electrophysiological evidence indicating that cerebellar nuclear stimulations have suppressive effects on limbic sites, including ACC and amygdala (Snider and Maiti 1976). In the same vein, smaller ACC volumes and greater posterior cerebellar volumes have been described in patients with Cushing's disease reporting depressive and anxiety symptoms as well as cognitive, affective, and personality disorders (Andela et al. 2013). Structural neuroimaging studies on patients affected by obsessive-compulsive disorder also indicate smaller ACC volumes associated with greater cerebellar GM volumes (de Wit et al. 2014), offering additional insights into *the* reciprocal structural relation between the cerebellum and limbic and para-limbic areas.

Intriguingly, the enlarged volumes in Crus 1 described in subjects with high alexithymic traits are nicely compatible with the functional findings by Moriguchi and Komaki (2013), who reported that people with high alexithymic traits show reduced neural response in the limbic system to external and internal emotional stimuli and conversely increased neural response in somatosensory and sensorimotor areas to stimuli closely associated with physical information. Note that subjects with high alexithymic traits exhibit hypersensitivity to physical sensations, associated with a tendency to rely on or to amplify physical symptoms. The network comprising the cerebellum and limbic system (and also the sensorimotor and prefrontal cortices) is involved in sensing and monitoring the physiological bodily conditions (Critchley and Garfinkel 2017; Moulton et al. 2011), in representing the interoception within the context of ongoing activities, and in feeling self- and externally induced emotions (Anders et al. 2004).

In the condition of efficient functioning, subjects have internal models of their internal or external environment that serve the function of representing it. Such internal models form embodied representations grounded in sensorimotor control loops, and these representations in turn are internally manipulated before or instead of acting directly on the environment, even if the final goal of this form of embodied emotion and cognition is acting on the environment (Barsalou 2008; Niedenthal et al. 2005; Pezzulo and Castelfranchi 2009).

On such a basis, alexithymia may be considered an altered embodiment process related to an altered perception of physiological correlates of the emotional activation, resulting in a deficit in emotional awareness. Karlsson et al. (2008) suggested that in highly alexithymic individuals the brain regions involved in bodily awareness may be hyperactive during emotional processing, possibly reflecting the alexithymic tendency to experience physical symptoms when emotionally aroused. In the same line, Zhang et al. (2011) interpreted the increases in GM density in relation to alexithymia as indicative of a greater reliance on bodily sensations during the subjective experience of emotion. Accordingly, a somatosensory amplification has been described in the presence of definite alexithymia (Lumley et al. 2005). Kano et al. (2007) described the aberrant manner of perceiving body signals of subjects with high alexithymic traits and reported positive associations between alexithymia scores and cerebellar regional cerebral blood flow (rCBF) following visceral stimulation. Furthermore, high cerebellar rCBF was reported in subjects with high alexithymic traits when viewing emotional facial expressions (Kano et al. 2003), recalling emotional autobiographic traces (Huber et al. 2002), or observing a classic mirror neuron task, as the observation of goal-directed hand actions (Moriguchi et al. 2009).

In the presence of alexithymia, an altered referential process can lead to emotions that are somato-sensorially perceived but not verbally expressed, *due* to not having words for the emotions or being without symbols for the somatic states. In line with the lack of emotional awareness, it has been described the lack of somatic awareness, the “alexisomia” (*Shitsu-taikan-sho* in Japanese). Such an intriguing psychological construct is characterized by difficulty in the awareness of somatic sensations, disconnection between cortical and subcortical systems, and homeostatic inadequacy by blunt interoception. Alexisomia might be an important variable in the pathology of psychosomatic disorders (Ikemi and Ikemi 1986; Moriguchi and Komaki 2013). Reduced interoceptive awareness featuring alexisomia would result by impairment of the senses necessary to maintain homeostasis (as hunger and sleepiness), the senses associated with adaptive processes to environmental changes normally felt as warning signs (such as fatigue), and the senses accompanying physical diseases (such as chill and pain). Ikemi and Ikemi (1986) added that individuals prone to *Shitsu-taikan-sho* show unhealthy and self-destructive lifestyles and have difficulties in awareness and expression of bodily feelings. Thus, if the awareness of bodily states, including autonomic and hormonal status, is the basis of emotional awareness, deficits of emotional awareness underlying alexithymia might be related to deficits of bodily sensation awareness underlying alexisomia. To exemplify this unhealthy condition, we can mention that patients with reduced interoceptive awareness may experience somatosensory amplification (the tendency to perceive normal somatic and visceral sensations as intense, disturbing, and noxious), accompanied by persistent pain, such as myalgia of some part of the body, or may not perceive their own somatic state properly. Considering the bottom-up component of the emotional expression, the altered awareness of bodily states featuring the alexisomia might be the rudimentary form of altered emotional awareness featuring alexithymia.

16.4 Hypnotizability as Embodied Psychological-Cognitive Process and Its Relation with the Cerebellum

Hypnotizability, or hypnotic susceptibility, is a term used to describe the degree to which a subject is responsive to suggestion, taking into account that not everyone is susceptible to hypnosis. In other words, hypnotizability is a personality construct that predicts the proneness to modify perception, memory, emotion, and behavior according to the content of specific imaginative suggestions after hypnotic induction as well as in the ordinary state of consciousness (Elkins et al. 2015). Hypnotizability can be assumed to be a psychological trait facilitating the embodiment of suggestions and the involuntariness in action. Indeed, differences in its main cognitive-emotional components (i.e., imagery, fantasy proneness, expectancy, attention/absorption, acquiescence, and motivation) are accompanied by differences in somatic and autonomic correlates, as sensorimotor integration, cardiovascular control, functional equivalence between imagery and perception (Santarcangelo and Scattina 2016). The degree of hypnotic susceptibility determines the differences in the ability of detachment from bodily signals, interoceptive sensitivity, tendency toward ideomotor behaviors, and in the way to represent and reconstruct sensorimotor information. In particular, the highly hypnotizable individuals exhibit higher proneness to modify memory, perception, and behavior according to specific imaginative suggestions and display greater embodiment of mental images related to both imagery or perception of a position of a body part (Ibáñez-Marcelo et al. 2019). The different embodiment of mental images supports the proneness to respond to sensorimotor suggestions and to report involuntariness in action featuring highly hypnotizable individuals. Additionally, different levels of hypnotizability are related to morpho-functional peculiarities of several brain areas. In particular, different activation and volumes not only of specific cortical regions, including the dorsolateral prefrontal cortex, inferior frontal gyrus, ACC, parietal and temporal regions, parahippocampal gyrus, and insula), but also of defined specific cerebellar areas have been described (Hoeft et al. 2012; Jiang et al. 2017; McGeown et al. 2015; Picerni et al. 2019). fMRI studies have shown that the report of involuntariness in action is associated with the activation of the parieto-cerebellar network, which differentiates the activations during suggestion-induced movements misattributed to an external source with respect to movements experienced as self-produced and controlled (Blakemore et al. 2003).

Subjects with different hypnotizability levels differ in sensorimotor integration, indicating the possible involvement of cerebellar networks in the sensorimotor, cognitive, and emotional aspects of hypnotizability (Santarcangelo and Scattina 2016). In particular, subjects with high hypnotic susceptibility exhibit a less strict postural and locomotor control, lower accuracy and higher variability in visuomotor tasks, higher blink rate, increased pain intensity, pre-eminent parasympathetic control of heart rate. Interestingly, they display smaller volumes in left cerebellar lobules IV/V and lobule VI (Picerni et al. 2019) (Fig. 16.1, lower part). Such volumetric differences closely fit with the functional topographic organization of cerebellar regions according to their anatomical connectivity with neocortical regions. In fact, the lobule VI represents the anterior boundary between overtly sensorimotor zones (i.e., lobules IV-V) and supramodal cognitive zones (i.e., lobule VII), so that sensorimotor tasks that involve complex, fast and sequenced movements activate specifically the lobule VI. Thus, reduced volumes of lobules IV–V and VI of subjects with high hypnotic susceptibility may sustain their altered sensorimotor processing.

Notably, lobules IV–VI are functionally linked to the insular cortex (Sultan et al. 2012), the integrative center for own-body representation and awareness that receives large quantities of interoceptive, autonomic, and emotional information from somatosensory and limbic areas, and links them with external elements in order to organize adaptive behaviors (Craig 2011). The insular cortex is involved in self-reflection, self-monitoring, and self-regulation, as well as in empathy, all processes that can be altered in hypnosis (Terhune and Hedman 2017).

By investigating the insular responses to sensory stimuli with affective valence in relation to the individual differences in emotional susceptibility, it has been demonstrated that weaker functional connections of the left anterior insula with left lobule IV are linked to higher emotional susceptibility (Ebisch et al. 2015). Such findings suggest that these changes could represent the correlate of the altered emotional processing reported in the presence of high levels of hypnotizability, when higher emotional intensity during imagery, sensitivity and empathy, tendency to somatic complaints, and vividness of pain imagery are present (Kirenskaya et al. 2011). Furthermore, an fMRI study on a sample of subjects with high levels of hypnotizability revealed parallel activations of the left insula and left cerebellum, besides prefrontal and parietal cortices, during both hypnotically and physically induced pain (Derbyshire et al. 2004).

Once more, it is important to emphasize the role of the cerebellum in forming internal models (forward or inverse) to adapt sensorimotor, cognitive, and emotional activities to information of internal and external environment (Ito 2008; Ramnani 2006). Even in the case of hypnotizability, the long-range signals from associative cortices may exert a relevant top-down control over the cerebellum broadly involved in the operational processing of information linked to movement, thought, and emotion. Once again, it has to be considered that the top-down processes work in concert with bottom-up mechanisms. The directionality of processing (bottom-up or top-down) depends on the hierarchical position of the cortical area from which the cerebellum receives its inputs relative to the cortical area to which the cerebellum directs its outputs, placing the cerebellum as a "sub-cortical hub" between hierarchically different cortical regions (Kellermann et al. 2012). Even if only speculatively, it is possible *to propose* that the individual differences in hypnotic susceptibility could be mediated by cortico-cerebello-cortical loops. The sensitivity of some neocortical regions might top-down modulate the activity of cerebellar lobules IV–VI, which in turn might bottom-up control other cortical regions.

16.5 Conclusion

Current psychological discourse debates emotions and psychological traits as 'embodied' phenomena, suggesting that the body helps the mind in shaping an emotional and cognitive response. The main models of embodiment describe the self as an integration of a social or conceptual self along with our physical self, suggesting that affective and psychological functions are not independent of sensorimotor functions. We use our own body and experiences to simulate information from other people's bodies to understand their emotions, thoughts, and behaviors. This idea of a strong mutual interaction between the embodiment processing and the cerebellum (Guell et al. 2018) underscores the role of the cerebellum in emotion and psychological traits.

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Part IV

Cerebellum and Emotion Disorders

17 The Cerebellum and Disorders of Emotion

Dennis J. L. G. Schutter

Abstract

Neuropsychological and experimental brain research have provided independent lines of evidence in support of cerebellar involvement in disorders of emotion. Medial cerebellar structures and their connections to the limbic system are involved in visceral aspects and the generation of emotions, whereas the posterolateral cerebello-thalamo-cortical loops are implicated in emotion regulation and subjective sense of control. Disturbances within these cerebellar-centred circuits are proposed to underlie homeostatic dysregulation and suboptimal predictive coding that provide a transdiagnostic mechanism by which the cerebellum may contribute to the vulnerability and persistence of mental disorders.

Keywords

Cerebellum · Disorder · Emotion · Homeostasis · Predictive coding

17.1 Introduction

According to the American Psychological Association (2021) psychological disorders are characterized by emotional reactions that are inappropriate or disproportionate to their cause. Whilst psychological disorders encompass a broad set of terms including emotional disturbance, behavioural and psychiatric conditions, and mental illness, its aetiology typically points towards issues in the responsivity, experience, and regulation of emotions. An important aspect of the nature of psychological disorders lies in its antonym which emphasizes effective functioning in daily activities and one’s ability to adapt to change and cope with adversity (American Psychiatric Association 2013). From this perspective, mental health — or the absence of emotional disturbance— can be understood along the lines of psychological resilience, which involves the facilitation of personal assets and protecting oneself from or limiting the impact of potential harmful effects of stressors (Kalisch et al. 2015). The ability to experience emotions and feelings comprises the backbone for both facing challenges and exploiting opportunities across different contexts. The continuous and active process of upheaval attributable to the mismatch between the current and desired state of an organism can be considered a basic mechanism for psychological well-being. The expression of adaptive behavioural responses to stress is proposed to reflect an important evolutionary principle, resulting in individuals being able to maintain stable behaviour or display behaviour that meets environmental demands as a function of their available internal resources. The degree to

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which an organism can meet the continuing challenge between stressors and available internal resources depends on a complex interplay between environmental load, learning from experience, and coping capacity (Schutter et al. 2015). The organism's ability to display situation-appropriate responses and downregulate stress is argued to reflect processes of adaptation and mental flexibility. As already mentioned, the context or environment makes up an important part of what is considered normal or abnormal when it comes to the experience of in particular negative emotions, or lack thereof, in, for example, shaping cognitive control processes and adaptive behavioural responses. In other words, extreme emotions and behaviours in response to extreme adversity can be considered normal and healthy reactions (Frankl 2006). However, when these emotions and behaviours arise outside the proper context they lose their adaptive value (Nesse 1999).

17.2 Evolutionary Science and the Psychology of Disorders

Emotions are phenotypes of the biological machinery that have been shaped through selection during the course of human evolution (Panksepp 2006). Evolutionary science aims to understand psychological disorders by addressing the proximate and ultimate causes of human behaviour. The study of proximate causation involves the systematic analysis of mechanistic causes of development and biological make-up of individuals ("ontogeny"). This is distinct from studies that address ultimate explanations aiming to understand the functional basis of human behaviour from the history of the evolution of a species or group ("phylogeny"). Thus, whereas the focus of ontogeny lies in the "how" question, phylogeny is concerned with addressing the "why" question (Tinbergen 1963).

Evolutionary psychiatrists and psychologists seek to explain psychological disorders based on the evolved functional characteristics of the human mind (Panksepp 2006). One of the implications of the phylogeny perspective is that, in agreement with Darwinian evolution theory, disorders are not intentional products of natural selection. Natural selection is tied to processes that promote reproduction, including random gene mutations that turned out to be beneficial for reproduction and survival of the species. However, natural selection can give rise to certain vulnerabilities that can contribute to maladaptive emotional, cognitive, and behavioural responses when an individual is exposed to new challenges and/or adversities. An influential evolutionary model proposes that negative emotions can lose their adaptive function and contribute to the development of psychological disorders (Nesse 1990). Emotions play a crucial role in guiding situation-appropriate behaviours that through the course of evolution have proven beneficial to the mammalian species. It is therefore not surprising that emotions are intrinsically tied to the brain's survival circuitry (LeDoux and Daw 2018). The neural core of the survival circuit which is part of our mammalian heritage consists of subcortical regions that include the amygdala, periaqueductal gray (PAG), hypothalamus, hippocampus, and brainstem nuclei, and are considered to be part of what Nesse calls the "smoke detector principle" (Nesse 2001). He illustrates this principle by arguing that many physiological responses and emotions, allegedly having their roots in the survival circuit, are part of coping mechanisms that come into play as soon as the brain's sensory modalities signal potential threat. In terms of signal detection theory, the threshold for threat appraisal is designed in such a manner that the brain is biased to generate many false alarms in the service of preventing a fatal miss. Furthermore, this threshold is dynamic in the sense that it is lowered in unsafe situations (i.e., high probability threat presence) and elevated in safe environments (i.e., low probability threat presence). The emergence of a complex cerebral cortex and consciousness in primates and humans not only facilitated the scaling of this threshold, but also greatly increased cognitive capacity associated with more accurate threat evaluation and coping strategies including the ability to anticipate future threats. Whilst this cortico-subcortical architecture has proven invaluable for the survival of the human species, such as by reaching the top of the food chain, these benefits come at a cost. Humans are vulnerable to emotional disorders and mental suffering which are even potentially lethal. For example, anticipating future stressful events (e.g., taking a final exam) can be helpful in finding effective coping strategies (e.g., study hard in advance) to deal with the potential negative consequence (e.g., failing the exam). However, this conscious awareness together with a low threshold for threat can also predispose to the development of excessive anxiety, irrational worrying, and rumination ("what-if" thinking) in the anticipation of future adversities that are highly unlikely. Additionally, this mental state is associated with increased feelings of hopelessness, mental fatigue, and loss of subjective feelings of control which are typical of mood disorders. Further, the subjective uncertainty can result in mannerisms, rituals, and stereotypical behavioural patterns, as seen in obsessive-compulsive disorder. These behaviours arguably result from a regression to an evolutionarily older and more primitive survival mode to cope with complex and challenging environments.

In sum, the workings of the human brain are the product of both proximate and ultimate processes which have contributed to our survival. However, as the organism is continuously pressured by new complex situations, this can cause a mismatch between evolved capacity of the brain and current environmental demands. This introduces vulnerability factors for the development of psychological disorders defined by subjectively experienced uncertainty, negative emotions, and depletion of coping resources.

17.3 Cerebellar Neuroscience of Emotion-Related Disorders

Available functional and anatomical evidence suggests that in addition to the cortico-subcortical circuitry, the cerebellum is part of the brain's survival and emotion regulation system shaped through natural selection. More specifically, the exceptional expansion of the prefrontal cortex in great apes and humans has been interpreted as a potential neural basis for the affective and cognitive distinctiveness in primates (Smaers et al. 2017). Furthermore, the development of the prefrontal cortex is considered to be part of a larger evolving network that in addition to the temporal and parietal cortical association areas includes the cerebellum (Balsters et al. 2010). Following these studies, recent work shows that the expansion of the major regions of the cerebello-cortical system in fact underwent the highest rate of evolution in humans as compared to other primates (Smaers and Vanier 2019). In addition, the cortical sheet of the cerebellum is much more tightly folded than that of the cerebrum. Structural reconstruction based on high-resolution post-mortem MRI scans indicates that the human cerebellum makes up almost 80% of the neocortical surface (Sereno et al. 2020). The relatively small size of the cerebellum at 10% of the total brain mass as compared to the size of the cerebral cortex at 75% of total brain mass underscores the computational strength of the cerebellum. Together, these findings have not only contributed to reconsideration of the role of the cerebellum in non-motor related functions, but in fact offer a neural foundation for complex human behaviour as well. It is not a coincidence that acquired cerebellar lesions can lead to emotional and cognitive disturbances which are remarkably similar to impairments following frontal lobe damage. The signs and symptoms associated with cerebellar damage in the more posterolateral regions (e.g., Crus I and II) are impairments in executive functioning, spatial cognition, language, and cognitive regulation (Schmahmann and Sherman 1998). Damage to medial cerebellar regions including the vermis is associated with emotion-related disturbances such as blunting of affect, anxiety, depression, impulsivity, irritability, and aggression (Schmahmann et al. 2007). The observation of cognitive abnormalities in association with posterolateral damage can be interpreted as functional disturbances within the cerebello-cortical system, whilst the relation between medial cerebellar lesions and emotion concurs with the existing anatomic connections between the vermis and subcortical structures. It should be noted that although the brain displays remarkable robustness to major perturbations to the system as shaped through the course of evolution, such a highly non-linear dynamic system is nonetheless vulnerable to minor perturbations that can trigger a cascade of failing processes (Doyle et al. 2005). Since the cerebello-cortical system continues to develop into childhood and adolescence (Tiemeier et al. 2010), early life adversities (big or small) can lead to suboptimal structural and functional characteristics that can predispose an individual to psychological disorders. In other words, psychopathological conditions can result from a combination of proximate and ultimate developmental trajectories. Furthermore, it has been suggested that the rapid evolution of the cerebello-cortical system has contributed to the evolutionary success of the human species as illustrated by scientific and technological innovations. However, the increasing complexity of our society and environment brings about new challenges associated with, for example, 24/7 economies in the Western society and overpopulation. These challenges typically cause a set of physiological processes, known as the stress response, which promote the organism to seek ways to effectively deal with them. However, early life chronic stress can not only have a negative impact on the developing brain and body but is also metabolically costly and together with the wearing out of coping strategies has a negative impact on resilience. The term allostasis, meaning "achieving stability through change" (Sterling and Eyer 1988), refers to the process by which the body responds to events in order to maintain internal bodily homeostasis (McEwen 1998). Allostatic load is the cost of chronic exposure to stress, and psychological disorders, like depression and anxiety, illustrate a loss of resilience and flexibility (McEwen 1998). Therefore, whereas depressive symptoms can be part of an adaptive response to withdraw and recuperate from an adverse event, their adaptive value goes awry when the depressive state loses its contextual meaning (Nesse 2000).

17.4 Disorders of Fear and Sadness

In addition to neuropsychological studies, there is ample evidence from structural and functional neuroimaging studies and early intracranial neurostimulation studies that demonstrate involvement of the cerebellum in human emotions and psychopathology (Schutter and van Honk 2005: Schutter 2013, 2020). For example, a recent meta-analysis of whole-brain resting-state functional MRI studies that explored differences in the amplitude of low-frequency fluctuations (ALFF) between patients with unipolar and bipolar disorder and healthy controls found, in addition to striatal, insular, and cortical differences, evidence for abnormal cerebellar activity (Gong et al. 2020). In particular, patients with major depressive disorder demonstrated decreased ALFF in bilateral cerebellum as compared to healthy controls. Patients diagnosed with bipolar disorder showed reduced ALFF in the left cerebellum in comparison to healthy controls. A conjunction analysis confirmed the lower ALFF in the left cerebellum together with increased ALFF in the insula and medial prefrontal cortical regions in both unipolar and bipolar disorder. The left-sided ALFF decreases were concentrated in lobule VI and Crus I, and the lower ALFF in the right cerebellum found in unipolar disorder was located in lobule VI (Gong et al. 2020). The abnormal intrinsic activity in the posterolateral regions of the cerebellum in both disorders is suggestive of a disruption of the cerebello-cortical system. These meta-analytic findings do not stand alone as numerous other studies support cerebellar eccentricities in mood disorders, including reduction of grey matter volumes and abnormal cerebellar functional connectivity (Schutter 2020). Inverse associations between cerebellar volumes and neuroticism in non-clinical samples together with reductions in emotion regulation capacity following disruptive repetitive transcranial magnetic stimulation over the cerebellum in healthy volunteers confirm the proposed link between the cerebellum and vulnerability to mood disorders (Schutter and van Honk 2009; Schutter et al. 2017; Adamaszek et al. 2017). As neuroticism is a personality trait characterized by worrying, self-doubt, behavioural inhibition, feelings of depression, and anxiety, a link between the cerebellum and anxiety disorder can be expected. Empirical support for this assumption comes from a systematic review and meta-analysis of voxel-based morphometry and task-based results that examined structural and functional differences between patients with generalized anxiety disorder and healthy controls (Kolesar et al. 2019). Results showed disorder-specific aberrations in limbic structures that included the hippocampus and amygdala, frontal cortical areas, and the cerebellum. In the case of the cerebellum, patients with generalized anxiety disorders showed lower-than-normal functional connectivity between the anterior lobe and the amygdala. Also, less recruitment of the anteromedial cerebellar lobule corresponding to the culmen of the vermis was seen during working memory, emotion modulation, and conflict tasks. Conversely, patients with generalized anxiety disorder exhibited greater functional connectivity and activity for congruency and conflict, and emotional face processing tasks in Crus II of the posterolateral cerebellum (Kolesar et al. 2019). Increased functional connectivity has also been found between posterolateral cerebellar activity and the dorsolateral prefrontal cortex in non-clinical individuals scoring high on behavioural inhibition (Caulfield et al. 2016). Together, these findings lend support to the involvement of the cerebello-cortical system in vigilance, executive control function, and emotion regulation in both clinical and non-clinical samples. Indeed, previous resting-state fMRI work indicates that the posterolateral regions of the cerebellum are part of the brain's executive control and salience network (Habas et al. 2009). Moreover, as a part of the saliency network, the connections of the vermis to limbic regions including the amygdala, hypothalamus, and hippocampus fit the idea of a cerebello-limbic pathway for interoceptive (visceral) and exteroceptive (sensory) processing. Such a pathway could involve (pre-attentive) emotion appraisal and internal homeostasis as well as motor coordination and preparation (Habas 2018; Schutter 2020).

17.5 Disorders of Disgust

Marked anxiety can lead to obsessions and irresistible urges to complete compulsive acts to alleviate feelings of distress. Obsessions are persistent thoughts about, for example, excessive fears of contamination and recurring doubts about danger. Compulsions are repetitive and stereotypical behaviours that an individual needs to perform in response to the obsession. In addition to fear, research supports the role of the emotion disgust in obsessive-compulsive disorder (OCD) related to contamination (Ludvik et al. 2015). From an evolutionary perspective, disgust helps to protect animals from ingesting potentially harmful substances and/or avoid physical contact with disease-causing pathogens (Kelly 2011). Thus, whilst disgust is an adaptive response, the earlier discussed low threshold for threat appraisal generating many false alarms as to prevent a highly unlikely fatal miss may turn into a maladaptive mechanism as exemplified by obsessions and compulsions. Following the discovery of a shared cortico-striatal-thalamo-cortical pathway and the insular cortex in disgust and obsessive-compulsive disorder (Berle and Phillips 2006), recent insights also point towards a role for the cerebellum (Eng et al. 2015). A meta-analysis of 54 task-based fMRI studies shows that OCD patients demonstrated hyperactivity in regions implicated in arousal, salience, and habitual responding (i.e., anterior cingulate cortex, insula, and striatum) and hypoactivity in regions implicated in cognitive and behavioural control (i.e., prefrontal cortex and striatum) (Rasgon et al. 2017). These findings indicate that OCD-related brain dysfunction involves heightened emotional responsivity and self-referential processing, enhanced habitual responding, and lower levels of cognitive control (Rasgon et al. 2017). With the notable exception of a study that found no differences in cerebellar activation to disgust-inducing pictures between OCD patients and healthy volunteers (Shapira et al. 2003), research on disgust-induced cerebellar activity in OCD is still lacking. It is evident that the cerebellum-disgust link in contamination OCD needs to be examined in more detail, but there is at least sufficient empirical ground to assume that the cerebellum is part of a disturbed affective-cognitive circuitry in OCD (Anticevic et al. 2014).

Larger functional connectivity between the nodular lobe and insula being predictive for greater reduction of aversive experiences (Bai et al. 2018) further hints towards a role of medial cerebellar structures in visceral and autonomic activity. Moreover, it provides a hypothetical link between disgust and somatic experiences like nausea in contamination OCD.

Finally, elevated connectivity between the cerebellum and the basal ganglia has been shown to correlate with less attentional set-shifting and cognitive flexibility in OCD (Vaghi et al. 2017).

17.6 Disorders of Anger

Aggression is a behavioural response to threat, frustration, provocation, or other aversive conditions. Roughly, two types of aggressions are distinguished: affective (defensive) and predatory aggression. Affective (reactive) aggression occurs in response to an imminent and often unescapable threat and is accompanied by sympathetic signs and high levels of experienced anger (Weinshenker and Siegel 2002). Predatory (proactive) aggression, on the other hand, is more appetitive and typically involves more goal-directed (premeditated) attack behaviors in the absence of sympathetic arousal and high levels of state anger (Weinshenker and Siegel 2002). The neural basis of reactive (affective) aggression originates in the fast-acting subcortical regions comprised of the amygdala, periaqueductal grey, and hypothalamus, whilst in proactive (predatory) aggression, the anterior cerebral cortical areas are also actively involved in the planning and control of goal-oriented behaviours. In comparison to other mammals, the well-developed anterior cerebral cortex of humans allows for more complex and sophisticated forms of aggression.

Involvement of the cerebellum in aggression dates back to invasive electric stimulation studies during the 1970s which demonstrated that exciting the fastigial nucleus of the deep cerebellar nuclei in cats elicits sham rage (Zanchetti and Zoccolini 1954) and attack behaviours (Reis et al. 1973). In a recent study in mice, optogenetic stimulation of Purkinje cell activity in the vermis was shown to significantly reduce attack behaviours towards an intruder, whereas optogenetic inhibition of Purkinje cell activity had the opposite effect and increased the number of attack behaviours (Jackman et al. 2020). The latter findings can be explained by the modulation of the inhibitory projections of the Purkinje cells to the fastigial nucleus. Furthermore, subdural electric stimulation of the vermis can lead to substantial improvements in aggression in severely behaviourally disturbed psychiatric patients (Heath 1977: Heath et al. 1980).

Electric stimulation of the anterior lobe has also been found to improve emotional control and reduced outbursts of aggression in patients with epilepsy (Cooper et al. 1976). Abnormalities of the vermis concur with the earlier discussed neuropsychological studies that found involvement of the vermis in emotion (Schmahmann and Sherman 1998), including anger and aggression (Schmahmann et al. 2007). Structural brain scans indicate that, in addition to cortico-subcortical abnormalities (Rogers and De Brito 2016), anomalies in the cerebellum are present in psychopathic, antisocial, and violent individuals. Bilateral grey matter volume reductions of the cerebellum have been reported in antisocial offenders and schizophrenic patients with a history of aggression (Bertsch et al. 2013: Puri et al. 2008). Similarly, smaller grey matter in posterolateral cerebellar hemispheres (e.g., Crus I) has been found in boys with conduct disorders (Dalwani et al. 2011: Zhang et al. 2018). In other studies, lower vermis volumes and larger bilateral grey matter volume in lobule IX have been reported in conduct disorder as compared to healthy controls (De Brito et al. 2009: Huebner et al. 2008). Furthermore, a recent study in healthy volunteers demonstrated a positive association between grey matter volume of the vermis and lowered behavioural inhibition, and an inverse relation between posterior lateral cerebellar regions and aggressive behaviour (Wolfs et al. 2022). Whilst the functional significance of these structural deviances remains elusive, the data suggest involvement of the cerebellum in the emotion anger and aggressive behaviour. A meta-analysis of fMRI studies is mostly in accordance with the structural findings showing involvement of the anterior and posterolateral cerebellar areas (Klaus and Schutter 2021). The posterolateral regions are suggested to be implicated in threat processing and the more cognitive aspects associated with anger (e.g., attentional bias). The anterior regions with their functional connections to the default mode and somatomotor network suggest involvement in mentalizing processes and execution of aggressive behaviour (Wong et al. 2019). In a script-driven imagery study, the recall of autobiographical memories of anger in a group of violent offenders activated the vermis and right lateral cerebellar hemisphere (Spoont et al. 2010). In addition, activation of the insula and a reduction of activity in the left inferior frontal gyrus were observed. The joint activation of the vermis and insula arguably denote the visceral representation and feeling of anger, whereas the increased activity in the right cerebellum together with reduced left inferior frontal gyrus activation may reflect cerebello-thalamo-cortical inhibition of the left-lateralized cortical approach (fight) system (Schutter 2020; Kruithof et al. in press).

It is proposed that the vermis and anterior lobe are suggested to be part of the (visceral) limbic regions implicated in fast pre-attentive and impulsive responses to imminent threat or provocation (affective aggression), whilst the posterolateral cerebellar hemispheres with its connections to the motor and prefrontal cortex provide a neural basis for top-down regulatory control mechanisms in predatory aggression (Kruithof et al. in press).

Intermittent-explosive disorder involves uncontrollable acts of aggression stemming from rapidly escalating feelings of frustration and anger that are out of proportion to the occasion. Subjective accounts of being thrown into a fit of rage or flying into a rage for no reason are exemplary for a hypersensitive subcortical anger circuit and lack of emotion regulation. This idea concurs with the symptom improvement of anger and aggression in response to subdural cerebellar neurostimulation in behaviourally disordered individuals (Heath 1977, 1980). However, cerebellar involvement in intermittent-explosive disorder remains a topic of future investigation.

17.7 Affective Predictive Coding Theory

Disorders of emotion can be defined as psychopathological conditions characterized by a mismatch between available resources and environmental demands in which the experience of emotions and feelings has lost its adaptive function in terms of guiding actions to resolve the mismatch and restore bodily homeostasis. The reciprocal monosynaptic connections of the cerebellum to the hypothalamus established in animals provide a neuroanatomic pathway for the cerebellar involvement in the metabolic, visceral, and endocrine processes associated with homeostatic functioning. Via basal pontine nuclei afferents, efferent connections to numerous other subcortical (e.g., the reticular formation, midbrain, basal ganglia, amygdala, and hippocampus) and cortical structures, (e.g., parietal, motor, and prefrontal cortex) form a highly complex neural circuit of cerebello-subcortical and cerebello-cortical loops (Stoodley and Schmahmann 2010).

The essentially uniform cellular architecture of the cerebellar cortex led to the concept of the universal cerebellar transform (UCT). It postulates that “a singular mechanism (...) performs its computation on different channels of information processing subserved by anatomically precise connections linking focal cerebellar regions with different cerebral areas. This enables the UCT to manifest as different functions, from movement coordination to cognition and emotion. In this view, different functions of the UCT (...), for instance, the regulation of rate, rhythm and accuracy of movement, and therefore the regulation of speed, capacity, consistence and appropriateness of emotions (Schmahmann 1991) are understood as different manifestations of the common mechanism." (Guell et al. 2018, page 143). The cerebellum is proposed to integrate multiple intero- and exteroceptive representations and coordinate cortical and subcortical information processing streams in support of appropriate (adaptive) behaviours in varying environmental contexts. In recent years, the uniform cellular organization of the cerebellar cortex has been challenged by research showing regional morphological differences in both the anterior-to-posterior and the medial-to-lateral planes of the mammalian cerebellar cortex (Cerminara et al. 2015). For example, greater density of Purkinje cells in the anterior as compared to the posterior lobe and the presence of larger Purkinje cells and higher granule cell density in the vermis as compared to the cerebellar hemispheres were reported. The physiological significance of the morphological differences implies the existence of functional specializations, which fits the idea of distinct cerebello-subcortical and cerebello-cortical anatomic topologies. The parallel fibres of the granule cells span across the regional morphological boundaries and may provide a cellular element of signal exchange and integration in the cerebellum. The conceptualization of the UCT was initially based on the cellular homogeneity of the cerebellar cortex, but the general principles of the UCT may find its origins in a small-world network-like architecture of the cerebellum. In agreement with the proposed UCT function and predictive coding theory, the functional role of the cerebellum in adaptive control within the sensorimotor domain is also applicable to the non-motor domain (Schmahmann 2010). Central to predictive coding is the idea of the brain operating as a system which constructs experience-based inferential models of the world to minimize uncertainty (Friston 2010). Prediction error signals that result from a mismatch between anticipated and actual outcome typically lead to a cascade of physiological processes and emotions that serve to restore bodily homeostasis through behavioural adaptation (Schutter 2016). The idea of reducing uncertainty defined as the inverse of variance is known as the error minimization routine of predictive coding (Friston 2010). This process is considered to form the basis of the organism's ability to construct and update inferential models that maximize the likelihood of successful adaptation under changing conditions.

The cerebellum receives affective and cognitive commands from cortical and subcortical areas to produce reward-punishment-based inferential models of the expected consequences of those commands (Moberget and Ivry 2016). Ultimately, these representations are internalised in separate functional neural units (microcomplexes) and used as inferential (prediction) models of behaviour (Sokolov et al. 2017). Prior work has demonstrated that microcomplexes are modifiable according to environmental cues (Ito 2008). This adaptive learning is arguably critical for optimizing behaviors according to context and mental flexibility (Schmahmann 2010). In other words, the cerebellum engages in estimates of probabilities and frequencies in situations of uncertainty which culminate in a behavioural response that is anticipated to produce the most likely outcome given time constraints and prior experience. The workings of the cerebellum may be compared with a Kalman filter which keeps track of the estimated state of the system and the variance or uncertainty of the estimate based on a series of measurements taken over time. The Kalman filter is comparable to the least-squares method in regression analyses, where the best fitting line is calculated on the basis of data points. Each data point represents the relationship between a known independent variable (input) and an unknown dependent variable (output) and would be an example of a so-called cerebellar heuristic (Schutter 2020). From a Bayesian perspective, feedback-related reward and punishment signals are proposed to serve important subcortical/limbic inputs to update the prior settings of the internal model in order to reduce uncertainty and promote context-appropriate behavioural outputs. Issues with updating these prior settings will affect the prediction error minimization routine and contribute to the experience of uncertainty, negative emotions, and loss of control, which arguably serve as vulnerability factors for the development of psychological disorders. The affective predictive coding theory of psychological disorders builds upon the central idea that the cerebellum is important for synchronising cortical cognitive and subcortical motivational information processing streams to fit contextual demands. In addition, the theory offers a transdiagnostic framework for why abnormalities in the UCT can result in disorganised thoughts and feelings, as well as the often experienced disconnection between (rational) thought and (irrational) feelings in disorders of emotion.

17.8 Conclusion

Psychological disorders can be understood as a product of proximate and ultimate processes in which the adaptive value of emotions and feelings has gone awry. Converging evidence from multidisciplinary research domains has established the involvement of the cerebellum in disorders of emotion. Whilst the cerebellar mechanisms in psychopathological conditions remain elusive, the well-established cerebellar prediction mechanisms in the sensorimotor domain can be extrapolated to the field of psychology and psychiatry and offer a cerebellar-oriented theoretical framework for understanding disorders of emotion as expressions of homeostatic dysregulation, mental flexibility, and loss of subjectively experienced control.

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18

Cerebellum and Neurorehabilitation in Emotion with a Focus on Neuromodulation

Kim van Dun, Mario Manto, and Raf Meesen

Abstract

More and more research has focused on the role of the cerebellum in emotions and social cognition. Structural cerebellar and cerebello-cerebral connectivity abnormalities have been identified in several prevalent neuropsychiatric conditions, which have in some cases even been linked to the severity of the emotional disorder.

Non-invasive brain stimulation (NIBS) techniques are currently used to modulate neuronal excitability and tune the connectivity within and between neuronal networks. Targeting the cerebellum with NIBS in order to improve emotions and social behavior in neuropsychiatric conditions seems to be a very interesting and innovative approach. Several studies have already explored the effect of cerebellar vermis stimulation in patients with schizophrenia with promising results. Other neuropsychiatric disorders such as bipolar disorder (BD), obsessive-compulsive disorder (OCD), major depressive disorder, or generalized anxiety disorder (GAD) have received less attention with respect to cerebellar stimulation, although the cerebellum has been implicated in these disorders. We will address NIBS and neuropsychiatric disorders in this chapter. Future research should focus on combining cerebellar NIBS with neuroimaging to unravel the specific role of the cerebellum in emotional disorders. Such studies will be very valuable in establishing causal relationships between the structural and functional abnormalities that can be observed in these disorders, and in the search for neurophysiological biomarkers for emotions. However, it is still unclear which stimulation parameters are optimal. Moreover, an important factor to consider when applying cerebellar NIBS in order to improve emotional or other functioning is cerebellar reserve. Although the cerebellum has a wide variety of plasticity mechanisms and its structural organization intrinsically incorporates a lot of redundancy, this redundancy can be depleted. A certain amount of cerebellar reserve should be preserved to successfully apply NIBS.

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Systematic studies are therefore needed to clarify the optimal stimulation parameters, and methods should be developed to quantify cerebellar reserve in order to estimate the possible added value of NIBS in the rehabilitation of emotions.

Keywords

Cerebellum · Emotion disorders · Neurorehabilitation · Non-invasive brain stimulation (NIBS)

18.1 Introduction

Identification of emotion disorders largely depends on self-report scales and is subjective by definition. Only the experience of the patient matters and so far no objective criteria can quantify the severity of the emotion disorder, although progress has been made in the understanding of the neurobiology of processing of emotions by the brain (Baek 2014). Emotion disorders are not only symptomatic of major psychiatric disorders, such as generalized anxiety disorder (GAD), depression, bipolar disorder (BD), or schizophrenia, they are also often observed in brain injury patients (Wilson et al. 2009) or other patient groups suffering from general disorders such as heart disease patients (Chauvet-Gelinier and Bonin 2017). Emotion disorders are particularly important to take into account when considering a rehabilitation strategy, given the impact of emotions on the quality of life in humans and social interactions.

In recent years, non-invasive brain stimulation techniques (NIBS) such as transcranial electrical stimulation (TES) and transcranial magnetic stimulation (TMS), have been increasingly used in rehabilitation sessions as an add-on therapeutic aid for a wide range of neurological, psychiatric, motor, and cognitive disorders. By using NIBS, clinicians and researchers aim to modulate neuronal excitability of specific regions and/or networks to improve cognitive, motor, or affective functioning in healthy and patient populations. Long-term after-effects are generated by using multiple sessions, which induces long-term potentiation (LTP)- and long-term depression (LTD)-like effects (TMS), and/or membrane potential changes and modulations of NMDA receptor efficacy (TES) (Sparing and Mottaghy 2008).

Different forms of NIBS exist that can excite or inhibit neuronal excitability in the targeted areas. For TMS, usually repetitive TMS (rTMS) is used in clinical settings, at high frequency (≥5 Hz) or at low frequency (~1 Hz). High frequency (HF) rTMS is assumed to be excitatory, while low frequency (LF) rTMS is assumed to be inhibitory (Tomlinson et al. 2013). Another form of TMS is theta-burst stimulation (TBS), which uses bursts of 3 pulses at 50 Hz and an inter-burst interval of 200 ms (5 Hz) instead of single pulses (Fig. 18.1). When applied in a continuous manner (cTBS), it induces inhibitory effects, but with intermittent pauses (iTBS), it can be used as excitatory (Tomlinson et al. 2013).

Different forms of TES also exist. Transcranial direct current stimulation (tDCS) is the most common one and can be applied in an excitatory (anodal) or inhibitory (cathodal) fashion by choice of electrode placement (Fig. 18.2). However, the distinction between excitatory anodal and inhibitory cathodal stimulation is not that clear when stimulating the cerebellum, although it appears that cerebellar ataxias benefit from anodal rather than cathodal stimulation (Oldrati and Schutter 2017). Transcranial alternating current stimulation (tACS) and transcranial pulsed current stimulation (tPCS), on the other hand, can be delivered in a frequency-specific manner and target intrinsic cortical oscillations. Much less is known about the working mechanisms of tACS and tPCS, as compared to tDCS. However, these might be interesting techniques to synchronize (or desynchronize) different areas, modulating the connectivity between those areas (Witkowski et al. 2016).

The cerebellum could be an interesting target for NIBS for several reasons. First, the cerebellum, and more specifically the posterior portion of the cerebellum, is situated at the back of the head right beneath the skull (van Dun et al. 2018a). Several modeling studies have shown that the posterior cerebellum can be easily targeted by tDCS (Parazzini et al. 2013, 2014; Rahman

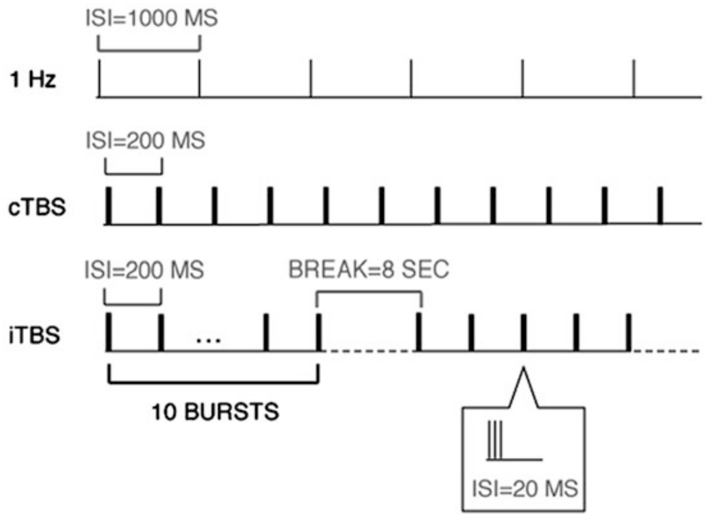

Fig. 18.1 Examples of different TMS protocols. The 1 Hz rTMS (top) with 1 s in between the pulses and TBS (middle, bottom) with 3-pulse bursts at 50 Hz every 200 ms with cTBS (middle) as a continuous train of bursts and iTBS (bottom) as separated trains of 10 bursts each with 8 s ISI. Adapted from Müller et al. (2013)

et al. 2014) and TMS (Hardwick et al. 2014; Sekino et al. 2006). Second, the cerebellum has numerous reciprocal connections with multiple motor and non-motor cerebral regions (Guell et al. 2018; Stoodley and Schmahmann 2009) (Fig. 18.3). Due to these connections, the cerebellum can be used as a 'window' to modulate distant cerebral regions that might be hard to reach using NIBS, or target neural networks comprising several cerebral areas (van Dun and Manto 2018). Third, though the cerebellum is a relatively small structure, likely more than 60% of all neurons are located in this structure, resulting in a very high neuronal density (Herculano-Houzel 2009).

Moreover, cerebellar neurons are highly organized and demonstrate a high level of plasticity, making them an interesting target for techniques aiming to alter neuronal excitability such as NIBS (van Dun and Manto 2018). Recently, the notion of cerebellar reserve has been introduced to describe the ability of the cerebellum to compensate or restore functions (Mitoma et al. 2021a) (Fig. 18.4). This notion is central to the understanding of how neurorehabilitation may impact cerebellar functions. The cerebellum is comprised of multiple microzones, i.e., the cerebellar functional units which perform the basic operations within the circuitry. These units are innervated by mossy fibers that convey both peripheral and central information. This information is integrated onto a single granular cell, that conveys this input onto several Purkinje cells via parallel fibers. Each microzone then combines the input of the parallel fibers with the input from the climbing fibers, before sending output to the deep cerebellar nuclei. Due to the complex organization of different types of input, a single microzone receives redundant information, which creates a lot of room for reorganization. Moreover, the circuitry is characterized by a co-operative interplay between a variety of plasticity mechanisms, such as spike timing-dependent plasticity, long-term potentiation (LTP), and long-term depression (LTD) (Mitoma et al. 2021b). This interplay is strongly involved in the generation of internal models and in continuous (motor) learning. When considering degenerative diseases or rehabilitation after an acute stroke, improvement of symptoms can be obtained via redistribution of synaptic weights and new synapse formation in the cerebellar cortex, but also by extra-cerebellar plasticity (Mitoma et al. 2021a).

The cerebellum is thus a highly modular and potentially reconfiguring brain structure, opening multiple doors for restorative therapies, including for disorders at the frontiers between neurobiology, neurology, and psychiatry, such as emotional disorders. The cerebellum has been implied in several emotional disorders, such as

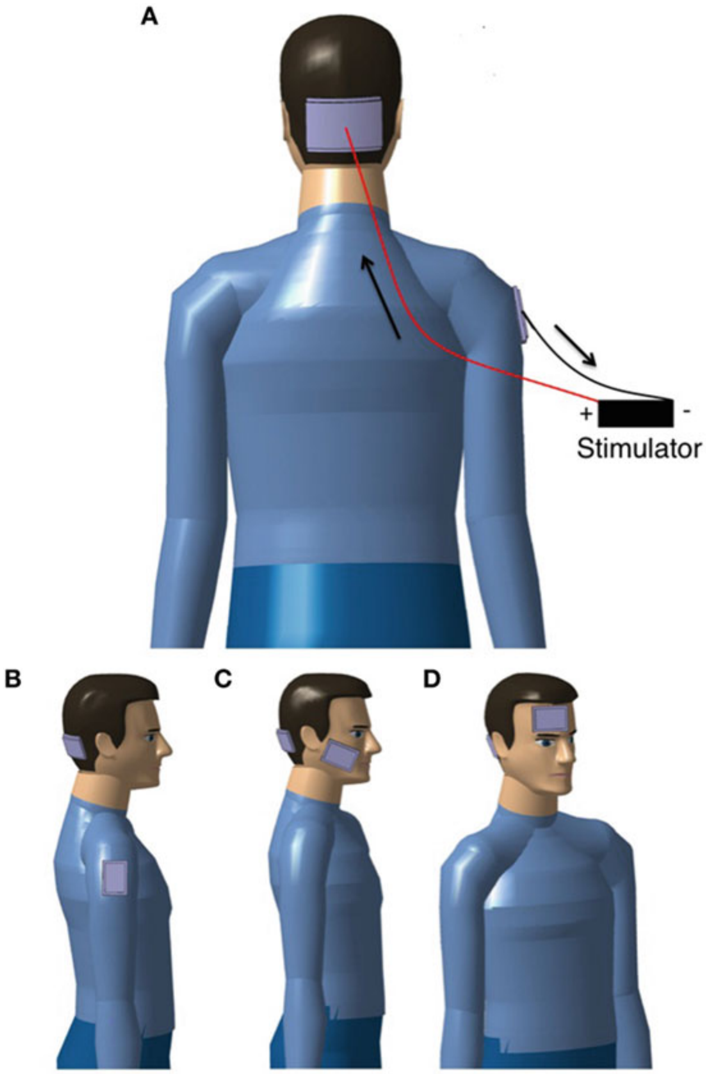

Fig. 18.2 Examples of set-ups to apply tDCS over the cerebellum. (**a**) Bilateral setup aiming to stimulate simultaneously the two cerebellar hemispheres and the vermis, the flow of the current is indicated with arrows for anodal stimulation of the cerebellum (for cathodal stimulation, the flow of the current is reversed); (**b–d**) unilateral set-ups (the target is one cerebellar hemisphere) with the reference electrode over (**b**) the deltoid muscle, (**c**) the buccinator muscle, and (**d**) the forehead/supraorbital area. For simplicity, the wires and stimulator are only shown in (**a**) (van Dun et al. 2016)

schizophrenia (Orlov et al. 2017), obsessive-compulsive disorder (OCD) (Xu et al. 2019), BD (Mills et al. 2005), major depressive disorder (Peng et al. 2011), and GAD (Yao et al. 2017), and cerebellar stimulation has already been proposed as a promising new tool in the rehabilitation of these neuropsychiatric disorders (van Dun et al. 2018a). Due to the plasticity of the cerebellum, and in part also due to the redundancy of the input, it might be possible to "reconfigure" abnormal cerebello-cerebral networks through behavioral therapy and NIBS. Recent research has identified the cerebellum as part of the neuronal networks involved in emotional processing (Adamaszek et al. 2017), and social cognition (Van Overwalle et al. 2020). Moreover, animal research has recently identified direct excitatory projections of the cerebellum to the ventral tegmental area, an area that has been implicated in reward, and in motivational and social behaviors (Carta et al. 2019). Given (1) this apparent role of the cerebellum in adequate social and emotional behavior, and (2) its high degree of plasticity, it seems a very interesting target for NIBS in neurorehabilitation of emotion disorders.

This chapter will provide an overview of the studies investigating cerebellar stimulation as a therapeutic aid for emotion disorders in

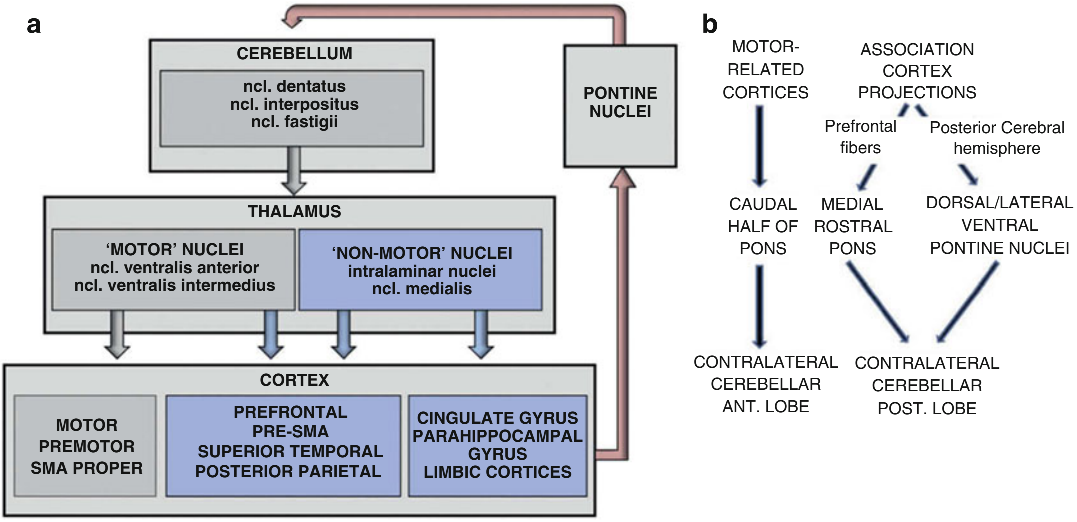

Fig. 18.3 (**a**) Diagram depicting the cerebello-cerebral connectivity network underlying cognitive and affective processes. The feedback or efferent loop originates from the deep nuclei of the cerebellum that project to the motor (gray arrows) and nonmotor (blue arrows) nuclei of the thalamus. In turn, the motor nuclei of the thalamus project to motor and premotor cortices (gray arrows) but also to nonmotor association cortices (blue arrows). The nonmotor nuclei of the thalamus project only to association cortices (blue arrows). After Schmahmann and Pandya (1997). Adapted from Mariën et al. (2013). (**b**) Topographic distribution of motor-related cortices and association cortex feedforward or afferent projections to the cerebellum. Both motor corticopontine projections and association cortex projections are somatotopically organized in the pons. See also Stoodley and Schmahmann (2010). Adapted from Grimaldi and Manto (2012)

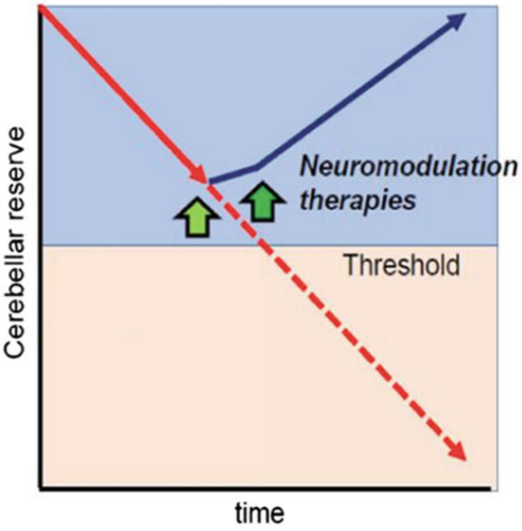

Fig. 18.4 Schematic illustration of the effects of neuromodulation therapies. Neuromodulation therapies can modify cerebellar symptoms if the cerebellar reserve is preserved. However, once the cerebellar reserve is depleted or below a certain threshold, no effect of neuromodulation therapies can be expected. Adapted from Mitoma et al. (2021a)

neuropsychiatric disorders. In addition, it will explore other possible avenues of emotional rehabilitation given the role of the cerebellum.

18.2 Cerebellar Stimulation and Emotional Disorders

18.2.1 Early Reports

Heath (1977) already showed that electrical stimulation of the cerebellum in patients with severe psychiatric illnesses could have a beneficial effect on affect and social behavior, resulting in disappearance of, amongst others, violence and uncontrollable aggression, although some controversies have been raised on direct clinical implications of such methods 40 years ago. The electrodes were placed subtentorially on the vermal and paravermal regions, targeting the rostral vermis. Previous experiments in animals had shown that stimulation of this region facilitated areas involved in the pleasure mechanisms while inhibiting areas involved in adversive emotion (Heath et al. 1978). A more recent study using excitatory HF rTMS over the cerebellar vermis in a healthy population, indeed showed an increased responsiveness to happy facial expressions (Schutter et al. 2009), while inhibitory LF rTMS over the cerebellar vermis seemed to increase negative mood induced by unpleasant pictures (Schutter and van Honk 2009).

In 2000, Schmahmann (Schmahmann 2000) published a paper in which he explicitly addressed the role of the cerebellum in affect and psychosis. Schmahmann described this role within the dysmetria of thought theory, which states that cerebellar malfunction leads to a lack of homeostasis in thought. Concerning psychiatric illnesses, this would mean that a mismatch between reality and the perceived reality of the patients causes the disturbances as observed in, for example, schizophrenia and BD (Schmahmann 2000). Schmahmann revisited the role of the cerebellum in neuropsychiatric disturbances in 2007, by describing the symptoms of patients (adults and children) with cerebellar damage (Schmahmann et al. 2007). Behaviorally, they observed “distractibility and hyperactivity, impulsiveness, disinhibition, anxiety, ritualistic and stereotypical behaviors, illogical thought and lack of empathy, as well as aggression and irritability. Ruminative and obsessive behaviors, dysphoria and depression, tactile defensiveness and sensory overload, apathy, childlike behavior, and inability to appreciate social boundaries and assign ulterior motives were also evident.” (Schmahmann et al. 2007). All these symptoms could be described as either exaggerated or diminished behavioral responses, as in line with the dysmetria of thought hypothesis. These behavioral changes were also primarily linked to lesions in the vermis and paravermian regions (Schmahmann et al. 2007). Based on these observations, Schmahmann et al. (2007) suggested the possible benefit of cerebellar stimulation, using contemporary non-invasive techniques such as TMS, in the treatment of psychiatric disorders.

In Table 18.1 you can find an overview of the cerebellar abnormalities linked to the emotion disorders discussed in this chapter, and which areas have been targeted with NIBS, together with some suggestions for future research.

18.2.2 Schizophrenia

The concept of cognitive dysmetria has been picked up early in the literature about schizophrenia (Andreasen et al. 1998). While discussing the origin of the broad spectrum of symptoms linked to schizophrenia, Andreasen et al. (1998) suggested a unitary model with an important role for the cortico-cerebellar-thalamic-cortical circuit. They hypothesized that cognitive dysmetria is the fundamental deficit in schizophrenia leading to a disruption of the coordination of mental processes (Andreasen et al. 1998). Recently, Brady et al. (2019) provided additional evidence for this hypothesis by showing that rTMS over the cerebellar vermis restored the prefrontal-cerebellar connectivity which was significantly related to the amelioration of the negative symptoms in 11 patients with schizophrenia.

Heath (1977) already included five patients with schizophrenia in his study using invasive cerebellar stimulation, showing a gradual, significant improvement of their symptoms in four of them. However, in a later study, Heath et al. (1980) stated that patients with schizophrenia seemed to respond less to cerebellar stimulation than other patient groups such as patients with depression or epilepsy and behavioral disorders.

Since then, multiple studies have used NIBS over the cerebellum in patients with schizophrenia to investigate its rehabilitative effects on cognition and affect (Escelsior et al. 2019). Most of them used a form of excitatory TMS ($n = 7$), but three applied a form of excitatory TES. As was shown in the systematic review of Escelsior et al. (2019), clinical changes of affect were predominantly seen in the domain of negative and depressive symptoms. However, Escelsior et al. (2019) already indicated that the methodological quality of the included studies was poor, with low sample sizes and only a few including randomization and a control group.

A more recent study by Chauhan et al. (2021) in 30 patients with treatment-resistant

Table 18.1 Overview of emotion disorders, the known neurophysiological change(s), and the proposed target (s) and NIBS

Emotion disorder	Neurophysiological change(s)	Target(s)	NIBS
Schizophrenia	– Disturbed prefrontal-cerebellar connectivity – Gray matter volume abnormalities in the cerebellum	Vermis	Excitatory NIBS
Bipolar disorder (BD)	– Altered white matter fronto-ponto-cerebellar connectivity	Prefronto-cerebellar network	tDCS
	– Decrease in gray matter density in parietal-occipital-cerebellar network	***Vermis***	***Excitatory TMS or TES***
Obsessive-compulsive disorder (OCD)	– Increased connectivity right putamen and left cerebellum	Right cerebellum	tDCS
	– Increased ventral loop + decreased dorsal loop – Hyperactivity in left orbitofrontal cortex + hypoactivity in right cerebellum	***Left cerebellum***	***LF rTMS***
Major depressive disorder	– Dysfunctional prefrontal-cerebellar network	Prefrontal regions	HF rTMS
		Prefronto-cerebellar network	***tDCS***
Generalized anxiety disorders (GAD)	– Abnormal cerebellar metabolism	Frontal cortex	Inhibitory and excitatory NIBS
	– Altered cerebello-cerebral functional connectivity – Cerebellar overactivation	***Cerebellum***	***Inhibitory NIBS***

Text in bold and italic are suggested targets and NIBS that have not yet been investigated

schizophrenia using a randomized double-blinded sham-controlled study failed to find an effect of iTBS over the cerebellum on any of the included clinical scores, including the positive and negative syndrome scale (PANSS), which has been used in most studies using cerebellar NIBS in patients with schizophrenia, when compared to the sham group (Chauhan et al. 2021). This seemingly contradicts the randomized rater-blind sham-controlled study of Garg et al. (2016), including 40 patients with schizophrenia. They showed a significant improvement in negative scores of the PANSS in the active group versus the sham group, using HF rTMS within the theta range (5–7 Hz). Considerable differences in methodology may account for this discrepancy, such as the used coil (figure-of-eight (Chauhan et al. 2021) vs double cone coil (Garg et al. 2016)), type of TMS (iTBS (Chauhan et al. 2021) vs HF rTMS (Garg et al. 2016)), stimulation intensity (80% RMT (Chauhan et al. 2021) vs 100% RMT (Garg et al. 2016)), session frequency (2 per day for 1 week (Chauhan et al. 2021) vs 1 per day for 2 weeks (Garg et al. 2016)), as well as the patient demographics such as older age and longer disease duration in Chauhan et al. (2021) with treatment resistance as an explicit inclusion criterium. This already shows the need for more systematic studies investigating the optimal stimulation settings to improve affective symptoms in patients with schizophrenia.

In conclusion, there already seems to be a general consensus to stimulate the cerebellar vermis in patients with schizophrenia, in order to improve affective and cognitive symptoms. Mostly, negative and depressive symptoms can be improved by stimulating the cerebellar vermis (Escelsior et al. 2019), but more systematic studies are needed to find the optimal stimulation parameters. In addition, randomized controlled studies should be used to investigate how robust these results are and whether it remains effective in patients with a long disease duration.

18.2.3 Bipolar Disorder (BD)

Bipolar disorder (BD) has been associated with schizophrenia based on clinical observations of Kraepelin in the early twentieth century (Bellivier et al. 2013). Structural imaging studies have added to this belief, based on structural abnormalities in both patient groups (Bellivier et al. 2013). However, it seems that while gray matter volume abnormalities in the cerebellum are consistently observed in patients with schizophrenia (Laidi et al. 2019), primarily white matter fronto-ponto-cerebellar connectivity alterations are observed in patients with euthymic BD (Argyropoulos et al. 2021). Moreover, white matter changes are most prominent in patients with predominantly manic or hypomanic episodes as opposed to patients with predominantly depressive episodes (Argyropoulos et al. 2021). Especially the right hemisphere networks seem to be related to (hypo)mania (Argyropoulos et al. 2021). In addition, gray matter concentration decrease in the parietal-occipital-cerebellar network has been associated with increased impulsivity in patients with BD (Lapomarda et al. 2021).

tDCS targeting the prefronto-cerebellar network in patients with BD has been shown to improve the lingering cognitive dysfunctions during the euthymic phase (Bersani et al. 2017; Martin et al. 2015; Minichino et al. 2015). However, the recent findings of Argyropoulos et al. (2021) and Lapomarda et al. (2021) suggest that the cerebellum is also heavily implicated in the affective dysregulation in patients with BD. NIBS targeting the cerebellum in order to induce long-lasting effects on the cerebello-cerebral connectivity, might also reduce the number of episodes or decrease the size of the rapid fluctuations in mood. Especially given the promising results of cerebellar vermis stimulation in patients with schizophrenia on negative and depressive symptoms, this neurorehabilitation strategy deserves further attention in patients with BD (van Dun et al. 2018a).

18.2.4 Obsessive-Compulsive Disorder (OCD)

Obsessive-compulsive disorder (OCD) is usually treated with serotonin reuptake inhibitors (SSRIs) and/or cognitive-behavioral therapy (CBT) (Hirschfeld et al. 2003). It has been shown that SSRIs can modulate abnormal functional connectivity patterns observed in patients with OCD (Anticevic et al. 2014). Besides global decreased connectivity between several cerebral areas, Anticevic et al. (2014) also demonstrated an increased connectivity between the right putamen and the left cerebellum, which was positively correlated with symptom severity.

CBT that focuses on identifying, challenging, and modifying dysfunctional beliefs has been recommended, as well as exposure, ritual prevention, and discussion of feared consequences and dysfunctional beliefs (Hirschfeld et al. 2003). This is in line with theories in cognitive rehabilitation of cerebellar patients, in which the patient is taught to act like an external cerebellum (Ruffieux et al. 2017; van Dun et al. 2018b).

Recently, the cerebellum has been implicated in compulsive and impulsive behaviors, as observed in patients with OCD (Miquel et al. 2019). Compulsivity and impulsivity have been linked to an imbalance between the dorsal frontal regions (under-activation) and the ventral striatal zones (over-activation) involved in behavioral control (Fineberg et al. 2010). Miquel et al. (2019) hypothesized that cerebellar dysfunction may lead to an increased basal ganglia-cerebellum connectivity (ventral loop), while decreasing prefrontal-cerebellum connectivity (dorsal loop), thereby inducing compulsive and impulsive behavior.

Therapy-refractory patients with OCD have also been treated with different forms of invasive and non-invasive stimulation techniques.

Deep brain stimulation (DBS) usually targets the dysfunctional orbito-fronto-striato-thalamo-cortical circuit and places the electrode in the internal capsule or the nucleus accumbens to inhibit the connections between the frontal lobe and the striatum (Blomstedt et al. 2013). The review of Blomstedt et al. (2013) showed a 50% reduction in OCD scores, depression, and anxiety in therapy-refractory patients with OCD, making DBS in this area an interesting approach for treating this patient group.

Several reviews have scrutinized the studies using TMS to treat patients with OCD (Hirschfeld et al. 2003; Berlim et al. 2013; Lusicic et al. 2018; Rodriguez-Martin et al. 2003). Almost all studies using TMS targeted the cortico-striato-thalamo-cortical circuit, focusing on the disturbed dorsal and ventral circuits, the sensorimotor circuit, and the affective anterior cingulate circuit (Lusicic et al. 2018). Surprisingly, none of the included studies targeted the cerebellum or a cerebello-cerebral circuit. De Vidovich et al. (2016), on the other hand, showed promising results of rTMS over the left cerebellum on impulsivity in patients with a borderline personality disorder. They speculated that rTMS over the left cerebellum facilitated the prefrontal cortex control, which could also be an interesting approach in patients with OCD (De Vidovich et al. 2016).

Concerning tDCS, a few studies have targeted the cerebellum intending to modulate the hyperactivity in the left orbitofrontal cortex and the hypoactivity in the right cerebellum as observed in patients with OCD (Brunelin et al. 2018). Although these studies seemed promising, with a decrease in OCD, depression, and/or anxiety scores (Alizadeh Goradel et al. 2016; Bation et al. 2016; Mondino et al. 2015), a more recent randomized controlled trial by Bation et al. (2019) failed to replicate the long-lasting effects on OCD scores of their open-label pilot study of 2016 (Bation et al. 2016). Only immediately after the tDCS treatment, a significant difference was observed between the real and the sham group (Bation et al. 2019). Moreover, a theoretical modeling study of Senço et al. (2015), based on DBS and rTMS studies in patients with OCD, described cathodal stimulation of the pre-supplementary area (preSMA) with an extracephalic reference electrode as the theoretically most ideal electrode placement to target the areas mostly related to OCD. However, it should be kept in mind that the cerebellum has been consistently ignored in TMS and DBS studies.

Though the cerebellum has not been investigated thoroughly as a target for invasive or non-invasive stimulation, the networks of interest in patients with OCD are strongly connected with the cerebellum (Miquel et al. 2019). Miquel et al. (2019) therefore already suggested to stimulate cerebellar activity to improve prefrontal functionality, thereby reducing OCD symptoms and possibly also depression and anxiety scores. However, the exact role of the cerebellum and which areas are (crucially) involved in OCD is still speculative. In order to formulate effective (neurostimulation) strategies targeting the cerebellum, this role should be elucidated (van Dun et al. 2018a).

18.2.5 Major Depressive Disorder

Major depressive disorder is one of the few disorders for which rTMS and tDCS have been officially recognized as a treatment option (Milev et al. 2016). Most guidelines recommend rTMS after treatment with an antidepressant has failed (Bayes and Parker 2018), and mention the left dorsolateral prefrontal cortex as the primary target (Wu and Baeken 2017).

However, it seems that the efficacy of HF rTMS over the left DLPFC is negatively correlated with the duration of the current depressive episode (Wu and Baeken 2017). The study of Wu and Baeken (2017) even linked rTMS treatment response to cerebellar metabolic activity and correlated this activity pattern to episode duration. Wu and Baeken (2017) speculated that a dysfunctional prefrontal-cerebellar network is implicated in major depressive disorder, which might still be improved by HF rTMS over the prefrontal regions in an early stage when functional connectivity between these regions is still largely intact. Although this is still speculative, a resting-state fMRI study by Guo et al. (2012) also identified the cerebellum as the sole area to differentiate responders and non-responders to antidepressants using coherence-based regional homogeneity.

Despite this evidence for the cerebellum being involved in the neuropathology of major depressive disorder and being a predictor for treatment response, few studies have targeted the cerebellum with NIBS in patients with major depressive disorder. Ho et al. (2014) explored alternative tDCS electrode positions among which also a frontal-cerebellar montage with the anode over the left dorsolateral prefrontal cortex and the cathode over the bilateral cerebellum. However, no significant improvement in mood was found using this montage (Ho et al. 2014).

In conclusion, the cerebellum seems to be involved in major depressive disorder and has currently received some attention as a biomarker to identify responders and non-responders to treatment. However, evidence for the validity of targeting the cerebellum with NIBS is scarce and needs further investigation. Especially in non-responders, targeting the entire fronto-cerebellar network seems promising, despite the negative results of the pilot study of Ho et al. (2014).

18.2.6 Generalized Anxiety Disorders (GAD)

Generalized anxiety disorders (GAD) are characterized by excessive worrying and anxiety about daily life matters (American Psychiatric Association 2013). GAD is usually treated psychologically rather than pharmacologically, predominantly using CBT (Cuijpers et al. 2014). One of the central premises of cognitive therapy is to reduce the symptoms by challenging the patient's usually unrealistic, thoughts (Beck and Beck 1979). For GAD, this premise was demonstrated by LaFreniere and Newman (2020).

Cerebellar metabolism abnormalities (Bonne et al. 2003; Sakai et al. 2005) and altered functional connectivity between the cerebellum and several cerebral regions (Yao et al. 2017; Nakao et al. 2011) have been observed in patients with anxiety disorders (van Dun et al. 2018a; Phillips et al. 2015). Anxiety disorders are also observed in patients with cerebellar (neurodegenerative) damage (Schmahmann et al. 2007). However, the exact role of the cerebellum in GAD is still unclear. It has been hypothesized that it is involved in the "fear network" and that an impaired exchange of information between the cerebellum and other areas of this network induces excessive anxiety (Yao et al. 2017). Diwadkar et al. (2017), on the other hand, demonstrated impaired memory control in patients with GAD with hypo-activation in the dorsal anterior cingulate, the ventral prefrontal cortex, and the cerebellum during the suppression of memories. Another plausible explanation, however, is the role of the cerebellum in sympathetic control (Phillips et al. 2015). Cerebellar hyperactivity has indeed been linked to increased blood pressure and heart rate (Critchley et al. 2000).

Few studies have used neurostimulation to treat GAD, primarily targeting the amygdala/limbic system through the frontal cortex, with promising results for both inhibitory and excitatory stimulation (Dilkov et al. 2017; Pallanti and Bernardi 2009; Shiozawa et al. 2014). Animal studies, however, have identified the cerebellum as an important contributor to these fear and anxiety networks (Moreno-Rius 2018). Taking together evidence from patient studies and animal studies, Moreno-Rius (2018) hypothesized that cerebellar overactivation lies at the basis of fear and anxiety in patients. By wrongfully recruiting threat memories, the cerebellum initializes forward models that are linked to situations that are perceived as a threat, thereby activating the entire fear and anxiety network (Moreno-Rius 2018). This interesting idea deserves further investigation and could lead to novel avenues for the treatment of GAD.

18.3 Conclusions and Future Directions

The cerebellum is gaining more and more attention in the field of neuropsychiatric disorders as a neural substrate of both cognitive and behavioral/affective symptoms in several patient populations (van Dun et al. 2018a; Adamaszek et al. 2017; Van Overwalle et al. 2020; Schmahmann et al. 2007; Phillips et al. 2015; Moreno-Rius 2018). For patients with schizophrenia, multiple studies have targeted the cerebellar vermis with promising results on negative and depressive symptoms (Escelsior et al. 2019). However, for other neuropsychiatric disorders, studies using cerebellar stimulation are scarce.

Given the role of the cerebellum as a predictor and controller of cognitive and affective cerebral processes, a dysfunctional cerebellum may result in a wide variety of emotional and behavioral disturbances (Schmahmann et al. 2007). This dysregulation can be seen as dysmetria of thought, with either hypermetric (exaggerated) or hypometric (diminished) behavior/affect (Schmahmann et al. 2007). Cognitive dysmetria has been explored explicitly in patients with schizophrenia (Andreasen et al. 1998). A causal relationship between a dysfunctional prefrontal-cerebellar network and severity of negative symptoms in patients with schizophrenia has been established by Brady et al. (2019). Similar theories and studies should be set up for other neuropsychiatric disorders to establish which networks are causally involved. By combining current non-invasive stimulation methods and neuroimaging techniques, more insight can be gained into the neural correlates of behavioral and affective disturbances. NIBS should therefore be used to establish these causal relationships by combining them with neuroimaging techniques. This knowledge will lead to effective strategies to apply NIBS as a therapy or as a therapeutic aid and might contribute to the identification of specific biomarkers for emotion. It should also be noted that patient-specific studies might be necessary, since NIBS might not have the same effect on healthy controls as compared to patient populations.

NIBS can be used to modulate cerebello-cerebral networks, which might have a beneficial effect on emotion disorders. However, other strategies could also be used to treat patients with emotion disorders. It has already been hypothesized that patients with cerebellar lesions are able to explicitly compensate for the loss of cerebellar function (Schmahmann 2010). By making the patients aware of the problem at hand, they can take over the role of the cerebellum in a conscious manner, they learn to act as an “external cerebellum.”(Ruffieux et al. 2017) This strategy has been explored in several patient populations and neurodevelopmental disorders for cognitive rehabilitation. Although the evidence was scarce, the best results seemed to be obtained by creating awareness and teaching the patients to self-monitor their behavior (van Dun et al. 2018b).

Especially for emotion disorders that are characterized by anxiety due to cognitive distortions, CBT has been shown to be effective (Hirschfeld et al. 2003; Cuijpers et al. 2014). A similar strategy as in cognitive rehabilitation might indeed be valuable in these emotion disorders, since the anxiety seems to be induced by faulty predictions about daily life situations (Moreno-Rius 2018). By creating awareness, patients could be taught to act as an external cerebellum to assess these situations in a conscious manner, for example by tracking the percentage of worries that did not come true (LaFreniere and Newman 2020).

Although it seems beyond doubt that the cerebellum is somehow involved in emotion regulation and social behavior (Adamaszek et al. 2017; Van Overwalle et al. 2020), the precise role of the cerebellum in emotion disorders has yet to be unraveled. Future studies should focus on the causal role of the cerebellum and combine NIBS with neuroimaging techniques in these patient populations. Other strategies, however, such as CBT that focus on creating awareness might also be an interesting avenue to explore for treating emotion disorders.

In addition, there is a major need to validate morphological and functional tools to quantify cerebellar reserve, not only for motor control studies but also for cognitive and emotion/affect investigations (Manto et al. 2021). Although the notion of cerebellar reserve is most relevant for cerebellar degenerative disorders or after acute cerebellar damage, it should also be investigated in the context of neuropsychiatric disorders. Disease duration does affect the efficacy of medication and NIBS interventions in neuropsychiatric patients. An estimation of cerebellar reserve might therefore also be relevant in these patient populations. Computational models likely have a great future here. This would have a critical impact in terms of planification of rehabilitation strategies tailored to each case encountered in daily practice. It is currently unclear what is the best method to modulate cerebellar networks for (a) disorders affecting primarily the cerebellar circuitry, and (b) disorders affecting remote regions and for which neuromodulation of the cerebellum is presumed to reduce symptoms.

There are also several unsolved questions regarding cerebellar NIBS and rehabilitation (Manto et al. 2021). Systematic studies are needed to determine the best montage, the ideal current intensity/density, the optimal session duration and frequency of the sessions, and the interaction with rehabilitation programs and/or medication. Additionally, some questions remain about the impact of anatomical variability (size and shape of the skull, cerebellar anatomy) between patients, the impact of NIBS itself on the electrical properties of the cerebrospinal fluid, and the quantification of the spreading of the current toward remote areas such as the basal ganglia, cerebral cortex, and spinal cord. There is therefore an urgent need to standardize protocols and plan large-scale sham-controlled double-blind trials to convince health authorities.

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Part V

Perspectives

Current and Future Perspectives of the Cerebellum in Affective Neuroscience

19

Michael Adamaszek, Mario Manto, and Dennis J. L. G. Schutter

Abstract

The importance of the cerebellum in basic as well as higher order domains of affect processing in the brain has been vividly elaborated and specified by the contributions collected in this book. Indeed, according to increasingly precise research findings in functional neuroimaging and functional neurophysiology, individually delineable areas of the cerebellum play a role in virtually all process levels of the responsible networks of emotion perception, attribution, and experience via a variety of reciprocal connections to the limbic system and distinct areas of the parietal, temporal, and prefrontal cortex. The works in this book identify alternative perspectives in neuroscience research that offer new directions in future investigations. Important aspects will be to pin down the precise cerebellar processes in multiple sensory integration and allocation in cognitive and affective evaluation, and also cognitive-affective as well as motor behavioral responses. In this context, imaging and electrophysiological techniques will highlight the spatial and temporal, and thus the topographic and topological, specificities of the cerebellar areas to the respective networks. In the final chapter, questions and suggestions for future neuroscientific investigations are identified, from whose developments several fields of neurological and psychological disciplines could benefit in order to open up therapeutic avenues for people with cerebellar disorders.

Keywords

Cerebellum · Cerebellar-cortico-limbic networks · Disorder · Emotion

We believe that the present compilation of basic and advanced principles of the cerebellum in emotive functions provides a timely and representative overview, fostering the fascinating development in neuroscience to unravel the neural mechanisms of human emotions. More specifically, appreciating the detailed outlining of the chapters in this book, the field is moving on to establish a more comprehensive understanding of the involvement of the cerebellum in many different avenues of emotion in the human brain. Overall, the emotional cerebellum appears both simple and complex at the same time. As the contributions in this book demonstrate, the

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cerebellum impacts a broad range of brain functions to basic as well as high-order affective processing domains, supporting the complex behavioral outcomes at the motor, cognitive, and emotion levels. With the growing evidence of neuroimaging, electrophysiological, and clinical study protocols, this book complements the ongoing research disentangling the underlying mechanisms and pathways of cerebellar actions in the widespread, even large-scaled neural affective and cognitive networks of the brain in different aspects of emotion.

Emotion is a complex construct and still an open area of research, including its precise frame of definition (Lindquist and Barrett 2012; Scarantino and de Sousa 2021). This debate should be kept in mind in particular in appreciating the hitherto findings, and of course the intention, to describe the specific role of the cerebellum in emotion. Moreover, capturing the specific cerebellar computations of emotion-related information is complicated by the fact that in most studies the involvement of the cerebellum in emotion processing is tied to the condition of correlative rather than constitutive findings, which often lead to a report besides the central scope of intended investigation of the cerebral activations. According to task-based fMRI studies and meta-analytic approaches including step-wise heuristic models (Ebneabbasi et al. 2021), five large-scale brain networks have been identified that govern basic emotion processing and emotion regulation. (1) The visual and (2) auditory cortical regions for registering sensory stimuli, whereby (3) the salient information is processed in the insula, anterior cingulate cortex (ACC), and various subcortical regions (e.g., hypothalamus), (4) the self-referential importance of a stimulus appraised in the medial prefrontal and posterior cingulate cortex (PCC), and (5) the emotional responses by the amygdala and fusiform gyri (Riedel et al. 2018). Following the growing literature of functional neuroimaging in emotion, the responsible neural networks of emotion processing in bottom-up levels and emotion regulation in top-down levels emerge as interrelated (Morawetz et al. 2017), in particular highlighting the strong interaction between the amygdala and PFC for guiding a scaled regulatory behavior (Doré et al. 2017). The amygdala is generally assumed to be involved in the encoding of motivationally relevant stimuli, therefore generating the expressive and affective characteristics of the emotional response, whereas the PFC (particularly the DLPFC and VLPFC) is associated with the modulation of appropriate emotional response (Dixon et al. 2017). Especially, the VLPFC with its specific role in evaluating the ongoing emotion response is expected to project the regulation urgency to DLPFC for emotion regulation initiation (Etkin et al. 2015). Thus, the functional connectivity between these cerebral structures, in particular between the amygdala and the prefrontal cortex, is presumed to be crucial in emotion perception and behavior and psychopathology (Ebneabbasi et al. 2021). As articulated in the chapter of Thomasson and Peron, the neuroscience of emotion has long been focusing on the cortico-limbic networks and less so on other potentially relevant regions including the basal ganglia and cerebellum. In fact, the close anatomical connections between the basal ganglia and cerebellum in conjunction with their reciprocal connections of the cerebellum provide a neuroanatomic blueprint for temporally structured event representations in the stage transition from the detection of salient (emotional) information to motivational tendencies and motor responses. According to previous data on emotion processing in the brain, early and late stages can be distinguished, which essentially characterize mechanisms of bottom-up and top-down control processes (Sabatinelli et al. 2013). The vermis and hemispheric areas of the cerebellum were identified as contributing to the functional stages identified for the cerebral process levels. Not only for the early steps of perception and recognition of emotional cues, but also for the late integrative stages of emotional evaluation (Adamaszek et al. 2013; Styliadis et al. 2015). Subsequently, cerebellar signal processing is important for the target processes within cerebral pathways for not only optimal emotional, but also cognitive and motor expressive behavior, including in a social context. In this context, distinct areas of the cerebellum are assigned a core mode of associative learning in emotion processing, which supports excitatory and inhibitory neural activities within task-dependent networks of motor, cognitive, and affective behavior (Adamaszek et al. 2017). More specifically, the cerebellar role in these different domains of emotion perception, recognition, and evaluation deems to be anchored within its fine adjusted connections to associative cortical brain regions, in particular the prefrontal and parietal areas, by driving the neural information along internal models as already built, or going to be build, within the responsible cerebral-cerebellar loops as part of the task-dependent large-scaled neural networks (Ito 2008). This assumption is in line with the proposal of the cerebellar role in interfacing and therefore supporting the predictive property of complex patterns of neural information along specific task-related brain networks. The intracerebellar distribution to these task-dependent network processing is nevertheless an exciting request in current research, in particular considering the meta-analysis data of evidence from neuroimaging about the cerebellar contributions to cognition, showing that there are both distinct and overlapping cerebellar regions involved across these tasks depending on task demands (Stoodley and Schmahmann 2009; Keren-Happuch et al. 2014). Neuroimaging analysis ruled out a map distribution for associative learning in the cerebellum with a medial-to-lateral cerebellar contribution along emotional, motor, and cognitive functions (Schmahmann et al. 2019), coupling distinct task-dependent cerebellar areas to nonmotor functions in parallel to the evolutionary development of the large nonmotor portions of the cerebellum, prefrontal, and association cortices, which is consistent with a phylogenetic expansion in size of the cerebellum parallel to the growth of the frontal cortex (D'Angelo and Casali 2013; Marek et al. 2018), and as a result representing a behavioural variable of brain evolution (Barton 2012). These observations might be of interest in particular for the cerebellar activities to various emotion domains, which should consider also the cognitive and motor aspects in specific behavior lines.

Numerous intriguing issues about the topographical organization of the cerebellum in the generation and experience of emotion have been provided in the chapter of Habas. The challenge of gathering available neuroimaging literature about the cerebellum and emotion has resulted in a considerable amount of data which points toward distinct areas of the cerebellum in emotion processing. However, there are still outstanding conceptual and methodological issues in neuroimaging research about precise cerebellar mechanisms in emotion that need to be addressed. For example, the vast majority of brain neuroimaging studies in affective neuroscience remains focused on the cortico-limbic networks. In addition, the cerebellum is also technically tied to a low signal-to-noise ratio of blood oxygenation level dependent (BOLD) due to location and complex folding. Furthermore, fMRI of the cerebellum in task-dependent recordings faces different metabolic patterns without aerobic glycolysis, leading to weak or even absent cerebellar activations when assessed by blood oxygenation levels (Marek et al. 2018). Finally, even though the cerebellum demonstrates a reliable, individual-specific network organization, across individuals the cerebellum is significantly more variable than the cerebral cortex (Marek et al. 2018). These individual differences in variability appear largest in the lateral posterior lobes of the cerebellum, and future studies have to establish whether or not the observed signal variability subserves functional relevance and, if so, how this is coupled to the cortical association networks. Despite these challenges, the overview by Habas of the topographic mapping and task-based functional imaging of the cerebellar lobules provides fairly clear-cut insights into the distinct functional contributions of the vermis and hemispheres. In particular, the connections of the vermis to a limbic core network and main intrinsic networks constitute an “emotional” part of the cerebellum. According to this assumed involvement in a general emotion network (GEN), the cerebellum deems to be implicated in a complex functional topography of basic emotions, which follows a multi-dimensional aspect subserved by a context-specific and dynamic recruitment of functionally connected networks (Raz et al. 2016). The topographically subdivided cerebellar areas could therefore be regarded as active integrators and part of bridging circuits contributing to different task- or situation-dependent actions, reflected by specific and variable recruitment and synchronization of distinct networks in charge of processing multiple dimensions, including arousal and valence of emotions. This idea nicely fits with the growing insights of the cerebellum to linear and parallel signal processing in cognitive and emotion processing, expressing a high degree of interindividual and task-dependent differences in brain activation patterns (Marek et al. 2018).

Approaching the neurophysiological signatures of the cerebellar role in the emotion-dedicated cortical-subcortical networks, the chapter of Adamaszek and Kirkby provided an extensive discussion of available EEG research. The authors show that sensitive early and late potentials of the cortical-subcortical EEG activities in emotion tasks are of concern in delineating cerebellar inputs in guiding the top-down control of incoming affective information along bottom-up stages of primary and visual and auditory associative areas in encoding and forwarding emotion processing in responsible networks of the human brain (Schutter and van Honk 2009; Adamaszek et al. 2015; Styliadis et al. 2015; Grass et al. 2016; Houston et al. 2018). In fact, research of the neurophysiology of the cerebellum in emotion processing has shown a bias to negative basic emotions such as anger and fear, prompting special involvement in unconscious and conscious processing in affective regulation in particular for predicting suitable motor and cognitive as well as affective patterns of the desired behavioral outcome. This interpretation concurs with evolutionary accounts on the rapid activation of fight-flight responses when facing immanent threat. Moreover, recent research has fostered the multiple representations of cognitive and affective processing engaging focal areas within different cerebellar regions in parallel. More precisely, gradient analysis of relationships between functionally distinct cerebellar regions emphasizes the existence of at least three nonmotor representations in the cerebellum and a cerebellar functional specialization following a graded organization of goal-directed (i.e., task-specific) and goal-undirected (i.e., task-specific) processing (Guell et al. 2018; Schmahmann et al. 2019). Notwithstanding the debated concepts on emotions related to valence and arousal, or the discussion about the neuropsychological assumption of distinct universal emotions (Lindquist et al. 2016), the cerebellum could be assumed to interface among the different neural signal processing involved in bottom-up and top-down control at the millisecond level, leading to unified perceptions and actions to emotional triggers (Freeman and Ambady 2011; Dolcos et al. 2020). This interface-like function is based upon complex integration of timing and sequential steps of sensory information processing, which are tied to specific cerebellar-cerebral feedforward processing involving the parietal and prefrontal cortex with its subregions of the DLPFC and VLPFC, and also the OFC. These areas are not only of specific importance to emotion processing with their leading role in emotion conjugation and control, but also as being functionally coupled to subcortical areas such as the amygdala and the basal ganglia subserving for the appraisal of emotion (Pessoa 2013; Ebneabbasi et al. 2021). The importance of delineating the underlying temporal dynamics of cerebellar input to the segregated large-scaled networks in emotion processing along perception, recognition, and expression might be of interest to get a better understanding of the functional deficits caused by cerebellar lesions, resulting in timing and/or impediments in synergy of signal processing within the responsible networks. The fact that cerebellar damage can lead to impairments in predictive computations and goal-directed behavior (Cabaraux et al. 2020) may offer therapeutic opportunities by way of promoting neuroplasticity in the affected areas.

The chapter of Han about the cerebellar contributions to morality points to the now increasingly recognized relationship of emotional aspects between moral reasoning and behavior, which allows for an alternative concept to be developed that includes emotion in moral functioning (Bebeau 2002; Kristjánsson 2007; Han 2014). In particular, the connections between Crus I and Crus II and the ventromedial areas of the prefrontal cortex and precuneus in conjunction with the default mode network (DMN) and the central executive networks (CEN) are implicated in the emotive and cognitive aspects of morality (Habas et al. 2009; Keren-Happuch et al. 2014; Van Overwalle et al. 2015). Crus I and Crus II appear to operate as a hub for the networks regulating cognitive and affective aspects of moral functioning. In consideration of Han's intriguing findings in his chapter, these two cerebellar areas within the right cerebellar hemisphere represent an exciting and potentially critical node in the neural circuitry underlying moral functioning. In concern to the role of the cerebellum in emotion in terms of its functional significance in human behavior, social cognition is one exciting subject of research (see a recent overview in Van Overwalle et al. 2020). The main focus of research has been on cognitive processes, revealing cerebellar activities to basic social skills like joint attention (Gordon et al. 2013), mentalizing and mirroring (Van Overwalle et al. 2014), and theory of mind (Mothersill and Donohoe 2016). Laricchiuta and colleagues discussed the possibility that the cerebellum could be an important hub associated with empathic abilities and social skills, impaired emotional identification and expression (e.g., alexithymia). This possibility is analyzed within the context of embodiment theory, which posits that cognitive and emotional processes are inherent parts of our biological constitution and depend on perceptual, somatosensory, motor, neuroendocrine, and autonomic nervous system activities (Critchley and Garfinkel 2017). Research has shown that the affective parts of empathy (e.g., feeling the emotion of the pain of others) are associated with activation of the posterior vermis, while the posterolateral regions, in particular Crus I and Crus II, show distinct activation when the cognitive aspects of empathy (e.g., understanding the emotion of another person) are involved. Additionally, D'Agata and Orsi in their chapter about the cerebellum in emotion recognition give a comprehensive overview in which they provided evidence for participation of the cerebellum in the underlying neural networks composed of the OFC, ACC, anterior insula, amygdala, lower ventral areas of the temporal lobes, fusiform gyrus, with their different activations along fast and slow neural strands (Adolphs 2009). Indeed, clinical and neurofunctional research has shown cerebellar involvement in the perception and evaluation of facial or bodily expressions (e.g., Schraa-Tam et al. 2012; Ferrucci et al. 2012), whereby the cerebellum takes part in the early and also late processing stages (Adamaszek et al., 2015). With the focus on the current aspects of cerebellar influences onto specific incoming sensory signals, the presumption of a specific role of the cerebellum in the perception and expression of music and art is congruent, with its demands of fine-graded resolution and its connections to forwarding to eligible brain regions, including the parietal, temporal, and prefrontal cortical parts in the further evaluation of artistic pieces and selection of suitable behavioral response. Similarly, the cerebellum has been proven to take part in several aspects of creativity in art, which involves a complex interplay between motor, cognitive, and emotional processes. In the chapter of Evers and Tölgyesi, the authors give a precise outlining of the cerebellar involvements not only in music perception and recognition, but also in production. They highlight specific network associations between certain parts of the cerebellum, in particular lobule VI and VII, the latter lobule with its Crus I and II, and the cerebral areas encompassing the frontoparietal and temporal cortex. In fact, the authors gathered a multitude of different components involved not only in music perception, including melody, harmony, rhythm, but also in the recognition of music chords, which emphasize the impact of memory and emotional processing to the temporal driven integration of sensory information during music perception and evaluation (Parsons 2001; Molinari et al. 2003; Paquette et al. 2017). Evers and Tölgyesi point out that from a topographical point of view, areas of the left hemisphere of the cerebellum deem to take a predominant role within music perception, which might be due to its specific role in low-pass filtered processes of prosodic and melodic properties, whereas the right hemisphere of the cerebellum might be more involved in segmental properties of music chords. A comparable topic related to the issue of cerebellar involvement in more complex functions was addressed in the chapter of the impact of the cerebellum in the experience of art, which follows the growing research field of neural underpinnings in aesthetics. According to the "aesthetic triad" of Chatterjee and Vartanian (2014), aesthetic experience represents the flexible interplay between the sensory-motor, emotion-evaluation, and meaning-knowledge levels along low- and high-level processes to aesthetic judgments in particular about visual and auditory stimuli from the occipital to frontal lobes (Boccia et al. 2016). Research on the role of the cerebellum in aesthetics has identified involvement of the posterior parts of the cerebellar hemispheres and sites within the vermis and paravermal regions. Thus, the cerebellum is suggested to be involved in the behavioral levels of creativity linking its unique cognitive and affective aspects (Petrosini et al. 2015), presumably by providing several internal models to solve the demands of motor, cognitive, and affective processing traces of the responsible networks in specific multimodal task processes (Ito 2008). Indeed, the reciprocal connections between the cerebellum and the lateral (DLPFC, IFG) and medial (vmPFC) areas of the PFC could, on the one hand, serve as an interface between intracerebellar convergence zones in order to progress to specific and novel outcomes within implicit and explicit processes of problem solving (Koziol and Lutz 2013) as a feature of creativity. On the other hand, the cerebellar contributions to art perception suggest similar modes of neural activities, as shown for other sensory processes with associative perception and recognition, such as emotional faces and vocalization. Therefore, activation of Crus I and II is frequently reported in specific fMRI tasks studying cerebral processing of emotion-laden visual and auditory art (e.g., Zeki et al. 2014), leading to the presumption that these cerebellar regions act as central hubs in diverse large-scaled neural networks. These cerebellar hubs arguably support aesthetic processing across different stimulus categories including not only paintings, music, and architecture, but also morality and mathematics (e.g., Kühn and Gallinat 2012; Vartanian and Kaufman 2013; Zeki et al. 2014). So art perception arguably involves the distribution of bottom-up and top-down processing stages that can be captured by early and late potential deflections in event-related potential protocols (Jacobsen 2013). The exact mechanisms of the responsible parts of the cerebellum serving as integrative modes need to be clarified in future studies.

One way of addressing the direct relationship between the cerebellum and the different emotion-related processing streams is with noninvasive brain stimulation techniques such as transcranial magnetic and direct current stimulation. These techniques can induce transient modulation of neural excitability of the human cerebellar cortex and associated (extracerebellar) regions. While cerebellar neurostimulation in the field of affective and clinical neuroscience is still in its initial phase, empirical evidence confirms direct involvement of the cerebellum in emotion and motivation. In addition, the chapter of Van Dun and colleagues deals with potential therapeutic options in affective disturbances in cerebellar disorders using transcranial magnetic and electric stimulation techniques. In consideration of the positive results described by Van Dun and colleagues in particular regarding cerebellar stimulation in the treatment of ataxia and emotion-related disorders, cerebellar stimulation protocols have been developed that may have neurorehabilitative potential. As Van Dun and colleagues outlined, the central aims of such neurorehabilitative approaches should be about targeting neural restoration of the responsible cerebellar circuitries. Moreover, specific psychological-oriented therapies, such as cognitive-behavioral therapy and/or goal management therapy to increase patient's awareness of acquired disabilities, may serve as a kind of "external cerebellum" as an additional mode of therapy through the implementation of self-monitoring strategies (Ruffieux et al. 2017). In fact, a combined setting including such cognitive-behavioral approaches, psychiatric and occupational therapies, and individual adapted medical and noninvasive stimulation may be particularly beneficial to establish clinically relevant effects. However, the therapeutic efficacy of these combined and add-on treatment approaches warrants further research.

Following the chapter of Van Dun and colleagues about rehabilitative issues in the context of the cerebellum and emotion, Evers and Tölgyesi in their chapter reported some fascinating study observations of therapeutic implications of music targeting the neural reorganization within the cerebellum or the affected cerebello-cerebral connections, which has been proven in different clinical entities such as Alzheimer's disease (King et al. 2019) or unresponsiveness wakefulness syndrome (Steinhoff et al. 2015). In sum, if plasticity of the brain following cerebellum lesions is a common characteristic (Bower and Parsons (2003), then the positive results of neurorehabilitative protocols for movement disabilities in cerebellar disorders may prompt comparable strategies for ameliorating deficits of perceiving and handling emotional cues (Ilg et al. 2014). According to the observation of cerebellar involvement in action perception coupling (APC) as an example of integration of motor and multisensory information (Christensen et al. 2014), a promising therapeutical approach might be a structured training of perceiving and evaluating visually presented scenes of daily situations with certain affective conditions or even practicing emotional facial expressions of basic emotions such as fear and anger.

Regarding the underlying mechanisms of the relevant cerebellar areas in guiding emotion processing, there is a highly uniform and stereotyped geometry at the microscopic level. The cerebellum can presumably be broken down to functional units, whereby several hundreds and thousands of multizonal microcomplexes serve as functional modules (D'Angelo and Casali 2013). Up to now, there is increasing evidence that the cerebellar areas work along corticonuclear microcomplexes subserving computational functions unique to the cerebellum. This overarching concept, known as the universal cerebellar transform (UCT), is considered a crucial feature of the cerebellum for the integration of internal representations with external stimuli and self-generated responses in an implicit and non-conscious manner (Schmahmann et al. 2019). Indeed, Baumann and Mattingley point out in their chapter that despite the value of a universal theory on cerebellar function, the unique contributions of the cerebellum (i.e., functional units) to specific functional domains are nonetheless important to consider. The authors show that the cerebellum partakes in several components of emotion processing, including physiological (bodily) responses underlying the "feeling" component of emotion, emotional expressions in social interactions, and cognitive appraisal processes linked to determine the significance of events and the subsequent regulation of emotions elicited by these events.

Similar to movement-related operations, the cerebellum coordinates and integrates cognitive and affective functions. Damage to the cerebellum can not only lead to ataxic motor symptoms (motor dysmetria), but also cause cognitive and emotional disturbances (dysmetria of thought) (Schmahmann 2021). Emotional dysmetria is now evolving. Within this framework, various hypotheses have been put forth that might form the basis of the UCT, such as error-based learning, error monitoring, forward control, prediction, timing, or sequencing (Argyropoulos et al. 2019). Notwithstanding the challenge to explain how a single brain structure whose neural circuitry is organized into uniform, repetitive pattern can play such an integral role in so many distinct functions and behaviors (Bower and Parsons 2003), the UCT model might be of relevance also to the cerebellar modes in emotion. This might be of interest for future research to further clarify the core computations and adaptability of the cerebellum in emotion and subsequent behavior. Sensitive clinical and neuropsychological assessments as well as fine-grained behavioral paradigms in functional neuroimaging targeting crucial cerebellar-cerebral pathways are warranted to address these questions on the specific intracerebellar computations of emotion and cognition

(Argyropoulos et al. 2019; Schmahmann et al. 2019). As the clinical impact of cerebellar-related impairments in emotion perception and experience are know well recognized at the neuropsychiatric level (Schmahmann and Sherman 1998; Wolf et al. 2009; Schutter 2016; Zhou et al. 2017; Schutter 2020; Schmahmann 2021), psychopathological conditions can be conceptualized as either an emotional overshoot (hypermetria) or undershoot (hypometria) for the five neuropsychiatric domains of the cerebellum, that is (1) attentional and (2) emotional control, (3) social skills, (4) psychosis spectrum disorders, and (5) autism spectrum disorders (ASD) (Argyropoulos et al. 2019). Indeed, neuropsychological and experimental brain research has provided independent lines of evidence in support of cerebellar involvement in disorders of emotion. Medial cerebellar structures and their connections to the limbic system are involved in visceral aspects and generation of emotions, whereas the posterolateral cerebello-thalamo-cortical loops are implicated in emotion regulation and subjective sense of control. Disturbances within these cerebellar-centered circuits are proposed to underlie homeostatic dysregulation and emotion dysregulation that may perhaps even provide a transdiagnostic mechanism by which the cerebellum contributes to neuropsychiatric conditions. As the dysmetria of thought concept defines psychological issues from a cognitive-centered perspective, the term dysmetria of affect may be a more appropriate term when the psychological disturbances find their (subcortical) origins in the generation and experience of emotional states (Schutter 2020). As such, the significance of different cerebellar areas in various domains of emotion, as presented in this book, is in accordance with the notification of clinically relevant sequelae of cerebellar caused emotion processing (Schmahmann and Sherman 1998), substantiating the high interest for ongoing and outstanding research. Therefore, several issues in affective and clinical neuroscience to uncover the cerebellar principles and mechanisms of emotions and related disorders remain to be clarified in future research:

- Topographical mapping and task-based functional imaging of the cerebellum have propagated the knowledge about intracerebellar areas not only in different categories of emotion such as valence and arousal, but also in combination to predominately cognitive processing modes. It would be interesting to clarify the specific topographical patterns of emotion processing within the responsible cerebellar regions in more detail, that is, by applying multivariate pattern analyses (Haxby et al. 2014). Moreover, it would be of interest to clarify the temporal features of each responsible cerebellar areas in more detail, capturing the task-dependent differences to each dynamic functional connectivity. In addition, intracerebellar connectivity between the medial and lateral regions, and the peculiarities of the regional overlaps, should be taken into account in future neuroimaging protocols. Finally, the importance of the intrinsic connectivity networks (ICN) subserving for maps of the cerebellum to various functional networks such as the default mode network (DMN), salience network (SN), and frontoparietal network (FPN) to certain associative processing in several domains such as creativity, imagination, or morality is warranted to be clarified.
- Clinical and neuroimaging studies should disentangle the specific characteristics of the cerebellum, in particular its connections to limbic areas and the frontoparietal and temporal cortex. In this sense, future studies should shed a light onto the specific spatial segregation to evolutionary new regions of the cerebellum in terms of functional connectivity with limbic versus association cortices.
- Does the cerebellum serve a more general role in emotion processing, or are there dedicated and functionally specialized regions? Moreover, how does the cerebellum contribute to the unconscious (subcortical) and conscious (cerebral cortical) processing streams?
- Additional studies with specific moral task conditions as well as protocols with focal noninvasive stimulation of the posterolateral

regions may obtain further detailed insights into the role of the cerebellum in morality.

- Concerning the higher order associative processing of emotion, more research is needed to get a better understanding of how the cerebellum learns to support the discrimination of emotional valence in associative processing of multifaceted sensory perception and evaluation in music and visual art. So while the cerebellum has been found to be involved in art perception, explicating the stages deemed crucial in recognizing and evaluating the emotion features warrants further systematic investigation. Moreover, what are the functional contributions of Crus I and II to networks such as the default mode network (DMN) and central executive network (CEN) in the context of cognitive and affective processes in creativity and aesthetic perception? Finalizing these roads to specific avenues of the cerebellum to art disciplines, suitable music and art training protocols serving for therapeutic applications in the use of active as well as passive therapies to enhance the neural organization of afflicted neural cortical-subcortical networks need to be clarified.
- Uncovering the precise role of the cerebellum in emotional prosody (i.e., the melodic and rhythmic features of speech that convey the emotional content) and the ability to recognize and describe one’s emotions (or lack thereof called alexithymia), as introduced in the chapter of Laricchiuta and colleagues, is an outstanding issue in language studies.
- How do microcomplexes regulate signals related to emotion and how the cerebellar modules interfere to smooth motor and behavior? Specifically, what is the role of the climbing and mossy fibers in relationship with emotional regulation, and how these fibers interact with the monoaminergic afferent system? And will it be possible to extract patterns of discharges of the cerebellar cortex noninvasively?
- Future studies are warranted to clarify individual parameters of transcranial cerebellar stimulation protocols, in particular the stimulation modes and target regions, which should be evaluated in more detail by neuroimaging approaches. In addition, neurorehabilitation protocols involving clinical physiatrist and occupational, psychological, and also individually tailored pharmacological treatment approaches should be evaluated in addressing affective disturbances following cerebellar disorders. Finally, the subdivision of the cerebellar syndrome into three subtypes (cerebellar motor syndrome, cerebellar vestibular syndrome, Schmahmann’s syndrome) can be used as a template to improve our handling of cerebellar disorders (Manto and Marien 2015).

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