

Magnetic Resonance Imaging in Assessing Chemotherapy-Induced Peripheral Neuropathy: Systematic Review

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Abstract: *Chemotherapy-induced peripheral neuropathy (CIPN) is a common side effect of many anticancer drugs that may cause various symptoms altering the quality of life. We conducted a systematic review to evaluate the peripheral and central nervous system changes associated with CIPN and detected by magnetic resonance imaging (MRI). Medical literature databases (PubMed, Scopus, Thomson Reuters - Web of Science and Embase) were searched for original studies reporting the use of MRI in the evaluation of CIPN. A total of 31 studies were identified and 9 were eligible for analysis. Results indicate few changes of the peripheral nervous system, most CIPN-associated nervous alterations involving pain processing areas and circuits inside the central nervous system. Distinct patterns of pain processing, changes in cerebral perfusion and gray matter density together with chronic activation of somatosensory areas have been observed in patients with CIPN compared to healthy subjects or cancer patients who did not develop CIPN. Identification of vulnerable brain areas and circuits may indicate future targets for novel therapies directed to prevent or treat CIPN. A preexisting vulnerability suggested by a unique pattern of brain activation following nociceptive stimulation prior to chemotherapy could help identify high-risk individuals, candidates to close monitoring and preventive strategies.*

Keywords: *chemotherapy induced peripheral neuropathy; magnetic resonance imaging; pain processing; cortical areas; preexisting vulnerability.*

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Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a common side effect of six anticancer drug groups like platinum-based antineoplastic agents, vinca alkaloids, epothilones (ixabepilone), taxanes, proteasome inhibitors (bortezomib) and immunomodulatory drugs (thalidomide) (Zajackowska et al., 2019). These drugs induce damage to the nervous system structures and lead to CIPN through various pathophysiological mechanisms involving microtubule disruption, oxidative stress, mitochondrial damage, altered ion channel activity, myelin sheath damage, DNA damage, immunological processes, and neuroinflammation (Avallone et al., 2022).

According to Burgess et al. (2021), the prevalence of CIPN after one month following the completion of chemotherapy is close to 68%, and it continues to persist in roughly one-third of patients beyond six months. This rate can vary significantly depending on the specific anticancer drugs and treatment regimen used, platinum agents being the most neurotoxic (at least grade 1 lesions in 70.9% of patients treated with oxaliplatin (Leonard et al., 2005) and 84% of patients treated with FOLFOX6 (Alejandro et al., 2013) after 1 month).

The diagnosis of CIPN typically involves a comprehensive evaluation (patient history, symptoms, neurologic examination, type, and dose of chemotherapy) and adjuvant investigations (vibratory perception threshold, nerve conduction studies, skin and nerve biopsies) but sometimes can be challenging as other causes of neuropathy should be ruled out before attributing the symptoms solely to chemotherapy.

CIPN can be a significant concern because it may cause various symptoms that can affect a patient's quality of life. The severity of CIPN can vary from person to person and may depend on factors such as the type of chemotherapy drug used, the dosage, the duration of treatment, and the individual's susceptibility to nerve damage. Several evaluation scales have been proposed to evaluate the severity of CIPN, the most widely used being

the Functional Assessment of Cancer Therapy (FACT)–Taxane scale, the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QOL)-CIPN twenty-item scale (CIPN 20), the National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI CTC-AE) scale and the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group—Neurotoxicity (FACT/GOG-Ntx) scale (Kanda et al., 2019).

The 2020 update of the American Society of Clinical Oncology (ASCO) guideline of prevention and management of CIPN (Loprinzi et al., 2020) indicated that there are currently no recommended agents for the prevention of CIPN and clinicians should evaluate whether it is appropriate to delay or reduce the dose, replace medications, or discontinue chemotherapy in patients experiencing intolerable neuropathy and/or functional impairment. For patients with cancer experiencing painful CIPN, ASCO recommends the use of duloxetine (intermediate evidence quality, moderate strength of recommendation). No clear evidence exists for other treatments still in clinical trial phase like exercise therapy, acupuncture, scrambler therapy, gabapentin, tricyclic antidepressants, and oral cannabinoids.

While acute forms of CIPN may reverse within a week, chronic forms (30-40% of cases) can persist even for more than one year after treatment completion (Beijers et al., 2014) and cause severe impairment in various aspects of life (functional, social, emotional, occupational).

The role of medical imaging in the diagnosis, severity rating and follow-up of CIPN has not yet been established. We consider that reproducible and non-invasive diagnostic methods are necessary to identify the neurological substrate of CIPN and vulnerable individuals, make a positive diagnosis, establish the management, and follow-up CIPN. We conducted a systematic review to evaluate the peripheral and central nervous system changes detected by magnetic resonance imaging (MRI) and associated with CIPN.

Materials and Methods

Search Strategy

Pubmed, Scopus, Embase and Web of Science (WOS) databases were searched from their inception to July 2023 for original studies, both prospective and retrospective (trial studies – randomized and prospective non-randomized, cross-sectional studies, case control, cohort) using the following queries: chemotherapy-induced peripheral neuropathy AND

magnetic resonance imaging (MRI), chemotherapy-induced peripheral neuropathy and functional magnetic resonance imaging (fMRI), chemotherapy-induced peripheral neuropathy AND Diffusion Tensor Imaging (DTI) returning the results displayed in Figure 1. No language limitation was applied. Relevant abstracts were included after content evaluation.

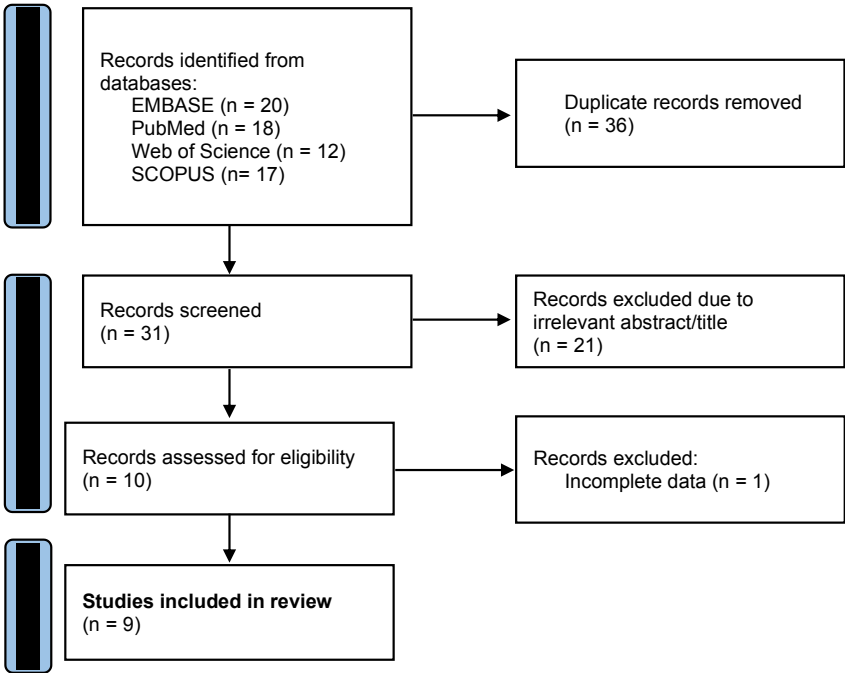


Figure 1. PRISMA flow diagram of selection process
(<http://prisma-statement.org/prismastatement/flowdiagram.aspx>).

Identified references were checked for duplicates and a total of 31 records resulted. All titles were screened manually for additional removal of 3 records. A total of 28 articles qualified for abstract evaluation. Another 18 articles were excluded due to absence of relevant information and failure to meet the inclusion criteria. One article was excluded because of incomplete data in the abstract and full text. Finally, 9 studies were included in the final analysis (Table 1). Two studies corresponded to presentations at the ASCO meeting not yet published in full text but containing relevant information in the abstract.

Inclusion and Exclusion Criteria

Included studies met the following criteria: (1) patients were adults with CIPN at least 18 years of age; (2) the study focused on the magnetic resonance imaging of the peripheral (PNS) and/or central nervous system (CNS) in patients diagnosed with a form of cancer who developed CIPN and completed chemotherapy or discontinued chemotherapy due to neurotoxicity; (3) the study provided neurotoxicity assessment criteria and MRI findings.

A study was excluded from the systematic review if (1) included patients with pre-existing peripheral neuropathy, diabetes, PNS/CNS involvement, prior neurotoxic chemotherapy; (2) provided incomplete data; (3) it was a low-quality investigation.

Data Extraction

Two investigators (R.O.C., C.F.) extracted the following data from each selected study: first author's surname, type of study, number of centers that provided data and the country(ies) the study was conducted in, sample size, cancer type, chemotherapeutic agents used, MRI protocol, neurotoxicity assessment criteria, MRI findings. When incomplete data was provided, the corresponding author was contacted.

Quality Assessment

The Critical Appraisal Skills Programme (CASP) Diagnostic Study Checklist was used to evaluate the quality of the included studies (Critical Appraisal Skills Programme UK) (Table 2). Two investigators independently evaluated selected articles (V.S. and D.V.S.). All studies managed to fulfill at least 7 domains.

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Table 1. Summary of selected studies

No	Authors	Type	No. of centers	CIPN patients no.	Age, years (mean $\pm$ SD)	Sex (% female)	Diagnosis	Chemotherapy agent	Neurotoxicity criteria	Structure of interest	MRI protocol	MRI aspect
1	Apostolidis et al., 2017	Prospective case-control	1 (Heidelberg, Germany)	20	58.9 $\pm$ 10.0	35%	Various cancers (>2)	Oxaliplatin	NCI CTC-AE scale	PNS – dorsal root ganglia morphological and functional changes	3D T2 inversion recovery SPACE, T2 with spectral fat saturation of both legs, DTI of both thighs	Dorsal root ganglia hypertrophy, heterogenous signal changes in sciatic nerve and branches, no change in FA and ADC.
2	Gimber et al., 2018	Prospective non-control (pilot study)	1 (Tucson, AZ, USA)	9	-	-	Various cancers (>2)	-	Vibratory perception threshold (VPT) > 25 Volts	PNS – posterior tibial nerve, medial and lateral plantar nerves	3D T2, 3D PSIF DWI, 2D DWI for DTI	No difference in FA and ADC.
3	Chalasani et al., 2020	Prospective non-control	1 (Tucson, AZ, USA)	14	52.9 $\pm$ 9.9	100%	Breast cancer	Paclitaxel, docetaxel	FACT/GOG-Ntx score $\geq$ 3 points	PNS – nerves in the ankle and mid-calf	2D axial T1, 2D axial T2, 3D PSIF DWI, 2D DWI for DTI (before and after chemotherapy)	FA decrease at mid-calf and ankle, greater reduction in patients who did not develop CIPN; unchanged ADC.
4	Boland et al., 2014	Cross-sectional screening study	1 (Sheffield, UK)	12	63 $\pm$ 2.5	33.33%	Multiple myeloma	Vincristine, thalidomide, bortezomib	TNS-reduced version score >2	CNS – response to heat pain stimulation	3D T1, 2D T2, T2* BOLD	Diminished activation right superior frontal gyrus, greater activation left precuneus, correlation of BOLD response with

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5	Nudelman et al., 2015	Prospective case-control	1 (Indianapolis, IN, USA)	24	49.4±7.9	100%	Breast cancer	Paclitaxel/docetaxel associated to other (doxorubicin, cyclophosphamide, cisplatin, carboplatin)	FACT/GOG-Ntx score	CNS – cerebral perfusion	Q2TIPS pulsed arterial spin labelling sequence, T1 MPRAGE, T2, FLAIR	TNS-reduced version score in the left operculo-insular cortex Increased perfusion in the left cingulate gyrus and right superior frontal gyrus at 1 month; decrease in gray matter density reduces patient symptom report.
6	Kleckner et al., 2017	Prospective case-control	1 (Rochester, NY, USA)	19	50±9	100%	Breast cancer	-	EORTC QLQ-CIPN20 sensory score >10	CNS - posterior insula – ACC connectivity	Resting fMRI (sequences not specified)	Reduced connectivity between the posterior insula and the ACC
7	Kleckner et al., 2021	Prospective case-control (pilot)	1 (Rochester, NY, USA)	11	63±12	54%	Various cancers (54% breast)	Taxane, platinum, bortezomib	EORTC QLQ-CIPN20 sensory score >10	CNS – brain sensory processing	Distinct attentional focus fMRI (somatosensory, interoceptive, visual attention) (sequences not specified)	Reduced increase in primary somatosensory activation during somatosensory attention, reduced increase in insula activation during interoceptive attention

8	Seretny et al., 2023	Prospective non-control	3 (Scotland, UK)	12	63.2±9.6	50%	Gynecological , colorectal cancers	Bortezomib, oxaliplatin, paclitaxel, docetaxol, cisplatin	EORTC Quality of Life Questionnaire CIPN 20	CNS – response to pain stimulation	T1 MPRAGE, T2* BOLD	Increased activity in response to pain stimulation prior to chemotherapy in the insula, thalamus, somatosensory cortex, and cerebellum.
9	Yeh et al., 2020	Prospective non-control (pilot)	1 (Baltimore, MD, USA)	6	57.15±9.74	75%	Various cancers (>2)	-	Rating CIPN symptoms (pain, numbness, tingling, stiffness) on a 0-10 scale	CNS – response to auricular point accupressure on ear points corresponding to the toes, soles, feet.	3D T1, T2* BOLD	Decrease in CIPN symptoms associated with changes in the connectivity and activity between ECN, SAL and BGN

- 2 *when range was reported, SD was considered as one fourth of the range of the data
- 3 ACC – Anterior Cingulate Cortex
- 4 ADC - Apparent Diffusion Coefficient
- 5 BGN – Basal Ganglia Network
- 6 BOLD – Blood Oxygen Level Dependent
- 7 CNS – Central Nervous System
- 8 ECN - Executive Control Network
- 9 EORTC - European Organization for Research and Treatment of Cancer
- 10 EPI – Echo Planar Imaging
- 11 FA - Fractional Anisotropy
- 12 FACT/GOG-NTx = Functional Assessment of Cancer Therapy/Gynecologic Oncology Group – neurotoxicity questionnaire
- 13 FLAIR – fluid-attenuated inversion recovery
- 14 MPRAGE – Magnetization Prepared Rapid Gradient Echo
- 15 NCI CTC-AE - National Cancer Institute Common Toxicity Criteria for Adverse Events Scale
- 16 PNS – Peripheral Nervous System
- 17 SAL - Saliency Network
- 18 SPACE - Sampling Perfection with Application-optimized Contrasts using different flip angle Evolution
- 19 TNS - Total Neuropathy Score
- 20 VPT – Vibration Perception Threshold

Table 2. Quality assessment using CASP Diagnostic Study Checklist (<https://casp-uk.net/casp-tools-checklists/>)

Study	1. Was there a clear question for the study to address?	2. Was there a comparison with an appropriate reference standard?	3. Did all patients get the diagnostic test and reference standard?	4. Could the results of the test have been influenced by the results of the reference standard?	5. Is the disease status of the tested population clearly described?	6. Were the methods for performing the test described in sufficient detail?	7. What are the results?	8. How sure are we about the results?	9. Can the results be applied to your patients/the population of interest?	10. Can the test be applied to your patient or population of interest?	11. Were all outcomes important to the individual or population considered?	12. What would be the impact of using this test on your patients/population?
Apostolidis et al., 2017	Yes	Yes	Yes	No	Yes	Yes	Dorsal root ganglia hypertrophy in oxaliplatin-induced peripheral neuropathy	Yes	Yes	Yes	Yes	Biomarker of CIPN
Gimber et al., 2018	Yes	Yes	Yes	No	Yes	Yes	Correlations between peripheral nerve FA and ADC measurements with CIPN	x	x	Yes	Yes	Further testing necessary
Chalasani et al., 2020	Yes	Yes	Yes	No	Yes	Yes	Peripheral nerve FA values indicative of CIPN	x	x	Yes	Yes	Further testing necessary
Boland et al., 2014	Yes	Yes	Yes	No	Yes	Yes	Unique pattern of central pain processing in patients with CIPN	Yes	Yes	Yes	Yes	Potential therapeutic target
Nudelman et al., 2015	Yes	Yes	Yes	Yes	Yes	Yes	Changes in cerebral perfusion and gray matter density in patients with	Yes	Yes	Yes	Yes	Biomarker of CIPN, potential therapeutic implications

Kleckner et al., 2017	Yes	Yes	Yes	Unable to estimate	Yes	No	CIPN Reduced connectivity in interoceptive brain circuitry patients with CIPN	Yes	x	Yes	Yes	Potential therapeutic target
Kleckner et al., 2021	Yes	Yes	Yes	Unable to estimate	Yes	No	Changes in somatosensory and interoceptive processing patients with CIPN	Yes	x	Yes	Yes	Potential therapeutic target
Seretny et al., 2023	Yes	Yes	Yes	No	Yes	Yes	Altered patterns of brain activity in response to nociceptive stimulation before chemotherapy patients who later developed CIPN	Yes	Yes	Yes	Yes	Identification of vulnerable individuals prior to therapy (potential prevention strategy)
Yeh et al., 2020	Yes	Yes	Yes	No	Yes	Yes	Changes in connectivity and activity of specific areas secondary to a novel therapeutic method	x	x	Yes	Yes	Potential novel therapeutic method

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Results

Peripheral Nervous System

Three studies examined peripheral nervous system (PNS) changes associated with CIPN by MRI.

The first was a German study conducted by Apostolidis et al. in 2017 and sought to evaluate the morphological and functional correlates of oxaliplatin-induced peripheral neuropathy (OXA-PNP) by magnetic resonance neurography (MRN) (Apostolidis et al., 2017). This prospective case-control study included 20 patients with various forms of cancer and OXA-PNP that were compared to 20 matched controls. CIPN was graded using NCI CTC-AE scale version 4.03. Patients underwent nerve conduction studies (NCS) of the sural, peroneal and tibial nerves and both patients and controls underwent high-resolution MRI of the lumbosacral plexus (3D T2-weighted inversion recovery SPACE), both thighs (DTI) and both legs (axial T2-weighted). The authors assessed dorsal root ganglia (DRG) volume, T2-weighted signal alterations and caliber of the sciatic, peroneal and tibial nerves and the fractional anisotropy (FA), radial diffusivity (RD), axial diffusivity (AD), and mean diffusivity (MD = apparent diffusion coefficient, ADC) of the peripheral nerves (sural, peroneal and tibial), and correlated DTI values with NCS results. DRG hypertrophy was identified as a significant morphological correlate of oxaliplatin induced CIPN. Sciatic nerve caliber, T2-weighted signal anomalies, FA, RD, AD and ADC of peripheral nerves did not correlate significantly with the presence of CIPN or with electrophysiological test results.

Two other studies were conducted in 2018 and 2020 in Tucson, AZ, USA by partially different teams (Gimber et al., 2019; Chalasani et al., 2020) and investigated the potential utilization of DTI as a predictive marker of the onset and severity of CIPN. The first pilot study (Gimber et al., 2019) only included 9 patients with various forms of cancer treated by chemotherapy, defined CIPN based on a vibratory perception threshold (VPT) score >25 Volts and imaged a total of 16 feet, 9 with CIPN and 7 without CIPN using morphological (3D T2-weighted turbo spin echo sampling perfection with application optimized contrasts using different flip angle evolution (SPACE) and 3D T2-weighted enhanced steady-state gradient echo reverse fast imaging with steady-state precession (PSIF) DWI with uniform fat suppression) and functional (2D axial diffusion-weighted imaging (DWI)) MRI sequences. Gimber et al. found no significant differences in FA or ADC between patients with and without CIPN for the

posterior tibial, medial plantar and lateral plantar nerves but identified a minor correlation between the left foot medial plantar nerve FA value and left foot lateral plantar nerve ADC value with VPT measurements thus motivating them to continue the study in 2020. In the newer study (Chalasani et al., 2020) they included 14 female patients with breast cancer treated with taxane. CIPN was graded using FACT&GOG-Ntx scale. Patients underwent pre- and post-chemotherapy MRI of both legs together with genotyping of single-nucleotide variations to detect known associations with CIPN. The MRI scanning protocol did not differ significantly from the previous study and the authors identified a significant decrease in mean FA values after chemotherapy was completed, greater for patients without CIPN. ADC values did not change significantly. The results reported by the three studies for the peripheral nerves are debatable as they are partially divergent, the first two indicated the absence of a correlation between FA and ADC values, CIPN symptoms and electrophysiological test results while the last one states that FA values decrease post-chemotherapy. At the same time, the first study evaluated only patients treated with oxaliplatin, the second study patients treated with various anticancer drugs and the last one only patients treated with taxane, the neurotoxic mechanism varying across anticancer drugs.

Central Nervous System

Our literature search identified six studies investigating the implication of the brain in CIPN.

The first study was conducted by Boland et al. in 2014 in Sheffield, United Kingdom. This research compared the activation of areas associated with central pain processing between 12 patients with multiple myeloma and CIPN induced by thalidomide, bortezomib or vincristine and 12 healthy volunteers. CIPN was affirmed based on a TNS-reduced version score >2. All subjects underwent sensory testing using Computer Assisted Sensory Evaluation (CASE) IV equipment, peripheral nerve conduction studies and fMRI scanning (3D T1, 2D T2, T2* BOLD sequences) with heat-pain stimulation of the right foot/thigh. Patients were asked to rate the perceived pain on a numerical scale from 0 to 10. Individuals experiencing CIPN demonstrated increased activity in the left precuneus and reduced activity in the right superior frontal gyrus, both in relation to the foot and thigh heat-pain stimulation, when compared to the control group of healthy participants. Additionally, increased activation in the left frontal operculum, situated near the insula, upon exposure to heat-induced pain in the foot was linked to more severe CIPN symptoms. This study suggests that patients

with CIPN develop a different pattern of pain processing compared to healthy controls.

Two years later, Nudelman et al. (2016) explored brain response to CIPN at Indiana University, Indianapolis, IN, USA. They compared brain perfusion between 24 patients with breast cancer who received chemotherapy and 23 patients with the same disease but treated without chemotherapy. CIPN was defined based on FACT/GOG-Ntx score. Brain perfusion and gray matter density were assessed at baseline, one month after treatment completion and 1 year after the 1-month evaluation. MRI scanning protocol involved Q2TIPS pulsed arterial spin labelling, T1 MPRAGE, T2, and FLAIR sequences. At 1 month after treatment completion, CIPN symptoms correlated with increased perfusion in regions associated with pain processing, bilateral superior frontal and cingulate gyri and the left middle and medial frontal gyri, correlation that was no longer demonstrated at the 1-year evaluation. Concerning gray matter density change, a decrease in density between the baseline and 1-month evaluation associated with decreased perfusion and lower CIPN severity.

Two other studies were conducted by Kleckner et al. in 2017 and 2021 in Rochester, NY, USA. Their first study investigated the potential impairment of interoceptive brain circuitry (connectivity between the posterior insula and anterior cingulate cortex (ACC) responsible for bodily sensations processing) as a substrate for CIPN symptoms. The authors compared the interoceptive brain circuitry between 19 women with breast cancer and CIPN symptoms (EORTC QLQ-CIPN20 sensory score >10), 31 women with breast cancer and no CIPN symptoms (EORTC QLQ-CIPN20 sensory score ≤10) and 280 healthy adults. The patients with breast cancer underwent fMRI before surgery, one month and one year after completion of chemotherapy. The fMRI scanning protocol was not described in the abstract. Cancer patients with CIPN had reduced connectivity between posterior insula and ACC while both cancer patients without CIPN and normal controls displayed positive connectivity. Their second study performed in 2021 evaluated 11 patients of both sexes and various forms of cancer before and 12 weeks after receiving taxane, platinum-based agents or bortezomib. Patients underwent fMRI (protocol not described) and brain activity was evaluated during three 20-seconds attentional focus tasks (somatosensory, interoceptive and visual attention). Patients with higher EORTC QLQ-CIPN20 sensory score registered both lower activation increases in primary somatosensory cortex (S1) and primary interoceptive cortex (mid/posterior insula) during specific attentional focus task and a

chronic somatosensory activation revealed by a paradoxical activation of the S1 during visual attentional focus task.

The results of the first four studies analyzed converge and prove an alteration of pain processing circuits in the brain in response to CIPN evolving either towards brain adaptation to pain or towards maintaining a chronic activation of somatosensory areas potentially responsible for the persistence of pain on the long term, after chemotherapy completion.

Seretny et al. (2023) went even further, beyond investigating CIPN induced impairment of pain processing areas and circuits. In a recent study published in 2023, they used fMRI in an attempt to identify if there is a pre-existing vulnerability to the development of CIPN. They performed a prospective study on 20 patients with various forms of cancer recruited from 3 sites across Scotland, UK and treated with neurotoxic chemotherapy. Patients underwent fMRI (T1 MPRAGE and T2* BOLD sequences) with nociceptive punctate stimulation above the right medial malleolus before starting chemotherapy at a center in Edinburgh, Scotland, UK. Of the 20 patients, 12 presented painful CIPN 9 months after chemotherapy based on the EORTC QLQ-CIPN20 score. Patients who developed CIPN displayed increased brain activity after nociceptive stimulation in the superior parietal lobule and angular gyrus bilaterally, occipital cortex bilaterally, left somatosensory cortex, right precentral gyrus, bilateral supplementary motor cortex, anterior and posterior insula subdivisions bilaterally, left caudate nucleus, left thalamus, left medial lemniscus, left middle and inferior frontal gyri, right medial superior frontal gyrus, right anterior cingulate gyrus, right inferior pons, right superior medulla, right inferior and middle temporal gyri, right precuneus, and right cerebellum. Patients that did not develop CIPN displayed increased brain activity in the occipital cortex bilaterally, left fusiform gyrus, left superior temporal gyrus, right superior parietal lobule and right angular gyrus, left postcentral gyrus, and the periaqueductal grey matter. Thus, Seretny et al. (2023) identified a preexisting completely different brain activation map in case of nociceptive stimulation in patients that later developed chronic CIPN.

Brain response to therapeutic methods has been assessed by a single study performed by Yeh et al. (2020) at the Johns Hopkins University, Baltimore, MD, USA. They analyzed 6 patients with various forms of cancer and suffering from CIPN. Patients evaluated their CIPN symptoms (pain, numbness, tingling, stiffness) on a 0-10 scale before and 4 weeks after Auricular Point Acupressure (APA) administered as a potential treatment for CIPN. fMRI involving 3D T1 and T2* BOLD sequences was performed before, during and 4 weeks after APA. Patients reported a significant clinical

amelioration ($\geq 30\%$ decrease in symptoms rating) following APA and fMRI identified a significant improvement of the connectivity of the basal ganglia network (BGN) to the salience (SAL) and language networks and within the executive control network (ECN) and SAL network post-APA (immediate or delayed) compared to the pre-APA status. These therapeutic induced changes suggest that brain connections involving insula, anterior cingulate and dorsolateral prefrontal cortices which are important in pain processing are subject to plasticity and potential therapeutic targets for ameliorating CIPN symptoms.

Discussion

Peripheral Nervous System

Diffusion tensor imaging (DTI) is an innovative functional MRI technique that has been developed using diffusion-weighted imaging principles. It leverages the directional variance of water molecule diffusion within tissues to reveal the microstructure of these tissues (Auriat et al., 2015). The diagnostic accuracy of DTI in diabetic peripheral neuropathy (DPN) has been assessed by several studies (Vaeggemose et al., 2017; Wang et al., 2022) that used 2 DTI parameters, ADC and FA, to evaluate the integrity of peripheral nerves and proved a significant decrease of FA values with increased ADC values in patients with severe DPN. The FA value indicates the directional sensitivity of water molecule diffusion and the anisotropy of peripheral nerves. Conversely, the ADC value indicates the extent or speed of water molecule diffusion, offering insights into the dimension of the cell membrane or myelin sheath diffusion barrier. For CIPN on the other hand, current evidence supporting a relationship between the same DTI parameters (FA and ADC values) and the occurrence and severity of CIPN is inconclusive. The different results could be explained by the different pathophysiological mechanisms. In case of DPN, both vascular factors and metabolic interactions play a role at every single stage leading to nerve fiber loss, microvascular defects in endoneurial vessels, arteriosclerosis and impaired blood flow with reduced oxygen tension translated through changes in water molecule diffusion (Tesfaye and Selvarajah, 2012). On the contrary, in CIPN the pathophysiological mechanisms are more complex and range from neuroinflammation, to altered ion channel activity, changes in intracellular systems (mitochondrial dysfunction, disruption of microtubules), microglial activation, impairment of sphingolipid metabolism, altered excitability, Wallerian degeneration (Avallone et al., 2022; Colvin, 2019). Thus, the effect and extent of water

molecule diffusion quantified by DTI is different in CIPN compared to DPN and FA and ADC values cannot be currently used to objectively confirm CIPN irrespective to the anticancer drug used. Further studies including more patients treated with the same class of chemotherapeutic drugs are necessary.

The hypertrophy of the dorsal root ganglion (DRG) in patients with CIPN was only identified and quantified by Apostolidis et al. and could be explained by the neuroinflammation caused by the penetration of the blood-nerve barrier by the chemotherapeutic drugs that accumulate in the DRG (Eldridge et al., 2020). Studies performed on mice identified increased levels of pro-inflammatory cytokines related to the recruitment of immune cells in the DRG following injection of oxaliplatin. The alterations noticed in the DRG might also arise from an inherent reaction of DRG cells following oxaliplatin treatment, rather than being a result of axonal degeneration (Calls et al., 2022). Macrophage infiltration into DRG was also described secondary to paclitaxel treatment (Zhang et al., 2016). The DRG is considered the main target of CIPN toxicity in case of taxanes, platinum-based drugs, alkylating agents, vinca alkaloids, proteasome inhibitors and immunomodulatory drugs (thalidomide) (Eldridge et al., 2020). The hypertrophy of the DRG could represent a potential biomarker of severe CIPN and could also be used as an argument for prescribing potential treatment methods like DRG stimulation or anti-inflammatory treatment (Ege et al., 2023).

Central Nervous System

Even if the damage and dysfunction of the peripheral nervous system are the main features of CIPN, the central nervous system (CNS) may also hold an important role in the pathophysiology of CIPN as a predisposing factor, through compensation, sensitization, and reorganization.

Patients with CIPN develop a particular pattern of central pain processing compared to healthy individuals which could explain the persistence of symptoms even after 6 months following the completion of chemotherapy in up to 1/3 of cases. Chronic pain in general is associated with altered activation of the precuneus, periaqueductal gray matter, superior frontal gyrus, primary somatosensory cortex, or operculo-insular cortex (Apkarian et al., 2005; Jaggi and Singh, 2011). The precuneus for example is involved in conscious pain perception and pain memory, its activation being potentially linked to pain memory retrieval upon new stimulation (Koyama et al., 2005; Kong et al., 2010). The operculo-insular cortex on the other hand is responsible for the intensity of perceived pain (Iannetti et al., 2005).

In case of the superior frontal gyrus, patients with CIPN investigated by Boland et al. registered a diminished functional response probably resulting from an adaptation to chronic pain. Hsieh et al. (1996) previously indicated a deactivation of the prefrontal cortex in response to pain in cluster headaches. An activation of the superior frontal gyrus was reported in response to pain only in healthy subjects (Fulbright et al., 2001). Even if chemotherapy drugs do not cross the blood-brain barrier, CIPN alters central pain perception and induces a long-term hypersensitivity to pain. The nociceptive brain circuits are not static and are subject to plasticity following chronic stimulation. Patients with CIPN register failure to activate or a chronic activation of the S1 cortex together with a reduced activation increase in primary interoceptive cortex (insula) during specific attentional tasks.

The alteration of the pain processing mechanisms was also confirmed by the cerebral perfusion study performed by Nudelman et al. (2016). They found significant perfusion changes in brain regions associated with central pain processing (superior temporal gyrus, precuneus) in acute CIPN (1 month after treatment completion), changes that regressed until the 1-year evaluation. A potential brain adaptation to CIPN could be represented by a decrease of gray matter density in the same areas (especially left cingulate gyrus, right superior frontal gyrus) at 1-month compared to baseline evaluation associated with reduced patient symptom report.

Seretny et al. (2023) suggest the existence of a predisposing state in patients who develop CIPN. In their study, increased brain activity in response to nociceptive stimulation was present in the insula, thalamus, somatosensory cortex, right medial superior frontal and right anterior cingulate gyri, right inferior and middle temporal gyri prior to chemotherapy in patients that later developed chronic CIPN. Prior studies linked the vulnerability to chronic pain to dysfunctions of the descending pain modulatory system (DPMS) and the reward system (Denk et al., 2014). The balance between the inhibitory and facilitatory outputs from the DPMS partially explains a person's pain perception. Alterations of DPMS and of its connections with pain-related brain regions have been identified in association with DPN (Segerdahl et al., 2018) and pelvic pain (Vincent et al., 2013). The medial prefrontal cortex is linked to the DPMS by the periaqueductal grey matter and is partially responsible for the cortical control of nociceptive processing. Altered connectivity between the medial prefrontal cortex and the periaqueductal grey matter could contribute to maladaptation to pain. No particular activation of these areas in response to nociceptive stimulation was noted prior to chemotherapy in patients that

later developed CIPN. On the contrary, patients that did not develop CIPN displayed increased brain activity in the periaqueductal grey matter potentially related to the capacity to activate the downward inhibitory components of the DPMS. Multiple areas linked to neuropathic pain states activated long before CIPN development – the insula, anterior cingulate cortex, right superior frontal gyrus. Abnormal activity in these areas has been identified by other reviewed studies after the onset of CIPN (Boland et al., 2014; Nudelman et al., 2016). The right superior frontal gyrus is particularly responsible for the cognitive aspect of pain and displays a decreased volume in neuropathic pain [Pan]. The reward system in the brain modulates pain and response to analgesia as pain relief is considered a reward by the brain and alterations of this system are partially responsible for chronification of pain (Wanigasekera et al., 2012). Anomalies of this system have not yet been identified in association with CIPN probably because the brain functional substrate implied in therapeutic response has not yet been assessed.

Up to date, a single study (Yeh et al., 2020) attempted an evaluation of the brain response to a potential therapeutic method - auricular point acupressure (APA) and identified on a limited number of patients changes in the connectivity within or between ECN, SAL and BGN immediately and delayed post-APA compared to the pre-APA status. The main areas critical to pain processing – the insula, anterior cingulate cortex, dorsolateral prefrontal cortex are part of these networks. Further studies performed on larger groups of patients and involving different therapeutic methods should be performed to objectivate the therapeutic response.

Conclusions

Despite being a disease of the peripheral nervous system, most CIPN-associated nervous alterations involve pain processing areas and circuits inside the central nervous system. Distinct patterns of pain processing, changes in cerebral perfusion and gray matter density in areas associated with pain processing together with chronic activation of somatosensory areas have been observed in patients with CIPN compared to healthy subjects or their counterparts treated with the same chemotherapeutic agent and who did not develop CIPN. Identification of brain areas involved in central pain processing associated with CIPN may indicate future targets for novel therapies directed to prevent or treat CIPN. A preexisting vulnerability to developing CIPN suggested by a unique pattern of brain activation following nociceptive stimulation before the onset of chemotherapy could facilitate a personalized approach and help

identify high-risk individuals candidates to close monitoring and preventive strategies.

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