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Central Pain Syndrome: Etiological Perspectives from the 3D Default Space Model of Consciousness

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Abstract

In this article, the mechanisms of central pain syndrome (CPS) are examined for the purpose of gaining insight into how a unified conscious experience arises from brain and body interaction. We provide a novel etiology for CPS via implementation of the previously proposed 3D Default Space (3DDS) consciousness model in which consciousness and body schema arise when afferent information is processed by corticothalamic feedback loops and integrated via the thalamus. Further, we propose the mechanisms by which CPS represents deficits in dynamic interactions between afferent and efferent signaling. Modern hypotheses of CPS suggest roles for maladaptive neuroplasticity, a deafferentated somatosensory cortex and/or thalamus, and reorganization along the sensory pathways of the spinothalamic tract in the pathogenesis of the painful sensations. We propose that CPS arises when painful sensory signals originating along the maladapted and/or dysfunctional spinothalamic tract become accentuated by the dominant top down mechanisms of the brain.

Keywords

Central Pain Syndrome, 3D Default Space, Thalamus, Consciousness, Spinothalamic Tract

1. Introduction

The nature of human consciousness has been debated and contemplated by philosophers, scientists, theologians, and mystics, yet the basis for its existence has remained a mystery. Human experience consists of sensory information from

outside the body as well as internal bodily information, including the body schema, a representation of the body shape and space [1]; thus, we define consciousness as the simple awareness of self and experience. The vast amount of afferent sensory input to the body must be directed to appropriate cortical areas, and is done so by the thalamus [2]. Malfunctions in thalamic routing/signaling have been shown previously to play a significant role in both central pain syndrome [3] and in the infrastructure of consciousness, by coordinating feedforward and feedback traffic with cortical areas and peripheral organs [4].

The thalamus integrates both peripheral and central neural traffic, effectively acting as the interface for bottom-up and top-down processing [5]. The dynamic oscillatory activity that forms the foundation of consciousness occurs in the gamma frequency range [6], and previous examinations of neurological disorders from the perspective of the 3DDS model suggest that failure of thalamic integration (*i.e.* afferent/efferent synchrony within this range of frequencies) may form the neurological basis for disorders such as phantom limb syndrome and contralateral neglect [7] [8]. In the present article, we argue that disruption of normal afferent/efferent oscillatory synchronization can lead to sensory experiences characteristic of central pain, and may in fact lend insights into the neurological basis of consciousness. Through this elucidation, we provide a novel look into how the top-down domination of sensory perception can lead to altered sensory experiences such as experienced in CPS.

2. 3D Default Space

The hypotheses proposed by Jerath *et al.* (2014, 2015) characterize a unique perspective on the nature of disorders with debated origin (including phantom limb syndrome and contralateral neglect) using a dynamic model of mind and consciousness [the 3D Default Space model (3DDS)]. The 3DDS model proposes that a 3D internal neural space is maintained and supplemented, or "filled in" with sensory information. The model further proposes that this 3D default space is the fundamental structure of consciousness and that all experience is contained within it. In previous work, we have proposed that the thalamus acts as the central hub of consciousness as it assists in processing sensory information in thalamocortical feedback loops, integrating this information into the 3D space [7] [9] (**Figure 1**).

The 3DDS model contends that the brain simulates the external physical world in an internal 3D space, which arises as a conscious experience [9] [10]. This is not only demonstrated by Contralateral Neglect and Phantom Limb syndromes, but by illusions that the average person can experience. These conditions are failures of the mind to correctly simulate the external world and are key in elucidating mechanisms of cognition [11]. In the case of Contralateral Neglect Syndrome, the external space on one side of the person's body fails to be reproduced in internal space, and in Phantom Limb Syndrome, false limbs are experienced that do not truly exist in external reality [12].

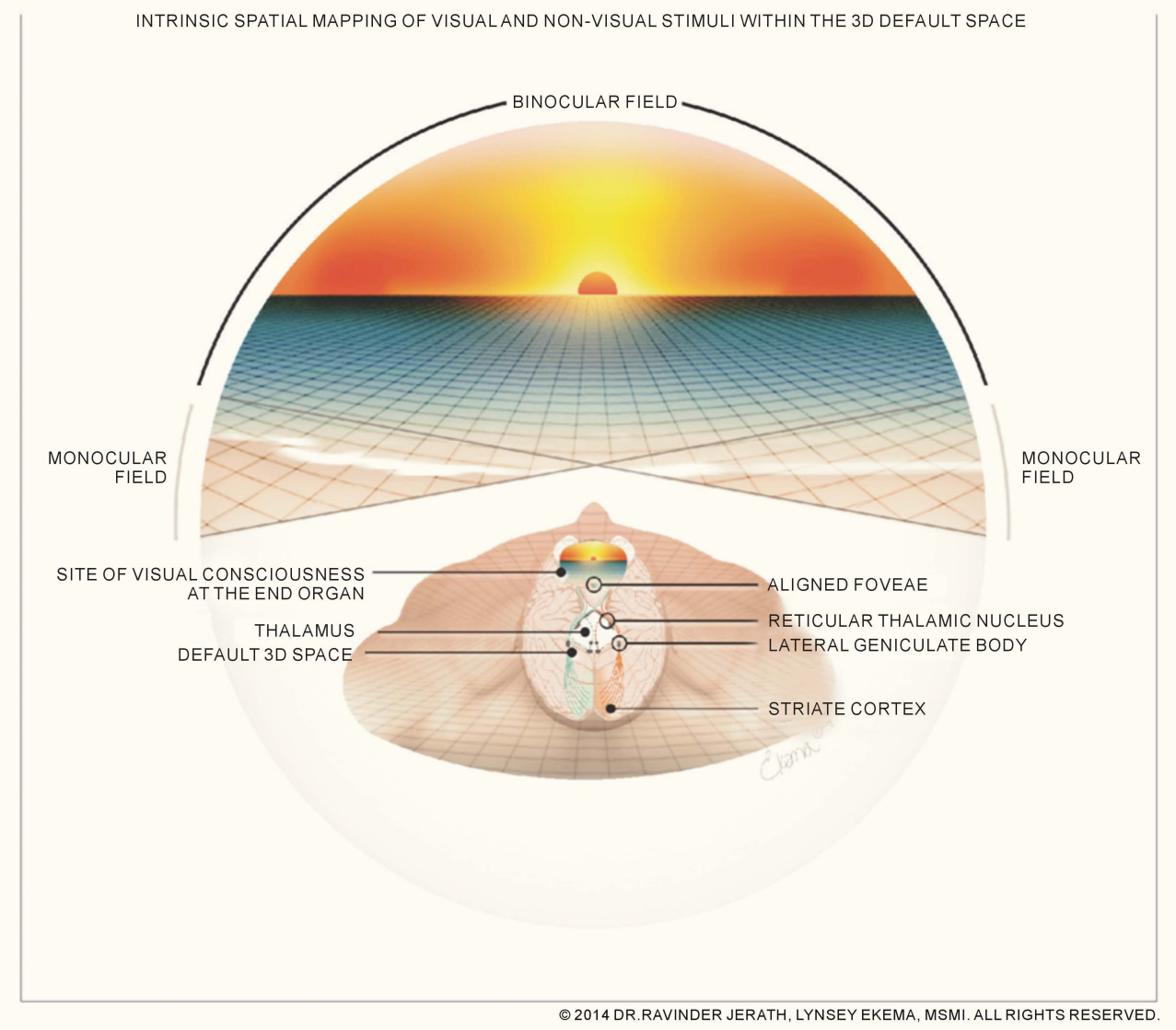

Figure 1. Mapping of sensory stimuli in the default space. This image illustrates how visual and non-visual sensation is mapped instantly and seamlessly within the internal 3D default space of the mind. Images that fall onto the fovea are processed along the visual pathways and monocular images converge in the visual cortex. These images are processed within corticothalamic feedback loops and integrated with other sensory stimuli into the default space by the thalamus. The result is a unified experience founded in a three-dimensional, internal space. Final processed sensation is experienced at the sensory organ of origin which allows incoming sensory stimuli to "fall into place" where it is expected [9].

3. Central Pain: History and Characteristics

CPS is a debilitating and chronic pain condition that results from a lesion or dysfunction within the central nervous system (CNS) [13]. The symptoms of central pain were first described as early as 1810, though the full concept of the syndrome was not developed until 1891. Through examining lesions in autopsy, Ludwig Edinger concluded that the pain that had been experienced by these patients was likely due to contact of the injured tissue with the sensory path of the CNS [3]. Subsequently, in 1906 a subset of CPS, found to involve in the thalamus, was described as "Thalamic Syndrome" [14], and Dejerine-Roussy Syn-

drome (now known as thalamic pain syndrome) was discovered to result from a stroke or tumor, damaging the sensory nuclei of the thalamus [15]. Today, the aforementioned syndrome terminology is medically obsolete, and simply "brain-central pain" and "cord-central pain" are used to differentiate the type and origin of central pain.

Central pain is characterized by chronic, excruciating pain, not in the damaged sensory tracts, but rather, in the areas associated with the damage on the contralateral side of the body [16] [17]. The experienced sensations consist mostly of pain; however, other sensations can include coldness, prickling, tingling, hyperpathia (increased sensitivity to light touch), sensory time lags, and altered spatial awareness and body schema [3] [18]. Painful symptoms include dysesthesia (acute pain sensations) and allodynia (pain from stimuli that normally does not cause pain), that can be elicited from a variety of stimuli including movement, temperature changes, stress, and even music [3] [15] [19] [20]. Delusions and tactile hallucinations such as Delusional Parasitosis have also been reported [21].

The majority of patients with CPS have suffered a spinal cord injury, though patients with multiple sclerosis or stroke also develop the condition [22]. Conventional medication has not been completely successful in ameliorating the pain of CPS [13] [18]; however, ablation or electrical stimulation of damaged thalamic tissue has been reported to provide some pain relief in those with thalamic damage [23] [24]. Pharmaceutical medications that have been successful in suppressing pain are those that reduce the hyperexcitability of neurons [25].

4. Somatosensory Pathway Anatomy and CPS Lesion Sites

In order to describe the mechanism and development of CPS, we explore the anatomy of the spinothalamic tract, as damage along this tract is the most commonly proposed cause of central pain [26]. The spinothalamic tract is a primary somatosensory pathway of the body and is responsible for mediating the conscious perception of pain [27]. The neurons of the spinothalamic tract are organized in 3 levels: 1) The first order neurons transmit sensory information from peripheral sensory structures to the dorsal horn of the spinal cord, 2) The second order neurons begin at the dorsal horn and contralaterally ascend to the thalamus, and 3) The third order neurons ascend ipsilaterally from the thalamus to terminate in the somatosensory cortex [27]. Specifically, it is the second order neurons of the spinothalamic tract that terminate in the ventral posterior inferior (VPI), ventral posterior lateral (VPL), and intralaminar nuclei of the thalamus [27]. These sites are the most commonly referenced thalamic areas that, when lesioned, lead to CPS.

Lesions anywhere along the spinothalamic tract or its cortical projections may lead to CPS, with area-specific damage accounting for the different symptoms of CPS [28]. Electrophysiological measurements in CPS patients indicate pathological alteration of thalamic circuits [29], and thalamic EEG recordings of syn-

drome patients have revealed abnormal activity in the form of excessive delta slow waves [24]. The sensory nuclei of the thalamus relay information in afferent/efferent pathways between the body and cortex, and are also involved in suppressing irrelevant information [2]. Given that the VPI and VPL nuclei are the thalamic terminal sites of the spinothalamic tract, they are thought to be crucial in the development of thalamic CPS [21]. In non-CPS individuals, neurons in the VPL display regular alpha waves at 10 Hz, whereas the neurons of the VPL in CPS patients fire brief bursts of high frequency action potentials, particularly in VPL regions that correspond to the painful body sites [29]. Additionally, lesions of spinothalamic tract can lead to the "deafferentation" of relay cells of the VPL and VPI seen in individuals with CPS [17]. CPS may also arise from damage to the thalamic reticular nucleus [30] which directs neural circuits required for object attention, and regulates corticothalamic feedback and feed-forward loops within the body [31].

5. Neuroplasticity and CNS Damage

Neuroplasticity is the brain's lifelong capacity to adapt to new conditions and learn new abilities from experience, through adaptive changes at both structural and functional levels [32]. This dynamic ability to change allows the brain to adjust its complex "circuitry" to a wide range of environmental pressures, including normal tasks such as learning, or in response to brain damage [33]. The nervous system's capacity to repair and reorganize after damage may explain how disruptions in the spinothalamic tract lead to characteristic symptoms of CPS. Neuronal plasticity indicates that the brain is not a hierarchy of individual modules, but is rather a set of dynamic, complex interconnected networks that maintain a neural homeostasis [34]. Several neurophysiological mechanisms may drive neuroplastic change in the CNS, including neuromodulation of synaptic excitability, reorganization of cortical sites, and the creation of new neurons [34]. Only in recent years has neuroplasticity been accepted by the scientific community as occurring in adults in response to brain damage, which can result in recovery of function [35]. Previously, the adult brain was thought to be somewhat fixed, with changes only happening through cortical development [32].

The central nervous system's astounding ability to compensate for injury through plasticity often results in recovery or improvement in CNS-damaged individuals [33]; in fact, rehabilitation programs can drive reorganization of cerebral networks often leading to functional improvements and recovery of function [34]. In the case of traumatic brain injury, damage to the sensorimotor cortex and associated disability can be overcome through use and development of compensatory motor patterns in nearby cortical areas [35]. A maladaptive role of neuroplasticity can occur, however, due to the improper rerouting of axons to unusual locations, maintenance of homeostasis, and reorganization of cortical sites [17] [36]. These spontaneous post-injury regenerative events can occur and

last for several months during the time when the injured brain is particularly malleable. The CNS areas surrounding a damaged area are inhibited from growth for approximately one month post-injury, before going through "waves" of growth promotion [35]. This temporal pattern dovetails the time delay in the development of central pain, with a third of thalamic stroke patients developing pain between 1 and 3 months, and 11% of patients developing pain after a full year [28]. Recent studies indicate that plastic alterations may also be induced in peripheral nerve terminals, enhancing the magnitude of nociception and therefore likely a factor in the development of persistent pain [27].

6. Current Hypotheses on the Etiology of Central Pain

The origins of the abnormal sensations and pain associated with CPS are not completely understood, but etiological theories do exist. Many authors have proposed the syndrome to be the result of abnormal thalamic activity due to a lack of afferent input [17] [37]. Other hypotheses suggest the condition results from damaged corticothalamic and/or spinothalamic networks, and other common explanations include maladaptive neuroplasticity as a source [17] [37]. Substantial thalamic damage can lead to sensory nerves randomly firing strong signals, which, if persistent, have the potential to release toxic levels of neurotransmitters [38]. These toxic levels may cause inactivated, nearby pain receptors to begin to fire as well [18]. Human experiments have shown that thalamic neuron misfiring and associated thalamocortical dysrhythmia is a likely source for neuropathic pain [39]. Moreover, disruption of modulatory function and gate control through thalamic damage is also an often cited mechanism for central pain [18].

Maladaptive plasticity is often cited as a cause of CPS due to the time delay in symptom development. Wang and Thompson (2008) assert the role of homeostatic plasticity in the thalamus as a likely source of CPS. Their hypothesis of homeostatic maintenance and post-lesion thalamic hyperexcitability was supported experimentally in spinal-lesioned rats. Additionally, in terms of the neurophysiological mechanism, they propose that compensatory thalamic hyperexcitability results from plastic changes in thalamic neurons and partial deafferentation over time. This, in turn, leads to an increased gain of somesthetic sensory relay function to the primary sensory cortices, and the heavy afferent signaling now reaching these sensory cortices is mistakenly perceived as painful stimuli [17]. Another modern hypothesis, attributing the development of CPS to maladaptive plasticity, adds to the previous assertion by suggesting that similar hyperexcitability develops in the cortical neurons due to deafferentation resulting from spinothalamic disruption. This hyperexcitability along with cortical reorganization is proposed to lead to the induction of spontaneous pain [36]. The reorganization of deafferentated cortex may "lock" the thalamus into the proposed hyperexcited state, resulting in disruptions in the synchrony of the afflicted corticothalamic loop [3]. Additionally, it has been suggested that the resulting abnor-

mal increases in the activity of the primary somatosensory cortex may underlie the painful symptoms of CPS [13], as this cortical region has been shown to encode stimulus intensity [40] and its nociceptive processing is somatically mapped [41].

We add to the current hypotheses regarding central pain by applying the 3DDS model to the current ideology revolving around CPS. We propose that, depending on the patient, various mechanisms may lead to CPS, although the majority of cases are due to the failure to suppress and properly process sensory information due to deafferentation and neuroplastic maladaptations. This proposition is based on modern theories of the development of CPS; however, we expand on these hypotheses by applying the 3DDS model in order to create a complete etiology and description of the mechanism. In order to thoroughly explain our hypothesis, we explore the healthy vs. CPS states of the human CNS through the lens of the model.

7. 3DDS Model and the Healthy State

According to the 3DDS model, healthy people are able to maintain an internal, near real time experience of the external world due to fast feedback/feedforward oscillatory loops between the body and cortex, coordinated by the thalamus [7] [9].

A normal sensory experience begins with the stimulation of the sensory organ, resulting in transduction of sensory information that travels along afferent pathways to the thalamus [2]. Here, it is directed to the appropriate cortical areas for processing [15]. The modern consensus is that brain-centric deduction of the processed sensory information is experienced by consciousness in the higher cognitive brain centers (**Figure 2**). The 3DDS model is not brain-centric and asserts that: 1) the processed information is then projected back to the original sensory organ by the thalamus on the efferent pathway via the fast oscillatory membrane potential activity; 2) this informational loop creates a synchronization of the afferent sensory information with the processed efferent; 3) the near real-time synchronization creates the conscious experience of that respective sensory organ by way of the membrane potential oscillations, with the oscillations of the every cell in the body resulting a unified conscious experience [10]. The oscillations between each sensory organ and corresponding cortical site are not isolated, but in sync with all of the other oscillatory activity throughout the nervous system and body [10].

The 3DDS model proposes that in the healthy neural system, new sensory information is integrated into the pre-existing 3D neural space maintained by corticothalamic oscillations. This 3D internal space contains what the mind simulates as the external world, and is constantly updated with new sensory information [9]. In the tactile sense, information is generated and perceived by a variety of sensory receptors including nociceptors, mechanoreceptors, and thermoreceptors that measure pain, stretching, and temperature respectively [42]. We

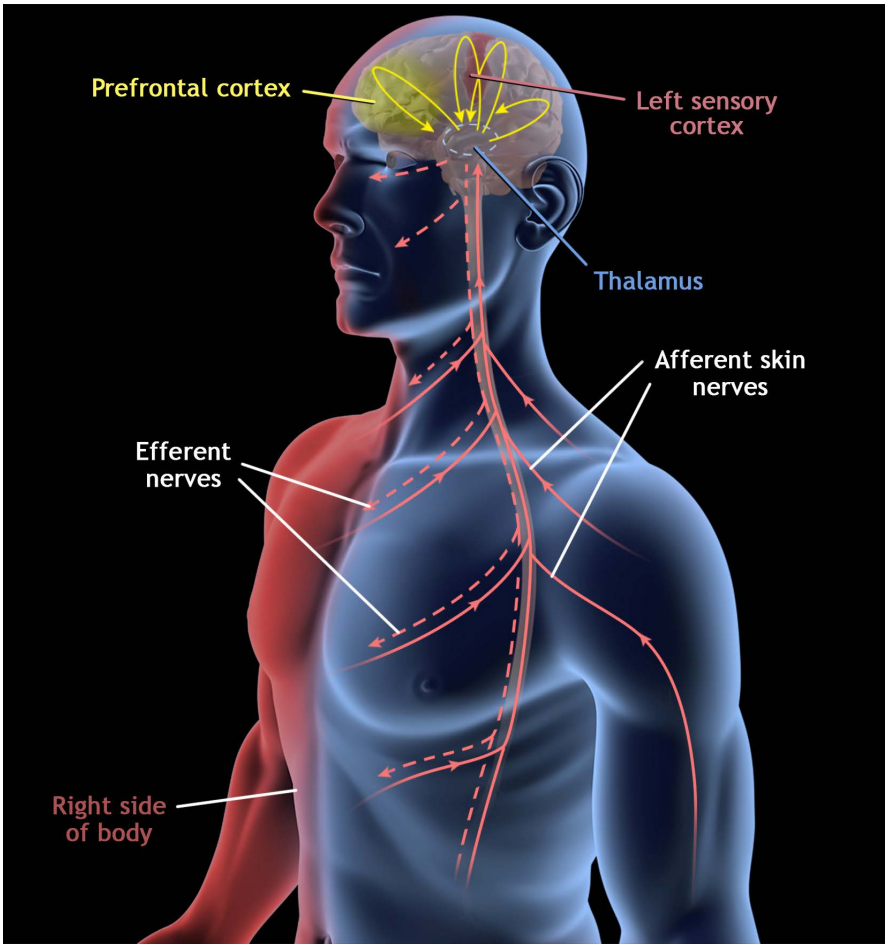

Figure 2. Model of the modern scientific view of sensation. This diagram illustrates the anatomy of the modern, brain-centric, scientific view of sensory information flow. Afferent sensory signals are balanced with homeostatic efferent information that can modulate sensory receptors. The afferent sensory stimuli are passed to cortical areas by the thalamus, where information is passed up a hierarchy of cognitive modules, ultimately leading to the conscious experience of sensory information. In this model, a balance between top-down and bottom-up information is achieved, neither showing dominance to each sensory system.

propose each of these receptor types oscillate at different frequencies on pathways directed by the sensory thalamic nuclei. The afferent and efferent oscillatory activity would not be balanced or coordinated without direction from the reticular formation [31], which is why lesions of this region may result in CPS. When observing CPS mechanisms in the context of the 3DDS model, it is important to note the dominance of top-down sensory processing in healthy as well injured patients.

The pre-existing oscillatory synchronization between the peripheral receptors and respective cortical sites (as coordinated by the thalamus) facilitates peripheral receptor preparation in terms of touch, pain, temperature, or other stimuli through top-down processes [43]. This allows the expected stimulation to "fall into place" into the 3DDS so it can be experienced in real time. The infor-

mation required to prepare the peripheral receptors is provided by the top-down dominated oscillatory synchronization between the peripheral receptors and the "adjacent" involved cortical areas [44]. This continuously maintained top-down projection of external space is consciously experienced as it is created, via "magnification" of the afferent, bottom-up, sensory signals processed under the influence of higher cognitive functions (such as attention and memory; **Figure 3**) [44]. Although the afferent signals are processed by the brain, they do not rise to conscious experience until after processing, at which point they are projected back to the original sensory receptors. The sensory receptors remain synchronized with cortical units via gamma wave oscillatory activity [45], which is

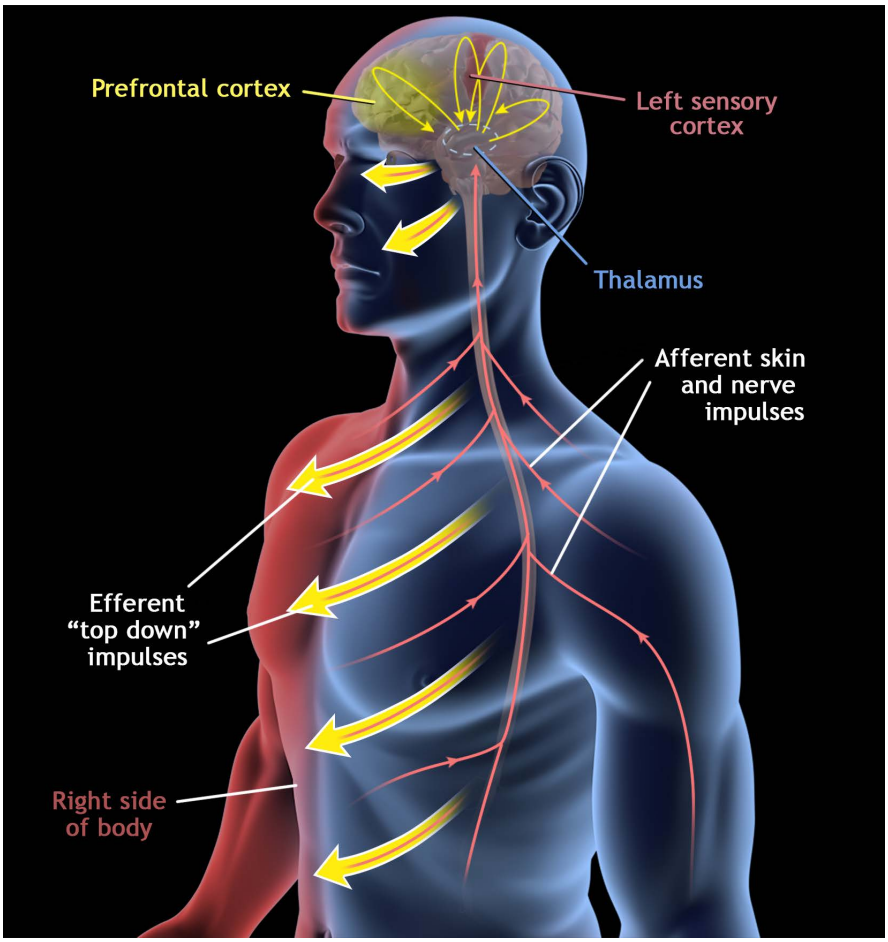

Figure 3. 3DDS model of sensation. This diagram illustrates the 3DDS model of sensory experience in which synchronization is maintained between the peripheral sensory organs and cortical areas. In the healthy individual, oscillatory synchronization is coordinated by the thalamus, and maintains a near real-time experience of each sensory modality. Synchronization of all oscillatory activity throughout the body is integrated by the thalamus to form a unified experience of the external world. The 3DDS model proposes that the sensory receptors receive dominant top-down efferent impulses from the cortex via the membrane potential oscillations. Subsequent synchronization between the sensory receptors and cortex (via the thalamus) creates awareness of the sensory information at the site of the receptors, thus leading to the potential for top-down input to influence new afferent stimuli.

driven in part by thalamic input to layer 5 neocortical pyramidal neurons [46]. We propose that, although afferent sensory information is normal in those with CPS, CNS participation in the processed efferent sensory impulses may disrupt normal gamma synchrony, and bring the abnormalities of the damaged neural network into the efferent sensory stream.

8. Hypothesis: Mechanism of Syndrome State and the 3DDS Model

In patients with CPS who have had an injury along the spinothalamic tract, there has been damage to the spine, thalamus, or cortex; however, signals from uninjured peripheral sensory receptors feeding into the lesioned areas continue [3] [28] [37]. Most often, pain and uncomfortable sensations of this syndrome take weeks, months, and even years to present [4] [19]. We agree with the modern theory that the time delay in symptom development is due to the nature of neuroplasticity of the brain [17] [18] [36]. Immediately after the development of a lesion along the spinothalamic tract, numbness is most often felt [12]. The numbness results from the absence of tactile signals reaching the brain due to deafferentation, similar to the effects produced by a large dose of local anesthetic [47]. Development of painful symptoms are likely a result of maladaptive plasticity, [17] and we build upon this modern assumption using the 3DDS model in order to elucidate the potential etiology of CPS.

Neuroplasticity is normally a beneficial brain characteristic [48], but in the case of CPS development it is maladaptive [17]. There are multiple proposed mechanisms of plastic change that could lead to CPS, including homeostatic plasticity, CNS reorganization, and the development of new network connections. These plastic mechanisms involve incessant afferent sensory information from the uninjured peripheral receptors and their deafferentated thalamic and cortical counterparts, which causes the formation of a painfully dysfunctional network over time [47]. Damage to the thalamus may lead to the failure to suppress and filter the continuing afferent signals, resulting in the development of alternate sensory routes. The signals may find their way through other undamaged thalamic nuclei that project the signals to other non-specific areas, including pain areas [18]. Thalamic damage may also lead its sensory modalities to become reorganized, causing non-painful stimuli to register as painful [29]. Due to the thalamic coordination of almost all sensory data [2], this reorganization or development of alternate sensory routes may lead stimulation originating from hearing music or even experiencing happiness to signal an experience of pain.

Homeostatic plasticity may contribute to CPS through hyper-amplification of tactile stimuli [17]. Due to the deafferentation of thalamic and cortical sites along a damaged spinothalamic tract, the neurons here see little activity, resulting in the adaptation of the homeostatic baseline, and ease in the potential for hyperexcitability [17]. The synchrony between the deafferentated thalamus and cortex becomes disturbed upon damage [3]. The change in thalamic excitability coincides with the reorganization of the cortical counterparts and the modern

assumption is that the cortex "locks" the thalamus in this hyperexcitable state [3]. Thus, a dysfunctional corticothalamic loop along the sensory pathways develops.

The 3DDS model is not in conflict with the modern theories of CPS. We argue, however, that these theories lack the full scope of the syndrome. By incorporating current theory with 3DDS model concepts, we arrive at a more complete etiology for CPS. Our model is differentiated from modern theories in the following ways: 1) it assumes pre-existing, dynamic, gamma oscillatory synchronization between the peripheral receptors and cortical sites, and 2) it is predominantly top-down in nature. These oscillations are constantly maintained to provide awareness of the relative sensory modalities [9]. The synchrony is damaged upon spinothalamic tract lesions leading to maladaptive plasticity and other mechanisms we have described. Over time, the corticothalamic loop becomes locked in a dysfunctional state. The currently accepted brain-centric view is that the final perception of pain due to CPS happens in the higher cortical structures after full processing. Our unified view of consciousness, however, involves the full functional sensory system in producing its perception. The brain-centric view of sensory information flow proposes a beginning and end; our assertion, to the contrary, is that there is a *circular* flow creating a unifying synchronization, which we propose is the foundation of consciousness.

The nature of the flow of information determines the nature of conscious experience. Information on the afferent pathway signals baseline subconscious and unconscious information. We assert that the afferent signals are amplified by the thalamus and cortex, leading to amplified sensory stimuli that are projected back to the periphery where they are incorporated with new sensory stimuli, and then sent back again on the afferent path. Because this synchronization is dominated by top-down modalities from involved cortical regions, the sensory information generated by the brain originates from pre-existing simulation from the external world. We propose this is what gives rise to conscious experience [43]. As the pain response becomes amplified by way of maladaptive recovery in the CNS of CPS patients, these painful stimuli are transferred back to the relevant nociceptors in the uninjured periphery via the efferent pathway (**Figure 4**). This oscillatory synchronization of peripheral receptors with cortical sites is integrated into the default space by the thalamus, and, through its dysfunction along the sensory tract, normally non-painful stimuli are magnified and are thus experienced as painful stimuli. The top-down dominance of the sensory stream leads pain centers such as the insula (which have become hypersensitive to pain) to project these pain stimuli to the peripheral receptors on a continuously maintained loop, creating a snowball-like effect of building pain. The 3DDS model etiology may lead to novel treatments geared toward preventing the magnified top-down stimuli from generating this painful cycle.

9. Conclusions

We have drawn support for the dynamic 3DDS model by applying its framework

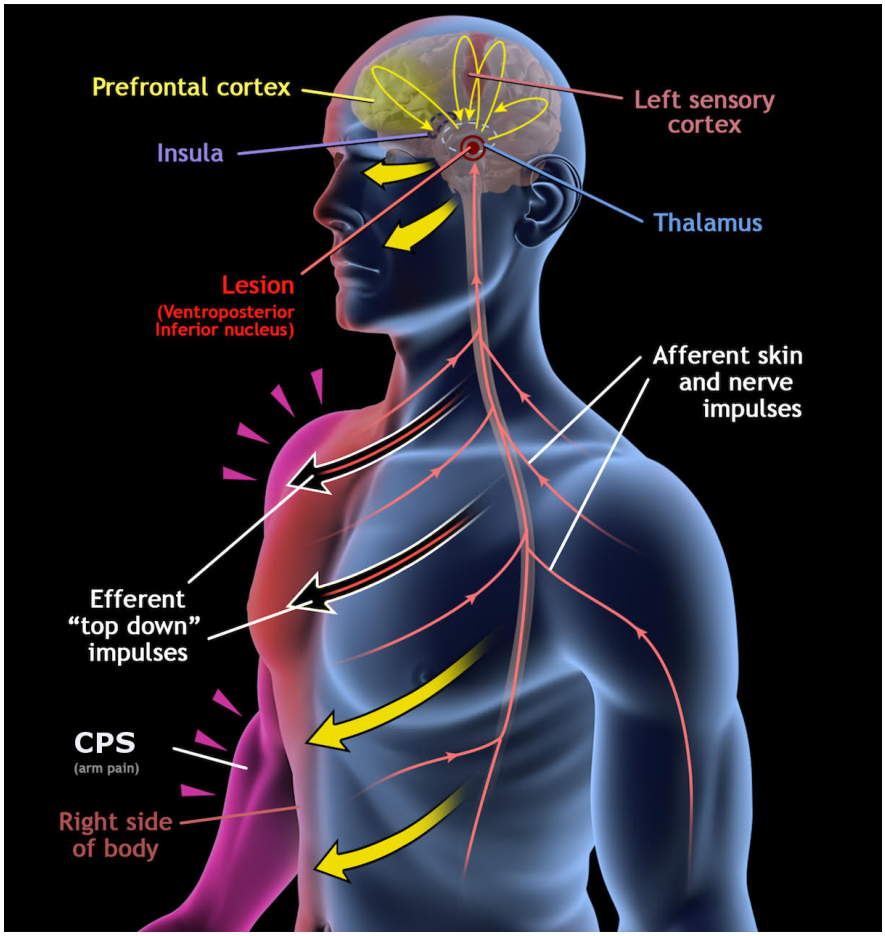

Figure 4. 3DDS model of CPS. This diagram illustrates the experience of central pain. In patients with central pain, the overriding system of top-down impulses dominates the sensory stream thus leading to dysfunctional cortical networks and subsequent altered sensory information along this efferent projection. In the model, the insula and sensory cortex are hyper-reactive in the presence of normal stimuli, presumably due to maladaptive plasticity and/or the development of alternate neural pathways (see text for details). The 3DDS model hypothesizes that malfunction along the spinothalamic tract would be projected back onto the sensory receptors from where the initial afferent sensory stimuli originated. Subsequent oscillatory synchronization between receptors and cortex would be dominated by the top-down efferent sensory information. In the figure, the CPS patient is shown with a lesion at the VPI of the thalamus (a common source of CPS). Over time, this leads to the insula and cortex receiving amplified information from the hyperexcitable thalamus in response to normal tactile stimuli.

to the current knowledge of CPS. In this syndrome, pain and uncomfortable sensations arise after damage to the central nervous system. We have explored the most common cause of central pain, lesions along the spinothalamic tract. The 3DDS model proposes that non-visual sensory information is relayed to the thalamus, processed by corticothalamic feedback loops, and integrated into the 3D default space by the thalamus. This integration occurs through pre-existing oscillations with the original sensory organ, dominated by top-down projections. The somatosensory cortex is synchronized with its respective receptor site by

these oscillations, essentially bringing the cortical information to the sensory receptor. In light of this concept, we have proposed a novel etiology for central pain syndrome, based on the modern hypothesis that damage along the spinothalamic tract disrupts the synchrony of sensory corticothalamic oscillations due to (partial) deafferentation of the thalamus and/or somatosensory cortex. This damage can be followed over time by several potentially exacerbating events: 1) maladaptive homeostatic plasticity, 2) the development of alternate routes around damaged pathways, and 3) the formation of new connections to inappropriate cortical areas, including those that influence pain. These new pathways and/or a hypersensitive thalamus/cortex allow the person to regain some sense of the body area with the original severed connection; however, this often results in the experience of extreme pain and uncomfortable sensations that become "locked" in by the reorganized corticothalamic loop.

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