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Review article

Oscillations and NMDA Receptors: Their Interplay Create Memories

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Abstract: Oscillatory activity is inherent in many types of normal cellular function. Importantly, oscillations contribute to cellular network activity and cellular decision making, which are driving forces for cognition. Theta oscillations have been correlated with learning and memory encoding and gamma oscillations have been associated with attention and working memory. NMDA receptors are also implicated in oscillatory activity and contribute to normal function and in disease-related pathology. The interplay between oscillatory activity and NMDA receptors are intellectually curious and a fascinating dimension of inquiry. In this review we introduce some of the essential mathematical characteristics of oscillatory activity in order to provide a platform for additional discussion on recent studies concerning oscillations involving neuronal firing and NMDA receptor activity, and the effect of these dynamic mechanisms on cognitive processing in health and disease.

Keywords: harmonic oscillator; NMDA Receptor; oscillations; memory; NMDA Receptors in Memory

1. Introduction

Complex systems, which include biological organisms, exhibit many dynamic qualities. For example, oscillatory activity characterizes several facets of normal cellular function, such as cell cycle regulation, gene expression, neurotransmission, cellular control of waking/sleeping cycles, and cell maintenance, to name a few. In particular, spiking patterns, membrane potential, and other cellular activity observed in neural tissues function rhythmically and repetitively about an equilibrium state and are thus said to also exhibit oscillatory behavior [1]. Moreover, oscillations contribute to cellular network activity and cellular decision making, which are associated with

pacemaker cells, the encoding and integration of sensory and signal transduction information, and locomotion and navigation. For example, theta oscillations (4–7 Hz) have been correlated with learning and memory encoding and gamma oscillations (30–60 Hz) have been associated with attention and working memory. Therefore, oscillatory activity appears to be a fundamental organizer of network information, which is a source of higher level cognitive function. Temporal variations in cell and network activity are essential to cell function and survival and also the adaptation of an organism to its environment. However, pathophysiological alterations to oscillatory activity appear to influence several clinical conditions, including hallucinations, bipolar disorders, seizure activity, additive behaviors, and navigational difficulties.

Interestingly, *N*-methyl-D-aspartate receptors (NMDA) receptors are implicated in oscillatory activity in several contexts, that is, in normal function and in disease-related pathology. The NMDA receptor has been well described [2] with regard to its biophysical properties and the molecular biology of the receptor-ion complex [3], and more recently a central role for NMDA receptors in oscillatory behaviors is emerging. For example, alterations in NMDA receptor-mediated oscillations have now been implicated in several affective disorders and in seizure disorders. Past studies demonstrated that NMDA receptor activation leads to the initiation and/or maintenance of *vital* cellular functions [4]. In addition, the NMDA receptor has been shown to play a role in diverse, but *fundamental* biological processes, such as synaptic plasticity, development, and memory [5–8]. Given this, it is not surprising that past investigations also report that modulation of NMDA receptor activity is associated with a variety of disease processes and conditions, including acute brain injury, epilepsy, Alzheimer's disease, chronic motor disorders, pain, and schizophrenia [9,10], which are likely intimately associated with oscillatory dynamics.

To develop an adequate description of how NMDA receptors contribute to oscillatory behaviors and ultimately cognition, an introduction to some of the mathematical characteristics detailing the nature of common linear oscillatory systems is first necessary. Therefore, this review will first define a few essential elements of oscillatory characteristics in order to provide a platform for additional discussion on recent studies concerning oscillations involving neuronal firing and NMDA receptor activity, and the effect of these dynamic mechanisms on cognitive processing in health and disease.

2. Simple Harmonic Motion

As oscillations may be described mathematically with respect to a temporal pattern of functional activity in systems such as mechanical vibrations, a working description of an oscillatory system will be introduced by discussing the mathematically well-known linear harmonic oscillator[1]. Harmonic oscillators describe mechanical systems that exhibit a rhythmic restoring force *F(x)* in response to a displacement *x* from an equilibrium position for an oscillating body. The simplest model of this type is the simple harmonic oscillator, which represents a system in which the periodic motion of the restoring force *F(x)* has a simple proportional relationship to the displacement of the system from its equilibrium position, and whose movement is driven only by *F(x)*. A typical mechanical system illustrating this type of motion is a point mass, *m*, attached to a spring with spring constant *k*. Thus for the simple harmonic oscillator, the restoring force is given by Hooke's law:

$$F(x) = -kx(t) \tag{1}$$

As evident in equation (1), any displacement *x* away from an equilibrium position results in a

[1] The discussion of the harmonic oscillator comes from the differential equations text 11. Nagle, R., Saff, B., Snider, A., *Fundamentals of differential equations and boundary value problems*. 6th ed. ed. 2012, Boston: Addison-Wesley.

proportional increase in *F(x)* directed back toward this position. As the mass reaches the equilibrium position, however, the mass maintains its momentum due to *F(x)* and thus continues past this position, introducing a negative displacement and a net restoring force directed again toward the equilibrium position. This continues until the system settles into a minimum energy state, that is until the momentum of the body dissipates and it once again settles into the equilibrium position.

For an undamped (i.e., simple) system as described above, however, the energy within the system is constant and thus the mass will continue to oscillate about the equilibrium position indefinitely. The travel of the mass in such a system is illustrative of an important characteristic of oscillatory behavior; the motion of a simple harmonic oscillator is *periodic*, as the motion of the body repeats every time period *T*. Thus we see a *sinusoidal* pattern of displacement as a function of time, where:

$$x(t) = A\sin(\omega t - \varphi) \tag{2}$$

In equation (2) we have the *angular* or *natural frequency* ω, which represents the rate at which the oscillating body moves about the equilibrium position in a period *T*; the amplitude or maximum size of oscillation A; and the *initial phase* φ corresponding to the initial displacement offset of the system.

The simple harmonic oscillator described thus far provides a mathematical model for illustrating the motion of simple systems such as small-amplitude pendulums or undamped (frictionless) spring-mass systems. Real-world systems require a more complex formalization of the mechanics of harmonic oscillation.

3. Damped and Forced Harmonic Motion

Real-world oscillators often involve forces that impede or amplify the motion of the oscillating body. Friction typically operates as the primary damping force, as it counteracts the movement of the oscillating body at all points. External stimulation may augment the motion of the oscillating body depending on the nature of the stimulation, such as by a rhythmic mechanical force. Damped harmonic oscillators model frictional force $F_f(t)$ as being proportional to the velocity of the oscillating body, and thus $F_f(t) = -bv(t)$, where b is the *damping coefficient*. Applying Newton's second law, the nature of the motion can be described as follows:

$$F_{net} = -kx - bv(t) = -kx - b\frac{dx}{dt} = m\frac{d^2x}{dt^2} \tag{3}$$

Where *v(t)* and *a(t)* in Newton's second law have been replaced by their respective displacement function derivatives. Rearranging equation (3) provides us with the following second-order differential equation:

$$\frac{d^2x}{dt^2} + 2\zeta\omega_0\frac{dx}{dt} + {\omega_0}^2x = 0 \tag{4}$$

Where ω_0 remains as the *undamped angular frequency* as in the simple harmonic oscillator, and $\zeta = \frac{b}{2\sqrt{mk}}$ represents the *damping ratio*. This equation incorporates the entirety of the motion of the system, relating the rates at which the displacement and velocity of the body changes with respect to time, $\frac{dx}{dt}$ and $\frac{d^2x}{dt^2}$ respectively, to the position of the body *x(t)*. Equation (4) also introduces a new constant involved in damped oscillatory motion, the damping ratio, which determines the behavior of the system with three possible states. Following are the solutions to equation (4) with the three varying cases of ζ:

$$x(t) = \begin{cases} c_1 e^{r_1 t} + c_2 e^{r_2 t}, & \zeta > 1 \\ e^{\frac{-bt}{2m}}(c_1 + c_2 t), & \zeta = 1 \\ A\, e^{\frac{-bt}{2m}} \sin\left(\frac{\sqrt{4mk - b^2}}{2m} t + \varphi_h\right), & \zeta < 1 \end{cases} \quad (5)$$

Over-damping occurs when $\zeta > 1$, which results in the system approaching a steady-state equilibrium position (as $t \to \infty$) without oscillating. Here we have that the system *x(t)* exponentially decays without oscillation. *Critical damping* occurs when $\zeta = 1$, resulting in a system that behaviors similar to an over-damped system, but with a much quicker return to equilibrium. Lastly, *under-damping* occurs when $\zeta < 1$, resulting in the system oscillating about the equilibrium position with a gradual loss of oscillation amplitude, which thus reaches the equilibrium position as $t \to \infty$. We can see from equation (5) that there is oscillatory behavior due to the *cosine* function, but we again see exponential decay due to frictional damping.

If in addition to an external force applying an impeding force on the motion of the body, an external force $F_{ext}(t)$ is applied as well, then the influence of this force must be accounted for in equation (4). Incorporating this force into equation (3), and then rearranging as was done to arrive to equation (4), we acquire the following second-order differential equation:

$$\frac{d^2x}{dt^2} + 2\zeta\omega_0 \frac{dx}{dt} + {\omega_0}^2 x = \frac{F_{ext}(t)}{m} \quad (6)$$

Of critical importance to consider in the case of forced oscillations is the nature of the external force. Of particular interest to a forced harmonic oscillator is the case in which the forcing force behaves as a harmonic driving force of the form $F_{ext}(t) = F_0 cos(\omega_d t)$. Using this driving force for $F_{ext}(t)$, and applying techniques of differential calculus to find a solution for *x(t)*, we acquire:

$$x(t) = A\, e^{\frac{-bt}{2m}} sin\left(\frac{\sqrt{4mk - b^2}}{2m} t + \varphi_h\right) + \frac{F_0}{\sqrt{(k - m\omega_d{}^2)^2 + b^2\omega_d{}^2}} sin(\omega_d t - \varphi) \quad (7)$$

Here it appears that the movement of the oscillating body described by *x(t)* has become quite complex. Without investigating the parameter-specific properties of equation (7), however, two very important characteristics of oscillatory behavior are readily exhibited: *transient* behavior and *steady-state* behavior. The first term in equation (7), $Ae^{\frac{-bt}{2m}} sin\left(\frac{\sqrt{4mk-b^2}}{2m} t + \varphi_h\right)$, is known as the *transient term*, which dictates the behavior of the system on short time scales with similar behavior as that exhibited in equation (5); the multiplicative ratio in the second term in equation (7), $\frac{F_0}{\sqrt{(k-m\omega_d{}^2)^2+b^2\omega_d{}^2}}$, is known as the *steady-state term* or *gain factor*, which defines the behavior of the system as $t \to \infty$. These terms essentially separate the influence on the oscillation of the body due to both the damping in the transient behavior of the system, and an external driving force in the steady-state behavior of the system.

Inspecting the transient term, we can see by comparing equation (7) to equation (5) that we have assumed a system in which under-damping occurs and thus exhibits oscillation transiently. If the system involves a damping ratio that results in over-damping or critical damping, then the transient term simply no longer provides a source of oscillation at short time scales and becomes simply an exponential decay as in equation (5). Regardless of this term damping behavior, however, the transient term tends toward 0 as $t \to \infty$ due to the exponential damping term, and thus only defines the behavior of the system for early time states of the system. Since $t \to \infty$ results in the transient term tending to 0, the system becomes defined only by the steady-state as *t* becomes large. As the transient term tends to dissipate over time, the steady-state term governs the oscillatory behavior of the system. By defining the function:

$$M(\omega_d) := \frac{1}{\sqrt{(k-m{\omega_d}^2)^2+b^2{\omega_d}^2}} \quad (8)$$

to represent the behavior of the steady-state term, we can determine the influence of the driving force on the system as a function of the driving force frequency ω_d. This function is known as a *resonance curve* or *frequency response curve*, which represents the alteration to the oscillation of the system by varying the frequency of the external driving force. Again using methods of differential calculus, it can be determined that this function $M(\omega_d)$ achieves a maximum at $\omega_{d_{max}}$ only when the system is under-damped. An important result of investigating the frequency response curve for a system allows for the identification of the system's *resonance frequency*, which occurs when the angular frequency of the driving function takes the value $\omega_d = \omega_{d_{max}}/2\pi$. At this frequency, the periodic behavior of the driving force matches that of the oscillating body given the parameters of the system, and thus maximally drives the oscillation of the system. This also affords a particularly interesting aspect of oscillatory behavior, wherein if the damping constant b is small (as in the under-damped case), and ω_d is close to the resonant frequency, the system tends toward large oscillations as $t \to \infty$ with larger oscillations as ω_d approaches the resonant frequency. This situation is governed by equation (7), and thus solving equation (6) for an under-damped system is justified.

Thus we see that the oscillatory behavior of the system is influenced by both inhibitory and driving forces in a number of different ways. The oscillations of the system behave uniquely at both short-term and long-term time scales, and the nature of the forces that drive the oscillation itself directly influence the rate and/or size of the systems oscillation.

4. Application to Neural Oscillations

Although there remains some further complexity in discussing harmonic oscillatory systems (e.g., quantum harmonic oscillators and parametric harmonic oscillators), the purpose of the present discussion is merely to motivate an initial description of the oscillatory behavior in neural systems. Attempts to model neural oscillations mathematically have remained within the field of dynamical systems, modeling the oscillatory activity using both linear and nonlinear systems, including using linear harmonic oscillators and limit cycle oscillators. In such an approach, however, the strategy remains the same: oscillatory systems are often described functionally by a system of differential equations, whose solutions (e.g. equation (7) representing the form of the solution to equation (6)) explicitly denote the nature of the oscillation as a function of some parameter. With this, the focus of identifying neural oscillations will be limited to a discussion of the parameters of the oscillations themselves, introduced above within the discussion of the harmonic oscillator above. Following a brief introduction to computational models of spiking activity, a description of general neural oscillations and their characteristics will be discussed.

Neuronal Models

The neural activity of a single neuron is rarely a representative model of the dynamics of a neural event, but is nonetheless essential in describing neuronal activity at both the single cell level and at the collective network level. In certain instances, oscillatory behavior of neuronal firing is relevant for long time-scale behavior. A brief introduction to these models will be followed with a description of a more widespread electrical description of neural oscillations.

For single cell representations, biological models of neurons mathematically describe the

functional activity of neurons often by modeling the pattern and rate at which they fire (or *spike*) with respect to specific neuronal properties (e.g., electrical characteristics) [12]. Thus we have systems that oscillate with respect to some parameter other than position *x(t)* as detailed in the harmonic oscillator, such as by determining an underlying rate equation with respect to some parameter of the system. Some of the more well-known and commonly used biological neuron models include: Integrate-and-fire models, which relate the general electrical properties (e.g., current and voltage) of the neuron to the frequency of the neuron firing; Hodgkin-Huxley models, which cumulatively relate the electrical properties of each ionic current to the frequency of firing over time; FitzHugh-Nagumo, Morris-Lecar, and Hindmarsh-Rose models, which all simplify and expand upon the equations of the Hodgkin-Huxley models [12,13]. These models illustrate the idea that the properties of the neuron may dictate the pattern at which it fires, and for certain systems, may operate periodically due to the nature of the solutions to the differential equations each model represents. As in the case of harmonic oscillators and limit cycle oscillators, the functional solution that represents the behavior of the system defines the characteristics of the oscillation, such as frequency, period, or amplitude.

The discussed models have also been extended to collectively describe neural network activity as in the Wilson-Cowan model, or the Kuramoto model, which describe network systems as a collection of coupled phase oscillators that operate as functions of circular phase rather than time. With this alteration, however, as in the case of the harmonic oscillator, a critical aspect of the system is the steady-state behavior of the system [14].

Neural Oscillations

We now move from an introduction of mathematical models of neural firing on to a more general description of oscillations in the brain. As many of these models illustrate, specific fluctuations to the electrical properties of neurons reflect the activity of neural activity as either a function of oscillation phase (as in the Kuramoto model) or time. This principle defines the basis for measuring brain activity with respect to electrical activity, illustrated by the temporal measurements of electrical activity recorded by an electroencephalograph (EEG). EEG readings give a representation of neural activity by defining the frequency with which the activity oscillates divided into bands through the use of spectral analysis (e.g., Welch or Fourier analysis) [15]. As spectral analysis represents an algorithm for dissecting a periodic function into its constituent trigonometric elements (e.g., a variation of equation (2)), the characteristic bands for activity illustrate many of the properties characteristic of the harmonic oscillator, such as its steady-state oscillation frequency. Given that we are particularly interested in steady-state behavior of the EEG recordings, however, ongoing brain activity is recorded as opposed to single time-point recordings or activity induced by a stimulus or task. This allows for an accurate representation of neural activity with respect to fluctuations in the oscillatory behavior of the signal frequency bands, such as fluctuations to frequency or amplitude, phase shifts (or *phase resetting*; i.e., resetting $\varphi = 0$ for each constituent signal in equation (2) for a simple sinusoid), and interference between simultaneous neural activity readings. The fluctuations and dynamics of the oscillations often represent different neural events. For instance, ensembles of neurons may coordinate their firing activity through phase resetting, resulting in the coordination of the transient (and similarly steady-state) behavior of constituent signals [16].

Not only have fluctuations in the parameters of the oscillatory behavior of neural activity been identified, but also typical frequency ranges corresponding to different generalized neural events as

well [15]. These bands are: the *delta* band, representing neural activity of frequency $f < 4\,Hz$; the *theta* band, representing neural activity within the range $4\,Hz < f < 7\,Hz$; the *alpha* band, representing neural activity within the range $7\,Hz < f < 14\,Hz$; the *beta* band, representing neural activity within the range $15\,Hz < f < 25\,Hz$; the gamma band, representing neural activity within the range $30\,Hz < f < 100\,Hz$ [15]. Although many cognitive activities have been identified to correspond to the above categorization scheme, a great deal of interest has also focused on how differences in oscillations operate in conjunction with NMDA receptor activity.

NMDA Receptors

A plethora of studies have documented the role of NMDA receptors in synaptic plasticity and memory in the brain. Activation of the NMDA receptor requires the binding of both glutamate and glycine and the depolarization of the cell membrane [17]. NMDA receptor activation and NMDA-mediated downstream signaling appear essential for normal synaptic function [17]. In addition, hippocampal synaptic plasticity, a fundamental *driver* of memory encoding, typically depends on NMDA receptor activation and calcium influx [18]. One widely accepted model of synaptic plasticity involves the experimental paradigms of long-term potentiation (LTP) and long-term depression (LTD) [8,19–21]. Numerous studies to date have shown that LTP is a result of brief bursts of high frequency electrical stimulation (e.g., 100 Hz), which lead to a long-lasting increases in the strength of synaptic transmission, and which is correlated with memory encoding and NMDA receptor activation. In addition, prolonged low frequency stimulation (e.g., 1 Hz) results in a reduction in synaptic transmission [8,18,21], which appears to be a cellular process for reversing memory encoding. LTP and LTD are both associated with increases in intracellular calcium ($[Ca^{++}]_i$) [10]; however, LTD is associated with much smaller increases (~750 nM for ~ 1 min) of $[Ca^{++}]_i$ than LTP (>10 μM for 5–6 secs) [22]. It is thought that the rise in postsynaptic $[Ca^{++}]$ required for CA1 hippocampal LTP induction is due to the entry of Ca^{++} via the NMDA receptor complex [23]. Calcium elevation is always required for LTP, but NMDA receptor activation is not required in every case. Several reviews have been written on LTP induction and the connection to NMDA receptor activation [8,18,21,24].

NMDA Receptor Subunits

NMDA receptors are assembled from combinations of NR1 and NR2A-D, and in some variants from NR3A or B subunits [25]. The NR1 subunit is encoded from one gene [26]; where studies have shown that there are eight different NR1 splice variants [26,27]. The NR2 subunits (2A-D) are encoded by 4 closely related genes [26,28]. Samples from rodent cortex typically consist of NR1, NR2A, and NR2B subunits. Studies thus far also report that the NMDA receptor is usually composed of a tetramer of NR1 and NR2 subunits (usually two NR1 and two NR2 subunits) where the presence of the NR1 subunit is required, but many other combinations are possible [27,29].

Pathological Activation of the NMDA Receptor

Under normal conditions, the NMDA receptor ion channel is physically blocked by the presence of Mg^{++} [4]. Upon simultaneous binding of glutamate and glycine, and also as a result of membrane depolarization, the Mg^{++} block is relieved and the NMDA receptor complex is activated, which allows calcium and other ions such as sodium to enter the cell via the NMDA channel. However,

during acute brain injury (e.g., stroke) or as a result of chronic disease (e.g., Alzheimer's disease), the NMDA receptor can become hyperactivated. When hyperactivation occurs, NMDA receptor mediated signaling triggers numerous excitotoxic processes leading to cell death. On the other hand, hypoactivation of the NMDA receptor may also lead to chronic diseases, such as schizophrenia [30,31]. Less is known about hypoactivation of the NMDA receptor and disease, but it does appear that a there is an optimal window of activity required for normal NMDA receptor function.

NMDA-Receptor Mediated Survival

Some types of synaptic function regulated by NMDA receptors have been claimed to promote nerve cell survival [32,33]. Because of this, the total blockade of NMDA-receptor-mediated synaptic transmission as a pharmacological treatment could be considered unfavorable for some neurological conditions. For example, complete blockade of NMDA receptor activity during acute injury, such as stroke or head trauma, or chronic conditions, such as Alzheimer's disease, might negatively affect endogenous mechanisms of neuroprotection mediated by NMDA receptor signaling. Of note is that the activation of NMDA receptors also leads to Ca^{++} entry through its channel, which in turn triggers the activation of extracellular signal-regulated kinase (ERK1/2) and Ca^{++}-calmodulin (CaM) kinase pathways that then lead to cAMP-response-element-binding protein (CREB) phosphorylation. This is important since CREB phosphorylation is linked to gene transcription and is known to be associated with cell survival. For example, studies show that CREB is activated by stimuli such as hypoxia-ischemia (HI), which is associated with cell survival at specific time points. Also, animals that lack CREB show neuronal apoptosis during critical developmental periods. Given this, it appears that NMDA-mediated CREB activation may contribute to ischemic tolerance for HI and may also help to regulate cell number.

NMDA Receptors and Oscillatory Dynamics

Data have been emerging since the 1990s that suggested NMDA receptors and other glutamatergic receptors play a role in oscillatory dynamics [34–37]. For example, Whittington et al. showed that [34], networks of inhibitory neurons can generate 40 Hz oscillations (gamma range) in pyramidal cells that can entrain their activity. Moreover, it was found that these oscillations occur in response to the activation of metabotropic glutamate receptors. In this study 40 Hz oscillations appeared to be a collective activity in networks of interneurons of the hippocampus. Moreover, the authors speculated that more far reaching synchrony might occur by oscillatory interactions between the hippocampus and the thalamus.

In a study by Jacobsen et al. [38] thalamic slice preparations were used to study spindle-like oscillations *in vitro* in the ferret. Oscillations of this kind have been referred to as sleep spindles and have been witnessed during non-rapid eye movement (non-REM) sleep. Although the significance of *sleep spindles* are not well understood, here they found that NMDA receptor activity contributed to the appearance of these oscillations. In addition, γ-aminobutyric acid (GABA) receptors and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors also contributed.

In another brain slice study by Middleton et al. [35], circuits in the entorhinal cortex and hippocampus were examined. These circuits were chosen since they generate 40 Hz activity independently of each other. Here they used the NMDA antagonist ketamine, which was known to affect memory, and found that this administration exposed an additional gamma rhythm at 25–35 Hz.

In other words, NMDA receptor modulation appeared to control switching between two distinct gamma rhythms and thus controlled activity between the entorhinal cortex and the hippocampus. These results could imply that the two different modes represent distinct cognitive processes. The findings also suggested that the strength and frequency of the nerve cell output from the entorhinal cortex was regulated by the intensity of the NMDA receptor activation.

Ketamine, a NMDA antagonist, has been used in other studies as well and Lazarewicz et al. [36] showed in an *in vivo* study with mice that ketamine modulates both theta and gamma oscillations. In this study, ketamine reduced the theta frequency band in background activity and in post-stimulus evoked activity, while in the gamma range, it enhanced both background and evoked power, but decreased relative induced power. Overall, these results suggested that NMDA receptors played a key role in controlling the balance between theta and gamma responses.

Additional studies using NMDA receptor ablation techniques have also showed alterations in oscillatory activity and in working memory. In a study by Korotkova et al. [39] NR1 subunits were removed from parvalbumin (PV)-positive interneurons. These mice were found to have alterations in theta and gamma oscillations and deficits in spatial working and in long term memory. In particular, theta rhythms were found to be diminished while gamma oscillations were increased. Other more recent work by Carlen et al. [40] generally support these findings by illustrating a critical role for NMDA receptors in PV neurons contributing to gamma oscillations in mice.

Additional studies have examined relationships between hallucinations and gamma oscillations. Interestingly, normal perception may emerge from the matching of information processing in the sensory cortex with information generated by previously stored memories from other cortical areas. To investigate how hallucinations may alter this process, Anver et al. [41] used rats *in vivo* and tested the effects of the NMDA antagonists ketamine and phencyclidine (PCP) in the visual cortex. Both agents are known to induce hallucinations and are associated with *hypersynchronization* in the gamma frequency band. In this study, it was found that the induced NMDA receptor hypofunction using ketamine and PCP caused phase coupling of two normally phase independent gamma generating networks (low frequency gamma, 34 Hz, and high frequency gamma, 54 Hz), which caused oscillation *hypersynchrony*. This suggested that perception may be altered thus leading to hallucinations when a mismatch occurs between sensory information processing and information processing from stored memories. In other words, the pharmacologically induced NMDA receptor hypofunction appears to couple the gamma oscillations from distinct networks (layer III and layer V) that are not typically coupled, thus leading to distorted perceptions, that is, hallucinations. In particular, the effect was mediated by *D*-serine-dependent NR2B subunit containing receptors and was reversed by increasing the rate of NMDA receptor activity.

Other studies have also reported that NMDA receptor blockade results in shifting oscillation synchronization. In a recent study by Wingerden et al. [42] single unit activity was recorded in rat neurons using tetrode technology (tetrodes are groups of four electrodes used for electrophysiology). In particular, neurons in the orbitofrontal cortex were recorded because of their role in odor processing and decision making and their ability to discriminate between cues. In this study they found that NMDA receptor blockade leads to hypersychronous phase locking (e.g., modulating firing rate by matching φ's as in equation (2)) in the theta, beta, and high frequency bands (i.e., 110–150 Hz). However NMDA blockade did not affect behavioral performance during task acquisition, but did attenuate changes in reaction time.

Characteristics of the Simple Harmonic Oscillator in NMDA Receptor Activity

As has been discussed, the oscillatory activity of NMDA receptors can be influenced by many characteristics of the immediate biological environment, and thus alterations to this environment may lead to a disruption to the rhythmicity of NMDA firing. To simplify the depth of discussion into the mathematics of describing NMDA receptor activity, the characteristics of oscillations will be inferred by using the harmonic oscillator described above. Wallén and Grillner [43] showed that when measuring NMDA activity with respect to cellular membrane potential in spinal cord tissue from the primitive vertebrate lamprey, the nature of the oscillations were altered by manipulating ion concentrations of Mg^{++} and Na^{+}, tetrodotoxin injection, and varied electrical current injection (both depolarizing and hyperpolarizing) into the measured cells. For instance, removal of either Mg^{++} or Na^{+} independently resulted in not only an increase in frequency of oscillation but also the introduction of oscillatory damping (e.g. see equations (5) and (7)) rather than spontaneous cessation. Particularly interesting, in the absence of Mg^{++}, electrical stimulation was unable to regenerate oscillatory activity regardless of the size of the injected current, despite showing that electrical stimulation influences the frequency of oscillation in baseline activity (presence of a standard physiological concentration of Mg^{++}). They showed that as Mg^{++} was re-introduced to the environment, spontaneous maintained (undamped) oscillatory activity without current injection occurred. Thus it appears that although electrical stimulation may act as a driving force for oscillations (e.g. $F_{ext}(t)$ in equation (6)), Mg^{++} is necessary for NMDA oscillation and the absence of Mg^{++} is inherently damping to NMDA activity. Similarly, Wang et al. [44] showed that Ca^{++} dynamics influences the shape of NMDA receptor activity, whereby the firing activity of the NMDA receptor becomes more 'spike-like' due to activation of Ca^{++}-dependent K^{+} channels.

Although the harmonic oscillator is an adequate introduction to the dynamics of oscillatory activity, and can explain some of the fundamental characteristics of real-world oscillatory systems as in NMDA receptors, they no longer provide an exact representation of activity due to the introduction of additional parameters (e.g. multiple ion channels influencing the activity of the NMDA receptor) and an inherent change to the nature (i.e., shape) of the oscillating function. As with neuron models described above, differential equations representing the dynamics of the system may result in the equations acquired in the harmonic oscillator for simple systems, but may warrant more complicated solutions in more complex systems. For instance, Lee et al. [45] utilized a biophysical model of NMDA receptor-mediated plasticity by modeling ion channel activity (for each Na^{+}, K^{+}, Ca^{++}), and AMPA receptor and NMDA receptor currents using differential calculus, and using these equations to dictate the times at which cells fire pre-synaptically and post-synaptically.

Effects on Navigation and Memory

Spatial navigation requires an animal to determine and maintain a trajectory from a point of departure to a target location. It also at times requires the memory of a learned route. A so-called *cognitive map* is thought to be utilized for navigation, which is dependent on recall of different types of memories. So called *place cells* in the hippocampus, appear to contribute to the formation of the cognitive map [46]. For example, allocentric navigation [47] is defined as the generation and use of cognitive maps that are not centered on the navigator (i.e., encodes the location of how one object is related to the location of another object). Or, an animal may remember a sequence of left and right movements in reference to *itself* (i.e., egocentric navigation) [47]. Studies have shown that the hippocampus plays a central role in the encoding of spatial information associated with both types of

spatial navigation [48], however, allocentric navigation appears to depend mostly on the hippocampus, whereas egocentric navigation also is regulated by parietal lobe and prefrontal regions of the brain.

In a recent study by Cabral et al. [37], navigational abilities were assessed after NMDA modulation. In this study, mice had a deletion of forebrain NMDA receptors, which resulted in an impairment in the ability of place cells to maintain a cognitive map based on sequence memory. In addition, oscillatory dynamics were altered by this deletion, which suggested that oscillations contribute to navigational capacity. The data are interesting since they also imply that place field maps change depending on the dominating gamma frequency.

5. Conclusions

Mechanisms of memory are far from being completely understood. However, oscillations of brain activity are a relatively new area of research and truly an added dimension of scientific thought with regard to their contribution to memory processing and cognition. The interplay between oscillatory activity and NMDA receptors also add an intellectually curious and fascinating dimension of inquiry in this area. As mathematical and experimental methods continue to develop and adequately unveil the mechanics of this interplay, our understanding of how oscillations and NMDA receptors interact in order to contribute to cognitive processing will most certainly lead to the discovery of novel targets for intervention in conditions where oscillations and NMDA receptor activity become altered by disease.

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Conflict of Interest

All authors declare no conflicts of interest in this paper.

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