

Pain processing in dementia and its relation to neuropathology

Erik JA Scherder, Joseph A Sergeant, and Dick F Swaab

Most clinical studies of pain in dementia have focused on assessment procedures that are sensitive to pain in “demented” or “cognitively impaired” elderly patients. The neuropathology of dementia has not played a major part in pain assessment. In this review, the neuropathological effects of dementia on the medial and the lateral pain systems are discussed. We focus on Alzheimer’s disease (AD), vascular dementia, and frontotemporal dementia. Lewy-body disease and Creutzfeldt-Jakob disease are briefly reviewed. The results of the studies reviewed show that, although the subtypes of dementia show common neuropathological features (such as atrophy and white-matter lesions), the degree by which they occur and affect pain-related areas determine the pattern of changes in pain experience. More specifically, in AD and even more so in frontotemporal dementia, a decrease in the motivational and affective components of pain is generally present whereas vascular dementia might be characterised by an increase in affective pain experience. Future studies should combine data from experimental pain studies and neuropathological information for pain assessment in dementia.

Lancet Neurol 2003; **2**: 677–86

One of the main findings of clinical studies on pain in dementia is that all demented patients are able to complete at least one of the available pain scales.^{1–3} The reliability of these scales decreases with progressive decline in cognitive function.^{2,3} Observation scales⁴ and autonomic responses to pain⁵ can provide valuable information on patients with poor communicative ability who have an advanced stage of dementia.

Research on pain and dementia has hardly gone beyond the development of new assessment procedures. An exception is the study by Benedetti and colleagues,⁶ who applied experimental pain stimuli to patients with Alzheimer’s disease (AD) and then related neuropathology to affective (pain tolerance) and discriminative (pain threshold) features of pain. The many components of pain include: sensory–discriminative, motivational–affective, cognitive–evaluative (such as memory for pain), and autonomic–neuroendocrine.^{7–9} Importantly, most pain scales have focused on sensory–discriminative and motivational–affective components,¹ whereas hardly any of the other domains have been studied. Little has been done to relate these domains to the neuropathological characteristics of specific subtypes of dementia.

The importance of relating neuropathology to pain in dementia has been emphasised in previous reviews.^{2,10–12}

Although a decrease in pain in AD is a consistent finding,^{6,13} an increase in pain may occur in vascular dementia¹⁰ and variant Creutzfeldt-Jakob disease (vCJD).¹⁴ It is an unfortunate misunderstanding, therefore, that the changes in pain processing in AD may be generalised to other types of dementia. However, most clinical studies on pain include both the “demented elderly” and the “cognitively impaired elderly” patients without more detailed information on the causes of their disorders.^{2,11} Information about the cause of the dementia is important, because it is related to neuropathology and, consequently, to possible changes in the patients’ pain. Our objectives in this review are: to extend our knowledge on the relation between neuropathology underlying the various subtypes of dementia and the components of pain processing; and to emphasise that, apart from the diagnosis of the type of dementia, insight into the functioning of pain-related areas and pathways is crucial for clinical practice. Within the nursing home environment, this insight can be gained by neuropsychological and neurological examination.

The medial and lateral pain systems

This review focuses on subcortical and cortical brain areas related to the medial and lateral pain system. For the sake of clarity, we have decided to mention only a few important areas at the level of the reticular formation and the mesencephalon. An extensive review of areas to which the spinoreticular tract and the spinomesencephalic tract project has been made before.¹⁵

The medial pain system (figure 1) includes the spinothalamic tract that projects directly to the intralaminar thalamic nuclei, the spinoreticular tract that projects to the reticular formation (eg, the parabrachial nucleus and the locus coeruleus), and the spinomesencephalic tract that projects to the mesencephalon (eg, the periaqueductal grey matter).¹⁵ There are many connections between the mesencephalon and reticular formation on one side and the intralaminar and medial thalamic nuclei on the other.¹⁵ Other areas that belong to the medial pain system are the thalamic ventral caudal parvocellular nucleus (VCPC) and

EJAS and JAS are at the Department of Clinical Neuropsychology, Vrije Universiteit, Amsterdam, and DFS is at the Netherlands Institute of Brain Research and the University of Amsterdam, Amsterdam, Netherlands.

Correspondence: Prof Erik JA Scherder, Department of Clinical Neuropsychology, Vrije Universiteit, Van der Boechorststraat 1, 1081 BT Amsterdam, Netherlands. Tel +31 20 4448761; fax +31 20 4448971; email EJA.Scherder@psy.vu.nl

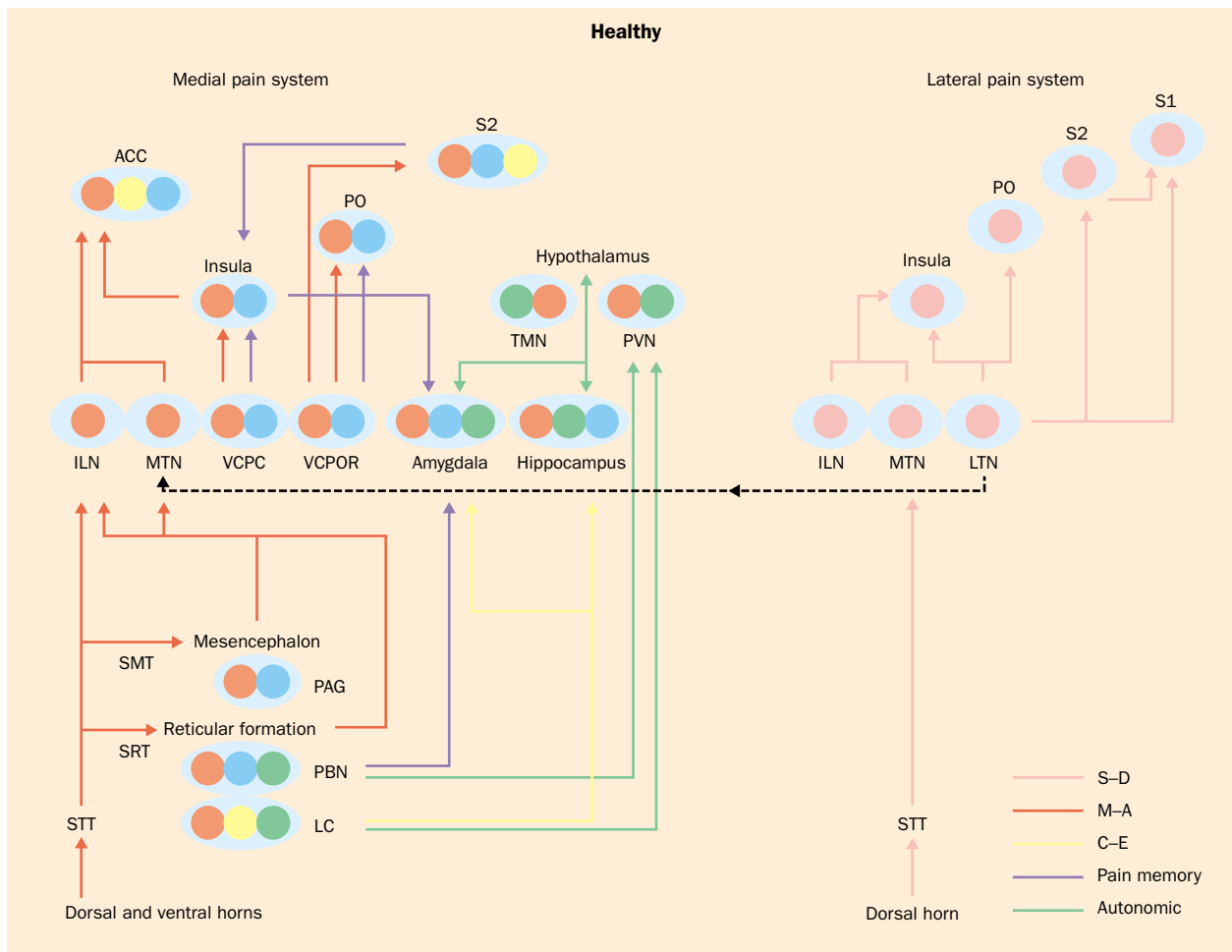


Figure 1. Subcortical and cortical areas and pathways of the medial and lateral pain systems. Most of the brain areas contribute to more than one pain pathway. PO=parietal operculum; TMN=tuberomammillary nucleus; PVN=paraventricular nucleus; ILN=intralaminar thalamic nuclei; MTN=medial thalamic nuclei; SMT=spinothalamic tract; PAG=periaqueductal grey; SRT=spinothalamic tract; PBN=parabrachial nucleus; STT=spinothalamic tract; LC=locus coeruleus. S-D=sensory-discriminative; M-A=motivational-affective; C-E=cognitive-evaluative systems.

the ventral caudal portae nucleus (VCPOR), the insula, parietal operculum, the secondary somatosensory cortex (S2), the anterior cingulate cortex (ACC), the amygdala, the hippocampus, and the hypothalamus.^{8,16,17} The insula, S2, and parietal operculum belong to the parasyllian area, and lesions in this area produce a change in pain perception.⁷

The lateral pain system consists of spinothalamic tract neurons that, through the lateral thalamus, project to the primary somatosensory area (S1), S2, parietal operculum, and the insula (figure 1).⁷

There are few connections between the lateral and medial pain system,¹⁶ except between the lateral and medial thalamic nuclei (see dotted line in figure 1). Disconnection of this link might be a cause of "central post-stroke pain".¹⁸

The many components of pain

The medial and lateral pain systems are involved in different features of pain. The medial pain system plays a crucial part in the motivational-affective and cognitive-evaluative features, the memory for pain, and the autonomic-neuroendocrine responses evoked by pain,

whereas the lateral pain system is particularly involved in the sensory-discriminative features of pain.^{8,16}

Sensory-discriminative

Through the spinothalamic tract, which originates in the dorsal horn, nociceptive stimuli are mediated to the lateral thalamus,¹⁵ and subsequently activate S2 and S1, either simultaneously or in a sequence with S2 as the primary target.⁷ Nociceptive stimuli also activate the parietal operculum and the insula through the lateral thalamus.^{7,19} A normal pain threshold might be dependent on the parietal operculum being intact.⁷ Furthermore, the parietal operculum is important for the recognition of location, intensity, and nature of nociceptive stimuli.⁷ The location and coding of nociceptive stimuli is done in a projection of the medial and intralaminar thalamic nuclei into the insula.⁸

Motivational-affective

Through inputs from the spinothalamic tract that originate from the dorsal and ventral horns, and through the

spinoreticular and spinomesencephalic tracts,¹⁵ the intralaminar and medial thalamic nuclei and the connected ACC, are involved in the motivational–affective features of pain.^{8,16,19} The thalamic VCPOR and VCPC have a strong affective pain component.²⁰ The VCPOR projects to the parietal operculum and S2 whereas the VCPC sends nociceptive information to the insula.^{7–9,16,20} Connections between the insula and the ACC have been found.⁸ In addition, the hypothalamus and the prefrontal cortex are involved in the motivational–affective components of pain.^{20,21} Specifically, the prefrontal cortex plays a part in the anticipation of affective painful stimuli.²¹

Cognitive–evaluative

The locus coeruleus mediates nociceptive information to the cortex thereby enabling attention to be given to pain.¹⁵ S2, and to a lesser extent the ACC, responds less to painful stimuli while doing a cognitive task.²² By receiving input from multiple pain pathways, originating from areas such as the spinal cord and the posterior parietal cortical areas where somatosensory input and cognitive processes, such as memory are integrated, the ACC has a crucial role in the processing of cognitive–evaluative features of pain.²³

Memory

Nociceptive information might be retained through input from the parabrachial nucleus to the amygdala.¹⁵ By stimulation of the VCPC and VCPOR, and consequently the insula and parietal operculum, respectively, people remember and experience affective pain that occurred earlier in life (eg, angina pectoris and labour pain).²⁰ The hippocampus and amygdala (medial-temporal lobe) are involved in the memory for pain through projections from S2 to the insula.²⁰ As described in the former section, by coordination of the cognitive–evaluative and somatosensory features of pain, the ACC, together with the prefrontal cortex, is involved in the assessment of future consequences of pain.²³

Autonomic response

At a mesencephalic level, the periaqueductal grey matter is involved in various autonomic processes.²⁴ At a higher level, through the hypothalamic–pituitary–adrenal axis, the hypothalamus plays a central part in aversive, autonomic–neuroendocrine responses to pain.⁹ Areas from the reticular formation (eg, the parabrachial nucleus and locus coeruleus) project to the hypothalamus.¹⁵ The hypothalamus has extensive reciprocal connections with the prefrontal cortex, the amygdala, and the hippocampus.^{9,25} Since the hypothalamus is a heterogeneous structure,²⁶ we will discuss the tuberomammillary nucleus and the paraventricular nucleus which are both particularly relevant for pain. The tuberomammillary nucleus contains histamine,²⁷ and the paraventricular nucleus is where oxytocin and arginine-vasopressin—which is partly colocalised with corticotropin-releasing hormone—are produced.^{28,29} Most pain-related areas contribute to more than one pain feature of pain (figure 1).

The medial and lateral pain system and neuropathology in dementia

The neuropathology of AD, vascular dementia, and frontotemporal dementia will be discussed exclusively with respect to areas of the lateral and medial pain system. The reason for focusing on these three types of dementia is, as far as we know, that one or more clinical studies with experimental data on changes in pain processing are available only for these subtypes of dementia. The combination of neuropathology and experimental data invites us to propose some cautious theoretical considerations concerning changes in the processing of pain.

Within the scope of the present review, it is worthwhile to discuss briefly other subtypes of dementia (ie, Lewy body disease), and sporadic CJD (sCJD) and vCJD. Although experimental data on pain are lacking, some clinical symptoms of these subtypes point to a change in pain processing, and emphasise the importance of the inclusion of neuropathology in studies of pain in dementia.

Alzheimer's disease

Neuropathology related to the medial and lateral pain system
Although the characteristic neuropathological hallmarks of AD are plaques, tangles,³⁰ and low neuronal metabolism,³¹ evidence suggests that the brains of many patients with AD contain vascular lesions,³² such as white-matter lesions.³³

In the medial pain system, neuronal loss has been found in the locus coeruleus.³⁴ Rüb and colleagues³⁵ observed cytoskeletal pathology in nuclei of the parabrachial region in a preclinical stage of AD and confirmed earlier findings by Parvizi and co-workers, who had made the same observation in the brains of people with Alzheimer's disease.³⁶ At a mesencephalic level, pathological changes were seen in the periaqueductal grey matter.²⁴ Furthermore, severe atrophy has been found in the thalamic medial and intralaminar nuclei, ACC, insula, amygdala, and hippocampus.^{35,37–39} In the hypothalamus, the histaminergic neurons of the tuberomammillary nucleus are affected (figure 2; table).²⁶ The paraventricular nucleus itself shows no degeneration; however, the corticotropin-releasing-hormone neurons are hyperactivated⁴⁰ resulting in hyperactivity of the hypothalamic–pituitary–adrenal axis and increased cortisol concentrations.^{26,41} Taken together, most of the areas of the medial pain system have been examined in AD and seem to be affected (figure 2; table).

The neuropathology of the lateral pain system in AD shows a somewhat different picture (figure 2). Neuropathology in the lateral thalamic nuclei in AD has hardly been examined. Braak and Braak³⁰ observed moderate numbers of neurofibrillary tangles and neuropil threads in the reticular nucleus, only in the final stage of AD. S1 is preserved in AD (figure 2; table).⁴² The high density of myelinated axons may protect S1 against the formation of neurofibrillary tangles.⁴³ This is also reflected in the preservation of connections between S1 and S2. S2 itself is more vulnerable to neurofibrillary tangles.⁴³

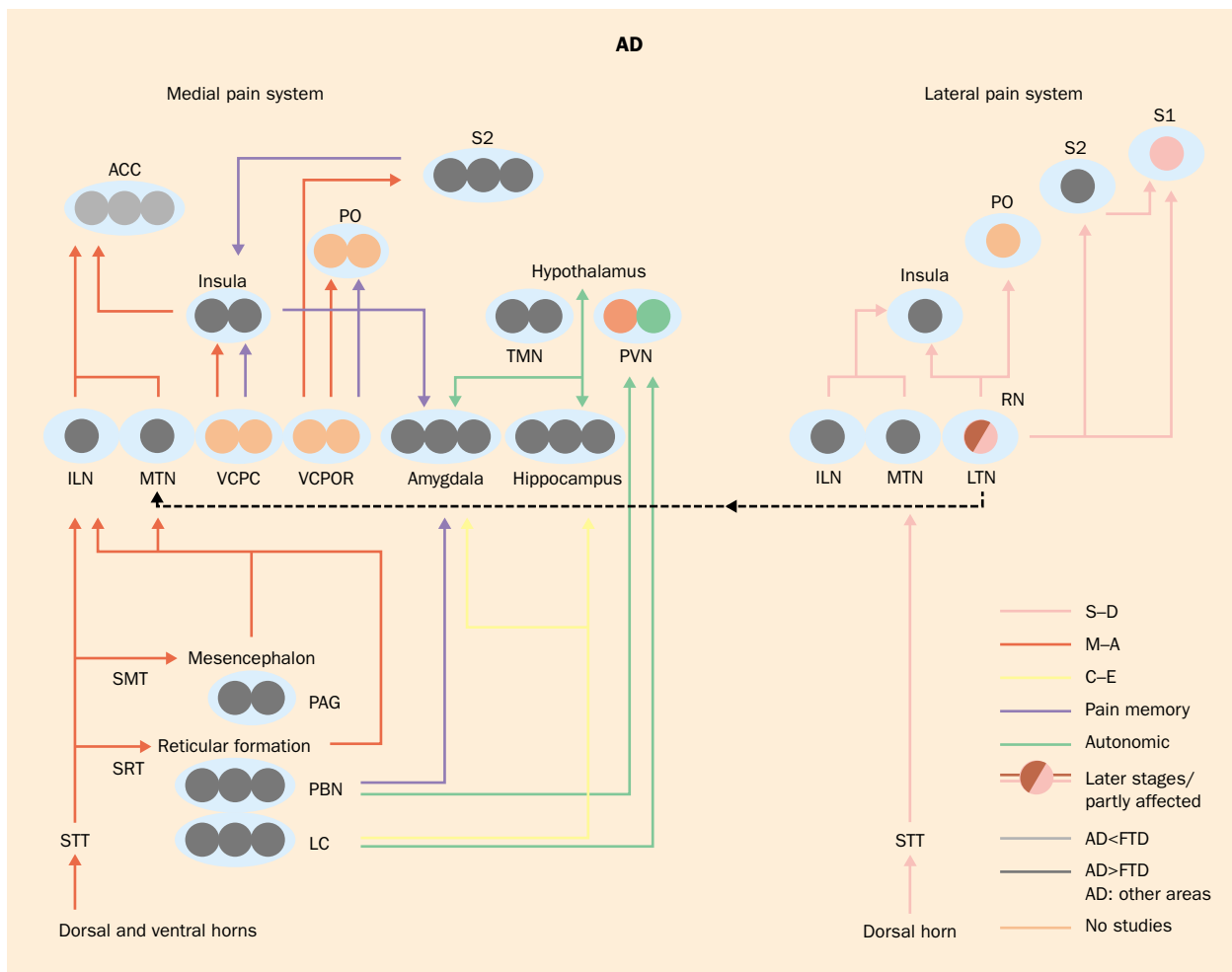


Figure 2. Subcortical and cortical areas and pathways of the medial and lateral pain systems in AD. Most of the areas belonging to the medial pain system are affected in AD PO=parietal operculum; TMN=tuberomammillary nucleus; PVN=paraventricular nucleus; RN=reticular nucleus; ILN=intralaminar thalamic nuclei; MTN=medial thalamic nuclei; SMT=spinomesencephalic tract; PAG=periaqueductal grey; SRT=spinothalamic tract; PBN=parabrachial nucleus; STT=spinothalamic tract; LC=locus coeruleus. S-D=sensory-discriminative; M-A=motivational-affective; C-E=cognitive-evaluative systems. Later stages/partly affected=information about pathology exists only for the thalamic reticular nucleus which is affected in the later stages of AD;³⁰ AD<FTD=affected less in AD than in frontotemporal dementia; AD>FTD=affected more in AD than in frontotemporal dementia.

Clinical studies

Patients with AD have fewer of the affective components of pain than non-demented elderly people.^{44,45} Similar results were obtained after minimising the influence of a possible decline in the memory for pain.¹³ The provocation of pain by electrical stimulation and ischaemia of the arm showed that, compared with the non-demented elderly, the pain threshold of patients with AD did not change (concurring with a relative sparing of S1). However, pain tolerance (pain affect) was significantly higher in patients with AD than in healthy control individuals.⁶ Autonomic responses were blunted by mild noxious stimulation, but seemed to be normal with pain at a high intensity.⁵ Measuring autonomic responses to pain in AD may, therefore, be helpful in the assessment of pain in non-communicative patients. As far we know, however, the cognitive-evaluative features of pain processing have not been examined in AD.

Theoretical considerations

In contrast to the discriminative-sensory features of pain (lateral pain system), one might expect a decline in motivational-affective and cognitive-evaluative features of pain, memory for pain, and autonomic responses to pain given the degeneration of the areas belonging to the medial pain system (figure 1, table). The normal autonomic reaction to extreme painful stimuli⁵ might be mediated by the unaffected hypothalamic paraventricular nucleus. In addition, both arginine-vasopressin and oxytocin have an antinociceptive effect^{46,47} and the number of arginine-vasopressin and oxytocin expressing neurons in the paraventricular nucleus remains unchanged in AD.²⁹ Moreover, the corticotropin-releasing-hormone neurons that produce analgesia⁴⁸ are hyperactive in AD.⁴⁰

Although neuropathology largely explains the clinically observed decline in the experience of motivational-affective aspects of pain in AD, the effect on the tuberomammillary

Brain areas of the medial and lateral pain system and the amount of involvement in the various types of dementia.

	Medial pain system										Lateral pain system			WMLs			
	LC	PBN	PAG	Thalamus MTN	ILN	VCN	Insula*	ACC	Hippocampus	Amygdala	Hypothalamus PVN	TMN	Prefrontal cortex		Thalamus LTN	S1	S2
AD	+	+	+	+	+	+	+	++	++		+	+		+	-	+	+
VaD										+Dis	+Dis	+Dis					++
FTD	-						+	++	+	+	+	++					+
LBD	+†						+‡	+†	+/-‡	+/-‡	+	+	+‡		-		+
sCJD				+		+					+	+					+
vCJD				+							++						++

No studies on the influence of one or more subtypes of dementia on the parietal operculum were found. In the lateral thalamic nuclei in AD, only the reticular nucleus is affected. VaD=vascular dementia; FTD=frontotemporal dementia; LBD=Lewy-body disease; LC=locus coeruleus; PBN=parabrachial nucleus; PAG=periaqueductal grey; MTN=medial thalamic nuclei; ILN=intralaminar nuclei; VCN=ventral caudal nucleus; ACC=anterior cingulate cortex; PVN=paraventricular nucleus; TMN=tuberomammillary nucleus; LTN=lateral thalamic nuclei; WML=white-matter lesion; -=unaffected; +=affected ++=strongly affected in comparison with other dementias; +Dis=affected by disconnection. *also part of the lateral pain system; †presence of Lewy Bodies; ‡grey matter atrophy.

nucleus-histaminergic system²⁶ and the presence of white-matter lesions may increase the experience of pain. In other words, although a decrease in motivational-affective pain might be characteristic for AD, an increase in the affective features of pain cannot be excluded.

Vascular dementia

Neuropathology related to the medial and lateral pain system

Vascular dementia is a highly heterogeneous disorder.³² In contrast to AD, frontotemporal dementia, and Lewy-body dementia, vascular dementia is primarily characterised by white-matter lesions^{39,50} and, to a lesser extent, by brain atrophy.^{33,51} Consequently, cognitive impairment may result from disruption of corticosubcortical circuits (deafferentiation), specifically frontosubcortical circuits,⁵² caused by small cortical infarcts or white-matter lesions.⁵³ A large infarct causes dementia when hypoperfusion and oxygen hypometabolism are present, particularly in the frontal lobe.⁵⁴

In the medial pain system, only a few pain-related areas have been described in vascular dementia (table). From caudal to rostral, Yang and colleagues⁵⁵ observed no significant neuronal loss in the locus coeruleus. Notably, a disconnection between the hippocampus and hypothalamus (figure 3) may cause overactivity in the hypothalamus-pituitary-adrenal axis,²⁵ which results in disturbed autonomic feedback,⁵⁶ and increased concentrations of corticotropin-releasing hormone.²⁵ There are no studies of the influence of vascular dementia on areas belonging to the lateral pain system.

Clinical studies

One study on pain included patients with "possible" vascular dementia.⁵⁷ These patients reported pain of a significantly higher intensity than non-demented elderly people and people with pain from chronic painful diseases, such as arthritis. However, one of the limitations of that study was that the diagnosis of vascular dementia was not confirmed by autopsy, and CT scans were unavailable. In short, of the five pain components, only preliminary information exists on how vascular dementia influences affective components of pain.

Theoretical considerations

Because infarctions of the brain can occur at many locations, they influence all five dimensions of pain (ie, the lateral and medial pain system). Disruption of connection in the cortex and between the cortex and subcortex by white-matter lesions⁵³ may increase the experience of pain in vascular dementia.¹⁰ This can occur, for instance, when white-matter lesions disrupt connections between S2 and the intralaminar thalamic nuclei (figure 3),⁵⁸ or when a lesion of the lateral spinothalamic cortical pathway to the parietoinsular system disinhibits the medial spinothalamic cortical pathway to the ACC (figure 3).⁵⁹ In both cases, deafferentiation by white-matter lesions produces "central post-stroke pain", which can occur 6 months or more after the event.¹⁸ This pain may be underreported owing to developing dementia. Headaches is another type of longterm post-stroke pain,¹⁸ which also occurs in patients who have not had stroke but who have deep white-matter lesions.⁶⁰

Although the neuropathology points to an increase, rather than a decrease, in the motivational-affective components of pain, a decrease in this part of pain can not be excluded given the hyperactivity in the hypothalamus-pituitary-adrenal axis and the resulting increased production of corticotropin releasing hormone.^{25,41} The pain pattern of vascular dementia is opposite to that of AD, implying that, although a decrease in affective pain experience is possible, an increase in suffering from pain occurs in vascular dementia.

Frontotemporal dementia

Neuropathology related to medial and lateral pain systems

Frontotemporal dementia is linked to chromosome 17 and is characterised by dementia, parkinsonism, and inclusion bodies that stain for phosphorylated neurofilaments. Several tau mutations are linked to frontotemporal dementia.⁶¹ In contrast to those with AD and vascular dementia, patients with frontotemporal dementia have the most severe atrophy in the frontal, lateral temporal, and parietal regions.⁶² White-matter lesions have been seen in frontotemporal dementia, although they are much less noticeable than in vascular dementia.⁵⁰

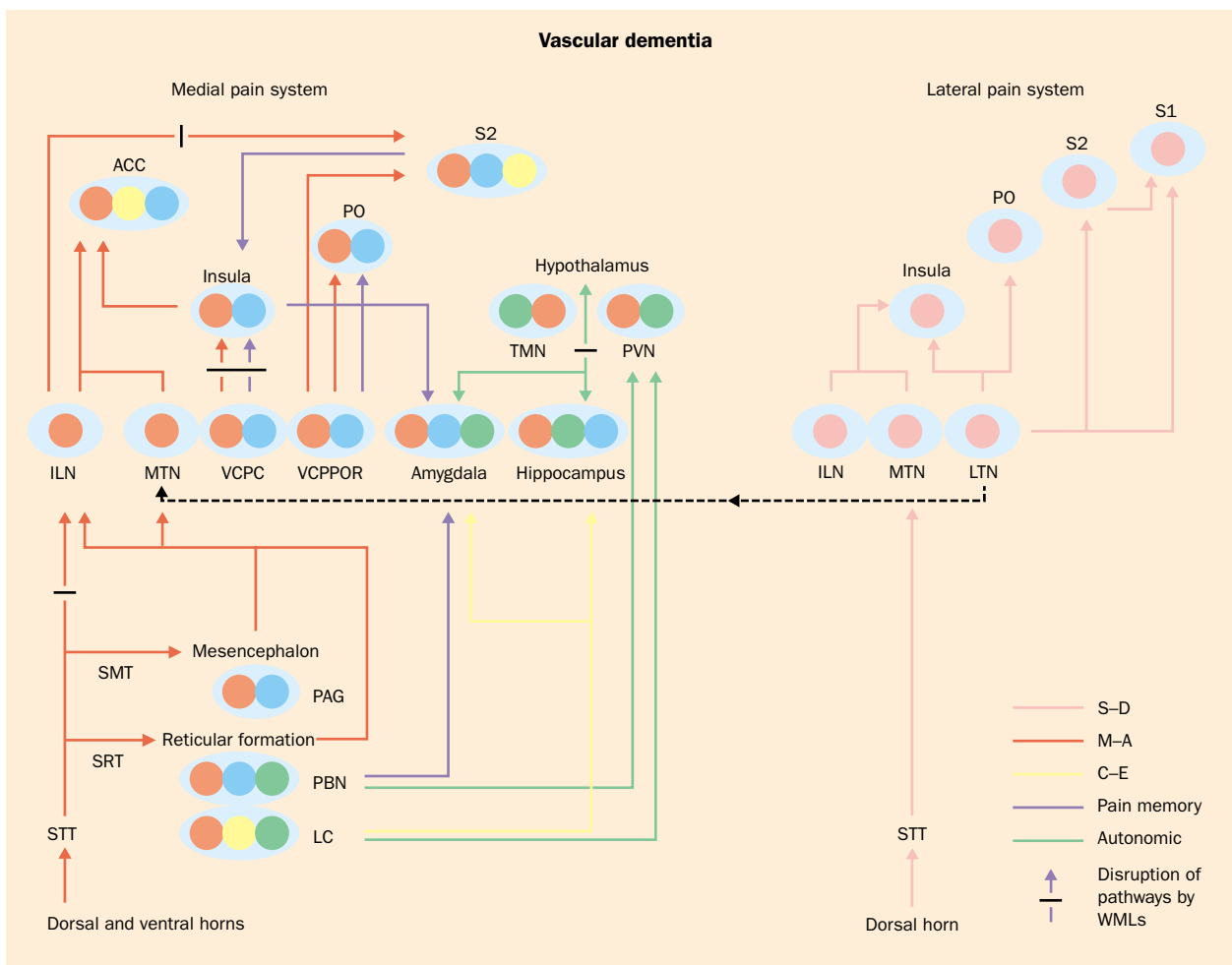


Figure 3. Subcortical and cortical areas and pathways of the medial and lateral pain systems in vascular dementia. Note the disconnections between the various brain areas that cause disruptions to pathways. PO=parietal operculum; TMN=tuberomammillary nucleus; PVN=paraventricular nucleus; ILN=intralaminar thalamic nuclei; MTN=medial thalamic nuclei; SMT=spinomesencephalic tract; PAG=periaqueductal grey; SRT=spinothalamic tract; PBN=parabrachial nucleus; STT=spinothalamic tract; LC=locus coeruleus. S-D=sensory-discriminative; M-A=motivational-affective; C-E=cognitive-evaluative systems; WMLs=white-matter lesions.

More specifically, in the medial pain system, brain atrophy was observed in the middle frontal gyrus, the insula, and the ACC.⁶³ Compared with patients with AD, patients with frontotemporal dementia had a more severe reduction in regional cerebral blood flow (rCBF) in the right medial prefrontal cortex, orbitofrontal cortex, and ACC (figure 4; table).⁶⁴ The rCBF in the anterior temporal cortex, which is located near the sylvian cortex, and, therefore, important for the processing of pain, is more reduced in frontotemporal dementia than it is in AD.⁶⁴ Varrone and colleagues⁶⁴ stated that the affected areas are strongly related to emotional states and motivation. By contrast, the amygdala and the hippocampus are more severely affected in AD than in frontotemporal dementia (figure 4; table).^{65,66} The highly fragmented and phase-advanced rest-activity rhythm⁶⁷ and the frequent occurrence of thyroid hormone abnormalities,⁶⁸ indicate involvement of the hypothalamus. The hypothalamus has not been studied systematically in frontotemporal dementia. Only one study was found in

which the locus coeruleus seemed to be spared in this disorder.⁶⁹ The relation between frontotemporal dementia and areas related to the lateral pain system has not been extensively studied.

Clinical studies

Only one study compared behavioural disturbances in frontotemporal dementia, AD, and vascular dementia, which included pain as a dependent variable.⁷⁰ The appreciation of nociceptive stimuli in frontotemporal dementia was significantly lower than in AD and vascular dementia, which was evidenced by severe burns after contact with hot water. This finding suggests that the disease process seriously damages the ability to anticipate danger (cognitive-evaluative) and to make timely withdrawal from hot water (sensory-discriminative). More research into the influence of frontotemporal dementia on the cognitive-evaluative and sensory-discriminative components and other features of pain is needed.

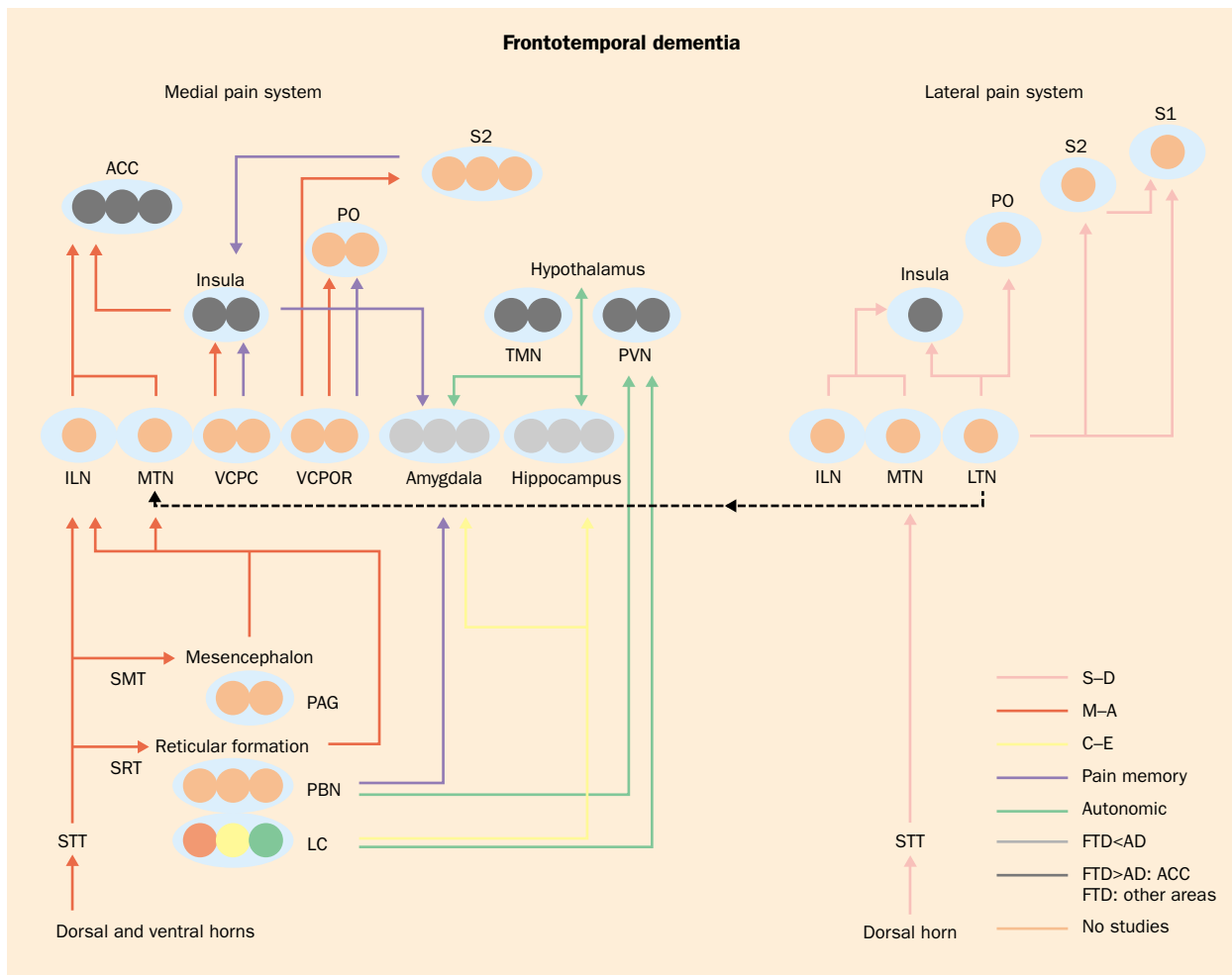


Figure 4. Subcortical and cortical areas and pathways of the medial and lateral pain system in frontotemporal dementia (FTD). Note that the prefrontal cortex which is more affected in FTD than in AD⁶⁴ is not indicated in the figure. PO=parietal operculum; TMN=tuberomammillary nucleus; PVN=paraventricular nucleus; ILN=intralaminar thalamic nuclei; MTN=medial thalamic nuclei; SMT=spinomesencephalic tract; PAG=periaqueductal grey; SRT=spinoreticular tract; PBN=parabrachial nucleus; STT=spinothalamic tract; LC=locus coeruleus. S-D=sensory-discriminative; M-A=motivational-affective; C-E=cognitive-evaluative system; FTD<AD=affected less in FTD than in AD; FTD>AD=affected more in FTD than in AD.

Theoretical considerations

Compared with AD, the degeneration of the ACC and the insula is severe in frontotemporal dementia, whereas atrophy of the amygdala and hippocampus is milder. One could argue that the cognitive-evaluative and motivational-affective aspects, as well as memory for pain, and autonomic-neuroendocrine responses to pain are especially prone to deterioration in frontotemporal dementia. There is overlap between AD and frontotemporal dementia in affected pain-related areas. However, the prefrontal cortex (not included in figures 1–4) plays a greater part in frontotemporal dementia than in AD, a finding that might explain why patients with the former experience fewer of the motivational-affective features of pain than patients with AD.⁷⁰

Pain assessment in the nursing home

In the nursing home, in addition to pain assessment tools, assessment instruments can be used that provide insight

into the functioning of a pain-related area itself or provide specific information about the processing of sensory stimuli. Those instruments include neuropsychological testing and a brief neurological examination, respectively.

Neuropsychological testing

Several brain areas of both the medial and lateral pain systems have a role in pain processing and cognition. The parietal operculum and S2 have a role in tactile object recognition,⁷ and the ACC is involved in the response interference task, the Stroop colour word test.^{71,72} The results of a specific cognitive test may be indicative of an area's role in pain processing. Because factors other than pain can cause poor test scores, only scores that meet the normal age-related measures are informative, because they reflect the integrity of all areas active during test performance, including the pain-related area under examination.

Neuropsychology is valuable as part of the comprehensive screening to provide a differential diagnosis in dementia.^{73,74} However, the strength of individual test scores in differential diagnosis is limited. For instance, patients with frontotemporal dementia were more impaired in verbal fluency than patients with AD in one study,⁷⁵ but not in another study.⁷⁶ Therefore, neuropsychological tests must include age and stage related dementia-specific expected values to differentiate between the various types of dementia. The final diagnosis, however, can only be made with autopsy.

Neurological examination

To date, studies on pain in dementia have failed to include a brief neurological examination assessing sensitivity to tactile stimuli, temperature, and pain. Such an examination could provide important additional information for the daily care of patients with dementia. For example, an increased reaction to an otherwise normal temperature or tactile stimuli, in combination with a reduced or abolished reaction to a pinprick, is indicative of allodynia, a type of pain associated with central post-stroke pain¹⁸ or mononeuropathy.⁷⁷ Allodynia helps explain why, despite a gentle approach, the patients react so aggressively when helped to bathe.

The contribution of neuropsychological testing and neurological examination to pain assessment in dementia is restricted. However, both techniques might provide insight into possible changes in an individual's experience of pain.

Discussion

Results from the studies reviewed here show that—although atrophy and white-matter lesions are neuropathological features common to all three dementia subtypes—the varying degree by which they occur and affect the different areas of the medial and lateral pain systems determines the pattern of changes in pain processing.

Both the neuropathology and the experimental data suggest the likelihood of a particular pain pattern for AD, vascular dementia, and frontotemporal dementia. Specifically, a decrease in the motivational–affective components of pain might prevail in AD, and to a greater degree in frontotemporal dementia, whereas patients with vascular dementia can have quite the opposite pain pattern (ie, an increase in affective pain experience).

However, generalisations regarding the dementia-specific patterns of pain presented here are made with caution. Some patients with AD or frontotemporal dementia experience greater pain due to such factors as the presence of white-matter lesions. Patients with vascular dementia may experience less pain due to hyperactivity in the hypothalamus–pituitary–adrenal axis and high corticotropin-releasing-hormone production.^{25,41} This point highlights the need for further development of pain assessment instruments. Specifically, in a clinical setting, where insight into the specific neuropathology is often difficult, new instruments, such as neurological and psychological tests can provide information about the

functioning of the pain-related brain area. Poor ability to do episodic memory tasks, in which the hippocampus and amygdala play a central part,⁷⁸ should alert medical staff that the patient may forget that they have pain.

Experimental data on pain in other subtypes of dementia such as Lewy-body dementia and CJD are currently lacking. However, it is interesting to present briefly the pain-related neuropathology in those types of dementia. This provides insight into the clinically observed reduction in pain perception in Lewy-body dementia and the occurrence of painful sensations in sCJD.

The extent of white-matter lesions in Lewy-body dementia is similar to that in AD.⁴⁹ More specifically related to the medial pain system, grey-matter atrophy was found in the parasyllian area⁷⁹ but not in the hippocampus or amygdala. High densities of Lewy bodies have been found in the amygdala, parahippocampal region, the ACC, the inferior temporal area, and the hypothalamus (not further specified; table).^{80,81} Lewy bodies have been identified in the locus coeruleus.⁸² With respect to measuring autonomic responses to pain, orthostatic hypotension impairs autonomic responses to pain in Lewy-body dementia.⁸³ Although not specifically related to Lewy-body dementia, Rüb and colleagues⁸⁴ observed a high density of Lewy bodies and Lewy neuritis in the medial thalamic nuclei of patients with Parkinson's disease. In the lateral pain system, S1 is preserved in Lewy-body dementia.⁸⁵ In Parkinson's disease, the primary sensory thalamic nuclei are relatively free of Lewy bodies and Lewy neuritis.⁸⁴ Atrophy and Lewy bodies particularly affect areas related to the medial pain system suggesting that almost all facets of pain, including its autonomic responses, may deteriorate in Lewy-body dementia. The predicted change in pain perception has been shown in only one case study thus far.⁸⁶ In that study, a patient with Parkinson's disease and Lewy-body dementia, who had an acute aortic dissection, indicated no experience of pain. The patient did not have diabetes. Typically, such a trauma coincides with the onset of acute pain.⁸⁶

In CJD, a distinction should be made between sCJD and vCJD, including the panencephalopathic type (pCJD).¹⁴ In the medial pain system in sCJD (table), neuronal loss has been observed in the ventral nuclear group of the thalamus, the thalamic reticular nucleus,⁸⁷ hypothalamus (not further specified)⁸⁸ and hippocampus.⁵⁴ In vCJD, the hippocampus and the medial thalamic nuclei show neuropathological changes.⁸⁹ Deep grey matter degeneration involving the medial thalamic nuclei, as well as severe white-matter changes, characterise pCJD,⁹⁰ although subcortical white-matter degeneration has also been observed in sCJD.⁹¹ Compared with sCJD, vCJD produces the most severe spongiform changes in the paraventricular nucleus of the hypothalamus.⁹² With respect to the lateral pain system, S1 might be preserved in sCJD.⁹³

Results of clinical studies reveal an early prevalence of affective pain in the limbs, trunk and face in vCJD,^{14,94,95} which distinguishes it from sCJD.¹⁴ Other sensory symptoms included hypersensitivity, feelings of coldness,

particularly in the feet, paraesthesia and numbness. These findings can be explained by the severe white-matter lesions that may provoke pain, for instance, by disrupting thalamocortical pathways or by degeneration of the paraventricular nucleus, which destroys its analgesic effect.

We stress that for the dementia subtypes reviewed here and for other subtypes of dementia (eg, semantic dementia), experimental studies are needed to examine possible change in one or more components of the medial and lateral pain system. Neuropathology has not been determined in many of pain-related areas (figures 2–4). Note, however, that several studies that did examine the neuropathology in pain-related areas used neuroimaging techniques.^{37–39} These findings should be confirmed by examination of the brain after death as has been done in some other studies.^{17,30,35,41} Future research should therefore include brain autopsy to relate the anatomical distribution of the lesions to the functional changes in pain modalities and to establish a final diagnosis of the type of dementia.

Currently, studies have focused on the assessment of various features of pain in demented patients. However, the double function of the pain-related area (ie, pain processing and cognition), implies that an improvement in cognition may coincide with an increase in pain. This may explain in part the observation that cognitive improvement by cholinesterase inhibitors, such as rivastigmine, coincides with an increase in pain reported.⁹⁶ The relation between the many features of pain, neuropathology, and new intervention strategies in dementia should become a goal for research.

Search strategy and selection criteria

Data for this review were selected from the personal files of the authors and in searches in MEDLINE and Web of Science. The search terms we used were “pain”, “medial pain system”, “lateral pain system”, “pain assessment”, “nociceptive stimuli”, “nociception”, “Alzheimer’s disease”, “vascular dementia”, “frontotemporal dementia”, “Lewy-body disease”, “sporadic Creutzfeldt-Jakob”, “variant Creutzfeldt-Jakob”, “atrophy”, “white-matter lesions”, “neuropsychological assessment”, and “cognition”. Moreover, we included all the areas belonging to the medial and lateral pain system separately and searched for studies in which these areas and adjacent pathways were examined with respect to the neuropathology in the various subtypes of dementia. We searched for studies in which the neuropathology of two or more dementias could be compared. Recent articles were preferentially selected.

Authors’ contributions

EJAS made the overall plan for the review, the relation between the clinical and neuropathological features (including four figures and one table), and the final version of the paper, incorporating the revisions from the other coauthors. JAS helped write the sections on neuropsychology, neurological examination, and concluding remarks. DFS wrote the sections on neuropathology and autonomic responses to pain.

Conflict of interest

We have no conflict of interest.

Role of the funding source

The work contributing to this review is supported by Fontis Amsterdam (EJAS), and RIDE-NWO, ISAO, Hersenstichting Nederland (DFS) which had no role in the preparation of the paper or the decision to submit it for publication.

References

- 1 Ferrell BA, Ferrell BR, Rivera L. Pain in cognitively impaired nursing home patients. *J Pain Symptom Manage* 1995; **10**: 591–98.
- 2 Scherder EJA. Low use of analgesics in Alzheimer’s Disease: possible mechanisms. *Psychiatry* 2000; **63**: 1–12.
- 3 Wynne CF. Comparison of pain assessment instruments. *Geriatr Nurs* 2000; **21**: 20–23.
- 4 Manfredi PL, Breuer B, Meier DE, Libow L. Pain assessment in elderly patients with severe dementia. *J Pain Symptom Manage* 2003; **25**: 48–52.
- 5 Rainero I, Vighetti S, Bergamasco B, Pinessi L, Benedetti F. Autonomic responses and pain perception in Alzheimer’s disease. *Eur J Pain* 2000; **4**: 267–74.
- 6 Benedetti F, Vighetti S, Ricco C, et al. Pain threshold and tolerance in Alzheimer’s disease. *Pain* 1999; **80**: 377–82.
- 7 Treede R, Apkarian AV, Bromm B, Greenspan JD, Lenz FA. Cortical representation of pain: functional characterization of nociceptive areas near the lateral sulcus. *Pain* 2000; **87**: 113–19.
- 8 Vogt BA, Sikes RW. The medial pain system, cingulate cortex, and parallel processing of nociceptive information. In: Mayer EA, Saper CB, eds. *Progress in brain research*, vol. 122. Amsterdam: Elsevier Science, 2000: 223–35.
- 9 Tsigos C, Chrousos GP. Hypothalamic-pituitary-adrenal axis, neuroendocrine factors and stress. *J Psychosom Res* 2002; **53**: 865–71.
- 10 Farrell MJ, Katz B, Helme RD. The impact of dementia on the pain experience. *Pain* 1996; **67**: 7–15.
- 11 Huffman JC, Kunik ME. Assessment and understanding of pain in patients with dementia. *Gerontologist* 2000; **40**: 574–81.
- 12 Pickering G, Eschaliar A, Dubray C. Pain and Alzheimer’s disease. *Gerontology* 2000; **46**: 235–41.
- 13 Scherder EJA, Bouma A, Slaets J, et al. Repeated pain assessment in Alzheimer’s Disease. *Dement Geriatr Cogn Disord* 2001; **12**: 400–07.
- 14 Prabhakar S, Bhatia R. Diagnosis of Creutzfeldt-Jacob disease. *Neurol India* 2001; **49**: 325–28.
- 15 Willis WD, Westlund KN. Neuroanatomy of the pain system and the pathways that modulate pain. *J Clin Neurophysiol* 1997; **14**: 2–31.
- 16 Sowards TV, Sowards MA. The medial pain system: neural representations of the motivational aspect of pain. *Brain Res Bull* 2002; **59**: 163–80.
- 17 Rüb U, Del Tredici K, Del Turco D, Braak H. The intralaminar nuclei assigned to the medial pain system and other components of this system are early and progressively affected by the Alzheimer’s disease-related cytoskeletal pathology. *J Chem Neuroanat* 2002; **23**: 279–90.
- 18 Widar M, Samuelson L, Karlsson-Tivenius S, Ahlström G. Long-term pain conditions after a stroke. *J Rehabil Med* 2002; **34**: 165–70.
- 19 Peyron R, Laurent B, Garcia-Larrea L. Functional imaging of brain responses to pain. A review and meta-analysis (2000). *Neurophysiol Clin* 2000; **30**: 263–88.
- 20 Hua SE, Garonzik IM, Lee JJ, Lenz FA. Microelectrode studies of normal organization and plasticity of human somatosensory thalamus. *J Clin Neurophysiol* 2000; **17**: 559–74.
- 21 Porro CA, Baraldi P, Pagnoni G, et al. Does anticipation of pain affect cortical nociceptive systems? *J Neurosci* 2002; **22**: 3206–14.
- 22 Petrovic P, Petersson KM, Ghatan PH, Stone-Elander S, Ingvar M. Pain-related cerebral activation is altered by a distracting cognitive task. *Pain* 2000; **85**: 19–30.
- 23 Price D. Psychological and neural mechanisms of the affective dimension of pain. *Science* 2000; **288**: 1769–72.
- 24 Parvizi J, Van Hoesen GW, Damasio A. Selective pathological changes of the periaqueductal gray matter in Alzheimer’s disease. *Ann Neurol* 2000; **48**: 344–53.
- 25 Swaab DF, Fliers E, Hoogendijk WJG, Veltman DJ, Zhou JN. Interaction of prefrontal cortical and hypothalamic systems in the pathogenesis of depression. In: Uylings HBM, Van Eden CG, De Bruin JPC, Feenstra MGP, Pennartz CMA, eds. *Progress in brain research*, volume 126. Amsterdam: Elsevier Science, 2000: 369–96.
- 26 Swaab DF. Neurobiology and neuropathology of the human hypothalamus. In: Bloom FE, Björklund A, Hökfelt T, eds. *Handbook of chemical neuroanatomy*, volume 13: the primate nervous system, part I. Amsterdam: Elsevier Science, 1997: 39–137.
- 27 Brown RE, Stevens DR, Haas HL. The physiology of brain histamine. *Prog Neurobiol* 2001; **63**: 637–72.
- 28 Raadsheer FC, Tilders FJ, Swaab DF. Similar age related increase of vasopressin colocalization in paraventricular corticotropin-releasing hormone neurons in controls and Alzheimer patients. *J Neuroendocrinol* 1994; **6**: 131–33.
- 29 Ishunina TA, Swaab DF. Neurohypophysial peptides in aging and Alzheimer’s disease. *Ageing Res Rev* 2002; **1**: 537–58.
- 30 Braak H, Braak E. Neuropathological staging of Alzheimer-related changes. *Acta Neuropathol* 1991; **82**: 239–59.
- 31 Swaab DF, Dubelaar EJJ, Hofman MA, Scherder EJA, Van Someren EJJW, Verwer RWH. Brain aging and Alzheimer’s disease: use it or lose it. In: Hofman MA, Boer GJ, Holtmaat AJGD, Van Someren EJJW, Verhaagen J, Swaab DF, eds. *Progress in brain research*, volume 138. Amsterdam: Elsevier Science, 2002: 343–73.
- 32 Jellinger KA. The pathology of ischemic-vascular dementia: an update. *J Neurol Sci* 2002; **203–204**: 153–57.
- 33 Scheltens P, Kittner B. Preliminary results from an MRI/CT-based database for vascular dementia and Alzheimer’s disease. *Ann N Y Acad Sci* 2000; **903**: 542–46.
- 34 Zarow C, Lyness SA, Mortimer JA, Chui HC. Neuronal loss is greater in the locus coeruleus than nucleus basalis and substantia nigra in Alzheimer and Parkinson diseases. *Arch Neurol* 2003; **60**: 337–41.
- 35 Rüb U, Del Tredici K, Schultz C, Thal DR, Braak E, Braak H. The autonomic higher order processing nuclei of the lower brain stem are among the early targets of the Alzheimer’s disease-related cytoskeletal pathology. *Acta Neuropathol* 2001; **101**:

- 555–64.
- 36 Parvizi J, Van Hoesen GW, Damasio A. Severe pathological changes of parabrachial nucleus in Alzheimer's disease. *NeuroReport* 1998; **9**: 4151–54.
- 37 Foundas AL, Leonard CM, Mahoney SM, Agee OF, Heilman KM. Atrophy of the hippocampus, parietal cortex, and insula in Alzheimer's disease: a volumetric magnetic resonance imaging study. *Neuropsychiatry Neuropsychol Behav Neurol* 1997; **10**: 81–89.
- 38 Rombouts SARB, Barkhof F, Witter MP, Scheltens P. Unbiased whole-brain analysis of gray matter loss in Alzheimer's disease. *Neurosci Lett* 2000; **285**: 231–33.
- 39 Callen DJA, Black SE, Gao F, Caldwell CB. Limbic system perfusion in Alzheimer's disease measured by MRI-coregistered HMPAO SPET. *Eur J Nucl Med* 2002; **29**: 899–906.
- 40 Raadsheer FC, van Heerikhuizen JJ, Lucassen PJ, Hoogendijk WJG, Tilders FJH, Swaab DF. Corticotropin-releasing hormone mRNA levels in the paraventricular nucleus of patients with Alzheimer's disease and depression. *Am J Psychiatry* 1995; **152**: 1372–76.
- 41 Swaab DF, Raadsheer FC, Enderst E, Hofman MA, Kamphorst W, Ravid R. Increased cortisol levels in aging and Alzheimer's disease in post-mortem cerebrospinal fluid. *J Neuroendocrinol* 1994; **6**: 681–87.
- 42 Dickson DW. Neuropathology of Alzheimer's disease and other dementias. *Clin Geriatr Med* 2001; **17**: 209–28.
- 43 Brückner G, Hausen D, Härtig W, Drlicek M, Arendt T, Brauer K. Cortical areas abundant in extra cellular matrix chondroitin sulphate proteoglycans are less affected by cytoskeletal changes in Alzheimer's disease. *Neuroscience* 1999; **92**: 791–805.
- 44 Scherder EJA, Bouma A, Borkent M, Rahman O. Alzheimer patients report less pain intensity and pain affect than non-demented elderly. *Psychiatry* 1999; **62**: 265–72.
- 45 Scherder EJA, Bouma A. Visual analogue scales for pain assessment in Alzheimer's disease. *Gerontology* 2000; **46**: 47–53.
- 46 Wahlbeck K, Sundblom M, Kalso E, Tigerstedt I, Rimón R. Elevated plasma vasopressin and normal cerebrospinal fluid angiotensin-converting enzyme in chronic pain disorder. *Biol Psychiatry* 1996; **40**: 994–99.
- 47 Lund I, Long-Chuan Y, Uvnäs-Moberg K, et al. Repeated massage-like stimulation induces long-term effects on nociception: contribution of oxytocinergic mechanisms. *Eur J Neurosci* 2002; **16**: 330–38.
- 48 Lariviere WR, Melzack R. The role of corticotropin-releasing factor in pain and analgesia. *Pain* 2000; **84**: 1–12.
- 49 Barber R, Scheltens P, Gholkar A, et al. White matter lesions on magnetic resonance imaging in dementia with Lewy bodies, Alzheimer's disease, vascular dementia, and normal aging. *J Neurol Neurosurg Psychiatry* 1999; **67**: 66–72.
- 50 Varma AR, Laitt R, Lloyd JJ, et al. Diagnostic value of high signal abnormalities on T2 weighted MRI in the differentiation of Alzheimer's, frontotemporal and vascular dementias. *Acta Neurol Scand* 2002; **105**: 355–64.
- 51 Bigler ED, Kerr B, Victoroff J, Tate DF, Breitner JCS. White matter lesions, quantitative magnetic resonance imaging, and dementia. *Alzheimer Dis Assoc Disord* 2002; **16**: 161–70.
- 52 Szirmai I, Vastagh I, Szombathelyi E, Kamondi A. Strategic infarcts of the thalamus in vascular dementia. *J Neurol Sci* 2002; **203–204**: 91–97.
- 53 Mori E. Impact of subcortical ischemic lesions on behavior and cognition. *Ann NY Acad Sci* 2002; **977**: 141–48.
- 54 Tanaka M, Okamoto K, Hirai S. Cerebral blood flow and oxygen metabolism in vascular dementia evaluated by positron emission tomography. *Ann NY Acad Sci* 2002; **977**: 135–40.
- 55 Yang Y, Beyreuther K, Schmitt HP. Spatial analysis of the neuronal density of aminergic brainstem nuclei in primary neurodegenerative and vascular dementia: comparative immunocytochemical and quantitative study using a graph method. *Anal Cell Pathol* 1999; **19**: 125–38.
- 56 Gottfries CG, Balldin J, Blennow K, et al. Regulation of the hypothalamic-pituitary-adrenal axis in dementia. *Ann NY Acad Sci* 1994; **746**: 336–44.
- 57 Scherder EJA, Slaets J, Deijen J-B, et al. Pain assessment in patients with possible vascular dementia. *Psychiatry* 2003; **66**: 133–45.
- 58 Schmahmann JD, Leifer D. Parietal pseudothalamic pain syndrome. *Arch Neurol* 1992; **490**: 1032–37.
- 59 Craig ADB. A new version of the thalamic disinhibition hypothesis of central pain. *Pain Forum* 1998; **7**: 1–14.
- 60 Fujishima M, Yao H, Terashi A, et al. Deep white matter lesions on MRI, and not silent brain infarcts are related to headache and dizziness of non-specific cause in non-stroke Japanese subjects. *Intern Med* 2000; **39**: 727–31.
- 61 Van Swieten JC, Stevens M, Rosso SM, et al. Phenotypic variation in hereditary frontotemporal dementia with tau mutations. *Ann Neurol* 1999; **46**: 617–26.
- 62 Varma AR, Adams W, Lloyd JJ, et al. Diagnostic patterns of regional atrophy on MRI and regional cerebral blood flow change on SPECT in young onset patients with Alzheimer's disease, frontotemporal dementia and vascular dementia. *Acta Neurol Scand* 2002; **105**: 261–69.
- 63 Rosen HJ, Gorno-Tempini ML, Goldman WP, et al. Patterns of brain atrophy in frontotemporal dementia and semantic dementia. *Neurology* 2002; **58**: 198–208.
- 64 Varrone A, Pappatà S, Caracò C, et al. Voxel-based comparison of rCBF SPET images in frontotemporal dementia and Alzheimer's disease highlights the involvement of different cortical networks. *Eur J Nucl Med* 2002; **29**: 1447–54.
- 65 Laakso MP, Frisoni GB, Könönen M, et al. Hippocampus and entorhinal cortex in frontotemporal dementia and Alzheimer's disease: a morphometric MRI study. *Biol Psychiatry* 2000; **47**: 1056–63.
- 66 Boccardi M, Pennanen C, Laakso MP, et al. Amygdaloid atrophy in frontotemporal dementia and Alzheimer's disease. *Neurosci Lett* 2002; **335**: 139–43.
- 67 Harper DG, Stopa EG, McKee AC, et al. Differential circadian rhythm disturbances in men with Alzheimer disease and frontotemporal degeneration. *Arch Gen Psychiatry* 2001; **58**: 353–60.
- 68 Smith JW, Evans AT, Costall B, Smythe JW. Thyroid hormones, brain function and cognition: a brief review. *Neurosci Biobehav Rev* 2002; **26**: 45–60.
- 69 Yang Y, Schmitt HP. Frontotemporal dementia: evidence for impairment of ascending serotonergic but not noradrenergic innervation. *Acta Neuropathol* 2001; **101**: 256–70.
- 70 Bathgate D, Snowden JS, Varma A, Blackshaw A, Neary D. Behaviour in frontotemporal dementia, Alzheimer's disease and vascular dementia. *Acta Neurol Scand* 2001; **103**: 367–78.
- 71 Bush G, Frazier JA, Rauch SL, et al. Anterior cingulate cortex dysfunction in attention deficit/hyperactivity disorder revealed by fMRI and the counting Stroop. *Biol Psychiatry* 1999; **45**: 1542–52.
- 72 Swick D, Jovanovic J. Anterior cingulate cortex and the Stroop task: neuropsychological evidence for topographic specificity. *Neuropsychologia* 2002; **40**: 1240–53.
- 73 Tomoeda CK. Comprehensive assessment for dementia: a necessity for differential diagnosis and management. *Semin Speech Lang* 2001; **22**: 275–88.
- 74 Storey E, Slavin MJ, Kinsella GJ. Patterns of cognitive impairment in Alzheimer's disease: assessment and differential diagnosis. *Front Biosci* 2002; **7**: 155–84.
- 75 Rascofsky K, Salmon DP, Ho GJ, et al. Cognitive profiles differ in autopsy-confirmed frontotemporal dementia and AD. *Neurology* 2002; **58**: 1801–08.
- 76 Diehl J, Kurz A. Frontotemporal dementia: patient characteristics, cognition, and behaviour. *Int J Geriatr Psychiatry* 2002; **17**: 914–18.
- 77 Petrovic P, Ingvar M, Stone-Elender S, Petersson KM, Hansson P. A PET activation study of dynamic mechanical allodynia in patients with mononeuropathy. *Pain* 1999; **83**: 459–70.
- 78 Killgore WDS, Casasanto DJ, Yurgelun-Todd DA, Maldjian JA, Detre JA. Functional activation of the left amygdala and hippocampus during associative encoding. *NeuroReport* 2000; **11**: 2259–63.
- 79 Burton EJ, Karas G, Paling SM, et al. Patterns of cerebral atrophy in dementia with Lewy Bodies using voxel-based morphometry. *Neuroimage* 2002; **17**: 618–30.
- 80 Piao Y-S, Wakabayashi K, Hayashi S, Yoshimoto M, Takahashi H. Aggregation of α -synuclein/NACP in the neuronal and glial cells in diffuse Lewy body disease: a survey of six patients. *Clin Neuropathol* 2000; **19**: 163–69.
- 81 Harding AJ, Broe GA, Halliday GM. Visual hallucinations in Lewy body disease relate to Lewy bodies in the temporal lobe. *Brain* 2002; **125**: 391–403.
- 82 Benecke R. Diffuse Lewy body disease: a clinical syndrome or a disease entity? *J Neurol* 2003; **250**: 139–42.
- 83 Mathias CJ. Neurodegeneration, parkinsonian syndromes and autonomic failure. *Auton Neurosci* 2002; **96**: 50–58.
- 84 Rüb U, Del Teddici K, Schultz C, et al. Parkinson's disease: the thalamic components of the limbic loop are severely impaired by α -synuclein immunopositive inclusion body pathology. *Neurobiol Aging* 2002; **23**: 245–54.
- 85 Mirzaei S, Knoll P, Koehn H, Bruecke T. Assessment of diffuse Lewy body disease by 2-[18F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG PET). *BMC Nucl Med* 2003; **3**: 1.
- 86 English P, Kishore M. Aortic dissection and rupture presenting as suprasternal bruising and neck swelling. *Age Ageing* 2002; **31**: 310–12.
- 87 Tschampa HJ, Herms JW, Schulz-Schaeffer WJ, et al. Clinical findings in sporadic Creutzfeldt-Jakob disease correlate with thalamic pathology. *Brain* 2002; **125**: 2558–66.
- 88 Rossi G, Giaccone G, Giampaolo L, et al. Creutzfeldt-Jakob disease with a novel four extra-repeat insertional mutation in the PrP gene. *Neurology* 2000; **55**: 405–10.
- 89 Yamada M, Itoh Y, Suematsu N, Matsushita M, Otomo E. Panencephalopathic type of Creutzfeldt-Jakob disease associated with cadaveric dura mater graft. *J Neurol Neurosurg Psychiatry* 1997; **63**: 524–27.
- 90 Carota A, Pizzolato GP, Gailloud P, et al. A panencephalopathic type of Creutzfeldt-Jakob disease with selective lesions of the thalamic nuclei in 2 Swiss patients. *Clin Neuropathol* 1996; **15**: 125–34.
- 91 Armstrong RA, Lantos PL, Cairns NJ. Spatial patterns of the vacuolation in subcortical white matter in sporadic Creutzfeldt-Jakob disease (sCJD). *Clin Neuropathol* 2002; **21**: 284–88.
- 92 Ironside JW. Neuropathology of variant Creutzfeldt-Jakob disease. *C R Biol* 2002; **325**: 27–31.
- 93 Aguglia U, Oliveri RL, Gambardella A, et al. Functional preservation of benzodiazepine receptors of the primary somatosensory cortex in Creutzfeldt-Jakob disease: a pharmacologic-evoked potential study. *Clin Neuropharmacol* 1996; **19**: 87–91.
- 94 Macleod M-A, Stewart GE, Zeidler M, Will R, Knight R. Sensory features of variant Creutzfeldt-Jakob disease. *J Neurol* 2002; **249**: 706–11.
- 95 Spencer MD, Knight RSG, Will RG. First hundred cases of variant Creutzfeldt-Jakob disease: retrospective case note review of early psychiatric and neurological features. *BMJ* 2002; **324**: 1479–82.
- 96 Birks J, Grimley Evans J, Iakovidou V, Tsolaki M. Rivastigmine for Alzheimer's disease (Cochrane Review). In: *The Cochrane Library*, Issue 2, 2003. Oxford: Update Software.