Neuroscience and Biobehavioral Reviews 103 (2019) 337–351

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Visual hallucinations, thalamocortical physiology and Lewy body disease: A review

Shooka Esmaeeli[a], Kathleen Murphy[a], Gabriel M. Swords[b], Baher A. Ibrahim[a,c], Jeffrey W. Brown[b], Daniel A. Llano[a,c,d,*]

[a] Department of Molecular and Integrative Physiology, University of Illinois at Urbana-Champaign, Urbana, IL, United States
[b] University of Illinois at Chicago College of Medicine, Chicago, IL, United States
[c] Beckman Institute for Advanced Science and Technology, University of Illinois at Urbana-Champaign, Urbana, IL, United States
[d] Carle Neuroscience Institute, Urbana, IL, United States

ARTICLE INFO

Keywords:
Dementia
Thalamus
Thalamic reticular nucleus
Lewy body
Hallucination
Acetylcholine

ABSTRACT

One of the core diagnostic criteria for Dementia with Lewy Bodies (DLB) is the presence of visual hallucinations. The presence of hallucinations, along with fluctuations in the level of arousal and sleep disturbance, point to potential pathological mechanisms at the level of the thalamus. However, the potential role of thalamic dysfunction in DLB, particularly as it relates to the presence of formed visual hallucinations is not known. Here, we review the literature on the pathophysiology of DLB with respect to modern theories of thalamocortical function and attempt to derive an understanding of how such hallucinations arise. Based on the available literature, we propose that combined thalamic-thalamic reticular nucleus and thalamocortical pathology may explain the phenomenology of visual hallucinations in DLB. In particular, diminished α7 cholinergic activity in the thalamic reticular nucleus may critically disinhibit thalamocortical activity. Further, concentrated pathological changes within the posterior regions of the thalamus may explain the predilection for the hallucinations to be visual in nature.

1. Introduction

Dementia with Lewy Bodies (DLB) is the second most common form of aging-related neurodegenerative dementia after Alzheimer's Disease (AD) and comprises up to 36% of autopsied dementia cases (McKeith et al., 2000a). DLB is a member of Lewy body diseases' (LBD) spectrum of degenerative illnesses along with Parkinson's Disease (PD) and Parkinson's Disease dementia (PDD) (McKeith, 2006). A core pathological feature in DLB is the cortical and subcortical accumulation of Lewy bodies (Burkhardt et al., 1988; Gibb et al., 1987; McKeith, 2006; Miners et al., 2014). The primary elements within Lewy bodies are α-synuclein and ubiquitin (Mukaetova-Ladinska and McKeith, 2006; Polymeropoulos et al., 1997; Spillantini et al., 1997; Zarranz et al., 2004) and Lewy body formation is thought to be related to α-synuclein functional disturbances (Zarranz et al., 2004), impaired clearance (Miners et al., 2014), increase in α-synuclein expression and/or decrease in its solubility (Mukaetova-Ladinska and McKeith, 2006). All of these mechanisms lead to the accumulation of both insoluble and soluble α-synuclein (Miners et al., 2014; Mukaetova-Ladinska and McKeith, 2006). Ultimately, the accumulation of α-synuclein is associated with mitochondrial dysfunction, oxidative stress and cellular decline (Dalfó et al., 2005; Hsu et al., 2000; Swerdlow, 2009).

Clinically, the key features of DLB are cognitive decline, parkinsonism, complex visual hallucinations as well as fluctuating arousal and cognition (Delli Pizzi et al., 2014; McKeith, 2006; Pletnikova et al., 2005). Rapid eye movement (REM) behavioral sleep disturbance is another important feature among DLB patients which can be present many years before the onset of the core symptoms (Boeve et al., 2004; Turner et al., 1997). The core cognitive features are deficits in attention and executive function, as well as deficits in memory retrieval and visuospatial dysfunction (Calderon et al., 2001; Ferman et al., 2006; Gomperts, 2016). The hallucinations are typically visual, though auditory hallucinations have been described (Ballard et al., 2001; Klatka et al., 1996; McKeith et al., 1992). The hallucinations are seen early in the illness, persist throughout its course, are often detailed and vivid, and commonly take the form of animals or people (Gomperts, 2016; McKeith, 2007; Mosimann et al., 2006). The presence of such hallucinations is associated with visuospatial perceptual deficits seen in these patients (Mori et al., 2000).

The presence of visual hallucinations strongly differentiates DLB

* Corresponding author at: Department of Molecular and Integrative Physiology, University of Illinois at Urbana-Champaign, Urbana, IL, United States.
E-mail address: d-llano@illinois.edu (D.A. Llano).

https://doi.org/10.1016/j.neubiorev.2019.06.006
Received 23 December 2018; Received in revised form 3 June 2019; Accepted 8 June 2019
Available online 10 June 2019
0149-7634/

from AD, particularly in the early stages of the illness (Ballard et al., 1999; Luis et al., 1999). Therefore, understanding the mechanisms underlying these hallucinations may provide specific insights into the pathophysiology underlying DLB. Unfortunately, the neural circuits responsible for the generation of visual hallucinations in DLB are not yet known. Given the role of the visual cortex, and in particular, regions in the inferior temporal cortex, in visual perception and object recognition, it is likely that areas of the occipital and/or inferior temporal cortices are active during visual hallucinations. Interestingly, cortical tangle pathology is inversely correlated with the presence of hallucinations in DLB patients (Ballard et al., 2004; Luis et al., 1999), as are subcortical occipital white matter abnormalities (Barber et al., 1999). These observations suggest that retention of functional cortical circuits and their subcortical connections is important for the production of visual hallucinations. In addition, fluctuations in the level of arousal and sleep disturbances, which are both seen when thalamocortical systems fail (Bassetti et al., 1996; Hermann et al., 2008; Schiff, 2008; Schiff and Plum, 2000), are commonly seen in DLB. These findings, together with longstanding hypotheses about the role of the thalamus in the production of hallucinations (Lee et al., 2003; Peláez, 2000) and findings reporting that enhanced thalamocortical connectivity is seen in patients with schizophrenia or taking hallucinogens (Anticevic et al., 2013; Preller et al., 2019; Schlösser et al., 2003), raise the possibility that hallucinations (and/or other symptoms) in DLB are caused by dysregulated thalamocortical circuitry.

The thalamus is a centrally located brain structure whose principal cells, thalamocortical neurons, project throughout the neocortex. Different thalamic nuclei project to different regions of the cerebral cortex in a roughly topographical and bidirectional fashion. The presumed functions of each thalamic nucleus mirror those of their cortical partners. Partially surrounding the thalamus is a sheet of GABAergic neurons known as the thalamic reticular nucleus (TRN). TRN neurons project to the thalamus and receive input from both thalamocortical neurons and the cortex, among other brain areas. Although early models of TRN organization postulated that TRN neurons were reciprocally connected with thalamocortical neurons – an organization leading to both physiological and pathological oscillations (Steriade et al., 1993a; Warren et al., 1994)– more recent work suggests that additional non-reciprocal circuits exist. In fact, multiple brain regions that influence cortical activation, such as the prefrontal cortex, amygdala, other thalamic regions and basal forebrain, may do so indirectly via their projections to the TRN (Crabtree et al., 1998; Crabtree and Isaac, 2002; Desilets-Roy et al., 2002; Kimura et al., 2007; Lam and Sherman, 2005, 2015; Lee et al., 2010; Pinault and Deschênes, 1998; Zikopoulos and Barbas, 2006). Such “open-loop” connectivity provides a potential substrate for long-range modulation of cortical activity, paradoxical enhancement of thalamocortical signal flow and propagation of signals across the thalamus (Brown et al., 2019; Gribkova et al., 2018; Willis et al., 2015). These findings comport with one of the hypothesized roles for the TRN which is to gate and modulate information flowing toward the cerebral cortex (Steriade and Llinás, 1988; Williams and Rakic, 1988; Wimmer et al., 2015). The TRN is also implicated in controlling the state of arousal and sleep (Steriade et al., 1993a) and dreaming (Solms, 2000).

The TRN may also control response mode in thalamocortical neurons. Thalamocortical neurons have two spiking response modes: bursting (when hyperpolarized) and tonic (when depolarized) (Sherman, 2001). Therefore, any hyperpolarizing stimulus (or potentially withdrawal of depolarizing stimulus) may change the spiking mode of thalamic neurons and their responsiveness to external stimuli - a point that will be returned to below.

Despite the parallels between thalamocortical physiology and the clinical findings in DLB, little is known about what changes in thalamocortical circuitry are found in DLB. A better understanding of how thalamocortical circuits malfunction in DLB may open the door to the development of novel therapeutic strategies to palliate the symptoms of DLB. Therefore, below we review the known literature about thalamocortical dysfunction in DLB and propose a model of thalamic circuit pathophysiology that may be responsible for a key symptom of DLB: visual hallucinations.

2. Changes to the thalamus in DLB

2.1. Anatomical/Biochemical studies

Several studies have revealed changes that occur in the thalamus in DLB patients. Swirski et al measured levels of amyloid-β and α-synuclein in thalamus and cortex from DLB and age-matched controls. They found elevated soluble amyloid-β1-40 and 1–42 and that the percentage of insoluble α-synuclein that was phosphorylated at serine 129 (P-129) was elevated in the thalamus of DLB subjects compared to controls (Swirski et al., 2014). Similarly, Miners et al. observed elevated levels of P-129 in the pulvinar nucleus (specific subnucleus not indicated in the publication) of the thalamus of DLB subjects relative to controls (Miners et al., 2014). These data suggest that the thalamus is a target of amyloid-β and α-synuclein pathology in DLB, though it should be noted that cortical pathology was generally more severe than thalamic pathology in both studies.

DLB-related pathology appears to be nonuniformly distributed in the thalamus, such that it is elevated in regions of the pulvinar nucleus, as well as the intralaminar nuclei. For example, a diffusion tensor imaging study on projection target-defined regions of the thalamus in DLB patients revealed changes in mean diffusivity across multiple thalamic regions. However, these changes were most prominent in the regions of the posterior thalamus (likely including the regions of the pulvinar) that project to the parietal and occipital cortices, and changes in mean diffusivity in these regions were positively correlated to the hallucinations item score on the neuropsychiatric index scale (Delli Pizzi et al., 2014). Several recent studies have examined the pathology of the visual thalamic nuclei: the lateral geniculate nucleus and the pulvinar, in DLB. Compared to AD and control subjects, the lateral pulvinar nucleus, which projects throughout the parietal visual association areas, showed significant cell loss in subjects with DLB, while the pulvinar generally showed increased α-synuclein deposition relative to controls and AD patients (Erskine et al., 2017), with similar trends seen across the analyzed subnuclei (anterior, medial, lateral – inferior nucleus not analyzed). In addition, whole pulvinar tissue showed a decrease in synaptic marker expression (including markers of inhibition) when compared to controls (Erskine et al., 2018). Interestingly, the lateral geniculate nucleus, which provides input to the primary visual cortex, appears spared in terms of pathological changes, when compared to AD subjects (Erskine et al., 2016). In addition, in a study of patients with Lewy Body spectrum diseases, when compared to the anterior and mediodorsal thalamic nuclei, the intralaminar nuclei were found to have increased susceptibility to DLB-related pathology. Intralaminar nuclei have been implicated in arousal and visual awareness (Purpura and Schiff, 1997; Schiff, 2008). The intralaminar nuclei most affected by α-synuclein deposition, and that showed the greatest degree of atrophy and cell loss, were the central lateral nucleus and cucullar nucleus. Degeneration of the latter structure, which projects to the amygdala, was also associated with the presence of visual hallucinations (Brooks and Halliday, 2009). These data suggest that synaptic physiology in regions of the thalamus specialized for arousal as well as visual processing and awareness is disrupted in DLB.

2.2. Perfusion imaging studies

Several studies have examined changes in regional blood flow in DLB and found changes in the thalamus and neocortex relative to controls. For example, Lobotesis et al observed decreased perfusion in the occipital lobe and relative preservation of thalamic perfusion using single photon emission computed tomography (SPECT) in DLB patients

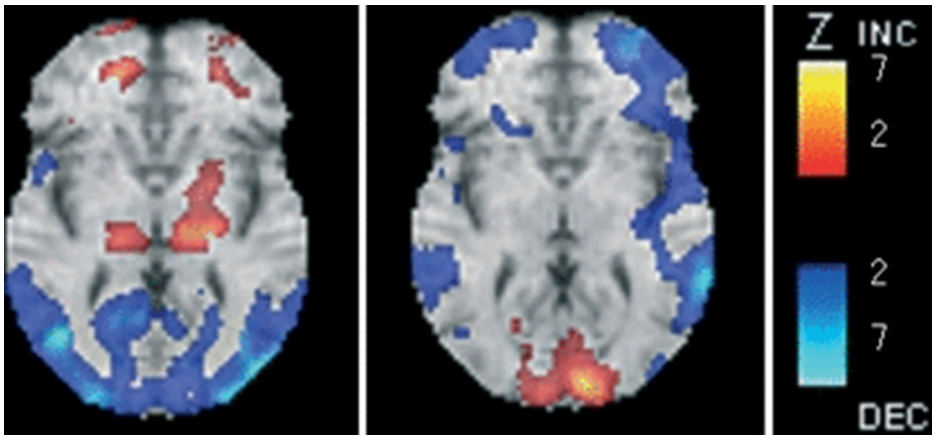

Fig. 1. Cerebral perfusion in DLB.
Changes in cerebral perfusion in DLB patients vs. controls (left) and AD patient vs. controls (right). Note the increase in perfusion of the thalamus and decrease in the occipital cortex in DLB. There are no significant changes in perfusion to deep gray matter in the AD brain, but decreases in temporal-parietal cortices are seen. Scale bar of Z-scores shown on the right. Used with permission from (Sato et al., 2007).

compared to AD patients and controls (Lobotesis et al., 2001). In addition, Sato et al explored characteristics of DLB perfusion changes using SPECT in 22 patients with DLB and 25 patients with AD. Similar to the Lobotesis study, they observed a significantly decreased perfusion in the occipital lobe and also reported a significant increase in perfusion in the deep gray matter (striatum and/or thalamus) in 18 DLB patients compared to 8 AD patients (See Fig. 1) (Sato et al., 2007). Relative preservation of thalamic perfusion in DLB relative to AD, while demonstrating prominent drops across posterior neocortical areas, was also reported by Tateno et al (Tateno et al., 2008). Similar increases in thalamic perfusion and metabolic activity were seen in earlier studies of PD patients using SPECT (Eidelberg et al., 1994; Imon et al., 1999). These data indicate that the perfusion signature in DLB is one of preservation of thalamic blood flow despite prominent drops across the temporo-occipital visual areas.

2.3. Acetylcholine, hallucinations, and cholinergic changes in the thalamus in DLB

Acetylcholine has been extensively implicated in altering states of consciousness and the production of hallucinations (Perry et al., 1999). For instance, antimuscarinics, such as scopolamine, have long been established to induce hallucinations (Safer and Allen, 1971) and restoration of synaptic acetylcholine via cholinesterase inhibitors is capable of attenuating hallucinations in patients with DLB, PDD, and AD (Cummings et al., 1993; Fabbrini et al., 2002; Fujita and Takebayashi, 2010; Maclean et al., 2001; McKeith et al., 2000b). It is notable that levodopa was not found to increase hallucinations in most DLB patients (Goldman et al., 2008), despite the purported role of dopamine in other forms of hallucinations. Atypical antipsychotics with efficacy against hallucinations in DLB, such as olanzapine, have been shown to cause striking increases in extracellular acetylcholine levels (Shirazi-Southall et al., 2002). In addition, patients with schizophrenia have long been established to have deficits in sensory gating (measured as deficits in P50 suppression) that respond to nicotinic stimulation (reviewed in (Martin et al., 2004)). That this nicotinic benefit is not attenuated with mecamylamine, an α4β2 antagonist, suggests that this deficit may be mediated by loss of α7 nicotinic receptors (Freedman et al., 1994). Collectively, these data suggest that dopamine may play less of a role in DLB-associated hallucinations than hallucinations seen in other conditions, and point to a key role for acetylcholine.

Cholinergic inputs to the thalamus are derived from the pedunculopontine and laterodorsal tegmental nuclei ((Mesulam et al., 1983; Sofroniew et al., 1985), and reviewed in (Varela, 2014; Yeomans, 2012)). In addition, the TRN receives dense cholinergic input mostly from the basal forebrain with a minority of cholinergic input from the pedunculopontine/laterodorsal tegmental nuclei (Hallanger et al., 1987). Thalamocortical neurons express both muscarinic (generally types M1-M3: (Breckinridge Carden and Bickford, 1999; Lord Plummer et al., 1999; Zhu and Uhlrich, 1998)) and nicotinic (mostly the α4β2 subtype in the body of the thalamus: (Chin et al., 2011; Hall et al., 1993) and the α7 receptor subtype in the TRN (Breese et al., 1997; Court et al., 1999; Ni et al., 2016; Quik et al., 2000)). M1, M2 and M3 receptors have been identified in the thalamus (Flynn and Mash, 1993), and acetylcholine generally depolarizes thalamocortical neurons via M1 or M3 receptors and therefore may shift thalamocortical cells from a bursting to a tonic state, though certain higher-order nuclei (those that receive sparse input from the sensory periphery) are hyperpolarized by acetylcholine via M2 receptors (Varela and Sherman, 2007) and others may show mixed responses (MacLeod et al., 1984). M4 receptors have also been identified in the thalamus, particularly in the inferior and lateral pulvinar of the primate (Ferrari-Dileo et al., 1994) though their functional significance is not yet known. M2 receptors are found on neurons in the TRN (Breckinridge Carden and Bickford, 1999; McCormick and Prince, 1986).

Neurons in the TRN show biphasic responses to pulses of acetylcholine: immediately after a pulse of acetylcholine, neurons depolarize, and then demonstrate long-lasting hyperpolarization (Sun et al., 2013). The depolarizing phase is sensitive to dihydro-beta-erythroidine, and therefore thought to be generated by α4β2 receptors, though some groups have speculated that α7 receptors play a role (Ni et al., 2016). As described above, α7 receptors are richly expressed in TRN neurons (Breese et al., 1997; Court et al., 1999; Ni et al., 2016; Quik et al., 2000), though are challenging to study given their rapid desensitization (Wang and Sun, 2005). Therefore, the functional role of α7 receptors in the TRN has been enigmatic. The late hyperpolarization is thought to be mediated by M2 muscarinic receptors (McCormick and Prince, 1986).

Multiple studies have documented changes in cholinergic function in DLB across the neocortex. For example, early studies documented significant loss of choline acetyltransferase activity across multiple neocortical areas (more pronounced in DLB than AD (Reid et al., 2000; Tiraboschi et al., 2000)) and that these drops are associated with the presence of visual hallucinations (Perry et al., 1990a, b). These drops, which were seen in an autopsy series in patients with end-stage disease, have been confirmed with in vivo imaging studies (Mazère et al., 2017). Nicotinic receptor subtypes appear to be more diminished than muscarinic receptors in DLB and the α7 receptor subtype appears to be more diminished than other neuronal nicotinic receptors, such as the α4β2 subtype (Colloby et al., 2006; Perry et al., 2000; Reid et al., 2000; Sabbagh et al., 2001). In addition, diminished cortical α7 and increased occipital α4β2 binding correlated with the presence of visual hallucinations (Court et al., 2001; O'Brien et al., 2008).

In the thalamus, similar to the neocortex, there is a pronounced overall drop in cholinergic innervation, as measured by imaging AChE activity in vivo, in DLB patients compared to either controls or AD patients (Kotagal et al., 2012). Regionally, cholinergic activity was

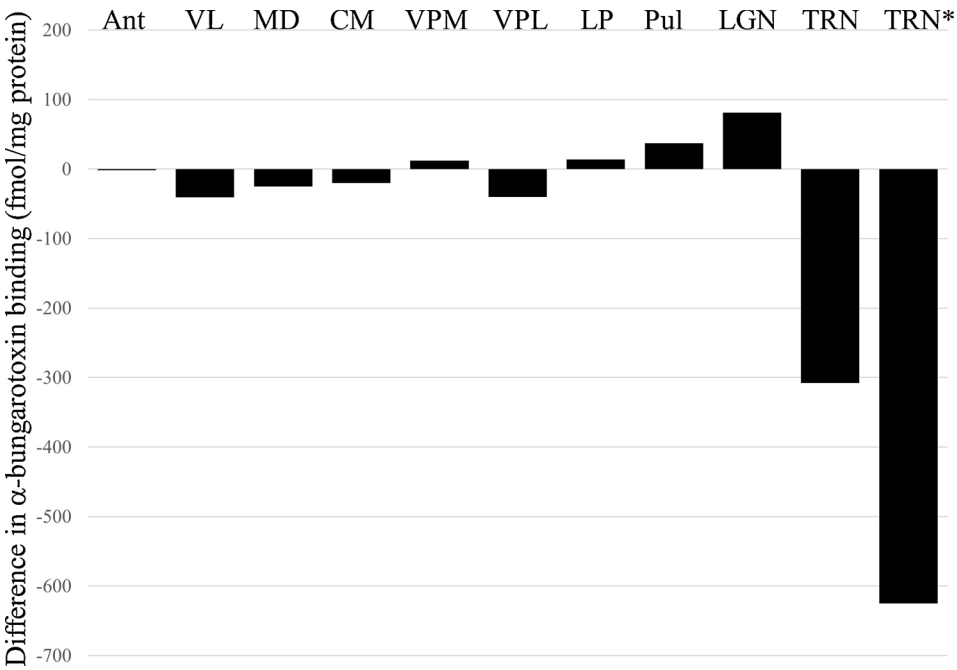

Fig. 2. Selective decline in α7 binding in the TRN in DLB patients.
Differences in α- bungarotoxin binding in various regions human thalamus expressed as difference in fmol/mg of protein. Only regions with at least 100 fmol/mg protein are shown. TRN* = TRN "high spots" correspond to areas with high baseline binding in the TRN. Abbreviations: Ant = anterior thalamic nucleus, VL = ventrolateral thalamic nucleus, MD = mediodorsal thalamic nucleus, CM = centromedial thalamic nucleus, VPM/L = ventral posterior medial/lateral nucleus, LP = lateral posterior nucleus, Pul = pulvinar (subnucleus not specified). Data replotted from (Court et al., 1999).

measured using choline acetyltransferase activity in the TRN, mediodorsal thalamus and centromedian thalamus in a small study (n = 5 DLB patients with parkinsonism, and n = 5 DLB patients without parkinsonism) and trends for a decrease were seen in the TRN and mediodorsal thalamic nuclei. These trends reached significance in PDD patients where the number of subjects was larger (n = 14, (Ziabreva et al., 2006)). This drop in cholinergic input to the thalamus appears to be reflected most strongly in the decline of α7 nicotinic receptors in the TRN (nearly 50% drop in α7 binding in DLB patients (Court et al., 1999), see Fig. 2) with relatively weak changes seen in α4β2 and α6 or α3 containing receptors (Bohr et al., 2005; Pimlott et al., 2004, 2006; Ray et al., 2004). Taken together, these findings point to a decline in cholinergic innervation of the thalamus and cortex in DLB, and indicate that α7 receptors in the TRN may be a particular point of vulnerability in DLB, potentially providing a substrate to the symptomatology described above.

Unfortunately, there is a paucity of information about muscarinic receptor changes within thalamic nuclei in DLB. In a study of M2 and M4 binding across anteroprincipal, mediodorsal and ventrolateral nuclei, only reductions in M4 binding were seen, and these only reached significance in the mediodorsal nucleus (Warren et al., 2007).

2.4. Serotonin, hallucinations, and serotonergic changes in the thalamus in DLB

Serotonin has been strongly implicated in the formation of hallucinations, particularly in the setting of schizophrenia or the use of hallucinogenic drugs (Marek, 2007). Hallucinogens such as lysergic acid diethylamide (LSD) and psilocybin are 5 H T2A agonists that excite infragranular pyramidal neurons in frontal and temporal cortices (Geyer and Vollenweider, 2008). Although a majority of 5 H T2A receptors are located in cortical areas, evidence from mRNA measurements in the rat brain have shown moderate levels in the TRN and ventrolateral geniculate nucleus (Pompeiano et al., 1994). Nichols argued that 5 H T2A receptor activation may lead to hallucinations via disruption of the TRN combined with increased thalamocortical excitability, potentially leading to the formation of coherent thalamocortical oscillations and subsequent formation of false percepts (Nichols, 2004). In addition, 5 H T1A receptors, which have been implicated in hallucinogenesis (Penington and Fox, 1994), have been identified in the primate thalamus in vivo (Yokoyama et al., 2016).

Most serotonin innervation of the thalamus is derived from the dorsal raphe nuclei (De Lima and Singer, 1987; Moore et al., 1978; Vertes, 1991; Yoshida et al., 1984) and innervation tends to be most dense in the intralaminar and higher-order nuclei, as well as in the lateral geniculate nucleus (Varela, 2014). Serotonin receptors comprise seven subfamilies (5 H T1-7). In the marmoset, the mRNA for only 5 H T1A, 5 H T1B, 5 H T6 and 5 H T7 have been identified across visual thalamic nuclei, while TRN neurons express 5 H T1A, 5 H T1B, 5 H T2A and 5 H T2B and appear to not express 5 H T6 or 5 H T7 receptors (McCormick and Wang, 1991; RodrÍguez et al., 2011; Shukla et al., 2014). It should be noted that mRNA expression within a thalamocortical neuron does not necessarily mean that the receptor will function in the thalamus (Fremeau et al., 1991). The receptor may be transported to the thalamocortical terminal, where presynaptic serotonin receptors may influence thalamocortical synaptic plasticity and, ultimately, cortical output (Barre et al., 2016; Marek et al., 2001). Supporting this idea is evidence that presynaptic 5 H T2A receptors on thalamocortical terminals may activate cortical neurons and contribute to the hallucinogenic effects of drugs that agonize 5 H T2A receptors (Marek et al., 2001).

The actions of serotonin on thalamocortical neurons are varied and depend on both the subnucleus of the thalamus and the species being investigated. Direct application of serotonin has been shown to both depolarize (via non-5 H T1A, 5 H T1 receptors (Pape and McCormick, 1989) or 5 H T7 receptors (Chapin and Andrade, 2001)), or hyperpolarize (via 5 H T1A-receptors (Monckton and McCormick, 2002; Varela and Sherman, 2008)) thalamocortical neurons as well as to increase activity of intrinsic GABAergic thalamic interneurons (Monckton and McCormick, 2002; Pape and McCormick, 1995), and may do so via 5 H T2A receptors (Crunelli and Di Giovanni, 2015). Serotonin also diminishes the impact of visual information on the lateral geniculate nucleus via presynaptic 5 H T1 receptors (5 H T1-subtype yet to be identified, (Chen and Regehr, 2003; Seeburg et al., 2004; Yang et al., 2014b)), thus potentially creating a deafferentation scenario and consequently promoting the formation of spontaneous visual percepts. The TRN also receives prominent serotonergic innervation which is at least as dense as principal thalamic nuclei (Lavoie and Parent, 1991; Morrison and Foote, 1986). Serotonergic innervation of the TRN derives from the dorsal raphe and supralemniscal nucleus and TRN dendrites

express 5 H T receptor subtypes that include 5 H T1A and 5 H T2A receptors (RodrÍguez et al., 2011). When applied at the level of the TRN, serotonin excites TRN neurons via 5 H T1C or 5 H T2 receptors (McCormick and Wang, 1991). In contrast, when applied at the site of reticulothalamic terminals in the dorsal thalamus, serotonin may decrease or increase GABA release via presynaptic 5 H T1A or 5 H T2A receptors, respectively (Goitia et al., 2016).

Serotonin pharmacology has also been implicated in DLB, and Lewy bodies occur in the dorsal and median raphe nuclei with marked reduction in 5 H T-positive cell bodies (Benarroch et al., 2007). To our knowledge, no studies exist that examine the changes in serotonin or its receptor levels in the thalamus in patients with DLB. However, the profound losses of serotonin neurons in the dorsal and median raphe suggest that changes in thalamic serotonin levels and/or receptor distribution would likely be seen. Outside of the thalamus, reductions of serotonin levels have been reported in the striatum and frontal cortex of DLB patients (Francis, 2009; Ohara and Kondo, 1998; Perry et al., 1993). Several studies have examined the relationship between serotonin levels in DLB patients and the likelihood of developing visual hallucinations. For example, Perry et al measured levels of the main metabolite of serotonin, 5-hydroxyindoleacetic acid (5-HIAA), as well as choline acetyltransferase, the main synthetic enzyme for acetylcholine, in the temporal cortex of DLB patients. Consistent with the literature reviewed above, they observed profound drops in choline acetyltransferase levels in the cortex of DLB patients relative to controls, as well as a drop in 5-HIAA levels. There was, however, relative preservation of 5-HIAA levels in those subjects with visual hallucinations (compared to the greater decline in choline acetyltransferase), suggesting that the balance of serotonin to acetylcholine metabolism may be the major determinant of whether hallucinations occur (Perry et al., 1990b). In a related study, Perry et al. used high performance liquid chromatography to measure neurotransmitter and metabolite levels in postmortem samples from the frontal cortex of DLB patients with and without visual hallucinations and found that 1) serotonin levels were reduced in DLB patients compared to controls and 2) that the ratio of 5-HIAA to serotonin was elevated in hallucinating relative to nonhallucinating patients (Perry et al., 1993). These data suggest that increased serotonin turnover is associated with hallucinations in DLB patients. With respect to receptor binding, 5 H T2 receptor levels were examined in the temporal cortex using autoradiography, and were found to be generally depressed in DLB patients relative to controls. However, similar to the Perry et al. 1990 study described above, there was a relative preservation of 5 H T2 binding in those subjects with visual hallucinations compared to those without (Cheng et al., 1991). Future work will determine whether similar changes are seen at the level of the thalamus.

2.5. Dopamine, hallucinations, and dopaminergic changes in the thalamus in DLB

Dopamine has long been implicated in the production of hallucinations based dopaminergic dysfunction in psychosis in schizophrenia (Kuepper et al., 2012), the efficacy of drugs to treat these symptoms via D2 receptor blockade (Miyamoto et al., 2005), and pharmacological induction of hallucinations seen with levodopa (Banerjee et al., 1989) as well as cocaine or amphetamine (Thirthalli and Benegal, 2006). Although traditionally the dopamine hypothesis of schizophrenia outlined excess dopamine in the mesolimbic pathway as the primary cause of positive symptoms, such as hallucinations (Davis and Kahn, 1991), recent evidence has implicated the nigrostriatal pathway—which has projections to the anterior caudate—as the potential primary site of dysfunction (Kuepper et al., 2012). In addition, it has been proposed that dopaminergic projections from the substantia nigra compacta may activate D2 and D4 receptors located in the TRN and suppress the synthesis of GABA resulting in disinhibition of thalamic relay neurons and thereby potentially contributing to positive symptoms of schizophrenia (Behrendt, 2006). Further, reductions in D2 and D3 binding have been observed in the brains of patients with schizophrenia, and these reductions were strongest in the thalamus (primarily in the pulvinar) in drug-naïve patients with schizophrenia (Buchsbaum et al., 2006). These data implicate a potential role for alterations in thalamic dopaminergic neurotransmission in generation of hallucinations.

The thalamus receives rich dopaminergic innervation, and this innervation is most densely found in midline and association nuclei and is derived from the hypothalamus, periaqueductal gray, ventral mesencephalon and lateral parabrachial regions (Sánchez-González et al., 2005). Multiple dopamine receptor subtypes have been identified in the thalamus. A strong signal for D1 receptor mRNA is found in the intralaminar nuclei as well as in the lateral geniculate and posterior thalamic nuclei, though weak binding to the D1 receptor was found in the thalamus, suggesting that much of the receptor expression was presynaptic at the targets of thalamic neurons in the cortex or basal ganglia (Fremeau et al., 1991). D2 receptor binding in the human thalamus is highest in the midline and intralaminar nuclei, and relatively low in the primary sensory nuclei and TRN (Rieck et al., 2004) though an older study reported stronger D2 binding in the lateral geniculate nucleus than other regions (Meador-Woodruff et al., 1991). mRNA for D5 receptors has primarily been localized to the parafascicular nucleus in the rat and not seen in other thalamic subnuclei (Meador-Woodruff et al., 1992). Lateral geniculate and primary somatosensory neurons are depolarized by dopamine via D1 receptors, and D2 receptors may directly increase the excitability of their parent thalamocortical neurons via alterations of potassium conductance (Govindaiah and Cox, 2005; Govindaiah et al., 2010b) or indirectly decrease thalamocortical cell firing via activation of local interneurons (Munsch et al., 2005). Mediodorsal thalamic neurons, similar to primary sensory neurons above, are directly excited by D2 agonists via a decrease in potassium conductance, but do not respond to D1 agonism (Lavin and Grace, 1998). In addition, similar to the effects of serotonin, dopamine tends to diminish retinogeniculate transmission via a combination of D1 and D2 receptors, possibly via presynaptic mechanisms (Govindaiah and Cox, 2006; Zhao et al., 2001). To our knowledge, no studies have been done specifically on the effects of dopamine on TRN neurons. However, it has been shown that D2 and D4 agonism can decrease the magnitude of tonic extrasynaptic inhibition induced by $GABA_A$ agonists (Yagüe et al., 2013), and that D4 agonism diminishes GABAergic inhibition in the TRN derived from the globus pallidus (Govindaiah et al., 2010a), suggesting that dopamine working across both the TRN and the dorsal thalamus can enhance TRN-based suppression of thalamocortical activity.

Thalamic dopamine abnormalities have also been found in DLB. For example, Piggot et al measured thalamic D2 receptor binding using post-mortem autoradiography in 18 cases of DLB, 13 cases of PDD, 6 PD without dementia features and 14 controls. DLB cases with parkinsonism had significantly elevated D2 receptor density in laterodorsal and ventrointermedius nuclei and DLB cases without parkinsonism did not show increased D2 density in any areas. The authors did not report any association between D2 receptor binding with cognitive decline or visual hallucinations, but D2 binding was reported significantly higher with increased extrapyramidal symptoms (Piggott et al., 2007). Although the mechanism of D2 receptor elevation is not known, the authors speculated that the increase may be compensatory and point out that similar increases in D2 density were seen in the striatum of DLB patients (Piggott et al., 1999). The findings that thalamic D2 receptor densities correlate better with parkinsonism rather than visual hallucinations are consistent with other studies showing that dopamine transporter density in the striatum correlates more strongly with parkinsonism than with neuropsychiatric features (Shimizu et al., 2017; Siepel et al., 2016; Ziebell et al., 2013), but see (Roselli et al., 2009).

2.6. NMDA receptors, hallucinations, and NMDA receptor changes in the thalamus in DLB

N-methyl-D-aspartate (NMDA) glutamate receptor hypoactivity has been implicated as a potential model of schizophrenia (Olney and Farber, 1995). Supporting this idea, drugs that antagonize the NMDA receptor, such as ketamine and phencyclidine, induce hallucinations (Mozayani, 2003; Powers III et al., 2015), alter thalamic and cortical rhythmicity (Lisman et al., 2010; Pinault, 2008), and block GABAergic neurons located in the TRN (Sharp et al., 2001). Furthermore, it has been suggested that disinhibition of the thalamus via NMDA antagonism at the level of the TRN may result in pathological activation of thalamocortical circuits potentially contributing to psychotic features of schizophrenia (Behrendt, 2006; Lladó-Pelfort et al., 2017). In fact, a recent modeling study suggested that downregulation of NMDA receptors on cortical interneurons or analogous hyperpolarization of TRN neurons may be sufficient to cause certain manifestations of schizophrenia such as smooth pursuit eye movement abnormalities or attentional dysregulation (John et al., 2018). In this context, it is notable that NMDA antagonism via the use of memantine (an NMDA-receptor antagonist drug approved for the treatment of AD), in at least one study has worsened hallucinations in DLB (Ridha et al., 2005), and another in AD patients (Monastero et al., 2007), but see (Meng et al., 2019) for reports of clinical benefit for memantine in DLB and PDD. However, it has also been posited that excessive disinhibition of thalamic relay cells alone would not be sufficient to produce hallucinations without pathological involvement of attentional mechanisms (Behrendt, 2006). Interestingly, blocking NMDA receptors through administration of ketamine has been shown to enhance dopamine release (Kegeles et al., 2000) suggesting cross-talk across neurotransmitter systems may contribute to the generation of hallucinations.

NMDA receptors are found throughout the thalamus (Clinton and Meador-Woodruff, 2004; Jones et al., 1998; Salt, 1986), and diminished thalamic expression of intracellular signaling molecules linked to NMDA receptors has been reported in individuals with schizophrenia (Clinton and Meador-Woodruff, 2004). NMDA receptors, along with other glutamate receptors, are found at corticothalamic synapses (Deschênes and Hu, 1990; Reichova and Sherman, 2004) and may be important for short-term plasticity at these synapses (Crandall et al., 2015; Fernandez et al., 2017). Diminished thalamic NMDA receptor function has been speculated to lead to disintegration of cortico-thalamocortical circuits (see section 4.0 below), leading to a breakdown in sensorimotor integration in schizophrenia (Vukadinovic, 2014). Therefore, it is possible that NMDA dysregulation can lead clinical manifestations in DLB. However, to our knowledge, no studies exist that examine the impact of DLB on thalamic NMDA receptor distributions.

3. Perception, perceptual deficits and hallucinations

It has been speculated that everyday perception is a result of the combination of external sensory input, internal object and scene representations and goal-directed attention (Collerton et al., 2005). This model implies that normal perception requires the fine coordination of bottom-up information from the sensory periphery and top-down modulatory influences, presumably from higher areas in the sensory hierarchy to lower areas (e.g., via corticocortical or corticothalamic projections). Deafferentation may then tip the balance in favor of internally-represented percepts. For example, Charles Bonnet syndrome is characterized by visual hallucinations in patients who typically have impairment at the level of the eye (most commonly age-related macular degeneration) and demonstrate hyperactivity in various portions of the visual association cortex (Howard et al., 1998; Schadlu et al., 2009) as well as the thalamus (Jang et al., 2011). Their hallucinations may be related to cortical release and consequent hyperexcitability of the cortex similar to that seen in phantom limb pain (Menon et al., 2003).

Neuromodulators, such as acetylcholine, have been speculated to play an important role in balancing bottom-up and top-down influences such that they may enhance signal-to-noise ratio (Everitt and Robbins, 1997; Hasselmo et al., 1997). For example, peduncular hallucinosis often presents with visual hallucinations as well as impaired arousal in patients with lesions in subcortical structures such as the reticular formation, raphe nuclei, substantia nigra, tegmentum, paramedian thalamic regions, and pulvinar (subnucleus not specified (Benke, 2006)). Of note, many patients who experience peduncular hallucinosis have abnormal sleep behavior and impaired episodic memory, similar to that observed in DLB. Manford and Andermann (1998) argued that the observed clinical sleep disturbances may be due to disruption of brainstem structures connected to midline thalamic nuclei and the TRN (Manford and Andermann, 1998). Thus, hallucinations may be related to inadequate arousal signals to the thalamus and cortex, diminishing appropriate integration of bottom-up and top-down inputs. Given that top-down influences likely modulate perception by building expectations about sensory stimuli, disruptions in acetylcholine may alter the relative certainty between bottom-up sensory information and top-down expectations (Angela and Dayan, 2002; Friston, 2005). As such, when uncertainty is high about bottom-up information, top-down biases may produce incorrect percepts based on an individual's expectations or memories of the perceptual scene. A corollary of this supposition is the finding that visual hallucinations diminish in Charles Bonnet patients when visual input is reduced to zero (i.e., when eyes are closed), which may signal an increase in certainty of the bottom-up signal being null (Collerton et al., 2005).

Supporting the notion that hallucinations can be related to the corrosion of bottom-up signals which may bias perception in favor of stored, top-down representations, is the finding that the perceptual capacities of individuals with hallucinations are often diminished. This sensory degradation is particularly evident in patients with established deafferentation syndromes, but is also found in individuals with schizophrenia. For example, in schizophrenia there are low-level auditory processing deficits such as diminished sensitivity to pure-tune stimuli (Mathew et al., 1993) and diminished pure-tone matching capacity (Rabinowicz et al., 2000). These deficits are compounded by higher-level auditory processing deficits, such as difficulties with speech perception (Bull and Venables, 1974; Hoffman et al., 1999). To our knowledge, despite extensive work documenting higher-order visual perceptual deficits in DLB (reviewed in (Collerton et al., 2003)), little work has been done to examine low-level visual perceptual abilities, such as visual detection tasks, in DLB patients (but see (Archibald et al., 2009) for evidence of retinal pathology PD). As suggested by Behrendt (Behrendt, 2006), these data point to a general uncoupling of sensory input to thalamocortical processing in hallucinating patients. It may be that mechanistically the uncoupling in different disorders is instantiated by different mechanisms, but that disruption of bottom-up perceptual processing is the common denominator among the hallucinating disorders.

3.1. Functional neuroimaging studies

To better understand the potential role of the thalamus in producing DLB-related hallucinations, here we briefly review the functional imaging literature with respect to thalamic activity during hallucinations. Most previous functional imaging work has focused on the role of the cortex in the production of hallucinations. This is in part due to early studies that showed that cortical stimulation, particularly in the temporal lobe, could cause hallucinations (Ishibashi et al., 1964; Penfield and Perot, 1963). Subsequent studies have revealed that regional cortical activation in hallucinating subjects is commensurate with the modality of hallucination (e.g., visual hallucinations activate areas of the visual cortex and visual association areas, etc. (Howard et al., 1998; Lennox et al., 2000; Shergill et al., 2001)). However, imaging studies have also implicated the thalamus in hallucinating states (Shergill et al., 2000). As discussed in Llano (2013), it is important to point out that

failure to see thalamic activation during a functional imaging study may be related to multiple factors: failure to examine thalamic regions of interest, the small size of thalamic nuclei relative to voxel size in functional imaging studies, the high variability of thalamic nuclear borders across subjects (Andrew and Watkins, 1969; Rademacher et al., 2002; Uylings et al., 2008) as well as the greater vulnerablity to movement artifacts induced by cardiac contractions than that observed in the cortex (Guimaraes et al., 1998). In addition, the thalamus shows different metabolic time profiles compared to neocortex (Llano et al., 2009), suggesting that thalamus-specific hemodynamic response functions may be needed. Finally, there may be differences in degree of regional activation that occur during cognitive tasks when comparing thalamus and cortex. For example, a small area of thalamic activation (measured in tens of microns) is sufficient to drive large cortical activations (measured in hundreds of microns) (Llano et al., 2009; Theyel et al., 2010).

Nevertheless, many studies have shown significant activation in the thalamus in actively hallucinating participants. For example, several studies have examined cerebral blood flow in subjects with Charles Bonnet hallucinations while the patients were actively hallucinating. In 2000, Adachi at el. studied five patients with Charles Bonnet syndrome using 123I-IMP SPECT and MRI. SPECT findings showed hyperperfusion in the thalamus bilaterally in four hallucinating patients compared to the non-hallucinating controls. The fifth patient had hyperperfusion in the right thalamus (Adachi et al., 2000). More recently, Jang et al. carried out a PET study to examine a subject with Charles Bonnet syndrome and observed left thalamic hyperperfusion compared to controls, which disappeared with successful pharmacological treatment (Jang et al., 2011). Similar thalamic hyperperfusion was seen in a hallucinating patient with PD (Goetz et al., 2014).

Three studies examining patients with schizophrenia also implicate the thalamus in hallucinations. In the case study published by Woodruff et al in 1994, a 48-year-old individual with schizophrenia was imaged using fMRI during a period of intermittent hallucinations and while not hallucinating. The investigators observed increased activity in the dorsomedial thalamus during hallucinations compared to non-hallucinating periods (Woodruff et al., 1994). Shergill et al. performed a similar study a few years later. This study examined six patients with schizophrenia using fMRI and found that the right thalamus showed a significant increase in activity in the ventral anterior nucleus during hallucinations (Shergill et al., 2000). Similar findings were reported by Silbersweig et al, who used H2(15)O PET to image five individuals with schizophrenia (Silbersweig et al., 1995). These converging data all point to an elevation of thalamic activity during hallucinations, though these studies cannot differentiate whether the hallucinations are triggered at the level of the thalamus or are a reflection (via corticothalamic projections) of ongoing hallucinations in the cortex.

3.2. Hallucinations in DLB vs. Other conditions

Throughout this report, by necessity, given the relatively small numbers of studies on DLB patients, we have looked to hallucinations in states other than DLB to understand the mechanisms of hallucinations in DLB. However, hallucinations in DLB have clinical characteristics that distinguish them from hallucinations seen under other conditions, and therefore may involve different underlying mechanisms. For example, hallucinations are seen at some point during the lifespan in a high fraction ($> 50\%$) of normal individuals without drug intoxications (McKellar, 1957; Posey and Losch, 1983). However, these hallucinations in these non-disease states are almost always seen at the borders of sleep (e.g., hypnogogic and hypnopompic hallucinations (Collerton et al., 2005)), and therefore may be attributable to alterations in thalamic state exhibited during sleep transitions, such as transitioning between rhythmic bursting and tonic firing modes. Hallucinogen-induced (e.g., LSD, psilocybin) hallucinations tend to be bizarre and distorted versions of reality (Collerton et al., 2005), rather than nonfrightening visions of relatively mundane objects seen in DLB. Therefore, the prominent antimuscarinic and 5 H T2 agonist properties of drug hallucinogens may not reflect mechanisms seen in DLB. Hallucinations seen in deafferentation states (Charles Bonnet hallucinations, tinnitus, phantom limb) tend to be more simple in form (ffytche, 2008). That is, they are more likely to represent features of objects (e.g., lines, tones, touch intensity) rather than whole objects, such as people or animals, seen in DLB. Therefore, their neural instantiations may involve different regions of the sensory hierarchy than those seen in DLB. Finally, in schizophrenia hallucinations are typically auditory, and are personal and negative in their content (Jones and Fernyhough, 2007), and therefore likely call upon auditory and limbic structures that are less likely to be involved in DLB. As a corollary, hallucinations in DLB tend to not provoke fear and anxiety to the same degree that hallucinations in schizophrenia do. It is possible that the additional biochemical abnormalities in schizophrenia such as dopaminergic hyperfunction or NMDA hypofunction may contribute to the affective component not present in DLB, though this hypothesis remains to be tested. In frontotemporal dementia, hallucinations are generally rare, but, when present are strongly associated with a hexanucleotide repeat expansion mutation in the C9orf72 gene (Devenney et al., 2014; Kertesz et al., 2013; Onofrj et al., 2015), which in this context has been associated with degeneration in the medial pulvinar (Vatsavayai et al., 2016). However, evidence for mutation in this gene is rare in DLB patients (Robinson et al., 2014; Snowden et al., 2012). Therefore, one needs to extrapolate with caution any mechanisms learned from the study of non-DLB patients to the biology of hallucinations in DLB.

4. Potential thalamic circuit abnormalities underlying visual hallucinations DLB

There are at least 20 different nuclei and subnuclei of the thalamus, and over the years multiple theories have been proposed to account for their roles in information processing. Early theories postulated that nuclei within the thalamus could be categorized as being part of a “core” vs. “matrix” region, based upon destination layer in the cortex (middle cortical layers for core and superficial layers for matrix) and staining density for the calcium-binding protein calbindin (high for matrix areas). In this organizational scheme, core areas carry specific information to the cortex, while matrix areas, via their more broadly distributed distal cortical terminations, synchronize activity across cortical areas (Jones, 2001). This scheme does not explicitly account for the considerable descending influence from the cortex onto thalamocortical neurons. Only the minority of inputs ($\sim 10\%$) onto thalamocortical neurons are derived from the sensory periphery, while the rest are derived from the cortex, TRN and ascending projections from monoaminergic and cholinergic nuclei (Erişir et al., 1997; Montero, 1991). A later model postulated that parvalbumin- and calbindin-positive regions of the thalamus divided thalamic nuclei into first-order and higher-order nuclei, such that first order nuclei receive their specific content-related signals from the sensory periphery (e.g., the retina for the lateral geniculate nucleus), while higher-order nuclei receive their specific content-related input from the cortex (e.g., the corticorecipient areas of lateral pulvinar for vision, see Figs. 3A and B). In this scheme, content-related signals to higher-order nuclei are derived from layer 5 of the cortex, while the more numerous layer 6 corticothalamic neurons play a modulatory role (Guillery and Sherman, 2002). The thalamus, therefore, acts as a conduit for information being transferred from one region of the cortex to another (Guillery and Sherman, 2002; Theyel et al., 2010). In more anterior regions of the thalamus, content-related input may be derived from other brain areas, such as cerebellum, basal ganglia and amygdala (Aggleton and Mishkin, 1984; Asanuma et al., 1983; Miyashita et al., 2007; Sakai et al., 1996; Sidibé et al., 1997), some of which may also manifest pathology in DLB (Higuchi et al., 2000; Popescu et al., 2004). These regions of the thalamus typically project to motor or prefrontal areas of cortex, though

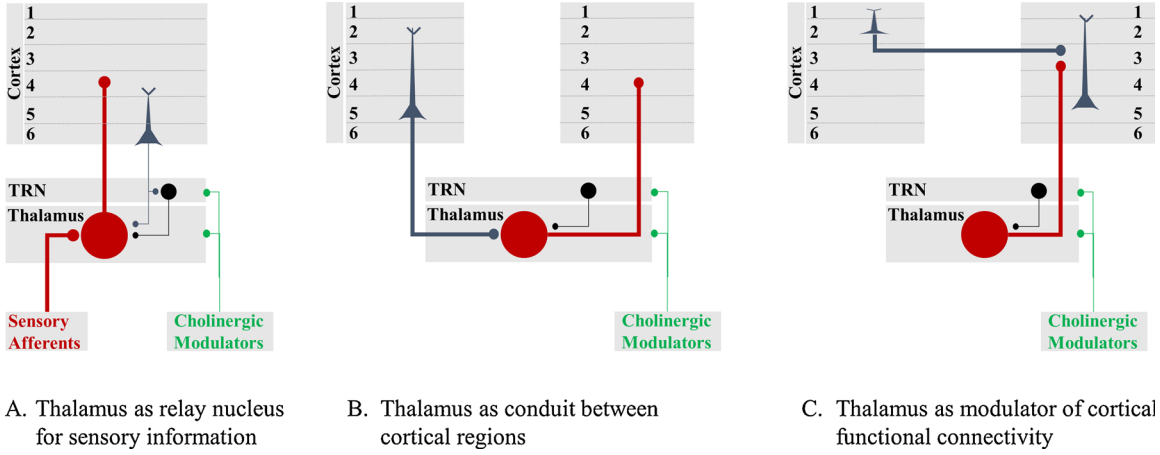

Fig. 3. Models of thalamic organization.
A) Thalamocortical neurons in principal relay nuclei (such as the lateral geniculate nucleus) send projections to layer 4 of the cortex. Also shown is a corticothalamic projection from layer 6 which branches to TRN, which in turn sends an inhibitory projection to the thalamocortical neuron. B) In higher order nuclei (such as the corticorecipient areas of lateral pulvinar), the thalamus may relay information from layer 5 neurons in one cortical area to layer 4 of another cortical area. C) An alternative model of function in higher order thalamic nuclei is to modulate the functional connectivity within or between regions of cortex. Corticothalamic projections to TRN and thalamocortical cells exist in models B and C, but were omitted for clarity. In all cases, both thalamocortical neurons and the TRN receive cholinergic input, as described in detail in the text. Note that this figure, as well as Fig. 4, only contains canonical inputs to layer 4.

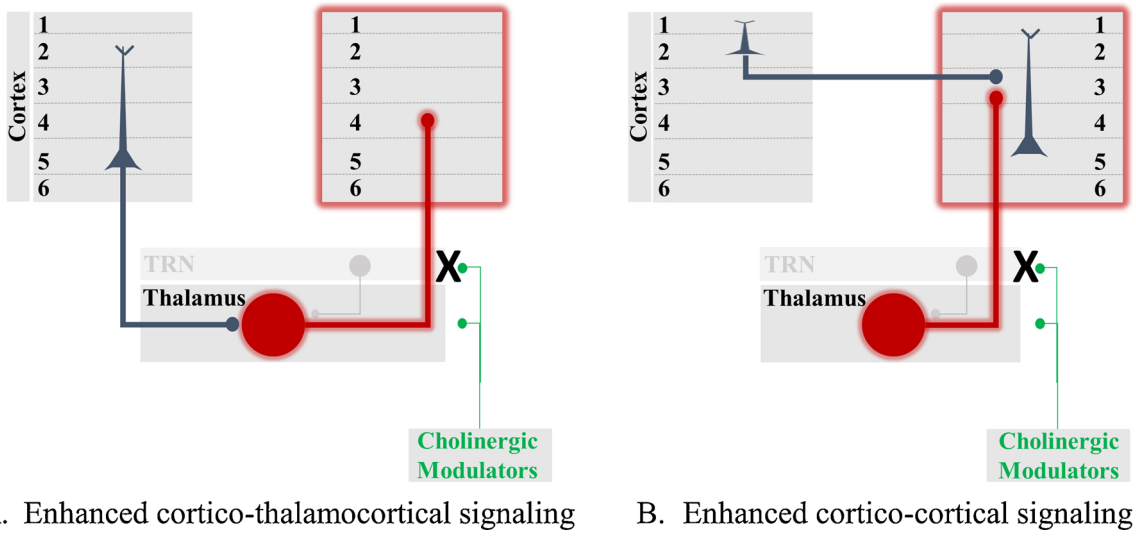

Fig. 4. Hypothesized impact of loss of α7 innervation of the TRN.
Shown are the models of non-primary thalamic nuclei (i.e., models B and C from Fig. 2). Loss of cholinergic innervation of the TRN (shown with an "X") leads to diminished activity of the TRN. This disinhibition of thalamocortical neurons (represented as a glowing thalamocortical neuron) increases the likelihood of an unselected cortical signal to activate a downstream cortical area (represented as a glowing gray box). This putative mechanism is shown for a cortico-thalamocortical mechanism of thalamic function (A) and a mechanism whereby the thalamus alters the functional connectivity between brain regions (B).

there is some evidence that rostral areas of the thalamus send projections to visual cortex (Rieck and Carey, 1985), which is presumably the most direct mediator of visual hallucinations. The schemes shown in Figs. 3A and 3B have been described as failing to capture the broader diversity of thalamocortical interactions that exist (Bickford, 2016; Clascá et al., 2012; Nakajima and Halassa, 2017). For example, thalamocortical neurons also project to layers 1, 5 and 6 (Bruno and Sakmann, 2006; Huang and Winer, 2000; Ji et al., 2015; Rezak and Benevento, 1979; Rubio-Garrido et al., 2007; Slater et al., 2019; Yang et al., 2014a; Zhao et al., 2009). These connections are not included in Fig. 3 (or Fig. 4) in order to focus on the impact of pathological change on canonical circuitry involving thalamus and cortex. It is not yet known if TRN projections to layer 4-targeted thalamocortical cells differs from that onto thalamocortical cells targeting other layers.

Recent data have suggested more nuanced functional organizational schemes for the thalamus and cortex. For example, Schmitt et al. demonstrated that the mediodorsal nucleus of thalamus played a key role of organizing prefrontal cortical activity in an attentional task (Schmitt et al., 2017). Similarly, and more relevant to the issue of visual hallucinations, Saalmann et al. demonstrated that the ventral portions of the pulvinar played an important function in synchronizing activity across multiple higher order visual cortical areas (Saalmann et al., 2012). These findings, coupled with diversity of thalamocortical projection termination patterns, have fueled proposed models of thalamocortical organization involving a mosaic of multiple thalamocortical organizational motifs, including those that involve point-to-point projections from thalamus to layer 4 of cortex, others involving potential cortico-thalamo-cortical connectivity, and others that link activity across cortical regions to enhance intracortical communication (Fig. 3C) (Bickford, 2016; Clascá et al., 2012; Nakajima and Halassa, 2017). However, specific mechanisms by which thalamocortical neurons can enhance cortico-cortical connectivity have not been

established.

In a mosaic-type of thalamic organization, multiple modes of thalamic function (and therefore dysfunction) are possible. For example, given the massive and heterogeneous cortical projections to the thalamus, the corticothalamic system has been speculated to be a substrate of a predictive coding mechanism (Rikhye et al., 2018). Predictive coding models postulate that one mechanism to disambiguate noisy stimuli is to use an internal model (a "prior" in a Bayesian framework) to bias sensory processing based on prior experiences (Friston and Kiebel, 2009; Malmierca et al., 2015; Mumford, 1991). In such a model, the thalamus could serve as a sensory processing station whose tuning properties are shaped by prior beliefs held by the cortex and/or a source of updates to shape belief networks in the cortex; in fact, there is evidence for both (Komura et al., 2013; Zhang and Yan, 2008). Importantly for this discussion, in a predictive coding framework, thalamic activity is tightly coupled to the fine balance of bottom-up and top-down information. It may be that any system that relies on perceptual inference, when the balance is shifted due to changes in excitatory or inhibitory tone, may be prone to hallucinate (Friston, 2005).

Another factor when considering thalamic dysfunction in the setting of hallucinations is the presence of bursting in thalamocortical neurons. Classically, bursting has been considered a hallmark of sleep and drowsiness, and therefore, a state in which sensory information is not being transmitted to cortex. In this formulation, bursting may also be seen under pathological states and bursting neurons, when adjacent to non-bursting thalamocortical projections, have been speculated to lead to cortical gamma activation, leading to false percepts (Jeanmonod et al., 1996; Llinás et al., 1999). There is some evidence for this mechanism in tinnitus (De Ridder et al., 2015; Sametsky et al., 2015), neuropathic pain (Hsieh et al., 1995; Walton et al., 2010) and Purkinje hallucinations (fictive visual percepts induced via patterns of light imposed upon the closed eye) (ffytche, 2008). Other formulations have speculated that thalamic bursting may carry sensory information (Lesica et al., 2006; Lisman, 1997; Person and Perkel, 2005; Reinagel et al., 1999; Swadlow and Gusev, 2001). In the case of DLB, the thalamus appears to be hypermetabolic (see Fig. 1, above), rather than hypometabolic, as occurs with Purkinje hallucinations and pain (ffytche, 2008; Hsieh et al., 1995). It is not yet known if bursting is associated with thalamic hyper- or hypo-metabolism, though it has been speculated that bursting leads to the latter (Llinás et al., 1999). Therefore, the notion that bursting drives hallucinations in deafferentation syndromes may not apply to hallucinations in DLB. It is not yet known if there is abnormal bursting in the thalamus of DLB patients. As described above, the most prominent neurochemical change in the thalamus in DLB is the withdrawal of acetylcholine on α7 receptors (see Fig. 2). Diminishment of acetylcholine at the level of the TRN, particularly on α7 receptors, would be expected to diminish thalamic bursting by dampening TRN influence on thalamocortical neurons. Since corticothalamic stimulation may inhibit thalamic relay cells via their projections to the TRN, in some cases with inhibition dominating over excitation (Destexhe et al., 1998; Lam and Sherman, 2009; Landisman and Connors, 2007; Von Krosigk et al., 1999; Paz et al., 2011), loss of TRN activity would be expected to cause corticothalamic fibers to cause net excitation of thalamocortical neurons. Thus, in DLB, a shift towards tonic thalamic firing may be seen, thereby releasing the brakes (normally imposed by the TRN) on unselected thalamic activations by corticothalamic inputs. Such a disruption would tip the balance in favor of cortical Bayesian priors, releasing stored cortical representations which may then propagate, potentially via cortico-thalamocortical pathways.

For this corticothalamic-based mechanism to explain visual hallucinations in DLB, there must 1) be a mechanism to hold pre-formed visual representations in the cerebral cortex and 2) be disruption of the comparison between corticothalamic inputs and ascending visual inputs. Common to all conscious experience and therefore likely common to all hallucinatory states is the activation of the cerebral cortex. In the absence of sensory stimuli, there is ongoing cortical activity (Kenet et al., 2003; Mao et al., 2001), and such cortical activity is characterized by being spontaneous and state-dependent (Hoffman et al., 2007; Kenet et al., 2003; Mao et al., 2001; Steriade et al., 1993b). This intrinsic cortical activity has been reported to be highly dependent on intracortical circuits (Ernst et al., 2001; Kenet et al., 2003; Sanchez-Vives and McCormick, 2000; Timofeev et al., 2000), which are felt to be the substrate for internal percepts (Nir and Tononi, 2010; Takeuchi et al., 2011). Imaging studies of spontaneous cortical activity have revealed that spontaneous spatiotemporal patterns of the population activity appear similar to those patterns measured during visual stimulation (MacLean et al., 2005; Miller et al., 2014; Sakata and Harris, 2009). Given that the cortical ensembles could be the main functional unit for perception (Buzsáki, 2010; Uhlhaas et al., 2009), the ability of thalamocortical afferents to activate the same cortical ensembles suggests that aberrant thalamocortical activation could release learned sensory representations in the cortex, leading to the experience of formed hallucinations. Thus, an important question remains: are there mechanisms to gate (or inhibit) learned sensory representations at the level of the thalamus?

4.1. Disrupted inhibitory control of the thalamus and visual hallucinations

The only output of the TRN is to provide hyperpolarizing influence onto thalamocortical neurons, though despite this relative simplicity of organization, the role of the TRN has long been enigmatic. The TRN has been speculated to play roles in multiple brain functions: maintenance of arousal (Llinás and Paré, 1991; Steriade et al., 1993a), selective attention (Crick, 1984; Guillery et al., 1998; Mc Alonan and Brown, 2002; McAlonan et al., 2006; Wimmer et al., 2015), the production of sleep spindles (Destexhe et al., 1994), shifting the firing state of thalamic neurons (Whitmire et al., 2017, 2016; Willis et al., 2015) and, under pathological conditions, the production of seizures (McCormick and Contreras, 2001) and sensory abnormalities in neurodevelopmental disorders such as autism (Krol et al., 2018). The TRN may also contain subnetworks subserving these myriad functions (Halassa et al., 2014; Kimura and Imbe, 2015).

Disrupted α7 cholinergic signaling mechanisms, and consequent disruptions in TRN function, have been speculated to contribute to circuit abnormalities in other hallucinating disorders, such as schizophrenia (Bencherif et al., 2012; Ferrarelli and Tononi, 2011; Pratt and Morris, 2015; Young and Wimmer, 2017). Evidence supporting TRN dysfunction in schizophrenia stems from studies showing 1) that human patients with schizophrenia show marked sensory gating abnormalities as measured by event-related potentials to paired stimuli (Light and Braff, 1999; Patterson et al., 2008), which is believed to be related to TRN function (Ferrarelli and Tononi, 2011; Krause et al., 2003; Tregellas et al., 2007) and 2) that patients with schizophrenia have marked sleep spindle abnormalities and that spindle deficits correlate with severity of positive symptoms (Ferrarelli et al., 2007, 2010; Ferrarelli and Tononi, 2017; Wamsley et al., 2012). As described above, a recent modeling study has found that downregulation of activity of TRN neurons (or of cortical inhibitory interneurons) led to abnormal eye movement output similar to that seen in schizophrenia. The authors further speculated that disinhibition at the level of the TRN could lead to the inability to focus attention; a deficit also seen in schizophrenia (John et al., 2018). In addition, levels of α7 nicotinic receptors, which are richly expressed in the TRN (Breese et al., 1997; Court et al., 1999; Ni et al., 2016; Quik et al., 2000; Spurden et al., 1997) are deficient in the TRN in schizophrenia (Court et al., 1999). Further, α7 polymorphisms are associated with sensory gating abnormalities in schizophrenia (Freedman et al., 2003). All of these findings are suggestive of a central deficit in TRN signaling as a putative mechanism underlying multiple symptoms of schizophrenia.

In the case of visual hallucinations in DLB, functional TRN abnormalities have been less extensively studied than in schizophrenia,

but there are data demonstrating severe sensory gating abnormalities in DLB patients (Perriol et al., 2005) compared to healthy controls and AD subjects. We are not aware of studies of sleep spindles in DLB. However, in PD patients, diminished frequency of sleep spindles is predictive of the later development of PDD (Latreille et al., 2015), a disease closely related to DLB. Further supporting the proposal that TRN-based cholinergic deficits are at the heart of visual hallucinations in DLB are studies demonstrating the efficacy of cholinesterase inhibitors for the treatment of hallucinations in this disorder (McKeith et al., 2000b; Satoh et al., 2010). Thus, these data suggest a model whereby α7 hypofunction at the level of the TRN leads to inadequate inhibition at the level of the thalamus. This disinhibition then may lead to disrupted comparison of top-down sensory predictions with bottom-up sensory input, leading to release of pre-formed patterns of activity across the visual cortex. See Fig. 4 for a representation of the impact of diminished cholinergic modulation of the TRN and resulting enhanced canonical cortico-thalamocortical (Fig. 4A) or cortico-cortical (Fig. 4B) signaling.

5. Conclusions and implications

Despite the wide-ranging pathology seen across cortical and subcortical sites and across multiple biochemical systems in DLB, converging lines of evidence suggest that a strong candidate for a circuit-level substrate for visual hallucinations is aberrant cholinergic, likely α7 nicotinic, signaling at the level of the TRN. The disrupted inhibition of thalamocortical neurons provides a trigger to release pre-formed patterns of cortical activity, leading to spontaneous false percepts. This hypothesis comports well with other recent proposals whereby a "leaky thalamus" leads to abnormal sensory processing as seen in disorders such as autism (Schmitt and Halassa, 2017; Wells et al., 2016). There are still many unanswered questions about this potential mechanism for hallucinations in DLB. First, it is not known if or how impoverished inhibition to a region of the thalamus could lead to spiking activity in thalamocortical cells in the absence of another input. Indeed, other thalamic models of hallucinations are based upon enhanced *hyperpolarization* triggering bursting activity in thalamocortical cells to trigger cortical activity (Llinás et al., 1999). Second, the impact cholinergic input to the TRN is still currently poorly understood. The presence of α7 receptors in the TRN has been established via receptor binding studies, but this presence does not establish if these receptors are actually postsynaptic. If they are presynaptic, given the range of excitatory and inhibitory inputs to any given TRN neuron, virtually any combination of effects of cholinergic deafferentation to the TRN is possible. Third, most synaptic physiology studies on the relevant structures have been conducted on young non-diseased laboratory animals. Clearly, species- and aging-related changes are likely to have an impact. For example, inhibitory interneurons are not present in most thalamic nuclei of the most commonly-studied species employed in basic studies (rodents) but comprise about 20% of the neuronal population in humans (Arcelli et al., 1997). Therefore, one would expect that the impact of TRN manipulations to differ between rodents and humans. In addition, cholinergic receptors in the thalamus are known to diminish with aging, and in very specific ways (Mitsis et al., 2009; Pilar-Cuéllar et al., 2008; Sottile et al., 2017a, b). Therefore, results from studies in young animals (or humans) may be difficult to extrapolate to an older population. Successful resolution of these questions will not only lead to a better understanding, and therefore potentially new treatments, for DLB, but may also shed light more broadly on the pathophysiology of hallucinations.

Future work will bring clarity to the questions raised above. Specifically, more direct measurements of thalamic function in patients with DLB such as analysis of spindle activity (which is tied to TRN activity) and correlations between spindle frequency and the likelihood of having visual hallucinations will prove informative. Direct recordings of thalamic activity in DLB, though done rarely in humans for clinical purposes, could also provide clarity, particularly on the issue of bursting. In addition, basic work to determine if thalamic bursting causes thalamic hyper- or hypometabolism would help in the interpretation of metabolic imaging studies in humans. Further, additional work on deficits in low-level vs. higher-level visual processing deficits will shed light on the levels at which visual processing (thalamic vs. cortical) are disrupted in DLB. Finally, clinical trials with α7 agonists to treat visual hallucinations in DLB may provide both mechanistic and therapeutic insight into this illness. Several α7 agonists have been developed and piloted for the treatment of cognitive deficits in schizophrenia and have favorable tolerability and pharmacokinetic profiles (Haig et al., 2016; Keefe et al., 2015; Walling et al., 2015), but to our knowledge, none have been tested yet in DLB.

References

Adachi, N., Watanabe, T., Matsuda, H., Onuma, T., 2000. Hyperperfusion in the lateral temporal cortex, the striatum and the thalamus during complex visual hallucinations: single photon emission computed tomography findings in patients with Charles Bonnet syndrome. Psychiatry Clin. Neurosci. 54, 157–162.

Aggleton, J., Mishkin, M., 1984. Projections of the amygdala to the thalamus in the cynomolgus monkey. J. Comp. Neurol. 222, 56–68.

Andrew, J., Watkins, E., 1969. A stereotactic atlas of the human thalamus and adjacent structures. A Variability Study. Williams and Wilkins.

Angela, J.Y., Dayan, P., 2002. Acetylcholine in cortical inference. Neural Netw. 15, 719–730.

Anticevic, A., Cole, M.W., Repovs, G., Murray, J.D., Brumbaugh, M.S., Winkler, A.M., Savic, A., Krystal, J.H., Pearlson, G.D., Glahn, D.C., 2013. Characterizing thalamocortical disturbances in schizophrenia and bipolar illness. Cereb. Cortex 24, 3116–3130.

Arcelli, P., Frassoni, C., Regondi, M., Biasi, S., Spreafico, R., 1997. GABAergic neurons in mammalian thalamus: a marker of thalamic complexity? Brain Res. Bull. 42, 27–37.

Archibald, N.K., Clarke, M.P., Mosimann, U.P., Burn, D.J., 2009. The retina in Parkinson's disease. Brain 132, 1128–1145.

Asanuma, C., Thach, W., Jones, E., 1983. Anatomical evidence for segregated focal groupings of efferent cells and their terminal ramifications in the cerebellothalamic pathway of the monkey. Brain Res. Rev. 5, 267–297.

Ballard, C., Holmes, C., McKeith, I., Neill, D., O'Brien, J., Cairns, N., Lantos, P., Perry, E., Ince, P., Perry, R., 1999. Psychiatric morbidity in dementia with Lewy bodies: a prospective clinical and neuropathological comparative study with Alzheimer's disease. Am. J. Psychiatry 156, 1039–1045.

Ballard, C.G., Jacoby, R., Del Ser, T., Khan, M.N., Munoz, D.G., Holmes, C., Nagy, Z., Perry, E.K., Joachim, C., Jaros, E., 2004. Neuropathological substrates of psychiatric symptoms in prospectively studied patients with autopsy-confirmed dementia with Lewy bodies. Am. J. Psychiatry 161, 843–849.

Ballard, C.G., O'Brien, J.T., Swann, A.G., Thompson, P., Neill, D., McKeith, I.G., 2001. The natural history of psychosis and depression in dementia with Lewy bodies and Alzheimer's disease: persistence and new cases over 1 year of follow-up. J. Clin. Psychiatry 62, 46–49.

Banerjee, A.K., Falkai, P.G., Savidge, M., 1989. Visual hallucinations in the elderly associated with the use of levodopa. Postgrad. Med. J. 65, 358–361.

Barber, R., Scheltens, P., Gholkar, A., Ballard, C., McKeith, I., Ince, P., Perry, R., O'brien, J., 1999. White matter lesions on magnetic resonance imaging in dementia with Lewy bodies, Alzheimer's disease, vascular dementia, and normal aging. J. Neurol. Neurosurg. Psychiatr. 67, 66–72.

Barre, A., Berthoux, C., De Bundel, D., Valjent, E., Bockaert, J., Marin, P., Bécamel, C., 2016. Presynaptic serotonin 2A receptors modulate thalamocortical plasticity and associative learning. Proc. Natl. Acad. Sci. 113, E1382–E1391.

Bassetti, C., Marhis, J., Gugger, M., Lovblad, K.O., Hess, C.W., 1996. Hypersomnia following paramedian thalamic stroke: a report of 12 patients. Ann. Neurol. 39, 471–480.

Behrendt, R.-P., 2006. Dysregulation of thalamic sensory 'transmission'in schizophrenia: neurochemical vulnerability to hallucinations. J. Psychopharmacol. 20, 356–372.

Benarroch, E.E., Schmeichel, A., Sandroni, P., Parisi, J.E., Low, P.A., 2007. Rostral raphe involvement in Lewy body dementia and multiple system atrophy. Acta Neuropathol. 114, 213–220.

Bencherif, M., Stachowiak, M.K., Kucinski, A.J., Lippiello, P.M., 2012. Alpha7 nicotinic cholinergic neuromodulation may reconcile multiple neurotransmitter hypotheses of schizophrenia. Med. Hypotheses 78, 594–600.

Benke, T., 2006. Peduncular hallucinosis. J. Neurol. 253, 1561–1571.

Bickford, M.E., 2016. Thalamic circuit diversity: modulation of the driver/modulator framework. Front. Neural Circuits 9, 86.

Boeve, B.F., Silber, M.H., Ferman, T.J., 2004. REM sleep behavior disorder in Parkinson's disease and dementia with Lewy bodies. J. Geriatr. Psychiatry Neurol. 17, 146–157.

Bohr, I., Ray, M., McIntosh, J., Chalon, S., Guilloteau, D., McKeith, I., Perry, R., Clementi, F., Perry, E., Court, J., 2005. Cholinergic nicotinic receptor involvement in movement disorders associated with Lewy body diseases. An autoradiography study using [125I] α-conotoxinMII in the striatum and thalamus. Exp. Neurol. 191, 292–300.

Breckinridge Carden, W., Bickford, M.E., 1999. Location of muscarinic type 2 receptors within the synaptic circuitry of the cat visual thalamus. J. Comp. Neurol. 410, 431–443.

Breese, C.R., Adams, C., Logel, J., Drebing, C., Rollins, Y., Barnhart, M., Sullivan, B.,

DeMasters, B.K., Freedman, R., Leonard, S., 1997. Comparison of the regional expression of nicotinic acetylcholine receptor α7 mRNA and [125I]-α-bungarotoxin binding in human postmortem brain. J. Comp. Neurol. 387, 385–398.
Brooks, D., Halliday, G.M., 2009. Intralaminar nuclei of the thalamus in Lewy body diseases. Brain Res. Bull. 78, 97–104.
Brown, J.W., Taheri, A., Kenyon, R.V., Berger-Wolf, T., Llano, D.A., 2019. A computational model of intrathalamic signaling via open-loop thalamo-reticular-thalamic architectures. bioRxiv 574178.
Bruno, R.M., Sakmann, B., 2006. Cortex is driven by weak but synchronously active thalamocortical synapses. Science 312, 1622–1627.
Buchsbaum, M.S., Christian, B.T., Lehrer, D.S., Narayanan, T.K., Shi, B., Mantil, J., Kemether, E., Oakes, T.R., Mukherjee, J., 2006. D2/D3 dopamine receptor binding with [F-18] fallypride in thalamus and cortex of patients with schizophrenia. Schizophr. Res. 85, 232–244.
Bull, H.C., Venables, P.H., 1974. Speech perception in schizophrenia. Br. J. Psychiatry 125, 350–354.
Burkhardt, C., Filley, C., Kleinschmidt-DeMasters, B., De la Monte, S., Norenberg, M., Schneck, S., 1988. Diffuse Lewy body disease and progressive dementia. Neurology 38 1520-1520.
Buzsáki, G., 2010. Neural syntax: cell assemblies, synapsembles, and readers. Neuron 68, 362–385.
Calderon, J., Perry, R., Erzinclioglu, S., Berrios, G., Dening, T., Hodges, J., 2001. Perception, attention, and working memory are disproportionately impaired in dementia with Lewy bodies compared with Alzheimer's disease. J. Neurol. Neurosurg. Psychiatr. 70, 157–164.
Chapin, E.M., Andrade, R., 2001. A 5-HT7 receptor-mediated depolarization in the anterodorsal thalamus. I. Pharmacological characterization. J. Pharmacol. Exp. Ther. 297, 395–402.
Chen, C., Regehr, W.G., 2003. Presynaptic modulation of the retinogeniculate synapse. J. Neurosci. 23, 3130–3135.
Cheng, A.V., Ferrier, I.N., Morris, C.M., Jabeen, S., Sahgal, A., McKeith, I.G., Edwardson, J.A., Perry, R.H., Perry, E.K., 1991. Cortical serotonin-S2 receptor binding in Lewy body dementia, Alzheimer's and Parkinson's diseases. J. Neurol. Sci. 106, 50–55.
Chin, C.-L., Carr, R.A., Llano, D.A., Barret, O., Xu, H., Batis, J., Koren, A.O., Seibyl, J.P., Marsh, K.C., Tamagnan, G., 2011. Pharmacokinetic modeling and [123I] 5-IA-85380 single photon emission computed tomography imaging in baboons: optimization of dosing regimen for ABT-089. J. Pharmacol. Exp. Ther. 336, 716–723.
Clascá, F., Rubio-Garrido, P., Jabaudon, D., 2012. Unveiling the diversity of thalamocortical neuron subtypes. Eur. J. Neurosci. 35, 1524–1532.
Clinton, S.M., Meador-Woodruff, J.H., 2004. Abnormalities of the NMDA receptor and associated intracellular molecules in the thalamus in schizophrenia and bipolar disorder. Neuropsychopharmacology 29, 1353.
Collerton, D., Burn, D., McKeith, I., O'Brien, J., 2003. Systematic review and meta-analysis show that dementia with Lewy bodies is a visual-perceptual and attentional-executive dementia. Dement. Geriatr. Cogn. Disord. 16, 229–237.
Collerton, D., Perry, E., McKeith, I., 2005. Why people see things that are not there: a novel perception and attention deficit model for recurrent complex visual hallucinations. Behav. Brain Sci. 28, 737–757.
Colloby, S.J., Pakrasi, S., Firbank, M.J., Perry, E.K., Piggott, M.A., Owens, J., Wyper, D.J., McKeith, I.G., Burn, D.J., Williams, E.D., 2006. In vivo SPECT imaging of muscarinic acetylcholine receptors using (R, R) 123I-QNB in dementia with Lewy bodies and Parkinson's disease dementia. Neuroimage 33, 423–429.
Court, J., Ballard, C., Piggott, M., Johnson, M., O'Brien, J., Holmes, C., Cairns, N., Lantos, P., Perry, R., Jaros, E., 2001. Visual hallucinations are associated with lower αbungarotoxin binding in dementia with Lewy bodies. Pharmacol. Biochem. Behav. 70, 571–579.
Court, J., Spurden, D., Lloyd, S., McKeith, I., Ballard, C., Cairns, N., Kerwin, R., Perry, R., Perry, E., 1999. Neuronal nicotinic receptors in dementia with Lewy bodies and schizophrenia. J. Neurochem. 73, 1590–1597.
Crabtree, J.W., Collingridge, G.L., Isaac, J.T., 1998. A new intrathalamic pathway linking modality-related nuclei in the dorsal thalamus. Nat. Neurosci. 1, 389–394.
Crabtree, J.W., Isaac, J.T.R., 2002. New intrathalamic pathways allowing modality-related and cross-modality switching in the dorsal thalamus. J. Neurosci. 22, 8754–8761.
Crandall, S.R., Cruikshank, S.J., Connors, B.W., 2015. A corticothalamic switch: controlling the thalamus with dynamic synapses. Neuron 86, 768–782.
Crick, F., 1984. Function of the thalamic reticular complex: the searchlight hypothesis. Proc. Natl. Acad. Sci. 81, 4586–4590.
Crunelli, V., Di Giovanni, G., 2015. Differential control by 5-HT and 5-HT1A, 2A, 2C receptors of phasic and tonic GABAA inhibition in the visual thalamus. CNS Neurosci. Ther. 21, 967.
Cummings, J.L., Gorman, D.G., Shapira, J., 1993. Physostigmine ameliorates the delusions of Alzheimer's disease. Biol. Psychiatry 33, 536–541.
Dalfó, E., Portero-Otín, M., Ayala, V., Martínez, A., Pamplona, R., Ferrer, I., 2005. Evidence of oxidative stress in the neocortex in incidental Lewy body disease. J. Neuropathol. Exp. Neurol. 64, 816–830.
Davis, K.L., Kahn, R.S., 1991. Dopamine in schizophrenia: a review and reconceptualization. Am. J. Psychiatry 148, 1474.
De Lima, A.D., Singer, W., 1987. The brainstem projection to the lateral geniculate nucleus in the cat: identification of cholinergic and monoaminergic elements. J. Comp. Neurol. 259, 92–121.
De Ridder, D., Vanneste, S., Langguth, B., Llinas, R., 2015. Thalamocortical dysrhythmia: a theoretical update in tinnitus. Front. Neurol. 6, 124.
Delli Pizzi, S., Franciotti, R., Taylor, J.-P., Thomas, A., Tartaro, A., Onofrj, M., Bonanni, L., 2014. Thalamic involvement in fluctuating cognition in dementia with Lewy bodies: magnetic resonance evidences. Cereb. Cortex 25, 3682–3689.
Deschênes, M., Hu, B., 1990. Electrophysiology and pharmacology of the corticothalamic input to lateral thalamic nuclei: an intracellular study in the cat. Eur. J. Neurosci. 2, 140–152.
Desilets-Roy, B., Varga, C., Lavallée, P., Deschênes, M., 2002. Substrate for cross-talk inhibition between thalamic barreloids. J. Neurosci. 22 RC218-RC218.
Destexhe, A., Contreras, D., Sejnowski, T.J., Steriade, M., 1994. A model of spindle rhythmicity in the isolated thalamic reticular nucleus. J. Neurophysiol. 72, 803–818.
Destexhe, A., Contreras, D., Steriade, M., 1998. Mechanisms underlying the synchronizing action of corticothalamic feedback through inhibition of thalamic relay cells. J. Neurophysiol. 79, 999–1016.
Devenney, E., Hornberger, M., Irish, M., Mioshi, E., Burrell, J., Tan, R., Kiernan, M.C., Hodges, J.R., 2014. Frontotemporal dementia associated with the C9ORF72 mutation: a unique clinical profile. JAMA Neurol. 71, 331–339.
Eidelberg, D., Moeller, J., Dhawan, V., Spetsieris, P., Takikawa, S., Ishikawa, T., Chaly, T., Robeson, W., Margouleff, D., Przedborski, S., 1994. The metabolic topography of parkinsonism. J.Cereb. Blood. Flow. Metab 14, 783–801.
Erişir, A., Van Horn, S.C., Sherman, S.M., 1997. Relative numbers of cortical and brainstem inputs to the lateral geniculate nucleus. Proc. Natl. Acad. Sci. 94, 1517–1520.
Ernst, U., Pawelzik, K., Sahar-Pikielny, C., Tsodyks, M., 2001. Intracortical origin of visual maps. Nature neuroscience 4, 431.
Erskine, D., Ding, J., Thomas, A.J., Kaganovich, A., Khundakar, A.A., Hanson, P.S., Taylor, J.P., McKeith, I.G., Attems, J., Cookson, M.R., 2018. Molecular changes in the absence of severe pathology in the pulvinar in dementia with Lewy bodies. Mov. Disord. 33 (6), 982–991.
Erskine, D., Taylor, J.P., Firbank, M.J., Patterson, L., Onofrj, M., O'brien, J.T., McKeith, I.G., Attems, J., Thomas, A.J., Morris, C.M., 2016. Changes to the lateral geniculate nucleus in A lzheimer's disease but not dementia with L ewy bodies. Neuropathol. Appl. Neurobiol. 42, 366–376.
Erskine, D., Thomas, A.J., Attems, J., Taylor, J.P., McKeith, I.G., Morris, C.M., Khundakar, A.A., 2017. Specific patterns of neuronal loss in the pulvinar nucleus in dementia with Lewy bodies. Mov.Disord. 32, 414–422.
Everitt, B.J., Robbins, T.W., 1997. Central cholinergic systems and cognition. Annu. Rev. Clin. Psychol. 48, 649–684.
Fabbrini, G., Barbanti, P., Aurilia, C., Pauletti, C., Lenzi, G., Meco, G., 2002. Donepezil in the treatment of hallucinations and delusions in Parkinson's disease. Neurol. Sci. 23, 41–43.
Ferman, T.J., Smith, G.E., Boeve, B.F., Graff-Radford, N.R., Lucas, J.A., Knopman, D.S., Petersen, R.C., Ivnik, R.J., Wszolek, Z., Uitti, R., 2006. Neuropsychological differentiation of dementia with Lewy bodies from normal aging and Alzheimer's disease. Cli.n Neuropsychol. 20, 623–636.
Fernandez, L.M., Pellegrini, C., Vantomme, G., Béard, E., Lüthi, A., Astori, S., 2017. Cortical afferents onto the nucleus Reticularis thalami promote plasticity of low-threshold excitability through GluN2C-NMDARs. Scientific reports 7, 12271.
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.
Ferrarelli, F., Tononi, G., 2011. The thalamic reticular nucleus and schizophrenia. Schizophrenia bulletin 37, 306–315.
Ferrarelli, F., Tononi, G., 2017. Reduced sleep spindle activity point to a TRN-MD thalamus-PFC circuit dysfunction in schizophrenia. Schizophr. Res. 180, 36–43.
Ferrari-Dileo, G., Waelbroeck, M., Mash, D.C., Flynn, D.D., 1994. Selective labeling and localization of the M4 (m4) muscarinic receptor subtype. Mol. Pharmacol. 46, 1028–1035.
ffytche, D.H., 2008. The hodology of hallucinations. Cortex 44, 1067–1083.
Flynn, D.D., Mash, D.C., 1993. Distinct kinetic binding propeties of N-[3H]-methylscopolamine afford differential labeling and localization of M1, M2, and M3 muscarinic receptor subtypes in primate brain. Synapse 14, 283–296.
Francis, P.T., 2009. Biochemical and pathological correlates of cognitive and behavioural change in DLB/PDD. J. neurolo. 256, 280–285.
Freedman, R., Adler, L.E., Bickford, P., Byerley, W., Coon, H., Cullum, C.M., Griffith, J.M., Harris, J.G., Leonard, S., Miller, C., 1994. Schizophrenia and nicotinic receptors. Harv. Rev. Psychiatry. 2, 179–192.
Freedman, R., Olincy, A., Ross, R.G., Waldo, M.C., Stevens, K.E., Adler, L.E., Leonard, S., 2003. The genetics of sensory gating deficits in schizophrenia. Curr. Psychiatry. Rep. 5, 155–161.
Fremeau, R.T., Duncan, G.E., Fornaretto, M.G., Dearry, A., Gingrich, J.A., Breese, G.R., Caron, M.G., 1991. Localization of D1 dopamine receptor mRNA in brain supports a role in cognitive, affective, and neuroendocrine aspects of dopaminergic neurotransmission. Proc. Natl. Acad. Sci. 88, 3772–3776.
Friston, K., Kiebel, S., 2009. Predictive coding under the free-energy principle. Philos. Trans. R. 364, 1211–1221.
Friston, K.J., 2005. Hallucinations and perceptual inference. Behav. Brain. Sci. 28, 764–766.
Fujita, Y., Takebayashi, M., 2010. Efficacy of low-dose donepezil for visual hallucinations in a patient with dementia with Lewy bodies. Psychiatry. Clin. Neurosci. 64 336-336.
Geyer, M.A., Vollenweider, F.X., 2008. Serotonin research: contributions to understanding psychoses. Trends. Pharmaco.l Sci. 29, 445–453.
Gibb, W., Esiri, M., Lees, A., 1987. Clinical and pathological features of diffuse cortical Lewy body disease (Lewy body dementia). Brain 110, 1131–1153.
Goetz, C.G., Vaughan, C.L., Goldman, J.G., Stebbins, G.T., 2014. I finally see what you see: parkinson's disease visual hallucinations captured with functional neuroimaging. Mov. Disord. 29, 115–117.
Goitia, B., Rivero-Echeto, M.C., Weisstaub, N.V., Gingrich, J.A., Garcia-Rill, E., Bisagno,

V., Urbano, F.J., 2016. Modulation of GABA release from the thalamic reticular nucleus by cocaine and caffeine: role of serotonin receptors. J. neurochem. 136, 526–535.
Goldman, J.G., Goetz, C.G., Brandabur, M., Sanfilippo, M., Stebbins, G.T., 2008. Effects of dopaminergic medications on psychosis and motor function in dementia with Lewy bodies. Mov. Disord.: official journal of the Movement Disorder Society 23, 2248–2250.
Gomperts, S.N., 2016. Lewy body dementias: dementia with Lewy bodies and Parkinson disease dementia. Continuum: Lifelong Learning in Neurology 22, 435.
Govindaiah, G., Cox, C.L., 2005. Excitatory actions of dopamine via D1-like receptors in the rat lateral geniculate nucleus. J.Neurophy. 94, 3708–3718.
Govindaiah, G., Cox, C.L., 2006. Depression of retinogeniculate synaptic transmission by presynaptic D2-like dopamine receptors in rat lateral geniculate nucleus. Eur. J. Neurol. 23, 423–434.
Govindaiah, G., Wang, T., Gillette, M.U., Crandall, S.R., Cox, C.L., 2010a. Regulation of inhibitory synapses by presynaptic D4 dopamine receptors in thalamus. J. Neurophy. 104, 2757–2765.
Govindaiah, G., Wang, Y., Cox, C., 2010b. Dopamine enhances the excitability of somatosensory thalamocortical neurons. Neuroscience 170, 981–991.
Gribkova, E.D., Ibrahim, B.A.E., Llano, D.A., 2018. A novel mutual information estimator to measure spike train correlations in a model thalamocortical network. J.Neurophy. 120, 2730–2755.
Guillery, R.W., Feig, S.L., Lozsádi, D.A., 1998. Paying attention to the thalamic reticular nucleus. Trend. Neurosci. 21, 28–32.
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.
Guimaraes, A., Melcher, J., Talavage, T., Baker, J., Ledden, P., Rosen, B., Kiang, N., Fullerton, B., Weisskoff, R., 1998. Imaging subcortical auditory activity in humans. Hum. Brain Mapp. 6, 33–41.
Haig, G., Wang, D., Othman, A.A., Zhao, J., 2016. The α7 nicotinic agonist ABT-126 in the treatment of cognitive impairment associated with schizophrenia in nonsmokers: results from a randomized controlled phase 2b study. Neuropsychopharmacology 41, 2893.
Halassa, Michael M., Chen, Z., Wimmer, Ralf D., Brunetti, Philip M., Zhao, S., Zikopoulos, B., Wang, F., Brown, Emery N., Wilson, Matthew A., 2014. State-dependent architecture of thalamic reticular subnetworks. Cell 158, 808–821.
Hall, M., Zerbe, L., Leonard, S., Freedman, R., 1993. Characterization of [3H] cytisine binding to human brain membrane preparations. Brain research 600, 127–133.
Hallanger, A.E., Levey, A.I., Lee, H.J., Rye, D.B., Wainer, B.H., 1987. The origins of cholinergic and other subcortical afferents to the thalamus in the rat. J. Comp. Neurol. 262, 105–124.
Hasselmo, M.E., Linster, C., Patil, M., Ma, D., Cekic, M., 1997. Noradrenergic suppression of synaptic transmission may influence cortical signal-to-noise ratio. J. neurophy. 77, 3326–3339.
Hermann, D.M., Siccoli, M., Brugger, P., Wachter, K., Mathis, J., Achermann, P., Bassetti, C.L., 2008. Evolution of neurological, neuropsychological and sleep-wake disturbances after paramedian thalamic stroke. Stroke 39, 62–68.
Higuchi, M., Tashiro, M., Arai, H., Okamura, N., Hara, S., Higuchi, S., Itoh, M., Shin, R.-W., Trojanowski, J.Q., Sasaki, H., 2000. Glucose hypometabolism and neuropathological correlates in brains of dementia with Lewy bodies. Exp. Neurol. 162, 247–256.
Hoffman, K.L., Battaglia, F.P., Harris, K., MacLean, J.N., Marshall, L., Mehta, M.R., 2007. The upshot of up states in the neocortex: from slow oscillations to memory formation. J.Neurosci. 27, 11838–11841.
Hoffman, R.E., Rapaport, J., Mazure, C.M., Quinlan, D.M., 1999. Selective speech perception alterations in schizophrenic patients reporting hallucinated “voices”. Am.J.Psy. 156, 393–399.
Howard, R., Brammer, M., David, A., Woodruff, P., Williams, S., 1998. The anatomy of conscious vision: an fMRI study of visual hallucinations. Nat. neurosci. 1, 738.
Hsieh, J.-C., Belfrage, M., Stone-Elander, S., Hansson, P., Ingvar, M., 1995. Central representation of chronic ongoing neuropathic pain studied by positron emission tomography. PAIN® 63, 225–236.
Hsu, L.J., Sagara, Y., Arroyo, A., Rockenstein, E., Sisk, A., Mallory, M., Wong, J., Takenouchi, T., Hashimoto, M., Masliah, E., 2000. α-Synuclein promotes mitochondrial deficit and oxidative stress. Am.J.path. 157, 401–410.
Huang, C.L., Winer, J.A., 2000. Auditory thalamocortical projections in the cat: laminar and areal patterns of input. J.Comp. Neurol. 427, 302–331.
Imon, Y., Matsuda, H., Ogawa, M., Kogure, D., Sunohara, N., 1999. SPECT image analysis using statistical parametric mapping in patients with Parkinson’s disease. J. Nuc. Med. 40, 1583.
Ishibashi, T., Hori, H., Endo, K., Sato, T., 1964. Hallucinations produced by electrical stimulation of the temporal lobes in schizophrenic patients. Tohoku. J. Exp Med. 82, 124–139.
Jang, J.-W., Youn, Y.C., Seok, J.-W., Ha, S.-Y., Shin, H.-W., Ahan, S.-W., Park, K.-Y., Kwon, O.-S., 2011. Hypermetabolism in the left thalamus and right inferior temporal area on positron emission tomography–statistical parametric mapping (PET–SPM) in a patient with Charles Bonnet syndrome resolving after treatment with valproic acid. J.Cli. Neurosci. 18, 1130–1132.
Jeanmonod, D., Magnin, M., Morel, A., 1996. Low–threshold calcium spike bursts in the human thalamus Common physiopathology for sensory, motor and limbic positive symptoms. Brain 119, 363–375.
Ji, X.-y., Zingg, B., Mesik, L., Xiao, Z., Zhang, L.I., Tao, H.W., 2015. Thalamocortical innervation pattern in mouse auditory and visual cortex: laminar and cell-type specificity. Cerebral Cortex 26, 2612–2625.
John, Y.J., Zikopoulos, B., Bullock, D., Barbas, H., 2018. Visual attention deficits in schizophrenia can arise from inhibitory dysfunction in thalamus or cortex. Comput. Psy. 2, 223–257.
Jones, E.G., 2001. The thalamic matrix and thalamocortical synchrony. Trend.Neurosci. 24, 595–601.
Jones, E.G., Tighilet, B., Tran, B.V., Huntsman, M.M., 1998. Nucleus-and cell-specific expression of NMDA and non-NMDA receptor subunits in monkey thalamus. J. Comp. Neu. 397, 371–393.
Jones, S.R., Fernyhough, C., 2007. Neural correlates of inner speech and auditory verbal hallucinations: a critical review and theoretical integration. Cli. Psy. Rev. 27, 140–154.
Keefe, R.S., Meltzer, H.A., Dgetluck, N., Gawryl, M., Koenig, G., Moebius, H.J., Lombardo, I., Hilt, D.C., 2015. Randomized, double-blind, placebo-controlled study of encenicline, an α7 nicotinic acetylcholine receptor agonist, as a treatment for cognitive impairment in schizophrenia. Neuropsychopharmacology 40, 3053.
Kegeles, L.S., Abi-Dargham, A., Zea-Ponce, Y., Rodenhiser-Hill, J., Mann, J.J., Van Heertum, R.L., Cooper, T.B., Carlsson, A., Laruelle, M., 2000. Modulation of amphetamine-induced striatal dopamine release by ketamine in humans: implications for schizophrenia. Bio. Psy. 48, 627–640.
Kenet, T., Bibitchkov, D., Tsodyks, M., Grinvald, A., Arieli, A., 2003. Spontaneously emerging cortical representations of visual attributes. Nature 425, 954.
Kertesz, A., Ang, L.C., Jesso, S., MacKinley, J., Baker, M., Brown, P., Shoesmith, C., Rademakers, R., Finger, E.C., 2013. Psychosis and Hallucinations in FTD with C9ORF72 mutation: A detailed clinical cohort. Cogn. Behav. Neurol. 26, 146.
Kimura, A., Imbe, H., 2015. Anatomically structured burst spiking of thalamic reticular nucleus cells: implications for distinct modulations of sensory processing in lemniscal and non-lemniscal thalamocortical loop circuitries. Eur. J Neurol. 41, 1276–1293.
Kimura, A., Imbe, H., Donishi, T., Tamai, Y., 2007. Axonal projections of single auditory neurons in the thalamic reticular nucleus: implications for tonotopy-related gating function and cross-modal modulation. Eur. J.Neurosci. 26, 3524–3535.
Klatka, L.A., Louis, E.D., Schiffer, R.B., 1996. Psychiatric features in diffuse Lewy body disease A clinicopathologic study using Alzheimer’s disease and Parkinson’s disease comparison groups. Neurology 47, 1148–1152.
Komura, Y., Nikkuni, A., Hirashima, N., Uetake, T., Miyamoto, A., 2013. Responses of pulvinar neurons reflect a subject’s confidence in visual categorization. Nat. neurosci. 16, 749.
Kotagal, V., Müller, M.L., Kaufer, D.I., Koeppe, R.A., Bohnen, N.I., 2012. Thalamic cholinergic innervation is spared in Alzheimer disease compared to parkinsonian disorders. Neurosci. Let. 514, 169–172.
Krause, M., Hoffmann, W.E., Hajós, M., 2003. Auditory sensory gating in hippocampus and reticular thalamic neurons in anesthetized rats. Biol. Psy. 53, 244–253.
Krol, A., Wimmer, R.D., Halassa, M.M., Feng, G., 2018. Thalamic reticular dysfunction as a circuit endophenotype in neurodevelopmental disorders. Neuron 98, 282–295.
Kuepper, R., Skinbjerg, M., Abi-Dargham, A., 2012. The dopamine dysfunction in schizophrenia revisited: new insights into topography and course. Current Antipsychotics. Springer, pp. 1–26.
Lam, Y.-W., Sherman, S.M., 2005. Mapping by laser photostimulation of connections between the thalamic reticular and ventral posterior lateral nuclei in the rat. J Neuroph. 94, 2472–2483.
Lam, Y.-W., Sherman, S.M., 2009. Functional organization of the somatosensory cortical layer 6 feedback to the thalamus. Cerebral cortex 20, 13–24.
Lam, Y.-W., Sherman, S.M., 2015. Functional topographic organization of the motor reticulothalamic pathway. J.neurophy. 113, 3090–3097.
Landisman, C.E., Connors, B.W., 2007. VPM and PoM nuclei of the rat somatosensory thalamus: intrinsic neuronal properties and corticothalamic feedback. Cerebral cortex 17, 2853–2865.
Latreille, V., Carrier, J., Lafortune, M., Postuma, R.B., Bertrand, J.-A., Panisset, M., Chouinard, S., Gagnon, J.-F., 2015. Sleep spindles in Parkinson’s disease may predict the development of dementia. Neurobiol.agi. 36, 1083–1090.
Lavin, A., Grace, A., 1998. Dopamine modulates the responsivity of mediodorsal thalamic cells recorded in vitro. J. Neurosci. 18, 10566–10578.
Lavoie, B., Parent, A., 1991. Serotoninergic innervation of the thalamus in the primate: an immunohistochemical study. J. Com. Neurol. 312, 1–18.
Lee, K.-H., Williams, L.M., Breakspear, M., Gordon, E., 2003. Synchronous gamma activity: a review and contribution to an integrative neuroscience model of schizophrenia. Brain Res. Rev. 41, 57–78.
Lee, S.C., Cruikshank, S.J., Connors, B.W., 2010. Electrical and chemical synapses between relay neurons in developing thalamus. J.phy. 588, 2403–2415.
Lennox, B.R., Park, S.B.G., Medley, I., Morris, P.G., Jones, P.B., 2000. The functional anatomy of auditory hallucinations in schizophrenia. Psy. Res.: Neuroimaging 100, 13–20.
Lesica, N.A., Weng, C., Jin, J., Yeh, C.-I., Alonso, J.-M., Stanley, G.B., 2006. Dynamic encoding of natural luminance sequences by LGN bursts. PLoS Biol 4, e209.
Light, G.A., Braff, D.L., 1999. Human and animal studies of schizophrenia-related gating deficits. Cur. Psy. Rep. 1, 31–40.
Lisman, J.E., 1997. Bursts as a unit of neural information: making unreliable synapses reliable. Trebd.Neurosci. 20, 38–43.
Lisman, J.E., Pi, H.J., Zhang, Y., Otmakhova, N.A., 2010. A thalamo-hippocampal-ventral tegmental area loop may produce the positive feedback that underlies the psychotic break in schizophrenia. Biol. Psy. 68, 17–24.
Lladó-Pelfort, L., Celada, P., Riga, M., Troyano-Rodríguez, E., Santana, N., Artigas, F., 2017. Effects of Hallucinogens on Neuronal Activity.
Llano, D.A., 2013. Functional imaging of the thalamus in language. Brain Language 126 (1), 62–72.
Llano, D.A., Theyel, B.B., Mallik, A.K., Sherman, S.M., Issa, N.P., 2009. Rapid and sensitive mapping of long-range connections in vitro using flavoprotein autofluorescence imaging combined with laser photostimulation. J. Neurophy. 101, 3325–3340.
Llinás, R.R., Paré, D., 1991. Of dreaming and wakefulness. Neuroscience 44, 521–535.

Llinás, R.R., Ribary, U., Jeanmonod, D., Kronberg, E., Mitra, P.P., 1999. Thalamocortical dysrhythmia: a neurological and neuropsychiatric syndrome characterized by magnetoencephalography. Proc.Nat. Aca. Sci. 96, 15222–15227.
Lobotesis, K., Fenwick, J., Phipps, A., Ryman, A., Swann, A., Ballard, C., McKeith, I., O'brien, J., 2001. Occipital hypoperfusion on SPECT in dementia with Lewy bodies but not AD. Neurology 56, 643–649.
Lord Plummer, K., Manning, K.A., Levey, A.I., Rees, H.D., Uhlrich, D.J., 1999. Muscarinic receptor subtypes in the lateral geniculate nucleus: a light and electron microscopic analysis. J. Com. Neurol. 404, 408–425.
Luis, C.A., Barker, W.W., Gajaraj, K., Harwood, D., Petersen, R., Kashuba, A., Waters, C., Jimison, P., Pearl, G., Petito, C., 1999. Sensitivity and specificity of three clinical criteria for dementia with Lewy bodies in an autopsy-verified sample. Int. J.Geriatric Psy. 14, 526–533.
MacLean, J.N., Watson, B.O., Aaron, G.B., Yuste, R., 2005. Internal dynamics determine the cortical response to thalamic stimulation. Neuron 48, 811–823.
Maclean, L.E., Collins, C.C., Byrne, E.J., 2001. Dementia with Lewy bodies treated with rivastigmine: effects on cognition, neuropsychiatric symptoms, and sleep. Int. Psy. 13, 277–288.
MacLeod, N., James, T., Starr, M., 1984. Muscarinic action of acetylcholine in the rat ventromedial thalamic nucleus. Exp. Brain Res. 55, 553–561.
Malmierca, M.S., Anderson, L.A., Antunes, F.M., 2015. The cortical modulation of stimulus-specific adaptation in the auditory midbrain and thalamus: a potential neuronal correlate for predictive coding. Front. Syst. Neurosci f9, 19.
Manford, M., Andermann, F., 1998. Complex visual hallucinations. Clinical and neurobiological insights. Brain: J. Neuro. 121, 1819–1840.
Mao, B.-Q., Hamzei-Sichani, F., Aronov, D., Froemke, R.C., Yuste, R., 2001. Dynamics of spontaneous activity in neocortical slices. Neuron 32, 883–898.
Marek, G., Wright, R., Gewirtz, J., Schoepp, D., 2001. A major role for thalamocortical afferents in serotonergic hallucinogen receptor function in the rat neocortex. Neuroscience 105, 379–392.
Marek, G.J., 2007. Serotonin and dopamine interactions in rodents and primates: implications for psychosis and antipsychotic drug development. Int. rev.neuro. 78, 165–192.
Martin, L.F., Kem, W.R., Freedman, R., 2004. Alpha-7 nicotinic receptor agonists: potential new candidates for the treatment of schizophrenia. Psychopharmacology 174, 54–64.
Mathew, V., Gruzelier, J.H., Liddle, P.F., 1993. Lateral asymmetries in auditory acuity distinguish hallucinating from nonhallucinating schizophrenic patients. Psy. Res. 46, 127–138.
Mazère, J., Lamare, F., Allard, M., Fernandez, P., Mayo, W., 2017. 123I-Iodobenzovesamicol SPECT imaging of cholinergic systems in dementia with Lewy bodies. J Nucl Med 58, 123–128.
Mc Alonan, K., Brown, V.J., 2002. The Thalamic Reticular Nucleus: More Than a Sensory Nucleus? Neuroscientist 8, 302–305.
McAlonan, K., Cavanaugh, J., Wurtz, R.H., 2006. Attentional modulation of thalamic reticular neurons. J. Neurosci. 26, 4444–4450.
McCormick, D., Wang, Z., 1991. Serotonin and noradrenaline excite GABAergic neurones of the guinea-pig and cat nucleus reticularis thalami. J. phy. 442, 235–255.
McCormick, D.A., Contreras, D., 2001. On the cellular and network bases of epileptic seizures. Ann. Rev. Physiol. 63, 815–846.
McCormick, D.A., Prince, D.A., 1986. Acetylcholine induces burst firing in thalamic reticular neurones by activating a potassium conductance. Nature 319, 402.
McKeith, I., 2007. Dementia with lewy bodies. Handbook of Clinical Neurology. Elsevier, pp. 531–548.
McKeith, I., Ballard, C., Perry, R., Ince, P., O'brien, J., Neill, D., Lowery, K., Jaros, E., Barber, R., Thompson, P., 2000a. Prospective validation of consensus criteria for the diagnosis of dementia with Lewy bodies. Neurology 54, 1050–1058.
McKeith, I., Del Ser, T., Spano, P., Emre, M., Wesnes, K., Anand, R., Cicin-Sain, A., Ferrara, R., Spiegel, R., 2000b. Efficacy of rivastigmine in dementia with Lewy bodies: a randomised, double-blind, placebo-controlled international study. The Lancet 356, 2031–2036.
McKeith, I., Fairbairn, A., Perry, R., Thompson, P., Perry, E., 1992. Neuroleptic sensitivity in patients with senile dementia of Lewy body type. Bmj 305, 673–678.
McKeith, I.G., 2006. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the Consortium on DLB International Workshop. J.Alzheimer's Dis. 9, 417–423.
McKellar, P., 1957. Imagination and thinking. A Psychological Analysis.
Meador-Woodruff, J.H., Mansour, A., Civelli, O., Watson, S.J., 1991. Distribution of D2 Dopamine Receptor mRNA in the Primate Brain.
Meador-Woodruff, J.H., Mansour, A., Grandy, D.K., Damask, S.P., Civelli, O., Watson Jr, S.J., 1992. Distribution of D5 dopamine receptor mRNA in rat brain. Neurosci. Let. 145, 209–212.
Meng, Y.H., Wang, P.P., Song, Y.X., Wang, J.H., 2019. Cholinesterase inhibitors and memantine for Parkinson's disease dementia and Lewy body dementia: a meta-analysis. Exp. Ther. Med. 17, 1611–1624.
Menon, G.J., Rahman, I., Menon, S.J., Dutton, G.N., 2003. Complex visual hallucinations in the visually impaired: the charles bonnet syndrome. Sur. Ophthalmol. 48, 58–72.
Mesulam, M., Mufson, E., Wainer, B., Levey, A., 1983. Central cholinergic pathways in the rat: an overview based on an alternative nomenclature (Ch1–Ch6). Neuroscience 10, 1185–1201.
Miller, J.-e.K., Ayzenshtat, I., Carrillo-Reid, L., Yuste, R., 2014. Visual stimuli recruit intrinsically generated cortical ensembles. Proc. Nat.Aca.Sci 111, E4053–E4061.
Miners, J.S., Renfrew, R., Swirski, M., Love, S., 2014. Accumulation of α-synuclein in dementia with Lewy bodies is associated with decline in the α-synuclein-degrading enzymes kallikrein-6 and calpain-1. Acta neuropa. Com. 2, 164.
Mitsis, E.M., Cosgrove, K.P., Staley, J.K., Bois, F., Frohlich, E.B., Tamagnan, G.D., Estok, K.M., Seibyl, J.P., van Dyck, C.H., 2009. Age-related decline in nicotinic receptor availability with [123I] 5-IA-85380 SPECT. Neu.agi. 30, 1490–1497.
Miyamoto, S., Duncan, G., Marx, C., Lieberman, J., 2005. Treatments for schizophrenia: a critical review of pharmacology and mechanisms of action of antipsychotic drugs. Mol. Psy. 10, 79.
Miyashita, T., Ichinohe, N., Rockland, K.S., 2007. Differential modes of termination of amygdalothalamic and amygdalocortical projections in the monkey. J. Comp. Neurol. 502, 309–324.
Monastero, R., Camarda, C., Pipia, C., Camarda, R., 2007. Visual hallucinations and agitation in Alzheimer's disease due to memantine: report of three cases. J. Neurol. Neurosurg. Psychiatry 78 546-546.
Monckton, J.E., McCormick, D.A., 2002. Neuromodulatory role of serotonin in the ferret thalamus. J Neurophys. 87, 2124–2136.
Montero, V., 1991. A quantitative study of synaptic contacts on interneurons and relay cells of the cat lateral geniculate nucleus. Exp. Brain Res. 86, 257–270.
Moore, R.Y., Halaris, A.E., Jones, B.E., 1978. Serotonin neurons of the midbrain raphe: ascending projections. J. Com. Neuro. 180, 417–438.
Mori, E., Shimomura, T., Fujimori, M., Hirono, N., Imamura, T., Hashimoto, M., Tanimukai, S., Kazui, H., Hanihara, T., 2000. Visuoperceptual impairment in dementia with Lewy bodies. Arch. Neuro. 57, 489–493.
Morrison, J.H., Foote, S.L., 1986. Noradrenergic and serotoninergic innervation of cortical, thalamic, and tectal visual structures in Old and New World monkeys. J.Com.Neuro. 243, 117–138.
Mosimann, U.P., Rowan, E.N., Partington, C.E., Collerton, D., Littlewood, E., O'Brien, J.T., Burn, D.J., McKeith, I.G., 2006. Characteristics of visual hallucinations in Parkinson disease dementia and dementia with Lewy bodies. Am. J. Geri. Psy. 14, 153–160.
Mozayani, A., 2003. Phencyclidine-effects on human performance and behavior. For. Sci. rev. 15, 61–74.
Mukaetova-Ladinska, E.B., McKeith, I.G., 2006. Pathophysiology of synuclein aggregation in Lewy body disease. Mech.agei. dev. 127, 188–202.
Mumford, D., 1991. On the computational architecture of the neocortex. Biolo. Cybe. 65, 135–145.
Munsch, T., Yanagawa, Y., Obata, K., Pape, H.C., 2005. Dopaminergic control of local interneuron activity in the thalamus. Eur. J. Neurosci. 21, 290–294.
Nakajima, M., Halassa, M.M., 2017. Thalamic control of functional cortical connectivity. Curr. Opi.Neuro. 44, 127–131.
Ni, K.-M., Hou, X.-J., Yang, C.-H., Dong, P., Li, Y., Zhang, Y., Jiang, P., Berg, D.K., Duan, S., Li, X.-M., 2016. Selectively driving cholinergic fibers optically in the thalamic reticular nucleus promotes sleep. Elife 5.
Nichols, D.E., 2004. Hallucinogens. Pharm. therapeutics 101, 131–181.
Nir, Y., Tononi, G., 2010. Dreaming and the brain: from phenomenology to neurophysiology. Trend. Cogni. Sci. 14, 88–100.
O'Brien, J.T., Colloby, S.J., Pakrasi, S., Perry, E.K., Pimlott, S.L., Wyper, D.J., McKeith, I.G., Williams, E.D., 2008. Nicotinic α4β2 receptor binding in dementia with Lewy bodies using 123I-5IA-85380 SPECT demonstrates a link between occipital changes and visual hallucinations. Neuroimage 40, 1056–1063.
Ohara, K., Kondo, N., 1998. Changes of monoamines in post-mortem brains from patients with diffuse Lewy body disease. Prog.Neuro-Psy.Biolo. psy. 22, 311–317.
Olney, J.W., Farber, N.B., 1995. Glutamate receptor dysfunction and schizophrenia. Arch.Gen. Psy 52, 998–1007.
Onofrj, M., Thomas, A., Martinotti, G., Anzellotti, F., Di Giannantonio, M., Ciccocioppo, F., Bonanni, L., 2015. The clinical associations of visual hallucinations. The Neurosci. Vis. Hall. 5, 91–117.
Pape, H.-C., McCormick, D., 1995. Electrophysiological and pharmacological properties of interneurons in the cat dorsal lateral geniculate nucleus. Neurosci. 68, 1105–1125.
Pape, H.-C., McCormick, D.A., 1989. Noradrenaline and serotonin selectively modulate thalamic burst firing by enhancing a hyperpolarization-activated cation current. Nature 340, 715.
Patterson, J.V., Hetrick, W.P., Boutros, N.N., Jin, Y., Sandman, C., Stern, H., Potkin, S., Bunney, W.E., 2008. P50 sensory gating ratios in schizophrenics and controls: a review and data analysis. Psy. Res. 158, 226–247.
Paz, J.T., Bryant, A.S., Peng, K., Fenno, L., Yizhar, O., Frankel, W.N., Deisseroth, K., Huguenard, J.R., 2011. A new mode of corticothalamic transmission revealed in the Grai4(-/-) model of absence epilepsy. Nature Neurosci. 14 (9), 1167–1173.
Peláez, J.R., 2000. Towards a neural network based therapy for hallucinatory disorders. Neural net. 13, 1047–1061.
Penfield, W., Perot, P., 1963. The brain's record of auditory and visual experience: a final summary and discussion. Brain 86, 595–696.
Penington, N.J., Fox, A.P., 1994. Effects of LSD on Ca++ currents in central 5-HT-containing neurons: 5-HT1A receptors may play a role in hallucinogenesis. J. Pharmacol. Exp. Ther. 269, 1160–1165.
Perriol, M., Dujardin, K., Derambure, P., Marcq, A., Bourriez, J., Laureau, E., Pasquier, F., Defebvre, L., Destee, A., 2005. Disturbance of sensory filtering in dementia with Lewy bodies: comparison with Parkinson's disease dementia and Alzheimer's disease. J.Neuro., Neurosur. Psy. 76, 106–108.
Perry, E., Marshall, E., Thompson, P., McKeith, I., Collerton, D., Fairbairn, A., Ferrier, I., Irving, D., Perry, R., 1993. Monoaminergic activities in Lewy body dementia: relation to hallucinosis and extrapyramidal features. J. Neural Trans.-Parkinson's Dis.Dementia Sec. 6, 167–177.
Perry, E., Martin-Ruiz, C., Lee, M., Griffiths, M., Johnson, M., Piggott, M., Haroutunian, V., Buxbaum, J.D., Nãsland, J., Davis, K., 2000. Nicotinic receptor subtypes in human brain ageing, Alzheimer and Lewy body diseases. Eur. J.pharm. 393, 215–222.
Perry, E., Walker, M., Grace, J., Perry, R., 1999. Acetylcholine in mind: a neurotransmitter correlate of consciousness? Trend. Neurosci 22, 273–280.
Perry, E.K., Kerwin, J., Perry, R.H., Irving, D., Blessed, G., Fairbairn, A., 1990a. Cerebral

cholinergic activity is related to the incidence of visual hallucinations in senile dementia of Lewy body type. Dementia and Geriatric Cogn. Disord. 1, 2–4.
Perry, E.K., Marshall, E., Kerwin, J., Smith, C.J., Jabeen, S., Cheng, A.V., Perry, R.H., 1990b. Evidence of a monoaminergic-cholinergic imbalance related to visual hallucinations in Lewy body dementia. J.Neuroche. 55, 1454–1456.
Person, A.L., Perkel, D.J., 2005. Unitary IPSPs drive precise thalamic spiking in a circuit required for learning. Neuron 46, 129–140.
Piggott, M., Marshall, E., Thomas, N., Lloyd, S., Court, J., Jaros, E., Burn, D., Johnson, M., Perry, R., McKeith, I., 1999. Striatal dopaminergic markers in dementia with Lewy bodies, Alzheimer's and Parkinson's diseases: rostrocaudal distribution. Brain 122, 1449–1468.
Piggott, M.A., Ballard, C.G., Dickinson, H.O., McKeith, I.G., Perry, R.H., Perry, E.K., 2007. Thalamic D2 receptors in dementia with lewy bodies, Parkinson's disease, and Parkinson's disease dementia. Int. J.Neuro. 10, 231–244.
Pilar-Cuéllar, F., Paniagua, M.Á., Díez-Alarcia, R., Dos_Anjos, S., Montori, S., Pérez, C.C., Fernández-López, A., 2008. Muscarinic receptor changes in the gerbil thalamus during aging. Brain res. 1243, 38–46.
Pimlott, S., Piggott, M., Owens, J., Greally, E., Court, J., Jaros, E., Perry, R., Perry, E., Wyper, D., 2004. Nicotinic acetylcholine receptor distribution in Alzheimer's disease, dementia with Lewy bodies, Parkinson's disease, and vascular dementia: in vitro binding study using 5-[125 I]-A-85380. Neuropsychopharmacology 29, 108.
Pimlott, S.L., Piggott, M., Ballard, C., McKeith, I., Perry, R., Kometa, S., Owens, J., Wyper, D., Perry, E., 2006. Thalamic nicotinic receptors implicated in disturbed consciousness in dementia with Lewy bodies. Neurobio.Dis. 21, 50–56.
Pinault, D., 2008. N-methyl d-aspartate receptor antagonists ketamine and MK-801 induce wake-related aberrant γ oscillations in the rat neocortex. Biolo. Psy. 63, 730–735.
Pinault, D., Deschênes, M., 1998. Anatomical evidence for a mechanism of lateral inhibition in the rat thalamus. Eur.J.Neurosci. 10, 3462–3469.
Pletnikova, O., West, N., Lee, M.K., Rudow, G.L., Skolasky, R.L., Dawson, T.M., Marsh, L., Troncoso, J.C., 2005. Aβ deposition is associated with enhanced cortical α-synuclein lesions in Lewy body diseases. Neuro.Agi. 26, 1183–1192.
Polymeropoulos, M.H., Lavedan, C., Leroy, E., Ide, S.E., Dehejia, A., Dutra, A., Pike, B., Root, H., Rubenstein, J., Boyer, R., 1997. Mutation in the α-synuclein gene identified in families with Parkinson's disease. Science 276, 2045–2047.
Pompeiano, M., Palacios, J.M., Mengod, G., 1994. Distribution of the serotonin 5-HT2 receptor family mRNAs: comparison between 5-HT2A and 5-HT2C receptors. Mol.Brain Res. 23, 163–178.
Popescu, A., Lippa, C.F., Lee, V.M.-Y., Trojanowski, J.Q., 2004. Lewy bodies in the amygdala: increase of α-synuclein aggregates in neurodegenerative diseases with tau-based inclusions. Arch. Neurol. 61, 1915–1919.
Posey, T.B., Losch, M.E., 1983. Auditory hallucinations of hearing voices in 375 normal subjects. Imag., cogn.pers. 3, 99–113.
Powers III, A.R., Gancsos, M.G., Finn, E.S., Morgan, P.T., Corlett, P.R., 2015. Ketamine-induced hallucinations. Psychopathology 48, 376–385.
Pratt, J.A., Morris, B.J., 2015. The thalamic reticular nucleus: a functional hub for thalamocortical network dysfunction in schizophrenia and a target for drug discovery. J. Psy. 29, 127–137.
Preller, K.H., Razi, A., Zeidman, P., Stämpfli, P., Friston, K.J., Vollenweider, F.X., 2019. Effective connectivity changes in LSD-induced altered states of consciousness in humans. Proc. Nat.Aca.Sci. 116, 2743–2748.
Purpura, K.P., Schiff, N.D., 1997. The thalamic intralaminar nuclei: a role in visual awareness. Neuro.-Baltimore- 3, 8–15.
Quik, M., Polonskaya, Y., Gillespie, A., Jakowec, M., Lloyd, G.K., Langston, J.W., 2000. Localization of nicotinic receptor subunit mRNAs in monkey brain by in situ hybridization. J.Com.Neuro. 425, 58–69.
Rabinowicz, E.F., Silipo, G., Goldman, R., Javitt, D.C., 2000. Auditory sensory dysfunction in schizophrenia: imprecision or distractibility? Arch.gen. Psy. 57, 1149–1155.
Rademacher, J., Bürgel, U., Zilles, K., 2002. Stereotaxic localization, intersubject variability, and interhemispheric differences of the human auditory thalamocortical system. NeuroImage 17, 142–160.
Ray, M., Bohr, I., McIntosh, J., Ballard, C., McKeith, I., Chalon, S., Guilloteau, D., Perry, R., Perry, E., Court, J., Piggott, M., 2004. Involvement of alpha6/alpha3 neuronal nicotinic acetylcholine receptors in neuropsychiatric features of Dementia with Lewy bodies:[(125) I]-alpha-conotoxin MII binding in the thalamus and striatum. Neuroscie. Lett. 372, 220–225.
Reichova, I., Sherman, S.M., 2004. Somatosensory corticothalamic projections: distinguishing drivers from modulators. J Neurophysiol 92, 2185–2197.
Reid, R.T., Sabbagh, M.N., Corey–Bloom, J., Tiraboschi, P., Thal, L.J., 2000. Nicotinic receptor losses in dementia with Lewy bodies: comparisons with Alzheimer's disease. Neuro.Agi. 21, 741–746.
Reinagel, P., Godwin, D., Sherman, S.M., Koch, C., 1999. Encoding of visual information by LGN bursts. J Neurophysiol 81, 2558–2569.
Rezak, M., Benevento, L., 1979. A comparison of the organization of the projections of the dorsal lateral geniculate nucleus, the inferior pulvinar and adjacent lateral pulvinar to primary visual cortex (area 17) in the macaque monkey. Brain Res. 167, 19–40.
Ridha, B., Josephs, K.A., Rossor, M., 2005. Delusions and hallucinations in dementia with Lewy bodies: worsening with memantine. Neurology 65, 481–482.
Rieck, R.W., Ansari, M., Whetsell Jr, W.O., Deutch, A.Y., Kessler, R.M., 2004. Distribution of dopamine D 2-like receptors in the human thalamus: autoradiographic and PET studies. Neuropsychopharmacology 29, 362.
Rieck, R.W., Carey, R.G., 1985. Organization of the rostral thalamus in the rat: evidence for connections to layer I of visual cortex. J. Comp. Neurol. 234, 137–154.
Rikhye, R.V., Wimmer, R.D., Halassa, M.M., 2018. Toward an integrative theory of thalamic function. Ann. Rev. Neurosci.
Robinson, A., Davidson, Y., Snowden, J.S., Mann, D.M., 2014. C9ORF72 in dementia with Lewy bodies. J. Neurol. Neurosurg. Psychiatry 85, 1435–1436.
RodrÍguez, J.J., Noristani, H.N., Hoover, W.B., Linley, S.B., Vertes, R.P., 2011. Serotonergic projections and serotonin receptor expression in the reticular nucleus of the thalamus in the rat. Synapse 65, 919–928.
Roselli, F., Pisciotta, N.M., Perneczky, R., Pennelli, M., Aniello, M.S., De Caro, M.F., Ferrannini, E., Tartaglione, B., Defazio, G., Rubini, G., 2009. Severity of neuropsychiatric symptoms and dopamine transporter levels in dementia with Lewy bodies: a 123I-FP-CIT SPECT study. Mov. Disord. 24, 2097–2103.
Rubio-Garrido, P., Pérez-de-Manzo, F., Clascá, F., 2007. Calcium-binding proteins as markers of layer-I projecting vs. Deep layer-projecting thalamocortical neurons: a double-labeling analysis in the rat. Neuroscience 149, 242–250.
Saalmann, Y.B., Pinsk, M.A., Wang, L., Li, X., Kastner, S., 2012. The pulvinar regulates information transmission between cortical areas based on attention demands. Science 337, 753–756.
Sabbagh, M., Reid, R., Hansen, L., Alford, M., Thal, L., 2001. Correlation of nicotinic receptor binding with clinical and neuropathological changes in Alzheimer's disease and dementia with Lewy bodies. J.Neur.Trans. 108, 1149–1157.
Safer, D.J., Allen, R.P., 1971. The central effects of scopolamine in man. Bio. Psy. 3 (4), 347–355.
Sakai, S.T., Inase, M., Tanji, J., 1996. Comparison of cerebellothalamic and pallidothalamic projections in the monkey (Macaca fuscata): a double anterograde labeling study. J. Comp. Neurol. 368, 215–228.
Sakata, S., Harris, K.D., 2009. Laminar structure of spontaneous and sensory-evoked population activity in auditory cortex. Neuron 64, 404–418.
Salt, T., 1986. Mediation of thalamic sensory input by both NMDA receptors and non-NMDA receptors. Nature 322, 263.
Sametsky, E.A., Turner, J.G., Larsen, D., Ling, L., Caspary, D.M., 2015. Enhanced GABAA-mediated tonic inhibition in auditory thalamus of rats with behavioral evidence of tinnitus. J.Neurosci. 35, 9369–9380.
Sánchez-González, M.Á., García-Cabezas, M.Á., Rico, B., Cavada, C., 2005. The primate thalamus is a key target for brain dopamine. J. Neurosci. 25, 6076–6083.
Sanchez-Vives, M.V., McCormick, D.A., 2000. Cellular and network mechanisms of rhythmic recurrent activity in neocortex. Nat. Neurosci. 3, 1027.
Sato, T., Hanyu, H., Hirao, K., Shimizu, S., Kanetaka, H., Iwamoto, T., 2007. Deep gray matter hyperperfusion with occipital hypoperfusion in dementia with Lewy bodies. Eur. J.Neuro. 14, 1299–1301.
Satoh, M., Ishikawa, H., Meguro, K., Kasuya, M., Ishii, H., Yamaguchi, S., 2010. Improved visual hallucination by donepezil and occipital glucose metabolism in dementia with Lewy bodies: the Osaki-Tajiri project. Eur. Neuro. 64, 337–344.
Schadlu, A.P., Schadlu, R., Shepherd, J.B., 2009. Charles Bonnet syndrome: a review. Curr. Opinion. Ophthalm. 20, 219–222.
Schiff, N.D., 2008. Central thalamic contributions to arousal regulation and neurological disorders of consciousness. Ann. New York Aca. Sci. 1129, 105–118.
Schiff, N.D., Plum, F., 2000. The role of arousal and "gating" systems in the neurology of impaired consciousness. J. Cli. Neuro. 17, 438–452.
Schlösser, R., Gesierich, T., Kaufmann, B., Vucurevic, G., Stoeter, P., 2003. Altered effective connectivity in drug free schizophrenic patients. Neuroreport 14, 2233–2237.
Schmitt, L.I., Halassa, M.M., 2017. Interrogating the mouse thalamus to correct human neurodevelopmental disorders. Mol. Psy. 22, 183.
Schmitt, L.I., Wimmer, R.D., Nakajima, M., Happ, M., Mofakham, S., Halassa, M.M., 2017. Thalamic amplification of cortical connectivity sustains attentional control. Nature 545, 219.
Seeburg, D.P., Liu, X., Chen, C., 2004. Frequency-dependent modulation of retinogeniculate transmission by serotonin. J. Neurosci. 24, 10950–10962.
Sharp, F.R., Tomitaka, M., Bernaudin, M., Tomitaka, S., 2001. Psychosis: pathological activation of limbic thalamocortical circuits by psychomimetics and schizophrenia? Trend.Neurosci. 24, 330–334.
Shergill, S., Cameron, L., Brammer, M., Williams, S., Murray, R., McGuire, P., 2001. Modality specific neural correlates of auditory and somatic hallucinations. J. Neuro. Neurosur. Psy. 71, 688–690.
Shergill, S.S., Brammer, M.J., Williams, S.C., Murray, R.M., McGuire, P.K., 2000. Mapping auditory hallucinations in schizophrenia using functional magnetic resonance imaging. Arch.Gen. Psy. 57, 1033–1038.
Sherman, S.M., 2001. Tonic and burst firing: dual modes of thalamocortical relay. Trend. Neurosci. 24, 122–126.
Shimizu, S., Hirose, D., Namioka, N., Kanetaka, H., Hirao, K., Hatanaka, H., Takenoshita, N., Kaneko, Y., Ogawa, Y., Umahara, T., 2017. Correlation between clinical symptoms and striatal DAT uptake in patients with DLB. Ann.Nuclear Med 31, 390–398.
Shirazi-Southall, S., Rodriguez, D.E., Nomikos, G.G., 2002. Effects of typical and atypical antipsychotics and receptor selective compounds on acetylcholine efflux in the hippocampus of the rat. Neuropsychopharmacology 26, 583–594.
Shukla, R., Watakabe, A., Yamamori, T., 2014. mRNA expression profile of serotonin receptor subtypes and distribution of serotonergic terminations in marmoset brain. Front. Neural Circuits 8, 52.
Sidibé, M., Bevan, M.D., Bolam, J.P., Smith, Y., 1997. Efferent connections of the internal globus pallidus in the squirrel monkey: I. Topography and synaptic organization of the pallidothalamic projection. J. Comp. Neurol. 382, 323–347.
Siepel, F.J., Dalen, I., Grüner, R., Booij, J., Brønnick, K.S., Buter, T.C., Aarsland, D., 2016. Loss of dopamine transporter binding and clinical symptoms in dementia with Lewy bodies. Mov. Disord. 31, 118–125.
Silbersweig, D.A., Stern, E., Frith, C., Cahill, C., Holmes, A., Grootoonk, S., Seaward, J., McKenna, P., Chua, S.E., Schnorr, L., 1995. A functional neuroanatomy of hallucinations in schizophrenia. Nature 378, 176.
Slater, B.J., Sons, S.K., Yudintsev, G., Lee, C.M., Llano, D.A., 2019. Thalamocortical and intracortical inputs differentiate layer-specific mouse auditory corticocollicular neurons. J. Neurosci. 39, 256–270.

Snowden, J.S., Rollinson, S., Lafon, C., Harris, J., Thompson, J., Richardson, A.M., Jones, M., Gerhard, A., Neary, D., Mann, D.M., 2012. Psychosis, C9ORF72 and dementia with Lewy bodies. J. Neurol. Neurosurg. Psychiatry 83, 1031–1032.
Sofroniew, M., Priestley, J., Consolazione, A., Eckenstein, F., Cuello, A., 1985. Cholinergic projections from the midbrain and pons to the thalamus in the rat, identified by combined retrograde tracing and choline acetyltransferase immunohistochemistry. Brain research 329, 213–223.
Solms, M., 2000. Dreaming and REM sleep are controlled by different brain mechanisms. Behav. Sci. 23, 843–850.
Sottile, S.Y., Hackett, T.A., Cai, R., Ling, L., Llano, D.A., Caspary, D.M., 2017a. Presynaptic neuronal nicotinic receptors differentially shape select inputs to auditory thalamus and are negatively impacted by aging. J. Neurosci. 37, 11377–11389.
Sottile, S.Y., Ling, L., Cox, B.C., Caspary, D.M., 2017b. Impact of ageing on postsynaptic neuronal nicotinic neurotransmission in auditory thalamus. J. Phys. 595, 5375–5385.
Spillantini, M.G., Schmidt, M.L., Lee, V.M.-Y., Trojanowski, J.Q., Jakes, R., Goedert, M., 1997. α-Synuclein in Lewy bodies. Nature 388, 839.
Spurden, D., Court, J., Lloyd, S., Oakley, A., Perry, R., Pearson, C., Pullen, R., Perry, E., 1997. Nicotinic receptor distribution in the human thalamus: autoradiographical localization of [3H] nicotine and [125I] α-bungarotoxin binding. J.Chem.Neuroanat. 13, 105–113.
Steriade, M., Llinás, R.R., 1988. The functional states of the thalamus and the associated neuronal interplay. Physiolo. Rev. 68, 649–742.
Steriade, M., McCormick, D.A., Sejnowski, T.J., 1993a. Thalamocortical oscillations in the sleeping and aroused brain. Science 262, 679–685.
Steriade, M., Nunez, A., Amzica, F., 1993b. A novel slow (< 1 Hz) oscillation of neocortical neurons in vivo: depolarizing and hyperpolarizing components. J.Neurosci. 13, 3252–3265.
Sun, Y.-G., Pita-Almenar, J.D., Wu, C.-S., Renger, J.J., Uebele, V.N., Lu, H.-C., Beierlein, M., 2013. Biphasic cholinergic synaptic transmission controls action potential activity in thalamic reticular nucleus neurons. J.Neurosci. 33, 2048–2059.
Swadlow, H., Gusev, A., 2001. The impact of' bursting' thalamic impulses at a neocortical synapse. Nat Neurosci 4, 402–408.
Swerdlow, R.H., 2009. Mitochondrial medicine and the neurodegenerative mitochondriopathies. Pharmaceuticals 2, 150–167.
Swirski, M., Miners, J.S., de Silva, R., Lashley, T., Ling, H., Holton, J., Revesz, T., Love, S., 2014. Evaluating the relationship between amyloid-β and α-synuclein phosphorylated at Ser129 in dementia with Lewy bodies and Parkinson's disease. Alzheimer's Res. therapy 6, 77.
Takeuchi, D., Hirabayashi, T., Tamura, K., Miyashita, Y., 2011. Reversal of interlaminar signal between sensory and memory processing in monkey temporal cortex. Science 331, 1443–1447.
Tateno, M., Utsumi, K., Kobayashi, S., Takahashi, A., Saitoh, M., Morii, H., Fujii, K., Teraoka, M., 2008. Usefulness of a blood flow analyzing program 3DSRT to detect occipital hypoperfusion in dementia with Lewy bodies. Prog. Neuro-Psychopharmacology and Biol. Psy. 32, 1206–1209.
Theyel, B.B., Llano, D.A., Sherman, S.M., 2010. The corticothalamocortical circuit drives higher-order cortex in the mouse. Nat Neurosci 13, 84–88.
Thirthalli, J., Benegal, V., 2006. Psychosis among substance users. Curr. Opi. Psy. 19, 239–245.
Timofeev, I., Grenier, F., Bazhenov, M., Sejnowski, T., Steriade, M., 2000. Origin of slow cortical oscillations in deafferented cortical slabs. Cerebral cortex 10, 1185–1199.
Tiraboschi, P., Hansen, L., Alford, M., Sabbagh, M., Schoos, B., Masliah, E., Thal, L., Corey-Bloom, J., 2000. Cholinergic dysfunction in diseases with Lewy bodies. Neurology 54 407-407.
Tregellas, J.R., Davalos, D.B., Rojas, D.C., Waldo, M.C., Gibson, L., Wylie, K., Du, Y.P., Freedman, R., 2007. Increased hemodynamic response in the hippocampus, thalamus and prefrontal cortex during abnormal sensory gating in schizophrenia. Schizophrenia research 92, 262–272.
Turner, R., Chervin, R., Frey, K., Minoshima, S., Kuhl, D., 1997. Probable diffuse Lewy body disease presenting as REM sleep behavior disorder. Neurology 49, 523–527.
Uhlhaas, P., Pipa, G., Lima, B., Melloni, L., Neuenschwander, S., Nikolić, D., Singer, W., 2009. Neural synchrony in cortical networks: history, concept and current status. Front. Integt. Neurosci. 3, 17.
Uylings, H., Amunts, K., Mohlberg, H., Pool, C., Zilles, K., Smeets, W., 2008. 3D probabilistic map of cytoarchitectonically defined human thalamic nuclei in standard MRI. Frontiers in Neuroinformatics. Conference Abstract: Neuroinformatics 2008.
Varela, C., 2014. Thalamic neuromodulation and its implications for executive networks. Front.Neural Cir. 8, 69.
Varela, C., Sherman, S.M., 2007. Differences in response to muscarinic activation between first and higher order thalamic relays. J. Neurophysi. 98, 3538–3547.
Varela, C., Sherman, S.M., 2008. Differences in response to serotonergic activation between first and higher order thalamic nuclei. Cerebral Cortex 19, 1776–1786.
Vatsavayai, S.C., Yoon, S.J., Gardner, R.C., Gendron, T.F., Vargas, J.N.S., Trujillo, A., Pribadi, M., Phillips, J.J., Gaus, S.E., Hixson, J.D., Garcia, P.A., Rabinovici, G.D., Coppola, G., Geschwind, D.H., Petrucelli, L., Miller, B.L., Seeley, W.W., 2016. Timing and significance of pathological features in C9orf72 expansion-associated frontotemporal dementia. Brain 139, 3202–3216.
Vertes, R.P., 1991. A PHA-L analysis of ascending projections of the dorsal raphe nucleus in the rat. J. Com. Neur. 313, 643–668.
Von Krosigk, M., Monckton, J., Reiner, P., McCormick, D., 1999. Dynamic properties of corticothalamic excitatory postsynaptic potentials and thalamic reticular inhibitory postsynaptic potentials in thalamocortical neurons of the guinea-pig dorsal lateral geniculate nucleus. Neuroscience 91, 7–20.
Vukadinovic, Z., 2014. NMDA receptor hypofunction and the thalamus in schizophrenia. Physio. Behav. 131, 156–159.
Walling, D., Marder, S.R., Kane, J., Fleischhacker, W.W., Keefe, R.S., Hosford, D.A., Dvergsten, C., Segreti, A.C., Beaver, J.S., Toler, S.M., 2015. Phase 2 trial of an alpha-7 nicotinic receptor agonist (TC-5619) in negative and cognitive symptoms of schizophrenia. Schizophrenia bulletin 42, 335–343.
Walton, K., Dubois, M., Llinas, R., 2010. Abnormal thalamocortical activity in patients with Complex Regional Pain Syndrome (CRPS) type I. Pain 150, 41–51.
Wamsley, E.J., Tucker, M.A., Shinn, A.K., Ono, K.E., McKinley, S.K., Ely, A.V., Goff, D.C., Stickgold, R., Manoach, D.S., 2012. Reduced sleep spindles and spindle coherence in schizophrenia: mechanisms of impaired memory consolidation? Biol. Psy. 71, 154–161.
Wang, H., Sun, X., 2005. Desensitized nicotinic receptors in brain. Brain Res. Rev. 48, 420–437.
Warren, N.M., Piggott, M.A., Lees, A.J., Burn, D.J., 2007. Muscarinic receptors in the thalamus in progressive supranuclear palsy and other neurodegenerative disorders. J.Neuropatho.Exp. Neuro. 66, 399–404.
Warren, R.A., Agmon, A., Jones, E.G., 1994. Oscillatory synaptic interactions between ventroposterior and reticular neurons in mouse thalamus in vitro. J. Neuro. 72, 1993–2003.
Wells, M.F., Wimmer, R.D., Schmitt, L.I., Feng, G., Halassa, M.M., 2016. Thalamic reticular impairment underlies attention deficit in Ptchd1 Y/− mice. Nature 532, 58.
Whitmire, C.J., Millard, D.C., Stanley, G.B., 2017. Thalamic state control of cortical paired-pulse dynamics. J.Neuro. 117, 163–177.
Whitmire, C.J., Waiblinger, C., Schwarz, C., Stanley, G.B., 2016. Information coding through adaptive gating of synchronized thalamic bursting. Cell reports 14, 795–807.
Williams, R.W., Rakic, P., 1988. Elimination of neurons from the rhesus monkey's lateral geniculate nucleus during development. J.Comp. Neuro. 272, 424–436.
Willis, A.M., Slater, B.J., Gribkova, E.D., Llano, D.A., 2015. Open-loop organization of thalamic reticular nucleus and dorsal thalamus: a computational model. J. Neuro. 114, 2353–2367.
Wimmer, R.D., Schmitt, L.I., Davidson, T.J., Nakajima, M., Deisseroth, K., Halassa, M.M., 2015. Thalamic control of sensory selection in divided attention. Nature 526, 705–709.
Woodruff, P., Brammer, M., Mellers, J., Wright, I., Bullmore, E., Williams, S., Colover, J., Lawrie, S., Abukmeil, S., 1994. Auditory hallucinations and perception of external speech. The Lancet 346, 1035–1036.
Yagüe, J.G., Cavaccini, A., Errington, A.C., Crunelli, V., Di Giovanni, G., 2013. Dopaminergic modulation of tonic but not phasic GABAA-receptor-mediated current in the ventrobasal thalamus of Wistar and GAERS rats. Exp. Neuro. 247, 1–7.
Yang, Q., Chen, C.-C., Ramos, R.L., Katz, E., Keller, A., Brumberg, J.C., 2014a. Intrinsic properties of and thalamocortical inputs onto identified corticothalamic-VPM neurons. Somatosensory & motor Res. 31, 78–93.
Yang, Y.C., Hu, C.C., Huang, C.S., Chou, P.Y., 2014b. Thalamic synaptic transmission of sensory information modulated by synergistic interaction of adenosine and serotonin. J.Neurochem. 128, 852–863.
Yeomans, J.S., 2012. Muscarinic receptors in brain stem and mesopontine cholinergic arousal functions. Muscarinic Receptors. Springer, pp. 243–259.
Yokoyama, C., Mawatari, A., Kawasaki, A., Takeda, C., Onoe, K., Newman-Tancredi, A., Zimmer, L., Onoe, H., 2016. Marmoset serotonin 5-HT1A receptor mapping with a biased agonist PET probe 18F-F13714: comparison with an antagonist tracer 18F-MPPF in awake and anesthetized states. Int. J. Neuropsychopharmacol. 19.
Yoshida, M., Sasa, M., Takaori, S., 1984. Serotonin-mediated inhibition from dorsal raphe nucleus of neurons in dorsal lateral geniculate and thalamic reticular nuclei. Brain Res. 290, 95–105.
Young, A., Wimmer, R.D., 2017. Implications for the thalamic reticular nucleus in impaired attention and sleep in schizophrenia. Schizophrenia Res. 180, 44–47.
Zarranz, J.J., Alegre, J., Gómez-Esteban, J.C., Lezcano, E., Ros, R., Ampuero, I., Vidal, L., Hoenicka, J., Rodriguez, O., Atarés, B., 2004. The new mutation, E46K, of α-synuclein causes parkinson and Lewy body dementia. Ann.Neuro. 55, 164–173.
Zhang, Y., Yan, J., 2008. Corticothalamic feedback for sound-specific plasticity of auditory thalamic neurons elicited by tones paired with basal forebrain stimulation. Cerebral Cortex 18, 1521–1528.
Zhao, C., Kao, J.P., Kanold, P.O., 2009. Functional excitatory microcircuits in neonatal cortex connect thalamus and layer 4. J.Neurosci. 29, 15479–15488.
Zhao, Y., Kerscher, N., Eysel, U., Funke, K., 2001. Changes of contrast gain in cat dorsal lateral geniculate nucleus by dopamine receptor agonists. NeuroReport 12, 2939–2945.
Zhu, J., Uhlrich, D., 1998. Cellular mechanisms underlying two muscarinic receptor-mediated depolarizing responses in relay cells of the rat lateral geniculate nucleus. Neuroscience 87, 767–781.
Ziabreva, I., Ballard, C.G., Aarsland, D., Larsen, J.-P., McKeith, I.G., Perry, R.H., Perry, E.K., 2006. Lewy body disease: thalamic cholinergic activity related to dementia and parkinsonism. Neuro.Agi. 27, 433–438.
Ziebell, M., Andersen, B.B., Pinborg, L.H., Knudsen, G.M., Stokholm, J., Thomsen, G., Karlsborg, M., Høgh, P., Mørk, M.L., Hasselbalch, S.G., 2013. Striatal dopamine transporter binding does not correlate with clinical severity in dementia with Lewy bodies. J.Nuc.Med. 54, 1072–1076.
Zikopoulos, B., Barbas, H., 2006. Prefrontal projections to the thalamic reticular nucleus form a unique circuit for attentional mechanisms. J. Neurosci. 26, 7348–7361.