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Cerebellar information flow in the thalamus: implications for cortical functions

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Cerebro–cerebellar interactions are becoming progressively more focused in their anatomical substrate but their functional meaning is still elusive. Here, we review current data on the cerebellar influence on cortical function, with special emphasis on the importance of the cerebellar input for cortical processing in primary motor and sensorimotor areas. Differences in the intracortical processing of cerebellar information are described and the possible role of the thalamus in controlling cerebro–cerebellar loops discussed.

Keywords: cognition, motor learning, somatosensory cortex, motor cortex, somatosensory evoked potentials

INTRODUCTION

In the past few decades we have witnessed a complete rethinking of our views on cerebellar functions. The traditional view that the cerebellum has roles in motor coordination and motor learning has been substituted by a more complex picture in which the cerebellum affects a wide range of cognitive, emotional and sensory functions (Schmahmann and Sherman, 1998; Molinari *et al.*, 2002; Ito, 2005; Ramnani, 2006). This 'expansion' of the cerebellum into new areas included one of the main interest of Mircea Steriade's lines of research; the role of the thalamus in sleep and consciousness (Steriade, 1995; Andre and Arrighi, 2003; Steriade, 2003). Despite earlier suggestions (Leiner *et al.*, 1991) and important contributions from lesion studies (Fiez *et al.*, 1992; Silveri *et al.*, 1994; Schmahmann and Sherman, 1997) indicating the expanded role of the cerebellum, the real shift from the old, motor-related to the new, cognitive-associated framework of cerebellar research occurred when functional neuroimaging data demonstrated the activity of the cerebellum in functions other than the motor domain (Desmond and Fiez, 1998; Barrios-Cerrejon and Guardia, 2001). This shifted the focus of cerebellar studies from interactions with subcortical structures to the cerebello–thalamo–cortical–ponto–cerebellar circuit. The cerebellum projects via the thalamus to multiple cortical areas (Sakai *et al.*, 1996) and receives cortical efferents from an even greater portion of the cerebral cortex through the pons (Schmahmann and Pandya, 1997). Nevertheless, information about the effects of cerebellar processing on cortical function is scarce and limited mostly to the motor cortex (Daskalakis *et al.*, 2004). The role of cerebellar input to prefrontal and parietal areas for both Cognitive and motor functions receives ever greater attention (Middleton and Strick, 2001; Blakemore and Sirigu, 2003; Clower *et al.*, 2005; Ramnani, 2006). However, little is known about the neurophysiological effects of cerebellar input on these cortices, especially in humans. In this paper we review data regarding the influence of cerebellar input on the cerebral cortex in humans by focusing on recent findings concerning cerebello–parietal interrelations. Furthermore, we discuss the possible links between differences in cerebello–thalamo–frontal and cerbello–thalamo–parietal circuits, and cerebellar influences on physiology of the parietal and frontal cortices.

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The cerebello–thalamo–cortico–cerebellar circuit

There have been many attempts to understand the connections between the cerebellum and the cerebral cortex. Thalamic terminals of cerebellar efferents have been described in primates (Asanuma *et al.*, 1983b) and corresponding areas evidenced in humans (Macchi and Jones, 1997). Tract-tracing studies using transneuronal transport of viruses in primates indicated that cerebellar information is funneled from the thalamus to motor, premotor (Hoover and Strick, 1999), prefrontal (Middleton and Strick, 2001) and parietal cortices (Clower *et al.*, 2005). Recently these findings have been confirmed in humans using functional connectivity magnetic resonance imaging (MRI) techniques (Allen *et al.*, 2005). Of particular interest is the supposed modular organization of the cerebello–thalamo–cortical loops (Steriade, 1995; Middleton and Strick, 2000; Cicirata *et al.*, 2005; Ramnani, 2006) that support parallel, segregated cortico–cerebellar interactions. The cerebello–thalamo–cortical arm is duplicated by the cortico–ponto–cerebellar arm, which has been investigated in detail in primates (Schmahmann and Pandya, 1997) and is now analyzed in humans using diffusion imaging RMI (Ramnani *et al.*, 2006). Both arms of the cerebello–cortical loop are organized in anatomically and functionally independent parallel channels (Middleton and Strick, 2000), and this segregation is maintained in the thalamus (Middleton and Strick, 1998). Although anatomically well defined in experimental models and partially defined in humans, the function of the cerebro–cerebellar interactions

remains elusive. In humans, technical advances in neurophysiological techniques have allowed non-invasive analyses of functional interactions between the cerebral cortex and cerebellum in healthy subjects and in patients with damaged cerebellar circuits (Di Lazzaro *et al.*, 1994a; Di Lazzaro *et al.*, 1994b; Di Lazzaro *et al.*, 1995; Restuccia *et al.*, 2001; Iwata and Ugawa, 2005).

Cerebellar input to the motor cortex

Physiologically, transcranial cerebellar stimulation reduces the excitability of the contralateral motor cortex. It is hypothesized that although deep cerebellar nuclei (DCN) have facilitatory effects on the contralateral cerebral cortex, the cerebellar cortex inhibits the activity of the nuclei. Considering this biological substrate, transcranial activation is thought to have a greater effect on the cerebellar cortex than on the deep nuclei, which would explain the prevalence of inhibitory effects on motor-cortex excitability. In line with this interpretation, magnetic cerebellar stimulation produces facilitatory effects on cortical excitability in patients with lesions that are limited to the cerebellar mantle with sparing of the deep nuclei (Di Lazzaro *et al.*, 1994a; Di Lazzaro *et al.*, 1994b). However, the picture is not so simple. Early, transitory, facilitatory effects were reported after electrical cerebellar stimulation in healthy subjects (Iwata *et al.*, 2004), and both facilitatory and inhibitory effects in M1 have been reported in the monkey after DCN stimulation (Holdefer *et al.*, 2000). Therefore, it seems that cerebellar input to the motor cortex might have opposite effects depending on the prevalence of either nuclear or cortical activity. Furthermore, the final effect of cerebellar activity might depend on the intrinsic organization of the target structures. For example, although excitatory in nature, the cerebello-thalamo-cortical pathway might exert inhibitory effects on the motor cortex by activating inhibitory circuits either in the thalamus or directly in the cortex (Daskalakis *et al.*, 2004). Despite the possible opposite effects of cerebellar input to the cerebral cortex, lesions of the cerebello-cortical pathway reduce the activity of the contralateral cerebral cortex. This is supported by several neuroimaging studies demonstrating reduction in cerebral blood flow in the cerebral cortex following a lesion of the contralateral cerebellum (Sonmezoglu *et al.*, 1993; Gomez-Beldarrain *et al.*, 1997). The general effects of lesioning cerebellar input can also be addressed by studying cortical physiology after focal cerebellar lesions. Using this approach we demonstrated (Di Lazzaro *et al.*, 1994a; Di Lazzaro *et al.*, 1994b) that the excitability of the motor cortex is reduced by damage to the contralateral cerebellar hemisphere (cortex plus nuclei). It has been proposed that cerebellar input influences both projection and local circuit cortical neurons in healthy subjects (Daskalakis *et al.*, 2004). However, the reduced excitability observed in cerebellar lesioned subjects was not related to changes in the activity of the inhibitory cortical circuits but to direct changes in cortical properties, particularly to a reduction of the intrinsic excitability of cortical neurons (Di Lazzaro *et al.*, 1995). Thus, considering the results in both healthy subjects and in subjects with cerebellar damage, we hypothesize that cerebellar input modulates the motor cortex both tonically, by enhancing excitability, and phasically, by inducing a transitory reduction of excitability in the motor cortex.

Modulation of motor cortex excitability by cerebellar-mediated somatosensory stimuli

It is known that peripheral manipulation of somatosensory input can modulate motor cortex physiology and motor performances in healthy subjects and stroke patients (Floel *et al.*, 2004). Animal studies have established that somatosensory stimulation influence motor-cortex excitability by modifying synaptic strength, which is achieved through co-activation of cortico-cortical and thalamo-cortical synapses on motor cortical neurons (Asanuma and Hunsperger, 1975). Projections from the somatosensory cortex are considered crucial for inducing such changes (Asanuma and Pavlides, 1997). Different lines of evidence support the importance of the cerebellar input to the cerebral cortex for motor cortex plasticity (Aumann, 2002; Molinari *et al.*, 2002) and for sensorimotor integration (Bower and Parsons, 2003). However, there is little data regarding the influence of the cerebellum on the interplay between somatosensory and motor cortices. Recently, the possible role of the cerebellum in the genesis of these effects has been addressed in rats (Ben Taib *et al.*, 2005; Oulad *et al.*, 2005). The sustained somatosensory stimulation evoked by repetitive stimulation of the sciatic nerve, enhanced the motor responses evoked by transcranial magnetic stimulation of the contralateral cortex (Luft *et al.*, 2002). This effect is lost if the cerebellar input to the motor cortex was blocked either by inactivation of the interpositus nucleus (Oulad *et al.*, 2005) or by surgical lesioning of a hemicerebellum (Ben Taib *et al.*, 2005). These data indicate the importance of cerebellar processing of sensory stimuli for the crosstalk between somatosensory and motor cortices.

Modulation of the physiology of the sensorimotor-cortex through cerebellar-mediated somatosensory stimuli

The posterior parietal cortex projects to the cerebellum via the pontine nuclei in a topographically organized manner (Schmahmann and Pandya, 1989). However, until recently the existence of a cerebellar return loop through the thalamus was less clear. Experimental data show the presence of disynaptic connections between DCN and partietal cortex through ventro lateral, and intralaminar nuclei in rodents (Giannetti and Molinari, 2002), carnivores (Wannier *et al.*, 1992b; Kakei *et al.*, 1995) and primates (Clower *et al.*, 2001; Clower *et al.*, 2005), and MRI data confirm the existence of different cerebello-parietal reverberating loops in humans (Allen *et al.*, 2005). Despite growing evidence to support the strict anatomical and reciprocal functional links between the parietal cortex and the cerebellum, the role of cerebellar input in parietal processing is obscure. Our group has investigated the influence of cerebellar computing on parietal somatosensory cortex neurophysiologically in patients with unilateral lesions of cerebellar circuits (Restuccia *et al.*, 2001). To analyze cerebellar influences on the cortical somatosensory processing we recorded cortical somatosensory evoked potentials (SEPs) and performed a dipolar source analysis of traces using brain electrical source analysis on patients with unilateral cerebellar damage. Early SEPs, namely the cortical N20 deflection, are thought to label the arrival of the afferent volley in the middle layers of the primary somatosensory

cortex (Allison *et al.*, 1992). By analyzing these we can assess the functionality of subcortical somatosensory pathways. SEPs occurring later than N20 are thought to be generated by intracortical processing of somatosensory input (Yamada *et al.*, 1984). Thus, they can be considered a reliable index of the functionality of the primary somatosensory cortex. By taking advantage of the unilaterality of the lesion (Restuccia *et al.*, 2001) we showed the cerebellar influence on cortical processing by comparing the SEPs evoked in the two hemispheres. Whereas early P14 and N20 responses were similar and, thus, considered to be unaffected by cerebellar damage, a significant reduction was observed in the N24 and P24 SEPs recorded from the hemisphere lacking cerebellar input. Dipolar source analysis confirmed this finding. Dipole 2, which is likely to generate both N24 and P24 waves, was indeed significantly smaller after stimulation of the side ipsilateral to the damaged hemicerebellum. P24 and N24 amplitudes were ascribed to the intensity of the electrotonic invasion of the apical dendrites due to current spread from the cell body with polarity inversion along the pyramidal cells of area 3b. Thus, we concluded that the cerebellar influence on the primary somatosensory cortex is located in the intracortical circuits, that is in the interneurons that are responsible for the inhibitory phase following arrival of the incoming volley from the thalamus (Restuccia *et al.*, 2001).

Some hints about the significance of the cerebellar contribution to parietal cortex processing of somatosensory stimuli derive from a MEG study by Tesche and Karhu (Tesche and Karhu, 2000). In their study Tesche and Karhu used a paradigm that compared responses after expected and unexpected sensory stimuli. In brief, the protocol was based on the delivery of somatosensory stimulations characterized by a regular train of pulse current. The random omission of a stimulus was inserted in the sequence. Using this paradigm, cortical- and cerebellar-evoked signals differed markedly depending on the predictability of the stimulus. After random-stimulus omission sustained oscillatory activity, which started before the next overt stimulus, was recorded in the cerebellum but not the somatosensory cortex. Thus, although the signal in the somatosensory cortex depends strictly on delivery of the stimulus, the cerebellar response is linked more to the expectancy of the sensory signal than to its presence. This neuronal coding can provide information for processing the temporal features of sensory stimuli and might represent short-term storage for identifying the predictability of a sequence of sensory stimuli. Considering its close relationship to the expectancy of a sensory signal, the cerebellar evoked response has been defined proactive, distinguishing it from the cortical somatosensory response, which is reactive to the stimulus (Ivry, 2000).

To analyze the ability of the somatosensory cortex to process incoming input in relation to the presence/absence of cerebellar processing, we recently analyzed the somatosensory mismatch negativity (s-MMN) component of event-related potentials (ERPs) in patients with unilateral cerebellar lesions (Restuccia *et al.*, 2006). Thus far, the mismatch negativity (MMN) response has been studied almost exclusively in its auditory modality. When unattended, deviant, acoustic stimuli are interspersed between regular, frequent, acoustic stimuli, the deviant ones usually elicit a frontotemporal negative response in the 120–180 msec latency range, labeled MMN (Naatanen and Escera, 2000). MMN is thought to be generated by an automatic cortical change-detection process in which there is a difference between current input and the representation of previous input. A comparison can be made only if a memory representation of the standard input is available together with the current input. In the auditory domain this process is thought to be sustained by a distributed network involving the auditory cortex, prefrontal cortex and parietal cortex (Alain *et al.*, 1998). In the somatosensory domain the MMN response has been analyzed poorly (Kekoni *et al.*, 1997; Shinozaki *et al.*, 1998; Kida *et al.*, 2001; Tamura *et al.*, 2004; Akatsuka *et al.*, 2005). Reports are inconsistent and there are fewer data on the brain circuits that sustain s-MMN (Reviewed by Restuccia *et al.*, 2006). By employing a large number of electrodes (31) and by careful analyses, consistent data on the physiological characteristics of the s-MMN were obtained first in healthy subjects. When the same protocol was applied to subjects with unilateral cerebellar lesions the generation of s-MMN was clearly abnormal only in the cortical hemisphere that lacked cerebellar input. This indicates that the cerebellum is involved in generating s-MMN, and supports the idea that subjects with cerebellar damage present altered cortical somatosensory processing. One of the classical ideas about cerebellar functioning is that the cerebellum acts as a comparator. Therefore, it is tempting to propose the cerebellar cortex is the site where the possible discordance between input from the deviant event and the sensory memory representation of the regular preceding stimulation is tested. Interactions between mossy and climbing systems, the so-called base and teaching lines, might be the structural base for these comparisons, in line with their hypothesized role in somatosensory associative learning (Ito, 2005).

THE CEREBELLAR—THALAMUS AND CEREBRO—CEREBELLAR INTERACTIONS

One concept is clear to cerebellar researchers and often appears as the opening statement of reviews on cerebellar function. The cerebellum presents a circuit that is uniform throughout its subdivisions, despite the different functions that require cerebellar processing, so it is conceivable that the same basic function is always performed independently by the systems involved. Differences in the final effect might depend on the structural and functional organization of the target structures. In this view, the thalamus, which is the first recipient of the cerebellar output directed to the cerebral cortex, is in a key position to modulate output according to the request of the target structure. This hypothetical function is in line with the known thalamic control of the peripheral volleys directed to the cortex (Cudeiro and Sillito, 2006) and with the different modes of terminations of cerebellar fibers in the thalamus. Although directed mainly to the ventrolateral nucleus (Asanuma *et al.*, 1983a), cerebellar fibers also synapse in the intralaminar (Bentivoglio *et al.*, 1988; Minciacchi *et al.*, 1991) and ventromedial nuclei (Jimenez-Castellanos and Reinoso-Suarez, 1985; Steriade, 1995). Furthermore, the different cerebellar recipient thalamo–cortical neurons might target different cortical layers (Rausell and Avendano, 1985; Molinari *et al.*, 1994). Thus, cerebellar input might have different effects in different cortical areas and also within the same zone, depending on which cerebello–thalamo–cortical channel is under consideration (Wannier *et al.*, 1992; Kakei *et al.*, 1995). Evidence of the variability of cerebro–cerebellar interactions in different behavioral

states and the importance of thalamic modulation over cerebellar output can be inferred from recordings of Purkinje cell excitability during the sleep–wake cycle. Andre and Arrighi (Andre and Arrighi, 2001) demonstrated that the response of Purkinje neurons to glutamate is reduced significantly during slow-wave sleep compared to waking and paradoxical sleep. Furthermore, because modulation of the Purkinje cell responsiveness was related to the intensity of slow-wave sleep, the authors suggested that the mechanisms controlling the sleep–wake cycle might also directly influence cerebellar cortex excitability. Similar sleep-related changes were reported in the thalamic gating of cerebellar input. Thus, it has been proposed that the entire cerebello–thalamo–cortical loop is involved in different brain functions depending on the different sleep–wake phases. In waking and paradoxical sleep a high level of signal transfer is active in cerebro–cerebellar circuits. In waking the correlation between cerebellar and cerebral cortical activity is established and has been related to different motor, cognitive and affective functions (Desmond and Fiez, 1998). As stated by Andre and Arrighi (Andre and Arrighi, 2003), the high activity in the cerebellum during paradoxical sleep, when sensory input and motor output are both impaired, is surprising. However, the explanation based on involvement of the cerebro–cerebellar circuit in the paradoxical sleep-related function of consolidating newly-formed memory traces seems reasonable (Andre and Arrighi, 2003). Furthermore, it is in line with increasing evidence of cerebellar involvement in imagery tasks, in which there is no relationship with either peripheral sensory input or overt motor acts (Oullier *et al.*, 2005; Battaglia *et al.*, 2006).

Similarly, neurophysiological data indicate that cerebellar input to primary motor and somatosensory cortices might act on different circuits. In the motor cortex, direct stimulation of the cerebellar cortex induces early, short-lived enhancement followed by more prolonged inhibition of cortex excitability. It was proposed that these effects are sustained by different intracortical circuits (Iwata and Ugawa, 2005). By contrast, chronic lack of cerebellar input reduces excitability of the primary motor cortex by affecting the intrinsic properties of pyramidal neurons (Di Lazzaro *et al.*, 1995). Although no data are available on the effects of cerebellar stimulation on the parietal cortex in humans, in cats cerebellar inputs to parietal areas 5 and 7 are functionally different and might be related to differences in the terminal distribution of thalamo–cortical fibers (Kakei *et al.*, 1995). In humans, chronic damage to the cerebellum induces modification of the excitability of local circuits without affecting the intrinsic properties of layer IV neurons (Restuccia *et al.*, 2001). Therefore, these data indicate that the cerebellar influence on different areas of the cerebral cortex is not uniform and that the thalamus might be the site where the cerebral cortex exerts its control over cerebro–cerebellar interplay.

CONCLUSIONS AND HYPOTHESIS

Despite the relatively simple structural organization of the cerebellum and the rapidly expanding knowledge about the cerebro–cerebellar circuits, the involvement of this structure in disparate functions ranging from motor control to language, and from memory to emotion constitutes a great challenge for our comprehension of cerebellar functioning. The general notion still holds that because the basic organization of the cerebellar circuits is maintained throughout all cerebellar subdivisions, the cerebellum must provide the same basic computing function in all contexts. In this paper we present evidence that different cerebro–cerebellar channels differ substantially in their functional organization. This supports the hypothesis that the thalamus and the thalamo–cortical systems exert at least partial control over the activation of the different cerebro–cerebellar loops.

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