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Causes and Consequences of Oscillations in the Cerebellar Cortex

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Cerebellar high-frequency oscillations have been observed for many decades, but their underlying mechanisms have remained enigmatic. In this issue of *Neuron*, two papers indicate that specific intrinsic mechanisms in the cerebellar cortex contribute to the generation of these oscillations. Middleton et al. show that $GABA_A$ receptor activation and nonchemical transmission are required for nicotine-dependent oscillations at 30–80 Hz and 80–160 Hz, respectively, while de Solages et al. provide evidence that recurrent inhibition by Purkinje cells is essential for oscillations around 200 Hz.

The olivocerebellar system and cerebral cortex are strongly connected through reverberating loops that are probably involved in sensorimotor control and cognitive processing (Figure 1A). So far, the vast majority of studies aimed at elucidating the mechanistic causes and functional consequences of the oscillations that occur within these systems have focused on the cerebral cortex (Sejnowski and Paulsen, 2006). Yet, the cerebellum also shows various sorts of oscillatory activities covering both the lower-frequency and the higher-frequency ranges (Table 1). At the lower frequencies these oscillations vary from slowly oscillating complex spike activities of Purkinje cells or slowly bursting activities of granule cells occurring at 2 to 10 Hz (delta band and theta band) to oscillating local field potentials that occur at 10 to 30 Hz (beta band). At the higher frequencies they vary from field oscillations at 30 to 80 Hz (gamma band) or 80 to 160 Hz (high-gamma band or very fast oscillations [VFOs]) to low-amplitude field potentials that oscillate at even higher frequencies of 160 to 260 Hz (here called very-high-frequency oscillations [VHFOs]). While it is clear that the preferred frequencies of the slowly oscillating complex spike activities and slow theta and beta rhythms originate in the inferior olive and granular layer, respectively (D'Angelo et al., 2001; Courtemanche and Lamarre, 2005; Van Der Giessen et al., 2008), the potential mechanisms that may underlie the high-frequency oscillations in the cerebellar cortex are largely unknown.

In this issue of *Neuron*, Middleton et al. (2008) and de Solages et al. (2008) show that these high-frequency rhythms can be generated without fast glutamatergic inputs to the cerebellum (cf. Cheron et al., 2008). Middleton et al. (2008) show in vitro in both murine and human tissue that one can induce field oscillations at the gamma and high-gamma band in coronal slices of crus I and II following application of physostigmine or nicotine, but not in coronal slices of other cerebellar regions or in sagittal slices in general. Using pharmacological blockage of $GABA_A$ receptors, these authors suggest that a combined input from GABAergic interneurons and Purkinje cells may be required to generate the gamma field potentials. The VFOs, on the other hand, may specifically require electrotonic coupling within a zonal region; the authors used five different types of gap junction blockers, and all of them affected the power of the VFOs. Moreover, they were able to show (in both molecular layer interneurons and a subset of Purkinje cells) so-called spikelets, which are subthreshold postjunctional potentials that usually reflect prejunctional full action potentials through a coupling mechanism. Combined with dye-coupling experiments, their data thus suggest that at least a subpopulation of Purkinje cells is directly coupled to molecular layer interneurons. Meanwhile, de Solages et al. (2008) investigated the potential mechanism underlying VHFOs. Using tetrode and multisite recordings in vivo, they show that VHFOs can occur in both anesthetized and awake rats and that they are probably largely

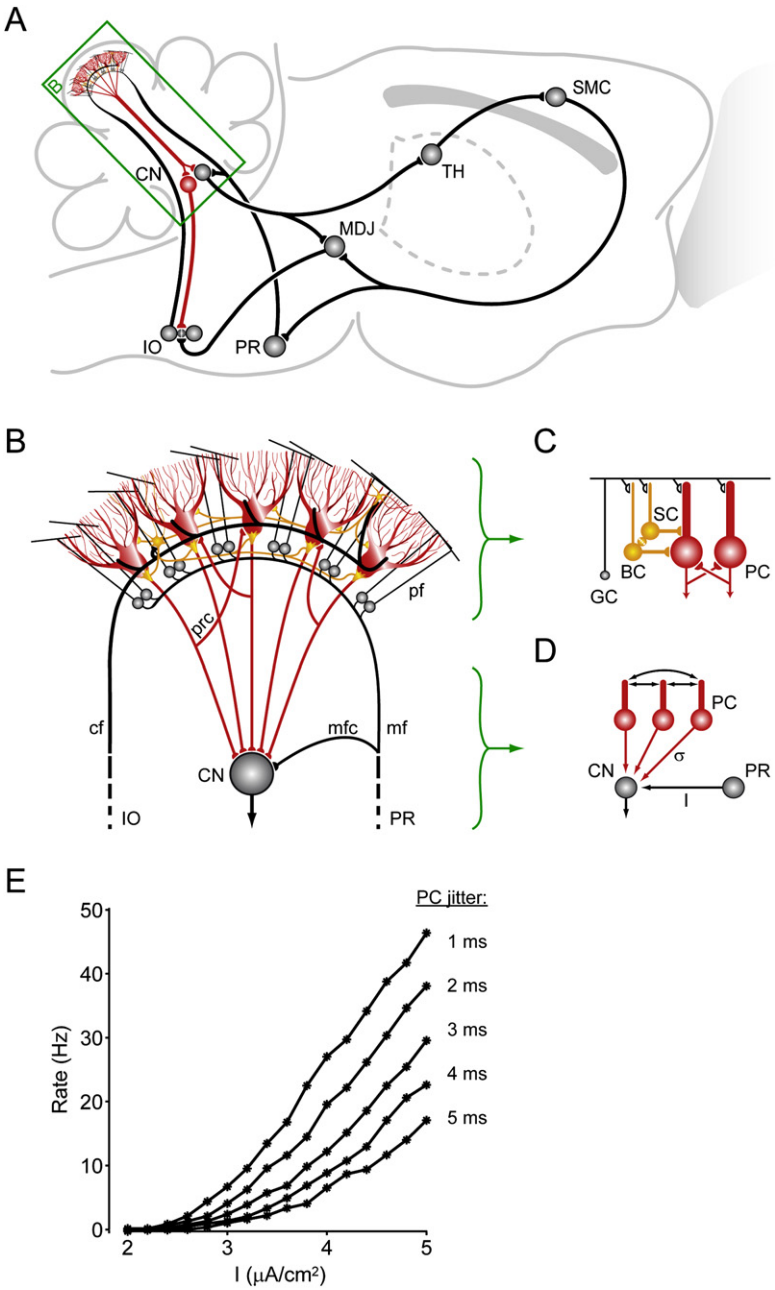

Figure 1. Schematic Drawing of Intracerebellar and Extracerebellar Connections Creating Local and Network Loops

(A) The cerebellum is connected with the cerebral cortex via the loops indicated. The cerebellar cortex receives main excitatory inputs (black) from the inferior olive (IO) and pontine regions (PR), and provides via the Purkinje cell axons an inhibitory feedback (red) to the cerebellar nuclei (CN). The outputs of the CN create a short loop by inhibiting the IO and two longer loops by exciting the mesodiencephalic junction (MDJ) and thalamus (TH). The TH excites various parts of the cerebral cortex such as the sensorimotor cortex (SMC), which in turn provides descending projections back to the PR and, via the MDJ, the IO. Note that the ultimate output connections of these systems, such as the pyramidal tract and oculomotor tracts that directly control the motor neurons, are not indicated in this drawing.

(B) Whereas the external IO and PR signals, which enter the cerebellum via the climbing fibers (cf) and the mossy fiber (mf)-parallel fiber (pf) pathway, are all excitatory, the local transmissions by the axons of the molecular layer interneurons (yellow) and recurrent collaterals (prc) of the Purkinje cells (red) are all inhibitory. Mossy fiber collaterals are indicated by mfc. Note that the climbing fiber collaterals and Golgi cell inhibition of granule cells (GC) are not depicted in this drawing.

(C) Molecular layer interneurons, i.e., basket cells (BC) and stellate cells (SC), are coupled by gap junctions (yellow), while Purkinje cells (PC) can influence one another via recurrent collaterals.

(D) As proposed in the main text and explained below, the level of synchrony in oscillating Purkinje cell activities might control the firing rate gain in the CN following excitation (I) by the mfcs. The PC spike-time dispersion (σ) is inversely related to the synchrony of this network oscillation.

(E) The CN firing rate versus mfc input current (I) plots are shown for different values of the PC jitter. As the jitter is decreased from 5 to 1 ms (from bottom to top), the gain of the CN responses to the excitatory mfc inputs is dramatically decreased. This interaction between mfc inputs and PC synchrony might be one of the potential mechanisms by which high-frequency oscillations in the cerebellar cortex exert their effects.

Panels (D) and (E) were modified from a cerebral network model with kind permission from Drs. Tiesinga and Sejnowski (see also Tiesinga et al., 2004 and Sejnowski and Paulsen, 2006).

reflecting Purkinje cell activities. Yet, they also show in an elegant fashion that the VHFOs can show fixed population frequencies independent from the firing rate of individual Purkinje cells. In contrast to that of the VFOs investigated by Middleton et al. (2008), the power of the VHFOs was reduced by complete blockage of all $GABA_A$ receptors. Since the power increased after pharmacological presynaptic suppression of the GABAergic input from the molecular layer interneurons alone, the authors suggest by exclusion that it must be the recurrent collaterals of the Purkinje cells that are essential for the generation of VHFOs. Due to the general sagittal orientation of the recurrent collaterals (Figure 1B), one might expect that the orientation of the VHFOs also follows a parasagittal-like pattern, but the authors convincingly show that the distribution is more patch-like. Thus, in this respect, the VHFOs more closely resemble the slower theta and beta oscillations generated in the granular layer, while the VFOs have a stronger tendency to follow the sagittal pattern of the slower oscillations generated in the olive (Table 1).

Even though the authors of both studies come a long way in elucidating the mechanisms underlying high-frequency oscillations in the cerebellum, a few issues remain to be resolved. The evidence that Middleton et al. (2008) provide for gap junctional coupling of Purkinje cells is certainly highly suggestive, but the strongest possible form of evidence for this phenomenon is still lacking: i.e., a direct demonstration of heptalaminar gap junctions

Table 1. Overview of Oscillatory Activities in Cerebellar Cortex and Their Presumptive Causes and Consequences

Oscillation Type	Frequency Band	Main Causal Substrates	Orientation in Cerebellar Cortex	Putative Functional Consequences	References
Complex spike oscillations (Delta/Theta)	1–4 Hz 4–9 Hz	olivary coupling and conductances	sagittal	- learning-dependent timing	Lang et al., 2006; Van Der Giessen et al., 2008
Theta oscillations	4–9 Hz	granule cell conductances	patchy	- assessment of sensory state - intermittent control of continuous movements	Hartmann and Bower, 1998 D'Angelo et al., 2001
Beta oscillations	10–30 Hz	granule cell and Golgi cell network	patchy	- cerebello-cerebral communication during sensorimotor processing and active and passive movements	Courtemanche and Lamarre, 2005 Soteropoulos and Baker, 2006
Gamma oscillations	30–80 Hz	molecular layer interneurons and Purkinje cells	transversal beam-like	?	Middleton et al., 2008
Very Fast Oscillations (VFO)	80–160 Hz	cerebellar cortical gap junctions	parasagittal-like	?	Middleton et al., 2008
Very High-Frequency Oscillations (VHFO)	160–260 Hz	recurrent collaterals	patch-like	?	de Solages et al., 2008

in the membrane of a Purkinje cell at the electron microscopic level. This final piece of evidence has been shown for coupling among molecular layer interneurons, but remains to be shown for any form of gap junction coupling with Purkinje cells. Moreover, once this observation is established, one should also attempt to find out which connexin is responsible for the formation of these gap junctions in adult animals and whether a knockout of this connexin leads indeed to an absence of VFOs. Similarly, it would strengthen their hypothesis if de Solages et al. (2008) could find an additional, more direct way to manipulate specifically the output of the recurrent collaterals of Purkinje cells. The evidence they provide here for the role of these collaterals in the generation of VHFOs is predominantly based on experiments in which they used the presynaptic endocannabinoid receptor agonist WIN 55,212-2 to suppress all inputs to Purkinje cells except that of the recurrent collateral input itself. However, WIN 55,212-2 also directly affects P-type calcium currents (Fisyunov et al., 2006), which are responsible for the majority of calcium influx in cerebellar Purkinje cells. So the finding that WIN 55,212-2 dramatically increases the oscillation power of VHFOs may not be solely due to a change in impact of the recurrent collaterals. In fact, a lack of calretinin and calbindin also directly leads to high-frequency oscillations, suggesting that a disturbance in calcium homeostasis in Purkinje cells can indeed also contribute to the generation of VHFOs (Cheron et al., 2008).

Regardless of the underlying mechanisms, questions remain as to what functions the various cerebellar oscillations may serve. Clearly, all oscillations generated in the cerebellar cortex, independent from whether they operate at low or high frequencies, will have to exert their effects in the end through the cerebellar and vestibular nuclei. The Purkinje cells form the sole output of the cerebellar cortex, and the neurons in the cerebellar and vestibular nuclei form, apart from the recurrent connections, their only target neurons (Figures 1A–1C). Since the firing rate and spike timing of these target neurons depend relatively strongly on the level of synchrony in their Purkinje cell inputs (Gauck and Jaeger, 2000), synchronized cerebellar oscillations may well in general evoke their effects downstream. So far, however, functional hypotheses have been virtually only proposed for cerebellar oscillatory activities that operate in the low frequency range. For example, synchronized delta and theta oscillations of complex spike activities generated in the inferior olive may be required for learning-dependent timing in response to unexpected events (Van Der Giessen et al., 2008), and local field potentials oscillating in the theta and beta band that are generated in the granular layer may be involved in preparing the system prior to the execution of movements (Courtemanche and Lamarre, 2005; Hartmann and Bower, 1998). Interestingly, the latter cerebellar cortical oscillations in the beta band synchronize optimally with those in the primary somatosensory cortex when the animal is expecting to make an active movement (Courtemanche and Lamarre, 2005), while single-unit activities of cerebellar nuclei neurons can synchronize with beta band field potentials in the primary motor cortex during the execution of a movement (Soteropoulos and Baker, 2006). So, at the lower frequencies, cerebellar oscillations can act in concert with oscillations in the cerebral cortex during specific stages of behavior.

But what about the higher frequencies as investigated by Middleton et al. (2008) and de Solages et al. (2008)? Can these high-frequency oscillations in the cerebellum also be related to behavioral paradigms? Data obtained with a recently developed space-time-frequency analysis method for MEG/EEG signals actually suggest that they in fact may do so at the level of the gamma and high-gamma band. Dalal and colleagues (2008) showed that the cerebellum reveals activities in the 65–90 Hz band or the 90–115 Hz band

during a self-paced finger movement task. Whether these high-frequency activities in the cerebellum can be coherent with those in other brain regions remains to be shown, but since Timofeev and Steriade (1997) demonstrated that thalamocortical cells show gamma band activities that are facilitated by their input from the cerebellar nuclei, this possibility should be looked into further. Whether a direct coherence between cerebellar and cerebral oscillating activities also occurs at the level of VHFOs is less clear at the moment. The finding that the power of the VHFOs in the awake rats was lower than that of the anesthetized rats (de Solages et al., 2008), and the fact that VHFOs spontaneously occur in mouse mutants with a compromised calcium metabolism in their cerebellar network, but not in their wild-type littermates (Cheron et al., 2008), raise doubts about this possibility. So, future studies should be designed to find out to what extent the high-frequency oscillations reflect merely an irrelevant echo of reverberating activities within the cerebellar cortex or cerebello-cerebral network, or whether they serve behaviorally relevant functions.

Still, one can easily imagine that they may contribute to signal processing in the cerebellar system in general. First, cerebellar oscillations operating at these high frequencies could, under particular circumstances, act well together with oscillations of lower frequencies at other regions (Jacobs et al., 2007; Canolty et al., 2006). In principle, such cross-frequency phase synchronization could even occur within the olivocerebellar system itself, in which for example the olivary neurons operate at the lower-frequency bands (Lang et al., 2006), while the Purkinje cells resonate at higher frequencies on the beat of the olivary climbing fiber rhythm. In this respect, it is important to note that the excitatory cerebellar nuclei neurons that project to the thalamus and the inhibitory nuclei neurons that provide feedback to the olive are innervated by the same individual Purkinje cell axons (Figure 1A), while the electrical architectures of these two types of neurons differ considerably in that they are better designed for tonic and phasic control, respectively (Uusisaari et al., 2007). So, different cerebellar rhythms may coexist and their underlying networks can still, at least partly, be shared. Second, apart from potential interactions with other oscillations, the high-frequency oscillations may also directly contribute to general computational processes including representation of information, regulation of information flow, and storage and retrieval of information (Sejnowski and Paulsen, 2006). For example, the information flow of the mossy fiber collateral input through the cerebellar nuclei neurons could benefit from a properly timed high-frequency oscillation in the inhibitory Purkinje cells such that the actual firing frequency of the nuclei neurons is largely dependent on the timing and phase of this oscillation (Figures 1D and 1E) (for analogy with cerebral cortical network model, see Tiesinga et al. [2004]). Similarly, the oscillations could help to retrieve information embedded in the temporal patterns of the simple spike activities by synchronizing their impact in the cerebellar nuclei neurons (Shin et al., 2007). Such patterns can show variances in the order of 5 to 10 ms, which are compatible with the ranges of high-frequency oscillations in the cerebellar cortex. Thus, it will be interesting to find out whether the high-frequency oscillations described here by Middleton et al. (2008) and de Solages et al. (2008) can indeed serve, just like the low-frequency oscillations, as a fundamental computational mechanism for the implementation of a temporal coding scheme that enables fast processing and memory retrieval.

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