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## The Thalamic Nexus: A Central Hub Integrating Respiration, Brain Oscillations, and Autonomic Control

Ravinder Jerath<sup>1\*</sup> and Varsha Malani<sup>2</sup>

<sup>1</sup>Charitable Medical Organization, Mind-Body and Technology Research, Augusta, GA, USA

<sup>2</sup>Masters Student Northeastern University, Boston, MA, USAj

**\*Corresponding author:** Ravinder Jerath, Professor in the pain diploma program Central University of Venezuela

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### Abstract

Historically, the thalamus has been categorized a sensory and motor relay nucleus to cortex given its positioning within the diencephalon and its connectivity; yet, this underestimates the thalamus as an interactive, integrative processing unit like the CPU for regulating communications between physiological endeavors and neurological engagement. Therefore, we hypothesize that the thalamus is a processing unit that transduces intrinsic, internal bodily rhythms at large and respiratory rhythms at small into brain rhythms for integration of physiological and neurological awareness for emotional engagement/reactive response and conscious cognizance. We support this through physical connections of anatomic connectivity including yet not limited to the thalamus' ability to process cardiorespiratory relevant information from periphery involvement and how it uses respiratory frequencies as a gating mechanism between thalamocortical neuronal firing and, thus, large scale brain dynamics that reveal brain state. We present observations through macroscopic anatomical connections from cranial vagus nerve-afferent fibers to brainstem nuclei to thalamic nuclei extending from brainstem regions to extensive cortical areas. Thereafter we develop a mechanism connection for the thalamus-as-processor functioning through the ability to regulate thalamocortical oscillations as a way to gate information, differentiate between sympathetic/para-sympathetic and voluntary/involuntary emotional responses/responses and establish a timeframe for awareness. Ultimately, we connect these findings clinically as we illustrate how thalamocortical dysrhythmia becomes a common denominator across various neurological disorders AND disorders of autonomic regulation, whilst vagus nerve stimulation and deep brain stimulation are two therapeutic approaches that target this anatomical connection to restore integrative capacity.

## Keywords

Physiological endeavors; Brain Oscillations; Autonomic Control.

## Introduction

Beyond the Relay—Thalamus as the Integrative Center of It All For years, the scientific community has defined the thalamus as the brain's "switchboard" [1,2]. According to such a highly reductionist characterization, the bilaterally symmetrical thalamic eggs positioned deep in the brain are a necessary way station for just about all sensory information/processing and motor commands—from seeing to hearing to taste and touch—that require redirection from peripheral and subcortical routes toward destination sites in the mantle cortex for effective communication and processing [3,4]. Yet while certain elements of such generalized definition are true—relaying is certainly an essential function of thalamic action—newer findings suggest an increasingly integrative definition. The thalamus is an integrating factor, a "gateway", a "conductor" that prioritizes, organizes, contextualizes for impactful impact, and fuses huge amounts of information to ultimately decide how we know what we know about our external environment and position within it [5,6,7]. Such intentionality increasingly mirrors systems neuroscience, the endeavor required to maintain stable conscious awareness in an ever-shifting environment supported by a constellation of physiological underpinnings [8,9].

At every single moment, one has to make sense of what's happening outside oneself and what's going on within—like heart rate and breathing patterns. This paper posits that there exists a master point—both anecdotally and tangibly—where this is possible—and that point is the thalamus. Its relative location in the geometric center of the brain with connective access to the entire cortical mantle through predominantly reciprocal connections [7], places it responsibly in an all-inclusive fashion across levels of perception and awareness. It internationalizes a globalized state of arousal, sleep, and consciousness [10,4]. Yet to characterize it as a "switchboard" is to belittle its clear functional importance. For example, it doesn't merely channel certain sounds—it fuses sounds together for those paying attention [11]. It doesn't send projections from cortex to thalamus; more often than not projections from cortex project onto itself through the thalamus than those projections projecting elsewhere [11,6].

This suggests an involved state-setting communication function as opposed to simply directing learned bytes of information from peripheral sources for further integration. Therefore, if thalamic functions serve as state-setting agents, then instead of just forwarding diverse bits of information which happen to be more relevant on their given path of least resistance for potential fully integrated higher-level engagement, the thalamus determines what state the cortex should be in for optimal operation based on how well it processes information relative to its most necessary functions—attention, focus, sleep, and its respective sensory modalities.

Unfortunately, when this state-setting agent malfunctions or goes offline, it either prevents any sensory compilation or renders overstimulation; such relevant dysfunction renders specific deficits attributable to non-functioning thalamic nuclei or comatose states when one no longer has access at all. But what establishes this state? This paper seeks to answer this question by suggesting that the primary mechanism by which this is accessible—to breath itself—is just as much a contributor in determining how effectively the

thalamus operates as it is a mechanism of intracortical functioning comparable to a perfectly regulated metronome for steady cadence.

## **The Architecture of Integration Thalamic Nuclei and Their Functional Circuits**

One's appreciation of the thalamus as an integrative center comes from an awareness of its internal structure. The thalamus is a paired gray matter structure of the diencephalon which is composed of nuclei (clusters) of neuronal cell bodies) with a relatively dense packing density [6]. The thalami are compartmentalized by the internal medullary lamina (Y-shaped sheet of white matter) into three main nuclear groups—the anterior, medial and lateral nuclear groups [6]. Furthermore, there are nuclei related to the thalamus closely positioned, intralaminar and midline nuclei (within the internal medullary lamina) and the thalamic reticular nucleus (TRN)—a shell of inhibitory cells that envelops the lateral part of the thalamus [6,12]. Thus, as a result of such compartmentalization, the thalamus functions in a specialized capacity which empowers it with the ability to process/release many streams of information simultaneously. Three categories of thalamic nuclei exist primarily to serve integration or relay purposes to and from the cortex and subcortex [6,13].

1. **Relay Nuclei:** This group of nuclei are classically known to investigators. They receive specific and dedicated inputs (i.e. one type of sensory input/input or motor input) and project to specific functionally relevant areas of the cerebral cortex.
2. **Association Nuclei:** This group is responsible for higher processing. They predominantly receive their inputs from the cerebral cortex (i.e. they project to the thalamus from cortical regions) and project back to more cortical "association areas" suggesting a regulatory role in integration and meaning-making across input sources, connecting multimodal processing for more higher order cognitive functions.
3. **Nonspecific Nuclei:** This is a diffuse group of nuclei which include intralaminar and midline nuclei which project to nonspecific areas throughout the entire cerebral cortex and other subcortical structures. They lend themselves to generalized functioning such as arousal, attention, and consciousness. Thus, these connections lend themselves to an understanding of how the thalamus can process information about respiration, what the brain is doing and autonomic functioning.

## **Detailed Examination of Key Nuclei**

### **Sensory relay nuclei**

The sensory relay nuclei are those nuclei which constitute the thalamus as a relay station for exteroceptive information. For example, the Ventral Posterior (VP) nucleus is the main thalamic relay for the somatosensory system. It consists of the ventral posterolateral (VPL) and ventral posteromedial (VPM) nuclei. The VPL relays non-conscious information about pain, temperature, touch, pressure, and proprioception from body to central nervous system via the spinothalamic tracts and medial lemniscus to more higher order regions. The information for face is relayed to VPM via trigeminothalamic pathways [6].

The Lateral Geniculate Nucleus (LGN) is the sole thalamic relay for vision, receiving projections from the retina via the optic tract and projecting to the primary visual cortex [6,14]. The Medial Geniculate Nucleus is the auditory relay, receiving projections from inferior colliculus of brainstem and projecting to the primary

auditory cortex of the temporal lobe [6,14]. Thus, while these nuclei are for specific modalities, they make up a relay station that only processes exogenous information from an otherwise sensitized inner environment. **Limbic and Association Nuclei** These nuclei pertain to the theme of this report because they connect sensation to emotion, cognition and autonomic regulation. The Anterior Nuclear Group (anteroventral, anteromedial, anterodorsal nuclei) are part of Papez circuit which is important for connecting emotions with memory. This nucleus receives a large input from the mammillary bodies of the hypothalamus via the mammillothalamic tract and projects to the cingulate gyrus which is a major limbic structure [6,12].

Thus, this circuit connects Papez Thalamus to circuits dedicated to true emotional processing and memory. The Mediodorsal (MD) Nucleus is arguably the most integrative nucleus of thalamus and has significant reciprocal connections with both prefrontal cortex (PFC) which houses executive function, as well as, amygdala and olfactory cortex [6,14].

Thus, MD nucleus integrates sensory experience or visceral experiences with emotional state for proper emotional regulation, planning, judgment and attention [6,14]. Midline and Intralaminar Nuclei (nucleus reuniens, paraventricular nucleus, central median-parafascicular complex [CM-Pf], central lateral [CL] nucleus) are "nonspecific systems". They receive input from many brain areas including reticular activating system of brainstem (arousal) and hypothalamus (autonomic/endocrine regulation), as well as pain tracts like spinothalamic tract [6,12]. Their diffuse projections to cortex and striatum essentially regulate general excitability of the cortex and therefore they are responsible for awareness or attention and autonomic drive [10,12].

**The Thalamic Reticular Nucleus (TRN)** The table below presents this nuclei's distinct role and connections relative to other thalamic nuclei. It is vital to distinguish TRN from all other thalamic nuclei. The TRN is a thin shell surrounding all of thalamus and it contains only GABAergic (inhibitory) neurons [6,13]. The TRN also does not project to cortex as it receives projections from cortex and other thalamic nuclei and then GABAergic (inhibitory) projections back into thalamus [6,4].

Therefore, it exists in an anatomical loop between the remainder of thalamus and cortex as thalamus' guardian. The TRN can inhibit specific thalamic nuclei for diminished or negated transmission of information while allowing projections through to reach the cortex. It serves as a "spotlight" onto information coming into and out of thalamus which gives a perspective by which thalamic information can be processed [7]. Ultimately, without TRN inhibition too much information would have free realm access to thalamus and be projected to cortex; thus, this facilitates brain rhythms and transitions through states.

	Key Afferents (Inputs)	Key Efferents (Outputs)	Primary Integrative Function
<b>Ventral Posterior Nucleus (VPL/VPM)</b>	Spinothalamic, medial lemniscus, and trigeminothalamic tracts [6].	Nucleus/Group	Relaying exteroceptive (touch, temp) and interoceptive (pain, pressure) somatic sensations for conscious perception.
<b>Mediodorsal Nucleus (MD)</b>	Amygdala, olfactory cortex, ventral pallidum, prefrontal cortex (reciprocal [6,14].	Prefrontal cortex (dorsolateral, orbitofrontal), cingulate gyrus,	Integrating sensory, visceral, and olfactory information with emotion, memory, and

		supplementary motor area [6].	executive function (attention, planning).
<b>Anterior Nuclei (AV, AM, AD)</b>	Mammillary bodies (hypothalamus) via mammillothalamic tract, hippocampus [6,12].	Cingulate gyrus, parahippocampal gyrus, prefrontal cortex (reciprocal) [6]	Key node in the Papez circuit for emotional processing, learning, and episodic memory.
<b>Midline &amp; Intralaminar Nuclei (Re, PV, CM-Pf, CL)</b>	Brainstem reticular formation, hypothalamus, periaqueductal gray, spinothalamic tract, basal ganglia [6,12].	Diffuse projections to cerebral cortex and striatum [10,6]	Regulating global cortical arousal, consciousness, attention, and providing autonomic drive.
<b>Thalamic Reticular Nucleus (TRN)</b>	Cerebral cortex, other thalamic nuclei, brainstem reticular formation [6].	Inhibitory (GABAergic) projections back to all other dorsal thalamic nuclei [6,4]	Gating and modulating all thalamocortical information flow; generating sleep rhythms and controlling attentional focus.

**Table 1:** Key Thalamic Nuclei in Respiration-Brain-Autonomic Integration.

### The ascending rhythm how cardiorespiratory signals modulate thalamic activity

Yet the brain doesn't function isolated from the rest of the world; it continuously communicates in bi-directional operation with the body. This occurs, for the most part, via the autonomic nervous system (ANS)—the primary control wiring of the body to achieve internal organismic homeostasis—which is divided into sympathetic ('fight-or-flight') and parasympathetic ('rest-and-digest') components [15]. While much of the ANS' involvement is honorary and reflexive, the brain constantly bombards the input of sensory information occurring in the viscera; therefore, it's appropriate to consider that each and every micro-moment has some virtual awareness of what's happening in the body—and therefore, such information serves an additional 'bottom-up' phenomenological awareness of data processing for adaptive governance. Thus, one of the central pathways is directed toward the thalamus. \\ Thalamic-Vagal Axis: The primary pathway of visceral sensory info occurs via vagus nerve (Cranial Nerve X). The vagus nerve contains nearly 75% of all the parasympathetic fiber nerves, making it a considerable sensory endeavor that 'vagabonds' (Latin: *vagus*) from the brainstem to innervate most of the heart, lungs and gastrointestinal tract [11]. It is the chief afferent pathway from cardiorespiratory levels and gastrointestinal levels to the Central Nervous System [11,16]. \\ Yet info transmission does not end at the periphery. Vagal afferent fibers project from the periphery back to the brainstem where they primarily synapse with Nucleus of Solitary Tract (NTS) [17,18]. The NTS serves as the first central processing unit of what is experienced sensorially in the viscera; it is an entry integrative center for autonomic information.

There is also other connected brainstem areas from which projections upward connect directly to the thalamus. There are substantial projections from these brainstem visceral nuclei to thalamic nuclei—as revealed by tracing studies—including basal aspect of ventral medial nucleus (VMB), midline thalamic nuclei and intralaminar thalamic nuclei [17]. Therefore, an anatomical superhighway exists via which cardiorespiratory information can—and does—arrive and affect thalamic centra. In addition, VNS (vagus nerve stimulation)—a therapeutic intervention for treatment of epilepsy and depression—intercepts this superhighway by sending electrical impulses via the vagus nerve back to the brain; thus, studies show that VNS can elicit potentials in the thalamus [17,24].

### Direct neuronal entrainment by bodily rhythms

The anatomical connectivity substantiating the organs to the thalamus is reinforced by overwhelming physiological support. For example, [25], only recently found—via intraoperative microelectrode recordings directly from human subjects—that a vast minority of individual neurons—about 70%—recorded from thalamic nuclei like the ventral intermedius nucleus [Vim] and ventral caudalis nucleus [Vc] and the neighboring subthalamic nucleus [STN] have their activity driven and locked to the cardiac and respiratory cycles. This is not a secondary or incidental phenomenon; rather, it's the overwhelmingly dominant type of subcortical activity located within these nuclei.

Moreover, these driving phenomena are specific. For example, certain nuclei fire faster upon inhalation and slow down thereafter; others fire less when someone inhales but then increases their firing upon exhalation. Some units become locked to systole and their firing changes during diastole [25]. Therefore, this means that the thalamus does not passively react to a heartbeat or respiration; instead, it actively responds to and acknowledges when certain phases of these actions occur. In addition, beyond this lock and specific firing in response to varying cycles, a substantial subset of these viscero-responsive units—30%—are multimodal; that is, their firing is driven by more than one endogenously-regulated phenomenon, like the heartbeat and respiratory cycle [25].

This is an important finding because it suggests that the thalamus is not merely a series of different stops through which interoceptive experiences must travel. Instead, it's an integrative hub through which information about the status of multiple organ systems comes together to form one composite image relative to what's going on in the body. This information complicates how we understand thalamic functions and interoception's role therein. While it's common knowledge that thalamus acts as a major relay station for exteroceptive senses, one could argue that it applies significantly more of its processing power to understanding where the body currently is in time and space. Ultimately, this is no minor or irrelevant function; rather, it serves as a fundamentally important component of thalamic operation. Therefore, the thalamus acts as an active transducer, transforming slow analog wavy impulses of breath and cardiac action into discrete digital firing rates which occur within specifically modulated action potentials. Such transformation is necessary to make sense of what the waves in the body mean as actual information in the brain, forming a simplified stabilized temporal signal by which cortical processing can be adjusted.

### The Language of Brain States Thalamocortical Oscillations

Brain activity is rhythmic. Different populations of neurons across the entirety of the cortex fire in synchrony to produce oscillatory activities operating at different frequencies—from slow waveforms accompanying sleep to fast, high frequency experiences with concentrated thought. Such brain waves are not a secondary byproduct of having access to the brain and functioning in it, but instead, the byproduct, a primary communicative and computational means between neurons [26]. The means by which such dissociated rhythms across the cortex are generated and integrated primarily occur from thalamic domains via thalamocortical loops, recurrently connected systems of circuitry [4,26].

### The pacemaker of the thalamocortical loop

The anatomical substrate through which these rhythms are generated and sustained exists as a reciprocated connection circuit that travels through thalamic nuclei and the overlying cortex. Thalamic neurons project to the cortex and cortical projects to the thalamic nuclei creating a reverberating loop that can produce rhythms

and sustain them over time [27]. The oscillatory patterns that emerge through these thalamocortical loops exist as the "cortex-thalamic dialect," yet how these oscillatory patterns emerge occur through differential firing characteristics at the level of individual thalamocortical neurons. Yet what is notable at the level of single thalamic neuron discharge, however, are two different but stable modes of electrophysiological firing which are determined by their gating mechanisms that specify and regulate information in relation to cognitive brain state [3,4].

1. **Tonic Firing Mode:** A thalamic neuron in tonic firing mode exists with a relatively depolarized membrane potential. It will produce a sustained train of action potentials (single spikes) relative to what it's been given as input representing relative intensity and timing. This sustained pattern is most effective for reliable processing of information. The tonic firing mode is the active/stimulated state of personality in which one is focused and aware [3,4]. The tonically firing thalamus means that the gate to the cortex is open.
2. **Burst Firing Mode:** The burst-firing mode relies upon a hyperpolarized state. Instead of producing sustained spikes or an action potential, the thalamic neuron produces high frequency burst firing (3-5 spikes at  $>100$  Hz) followed by more silent operations. This burst indicates more potentiated a change for input but represents poorly the internal temporal organization of that input. Thus, without sustained attention, the burst serves as a good lookout or alarm, although effectively it closes down the cortex for continual projection away from its attentional awareness [3,4]. The burst-firing thalamus represents typical function associated with sleep and disconnection.

Thus, the difference between these states and how the thalamus interprets overall functioning of the state comes from a transition from one mode to another. As such, this transition occurs mediated by two lines of opposing force. First, ascending activating systems that arise from within the brainstem rely upon nociceptive neurotransmitters like acetylcholine and norepinephrine to effectively depolarize the thalamic neurons such that they remain in their tonic firing state associated with awareness [4]. Conversely, an inhibitory (GABAergic) push from within the TRN serves to hyperpolarize these thalamocortical neurons into their burst-firing states. The bursting then emitted via the TRN serves to create sleep spindles (7-15 Hz oscillations), typical of non-REM sleep and stabilization of when the cortex disconnects rhythmically from external stimulus [27,4].

### **Infraslow oscillations (ISOs) and the default mode network (DMN)**

Above and beyond the rapid firing associated with sleep and wakefulness, there exists a more rudimentary rhythm: the infraslow oscillation (ISO). Below 0.1 Hz (i.e. tens of seconds to minutes periods), ISOs are often found in spontaneous brain activity, present in scalp EEG measurement as well as in blood-oxygen-level-dependent (BOLD) signal during subtle magnetic resonance imaging (fMRI) [28,29,26].

Moreover, the thalamus has been correlated as a great source of this fundamental oscillation. In vitro studies show that thalamic slices can generate powerful ISOs on their own in vitro, suggesting that the ISO is part and parcel of thalamic circuitry [28,30]. However, *in vivo*, such thalamic ISOs are not unconnected; instead, they are massively coupled to large-scale resting-state networks, the greatest being the Default Mode Network [31,29]. This network is comprised of the posterior cingulate cortex and medial prefrontal cortex and is most highly activated when one is at rest and mind-wandering, thus engaged in self-referential thought. The thalamic ISOs organize thalamocortical coupling, intralaminar activity, and thus support the speculation that

they mediate and orchestrate neuroplastic phenomena during sleep—memory consolidation [29].

Thus tonic-firing, bursting, sleep spindles and ISOs emerge not as correlates of brain state but as constitutive elements of brain state. The brain is not just awake; it's flooded with ascending modulatory systems that catapult the thalamus into a tonic-firing pattern—this is being awake, purposefully attending to the external world. In parallel, without TRN-facilitated burst firing, there is no sensory disconnection that we understand to be sleep. This raises an issue about how we control brain state that needs to be reconsidered: if this oscillation is the syntax for how the brain operates, then what master signal tells the thalamus when to use which "words" of this language?

### **The Nexus of Control Respiratory Entrainment of Thalamocortical Dynamics**

These principles converge to generate a unified brain-body model emerging from thalamus. Breathing is a continuously updated, cyclical input which is the global principle of thalamocortical organization—breathing is the temporal input that links physiological to psychological state. The thalamus gets kept in the loop about the cycle of breathing via two redundant streams of information. First, as established, a "bottom-up" afferent stream travels via vagus nerve into the NTS and then thalamic nuclei conveying the state of the lungs and airways Second, a "top-down," or efferent pathway emerges from the thalamus where breathing rhythm generators are located. The pre-Bötzinger complex in the medulla generating the basic inspiratory rhythm sends projections down to spinal motor neurons innervating diaphragm movement, but it also sends efferent copies corollary discharges up to suprathalamic structures including the central medial thalamus [32].

Thus, thalamus gets an important moment-to-moment stream of volition and its sensory outcome. Breathing as a Thalamic Global Organizer of Brain Rhythms Such rhythmic input into thalamus has global repercussions. For example, MEG data show that phase of slow respiratory rhythm (typically  $\sim$ 0.2–0.3 Hz) correlates with amplitude shifts across all canonical frequency bands apparent in human electrophysiology (delta, theta, alpha, beta, gamma) [33,32]. This is called phase-amplitude coupling which serves as a modulation force for a broad network of cortical and subcortical agencies. For example, strength of higher-order gamma oscillations—those associated with local computation/engaged thought—might reliably elevate during exhalation and decrease during inhalation [33].

Therefore, the fastest rhythms of thought are gated by the slowest of all rhythms: breathing. The Thalamic Mechanism of Respiratory Gating Yet it's thalamus that guides this organizing principle. The integrative hypothesis of this model is as follows: converging input in rhythm from afferent vagal pathways and efferent respiratory centers rhythmically modulate resting membrane potential of thalamocortical neurons. This rhythmic change relative to resting membrane potential is the cue that biases the state of firing along bipolar tonic versus burst firing states [34,4].

For example, the physiological state associated with slow controlled exhalation—increased parasympathetic (vagal) tone—may render a slightly depolarized thalamocortical neuron which supports tonic firing—for this mode opens the thalamic gate to effective transmission to cortex and represents a temporal aperture most conducive to attentional concentration and focused representational processing. In contrast, the state associated with inhalation may have a more hyperpolarized resting membrane potential that biases higher access to burst firing; this places thalamocortical functioning in a "sleeping on the job" mode—it's gainfully attentive to novel perspectives but disinterested in processing new stimuli as compared to stimuli that it has

already engaged with or concurrently engaging with. The result of this mechanism is a dynamic breath-by-breath gating of all information turning to cortex. The thalamus—and thus, access to cortex—is rhythmically confined to a more open configuration through the waves of respiration.

Not only does this determine whether something is engaged with, but when and how this engagement occurs by providing direct access to new neurophysiological relations between breathing pattern, attentional vs. perceptual orientation [25]. This elevates respiration from yet another interoceptive signal to process to the status of the brain's intrinsic metronome. It has predictable, consistent and stable temporal signal that provides scaffolding by which newer and faster cognitive functions are built upon. By creating high windows of excitability that are phase-locked consistently and repeatedly across cortical regions corresponding to breathing patterns, this thalamic system may resolve a key "binding problem" in neuroscience—not just binding spatial features together for coherent object representation but binding timely perception-action cycles together for coherent moments within intentional experience. This conclusively explains why when information is bound together across simultaneously relevant time frames—such as memory retrieval or reaction times—it can be profoundly contingent on one's place in breathing cycles [35]. Breathing—and through thalamus—creates a fundamental temporal architecture for conscious cognition.

### **The Affective Loop Thalamic Integration of Emotion and Autonomic Output**

Human beings don't just think or feel. They exist, essentially, as emotional creatures. While the thalamus relays information between various points for best sensorimotor integration and interoception, it's one part of many requisite components for emotional generation and subsequent, autonomic response. The thalamus stands at a crossroads where information—dissociated sensory data—can travel down common paths of intersection for immediate reflexive emotional response or, learned, conscious emotional regulation. The Thalamo-Amygdala "Low Road": A Fast Track to Generate Emotion One of the most important pathways to emotion generation and processing occurs via a monosynaptic pathway between the sensory thalamic nuclei and amygdala, an emotion generation and processing nucleus of the limbic system with a central nucleus, basolateral nucleus, medial nucleus among others, responsible for fear and emotion association [36]. Thus, this thalamo-amygdala connection is the "low road" of emotional awareness, a fast, almost low-res understanding of the world around it.

For example, when something bad may happen—a sound of thunder—the amygdala can receive information quicker than the auditory cortex [36]. The auditory thalamus (MGN), for example, can send an impulse into the amygdala before it can grasp the sound fully—before it travels to the auditory cortex and back—to give an almost anticipated, yet quick-but-effective, defensively cautious response. The central nucleus of the amygdala sends fibers to the hypothalamus and brainstem autonomic areas to mediate general "fight-or-flight" response to increased heart rate, blood pressure and respiration [36,37]. Thus, this pathway offers speediness for emotional awareness over authenticity. Simultaneously with the low road—and the thalamus, however—the high road is paved for emotional processing. Thalamo-Cortico-Amygdala Generation and Regulation Simultaneously with the low road, however, emerges the "high road" of emotional processing relative to cognition.

The thalamus transmits sensory output to the associated primary sensory cortex (auditory cortex, for example) where it can then be more thoroughly contextualized with more data through more complicated processing [36]. Thus, information travels back to association cortices and prefrontal cortices (PFC) so the

stimulus can be appreciated under a larger umbrella. Thus, a slower more deliberate process allows top-down regulation of initial emotional responses. Since the thalamus operates with MD nucleus also associated with these functions, it becomes clear how simultaneous operations occur interconnectedly [6,12]. The Mediodorsal (MD) nucleus of the thalamus and PFC create a reciprocal loop which allows for such regulation [12]. The MD nucleus receives the information from the amygdala and other limbic components relative to emotion-charged events and sends them to the PFC for awareness to consideration and decision making/planning for the future [6,37]. The PFC can then convey inhibitory signals to the amygdala—typically this same thalamic route—to tone down an inappropriate or overstimulated fear response [35].

Thus, without this circuit for critical awareness relative to engaging with motion-response immediacy would allow everyone an automatic negative reaction to something scary without means for higher reflection and overarching control. The Insula and Conscious Sensation Finally, the last aspect of the affective loop is conscious awareness of one's internal states facilitated largely through the insula [19]. For example, when one has "butterflies" in their stomach, it's not merely metaphorical from nervousness but literally feeling what's happening within. Part of this development comes through interoceptive sensation—pain/temperature/pressure/visceral VPM and other nuclei—being relayed from thalamus to insula's posterior [6,19].

This is part of a thalamo-insular pathway that generates awareness from autonomic responses and then subjective experienced emotion. Thus, the thalamus not only serves as mediator for reflex and regulation but generation as well. For example, when it receives sensory experience that could reflexively activate emotional response, it does both simultaneously. It creates a fast reflexive autonomic response via "low road" to act on message and then sets up gradual understanding via "high road". It doesn't stop there, however, if there's generated flagging awareness—or interoception from second part of affective loop—about it. Whether someone determines it's appropriate or not then impacts both emotional output and subsequent integration of emotively+cognitively perceived response nearly regardless if it's challenged autonomically first or after emotional regulation subsequently assessed.

However, what biases action over assessment depends not upon reliability but instead where the thalamus is at its own regard. If breath is quickened and shallow as anxiety or high arousal has emerged—whereas before it was situated steadily in awareness—it could help facilitate speedier intension through thalamoamygdala route but if breath remains slowed and deep it might give benefit more toward proactive/top-down assessment through thalamo-cortical route. But since it's active all the time—and thus mediating all affective experience—it breathes—and thus across all emotional experience at its center of control.

## Functional and Clinical Perspectives

The thalamic model of respiration, oscillations and autonomic involvement stands as a convincing organizing method for healthy physiology, clinical disorder origins and treatment responses. It substantiates a neurophysiological meaning of millennial endeavors from breath work to meditation and the pathophysiology of thalamocortical circuit dysrhythmias. Breath Work from Pranayama to Neurology: A Breath Work Model Mind-body interventions from pranayama (yogic breathing) to mindfulness meditation have culturally existed for generations across nations with emotive management and anxiety reduction as primary factors [38,39,40].

The above organizing model substantiates this capacity. Breath mastery—volitional, slow, deep breathing—engages the vagal-thalamic axis. Breath mastery is volitional; thus, it heightens vagal afferent traffic to the nucleus tractus solitarius (NTS) and subsequently the thalamus creating a parasympathetic conversion of autonomic regulation [40,39]. Such powerful oscillatory input dominates thalamocortical oscillation governing determinants. Slow breathing fosters hypothesized tonic firing of thalamic neurons, increasing amplitude at the "high road" routing governance between thalamus, prefrontal cortex (PFC) and amygdala [35,39]. Therefore, when individuals slow their breathing, the PFC has increased top-down governance over the amygdala. This translates subjectively into reduced anxiety and a well-regulated autonomic state [39].

Essentially, breath work provides access to the thalamus' ability to set the state so that intentional breath aligns that capacity with psychological needs. Thalamic Dysrhythmias and Autonomic Dysfunction When the thalamic pacemaker is disturbed or become dysrhythmic, dysfunction transpires that can prompt deviant sensory awareness or consciousness but more challenging issues that dictate how the body functions beyond neurological peripherally. As such, many neurological and psychiatric disorders can be explored through thalamocortical dysrhythmia phenomena [41].

**Fatal Familial Insomnia.** An example of catastrophic thalamic failure occurs as this genetic prion disease. The increase of prion proteins creates a dysfunction cascade—especially in the mediodorsal and anterior thalamic nuclei—which creates an irreversible sleep-wake cycle and excessive autonomic hyperactivity—most critically but not exclusively treatment refractory insomnia, hypertension, hyperhidrosis [42]. Such paths of dysfunction clarify why the thalamus is necessary for sleep rhythms and thalamically produced stabilization of autonomic function.

**Epilepsy and Migraine.** The thalamus is crucially involved in seizures disorders and migraine. The thalamic reticular nucleus (TRN) has vast inhibitory power over thalamic relays; thus, it may be the ictus behind anecdotal generalized spike-wave discharges characteristic of absence epilepsy [13]. For migraine pathophysiology, abnormally low frequency oscillations in thalamocortical networks are supposed to contribute to light (photophobia) and sound sensitivity (phonophobia) degrees in headaches which implies dysfunctioning sensory thalamic gating [5,41].

**Dyspnea Air Hunger.** Breathlessness or "air hunger" emerges as a painful symptom across the dyspnea cardiorespiratory disease spectrum. For example, in experimental studies on air hunger, deep brain stimulation (DBS) targeting motor thalamus (ventral intermediate nucleus, VIM) dramatically reduces elicited air hunger [43]. Thus, research has concluded that a centralized node in hierarchical circuitry mediating air hunger is the thalamus processing the gap between respiratory perception and urge feedback into an undesirable conscious phenomenon; thus, air hunger can be lessened when its sensory gating ability is targeted by thalamic DBS.

## **Therapeutic Neuromodulation: Targeting the Thalamic Nexus**

The thalamus' central role in such disease processes substantiates it as a neuromodulatory target. **Vagus Nerve Stimulation (VNS):** The VNS is an FDA-approved intervention for drug-refractory epilepsy and drug-refractory depression; clinically, VNS seems to have its interventionary effect via takeover of the vagal-thalamic pathway [24]. This implantable device provides rhythmic electrical stimulation to the vagus nerve

and creates an averted homeostatic signal to the nucleus tractus solitarius (NTS)—a region of the brain that shares great connection with the thalamus—and thus to the thalamus proper. The clinical literature proves that such modulation of metabolism through VNS alters thalamic absorption and thalamocortical functional connectivity relative to the limbic system and DMN, stabilizing and restoring pathological rhythms of the brain so that interconnectedness, in otherwise disrhythmic response, may be reinforced [44,45].

**Deep Brain Stimulation (DBS):** This technique requires surgical implantation of the electrode(s) within specific cerebral targets. DBS is indicated for movement disorders, as well—VIM of thalamic motor nuclei is the DBS target—and has been examined in disorders of consciousness via intralaminar nuclei targeting [10,42]. Both therapeutic modalities attempt high-frequency electrical stimulation as a "jab" to override or "jam" disrhythmic impulses traveling the thalamocortical circuit to reset a more stabilized conversation in response. Such clinical application shows how important the thalamus is to central pathology. Therefore, making the thalamus an integrative hub better clarifies pathophysiology for various conditions while also allowing successful rehabilitation of the rhythm of the conversation that matters most—mind and body.

## Conclusion

### The thalamus as a conscious sentinel

Thus, we must revise our definition of the thalamus considering these findings: it is more than a grossly oversimplified vestibular regulator; it is a dynamic, computational hometown of ourselves as sentient beings at the intersection of body and mind. As the master conductor for brain dynamics operating on a globalized function, the thalamus is what best asserts itself as the integrative entity between the two worlds—from its highly nuanced nuclear composition to its highly interconnected reciprocal projections to cortical regions as well as its position in regulating global states of brain functioning.

Ultimately, this thesis seeks to explain how the thalamus acts as the master conductor for brain-wide dynamics employing respiration—the most ubiquitous, automatic beat we have—that serves as a master clock signal. What we do, we do on a breath—by—breath basis, and in so doing, the thalamus is continually fed surrounding streams of rhythmic information about what's going on in our bodies projected upon it via afferent channels of sensory modalities as well as efferent copies of motor outputs tasked with implementation. It takes this dynamic, changing rhythm and renders it into a discrete, digitized currency of healthy neuronal firing pattern. Thus, the thalamus becomes both a regulator and responsive component for how fast its neurons fire via rhythmic gating to position itself as a proactive means of organization sourced from this metronomic function to organize thalamocortical oscillations to regulate state of arousal, attentional capacity, and perceptual consciousness—all of which exist in temporally bound nowhere to go but here modalities of information exchange.

All information exchange must find somewhere to go, and thus relative awareness travels across thalamic nuclei loops—some faster than others compared to slow relative engagement for valenced emotional response or conscious response appraisal and access to regulation—and thus everything the body senses must integrate with everything the mind feels. Yet it is not merely an option; as suggested through thalamocortical dysrhythmias, failure to integrate makes individuals vulnerable to disruptive multimodal conditions/AUT. Yet careful calibrations—whether mindfulness based breathing exercises or implantation of electrodes in the thalamic cavity seeking a new normative coupling between respiration and thalamocortical

oscillations—allow such individuals to sense a new found comfort. Longitudinal studies are needed to help tease apart this system.

The next step would be high-resolution human neuroimaging to determine precise phase relationships between breath, areas of thalamic nuclei and their corresponding cortical networks as well as further determinations about their modulating neurochemicals that help set thalamic state. Ultimately, however, in conjunction with theoretical studies and quality of life enhancement based on increased intervention helps not only further the theoretical approach to consciousness research but create new and non-invasive approaches for neuromodulatory intervention for said nexus to help mind with body rhythms to heal brain. The thalamus is no longer just a gatekeeper; it's the master conductor of the conscious orchestra with breath rhythms blended with body parts, body attributes and body functions creating the symphony that is the mind.

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