# Dynamics of the Inferior Olive Oscillator and Cerebellar Function

Dimitar Kostadinov, Alexandre Mathy, and Beverley A. Clark

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**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 the 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 the burst, implicating them in important downstream effects in the cerebellar cortex, such as complex spike timing, synchrony, and synaptic plasticity. STOs and the coupling between

D. Kostadinov · A. Mathy · B. A. Clark (✉)
Wolfson Institute for Biomedical Research, University College London, London, UK
e-mail: dimvladkost@gmail.com; Ardm2@cantab.net; b.clark@ucl.ac.uk



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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.

**Keywords**

ADP (after depolarization) · AHP (after hyperpolarization) · AMPA · Calcium-activated potassium channels · $Ca_v2.1$ · $Ca_v3.1$ · Climbing fiber · Clock · Complex spike · Deep cerebellar nuclei · Dorsal cap of Kooy · Electrical coupling · Endocannabinoid · GABA · Gap junctions · Glutamate · Harmaline · Hyperpolarization-activated cation channel · Inferior olivary nuclei · Inferior olive · NMDA · Olivocerebellar loop · Olivocerebellar system · P/Q type calcium channel · Plasticity · Purkinje cell · Rebound depolarization · Rhythmic activity · Serotonin · Subthreshold oscillations · Synchronization · T-type calcium channel · Tremor

## 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 delivers 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; Marr 1969; Ito 2001). 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 (Lang et al. 2017). Secondly, synchronous complex spike activity can occur across spatially organized populations of Purkinje cells, allowing climbing fiber input to assemble functional circuit modules in cerebellar cortex. Both of these complex spike characteristics must arise as a result of the intrinsic and network properties of the neurons of the inferior olivary nuclei in the brainstem, whose axons form the climbing fibers.

The intimate association between the cerebellum and the inferior olivary nuclei (IO) of the brainstem was recognized long before electrophysiological recordings or detailed anatomical data were available, mostly from studies where cerebellar lesions resulted in degeneration of this nucleus (Ramon and Cajal 1909; Keller 1901; Klimoff 1899). The substrate for this relationship became clear with the discovery that the climbing fiber pathway is composed of the axons of olivary

neurons (Eccles et al. 1966; Szentagothai and Rajkovits 1959), and that activity in the cerebellar cortex is in turn fed back to the IO via the inhibitory output of the cerebellar nuclei (CbN) (De Zeeuw et al. 1989) in a topographically organized manner (APPS and Garwicz 2005; De Zeeuw et al. 1998; Szentagothai and Rajkovits 1959). One of the main functions of this *olivocerebellar system* is thought to be generating spatiotemporal patterns of neural activity (Jacobson et al. 2008) that, ultimately, adjust the output of the motor system to optimize behavioral output. Underlying this view is the ever-increasing evidence that the IO has remarkable oscillatory properties, suggesting that the olive could have a clock-like function that provides a timing signal for coordination of cerebellar activity. This is a controversial view, however, and is not widely accepted. This chapter reviews 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 at the base of the medulla oblongata, the inferior olives are composed of four subnuclei: the principal olive, the medial and dorsal accessory olives (Fig. 1a), and the dorsal cap of Kooy (De Zeeuw et al. 1998). The neurons 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. 1b) (Scheibel and Scheibel 1955). The cells make no chemical synapses between each other, but are extensively electrotonically coupled by gap junctions (Sotelo et al. 1974; Llinas 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 of groups of coupled olivary neurons innervate Purkinje cells in a sagittally oriented band of cerebellar cortex called a microzone (APPS and Garwicz 2005), and these Purkinje cells target neurons in the CbN that in turn projects to the same area of the IO, forming an olivocerebellar loop (De Zeeuw et al. 1989). Olivary axon collaterals also project directly to the CbN (De Zeeuw et al. 1997). The inferior olive receives direct excitatory input from spinal afferents and from 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. 1c) (De Zeeuw et al. 1989).

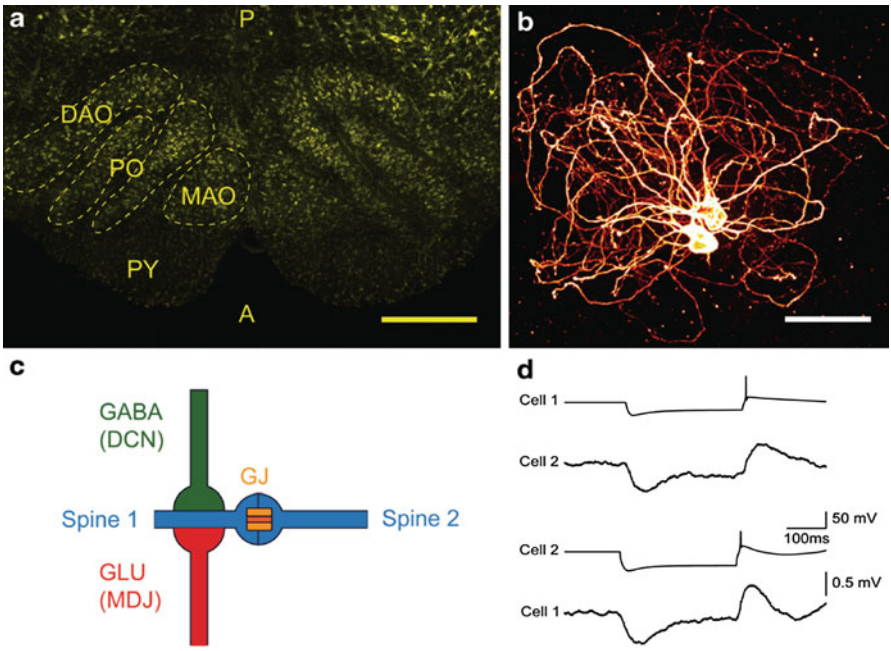


**Fig. 1** Anatomy of the inferior olive. (**a**) Nissl stain of a transverse section through the medulla oblongata showing the subnuclei of the inferior olive. *MAO* medial accessory olive, *DAO* dorsal accessory olive, *PO* principal olive, *P* posterior, *A* anterior (scale bar 500 μm). (**b**) Two adjacent olivary neurons filled with biocytin (scale bar 50 μm). (**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) (Mathy and Clark, unpublished data)

Importantly, the inferior olive also receives a dense serotonergic input from other brainstem 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, large calcium-activated potassium channels (BK), and hyperpolarization-activated cation channels ($I_h$) in the dendrites; and low-threshold calcium channels, small 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.

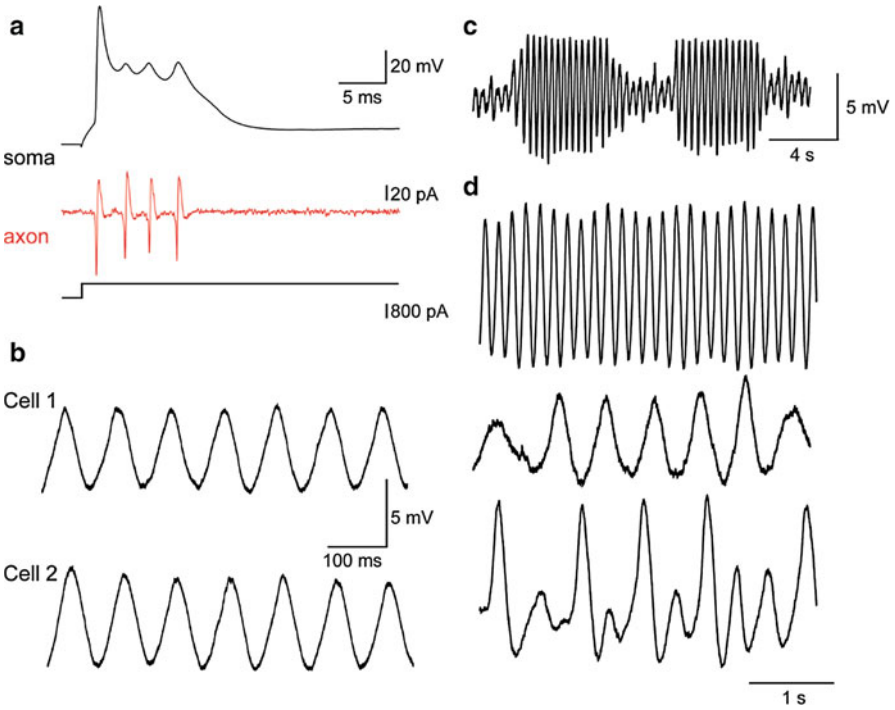


**Fig. 2** Excitable properties of olivary neurons. (**a**) Simultaneous patch clamp recordings from the soma (whole-cell) and axon (cell attached) of an olivary neuron in vitro. Depolarization by a somatic current step triggers a large amplitude action potential followed by and after depolarization 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 olivary recording in which the STOs shows prominent intermittent amplitude modulation. (**d**) Recording from three olivary neurons in vitro, demonstrating diversity in shape and frequency of STOs

Understanding what drives cells to transition between these states is essential to determining the influence of climbing fiber activity on cerebellar output.

When olivary neurons are depolarized to spike threshold, a complex somatic response occurs (Fig. 2a), consisting of an initial fast sodium spike followed by a broad after depolarization (ADP) on which several 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 (Mathy et al. 2009; Maruta et al. 2007; 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, 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 periodicity of this rhythmic firing.

## 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. 2b). STOs have been observed in vitro in isolated brain slices (Leznik and Llinas 2005; Welsh et al. 2011; Bal and McCormick 1997; Benardo and Foster 1986; Llinas and Yarom 1986; Devor and Yarom 2002a, b; Leznik et al. 2002; Placantonakis et al. 2006, 2000; Long et al. 2002; Choi et al. 2010; Bleasel and Pettigrew 1992; Mathy et al. 2009; Placantonakis and Welsh 2001) 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. 2c, d) and can be categorized into two main types in vivo (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. 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 (>85%) neurons (Benardo and Foster 1986; Khosrovani et al. 2007). These differences may be due to various factors including the species employed, the details of the slice preparation and anesthesia

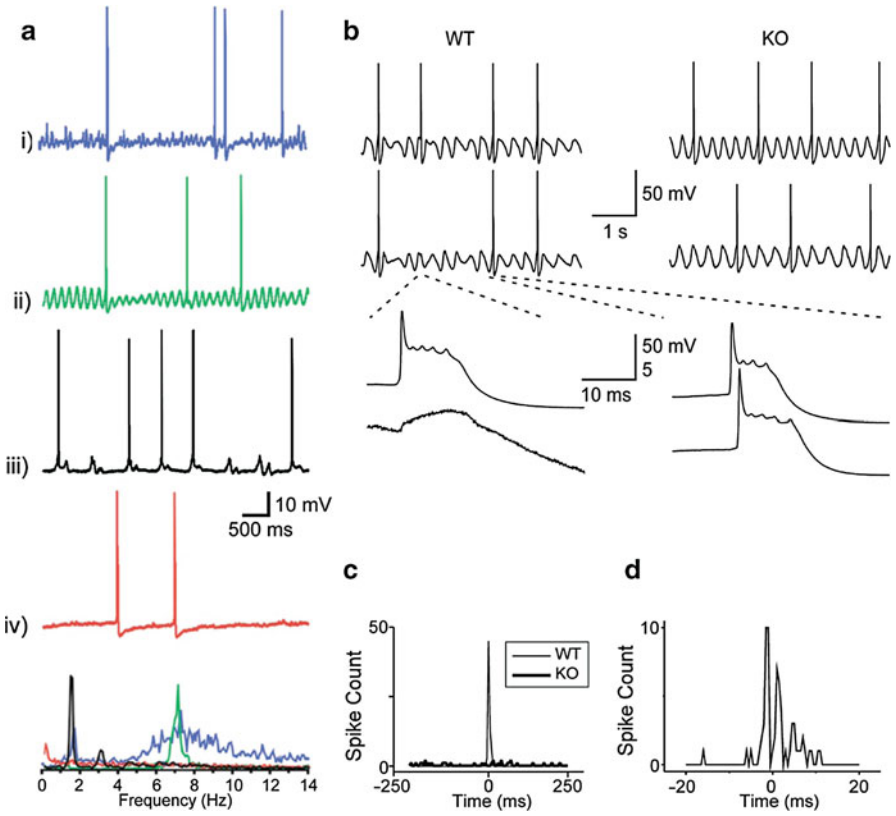


**Fig. 3** Oscillations, coupling, and spike output in the IO. (**a**) Different types of subthreshold activity and spontaneous firing observed using whole cell patch clamp recording in vivo. (From Khosrovani et al. 2007 copyright 2007 National Academy of Sciences, USA) (i) a neuron showing both SSTOs and LTOs, (ii) a neuron showing SSTOs alone, (iii) LTO activity, (iv) 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 knock-out 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 people in the knock-out. (**d**) Same data shown with finisher temporal resolution (0.5 ms bin width). (From Long et al. 2002, permission requested)

protocols used, as well as the criteria applied for positively identifying the presence of STOs. Importantly, the cells of dorsal cap of Kooy does 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. Along with 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 as a role in their generation as they are resistant to the sodium channel antagonist tetrodotoxin. They are, however, sensitive to calcium channel blockers or removal of calcium from the extracellular medium (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; Leznik and Llinas 2005; Long et al. 2002). 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 knock-out mice, one lacking the high-threshold P/Q-type ($Ca_v2.1$) calcium channel and the other the low-threshold T-type ($Ca_v3.1$) channel, it was 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). Diversity in $Ca_V3.1$ channels has been directly linked to the variability of STOs across olivary nuclei (Bazzigaluppi and De Jeu 2016). Harmaline administration to $Ca_v3.1$ knock-out mice fails to induce tremor, suggesting that the pharmacological induction of STOs is via modulation of the T-type calcium current, most likely though 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; Matsumoto-Makidono et al. 2016) both by keeping the membrane potential within the window for T-type calcium channel activation and by providing a resonant 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 (Devor and Yarom 2002a, b; Benardo and Foster 1986; 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 channels 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, 18β-glycyrrhetinic acid (18β-GA), which substantially reduces dye-coupling between olivary neurons, enhances the voltage dependence of the amplitude of STOs and increases their frequency (Leznik and Llinas 2005). Both these effects can be explained by the removal of the dampening effect of the coupling conductance and the loss of enhanced trans junctional current across the gap junctions at potentials more positive and more negative than the membrane potentials of coupled cells (Levitan et al. 1970). In connexin 36 knock-out mice, intrinsic oscillations are still present, displaying a similar voltage dependence to those in the presence of 18β-GA, but are not synchronized between cells (Long et al. 2002) (Fig. 3b–d). Possible compensatory mechanisms observed in these knock-out 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; Ozden et al. 2009; Bell and Kawasaki 1972). 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. 2011). The voltage-sensitive dye studies, however, conclude that a synchronous cluster extends beyond this small neighborhood, and can contain between 100 and 2000 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 (although see (Garden et al. 2017, 2018)), 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). More 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. 4a, b). 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). Consistent with this idea, recent studies of visuomotor adaptation in monkeys have shown that the duration and timing of complex spikes induced by visuomotor errors are correlated, and that strong complex spike activation triggers greater plasticity and adaptation (Herzfeld et al. 2018; Yang and Lisberger 2014).

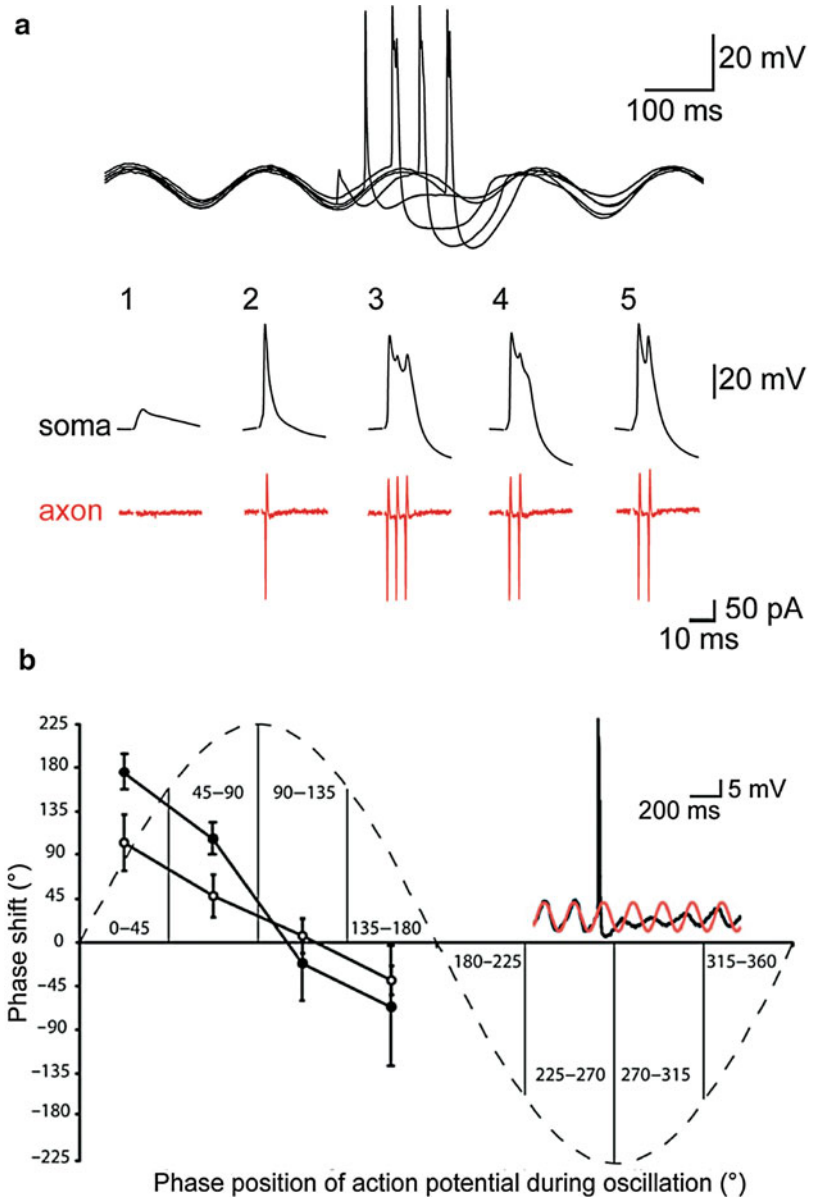


**Fig. 4** (**a**) Dependence of number of output spikes on STO phase. Top panel shows overlay of five somatic responses of an olivary neuron in vitro to synaptic stimulation during STOs generated by sinusoidal (5 Hz) current injection. EPSPs were triggered by single synaptic stimuli (arrow heads), timed 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)

## 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.

Activation of glutamate receptors has also been shown to affect oscillations in several different ways. Glutamatergic input activates both AMPA and NMDA receptors in IO cells (Best and Regehr 2008). In vitro application of NMDA receptor antagonists have 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 that persist even in acute brain slices. 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. 5a). Importantly, synaptic input that is large enough to trigger an action potential causes a phase reset of the STOs, advancing the oscillation so that regardless of the phase at which the spike is triggered, the emerging oscillation is consistently at the same phase (Khosrovani et al. 2007). 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 (Llinas 2009).

More recently, two studies have addressed how excitatory inputs to olivary neurons, acting through NMDA receptors, can trigger long-term changes in coupling and subthreshold oscillations (Mathy et al. 2014; Turecek et al. 2014). Interestingly, these two studies found that the effects of NMDA-dependent excitatory inputs can

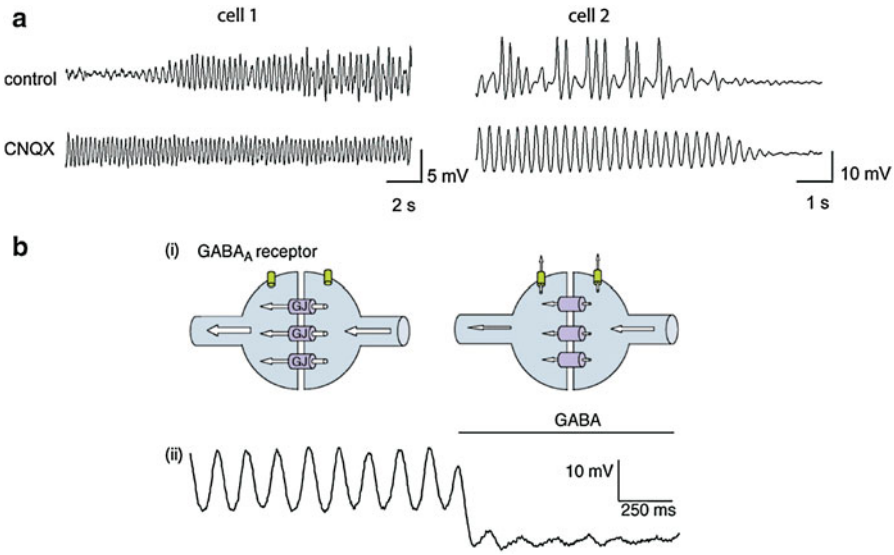


**Fig. 5** Control of STOs by glutamate and GABA. (**a**) Bath application of CNQX stabilizes the frequency and amplitude of STOs in vitro. Two example patch clamp recordings in separate olivary slices (left, right) in the absence (top) and presence (bottom) of CNQX (40 μM). CNQX blocks the frequency modulation in both cases but does not prevent intermittence of oscillations (seen on the right). (**b**) GABA suppression of STOs: (i) Schematic illustration of the proposed shunting effect of GABA conductance on coupling between olivary neurons. Activation of $GABA_A$ 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). (ii) Whole cell recording from an olivary neuron shows that application of GABA can suppress STOs

have opposing effects on coupling that depend on the frequency of stimulation. Activation of these inputs at low frequencies (1 Hz) caused a long-lasting decrease in the coupling coefficient between recorded pairs without changing the efficacy of chemical transmission. This decrease does not depend on action potential generation but does depend on calcium entry and activation of CaMKII (Mathy et al. 2014). In contrast, activating excitatory inputs at higher frequencies (9–50 Hz) or directly applying NMDA increased the electrical coupling between olivary neurons that were initially coupled weakly, again via a CaMKII-dependent mechanism (Turecek et al. 2014). Because these weakly coupled neurons tend to be further away from each other, this form of plasticity may expand the effective network of coupled neurons. Perhaps due to this network expansion, NMDA application also caused a synchronization of STOs. Together, these studies provide a mechanism by which excitatory input can dynamically modulate the size of coupled olivary networks, with strong excitatory input expanding these networks and weak input exerting homeostatic normalization of this expansion.

The inhibitory pathway from the cerebellar nuclei to the IO (nucleo-olivary pathway) 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. 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 CbN 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 $GABA_A$ 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). More recently, the influence of inhibitory cerebellar input on olivary neurons was probed using a combination of optogenetic activation of this pathway and paired recordings of olivary neurons (Lefler et al. 2014). Activating this pathway did indeed caused a decrease in coupling between olivary neurons and abolished STOs for the duration of stimulation, over time scales of tens to hundreds of milliseconds. The time course of the STO blockade showed variable onset and offset timing, consistent with reports of asynchronous GABA release exerting a slow but prolonged influence on olivary neurons (Best and Regehr 2009).

Thus, extrinsic input to the olive can modify coupling between olivary neurons and STOs on multiple time scales. How these different inputs interact with each other and how they are engaged in vivo to influence cerebellar function and, ultimately, behavior remain a topic for future 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 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 (Lang et al. 1999; Llinas and Sasaki 1989; Welsh et al. 1995), 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, auto-correlograms 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 (Keating and Thach 1995, 1997; Armstrong and Rawson 1979) 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 (Lang et al. 2006b; Marshall and Lang 2004). 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, complex spikes occur synchronously in Purkinje cells, with a spatial organization limited to a sagittal strip of approximately 50 μm (Ozden et al. 2009; Schultz et al. 2009; Lang et al. 1999; Bell and Kawasaki 1972). Even asynchronous climbing fibers can fire at fixed time intervals with respect to each other (Jacobson et al. 2009), likely reflecting fixed phase offsets between olivary neurons oscillating at the same frequency. Clearly, complex spike synchrony will result 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 an open 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 CbN form one arm of the olivocerebellar loop, a patch of IO could dynamically self-regulate its own pattern

of synchrony (Marshall and Lang 2009). This had led several groups to theorize that the olivocerebellar system can generate different spatiotemporal patterns of climbing fiber activation relevant for the coordination of a particular 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 CbN (Hoebeek et al. 2010)) than does the PF pathway, which can only weakly modulate the intrinsic firing of Purkinje cells.

## Conclusion

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 (Khosrovani et al. 2007; Lang et al. 2006a; Lampl and Yarom 1997). 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 begin to able to make sense of this elegant, yet perplexing, neuronal machine.

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