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The thalamus as a relay station and gatekeeper: relevance to brain disorders

Abstract: Here, we provide a review of behavioural, cognitive, and neural studies of the thalamus, including its role in attention, consciousness, sleep, and motor processes. We further discuss neuropsychological and brain disorders associated with thalamus function, including Parkinson's disease, Alzheimer's disease, Korsakoff's syndrome, and sleep disorders. Importantly, we highlight how thalamus-related processes and disorders can be explained by the role of the thalamus as a relay station.

Keywords: Alzheimer's disease; consciousness; hemiballismus; Korsakoff's syndrome; Parkinson's disease; relay station; sleep; thalamus; Tourette syndrome.

Introduction

The goal of this review is to provide a unified account of the role of the thalamus across a range of behavioural processes and how these processes impact brain disorders associated with thalamus dysfunctions. We start by providing a brief summary of the thalamus. We then discuss cognitive processes that are associated with the thalamus, such as attention and consciousness, as well as other perceptual, cognitive, and motor processes. How these processes relate to the notion of the thalamus as an integral component of cortical function will also be addressed. Finally, we discuss brain disorders that are associated

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with thalamus dysfunction. Although there are some review papers regarding the thalamus and its 'gatekeeper' or 'relay station' role, it is argued that these ideas are not separate, but rather that both these ideas highlight the crucial role that the thalamus plays in information processing for cognitive and behavioural functions.

Anatomy and physiology

The thalamus has many nuclei that play key roles in perceptual, motor, emotional, and cognitive processes (Bushnell and Duncan, 1989; Ab Aziz and Ahmad, 2006; Saalmann and Kastner, 2011). Figure 1 illustrates the major subsections of the thalamus structure. The thalamus is located between the cortex and the midbrain and has direct connectivity to many subcortical structures, such as the basal ganglia, amygdala, cerebellum, and cerebral cortex, which is responsible for higher-level functions. Hence, it is often considered to be a relay station that acts as a gatekeeper for information processing throughout the brain.

Specific areas of the thalamus receive afferent input and send efferent projections to distinct areas of the cortex, forming the purported cortico-thalamo-cortical pathways (Theyel et al., 2010; Purushothaman et al., 2012; Saalmann et al., 2012). A large component of the function of individual thalamic relays is defined by its particular type of driver input (Sherman and Guillery, 2006). Importantly, the thalamus is often divided into two subregions: first- and higher-order relays. See Figure 2 for an illustration.

First-order relays are some of the more established regions including sensory-related nuclei, such as the lateral geniculate (in the visual thalamus), the ventral division of the medial geniculate (in the auditory thalamus), and the ventral posterior nuclei (in the somatosensory thalamus). The lateral geniculate body receives afferents from the retina and sends efferents to the primary visual area. In contrast, the medial geniculate body receives afferents from auditory stimuli and sends efferents to the auditory section of the temporal lobe. Ventral posterior nuclei receive afferent input from the face and olfactory system via the medial nuclei (VPM) or from the trunk via the lateral nuclei (VPL). Consequently, the VPM send efferents to the parietal cortex, whereas the VPL send

Figure 1: Structure of the thalamus.

Figure 2: First- and higher-order thalamic relays.

efferents to the parietal lobe (Sherman and Guillery, 2006; Saalmann, 2014). Therefore, first-order relays are often the 'first stop' as they transmit information from sensory systems to the cerebral cortex.

In contrast, higher-order thalamic nuclei, including the pulvinar, mediodorsal, intralaminar, and midline, receive major input from the cortex and project back to the cerebral cortex (Sherman and Guillery, 2006; Saalmann, 2014). For example, the ventrolateral and ventromedial thalamic nuclei project to motor cortical areas (Bosch-Bouju et al., 2013). In contrast, the mediodorsal thalamic nucleus is connected with the prefrontal cortex, including dorsolateral regions (Saalmann and Kastner, 2011; Mitchell and Chakraborty, 2013).

First-order and higher-order relays are separate stages of a singular process. That is, first-order relays route somatosensory information to respective cortical areas, whereas higher-order relays relay processed information from layer five of a single cortical area to the middle levels of another cortical area. All thalamic relays (i.e. both first and higher order) receive feedback from layer six of the cortex. Higher-order relays are often acknowledged as being modulatory in nature as they are actively involved in routing feedback (Sherman and Guillery, 2006). Sherman and Guillery (2006) acknowledge that this is a simplified overview as the functioning of the thalamus is somewhat more complex.

Further, the thalamus is highly interconnected with many subcortical structures, including the basal ganglia, amygdala, hippocampus, cerebellum, as well as deep midbrain nuclei (Hendry et al., 1979; Pessoa and Adolphs, 2010; Bosch-Bouju et al., 2013). These connections suggest that the thalamus plays a role in processes mediated by these subcortical structures, such as basic emotions, memory, and motor processes. Although the exact function of the interrelationship among thalamus-subcortical regions is not known, it is suggested that the thalamus impacts information processing in these subcortical structures in a similar fashion as it impacts cortical function (Poulet et al., 2012).

As for the basal ganglia, the striatum (i.e. the input structure of the basal ganglia) sends projections to the globus pallidus internal segment and substantia nigra pars reticulata via two pathways: the indirect pathway and the direct pathway. The indirect pathway involves the globus pallidus external segment and the subthalamic nucleus (STN), which both send projections and inhibit the thalamus (Wickens, 1997). In contrast, the direct pathway involves the striatum, which inhibits the globus pallidus internal segment, which in turn inhibits the thalamus. Further, it was found that the thalamus sends projections to the striatum, thus suggesting that the thalamus controls information processing in the basal ganglia (Matsumoto et al., 2001). Matsumoto et al. (2001) argue that the relevant sensory information that guides action selection processes is projected from the thalamus to the striatum. Importantly, it is not known if there are dissociable functions of cortical and thalamic pathways to the striatum. Like the basal ganglia, it has been found that the medial dorsal region of the thalamus receives dopamine from the midbrain regions, including the ventral tegmental area (García-Cabezas et al., 2009), suggesting that thalamic dopamine plays a role in dopamine-related disorders such as addiction, schizophrenia, and Parkinson's disease (Sánchez-González et al., 2005).

Like the basal ganglia, similar kinds of connectivity with the thalamus are found with other subcortical structures, including the hippocampus, amygdala, and cerebellum (Middleton and Strick, 2000; Houk et al., 2007). Input from these structures project to different thalamic nuclei before reaching the cortex. For example, imaging and correlational studies in humans support connectivity between the thalamus and hippocampus (Stein et al., 2000). It was also found that the medial dorsal thalamus sends input from the amygdala to the frontal cortex and limbic system (Tham et al., 2009).

In sum, studies such as the ones described above have established how neural connections between subcortical and cortical areas nearly always pass through the thalamus. Yet the functional roles of the thalamus are poorly understood. However, based on the known patterns of connectivity, there is evidence that suggests that the thalamus functions as a relay station (or as a 'secretary' of the cortex and perhaps subcortical structures), as we discuss below.

Cognitive functions of the thalamus

Areas of focus

Four main areas of focus are examined within this section: first, the pulvinar region (PUL), which is a higher-order relay with afferent pathways from the occipital cortex, parietal lobes, and temporal lobes and efferent pathways from the occipital cortex, parietal lobes, and temporal lobes; second, the centromedian nucleus (CM), which has afferent pathways from the cerebral cortex, vestibular nuclei, globus pallidus, superior collicullos reticular formation, and spinothalamic tract and has efferent pathways from the STN and putamen; third, the media dorsal nucleus (MD), which is a higher-order relay with afferent pathways from the hypothalamus and prefrontal cortex and efferent pathways from the prefrontal cortex; fourth, the ventral lateral nucleus (VL), which is a higher-order relay with afferent pathways from the basal nuclei and efferent pathways to the primary motor cortex and premotor cortex.

The thalamus plays a role in multiple cognitive functions, including memory, attention, perception, motor planning, and language processing. It is this integration that gives rise to the notion that the thalamus does function as a relay station (Wilke et al., 2010; Ford et al., 2013). The role of the thalamus can also be understood by studies showing that lesions to the thalamus

can cause cognitive and memory deficits (Mitchell and Gaffan, 2008) and that higher-order thalamic lesions perturb cortico-cortical information transmission (Purushothaman et al., 2012). For example, patients with pulvinar lesions exhibit deficits both in coding spatial information in the contralesional visual field and in filtering distractor information (Saalmann and Kastner, 2011). Bradfield et al. (2013) review evidence from rodent studies that indicate that the intralaminar thalamic nucleus and the parafascicular thalamus are mediators of behavioural flexibility, whereas the mediodorsal thalamic nucleus plays a key role in acquiring goal-directed behaviour.

Learning is another process that can be mediated by the thalamus. The mediodorsal thalamus plays an important role in free operant behavioural tasks. More specifically, it was found to be important for both the acquisition of goal-directed behaviour and the regulation of stimulus-outcome and response-outcome contingencies (Ostlund and Balleine, 2008; Bradfield et al., 2013). Habib et al. (2013) reported that fear conditioning (i.e. learning that a conditioned stimulus that comes before an aversive unconditioned stimulus is also aversive) and safety learning (i.e. learning that a conditioned stimulus that comes after an unconditioned stimulus is safe) lead to different molecular changes in the auditory thalamus. That is, safety learning led to a decrease in the level of ABL1 protein in the thalamus, whereas fear conditioning did not (Habib et al., 2013). This finding suggests that different neural mechanisms may be involved when the same stimuli are presented differently. These alternative mechanisms may then lead to differences in memory formation.

There are various types of motor processes that are affected by the thalamus. For example, Ostendorf et al. (2013) further investigated previous findings that indicated that oculomotor commands produce corollary discharge signals that are transmitted from the thalamus to frontal cortices. They examined whether perceptual matching of visual input before and after an eye movement is impaired due to damage to the pathway between these brain regions. The findings suggest that this pathway and the transmission of corollary discharge are essential in order for individuals to predict the consequences of oculomotor actions. Based on data from clinical subjects with thalamic lesions, Ostendorf et al. (2013) concluded that the central thalamus makes an important contribution to predicting the perceptual consequences of eye movements.

Indeed, the thalamus appears to mediate the influence of cognitive processes on motor control. Thalamic neurons that receive input from the cerebellum, for example, may assist visuomotor control, such as making self-timed movements. Studies that focus on the cerebello-cortical pathways identify the role of the central and VL thalamus in the modulation of movement processing based on cognitive requirements (Prevosto and Sommer, 2013). Minamimoto et al. (2014) showed that the CM in the intralaminar thalamus plays a role in counteracting behavioural biases, which contributes to flexible behaviour via interactions with the basal ganglia. One study examined the role of the thalamic centromedian in the counteracting process, in which preaction bias is not valid in unexpected situations and is therefore replaced by a more appropriate action (Minamimoto et al., 2014). This study tested monkeys who performed a Go-Nogo task in small and large reward conditions. The results indicated that the thalamic centromedian was involved in signalling the occurrence of a discrepancy between preaction bias and an environmental demand, as well as the withdrawal of the preaction bias in favour of a more appropriate action.

The thalamus also plays a role as the central monitor for language-related processes (Klostermann et al., 2013). Encompassing a number of thalamic nuclei, including the pulvinar, mediodorsal, and ventral intermediate nuclei, Klostermann et al. (2013) discuss contributions of the thalamus and basal ganglia to language perception and production. Cortical language operations are engaged and disengaged by thalamic nuclei, such that human language is a product of subcortical and cortical regions of the brain (Klostermann et al., 2013). The thalamus contributes to language capacities due to both its functions related to the control and regulation of information from one cortical area to another and its interconnections with Broca's area, which plays a key role in language production (Ford et al., 2013; Bohsali et al., 2015).

The mediodorsal thalamus has a role in declarative memory processes (Van der Werf et al., 2000). More specifically, the mediodorsal thalamus processes the content of information for both storage and recall. The retrieval of stored information may involve the production and guidance of strategies by the mediodorsal thalamus (Mitchell and Chakraborty, 2013). The anterior thalamic nuclei were also found to play a role in memory and spatial navigation. As for memory processes, Jankowski et al. (2013) argue that the anterior thalamus and its interactions with the hippocampus and cortex is crucial for memory processing and spatial navigation in rodents. This is due to evidence of oscillatory activity at theta frequencies in the anterior thalamus.

Thalamus, prefrontal cortex, and working memory

Area of focus

The MD is examined within this section. It is a higher-order relay with afferent pathways from the hypothalamus and prefrontal cortex. It also has efferent pathways to the prefrontal cortex. Its primary functions involve memory, attention, and abstract thinking.

Similar to the prefrontal cortex, different types of studies have shown that the thalamus plays a key role in working memory. When monkeys performed spatial working memory tasks, the mediodorsal neurons of the thalamus exhibited directionally selective sustained delay-period activity, which is related to the temporary maintenance of information. This is similar to delay activity reported in many cortical regions, including the dorsolateral prefrontal cortex and the medial temporal cortex (Goldman-Rakic, 1995; Constantinidis et al., 2001; Ranganath and D'Esposito, 2001). Mediodorsal neurons of the thalamus play an important role in prospective motor aspects of working memory (Funahashi, 2013). Mediodorsal neurons have been shown to modulate their spike rate during different cue, delay, and response periods in monkeys trained in delayed response tasks (Saalmann, 2014). This delay period activity within the thalamus is an indication of its role in working memory (Saalmann, 2014).

The mediodorsal nucleus may play a role in representational plasticity within the prefrontal cortex (Van der Werf et al., 2000). Deep brain stimulation (DBS) of the mediodorsal nucleus was found to improve prefrontal functioning (Baxter, 2013), suggesting that it plays a role in cognitive processes. The various effects of lesions to the mediodorsal thalamus support its role in memory and other cognitive processes (Mitchell and Chakraborty, 2013). The mediodorsal thalamus regulates both the plasticity within the prefrontal cortex and the flexibility of prefrontal-dependent operations Baxter (2013). Funahashi (2013) argues that the mediodorsal thalamus contributes to spatial working memory, including how the interaction between the thalamus and prefrontal cortex can enable sensory-to-motor transformations of maintained information. Finally, Saalmann (2014) proposes that the mediodorsal thalamus regulates the synchrony between neurons in the prefrontal cortex, which consequently influences their exchange of information according to cognitive control demands.

The thalamus and attention

Area of focus

The lateral geniculate nucleus (LGN) is examined in this section. It a first-order relay with afferent pathways from the retina. It has efferent pathways to the primary visual area. The primary function of the LGN involves relaying visual information to the primary visual area. In contrast, the thalamic reticular nucleus (TRN) is a higher-order relay. It has afferent pathways from the cerebral cortex and dorsal thalamic nuclei. It also has efferent pathways from dorsal thalamic nuclei.

Attention, described simply, is the selective processing of sensory or conceptual information in the brain. The thalamus is often described as a 'gateway' of such information processing, since it has feedforward and feedback connections to the brainstem and to cortical areas (Ward, 2013). Visual attention provides a good example of the role of the thalamus in the modulation of visual information. Each eye has over 125 million receptors that send sensory information via the optic nerve to the LGN in the thalamus (Hubel, 1995). The neurons are organized topographically in the LGN, reflecting the arrangement of the receptors on the retina, but this organization tends to be less pronounced as neurons travel through the visual cortex. Since almost all visual information passes through the thalamus, it is considered to have an important role in vision and visual attention.

Studies by Kastner et al. (2006) have confirmed that the LGN supports attentional modulation of neural signals that come from the eyes. This makes the LGN one of the first areas where feedback signals from the visual cortex and higher cortical areas modulate the processing of visual information. The forms of modulation that can occur in the LGN include the enhancing of neural signals for attended stimuli and an attenuating of responses for ignored stimuli. The TRN in particular is believed to be responsible for sending inhibitory signals to the LGN (McAlonan et al., 2006). The TRN has an important role in attention, and some would argue that it is the locus of the 'attentional spotlight' (Crick, 1984).

Another example of how the LGN helps determine visual experience is by examining cases of binocular rivalry, which is when there are conflicting sources of information coming from each eye (generally a manipulation done in a laboratory setting when studying the visual system). During binocular rivalry, only one of the images is perceived at a given time. That is, one image shifts in dominance over time rather than producing a percept where

the two conflicting images mesh into one. For example, if one eye receives an image of a house and another receives an image of a face, the percept is of one or the other, never both at the same time (e.g. resulting in an odd house with a face). Binocular rivalry induces the suppression of one of the images, and brain imaging studies indicate that the LGN is involved in this suppressive signal processing that tries to resolve conflicting information (Wunderlich et al., 2005).

The thalamus is connected to the brainstem and thus receives sensory signals from the rest of the body. It also has connections to all cortical areas, to which it sends signals as well as receives them, which is why it is often described as a 'relay' station. This organization where both feedforward and feedback signals converge is a signature of attentional modulation and makes the thalamus a candidate location for processing all forms of attention. For example, it can also process emotional signals from the amygdala that can influence behavioural responses, even outside of conscious awareness (Tamietto and de Gelder, 2010).

For these reasons, the thalamus is also described as a 'gatekeeper' for the information processed by visual attention, some of which may eventually reach visual conscious awareness. It is more likely, however, that the thalamus is part of a group of cortical and subcortical areas that work collectively to modulate attentional processing and provide the contents of visual awareness (Kastner et al., 2006). The thalamus appears to have many important connections to the motor circuitry found in the brain stem and spinal cord, suggesting a close relationship between sensory information and the motor system (Guillery and Sherman, 2002b; Sherman and Guillery, 2006). Recently, there has been evidence for different pathways that indicate a separating of information pathways, with some reaching perception and others going to inform systems involved in the execution of eye movements (Spering and Carrasco, 2015). This could be the result of earlier connections from the retina directly to the superior colliculus and brainstem (with connections to the middle temporal area, or V5), thereby not passing through the thalamus in order to allow information to be more readily available for the motor system. More empirical support is required, but this organization could explain why there are often dissociations between what reaches awareness and what can inform actions (with unconscious processing often influencing action). Nevertheless, the location of the thalamus and its interconnectedness with the brainstem and cortical areas make it a central area where very early feedback modulation of feedforward neural signals can occur, making it important for attention.

The thalamus and consciousness

Related to the role of modulating attention, the thalamus may also help support conscious awareness. Something as complex as consciousness, which includes the subjective phenomenal experience of sensory and conceptual information, will not be constrained to one specific area within the brain. Nevertheless, research does indicate that the thalamus plays an important role in consciousness (Crick and Koch, 2003; Seth et al., 2005). Specific areas of the thalamus are responsible for certain forms of processing, such as the influence of the LGN on visual awareness (Kastner et al., 2006). Since the thalamic nuclei have projections to and from all cortical areas, it seems to be a good candidate for a mechanism that enables the integration of all of these different forms of information, which may be through a synchrony of neural activations (for a review, see Ward, 2011).

There are many definitions of consciousness in the philosophical literature (see for example Kriegel, 2015), but two main distinctions are important to identify here: phenomenal and access. Phenomenal consciousness is what most people mean when they use the term consciousness – it is the subjective experience of being aware of a certain thought, sensation, or feeling. It is what you are experiencing as you read this sentence and includes all experienced sensations, like the sound of the refrigerator in the background and the chair against your back and the slight feeling of hunger in your stomach. Phenomenal consciousness also includes forms of meta-consciousness, where one is conscious and aware of the contents of consciousness as proposed in higher-order theories (see Rosenthal, 2002); it also includes self-consciousness, which helps differentiate the self as distinct from other things in the world. Access consciousness, on the other hand, does not necessarily include subjective experience – it is a form of consciousness that allows representational content to be made available for use by various cognitive systems for thought and action (Block, 1995). In this sense, the distinctive features of access consciousness relate to attention due to their role in processing information within the brain in a task-relevant manner in order to guide action and thought. It is assumed that both phenomenal and access consciousness are processed and supported by the thalamus. For our purposes, exploring the thalamus in terms of phenomenal consciousness suffices.

One way to study consciousness in the thalamus is to examine how anaesthesia induces unconsciousness (Alkire et al., 2008; Mashour and Alkire, 2013a,b). The administration of anaesthesia (e.g. propofol) reduces

the interconnectivity between the thalamus and cortical areas. This reduced interconnectivity is due to suppressed activity within the 'nonspecific division' of the thalamocortical system (Liu et al., 2013). This in turn inhibits the ability to integrate information within the thalamus, which leads to unconsciousness. Thus, such studies seem to indicate that an important function of the thalamus is to help integrate sensory information. This is also relevant for understanding how some patients may experience vegetative states. Damage to the thalamus produces major disturbances to consciousness because without interconnectivity, the various areas of the brain cannot communicate to each other (Llinás et al., 1998). On the other hand, damage to other brain areas, such as parts of the cortex, may have limited or no effect on consciousness (Seth et al., 2005).

The thalamus also appears to be involved in self-awareness. Having a representation of the self may rely on signals from the thalamus, which seems to be integral to conscious forms of attention (Bruya, 2010). The Triangular Circuit Theory (LaBerge, 1997, 2001) argues that consciousness requires activations of various areas responsible for attentional selection, enhancement, and control, in addition to a representation of the self in relation to the objects of attention. That is, without a representation of the self, one cannot experience consciousness. The thalamus is considered to be a core part of this circuitry that is responsible for both attentional processing and self-awareness (LaBerge, 1997). Whether self-awareness is crucial for having the phenomenal experience of consciousness is debateable, but self-awareness does represent a type of phenomenal consciousness that can be observed in humans and even some mammals (e.g. apes) and birds (e.g. grey parrots).

Theories of consciousness in other animals also suggest that it may rely on the thalamus. For example, Bayne's (2007) theory of Creature Consciousness specifies whether or not an organism can be said to be phenomenally conscious by requiring two primary components: the mechanisms responsible for providing the contents of consciousness (e.g. neural inputs from different sensory processing areas) and the integrative mechanisms that generate the 'phenomenal field' (i.e. of what it is like to be in a state), which may be related to activity in the thalamus. Indeed, some argue that the higher thalamus and thalamocortical activity are both critical for human and animal consciousness and can be used as criteria for determining animal consciousness (Seth et al., 2005; Boly et al., 2013). While the evidence for the role of the thalamus in consciousness is not conclusive, there is good empirical support for recognizing its importance in the modulation of information that becomes part of conscious experience.

In addition to the Triangular Circuit and Creature Consciousness theories, there are several other theories that include the thalamus as part of the neural network required for consciousness. The Information Integration Theory, for example, proposes that the thalamocortical system plays an important role in the integration of information and is therefore crucial for consciousness (Tononi, 2004). According to this theory, the thalamus is a centre of activity where neural signals converge to integrate information (Tononi and Edelman, 1998; Alkire et al., 2008). Along these lines, the thalamic Dynamic Core Theory of consciousness argues that synchronized neuronal activity within the dorsal thalamic neurons is required for consciousness (Ward, 2011). That is, consciousness is associated with a state when neuronal signals occur in synchrony, which may also be regarded as the integration process.

The Global Workspace Theories (e.g. Newman et al., 1997; Dehaene and Naccache, 2001; Baars, 2005) also require the processing of information by the thalamus, cortical regions, and some type of working memory. The thalamus seems to be important in modulating the flow of information and the level of alertness associated with this processed information (León-Domínguez et al., 2013). Ultimately, the complete thalamocortical network is crucial for consciousness. That is, the cortical areas engage in the interpretation of information and provide the contents of conscious experience, whereas the thalamus helps integrate information, modulates what enters awareness, and determines the level of awareness produced by this information (Ward, 2011; León-Domínguez et al., 2013). Consciousness is not reliant solely on thalamic activity, but it does seem to be a crucial part of the formula.

Thalamus as a relay station

Sherman and Guillery (2002) suggest that all thalamic nuclei are relay nuclei. However, this does not mean that that all thalamic nuclei are the same. According to Sherman and Guillery (2002), there are broadly two types of thalamic nuclei: first-order relays and higher-order relays. First-order relays carry information from the sensory periphery (e.g. visual and auditory channels) and other parts of the brain such as the cerebellum. An example of a first-order relay is the lateral geniculate, which is involved in the relay of visual information. In contrast, higher-order relays receive information from the cerebral cortex. The PUL is an example of a high-order

relay. Sherman and Guillery (2002) suggest that these higher-order relays make up the largest percentage of the thalamus within primates. Higher-order relays play a dynamic role in corticocortical communication, such that they do not just passively relay information, rather they actively control the passage of information from one cortical area to another.

Based on its functions and its anatomical connections within the brain, it has been suggested that the thalamus plays a role in routing information across cortical and subcortical structures (Saalmann et al., 2012; Xu and Südhof, 2013). This role may involve a flexible synchronization of neurons and the configuration of brain networks for the current behavioural context. In other words, the thalamus may activate some cortical areas and deactivate others. Thus, relevant information that is selectively projected to the cortex depends on the context and the task at hand (Saalmann et al., 2012; Xu and Südhof, 2013).

Specifically, as discussed above, a key function of the thalamus is to relay sensory and motor information to the cerebral cortex. All sensory systems, except the olfactory system, include a thalamic nucleus that receives and transmits sensory signals to relevant cortical areas. Information that comes from the sensory periphery (e.g. visual, auditory), cerebellum, and the mammillary bodies is relayed to the cortex via 'first-order relays' in the thalamic nuclei, whereas information that comes from the cerebral cortex is relayed via 'higher-order relays' (Guillery, 1995; Guillery and Sherman, 2002a). For example, visual information from the retina is first transmitted to the LGN of the thalamus, from which it is then sent to the primary visual cortex.

The thalamus has been referred to as the 'ultimate gatekeeper' due to its important role in sending information from the sensory periphery to the correct areas of the cortex (Steriade and Llinás, 1988; Edelman, 2003). This is similar to arguments that the thalamus functions as a threshold to decide which information should and should not be projected to the cortex or other brain regions (Edelman, 2003). The evidence reviewed above highlights the thalamus's role in sleep, controlling unconsciousness under anaesthesia, and selectively transferring information for attentional processing and consciousness, all of which support its characterization as a gatekeeper and relay station.

Controlling the transfer of information across the brain is related to successful performance in various processes, including perceptual, emotional, motor, and cognitive processes. For example, the brain must decide which perceptual input should be transferred to the cortex for further processing, which motor plans to be implemented, and which information to be maintained in long-term memory storage. The same applies to higher cognitive processes, such as consciousness, as this also involves awareness of only some information.

As discussed above, there are many theories that attempt to explain the role of the thalamus in consciousness, including the Triangular Circuit, Creature Consciousness, Information Integration, Dynamic Core, and Global Workspace Theories. These theories argue that consciousness is related to the thalamus's role in the activation of various areas, integration of information across different areas, modulation of information flow, and synchronized neuronal activity. It is possible that these same theories also explain the thalamus's role in other behavioural processes, including motor and cognitive processes (although these processes have received less attention in the field in comparison to consciousness). The role of the thalamus in consciousness uniquely highlights the integral and critical nature of its role in normal cognitive and motor function.

Viewing the thalamus as a relay station highlights its role in the processing of many different forms of information, including those related to motor processes, cognition, emotion, learning, pain, attention, and consciousness. In all of these processes, it seems that the thalamus sets the threshold and decides whether it should relay the information to other brain areas. Importantly, we argue that the two theories of the thalamus as a gatekeeper and relay station are not necessarily separate, but rather they are part of one mechanism allowing the brain to continue to select behaviourally relevant information. Its gatekeeping ability relies on its interconnectivity within the brain, which allows it to relay relevant information effectively. The role of the thalamus can be further understood by examining neurological disorders as well as thalamic damage.

Thalamus-related disorders

The critical nature of the thalamus to major cognitive and motor processes as evidenced above can be further shown by examining cases where the thalamus has sustained damage or there are other abnormalities present. Below, we will discuss thalamus-related brain disorders through a wider anatomical and physiological standpoint of movement and cognitive disorders. One way to better understand how the thalamus contributes to cognitive and motor processes is to examine cases in which there is damage or abnormalities present in the thalamus. Below, we discuss various brain disorders and specific dysfunctions that are related to abnormalities in the thalamus.

Specific dysfunctions

Specific damage to the various nuclei generates different symptoms depending on the specific nuclei and the type of interaction between them. For example, a vascular lesion within the tuberothalamic region impairs arousal and orientation, as well as leading to problems with learning and general memory. Furthermore, damage to these particular nuclei can also lead to personality and executive function impairment. These issues, when encountered, highlight the importance that the thalamus has on not only simple relaying of information but also on the active filtering of appropriate information for processing.

A vascular infarct event within the parademian region can also cause decreased arousal, as well as impaired learning and issues with general memory. Damage to the thalamus can also cause problems with language, specifically lesions within the left paramedian, as well as left tuberothalamic nuclei. Furthermore, damage to the right side of the thalamus can cause issues with vision and spatial orientation. Finally, damage to the posterior choroidal region can cause a variety of different issues, including dystonia, tremors, visual field disturbances, and weakness (Schmahmann, 2003). These specific disturbances within the thalamus highlight and pinpoint the exact pathways and the exact functions related to those pathways. These specific examples, coupled with the general evidence above, showcase the importance of the thalamus. That is, not only is the thalamus an important mediator, but it also provides essential control over filtering of information for continued processing of sensory data.

Movement disorders

There are various movement disorders that are connected to thalamic dysfunction. These include Parkinson's disease, Tourette syndrome (TS), and hemiballismus.

STN: Hemiballismus

This particular type of movement disorder is one of the most dramatic. It is characterized by a repetitive but unique set of involuntary wavelike movements located within the proximal portion of the limbs (Handley et al., 2009). The most common cause of hemiballismus is stroke, with an incident rate of approximately 0.45 per 100 000 cases. It is believed that lesions to the cerebral cortex, subcortical areas, midbrain, striatum, and thalamus can cause

hemiballismus. The main causal area for the manifestation of hemiballismus is considered to be the STN. Lesions in this area can occur due to diabetes, hypertension, and smoking (Etemadifar et al., 2012). This specific dysfunction also highlights the role that the thalamus has on higher-order functions such as language. Language production and comprehension occur in disparate parts of the brain, although as can be detailed from this specific dysfunction, the thalamus is tightly involved with these actions (Etemadifar et al., 2012).

In the particular case that Etemadifar et al. (2012) were investigating, the region that was damaged by an infarction was the left subthalamic area. This resulted in right side hemiballismus, as well as behavioural changes demonstrated by irritability, anxiety, and some aggressive and obscene speeches. A further study showed that an ischemic infarct of the right thalamus resulted in hemiballismus, as well as behavioural changes including elation, disrupted sleep, and aggrandised sense of self (Kulisevsky et al., 1993). These two cases of hemiballismus provide further support to the notion that the thalamus plays a crucial role in the efficient running of cognitive and motor functions (Kulisevsky et al., 1993; Etemadifar et al., 2012).

Caudate Nucleus: TS

The clinical landscape for TS is characterised by the uncontrollable occurrence of motor and vocal tics. These tics can be described as sudden and repetitive movements and/or vocalisations that can differ across both intensity and frequency. Furthermore, these tics often occur after an urge or sensation that can foretell the actual tic. The clinical onset of this condition is usually in early childhood, and there are several comorbid behavioural disorders that are very common with people who have TS. These related behavioural disorders include attention deficit hyperactivity disorder, obsessive-compulsive disorder, and occurrences of self-damage behaviour (Leckman et al., 2010).

Much of the neurophysiological underpinnings of TS are still unknown. However, a dysfunction of the basal ganglia and the parallel striatal-thalamic-cortical circuits seem to play a critical role in the disorder (Leckman et al., 2010). Numerous studies have identified structural changes within the basal ganglia in TS patients. For instance, Peterson et al. (2003) identified a consistent but mild decrease in basal ganglia volume across 150 TS patients. These findings were most visible in the caudate of children. These results support the

findings of Hyde et al. (1995) that sufferers who were more affected had a smaller right caudate (Bloch et al., 2005; Roessner et al., 2011). Relatively few studies have specifically examined the thalamus in TS sufferers. The studies that have been conducted exhibit somewhat contradictory results. However, Lee et al. (2005) did find that young Taiwanese boys with TS had a larger left hemithalami. Furthermore, the magnetic resonance imaging analysis of Miller et al. (2010) found a 5% increase in thalamic volume. They concluded that these differences were not due to IQ, other disorders, or other treatments (Miller et al., 2010).

There are various treatments that have been shown to be successful in helping to alleviate the suffering of people with TS. DBS has been promoted as an option for TS sufferers who have been resistant to other forms of treatment Vandewalle et al., (1999). Some studies conducted a double blind randomised cross-over trial testing the ability of DBS in TS sufferers. The specific region examined was the CM–substantia periventricularis–nucleus ventro-oralis internus crosspoint in the thalamus. There are also other studies that promote the ability of DBS for the thalamus to help diminish the occurrence of tics in TS sufferers (see Temel et al., 2004; Ackermans et al., 2006; Rotsides and Mammis, 2013).

Therefore, although the thalamus is not directly responsible for TS, the striatal-thalamic-cortical circuits may very well be involved in the disorder. Furthermore, it has been shown that DBS of the thalamus can improve the occurrences of tics in TS sufferers that are treatment resistant. DBS seems to be at least nominally successful in treating disorders that involve the thalamus, which adds further evidence to the thalamus not only being a passive relay but also an active participant (Vandewalle et al., 1999). These findings provide an excellent insight into exactly how tightly integrated the thalamus is in overall brain functionality and how important the thalamus is for coordinated and voluntary movement.

Multiple areas: Parkinson's disease

The clinical diagnosis of Parkinson's disease involves the identification of motor symptoms including rigidity, resting tremor, bradykinesia, and postural instability (Gelb et al., 1999). The cause of these motor symptoms is typically explained by the loss of dopaminergic regulation in the basal ganglia (Zaidel et al., 2009). Research suggests, however, that abnormalities in the thalamus can also cause these motor symptoms. For instance, findings indicate that the overall shape of the thalamus is different

in Parkinson's disease patients compared to healthy controls (McKeown et al., 2008). That is, there were significant shape differences between the left and right thalamus in patients with Parkinson's disease compared to healthy controls. Also, tremor-dominant patients with Parkinson's disease exhibit structural changes in the posterior region of the ventral cell mass and hypermetabolism of the lateral region of the ventral cell mass (Kassubek et al., 2002). These results suggest a site of nondopaminergic degeneration in Parkinson's disease.

Research also indicates that patients with Parkinson's disease exhibit reduced thalamic volume. For example, neuronal loss was found in selected intralaminar nuclei in patients with Parkinson's disease (Henderson et al., 2000). This cell loss was greatest in the large centromedian/parafascicular complex and central lateral region of the thalamus. There was also a reduced number of neurons in the caudal intralaminar nuclei (40–55%) in patients with Parkinson's disease. Additionally, Lewy bodies (i.e. abnormal deposits of protein) were found in the limbic thalamic nuclei and the caudal intralaminar nuclei. Loss of thalamic volume has also been found to be associated with freezing of gait in patients with nondemented Parkinson's disease (Sunwoo et al., 2013).

Other findings indicate a reduction in serotonin transporter in the thalamus in tremor-dominant Parkinson's disease patients (Caretti et al., 2008). Therefore, serotonin may play a role in the development of resting tremor in the early stages of Parkinson's disease. This is in agreement with studies showing that the thalamus plays a role in tremor (Kassubek et al., 2002; Probst-Cousin et al., 2003; Weinberger et al., 2009; Zaidel et al., 2009; Mure et al., 2011; Helmich et al., 2012).

These findings suggest Parkinson's disease symptoms may be caused by abnormalities in the thalamus, rather than solely being related to abnormalities in the basal ganglia, substantia nigra, brain stem, or limbic or neocortical brain regions. According to Halliday (2009), neurodegenerative changes in the motor and midline regions of the thalamus influence motor cortical excitability, which leads to the observed symptoms of Parkinson's disease. Therefore, besides the basal ganglia, the thalamus may have a more central role in the aetiology of Parkinson's disease symptoms because of its impaired ability to relay information.

Various existing therapies for Parkinson's disease have targeted the thalamus, including thalamotomy and DBS to the thalamus (Speakman, 1963; Tasker et al., 1983; Ohye et al., 2012). These were particularly effective for the treatment of tremor. For example, one study found that thalamic DBS was very effective at managing resting

tremor more so than for akinesia and rigidity (Benabid et al., 1996), although not all studies support this conclusion (see Yamada et al., 2014).

Sleep disorders

The thalamus has an important role in sleep production. During the early stages of non-rapid eye movement (REM) sleep, thalamic GABAergic inhibitory reticular neurons (RE neurons, which are in the rostral, lateral, and ventral parts of the thalamus) are activated with thalamocortical neurons. Hyperpolarisation of the thalamocortical system leads to a reduction in synaptic responsiveness and a halt to the bidirectional flow of information. Low- and high-frequency spindles are created by RE neurons and have a role in the activation, maintenance, and advancement of non-REM sleep into later stages (Steriade et al., 1993). These spindles are bursts of oscillatory activity between the RE neurons and thalamocortical neurons. It is necessary that excitatory input to the thalamus from the cerebral cortex is suppressed and all stimuli from sensorimotor inputs must be reduced in order for hyperpolarisation of the RE neurons to occur.

Abnormalities in the thalamus can lead to problems in sleep initiation and maintenance. For instance, problems with the spindles (e.g. reduced number) can lead to problems with non-REM sleep such as delayed sleep onset and constant awakenings (De Gennaro and Ferrara, 2003; Urakami, 2008). Although unilateral thalamic stroke patients show no ipsilateral decrease or absence of sleep spindles, patients with thalamic lesions to both hemispheres show a decrease in spindles (Santamaria et al., 2000). Findings indicate that paramedian thalamic stroke can lead to increased sleep duration, increased sleep fragmentation, and decreased spindles (Guilleminault et al., 1993; Bassetti et al., 1996; Santamaria et al., 2000).

Fatal thalamic insomnia patients exhibit a decrease in slow wave sleep, absence of spindles, and abnormal REM sleep. This may be due to neuronal loss to the anterior and dorsomedial nuclei of the thalamus (Tinuper et al., 1989). The disruption of thalamic sleep-generating mechanisms may also cause hypersomnia, which consists of excessive sleepiness during the daytime and prolonged sleep (Guilleminault et al., 1993; Bassetti et al., 1996).

Korsakoff's syndrome

Korsakoff's syndrome is a memory disorder that can involve both anterograde and retrograde amnesia (Kopelman, 1995). It is typically preceded by Wernicke's encephalography, which is a neuropsychiatric condition that is caused by deficits in thiamine (Victor et al., 1989). There have been numerous studies and debate concerning the neural systems and pathways that produce the memory deficits observed in Korsakoff's syndrome (for a review, see Fama et al., 2012). The thalamus has consistently been identified as a critical brain region for memory impairment in patients with Korsakoff's syndrome (Victor et al., 1971).

Neuroimaging and neuropathological studies have identified the mediodorsal nucleus of the thalamus (Shimamura et al., 1988; Victor et al., 1989), the parataenial nucleus of the thalamus (Mair et al., 1979; Mayes et al., 1988), and nuclei in the midline of the thalamus (Visser et al., 1999) as probable neural substrates for anterograde amnesia observed in patients with Korsakoff's syndrome. It has been argued that neuronal loss in anterior thalamic nuclei explains anterograde amnesia in patients with alcoholic Korsakoff's psychosis (Harding et al., 2000). Furthermore, neuroimaging studies have indicated that lesions in the mammillo-thalamic tract result in Korsakoff's syndrome (Yoneoka et al., 2004). Findings from psychologists and neuroscientists studies suggest that hypometabolism in the thalamus is associated with permanent amnesia (Aupée et al., 2001; Reed et al., 2003). Lastly, anterograde amnesia observed in Korsakoff's syndrome is associated with disruptions in the connections between the thalamus and other brain regions such as the hippocampus, mammillary bodies, frontal lobes, and medial temporal cortices (Aggleton and Brown, 1999; Savage et al., 2012).

Alzheimer's disease

Alzheimer's disease is a neurodegenerative disorder that is characterized by gradual cognitive decline. The neuropathology of Alzheimer's disease consists of atrophy, increased presence of neurofibrillary tangles, and amyloid plaques (Braak and Braak 1991a). Research has typically focused on the hippocampus and the amygdala as brain regions that are vulnerable to these pathologies (e.g. de Leon et al., 1993; Horinek et al., 2007). Consequently, the thalamus has received less attention. Research suggests, however, that Alzheimer's disease also causes abnormalities to the thalamus.

Alzheimer's disease affects limbic nuclei of the thalamus (Braak and Braak 1991b). That is, amyloid and neurofibrillary changes develop in the thalamus, which may consequently disrupt the transmission of information through limbic systems (Braak and Braak 1991b).

Neuronal loss occurs in the anterodorsal nucleus and the CM of the thalamus (Xuereb et al., 1991). Thalamus volume is reduced in patients with Alzheimer's disease, which has been found to be associated with impaired global cognitive performance (de Jong et al., 2008). Furthermore, thalamic atrophy found in Alzheimer's disease may lead to degenerative changes in the hippocampal-thalamic network (Zarei et al., 2010). Examination of the volume of the thalamus revealed that atrophy was common in this network in early Alzheimer's disease (Zarei et al., 2010). These findings suggest that degenerative decline in the thalamus may lead to further cognitive decline in Alzheimer's disease.

Thalamus, an integral component

The common thread throughout this paper has been the notion that the thalamus is not only a passive relay but that it also has an active influence over multiple sensory modalities, as well as control over voluntary coordinated action. The above evidence highlights that the thalamus is an integral component and acts as both a simple relay as well as an active gatekeeper. It is notable how specific areas of cognition, perception, and motor control are affected by specific points of damage to the thalamus. For example, damage to the left paramedian and the left tuberothalamic nuclei area can lead to issues with language production and comprehension, while damage to the parademian region can impact general memory and arousal (Schmahmann, 2003). Disorders such as Parkinson's disease and hemiballismus add to the idea that the thalamus is actively involved in voluntary and involuntary movement. Additionally, the investigation of Alzheimer's disease and TS suggests that the thalamus is involved in not only movement but also language and memory.

The effects of these neurological disorders have shown that the thalamus is a crucial component of the brain that contributes to successful cognitive and motor functionality. The thalamus is not only a simple 'relay station', rather it also plays a crucial role in selectively filtering information for further processing. This selective filtering of information means that it has an 'active' role in determining responses to external stimuli. The active involvement of the thalamus in major areas of brain functionality highlights how integral the thalamus is for language, perception, movement, and consciousness.

References

Ab Aziz, C.B. and Ahmad, A.H. (2006). The role of the thalamus in modulating pain. Malays. J. Med. Sci. *13*, 11–18.

Ackermans, L., Temel, Y., Cath, D., van der Linden, C., Bruggeman, R., Kleijer, M., Nederveen, P., Schruers, K., Colle, H., Tijssen, M.A., et al. (2006). Deep brain stimulation in Tourette's syndrome: two targets? Mov. Disord. *21*, 709–713.

Aggleton, J.P. and Brown, M.W. (1999). Episodic memory, amnesia, and the hippocampal–anterior thalamic axis. Behav. Brain Sci. *22*, 425–444.

Alkire, M.T., Hudetz, A.G., and Tononi, G. (2008). Consciousness and anesthesia. Science *322*, 876–880.

Aupée, A.M., Desgranges, B., Eustache, F., Lalevée, C., de la Sayette, V., Viader, F., and Baron, J.C. (2001). Voxel-based mapping of brain hypometabolism in permanent amnesia with PET. Neuroimage *13*, 1164–1173.

Baars, B.J. (2005). Global workspace theory of consciousness: toward a cognitive neuroscience of human experience. Prog. Brain Res. *150*, 45–53.

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

Baxter, M.G. (2013). Mediodorsal thalamus and cognition in non-human primates. Front. Syst. Neurosci. *7*, 38.

Bayne, T. (2007). Conscious states and conscious creatures: explanation in the scientific study of consciousness. Philos. Perspect. *21*, 1–22.

Benabid, A.L., Pollak, P., Gao, D., Hoffmann, D., Limousin, P., Gay, E., Payen, I., Benazzouz, A., and Benazzouz, A. (1996). Chronic electrical stimulation of the ventralis intermedius nucleus of the thalamus as a treatment of movement disorders. J. Neurosurg. *84*, 203–214.

Bloch, M.H., Leckman, J.F., Zhu, H., and Peterson, B.S. (2005). Caudate volumes in childhood predict symptom severity in adults with Tourette syndrome. Neurology *65*, 1253–1258.

Block, N. (1995). On a confusion about a function of consciousness. Behav. Brain Sci. *18*, 227–247.

Bohsali, A.A., Triplett, W., Sudhyadhom, A., Gullett, J.M., McGregor, K., FitzGerald, D.B., Mareci, T., White, K., and Crosson, B. (2015). Broca's area-thalamic connectivity. Brain Lang. *141*, 80–88.

Boly, M., Seth, A.K., Wilke, M., Ingmundson, P., Baars, B., Laureys, S., Edelman, D.B., and Tsuchiya, N. (2013). Consciousness in humans and non-human animals: recent advances and future directions. Front. Psychol. *4.*.

Bosch-Bouju, C., Hyland, B.I., and Parr-Brownlie, L.C. (2013). Motor thalamus integration of cortical, cerebellar and basal ganglia information: implications for normal and parkinsonian conditions. Front. Comput. Neurosci. *7*, 163.

Braak, H. and Braak, E. (1991a). Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol. *82*, 239–259.

Braak, H. and Braak, E. (1991b). Alzheimer's disease affects limbic nuclei of the thalamus. Acta Neuropathol. *81*, 261–268.

Bradfield, L.A., Hart, G., and Balleine, B.W. (2013). The role of the anterior, mediodorsal, and parafascicular thalamus in instrumental conditioning. Front. Syst. Neurosci. *7*, 51.

Bruya, B. (2010). Effortless Attention: A New Perspective in the Cognitive Science of Attention and Action (Cambridge, MA: MIT Press).

Bushnell, M.C. and Duncan, G.H. (1989). Sensory and affective aspects of pain perception: is medial thalamus restricted to emotional issues? Exp. Brain Res. 78, 415–418.

Caretti, V., Stoffers, D., Winogrodzka, A., Isaias, I.U., Costantino, G., Pezzoli, G., Ferrarese, C., Antonini, A., Wolters, E.C., and Booij, J. (2008). Loss of thalamic serotonin transporters in early drug-naïve Parkinson's disease patients is associated with tremor: an [(123)I]β-CIT SPECT study. J. Neural Transm. 115, 721–729.

Constantinidis, C., Franowicz, M.N., and Goldman-Rakic, P.S. (2001). The sensory nature of mnemonic representation in the primate prefrontal cortex. Nat. Neurosci. 4, 311–316.

Crick, F. (1984). Function of the thalamic reticular complex: the search-light hypothesis. Proc. Natl. Acad. Sci. USA 81, 4586–4590.

Crick, F. and Koch, C. (2003). A framework for consciousness. Nat. Neurosci. 6, 119–126.

De Gennaro, L. and Ferrara, M. (2003). Sleep spindles: an overview. Sleep Med. Rev. 7, 423–440.

de Jong, L.W., van der Hiele, K., Veer, I.M., Houwing, J.J., Westendorp, R.G.J., Bollen, E.L.E.M., de Bruin, P.W., Middelkoop, H.A.M., van Buchem M.A., and van der Grond, J. (2008). Strongly reduced volumes of putamen and thalamus in Alzheimer's disease: an MRI study. Brain 131, 3277–3285.

de Leon, M.J., Golomb, J., Convit, A., DeSanti, S., McRae, T.D., and George, A.E. (1993). Measurement of medial temporal lobe atrophy in diagnosis of Alzheimer's disease. Lancet 341, 125–126.

Dehaene, S. and Naccache, L. (2001). Towards a cognitive neuro-science of consciousness: basic evidence and a workspace framework. Cognition 79, 1–37.

Edelman, G.M. (2003). Naturalizing consciousness: a theoretical framework. Proc. Natl. Acad. Sci. USA 100, 5520–5524.

Etemadifar, M., Abtahi, S.H., Abtahi, S.M., Mirdamadi, M., Sajjadi, S., Golabbakhsh, A., Savoj, M.-R., Fereidan-Esfahani, M., Nasr, Z., and Tabrizi, N. (2012). Hemiballismus, hyperphagia, and behavioral changes following subthalamic infarct. Case. Rep. Med. 2012, 768580.

Fama, R., Pitel, A.-L. and Sullivan, E.V. (2012). Anterograde episodic memory in Korsakoff syndrome. Neuropsychol. Rev. 22, 93–104.

Ford, A.A., Triplett, W., Sudhyadhom, A., Gullett, J., McGregor, K., FitzGerald, D.B., Mareci, T., White, K., and Crosson, B. (2013). Broca's area and its striatal and thalamic connections: a diffusion-MRI tractography study. Front. Neuroanat. 7, 8.

Funahashi, S. (2013). Thalamic mediodorsal nucleus and its partici-pation in spatial working memory processes: comparison with the prefrontal cortex. Front. Syst. Neurosci. 7, 36.

García-Cabezas, M.Á., Martínez-Sánchez, P., Sánchez-González, M.Á., Garzón, M., and Cavada, C. (2009). Dopamine innerva-tion in the thalamus: monkey versus rat. Cereb. Cortex (New York, NY) 19, 424–434.

Gelb, D.J., Oliver, E., and Gilman, S. (1999). Diagnostic criteria for Parkinson disease. Arch. Neurol. 56, 33–39.

Goldman-Rakic, P.S. (1995). Cellular basis of working memory. Neuron 14, 477–485.

Guilleminault, C., Quera-Salva, M.-A., and Goldberg, M.P. (1993). Pseudo-hypersomnia and pre-sleep behaviour with bilateral paramedian thalamic lesions. Brain 116, 1549–1563.

Guillery, R.W. (1995). Anatomical evidence concerning the role of the thalamus in corticocortical communication: a brief review. J. Anat. 187, 583–592.

Guillery, R.W. and Sherman, S.M. (2002a). Thalamic relay functions and their role in corticocortical communication: generalizations from the visual system. Neuron 33, 163–175.

Guillery, R.W. and Sherman, S.M. (2002b). The thalamus as a moni-tor of motor outputs. Philos. Trans. R. Soc. Lond. B. Biol. Sci. 357, 1809–1821.

Habib, M.R., Ganea, D.A., Katz, I.K., and Lamprecht, R. (2013). ABL1 in thalamus is associated with safety but not fear learning. Front. Syst. Neurosci. 7, 5.

Halliday, G.M. (2009). Thalamic changes in Parkinson's disease. Parkinsonism Relat. Disord. 15, S152–S155.

Handley, A., Medcalf, P., Hellier, K., and Dutta, D. (2009). Movement disorders after stroke. Age Ageing 38, 260–266.

Harding, A., Halliday, G., Caine, D., and Kril, J. (2000). Degeneration of anterior thalamic nuclei differentiates alcoholics with amnesia. Brain 123, 141–154.

Helmich, R.C., Hallett, M., Deuschl, G., Toni, I., and Bloem, B.R. (2012). Cerebral causes and consequences of parkinsonian resting tremor: a tale of two circuits? Brain 135, 3206–3226.

Henderson, J.M., Carpenter, K., Cartwright, H., and Halliday, G.M. (2000). Loss of thalamic intralaminar nuclei in progressive supranuclear palsy and Parkinson's disease: clinical and thera-peutic implications. Brain 123, 1410–1421.

Hendry, S.H.C., Jones, E.G., and Graham, J. (1979). Thalamic relay nuclei for cerebellar and certain related fiber systems in the cat. J. Comp. Neurol. 185, 679–713.

Horinek, D., Varjassyova, A., and Hort, J. (2007). Magnetic reso-nance analysis of amygdalar volume in Alzheimer's disease. Curr. Opin. Psychiatry 20, 273–277.

Houk, J.C., Bastianen, C., Fansler, D., Fishbach, A., Fraser, D., Reber, P.J., Roy, S.A., and Simo, L.S. (2007). Action selection and refinement in subcortical loops through basal ganglia and cerebellum. Philos. Trans. R. Soc. Lond. B. Biol. Sci. 362, 1573–1583.

Hubel, D.H. (1995). Eye, Brain, and Vision (New York: Scientific American Library).

Hyde, T.M., Stacey, M.E., Coppola, R., Handel, S.F., Rickler, K.C., and Weinberger, D.R. (1995). Cerebral morphometric abnormalities in Tourette's syndrome: a quantitative MRI study of monozy-gotic twins. Neurology 45, 1176–1182.

Jankowski, M.M., Ronnqvist, K.C., Tsanov, M., Vann, S.D., Wright, N.F., Erichsen, J.T., Aggleton, J.P., and O'Mara, S.M. (2013). The anterior thalamus provides a subcortical circuit supporting memory and spatial navigation. Front. Syst. Neurosci. 7, 45.

Kassubek, J., Juengling, F.D., Hellwig, B., Spreer, J., and Lucking, C.H. (2002). Thalamic gray matter changes in unilateral Parkin-sonian resting tremor: a voxel-based morphometric analysis of 3-dimensional magnetic resonance imaging. Neurosci. Lett. 323, 29–32.

Kastner, S., Schneider, K.A., and Wunderlich, K. (2006). Beyond a relay nucleus: neuroimaging views on the human LGN. Prog. Brain Res. 155, 125–143.

Klostermann, F., Krugel, L.K., and Ehlen, F. (2013). Functional roles of the thalamus for language capacities. Front. Syst. Neurosci. 7, 32.

Kopelman, M.D. (1995). The Korsakoff syndrome. Br. J. Psychiatry 166, 154–173.

Kriegel, U. (2015). The Varieties of Consciousness (New York, NY: Oxford University Press).

Kulisevsky, J., Berthier, M.L., and Pujol, J. (1993). Hemiballismus and secondary mania following a right thalamic infarction. Neurology 43, 1422–1424.

LaBerge, D. (1997). Attention, awareness, and the triangular circuit. Conscious. Cogn. 6, 149–181.

LaBerge, D. (2001). Attention, consciousness, and electrical wave activity within the cortical column. Int. J. Psychophysiol. 43, 5–24.

Leckman, J.F., Bloch, M.H., Smith, M.E., Larabi, D., and Hampson, M. (2010). Neurobiological substrates of Tourette's disorder. J. Child Adolesc. Psychopharmacol. 20, 237–247.

Lee, C.C., Chou, I.C., Tsai, C.H., Wang, T.R., Li, T.C., and Tsai, F.J. (2005). Dopamine receptor D2 gene polymorphisms are associated in Taiwanese children with Tourette syndrome. Pediatr. Neurol. 33, 272–276.

León-Domínguez, U., Vela-Bueno, A., Froufé-Torres, M., and León-Carrión, J. (2013). A chronometric functional sub-network in the thalamo-cortical system regulates the flow of neural information necessary for conscious cognitive processes. Neuropsychologia 51, 1336–1349.

Liu, X., Lauer, K.K., Ward, B.D., Li, S.-J., and Hudetz, A.G. (2013). Differential effects of deep sedation with propofol on the specific and nonspecific thalamocortical systems a functional magnetic resonance imaging study. Anesthesiology 118, 59–69.

Llinás, R., Ribary, U., Contreras, D., and Pedroarena, C. (1998). The neuronal basis for consciousness. Philos. Trans. R. Soc. Lond. B. Biol. Sci. 353, 1841–1849.

Mair, W.G., Warrington, E.K., and Weiskrantz, L. (1979). Memory disorder in Korsakoff's psychosis: a neuropathological and neuropsychological investigation of two cases. Brain 102, 749–783.

Mashour, G.A. and Alkire, M.T. (2013a). Consciousness, anesthesia, and the thalamocortical system. Anesthesiology 118, 13–15.

Mashour, G.A. and Alkire, M.T. (2013b). Evolution of consciousness: Phylogeny, ontogeny, and emergence from general anesthesia. Proc. Natl. Acad. Sci. USA 110, 10357–10364.

Matsumoto, N., Minamimoto, T., Graybiel, A.M., and Kimura, M. (2001). Neurons in the thalamic CM-Pf complex supply striatal neurons with information about behaviorally significant sensory events. J. Neurophysiol. 85, 960–976.

Mayes, A.R., Meudell, P.R., Mann, D., and Pickering, A. (1988). Location of lesions in Korsakoff's syndrome: neuropsychological and neuropathological data on two patients. Cortex 24, 367–388.

McAlonan, K., Cavanaugh, J., and Wurtz, R.H. (2006). Attentional modulation of thalamic reticular neurons. J. Neurosci. 26, 4444–4450.

McKeown, M.J., Uthama, A., Abugharbieh, R., Palmer, S., Lewis, M., and Huang, X. (2008). Shape (but not volume) changes in the thalami in Parkinson disease. BMC Neurol. 8, 1–8.

Middleton, F.A. and Strick, P.L. (2000). Basal ganglia and cerebellar loops: motor and cognitive circuits. Brain Res. Brain Res. Rev. 31, 236–250.

Miller, A.M., Bansal, R., Hao, X., Sanchez-Pena, J.P., Sobel, L.J., Liu, J., Xu, D., Zhu, H., Chakravarty, M.M., Durkin, K., et al. (2010). Enlargement of thalamic nuclei in Tourette syndrome. Arch. Gen. Psychiatry 67, 955–964.

Minamimoto, T., Hori, Y., Yamanaka, K., and Kimura, M. (2014). Neural signal for counteracting pre-action bias in the centromedian thalamic nucleus. Front. Syst. Neurosci. 8, 3.

Mitchell, A.S. and Chakraborty, S. (2013). What does the mediodorsal thalamus do? Front. Syst. Neurosci. 7, 37.

Mitchell, A.S. and Gaffan, D. (2008). The magnocellular mediodorsal thalamus is necessary for memory acquisition, but not retrieval. J. Neurosci. 28, 258–263.

Mure, H., Hirano, S., Tang, C.C., Isaias, I.U., Antonini, A., Ma, Y., Dhawan, V., and Eidelberg, D. (2011). Parkinson's disease tremor-related metabolic network: characterization, progression, and treatment effects. Neuroimage 54, 1244–1253.

Newman, J., Baars, B.J., and Cho, S.-B. (1997). A neural global workspace model for conscious attention. Neural Netw. 10, 1195–1206.

Ohye, C., Higuchi, Y., Shibazaki, T., Hashimoto, T., Koyama, T., Hirai, T., Matsuda, S., Serizawa, T., Hori, T., Hayashi, M., et al. (2012). Gamma knife thalamotomy for Parkinson disease and essential tremor: a prospective multicenter study. Neurosurgery 70, 526–535; discussion 535–526.

Ostendorf, F., Liebermann, D., and Ploner, C.J. (2013). A role of the human thalamus in predicting the perceptual consequences of eye movements. Front. Syst. Neurosci. 7, 10.

Ostlund, S.B. and Balleine, B.W. (2008). Differential involvement of the basolateral amygdala and mediodorsal thalamus in instrumental action selection. J. Neurosci. 28, 4398–4405.

Pessoa, L. and Adolphs, R. (2010). Emotion processing and the amygdala: from a 'low road' to 'many roads' of evaluating biological significance. Nat. Rev. Neurosci. 11, 773–783.

Peterson, B.S., Thomas, P., Kane, M.J., Scahill, L., Zhang, H., Bronen, R., King, R.A., Leckman, J.F., and Staib, L. (2003). Basal ganglia volumes in patients with Gilles de la Tourette syndrome. Arch. Gen. Psychiatry 60, 415–424.

Poulet, J.F., Fernandez, L.M., Crochet, S., and Petersen, C.C. (2012). Thalamic control of cortical states. Nat. Neurosci. 15, 370–372.

Prevosto, V. and Sommer, M.A. (2013). Cognitive control of movement via the cerebellar-recipient thalamus. Front. Syst. Neurosci. 7, 56.

Probst-Cousin, S., Druschky, A., and Neundorfer, B. (2003). Disappearance of resting tremor after "stereotaxic" thalamic stroke. Neurology 61, 1013–1014.

Purushothaman, G., Marion, R., Li, K., and Casagrande, V.A. (2012). Gating and control of primary visual cortex by pulvinar. Nat. Neurosci. 15, 905–912.

Ranganath, C. and D'Esposito, M. (2001). Medial temporal lobe activity associated with active maintenance of novel information. Neuron 31, 865–873.

Reed, L.J., Lasserson, D., Marsden, P., Stanhope, N., Stevens, T., Bello, F., Kingsley, D., Colchester, A., and Kopelman, M.D. (2003). FDG-PET findings in the Wernicke-Korsakoff syndrome. Cortex 39, 1027–1045.

Roessner, V., Overlack, S., Schmidt-Samoa, C., Baudewig, J., Dechent, P., Rothenberger, A., and Helms, G. (2011). Increased putamen and callosal motor subregion in treatment-naive boys with Tourette syndrome indicates changes in the bihemispheric motor network. J. Child Psychol. Psychiatry 52, 306–314.

Rosenthal, D.M. (2002). How many kinds of consciousness? Conscious. Cogn. 11, 653–665.

Rotsides, J. and Mammis, A. (2013). The use of deep brain stimulation in Tourette's syndrome. Neurosurg. Focus 35, E4. Doi: 10.3171/2013.8.FOCUS13292.

Saalmann, Y.B. (2014). Intralaminar and medial thalamic influence on cortical synchrony, information transmission and cognition. Front. Syst. Neurosci. *8*, 83. Doi: 10.3389/fnsys.2014.00083.

Saalmann, Y.B. and Kastner, S. (2011). Cognitive and perceptual functions of the visual thalamus. Neuron *71*, 209–223.

Saalmann, Y.B., Pinsk, M.A., Wang, L., Li, X., and Kastner, S. (2012). Pulvinar regulates information transmission between cortical areas based on attention demand(s). Science (New York, NY) *337*, 753–756.

Sánchez-González, M.Á., García-Cabezas, M.Á., Rico, B., and Cavada, C. (2005). The primate thalamus is a key target for brain dopamine. J. Neurosci. *25*, 6076–6083.

Santamaria, J., Pujol, M., Orteu, N., Solanas, A., Cardenal, C., Santacruz, P., Chimeno, E., and Moon, P. (2000). Unilateral thalamic stroke does not decrease ipsilateral sleep spindles. Sleep *23*, 333–339.

Savage, L.M., Hall, J.M., and Resende, L.S. (2012). Translational rodent models of Korsakoff syndrome reveal the critical neuroanatomical substrates of memory dysfunction and recovery. Neuropsychol. Rev. *22*, 195–209.

Schmahmann, J.D. (2003). Vascular syndromes of the thalamus. Stroke *34*, 2264–2278.

Seth, A.K., Baars, B.J., and Edelman, D.B. (2005). Criteria for consciousness in humans and other mammals. Conscious. Cogn. *14*, 119–139.

Sherman, S.M. and Guillery, R.W. (2002). The role of the thalamus in the flow of information to the cortex. Philos. Trans. R. Soc. Lond. B. Biol. Sci. *357*, 1695–1708.

Sherman, S.M. and Guillery, R.W. (2006). Exploring the Thalamus and its Role in Cortical Function (Cambridge, MA: MIT Press).

Shimamura, A., Jernigan, T., and Squire, L. (1988). Korsakoff's syndrome: radiological (CT) findings and neuropsychological correlates. J. Neurosci. *8*, 4400–4410.

Speakman, T.J. (1963). Results of thalamotomy for Parkinson's disease. Can. Med. Assoc. J. *89*, 652–656.

Spering, M. and Carrasco, M. (2015). Acting without seeing: eye movements reveal visual processing without awareness. Trends Neurosci. *38*, 247–258.

Stein, T., Moritz, C., Quigley, M., Cordes, D., Haughton, V., and Meyerand, E. (2000). Functional connectivity in the thalamus and hippocampus studied with functional MR imaging. Am. J. Neuroradiol. *21*, 1397–1401.

Steriade, M. and Llinás, R.R. (1988). The functional states of the thalamus and the associated neuronal interplay. Physiol. Rev. *68*, 649–742.

Steriade, M., McCormick, D.A., and Sejnowski, T.J. (1993). Thalamocortical oscillations in the sleeping and aroused brain. Science *262*, 679–685.

Sunwoo, M.K., Cho, K.H., Hong, J.Y., Lee, J.E., Sohn, Y.H., and Lee, P.H. (2013). Thalamic volume and related visual recognition are associated with freezing of gait in non-demented patients with Parkinson's disease. Parkinsonism Relat. Disord. *19*, 1106–1109.

Tamietto, M. and de Gelder, B. (2010). Neural bases of the nonconscious perception of emotional signals. Nat. Rev. Neurosci. *11*, 697–709.

Tasker, R.R., Siqueira, J., Hawrylyshyn, P., and Organ, L.W. (1983). What happened to VIM thalamotomy for Parkinson's disease? Appl. Neurophysiol. *46*, 68–83.

Temel, Y., van Lankveld, J.J., Boon, P., Spincemaille, G.H., van der Linden, C., and Visser-Vandewalle, V. (2004). Deep brain stimulation of the thalamus can influence penile erection. Int. J. Impot. Res. *16*, 91–94.

Tham, W.W.P., Stevenson, R.J., and Miller, L.A. (2009). The functional role of the medio dorsal thalamic nucleus in olfaction. Brain Res. Rev. *62*, 109–126.

Theyel, B.B., Llano, D.A., and Sherman, S.M. (2010). The corticothalamocortical circuit drives higher-order cortex in the mouse. Nat. Neurosci. *13*, 84–88.

Tinuper, P., Montagna, P., Medori, R., Cortelli, P., Zucconi, M., Baruzzi, A., and Lugaresi, E. (1989). The thalamus participates in the regulation of the sleep-waking cycle. A clinicopathological study in fatal familial thalamic degeneration. Electroencephalogr. Clin. Neurophysiol. *73*, 117–123.

Tononi, G. (2004). An information integration theory of consciousness. BMC Neurosci. *5*, 42.

Tononi, G. and Edelman, G.M. (1998). Consciousness and the integration of information in the brain. Adv. Neurol. *77*, 245–280.

Urakami, Y. (2008). Relationships between sleep spindles and activities of cerebral cortex as determined by simultaneous EEG and MEG recording. J. Clin. Neurophysiol. *25*, 13–24.

Van der Werf, Y.D., Witter, M.P., Uylings, H.B., and Jolles, J. (2000). Neuropsychology of infarctions in the thalamus: a review. Neuropsychologia *38*, 613–627.

Vandewalle, V., van der Linden, C., Groenewegen, H.J., and Caemaert, J. (1999). Stereotactic treatment of Gilles de la Tourette syndrome by high frequency stimulation of thalamus. Lancet *353*, 724.

Victor, M., Adams, R.D., and Collins, G.H. (1971). The Wernicke-Korsakoff Syndrome (Philadelphia, PA: FA Davis Company).

Victor, M., Adams, R., and Collins, G. (1989). The Wernicke-Korsakoff Syndrome and Related Neurologic Disorders due to Alcoholism and Malnutrion (Philadelphia, PA: FA Davis Company).

Visser, P.J., Krabbendam, L., Verhey, F.R.J., Hofman, P.A.M., Verhoeven, W.M.A., Tuinier, S., Wester, A., Den Berg, Y.W.M.M.V., Goessens, L., Werf, Y., and Jolles, J. (1999). Brain correlates of memory dysfunction in alcoholic Korsakoff's syndrome. J. Neurol. Neurosurg. Psychiatry *67*, 774–778.

Ward, L.M. (2011). The thalamic dynamic core theory of conscious experience. Conscious. Cogn. *20*, 464–486.

Ward, L.M. (2013). The thalamus: gateway to the mind. Wiley Interdiscip. Rev. Cognitive Sci. *4*, 609–622.

Weinberger, M., Hutchison, W.D., Lozano, A.M., Hodaie, M., and Dostrovsky, J.O. (2009). Increased gamma oscillatory activity in the subthalamic nucleus during tremor in Parkinson's disease patients. J. Neurophysiol. *101*, 789–802.

Wickens, J. (1997). Basal ganglia: structure and computations. Netw. Comput. Neural Syst. *8*, R77–R109.

Wilke, M., Turchi, J., Smith, K., Mishkin, M., and Leopold, D.A. (2010). Pulvinar inactivation disrupts selection of movement plans. J. Neurosci. *30*, 8650–8659.

Wunderlich, K., Schneider, K.A., and Kastner, S. (2005). Neural correlates of binocular rivalry in the human lateral geniculate nucleus. Nat. Neurosci. *8*, 1595–1602.

Xu, W. and Südhof, T.C. (2013). A neural circuit for memory specificity and generalization. Science (New York, NY) *339*, 1290–1295.

Xuereb, J.H., Perry, R.H., Candy, J.M., Perry, E.K., Marshall, E., and Bonham, J.R. (1991). Nerve cell loss in the thalamus in Alzheimer's disease and Parkinson's disease. Brain *114*, 1363–1379.

Yamada, K., Hamasaki, T., and Kuratsu, J. (2014). Thalamic stimulation alleviates levodopa-resistant rigidity in a patient with non-Parkinson's disease parkinsonian syndrome. J. Clin. Neurosci. *21*, 882–884.

Yoneoka, Y., Takeda, N., Inoue, A., Ibuchi, Y., Kumagai, T., Sugai, T., Takeda, K., and Ueda, K. (2004). Acute Korsakoff syndrome following mammillothalamic tract infarction. Am. J. Neuroradiol. *25*, 964–968.

Zaidel, A., Arkadir, D., Israel, Z., and Bergman, H. (2009). Akineto-rigid vs. tremor syndromes in Parkinsonism. Curr. Opin. Neurol. *22*, 387–393.

Zarei, M., Patenaude, B., Damoiseaux, J., Morgese, C., Smith, S., Matthews, P.M., Barkhof, F., Rombouts, S.A., Sanz-Arigita, E., and Jenkinson, M. (2010). Combining shape and connectivity analysis: an MRI study of thalamic degeneration in Alzheimer's disease. Neuroimage *49*, 1–8.