

Alexandre Mathy and Beverley A. Clark

---

## Abstract

The inferior olive gives rise to the climbing fiber input to cerebellar Purkinje cells and is therefore the source of one of the most powerful synapses in the brain, generating a large burst of Purkinje cell activity referred to as the complex spike. The timing of complex spikes plays a key role in theories of cerebellar function and the determinants of the temporal output structure of neurons of the inferior olive are thus of critical importance. Olivary neurons display spontaneous subthreshold oscillations (STOs) that are generated by the interplay of intrinsic voltage- and calcium-gated conductances and electrotonic coupling between groups of neurons that consequently oscillate in synchrony. Olivary action potentials are also complex, consisting of an initial spike followed by a plateau potential that drives a burst of axonal action potentials. The STOs can influence the timing of spike output and the number of spikes in this burst, implicating them in important downstream effects in the cerebellar cortex, such as complex spike timing and synchrony, and synaptic plasticity. STOs and the coupling between olivary neurons can be modified by extrinsic input, a key candidate being the afferent inhibitory connections forming the descending limb of the olivocerebellar loop. This may result in an olivary network with dynamic properties, which has led to theories of the olivocerebellar system as a generator of spatiotemporal patterns of firing. This chapter discusses evidence for these and competing models, as well as their implications for the production of motor rhythms.

---

A. Mathy • B.A. Clark (✉)

Wolfson Institute for Biomedical Research, University College London, Gower Street, London, WC1E 6BT, UK

e-mail: ardm2@cantab.net, b.clark@ucl.ac.uk

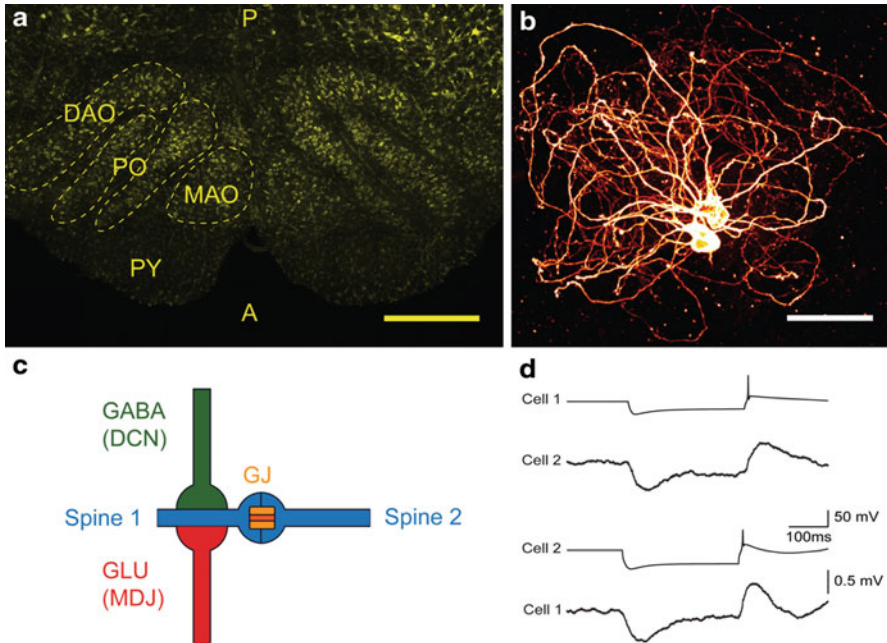
## Introduction

The climbing fiber input to cerebellar Purkinje cells represents one of the strongest synaptic connections in the brain, generating unitary postsynaptic excitatory conductances so powerful that this single input generates a massive spike burst known as the complex spike, accompanied by widespread increases in intracellular calcium concentrations. The magnitude of this response alone implies that it represents a very important signal within the cerebellar system, and as such it has been proposed to have a range of important functions including acting as an error signal to trigger associative plasticity at parallel fiber synapses (Albus 1971; Ito 2001; Marr 1969). However, the climbing fiber signal is not only very large but is attributed with two other important features: firstly, under some circumstances, complex spikes can be periodic, suggesting that they represent a timing signal that regulates Purkinje cell output. Secondly, synchronous complex spike activity can occur across organized populations of Purkinje cells and so it is possible that climbing fiber input may assemble certain functional subpopulations. The source of both of these complex spike characteristics must reside in the properties of the neurons of the inferior olivary nuclei in the brainstem, which give rise to the climbing fibers.

The intimate association between the cerebellum and the inferior olivary (IO) nuclei of the brainstem was recognized long before electrophysiological recordings or detailed anatomical data were available, mostly from the studies where cerebellar lesions resulted in degeneration of this nucleus (Klimoff 1899; Keller 1901; Ramon y Cajal 1909). The substrate for this relationship became clear with the discovery that the climbing fiber pathway is composed of the axons of olivary neurons (Szentagothai and Rajkovits 1959; Eccles et al. 1966), and that activity in the cerebellar cortex is in turn fed back to the IO via the inhibitory output of the deep cerebellar nuclei (DCN) (de Zeeuw et al. 1989) in a topographically organized manner (Szentagothai and Rajkovits 1959; De Zeeuw et al. 1998; Apps and Garwicz 2005). Often referred to as the *olivocerebellar system*, one of its presumed functions is the generation of spatiotemporal patterns of neural activity (Jacobson et al. 2008) that, ultimately, modulates the output of the motor system to produce smooth movement. Underlying this view is the ever-increasing evidence that the IO has remarkable oscillatory properties, tempting the researchers to see the olive as a kind of clock that can provide a timing signal for coordination of cerebellar activity. This is a controversial view, however, and is not widely accepted. This chapter will review the evidence for the existence of such a clock, what makes it tick, and how it may direct cerebellar responses.

## Basic Features of the Inferior Olive

Located bilaterally in the medulla oblongata, the inferior olives are composed of four subnuclei: the Principal Olive, the Medial and Dorsal Accessory Olives (Fig. 44.1a), and the Dorsal cap of Kooy (De Zeeuw et al. 1998). The neurons



**Fig. 44.1** Anatomy of the inferior olive. (a) Nissl stain of a transverse section through the medulla oblongata showing the subnuclei of the inferior olive. *MAO* medial accessory olive, *DAO* dorsal accessory olive, *PO* principal olive, *P* posterior, *A* anterior (scale bar 500  $\mu\text{m}$ ). (b) Two adjacent olivary neurons filled with biocytin (scale bar 50  $\mu\text{m}$ ). (c) Olivary neurons are electrically connected via gap junctions between their spines, which also receive both excitatory and inhibitory input, forming a trisynaptic junction. (d) Whole cell patch clamp recording from a pair of coupled olivary neurons showing bidirectional transfer of slow voltage components in response to a current injection in one and then the other neuron, but little coupling of action potentials (seen here as rebound spikes)

contained in these nuclei are almost exclusively projection neurons, and can be divided into two morphologically distinct populations defined by their dendritic arborizations: a phylogenetically more ancestral type carrying a small number of straight dendrites, and a type with a more complex dendritic tree characterized by multiple curling dendrites (Fig. 44.1b) (Scheibel and Scheibel 1955). The cells make no chemical synapses between each other, but are extensively electrotonically coupled by gap junctions (Llinas et al. 1974; Sotelo et al. 1974). These are thought to be composed principally of connexin 36 and to occur mainly between dendritic spines (De Zeeuw et al. 1995, 1997).

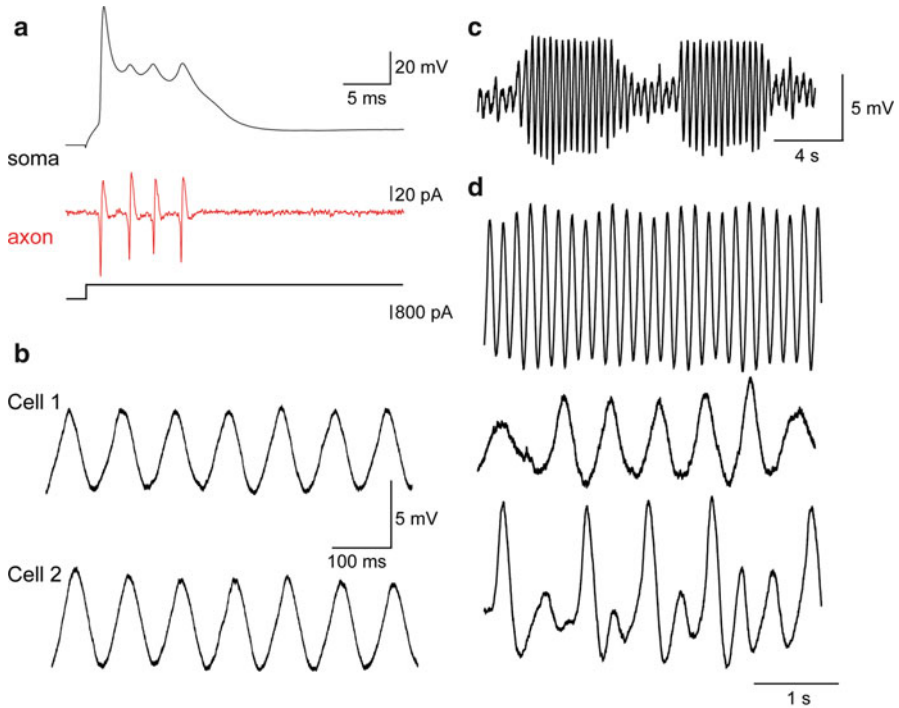
The axon of each olivary neuron ascends across the midline of the brainstem, where it ultimately branches to form approximately ten collaterals, each of which extends into the cerebellar cortex as a climbing fiber and innervates a single Purkinje cell. The climbing fibers from a given olivary neuron innervate a sagittally oriented band of cerebellar cortex called a microzone (Apps and Garwicz 2005) and the activity of Purkinje cells in this zone targets the DCN

which in turn projects to the same area of the IO, thereby closing an olivocerebellar loop (De Zeeuw et al. 1989). Olivary axon collaterals also project directly to the DCN (De Zeeuw et al. 1997). The inferior olive receives direct excitatory input from spinal afferents and cortical areas, and these two sources are shown to converge in the IO (Pardoe et al. 2004). The principal and accessory olives receive considerable multimodal sensory input via these pathways (Armstrong 1974; Gellman et al. 1983). Both inhibitory and excitatory inputs innervate the dendritic spines of IO neurons frequently forming a trisynaptic glomerular structure containing a dendrodendritic gap junction as well as chemical synapses (Fig. 44.1c) (De Zeeuw et al. 1989). Importantly, the inferior olive also receives a dense serotonergic input from other brain stem nuclei (Takeuchi and Sano 1983; Bishop and Ho 1986).

## Excitable Properties of IO Neurons

The excitable properties of olivary neurons result from a rich interaction between a number of different voltage-gated conductances: high-threshold calcium channels, calcium-activated potassium channels (BK), and hyperpolarization-activated cation channels ( $I_h$ ) in the dendrites and low-threshold calcium channels, calcium-activated potassium channels (SK), and sodium channels in the soma (Llinas and Yarom 1981a, b; Bal and McCormick 1997). The relative availability of this complex variety of channels, in conjunction with the electrical coupling between cells, means that olivary neurons can display a range of activity states including quiescence, subthreshold oscillations (STOs), and rhythmic firing. Understanding what drives these cells to transition between these activity states is essential to determining the role of climbing fiber activity in cerebellar function.

When olivary neurons are depolarized to spike threshold, a complex somatic response occurs (Fig. 44.2a), consisting of an initial fast sodium spike followed by a broad after-depolarization (ADP) on which a number of high-frequency (130–450 Hz) spikelets are superimposed. This is usually followed by a prolonged after-hyperpolarization (AHP). Both the fast sodium spike and the spikelets of the plateau phase originate in the axon as full amplitude action potentials (Mathy et al. 2009; Crill 1970) and drive a burst of multiple excitatory postsynaptic potentials (EPSPs) in their Purkinje cell targets (Maruta et al. 2007; Mathy et al. 2009; Armstrong and Rawson 1979). High-threshold dendritic calcium currents generate the ADP (Llinas and Yarom 1981a) and, while they sustain depolarization at the soma, their effect is attenuated at the axon spike initiation zone (Mathy et al. 2009). Consequently, while somatic sodium channels remain largely inactivated during this phase, axonal sodium channels remain available at sufficient density to sustain a high-frequency burst of axonal spikes, manifest at the soma as small spikelets. The ADP is curtailed by large and small calcium-activated potassium channels that underlie the AHP (Llinas and Yarom 1981a; Benardo and Foster 1986; Lang et al. 1997). The presence of low-threshold (T-type) calcium channels at the soma, which become de-inactivated by the AHP, can give rise to a rebound depolarization which,



**Fig 44.2** Excitable properties of olivary neurons (a) Simultaneous patch clamp recordings from the soma (whole cell) and axon (cell attached) of an olivary neuron in vitro. Depolarization by a somatic current step triggers a large amplitude action potential followed by an after-depolarization upon which are superimposed small wavelets. In the axon, these are full amplitude action potentials (from Mathy et al. 2009 copyright 2009 Cell Press). (b) Paired recording from two olivary neurons in vitro showing synchronous sinusoidal STOs of the membrane potential. (c) Example of olivary recording in which the STOs show prominent intermittent amplitude modulation. (d) Recording from three olivary neurons in vitro, demonstrating diversity in shape and frequency of STOs

if large enough, will trigger another spike and the cycle may be repeated, generating rhythmic firing.  $I_h$  regulates the rate of rise of the rebound depolarization (Bal and McCormick 1997) and so can modulate the firing frequency.

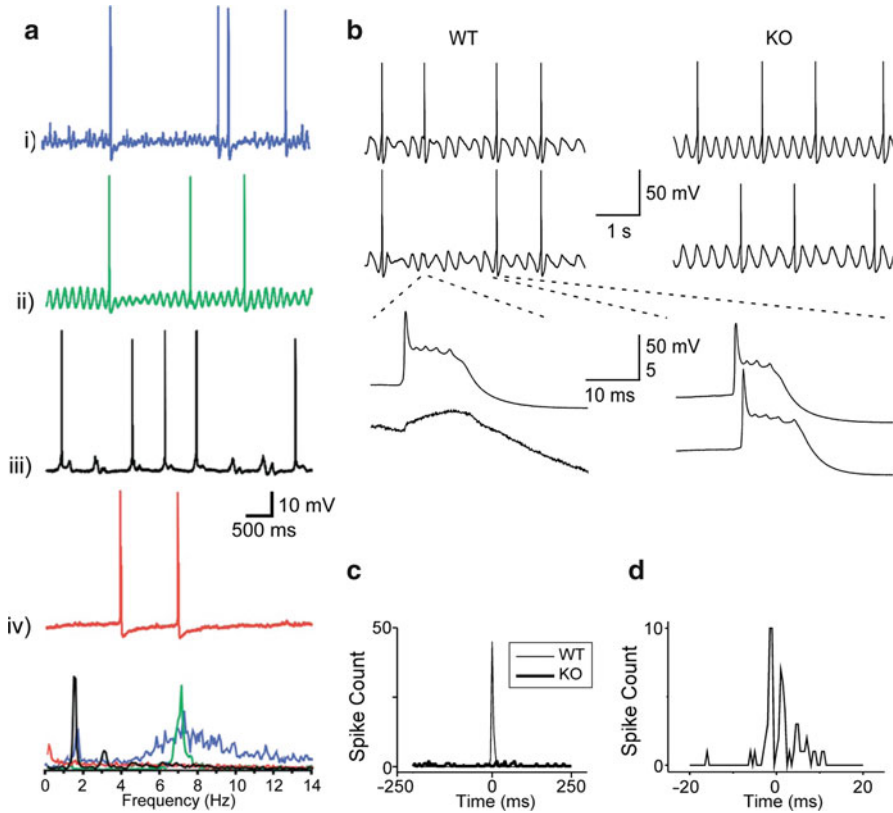
### Subthreshold Oscillations

Administration of harmaline, an alkaloid drug that induces a fine motor tremor at a frequency of around 10 Hz (de Montigny and Lamarre 1973, 1974; Llinas and Volkind 1973), was found to cause rhythmic activity at the same frequency in cerebellar cortex and in inferior olive. The activity in Purkinje cells was entirely composed of complex spikes with suppression of simple spikes and, since cerebellar but not olivary rhythmic activity was curtailed by surgical separation of the

cerebellar cortex from the brain stem, the olivary neurons were confirmed to be the source of this activity. The concurrent tremor and rhythmic spike output was interpreted as evidence that oscillatory activity in the IO could be important in the generation of motor programs.

It is now well established that olivary neurons can spontaneously generate endogenous STOs (see Fig. 44.2b), which can also be induced by harmaline. STOs have been observed *in vitro* in isolated brain slices (Benardo and Foster 1986; Llinas and Yarom 1986; Bleasel and Pettigrew 1992; Bal and McCormick 1997; Placantonakis et al. 2000; Placantonakis and Welsh 2001; Devor and Yarom 2002a, b; Leznik et al. 2002; Long et al. 2002; Leznik and Llinas 2005; Placantonakis et al. 2006; Mathy et al. 2009; Choi et al. 2010; Welsh et al. 2011) across several species (guinea pig, rat, mouse, ferret, monkey) and, more recently, *in vivo* in anesthetized animals (Chorev et al. 2007; Khosrovani et al. 2007; Van Der Giessen et al. 2008). They occur at 1–10 Hz, are 1–20 mV in amplitude, are often sinusoidal in character, and are found in all olivary subnuclei except the Dorsal Cap of Kooy. The STOs are heterogeneous (Fig. 44.2c, d); *in vivo* they can be categorized into two main types (Devor and Yarom 2002a, b; Khosrovani et al. 2007): LTOs (low-threshold oscillations in the 1–3 Hz range) and SSTOs (sinusoidal subthreshold oscillations in the 6–9 Hz range) (Fig. 44.3a). They can be transient or sustained and can show continual amplitude modulation over time. How ubiquitous STOs are to olivary neurons is not yet clear. Their occurrence varies considerably between reports with some studies describing relatively infrequent STOs (Llinas and Yarom 1986) requiring hyperpolarizing current injections, synaptic stimulation, or increased extracellular potassium concentrations to trigger them, while others show that they occur in most neurons sampled (e.g., 90% Benardo and Foster 1986, 85% in (Khosrovani et al. 2007)). These differences may be due to various factors including the species employed, the details of the slice preparation and anesthesia protocols used, as well as the criteria applied for positively identifying the presence of STOs. Importantly, the cells of Dorsal Cap of Kooy do not generate any subthreshold oscillations (Urbano et al. 2006), indicating that the floccular olivocerebellar system (involved in eye movements) may operate using different principles in comparison to the rest of this network. As well as variability in occurrence, the character of the oscillations is also somewhat controversial. In some cases, highly stable STOs are observed that persist throughout a recording (Khosrovani et al. 2007), while in others, oscillations are either frequently interrupted by periods of quiescence or they show considerable amplitude and frequency modulation (Devor and Yarom 2002b; Chorev et al. 2007). What underlies the STOs, their initiation, maintenance, amplitude, and frequency is fundamental to their proposed role of rhythm generators in the olivocerebellar system.

All of the voltage- and calcium-dependent conductances involved in generating olivary spike output could potentially be involved in generating these STOs. The original observations of STOs in inferior olivary slices demonstrated that voltage-gated sodium currents do not play a role in their generation they are resistant to the sodium channel antagonist tetrodotoxin. They are, however, sensitive to calcium



**Fig. 44.3** Oscillations, coupling, and spike output in the IO. (a) Different types of subthreshold activity and spontaneous firing observed using whole cell patch clamp recording in vivo (from Khosrovani et al. 2007 copyright 2007 National Academy of Sciences, USA): (1) a neuron showing both SSTOs and LTOs; (2) a neuron showing SSTOs alone; (3) LTO activity; (4) a neuron showing no STOs of either variety. Power spectra of the four recordings. (b) Action potential synchrony during oscillations in coupled olivary neurons. Paired whole cell recordings in vitro from wild-type (WT, *left*) and connexin-36 knockout mice. STOs are present in both mouse strains but are only synchronous in the wild-type. Lower panel shows that, in WT, spontaneous action potentials in one cell are accompanied by either junctional potentials (*left*) or action potentials (*right*) in the coupled cell. (c) Spike cross-correlogram (5 ms bin width) of the data shown in **b** shows a peak at 0 ms in WT indicating spike synchrony, but no peaks in the knockout. (d) Same data shown with finer temporal resolution (0.5 ms bin width) (reproduced with permission, Long et al. 2002)

channel blockers or removal of calcium from the bath (Benardo and Foster 1986; Llinas and Yarom 1986). Injection of either depolarizing or hyperpolarizing current injection does not block the STOs but changes their amplitude and shape. The relationship between amplitude and membrane potential is parabolic, with a maximum close to the resting potential (Benardo and Foster 1986; Long et al. 2002; Leznik and Llinas 2005). The smaller amplitudes at more depolarized and

hyperpolarized potentials are consistent with a change in availability of the high- and low-threshold voltage-gated calcium channels present in olivary neurons.

By using two lines of knockout mice, one lacking the high-threshold P-/Q-type ( $\text{Ca}_v2.1$ ) calcium channel and the other the low-threshold T-type ( $\text{Ca}_v3.1$ ) channel it has recently been shown that, while both of these conductances are certainly involved in STO generation, lack of the T-type channel has the most deleterious effects by greatly reducing the number of oscillating cells and strongly suppressing the amplitude of remaining oscillations which also become voltage-independent (Choi et al. 2010). Harmaline administration to the  $\text{Ca}_v3.1$  knockout mice fails to induce tremor, suggesting that the mechanism underlying the action of this drug is a reduction in the threshold for T-type calcium channel activation (Park et al. 2010). As with rhythmic firing,  $I_h$  also plays a key role in STO generation (Bal and McCormick 1997) both by keeping the membrane potential within the window for T-type calcium channel activation and by providing the initial depolarizing trajectory out of the hyperpolarizing phase to reach T-type channel threshold. This generates STOs of a higher frequency than could be achieved with calcium channels and calcium-activated potassium channels alone. In simple terms, STOs are principally generated by low-threshold calcium spikes that are regulated by SK-type calcium-activated potassium channels and  $I_h$ . When SK channels are blocked in the IO, the rate of complex spike activity in cerebellum increases, but it loses rhythmicity (Lang et al. 1997).

### Gap Junctions and Synchrony

In addition to their reliance on intrinsic voltage-gated conductances, there is strong evidence that STOs are also a network phenomenon driven via the electrotonic coupling between IO cells. STOs are tightly synchronized among groups of coupled IO neurons (Benardo and Foster 1986; Devor and Yarom 2002a, b; Long et al. 2002) indicating that the intrinsically generated currents can also flow within the network. During development, oscillations emerge at the same stage as gap junctions, despite the earlier presence of the voltage-gated channel conductances that drive them (Bleasel and Pettigrew 1992). This leads to the question: Are STOs the result of summed network activity or are individual olivary neurons capable of generating STOs in isolation? Although depolarization and hyperpolarization reduce the amplitude and modulate the frequency of STOs, they cannot be blocked completely by changes in the membrane potential (Benardo and Foster 1986) which would be expected to suppress the voltage-gated channels involved in their generation. A gap junctional blocker,  $18\beta$ -glycyrrhetic acid ( $18\beta$ -GA), which substantially reduces dye-coupling between olivary neurons, enhances the voltage-dependent changes in amplitude and frequency of STOs (Leznik and Llinas 2005), leading to their absence at more positive and negative membrane potentials. In connexin 36 knockout mice, the oscillations are still present, displaying a similar voltage dependence to those in  $18\beta$ -GA, but are not synchronized between cells (Long et al. 2002) (Fig. 44.3b–d). Possible compensatory mechanisms observed in these knockout mice, including changes in both morphology and excitability, makes the interpretation of the effects of removing connexin 36 problematic



(De Zeeuw et al. 2003). However, the use of lentiviral-mediated knockdown of connexin 36 in the IO has confirmed that, in order to support STOs, olivary neurons do need to be coupled to a small ensemble of other IO cells (Placantonakis et al. 2006). It seems, therefore that, while olivary neurons are intrinsically oscillatory, sustained large amplitude oscillations may only occur when the cells are part of a coupled neuronal ensemble supporting intercellular current flow (Lampl and Yarom 1997; Manor et al. 2000).

The synchronization of oscillations in the IO results in temporal coherence of complex spike activity across populations of Purkinje cells beyond the microzonal organization of a single olivary projection (Lang et al. 1999; Schultz et al. 2009; Bell and Kawasaki 1972; Ozden et al. 2009). Voltage-sensitive dye imaging in IO slices has been used to characterize the spatial profile of STO synchrony across the olivary network with some mixed results. In one case (Leznik et al. 2002), after a brief electrical stimulus, the IO showed synchronous STO clusters, estimated to contain many hundreds of neurons, which were reliant on gap junction connectivity (Leznik and Llinas 2005). In another case (Devor and Yarom 2002b), patches of spontaneous or stimulus-evoked STOs were observed within which the oscillations were not spatially stationary but instead propagated rapidly in a wave-like manner throughout the local network resulting in the establishment of phase differences between cells. In agreement with this, *in vivo* multi-electrode array recordings of Purkinje cell complex spike activity in awake rats (Jacobson et al. 2009) suggest that, rather than being exactly in phase, stable phase differences can exist between neurons which oscillate at the same frequency. A networked compartmental model of olivary neurons (Schweighofer et al. 1999) demonstrated that these phase differences can be achieved by variations in coupling strength between the oscillating neurons.

It is still unresolved how large an oscillating cluster of cells is. A dye-coupling study suggests olive cells are directly coupled to a varying small number of cells (up to 35) contained within their dendritic field (Hoge et al. 2010). The voltage-sensitive dye studies, however, conclude that a synchronous cluster extends beyond this small neighborhood, and can contain between 100 and 2,000 cells (Leznik and Llinas 2005; Devor and Yarom 2002b). It is also known that olivary dendrites can sometimes extend across the midline to make contacts with the contralateral olive (De Zeeuw et al. 1996), which is reflected in the presence of bilateral climbing fiber synchrony in the cerebellum.

## Oscillations and Olivary Output

What is the impact of STOs on olivary spike output? There is much support for the idea that they precisely and periodically time output (the “clock” hypothesis), with spikes occurring solely at the peak of any cycle, but this is controversial. While olivary neurons have been shown *in vivo* to preferentially fire at the crest of an oscillation (Chorev et al. 2007), spikes can also occur across a broader range of the oscillatory cycle (Khosrovani et al. 2007). These differences may be due, at least in part, to the variation in STO amplitude, with larger and faster rising STOs leading to

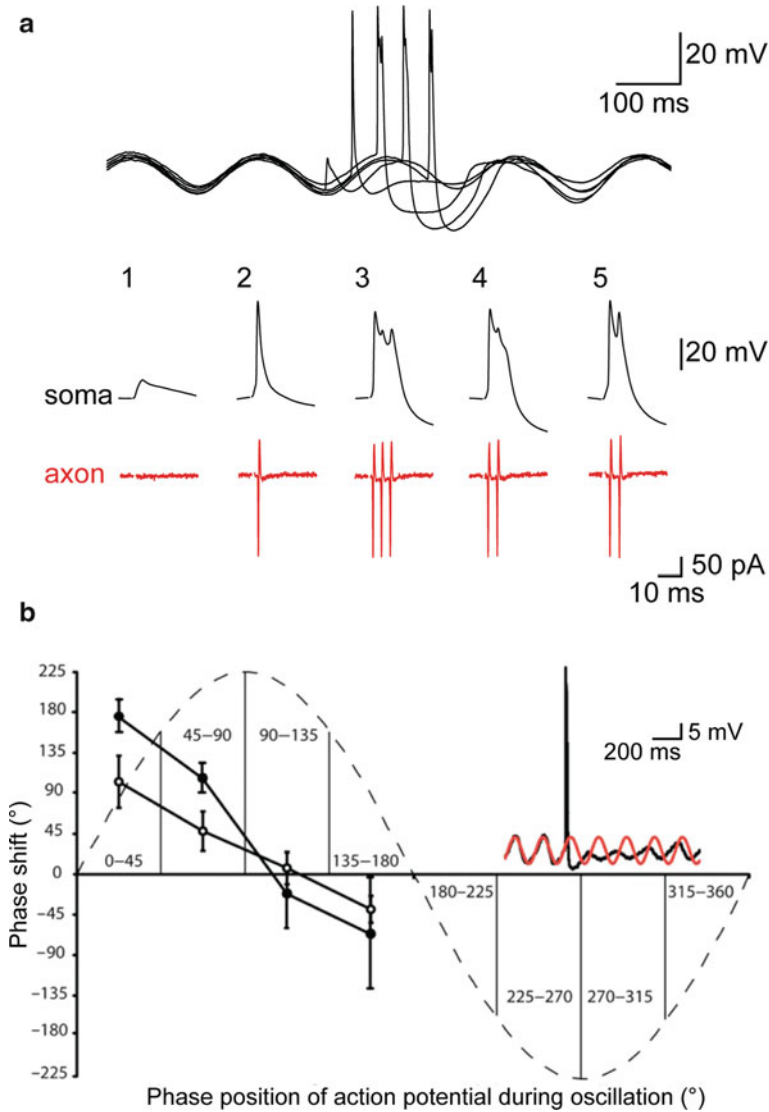
peak-locked spikes and smaller, slower STOs showing more variation in spike timing. Little is known about the synaptic weight of excitatory inputs to olivary neurons, but synaptic diversity will also likely play a role in timing of output relative to STO phase. It is by now certainly clear that IO neurons do not function as simple, autonomous pacemaker cells. Block of glutamatergic input into the IO showed that in vivo firing rates drop by 50% (Lang 2001), indicating that spike output is both extrinsically and intrinsically generated. It has been argued, based on observations in vitro, that afferent-evoked responses are delayed until the peak of an oscillation (Lampl and Yarom 1993) but the mechanism for this is poorly understood and this is not consistently observed (Mathy et al. 2009). This idea is also contradicted by data showing that, in vivo, olivary neurons respond with short latencies to somatosensory stimuli (Gellman et al. 1985). Recent findings suggest that, rather than restricting spike output to occur only at the peak of the oscillation, the cycle phase at which excitation occurs can determine the number of axonal spikes initiated during the complex burst response of an olivary neuron (Fig. 44.4a). This could provide a means by which the cerebellar cortex could extract information about the cycle origin of climbing fiber input and, as a consequence, attribute new learning rules that incorporate this information (Mathy et al. 2009).

## Extrinsic Control of Oscillations

If, as many suspect, subthreshold oscillations are the substrate for generating motor rhythms, it is important to know what can modify and shape them. The variability of the oscillations within and between cells suggests that modulation occurs physiologically. The plausible loci for affecting the oscillations are the ion channels involved in rhythmogenesis, the afferent synaptic pathways into the nucleus, and the electrical coupling between the neurons.

It is discussed above how pharmacological and genetic approaches have dissected out the ion channels responsible for generating STOs. Whether modulation of these channels is engaged physiologically for shaping oscillations is as yet unknown, but plausible. For instance, it is known that the  $I_h$  current – important in the generation of oscillations – is extremely plastic in other neurons (van Welie et al. 2004). Recently, it was shown in monkeys that chronic alcohol abuse followed by abstinence can modulate both  $I_h$  and the low-threshold calcium current in the olive, and this might underlie the intention tremor that alcoholics can experience upon withdrawal (Welsh et al. 2011).

The IO receives a significant serotonergic input from the nucleus reticularis paragigantocellularis (Bishop and Ho 1984, 1986). In vitro application of serotonin suppresses oscillations (Placantonakis et al. 2000), thought to be via potentiation of  $I_h$  and suppression of the T-type calcium current. Interestingly, serotonin also strongly suppresses excitatory synaptic inputs in the IO (Best and Regehr 2008) through a retrograde, endocannabinoid mediated pathway. In vivo recordings have provided conflicting data as to whether serotonin decreases (Headley et al. 1976) or increases (Sugihara et al. 1995) rhythmicity in the olive.



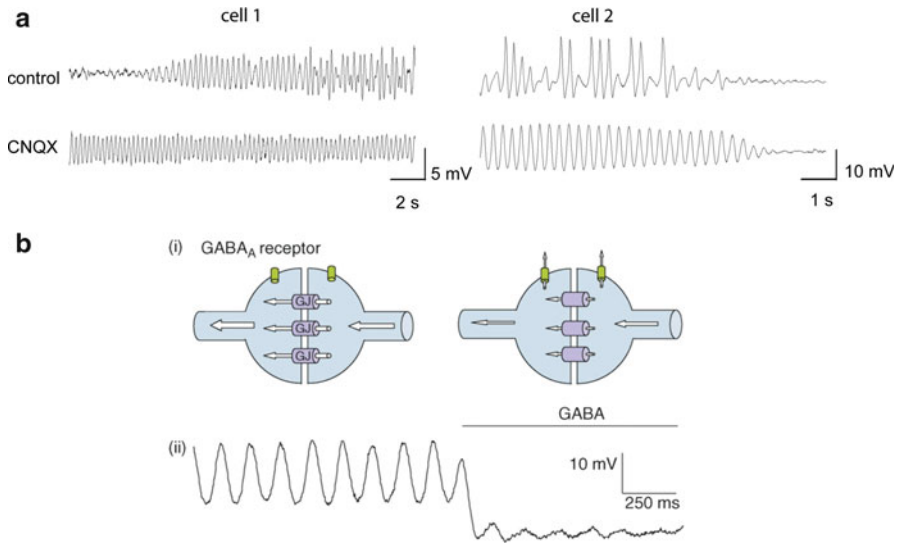
**Fig. 44.4** (a) Dependence of number of output spikes on STO phase. *Top panel* shows overlay of five somatic responses of an olivary neuron in vitro to synaptic stimulation during STOs generated by sinusoidal (5 Hz) current injection. EPSPs were triggered by single synaptic stimuli (*arrow heads*), timed to occur at different phases of the STO. *Lower panel*: same somatic responses on an expanded timescale and, below, simultaneously recorded axonal spikes from the same cell (from Mathy et al. 2009 copyright 2009 Cell Press). (b) In vivo phase response curves generated from neurons showing SSTOs with spontaneous (*open circles*) or stimulated (peripheral stimulation, *closed circles*) action potentials. The phase of the oscillation was reset when the spikes did not occur at the peak of the STOs. Inset shows recorded membrane potential (*black*) superimposed with a sinusoidal fit (*red*) to the data prior to the occurrence of the action potential (from Khosrovani et al. 2007 as above)

Interestingly, activation of glutamate receptors has also been shown to interfere with oscillations in several different ways. Glutamatergic input will activate both AMPA and NMDA receptors in IO cells (Best and Regehr 2008). In vitro application of NMDA receptor antagonists has been shown to block STOs, while application of NMDA causes oscillations sensitive to L- and P-type calcium channel antagonists (Placantonakis and Welsh 2001) but not to TTX. This seems to implicate excitatory input in the generation of STOs via a calcium current. Blocking AMPA receptors with CNQX, on the other hand, stabilizes the oscillations (Devor and Yarom 2002b), which could plausibly be due to an increased input resistance and a reduced shunting of the intercellular currents through gap junctions (Fig. 44.5a). When a large excitatory input triggers a spike, the subthreshold oscillation resets to a given phase (Khosrovani et al. 2007; Llinas 2009). In other words, depending at which oscillatory phase the spike occurs, the oscillation is advanced so that after the spike the oscillation is always at the same phase (Fig. 44.4b). This is a network phenomenon affecting many cells simultaneously, and has been hypothesized to represent the retrieval of a new motor program in the olivocerebellar system.

The inhibitory pathway from the deep cerebellar nuclei to the IO is thought to play a key role in gating responses to excitatory input (Kim et al. 1998) and may do this to some extent by influencing the STOs (Fig. 44.5b). The peculiar synaptic organization within the olive, with GABAergic synapses placed adjacent to gap junctions, led to the suggestion in the 1970s that a role of inhibitory input from the DCN might be to uncouple the olivary neurons by shunting intercellular currents (Llinas et al. 1974), thereby reducing the size of oscillating neuronal assemblies and dampening the amplitude of the oscillations themselves (Jacobson et al. 2008). Subsequently it has been shown that, in vitro, blocking GABA<sub>A</sub> receptors creates more synchronous clusters of olive cells as visualized by voltage-sensitive dyes (Leznik et al. 2002), while local GABA application abolishes the STOs (Devor and Yarom 2000). It is not yet known whether physiological inhibitory input is sufficient either in time course or distribution to mediate these effects. If this is the case, then other physiological modifiers of gap junction coupling might be expected to influence both the STOs and their synchrony across the olivary network. Mammalian gap junctions are known to be modulated by intracellular pH, calcium and membrane potential, among other things (Connors and Long 2004). Intriguingly, thalamic neurons have recently been shown to undergo activity-dependent depression of intercellular coupling (Landisman and Connors 2005). Whether these phenomena are important within the IO requires further study.

## Rhythmicity and Synchrony in the Climbing Fiber System

Determining how inferior olive spike output is timed relative to STOs is central to understanding the role played by the climbing fiber signal in cerebellar function. While the evidence for STOs in olivary neurons is compelling, the relationship



**Fig. 44.5** Control of STOs by glutamate and GABA. **(a)** Bath application of CNQX stabilizes the frequency and amplitude of STOs *in vitro*. Two example patch clamp recordings in separate olivary slices (*left, right*) in the absence (*top*) and presence (*bottom*) of CNQX (40  $\mu$ M). CNQX blocks the frequency modulation in both cases but does not prevent intermittence of oscillations (seen on the *right*). **(b)** GABA suppression of STOs: (1) Schematic illustration of the proposed shunting effect of GABA conductance on coupling between olivary neurons. Activation of GABA<sub>A</sub> receptors on gap junction (GJ) connected dendritic spines results in shunting of current flow via the open chloride-permeable channels, resulting in less current flow between the coupled cells (*white arrows*). (2) Whole cell recording from an olivary neuron shows that application of GABA can suppress STOs (reproduced with permission, Jacobson et al. 2008)

between these and complex spike timing in the cerebellar cortex is not clear-cut. In the absence of direct intracellular recordings from the IO, the simplest predictor of olivary STOs would be the presence of rhythmic or periodic complex spike activity in cerebellar cortex but the prevalence of complex spike rhythmicity cannot be agreed on (Kitazawa and Wolpert 2005). Periodicity in complex spike activity has been demonstrated in awake animals during behavior and rest (Llinas and Sasaki 1989; Welsh et al. 1995; Lang et al. 1999), but this periodicity varies considerably across Purkinje cells, and is strongest when the behavior itself is rhythmic. In rats, olivary neurons fire rhythmically during the step cycle (Smith 1998), but rhythmic complex spikes are not seen during locomotion in cats (Armstrong et al. 1988). Another study in cat (Bloedel and Ebner 1984) found that, despite there being no rhythmicity in complex spikes in response to forepaw displacement, autocorrelograms of the PSTH over many trials show two to four peaks, indicating that there are rhythmic increases in excitability of IO neurons after a sensory input. This could be explained by the phase-resetting phenomenon discussed above. Importantly, recordings in awake monkeys and cats (Armstrong and Rawson 1979; Keating and Thach 1995, 1997) show no periodicity in complex spike

activity in single Purkinje cells. A modeling study (Schweighofer et al. 2004) suggests that the firing of the olive is not periodic, but chaotic; so that the precise timing of the spikes can maximize the information transmitted through the olive despite occurring at low frequencies. It should be borne in mind that, while observed CS rhythmicity may indeed reflect the presence of STOs in the IO, it might also reflect rhythmic firing generated by another rhythmic input. Likewise, a lack of CS rhythmicity does not necessarily indicate the absence of STOs. Intracellular recordings from IO neurons are challenging and those that have been made, while showing clear STOs, have been carried out in anesthetized preparations. If oscillations are suppressed during action, testing the relationship between STOs and IO spike output while an animal performs a simple behavior may provide the missing piece of the puzzle.

Given the efficacy of afferent excitation in triggering olivary output, other brain areas may drive the olivocerebellar system to the beat of their own drum. It has been suggested, for example, that the IO acts as a resonating circuit, preferentially transmitting input within a certain bandwidth from the motor cortex to the cerebellum, and that this gating shapes the frequencies at which the cortex is able to generate motor output (Marshall and Lang 2004; Lang et al. 2006b). The peak of the frequency response curve resides close to 10 Hz, which is consistent with common frequencies of olivary STOs.

Physiologically relevant periodicity in olivary output may be disputed, but it has consistently been shown that groups of olivary neurons fire together: in the cerebellar cortex, Purkinje cells within a 500  $\mu\text{m}$  sagittal strip discharge complex spikes in synchrony (Bell and Kawasaki 1972; Lang et al. 1999; Ozden et al. 2009; Schultz et al. 2009). A recent study suggests that even asynchronous climbing fibers fire at fixed time intervals with respect to each other (Jacobson et al. 2009) which is proposed to reflect fixed phase offsets between olivary neurons oscillating at the same frequency. Synchrony results from a combination of the electrotonic coupling between IO cells (Blenkinsop and Lang 2006), the subthreshold oscillations themselves (Lang et al. 1997), the branching of a single olivary axon into multiple climbing fibers (Lang et al. 2006a), and shared excitatory synaptic input between neighboring olivary neurons (Kistler et al. 2002). The fact that rodents and humans with impaired gap junction function show motor learning deficits is an indication that synchronous olivary activity is important for normal cerebellar function (Van Der Giessen et al. 2008; van Essen et al. 2010). This is supported by the finding that, in rats with impaired electrotonic coupling in inferior olive, there is a reduction in coherence across muscle groups during harmaline-induced tremor (Placantonakis et al. 2004).

An important feature of complex spike synchrony is that the populations involved are not fixed, but can change during behavior (Welsh et al. 1995). How this occurs is still open to question but synaptic input is a key candidate. Blocking either excitatory or inhibitory receptors in the inferior olive increases the synchronicity with which the cells fire (Lang 2002). This has been posited to be due to shunting of intercellular current by activated synapses located within the trisynaptic junctions. Furthermore, since the inhibitory afferents from the DCN is one arm of

the olivocerebellar loop, a patch of IO could be regulating its own pattern of synchrony dynamically (Marshall and Lang 2009). This had led several groups to theorize that the olivocerebellar system is capable of dynamically generating different spatiotemporal patterns of climbing fiber activation relevant for the coordination of synergistic muscle activity (Jacobson et al. 2008; Llinas 2009). The rationale for taking this olive-centric view of the system is that the climbing fiber system has a much more dramatic effect on the output of the cerebellum (via the CF pause) (Davie et al. 2008), the modulation of PC bistability (Loewenstein et al. 2005), and rebound firing in the DCN (Hoebeek et al. 2010) than does the PF pathway, which can only weakly modulate the intrinsic firing of Purkinje cells.

---

## Conclusions

This chapter reviews the remarkable properties of the inferior olive and its role in the motor system, showing that subthreshold oscillations present at frequencies of 1–10 Hz are intrinsic and reinforced by gap junction coupling, and that these oscillations can shape the climbing fiber output to the cerebellum by imposing rhythmicity and synchrony in sagittal bands in the cortex. Many other brain circuits employ oscillations (Buzsaki and Draguhn 2004), but the independence of extrinsic input is a rare feature of this system. Is the olive a clock? While this may be a good metaphor for, say, pacemaker cells in the sinoatrial node of the heart, it is likely too simplistic a description of the olive. While there is no doubt that, via its oscillatory activity, the olive can generate an intrinsic timing signal, it is also robustly activated by excitatory afferents responding vigorously and with short latency to minute peripheral stimuli (Gellman et al. 1985), especially when such stimuli are not expected by the animal. The effective silencing of the IO during expected sensory input suggests that signaling unanticipated events is a key function of this structure (Devor 2002).

Early theories of the cerebellum suggested that the main role of the climbing fiber input is to provide a teaching signal to adjust the weights of parallel fiber synapses in order to modulate Purkinje cell simple spike output (Marr 1969). Modern variants see the cerebellum as an adaptive filter for tuning motor output (Dean et al. 2010). Some of the best evidence for these theories comes from the floccular system for adjusting eye movements (Ito 1970), however, and as discussed above, the relevant climbing fibers originate in the Dorsal Cap of Kooy, an area of the olive which does not generate subthreshold oscillations (Urbano et al. 2006). This may therefore not represent a universal model for the olivocerebellar system – if indeed such a model can exist. It has been argued elsewhere (Mathy et al. 2009) that it is important that future cerebellar learning theories take into account the dynamic properties of the IO, since it is clear that precise timing must play a role in complex motor output. There is much evidence, however, to support the view that the olivocerebellar system behaves as a resonant circuit, which can amplify input signals within a relevant frequency range (LampI and Yarom 1997; Lang et al. 2006a; Khosrovani et al. 2007). Whether, as has been suggested

(De Zeeuw et al. 2011), it can also stably and reproducibly generate spatiotemporal patterns of activity in the cerebellum remains to be shown conclusively. Experimental interventions are needed that can precisely manipulate the output of the olivocerebellar system and quantify the effect on, for example, motor behavior. Furthermore, this hypothesis requires an elaborate learning process distributed across the network and a mechanism to select the correct activity pattern for the intended behavior – two aspects which require further theoretical refinement and experimental confirmation. More pressingly, we need to know how subthreshold oscillations relate to activity in the awake animal. Only then will neuroscientists be able to make sense of this elegant, yet perplexing, neuronal machine.

---

## References

- Albus J (1971) A theory of cerebellar function. *Mathematical Biosciences* 10:25–61
- Apps R, Garwicz M (2005) Anatomical and physiological foundations of cerebellar information processing. *Nat Rev Neurosci* 6(4):297–311
- Armstrong DM (1974) Functional significance of connections of the inferior olive. *Physiol Rev* 54(2):358–417
- Armstrong DM, Rawson JA (1979) Activity patterns of cerebellar cortical neurones and climbing fibre afferents in the awake cat. *J Physiol* 289:425–448
- Armstrong DM, Edgley SA et al (1988) Complex spikes in Purkinje cells of the paravermal part of the anterior lobe of the cat cerebellum during locomotion. *J Physiol* 400:405–414
- Bal T, McCormick DA (1997) Synchronized oscillations in the inferior olive are controlled by the hyperpolarization-activated cation current  $I(h)$ . *J Neurophysiol* 77(6):3145–3156
- Bell CC, Kawasaki T (1972) Relations among climbing fiber responses of nearby Purkinje cells. *J Neurophysiol* 35(2):155–169
- Benardo LS, Foster RE (1986) Oscillatory behavior in inferior olive neurons: mechanism, modulation, cell aggregates. *Brain Res Bull* 17(6):773–784
- Best AR, Regehr WG (2008) Serotonin evokes endocannabinoid release and retrogradely suppresses excitatory synapses. *J Neurosci* 28(25):6508–6515
- Bishop GA, Ho RH (1984) Substance P and serotonin immunoreactivity in the rat inferior olive. *Brain Res Bull* 12(1):105–113
- Bishop GA, Ho RH (1986) Cell bodies of origin of serotonin-immunoreactive afferents to the inferior olivary complex of the rat. *Brain Res* 399(2):369–373
- Bleasel AF, Pettigrew AG (1992) Development and properties of spontaneous oscillations of the membrane potential in inferior olivary neurons in the rat. *Brain Res Dev Brain Res* 65(1):43–50
- Blenkinsop TA, Lang EJ (2006) Block of inferior olive gap junctional coupling decreases Purkinje cell complex spike synchrony and rhythmicity. *J Neurosci* 26(6):1739–1748
- Bloedel JR, Ebner TJ (1984) Rhythmic discharge of climbing fibre afferents in response to natural peripheral stimuli in the cat. *J Physiol* 352:129–146
- Buzsaki G, Draguhn A (2004) Neuronal oscillations in cortical networks. *Science* 304(5679):1926–1929
- Choi S, Yu E et al (2010) Subthreshold membrane potential oscillations in inferior olive neurons are dynamically regulated by P/Q- and T-type calcium channels: a study in mutant mice. *J Physiol* 588(Pt 16):3031–3043
- Chorev E, Yarom Y et al (2007) Rhythmic episodes of subthreshold membrane potential oscillations in the rat inferior olive nuclei in vivo. *J Neurosci* 27(19):5043–5052
- Connors BW, Long MA (2004) Electrical synapses in the mammalian brain. *Annu Rev Neurosci* 27:393–418



- Crill WE (1970) Unitary multiple-spiked responses in cat inferior olive nucleus. *J Neurophysiol* 33(2):199–209
- Davie JT, Clark BA et al (2008) The origin of the complex spike in cerebellar Purkinje cells. *J Neurosci* 28(30):7599–7609
- de Montigny C, Lamarre Y (1973) Rhythmic activity induced by harmaline in the olivo-cerebello-bulbar system of the cat. *Brain Res* 53(1):81–95
- De Montigny C, Lamarre Y (1974) Activity in the olivo-cerebello-bulbar system of the cat during ibogaline- and oxotremorine-induced tremor. *Brain Res* 82(2):369–373
- De Zeeuw CI, Holstege JC et al (1989) Ultrastructural study of the GABAergic, cerebellar, and mesodiencephalic innervation of the cat medial accessory olive: anterograde tracing combined with immunocytochemistry. *J Comp Neurol* 284(1):12–35
- De Zeeuw CI, Wylie DR et al. (1995) Phase relations of Purkinje cells in the rabbit flocculus during compensatory eye movements. *J Neurophysiol* 74:2051–2064
- De Zeeuw CI, Lang EJ et al (1996) Morphological correlates of bilateral synchrony in the rat cerebellar cortex. *J Neurosci* 16(10):3412–3426
- De Zeeuw CI, Van Alphen AM et al (1997) Climbing fibre collaterals contact neurons in the cerebellar nuclei that provide a GABAergic feedback to the inferior olive. *Neuroscience* 80(4):981–986
- De Zeeuw CI, Simpson JI et al (1998) Microcircuitry and function of the inferior olive. *Trends Neurosci* 21(9):391–400
- De Zeeuw CI, Chorev E et al (2003) Deformation of network connectivity in the inferior olive of connexin 36-deficient mice is compensated by morphological and electrophysiological changes at the single neuron level. *J Neurosci* 23(11):4700–4711
- De Zeeuw CI, Hoebeek FE et al (2011) Spatiotemporal firing patterns in the cerebellum. *Nat Rev Neurosci* 12(6):327–344
- Dean P, Porrill J et al (2010) The cerebellar microcircuit as an adaptive filter: experimental and computational evidence. *Nat Rev Neurosci* 11(1):30–43
- Devor A (2002) The great gate: control of sensory information flow to the cerebellum. *Cerebellum* 1(1):27–34
- Devor A, Yarom Y (2000) GABAergic modulation of olivary oscillations. *Prog Brain Res* 124:213–220
- Devor A, Yarom Y (2002a) Coherence of subthreshold activity in coupled inferior olivary neurons. *Ann N Y Acad Sci* 978:508
- Devor A, Yarom Y (2002b) Generation and propagation of subthreshold waves in a network of inferior olivary neurons. *J Neurophysiol* 87(6):3059–3069
- Eccles JC, Llinas R, Sasaki K (1966) The excitatory synaptic action of climbing fibres on the purkinje cells of the cerebellum. *J Physiol* 182:268–296
- Gellman R, Houk JC et al (1983) Somatosensory properties of the inferior olive of the cat. *J Comp Neurol* 215(2):228–243
- Gellman R, Gibson AR et al (1985) Inferior olivary neurons in the awake cat: detection of contact and passive body displacement. *J Neurophysiol* 54(1):40–60
- Headley PM, Lodge D et al (1976) Drug-induced rhythmical activity in the inferior olivary complex of the rat. *Brain Res* 101(3):461–478
- Hoebeek FE, Witter L et al (2010) Differential olivo-cerebellar cortical control of rebound activity in the cerebellar nuclei. *Proc Natl Acad Sci USA* 107(18):8410–8415
- Hoge G, Davidson KG et al (2010) The extent and strength of electrical coupling between inferior olivary neurons is heterogeneous. *J Neurophysiol* 105:1089–1101
- Ito M (1970) Neurophysiological aspects of the cerebellar motor control system. *Int J Neurol* 7(2):162–176
- Ito M (2001) Cerebellar long-term depression: characterization, signal transduction, and functional roles. *Physiol Rev* 81:1143–1195
- Jacobson GA, Rokni D et al (2008) A model of the olivo-cerebellar system as a temporal pattern generator. *Trends Neurosci* 31(12):617–625

- Jacobson GA, Lev I et al (2009) Invariant phase structure of olivo-cerebellar oscillations and its putative role in temporal pattern generation. *Proc Natl Acad Sci USA* 106(9):3579–3584
- Keating JG, Thach WT (1995) Nonclock behavior of inferior olive neurons: interspike interval of Purkinje cell complex spike discharge in the awake behaving monkey is random. *J Neurophysiol* 73(4):1329–1340
- Keating JG, Thach WT (1997) No clock signal in the discharge of neurons in the deep cerebellar nuclei. *J Neurophysiol* 77(4):2232–2234
- Keller R (1901) Ueber die Folgen von Verletzungen in der Gegend der unteren Olive bei der Katze. *Arch f Ana. u Physiol Anat Abth* 17:177–249
- Khosrovani S, Van Der Giessen RS et al (2007) In vivo mouse inferior olive neurons exhibit heterogeneous subthreshold oscillations and spiking patterns. *Proc Natl Acad Sci USA* 104(40):15911–15916
- Kim JJ, Krupa DJ, Thompson RF (1998) Inhibitory cerebello-olivary projections and blocking effect in classical conditioning. *Science* 279:570–573
- Kistler WM, De Jeu MT et al (2002) Analysis of Cx36 knockout does not support tenet that olivary gap junctions are required for complex spike synchronization and normal motor performance. *Ann N Y Acad Sci* 978:391–404
- Kitazawa S, Wolpert DM (2005) Rhythmicity, randomness and synchrony in climbing fiber signals. *Trends Neurosci* 28(11):611–619
- Klimoff J (1899) Ueber die Leitungsbahnen des Kleinhirns. *Arch f Anat u Physiol Anat Abth* 1078:11–27
- Lamp I, Yarom Y (1993) Subthreshold oscillations of the membrane potential: a functional synchronizing and timing device. *J Neurophysiol* 70(5):2181–2186
- Lamp I, Yarom Y (1997) Subthreshold oscillations and resonant behavior: two manifestations of the same mechanism. *Neuroscience* 78(2):325–341
- Landisman CE, Connors BW (2005) Long-term modulation of electrical synapses in the mammalian thalamus. *Science* 310(5755):1809–1813
- Lang EJ (2001) Organization of olivocerebellar activity in the absence of excitatory glutamatergic input. *J Neurosci* 21(5):1663–1675
- Lang EJ (2002) GABAergic and glutamatergic modulation of spontaneous and motor-cortex-evoked complex spike activity. *J Neurophysiol* 87(4):1993–2008
- Lang EJ, Sugihara I et al (1997) Differential roles of apamin- and charybdotoxin-sensitive K<sup>+</sup> conductances in the generation of inferior olive rhythmicity in vivo. *J Neurosci* 17(8):2825–2838
- Lang EJ, Sugihara I et al (1999) Patterns of spontaneous purkinje cell complex spike activity in the awake rat. *J Neurosci* 19(7):2728–2739
- Lang EJ, Llinas R et al (2006a) Isochrony in the olivocerebellar system underlies complex spike synchrony. *J Physiol* 573(Pt 1):277–279, Author reply 281–272
- Lang EJ, Sugihara I et al (2006b) Olivocerebellar modulation of motor cortex ability to generate vibrissal movements in rat. *J Physiol* 571(Pt 1):101–120
- Leznik E, Llinas R (2005) Role of gap junctions in synchronized neuronal oscillations in the inferior olive. *J Neurophysiol* 94(4):2447–2456
- Leznik E, Makarenko V et al (2002) Electrotonically mediated oscillatory patterns in neuronal ensembles: an in vitro voltage-dependent dye-imaging study in the inferior olive. *J Neurosci* 22(7):2804–2815
- Llinas RR (2009) Inferior olive oscillation as the temporal basis for motricity and oscillatory reset as the basis for motor error correction. *Neuroscience* 162(3):797–804
- Llinas R, Sasaki K (1989) The functional organization of the olivo-cerebellar system as examined by multiple Purkinje cell recordings. *Eur J Neurosci* 1(6):587–602
- Llinas R, Volkind RA (1973) The olivo-cerebellar system: functional properties as revealed by harmaline-induced tremor. *Exp Brain Res* 18(1):69–87
- Llinas R, Yarom Y (1981a) Electrophysiology of mammalian inferior olivary neurones in vitro. Different types of voltage-dependent ionic conductances. *J Physiol* 315:549–567

- Llinas R, Yarom Y (1981b) Properties and distribution of ionic conductances generating electrosensitiveness of mammalian inferior olivary neurones in vitro. *J Physiol* 315:569–584
- Llinas R, Yarom Y (1986) Oscillatory properties of guinea-pig inferior olivary neurones and their pharmacological modulation: an in vitro study. *J Physiol* 376:163–182
- Llinas R, Baker R et al (1974) Electrotonic coupling between neurons in cat inferior olive. *J Neurophysiol* 37(3):560–571
- Loewenstein Y, Mahon S et al (2005) Bistability of cerebellar Purkinje cells modulated by sensory stimulation. *Nat Neurosci* 8(2):202–211
- Long MA, Deans MR et al (2002) Rhythmicity without synchrony in the electrically uncoupled inferior olive. *J Neurosci* 22(24):10898–10905
- Manor Y, Yarom Y et al (2000) To beat or not to beat: a decision taken at the network level. *J Physiol Paris* 94(5–6):375–390
- Marr D (1969) A theory of cerebellar cortex. *J Physiol* 202(2):437–470
- Marshall SP, Lang EJ (2004) Inferior olive oscillations gate transmission of motor cortical activity to the cerebellum. *J Neurosci* 24(50):11356–11367
- Marshall SP, Lang EJ (2009) Local changes in the excitability of the cerebellar cortex produce spatially restricted changes in complex spike synchrony. *J Neurosci* 29(45):14352–14362
- Maruta J, Hensbroek RA et al (2007) Intraburst and interburst signaling by climbing fibers. *J Neurosci* 27:11263–11270
- Mathy A, Ho SS et al (2009) Encoding of oscillations by axonal bursts in inferior olive neurons. *Neuron* 62(3):388–399
- Ozden I, Sullivan MR et al (2009) Reliable coding emerges from coactivation of climbing fibers in microbands of cerebellar Purkinje neurons. *J Neurosci* 29(34):10463–10473
- Pardoe J, Edgley SA et al (2004) Changes in excitability of ascending and descending inputs to cerebellar climbing fibers during locomotion. *J Neurosci* 24:2656–2666
- Park YG, Park HY et al (2010) Ca(V)<sub>3.1</sub> is a tremor rhythm pacemaker in the inferior olive. *Proc Natl Acad Sci USA* 107:10731–10736
- Placantonakis D, Welsh J (2001) Two distinct oscillatory states determined by the NMDA receptor in rat inferior olive. *J Physiol* 534(Pt 1):123–140
- Placantonakis DG, Schwarz C et al (2000) Serotonin suppresses subthreshold and suprathreshold oscillatory activity of rat inferior olivary neurones in vitro. *J Physiol* 524(Pt 3):833–851
- Placantonakis DG, Bukovsky AA et al (2004) Fundamental role of inferior olive connexin 36 in muscle coherence during tremor. *Proc Natl Acad Sci USA* 101(18):7164–7169
- Placantonakis DG, Bukovsky AA et al (2006) Continuous electrical oscillations emerge from a coupled network: a study of the inferior olive using lentiviral knockdown of connexin36. *J Neurosci* 26(19):5008–5016
- Ramon y Cajal S (1909) *Histologie du système nerveux de l'homme et des vertébrés*. Maloine, Paris.
- Scheibel ME, Scheibel AB (1955) The inferior olive: a golgi study. *J Comp Neurol* 102(1):77–131
- Schultz SR, Kitamura K et al (2009) Spatial pattern coding of sensory information by climbing fiber-evoked calcium signals in networks of neighboring cerebellar Purkinje cells. *J Neurosci* 29(25):8005–8015
- Schweighofer N, Doya K et al (1999) Electrophysiological properties of inferior olive neurons: a compartmental model. *J Neurophysiol* 82(2):804–817
- Schweighofer N, Doya K et al (2004) Chaos may enhance information transmission in the inferior olive. *Proc Natl Acad Sci USA* 101(13):4655–4660
- Smith SS (1998) Step cycle-related oscillatory properties of inferior olivary neurons recorded in ensembles. *Neuroscience* 82(1):69–81
- Sotelo C, Llinas R et al (1974) Structural study of inferior olivary nucleus of the cat: morphological correlates of electrotonic coupling. *J Neurophysiol* 37(3):541–559
- Sugihara I, Lang EJ et al (1995) Serotonin modulation of inferior olivary oscillations and synchronicity: a multiple-electrode study in the rat cerebellum. *Eur J Neurosci* 7(4):521–534

- Szentagothai J, Rajkovits K (1959) Uber den ursprung der kletterfasern des kleinhirns. *Z Anat EntwGesch* 121:130–141
- Takeuchi Y, Sano Y (1983) Immunohistochemical demonstration of serotonin-containing nerve fibers in the inferior olivary complex of the rat, cat and monkey. *Cell Tissue Res* 231:17–28
- Urbano FJ, Simpson JI et al (2006) Somatomotor and oculomotor inferior olivary neurons have distinct electrophysiological phenotypes. *Proc Natl Acad Sci USA* 103(44):16550–16555
- Van Der Giessen RS, Koekkoek SK et al (2008) Role of olivary electrical coupling in cerebellar motor learning. *Neuron* 58(4):599–612
- van Essen TA, van der Giessen RS et al (2010) Anti-malaria drug mefloquine induces motor learning deficits in humans. *Front Neurosci* 4:191
- van Welie I, van Hooft JA et al (2004) Homeostatic scaling of neuronal excitability by synaptic modulation of somatic hyperpolarization-activated Ih channels. *Proc Natl Acad Sci USA* 101(14):5123–5128
- Welsh JP, Lang EJ et al (1995) Dynamic organization of motor control within the olivocerebellar system. *Nature* 374(6521):453–457
- Welsh JP, Han VZ et al (2011) Bidirectional plasticity in the primate inferior olive induced by chronic ethanol intoxication and sustained abstinence. *Proc Natl Acad Sci USA* 108(25):10314–10319