Mechanisms underlying cortical resonant states: implications for levodopa-induced dyskinesia

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Mechanisms underlying cortical resonant states: implications for levodopa-induced dyskinesia

Abstract: A common observation in recordings of neuronal activity from the cerebral cortex is that populations of neurons show patterns of synchronized oscillatory activity. However, it has been suggested that neuronal synchronization can, in certain pathological conditions, become excessive and possibly have a pathogenic role. In particular, aberrant oscillatory activation patterns have been implicated in conditions involving cortical dysfunction. We here review the mechanisms thought to be involved in the generation of cortical oscillations and discuss their relevance in relation to a recent finding indicating that high-frequency oscillations in the cerebral cortex have an important role in the generation of levodopa-induced dyskinesia. On the basis of these insights, it is suggested that the identification of physiological changes associated with symptoms of disease is a particularly important first step toward a more rapid development of novel treatment strategies.

Keywords: basal ganglia; dopamine; motor cortex; neuronal circuits; oscillations; Parkinson's disease.

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Introduction

Already the very early experiments involving electrophysiological measurements of brain activity in awake subjects revealed that the electrical activity of neurons in the cortical sheet tends to synchronize into rhythmical patterns that vary with the state of the brain. It was shown that factors like the presence of sensory input (Adrian and Matthews, 1934), physical activity (Jasper and Penfield, 1949) or even the general alertness and attention of the subject being examined (Berger, 1929) strongly influenced the type of oscillatory patterns that could be detected when electrodes are placed on the scalp or directly on the surface of the brain. These findings generated a great interest among many researchers, and several hypotheses regarding the functional significance of this physiological phenomenon have since been put forward (Gray and Singer, 1989; Murthy and Fetz, 1992; Llinás and Ribary, 1993; Sanes and Donoghue, 1993; Sarnthein et al., 1998). Indeed, the study of the functional significance of oscillatory patterns has continued into modern times and is currently a very active field of research. However, others have pointed out that oscillations should arise spontaneously in any highly interconnected dynamic network. Therefore, they may not necessarily reflect an important aspect of the information processing in neuronal circuits but could instead be more of an epiphenomenon. In this view, no significant insights should come from the study of neural oscillations and their underlying mechanisms (Shadlen and Movshon, 1999; Singer, 1999). Nevertheless, it is generally agreed that the degree of temporal synchronization of synaptic inputs to any given neuron should ultimately strongly affect its probability of activation. Hence, it is expected that oscillations involving periodic activation of a large population of neurons in the end should have demonstrable effects on neuronal information processing in downstream neuronal circuits.

In parallel to the investigations aimed at resolving the possible functional implications of oscillatory activity patterns in different physiological processes, several researchers have begun exploring a possible pathophysiological role of synchronized oscillatory activity in various disease conditions. In particular, electrophysiological studies in Parkinson's disease (PD) patients and in animal models of PD have suggested that rhythmic synchronization of neural activity may have a direct pathophysiological role. Several electrophysiological studies using animal models of PD have concluded that neuronal activity patterns in the parkinsonian state show an excessive synchronized oscillatory activity in practically all parts of the corticobasal ganglia circuits (Bergman et al., 1994; Nini et al., 1995; Sharott et al., 2005; Costa et al., 2006). Similar activity patterns have also been observed in PD patients where electrophysiological recordings have been obtained in conjunction with the implantation of deep brain stimulation (DBS) electrodes (Levy et al., 2000,

2002). Specifically, synchronization of neuronal activity at lower frequencies, as measured by the power of local field potential (LFP) signals in the 8- to 35-Hz frequency band, has been suggested to directly correlate with the severity of motor symptoms in PD patients (Kühn et al., 2006). In line with these results, it has been established that both dopamine replacement therapy and DBS reduce the amplitude of low-frequency LFP oscillatory activity in the basal ganglia along with providing clinical improvements (Brown et al., 2001, 2004; however, see also Rossi et al., 2008).

In a recently published study employing a rodent model of PD, we could confirm that low-frequency oscillations in corticobasal ganglia circuits is a key feature of the parkinsonian state (Halje et al., 2012). More unexpectedly, we could also establish that a different type of high-frequency narrow-band oscillation at ~80 Hz was strongly associated with dyskinetic motor symptoms induced by pharmacological dopamine replacement therapy. The strong association between the cortical high-frequency oscillation and levodopa-induced dyskinetic symptoms in these animals was further corroborated by the finding that a local pharmacological blockade of dopamine type 1 receptors applied directly to the cortical surface, within minutes proved to concomitantly attenuate both the resonant oscillations and dyskinetic symptoms.

These findings are here further discussed in the broader context of network oscillations with possible links to disease conditions and implications for neuromodulatory and pharmacological treatment strategies.

Origins of oscillatory activity in networks of neurons

In individual neurons, synchronized synaptic input generally has a strong influence on the probability of reaching the threshold of action potential generation. Yet, periodically occurring waves of synaptic activation tend to have highly differential postsynaptic effects in the sense that certain input frequencies cause a larger membrane depolarization than others. These frequency response characteristics result from high- and low-pass filtering properties of the different cellular elements of the neuron, which, in turn, stem from the specific distribution of ionic conductances over the plasma membrane and the passive resistive properties of different dendritic regions. Such cellular resonance properties cannot only be detected in subthreshold membrane oscillations, but can also be measured directly in input-output relations of neuronal spiking patterns (Richardson et al., 2003; Cardin et al., 2009). Moreover, even in the absence of synchronized input, preferred frequencies of spiking activity may be displayed, such as in rhythmically bursting neurons. Thus, input-output properties and firing characteristics of individual neurons may have resonance-like or pacing properties that can allow it to act as a pacemaker for an entire network (Llinás, 1988; Hutcheon and Yarom, 2000).

In a network of reciprocally connected neurons, the precise timing of spiking activity will consequently have a critical effect on the probability of inducing an oscillatory state (Ermentrout and Kopell, 1991). In effect, the functional coupling between individual neurons will be dynamic and depend on factors like the activation time constants of the individual neurons (resulting from synaptic latencies and rise and decay times of the involved ion channels) and duration of post-activity refractory periods as well as conduction delay times between the pairs of interconnected neurons. Given this large parameter space, any combination of reciprocally connected excitatory or inhibitory neuronal populations can theoretically enter into states characterized by oscillatory spiking activity of the single neurons at resonance frequencies that are determined by the specific temporal characteristics of the neuronal subgroup. In addition, however, because large-scale oscillatory activity patterns, such as those that are recorded in LFPs, reflect the summed activity of many thousands of neurons, these network oscillations must also include a synchronization mechanism involving large populations of neurons. Notably, even a very weak entrainment of the spiking in individual cells to the surrounding LFP oscillation (where most spikes do not occur in a strict relation to the phase of the LFP and often only every few cycles) can lead to strong oscillations on a population level – a phenomenon referred to as sparse synchronization (Brunel and Wang, 2003; Wang, 2010).

Origins of oscillatory activity in the cerebral cortex

It should be noted that network oscillations in a specific structure of the nervous system may principally originate from interactions between different cell groups within this volume, but will often also involve interactions with regionally distinct but anatomically connected structures. For the cerebral cortex, this implies that oscillations resulting from thalamic input in many behavioral states are intermingled with intrinsically generated activity patterns.

When considering mechanisms underlying intrinsically generated synchronized cortical oscillatory activity, interactions between populations of excitatory principle cells and/or inhibitory interneurons have been regarded as important to a varying degree depending on the type of oscillation that is being studied. By employing computer models and incorporating data from intracellular recordings of *in vitro* studies, an increased understanding of how interactions between different cell types contribute to cortical network oscillations has emerged (Wang and Buzsáki, 1996; Wang, 2010). On the basis of these studies, it has been suggested that whereas mutual excitation between pyramidal cells primarily generates network oscillations in the frequency range <15 Hz (Gutfreund et al., 1995), interaction between excitatory pyramidal cells and inhibitory interneurons and mutual inhibition between inhibitory interneurons can support faster oscillations even in the high gamma range (Whittington et al., 1995; Jefferys et al., 1996). However, for high-frequency oscillations close to or above 100 Hz, it is less clear to what extent signaling through chemical synapses makes a significant contribution, or whether electrical coupling through gap junctions between fast-spiking interneurons is the principal mechanism at work (Galarreta and Hestrin, 1999; Gibson et al., 1999).

When investigating intrinsic oscillatory mechanisms, experimental evidence has been obtained not only from the neocortex but also from parts of the allocortex – in particular the hippocampal formation. Although differences exist between the populations of cells constituting the core networks of these cortical regions, certain similarities in the basic intrinsic mechanisms underlying synchronized oscillations can nevertheless be identified. Specifically, inhibitory interneurons are, alone or in interaction with excitatory principal cells, chiefly responsible for generating synchronized gamma activity, and in particular, persistent high-frequency oscillations seem to require gap-junction conductances (Klausberger et al., 2003; Hájos et al., 2004; Whittington et al., 2011). It should also be pointed out that external pacing probably has an important role for inducing oscillatory activity in the hippocampus and is thought to be primarily mediated via input from the entorhinal cortex and medial septal regions for gamma and theta oscillations, respectively (Buzsáki, 2002; Csicsvari et al., 2003).

Regarding the role of the cortico-thalamocortical system in the generation of synchronized activity, several mechanisms remain to be explored. Oscillations associated with deep sleep stages (sleep spindles, delta waves and slow oscillations) have been relatively well characterized (Steriade, 2006), but this network also seems to have a powerful influence on the generation of gamma activity in the cortex in vigilant states. In this context, it may be of particular importance that thalamocortical relay cells have a propensity to switch into a tonically firing mode (~40 Hz) when being depolarized by afferents ascending from brain stem-activating systems. Moreover, corticothalamic feedback may in turn cause large ensembles of thalamic neurons to become entrained to this gamma rhythm, which then will spread to larger cortical areas (Jones, 2009).

In summary, interactions between cell groups within the cerebral cortex on the one hand and between cortical cells and neurons in external structures on the other hand jointly create dynamic activity patterns depending on the behavioral state. Rhythmic synchronized activity arising from these processes can often be recorded as the summed activity from large neuronal populations in the form of LFP or electroencephalogram EEG dynamics.

Cortical oscillations involving large neuronal populations

Having considered the possible underlying mechanisms of cortical oscillations in general, it is instructive to review how cortical rhythms have been classified by researchers and clinicians using population activity recordings as a tool to probe cortical function.

Although it has been noted that during anesthesia and in certain sleep stages neurons in the mammalian cortex tend to synchronize their firing, resulting in slow oscillations (<15 Hz) of the field potential that are clearly visible even in raw EEG traces (Timofeev and Bazhenov, 2005), the picture is generally fundamentally different during awake and active periods in healthy subjects (Steriade, 1993, 2000). In active states, neurons typically fire asynchronously without any striking high-voltage features in the recorded field potential. During such periods, the relative power of different frequency components of the recorded population activity decreases smoothly with frequency so that the spectral content of the signal is well approximated by a $1/f$ distribution, a feature resembling that of pink noise (Barlow, 1993). However, a handful of oscillatory phenomena break this norm. The most prominent one is probably the posterior alpha rhythm (7–13 Hz), which is inversely correlated with processing of (or attention to) visual stimuli (Nunez et al., 2001). These nearly sinusoidal oscillations typically last for several seconds and wax and wane in a spindle-like fashion (Nunez et al., 2001; Niedermeyer and Lopes da Silva, 2005). The origin

of this posterior alpha rhythm is still a matter of debate, although both intracortical and cortico-thalamocortical visual circuits seem to be essential for the generation of this wave (Lopes da Silva and Storm Van Leeuwen, 1977; Niedermeyer and Lopes da Silva, 2005).

Another strong oscillation, called the mu rhythm, can be recorded in the sensorimotor cortex (Gastaut, 1952; Chatrian et al., 1959) and is believed to be generated by circuits in the sensorimotor cortex and in corticobasal ganglia-thalamic circuits (Nunez et al., 2001; Nicolelis and Fanselow, 2002; Courtemanche et al., 2003). Its fundamental frequency overlaps with the posterior alpha rhythm, but some key differences exist: First, the mu rhythm is modulated by motor activity or sensorimotor-related processing rather than visual. Second, the mu rhythm is less sinusoidal and is often described as having a spike-wave shape (hence the alternate names 'wicket rhythm' or 'rythme en arceau'). In the rodent literature, the same rhythm is often referred to as high-voltage spindles (Kandel and Buzsáki, 1997). Its shape implies that the mu rhythm does not consist of one pure frequency; rather, it is the superposition of a fundamental frequency and several harmonic overtones to the fundamental frequency. This is also what is usually observed in power spectra of the mu rhythm (Hari and Salmelin, 1997). These overtones occasionally lose their phase-locking to the fundamental frequency and instead appear as independent oscillations in the beta band (Pfurtscheller 1981; Tiihonen 1989). Such differences can further complicate the classification and have led different authors to report on the same oscillatory phenomenon with references to mu, alpha and beta rhythm. Another parallel to alpha rhythm is that the mu rhythm follows a similar pattern of 'suppression during activation'; that is, the amplitude is reduced during action execution or touch (Hari and Salmelin, 1997). In addition, the mu rhythm has been linked to a wide range of processes involving sensorimotor transformations, for example, passive movements (Arroyo et al., 1993), action observation (Gastaut et al., 1952; Gastaut and Bert, 1954) and several action-related cognitive tasks, such as motor imagery (Pfurtscheller and Neuper, 1997) and biological motion perception (Ulloa and Pineda, 2007).

In contrast, high-voltage oscillations in the gamma band (>30 Hz) are typically not found in healthy subjects. However, since the 1980s, evidence has accumulated for an oscillatory phenomenon around 40 Hz observable after spectral analysis or spike-triggered average of LFPs. Gamma oscillations of this type are distinct from asynchronous broad-band activity in the gamma band (Buzsáki and Wang, 2012). In many of the experiments the reported gamma oscillations can be described as stimulus-evoked resonances in the visual system (Eckhorn et al., 1988; Gray et al., 1989; Hoogenboom et al., 2006), but similar oscillations have also been found in several other cortical areas and related structures, including sensorimotor cortex, entorhinal cortex, amygdala and hippocampus (Buzsáki and Wang, 2012). These gamma oscillations, or at least the gamma band power, has been shown to correlate with both activity and increased attention (Herculano-Houzel et al., 1999). In other words, they generally follow an opposite modulation pattern compared to the oscillations below ~30 Hz. On the basis of these findings, gamma oscillations have been implicated in a wide range of perceptual and cognitive functions, such as feature binding, attention and working memory, and on a mechanistic level, it has been hypothesized that gamma oscillations facilitate the grouping of information through selective entrainment of the relevant cell assemblies (Fries, 2009).

Oscillations in corticobasal ganglia circuits

Besides the corticothalamic projection, the frontal cortex is also densely connected with the basal ganglia, which are critically involved in the control of motor behavior. The cerebral cortex projects in a convergent fashion to the main input structure of the basal ganglia – the striatum – but also, via the hyperdirect pathway, to the subthalamic nucleus (STN).

Although oscillations in basal ganglia circuits clearly are a common phenomenon in healthy subjects (Bevan et al., 2002; Courtemanche et al., 2003; Leventhal et al., 2012), discussions on the origins of network oscillations often use the physiological changes associated with PD as a starting point because basal ganglia oscillatory activity appears to be a hallmark of this disease. The frequency range where excessive oscillatory activity has been reported in PD patients and in animal models of the disease is often referred to as the beta band, but in reality it typically spans the somewhat wider 8- to 30-Hz interval (Hammond et al., 2007; Fuentes et al., 2010) (perhaps suggesting a possible involvement of pathologically enhanced mu rhythms). When trying to identify the underlying mechanisms generating oscillatory patterns, it should be noted that practically all the involved structures are most likely affected by the substantial loss of midbrain dopaminergic innervation that is associated with the disease (Rommelfanger and Wichmann, 2010). Nevertheless, it is a common opinion that cells in the striatum might be particularly influenced by the loss of

dopaminergic input in PD (Wilson and Kawaguchi, 1996; Grillner et al., 2005).

Along this line of reasoning, it has been hypothesized that the aberrant beta oscillations that are characteristic of PD may originate intrinsically in the striatum. Experiments in mice have revealed that chronic dopamine depletion increases the functional connectivity between striatal fast-spiking interneurons and the group of medium spiny neurons (MSNs) that project to the external segment of the globus pallidus (GPe), a part of the indirect basal ganglia pathway. These changes were shown to be sufficient to increase the synchrony between the GPe-projecting MSNs in a computer model of the striatal network incorporating interneurons and MSNs (Gittis et al., 2011). Similar findings have been made using acute pharmacological manipulations of cholinergic striatal interneurons leading to the induction of striatal beta oscillations (McCarthy et al., 2011). It may be of particular relevance that cells in the indirect pathway of the basal ganglia are easily entrained to the beta rhythm, because the reciprocal connections between the GPe and the STN have been proposed to be a key element in maintaining and further amplifying network oscillations.

Indeed, the recurrently connected network of excitatory and inhibitory neurons in the STN and the GPe has in itself been suggested to be a core element in the generation of basal ganglia oscillations (Bevan et al., 2002). Initial experiments in organotypic cultures of neurons from cortex, striatum, STN and GPe appeared to support a rhythmogenic mechanism in the interaction between GPe and STN (Plenz and Kital, 1999). However, because later experiments using brain slices with intact connectivity between the two nuclei have not provided further evidence in support of this hypothesis (Loucif et al., 2005; Wilson et al., 2006) it is probable that the basal ganglia network dynamics seen in PD is not generated by GPe-STN interaction alone.

Other hypotheses are emphasizing an important role of the cortex by stating that PD beta oscillations originate from cortical patterning of striatal and, perhaps more importantly, subthalamic activity (Bevan et al., 2006). For example, both STN and GPe have been shown to fire action potentials coherently with cortical slow oscillations under the influence of cortical input (Magill et al., 2000, 2001). In this network, the GPe could have a central function in enhancing oscillatory activity in two ways: first, by increasing the capability of the rhythmic excitation from the cortex to drive coherent rhythmic activity in the STN via its recurrent connections with the STN (Baufreton et al., 2005) and second, through increased transmission of cortical activity to the STN via the striatum (Tseng et al., 2001), thus suggesting that a combination of mechanisms involving certain elements of all the above-mentioned hypotheses is at work.

Finally, it should be emphasized that although low-frequency oscillations have caught a lot of attention, higher oscillation frequencies are also present in different parts of the basal ganglia circuit. For example, recordings from rodent striatum have shown both broadband and more narrowly tuned gamma oscillations in corticostriatal circuits in active states, during attentive task performance and in association with initiation of movements (Masimore et al., 2005; Costa et al., 2006; van der Meer, 2009). Also, in recordings from the STN or the thalamus, several types of gamma rhythms have been found that can be linked not only to diverse functions such as motor acts and parkinsonian tremor, but also to higher mental processes (Brown and Marsden, 1998; Brown et al., 2002; Kempf et al., 2009; Weinberger et al., 2009).

Levodopa-induced cortical oscillations

In our recently published study (Halje et al., 2012) referred to above, it was evident that symptoms of levodopa-induced dyskinesia were tightly associated with strong resonant high-frequency oscillations in the primary motor cortex of the lesioned (parkinsonian) hemisphere. The oscillation frequency was essentially the same in all animals and in all experiments (80.9±2.7 Hz) and persisted throughout the entire dyskinetic period (lasting typically ~2h). This resonance could also be detected in striatal recordings of dyskinetic animals, indicating that the oscillation could be passed on to downstream structures. However, resonant oscillations were never detected in the intact (non-parkinsonian) hemisphere or in levodopa-treated non-dyskinetic parkinsonian animals.

The cellular mechanisms underlying this population activity were closely investigated. First, the 462 single units recorded were divided into putative pyramidal cells and interneurons in the primary motor cortex, and medium spiny neurons and fast-spiking interneurons for cells recorded in the dorsolateral striatum based on spike shape features, according to previously described methods (Bartho 2004; Gage 2010). In order to detect changes that could potentially explain the resonant oscillation, the firing characteristics of the cells in the different cell groups were then evaluated during the untreated baseline period and following levodopa treatment. It was noted that no major changes could be detected with

regard to the average firing rates of the cells belonging to the different cell groups. Approximately equal fractions of cells increased or decreased their firing rate compared to the untreated state in both the intact and the lesioned hemisphere, making population rate changes a less likely underlying mechanism. In a few cells of the lesioned hemisphere, pacemaker-like firing could be established when the resonant oscillation was present, suggesting that these cells could be involved in driving the entire network. However, action potentials were not elicited in every cycle of the population oscillation, and it is possible that these cells primarily follow rather than independently generate the population rhythm. Indeed, we could find a substantial fraction of cells belonging to all the different putative cell classes becoming significantly entrained to the 80-Hz oscillation in both cortex and striatum of the lesioned hemisphere. When analyzing the phase relations of the action potentials of the different cell groups to probe for a tendency for a grouped reciprocal excitatory-inhibitory interaction or phase-locked synchronized firing involving specific cell-types (Hájos et al., 2004), we could, however, not find any apparent grouping patterns. The 80-Hz entrained cells were therefore analyzed in further detail and it was concluded that in one respect the cells of the parkinsonian motor cortex, where the resonant oscillation was the strongest, appeared to differ from cells in the ipsilateral parkinsonian striatum and cells in structures in the intact hemisphere – the cortical cells often showed a shift from a strong low-frequency entrainment to high-frequency entrainment in association with levodopa-induced dyskinesia. It can therefore be speculated that this group of cells that appear to be very sensitive to the surrounding LFP oscillations may have a particularly important role both in the generation of synchronized low-frequency oscillations in the parkinsonian state and in maintaining the high-frequency oscillation associated with dyskinetic symptoms. Because, on a single-cell level, firing was sparse in relation to the 80-Hz population oscillation, this in addition suggests that a large network of neurons is required to generate the strong oscillation recorded in the LFP. On the basis of these findings, it can be hypothesized that dopamine replacement therapy used in symptomatic treatment of PD switches the system from a state dominated by excessive low-frequency oscillatory activity, perhaps in particular sustained by the group of entrainment-sensitive cells, to a more excitable network state where resonance properties of single cells and on a network level facilitate the induction of 80-Hz oscillations. However, it should be emphasized that because neuronal recordings have not yet been obtained in other structures of the basal ganglia loop during dyskinesia in this animal model it is too early to conclude that intrinsic cortical mechanisms are solely responsible for the generation of this peculiar phenomenon. The fact that a local pharmacological blockade of dopamine receptors in the cerebral cortex effectively attenuated dyskinetic symptoms proves that the cortical oscillation has a strong causal link to the dyskinetic symptoms but does not rule out that other parts of the basal ganglia circuit have an important role in producing the excitable cortical state leading to induction of network oscillations. Indeed, recordings obtained in patients implanted with DBS devices show that similar oscillations are often detectable in the subthalamic nucleus following levodopa treatment (Williams et al., 2002; Brown and Williams, 2005). Thus, when taking the established strong effect on cortical activity induced by activity changes in different parts of the basal ganglia into account, it seems highly probable that activity changes in several of these tightly interconnected structures act together to generate this state (Carta et al., 2006).

The role of dopamine in cortical oscillations

Although the bioactive role of dopamine in the central nervous system was convincingly proven half a century ago (Carlsson et al., 1958), the electrophysiological effects of dopamine on different cell populations are, perhaps surprisingly, still relatively poorly understood. A number of points, however, are generally agreed upon: First, in contrast to transmitter substances such as acetylcholine, glutamate or γ-aminobutyric acid (GABA), dopamine is not a neurotransmitter acting on fast ionotropic receptors (Lachowicz and Sibley, 1997; Missale et al., 1998). Second, dopamine release alone has a relatively moderate direct excitatory and/or inhibitory effect, causing only minor changes in postsynaptic membrane potential (typically a few millivolts) or suppression of spontaneous firing (Herrling and Hull, 1980; Bernardi et al., 1982). Finally, if dopamine is co-applied with a fast-acting neurotransmitter like glutamate or GABA, dopamine can efficiently modulate the effect of the fast neurotransmitter even at very low concentrations (Chiodo and Berger, 1986; Surmeier et al., 2007). It has therefore been argued that the principal role of dopamine in neuronal signaling should be considered that of a neuromodulator (Vives and Mogenson, 1986; Waszczak and Walters, 2013).

The dopaminergic innervation of the cerebral cortex stems from the mesocortical and to some extent the mesolimbic projection from cell groups in the midbrain

ventral tegmental area (A10) (Oades and Halliday, 1987). Although in both rodents and primates almost all parts of the cerebral cortex have been found to receive a subset of these dopaminergic projections, there are notable differences in the termination density of dopaminergic fibers between different cortical regions in both groups of animals (Kehr et al., 1976; Brown et al., 1979). Direct measurements of dopamine levels in the cortex have revealed that the highest concentrations can be detected in the prefrontal region. In more posterior regions, dopamine levels gradually decline until they reach their lowest level in the occipital lobe. Furthermore, the distribution of dopamine receptors in the cortical layers is differing between different cortical regions and shows, similar to the laminar distribution of terminals, certain interspecies differences. In relation to the topics discussed in the present review, it is of particular interest to note that the distribution of the dopamine receptor type 1 (D1R) and type 2 (D2R) in the primary motor cortex of rats resembles the cortical pattern of dopaminergic termination, which has a stronger projection to the deeper cortical layers (V/VI) (Martres et al., 1985; Dawson et al., 1986). In addition, the relative density of D1Rs in the motor cortex and in other cortical regions is higher than that of D2Rs (Gaspar et al., 1995). In primates, however, the D1R distribution in the motor cortex differs from rats in the sense that receptors are primarily located in the more superficial layers (I–III), whereas the D2R pattern rather resembles the one found in rats (layer V) (Lidow et al., 1991; Luft and Schwarz, 2009). To make a prediction regarding the network response to cortical dopaminergic stimulation is rather difficult because, in the cerebral cortex, both receptor types are expressed by the interconnected pyramidal cells and inhibitory interneurons (Vincent et al., 1995). In fact, several different factors appear to influence the effects even on a single-cell level (Servan-Schreiber et al., 1990; Goldman-Rakic et al., 2000). D1R activation can, for example, have opposing effects depending on the level of stimulation. Furthermore, the effect of dopaminergic activation may change over time in the same cell, and the dopaminergic effect may depend on the activity/depolarization level of the postsynaptic cell as well as the frequency of synaptic activity. Finally, effects may persist long after dopamine clearance, thereby creating complicated time dependencies related to the slow release of dopamine in the cortex [for a more comprehensive discussion on the mechanisms of dopaminergic modulation in the cortex and a summary of dopaminergic effects on cellular physiology, we would like to refer to the review by Seamans and Yang (2004)].

Inspired by the complex but evidently critical role of dopamine in the cerebral cortex, in the above-mentioned study we therefore further investigated the role of dopamine in the cortex in this rodent model of PD. After establishing dopaminergic lesions following 6-hydroxydopamine (6-OHDA) injections targeting the medial forebrain bundle, histological analyses of the cortex revealed that virtually all dopaminergic terminals were eliminated. Despite this severe dopaminergic denervation, we could not detect any reduction in the expression density of postsynaptic D1Rs. Interestingly, almost identical changes have been reported to occur in the striatum of 6-OHDA-lesioned animals (Muriel et al., 1999), leading to the hypothesis that an imbalance between pre- and postsynaptic elements of the dopamine synapse may in turn bring about a sensitization in the postsynaptic response to dopaminergic signaling. Our additional finding that c-fos expression in both the striatum and the primary motor cortex is increased following levodopa administration may thus suggest that changes leading to a sensitized state occur in parallel in both structures. Whereas a sensitization to dopamine in the striatum, involving mechanisms downstream of the D1R, has been claimed to be an important factor behind levodopa-induced dyskinetic symptoms (Cenci and Konradi, 2010), we decided to also evaluate the effect of direct pharmacological manipulation of dopaminergic neurons in the cerebral cortex in dyskinetic animals. Interestingly, topical application of the D1R antagonist SCH23390 onto the cortical surface resulted in a rather robust suppression of the resonant oscillation together with alleviation of dyskinetic symptoms within a few minutes after injection in all dyskinetic animals. On a methodological point, it is worth noting that it cannot be entirely ruled out that the D1R antagonist could have affected receptors outside the cortical area directly subjected to drug application due to diffusion of the drug in the brain tissue. Yet, it is reasonable to assume that the main effect was caused by pharmacological effects close to the injection site (the total volume injected was 10 µl, and injection of an equally soluble small-molecule dye in control experiments resulted in staining of adjacent cortical areas but very limited penetration to deeper tissue). In any case, antagonizing the levodopa-induced stimulation of D1Rs in the motor cortex and adjacent regions was clearly sufficient to suppress the strong 80-Hz oscillation in dyskinetic animals.

Dopaminergic cells in the nigrostriatal pathway show a faster and more severe degeneration in PD than the mesocortical counterpart (Hirsch, 1994). For this reason, dopamine deficiency involving the ventral tegmental area has often been overlooked (however, see also Gaspar et al., 1991; Hirsch, 1994; Moore et al., 2008). Given these different temporal profiles of neurodegeneration in the

two pathways that primarily affects cortex and striatum, respectively, it could be speculated that an accompanying gradual sensitization to dopamine in the two structures with an equally differing temporal profile follows. After several years of dopamine replacement therapy, the sensitization to dopamine in the cerebral cortex could then reach a threshold level at which the drug dose needed to achieve the therapeutic prokinetic effect in basal ganglia circuits has become sufficient to cause resonant cortical oscillations that result in dyskinetic symptoms.

Parallels to other conditions involving cortical dysfunction

In the context of dysfunctional dopaminergic modulation of cortical activity resulting in altered gamma oscillations, it is important to discuss the parallels to schizophrenia, which is known to be characterized by these same traits (Uhlhaas and Singer, 2010). The positive symptoms of schizophrenia include auditory hallucinations, delusions and thought disorder, whereas negative symptoms include anhedonia and apathy. Thus, whereas the collection of symptoms to a certain extent is qualitatively different from those seen in levodopa-induced dyskinesia, several lines of evidence nonetheless indicate that an excessive dopaminergic signaling is a central part of this disorder as well. For example, postmortem and positron emission tomography studies have shown that dopamine levels and dopamine receptor densities are elevated in schizophrenic patients (Davis et al., 1991). Accordingly, both typical and atypical antipsychotic medications act on cortical dopamine receptors (Da Silva Alves et al., 2008). Also, amphetamine and many other substances that increase synaptic dopamine signaling worsen psychotic symptoms in schizophrenic patients and can induce psychotic states in the healthy subject (Lieberman et al., 1990; Dalmau et al., 1999; Kapur and Seeman, 2002). At least two widely reported electrophysiological indicators of schizophrenia can be readily linked to altered dopamine signaling: the error-related negativity (ERN) and the auditory steady-state response (ASSR). The ERN is a deflection in the event-related potential that appears when a person commits an error in a choice task. The ERN is reduced in schizophrenic patients but is partially normalized by medication (Bates et al., 2004; Simmonite et al., 2012). It is likely generated in the anterior cingulate cortex by processes triggered by decreased firing of dopaminergic cells in the ventral tegmental area (Holroyd and Coles, 2002; Jocham and Ullsperger, 2009). The ASSR is an oscillation in auditory cortex evoked by repetitive auditory stimulation at a fixed frequency. The response is most consistent around 40 Hz (Picton et al., 1987), suggesting that the neural network has a resonance at this particular frequency, which is also consistent with other experimental and theoretical data (Wang and Buzsáki, 1996; Cardin et al., 2009). As discussed above, previous studies suggest that the 40-Hz oscillation is primarily driven by mutually connected inhibitory interneurons. It is therefore interesting to note that the ASSR is reduced in schizophrenic patients at 40 Hz, but not at lower frequencies (Kwon et al., 1999), indicating that dysfunction in the rhythmic activity of inhibitory interneurons could be a central component of the disease. Moreover, studies on the genetics of schizophrenia also point to the same group of interneurons (Harrison and Weinberger, 2005; Stefansson et al., 2008; Marín, 2012). Although there is at present insufficient evidence to conclude that alterations in dopamine signaling are the underlying cause of the abnormal gamma oscillations observed in schizophrenic patients, this tentative link to our finding that excessive dopamine can induce cortical resonant states is nevertheless highly interesting. A common mechanism behind dopamine-induced cortical resonance and the schizotypal ASSR, which is related to dopaminergic effects on the interneuron population, could provide clues as to why antipsychotic drugs often cause dyskinesia after long-term treatment.

Finally, any general discussion on cortical oscillatory phenomena would be incomplete without a reference to epilepsy. However, it should be acknowledged that epilepsy encompasses a number of different disorders, and some of these include components that are probably less relevant for the current review, for example, seizures induced by severe structural damage, abnormal metabolic states or conditions including severe convulsive seizures causing comatose states. However, it is possible that some of the electrophysiological mechanisms underlying other types of epilepsy, such as focal epilepsy or absence seizures, could be shared between the states of excessive cortical synchronization discussed herein. Two specific links to the mechanisms discussed in this review deserve to be mentioned. First, although a general imbalance between inhibitory and excitatory neurotransmitter systems of the cortical network is probably fundamental to the increased excitability in epilepsy, the synchronization of cortical activity is thought to specifically depend on synaptic and gap junction-mediated signaling between inhibitory interneurons (Uhlhaas and Singer, 2006). Second, the abnormal synchronization observed in absence epilepsy is thought to be generated via interacting intrinsic

cortical mechanisms and highly synchronized oscillations in the thalamocortical network (Niedermeyer and Lopes da Silva, 2005). Further studies will, however, be needed to clarify if the high-frequency oscillations that are detectable in the EEG before and during epileptic events can be mechanistically linked to gamma oscillations in disease conditions involving dopaminergic dysregulation. For a more in-depth comparative review on synchronized states in epilepsy and other disorders we would like to refer the reader to Uhlhaas and Singer (2006).

Breaking the waves – a neuromodulatory approach

In Parkinson patients, symptoms can be treated through electrical stimulation of subcortical structures such as parts of the thalamus, the STN or the internal part of the globus pallidus (GPi) (Moro and Lang, 2006). The initial intent of using high-frequency stimulation of these deep structures was to achieve a reversible functional inactivation mimicking the targeted lesions that had previously been shown to alleviate symptoms in animal models of PD and in late-stage PD patients (Benabid et al., 1987, 1989; Bergman et al., 1990; Aziz et al., 1991). In this perspective, applying an electrical stimulation in order to block the neuronal activity clearly presents a more attractive alternative. However, subsequent investigations of the mechanistic explanation for the alleviation of symptoms made it apparent that the full functional effect of high-frequency DBS is, in fact, a lot more complex. The activation of axons in the vicinity of the electrode has been shown to cause concurrent anterograde/retrograde activation or inactivation of neurons in several more distant targets and has in addition long- and short-term effects on synaptic transmission (Deniau et al., 2010). In an alternative view, less emphasis has been put on the importance of induced changes in neuronal activity in terms of mean firing rates. Instead, it has been argued that the main mechanism of action is related to a desynchronization of oscillatory activity patterns in the basal ganglia and connected networks (Kühn et al., 2008). Because low-frequency oscillations in sensorimotor networks have long been known to be associated with inactive states, and strong coherent oscillations of this type have often been observed in Parkinson patients, it has been hypothesized that excessive low-frequency oscillations could have a pathogenic role in PD (Brown, 2003; Marceglia et al., 2006; Hammond et al., 2007; Fuentes et al., 2010). According to this hypothesis, neuronal circuits may become locked in an inactive state through excessive synchronization, thereby preventing the physiological transition required for initiation of voluntary movements. Researchers have consequently also been evaluating less invasive methods to obtain desynchronization. In particular, because sensory stimulation of somatosensory afferent pathways has long been known to interfere with rhythmic cortical activity (see, for example, Adrian and Matthews, 1934; Chatrian et al., 1959), extracranial stimulation of afferent pathways has been evaluated as a means to interfere with excessive synchronized oscillatory activity. This method has, for example, been shown to block epileptic seizures in both animal models and in a few clinical trials of epilepsy (Fanselow et al., 2000; DeGiorgio et al., 2003, 2006). In PD, a similar approach using spinal cord stimulation (SCS) has been tested for the purpose of interfering with synchronized low-frequency oscillations characteristic of the parkinsonian state. Good results were initially achieved in rodent models of PD (Fuentes et al., 2009), and more recently, clinically validated effects have also been reported (Agari and Date, 2012; Fénelon et al., 2012; Hassan et al., 2013; see also Nicolelis et al., 2010). In the treatment of levodopa-induced dyskinesia, however, stimulation of afferent pathways remains to be evaluated. In contrast, the beneficial effects of DBS in treatment of dyskinesia are well documented and are generally thought to be twofold. First, the alleviation of parkinsonian symptoms allows for a reduction in medication, and second, the stimulation has a direct antidyskinetic effect. Accordingly, high-frequency stimulation of the STN and parts of the globus pallidus (in particular GPi) are both regarded as useful complementary treatment options to pharmacological interventions (although it is still unclear which is the better target) (Toda et al., 2004). If the high-frequency cortical oscillations found in dyskinetic rats is indeed a causal mechanism underlying levodopa-induced dyskinesia, it is of key importance to investigate if the beneficial effects of STN/GPi stimulation include a suppression of 80-Hz oscillations either indirectly or, in the case of STN, perhaps directly through retrograde activation of the hyperdirect cortico-subthalamic pathway (Li et al., 2007; Gradinaru et al., 2009; Deniau et al., 2010).

Breaking the waves – a pharmacological approach

In levodopa-treated dyskinetic rats, we could effectively alleviate symptoms through topical application of the highly selective D1R antagonist SCH23390 onto the cortical surface

concomitant with an interruption of cortical high-frequency oscillations. Although these results may be taken to indicate that pharmacological interventions directed at dopaminergic signaling in the cerebral cortex could potentially be used in the treatment of dyskinesia, it should be pointed out that a reduced antiparkinsonian effect of levodopa treatment could also follow. For this reason, it would be desirable to more directly target molecular elements required to sustain the resonant state. As discussed above, different synchronization mechanisms are typically at work depending on the frequency of the network oscillation. Because synaptic and gap junction-mediated coupling between GABAergic fast-spiking interneurons has been claimed to be of particular importance for high oscillation frequencies (Wang, 2010), this transmission may constitute a potential pharmaceutical target in future drug development.

Importantly, however, several substances have already been evaluated for treatment of dyskinesia in different animal models and in clinical trials (Huot et al., 2013). Although side effects or insufficient drug efficacy have turned out to be major limitations to many of these candidate drugs, it is still of great importance to further investigate the physiological changes associated with the partial alleviation of symptoms that has been reported. In particular, the weak *N*-methyl-D-aspartate antagonist amantadine is considered efficacious in the treatment of levodopa-induced dyskinesia, also when evaluated by means of evidence-based review techniques (Goetz et al., 2005). For this drug, it is particularly interesting to note that a direct link to resonant cortical oscillations may exist, as the antidyskinetic effect of amantadine can be potentiated in nonhuman primates when combined with the antiepileptic drug levetiracetam (Hill et al., 2004). Levetiracetam is indicated for the treatment of refractory partial epilepsy and can reduce neuronal synchronization in animal models of epilepsy, in part through interference with synaptic release mechanisms (Klitgaard et al., 2003). Finally, understanding the differential actions of drugs in different central nervous system structures may provide important clues on how to tailor compounds to achieve more specific actions (Huot et al., 2011; Ostock et al., 2011). To make such investigations more effective, the identification of neurophysiological phenomena associated with dyskinetic symptoms will be an important complement to standard behavioral readouts. On the basis of our previous findings and the mechanisms discussed in this review, we suggest that cortical oscillations may provide a useful biomarker to this aim.

Conclusions

Taken together, several lines of evidence indicate that aberrant activity patterns may have an important pathophysiological role in a number of psychiatric and neurological conditions. In PD, part of the beneficial effect in symptomatic treatment of the disease based on both dopamine replacement therapy and DBS/SCS may be due to a suppression of synchronized oscillations. Similarly, in animal models of levodopa-induced dyskinesia, a pharmacological interruption of resonant high-frequency oscillations proved to alleviate dyskinetic symptoms. Unfortunately, very little is known about the mechanisms causing these abnormal activity patterns. Thus, clarifying the importance and the mechanistic underpinnings of the physiological phenomena associated with symptoms of disease should be a key goal in research aimed at improving treatment of these conditions.

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