


# Bottom-up gamma and bipolar disorder, clinical and neuroepigenetic implications

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**Objectives:** This limited review examines the role of the reticular activating system (RAS), especially the pedunculo-pontine nucleus (PPN), one site of origin of bottom-up gamma, in the symptoms of bipolar disorder (BD).

**Methods:** The expression of neuronal calcium sensor protein 1 (NCS-1) in the brains of BD patients is increased. It has recently been found that all PPN neurons manifest intrinsic membrane beta/gamma frequency oscillations mediated by high threshold calcium channels, suggesting that it is one source of bottom-up gamma. This review specifically addresses the involvement of these channels in the manifestation of BD.

**Results:** Excess NCS-1 was found to dampen gamma band oscillations in PPN neurons. Lithium, a first line treatment for BD, was found to decrease the effects of NCS-1 on gamma band oscillations in PPN neurons. Moreover, gamma band oscillations appear to epigenetically modulate gene transcription in PPN neurons, providing a new direction for research in BD.

**Conclusions:** This is an area needing much additional research, especially since the dysregulation of calcium channels may help explain many of the disorders of arousal in, elicit unwanted neuroepigenetic modulation in, and point to novel therapeutic avenues for, BD.

## KEYWORDS

Arousal, binding, Ca<sup>2+</sup> channels, gamma oscillations, lithium, NCS-1, neuroepigenetics, preconscious awareness, REM sleep, waking

## 1 | INTRODUCTION

### 1.1 | Sleep dysregulation in bipolar disorder (BD)

The wake-sleep patterns manifested in the EEG of bipolar disorder (BD) patients include fragmented sleep, decreased slow wave sleep, increased vigilance, and increased REM sleep drive.<sup>1-3</sup> More specifically, adults with BD manifest reduced sleep duration and delayed sleep onset during episodes of mania, which show decreased REM sleep latency and increased REM sleep duration. On the other hand, during episodes of depression, BD patients experience

insomnia or hypersomnia, also with decreased REM sleep latency and increased REM sleep density.<sup>1,3-5</sup> Recent analyses described fragmented sleep (characterized by increased sleep onset, waking after sleep onset, and overall sleep efficiency) in BD.<sup>6,7</sup> These patients also show decreased habituation of the arousal-related P50 potential in a paired stimulus paradigm,<sup>8,9</sup> indicative of a sensory gating deficit, along with increased startle response,<sup>10</sup> and dysregulation of blink reflexes,<sup>11</sup> indicative of exaggerated reflexes. *All of these symptoms are suggestive of hyper-arousal as a hallmark of the disease.* Importantly, reduced maintained gamma band activity

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has been reported in BD patients.<sup>12</sup> That is, while patients have hyper-arousal, waking is marked by erratic maintenance of high frequency activity. As we will see below, hyper-arousal and decreased maintenance of gamma band activity can account for many of the symptoms in BD, including wake-sleep, arousal, and cognitive symptoms.

## 1.2 | Tonic and phasic arousal and hyper-arousal

The reticular activating system (RAS) exhibits both phasic and tonic actions. On the one hand, it is in charge of relaying sudden or startling stimuli to elicit both cortical activation and reticulospinal motor readiness, and on the other hand, it is in charge of keeping us awake on a continuous basis.<sup>13</sup> The first description of the RAS suggested that it specifically participates in “tonic or continuous” arousal.<sup>14</sup> In addition, it was found that lesions of this region could eliminate tonic arousal.<sup>15</sup> Therefore, these tonic mechanisms help maintain gamma band activity for prolonged periods and are critically important for such functions as perception, learning, and memory, not to mention consciousness. It has been suggested that consciousness is associated with *continuous* gamma band activity, as opposed to an interrupted pattern of activity.<sup>16</sup> The lack of consistent gamma band activity would alter waking and REM sleep drive, decrease binding of perceptions, decrease the ability to attend, etc., thus accounting for a number of symptoms in BD. Transitions between mania and depression could well be related to shifts in arousal levels, as would erratic energy and activity levels. In addition, sudden stimuli activate ascending RAS projections to the thalamus and then the cortex to induce cortical arousal, and simultaneously activate descending projections that influence the spinal cord in the form of postural changes in tone resulting from the startle response, as well as trigger locomotor events in fight-vs-flight responses.<sup>13</sup> Dysregulation of this system thus can elicit a host of abnormal sensory and motor (reflex) responses, both tonic and phasic, that can account for a number of symptoms expressed in BD.

## 2 | METHODS

We have reviewed a limited series of articles describing both basic science and clinical data related to the underlying mechanisms of BD. In addition, cross-references were searched from identified papers related to calcium channels involved in intrinsic gamma oscillations, especially neuronal calcium sensor protein 1 (NCS-1). Papers not addressing the role of calcium channels in BD were excluded based on initial screening of titles and abstracts, and subsequently selection was based on the concept of “bottom-up gamma” and new experiments describing a mechanism of action of lithium, and gamma oscillations and their epigenetic modulation in the PPN.

## 3 | RESULTS

### 3.1 | Bottom-up gamma

#### 3.1.1 | What does it do?

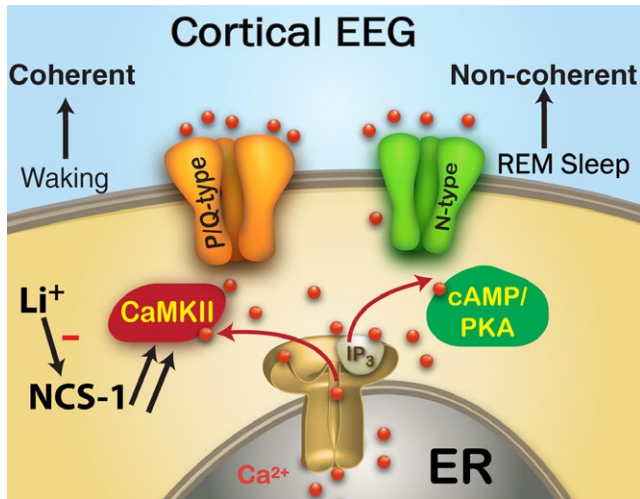
Recent studies suggest that feed forward signals from the brainstem and feedback signaling from the cortex use different frequency channels, specifically gamma and beta frequencies, respectively.<sup>17</sup> On the one hand, bottom-up gamma or feed forward brain processes depend on sensory events that activate lower brain centers and the information rises to succeeding higher centers to promote perception. On the other hand, top-down beta or feedback processing refers to the influence imposed by higher centers on the perception of and attention to sensory stimuli. Gamma/beta oscillations are known to participate in perception, problem solving, and memory.<sup>18-21</sup> Synchronous or coherent beta/gamma band activation in thalamocortical networks,<sup>22</sup> and other neuronal groups is thought to contribute to the merger, or “binding”, of information originating from separate regions, necessary for unified perception.<sup>23</sup> Moreover, beta/gamma oscillation deficits have been suggested as a pathophysiologic feature of diseases like schizophrenia and Alzheimer's disease.<sup>24,25</sup>

#### 3.1.2 | Where does it come from?

Gamma oscillations are thought to emerge from the dynamic interaction between intrinsic neuronal and synaptic properties of thalamocortical networks.<sup>22</sup> That is, synaptic connections alone may not be able to maintain firing at gamma frequencies (~30-90 Hz), so that intrinsic membrane properties also appear essential to the maintenance of gamma band activity.<sup>26,27</sup> Thus, the ability of cells with intrinsic membrane properties, coupled with synaptic interactions, is what allows the circuit as a whole to fire at a preferred frequency, and is essential to maintaining frequencies in the beta/gamma range. At the thalamic level, thalamocortical excitatory neurons have intrinsic properties needed to generate subthreshold gamma band membrane oscillations.<sup>28</sup>

However, the cortex and thalamus are not the only regions capable of generating beta/gamma frequency oscillations. For example, the hippocampus and cerebellum have the intrinsic and synaptic properties necessary to generate gamma band oscillatory activity. Hippocampal oscillatory activity in the gamma range (30-60 Hz) has been extensively described to be functional associated with entorhinal cortex afferents.<sup>29</sup> Gamma band activity in the hippocampal cornu ammonis 1 (CA1) subfield was divided into fast (>65 Hz) and slow (~25-60 Hz) frequency components differentially coupling CA1 and CA3 subfields.<sup>30</sup> These different frequency bands have been proposed to “bind” CA1 fast gamma oscillations with very high frequency activity from entorhinal cortex (in charge of providing information about object and place recognition in rodents<sup>31</sup>), whereas CA1 slow gamma oscillations would be locked to the slower frequencies present in the CA3 area in charge of memory storage.<sup>32</sup>

Gamma band power also has been described in the olivocerebellar system.<sup>33,34</sup> Cortico-cerebellar coherence at gamma frequencies is



**FIGURE 1** Waking vs REM sleep gamma mechanisms. The Cortical EEG looks the same during waking and REM sleep, but it is coherent across regions during waking and non-coherent during REM sleep. The cortical EEG, therefore, is driven by the RAS, which regulates waking and sleep. Cells in the PPN modulate gamma oscillations during waking through P/Q-type calcium channels that are under the control of CaMKII, while cells in the PPN that modulate REM sleep do so through N-type calcium channels that are under the control of cAMP/PKA. In BD, NCS-1 is over expressed (note double arrows to denote over expression) and its excess decreases CaMKII and P/Q-type driven gamma oscillations to decrease the maintenance of gamma band activity during waking. This may also lead to excessive REM sleep drive. Li<sup>+</sup> inhibits the action of over expressed NCS-1 in order to restore the generation of gamma band oscillations during waking [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

evident in monkeys during performance of a manual precision grip task,<sup>35</sup> and cerebello-thalamic activity is synchronized with neocortical activity at gamma frequencies.<sup>36</sup> Thus, it has been proposed that both cerebellar and thalamocortical networks might oscillate at the same frequencies to enable information exchange and processing among these brain areas.<sup>34</sup>

Importantly, it has been shown that beta/gamma band activity in the motor cortex lags behind coherent activity in the basal ganglia.<sup>37</sup> This led to the suggestion that motor cortex beta/gamma synchronization reflects a momentary arousal-related event for enabling the initiation of movement.<sup>38,39</sup> That is, structures such as the RAS, that mediates arousal, and thalamus, that carries afferent information, may play an early permissive role in the control of movement. Moreover, there are several other regions generating gamma band activity besides the cortex and thalamus, including the hippocampus, cerebellum, basal ganglia, and importantly, the RAS.

## 3.2 | Gamma during waking vs during REM sleep

### 3.2.1 | Two types of high threshold calcium channels

The PPN is the only nucleus in the RAS that is active during states of high frequency (beta/gamma) EEG activity as in waking and

REM sleep. Paradoxically, the EEG during the two markedly different states is identical, but, is beta/gamma band activity during waking really the same as during REM sleep? In general, recordings of PPN neurons during sleep-wake states revealed neurons that were active during waking and REM sleep, referred to as “Wake-REM on” cells, others were active only during REM sleep, referred to as “REM on” cells, and yet others were active only during waking, referred to as “Wake on” cells, and none were more active during slow wave sleep.<sup>40-43</sup> Gamma band activity has been observed in the cortical EEG of the cat in vivo when the animal is active<sup>44</sup>; in the region of the PPN in humans during stepping, but not at rest<sup>45</sup>; and firing at low frequencies ~10 Hz at rest in the primate, but firing at gamma band frequencies when the animal woke up, or when the animal began walking on a treadmill.<sup>46</sup> Thus, the same cells were involved in both arousal and motor control in the PPN in vitro, in vivo, and across species, including man.

Our findings established that all PPN neurons fired maximally at beta/gamma frequencies,<sup>47</sup> that all PPN neurons manifested beta/gamma frequency intrinsic membrane oscillations,<sup>48</sup> and that these oscillations were mediated by high threshold, voltage-dependent N- and P/Q-type calcium channels.<sup>27</sup> We found that these channels were distributed along the dendrites of PPN neurons,<sup>50</sup> and that some cells exhibited both N- and P/Q-type calcium channels, some had only N-type channels, and some had only P/Q-type channels.<sup>51,52</sup> We suggested that these three cell types represented neurons that were active in relation to waking and REM sleep (N+P/Q cells = “Wake-REM on” cells), only during REM sleep (N-only = “REM on” cells), or only during waking (P/Q only = “Wake on” cells), respectively.<sup>51-54</sup>

### 3.2.2 | Two intracellular pathways

In freely moving animals, injections of glutamate into the PPN increased both waking and REM sleep,<sup>55</sup> but injections of NMDA, one glutamatergic receptor agonist, increased only waking,<sup>56</sup> while injections of kainic acid (KA), another glutamatergic receptor agonist, increased only REM sleep.<sup>57</sup> These data indicated a differential control of waking vs REM sleep by different glutamatergic receptor subtypes. Protein kinase C (PKC), which modulates KA receptors, enhances N-type channel activity and has no effect on P/Q-type channel function,<sup>58</sup> however, calmodulin dependent kinase II (CaMKII), which modulates NMDA receptors, was shown to modulate P/Q-type channel function.<sup>59</sup> These results suggest that the two high threshold calcium channel types are modulated by different intracellular pathways, N-type by the cAMP/PK pathway, and P/Q-type via the CaMKII pathway. The implications from all of these results is that there is a “waking” pathway mediated by CaMKII and P/Q-type channels and a “REM sleep” pathway mediated by cAMP/PK and N-type channels, moreover, different PPN cells fire during waking (those with N+P/Q and only P/Q-type) or REM sleep (those with N+P/Q and only N-type) or both (N+P/Q).<sup>13,53,54</sup>

### 3.2.3 | Is gamma from the PPN manifested in the cortical EEG?

Recent findings showed that gamma band activity at the level of the cortex during waking is characterized by coherence across regions, but gamma band activity in the cortex during REM sleep has an absence of coherence.<sup>60</sup> Thus, since the brainstem is the origin of REM sleep drive, it is clear that the manifestation of gamma band activity during REM sleep at the level of the cortex begins in the brainstem. We assume that the manifestation of gamma band activity during waking is at least in part originating in the brainstem as well. Moreover, injections of the cholinergic agonist carbachol induced REM sleep with cataplexy that is characterized by decreased gamma band coherence in the cortex.<sup>61</sup> Therefore, this line of evidence suggests that, not only do brainstem centers drive gamma band activity that is manifested in the cortical EEG, but during waking, brainstem-thalamic projections include coherence across regions, and during REM sleep, which is controlled by the Subcoeruleus region (lesion of this region eliminates REM sleep, and injection of carbachol into it induces REM sleep), drives cortical EEG rhythms without coherence.<sup>62,63</sup>

Figure 1 shows the proposed organization of the differential control of beta/gamma band activity during waking through P/Q-type calcium channels that are modulated by intracellular CaMKII, while activity during REM sleep through N-type channels is modulated by cAMP/PKA. As far as the cortical EEG is concerned, waking drive from the PPN through the intralaminar thalamus induces coherent cortical gamma band activity, but REM sleep drive, presumably through the Subcoeruleus nucleus, induces cortical gamma band activity without coherence across regions. Included in this figure is the role of neuronal calcium sensor protein 1 (NCS-1) in modulating P/Q-type channels, and that of lithium, which inhibits the action of NCS-1.

## 3.3 | Neuronal calcium sensor protein 1 (NCS-1)

### 3.3.1 | Role of NCS-1

NCS-1 is expressed in the brain and heart, where it has been identified as a regulator of cardiac  $Ca^{2+}$  signaling.<sup>64,65</sup> Furthermore, a study on immature hearts reported that NCS-1 interacts with inositol 1,4,5-triphosphate receptor protein (InsP3R).<sup>65</sup> NCS-1 is known to enhance the activity of InsP3Rs,<sup>66</sup> thus amplifying  $Ca^{2+}$  signaling through these receptors. Importantly, InsP3Rs are present in the PPN.<sup>67</sup> Stimulation of InsP3 levels resulted in phosphorylation of CaMKII, which was enhanced by NCS-1 over expression. These results indicate that a functional link exists between NCS-1, InsP3 function, and CaMKII activation that potentially affect global  $Ca^{2+}$  signaling.<sup>64,65</sup> However, NCS-1 is known to interact with many other target proteins in the brain, including 1-phosphatidylinositol 4-kinase,<sup>68,69</sup> dopamine D2 receptors,<sup>70</sup> as well as voltage-gated  $Ca^{2+}$ ,<sup>71-74</sup> and  $K^+$  channels.<sup>64,74</sup>

We discovered that intracellular NCS-1 had a concentration-dependent effect on beta/gamma oscillatory activity in PPN neurons.<sup>75,76</sup> While lower levels of NCS-1 enhanced oscillation amplitude at long latency, higher levels of NCS-1 had an early enhancing effect of oscillation amplitude that was followed by an inhibitory effect, ultimately reducing the amplitude of gamma oscillations. Strikingly, the time course of the calcium current block was similar to the high level NCS-1 effect on oscillation amplitude, but both of these effects were faster than the one observed for the enhancement of gamma band amplitude, suggesting that multiple intracellular mechanisms may mediate the NCS-1 effects on PPN oscillations. We concluded that NCS-1 at optimal concentrations will help maintain gamma band oscillations dependent on P/Q-type calcium channels, but excessive levels of NCS-1 will lead to a decrease or interrupted pattern of waking-related (P/Q-type channel-mediated) gamma band activity. However, since NCS-1 is also known to down regulate N-type calcium channels,<sup>77</sup> we assumed that these are the channels being blocked by NCS-1 to reduce calcium currents. Therefore, we suggested that NCS-1 will also down regulate N-type calcium channel REM sleep-related gamma oscillations.<sup>75,76</sup> This implies a push-pull effect in which appropriate levels of NCS-1 will promote P/Q-type channel oscillations as in waking, and suppress N-type channel oscillations as in REM sleep.

### 3.3.2 | Over expression in BD

In addition to the symptoms described at the beginning of this article, the symptoms of BD also include disturbances in cognition. These include sleep and circadian disturbances, but also emotional dysregulation, and cognitive impairments.<sup>1,78-80</sup> For example, attention and memory deficits, impairment in verbal recall and fine motor skills, and disturbance of sustained attention are present during depressive episodes, whereas during mania, episodes of dysfunction in attention, complex processing, memory, and emotional processing are manifested.<sup>79</sup> Cognitive deficits are evident even during euthymia, when executive function, verbal memory, sustained attention, visual memory, and verbal fluency are disturbed.<sup>80</sup> Many of these symptoms, however, can be accounted for by dysregulation of gamma band activity.

Human postmortem studies reported increased expression of high affinity, low capacity NCS-1 in the brains of some BD and schizophrenic patients.<sup>81</sup> However, although the average levels were elevated, some patients manifested NCS-1 levels close to normal values. Therefore, either the expression levels are chronically elevated only in some patients, or death in some patients occurred when levels were close to normal, implying that levels fluctuate. Which option may be correct remains to be determined. Given the paucity of research in this area, we can only speculate, but there are a number of potentially productive lines of research that could lead to better therapeutic options.

Given the foregoing, we assume that during normal waking, normal levels of NCS-1 will promote P/Q-type channel function and suppress N-type channel function, thus helping maintain the

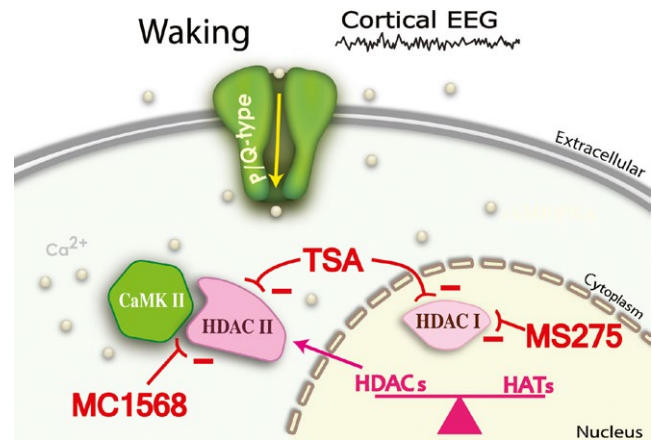
awake state. During sleep, NCS-1 levels probably decrease, removing waking drive and disinhibiting N-type channel activity, which presumably promotes REM sleep. What happens if NCS-1 levels are increased such as in over expression? Excessive NCS-1 levels during waking would decrease waking drive through suppression of gamma activity. At the same time, there may be some inactivation of the inhibitory effects of NCS-1 on N-type channels, permitting REM sleep drive to increase. Under these circumstances, perception and consciousness would be interrupted during waking, leading to attentional and cognitive disturbances. In addition, REM sleep drive may be increased during waking, leading to misperception and perhaps hallucinations. Therapies that normalize sleep-wake states would certainly help reduce some of these symptoms.

### 3.3.3 | Effects of lithium

Lithium was by chance found to treat the mood disturbances in BD, and it is an ion that remains one of the best treatment options, although it is limited by side effects.<sup>82</sup> Lithium may act by inhibiting the interaction between NCS-1 and InsP3.<sup>83</sup> Our findings demonstrated that lithium suppressed the effects of NCS-1 on gamma oscillations in a concentration-dependent manner.<sup>75,76</sup> These results provide a physiological mechanism (gamma band dysregulation) that can account for many of the symptoms of the disease, as well as a rationale for the effective treatment of BD with lithium by down regulating NCS-1, and promoting the maintenance of gamma band activity. If lithium levels are too high, then the suppression would lead to sleepiness and other adverse effects, if too low, there would be insufficient suppression of over expressed NCS-1 (see Figure 1). Such a mechanism helps explain the need for therapeutic levels of lithium to be monitored in order to remain at an effective range. A number of other agents are also used successfully, including anticonvulsants and antipsychotics, which are beyond the scope of the present article. Fortunately, for many patients such therapies do allow them to function more normally and lead productive lives.

### 3.3.4 | Neuroepigenetic modulation of PPN neurons

Epigenetic mechanisms, that is, histone posttranslational modification and DNA methylation, play a role in regulating gene expression in response to environmental stimuli, such as learning, stress, or drugs of abuse.<sup>84</sup> Acetylation of histones is associated with the modulation of transcription by relaxing chromatin structure that would increase the accessibility of transcription factors to their target genes, and also by direct acetylation of transcription factors and other proteins.<sup>85</sup> Histone acetylation is controlled by the balance between two families of enzymes, the histone acetyltransferases (HATs) and the histone deacetylases (HDACs). The antagonism between these enzymes is a key regulatory mechanism for many cellular processes and disease states. HDACs have been classified into four classes, with Class I HDACs localized in the nucleus, but Class IIs shuttle between the nucleus and the



**FIGURE 2** P/Q-type channels, CaMKII, and HDAC Class II interactions. During waking, gamma oscillations mediated by P/Q-type Ca<sup>2+</sup> channels lead to Ca<sup>2+</sup> entry and interaction with CaMKII. In turn, CaMKII leads to phosphorylation of HDAC Class IIs that have left the nucleus (while HDAC Class Is remain in the nucleus). The complex between CaMKII and HDAC Class IIs is maintained by Ca<sup>2+</sup> entry, in the case of P/Q-type channels, specifically during waking. Deacetylation of histones facilitates transcription. MC1568, a HDAC Class IIb inhibitor blocked oscillations, while MS275, a HDAC Class I inhibitor did not affect oscillations.<sup>88</sup> The minus (-) signs denote inhibition by TSA of HDAC class I and HDAC class II; inhibition of HDAC class I by MS275' and inhibition of HDAC class II by MC1568 [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

cytoplasm where they can modify non-histone proteins. HDAC inhibitors are candidates for treating cancer and several neurodegenerative disorders.<sup>86</sup> However, these produce a range of side effects, including fatigue, seizures, somnolence, and gait problems.<sup>87</sup> That is, these HDAC inhibitors may affect arousal.

We studied whether PPN intrinsic gamma oscillations that are involved in arousal are affected by inhibition of histone deacetylation. Our results showed that, (a) acute *in vitro* exposure to the histone acetylation inhibitor trichostatin A (TSA) led to the elimination of high threshold, voltage-dependent Ca<sup>2+</sup> channel-mediated intrinsic membrane oscillations, specifically in the gamma band range but not lower frequencies, (b) pre-incubation with TSA led to a similar decrease specifically in gamma band oscillations, (c) a significant reduction in Ca<sup>2+</sup> currents was elicited by the same histone acetylation inhibitor, (d) a HDAC Class I inhibitor, MS275, failed to affect intrinsic gamma oscillations in PPN neurons, and (e) a HDAC Class IIb inhibitor, MC1568, blocked gamma oscillations.<sup>88</sup> These results suggest that there is a specific effect on gamma band oscillations when histone deacetylation via HDACIIb is blocked, suggesting that gamma oscillations related to arousal could be modulated by the balance between histone acetylation and deacetylation.

Acetylation and deacetylation of histone proteins in the brain represents one of the most significant neuroepigenetic mechanisms for the control of gene expression. The fact that the PPN modulates both waking and REM sleep, the two states with prominent EEG gamma band activity, suggests that TSA blockade of intrinsic

**TABLE 1** Neuroepigenetic effects of histone deacetylases in PPN gamma oscillations<sup>88</sup>

Agent	Conc'n role		Effect
Trichostatin A (TSA)	1 μmol/L	Inhibits HDAC class I	No effect on oscillations
		Inhibits HDAC class II	Blocks oscillations
MC1568	1 μmol/L	Inhibits HDAC class IIa	Blocks oscillations
MS275	500 nmol/L	Inhibits HDAC class I	No effect on oscillations
Tubastatin A	150 nmol/L	Inhibits HDAC class IIb	No effect on oscillations
KN-93	1 μmol/L	Inhibits CaMKII	Reduced effects of TSA

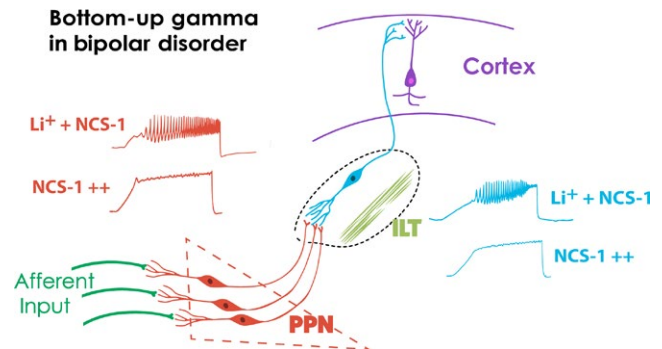
HDAC class Is remains in the nucleus while HDAC class IIs can move to cytoplasm.

membrane gamma oscillations eliminates a major process subserved by gamma band frequency activity, arousal. Our discovery suggests that this constant flow of continuous sensory information through the induction of gamma oscillations may be modulating the transcription of genes in PPN neurons.<sup>88</sup> This represents a potential neuroepigenetic mechanism not previously considered, but which carries significant implications. The constant flow of afferent information, termed bottom-up gamma,<sup>62</sup> may be providing ongoing remodeling of the neurons in this part of the RAS, a kind of daily update of sensory experience. Figure 2 is a diagram of the relationship between P/Q-type  $Ca^{2+}$  channels, CaMKII, and the interaction with HDAC Class IIs. Table 1 summarizes the effects of the agents used in this study.<sup>88</sup>

In BD, therefore, maintaining an appropriate level of gamma oscillations is essential to the sculpting of neurons taking place through genetic modification. Long-term dysregulation of this process may physically transform neurons exposed to over expression of NCS-1 and its effects on gamma oscillations, requiring extended treatment to correct these distortions. Stabilizing the manifestation of gamma oscillations during waking is essential to combating the debilitating effects of decreased or interrupted gamma band activity.

## 4 | DISCUSSION

Figure 3 depicts one origin of bottom-up gamma via sensory afferents that induce gamma oscillations in PPN neurons. These PPN cells project to the parafascicular nucleus in the intralaminar thalamus (ILT), that also manifests N- and P/Q-type calcium channel-mediated gamma oscillations,<sup>89</sup> and these channels are located all along the dendrites of Pf neurons.<sup>90</sup> The ILT projects arousal-related input to upper layers of the cortex, providing the context of sensory perception.<sup>22,23</sup> In BD, the effects of over expressed NCS-1 in suppressing intrinsic membrane gamma oscillations in the PPN, and presumably in its ascending target, the Pf, would decrease gamma maintenance at the level of the cortex. However, with lithium treatment, appropriate gamma oscillation amplitudes are presumably restored in the PPN and Pf, among other regions.



**FIGURE 3** Bottom-up gamma in bipolar disorder. Afferent input helps activate PPN neurons that manifest intrinsic gamma band oscillations through high threshold, voltage-dependent calcium channels. These cells project to the intralaminar thalamus (ILT)<sup>89,90</sup> that also manifests these calcium channels to drive cortical activity by terminating in layers I and II. When NCS-1 is over expressed (NCS-1 with multiple ++), these oscillations are reduced, but  $Li^+$  therapy ( $Li^+$  + NCS-1) will restore intrinsic gamma band oscillations, perhaps both in the PPN (left side, red records) and ILT (right side, blue records), among other regions. We assume that too much  $Li^+$  will over inhibit NCS-1 and decrease oscillations, while too little  $Li^+$  will not overcome the suppression of oscillations by over expressed NCS-1. This suggests, in keeping with standard therapy, that concentrations of  $Li^+$  should be maintained at an optimal level [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

These suggestions provide a direction for determining, for example, the role of N-type and P/Q-type calcium channel expression in BD, which has not been explored. The role of intracellular pathways through CaMKII and cAMP/PKA in BD require further attention, as does the modulation of levels of NCS-1 and InsP3. For example, are the effects of NCS-1 mediated by its interaction with InsP3? Will blockade of InsP3 have similar effects as blocking NCS-1? These and additional questions remain, but the discoveries described herein provide, (a) a physiological mechanism that accounts for many of the symptoms of the disease, and (b) multiple novel directions for developing more effective treatments for BD.

Such efforts are important because disturbances in gamma band maintenance at the level of the PPN will disrupt a basic survival process. The ubiquitous generation of gamma band activity by all PPN

neurons has been proposed, not to participate in the temporal process of sensory binding as in the cortex, but to underlie the more basic process of preconscious awareness.<sup>13,27</sup> Briefly, the act of waking up has a complex role since it needs to integrate the world with ourselves, while we use other parts of our brains to formulate our plans and desires. Preconscious awareness is a process in which we may not be paying attention to some of these plans and desires, that is, we are not consciously attending to a mass of information that we nevertheless process preconsciously. That is, the RAS is involved in subliminally formulating movements and actions of which we are not consciously (but only preconsciously) aware. We suggested that the manifestation of this process is “bottom-up gamma”.<sup>26,27</sup> This expands the role of the background of activity in the RAS as not only allowing afferent information to flow into the brain, but in establishing the background of activity on which we superimpose volition and free will, pre-consciously. If this process is impaired in BD, the distortions in perception, attention, and formulation of actions will be massively disturbing.

## 5 | CONCLUSION

PPN gamma activity may participate in a process that provides the essential stream of information necessary for the formulation of many of our actions. Preconscious awareness is the state that allows us to reliably assess the world around us on a continuous basis, providing a unifying picture and promoting survival. Although this process does not involve selective attention to specific stimuli, it provides the background upon which we assess our environment and act upon it. Without this function, our very survival is at risk. Interruptions in this process, therefore, will markedly disrupt perception as well as planning of motor strategies, adding uncertainty to the wildly shifting world of the BD patient. Dysregulation of preconscious awareness may not only disturb but create the rollercoaster mood swings in this condition.

## CONFLICT OF INTEREST

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial or non-financial interest in the subject matter or materials discussed in this manuscript.

## AUTHOR CONTRIBUTIONS

Dr. Garcia-Rill participated in generating the review, designing the layout, and verifying content. Dr. D'Onofrio participated in the original data acquisition, data analysis, and manuscript review. Ms Mahaffey participated in the original data analysis, manuscript review, and figure design and generation. Dr. Lee participated in generating the review, designing the layout and verifying content. Dr. Urbano participated in generating the review, designing the layout and verifying content.

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