Published in final edited form as:
Brain Res Rev. 2010 October 5; 65(1): 14–27. doi:10.1016/j.brainresrev.2010.05.005.

The Cerebellum and Pain: Passive Integrator or Active Participator?

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Abstract

The cerebellum is classically considered to be a brain region involved in motor processing, but it has also been implicated innon-motor, and even cognitive, functions. Though previous research suggests that the cerebellum responds to noxious stimuli, its specific role during pain is unclear. Pain is a multidimensional experience that encompasses sensory discriminative, affective motivational, and cognitive evaluative components. Cerebellar involvement during the processing of pain could thus potentially reflect a number of different functional processes. This review will summarize the animal and human research to date that indicates that (1) primary afferents conduct nociceptive (noxious) input to the cerebellum, (2) electrical and pharmacological stimulation of the cerebellum can modulate nociceptive processing, and (3) cerebellar activity occurs during the presence of acute and chronic pain. Possible functional roles for the cerebellum relating to pain will be considered, including perspectives relating to emotion, cognition, and motor control in response to pain.

Keywords

cerebellum; pain; nociception; nociceptive; nocifensive; noxious

1. Introduction

The cerebellum is implicated in several neurological and psychiatric disorders (Gilman, 2000; Schmahmann, 2004). It is involved in a number of integrative functions, including: memory, associative learning, motor control (Ito, 2006; Schmahmann, 1991; Stoodley and Schmahmann, 2009), and more recently in somatosensory processing, including nociception (Saab and Willis, 2003). Nociception represents the neural circuitry that underlies the perception of pain, a multidimensional experience that encompasses sensory discriminative, affective motivational, and cognitive evaluative components (Melzack and Casey, 1968). Though most fMRI studies of pain show activation in the cerebellum (Table 1) (Apkarian et al., 2005; Borsook et al., 2008; Peyron et al., 2000), little is known about the specific role of

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The authors declare no conflicts of interest regarding the contents of this manuscript.

the cerebellum in nociceptive processing. The purpose of this review is to summarize recent findings that suggest that the cerebellum may have a role in nociceptive processing and in pain. The review will cover a basic overview of the anatomy and connectivity of the cerebellum, the evidence that nociceptive afferents project to the cerebellum, the modulatory effects of cerebellar stimulation on nociceptive processing, how cerebellar activity has been linked to the perception of pain, and what pain-related activation in the cerebellum could functionally reflect.

2. Overview of Cerebellar Anatomy

The neural circuitry in the cerebellar cortex has a uniform structure featuring a three-layered sheet (Figure 1) (Eccles et al., 1967;Palay and Chan-Palay, 1974;Voogd and Glickstein, 1998). Purkinje cells are the largest neurons in the cerebellum in terms of cell body diameter. Their cell bodies are aligned in a single row to make up the Purkinje cell layer in the cerebellar cortex. Purkinje cells are inhibitory and provide the sole neural output from the cerebellar cortex. In terms of gross morphology, the human cerebellum is comprised of two hemispheres of complex folia joined across the midline by the vermis, with an anterior, a posterior, and a flocculonodular lobe. These three lobes are further divided into 10 lobules, designated I to X (Schmahmann et al., 2000).

The main ascending input routes to the cerebellum are through the mossy fibers, climbing fibers, and diffuse mono-aminergic and cholinergic afferents. Mossy fibers convey excitatory neural input from the pontine nuclei to granule cells, the axons of which ascend into the molecular layer and bifurcate to form parallel fibers that synapse on the distal dendrites of the Purkinje cells. Climbing fibers also provide excitatory cerebellar afferents, conveying input from the inferior olive to Purkinje cells directly. Both the mossy fibers and climbing fibers also send collateral projections to the deep cerebellar nuclei. The deep cerebellar nuclei project to brainstem nuclei and the thalamus, which relays these projections to different parts of the cerebral cortex.

3. Cortical and Sub-cortical Connectivity to and from the Cerebellum

The cerebellum receives massive cortical input through two major relays in the brainstem: the pontine nuclei and the inferior olive (Figure 2). With the identification of cortical connections to and from the cerebellum, distinctive cerebrocerebellar loops have been discovered that have been proposed to process motor control and cognitive functions (Jissendi et al., 2008;Kelly and Strick, 2003;Middleton and Strick, 2001;Schmahmann, 1996;Schmahmann and Pandya, 1997). Different parts of the cerebellum have anatomical and functional connectivity with specific cortical regions, indicating that the cerebellum has functional zones that may relate to the topography of its cortical connections (Habas et al., 2009;Krienen and Buckner, 2009;O'Reilly et al., 2009;Sasaki et al., 1975;Schmahmann, 1996). A brief review of these connections will help define the possible pain-related functions that the cerebellum may process.

In the primate, the pontine nuclei receive extensive and diverse neural input from the cerebral cortex before sending mossy fiber input to the cerebellum through the middle cerebellar peduncle. Based on their areas of origin, cortical projections to the pons convey several different types of functional inputs that may pertain to pain, including motor, somatosensory, visuo-spatial, and cognitive information. Cerebral cortical efferents classically related to motor function arise from the primary motor cortex, premotor cortex, supplemental motor area, and frontal eye fields; while projections to the pons from traditionally somatosensory-related cortical areas arise from the primary somatosensory cortex and superior parietal lobule (Brodal, 1978; Glickstein et al., 1985; Jansen and Brodal, 1940; Nyby and Jansen, 1951; Schmahmann, 1996; Schmahmann and Pandya, 1997; Shook

et al., 1990). The pons also receives cortical inputs from association areas relevant to cognition and/or visuo-spatial processing such as the inferior parietal lobule, parahippocampal gyrus, dorsolateral prefrontal cortex (DLPFC), and other regions within the prefrontal cortex (Brodal, 1978; Dum and Strick, 2003; Hartmann-von Monakow et al., 1981; May and Andersen, 1986; Middleton and Strick, 2001; Ramnani et al., 2006; Schmahmann and Pandya, 1997; Strick et al., 2009; Wiesendanger et al., 1979). The DLPFC efferents to the cerebellum are particularly interesting, given that it is a region implicated in cognitive control (Koechlin et al., 2003; MacDonald et al., 2000), as well as pain modulation (Apkarian et al., 2004; Lorenz et al., 2003; Wager et al., 2004; Zubieta et al., 2005). The DLPFC is part of a closed cerebrocerebellar loop (Kelly and Strick, 2003), which suggests that the cerebellum may have a feedback modulatory role in nociceptive processing.

The inferior olive, which sends climbing fiber input to the cerebellum through the inferior cerebellar peduncle, receives input from both cortical and subcortical sources. It receives most of its descending input from the parvicellular red nucleus, which in turn receives input from primary motor cortex, supplementary motor cortex, premotor cortex, primary somatosensory cortex, and the superior parietal lobe (Schmahmann, 1996). In addition to red nucleus input, the inferior olive also receives projections from zona incerta (Cintas et al., 1980; Saint-Cyr and Courville, 1980), which has a role in the expression of chronic pain (Masri et al., 2009). The periaqueductal gray (PAG), a brainstem structure related to descending pain modulation (Fields, 2000), sends projections to the inferior olive as well (Holstege, 1988; Rutherford et al., 1984; Van Bockstaele et al., 1991). Based on these connections, the red nucleus-inferior olive system seems to convey motor and some sensory efferents to the cerebellum, while the zona incerta and PAG inputs may have a role in the modulation of nociceptive processing.

4. Nociceptive Cerebellar Afferents

Though neuroanatomical tracers have shown that the cerebellum receives inputs from cutaneous primary afferents (Edgley and Gallimore, 1988; Randic et al., 1981; Snyder et al., 1978), direct evidence that it receives nociceptive afferents comes from electrophysiological studies. These studies suggest that afferent input from nociceptors reach the cerebellum, as stimulation of nociceptors evokes neural activity in the cerebellum (Figure 3) (Ekerot et al., 1987a; Ekerot et al., 1987b; Hayashi et al., 1984; VanGilder and Fitzmartin, 1973; VanGilder, 1975; Wu and Chen, 1990; Wu and Chen, 1992). In cats, stimulation of cutaneous A-delta and C fiber nociceptors activates climbing fibers that terminate on Purkinje cells in the cerebellar anterior lobe ipsilateral to stimulation (Ekerot et al., 1987a; Ekerot et al., 1987b). C fiber nociceptors convey neural input through the postsynaptic dorsal columns as part of a proposed spino-olivocerebellar pathway (Ekerot et al., 1991). In addition to climbing fiber input, C-fiber nociceptors may also act through mossy fibers to reach Purkinje cells in the cerebellum (Wu and Chen, 1992). In rats, noxious colorectal distention activates visceral nociceptive-specific neurons in the lateral medullary reticular formation, including several with direct projections to the cerebellar vermis (Ness et al., 1998). Likewise, nociceptive visceral stimulation can modulate Purkinje cell activity in the posterior cerebellar vermis (Saab and Willis, 2001). However, evidence of how nociceptive information is encoded once it reaches the cerebellum is lacking.

5. Nociception is Modulated by Cerebellar Stimulation

Inferences from electrical and/or pharmacological stimulation of different parts of the cerebellum imply a modulatory role in nociceptive processing(Table 2). Electrical stimulation of the cerebellar lateral nucleus in rats modulates the encoding of noxious stimuli in intralaminar parafasicular neurons in the thalamus (Liu et al., 1993). In squirrel

monkeys, electrical stimulation of the intermediate portion of the anterior cerebellar lobe can raise nociceptive thresholds to tail shock (Siegel and Wepsic, 1974). Microinjection of morphine into the anterior portion of the cerebellum of rats results in acute analgesia that is reversible by both systemic naloxone and electrical stimulation at the site of the microinjection (Dey and Ray, 1982). Stimulation of rat cerebellar cortex using electrical stimulation or chemical stimulation using D,L-homocysteic acid (DLH), a non-specific glutamate receptor agonist, increases neural responses to a noxious visceral stimulus in and around the termination sites of nociceptive afferents in the spinal cord (Saab and Willis, 2001). Chemical stimulation using DLH applied to the rat cerebellar cortex increases visceral nociceptive reflexes, whereas DLH applied to the cerebellar fastigial nucleus decreases these reflexes (Saab and Willis, 2002). This inhibitory effect led the authors to suggest that the cerebellum may engage the pain modulating circuitry in the brainstem (Fields, 2000), which includes the PAG and rostral ventromedial medulla. Perhaps related, a clinical study has demonstrated functional changes in primary somatosensory cortex following unilateral cerebellar lesions, though without accompanying perceptual changes (Restuccia et al., 2001). Though cerebellar activation through electrical and/or chemical means influences nociceptive processing, its role in the experience of pain is still not well defined.

6. Cerebellar Activity and the Perception of Pain

Though pain neuroimaging studies often report cerebellar activation (Figure 4; Table 1), fMRI has only recently been applied to specifically addressing the nociceptive activity in the cerebellum and its relationship to pain. Helmchen and colleagues have identified differential patterns of cerebellar responses to innocuous and noxious thermal stimuli (Helmchen et al., 2003;Helmchen et al., 2004). Evidence suggests that nociceptive-specific activation is processed in the deep cerebellar nuclei, anterior vermis, and bilaterally in cerebellar hemispheric lobule VI (Helmchen et al., 2003). This dataset also indicated that in response to a 48.5^{o}C stimulus, ipsilateral hemispheric lobules III-VI were significantly more active in subjects experiencing high pain vs. low pain. This was the first study to explicitly link nociceptive activity in the cerebellum with pain perception. In a follow-up study, cerebellar activity in lobule VI and the anterior vermis varied with pain ratings, but only when the stimuli were self-administered by the subjects being scanned (Helmchen et al., 2004). This contrasts with their earlier study, which found significant effects of pain intensity when stimuli were applied by the experimenters. This discrepancy between the two studies is not explained, and suggests that the cerebellum's capacity for basic nociceptive encoding needs to be further explored.

Data from our lab suggest that the pattern of cerebellar activation in patients who have neuropathic pain affecting the maxillary division of the trigeminal nerve (V2) is altered relative to healthy subjects (Borsook et al., 2008). In healthy subjects, noxious heat produced increased activation in areas thought to be involved in cognitive processing (lobules Crus II and VIIB), as well as sensory-motor integration (lobule VI) (Grodd et al., 2001; Schmahmann, 1996; Stoodley and Schmahmann, 2009; Timmann et al., 2009). Brush stimuli applied to the affected V2 region produced allodynia (pain to a normally innocuous stimulus) in these subjects and resulted in activation in areas involved in sensory-motor integration (lobules IV, V, and VI), secondary sensory processing (lobule VIIIB), cognition (lobules VIIB, Crus I, Crus II), and the dentate nucleus. Only painful stimuli triggered activation of cerebellar areas related to cognitive processing, while innocuous brushing did not. By contrast, painful heat and painful brushing in chronic neuropathic pain patients both activated cerebellar areas related to cognitive processing. This suggests that cognitive processing areas in the cerebellum may be related to the encoding of pain, possibly as a cognitive modulator.

7. Functional Aspects of the Cerebellum Non-specific to Pain

The cerebellum has been correlated with a wide variety of different cortical functional areas (Habas et al., 2009; Krienen and Buckner, 2009; O'Reilly et al., 2009; Stoodley and Schmahmann, 2009; Strick et al., 2009). While the cerebellum appears to activate during the perception of pain, noxious stimuli may activate other processes related to pain, but not necessarily exclusive to it. Since pain itself is a multidimensional experience, other such functional processes that could be elicited include motor control, anticipation of pain, and negative emotions. Cerebellar activation could thus relate to aspects related to the pain experience separate from sensory discrimination. These may include nocifensive withdrawal responses, anticipation, emotion, and sensory-motor integration (Figure 5).

7.1. Withdrawal Responses

Lesions of the cerebellum can reduce the magnitude of a patient's withdrawal from a noxious stimulus, though such patients do not show overt signs of altered sensation (Holmes, 1939). This observation led to the conclusion that the cerebellum is related more specifically to the generation of a motor response to pain than to pain itself. Indeed, imagining the execution of a motor task can activate the cerebellum (Boly et al., 2007; Lotze et al., 1999; Luft et al., 1998), but Holmes' now classic finding does not rule out the possibility of a cerebellar role in nociceptive processing. More recently, the act of discriminating sensory information was found to significantly increase cerebellar activation (Gao et al., 1996). When a cutaneous discrimination task was added to a sensory experience, whether experimenter-applied or subject-initiated, cerebellar activation was significantly increased, suggesting a role for the cerebellum in sensory processing. Furthermore, a passive manipulation of limb position by an experimenter produces cerebellar activation similar to voluntary movement of the limb (Jueptner and Weiller, 1998). Together, these findings suggest that cerebellar activity observed during the execution of a motor task may be attributable to sensory processing. Thus far, functional imaging studies are often unable to differentiate cerebellar activation due to motor withdrawal vs. nociceptive sensory processing when using painful stimuli (Dimitrova et al., 2003; Maschke et al., 2002).

7.2. Inhibition of Nocifensive Behaviors/"Remaining Still"

Cerebellar responses to noxious stimuli in neuroimaging studies have often been ascribed to the inhibition of an escape response. Indeed, all human imaging studies include instructions to their subjects to remain still during scanning, which can be demanding during the application of painful stimuli. Stimulation of the PAG can lead to inhibition of withdrawal responses to nociceptive stimuli (Fields, 2000), which may involve the cerebellum. In a rodent model, chemical activation of the PAG by DLH has been shown to directly inhibit nociceptive input to the cerebellum, perhaps to help the animal disengage from an inescapable stressor (Cerminara et al., 2009). A pain study using human volunteers could theoretically engage a similar PAG-cerebellar process to reduce responsiveness to external stimuli. However, a reduction in nociceptive input to the cerebellum would seem to better explain a decrease in cerebellar cortical evoked potential amplitude rather than an increase, as was observed in the DLH study. During pain, increased cerebellar activation that would relate to inhibition of a motor response thus seems to require a mechanism separate from PAG-induced inhibition of cerebellar afferents.

The voluntary inhibition of a motor response to pain does not fully explain cerebellar activation during pain, since noxious heat can produce cerebellar activation even when subjects are under general anesthesia(Hofbauer et al., 2004). In this positron emission tomography study, noxious thermal stimuli were applied to the forearms of 15 healthy subjects while they were infused with different concentrations of propofol, a general

anesthetic. When subjects were deeply sedated, noxious heat evoked significant cerebellar activation comparable in magnitude to when they were free of sedation. Interestingly, the cerebellum also showed activation with noxious heat when subjects were completely unconscious. Note that with deep sedation, almost half of the subjects showed involuntary movements of their limbs in response to noxious heat. Together, these results suggest that cerebellar activation to noxious heat: (1) can be involuntary; (2) is present in the absence of inhibition of movement; and (3) does not require the conscious perception of pain. Unfortunately, few if any other studies like this have been conducted to address the necessity of consciousness for cerebellar activation. Future research in this regard may help uncover the cerebellum's role during nociceptive processing.

7.3. Anticipation of Pain

As well as being active during a painful event, the cerebellum shows activation during the anticipation of pain in humans with fMRI (Ploghaus et al., 1999). When subjects were shown a light cue to signal impending pain, the ipsilateral posterior cerebellum was active. During painful heat stimulation, a wholly different region of the cerebellum was active: bilateral anterior cerebellum. Yet in this study, the functional role of this cerebellar activation was ascribed to the motor response/preparation to painful stimuli. Another possibility is that the cerebellum is involved in pre-attentive detection of somatosensory input changes, as indicated by a recent mismatch negativity study (Restuccia et al., 2007). Considering the separate spatial locations of the anticipatory and pain activations, multiple parts of the cerebellum seem to respond to a painful event in different ways.

The cerebellum appears to have a more prominent role in processing unanticipated events than anticipated events, though it activates during the anticipation of an event before it occurs. In a recent imaging of spontaneous trigeminal neuralgia, also known as "*tic doloureux*" (Borsook et al., 2007b), no activation was observed in the cerebellum following self-triggered (expected) tics, but activation was observed following spontaneous (unexpected) tics. This information suggests that the cerebellum processes anticipated events differently than unanticipated events, akin to the relationship between efference copy and predicted sensory outcome (Sperry, 1950; Von Holst, 1954), and is perhaps involved in the preparation of impending pain. This indicates a role in processing anticipated sensory input with a high level of temporal accuracy, with optimization of temporal responses of anticipated events in the sensory and integrative systems (Blakemore et al., 1998; Ohyama et al., 2003; Tesche and Karhu, 2000). This putative comparative role of the cerebellum, in which the anticipation of pain is compared with the actual experience of pain, has not been thoroughly researched.

7.4. Emotional Aspects of Pain

In addition to responses to painful stimuli, cerebellar activation is also observed in studies of pain empathy (Jackson et al., 2005; Moriguchi et al., 2007; Singer et al., 2004), fear (Murphy et al., 2003), and in generalized emotional perception (Bermpohl et al., 2006; Konarski et al., 2005; Murphy et al., 2003). Cerebellar activation with pain empathy, regardless whether it is an affective or cognitive process, gives further indication that the cerebellum processes more than motor function. Thus far, cerebellar responses to pain have not been compared to other forms of aversive stimuli, such as aversive pictures that also activate the cerebellum (Bermpohl et al., 2006). Such a comparison would help determine whether the cerebellum responds to pain specifically, or encodes it as a generalized aversive stimulus.

7.5. Integrative Functions

The cerebellum may have an integrative function that combines and coordinates a variety of functional inputs for a supramodal process. A possible role of the cerebellum in pain processing may be considered in light of the "*dysmetria of thought*" hypothesis (Schmahmann, 1991; Schmahmann, 2004). This hypothesis posits that the cerebellum has a fundamental function to optimize performance by automatically modulating behavior according to context, and is disrupted when the cerebellum is damaged. This hypothesis is built upon the Universal Cerebellar Transform, which theorizes that the cerebellum has a singular generalizable function that is applied to a variety of different types of functional inputs (Schmahmann, 2004). The dysmetria of thought hypothesis may be applied to learned behaviors in pain (sensory) processing, as cerebellar processing may influence monitoring and adjusting sensory acquisition (Bower, 1997). The cerebellum may be involved in processing motor control error signals in state estimation (Miall and King, 2008; Wolpert and Miall, 1996), and may be a comparator for errors in somatosensory processing (Apps and Garwicz, 2005; Eccles et al., 1967; Ekerot et al., 1987a). Such error signals may play a role in wrongly executed movements. While this hypothesis was originally related to somatosensory inputs to the cerebellum, it may also apply to nociceptive inputs (Cerminara et al., 2009).

7.6. Cerebellum and Pain Co-morbidities

Given that chronic pain conditions are co-morbid with psychiatric disorders (Gureje et al., 2001; Haley et al., 1985; Wilson et al., 2002), the cerebellum is interestingly linked to depression as well as pain. Sensory and affective neural systems involved with processing pain can become altered with chronic pain, resulting in the development of psychiatric illnesses, such as depression (Borsook et al., 2007a). Abnormal cerebellar responses to the anticipation of noxious stimuli have been suggested to be a potential marker for depression (Smith et al., 2002). Furthermore, patients with depression have a tendency for increased resting activity in the anterior cerebellum, as well as abnormal responses to stimuli evoking positive and negative affect (Fitzgerald et al., 2008). This suggests that in addition to being co-morbid, pain and depression may share a common mechanism within the cerebellum.

8. Conclusions

An improved knowledge of the cerebellar function in relation to pain has potential implications for the discovery of new understanding for pain control. Currently, less than a handful of studies have even attempted to discern the function of the cerebellum in regards to pain. Pain does not necessarily have a singular impact on what may be a variety of cerebellar functions, given that pain is a multi-dimensional experience itself. Based on relatively scant evidence, we speculatively propose that the cerebellum is an integrator of multiple effector systems including affective processing, pain modulation, as well as sensorimotor processing. The cerebellum appears to play a cross-modal modulatory role in regards to pain, with noxious stimuli impacting the processing of generalized aversion as well as sensorimotor adaptations to pain and/or injury. Clearly, more research in this domain is required to explicitly define the significance of nociceptive processing in the human cerebellum. The role of the cerebellum as it pertains to motor control in response to nociceptive stimuli also needs further study. Such research may lead to an enhanced understanding of perturbations in chronic pain states which appear to have altered cerebellar functionality (Borsook et al., 2008).

Acknowledgments

This work has been supported by a K01 grant from NIDA to EA (DA25289), a K24 grant from NINDS to DB (NS064050), and the Birmingham foundation and the MINDLink foundation (JDS).

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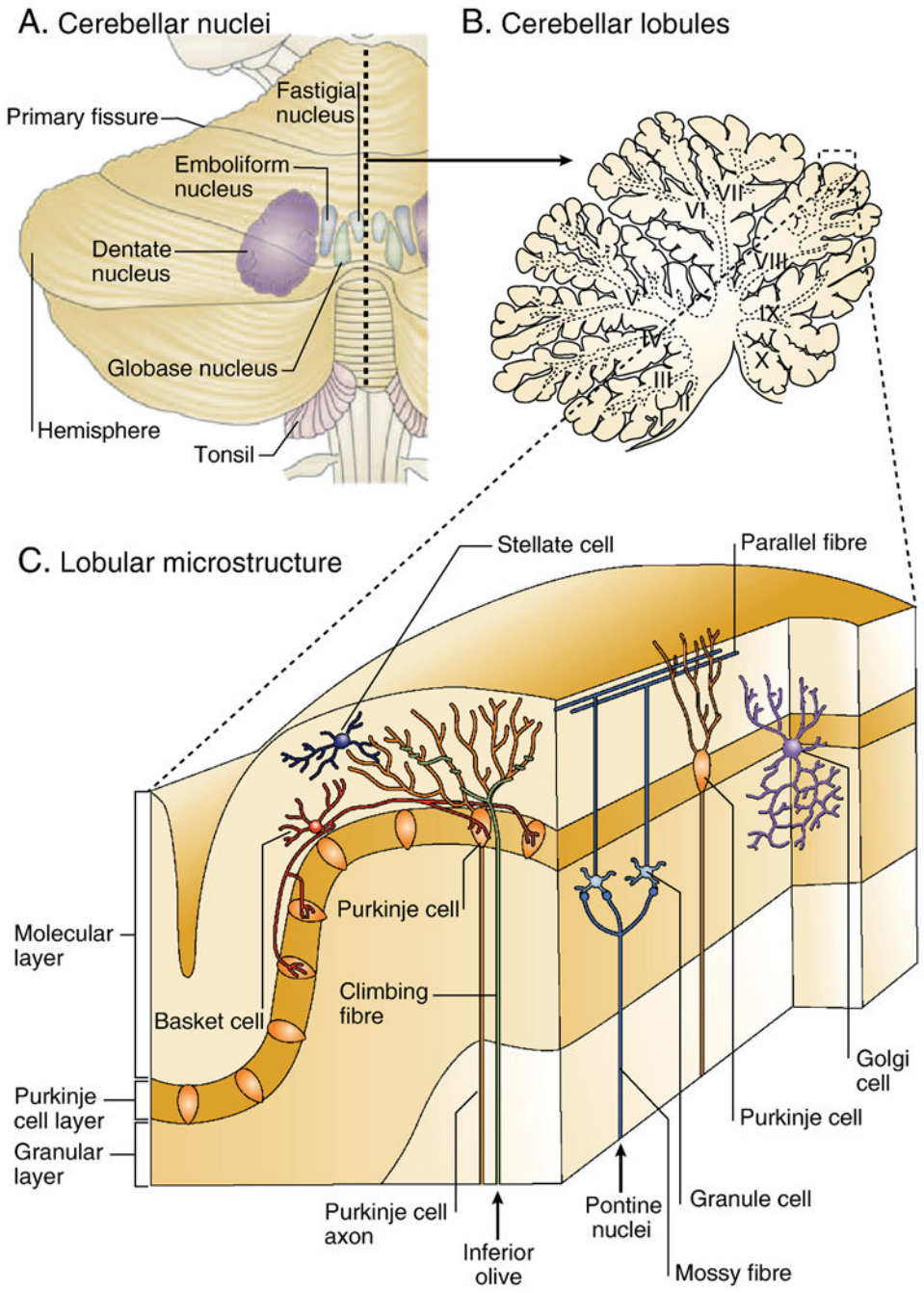

Figure 1.

Cerebellar Anatomy. A) Location of the cerebellar nuclei beneath the cerebellar cortex, as viewed from the posterior aspect of the human cerebellum. B) Lobular organization of the human cerebellum. C) Magnified view of the microstructural organization of a representative lobule, highlighting the Purkinje cells and the main cerebellar inputs from the inferior olive and pontine nuclei. Figure modified with permission **[pending]** from (Ramnani, 2006).

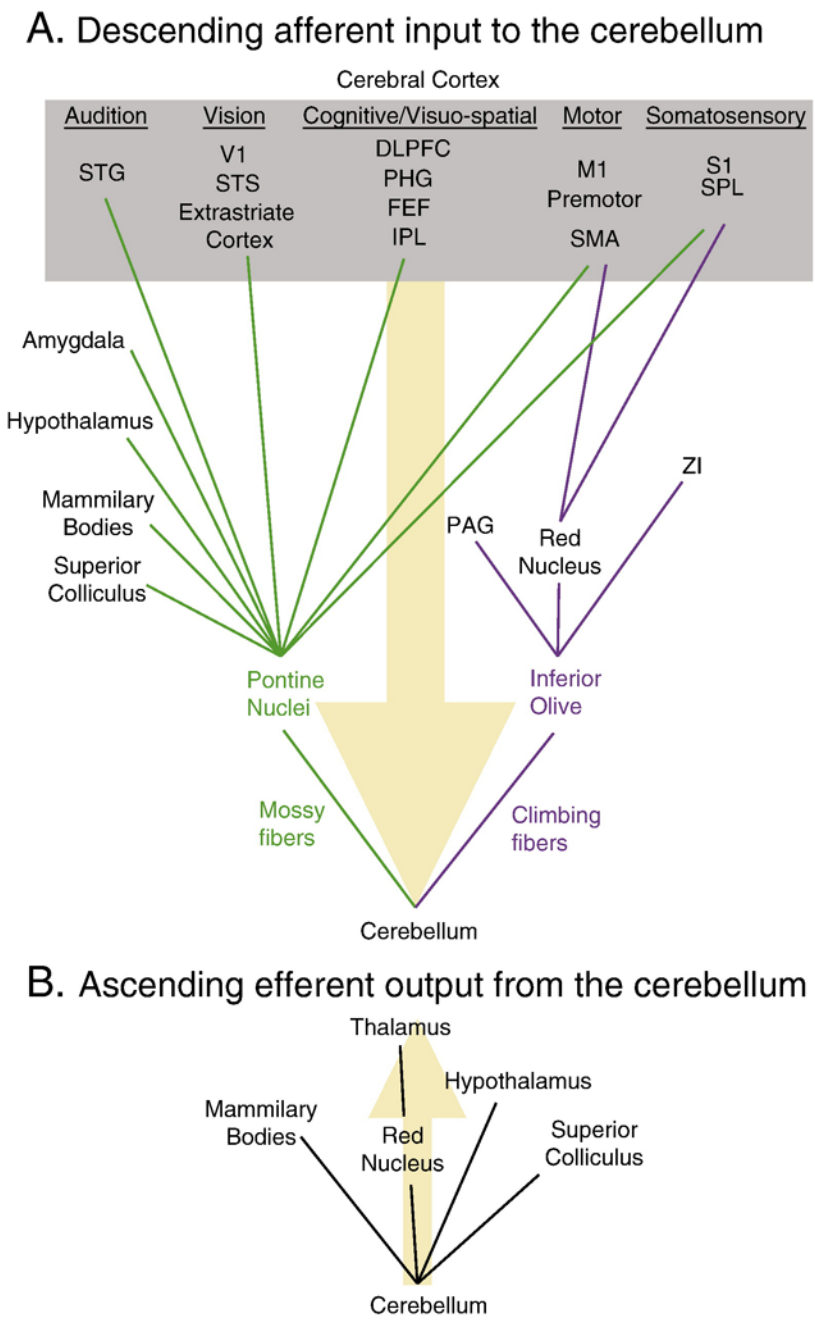

Figure 2.

Cortical and sub-cortical connectivity to and from the cerebellum. A) Descending afferent input to the primate cerebellum (orange arrow). Cortical (gray box) and sub-cortical areas send neural inputs to the cerebellum through either the pontine nuclei (green) and inferior olive (purple). Descending connectivity based on (Cerminara et al., 2009; Schmahmann, 1996). B) Ascending efferent output from the primate cerebellum (orange arrow). Ascending connectivity based on (Haines and Dietrichs, 1984; Haines et al., 1997; May et al., 1990; Schmahmann, 1996). Abbreviations: dorsolateral prefrontal cortex (DLPFC), frontal eye fields (FEF), inferior parietal lobule (IPL), primary motor cortex (M1), periaqueductal gray (PAG), parahippocampal gyrus (PHG), primary somatosensory cortex (S1), supplementary

motor area (SMA), superior parietal lobule (SPL), superior temporal gyrus (STG), superior temporal sulcus (STS), primary visual cortex (V1), zona incerta (ZI).

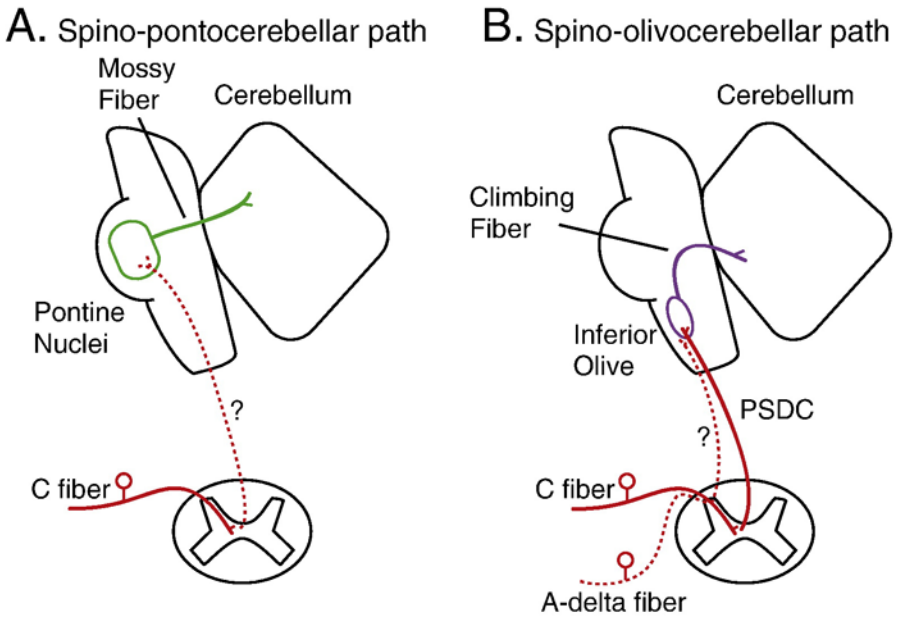

Figure 3.

Cutaneous nociceptive afferents to the cerebellum. A) Spino-pontocerebellar path. Stimulation of C fiber nociceptors activates mossy fibers that project to the cerebellum through an unknown pathway. B) Spino-olivocerebellar path. C fiber nociceptors convey neural input through the post-synaptic dorsal column (PSDC) in the spinal cord to the inferior olive to activate climbing fibers that project to the cerebellum. A-delta fiber nociceptors stimulation activates climbing fibers through an unknown pathway.

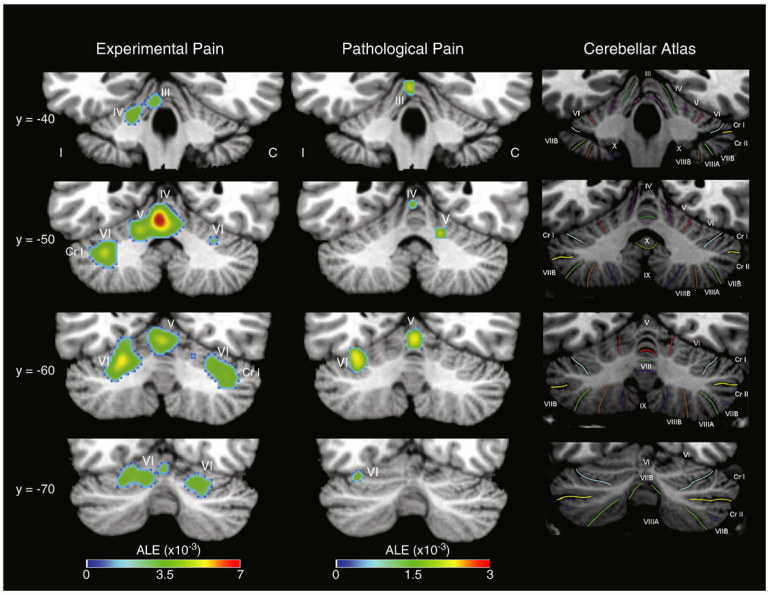

Figure 4.

Activation estimate likelihood (ALE) meta-analysis of cerebellar activations reported by experimental (n=56 experiments, 195 foci) and pathological pain studies (n=20 experiments, 54 foci). ALE is a quantitative meta-analysis method that statistically evaluates the spatial distribution of activation foci across studies (Turkeltaub et al., 2002). Activation foci from experimental and pathological pain studies (Table 1) were entered as coordinates in Montreal Neurological Institute (MNI) space. Foci originally reported in Talairach coordinates were transformed into MNI space using the "Convert Foci" tool in GingerALE 2.0 (www.brainmap.org/ale/), which considers the analysis software used for spatial normalization in the reporting paper (i.e. FSL/SPM/Other). After MNI transformation, images were oriented such that the side of unilateral pain always occurred on the same side of the image (left). ALE maps were generated using GingerALE (Eickhoff et al., 2009; Laird et al., 2005), with a false discovery rate of $p<0.001$ and a minimum cluster volume of 150 mm^3. ALE maps are displayed on the Colin27 in MNI space via Mango (ric.uthscsa.edu/mango/). The "Cerebellar Atlas" images in the right column show the corresponding slices from the MRI Atlas of the Human Cerebellum (Schmahmann et al., 2000). Experimental and pathological pain both activates vermal lobules IV/V, and bilateral hemispheric lobule VI. Abbreviations: contralateral to pain (C), Crus I (Cr I), ipsilateral to pain (I).

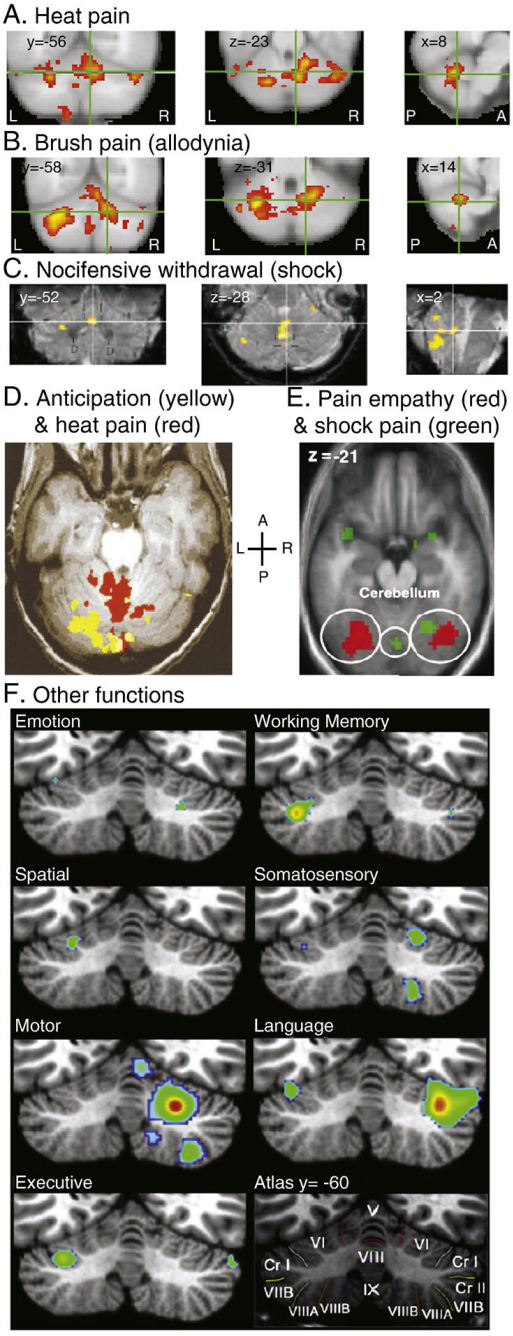

Figure 5.

Cerebellar fMRI activation relating to pain, motor, and non-motor functions. A) Noxious thermal stimuli (pain threshold +1°C) applied to the right side of the face in neuropathic pain patients (Borsook et al., 2008) **[with permission pending]**. Crosshairs indicate approximate location of globose/fastigial deep cerebellar nuclei. B) Brushing of allodynic (painfully sensitive) skin on the right side of the face in neuropathic pain patients (Borsook et al., 2008) **[with permission pending]**. Crosshairs indicate approximate location of dentate deep cerebellar nucleus. C) Nociceptive leg withdrawal from noxious electrical stimuli applied to the left tibial nerve (Dimitrova et al., 2003) **[with permission pending]**. Crosshairs indicate approximate location of fastigial deep cerebellar nuclei. D) Anticipation

of painful heat (yellow) and application of painful heat to the dorsum of the left hand (red) (Ploghaus et al., 1999) **[with permission pending]**. E) Observing one's partner feeling pain (red) and experiencing pain oneself (green) from noxious electrical stimuli applied to the dorsum of the right hand (Singer et al., 2004) **[with permission pending]**. F) ALE meta-analysis of cerebellar activation elicited by a variety of tasks (Stoodley and Schmahmann, 2009) **[with permission pending]**. Abbreviations: anterior (A), left (L), posterior (P), right (R).

Table 1

Functional neuroimaging of cerebellar activation in experimental and pathological pain studies.

A. Experimental pain					
Paper	**Method**	**Subjects**	**Stimulation**	**Site**	**Foci**
(Casey et al., 1996)	PET	9 (3F)	Thermode	L arm	1 (C)
			Cold water bath	L hand	1 (C)
(Hsieh et al., 1996)	PET	4 (3F)	Ethanol injection	R arm	2 (I)
(Svensson et al., 1997)	PET	11M	Laser	L arm	1 (I)
			Electric	L arm	1 (I)
(Xu et al., 1997)	PET	6M	Laser	L hand	2 (B)
(Derbyshire and Jones, 1998)	PET	12M	Hot water bath	R hand	1 (I)
(Iadarola et al., 1998)	PET	13 (5F)	Capsaicin injection	L arm	5 (B)
(May et al., 1998b)	PET	7M	Capsaicin injection	R forehead	3 (B)
(Paulson et al., 1998)	PET	10M	Thermode	L arm	2 (I)
		10F	Thermode	L arm	3 (B)
(Svensson et al., 1998)	PET	10 (4F)	Thermode (Tonic)	R arm	1 (I)
			Thermode (Phasic)	R arm	1 (I)
(Becerra et al., 1999)	fMRI	6M	Thermode (4x)	L arm	1 (I)
			Thermode (3x)	L arm	1 (I)
(Coghill et al., 1999)	PET	16 (7F)	Thermode	R arm	2 (B)
(Peyron et al., 1999)	PET	12 (?F)	Thermode	R arm (L flipped)	1 (B)
(Becerra et al., 2001)	fMRI	8M	Thermode	L hand	3 (B) early
					5 (B) late
(Casey et al., 2001)	PET	14 (4F)	Thermode	L arm	2 (B)
(Coghill et al., 2001)	PET	9 (5F)	Thermode	R arm	17 (B)
				L arm	15 (B)
(Witting et al., 2001)	PET	8 (2F)	Capsaicin injection	L arm	1 (C)
(Bingel et al., 2002)	fMRI	14 (1F)	Laser	R/L hand	2 (B)
(Brooks et al., 2002)	fMRI	18 (6F)	Thermode	R hand	2 (B)
				L hand	1 (I)
(Derbyshire et al., 2002)	PET	16 (11F)	Thermode	R hand	1 (C)
(Dimitrova et al., 2003)	PET	16 (5F)	Electric	L tibial nerve	13 (B)

A. Experimental pain					
Paper	**Method**	**Subjects**	**Stimulation**	**Site**	**Foci**
(Helmchen et al., 2003)	fMRI	12 (3F)	Thermode	R hand	16 (B)
(Koyama et al., 2003)	fMRI	9 (3F)	Thermode	R calf	1 (I)
(Nemoto et al., 2003)	PET	12 (6F)	Laser	R arm	2 (B)
(Strigo et al., 2003)	fMRI	7 (3F)	Balloon	Esophagus	4 (B)
			Thermode	Upper chest	5 (B)
(Derbyshire et al., 2004)	fMRI	8 (5F)	Thermode	R hand	1 (I)
(Giesecke et al., 2004)	fMRI	11 (4F)	Pressure	L finger	1 (I)
(Helmchen et al., 2004)	fMRI	16M	Thermode	R hand	2 (I)
(Ibinson et al., 2004)	fMRI	6 (3F)	Electric	R median nerve	1 (I)
(Kupers et al., 2004)	PET	10 (4F)	HT-saline injection	R face	3 (B)
(Wager et al., 2004)	fMRI	24 (?F)	Electric	R wrist	6 (I)
		23 (?F)	Thermode	L arm	6 (I)
(Botvinick et al., 2005)	fMRI	12F	Thermode	L hand	1 (I)
(Koyama et al., 2005)	fMRI	10 (2F)	Thermode	R leg	3 (B)
(Wiech et al., 2005)	fMRI	15 (5F)	Thermode	L arm	8 (C)
(Albuquerque et al., 2006)	fMRI	8F	Thermode	R face	2 (B)
(Carlsson et al., 2006)	fMRI	10 (3F)	Electric	R wrist	3 (B)
(Choi et al., 2006)	fMRI	18F	Hot water bath	L finger	3 (B)
(Farrell et al., 2006)	fMRI	10M	Pressure	L finger	1 (I)
(Kong et al., 2006)	fMRI	8M	Thermode	R arm	2 (B)
(Ruehle et al., 2006)	fMRI	13 (9F)	Electric (ICS)	R foot	3 (B)
			Electric (TCS)	R foot	3 (B)
(Oshiro et al., 2007)	fMRI	12 (6F)	Thermode	L leg	2 (B)
(Seminowicz and Davis, 2007)	fMRI	23 (12F)	Electric	L median nerve	0 (C)**
(Staud et al., 2007)	fMRI	13F	Thermode	R foot	1 (I)
(Borsook et al., 2008)	fMRI	12 (3F)	Thermode	R face	4 (B)*
(Helmchen et al., 2008)	fMRI	14M	Thermode	L hand	9 (B)
			Laser	L hand	9 (B)
(Tseng et al., 2009)	fMRI	12 (6F)	Thermode	R foot	2 (B)
B. Pathological pain					

Brain Res Rev. Author manuscript; available in PMC 2011 October 5.

Brain Res Rev. Author manuscript; available in PMC 2011 October 5.

A. Experimental pain

Paper	**Method**	**Subjects**	**Stimulation**	**Site**	**Foci**
Paper	Method	Subjects	Condition	Stimulation	Site	Foci
(Hsieh et al., 1995)	PET	4 (1F)	Neuropathy (L)	Spontaneous pain	L	1 (I)
		4 (3F)	Neuropathy (R)	Spontaneous pain	R varied	1 (C)
		8 (4F)	Neuropathy (R+L)	Spontaneous pain	R+L varied (no flip)	1
(May et al., 1998a)	PET	9M	Cluster headache	Triggered headache	L (R flipped)	1 (C)
(Petrovic et al., 1999)	PET	5 (3F)	Neuropathy	Brushallodynia (vs. rest)	R varied (L flipped)	4 (B)
				Brush allodynia (vs. touch)	R varied (L flipped)	4 (B)
(Derbyshire et al., 2002)	PET	16 (12F)	Back pain	Thermode	R hand	1
(Giesecke et al., 2004)	fMRI	11 (8F)	Back pain	Pressure	L finger	1 (I)
		16 (12F)	Fibromyalgia	Pressure	L finger	1 (I)
(Albuquerque et al., 2006)	fMRI	8F	Burning mouth	Thermal hyperalgesia	R face	1 (C)
(Becerra et al., 2006)	fMRI	6 (5F)	Neuropathy	Cold allodynia	R face	1 (I)*
				Brush allodynia	R face	2 (B)*
				Thermal hyperalgesia	R face	2 (B)*
(Ducreux et al., 2006)	fMRI	6 (?F)	Syringomyelia	Cold allodynia	R hand (L flipped)	1 (C)
(Schweinhardt et al., 2006)	fMRI	8 (4F)	Neuropathy	Brush allodynia	R hand (L flipped)	2 (B)
(Witting et al., 2006)	PET	9 (3F)	Neuropathy	Brush allodynia	L varied (R flipped)	1 (I)
(Geha et al., 2007)	fMRI	11 (10F)	PHN	Spontaneous pain	L varied (R flipped)	1 (I)*
(Borsook et al., 2008)	fMRI	6 (5F)	Neuropathy (R)	Thermode	R face	8 (B)*
				Brush allodynia	R face	19 (B)*
(Geha et al., 2008)	fMRI	11 (9F)	PHN	Brush allodynia	L varied (R flipped)	1 (C)*

*Continuous pain ratings collected during imaging.

**Did not report activation foci coordinates.

Abbreviations: B=bilateral, C=contralateral to stimuli, HT-saline=hypertonic saline, I=ipsilateral to stimuli, ICS=intracutaneous stimulation, TCS=transcutaneous stimulation

*Continuous pain ratings collected during imaging.

Abbreviations: B=bilateral, C=contralateral to stimuli, HT-saline=hypertonic saline, I=ipsilateral to stimuli, ICS=intracutaneous stimulation, PHN=postherpetic neuralgia

Table 2

Cerebellar stimulation modulates nociception.

Stimulus	Cerebellar site	Effect	Nociception	Animal	Paper
Electric	Anterior lobe (intermediate part)	Increased tail shock thresholds	↓	Squirrel Monkeys	(Siegel and Wepsic, 1974)
Morphine	Anterior (culmen region)	Increased acute analgesia	↓	Rats	(Dey and Ray, 1982)
Electric	Lateral nucleus	Modulated parafasicular neurons, Intralaminar thalamus	↑/↓	Rats	(Liu et al., 1993)
Electric	Posterior vermis (lobule VI)	Increased midline neuron activity in lumbosacral spinal cord	↑	Rats	(Saab and Willis, 2001)
DLH	Posterior vermis (lobule VI)	Increased midline neuron activity in lumbosacral spinal cord	↑	Rats	(Saab and Willis, 2001)
DLH	Cortex (vermis, lobule VIII)	Increased nociceptive reflexes (abdominal)	↑	Rats	(Saab and Willis, 2002)
DLH	Fastigial nucleus	Decreased nociceptive reflexes (abdominal)	↓	Rats	(Saab and Willis, 2003)

*DLH (D, L homocysteic acid) = nonspecific glutamate receptor agonist