

# Chapter 12

## Cerebello-Cerebral Feedback Projections

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**Abstract** The functional neuroanatomy of cerebellar systems has been extensively studied during the past decades by means of experimental animal studies, anatomo-clinical studies, as well as structural and functional neuroimaging studies in patients and healthy subjects. Within a system of closed-loop circuits, this wealth of studies identified reciprocal projections between the cerebellar structures and the supratentorial areas subserving sensorimotor, cognitive, and affective function. It has been shown that cerebellar output is mediated by the deep cerebellar nuclei, mainly by the dentate nucleus (DN), which project to the supratentorial cortex via the thalamus (cerebello-thalamo-cortical pathway). In turn, the cortical areas that are the target of cerebellar output project back to the cerebellum via the pons (cortico-ponto-cerebellar pathway). Regions of the cerebellar cortex that receive input from a specific supratentorial area, are the same regions that project back to that supratentorial area, thus forming closed-loop circuits. These projections are largely crossed, connecting the cerebral hemispheres primarily with the contralateral cerebellar hemispheres.

**Keywords** Corticocerebellar pathways • Cerebello-cerebral network • Dentate nucleus • Functional neuroanatomy

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## 12.1 Introduction

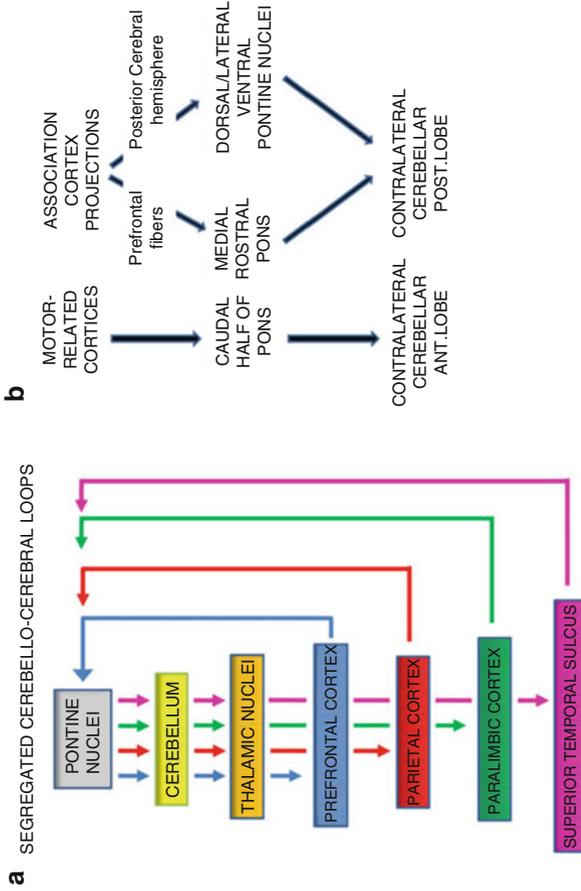
The functional neuroanatomy of cerebellar systems has been extensively studied during the past decades by means of experimental animal studies, anatomoclinical studies, as well as structural and functional neuroimaging studies in patients and healthy subjects. Within a system of closed-loop circuits, this wealth of studies identified reciprocal projections between the cerebellar structures and the supratentorial areas subserving sensorimotor, cognitive, and affective function. It has been shown that cerebellar output is mediated by the deep cerebellar nuclei, mainly by the dentate nucleus (DN), which project to the supratentorial cortex mainly via the thalamus (cerebello-thalamo-cortical pathway). In turn, the cortical areas that are the target of cerebellar output project back to the cerebellum via the pons (cortico-ponto-cerebellar pathway) (Schmahmann and Pandya 1995; Stoodley and Schmahmann 2010; Strick et al. 2009). Kelly and Strick (2003) demonstrated that the regions of the cerebellar cortex that receive input from a specific supratentorial area, are the same regions that project back to that supratentorial area, thus forming closed-loop circuits (Allen and Tsukahara 1974). These projections are largely crossed, connecting the cerebral hemispheres primarily with the contralateral cerebellar hemispheres (Stoodley and Schmahmann 2010). These crossed cerebello-cerebral projections are visualised in Fig. 12.1.

## 12.2 Projections

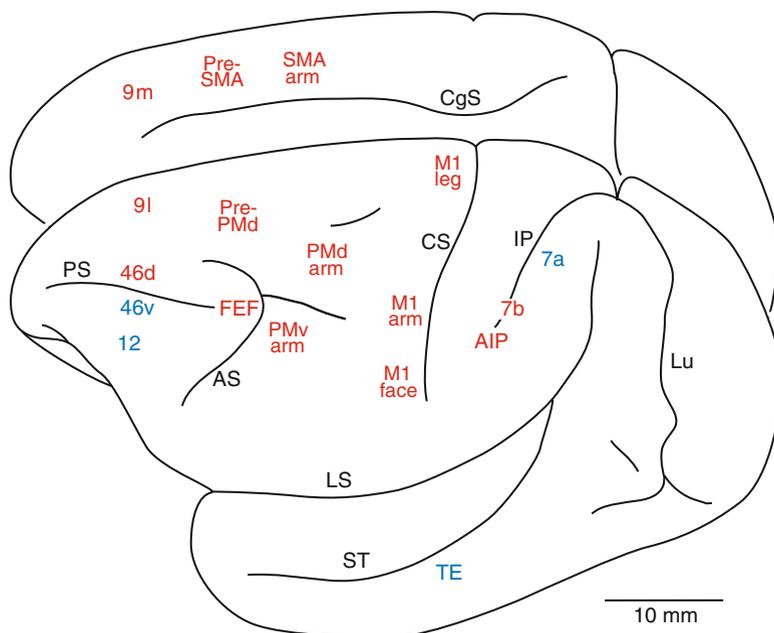
Over the past decades neuroanatomical studies established the foundation to substantially modify the traditional view of the cerebellum as a sole coordinator of sensorimotor function by showing that the cerebellum, in addition to the motor areas, also targets some associative areas crucially implicated in cognition and affect (Strick et al. 2009). Tracing methods in primates (Middleton and Strick 2001; Dum and Strick 2003; Akkal et al. 2007) linked the cerebellum to both frontal motor and premotor areas, and associative prefrontal and parietal regions (Strick et al. 2009; Habas et al. 2013). Some of the targeted cortical areas are visualised in Fig. 12.2.

Output channels from the DN are segregated. Projections to the motor areas originate from the dorsal portions of the DN, while projections to the associative cortices originate from the ventral portions of the DN (Dum and Strick 2003; Strick et al. 2009).

This means that the DN contains anatomically separate and functionally distinct motor and nonmotor domains (Dum and Strick 2009). This division is also represented by a neurochemically different composition within the DN, as shown by immunostaining with antibodies (Strick et al. 2009). Functional connectivity Magnetic Resonance Imaging (fcMRI) and Diffusion Tensor Imaging (DTI)-based tractography studies have confirmed these connections in primates, and in the



**Fig. 12.1** (a) Illustration of the segregated loops between the cerebellum and prefrontal cortex, parietal cortex, paralimbic cortex and superior temporal sulcus (Adapted from Grimaldi and Manto (2011)). (b) Topographic distribution of motor-related cortices and association cortex projections to the cerebellum. Both motor corticopontine projections and association cortex projections (from prefrontal, posterior parietal, superior temporal, parastriate, parahippocampal, and cingulate regions) are somatotopically organised in the pons (See also Stoodley and Schmahmann (2010). Adapted from Grimaldi and Manto (2012))



**Fig. 12.2** Targets of cerebellar output. *Red labels* indicate areas of the cerebral cortex that are the target of cerebellar output. *Blue labels* indicate areas that are not the target of cerebellar output. These areas are indicated on lateral and medial views of the cebus monkey brain. The numbers refer to cytoarchitectonic areas. *AIP* anterior intraparietal area, *AS* arcuate sulcus, *CgS* cingulate sulcus, *FEF* frontal eye field, *IP* intraparietal sulcus, *LS* lateral sulcus, *Lu* lunule sulcus, *M1*, face, arm, and leg areas of the primary motor cortex, *PMd arm* arm area of the dorsal premotor area, *PMv arm* arm area of the ventral premotor area, *PrePMd* predorsal premotor area, *PreSMA* presupplementary motor area, *PS* principal sulcus, *SMA arm* arm area of the supplementary motor area, *ST* superior temporal sulcus, *TE* area of inferotemporal cortex (Adapted from Strick et al. (2009))

human brain (Habas et al. 2013; Schlerf et al. 2014). DTI-based tractography is an important tool to track direct corticocerebellar pathways in humans. However, due to its low spatial resolution, partial coverage of the brain, and impossibility to track in low anisotropic regions, the technique faces a number of limitations preventing a full mapping of all the corticopontocerebellar fibers (Habas et al. 2009). Functional connectivity studies additionally indicate the existence of indirect connections that could be mediated by a third region. Both methods (functional connectivity and tractography) are therefore complementary and offer excellent opportunities to disentangle all cerebello-cerebral functional networks.

A motor/nonmotor subdivision also holds within the cerebellum. The sensorimotor cerebellum, which projects to the motor areas via the dorsal part of the DN, is primarily situated in the hemispheric parts of lobules IV/V/VI and VIII (Habas et al. 2013). There is little to no overlap between this sensorimotor network and the cognitive neocerebellar regions found to participate in the right/left executive control

networks involved in working memory, attention, response selection, and flexibility (especially crus I and II), the salience network required for processing and integration of interoceptive, autonomic, and emotional information (lobule VI), and the default-mode network involved in stream of consciousness, mental imagery, episodic memory retrieval, and self-reflection (lobule IX) (Habas et al. 2009, 2013). Therefore a functional dichotomy is suggested between the anterior cerebellum (lobules I-V) and lobule VIII, which are part of the sensorimotor network, and lobules VI and VII (including Crus I and II, and lobule VIIIB), and possibly also lobule IX, contributing to higher-level processing (Stoodley and Schmahmann 2010).

### 12.2.1 *Sensorimotor Network*

Functional connectivity studies have shown that the sensorimotor network consists of cortical and subcortical structures comprising: the sensorimotor cortex (M1/S1), the premotor cortex (BA 6), the supplementary motor area (SMA), the anterior cingulate cortex (BA 24), the occipital cortex (BA 19/37), the temporal cortex (BA 21), the insula, the lentiform and caudate nuclei, the ventral thalami, the rostral part of the left red nucleus, and the bilateral hemispheric portions of lobules IV/V/VI and VIII of the cerebellum (Habas et al. 2009, 2013).

Virus tracing studies in primates found direct projections of the dorsal part of the DN to M1, the ventral premotor area (PMv), and the SMA (Strick et al. 2009). DTI-based tractography confirmed the connections between the DN and the supratentorial sensorimotor areas M1/S1 via the ventral part of the thalamus (Habas et al. 2013).

### 12.2.2 *Cognitive Networks*

Three different cognitive networks have been studied by means of functional connectivity studies: (1) *the default-mode network*, (2) *the executive network*, and (3) *the salience network*. *The default-mode network* consists at the cortical level of the prefrontal cortex (BA 9/10, 32), the superior parietal cortex (BA 7), the angular gyrus (BA 39), the posterior cingulate cortex (BA 23/31), the retrosplenial cortex (BA 29/30), the medial temporal lobe, and the ventral temporal cortex (BA 20). At the subcortical level this network includes the thalamus, the left red nucleus, the midbrain and both caudodorsal hemispheres of lobule IX, and a small cluster in the right hemisphere of lobule VIIIB) of the cerebellum (Habas et al. 2009). *The executive network* consists of a right (RECN) and a left (LECN) executive network. These networks entail the following cortical and subcortical areas: the prefrontal cortex (LECN: BA 45/46, 9, and 8; RECN: BA 44/45/46), the orbitofrontal cortex (BA 47), the superior parietal cortex (BA 7), and the angular gyrus (BA 39), the caudate nucleus, and primarily crus I and crus II of the cerebellum with limited extensions into lobules VI and VIIIB and the rostral hemisphere of lobule IX (Habas et al. 2009).

The RECN additionally activates the caudal cingulate cortex (BA 23 bilaterally), the supramarginal gyrus (BA 40), and the left red nucleus. *The salience network* comprises functional connectivity between the medial frontal cortex (BA 32), the dorsal anterior cingulate cortex (BA 24), the dorsolateral prefrontal cortex (BA 46), the frontoinsula cortex (BA 47/12), the thalamus, the red nuclei with a left predominance, and the lateral and ventral parts of both hemispheres of lobule VI of the cerebellum, more laterally located and closer to the posterosuperior fissure than the sensorimotor network (Habas et al. 2009).

Virus studies traced projections from the cerebellum to prefrontal areas BA 8A, 9/9 m, 10 and 46d (Strick et al. 2009; Schmahmann and Pandya 1995). Projections were also found to the preSMA, which can be regarded as a region of the associative prefrontal cortex instead of a motor area since it is densely interconnected with the prefrontal areas (Stoodley and Schmahmann 2010; Strick et al. 2009). In addition to the prefrontal cortex, the cerebellum is also connected with the posterior parietal cortex (BA 7b), the anterior intraparietal area, and possibly also with the medial and lateral banks of the intraparietal sulcus. Cerebellar projections to the parietal lobe, however, are complex and currently still incompletely understood (Strick et al. 2009). Tractography confirms the connectivity between the DN and the temporal, prefrontal (BA 9), and parietal (BA 7) cortices (Habas et al. 2013).

## 12.3 Conclusion

Neuroanatomical studies in primates, and functional connectivity analyses and DTI-based tractography studies in humans have confirmed a crossed closed-loop cerebello-cerebral feedback projection system. These dense connections not only link the cerebellum with the supratentorial motor areas such as M1/S1, but also with the associative cortical areas in the frontal, temporal, and parietal lobes. Due to these connections the cerebellum participates in the sensorimotor network, as well as in cognitive networks such as the default-mode network, the executive network, and the salience network.

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