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Review article

Changes in the central nervous system in diabetic neuropathy

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ABSTRACT

One of the most common chronic complications arising from diabetes is diabetic peripheral neuropathy. Depending on research statistics, approximately half of the people who have diabetes will suffer from diabetic peripheral neuropathy over time, which manifests as abnormal sensations in the distal extremities, and about 25%–50% of these patients have symptoms of neuralgia, called painful diabetic neuropathy. These patients often exhibit adverse emotional conditions, like anxiety or depression, which can reduce their quality of life. The pathogenesis of diabetic peripheral neuropathy is complex, and although persistent hyperglycemia plays a central role in the development of diabetic peripheral neuropathy, strict glycemic control does not eliminate the risk of diabetic peripheral neuropathy. This suggests the need to understand the role of the central nervous system in the development of diabetic peripheral neuropathy to modulate treatment regimens accordingly. Magnetic resonance imaging not only allows for the noninvasive detection of structural and functional alterations in the central nervous system, but also provides insight into the processing of abnormal information such as pain by the central nervous system, and most importantly, contributes to the development of more effective pain relief protocols. Therefore, this article will focus on the mechanisms and related imaging evidence of central alterations in diabetic peripheral neuropathy, especially in painful diabetic neuropathy.

1. Introduction

Diabetic peripheral neuropathy (DPN) is the most common of the various complications of diabetes, affecting approximately 30% of people with diabetes and more than 50% of diabetics over the age of 50 [1–3]. Distal symmetric polyneuropathy is the most prevalent of these, comprising approximately 75% of diabetic neuropathies [4]. It mainly presents with symmetric sensory deficits in the lower extremities, such as numbness, pain, ankylosis, etc. Half of the patients may be asymptomatic, and if unrecognized and without preventive foot care, they may be at risk of a foot injury, which may lead to amputation in severe cases, severely affecting the quality of life. The predominance of peripheral neuropathy symptoms in DPN has led to a neglected impact on the central nervous system (CNS).

Ryan found in 1992 that DPN was strongly associated with reduced psychomotor efficiency on neuropsychological tests, suggesting a link between DPN and mild neuropsychological dysfunction [5]. As the magnetic resonance imaging (MRI) technique developed, Eaton applied MRI, which revealed a significant reduction in the overall spinal cord cross-sectional area at C4/5 and T3/4 in patients with DPN compared to diabetic patients without DPN, suggesting for the first time that DPN involves the CNS [6]. Subsequently, a

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growing body of evidence has identified CNS involvement in DPN, involving structural damage to central sensory pathways (spinothalamic tract and medial lemniscus), thalamic neuronal dysfunction, abnormal thalamic blood perfusion in patients with painful diabetic neuropathy (PDN), and reduced gray matter volume in the primary somatosensory cortex [7–11]. These discoveries offer a completely new direction for DPN research: some of the mechanisms that produce sensory impairment and pain may be in the CNS, like the spinal cord, thalamus, and cerebral cortex, suggesting ideas for developing new, more targeted treatment options.

2. Pathogenic mechanisms

The mechanisms underlying DPN have not yet been elucidated, but it is thought to be mainly related to a series of pathophysiological changes caused by hyperglycemia, lipid metabolism disorders, and abnormal insulin signaling pathways, including polyol pathway, glycolytic pathway, hexosamine pathway, protein kinase C (PKC) pathway, advanced glycation end products (AGEs) pathway, toll-like receptor 4 (TLR4) signaling pathway and oxidized low-density lipoproteins receptor 1 (LOX1) signaling pathway. They act individually or together to cause endoplasmic reticulum stress, mitochondrial dysfunction, DNA damage, and enhanced inflammatory signaling. In addition, impaired insulin signaling and impaired diabetic microcirculation can also lead to an irreversible impairment of neurons, glial cells, and vascular endothelial cells, contributing to the progression of DPN (Feldman et al., 2017). For patients with PDN, the causes of pain are related to peripheral sensitization and central sensitization in addition to the appeal mechanism (Fig. 1).

2.1. Peripheral sensitization mechanism

Peripheral sensitization refers to the increased sensitivity of injurious sensory neurons to afferent signals, as evidenced by the

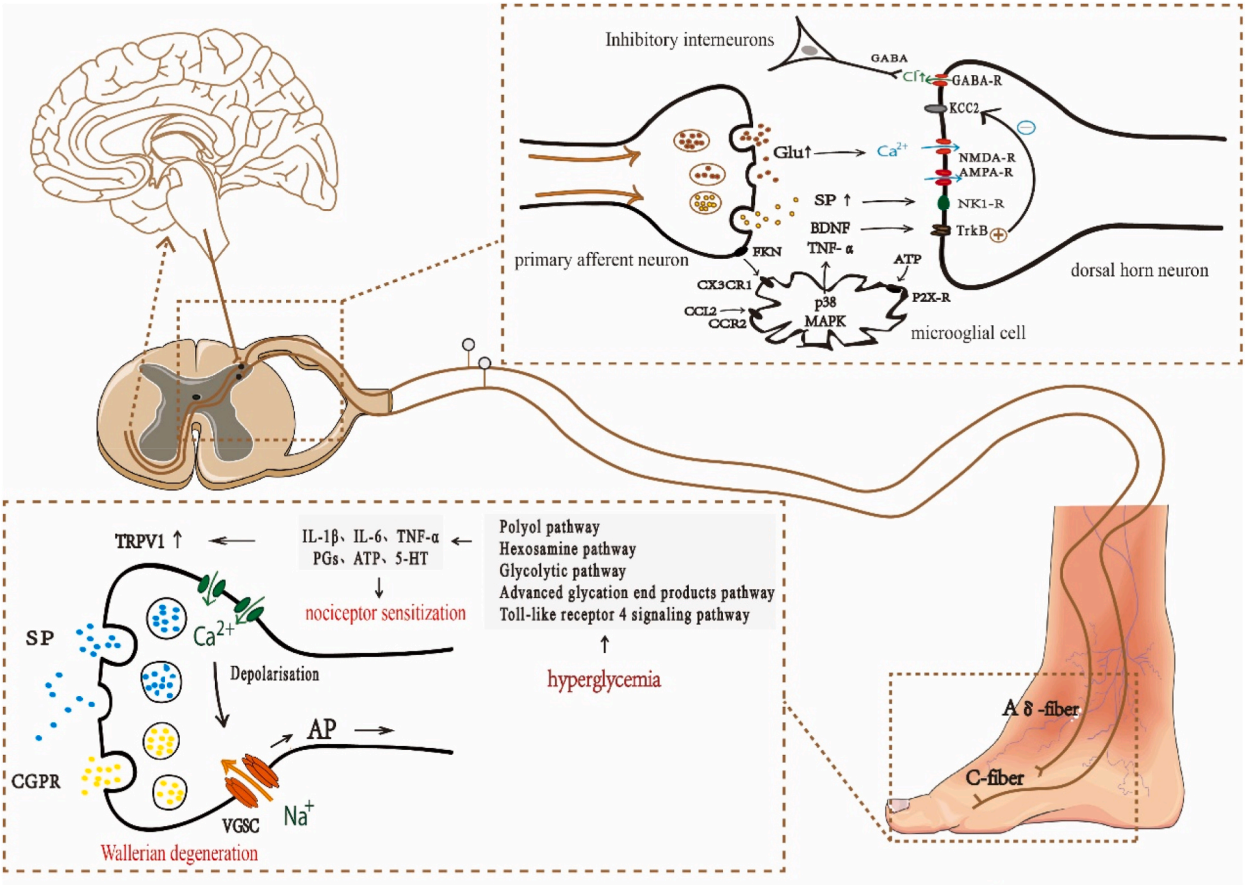

Fig. 1. Peripheral and central mechanisms of PDN. GABA, γ-aminobutyric acid; GABA-R, GABA receptor; KCC2, chloride potassium symporter; NMDA-R, N-methyl-*d*-aspartate receptor; AMPA-R, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; NK1-R, neurokinin 1 receptor; TrkB, tyrosine kinase B; Glu, glutamic acid; SP, substance P; BDNF, brain-derived neurotrophic factor; TNFα, tumor necrosis factor-alpha; FKN, fractalkine; CX3CR1, FKN receptor; CCL2, C–C motif ligand-2; CCR2, CCL2 receptor; p38MAPK, p38 mitogen-activated protein kinase; ATP, adenosine triphosphate; TRPV1, transient receptor potential vanilloid 1; CGRP, calcitonin gene-related peptide; VGSC, voltage-gated sodium channel; IL-1β, interleukin 1β; AP, action potential; PGs, prostaglandins; IL-6, interleukin 6; 5-HT, 5-hydroxytryptamine.

hyperexcitability of primary afferent neurons and a decrease in their activation threshold. It is associated with ectopic discharges following nerve injury, inflammatory responses at the site of injury, and changes in pain signaling.

2.1.1. Transient receptor potential vanilloid type-1

Transient receptor potential vanilloid type-1 (TRPV1) is closely associated with the perception of injurious impulses and the production of nociception in humans and is widely distributed in injurious receptor neurons, like the dorsal root ganglion (DRG) [12]. found that in a mouse model of PDN, oxidative stress led to a significant increase in TRPV1 expression in the DRG, and TRPV1 activation could regulate Ca^{2+} inward flow by upregulating voltage-dependent calcium channels (VDCC). The use of TRPV1 antagonist and antioxidant noopept can reduce Ca^{2+} concentration and apoptosis rate in DRG and effectively alleviate the nociceptive sensitization caused by nerve injury. In addition, TRPV1 activation also releases calcitonin gene-related peptide (CGRP), substance P (SP), etc. Increased release of CGRP and SP activates various immune cells and promotes the release of inflammatory factors, which further enhances TRPV1 activation, resulting in a positive feedback loop [13]. The anticonvulsant drugs pregabalin and gabapentin can exert analgesic effects by selectively blocking VDCC containing α2δ-1 subunits, reducing Ca^{2+} inward flow and thereby decreasing the release of glutamate, norepinephrine (NE), and SP. Several high-quality clinical studies have supported the role of pregabalin and gabapentin in the treatment of PDN [14], and the American Diabetes Association (ADA) Standards of Care in Diabetes-2023 recommend gabapentinoids as initial treatment for diabetic neuropathic pain [15].

2.1.2. Ectopic discharge activity

After peripheral nociceptive afferent fiber injury, distal axons at the injury site undergo Wallerian degeneration, and proximal residual axons and DRG cytosol spontaneously generate ectopic discharge. The altered expression of voltage-gated sodium channels (VGSC) plays an important role in ectopic discharges. There are multiple VGSCs distributed on DRG, among which pain-related studies are mainly concentrated in Nav1.3, Nav1.7, and Nav1.8. The role of Nav1.3 in pain is controversial. Nav1.3 expression is higher in immature embryonic DRG, decreases progressively during development, and significantly decreases in mature DRG expression [16]. The significant upregulation of Nav1.3 after nerve injury suggests that the re-expression of Nav1.3 may contribute to the altered excitability of DRG. NaV1.8 has electrophysiological properties of slow activation and rapid deactivation, with high activation and steady-state deactivation voltage thresholds, and can maintain a depolarized state continuously. NaV1.8-induced sustained sodium inward flow is one of the mechanisms leading to abnormal neuronal firing. Intrathecal injection of specific antisense oligodeoxynucleotides into the nerve sheaths of a spinal nerve ligation (SNL) rat model inhibited the expression of Nav1.8, thereby reducing the symptoms of nociceptive sensitization in neuropathic rats [17]. Nav1.7 has an important role in nociceptive perception, and Nav1.7 inactivating mutations result in nociceptive deficits in patients [18]. A study found that, compared with a placebo, the application of lacosamide reduced pain in patients with Nav1.7-associated small nerve fiber lesions, suggesting that targeted therapeutic agents for Nav1.7 may be more effective analgesics [19]. In addition to preclinical studies, five moderate-quality studies in PDN-related clinical studies have been found to support that sodium channel blockers can mitigate diabetic neuropathic pain [14]. Furthermore, as mentioned above, inflammatory stimulation leads to activation of TRPV1 channels, causing increased VDCC expression and promoting Ca^{2+} inward flow, which not only causes increased Ca^{2+}-dependent excitatory neurotransmitter release but also provides a generator potential for activation of the VGSC, further contributing to the generation of ectopic discharge activity.

2.2. Central sensitization mechanism

The main feature of the central sensitization mechanism is the plasticity changes in synaptic transmission. Alterations in central neuroplasticity triggered by peripheral injurious stimuli are common not only in the spinal cord but also in different brain regions, including the thalamus, brainstem, and cerebral cortex.

2.2.1. Central sensitization of spinal cord segments

Peripheral nerve injury causes a massive release of the excitatory neurotransmitters glutamate and SP at the central end of the nociceptive afferent terminals. Glutamate binds to alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors and N-methyl-*d*-aspartate (NMDA) receptors on spinal dorsal horn neurons, enhancing synaptic efficacy, causing Ca^{2+} inward flow, and activating intracellular signaling pathways capable of initiating and maintaining central sensitization. At the same time, SP can act on neurokinin 1 (NK-1) receptors, activate PKC, and cause depolarization of the cell membrane of postsynaptic projection neurons by phosphorylating NMDA receptors, removing the voltage-dependent blockade of NMDA receptors by Mg^{2+}, thus generating a greater inward current [20]. In addition, PKC also phosphorylatesγ-aminobutyric acid (GABA) receptors, reducing their ability to bind GABA, thereby reducing the efficacy of GABA-inhibitory interneurons to hyperpolarize sensory neurons in the dorsal horn of the spinal cord. It was found that apoptosis of GABA-inhibitory interneurons occurred after peripheral nerve injury, as evidenced by the appearance of dark neurons in layers I and II of the dorsal horn of the spinal cord, which may be due to the opening of NMDA receptors and a large Ca^{2+} influx that triggers a neurotoxic response [21]. Ketamine is an anesthetic agent that has been shown to exert potent analgesic effects by antagonizing NMDA receptors, and is effective for a variety of acute and chronic pains [22].

Microglia are also involved in the central sensitization process. After peripheral nerve injury, the chemokine fractalkine (FKN) binds to its receptor CX3CR1 and the C–C motif ligand-2 (CCL2) binds to its receptor CCR2, activating microglia and subsequently triggers the p38 mitogen-activated protein kinase (p38MAPK) signaling pathway to release pro-inflammatory mediators, such as interleukin 1β (IL-1β), among others [23]. In addition, microglia activation also releases brain-derived neurotrophic factor (BDNF), which can bind to its receptor tyrosine kinase B (TrkB) and inhibit the expression and function of K–Cl cotransporter isoform 2 (KCC2)

in the dorsal horn of the spinal cord. Among them, KCC2 has mainly enriched GABA receptor-containing neurons and can reduce intracellular Cl^- concentration. Activation of the BDNF-TrkB pathway leads to downregulation of KCC2 expression, resulting in disruption of spinal Cl^- homeostasis, weakening the inhibitory effect of intermediate inhibitory neurons and promoting the onset of pain [24].

The periaqueductal gray (PAG) receives nociceptive information from higher nociceptive centers such as the frontal lobe, insula cortex, thalamus, and amygdala, and then sends fibers to the dorsal horn of the spinal cord to enhance or diminish the pain response by releasing neurotransmitters such as 5-hydroxytryptamine (5-HT), NE, or excite inhibitory neurons in the dorsal horn to modulate or inhibit the upstream nociceptive information. Under physiological conditions, the downstream inhibitory effect is predominant, but the function of the downstream inhibitory system may be altered after neurological injury, as neurotransmitter and receptor changes inhibit the effectiveness of the downstream inhibitory pathways of 5-HT and NE, thus causing sensitization of the dorsal horn of the spinal cord [25,26]. Antidepressants serotonin and noradrenaline reuptake inhibitors (SNRIs), such as duloxetine, can provide analgesia by inhibiting the reuptake of 5-HT and NE in the downstream inhibitory pathway and enhancing the inhibitory effect of the downstream inhibitory pathway [27], and there are several high-quality clinical studies supporting the role of duloxetine in the treatment of DPN pain [14]. Selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine and paroxetine also have enhanced effects on the downstream inhibitory pathway. The study found that microinjections of paroxetine into the primary sensory cortex of mice reduced thermal nociceptive hyperalgesia [28]. However, the effectiveness of SSRIs in analgesia is controversial. It was found that 5-HT agonists can aggravate pain by increasing the release of SP. This may be related to the involvement of 5-HT in pain inhibition in addition to pain facilitation [29]. Therefore, SSRIs remain to be investigated in the treatment of DPN pain. PDN patients who experience chronic pain for a long time are often accompanied by psychiatric problems such as anxiety and depression. Antidepressants have been found to have not only antidepressant effects but also analgesic effects, and the 2023 ADA guidelines have suggested that SNRIs, tricyclic antidepressants, can be an effective initial treatment for PDN [15], but the related mechanism research is very limited and is currently mainly thought to be related to the enhancement of 5-HT and NE functional transmission of the downstream inhibitory pathway. The analgesic effects of antidepressants on CNS can be further explored in the future using MRI imaging.

2.2.2. Central sensitization above the spinal cord

The thalamus, cortex, and other higher centers above the spinal cord level not only passively receive pain information afferents, but also actively participate in pain information generation and transmission. Increased postsynaptic Ca^{2+} inward flow in dendritic spines in the anterior cingulate cortex of the cerebral cortex after nerve injury induces long-term potentiation (LTP) of cingulate synaptic transmission and enhances pre- and postsynaptic currents, a process that involves activation of AMPA receptors, extracellular signal-regulated kinase (ERK) and calcium-dependent adenylate cyclase-1 (AC-1) [30]. Neuroimaging studies have also shown changes in the structure and function of higher centers involved in nociceptive information processing [31]. At present, many mechanisms of central sensitization are still unknown or contradictory, and more experimental studies are still needed.

3. MRI study of CNS changes in DPN

Since the introduction of MRI, a large number of related technical innovations and developments have enabled in vivo imaging techniques to be widely used in clinical practice. One of its main advantages is the richness of imaging modalities, and the use of multimodal MRI has become an important research tool in several research fields, especially in neurological and psychiatric diseases. Conventional structural imaging probes the morphological structural properties of the brain mainly through brain tissue proton density, T1 relaxation time and T2 relaxation time. Diffusion tensor imaging (DTI) can investigate the microstructural properties of the brain and the integrity of white matter nerve fiber bundles by detecting the activity of water molecules in the brain. Magnetic resonance spectroscopy (MRS) can be used to detect changes in the levels of certain metabolites in the brain and to study diseases from the perspective of energy metabolism and biochemical metabolism. Functional magnetic resonance imaging (fMRI) is mainly used to study the neural activity of the brain based on blood oxygenation level-dependent (BOLD) contrast. It can be divided into two categories, one is task-based fMRI, which is used to study the neural activity of the brain under certain stimulation or task conditions and is used to reflect the specific functions of different brain regions. The other type is resting-state fMRI, which is mainly used to study the spontaneous neural activity of the brain in the absence of any cognitive task and to respond to the connectivity of functional networks in the brain. Today advances in multimodal MRI allow us to study the structural and functional effects of DPN on the CNS in greater detail, providing a valuable imaging basis for diagnosis and severity assessment, and thus for early intervention and treatment.

3.1. Spinal cord

Currently, with the development of MRI techniques, there is increasing evidence of central alterations in DPN. Comparing patients with DPN to non-DPN patients [6], found by MRI techniques that the cross-sectional area of the C4/5, and T3/4 overall spinal cord was significantly reduced in patients with advanced DPN. To further clarify the extent of spinal cord involvement early in the disease [32], studied the changes in spinal cord cross-sectional area in patients with subclinical DPN and found that DPN patients, even those with subclinical DPN, had a lower spinal cord cross-sectional area than healthy controls and diabetic patients without DPN. This suggests that atrophy of the spinal cord, which implies the loss of primary sensory neurons and leads to the abnormal transmission of sensory signals, may have occurred at an early stage when peripheral nerve injury is relatively modest. Furthermore [33], performed task-based fMRI by low-frequency electrical stimulation and found that both DPN patients with disease duration up to 6 months and healthy subjects had activation signals in the thoracolumbar spine, with signals mainly concentrated in the T12-L1 vertebral segments,

and that the mean T11 and L1 signal changes were higher in DPN patients than in healthy subjects and positively correlated with total cholesterol and blood glucose levels. This may be related to the increased release of SP induced by electrical stimulation, which increased local blood flow and altered neuronal excitability. This suggests that DPN patients may have hyperexcitability of primary afferent nerves in the early stage of the disease, and fMRI may play some value in the detection of early DPN.

3.2. Axonal pathways to the thalamus and cortex

As mentioned earlier, DPN is not only limited to peripheral nerves but also involves the spinal cord, which is an important bridge between peripheral nerve tissue and the brain, and it is tempting to speculate whether the central involvement of DPN is limited to spinal cord levels or continues further along the conduction pathway through the brainstem to the thalamus and then to the sensory cortex. Earlier, [34] found dysfunction of sensory transmission pathways in DPN patients using somatosensory evoked potentials (SEPs), and the extent of the dysfunction depended on the degree of peripheral neuropathy. We know that the human CNS has two main upstream sensory transmission pathways: 1. The spinothalamic tract and its thalamocortical pathway (spino-thalamic-cortical (STC)), which mainly transmits pain, temperature, and crude touch sensations in the trunk and extremities; 2. The medial lemniscus and its thalamocortical pathway (medial lemniscus-thalamic-cortical, MLTC)) mainly transmit proprioceptive and fine tactile sensations. To further investigate the microstructural changes of the superior sensory transmission bundle in DPN patients [7], found that the fractional anisotropy (FA) values of the left STC and MLTC were significantly reduced in DPN patients compared to diabetic patients without DPN based on DTI, and the FA values were positively correlated with myelin integrity, fiber density, and parallelism, which indicated that the integrity of the left superior sensory transmission bundle was impaired in DPN patients and suggested that DPN not only occurs in primary neurons but also involves secondary and tertiary neurons. Furthermore, as stated in the previous mechanistic content, the central sensitization mechanism of PDN is closely related to the dysfunction of the nociceptive downstream regulatory system involving the PAG. Segerdahl et al. (2018) found that the functional connectivity of the ventral lateral region of the PAG was enhanced in PDN patients by fMRI and positively correlated with the nociceptive response, confirming that the PAG, together with the anterior cingulate gyrus, amygdala, and hypothalamus, mediates the production of nociceptive sensitization. In the future, the DTI technique can be further utilized to clarify the extent of damage to the nociceptive pathways in PDN, which plays an important role in understanding the central mechanisms of PDN.

3.3. Thalamus

The projections of the ascending sensory pathways of the spinal cord terminate in the ventroposterior lateral thalamic subnucleus. The thalamus serves as an important sensory transmission relay station, projecting information to the sensory cortex through initial analysis and integration. Therefore, it is particularly important to clarify whether the thalamus, the sensory gateway to the brain, is also functionally impaired. MRI perfusion-weighted imaging (PWI) correlation studies have found increased thalamic perfusion in patients with PDN compared to patients with painless DPN [32]. At present, the cause of thalamic hyperperfusion in PDN is unknown and may be related to increased thalamic excitability and abnormal discharge activity. In the future, animal experiments can be further improved to clarify the relevant mechanisms and provide new ideas for the development of more effective analgesic protocols. A study using resting-state fMRI found that the ventral posterior lateral thalamic nucleus, the dorsal medial thalamic nucleus, and other brain regions such as the cerebral cortex were less functionally connected in PDN patients compared to healthy subjects, suggesting that chronic pain may reduce the connection between the thalamus and the cortex, resulting in impaired function of the central pain feedback system [35]. In addition, using MRS [36], found that the thalamic NAA/Cr and NAA/Cho ratios were significantly decreased in the PDN group compared with those of patients with painless DPN. N-acetyl aspartate (NAA) is considered to be an indicator of neuronal structure and function, and the decrease in NAA/Cr and NAA/Cho ratios suggests structural and functional damage to thalamic neurons. This suggests that one of the causes of nociceptive hypersensitivity in PDN patients may be damage to thalamic neurons, which reduces the volume of thalamic gray matter and the connection between the thalamus and the cerebral cortex, affecting the feedback of nociceptive information from the thalamus. However [9,37], using MRS found that the thalamus and somatosensory cortex NAA/Cr ratios were higher in the PDN group than in the painless DPN group. The inconsistent results of these studies may be related to the choice of echo time and technical parameters of MRS acquisition as well as the size of the study sample. In summary, MRS can noninvasively detect thalamic metabolic abnormalities in PDN patients, and NAA/Cr and NAA/Cho ratios are expected to be used as imaging indicators for measuring the degree of pain in PDN patients, as well as the efficacy of analgesic drugs, but this may require support from larger samples, multicenter studies, and more detailed specifications for MRS acquisition.

3.4. Higher brain centers

[8] found reduced gray matter volume in the primary somatosensory cortex (S1), supramarginal gyrus, and cingulate cortex in patients with type 1 diabetes mellitus (T1DM) with peripheral neuropathy based on voxel-based morphometry (VBM) analysis. As T1DM and type 2 diabetes mellitus (T2DM) have different pathogeneses, it is unclear whether the cerebral cortex of T2DM patients with peripheral neuropathy behaves similarly. Therefore, Zhang et al. investigated the differences in brain structure between DPN patients and healthy subjects and divided the DPN group into a painless DPN group and a PDN group. It was found that painless DPN patients and PDN patients had thinner cerebral cortex and increased cortical surface area compared to normal controls. In addition, the cortical damage in PDN patients was mainly located in brain areas related to nociceptive perception, such as the thalamus, PAG, prefrontal cortex and cingulate gyrus. However, there was no significant difference in brain structure between patients with painless

DPN and PDN (Fig. 2). Cortical thinning is considered to be associated with demyelination and neuronal death, whereas the expansion of cortical surface area may be associated with gliogenesis, synaptogenesis, and intracortical myelination. This suggests that long-term chronic inflammatory stimulation leads to increased axonal damage and abnormal firing activity in primary sensory neurons, which in turn transmits a large number of peripheral injurious signals into the CNS and activates microglia, resulting in neuronal damage or even death, which in turn affects the thickness of the cerebral cortex. And the site of cortical damage in DPN patients suggests us that pain perception and pain modulation-related pathways may be abnormal in PDN patients. Meanwhile, in the same study population [38], discovered a significant decrease in cortical thickness in DPN patients based on a human brain connectomics study, mainly in some brain regions related to sensorimotor function and pain, which is consistent with a previous study by Zhang. In addition, they found differences between the number and distribution of hubs in the networks of DPN patients and healthy controls, with DPN patients not only having new hubs (mainly in the prefrontal gyrus, superior temporal sulcus, insula cortex, and sphenoid gyrus) but also missing some of the hubs that were previously present, such as the left pars orbitalis and left rostral anterior cingulate cortex. This may be due to pain and cognitive dysfunction, or it may be due to reduced cortical thickness and impaired function of the associated brain regions in DPN patients, with the brain compensating to produce new nodes to maintain normal function.

A task-based fMRI study found that brain regions involved in somatosensory pathways (right insular cortex, left caudate nucleus, frontal gyrus, and cingulate gyrus) as well as higher brain regions associated with cognitive function (left hippocampus and left cingulate gyrus) showed greater activation in DPN patients than in non-DPN patients and normal controls after applying multiple thermal stimuli to the lower extremities, suggesting that CNS damage in DPN patients is probably not restricted to motor- and sensory-related cortical areas but that cognitively related areas like the hippocampus or cingulate gyrus may also be influenced by DPN [40]. A default mode network (DMN) has the functions of internal and external environment monitoring, emotional processing, self-reflection, maintenance of conscious awareness, and situational memory extraction [41]. showed that repeated pain stimulation altered the activity of brain networks such as the DMN and that cognitive-behavioral treatment could reverse such brain alterations. This suggests that pain and attention interact, with pain interfering with attentional and cognitive processes and cognitive tasks alleviating pain, and that chronic pain states in PDN patients may be associated with deficits in cognitive and attentional networks and abnormalities in the pain modulation system. Therefore, fMRI can be used as a method to study functional alterations in the brain in the nociceptive network to further reveal the central mechanisms of diabetic pain production.

[35] found reduced connections of the DMN to primary sensorimotor areas and cingulate cortex, as well as to the left temporo-occipital cortex, and increased connections to the lateral thalamus and bilateral insula in the corresponding areas of the left

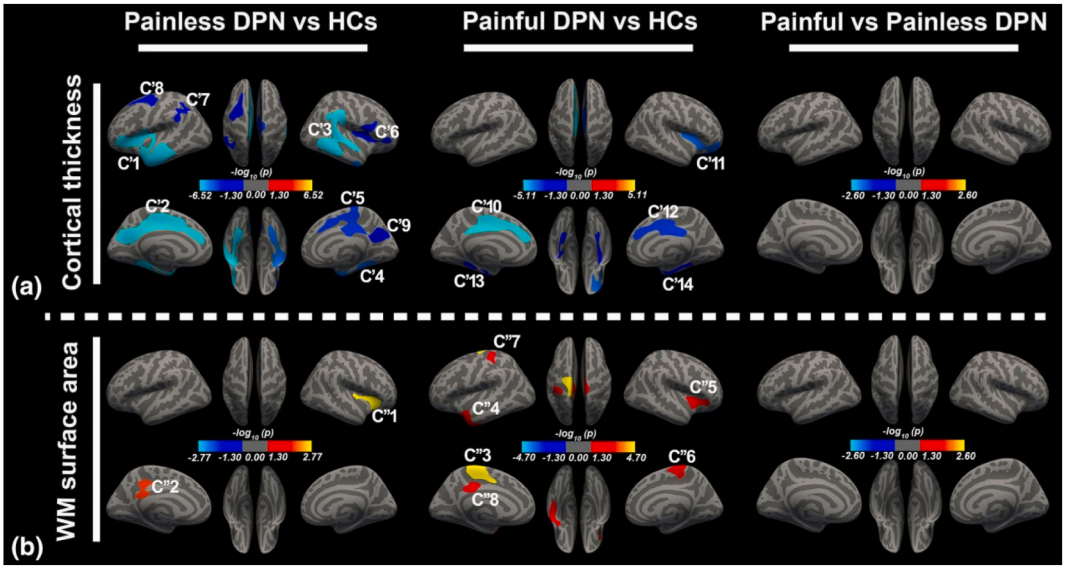

Fig. 2. Paired group comparisons of cortical thickness and cortical surface area [39] CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/). (a) Brain regions with altered cortical thickness between groups; (b) Brain regions with altered cortical surface area between groups. Significance is represented on a log (p value) scale, in which positive values (warm colors) are assigned to the painless DPN > HCs, painful DPN > HCs, and painful DPN > painless DPN clusters and negative values (cold colors) are assigned to the painless DPN < HCs, painful DPN < HCs, and painful DPN < painless DPN clusters. C′1, anterior temporal lobe and insula; C′2, cingulated cortex; C′3, inferior parietal lobule, and lateral temporal lobe; C′4, medial temporal lobe (parahippocampal gyrus and fusiform gyrus); C′5, paracentral lobule and cingulated cortex; C′6, insula and inferior frontal gyrus; C′7, inferior frontal gyrus; C′8, superior frontal gyrus; C′9, precuneus; C′10, cingulated cortex; C′11, prefrontal lobe, and insula; C′12, anterior cingulated cortex, and middle cingulated cortex; C′13, medial temporal lobe (parahippocampal gyrus and fusiform gyrus); C′14, medial temporal lobe (parahippocampal gyrus and fusiform gyrus); C″1, insula; C″2, posterior cingulated cortex; C″3, paracentral lobule, precentral gyrus, and postcentral gyrus; C″4, temporal lobe; C″5, insula; C″6, paracentral lobule, precentral gyrus, and postcentral gyrus; C″7, postcentral gyrus; C″8, posterior cingulated cortex. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

dorsolateral prefrontal and posterior parietal cortex in PDN patients, suggesting that pain may be the result of abnormal functional connectivity of the DMN. These brain regions have organized brain network activity during waking and resting states and are more active than under task load. This may explain why PDN patients often feel pain more at night than during daily activities. In addition, there are different sensory characteristics in DPN, and quantitative sensory testing (QST) is widely used in the study of pain. Patients with painful DPN can be classified into two pain phenotypes by QST, irritable nociceptor (IR) and nonirritable nociceptor (NIR). Researchers have found that patients with the IR phenotype respond to lidocaine treatment and that the functional connections between the insular cortex and the limbic system (orbitofrontal cortex, amygdala, cingulate cortex, and vomeronasal nucleus) in these patients are significantly enhanced [42]. The insular cortex is essential for the perception and processing of unpleasant emotions caused by chronic pain. This suggests that in the future, objective imaging markers can be established based on the response of fMRI to different pain stimuli to detect the "critical state" of nociceptive hypersensitivity at an early stage, providing a valuable imaging basis for diagnosis and severity assessment, leading to early intervention and treatment.

4. Central alterations in autonomic neuropathy

Autonomic neuropathy is another serious complication of diabetic neuropathy, especially cardiovascular autonomic neuropathy (CAN), which causes high mortality and can lead to spontaneous respiratory arrest and sudden death of unknown origin and therefore has received the attention of many researchers [43]. Studies have demonstrated that the central autonomic network includes the prefrontal cortex (anterior cingulate cortex, insula, orbitofrontal and ventral medial cortex), limbic system (amygdala and hypothalamus), and brainstem regions (PAG and ventral medial medulla) [44,45].

The limbic system is also known as the "visceral brain" due to its extensive influence on visceral activity and has a significant impact on the body's instinctive behavioral and emotional responses. The hypothalamus is the highest subcortical regulator of visceral activity and can indirectly influence cardiovascular activity through the cardiovascular centers of the brainstem and is involved in some basic cardiovascular reflexes, as well as in the regulation of mood changes and behavior. In addition, the medulla oblongata of the brainstem contains many regions related to cardiovascular, respiratory, and digestive activities and the reflex regulation of many basic vital phenomena. The reflex activity of autonomic nerves is mostly carried out in the medulla oblongata. Considering that various regions of the brain collaborate in processing information and that there is a large overlap between the central autonomic nervous system and the brain regions involved in DPN, we can expect that diabetic patients with autonomic neuropathy may also have central abnormalities. To test this idea [46], evaluated cognitive function and short- and long-term memory in 20 patients with autonomic neuropathy (average age 60) and found that patients with autonomic neuropathy performed worse on tests of cognitive function related to visual memory than non-autonomic neuropathy patients. However [47], studied 5047 middle-aged diabetic patients with a disease duration $<$10 years in terms of cognitive profile and CAN and found that RMSSD or SDNN, indicators of heart rate variability that assess autonomic function, did not correlate with cognitive decline in middle-aged diabetic patients. This study, like the Whitehall II study, did not find a relationship between CAN as assessed by heart rate variability and cognitive dysfunction in middle-aged adults [48]. These conflicting findings are probably associated with the choice of patient age groups, so further investigation into the cognitive function of elderly autonomic neuropathy patients and their altered brain structure is still needed.

5. Conclusions

The development of MRI techniques has allowed us to recognize that DPN is no longer restricted to peripheral nerve damage but also has CNS involvement, and central lesions are not solely secondary to peripheral neuropathy. Atrophy of functional areas of the brain and spinal cord, alterations in the composition of functional area compounds, changes in neural activity, and abnormalities in blood perfusion are all imaging manifestations of central involvement. Although the analgesic effects of antidepressants and gabapentin analogs are now well established, these drugs have significant side effects, and more relevant MRI studies are currently available in small clinical samples and lack animal MRI studies. Therefore, we still need further prospective, multifaceted, and multifunctional MRI data to investigate whether the central lesions in DPN are "dying back" or "concomitant" processes to help reduce the burden of DPN.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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