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Review

Abnormalities in thalamic neurophysiology in schizophrenia: Could psychosis be a result of potassium channel dysfunction?

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ABSTRACT

Psychosis in schizophrenia is associated with source-monitoring deficits whereby self-initiated behaviors become attributed to outside sources. One of the proposed functions of the thalamus is to adjust sensory responsiveness in accordance with the behavioral contextual cues. The thalamus is markedly affected in schizophrenia, and thalamic dysfunction may here result in reduced ability to adjust sensory responsiveness to ongoing behavior. One of the ways in which the thalamus accomplishes the adjustment of sensory processing is by a neurophysiological shift to post-inhibitory burst firing mode prior to and during certain exploratory actions. Reduced amount of thalamic burst firing may result from increased neuronal excitability secondary to a reported potassium channel dysfunction in schizophrenia. Pharmacological agents that reduce the excitability of thalamic cells and thereby promote burst firing by and large tend to have antipsychotic effects.

Contents

1. Introduction: source-monitoring in schizophrenia

Schizophrenia is a heterogeneous disease entity associated with a wide range of symptoms that include psychotic symptoms such as hallucinations, passivity phenomena, delusions as well as a number of cognitive and affective deficits (American Psychiatric Association, 2000). Psychosis in schizophrenia can include bizarre involuntary experiences such as fixed false beliefs that one's own actions (somatic passivity) or even thoughts are controlled by someone else. The historical integrated model of schizophrenia, as shown in Fig. 1, places an emphasis on the projections from the temporal lobe (entorhinal cortex, subicular region, and hippocampal formation) to the nucleus accumbens and the mesolimbic dopaminergic pathway. It also implicates the role of the frontal cortex, and its links with the basal ganglia and the mesocortical dopaminergic pathway (Gray, 1998). Overwhelmingly, the pathways that are still considered most likely to determine schizophrenia symptomatology are those that involve dopaminergic transmission. In particular, there appears to be an inverse reciprocal link between dopaminergic transmission in the frontal cortex and the nucleus accumbens (Fig. 1). Dopaminergic release in the nucleus accumbens, inhibits the GABAergic output from the accumbens to the ventral pallidum and also probably contributes (via the pallidal projection to thalamic reticular nuclei, and from there to thalamic relay nuclei) to increased activity in the neocortex. Notwithstanding these intricate models, multiple authors

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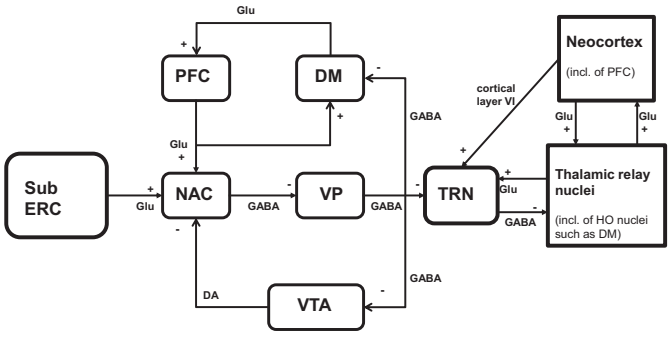

PFC = prefrontal cortex; DM = dorsomedial thalamic nucleus; VP = ventral pallidum; HO = higher order relay nuclei; VTA = the ventral tegmental area (e.g. dopaminergic nucleus A 10); GLU, GABA, DA = the neurotransmitters glutamate, gamma-aminobutyric acid, and dopamine; + = excitation; – = inhibition.

Fig. 1. Diagram showing cortical and thalamic connections thought to be involved in schizophrenia: connections from the subiculum (Sub) and entorhinal cortex (ERC) to the nucleus accumbens (NAC) component of the basal ganglia, and from that system to the nucleus reticularis thalami (TRN) and thalamocortical pathways. In addition to inhibitory ventral pallidal (VP) projections, the TRN also receives excitatory inputs from the cortical layer VI and from the thalamus. Note that the connections between the prefrontal cortex (PFC) and the dorsomedial thalamic nucleus (DM) are here shown twice: firstly as part of the general thalamocortical network (on the right) and then again separately and individually (middle part of the figure), in order to highlight important connections between the PFC and the NAC. VTA, ventral tegmental area (e.g. dopaminergic nucleus A 10); GLU, GABA, DA, the neurotransmitters glutamate, gamma-aminobutyric acid, and dopamine; +, excitation; –, inhibition. Adapted from Gray (1998) with permission.

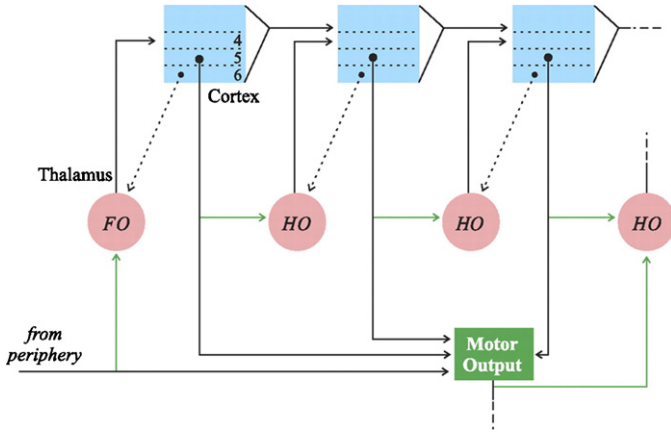

Fig. 2. Simplified schema of corticothalamic projections. Of particular note are following points: the layer V cortical pyramidal neurons control the motor output and some also branch and innervate the higher order (HO) nuclei in the thalamus. The HO nuclei project to the cortex, and therefore, are proposed to be important for informing wider cortical areas about the behavioral context in an ongoing manner. Different cortical areas can also inform each other about the ongoing motor output via direct cortico-cortical connections. Note that the HO nuclei are notably affected in schizophrenia compared with the first order (FO) nuclei. Another important point is that cortical layer VI projects to the thalamus where it modulates neuronal responsiveness.

Adapted with permission from Sherman and Guillery (2011).

have also hypothesized that some of the psychotic symptoms may singularly result from a failure of internal motor monitoring mechanisms (Feinberg, 2011; Frith et al., 2000; Malenka et al., 1986; Vukadinovic, 2011). This proposed functional brain mechanism has been termed corollary discharge, efference copy (Feinberg, 2011) and internal forward model system (Frith et al., 2000). Despite the different terms used, the underlying concept is shared and involves utilization of a copy of ongoing motor instructions for the preparation of the sensory structures that will be affected by the execution of those instructions (Fuster, 2008). In this way, the sensory consequences of motor outputs are anticipated, which also enables their recognition as one's own. In schizophrenia, the proposed impaired monitoring of ongoing motor instructions sent from higher to the lower motor centers in the brainstem and the spinal cord could result in the failure to recognize one's own motor output as such (Fig. 2; Vukadinovic, 2011), which could in turn lead to misattribution of its sensory consequences to an outside source. Consistent with this idea, the illness has been associated with so called source-monitoring deficits (Anselmetti et al., 2007; Brebion et al., 2000; Franck et al., 2001; Keefe et al., 1999, 2002) whereby self-initiated actions become misattributed to external sources. More specifically, there is evidence that such source-monitoring deficits underlie auditory hallucinations (Ford et al., 2002, 2007; Johns et al., 2001; Woodward et al., 2008). As suggested in these reports, self-generated thoughts and speech may become misattributed to an outside agency, which may underlie the experience of hearing voices. In summary, some psychotic phenomena in schizophrenia may reflect a deficiency in the mechanisms that in healthy individuals monitor ongoing motor instructions and prepare the sensory apparatus for the consequences of self-initiated activity. It should be noted, however, that physiological correlates of this proposed functional mechanism have not yet been identified.

2. Thalamus and internal monitoring of actions

It has been suggested that the thalamus may be important for the monitoring of ongoing motor instructions to lower motor centers in the brain stem and the spinal cord (Guillery and Sherman, 2002; Sherman and Guillery, 2006). The thalamus can be subdivided into a number of distinct nuclei, and these can be further classified as first order (FO) or higher order (HO) nuclei. The FO thalamic nuclei receive ascending sensory afferents and then project to the corresponding primary sensory cortex. In contrast the HO nuclei receive their main inputs from collateral branches of descending layer V cortical neurons, and then relay this input back to the cortex. It should be noted that neocortical layer V is the main cortical output layer to subcortical extra-diencephalic motor centers. This pattern of connectivity suggests that the thalamus and especially its HO nuclei, should not be only viewed as a relay for sensory information. In addition, thalamus can also be seen as an important relay node that informs wider cortical areas about efferent motor instructions sent from the cortex to the lower centers involved in motor control (Fig. 2; Guillery and Sherman, 2010). As the anatomical structure that relays both, copies of efferent motor instructions as well as ascending sensory inputs, the thalamus may play an important part in the integration of self-initiated cortical motor outputs with sensory consequences that these instructions may result in. Neuromodulatory cortical inputs to thalamus, on the other hand, are thought to originate from the corticothalamic layer VI projections that have no extra-diencephalic projections (Sherman and Guillery, 2006).

This novel concept for thalamic structure and function (Fig. 2; Guillery and Sherman, 2010) is by and large consistent with some incoming experimental data in literature. Various studies demonstrated that the thalamus is involved in the performance of saccadic double-step tasks, in which correct performance of the second task requires successful internal monitoring of the motor execution of the first task, without reliable retinal information (Bellebaum et al., 2005; Ostendorf et al., 2010; Wurtz and Sommer, 2004). For example, Wurtz and Sommer (2004) found that monkeys could not correctly perform the second task when a HO thalamic nucleus, the mediodorsal (MD) nucleus, was pharmacologically inactivated. They concluded that the inactivation of the MD impaired a transthalamic pathway between the superior colliculus that initiates saccades and the frontal eye fields that may be involved in the motor planning of the second saccade. Similarly, Bellebaum et al

(2005) found that human patients with thalamic lesions could not accurately perform the second saccadic task. Additionally, Ostendorf et al. (2010) reported a patient with unilateral central thalamic lesion that included the MD nucleus who exhibited errors in double-step tasks and in determining the locations of visual stimuli. Interestingly, the patient attributed the resulting errors to external causes such as stimulus changes. Finally, Tanibuchi and Goldman-Rakic (2003) recorded primate MD neuron activities during various visual tasks and found that a large number of recorded cells displayed pre-saccadic burst firing that was specific for the direction of the upcoming saccade. In summary, there is experimental evidence that the HO thalamic nuclei may be involved in the internal monitoring of ongoing motor instructions in addition to the preparation of cortical sensory neurons for the consequences of self-initiated activity. Moreover, impairment in the ability of the HO nuclei to fulfill this role could result in errors during tasks that require internal motor monitoring as well as incorrect attribution of the sensory consequences of these errors to outside sources (Ostendorf et al., 2010).

As it has been argued elsewhere (Vukadinovic, 2011), neuroimaging and post-mortem studies in schizophrenia have found reduced thalamic volumes, with the HO nuclei preferentially affected in relation to the FO nuclei (Andrews et al., 2006; Danos et al., 2003; Brickman et al., 2004; Byne et al., 2009). The two HO nuclei that appear to be notably affected are the MD and the pulvinar nuclei (Byne et al., 2009). In particular the MD nucleus, which is extensively interconnected with the prefrontal cortex (PFC) (Fig. 1), has been noted to be affected in schizophrenia, both in terms of volume and cell loss (for a review see Alelu-Paz and Gimenez-Amaya, 2008). The PFC is important for executive functions including motor control and planning (Fuster, 2008). In a functional neuroimaging study, metabolic disconnection was reported between the left MD nucleus and the frontotemporal cortical regions in schizophrenia (Mitelman et al., 2005). These findings taken together are consistent with the view that some of the symptoms in schizophrenia could perhaps be understood as a failure to monitor ongoing motor behavior. The reduced volume of the HO nuclei in general, or the MD nuclei in particular, may be associated with their reduced ability to inform wider cortical areas about ongoing motor instructions that other cortical areas are sending to their lower motor targets. Consequently, this may mean that the sensory cortical areas have reduced ability to recognize sensory consequences of self-initiated actions. It is further conceivable that the re-afferent sensory inputs may therefore be misattributed to an outside agency resulting in psychotic experiences mimicking passivity phenomena (Feinberg, 2011; Frith et al., 2000; Malenka et al., 1986; Vukadinovic, 2011). In yet another neuroimaging study, Kumari et al. (2010) reported that impaired speech self-monitoring in schizophrenia was associated with hypoactivation of a neural network comprised of the thalamus (medial geniculate nucleus, pulvinar) and frontotemporal cortical regions. They concluded that poor speech self-monitoring and positive symptoms, including auditory hallucinations, share a common neuronal activation abnormality thereby further implicating the thalamus in the pathophysiology of psychosis. Outlining the review of neuroscientific data to follow, subsequent sections consider the organization of thalamic reticular nucleus, thalamocortical connectivity and argue which neurotransmitter models of schizophrenia may be consistent with reduced thalamic burst firing. A detailed account of important aspects of thalamic neurophysiology that have potential relevance for understanding the role of the thalamus in internal motor monitoring can be found in an earlier report (Vukadinovic, 2011). This review will only briefly appraise the relevant neuroscientific data pertaining to it while shifting the focus to the recently reported dysfunction of potassium channels (Huffaker et al., 2009), which is thought to impair the thalamic mechanisms for internal motor monitoring. It is further argued that addressing the resulting abnormality in potassium conductance may constitute a potential mechanism of action of some of the current, but also of the future antipsychotic agents.

3. The thalamic reticular nucleus and its role in thalamic neurophysiology

In addition to the subdivision of thalamic nuclei in FO and HO, the thalamic reticular nucleus (TRN) and its impact on thalamocortical neurophysiology is another important concept for the purposes of the current review. The TRN is a thin sheet of gamma amino butyric acid (GABA)ergic neurons that lies laterally adjacent to the rest of the thalamus (Sherman and Guillery, 2006). It receives inputs from excitatory thalamocortical and corticothalamic layer VI projections that pass through it on their way to the thalamus (Fig. 1), as well as neuromodulatory projections from various subcortical structures such as the basal forebrain and the brain stem. It in turn tends to reciprocate its thalamic projections where its effect is to hyperpolarize thalamocortical neurons. The TRN tends to be topographically organized in terms of the projections it receives from the cortex and its connections with the thalamus. Pinault (2011) recently described the TRN as a combinatorial matrix that assists in the regulation of thalamocortical information flow. It occupies a strategic position between the cortex and the rest of the thalamus where various corticothalamic and thalamocortical projections converge while giving off collaterals. PFC was also reported to have widespread projections to the TRN that extend into the sensory sectors of the nucleus (Zikopoulos and Barbas, 2007). This may be taken to further implicate the TRN in the integration of ascending sensory information with ongoing efferent output from structures involved in motor planning and control.

One of the functions of the TRN is the control of the firing mode of thalamocortical cells (Kim et al., 1997; Sherman and Guillery, 2006; Pinault, 2011). Namely, thalamic neurons display two modes of firing, the so called tonic and burst firing modes (Steriade, 2006). When relatively depolarized, thalamic cells respond to incoming inputs tonically, and the number of action potentials they display is proportional to their excitatory inputs. Alternatively, when in a relatively hyperpolarized state for at least 100 ms, they respond with a burst of action potentials. Namely, sustained hyperpolarization de-inactivates the low threshold calcium channels and the resulting influx of calcium into the cell is termed low threshold calcium spike, which depolarizes the cell. The neuron then responds with a burst of action potentials in response to further depolarization. The state of thalamocortical cells, and consequently, their mode of firing is determined by the firing of their inhibitory inputs, which include the reticulothalamic inputs (Kim et al., 1997). More sustained firing of those inhibitory cells tends to favor the sustained hyperpolarization of thalamocortical cells, and therefore, also the burst firing mode. Importantly, like the thalamocortical cells, the TRN neurons also have the ability to fire in the tonic or burst modes (Sherman and Guillery, 2006). The burst firing mode in the thalamus occurs rhythmically during the slow wave sleep while its occurrence in the awake state has been described as arrhythmic (Sherman, 2001).

4. The TRN and schizophrenia

In two recent studies, Ferrarelli et al. (2007, 2010) found that sleep spindles were reduced in a vast majority of patients with schizophrenia and that their reduction was correlated with the positive symptoms. The second study further determined that antipsychotic medications and overall intelligence did not fully account for this finding (Ferrarelli et al., 2010). Sleep spindles are 11–16 Hz oscillatory bursts of synchronous neuronal firing lasting

up to several seconds and involving the thalamus and the cortex (Steriade, 2006). They are found in the stages 2 and 3 of non-rapid eye movement sleep (NREM). The TRN is crucial for their generation and propagation, but their initiation is thought to involve the cortex. Sleep spindles are grouped by slow cortical oscillations, which are seen during slow wave sleep (Mölle et al., 2002; Steriade, 2003). Slow oscillations are associated with rhythmic shifts of cortical pyramidal cells between a hyperpolarized "down" state (−70 to −80 mV) and a more depolarized "up" state, which is near the spike threshold. When in the "up" state, populations of cortical cells are more likely to spontaneously fire a burst of action potentials. Conceivably, the high frequency discharge of layer VI thalamocortical neurons during the "up" state could stimulate post-synaptic group II mGluR. Namely, high frequency glutamatergic firing has been found to activate group II mGluRs in the thalamus (Govindaiah and Cox, 2006a), and more specifically, also in the TRN (Alexander and Godwin, 2006; Turner and Salt, 2003). Moreover, the stimulation of group II mGluRs has been found to hyperpolarize TRN neurons in a sustained manner by increasing potassium conductance, which could cause a shift to the burst firing mode (Cox and Sherman, 1999). The shift of TRN neurons to the burst firing mode has been found to be involved in spindle initiation (Bazhenov et al., 2000). The burst firing of the TRN neurons in turn causes sustained hyperpolarization of thalamocortical cells (Kim et al., 1997; Turner and Salt, 2003) and their shift to the burst firing mode (Steriade, 2003, 2006). The burst firing of thalamocortical cells then recruits more cortical and TRN neurons. With each subsequent cycle of firing, greater numbers of thalamic and cortical neurons are recruited into the oscillatory spindle activity. During NREM sleep, when the cholinergic tone is relatively low, the cells in the TRN tend to be relatively depolarized compared to thalamocortical cells, which is thought to increase the likelihood that the spindle activity will spread (Steriade, 2006). Alternatively, when the cholinergic tone is higher in the awake state and rapid eye movement sleep, the post-inhibitory burst firing in the thalamus remains more localized.

In summary, sleep spindle initiation may depend on the ability of TRN neurons to become hyperpolarized in a sustained manner by activation of post-synaptic group II mGluR during high frequency firing of the neuromodulatory layer VI corticothalamic cells. Subsequently, the TRN neurons shift their firing mode to the post-inhibitory bursting thereby initiating spindling. Other spindle parameters such as amplitude and duration were reported as reduced in schizophrenia suggesting that both spindle initiation and propagation are affected. In view of the proposed scenario for spindle initiation, this could suggest that schizophrenia may in some patients be associated with reduced ability of the TRN to switch to the burst firing mode. In this context, it is interesting to note that a selective group II mGluR receptor agonist LY2140023 has been found to be an effective antipsychotic in an animal (Moghaddam and Adams, 1998) and a human study (Patil et al., 2007). Its efficacy was reported to be comparable to that of olanzapine.

The results of the genetic study by Huffaker et al. (2009) may offer some insight into the pathophysiological mechanisms behind the noted reduced ability of TRN neurons to become hyperpolarized in schizophrenia as well as to display the post-inhibitory burst firing. In this seminal study, schizophrenia was shown to be associated with single nucleotide polymorphisms in the *KCNH2* gene that encodes ether-a-go-go-related (ERG) potassium channels. These channels are believed to be involved in the modulation of neuronal firing. Furthermore it was shown that in the brains of schizophrenic patients an isoform of the *KCNH2*, the *KCNH2*-3.1, was markedly overexpressed. The *KCNH2*-3.1 encoded isoform lacks a domain that plays a part in the slow deactivation of ERG potassium channel. Consequently, its overexpression may lead to rapid deactivation of outward potassium currents, which in turn may result in increased neuronal excitability and reduced neuronal ability to remain hyperpolarized in a sustained manner. Interestingly, the ERG family of potassium channels is distributed differentially in the brain and is found in the cerebral cortex, hippocampus, TRN, paraventricular nucleus of the hypothalamus, cerebellum and several brain stem nuclei (Papa et al., 2003; Saganich et al., 2001). This pathomechanism may underlie the reported observed reduction in sleep spindles in schizophrenia in certain genetically predisposed patients (Ferrarelli et al., 2007, 2010). One can possibly extrapolate these findings further to also account for some of the psychotic phenomena in schizophrenia.

5. Thalamic burst firing and internal monitoring of actions

Krahe and Gabbiani (2004) suggested that thalamic neurons possess the ability to neurophysiologically shift to the burst mode depending on the ongoing behavioral context. This change further impacts how sensory information is being processed with enhanced ability of the thalamocortical cells to detect relevant sensory signals (Crick, 1984; Destexhe and Sejnowski, 2002; Krahe and Gabbiani, 2004; Sherman and Guillery, 2006). For example, the switch to the burst firing mode has been found to occur immediately prior to, as well as during, an important exploratory behavior in rodents termed whisker twitching, which consecutively resulted in improved signal detection (Fanselow et al., 2001; Nicolelis and Fanselow, 2002). More specifically, the rat trigeminal somatosensory system was studied and it was shown that whisker twitching was associated with burst firing of the thalamocortical neurons in the ventral posterior medial nucleus (VPM). It was also shown that the shift to the burst firing was triggered by descending corticothalamic input from the primary somatosensory cortex (S1). Although the reported studies did not detail which S1 cortical layer was the likely source of the corticothalamic projections, we propose the layer VI pyramidal neurons as the most likely culprit here. These layer VI neurons are known to give off collaterals to the TRN on their way to the VPM. Moreover, the primary motor cortex (M1) sends projections to the neuromodulatory corticothalamic layer VI neurons in the S1 that project to the VPM (Zhang and Deschenes, 1998). This connectivity pattern may go some way towards explaining how it was possible for the neurophysiological shift to occur prior to the onset of whisker movements, possibly also suggesting that the shift might have involved internal monitoring of ongoing vibrissal motor instructions. In summary, all of these factors the onset of the whisking movement, the ability of the thalamic cells to respond to sensory stimuli with a burst of action potentials and increased sensitivity to the incoming sensory stimuli, might be synchronized under cortical influence. One could take this theoretical construct to imply that the rat somatosensory system has an active role in perception; it might be able to shift thalamic physiologic mode of responsiveness in accordance with self-initiated motor output during an exploratory behavior. Further in support of this claim, pharmacological inactivation of the S1 was shown to abolish the whisker twitching behavior (Fanselow et al., 2001).

Another study that implicated the switch to burst firing mode in the thalamus in accordance with ongoing motor instructions was reported by Zhu and Lo (1998). In anesthetized rabbits, they electrically stimulated the deep layers of superior colliculus and simultaneously recorded cells in the lateral pulvinar (LP) nucleus of the thalamus as well as TRN neurons in the visual sector of the TRN. It should be noted that the deep layers of the superior colliculus control saccadic eye movements, and they have also been found to project to the LP in the primates (Berman and Wurtz, 2010). The LP in turn projects to the cortex with the thalamocortical projections also innervating the TRN on their way to their cortical targets. The TRN likely reciprocates the innervation with GABAergic reticulothalamic projections back to the LP. The authors of this study

found that the stimulation of the deep superior collicular layers resulted in hyperpolarization and post-inhibitory burst firing in the recorded cells of the visual TRN and the LP. The hyperpolarization and the subsequent burst firing had shorter latencies in the TRN, which led the authors to conclude that the burst firing of the TRN neurons evoked hyperpolarization and the switch to the burst firing mode in the LP. Based on these results, they suggested that the switch to the burst firing mode occurs simultaneously with saccade initiation, and that it may modulate sensory responsiveness in the visual system in such a way as to amplify salient visual information. Their suggestion is in keeping with that of Fanselow et al. (2001). Notably, in both studies, it is implied that excitatory corticothalamic (Fanselow et al., 2001) and thalamocortical (Zhu and Lo, 1998) projections cause hyperpolarization and subsequent switch to the burst firing mode by as of yet unidentified mechanisms. Finally, Fuster (2008) similarly reported that initiation of motor actions in primates is preceded by acceleration in the firing of some pyramidal neurons in the PFC, which the author termed the motor-coupled cells. As the PFC projections to the TRN have been found to overlap with ascending sensory pathways in the thalamus (Zikopoulos and Barbas, 2007), it is also taken here that the PFC burst firing may result in thalamic burst firing in the sensory pathways. All of this presumably with a task of preparing the sensory cortical areas for re-afferent signals from self-initiated behaviors.

Correspondingly to the mechanism behind the genesis of sleep spindles (Steriade, 2003, 2006), we suggest that the accelerating discharge of some cortical pyramidal cells in preparation for an action (Fuster, 2008) activates the inhibitory post-synaptic group II mGluRs in the TRN, which have been found to be activated by high levels of glutamatergic activity (Alexander and Godwin, 2006; Turner and Salt, 2003). Thus, one can postulate that what occurs during internal motor monitoring and spindle initiation is probably mechanistically related at the level of the thalamus. This potentially 'shared' mechanism may involve the activation of group II mGluRs on TRN neurons by high frequency firing of corticothalamic layer VI cells and their subsequent sustained hyperpolarization followed by the switch to the burst firing mode. The burst firing may then propagate to their thalamocortical target cells. Interestingly, the primate PFC layer V projections, unlike those of other cortical areas, were also shown to give off some synapses in the TRN (Zikopoulos and Barbas, 2007).

6. Neurotransmitter models of schizophrenia may be consistent with reduced thalamic burst firing

In the previous sections, a tentative association was proposed for patients with schizophrenia and the KCNH2-3.1 overexpression in the TRN, with the faulty internal motor monitoring intimated to underlie some of the illness-related psychotic phenomena. The proposal that certain psychotic phenomena are associated with reduced thalamic burst firing may also be consistent with two influential neurotransmitter models of the illness. Buzsaki (1991) reported that the N-methyl-D-aspartate (NMDA) receptor antagonist ketamine reduced the amount of burst firing in the rat thalamus. Following from this, the NMDA-hypofunction model of schizophrenia (Kehrer et al., 2008) would predict a reduction of thalamic burst firing in the illness. In keeping with this, administration of another NMDA antagonist, phencyclidine (PCP), has been found to reduce metabolism in several rat brain areas including the TRN (Cochran et al., 2003). Here one can argue that if schizophrenia is associated with NMDA-hypofunction, the illness may also involve reduced metabolism and hypoactivity in the TRN, and consequently, reduced firing of the GABAergic TRN neurons. The decrease in the firing of TRN neurons could in turn result in reduced thalamocortical post-inhibitory burst firing. Sharp et al. (2001) reported that administration of the NMDA antagonists MK801 into the rat thalamic anterior nucleus (AN) caused injury in the limbic cortex. This was preventable by injecting the GABAergic agonist muscimol. Of note is that thalamic GABAergic inhibitory neurons in rodents are found almost exclusively in the TRN (Sherman and Guillery, 2006) and the LGN (Zhu and Lo, 1999). Sharp et al. (2001) concluded that NMDA blockade reduced the firing of TRN neurons and thereby resulted in dysregulation of thalamocortical neuronal firing, which consequently caused the cortical injury. They further hypothesized that NMDA-hypofunction in schizophrenia may result in psychosis due to decreased ability of inhibitory GABAergic neurons in the thalamus to regulate thalamocortical neurotransmission. As GABAergic thalamic neurons have been shown to regulate the firing mode of thalamocortical cells (Kim et al., 1997), their hypothesis could be expanded by stating that the proposed NMDA-hypofunction in schizophrenia may be consistent with dysregulation of the thalamocortical firing mode.

It has also been reported that antidopaminergic drugs increase the amount of burst firing in the rodent thalamus (Buzsaki, 1990). In view of the proposed dopaminergic hyperactivity (e.g. from the spontaneously active dopamenergic neurons of A10 nucleus in the VTA, also see Fig. 1) in schizophrenia, this finding could lead one to suspect that the thalamic burst firing might also be reduced in the illness. Interestingly, in primates the thalamus is a key dopaminergic target with the high density of dopaminergic innervation in the MD and the lateral posterior HO nuclei (Sanchez-Gonzalez et al., 2005). In humans, Rieck et al. (2004) reported heterogeneous distribution of D2-like dopamine receptors in the thalamus with highest densities in the midline thalamic nuclei, moderate densities in the MD and AN and lower densities in the rest of the thalamus. These studies suggest that dopamine may play an important role in the regulation of thalamocortical information flow, but hitherto little is known about the exact mechanism. The blockade of the D2 receptors by antipsychotic drugs presents the mainstay of pharmacological treatment of schizophrenia (Seeman et al., 1975) and this further suggests the importance for elucidation of the very role for dopamine in the thalamus. In post-mortem studies, Seeman et al. (1993) have reported increased density of D2-like receptors in schizophrenia. More specifically, they reported that the D2 and D3 receptors were increased by 10% while the D4 receptor was increased six-fold. The D4 receptors are thought to be localized on GABAergic neurons in various regions of the human brain, including the TRN. The antipsychotic clozapine has a high affinity for this receptor (Mrzljak et al., 1996). Floran et al. (2004) reported that the D2-like receptor agonist quinpirole reduced GABA release in the rat TRN. This effect was blocked by specific D4 antagonists L745,870 and U101958 suggesting that the effect on GABA release was mediated by the D4 receptors. Similar findings were reported by Govindaiah et al. (2010a), which raises the possibility that the reported marked increase in the D4 receptors in schizophrenia (Mrzljak et al., 1996) might be associated with reduced GABA release in the TRN. This could theoretically lead to decreased burst firing of the TRN neurons and the thalamocortical cells. However, this argument is perhaps rendered somewhat inconsequential in the view that the specific D4 receptor antagonist L745,870 was found ineffective in treatment of schizophrenia (Kramer et al., 1997).

In a recent study of the effects of dopamine on the rat ventrobasal thalamus, it was found that dopamine enhances the excitability of somatosensory thalamocortical neurons (Govindaiah et al., 2010b). The stimulation of both D1 and D2 dopamine receptors resulted in some membrane depolarization, which was, however, more marked with D1 stimulation. The D2 receptor agonist quinpirole increased action potential discharge by reducing slowly inactivating outward potassium current, which is associated with an excitatory effect. The increase in action potential discharge with quinpirole could be reversed with the selective

antidopaminergic-dopamine D2 antagonist sulpride. A number of studies suggest that dopamine may have an excitatory effect on thalamic relay cells in the rat LGN (Govindaiah and Cox, 2006b; Rogawski and Aghajanian, 1980) and that the excitatory effect may be mediated by D2 receptor stimulation in rats (Albrecht et al., 1996) and cats (Zhao et al., 2002). In a study of the rat HO MD nucleus, Lavine and Grace (1998) found that quinpirole had hyperpolarizing and depolarizing effects on different subsets of relay cells, which resulted from changes in membrane potassium conductance. A subset of cells that exhibited hyperpolarization in response to D2 stimulation were also treated with antipsychotic agents haloperidol and clozapine, which were shown to reverse the hyperpolarization. They, however, did not have an effect on the resting membrane potential in absence of quinpirole.

The results of some of the reviewed studies of the effects of dopamine on the excitability of thalamocortical cells suggest the neuromodulatory role for dopamine. Dopamine has been associated with relative depolarization of thalamic relay cells (Govindaiah and Cox, 2005, 2006b; Rogawski and Aghajanian, 1980; Zhao et al., 2002), with decreased membrane potassium conductance and with increased excitability of the thalamocortical cells (Govindaiah et al., 2010b). All of these effects favor tonic firing mode (McCormick, 1992) and it could be argued that the proposed dopamine hyperactivity in schizophrenia may be consistent with a reduction in thalamic burst firing in this illness. Moreover, the reported reduction in GABA release in the TRN in response to D4 receptor stimulation (Floran et al., 2004; Govindaiah et al., 2010a) could further suggest that higher levels of dopaminergic neurotransmission may result in decreased burst firing of the TRN neurons and subsequent reduction of burst firing of thalamocortical cells. To recapitulate, the reduced tendency of thalamic relay neurons to switch to the burst firing mode in schizophrenia may impair the ability of populations of thalamocortical cells to adjust their firing mode to the overall behavioral context (Krahe and Gabbiani, 2004) and possibly also help to generate psychotic symptoms such as hallucinations and passivity phenomena.

7. Possible additional pharmacological targets suggested by thalamic abnormalities in schizophrenia

D2 receptor stimulation by quinpirole in the thalamus, as previously discussed, may increase neuronal excitability of the relay cells by reducing the slowly inactivating potassium current, and this effect could be reversed with the selective antidopaminergic-dopamine D2 receptor antagonist sulpiride (Govindaiah et al., 2010b). Thus, the proposed dopamine hyperactivity in schizophrenia may be consistent with a relative increase in the excitability of thalamic relay neurons, and therefore, also with reduced tendency to display the post-inhibitory burst firing mode. Apart from the already mentioned genetic study by Huffaker et al. (2009), possible etiological relevance of the potassium channels for psychosis in schizophrenia was also suggested by the significant improvement in positive symptoms in patients on haloperidol who were additionally given diazoxide, the potassium channel activator (Akhondzadeh et al., 2002). Moreover, another potassium channel opener, the antiepileptic drug retigabine, was recently reported to have antipsychotic properties in animal models of schizophrenia (Sotti et al., 2009). Conversely, levetiracetam, a relatively new antiepileptic drug, shown to cause reduction in neuronal voltage-operated potassium currents (Madeja et al., 2003), was recently identified to have pro-psychotic effects in some susceptible patients (Rosenzweig et al., 2009; Wade et al., 2010). One possibility of how the potassium channel openers may exert their antipsychotic effects is by potentiating sustained hyperpolarization due to increased potassium conductance and consequent enhancement of the burst firing in the TRN and the rest of the thalamus.

Mooney et al. (2004) showed that acetylcholine depolarized the FO thalamic nuclei. Somewhat surprisingly, it hyperpolarizes TRN neurons (Sherman and Guillery, 2006), as well as a significant portion of the HO thalamic nuclei (Mooney et al., 2004; Varela and Sherman, 2007). These results were taken to suggest that acetylcholine acted to increase the overall likelihood of the TRN and the HO thalamic nuclei to respond in burst firing mode to any incoming excitatory inputs while also decreasing their overall input resistance (Varela and Sherman, 2007). In addition, it was proposed that acetylcholine may exert the hyperpolarizing effects in the thalamus by stimulating the muscarinic M2 receptors, which then increase potassium conductance (Mooney et al., 2004; Sherman and Guillery, 2006; Varela and Sherman, 2007). The muscarinic M2 receptors are found in greater numbers in the HO nuclei compared with FO nuclei (Ramcharan et al., 2005), which may also account for the differential effect of acetylcholine on the FO and the HO thalamic relays. These findings are potentially relevant to the genesis of psychosis as partial M2 and M4 agonists PTAC and BuTAC have been found to have antipsychotic properties in rodents (Bymaster et al., 1998; Jones et al., 2005; Raedler et al. 2007; Rasmussen et al., 2001). Furthermore, clozapine, a highly efficacious antipsychotic (Lieberman et al., 2005) and its major metabolite N-desmethylclozapine are thought to act as partial muscarinic receptor agonists (for a review see Raedler et al., 2007). Thus it is feasible that partial muscarinic agonists may also exert their antipsychotic effect by increasing burst firing in the thalamic HO nuclei.

Pharmacological stimulation of GABAB receptors is known to increase potassium conductance (McCormick, 1992) and to hyperpolarize thalamocortical cells leading to their burst firing (Crunelli and Leresche, 1991; Kim et al., 1997). Significantly, the GABAB agonists CGP44532 and GABAB positive modulator GS39783 have also been found to have antipsychotic effects in rodent models of psychosis (Wieronska et al., 2011). Baclofen, the GABAB agonist, was reported to have an antipsychotic efficacy in humans (for a review see Daskalakis and George, 2009) and the emergence of frank psychotic symptomatology was reported following its sudden withdrawal in otherwise psychiatrically intact patients (D'Aleo et al., 2007; Malhotra and Rosenzweig, 2009). Daskalakis and George (2009) in their review propose that clozapine may exert some of its antipsychotic effects additionally by modulating the GABAB receptor. Hence, clozapine might act as a burst-promoting agent that interacts with multiple metabotropic receptors (D2-like, M2, GABAB), which in turn may explain its noted superior antipsychotic efficacy.

Finally, stimulation of adenosine A1 receptors in the thalamus produced a hyperpolarizing effect via an increase in potassium conductance (McCormick, 1992). In animal models of schizophrenia adenosine A1 and A2 receptor agonists were shown to have antipsychotic properties (Browne and Welch, 1982; Kafka and Corbett, 1996; Popoli et al., 1997; Rimondini et al., 1997; Sillis et al., 1999; for a review see Lara et al., 2006). Moreover, there is some evidence that add-on therapy with agents that increase adenosine levels, such as dipyridamole and allopurinol, has beneficial effects on positive symptoms in patients with schizophrenia (Akhondzadeh et al., 2000, 2005; Brunstein et al., 2001, 2004; Lara et al., 2001).

8. Conclusion

Many of the biological abnormalities identified in studies of patients with schizophrenia highlight individuals liability to experience some of the psychotic symptoms at times of increased stress and anxiety by disrupting the balance between intrinsic activation of and external constraints upon the thalamocortical

activation (Behrendt, 2010). Correspondingly, the following neuropathophysiological model of schizophrenia is proposed herein: in some genetically predisposed patients the possible overexpression of the *KCNH2*-3.1 isoform of the ERG potassium channel in the TRN (Huffaker et al., 2009; Papa et al., 2003; Saganich et al., 2001) along with the hyperdopaminergic state in the thalamus may all conspire to rapidly deactivate outward potassium currents (Govindaiah et al., 2010b). This can in turn lead to increased neuronal excitability and the inability of TRN and thalamocortical neurons to remain hyperpolarized in a sustained manner. As a result, the ability of the thalamus to generate the burst firing mode will also likely be diminished, something which is circumstantially suggested by the reported reduction in sleep spindles in schizophrenia (Ferrarelli et al., 2007, 2010). As the shift to the burst firing in the thalamus occurs in accordance with the behavioral context with consequences for detection of sensory stimuli (Krahe and Gabbiani, 2004), the reduction in the burst firing mode could underpin the genesis of psychotic symptoms in genetically vulnerable individuals.

In keeping with this proposed construct, agonists at metabotropic receptors that increase potassium conductance and thereby cause sustained hyperpolarization in the thalamus (and/or the TRN) commonly tend to have antipsychotic properties. It is suggested that their antipsychotic properties are derived from the restoration of the ability of the thalamus to generate the burst firing mode, making it more responsive to the behavioral contextual cues. The examples of metabotropic receptors that can cause sustained hyperpolarization by increased potassium conductance in the thalamus include M2, A1, group II mGluR, GABAB (see discussion above). In addition, there is evidence that more specific potassium channel openers, such as diazoxide and an antiepileptic drug retigabine, also have an antipsychotic efficacy in humans and in animal models of psychosis (Akhondzadeh et al., 2002; Sotti et al., 2009). Equally, D2 receptor antagonists may exert their antipsychotic effects by reducing D2-mediated rapid deactivation of slowly deactivating outward potassium current (Govindaiah et al., 2010b). In conclusion, we propose that those agents that increase the likelihood of thalamocortical and/or TRN neurons to stay relatively hyperpolarized, and that thereby promote burst firing in the thalamus, may have an antipsychotic propensity. Taken as a whole, the neuroscientific and clinical data reviewed here offer further support to the old notion that the faulty and impaired internal thalamic motor monitoring can lead to genesis of certain psychotic symptoms, such as hallucinations and passivity phenomena.

Conflicts of interest

The authors do not have any conflicts of interest to report.

References

Akhondzadeh, S., Shasavand, E., Jamilian, H., Shabestari, O., Kamalipour, A., 2000. Dipyridamole in the treatment of schizophrenia: adenosine–dopamine receptor interactions. J. Clin. Pharm. Ther. 2, 131–137.

Akhondzadeh, S., Mojtahedzadeh, V., Mirsepassi, G.R., Moin, M., Amini-Nooshabadi, H., Kamalipour, A., 2002. Diazoxide in the treatment of schizophrenia: novel application of potassium channel openers in the treatment of schizophrenia. J. Clin. Pharm. Ther. 27 (6), 453–459.

Akhondzadeh, S., Safarcherati, A., Amini, H., 2005. Beneficial antipsychotic effects of allopurinol as add-on therapy for schizophrenia: a double blind, randomized and placebo controlled trial. Prog. Neuropharmacol. Biol. Psychiatry 2, 253–259.

Albrecht, T., Quäschling, U., Zippel, U., Davidowa, H., 1996. Effects of dopamine on neurons of the lateral geniculate nucleus: an iontophoretic study. Synapse 23, 70–78.

Alelu-Paz, R., Gimenez-Amaya, J.M., 2008. The mediodorsal thalamic nucleus and schizophrenia. J. Psychiatry Neurosci. 33 (6), 489–498.

Alexander, G.M., Godwin, D.W., 2006. Unique presynaptic and postsynaptic roles of group II metabotropic glutamate receptors in the modulation of thalamic network activity. Neuroscience 141, 501–513.

American Psychiatric Association, 2000. Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Text Revision, American Psychiatric Association, Washington, DC.

Andrews, J., Wang, L., Csernansky, J.G., Gado, M.H., Barch, D.M., 2006. Abnormalities of thalamic activation and cognition in schizophrenia. Am. J. Psychiatry 163, 463–469.

Anselmetti, S., Cavallaro, R., Bechi, M., Angelone, S.M., Ermoli, E., Cocchi, F., Smeraldi, E., 2007. Psychopathological and neuropsychological correlates of source monitoring impairment in schizophrenia. Psychiatry Res. 150, 51–59.

Bazhenov, M., Timofeev, I., Steriade, M., Sejnowski, T., 2000. Spiking–bursting activity in the thalamic reticular nucleus initiates sequences of spindle oscillations in thalamic networks. J. Neurophysiol. 84, 1076–1087.

Behrendt, R.P., 2010. Contribution of hippocampal region CA3 to consciousness and schizophrenic hallucinations. Neurosci. Biobehav. Rev. 34, 1121–1136.

Bellebaum, C., Daum, I., Koch, B., Schwartz, M., Hoffman, K.-P., 2005. The role of the human thalamus in processing corollary discharge. Brain 128, 1139–1154.

Berman, R.A., Wurtz, R.H., 2010. Functional identification of a pulvinar path from superior colliculus to cortical area MT. J. Neurosci. 30 (18), 6342–6354.

Brebion, G., Amador, X., David, A., Malaspina, D., Sharif, Z., Gorman, J.M., 2000. Positive symptomatology and source-monitoring failure in schizophrenia—an analysis of symptom-specific effects. Psychiatry Res. 95 (2), 119–131.

Brickman, A.M., Buchsbaum, M.S., Shihabuddin, L., Byne, W., Newmark, R.E., Brand, J., Ahmed, S., Mitelman, S.A., Hazlett, E.A., 2004. Thalamus size and outcome in schizophrenia. Schizophr. Res. 71, 473–484.

Browne, R.G., Welch, W.M., 1982. Stereoselective antagonism of phencyclidine's discriminative properties by adenosine receptor agonists. Science 4565, 1157–1159.

Brunstein, M.G., Belmonte-d-Abreu, P., Souza, D.O., Lara, D.R., 2001. Therapeutic benefit of adjunctive dipyridamole in schizophrenia is probably due to adenosine–glutamate interactions. J. Clin. Pharm. Ther. 2, 155–156.

Brunstein, M.G., Ghisolfe, E.S., Ramos, F.L., Lara, D.R., 2004. Clinical trial for allopurinol adjuvant therapy for poorly responsive schizophrenia. Schizophr. Res., S142.

Buzsaki, G., 1990. Petit mal epilepsy and parkinsonian tremor: hypothesis of a common pacemaker. Neuroscience 36 (1), 1–14.

Buzsaki, G., 1991. The thalamic clock: emergent network properties. Neuroscience 41 (2/3), 351–364.

Bymaster, F.P., Shannon, H.E., Rasmussen, K., Delapp, N.W., Mitch, C.H., Ward, J.S., Calligaro, D.O., Ludvigsen, T.S., Sheardown, M.J., Olesen, P.H., Swedberg, M.D., Sauerberg, P., Fink-Gensen, A., 1998. Unexpected antipsychotic-like activity with the muscarinic receptor ligand (5R,6R)6-(3-propylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo[3.2.1]octane. Eur. J. Pharmacol. 356, 109–119.

Byne, W., Hazlett, E.A., Buchsbaum, M.S., Kemether, E., 2009. The thalamus and schizophrenia: current status of research. Acta Neuropathol. 117, 347–368.

Cochran, S.M., Kennedy, M., McKerchar, C.E., Steward, L.J., Pratt, J.A., Morris, B.J., 2003. Induction of metabolic hypofunction and neurochemical deficits after chronic intermittent exposure to phencyclidine: differential modulation by antipsychotic drugs. Neuropsychopharmacology 28, 265–275.

Cox, C.L., Sherman, S.M., 1999. Glutamate inhibits thalamic reticular neurons. J. Neurosci. 19, 6694–6699.

Crick, F., 1984. Function of the thalamic reticular complex: the searchlight hypothesis. Proc. Natl. Acad. Sci. U. S. A. 81, 4586–4590.

Crunelli, V., Leresche, N., 1991. A role for GABAB receptors in excitation and inhibition of thalamocortical cells. Trends Neurosci. 14 (1), 16–21.

D'Aleo, G., Cammaroto, S., Rifici, C., Marra, G., Sessa, E., Bramanti, P., Di Bella, P., 2007. Hallucinations after abrupt withdrawal of oral and intrathecal baclofen. Funct. Neurol. 22, 81–88.

Danos, P., Baumann, B., Kramer, A., Bernstein, H.G., Stauch, R., Krell, D., Falkai, P., Bogerts, B., 2003. Volumes of association thalamic nuclei in schizophrenia: a postmortem study. Schizophr. Res. 60, 141–155.

Daskalakis, Z.J., George, T.P., 2009. Clozapine, GABA B, and the treatment of resistant schizophrenia. J. Clin. Pharm. Ther. 86, 442–446.

Destexhe, A., Sejnowski, T.J., 2002. The initiation of bursts in thalamic neurons and the cortical control of thalamic sensitivity. Philos. Trans. R. Soc. Lond. B 357, 1649–1657.

Fanselow, E.F., Sameshima, K., Baccala, L.A., Nicolelis, M.A.L., 2001. Thalamic bursting in rats during different awake behavioral states. Proc. Natl. Acad. Sci. U. S. A. 98 (26), 15330–15335.

Feinberg, I., 2011. Corollary discharge, hallucinations and dreaming. Schizophr. Bull. 37 (1), 1–3.

Ferrarelli, F., Huber, R., Peterson, M.J., Massimini, M., Murphy, M., Riedner, B.A., Watson, A., Bria, P., Tononi, G., 2007. Reduced sleep spindle activity in schizophrenia patients. Am. J. Psychiatry 164, 483–492.

Ferrarelli, F., Peterson, M.J., Sarasso, S., Riedner, B.A., Murphy, M.J., Benca, R.M., Bria, P., Kalin, N.H., Tononi, G., 2010. Thalamic dysfunction in schizophrenia suggested by whole-night deficits in slow and fast spindles. Am. J. Psychiatry 167, 1339–1348.

Floran, B., Floran, L., Erlij, D., Aceves, J., 2004. Activation of dopamine D4 receptors modulates [3H]GABA release in slices of the rat thalamic reticular nucleus. Neuropharmacology 46 (4), 497–503.

Ford, J.M., Mathalon, D.H., Whitfield, S., Faustman, W.O., Roth, W.T., 2002. Reduced communication between frontal and temporal lobes during talking in schizophrenia. Biol. Psychiatry 52, 485–492.

Ford, J.M., Gray, M., Faustman, W.O., Roach, B.J., Mathalon, D.H., 2007. Dissecting corollary discharge dysfunction in schizophrenia. Psychophysiology 44, 522–529.

Franck, N., Farrer, C., Georgieff, N., Marie-Cardine, M., Dalery, J., d'Amato, T., Jeannerodm, M., 2001. Defective recognition of one's own actions in schizophrenic patients. Am. J. Psychiatry 158, 454–459.
Frith, C.D., Blackemore, S.J., Wolpert, D.M., 2000. Explaining the symptoms of schizophrenia: abnormalities in the awareness of action. Brain Res. Rev. 31, 357–363.
Fuster, J.M., 2008. The Prefrontal Cortex, 4th ed. Elsevier, London, UK.
Govindaiah, G., Cox, C.L., 2005. Excitatory actions of dopamine via D1-like receptors in the rat lateral geniculate nucleus. J. Neurophysiol. 94 (6), 3708–3718.
Govindaiah, G., Cox, C.L., 2006a. Metabotropic glutamate receptors differentially regulate GABAergic inhibition in thalamus. J. Neurosci. 26 (52), 13443–13453.
Govindaiah, G., Cox, C.L., 2006b. Excitatory actions of synaptically released catecholamines in the rat lateral geniculate nucleus. Neuroscience 137, 671–683.
Govindaiah, G., Wang, T., Gilette, M.U., Crandall, S.R., Cox, C.L., 2010a. Regulation of inhibitory synapses by presynaptic D4 dopamine receptors in thalamus. J. Neurophysiol. 104, 2757–2765.
Govindaiah, G., Wang, Y., Cox, C.L., 2010b. Dopamine enhances the excitability of somatosensory thalamocortical neurons. Neuroscience 170 (4), 981–991.
Gray, J.A., 1998. Integrating schizophrenia. Schizophr. Bull. 24, 249–266.
Guillery, R.W., Sherman, S.M., 2002. Thalamic relay functions and their role in corticocortical communication: generalizations from the visual system. Neuron 33, 163–175.
Guillery, R.W., Sherman, S.M., 2010. Branched thalamic afferents: what are the messages that they relay to the cortex? Brain Res. Rev. 66, 205–219.
Huffaker, S.J., Chan, J., Nicodemus, K.K., Sambataro, F., Yang, F., Mattay, V., Lipska, B.K., Hyde, T.M., Song, J., Rujescu, D., Giegling, I., Mayilyan, K., Proust, M.J., Soghoyan, A., Caforio, G., Callecott, J.H., Bertolino, A., Meyer-Lindenberg, A., Chang, J., Ji, Y., Egan, M.F., Goldberg, T.E., Kleinman, J.E., Lu, B., Weinberger, D.R., 2009. Primate-specific, brain isoform of KCNH2 affects cortical physiology, cognition, neuronal repolarization and risk of schizophrenia. Nat. Med. 15, 509–518.
Johns, L.C., Rossell, S., Frith, C., Agmad, F., Hemsley, D., Kuipers, E., McGuire, P.K., 2001. Verbal self-monitoring and auditory verbal hallucinations in patients with schizophrenia. Psychol. Med. 31, 705–715.
Jones, C.K., Eberle, E.L., Shaw, D.B., McKinzie, D.L., Shannon, H.E., 2005. Pharmacologic interactions between the muscarinic cholinergic and dopaminergic systems in the modulation of prepulse inhibition in rats. J. Pharmacol. Exp. Ther. 312, 1055–1063.
Kafka, S.H., Corbett, R., 1996. Selective adenosine A2A receptor–dopamine D2 receptor interactions in animal models of schizophrenia. Eur. J. Pharmacol. 2–3, 147–154.
Keefe, R.S., Arnold, M.C., Bayen, U.K., Harvey, P.D., 1999. Source-monitoring deficits in patients with schizophrenia: a multinomial modeling analysis. Psychol. Med. 29 (4), 903–914.
Keefe, R.S., Arnold, M.C., Bayen, U.K., McEvoy, J.P., Wilson, W.H., 2002. Source monitoring deficits for self-generated stimuli in schizophrenia: multinomial modeling of data from three sources. Schizophr. Res. 57, 51–67.
Kehrer, C., Maziashvili, N., Dugladze, T., Gloveli, T., 2008. Altered excitatory-inhibitory balance in the NMDA-hypofunction model of schizophrenia. Front. Mol. Neurosci. 1 (6), 1–7.
Kim, U., Sanchez-Vives, M.V., McCormick, D.A., 1997. Functional dynamics of GABAergic inhibition in the thalamus. Science 278 (5335), 130–134.
Krahe, R., Gabbiani, F., 2004. Burst firing in sensory systems. Nat. Rev. Neurosci. 5, 13–23.
Kramer, M.S., Last, B., Getson, A., Reines, S.A., 1997. The effects of a selective D4 dopamine receptor antagonist (L745,870) in acutely psychotic inpatients with schizophrenia. Arch. Gen. Psychiatry 54 (6), 567–572.
Kumari, V., Fannon, D., Ffytuche, D.H., Raveenrdran, V., Antonova, E., Premkumar, P., et al., 2010. Functional MRI of verbal self-monitoring in schizophrenia: performance and illness-specific effects. Schizophr. Bull. 36 (4), 740–755.
Lara, D.R., Brunstein, M.G., Ghisolfi, E.S., Lobato, M.I., Belmonte-de-Abreu, P., Souza, D.O., 2001. Allopurinol augmentation for poorly responsive schizophrenia. Int. Clin. Psychopharmacol. 4, 235–237.
Lara, D.R., Dall-Egna, O.P., Ghisolfi, E.S., Brunstein, M.G., 2006. Involvement of adenosine in the neurobiology of schizophrenia and its therapeutic implications. Prog. Neuropsychopharmacol. Biol. Psychiatry 30, 617–629.
Lavine, A., Grace, A.A., 1998. Dopamine modulates the responsivity of mediodorsal thalamic cells recorded in vitro. J. Neurosci. 18 (24), 10566–10578.
Lieberman, J.A., Stroup, T.S., McEvoy, J.P., Swartz, M.S., Rosenheck, R.A., Perkins, D.O., Keefe, R.S., Davis, S.M., Davis, C.E., Lebowitz, B.D., Severe, J., Hsiao, J.K., 2005. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N. Engl. J. Med. 353 (12), 1209–1223.
Madeja, M., Margineanu, D.G., Gorji, A., Siep, E., Boerrigter, P., Klitgaard, H., Speckmann, E.J., 2003. Reduction of voltage-operated potassium currents by levetiracetam: a novel antiepileptic mechanism of action? Neuropharmacology 45, 661–671.
Malenka, R.C., Angel, R.W., Thieman, S., Weitz, C.J., Berger, P.A., 1986. Central error-correcting behavior in schizophrenia and depression. Biol. Psychiatry 21, 263–273.
Malhotra, T., Rosenzweig, I., 2009. Baclofen withdrawal causes psychosis in otherwise unclouded consciousness. J. Neuropsychiatry Clin. Neurosci. 21, 476.
McCormick, D.A., 1992. Neurotransmitter actions in the thalamus and cerebral cortex and their role in neuromodulation of thalamocortical activity. Prog. Neurobiol. 39, 337–388.
Mitelman, S.A., Byne, W., Kemether, E., Hazlett, E.A., Buchsbaum, M.S., 2005. Metabolic disconnection between the mediodorsal nucleus of the thalamus and cortical Brodmann's areas of the left hemisphere in schizophrenia. Am. J. Psychiatry 162, 1733–1735.
Moghaddam, B., Adams, B.W., 1998. Reversal of phencyclidine effects by a group I metabotropic glutamate receptor agonist in rats. Science 281, 1349–1352.
Mölle, M., Marshall, L., Gais, S., Born, J., 2002. Grouping of spindle activity during slow oscillations in human non-rapid eye movement sleep. J. Neurosci. 22 (24), 10941–10947.
Mooney, D.M., Zhang, L., Basile, C., Senatorov, V.V., Ngsee, J., Omar, A., Hu, B., 2004. Distinct forms of cholinergic modulation in parallel thalamic sensory pathways. Proc. Natl. Acad. Sci. U. S. A. 101, 320–324.
Mrzljak, L., Bergson, C., Pappy, M., Huff, R., Levenson, R., Goldman-Rakic, P.S., 1996. Localization of dopamine D4 receptors in GABAergic neurons of the primate brain. Nature 381, 245–248.
Nicolelis, M.A.L., Fanselow, E.F., 2002. Dynamic shifting in thalamocortical processing during different behavioural states. Philos. Trans. R. Soc. Lond. B 357, 1753–1758.
Ostendorf, F., Liebermann, D., Ploner, C.J., 2010. Human thalamus contributes to perceptual stability across eye movements. Proc. Natl. Acad. Sci. U. S. A. 107 (3), 1229–1234.
Papa, M., Boscea, F., Canitano, A., Castaldo, P., Selletti, S., Annunziato, L., Taglealatela M., 2003. Expression pattern of the ether-a-gogo-related (ERG) K+ channel-encoding genes ERG1, ERG2, and ERG3 in the adult rat central nervous system. J. Comp. Neurol. 466, 119–135.
Patil, S.T., Zhang, L., Martenyi, F., Lowe, S.L., Jackson, K.A., Andreev, B.V., Avedisova A.S., Bardenstein, L.M., Gurovich, I.Y., Morozova, M.A., Mosolov, S.N., Neznanov N.G., Reznik, A.M., Smulevich, A.B., Tochilov, V.A., Johnson, B.G., Monn, J.A. Schoepp, D.D., 2007. Activation of mGlu2/3 receptors as a new approach to treat schizophrenia: a randomized phase 2 clinical trial. Nat. Med. 13, 1102–1107.
Pinault, D., 2011. Dysfunctional thalamus-related networks in schizophrenia. Schizophr. Bull. 37 (2), 238–243.
Popoli, P., Reggio, R., Pezzola, A., 1997. Adenosine A1 and A2 receptor agonists significantly prevent the electroencephalographic effects induced by MK-801 in rats. Eur. J. Pharmacol. 2–3, 143–146.
Raedler, T.J., Bymaster, F.P., Tandon, R., Copolov, D., Dean, B., 2007. Towards a muscarinic hypothesis of schizophrenia. Mol. Psychiatry 12, 232–246.
Ramcharan, E.J., Gnadt, J.W., Sherman, S.M., 2005. Higher-order thalamic relays burst more than first-order relays. Proc. Natl. Acad. Sci. USA 102 (34), 12236–12241.
Rasmussen, T., Fink-Gensen, A., Sauerberg, P., Swedberg, M.D., Thomsen, C., Sheardown, M.G., Jeppesen, L., Calligaro, D.O., DeLapp, N.W., Whitesitt, C., Ward, J.S. Shannon, H.E., Bymaster, F.P., 2001. The muscarinic receptor agonist BuTAC, a novel potential antipsychotic, does not impair learning and memory in mouse passive avoidance. Schizophr. Res. 49, 193–201.
Rieck, R.W., Ansari, M.S., Whetsell, W.O., Deutsch, A.Y., Kessler, R.M., 2004. Distribution of dopamine D2-like receptors in the human thalamus: autoradiographic and PET studies. Neuropsychopharmacology 29, 362–372.
Rimondini, R., Ferre, S., Ogren, S.O., Fuxe, K., 1997. Adenosine A2A agonists: a potential new type of atypical antipsychotic. Neuropsychopharmacology 2, 82–91.
Rogawski, M.A., Aghajanian, G.K., 1980. Activation of lateral geniculate neurons by norepinephrine: mediation by an alpha-adrenergic receptor. Brain Res. 182, 345–359.
Rosenzweig, I., Valentin, A., Brex, P.A., Elwes, R.D., Alarcon, G., 2009. Face-related ictal hallucinations and illusions and reflex-type phenomena. J. Neuropsychiatry Clin. Neurosci. 21, 469–470.
Saganich, M.J., Machado, E., Rudy, B., 2001. Differential expression of genes encoding subthreshold-operating voltage-gated K+ channels in brain. J. Neurosci. 21, 4609–4624.
Sanchez-Gonzalez, M.A., Garcia-Cabezas, M.A., Rico, B., Cavada, C., 2005. The primate thalamus is a key target for brain dopamine. J. Neurosci. 25 (26), 6076–6083.
Seeman, P., Chau-Wong, M., Tedesco, J., Wong, K., 1975. Brain receptors for antipsychotic drugs and dopamine: direct binding assays. Proc. Natl. Acad. Sci. U. S. A. 72, 4376–4380.
Seeman, P., Guan, H.C., Van Tol, H.H.M., 1993. Dopamine D4 receptors elevated in schizophrenia. Nature 365, 441–445.
Sharp, F.R., Tomitaka, M., Bemaudin, M., Tomitaka, S., 2001. Psychosis: pathological activation of limbic thalamocortical circuits by psychomimetics and schizophrenia? Trends Neurosci. 24 (5), 330–334.
Sherman, S.M., 2001. Tonic and burst firing: dual modes of thalamocortical relay. Trends Neurosci. 24 (2), 122–126.
Sherman, S.M., Guillery, R.W., 2006. Exploring the Thalamus and its Role in Cortical Function, 2nd ed. The MIT Press, Cambridge, MA.
Sherman, S.M., Guillery, R.W., 2011. Distinct functions for direct and transthalamic corticocortical connections. J. Neurophysiol. 106, 1068–1077.
Sillis, T.L., Azampanah, A., Fletcher, P.J., 1999. The adenosine A1 receptor agonist N6-cyclopentyladenosine blocks the disruptive effect of phencyclidine on prepulse inhibition of the acoustic startle response in the rat. Eur. J. Pharmacol. 3, 325–329.
Sotti, F., Damgaard, T., Montezinho, L.P., Mork, A., Olsen, C.K., Bundgaard, C. Husum, H., 2009. Antipsychotic-like effects of retigabine [N-(2-amino-4-(fluorobenzylamino)-phenyl)carbamic acid ester], a KCNQ potassium channel opener, via modulation of mesolimbic dopaminergic neurotransmission. J. Pharmacol. Exp. Ther. 328 (3), 951–962.
Steriade, M., 2003. Neuronal Substrates of Sleep and Epilepsy. Cambridge University Press, Cambridge, UK.

Steriade, M., 2006. Grouping of brain rhythms in corticothalamic systems. Neuroscience 137, 1087–1106.
Tanibuchi, I., Goldman-Rakic, P.S., 2003. Dissociation of spatial-, object-, and sound-coding neurons in the mediodorsal nucleus of the primate thalamus. J. Neurophysiol. 89, 1067–1077.
Turner, J.P., Salt, T.E., 2003. Group II and III metabotropic glutamate receptors and the control of nucleus reticularis thalami input to rat thalamocortical neurones in vitro. Neuroscience 122, 459–469.
Varela, C., Sherman, S.M., 2007. Differences in response to muscarinic activation between first and higher order thalamic relays. J. Neurophysiol. 98, 3547–3583.
Vukadinovic, Z., 2011. Sleep abnormalities in schizophrenia may suggest impaired trans-thalamic cortico-cortical communication: towards a dynamic model of the illness. Eur. J. Neurosci. 34 (7), 1031–1039.
Wade, J.F., Dang, C.V., Nelson, L., Wasserberger, J., 2010. Emergent complications of the newer anticonvulsants. J. Emerg. Med. 38, 231–237.
Wieronska, J.M., Kusek, M., Tokarski, K., Wabno, J., Froesti, W., Pilc, A., 2011. The GABA B receptor agonist CGP44532 and the positive modulator GS39783 reverse some behavioural changes related to positive syndromes of psychosis in mice. Br. J. Pharmacol. 163 (5), 1034–1047.
Woodward, T.S., Weinstein, S., Cairo, T.A., Metzak, P., Ngan, E.T.C., Kumar, D., 2008. Hallucinations are associated with aberrant activation in inner speech regions during source monitoring. Schizophr. Res. Suppl. 102 (2), 96.
Wurtz, R.H., Sommer, M.A., 2004. Identifying corollary discharges for movement in the prime brain. Prog. Brain Res. 144, 47–60.
Zhang, Z.W., Deschenes, M., 1998. Projections to layer VI of the posteromedial barrel field in the rat: a reappraisal of the role of corticothalamic pathways. Cereb. Cortex 8 (5), 428–436.
Zhao, Y., Kerscher, N., Eysel, U., Funke, K., 2002. D1 and D2 receptor-mediated dopaminergic modulation of visual responses in cat dorsal lateral geniculate nucleus. J. Physiol. 539 (1), 223–238.
Zhu, J.J., Lo, F.S., 1998. Control of recurrent inhibition of the lateral posterior-pulvinar complex by afferents from the deep layers of the superior colliculus of the rabbit. J. Neurophysiol. 80, 1122–1131.
Zhu, J.J., Lo, F.S., 1999. Three GABA receptor-mediated postsynaptic potentials in interneurons in the rat lateral geniculate nucleus. J. Neurosci. 19 (14), 5721–5730.
Zikopoulos, B., Barbas, H., 2007. Circuits for multisensory integration and attentional modulation through the prefrontal cortex and the thalamic reticular nucleus in primates. Rev. Neurosci. 18, 417–438.