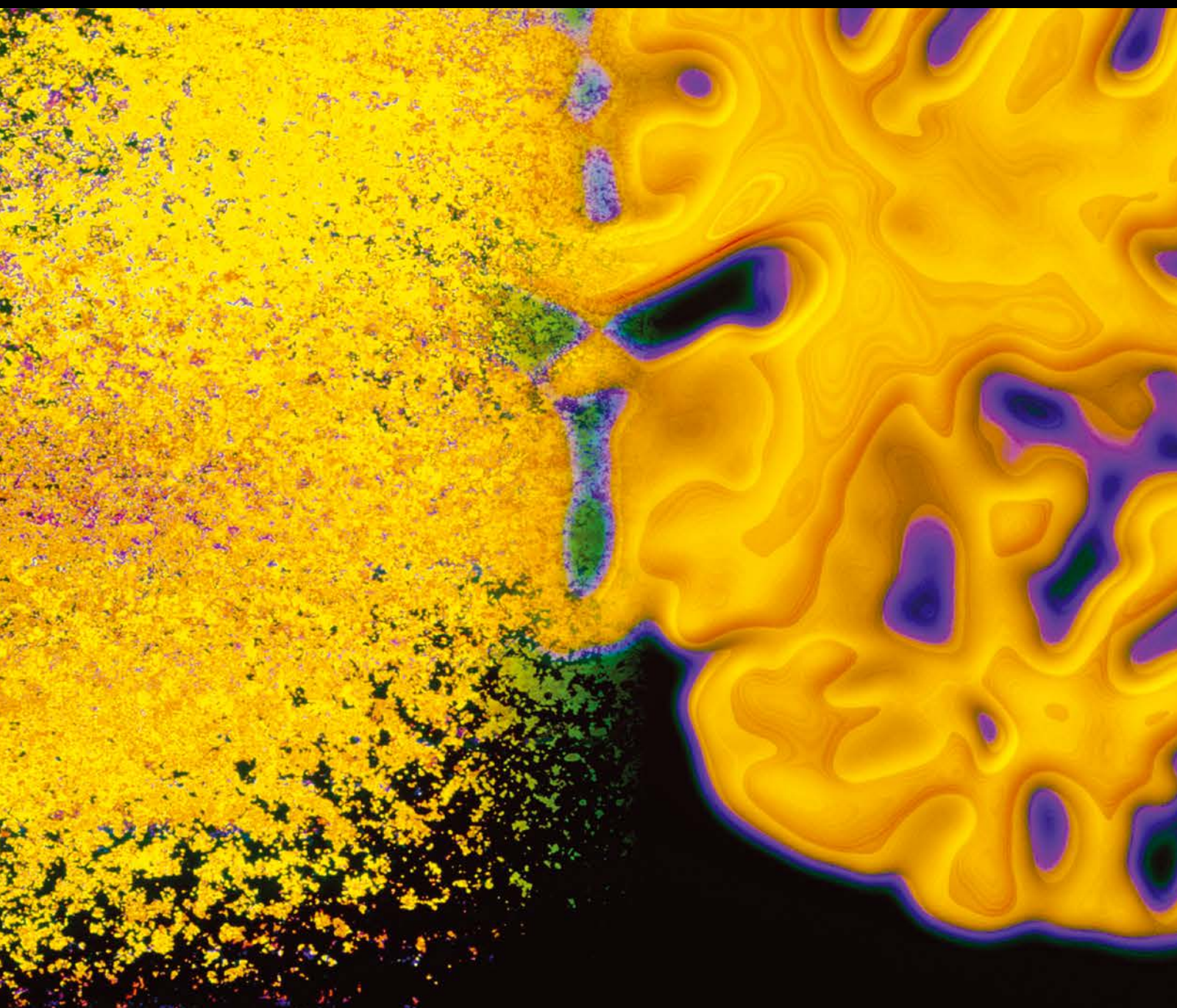
Behavioural Neurology

Pain Assessment in Neurodegenerative Diseases

Guest Editors: Marina de Tommaso, Lars Arendt-Nielsen, Ruth Defrin, Miriam Kunz, Gisele Pickering, and Massimiliano Valeriani



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Editorial Board

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Editorial

Pain Assessment in Neurodegenerative Diseases

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In recent years neurodegenerative diseases deserved growing attention for the progressive lengthening of human survival and the increasing prevalence of age-related brain disorders. Increasing competence is required by clinicians in regard to the different aspects of these chronic disabling disorders, as psychiatric and cognitive aspects, motor impairment, and pain. Diseases as dementia and motoneuronal and extrapyramidal disorders are opening a new scenario on pain syndromes, which represent an underestimated problem as the link between pathology and the pain experience is most often difficult to establish. This special issue was hosted by a panel of pain specialists around Europe and Israel, who shared common scientific interests on different aspects of pain, being particularly involved in researches on pain assessment and diagnosis in neurodegenerative diseases and especially dementia.

The issue contains a comprehensive review on pain aspects in common and rare neurodegenerative disorders where pain has recently emerged as a frequent symptom, although main treatments are exclusively focusing on cognitive or motor impairment and hence leave pain out of the guidelines. In Alzheimer disease, pain symptoms are not clearly expressed, so the few clinical scales actually used and in course of validation have the special aim to recognize features of sufferance. In Parkinson's disease and amyotrophic lateral sclerosis, pain has been described as a frequent associated condition, while few specific scales were employed and pain treatment is not guided by any quantitative assessments. In the review, the search for studies assessing the frequency and the clinical features of pain in these syndromes leads to the conclusion that it is a poorly studied symptom, despite its potential impact on the outcome of the diseases and main implication on the patients' quality of life. Up to now the available studies on the pathophysiological basis of pain in these disorders are inconclusive, and only few indications are present in regard to guiding the pharmacological approaches. The review outlined the need of a more focused attention by clinicians and researches on this emerging problem in the management of neurodegenerative diseases and the use of quantitative tools to evaluate the pain symptoms.

In addition, some original articles have also been included in this special issue to support this concept.

Since the first reports of altered pain responses in patients with cognitive impairment were published, the question has arisen, whether there might be certain cognitive domains (e.g., memory, attention, and executive functioning) that might best explain these alterations in pain responses. Kunz et al. [1] previously investigated this in a group of patients suffering from either mild cognitive impairment or dementia and found that "executive functioning" was the cognitive domain that best explained dementia-related alterations in pain responsiveness. In the present special issue, J. M. Oosterman et al. followed this approach and investigated which role executive functioning plays in explaining variations

in self-report and facial expression to pain in a group of 52 older individuals. Facial expression and self-report were assessed in response to pressure pain of different intensities and these pain responses were then related to different domains of cognitive functioning. The authors could show that executive functioning (especially cognitive inhibition) indeed played an important role in explaining variations in pain responsiveness in older individuals. The poorer the ability for cognitive inhibition was, the stronger the facial expressions of pain across pain intensities were. Or in other words, impairment in executive functioning leads to a more pronounced communication of pain via the face. This study highlights the need to include tests of cognitive functions when assessing pain in older individuals.

T. F. Habiger et al. examined the complex relationship between pain, neuropsychiatric symptoms, and agitation in people with dementia. The authors performed a cluster randomized controlled trial and showed that in nursing homes patients with dementia exhibited reduced agitation, aberrant motor behaviour, and psychosis when they received pain treatment. This important trial suggests that pain is linked to psychosis and agitation among patients with dementia. In addition, the authors showed that opioid analgesics did not increase the prevalence of hallucination or delusion. These observations are particularly pivotal to provide adequate pain care in this vulnerable population.

M. W. de Vries et al. provided a good example of the difficulties of pain assessment in patients with cognitive impairment and their possible solution. They studied 153 patients with moderate to severe cognitive impairment by using the Orofacial Pain Scale for Non-Verbal Individuals (OPS-NVI). The "chewing" subscale was demonstrated to be reliable in assessing orofacial pain by means of the mere observation of video clips. Orofacial pain can be extremely frequent in elderly patients who have lost the capability to express it. Therefore, the development of behavioural scales able to reveal pain in these patients is mandatory to improve their quality of life. Of course, these tools need to prove their efficacy in large samples of patients, such as that investigated in this study.

Finally, one study by M. de Tommaso et al. reports original data on pain assessment in a rare disease such as Huntington's disease (HD). In HD motor symptoms as dystonia and hyperkinesis may be a potential cause of pain, but this has been only rarely reported in such disorder, suggesting a substantial dysfunction in pain expression. The present study reports the results of the application of a neurophysiological method as laser evoked potentials (LEPs) in early HD patients and genetically predisposed subjects in a presymptomatic phase. The LEPs showed clear abnormalities in both patients and those presymptomatic subjects who approached clinical onset, suggesting that the dysfunction of pain pathways is an early phenomenon which can influence sensory motor integration and the global outcome of the disease.

In conclusion, this special issue adds a small but potentially useful piece to the puzzle of pain expression and pain treatment in patients with cognitive and communication disorders, contributing to the understanding and management of the complex clinical aspects of pain in neurodegenerative diseases, a field which should receive more attention in the future.

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Ruth Defrin
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Review Article

Pain in Neurodegenerative Disease: Current Knowledge and Future Perspectives

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Neurodegenerative diseases are going to increase as the life expectancy is getting longer. The management of neurodegenerative diseases such as Alzheimer's disease (AD) and other dementias, Parkinson's disease (PD) and PD related disorders, motor neuron diseases (MND), Huntington's disease (HD), spinocerebellar ataxia (SCA), and spinal muscular atrophy (SMA), is mainly addressed to motor and cognitive impairment, with special care to vital functions as breathing and feeding. Many of these patients complain of painful symptoms though their origin is variable, and their presence is frequently not considered in the treatment guidelines, leaving their management to the decision of the clinicians alone. However, studies focusing on pain frequency in such disorders suggest a high prevalence of pain in selected populations from 38 to 75% in AD, 40% to 86% in PD, and 19 to 85% in MND. The methods of pain assessment vary between studies so the type of pain has been rarely reported. However, a prevalent nonneuropathic origin of pain emerged for MND and PD. In AD, no data on pain features are available. No controlled therapeutic trials and guidelines are currently available. Given the relevance of pain in neurodegenerative disorders, the comprehensive understanding of mechanisms and predisposing factors, the application and validation of specific scales, and new specific therapeutic trials are needed.

1. Introduction

Neurodegenerative diseases are going to increase in parallel to the lengthening of survival. The most common of them become more prevalent with age being accompanied by progressive motor and cognitive impairment. The management of neurodegenerative diseases as Alzheimer's disease (AD) and other dementias, Parkinson's disease (PD) and PD related disorders, motor neuron diseases (MND), Huntington's disease (HD), spinocerebellar ataxia (SCA), and spinal muscular atrophy (SMA), is mainly addressed to motor and cognitive impairment with special care to the vital functions as breathing and feeding. Many of these patients complain of painful symptoms though their origin is variable, and their presence is frequently not considered in the treatment guidelines, leaving their management to the decision of the clinicians alone. In some neurodegenerative diseases as Parkinson's disease, pain has recently been recognized as a frequent and invalidating symptom [1]. In general, pain treatment should mainly be based on its pathophysiological mechanisms. According to the International Association for the Study of Pain (IASP), pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage [2]. Most pain syndromes are neuropathic or nociceptive in their origin. While central and peripheral neuropathic pain are caused by a lesion

or disease of the central or peripheral somatosensory nervous system, respectively, the nociceptive pain arises from actual or threatened damage to nonneural tissue and is due to the activation of nociceptors [3]. Thus, nociceptive pain occurs in patients with a normally functioning somatosensory nervous system [3]. Neurodegeneration may specifically involve the somatosensory system, thus making a neuropathic origin of pain very likely, or it may affect cortical and subcortical structures involved in pain modulation. Motor impairment with muscular tone abnormalities and reduced active mobility may cause osteoarticular problems with local inflammation and nociceptive pain. In many neurodegenerative conditions, the origin of pain is complex, often multifactorial and hardly classifiable as merely neuropathic or nociceptive. In addition, there are few evidences on frequency and characteristics of pain symptoms in neurodegenerative disorders and on their impact on the disease outcome. An IASP task force [4] has revised the clinical and instrumental assessment of chronic pain as well as its therapeutic management so a systematic application of these guidelines to chronic pain in neurodegenerative diseases should be within reach. However, pain assessment may be hampered by the impairment of cognitive and motor performances so special recommendation should be provided upon approaching this important aspect of neurodegenerative diseases.

The present review focuses on chronic pain in main neurodegenerative diseases addressing the current knowledge about pain frequency and clinical features, clinical and instrumental assessment, possible pathophysiological mechanisms, and the current evidence on pain therapeutic management. Also the main limitations of the present studies and the future research direction and perspectives are considered.

We also dedicated a section to rare neurodegenerative conditions where pain was not extensively assessed.

This was a narrative review based on PubMed search by the following key words: pain, pain frequency, pain features, pain treatment and Alzheimer disease, Parkinson's disease, extrapyramidal disorders, motor neuron disease, and spinocerebellar ataxia. There was no time limit for the research, starting form the first date reported by PubMed.

2. Alzheimer Disease and Other Dementias

Dementia refers to a broad category of brain neurodegenerative diseases that are accompanied by loss of ability in memory function, attention, executive function, orientation, language, and other cognitive domains as well as by changes in mood and behavior, which increase across the course of dementia. There are an estimated 35 million people with dementia in the world. The most common type of dementia is Alzheimer's disease. Other forms of dementia are vascular dementia, frontotemporal dementia, and Lewy body dementia. Given that the prevalence rate of dementia is tightly linked to ageing, the increase of ageing population is the main reason for the predicted substantial growth in the number of people affected by dementia. Not only do prevalence rates of dementia increase with age, but also the prevalence rates of pain are strongly linked to ageing [5]. Given that both the prevalence rates of dementia and pain increase with age, it appears that pain is highly common among people suffering from dementia. The difficulty is, however, that patients with dementia (particularly those in the advanced stages of the disease) are often unable to use self-report to communicate their suffering, and thus their pain is often overlooked and remains untreated [6].

2.1. Pain Frequency and Clinical Features. Due to their advanced age, individuals with dementia often suffer from multiple morbidities associated with pain. However, the exact pain prevalence in dementia is unknown due to the lack of self-report in this patient group as mentioned previously. Studies using observational tools to assess pain indicate that about 50% of patients with dementia living in nursing homes are suffering from pain [13, 28]. This is in line with prevalence rates reported about nursing home patients, independently of their cognitive status. Yet, the prevalence of pain among patients with dementia is associated with the severity of the condition. In fact, between 45% and 83% of the patients living in nursing homes experience acute or chronic pain [29]. Most of these patients (about 94%) were reported to suffer from persistent pain (3–6 months or more). The causes of pain among patients with dementia living in nursing homes include but are not restricted to genitourinary infections, pathologies in the musculoskeletal system [30], pressure ulcers [31], and skin diseases, with the latter of which found in 95% of the patients and described as one of the most prevalent health problems in this population [32].

Several studies have estimated the prevalence rates of pain among patients with dementia who are living at home. These prevalence rates are listed in Table 1 [7–13]. What appears evident is that the rates vary across studies, depending on whether they are based on the self-report or on the caregivers' report. Overall, at least 50% of the community dwelling patients with dementia seem to be suffering from pain. Considering the aforementioned studies, pain is highly prevalent among patients with dementia whether living in nursing homes or living at home, and thus its management required careful assessment and monitoring.

2.2. Clinical and Instrumental Assessment. Given the high prevalence of pain in the elderly, proper assessment of pain by observers such as health care professionals or family members is required for successful pain treatment. Due to the subjective and complex nature of the pain experience, assessing patients' pain is often a challenge. The more severe the cognitive impairment is and hence the more severe the loss of self-report is, the greater the challenge is [33]. In such instances, caregivers should rely less on self-report and more on behavioral indicators of pain. Facial expressions in particular seem to provide a valid indication of the patients' pain. Patients with dementia display the same types of facial movements in response to pain as cognitively intact individuals [34, 35]. Thus, the pain-peculiarity of their facial expression is not reduced. This finding implies that facial expressions of pain have the potential to serve as an alternative pain indicator in patients with dementia. Other means to indirectly assess pain are various behavior rating scales (for comprehensive reviews, see, e.g., Herr et al. [36]

Table 1: Summary of the studies on the prevalence of pain among patients with dementia living at home or in nursing homes. Features and location of pain were not available.

	Study design	Number of patients and controls	Assessment method	Frequency of pain
Barry et al. [7]	Observational	Patients: 75 Controls: 0	Interview with patients and caregivers	*Daily pain* Patients' report: 57% Caregivers' report: 71%
Barry et al. [8]	Observational	Patients: 42 Controls: 0	Interview with patients, nurses, and relatives	*Daily pain* Patients' report: 38% Nurses' report: 69% Relatives' report: 75%
Hunt et al. [9]	Observational	Patients: 802 Controls: 802	Interview with patients	*Bothersome pain* Patients' report: 64% Controls' report: 55%
Werner et al. [10]	Observational	Patients: 141 Controls: 55	Category rating scale	*Pain is experienced* Patients' report: 21% Patients' and Caregivers' report: 46% Controls' report: 48.1
Mäntyselkä et al. [11]	Observational	Patients: 75 Controls: 446	Interview with the patients	*Any pain* Patients' report: 43% Controls' report: 69%
Shega et al. [12]	Observational	Patients: 150 Controls: 0	Interview with patients and caregivers	*Pain right now* Patients' report: 32% Caregivers' report: 52%
Zwakhalen et al. [13]	Observational	Patients: 117 Controls: 0	Observational pain scale	*Experience of pain to some extent* Nurses' observations: 47%

and Zwakhalen et al. [13]). However, the validation process of these scales has just started. Although the first results are promising, future studies are needed to define which items are able to discriminate between pain behavior and behaviors related to other aspects of unmet needs in patients with dementia. Within a European initiative (COST TD1005), researchers across Europe have started to investigate which behavioral items can indeed validly indicate the presence of pain in patients with different types of cognitive impairment. The process is still ongoing [37] but will hopefully be completed within the next 1-2 years.

2.3. Possible Pathophysiological Mechanisms. Only a few experimental studies have tried to investigate how dementia affects the processing of nociceptive information with most studies focusing on patients with Alzheimer's disease (for a comprehensive review, see Defrin et al. [38]). Alarmingly, the majority of the experimental findings seem to suggest that the processing and the experience of pain are not diminished in patients with mild-to-moderate forms of dementia. On the contrary, the pain experience might even be enhanced. It has been reported that patients with dementia respond to noxious stimulation with more enhanced facial responses [34, 35] and pain withdrawal reflexes [35] compared with cognitively intact peers. Functional magnetic resonance imaging (fMRI) studies showed that brain activity in response to noxious stimulation is preserved and even elevated in patients with mild forms of Alzheimer's disease [39, 40] corroborating findings based on facial and reflexive expressions. Using evoked related potentials (ERPs), one study found no difference in peak amplitude between patients and controls [41] and one study failed to induce pain-evoked potentials in the subgroup of patients with severe dementia [42]. The widespread brain damage occurring in the course of dementia might possibly affect descending pain modulation pathways most strongly in mild-to-moderate stages of dementia, which in turn lead to reduced inhibitory control over the pain system and increased pain processing. In later stages of dementia, the ascending pain pathways might be affected more severely, resulting in reduced pain processing. However, this is only speculative since research on patients at severe stages of dementia is lacking.

2.4. Current Evidence on Pain Therapeutic Management. Recent reviews on pain management in patients with dementia point to a severe lack of effective assessment and treatment in different clinical settings and to the conclusion that even today patients with dementia are still undertreated for pain compared with nondemented elderly individuals [43, 44]. However, this seems to be slowly changing. Two studies from Scandinavia [45, 46] found that patients with dementia received even more analgesic drugs (mostly paracetamol) compared with those without dementia. The increased dosage was administered even though the patients reported pain less frequently, and the prevalence of the pain related diagnoses was similar compared with persons without

dementia. Beyond being very promising, these results clearly suggest that the research findings of the last decades—which reported an undertreatment of pain in dementia—have already impacted the clinical practice and have led to an intensification of pain management in this frail patient group.

2.5. Main Limitations of the Present Studies and Future Directions. In the last two decades, much effort has been invested to better understand how dementia affects the pain processing as well as its assessment. Up to now, an impressive number of pain behavior rating scales have been developed trying to assess pain based on nonverbal behavior. However, the validity, usability, and feasibility of these scales are still unsatisfactory, and they are not often used in the clinical practice. Moreover, dementia is a very broad concept that includes not only various types of neurodegenerative processes affecting different brain areas but also different degrees of cognitive decline. Most studies do not differentiate between different types or stages of dementia. Moreover, research investigating patients with dementia at the last stage of the disease is still mostly lacking, and, therefore, we do not know how pain processing might be altered in these very fragile patients. Moreover, it is an alarming fact that patients with dementia are still excluded from high quality randomized controlled trials of pain treatment. This underlines the comprehensive need of research as well as excellent implementation concepts for pain assessment and pain treatment in elderly individuals with dementia.

3. Parkinson's Disease and Other Extrapyramidal Disorders

Patients with Parkinson's disease (PD) often experience pain. By now, pain is commonly accepted to represent one of the PD nonmotor symptoms having a remarkable impact on the PD patients' quality of life. While pain was considered initially as an epiphenomenon of the motor impairment characteristic of the disease, the attention toward this symptom has increased in the last ten years. Two main elements led clinical and research efforts to understand the pain mechanisms in PD: (1) the higher prevalence of pain in PD patients compared to that in the healthy elderly subjects and (2) the involvement of nondystonic body parts, which means that pain is possibly linked to the intrinsic pathophysiological mechanisms of the disease.

3.1. Pain Frequency and Clinical Features. Pain in PD is commonly assessed according to Ford's scheme [47]. Five different types of pain can be recognized: (1) musculoskeletal, (2) radicular-neuropathic, (3) dystonic, (4) central neuropathic, and (5) akathisia pain. Whether the classical distinction between the nociceptive and the neuropathic pain is used or not, most Parkinsonian patients refer a nociceptive pain, which can be mainly musculoskeletal and visceral. Musculoskeletal pain derives from abnormal postures of the dystonic body parts, rigidity, and akinesia. Visceral pain is often the consequence of the abnormal function of the vegetative nervous system typical of the disease [48]. In PD, an example of neuropathic pain is represented caused by nerve root irritation following the abnormal posture and motor activity of the Parkinsonian patients. However, most papers on PD pain consider also a far less defined "central neuropathic" pain. This is poorly localized and often described as "boring," "constant," and "burning" [49]. The classification of this "central pain" is questionable according to the commonly accepted definition of neuropathic pain as being due to a lesion or a disease of the somatosensory system [3]. Although a clear sensory deficit cannot be demonstrated in PD patients with central pain, there are evidences linking this kind of pain to basal ganglia dysfunctions [50] and abnormal nociception [51].

Although several studies investigated the epidemiologic characteristic of pain in PD, the exact prevalence of this disabling symptom is not definitely known, ranging from 30% to 80% [49]. A recent meta-analysis [52] identified 8 studies which met the criteria of the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool. In these studies, the average prevalence of pain was 67.6%, ranging from 40% to 85%. As for the location, the pain was prevalently referred to the lower limbs (47.2%) while it involved less frequently the back (14.3%), the upper limbs (13.4%), and the neck/shoulder region (12.4%). The most frequently reported type of pain was the musculoskeletal one (46%) followed by dystonic (19.6%) and radicular (9.1%) pain. Central neuropathic pain was found in 5.6% of PD patients. Interestingly, the only available community study performed in Norway by Beiske et al. [1] reports the highest prevalence of pain in PD as compared to healthy subjects (83% versus 30%). Valkovic et al. [16] have very recently investigated the modifications in the prevalence of pain during the disease progression. Interestingly, all the 4 Parkinson-related types of pain considered in this study (musculoskeletal, dystonic, radicular, and neuropathic) were more prevalent in the advanced stages of PD confirming their strict relationship with the disease.

It should be mentioned that a couple of studies failed in showing a higher prevalence of pain in PD patients compared to that in healthy subjects [53, 54]. In these studies, however, the prevalence of pain was very low in PD patients as compared to other studies or high in healthy subjects thus suggesting an ascertainment bias [15] (Table 2).

3.2. Clinical and Instrumental Assessment. Though pain is very prevalent in PD, in most studies rating scales not specific for this disease were used. Only a very recent multicenter study published the first PD pain specific scale [55]. King's Parkinson's Disease Pain Scale (KPPS) is an interview-based scale used to explore the frequency, intensity, and location of each type of PD pain. Moreover, it also rates the pain modifications associated with motor fluctuations in PD.

3.3. Possible Pathophysiological Mechanisms. Although the epidemiological data support the linkage between at least certain types of pain and the biological background of the disease, the pathophysiological mechanisms of pain in PD patients are far from being ascertained. According to the current idea, abnormal nociceptive mechanisms, which could

Table 2: Summary of studies on the prevalence and features of pain among patients with Parkinson's disease.

	Study design	Number of patients and controls	Assessment methods	Frequency of pain	Feature and location of pain
Nègre-Pagès et al. [14]	Observational	450	Visual analogue scale	278 patients (61.8%)	*PD related (167 patients)* *Other types (111 patients)*
Defazio et al. [15]	Case control	402	Visual analogue scale	*281 patients (69.9%) and 199 controls (62.8%)*	*Nondystonic (267 patients)* *Dystonic and nondystonic (14 patients)*
Beiske et al. [1]	Observational	176	Structured interview (SF-36)	*147 patients (83%)*	Musculoskeletal (103 patients) Dystonic (59 patients) Radicular (0 patients) Central (15 patients)
Valkovic et al. [16]	Observational	100	Brief Pain Inventory Leeds assessment of neuropathic symptoms and signs	*76 patients (76%)*	Musculoskeletal (41%) Radicular (27%) Central (22%) Dystonic (17%) Others (31%)
Tinazzi et al. [17]	Observational	117	Visual analogue scale	*47 patients (40%)*	Dystonic (19 patients) Musculoskeletal (22 patients) Radicular (4 patients) Central (2 patients)

predispose patients to develop spontaneous pain, could be found in PD. This is suggested by psychophysical and neurophysiologic studies in PD patients without pain [15]. Reduced thresholds to different pain modalities were found in PD patients without pain compared with the control subjects [17, 51, 56–63]. Moreover, the laser evoked potential (LEP) amplitude assessing the pain matrix function was reduced in the pain-free PD patients [51] even in the early stages of the disease [58]. As for the role of dopamine in the development of PD pain, the available results are not univocal. Indeed, elements suggesting dopamine importance are represented by the more frequent involvement of the affected side in hemi-Parkinson and the pain modifications according to the PD motor fluctuations [14, 64]. However, the psychophysical and neurophysiologic abnormalities shown in PD patients cannot generally recover after dopamine administration [65]. Monoaminergic systems different from the dopaminergic one could be involved in the pathophysiology of pain in PD.

Finally, it is worth mentioning that a reduction of small unmyelinated fibers was reported in PD both in the skin biopsy [66] and in cornea [67]. However, the meaning of the peripheral fiber reduction in the neurophysiological findings is not clear since the last ones seem most dependent on central nervous system modifications.

3.4. Current Evidence on Pain Therapeutic Management. No systematic study on pain treatment in PD is currently available. However, it is conceivable that the treatment strongly depends on the type of pain. Broen et al. [52] reviewed 3 studies, which provided some data. According to them, 37.6% of the PD patients use nonopioid analgesic while 13.5% of them use opioids and 11.8% of them use antidepressant and/or anticonvulsive drugs. Kass-Iliyya et al. [67] described an analgesic effect of the deep brain stimulation (DBS) indicated for the improvement of the motor symptoms. Eight patients, having undergone DBS electrode implant within the subthalamic nucleus, showed an increase of the pain threshold when the DBS was switched on as compared to what happened with the stimulator off. Moreover, the authors used the positron emission tomography to investigate the cerebral activity related to central neuropathic pain in PD patients. It was found that the DBS could reduce the brain activity related to pain.

3.5. Main Limitations of Present Studies and Future Direction. In conclusion, pain in PD has become an important element to be considered in the clinical practice since it can worsen the general impairment of the patients. In spite of the number of papers published in the last years, there are still some points which should be improved. Firstly, there is still the tendency to consider the different types of PD pain together in many studies. This can prevent the correct identification of the pathophysiological mechanisms and the best treatments that are unlikely to be the same for musculoskeletal, dystonic, and neuropathic pain. Secondly, the KPPS, which represents the first specific PD pain scale, was published in 2016 [55] while pain was previously assessed on the basis of the examiner's experience or by using some questionnaires not specific for PD. This has surely hampered a systematic classification of pain in PD, which represents the mandatory background for any effective treatment.

4. Other Extrapyramidal Disorders

Although pain is often reported by patients with extrapyramidal disorders different from PD, there are only few studies

dealing with pain in these conditions. Few studies dealt with pain frequency and features in patients with Huntington's disease (HD). Some clinical reports suggested that pain may not be sufficiently manifested and treated in HD patients and that it may be an underestimated problem [68, 69]. In a study conducted by laser evoked potentials, HD patients in the early stages of the disease showed increased LEPs latencies, inversely correlated with their functional capacities [70]. In that study, only 3 out of 28 patients complained of pain despite the presence of possible postural and muscle skeletal abnormalities. This preliminary observation may support the need of more extensive multicentric observational controlled studies. There is a consistent amount of studies indicating that HD patients show a deficit in recognizing negative emotions and pain of others [71, 72]. The impaired processing of negative experiences may thus be supported by an altered influence of basal ganglia on cortical areas devoted to the elaboration of stimuli requesting an aversive motor response as in the case of painful stimuli [73]. The disturbed processing of negative stimuli including pain may interfere with sensory-motor integration [70, 74] and contribute to the global worsening of the disease as suggested by the correlation found between LEPs abnormalities and disability in HD patients [70].

Some data have been collected for Cervical Dystonia (CD), which is characterized by involuntary twisting neck movements and abnormal head postures [75]. Early studies reported pain in around 70% of CD patients [76, 77]. More recently, Charles et al. [78] published epidemiological data from 1,037 CD patients included in a USA registry (Cervical Dystonia Patient Registry for Observation of OnabotulinumtoxinA efficacy—CD PROBE). At baseline, that is, before OnabotulinumtoxinA treatment, 88.9% (922/1037) of the patients reported pain related to CD. In particular, 70.7% (733/1037) reported moderate or severe pain intensity while 29.3% (304/1037) reported no pain or had only a mild pain intensity. Interestingly, the patients with no/mild pain were older than those with moderate/severe pain, while no difference between groups was found in the onset age or the duration of the disease. Unfortunately, no systematic pain classification, including also a possible separation between different types of pain (according to the model reviewed above for pain in PD), has been performed in CD. This contributes to the uncertainty about the pathophysiological mechanisms subtending pain in this condition. Indeed, it is conceivable that pain in CD can be due to the abnormal contraction of the dystonic muscles. However, this possibility has been challenged by the observation that botulinum toxin treatment does not always reduce pain [79, 80]. Moreover, pain is not always correlated with the severity of dystonia in the neck muscles [81]. These elements could lead to hypothesizing a susceptibility of the nociceptive system in CD similar to that demonstrated in PD. Tinazzi et al. [82, 83] recorded LEPs in 20 CD patients by stimulating the skin overlying both painful and nonpainful muscles. They failed to show any abnormality of the nociceptive input processing in these patients making the hypothesis of a central sensitization of the pain matrix in CD unlikely. However, it has to be mentioned that partially different results were obtained in patients with nonpainful hand dystonia by using the contact heat evoked potentials (CHEPs) [84]. Indeed, 6 out of 10 patients showed reduced amplitude of their pain related brain responses to stimulation of the dystonic hand.

Pain was described as a common symptom also in multiple system atrophy (MSA) [85, 86]. This finding was confirmed by a more recent study comparing 21 MSA patients with 65 PD patients [87]. Pain prevalence was similar between MSA (81%) and PD (89%) patients, as well as the scarce response of pain to dopamine administration in both conditions. In MSA, the pathophysiology of pain could be similar to that in PD, involving basal ganglia degeneration. This is suggested by the results of a neurophysiological study exploring pain processing in MSA and PD patients by using the nociceptive withdrawal reflex (NWR) recording [88]. MSA patients showed facilitation of a series of pain responses as compared to healthy subjects. However, no difference was found between MSA and PD patients in terms of neurophysiological abnormalities.

The progressive supranuclear palsy (PSP) is even less investigated than the previously reviewed conditions. The few available data suggest that pain in PSP is far less prevalent than that in PD [87, 88]. However, the only neurophysiological study in PSP showed a lower pain threshold in PSP patients than that in control subjects suggesting that the apparently low prevalence of pain in this condition could be related to the early cognitive impairment of the patients [88].

5. Motor Neuron Disease: Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS), also known as motor neuron disease (MND), is the most common neurodegenerative disorder of the motor system in adults. ALS is characterized by a degeneration of primary motor neurons in the cortex, brainstem, and spinal cord. The amyotrophy (atrophy of muscle fibers) leads to muscular paralysis due to loss of innervating motor neurons. The lateral sclerosis typical of the disease refers to the upper motor neuron axonal loss and the hardening of corticospinal tracts and the resultant gliosis [89, 90]. These changes can lead to a number of debilitating conditions that reflect aberrant functioning in both upper and lower motor neurons. These characteristic features of ALS are also accompanied by a number of secondary conditions that can be just as burdensome as those symptoms directly associated with the disorder. Although degeneration of motor neurons is pivotal in ALS, it is actually considered a multisystemic disorder involving sensory system. A spinocerebellar pathway (Clarke's column) taking origin in the spinal cord segments is consistently affected in pathological studies of ALS, which may underlie the early symptom of impaired balance often reported by patients at diagnosis [90]. In addition, clinicians have long noted minor sensory and autonomic involvement in patients with ALS [91] and small fiber neuropathy was found in skin biopsies in 79% of ALS patients [92]. The link between ALS and frontotemporal dementia represents an extension of ALS as a motor system disease to the frontal and temporal

lobes, which are brain areas involved in the expression of thought, planning, personality, and speech, all aspects of brain function that may interfere with pain perception [93]. The complexity of ALS pathophysiology and clinical appearance justifies the need to manage associate symptoms including pain.

5.1. Pain Frequency and Clinical Features. Thirty years ago, pain was reported to occur in ASL patients [94]. In the following years, some studies dealt with the frequency of pain in ALS patients, though most of them were conducted in small cohorts of patients in different stages of the disease; in addition, the case control design was sometimes omitted. In most studies, the usual classification in nociceptive and/or neuropathic pain was not used. Ganzini et al. [18] evaluated pain in ALS patients with direct interviews and questionnaires to caregivers. They found that both methods showed high representation of painful symptoms as causes of invalidity (Table 3). A case control study on neuromuscular diseases found that pain was present in 73% of the total population (193 patients) with ALS patients showing the greatest pain interference [19]. The pain was especially located in the back and shoulder, followed by neck, buttock and hip(s), feet, arm(s), and hand(s) [19]. Shoulder pain was also observed in 43 out of 193 ALS patients, independently of age, gender, and phenotype [20].

In a case control study, Chiò et al. [21] found that ALS patients reported pain more frequently than control subjects. Pain was correlated with the disease stage and invalidity. In an observational study on a small ALS series (42 patients), 19 experienced pain, which worsened the quality of life [22]. Rivera et al. [23] used the neuropathic pain scale [95] to study pain in 63 ALS patients in different stages of the disease. They found that about half of patients reported neuropathic pain, which was invalidating since it was present even in the early stages of the disease (Table 1). Pizzimenti et al. [24] observed pain in 72% of 36 ALS patients causing depression and a significant decline of the quality of life. More recently, Wallace et al. [25] specified that in 81% of 41 ALS patients complaining of pain this did not have neuropathic characteristics. In another recent study, 78% of the examined patients complained about pain, which interfered with the quality of life, sleep, and mood [26]. The lack of correlation between severity of pain and disease duration was also reported in this latter study (Table 3). Another study applied the DN4 test for neuropathic pain scoring [96] in 92 ALS patients, who reported only rare symptoms of neuropathic origin [27]. Summarizing, both observational and case control studies reported a high frequency of pain in ALS patients from around 20% in retrospective studies to 80% in case control ones. Characteristics of pain symptoms have been collected with different scales though the most recent studies seemed to suggest the nonneuropathic origin of pain.

5.2. Clinical and Instrumental Assessment. As reported above, different scales were used to assess the pain features in ALS patients (Table 3). The short form of BPI was generally applied [97] while only few studies assessed the neuropathic origin of pain with specific questionnaires as DN4 or neuropathic pain scales [96] (Table 3). In most studies, the factors aggravating pain, such as depression and sleep disturbances, were also assessed.

Neurophysiological studies and in particular electromyography and electroneurography are routinely applied for diagnostic purposes to explore motor system in ALS patients [98] while the employment of methods for the specific assessment of nociceptive pathways functions was rarely reported though it would be useful to improve the knowledge about pain pathophysiology and its management. Contact heat evoked potentials were used to explore noxious stimuli conduction along the C-fibers in 60 ALS patients versus 60 controls, and no significant abnormality was found in patients corroborating the hypothesis of an intact nociceptive system [99]. These results were not confirmed in a CO2 laser evoked potentials (LEPs) study conducted in 23 ALS patients [100], who showed an increase in LEPs latencies but also in the amplitude of the earlier latency N1 potential. This is a contradictory result possibly explained by a probable dysfunction of the nociceptive pathways at subcortical level [101], coexisting with enhanced excitability of the nociceptive cortex as a result of motor cortex degeneration. In that study, 19 patients complained about pain, which was usually of the musculoskeletal type supporting the hypothesis that, also in the presence of signs of nociceptive system dysfunction, pain is an indirect consequence of motor impairment [100]. Small fiber involvement was demonstrated by skin biopsy. Weis et al. [92] found a significant reduction in the epidermal nerve fiber density in the distal calf of patients with ALS, which was recently confirmed in another study based on skin biopsy and Quantitative Sensory Testing (QST). In this last study, only patients with spinal onset, but not those with bulbar form, showed an impairment of the thermal sensitivity and distal C afferents [102]. Moreover, a sensitive axonal involvement may be a feature of ALS subtypes.

5.3. Possible Pathophysiological Mechanisms. Clinical studies seem to indicate the nonneuropathic origin of pain in the majority of ALS patients though the complexity of this multisystemic degenerative disorder may account for a dysfunction of the nociceptive system at both peripheral and central level. The neuropathic components of ALS-related pain can be present even in the early phases of the disease and worsen the musculoskeletal pain. The presence of the nociceptive afferents dysfunction in ALS is suggested by both skin biopsies and QST especially in the spinal onset phenotype [18, 102]. In addition, the complex interaction between the motor and sensory cortex may cause disinhibition and hyperactivation of sensory functions in order to improve sensory-motor integration in a situation of motor failure [103, 104]. This could explain the increased amplitude of LEPs [100] and SEPs [105] observed in the early stages of the disease.

5.4. Current Evidence on Pain Therapeutic Management. A recent Cochrane review [106] reported that there is no evidence from randomized controlled trials about the management of pain in ALS so no guidelines on this important aspect of the disease are available for clinicians. In an

Table 3: Summary of studies on the prevalence and features of pain among patients with amyotrophic lateral sclerosis.

	Study design	Number of patients and controls	Assessment methods	Frequency of pain	Feature and location of pain
Ganzini et al. [18]	Observational	100 patients	Interview to patients and caregivers	19% reporting moderate to severe pain	Not reported
Jensen et al. [19]	Observational	193 patients with neuromuscular disease (30 ALS)	Neuropathic pain scale, Brief Pain Inventory, quality of life (SF-36)	60% of ALS patients	"Deep," "tiring," "sharp," and "dull" Localized in the back, leg, shoulder, and neck (total of patients with neuromuscular disease)
Ho et al. [20]	Retrospective	193 patients	Standard medical records	23%	Shoulder pain
Chiò et al. [21]	Case control	160 patients	Brief Pain Inventory	56.9%	Pain more frequent in the extremities
Pagnini et al. [22]	Observational	40 patients	Italian Pain Questionnaire, McGill Quality of Life Questionnaire	51.2%	"Nagging," "sore," "periodic," "annoying," "exhausting," "enduring," "debilitating," and "worrying"
Rivera et al. [23]	Observational	63	Neuropathic pain scale	50%	Neuropathic pain
Pizzimenti et al. [24]	Observational	36	Neuropathic Pain Symptom Inventory (2 items)	71%	Localized in scapular-humeral area and lower limb
Wallace et al. [25]	Case control	42	Brief Pain Inventory PainDETECT Questionnaire	85%	Nonneuropathic: cramping, aching, tiring, sharp, and tender
Hanisch et al. [26]	Case control	46	Brief Pain Inventory	78%	Cramps
Moisset et al. [27]	Observational	93	DN4 questionnaire	66%	9% neuropathic pain

observational study, 17 out of 36 ALS patients complaining about pain received treatment with nonsteroidal anti-inflammatory drugs, opioid, or antiepileptics with unspecified results [24]. In another observational study, 63% of 91 ALS patients suffering from pain were under treatment in most of the cases with nonsteroidal anti-inflammatory drugs and nonopioid analgesics [21]. Cramps are currently treated by carbamazepine or phenytoin [107]. In a hospice study, where more than 80% of the patients received the analgesic therapy at least once a day, opioids offered benefit to about 70% of the patients with advanced motoneuronal disease [108, 109]. The treatment of spasticity by intrathecal baclofen may also alleviate pain though this aspect was rarely considered [110]. In addition, although riluzole is actually indicated as the only available disease-modifying medication and confers a little survival advantage, the effects of symptomatic treatment on pain remain unclear [111]. Again, pain associated with ALS is believed to be largely due to immobility. Physiotherapy, stretching, and range of motion exercises used in combination with pharmacotherapies to prevent contractures and reduce cramping and spasticity can be effective for associated pain [107, 112].

5.5. Main Limitations of Present Studies and Future Directions. ALS is a complex disorder where pain is currently considered an important but not primary end point in current management. Studies on pain frequency in ALS present the limits to be conducted in single centers in small samples, to rarely have a reliable control population, to be frequently retrospective, and to use usually nonvalidated methods for pain evaluation so the real impact of pain symptoms on the global burden of the disease is still unknown. Neurophysiological examination is limited to standard examination of sensory neurography, and the few studies with neurophysiological techniques exploring the nociceptive and nonnociceptive somatosensory system were conducted in small cohorts of patients in different stages of the disease. Controlled randomized trials on different pain killers are still lacking, and pain was considered only in some studies focusing on the global management of ALS.

Considering the impact of pain on the total outcome of ALS, a systematic clinical approach with specific scale for pain features and invalidity should be used in patients who report painful symptoms. A neurophysiological assessment of sensory functions by means of somatosensory nociceptively

and nonnociceptively evoked responses might complete the standard examination [98]. The effects of treatments on pain should be considered, and specific, controlled trials are needed.

Although *Cannabis* may potentially represent a therapeutic opportunity for many ALS symptoms including pain [113, 114], evidence on its efficacy is presently scarce and based only on one controlled study in a small patient group, with negative results on pain release [115]. Angiotensin-converting enzyme inhibitors may be also a potential approach to neurodegenerative disorders and neuropathic pain [116]. In addition, physical therapy and the other nonpharmacological approach would be finalized toward pain symptoms improvement.

6. Other Rare Neurodegenerative Conditions

6.1. Spinocerebellar Ataxia (SCA). Among the neurodegenerative hereditary cerebellar ataxia conditions, there are at least 36 different forms of autosomal dominant cerebellar ataxia (ADCA), 20 autosomal recessive cerebellar ataxia conditions, two X-linked ataxia conditions, and several forms of ataxia associated with mitochondrial defects [117].

A number of disease entities present with the ADCA phenotype such as spinocerebellar ataxia (SCA) conditions, dentatorubral-pallidoluysian atrophy, episodic ataxia, and autosomal dominant spastic ataxia. SCA conditions can be divided by the mode of inheritance into autosomal dominant, autosomal recessive, or sporadic conditions. There are many types of spinocerebellar ataxia and about 30 different gene mutations, 22 different genes, and 10 different gene loci have been identified, but the numbers continue to grow [118–120].

The definition of SCA conditions, despite significant progress in their understanding, is still imprecise, but the development of genetic profiling has made genetic classifications possible, which allows estimating the underlying etiology in 60% of the patients [121]. SCA disorders are a group of neurodegenerative disorders with clinical, genetic, and neuropathological heterogeneity being characterized by ataxia and other neurological signs such as oculomotor disturbances, cognitive deficits, pyramidal and extrapyramidal dysfunction, and bulbar, spinal, and peripheral nervous system involvement [122]. The prevalence of ADCA conditions is estimated to be around 3 in 100000, but it is highly variable depending upon the geographical area [123, 124].

As compared with other neurodegenerative disorders such as Parkinson's disease, quantitative and validated assessment tools are less developed [125]. The patients generally experience problems with mobility, usual activities, pain/discomfort, depression/anxiety, and self-care. Different population surveys have shown that 19 to 64% of patients report pain as a problem in selected SCA conditions [126]. In the same study, multivariate analysis revealed three independent predictors of subjective health status: ataxia severity, extent of noncerebellar involvement, and the presence of depressive syndrome. Although pain is not a primary invalidating factor in such patients, it may influence the quality of life as part of depression-related symptoms cohort and noncerebellar features.

In a recent systematic review reporting data from 1062 publications and 12141 patients with different neuromuscular disorders, pain was found to be reported in 1 among 30 SCA sufferers [127]. However, pain may often be underestimated though it can be severe when related to dystonia. In SCA conditions, pain can be misdiagnosed and mistreated but successfully ameliorated by, for example, botulinum toxin therapy [128].

There are currently no cures for SCA and treatments (pharmacological therapy and physiotherapy) target the symptoms such as pain, spasticity, tremor, stiffness, postural balance, gait disabilities, sleep problems, and depression. However, there are some very preliminary and nonvalidated data suggesting the use of umbilical cord mesenchymal stem cells in SCA [129].

6.2. Spinal Muscular Atrophy (SMA). Spinal muscular atrophy (SMA) is an autosomal, recessive, severe neuromuscular, degenerative disease characterized by loss of alpha motor neuron function in the spinal cord resulting in progressive proximal symmetrical muscle weakness often greater in the legs than in arms, atrophy, and paralysis and eventually in impairment of respiration and dysphagia. SMA is the second most common lethal, autosomal, recessive disorder in Caucasians with an incidence of approximately 1/6000 and a carrier frequency of 1/50 [130]. The muscle weakness can cause contracture formation, spinal deformity, limited mobility, and activities of daily living and eventually cause pain.

Engel et al. [131] found chronic pain in most patients classified as "other MND" including the CMT disease, all forms of spinal muscular atrophy, and many forms of mitochondrial and congenital myopathies. Pain was most frequently reported in the legs with a mild intensity (1.3, range 0–6 on the 0–11 numerical scale) [131].

7. Conclusions

Neurodegenerative diseases represent a social, medical, and economic problem and constitute a main field of interest for neurologists. Pain may be one of the most debilitating symptoms and a mode to express subjective discomfort and sufferance. Motor and sensory deficit may directly cause pain as in amyotrophic lateral sclerosis, Parkinson's disease, spinal cerebellar ataxia, and hereditary neuropathies where the subjective expression may be limited by the motor impairment. In demented patients, pain may be caused by different factors as age-related muscle skeletal degeneration, immobility, or neurodegeneration in brain areas involved in pain inhibition though subjective sufferance manifestation may be limited by cognitive impairment. The present review outlined a general medical carelessness with regard to pain as attention is especially pointed to the main illness symptoms. However, in many conditions such as Parkinson's disease, amyotrophic lateral sclerosis, and chronic familiar polyneuropathy, pain is largely represented among patients pending its specific assessment. Even in Alzheimer's disease, if special care is provided and specific scales are used, pain appears not to

be a secondary problem but instead it appears worthy of full consideration. In rare conditions as Huntington's disease, pain expression may be also limited, and its causes would be underestimated and neglected. As a consequence of the scarce attention generally dedicated to pain, no controlled trials and specific treatment guidelines are available, and pain therapy is generally based on the symptomatic approach by analgesics and anti-inflammatory drugs without a systematic consideration of the causal mechanisms. Current evidences about the relevance of pain in neurodegenerative disorders indicate the opportunity of a full involvement of neurologists in pain management taking into consideration its causes and mechanisms giving special attention to predisposing factors symptoms, employing and validating specific scales performing the clinical and instrumental assessment of sensory functions promoting therapeutic trials by means of pharmacological and nonpharmacological approach. Considering the centrality of pain in individual suffering, the question "Do you feel, or did he/she feel pain?" followed by a careful observation and consideration of the contribution of painful symptoms to the global burden of the disease should be included in the routine assessment of neurodegenerative diseases to finalize the best therapeutic choice.

Competing Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Clinical Study

The Interactive Relationship between Pain, Psychosis, and Agitation in People with Dementia: Results from a Cluster-Randomised Clinical Trial

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Background. Neuropsychiatric symptoms are common in people with dementia, and pain is thought to be an important underlying factor. Pain has previously been associated with agitation, and pain treatment has been shown to ameliorate agitated behaviour. So far, the association between pain and psychosis and the effect of pain treatment on psychotic symptoms is unclear. Furthermore, the impact of opioid treatment on psychosis is not established. *Aim*. To investigate the efficacy of a stepwise protocol for treating pain (SPTP) on psychosis and agitation measured with the Neuropsychiatric Inventory, Nursing Home version, and to explore the impact of opioid analgesics on psychosis. *Method*. Secondary analyses are from a cluster-randomised controlled trial including 352 patients with advanced dementia and agitation from 18 nursing homes in Western Norway. The intervention group received pain treatment according to SPTP. *Results*. Pain was associated with disinhibition (adjusted OR: 1.21, 95% CI: 1.10–1.34) and irritability (adjusted OR: 1.10, 95% CI: 1.01–1.21) at baseline. Pain treatment reduced agitation ($p < 0.001$, df = 1; 300) and aberrant motor behaviour ($p = 0.017$, df = 1; 300). Psychosis was reduced in people with at least one symptom at baseline ($p = 0.034$, df = 1; 135). The use of opioid analgesics did not increase psychotic symptoms. *Study Registration*. This trial is registered with ClinicalTrials.gov (NCT01021696), Norwegian Medicines Agency, EudraCT (EudraCTnr: 2008-007490-20).

1. Introduction

Neuropsychiatric symptoms (NPS) are a feature in many neurodegenerative diseases, among other dementia, where over 90% of patients suffer from at least one NPS during the course of their disease [1]. NPS can be distressing for both patients and family alike and is often the main reason for admission to a nursing home (NH) [2]. NPS can be clustered in different ways. These clusters are most commonly defined by symptoms that present concurrently, like mood symptoms such as depression and anxiety, agitation symptoms such as aggression and irritability, and psychosis symptoms such as delusion and hallucination [3–6].

The aetiology of NPS is largely unknown, but factors like neuropathological changes in the brain, unmet psychosocial needs, and pain are thought to play a role [7]. Despite the multiple potential underlying factors, NPS are often treated with antipsychotic drugs with potential harmful side effects [8]. This highlights the importance of investigating the relationship between NPS and possible underlying treatable causes, such as pain, to avoid unnecessary antipsychotic drug use [9–11].

People in the later stages of dementia often reside in NHs and frequently experience pain, with 30–60% suffering daily from pain [12–14]. The cognitive decline with a subsequent loss of communicative abilities puts people with dementia at an increased risk of suffering from untreated pain [15, 16]. Research demonstrates that pain in people with dementia can act as a trigger for NPS such as agitation and mood symptoms [17, 18]. However, the relationship between pain

and psychosis symptoms is less well studied, and only an association between pain and delusion has previously been described. Tosato et al. investigated the association between pain and NPS in NH patients with cognitive impairment and found pain to be associated with delusion [19]. In contrast, Cohen-Mansfield et al. found no association between pain and psychosis symptoms in an adult day care population (≥60 years old) residing in the community [20].

Our own research demonstrated the efficacy of individual pain treatment on behavioural disturbances in NH patients with advanced dementia and found that pain treatment ameliorated agitation as assessed by the Cohen-Mansfield Agitation Inventory (CMAI) [9]. Secondary analyses showed that pain treatment also reduced verbal aggression and restlessness [10]. Mood symptoms such as depression, sleep and appetite disturbances, measured with the Neuropsychiatric Inventory, Nursing Home version (NPI-NH) [11], and pain intensity assessed by the Mobilisation Observation Behaviour Intensity Dementia-2 (MOBID-2) Pain Scale [13] were also found to be reduced. The effect of pain treatment on psychosis and agitation symptoms measured by NPI-NH has, however, not yet been investigated.

Although there are no official guidelines for pain treatment in people with dementia, the use of opioid analgesics in pain treatment is recommended in guidelines for older people [21–23]. However, some physicians can be reluctant to prescribe these drugs, often due to the fear of possible side effects such as delirium, which also includes psychotic symptoms such as hallucination and delusion [24, 25]. The association between opioid analgesics and psychosis can therefore give relevant information regarding delirium as a potential side effect of opioid drug use.

The primary aim of this study was to investigate the efficacy of pain treatment on psychosis and agitation and the association between pain, psychosis, and agitation in people with advanced dementia. In addition, we investigated whether the use of opioid analgesics increased the prevalence of delusion and hallucination in people with dementia. We hypothesized an association between pain and agitation at baseline, but not between pain and psychosis, and suggested that pain treatment will reduce symptoms of agitation, but not symptoms of psychosis. We also hypothesized that the use of opioid analgesics does not increase the prevalence of hallucination and delusion.

2. Method

We conducted secondary analyses from a cluster-randomised controlled trial (RCT), investigating the efficacy of treating pain on behavioural disturbances in NH patients with advanced dementia from 18 NHs in Western Norway. For a more detailed description of the study procedure, we refer to previous publications [9, 11, 13]. In brief, patients included in this study had moderate to severe dementia as defined by the Diagnostic and Statistical Manual of mental disorders, 4th edition (DSM-IV); Functional Assessment Staging Test (FAST) score ≥ 4 [26]; Minimental State Examination (MMSE) score ≤ 20 [27], and clinically relevant behavioural disturbances as defined by a score ≥ 39 on CMAI [28]. Patients were excluded if they had an advanced medical disorder with expected survival ≤ 6 months, severe psychiatric or neurological disorder, hepatic or renal failure, a score ≥ 8 on the aggression item of the NPI-NH, with aggression as the predominant symptom [29], or allergy to paracetamol, morphine, buprenorphine, or pregabalin.

2.1. Study Design. Each NH unit was defined as a single cluster and was randomised to either intervention or control. Randomisation was performed by a statistician using Stata version 8, by generating a list of random numbers used for allocating each cluster to either intervention or control. The intervention group received individual pain treatment according to a stepwise protocol for treating pain (SPTP) for 8 weeks, followed by a 4-week washout period where analgesics were reverted back to preintervention treatment. The control group received treatment as usual. The SPTP was based on recommendations made by the American Geriatrics Society [22]. According to assessment of current medication and degree of pain, the patient was allocated to one of four steps, receiving either paracetamol (Paracetamol®), extended release morphine (Dolcontin®), buprenorphine transdermal patch (Norspan®) for patients with swallowing difficulties, or pregabalin (Lyrica®) for patients with suggested neuropathic pain. Physicians were instructed to keep the prescription unchanged if possible. Use of as-needed analgesics was not prohibited and was monitored during the study.

2.2. Outcome Measures. The primary outcome measure was NPS as measured by the NPI-NH [29]. The NPI-NH rates the frequency (F) and severity (S) of twelve different NPS. Frequency is rated on a scale from 1 to 4, where 1 represents occasionally (less than once a week) and 4 represents very frequent (daily or more often). Severity is measured on a scale from 1 to 3, where 1 represents mild (causes little stress for the patient) and 3 represents severe (puts very much stress on the patient and cannot easily be diverted by caregivers). The frequency and severity scores are multiplied ($F \times S$) to give an item score for each NPS, where a score ≥ 4 was viewed as a clinically significant symptom [30].

The NPS measured by NPI-NH were clustered in three groups: agitation (aggression, disinhibition, irritability, and aberrant motor behaviour), psychosis (delusion, hallucination, and euphoria), and mood (depression, anxiety, apathy, and sleep and appetite disturbances), according to factor analyses by Cheng et al. [6].

Pain intensity was assessed by the MOBID-2 Pain Scale [31–33]. This is a nursing staff-administered pain tool, consisting of two parts. The first part assesses pain originating from the musculoskeletal system during five active guided movements. The second part assesses pain that might be related to internal organs, head, and skin based on the caregivers' observation during the last week. Taking all items into account, the caregiver rated the patients' pain on a Numerical Rating Scale (NRS) ranging from 0 to 10, where 0 represented no pain and 10 the worst pain imaginable. This tool has been

thoroughly tested for its psychometric properties and showed good validity, reliability, and responsiveness [32, 33].

All assessments were conducted at baseline and Weeks 2, 4, 8, and 12 by the primary caregivers who knew the patient best in collaboration with a specialised study nurse.

2.3. Statistics. Differences in baseline characteristics were explored using an independent sample t-test for normally distributed variables; a Chi-squared test was used for categorical variables, and a Mann-Whitney U test was used for nonparametric variables. Associations between pain, psychosis, and agitation at baseline were investigated by using crude and adjusted logistic regression. Each symptom of psychosis and agitation represented the dependent variable, while total pain intensity, assessed by MOBID-2, represented the explanatory variable. Associations were adjusted for age, gender, dementia severity (assessed by MMSE and FAST), and activities of daily living (ADL) function assessed by Barthels ADL index [34]. The changes in $F \times S$ score between the intervention and control groups from baseline to Week 8 were compared using the Mann-Whitney U test. The association between opioid analgesics and delusion and hallucination was evaluated at baseline and Week 8 using logistic regression. Associations were adjusted for age, gender, dementia severity (MMSE and FAST), ADL function (Barthels ADL index), and pain intensity (MOBID-2). Statistic calculations were performed using the Statistical Package for Social Sciences (SPSS) version 22.

3. Ethics

Informed consent was obtained from patients who were cognitively able to understand the possible risks and benefits of the study. Consent was, if possible, obtained in a meeting where next of kin was present as well. A presumed consent was obtained from next of kin, or a legal guardian, if the patient was not able to give an informed consent. All consents were obtained in accordance with local law, approved by the Regional Ethical Committee for Medical Ethics in Western Norway (REK-Vest 248.08), and authorised by the participating institutions' review board.

4. Results

Three hundred and fifty-two patients from 60 NH units were included. Units were randomised to either intervention or control, generating 177 patients in the control group and 175 patients in the intervention group. With the exception of age ($p = 0.022$), we found no differences between the two groups. Baseline characteristics are described in Table 1. During the intervention period, 13 patients in the control and 25 in the intervention group were excluded, with no significant differences between the two groups [9]. At baseline, 71 people in the control group (40%) and 83 people in the intervention group (47%) had one or more symptoms of psychosis, while 128 people in the control group (72%) and 137 people in the intervention group (78%) had one or more symptoms of agitation. The most prevalent symptom was irritability (48%), while the least prevalent one was euphoria (9%).

Table 1: Sample characteristics of patients at baseline.

	Control ($n = 177$)	Intervention ($n = 175$)	df	p
Age (SD)[a]	86.5 (6.7)	84.9 (7.0)	350	0.022
Women (%)[b]	131 (74.0)	131 (74.9)	1	0.856
FAST (SD)[c]	6.0 (0.7)	6.1 (0.7)	349	0.057
MMSE (SD)[c]	8.4 (6.7)	7.5 (6.5)	346	0.177
Barthels ADL total score (SD)[c]	8.6 (5.6)	7.9 (5.7)	339	0.216
CMAI total score (SD)[c]	56.2 (16.1)	56.5 (15.2)	349	0.487
MOBID-2 (SD)[c]	3.7 (2.5)	3.8 (2.7)	325	0.988
Medications (SD)[c]	3.6 (1.6)	3.4 (2.1)	318	0.146
Analgesics (%)[b]	122 (68.9)	117 (66.9)	1	0.404
Paracetamol (%)[b]	94 (53.1)	99 (56.6)	1	0.665
Opioids (%)[b]	51 (28.8)	43 (24.6)	1	0.292
NSAIDS (%)[b]	9 (5.1)	13 (7.4)	1	0.364
Psycholeptics (%)[b]	112 (63.3)	104 (59.4)	1	0.458
Antipsychotics (%)[b]	13 (7.3)	17 (9.7)	1	0.465
Anxiolytics (%)[b]	86 (48.6)	80 (45.7)	1	0.589
Psychosis symptoms (%)[b]	71 (20.2)	83 (23.6)	1	0.209
Delusion (%)[b]	49 (27.7)	66 (37.7)	1	0.056
Hallucination (%)[b]	29 (16.4)	32 (18.3)	1	0.690
Euphoria (%)[b]	15 (8.5)	16 (9.1)	1	0.864
Agitation symptoms (%)[b]	128 (36.4)	137 (38.9)	1	0.285
Agitation/aggression (%)[b]	74 (41.8)	85 (48.6)	1	0.253
Disinhibition (%)[b]	56 (31.6)	59 (33.7)	1	0.760
Irritability (%)[b]	84 (47.5)	85 (48.6)	1	0.956
Aberrant motor behaviour (%)[b]	57 (32.2)	65 (37.1)	1	0.388

[a]Independent-samples t-test.
[b]Pearson's Chi-squared test.
[c]Mann-Whitney U test.

Related to symptoms of psychosis, no associations were found between pain and symptoms of psychosis at baseline. During the intervention period, no reduction in the psychosis cluster ($p = 0.091$, df = 1; 300), delusion ($p = 0.052$, df = 1; 300), hallucination ($p = 0.832$, df = 1; 300), and euphoria ($p = 0.507$, 1; 300) was observed in response to individual pain treatment compared to the control group from baseline and to Week 8 (Table 2, Figures 1–3). However, for people with one or more symptoms of psychosis at baseline, a decrease was observed in the psychosis cluster ($p = 0.034$, df = 1; 135) and delusion ($p = 0.031$, df = 1; 135) in the intervention group compared with the control group (Table 3, Figure 7).

At baseline, the adjusted logistic regression analysis showed a positive association between disinhibition and level of pain (OR: 1.18, aOR: 1.21, 95% CI: 1.10–1.34, and $p < 0.001$) and between irritability and level of pain (OR: 1.11, aOR: 1.10, 95% CI: 1.01–1.21, and $p = 0.032$), adjusted for confounders. During the intervention period, a decrease in the agitation cluster ($p < 0.001$, df = 1; 301), agitation/aggression ($p = 0.001$, df = 1; 301), and aberrant motor behaviour ($p = 0.017$, df = 1; 301) was found in the treatment group compared to

Table 2: Efficacy of treating pain on psychosis and agitation.

	Baseline			8 weeks			
	Control ($n = 177$)	Intervention ($n = 175$)	p^a	Control ($n = 157$)	Intervention ($n = 146$)	p^a	p change^b
NPI total score	31.4 (21.4)	34.8 (21.9)	0.132	26.6 (20.1)	18.9 (17.5)	<0.001	<0.001
Psychosis cluster	4.8 (5.8)	6.1 (6.9)	0.087	3.7 (4.9)	3.9 (5.5)	0.682	0.091
Delusion	2.6 (3.8)	3.6 (4.3)	0.030	2.0 (3.1)	2.0 (3.2)	0.813	0.052
Hallucination	1.5 (2.9)	1.8 (3.2)	0.427	1.1 (2.3)	1.4 (2.7)	0.405	0.832
Euphoria	0.7 (2.0)	0.8 (2.2)	0.887	0.6 (1.9)	0.5 (1.8)	0.123	0.507
Agitation cluster	13.4 (10.9)	14.8 (10.9)	0.155	11.3 (10.9)	7.8 (8.3)	0.007	<0.001
Agitation/aggression	3.7 (3.9)	4.2 (4.3)	0.373	3.4 (3.8)	2.1 (3.1)	0.001	0.001
Disinhibition	3.0 (4.0)	2.9 (3.8)	0.922	2.6 (3.9)	1.7 (3.0)	0.061	0.293
Irritability	3.7 (3.7)	4.2 (4.1)	0.338	3.0 (3.4)	2.3 (3.1)	0.092	0.093
Abb. motor behaviour	3.0 (4.5)	3.5 (4.7)	0.328	2.4 (3.7)	1.7 (3.6)	0.052	0.017

[a]Calculated by analyzing the difference between the intervention group and control group at each measurement point using the Mann-Whitney U test.
[b]Calculated by analyzing the difference in change of NPI-NH score in the intervention group versus the control group from baseline to Week 8 using the Mann-Whitney U test.

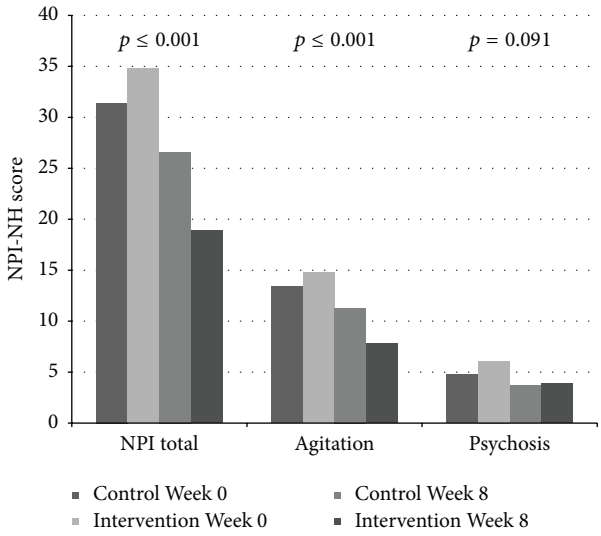

Figure 1: The efficacy of treating pain on psychosis and agitation.

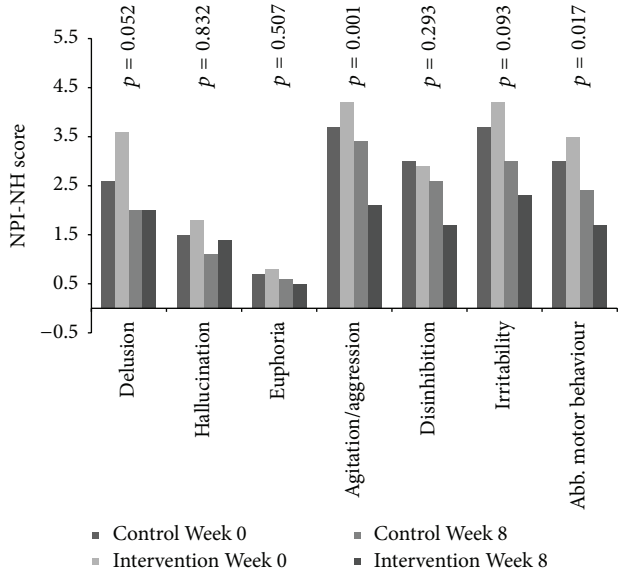

Figure 2: The efficacy of pain treatment on individual neuropsychiatric symptoms.

the control group (Table 2, Figures 1, 2, 4, 5, and 6). For people with one or more symptoms of agitation at baseline, a decrease during the intervention period was observed in the agitation cluster ($p < 0.001$, df = 1; 228), agitation/aggression ($p = 0.004$, df = 1; 228), and aberrant motor behaviour ($p = 0.007$, df = 1; 228) in the treatment group compared with the control group (Table 3, Figure 8).

At baseline, the use of opioid analgesics was not associated with the prevalence of delusions (OR: 0.97, aOR: 0.96, 95% CI: 0.56–1.65, and $p = 0.870$) or hallucination (OR: 0.76, aOR: 0.69, 95% CI: 0.34–1.41, and $p = 0.314$). Following the intervention period at Week 8, opioids were not associated with the prevalence of delusion (OR: 1.90, aOR: 1.89, 95% CI: 0.72–4.98, and $p = 0.200$) or hallucination (OR: 1.05, aOR: 1.26, 95% CI: 0.39–4.09, and $p = 0.700$).

5. Discussion

This study aimed to investigate the relationship between pain, psychosis, and agitation, the efficacy of treating pain on psychosis and agitation, and the potential impact of opioid analgesics on the development of hallucination and delusion in NH patients with advanced dementia.

The study showed that treatment of pain ameliorates the prevalence of psychosis and delusion in people with dementia who presented at least one psychosis symptom at baseline. It is also established that, in this study, opioid analgesics did not increase the prevalence of hallucination or delusion. These findings confirmed the hypothesis that pain is a potential underlying cause for psychosis and that proper pain management is needed in order to avoid psychotic symptoms. This provides important information for clinicians when pharmacological treatment options for pain are to be evaluated. Some clinicians can be reluctant to prescribe opioid analgesics for pain treatment of people with dementia, often due to fear of anticholinergic side effects, such as delirium [24]. Finally, we found that pain treatment

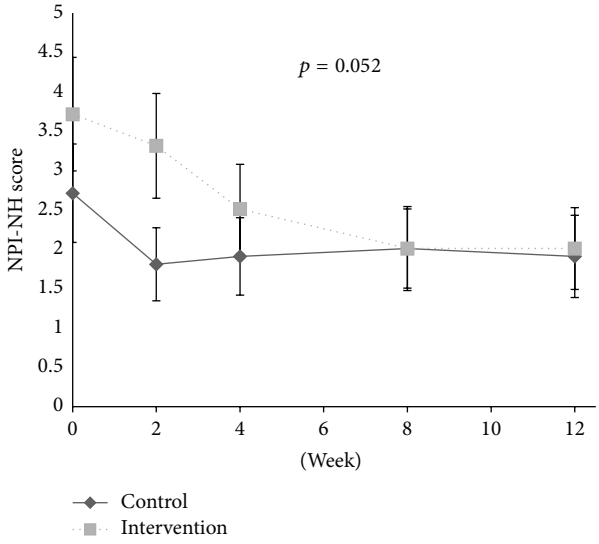

Figure 3: Development of delusion during the intervention and washout period.

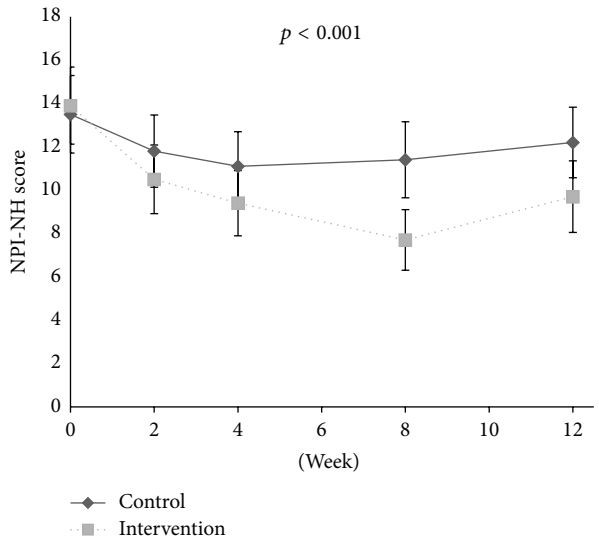

Figure 4: Development of agitation scores in clusters during intervention and washout period.

reduced agitation, aggression, and aberrant motor behaviour. This underlines previous findings where pain was found to be an important underlying cause for agitation assessed with CMAI in people with dementia. These findings highlight the fact that proper pain assessment should be a prerequisite when deciding treatment options for agitation in people with dementia.

The current study was the first parallel group-controlled trial investigating the efficacy of analgesics on psychotic symptoms in people with advanced dementia. Although individual pain treatment reduced psychosis in people with psychotic symptoms, pain was, interestingly, not cross-sectionally associated with hallucination and delusion at baseline. Tosato et al. used data from the Minimum Data Set (MDS) and investigated the relationship between pain

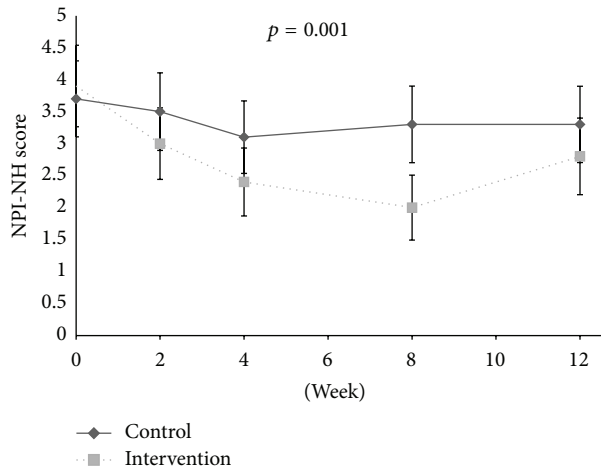

Figure 5: Development of agitation/aggression during the intervention and washout period.

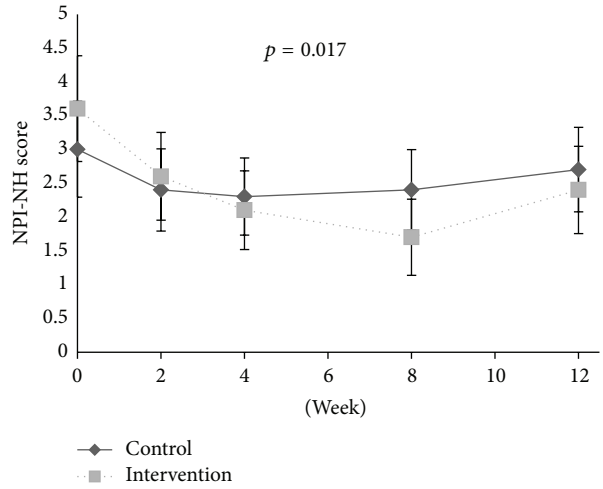

Figure 6: Development of aberrant motor behaviour during the intervention and washout period.

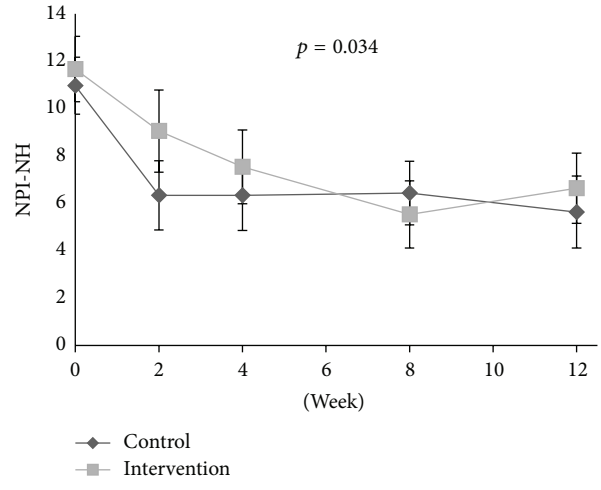

Figure 7: Development of the psychosis cluster in patients with one or more clinically significant NPS of psychosis at baseline (NPI-NH ≥ 4).

Table 3: Efficacy of treating pain on psychosis and agitation in patients presenting one or more clinically significant symptoms at baseline (NPI-NH ≥ 4).

	Baseline (SD)			8 weeks (SD)			
	Control ($n = 71$)	Intervention ($n = 83$)	p^a	Control ($n = 67$)	Intervention ($n = 70$)	p^a	p change^b
Psychosis cluster	10.5 (4.7)	11.6 (5.9)	0.314	6.4 (5.3)	5.6 (6.1)	0.148	0.034
Delusion	5.6 (4.2)	6.9 (4.0)	0.043	3.2 (3.7)	2.9 (3.6)	0.770	0.031
Hallucination	3.2 (3.8)	3.3 (4.0)	0.813	2.1 (3.1)	2.1 (3.3)	0.987	0.925
Euphoria	1.7 (2.9)	1.4 (3.1)	0.211	1.0 (2.2)	0.5 (1.9)	0.027	0.758
	Control ($n = 128$)	Intervention ($n = 137$)	p^a	Control ($n = 117$)	Intervention ($n = 113$)	p^a	p change^b
Agitation cluster	17.4 (9.7)	18.0 (9.6)	0.422	14.0 (11.0)	8.8 (8.8)	<0.001	<0.001
Agitation/aggression	4.7 (4.0)	5.1 (4.2)	0.441	4.2 (4.0)	2.5 (3.3)	0.001	0.004
Disinhibition	3.9 (4.3)	3.5 (4.0)	0.618	3.3 (4.2)	1.9 (3.2)	0.008	0.211
Irritability	4.8 (3.6)	5.1 (4.1)	0.664	3.6 (3.6)	2.6 (3.2)	0.023	0.183
Abb. motor behaviour	4.0 (4.7)	4.3 (4.9)	0.639	2.9 (3.9)	1.8 (3.5)	0.008	0.007

[a]Calculated by analyzing the difference between the intervention group and control group at each measurement point using the Mann-Whitney U test.
[b]Calculated by analyzing the difference in change of NPI-NH score in the intervention group versus the control group from baseline to Week 8 using the Mann-Whitney U test.

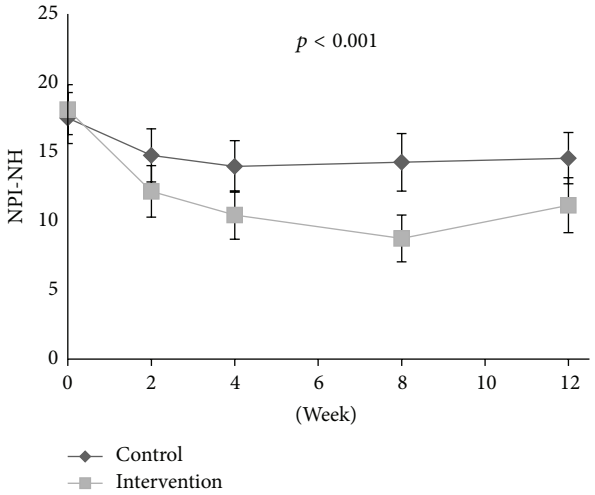

Figure 8: Development of the agitation cluster in patients with one or more clinically significant NPS of agitation at baseline (NPI-NH ≥ 4).

and psychiatric symptoms in 2822 NH residents with cognitive impairment and found an association between pain and delusion but not between pain and hallucination [19], contrary to our results. In Tosato's study, the interRAI MDS 2.0 instrument for long-term facilities was used to measure psychosis and pain, while our study used the MOBID-2 Pain Scale to measure pain. Cohen-Mansfield et al. also investigated the association between pain, delusion, and hallucination in an adult day care population and found no association between pain and delusion or pain and hallucination [20]. However, in contrast to our study, these people were not residing in NHs and patients suffering from dementia were not analyzed as a separate group. The study used the Behavioural Pathology in Alzheimer's disease rating scale to measure psychosis and a questionnaire, based on the short form of the McGill Pain Questionnaire, distributed to family and caregivers to measure pain. Pain should be measured by a tool thoroughly tested for psychometric properties, and among the measurement tools used, only MOBID-2 has been tested for validity, reliability, and responsiveness [32, 33].

We used a symptom clustering largely based on a factor analyses of the NPI-NH by Cheng et al., where the symptoms were clustered in three main groups: agitation, mood, and psychosis [6]. This clustering makes "clinical sense" and is in line with other previous studies. Hollingworth et al. grouped delusion and hallucination in a psychosis cluster, aggression and irritability in an agitation cluster, and disinhibition, euphoria, and aberrant motor behaviour in a behavioural dyscontrol cluster [3]. In a four-factor solution, Selbæk and Engedal grouped hallucination and delusion as a psychosis cluster and aggression, irritability, disinhibition, and aberrant motor behaviour in an agitation cluster [4]. Overall, the clusters may be viewed as merely theoretical constructs and changes assessed over time [4].

The reduction in psychosis was largely attributed to the reduction of delusion, as neither hallucination nor euphoria was reduced in response to pain treatment. This indicates that hallucination and euphoria may not be associated with pain. Traditionally, antipsychotics are recommended for short-time treatment of psychosis, also in people with dementia, despite potential harmful side effects and increased mortality [8]. Our results suggested that hallucination and euphoria were not associated with pain, making the use of antipsychotics in treatment of hallucination and euphoria more warranted than in treatment of delusion.

The use of opioid analgesics did not increase the prevalence of delusion or hallucination at baseline, or after the 8-week intervention. This is of key importance, because opioid analgesics such as morphine or buprenorphine can have multiple side effects such as confusion and delirium caused by anticholinergic activity [24]. Notably, delirium, psychosis, and depression have several similarities in people with dementia, making them difficult to distinguish and diagnose. This highlights the importance of trained staff in order to discriminate between the more acute state delirium and more chronic symptoms in dementia [25].

The reduction of agitation in response to pain treatment was fairly expected, as previous analyses on the study population have shown a decrease in behavioural disturbances, especially agitation, as measured using CMAI [9, 10]. NPI-NH does however measure more specific symptoms in contrast to CMAI, which measures more specific behavioural items. Therefore, the efficacy of pain treatment on the specific symptom aberrant motor behaviour is an interesting finding, supported by previous studies which found that pain treatment may reduce agitation. An article by Flo et al. reviewed studies on pain management in people with dementia and found that pharmacological pain treatment could reduce agitation [17]. Achterberg et al. reviewed the efficacy of pain management in people with dementia and found that pain can be a possible underlying cause for agitation and that a thorough pain assessment and management can ameliorate agitation [16]. The present analyses also found that there was an association between pain and disinhibition and irritability at baseline. While previous studies have found an association between pain and agitation, the direct association between pain, disinhibition, and irritability has not previously been described [17, 18, 35]. Our results showed that NPS associated with pain at baseline, like irritability and disinhibition, were not reduced in response to pain treatment. Results also showed that NPS not associated with pain at baseline, like agitation and delusion, were reduced in response to pain treatment. This paradox simply highlights the complex aetiology of NPS of agitation, and a thorough assessment of all possible underlying causes is important when deciding on possible treatment options for neuropsychiatric symptoms in people with dementia. Pain and behaviour are strongly intertwined, and the efficacy of both behavioural interventions and pain medication can improve both pain and behaviour [36].

Strengths and Limitations. This is the first RCT investigating the efficacy of treating pain on psychosis. Results came from secondary analyses from a previous study where CMAI was the primary outcome and NPI-NH was a secondary outcome. Inclusion criteria were therefore based on behavioural disturbances measured using CMAI. The number of study participants was also a limitation, as the group of patients with psychosis at baseline were a subgroup of the original population and a small sample. Despite this, the study is still the largest RCT investigating the efficacy of treating pain on psychosis and agitation.

6. Conclusion

Pain seems to be an underlying cause of psychosis and especially delusion. In addition, pain seems to be an underlying cause of agitation, such as aberrant motor behaviour. Thus, proper pain assessment is needed when treating these symptoms in people with dementia. The use of opioid analgesics does not seem to increase the prevalence of delusion and hallucination; therefore, the reluctance to use them may not necessarily be to the benefit of the patient.

Ethical Approval

The study was approved by the Regional Ethical Committee for Medical Research of Western Norway (248.08).

Competing Interests

The authors declare that there are no competing interests regarding the publication of this paper.

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Research Article

The Influence of Executive Functioning on Facial and Subjective Pain Responses in Older Adults

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Cognitive decline is known to reduce reliability of subjective pain reports. Although facial expressions of pain are generally considered to be less affected by this decline, empirical support for this assumption is sparse. The present study therefore examined how cognitive functioning relates to facial expressions of pain and whether cognition acts as a moderator between nociceptive intensity and facial reactivity. Facial and subjective responses of 51 elderly participants to mechanical stimulation at three intensities levels (50 kPa, 200 kPa, and 400 kPa) were assessed. Moreover, participants completed a neuropsychological examination of executive functioning (planning, cognitive inhibition, and working memory), episodic memory, and psychomotor speed. The results showed that executive functioning has a unique relationship with facial reactivity at low pain intensity levels (200 kPa). Moreover, cognitive inhibition (but not other executive functions) moderated the effect of pressure intensity on facial pain expressions, suggesting that the relationship between pressure intensity and facial reactivity was less pronounced in participants with high levels of cognitive inhibition. A similar interaction effect was found for cognitive inhibition and subjective pain report. Consequently, caution is needed when interpreting facial (as well as subjective) pain responses in individuals with a high level of cognitive inhibition.

1. Introduction

In the general population, the self-report of pain is typically viewed as the golden standard in pain assessment. In dementia, however, these self-reports are limited by the strong cognitive decline accompanying the disease, as it impairs language capacities and thereby the patients' ability to communicate about their pain. Moreover, dementia causes a reduction in abstraction abilities, which reduces the patients' ability to comprehend and thereby use pain scales to indicate their pain. Experts have therefore recently identified pain behaviors as being crucial in order to obtain reliable and valid pain assessments in dementia. Facial expressions form an important part of pain behaviors in the assessment of pain. Facial responses are not compromised by language impairments and, according to some studies, may be less dependent on the desire of expressing pain since facial expression is a rather automatic process [1, 2]. As a result, facial expressions should be less influenced by cognitive decline and are believed to validly indicate pain in patients with dementia [3].

However, although facial expressions of pain are thought to be relatively unaffected by cognitive decline compared to self-report, there is evidence that facial expressions are not completely unrelated to cognitive performance. Keltner and coworkers [4] examined facial expressions in adolescents with internalizing and externalizing problems and emphasized the role of impulse control and inhibition, important prefrontally mediated executive control functions, in the display of emotions. Several other studies examined cognitive and neural correlates of expression suppression, detecting strong associations with prefrontal brain structures and executive control functions [5, 6]. Similar results have been obtained for pain-specific facial expressions: two neuroimaging studies [7, 8] revealed that the suppression of facial pain expressions in low expressive individuals was related

to activation in the medial frontal cortex, a structure that is known to be involved in motor and behavioral inhibition [9–11]. This suggests that the degree to which we facially express pain might be related to executive functioning and potentially specifically to inhibitory processes, with low executive functioning leading to higher degrees of expressivity. The reason for this relation might be that we learn in our childhood to control and adjust our facial expressions according to social display rules [12, 13]. According to these social rules, we learn that we should inhibit the facial expression of negative affect, for example, the expression of pain. Depending on our executive functioning, we might be more or less capable of acting upon these rules and inhibit our facial expression of pain. Taken together, several studies suggest that executive functioning, which is strongly dependent on prefrontal cortex functioning, influences the extent to which facial expressions of pain are displayed. Moreover, executive control functions may act as a moderator in the relationship between the level of noxious intensity and the corresponding facial expressions [7].

The goal of the present study was to add to our understanding of how cognitive functioning (especially executive functioning) affects the self-report and facial expression of pain. Studies so far mainly assessed facial expression of pain using the Facial Action Coding System (FACS) [14]. This is a fine-grained analysis system that is, due to being very time consuming, not feasible for use in clinical practice. We therefore decided to investigate the effect of cognitive functioning on observable facial expressions using facial items extracted out of existing observational pain assessment scales. The following hypotheses were tested: (i) first, we expected that a decline in executive control predicts an increase in facial expressions following painful stimulation. (ii) Second, we tested whether this relationship was specific for executive functioning and not an unspecific relation between facial expression and other functions that commonly decline in aging, such as psychomotor speed and episodic memory. (iii) Finally, we examined whether executive functioning moderates the relationship between facial pain expressions and noxious intensity, with those participants with high levels of executive control showing a reduced relationship between facial expressions and stimulus intensity.

As the dementia process induces severe cognitive decline, which hinders both pain report and neuropsychological functions to be reliably assessed, we focused on normal aging adults, as this population is still able to provide reliable pain reports and to undergo a neuropsychological examination. Moreover, we focused on a wide age range, as from the age of 50 years onward a significant decline in cognitive functions, including executive control, can be detected [15, 16]. Therefore, participants from the ages of 50 years and older were included in this study.

2. Methods

2.1. Participants. Fifty-two older adults between the ages of 50 and 93 years were recruited for this study. Participants were volunteers recruited through advertisements in a local newspaper and through oral advertisement; in addition, some volunteers were acquaintances of the researcher. Education was measured using an ordinal rating scale that ranges from 1 to 7. Here, score 1 represents incomplete primary education, score 2 reflects primary education, score 3 reflects incomplete lower secondary education, score 4 reflects lower general secondary education, score 5 reflects vocational education, score 6 reflects higher general secondary/higher vocational/preuniversity education, and score 7 represents an academic degree [17]. Exclusion criteria were the presence of chronic pain, depression, stroke, a neurological disorder, and daily use of analgesic medication. Furthermore, global cognitive functioning was measured using the Mini Mental State Examination (MMSE) [18]. This test was included to detect the possible presence of severe cognitive problems (score < 24), which was also reason for exclusion from the study. One patient used naproxen and was therefore excluded from the study. All participants gave written informed consent prior to participation. The study protocol was approved by the Institutional Review Board of the Radboud University Nijmegen.

2.2. Neuropsychological Examination. All neuropsychological tests were administered in a fixed order. This was necessary to include a fixed delay between immediate and delayed memory testing (see Section 2.2.2.) and to ascertain that this period was filled with the same task demands for all participants. Neuropsychological examinations were conducted by psychology students trained by the principal investigator (JMO). In addition, the administration of the tests was performed in accordance with the standardized instructions as outlined in the manual of the specific tests. The total testing time was, overall, less than one hour.

2.2.1. Executive Functioning. Since executive functioning was our main focus, we employed three tasks to assess this heterogeneous domain. These were the Stroop task, the Digit Span Backward task, and the Zoo Map task. The Stroop task was employed as a measure of cognitive inhibition [19], assessing inhibition of prepotent responses. In short, this test consists of three cards, with each card containing 100 stimuli. The first Word card consists of color words written in black ink, which the participant has to read aloud as fast as possible. The second Color card consists of colored blocks which have to be named as fast as possible. The final Color/Word card contains color names written in an incongruent ink color; here the ink colors have to be named, while reading of the color names has to be suppressed. Participants were instructed to read the words or name of the color as fast as possible. Response times till completion of each card were assessed. The interference score (time needed for the Stroop Color/Word card divided by the time needed for the Stroop Color card) was used for the analyses. It is crucial to note that an increase in the interference score actually reflects worse interference control performance, as participants need more time to complete to complex Color/Word card compared to the time needed to complete the Color card. Working

memory was measured with the Digit Span Backward test [20]. Here, series of digits are read aloud to the participants, with the approximate speed of one digit per second, and the participant is requested to repeat these digits in the reversed order. This test starts with 2 digits, which increase in length following successful repetition of at least 1 series. The total number of correctly reproduced series of digits was used as outcome measure. Planning was measured with the Zoo Map, a test that is part of the Behavioural Assessment of the Dysexecutive Syndrome battery [21]. This test consists of an unstructured and a structured part; in both parts, participants are instructed to plan their route through a map of the zoo, visiting a selection of places while bypassing others. While planning the route, participants also need to obey to certain rules (e.g., certain paths can be used only once). In the unstructured part, no information about the exact order is given as participants have to come up with this order themselves, whereas in the structured part the order is explicitly stated. Points are given to places that are visited in the right order, whereas points are deducted in case an error is made. The total score (with a maximum of 16) was used for the current analysis.

2.2.2. Memory Functioning. In addition to these executive function tasks, episodic memory was measured since this function is known to decline with aging as well [22]. Both the Auditory Verbal Learning Test (AVLT) [23] and the Story Recall test (of the Rivermead Behavioural Memory Test (RBMT)) [24] were used for this purpose. The AVLT, measuring memory for unrelated words, consists of a list of 15 words, which are read aloud five times to the participant. Following each presentation, immediate recall is tested, and a total immediate recall score based on the five presentation times is calculated. In addition, delayed recognition was unexpectedly tested after an interval of approximately 15–20 minutes. Story Recall measures memorization of related information that is presented in the form of a story. After an entire story (consisting of 21 distinct elements) has been read aloud by the experimenter, immediate recall is tested. Again, after a delay of approximately 15 minutes, delayed recall is unexpectedly tested.

2.2.3. Psychomotor Speed. Finally, psychomotor speed, a function very sensitive to the age-related decline [25], was assessed using the Word and Color cards of the Stroop test.

2.2.4. Data Processing. For further analyses, standardized scores were calculated for the cognitive outcome measures in order to create cognitive domain scores, so as to reduce the number of statistical tests necessary (which reduces risk of type I error). Hence, an executive domain score (consisting of Stroop interference, Digit Span Backward, and the Zoo Map test), a memory domain score (AVLT immediate recall and delayed recognition, Story Recall immediate and delayed recall), and a psychomotor speed domain score (Stroop Word and Color card) were calculated. Cronbach's alpha was calculated to test reliability of these domains, in order to determine whether it was appropriate to use these domains for the analyses. As previous studies indicated that specifically cognitive inhibition may play a unique role in facial expressiveness, the executive function measures were also examined separately.

2.3. Mechanical Stimuli. Perception of noxious mechanical pressure was administered using a Wagner FPX™ Algometer. Three pressure intensities (50 kPa, 200 kPa, and 400 kPa) were applied in increasing order to both trapezius muscles, yielding a total of six stimuli. These stimulations always commenced on the dominant side. Pressure levels were built up rapidly (within 2 s) and were continued for approximately 5 s. The stimulation intensities were chosen to induce no pain (50 kPa), slight pain (200 kPa), and moderate pain sensations (400 kPa), respectively. In between stimulus applications, pain ratings were recorded, producing short intervals of 10–20 s.

All stimulation sessions were conducted by trained psychology students who also conducted the neuropsychological tests. We used a standardized protocol, and the students performed extensive practice sessions prior to starting the study to assure that they complied to this protocol.

2.4. Facial Pain Expression. Facial expressions were videotaped during the mechanical pain test and during a baseline period using a camera that was located in front of the participant at a distance of approximately 1.5 meters. Participants were instructed to maintain focus to a predefined location in front of them, in order to guarantee a frontal view and to avoid talking while pressure was applied. Facial expressions were analyzed offline in time windows of 7 seconds (covering the stimulation period or, in case of baseline trials, the time period before starting the pressure stimulation) using facial descriptors extracted out of existing observational pain assessment scales. This extraction has led to the development of the Pain Assessment in Impaired Cognition (PAIC) metatool [26] as part of a European funded COST action (TD1005) and we used all facial items of this PAIC tool (see Table 1). All facial expressions were rated by an independent rater, trained by the principal investigator (JMO), who was blinded towards the study questions and expectations. In addition, this rater was blinded to study outcomes (e.g., the level of cognitive performance of each participant). To get an indication of interrater reliability, a subset of videos (of 20 participants) was additionally rated by a second rater, namely, one of the psychology students involved in the study. For further analyses, we wanted to select those facial items that are able to differentiate between painful and nonpainful states to form a composite score of pain-indicative facial responses. Following previous approaches [3] we calculated which of the facial items are observed in at least 5% of the 400 kPa trials and which of these items are observed more frequently in response to 400 kPa stimulation compared to baseline (see Table 1). Only these items (they are shaded in grey in Table 1) were summarized to form a pain-indicative facial expression score. Average pain-indicative facial expressions were calculated for each

Table 1: Observation of facial items within the painful trials (400 kPa) in 51 participants. Selection of pain-indicative items was based on frequency of occurrence (>5%) as well as on a more frequent occurrence during pain compared to baseline (effect size $d \geq 0.5$).

Facial items	Percentage of occurrence[a]	Effect size (Cohen's d)
Pained expression	11.8	*d = 0.44*
Frowning	**12.8**	**d = 0.51**
Narrowing eyes	**17.3**	**d = 0.59**
Closing eyes	5.0	*d = 0.25*
Raising upper lip	**16.7**	**d = 0.53**
Opened mouth	**33.3**	**d = 0.85**
Tightened lips	**19.6**	**d = 0.58**
Clenched teeth	<5%	—
Empty gaze	50.0	*d = 0.32*
Seeming disinterested	<5%	—
Pale face	<5%	—
Teary eyed	<5%	—
Looking tense	**12.8**	**d = 0.52**
Looking sad	<5%	—
Looking frightened	<5%	—

[a]Percentage refers to the percentage of occurrence within the painful (400 kPa) trials. Effect sizes for frequency differences between "baseline" and "400 kPa" trials are given. Medium and strong effect sizes ($d \geq 0.5$) are marked in bold.

of the stimulus intensities, resulting in one average pain-indicative expression for 50 kPa pressure, one for 200 kPa pressure, and one for 400 kPa pressure. Reliability between the two raters for these pain-indicative expressions, expressed by intraclass correlations (ICC) for each of the pressure intensities, revealed fair agreement between both raters (ICC of 0.43, 0.34, and 0.48 for 50 kPa, 200 kPa, and 400 kPa, resp.).

2.5. Self-Report. After each stimulation, participants rated their pain using a 0–10 numerical rating scale (NRS). Average NRS pain scores were calculated for each of the stimulus intensities, resulting in one average NRS pain score for 50 kPa pressure, one for 200 kPa pressure, and one for 400 kPa pressure.

2.6. Statistical Analysis. (i) To test the hypothesis that a decline in executive control is associated with increased facial expressions of pain and increased NRS scores, regression analyses were employed, entering the executive function scores as predictor variables and facial expressions or NRS ratings, respectively, as criterion variables. Given that we applied 2 pressure intensities that lay in the noxious range (200 and 400 kPa), analyses were conducted separately for facial and subjective responses to 200 kPa and 400 kPa, respectively, resulting in 2 (NRS scores, facial expression) × 2 (200, 400 kPa) = 4 regression analyses.

(ii) To test whether potential associations are indeed specific for executive functioning, as was suggested by previous studies, we conducted blockwise regression analyses, this time entering memory and speed function in the first block of predictors and executive functioning in the second block. This allows us to test whether executive functioning can add predictive power beyond that already explained by memory and speed performances. Again, analyses were conducted separately for NRS ratings and facial expressions and separately for the 2 noxious intensities.

(iii) In order to examine whether cognition moderates the relationship between pressure intensity and facial and subjective pain responses, repeated measures analysis was employed with pressure intensity (50 kPa, 200 kPa, and 400 kPa) as within-subjects variable and the executive functioning scores as covariates. This analysis was conducted twice, once with the NRS scores as dependent variable and once with the facial expression scores as dependent variable.

Analyses were conducted with SPSS 22 and alpha level was set to 0.05. In case of directed hypotheses, we used one-sided testing.

3. Results

Participant characteristics, together with the results from the pain assessment and the neuropsychological examination, can be found in Table 2. For one participant, the facial expressions at 200 kPa pressure intensity could not be rated (due to talking during the stimulation and turning the head downwards). Cronbach's alpha indicated good to excellent reliability of the memory ($\alpha = 0.86$) and psychomotor speed ($\alpha = 0.91$) domains. Reliability of the executive function domain, however, was low ($\alpha = 0.44$), based on which we decided not to use the executive domain score but only focus on the separate executive tests as independent predictors.

3.1. Relationship between Executive Functioning and Facial as well as Subjective Responses to Pain (i). Results from the regression analyses are presented in Table 3. As expected, we found significant associations between executive functioning and responses to painful pressure stimulation. With regard to the NRS ratings, these associations were significant for both mild (200 kPa) and moderate (400 kPa) pressure pain. In contrast, we only found a significant association between executive functioning and facial expression for mild pain stimulation. As can be seen in Table 3, the worse somebody performed in the Stroop interference test (i.e., a higher interference score), the greater the facial expression in response to 200 kPa pressure was. No significant associations were found for facial responses to the moderate pain intensity.

3.2. Specificity of the Relationship between Executive Functioning and Facial as well as Subjective Responses to Pain (ii). Results of the blockwise regression analyses are displayed in Table 4. As can be seen, executive functioning only added explanatory value in addition to memory and speed functioning in explaining variance in facial responses to mild painful stimulation (200 kPa). In contrast, variation in

Table 2: Characteristics, pain NRS, and facial expression scores of the participants.

Variable	*N*	
Age (yrs)	51	66.7 (12.0)
Sex (M/F)	51	26/25
MMSE	51	28.7 (1.4)
Education	51	5 (2)
NRS 50 kPa	51	1.2 (1.6)
NRS 200 kPa	51	2.9 (2.3)
NRS 400 kPa	51	5.0 (2.6)
Facial expressions 50 kPa	51	0.4 (0.6)
Facial expressions 200 kPa	50	0.7 (0.9)
Facial expressions 400 kPa	51	1.2 (1.4)
Stroop Word card (s)	51	55.9 (15.9)
Stroop Color card (s)	51	67.3 (20.1)
Stroop Color/Word card (s)	51	127.5 (95.2)
Zoo Map score	51	11.0 (4.0)
Digit Span Backward	51	5.8 (2.3)
AVLT immediate recall	51	38.6 (11.1)
AVLT delayed recognition	51	27.3 (2.9)
RBMT immediate story recall	51	7.5 (3.4)
RBMT delayed story recall	51	6.3 (3.2)

Descriptive represent means (±SD), with the exception of sex, where frequencies (male (M)/female (F)) are presented, and education where the median score (IQR) is presented. The facial expression scores represent the average number of pain-specific expressions. AVLT: Auditory Verbal Learning Test; MMSE: Mini Mental State Examination; NRS: numerical rating scale; RBMT: Rivermead Behavioural Memory Test; s: seconds; yrs: years.

facial responses to 400 kPa and variances in subjective ratings were not better explained by executive functioning than by memory and speed functioning.

3.3. Covariate Analyses (iii): Does Executive Functioning Moderate the Relationship between Noxious Intensity and Subjective Responses? Repeated measures analysis, with pressure intensity as within-subjects variable, the NRS scores as dependent variable, and the executive function measures as covariates, revealed a significant interaction between the Stroop interference score and pressure intensity ($F(1.32, 61.82) = 11.51$, $p < .001$, $\eta^2_p = .20$, and Greenhouse-Geisser corrected). To further examine this interaction effect, three equal-sized Stroop interference groups were created and the analysis was repeated for each group separately (characteristics of these groups are presented in Table 5). For the sake of clarity, we refer to these groups in terms of interference control capabilities. Thus, participants with low interference scores (i.e., less slowing on the complex Stroop Color/Word card) are referred to as having high interference control capabilities. Stated otherwise, these high interference control participants have good executive, inhibitory abilities. Likewise, participants with high interference scores actually have low interference control (i.e., worse executive control), suggesting substantial slowing on the complex Stroop Color/Word card. In all

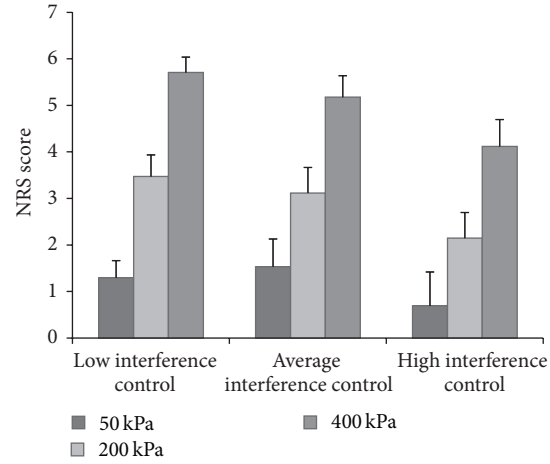

Figure 1: Numerical rating scale (NRS) scores at different pressure intensities of participants with low ($n = 17$), average ($n = 17$), and high ($n = 17$) levels of inhibitory control.

groups, a significant effect of pressure intensity was found, showing increasing NRS scores from 50 to 200 and from 200 to 400 kPa. Results are presented in Figure 1; as can be seen, the groups with average and lowest (i.e., worse) interference control capacities showed comparable increases in NRS scores as the pressure intensity increased. However, the group with the high level of interference control showed a less strong increase in NRS scores as the pressure intensity increased.

The Digit Span Backward and the Zoo test did not interact with the effect of pressure intensity on subjective ratings (all p values $> .05$).

3.4. Covariate Analyses (iii): Does Executive Functioning Moderate the Relationship between Noxious Intensity and Facial Expressions? A same repeated measures analysis, now with facial expressions as dependent variable, demonstrated a significant effect of pressure intensity ($F(1.23, 56.58) = 4.37$, $p < .05$, $\eta^2_p = .09$, Greenhouse-Geisser corrected). Repeated contrasts showed that an increase in pressure intensity from 50 to 200 kPa ($p < .001$) and from 200 to 400 kPa ($p < .05$) induced a significant increase in facial expressions. With regard to the interactions between pressure intensity and the cognitive constructs, the interaction with the Stroop interference score ($F(1.23, 56.58) = 7.74$, $p < .01$, $\eta^2_p = .14$, and Greenhouse-Geisser corrected) was significant. Further examination of the facial expressions for each interference control group separately showed a significant effect of intensity in the low interference control group ($F(1.63, 24.40) = 4.76$, $p < .05$, and $\eta^2_p = .24$) but not in the average ($F(1.14, 18.30) = 2.20$, $p = .15$, $\eta^2_p = .12$, and Greenhouse-Geisser corrected) or high ($F(1.13, 18.11) = 3.38$, $p = .08$, $\eta^2_p = .17$, and Greenhouse-Geisser corrected) interference control groups. As can be seen in Figure 2, the increase in facial expressions from nonnoxious (50 kPa) to slight (200 kPa) and moderate (400 kPa) pain appears to

Table 3: Association between executive functioning and facial or subjective responses to noxious stimulation (200 and 400 kPa).

Criterion variable	N	Pressure intensity	β			r	R^2	F	p
			Stroop interference	Digit Span Backward	Zoo Map test				
Facial expression	50	200	.575	.054	−.203	.596	.355	8.438	**<.001**
	51	400	−.124	−.233	.123	.223	.050	.820	.244
NRS score	51	200	.299	−.281	.055	.446	.199	3.894	**.007**
	51	400	.321	−.231	.170	.435	.190	3.664	**.008**

NRS: numerical rating scale.

Table 4: Specificity of the association between executive functioning and facial or subjective responses to noxious stimulation (200 and 400 kPa).

Criterion variable	Pressure intensity	N		Predictor variables	R^2	ΔR^2	Significance of ΔR^2 (p)
Facial expression	200	50	Block 1	Memory & speed	.349		
		50	Block 2	Executive functioning	.438	.089	**.044**
	400	51	Block 1	Memory & speed	.005		
		51	Block 2	Executive functioning	.067	.063	.198
NRS rating	200	51	Block 1	Memory & speed	.307		
		51	Block 2	Executive functioning	.335	.028	.293
	400	51	Block 1	Memory & speed	.229		
		51	Block 2	Executive functioning	.281	.052	.184

Results of blockwise regression analyses are presented. NRS: numerical rating scale.

Table 5: Characteristics of the three interference control groups.

Variable	Low interference control	Average interference control	High interference control	Statistical test
N	17	17	17	—
Age	74.0 (12.3)	67.5 (11.5)	58.6 (6.5)	$F(2, 48) = 9.3$, $p < .001$
Sex (M/F)	9/8	11/6	6/11	$X^2(2) = 3.0$, $p = .23$
MMSE	28.4 (1.5)	28.6 (1.8)	29.1 (0.9)	$F(2, 48) = 1.0$, $p = .37$
Education	4 (1.5)	5 (2)	6 (2.0)	$X^2(2) = 3.9$, $p = .14$
Stroop interference score	2.26 (1.85–4.66)	1.71 (1.54–1.84)	1.41 (1.18–1.54)	—

Means (±SD) are presented for age and the MMSE, means (range) for the Stroop interference score, frequencies for sex, and median score (IQR) for education. F: females; M: males; MMSE: Mini Mental State Examination; N: number of participants.

be significantly larger in the group with the lowest (i.e., worst) level of interference control. This increase was less pronounced in the average and high interference control groups.

The Digit Span Backward and the Zoo test did not interact with the effect of pressure intensity on facial expressions (all p values > .05).

4. Discussion

The present study examined the interrelatedness between cognitive functioning, noxious intensity, and facial expressions of pain in elderly people. Our primary goal was to investigate whether executive function in particular would show a relationship with facial expressions following painful stimulation and if these functions moderated the effect of noxious intensity on facial expressiveness. Moreover, given that subjective pain reports are regarded as being prone to the age-related cognitive decline, in contrast to the more automatically generated facial expressions [1, 2, 27], we expected that cognitive correlates would be more pronounced for these subjective reports than for facial expressions.

Overall, the results showed that variations in subjective and facial responses to noxious stimulation could indeed be explained by executive functioning. The associations were strong for subjective responses, whereas only variations in facial expressiveness to mild noxious stimuli were significantly associated with executive functioning. However, when investigating how specific the associations were for executive functioning compared to the neuropsychological domains "memory" and "speed," we only found a specific association between executive functioning and facial expressiveness (to mild pain). Here, executive functioning still added explained variance even when controlling for memory and speed

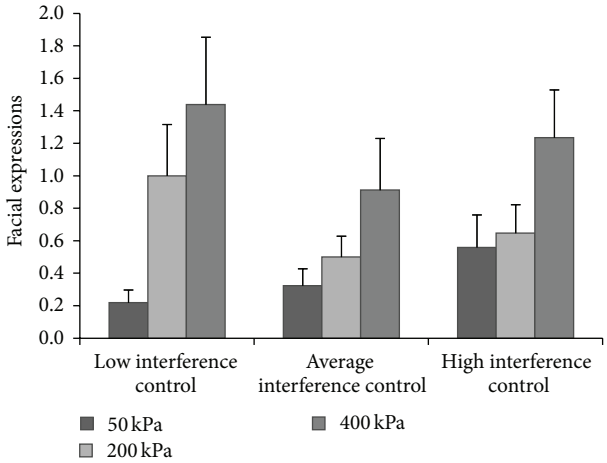

Figure 2: Facial expressions at different pressure intensities of participants with low ($n = 16$), average ($n = 17$), and high ($n = 17$) levels of inhibitory control.

performances. In contrast, variance in self-report ratings to noxious stimulation was sufficiently explained by memory and speed performances.

In addition to these regression analyses, we also investigated whether executive functioning might moderate the association between noxious intensity and facial as well as subjective responses using covariate analyses of variance. We found that the interference score as measured with the Stroop test significantly moderated the relationship between pressure intensity and both the subjective pain report and the facial expressions. These interactions indicated that those older adults with better interference control abilities show a less pronounced increase in both the pain report and the facial expressions following painful stimulation, when compared to elderly people with a lower (i.e., worse) level of interference control. A further comparison of these subgroups showed that the only significant group difference was one in age, which supports the notion that it is an age-related decline in inhibition capability that plays an important role in the facial expressions of pain. Moreover, as the interaction effect was isolated to the Stroop task (other executive tasks did not demonstrate an interaction with the facial or subjective expression of pain), we believe that it does not reflect a general effect of age. If it were a general age effect, other executive tests should have also yielded significant interaction effects.

The interpretation of these findings has crucial clinical implications. The relationship between subjective pain ratings and executive functioning appears to be nonspecific: although significant associations with executive control were found, they disappeared after the significant confounding effect of memory and psychomotor speed was included. Hence, regardless of the specific cognitive domain, a general relationship is present where cognitive decline is associated with higher NRS scores. This contrasts with findings for facial expressions, where a unique association with executive functioning was found.

Furthermore, the current study suggests that the level of cognitive inhibition is crucial for the extent to which facial expressions of pain are displayed. A previous study in healthy participants already suggested that cognitive inhibition, as measured with the Stroop interference control score, but not other executive functions such as shifting, working memory, and planning, is associated with experimental pain sensitivity [28]. The current study extends these findings, by demonstrating that interference control may play an important role not only in reporting the severity of pain, but also in the extent to which facial expressions indicative of increasing levels of pain are displayed. More specifically, older adults with high levels of cognitive inhibition may report less pain but also display less facial indicators of pain as the intensity levels increase. How to interpret these finding is currently unclear; it could, for example, indicate that adults with higher levels of interference control can better control their pain, resulting in lower pain reports and less facial pain expressions being displayed, whereas pain levels may be increased in those with lower levels of this control. An alternative interpretation, however, is that people with better interference control are primarily better at inhibiting their pain expressions (both verbal and facial), even though they experience the same level of pain as do older adults with lower levels of interference control. From this perspective, these older adults simply inhibit their explicit expression of pain, but not the *experience of pain* [29], and measuring pain through facial pain expressions might be best applicable in subjects who are not capable of effective inhibition, such as young children and cognitively impaired patients [30]. This is very promising because it indicates that the cognitive decline in patients with dementia (especially the decline in executive functioning) affects the facial expression in a way that makes the facial expression a better indicator of pain and its intensity.

Finally, some other findings deserve attention in the discussion regarding interpretation of facial expressions of pain. First of all, the low interference control group demonstrated increased facial expressions but similar NRS scores compared to the participants with average levels of interference control. This might indicate that this group is specifically unable to inhibit their facial expression to painful stimulation but does not actually experience more pain. Second, given that facial expressions were reduced and did not increase substantially across intensities in the high cognitive inhibition group, interpreting pain based on the facial expressions in adults with high levels of cognitive inhibition could result in an *underestimation* of the amount of pain that is experienced. This is however purely speculative; one potential solution to elucidate this would be to use personalized pain measurements, such as establishing the stimulus intensity of very mild (e.g., NRS score of 2), mild (NRS score of 4), and moderate (NRS score of 6) pain for each individual separately and then to examine whether and how facial expressions change according to the level of interference control.

In contrast to "interference control" the other types of executive functioning (planning and working memory ability) were less strongly related to facial reactivity to pain. It is possible that the commonly assumed heterogeneous nature of executive functioning is also evident in distinct associations with regard to pain outcomes. This suggests that whereas

interference control may show an inverse relationship with the level of pain that is reported and facially expressed, this association may be different for other frontal functions. In the existing literature, also indirect evidence for a heterogeneous link between the frontal lobes and pain can be found. Patients with frontotemporal dementia, for example, who normally show severe frontal brain damage, have been shown to display reduced pain awareness as indicated by patients' proxies [31] and increased experimental pain threshold and tolerance levels [32]. Apparently, in these patients reduced frontal lobe functioning is associated with reduced pain, whereas in the current and previous [28] studies, a reversed effect was reported with regard to the relationship between interference control and pain.

Some limitations of the present study need to be addressed. First, participants were instructed to refrain from talking. This might have caused subjects to keep a still face in general and to consciously inhibit facial pain expressions. The fact that the level of facial expressions was generally low might also be related to this point. It is crucial to realize though that the threshold for facial expression of pain is much higher than the subjective pain threshold. That means that individuals just start to facially express their pain once the pain is of moderate or sometimes even strong intensity [33]. Thus, although facial expressions have a very low sensitivity for mild pain experiences, they have a much better reliability for moderate and high pain intensities. One important reason for this is that we learn across childhood to inhibit the expression of negative affect (based on social display rules), including pain [34]. However, since a comparable interaction was found between interference control and the subjectively reported pain, we feel that the observed interaction between interference control and the facial expressions of pain is reliable.

A second drawback of the current study is that the intensities of the applied stimuli were rather low so that some subjects might not have experienced any noteworthy pain. This impression was supported by several participants hesitating or looking doubtful about their pain ratings, especially on the second intensity, as if they were expected to feel actual pain and give higher ratings than on the first occasion but did not really perceive the stimulus as painful. Nonetheless, the fact that we did find a comparable effect of interference control on the increase in pain responses, whether measured by report (subjective) or by facial expressions (objective), supports reliability of our findings.

Third, all stimulation intensities were applied in the same ascending order to prevent that a first stimulation at a high intensity might have an analgesic or even induce a hyperalgesic effect for subsequent lower-level stimulations. Stated otherwise, starting with, for example, 400 kPa stimulation intensity might mask or exacerbate responses to subsequent lower stimulation levels. Although there was a clear rationale for using this fixed order, it might have influenced how participants reacted to the pain. A solution would be to let participants first get accustomed to different pressure intensities, in order to increase reliability of the pain assessment protocol. Regarding the rating of the facial expressions, this was also always accomplished in a fixed order. Hence, the rater may have been influenced by expectations regarding facial expression as the pressure intensity increased. Nonetheless, as the rater was blinded to all study outcomes (e.g., cognitive test results), it is unlikely that expectations of the rater can explain the observed interaction with the interference control score.

Finally, the current study examined only elderly people that were not diagnosed with a neurodegenerative disorder. In order to generalize the results to other populations such as children or patients with dementia, a replication within these populations is necessary.

5. Conclusion

The present study indicates that cognitive inhibition moderates the effect of stimulus intensity on pain ratings and facial expressions. Nonetheless, the results also indicate that, in contrast to subjective pain ratings, facial expressions are less likely to be influenced by a general cognitive decline, supporting the clinical utility of these expressions for pain assessment purposes in populations with limited communicative abilities. Future studies are needed, addressing these associations in diverse populations.

Competing Interests

The authors declare that there are no competing interests regarding the publication of this paper.

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Research Article

Laser Evoked Potentials in Early and Presymptomatic Huntington's Disease

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Pain was rarely studied in Huntington's disease (HD). We presently aimed to extend our previous study on pain pathways functions by laser evoked potentials (LEPs) to a larger cohort of early unmedicated HD patients and a small group of presymptomatic HD (PHD) subjects. Forty-two early HD patients, 10 PHD patients, and 64 controls were submitted to LEPs by right-hand stimulation. Two series of 30 laser stimuli were delivered, and artifact-free responses were averaged. The N1, N2, and P2 latencies were significantly increased and the N2P2 amplitude significantly reduced in HD patients compared to controls. In the HD group, the LEPs abnormalities correlated with functional decline. PHD subjects showed a slight and insignificant increase in LEPs latencies, which was inversely correlated with the possible age of HD clinical onset. Data of the present study seem to suggest that the functional state of nociceptive pathways as assessed by LEPs may be a potential biomarker of disease onset and progression. The assessment of pain symptoms in premanifest and manifest HD may also open a new scenario in terms of subtle disturbances of pain processing, which may have a role in the global burden of the disease.

1. Introduction

Huntington's disease (HD) is an inherited autosomal dominant disorder, the phenotypic expression of which consists of invalidating motor, cognitive, and psychiatric symptoms, linked to the progressive dysfunction and neuronal death in corticostriatal circuits [1]. The causative gene (mutated huntingtin, HTT) is inherited in 50% of first-degree relatives, and the genetic test provides for the individuation of presymptomatic subjects. The onset of HD is associated with the first appearance of chorea movements while the possible early cognitive or psychiatric impairment is frequently supposed in clinical practice, before HD diagnosis is done [2]. The CAG replication may predict age at onset [3], but the early stage of neurodegeneration and pathophysiological changes is not evident in clinical practice [4]. The best clinical and instrumental assessment of the presymptomatic stage may provide for a combination of potential biomarkers and improve the knowledge about the neuronal circuits which are affected by mutated HTT even before motor symptoms appear.

Pain is a fundamental function of life, and nociceptive inputs are conducted via specific pathways (the spinothalamic tract) and processed at cortical level by the so-called pain matrix, which includes both cortical areas specifically devoted to pain processing and associative areas integrating salient stimuli for the potential motor response [5]. Increasing interest is growing toward pain expression in different types of dementia [6]. Pain has been also extensively evaluated in extrapyramidal disorders as Parkinson's disease, given that patients report pain symptoms even in the early stage [7], while very few reports focused on the pain in HD patients, despite motor symptoms as dystonia or muscle skeletal damage consequent to postural abnormalities that would cause discomfort. Scherder and Statema [8] described pain in 11 among 19 patients with advanced HD, which had been underestimated and not successfully treated. In a previous study, we examined a cohort of 28 HD patients

by means of laser evoked potentials, which are a reliable tool for the detection of pain pathways dysfunctions at both peripheral and central level [9, 10]. In that study, we found prolongation of N2 and P2 cortical waves, which was correlated with disease severity [9]. Slowing of pain processing may interfere with sensory-motor integration [11] with an impact on the general outcome of the disease, even in the early stage. A general impairment in negative emotion recognition including empathy for pain was also found in manifest HD [12], so it is conceivable that the cortical processing of negative stimuli potentially preceding an adversative motor response may be an early phenotypic HD expression.

In the present study, we aimed to confirm the previous laser evoked potentials findings [9], by the evaluation of a new larger cohort of early nonmedicated HD patients and a small sample of genetically predisposed relatives, in order to establish whether the slowing of pain processing may be present in the early and presymptomatic phase of HD.

2. Methods

2.1. Subjects. Forty-five consecutive nonmedicated HD patients, who came for the first time to our HD regional referral center, were enrolled. Twenty relatives who voluntarily decided to be submitted to the genetic test were examined by means of laser evoked potentials (LEPs). Only the 10 cases that presented with CAG replication ≥39, without current clinical signs of HD onset, were included in the PHD group. The criterion for HD onset was the appearance of chorea movements [2]. Sixty-four healthy volunteers, selected among the hospital staff, were examined. Exclusion criteria were the current use of CNS drugs, the evidence of general medical and other neurological diseases, including present peripheral neuropathies and metabolic diseases as diabetes and chronic renal failure with potential risk for these conditions, a history of HD > 5 years, and a Mini-Mental State Examination score ≤26. We did not exclude patients with chronic lumbar and sacral radiculopathies from spondylarthrosis, which would not interfere with LEPs from hand stimulation. Three HD patients were excluded for severe chorea which disturbed the LEPs recording.

Demographic and clinical data are reported in Table 1. The HD patients were older compared to both PHD and controls. Considering that a linear correlation was present between main LEPs features and age, this was introduced as a covariate in statistical comparisons (see below). For PHD, the presumable age of onset was computed, applying the formula $\log(\text{age}) = \alpha + \beta(\text{CAG number repeats})$, where $\alpha = 6.16$ and $\beta = -0.053$ [3]. We considered the difference in years between the current age and the presumable age of disease onset, as the expected time of illness onset.

2.2. Clinical Evaluation. All patients and PHD patients were submitted to the Mini-Mental State Examination (MMSE) [13] to exclude severe cognitive impairment.

In addition, patients and PHD cases underwent the motor section of Unified Huntington's Disease Rating Scales (UHDRS) [14] and the Total Functional Capacity Scale [15]. The sensory functional status was assessed in HD patients, PHD patients, and controls by clinically standardized evaluation to explore touch, pinprick, pressure, cold, heat, and vibration. To evaluate the presence and characteristic of pain, the short form of Brief Pain Inventory (BFP) [16] was applied to HD and PHD subjects. Chronic pain was assessed according to the IASP (International Association for the Study of Pain) criteria [17]. The Ethical Committee of Bari Policlinico General Hospital approved the study, and each subject signed an informed consent.

2.3. CO_2 Laser Stimulation and LEPs Recording. LEPs were recorded in the Laboratory of Neurophysiopathology of the Pain Unit of our department.

Each subject was seated in a comfortable chair, positioned in a quiet room with an ambient temperature of 21–23°C, in an awake and relaxed state. Subjects and experimenters wore protective goggles during data acquisition. The pain stimulus was a laser pulse (wavelength: 10.6 μm) generated by a CO_2 laser (Neurolas; Electronic Engineering, Florence, Italy; http://www.elengroup.com/). The location of the impact on the skin was slightly shifted between two successive stimuli, to avoid the sensitization of the nociceptors. The CO_2 laser stimuli were delivered at fixed 25 ms duration, while intensity was changed in increasing steps of 1,5 Watts in order to individuate the pain threshold, judged by a 10-point verbal analog scale in which "0" corresponds to no sensation, "4" to the pain threshold (painful pinprick), and "10" to intolerable pain. We paid attention to settling the laser power at 1,5 Watts, 1 step above the individual pain threshold in all cases [18], with a VAS value of 5-6 in more than 50% of 20 stimuli. We placed four electrodes at Cz, T3, T4, and Fz positions, with the reference electrode at the nasion; the T3 and T4 electrodes were referred offline to Fz, in order to detect the N1 component [10]. Another electrode was placed above the right eye to record the electrooculogram. Signals were amplified, filtered (0.5–80 Hz), and stored in a biopotential analyzer (Micromed System Plus, Italy). Two series of 30 laser pulses were applied to the dorsum of the right hand, with an interstimulus interval of 10 sec and an interseries interval of at least 5 min. Patients and healthy controls were requested to pay attention to the stimuli. At the end of each stimulation series, all subjects were requested to rate the pain induced on average by the 30 laser stimuli, using a 0–100 visual analog pain scale (laser pain VAS), in which the white color corresponded to 0 (no pain) and intense red to 100 (the most severe pain imaginable). Patients and controls were requested to individuate the number which corresponded to the color expressing the intensity of the perceived laser pain. Although many patients and controls were also submitted to LEPs recording from left-hand stimulation, in other cases, the short time available for examination did not enable completing the two hands, so in the present study, we decided to report only the results from the right-hand stimulation.

All cases included in the study were also submitted to standard electroneurography, in order to exclude peripheral neuropathies. The standard neurophysiological examination was normal in all HD patients, PHD patients, and controls.

Table 1: Demographic and clinical data in normal subjects (N), Huntington's disease (HD) patients, and presymptomatic Huntington's disease (PHD) patients. The ANOVA analysis shows that age was different among groups. TFC score: total functional capacity score; UHDRS: Unified Huntington's Disease Rating Scale; MMSE: Mini-Mental State Examination. The CAG range is reported. For time from or before illness onset, the range is reported in parentheses. In PHD, negative values indicate the supposed years before clinical HD diagnosis.

	Age	Sex	CAG	Illness onset (years)	UHDRS motor section	TFC score	MMSE	Chronic pain (number)
N	42 ± 16.35	34 F 30 M						
HD	54 ± 11.50	20 F 22 M	39–56	3.23 ± 2.11 (1,5)	32.93 ± 18.97	8.92 ± 3.33	27.1 ± 1.8	3 (mixed pain (2) and fibromyalgia syndrome (1))
PHD	36.62 ± 8.61	5 F 5 M	39–51	−12.20 ± 9.6 (−1, −21)	4.1 ± 4.33	13 ± 0	29.9 ± 0.31	0
	ANOVA $F = 11.60$ $p < 0.001$	Chi square: 0.99 ns						

2.4. LEPs Analysis. An investigator blind to the clinical condition analyzed the LEPs for 1 s, with a 100 ms prestimulus time, at a sampling rate of 512 Hz. All runs containing transient activities that exceeded 65 μV at each recording channel were excluded from the average by an automatic artifact rejection algorithm. In addition, further artifacts were visually inspected and an average of at least 15 artifact-free responses was obtained offline. We performed the baseline correction feature by the subtraction of the DC offset in the 1 sec poststimulus time, according to ASA software, vers. 4.7.3, by ANT neuro (http://www.ant-neuro.com/). For each stimulation site, an average across the two series of stimuli was obtained.

LEPs were identified based on their latency and distribution, and three responses were labeled according to Valeriani et al. [19]. The N2 and P2 components were detected at the vertex (Cz), as a positive-negative complex in the time range 180–450 msec, while the N1 component was checked at T3-Fz, as a smaller negative wave in the latency range 150–250 msec [9, 19]. Absolute latencies of the scalp potentials were measured at the highest peak of each response component. The amplitude of the N1 was measured from the baseline while the peak-to-peak amplitude was considered for the N2/P2 complex.

2.5. Statistical Analysis. One-way ANOVA with diagnosis (HD versus PHD versus N) as factor and main LEPs features as variables was performed. In control subjects, there was a linear correlation between age and main LEPs features (linear regression test for N2P2 amplitude $F = 24.56$, $p < 0.0001$; N1 amplitude $F = 7.58$, $p = 0.008$; N1 latency $F = 4$, $p = 0.049$; N2 latency $F = 4.92$, $p = 0.03$, P2 latency $F = 5.69$, $p = 0.02$) so age was included as covariate in ANOVA analysis.

The post hoc Bonferroni test was also employed among groups. In HD group, the correlation between LEPs values and main clinical features was done by means of Pearson correlation test. In PHD, the expected time of illness onset, as well as the UHDRS motor section, was also correlated with LEPs latencies and amplitudes by the partial correlation test, subtracting the age effect. The SPSS vers. 21 was used.

3. Results

3.1. Clinical Examination. Main clinical features of patients and presymptomatic HD subjects are reported in Table 1. In 6 out of 10 pre-HD patients, few nonspecific motor abnormalities, as slight oculomotor slowing, were present. The expected time of illness onset varied from 1 to 21 years. The MMSE was normal in all PHD cases. Only 3 HD patients reported chronic pain, 2 of mixed nociceptive neuropathic type (low back pain with lumbar radiculopathy from spondyloarthosis) and 1 HD patient, female, who suffered from diffuse muscle skeletal pain (fibromyalgia). No PHD subject suffered from chronic pain. Considering the small number of patients complaining of pain, the BPI items were not reported.

3.2. Laser Evoked Potentials. The LEPs features, including pain threshold and VAS values, are summarized in Table 2.

HD patients presented with significant prolongation of LEPs components latencies and a reduction of N2P2 vertex complex amplitude, in respect to controls (Table 2). A slight LEPs latency increase was present in PHD subjects, where values were in an intermediate range between patients and controls, so they did not differ either from patients or from controls, as shown by the Bonferroni test results (Table 2, Figure 1). The N2P2 amplitude was similar to controls, but not significantly different from HD group. The analysis of single PHD cases showed that subjects who were hypothetically near to the clinical onset of the disease had N2 and P2 latencies in the upper limit of normality (Figures 2(a), 2(b), and 2(c)).

3.3. Correlations between LEPs and Clinical Features. In HD patients, the P2 latency was negatively correlated with

Table 2: Laser evoked potentials features, including laser pain threshold and subjective perception (expressed by visual analog scale (VAS) from 0 to 100) in Huntington's disease (HD) subjects, presymptomatic Huntington's disease (PHD) subjects, and normal controls (N). The results of one-way ANOVA and post hoc Bonferroni test are reported. Significant results are reported in bold font.

Diagnosis	Pain threshold (Watt)	VAS	N1 (msec)	N1 (μV)	N2 (msec)	P2 (msec)	N2P2 (μV)
HD: 43							
Mean	13.5	45	202.45	3.77	250.628	351.69	8.74
SD	5.5	22.2	32.241	2.31	47.76	66.73	6.06
N: 64							
Mean	13.1	43.05	171.00	4.68	227.82	320.13	17.26
SD	4.8	24.46	31.128	3.12	23.68	27.06	11.68
PHD: 10							
Mean	12.9	41.3	185.30	4.20	241	346.1	14.22
SD	5.6	19.14	26.403	3.85	32.9	42.77	11.82
ANOVA (age as covariate)							
F		0.98	7.16	1.73	5.52	5.63	5.83
DF		2	2	2	2	2	2
p		ns	**0.001**	ns	**0.005**	**0.005**	**0.004**
Bonferroni							
N versus HD patients		ns	**0.001**	ns	**0.004**	**0.004**	**0.003**
N versus PHD patients		ns	ns	ns	ns	ns	ns
HD patients versus PHD patients		ns	ns	ns	ns	ns	ns

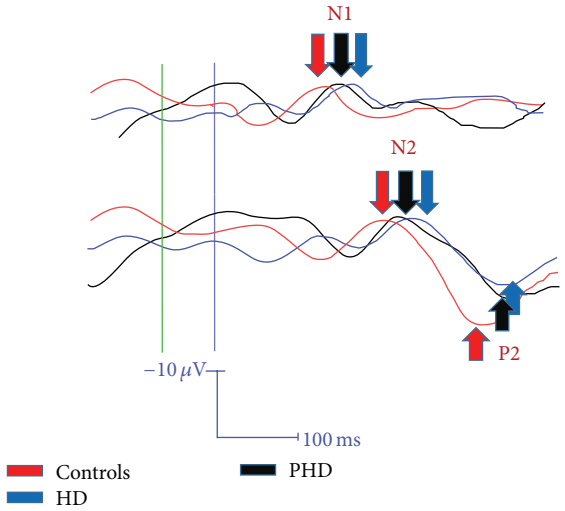

Figure 1: Grand average of N2P2 vertex complex computed in normal subjects (N) (64), HD (Huntington's disease) patients (43), and PHD (presymptomatic HD) subjects (10). The N2 and P2 components are indicated with colored arrows.

functional capacities (Pearson correlation: −0.434, $p < 0.01$), expressed by the Total Functional Capacity score; the N2 and N1 latencies were also negatively correlated with the TFC score (N2: −0.327, $p < 0.05$; N1: −0.321, $p < 0.05$); the N2P2 amplitude was positively correlated with the TFC (0.338, $p < 0.05$).

In PHD, the expected time of illness onset was negatively correlated with motor abnormalities and N1, N2, and P2 latencies. The UHDRS motor section was not correlated with the LEPs features (Table 3).

4. Discussion

In this study, we confirmed LEPs abnormalities in early HD. In fact, the increased LEPs latencies previously observed in a smaller cohort [9] were confirmed in the present HD group. A significant N2P2 amplitude reduction emerged in the present HD cohort. The consistency of actual results was based on the increased number of HD patients and the exclusion of confounding factors, as the use of centrally acting drugs. The amplitude reduction did not involve the early N1, possibly because this wave is smaller and more variable than the vertex complex [10]. However, both the early temporal and the late vertex components were affected by latency increase, which could suggest A-delta fibers dysfunction at the peripheral level. Given that we carefully avoided including patients affected by peripheral neuropathies and that standard electroneurography examination was normal in all cases, central delay in nociceptive inputs processing may be rather supposed, though the exact mechanism by which the genetic abnormality subtending HD may affect noxious stimuli processing is presently unknown. Although no LEP component may be generated from the basal ganglia [20], these receive all types of somatosensory information in order to modulate nociceptive cortex and organize the possible motor response against potentially dangerous events [21, 22]. Slowing of cortical response to nociceptive stimuli may interfere with sensory-motor integration and affect voluntary motor planning [11]. This phenomenon seems to involve either the early cortical functions of stimulus detection

Table 3: Partial correlation test between laser evoked potentials latencies and amplitudes and expected time of illness onset in 10 presymptomatic HD (PHD) cases (age effect was subtracted). UHDRS: Unified Huntington's Disease Rating Scale.

		UHDRS motor section	N2	P2	N1	N2P2
PHD	10 (DF: 7)	−0.714	−0.723	−0.732	−0.636	0.412
		$p < 0.05$	$p < 0.05$	$p < 0.05$	$p < 0.05$	ns

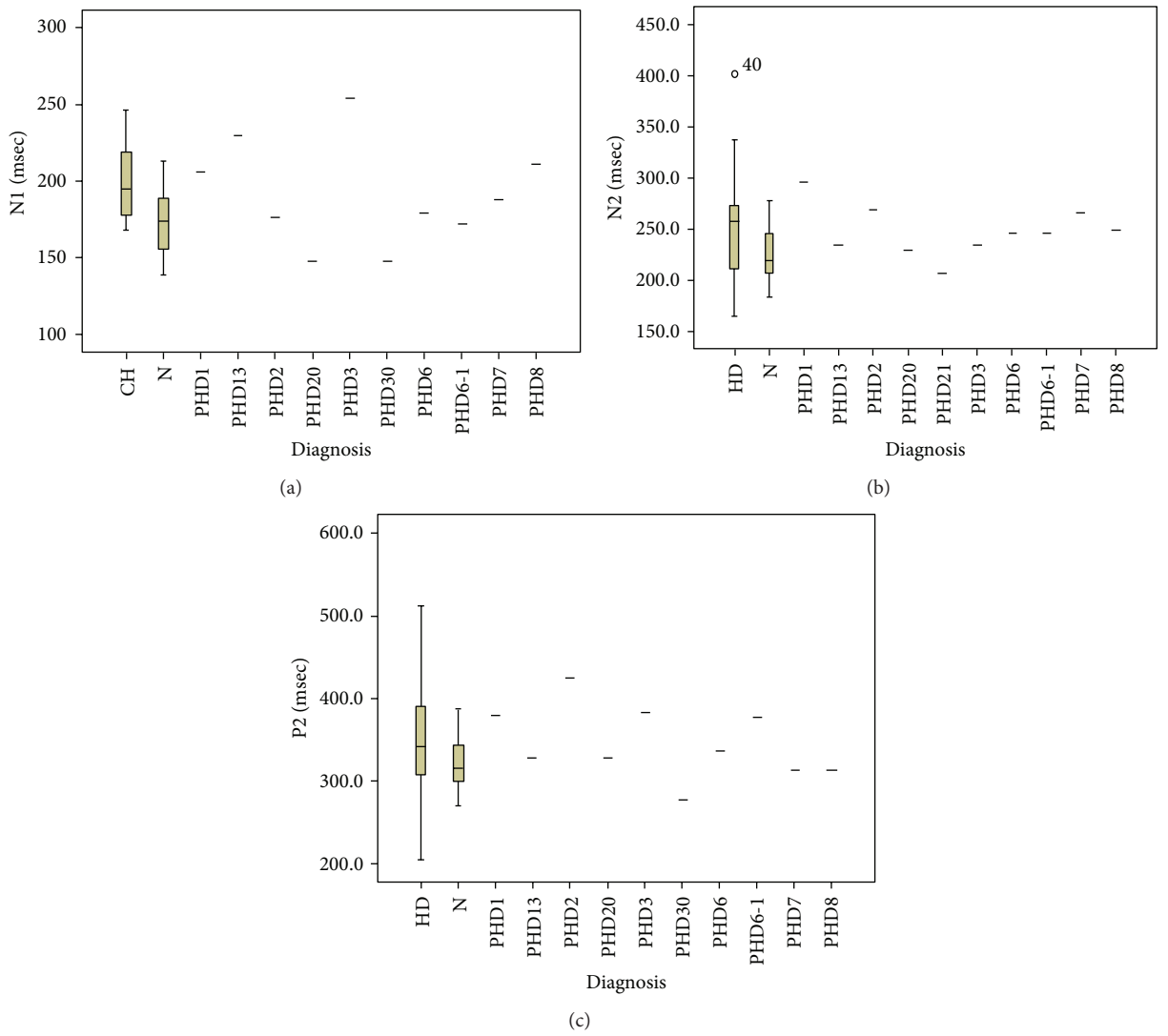

Figure 2: The N1 (a), N2 (b), and P2 (c) latency values are shown for single PHD (presymptomatic HD) cases and N (normal) and HD groups (95% CI). The values are corrected for age. The numbers following the PHD title expressed the expected time of illness onset (in years). Only the PHD21 case, who was an 18-year-old girl, showed values in the lower normal limits. The cases PHD1, PHD2, and PHD3 with a risk for manifest chorea within little time presented with P2 latency in the upper normal limits. The case PHD1 showed significant prolongation of N2 latency. The case PHD2 had significant prolongation of N1 latency.

and discrimination, expressed by the N1 wave, or the late vertex N2P2 response induced by the attention and arousal toward relevant stimuli, worthy of possible motor reaction [23, 24]. The impairment of painful stimuli transmission may also cause the cortical degeneration responsible for the LEPs amplitude reduction observed in our HD patients. This abnormal functioning of nociceptive transmission may impair pain feeling and expression, possibly explaining the low number of patients complaining of chronic pain in our HD group, though this finding is not conclusive and needs to be confirmed in larger and normal population controlled studies. The expression of pain is currently a challenge for the management of dementia and neurodegenerative disorders [6]. A possible disturbance in pain symptoms expression was rarely reported in HD [8], with the possibility that even visceral pain would be underestimated and not

appropriately treated [25]. In accord with previous results, we did not observe sensory disturbances in our patients [9]. Besides, the laser pain threshold and perception were within normal limits, suggesting that the LEPs abnormalities we observed were not associated with an evident sensory deficit. Despite this, we confirmed that LEPs abnormalities were correlated with impairment in functional capacities, in accord with a previous study [9], while no correlation was found with motor impairment or chorea. The slowing in nociceptive inputs processing may not be a consequence of motor disturbances, but an independent phenomenon which may negatively influence sensory-motor integration, motor planning, and ability in daily living. Accordingly, a progressive reduction of cortical somatosensory evoked potentials in parallel with functional impairment evolution was observed in longitudinal studies of HD patients [26]. Moreover, the deterioration of pain transmission may evolve with the progression of neurodegeneration and the global worsening of the disease, being a phenotypical manifestation of the genetically induced brain changes. In our HD series, the lack of correlation between LEPs abnormalities and illness duration may be explained by the scarce reliability of this feature in marking the real beginning of the disease, with functional capacities being a more consistent sign of disease progression. The slowing in nociceptive inputs processing may be supported by a general impairment in somatosensory or even cognitive functions. However, most of the studies on somatosensory evoked potentials in HD reported a progressive amplitude reduction rather than latency prolongation even in the early phase [26]. Cognitive event-related potentials, as P300, did not show clear abnormalities in early HD [27]. In addition, our patients were not affected by relevant cognitive decline. Although our study lacks control sessions including the not nociceptive somatosensory system and cognitive event-related responses (which were avoided for the long and exhausting procedure), data from other studies on these neurophysiological examinations seem to support the hypothesis that in the early HD the slowing of pain pathways may precede other systems' dysfunction. In regard to presymptomatic HD, very few subjects in PHD state were examined, though the present results seem worthy of discussion and further confirmation in enlarged groups. Based on actual age and CAG expansion [3], our presymptomatic subjects were different in regard to the possible age of clinical onset. Slight motor symptoms as oculomotor disturbances were observed in few HD relatives, being not so relevant to be attributed to HD onset [2]. This slight motor impairment was correlated with risk age, which confirmed that the genetically induced pathological process and huntingtin abnormal functions may start before chorea appearance [2]. In PHD subjects, LEPs latencies were not significantly different either from normal controls or from HD patients. Although the statistical analysis could be affected by the small number of PHD subjects, single cases possibly approaching the clinical diagnosis of HD presented with prolongation of all LEPs waves, which negatively correlated with the supposed time before clinical diagnosis. Early brain degeneration starting before chorea appearance may negatively influence the processing of painful stimuli [28]. The phenotypic expression of presymptomatic HD is useful to apply the potential neuroprotective therapies, so many studies focused on the biomarkers of neurodegeneration [29]. In our small presymptomatic cohort, LEPs latencies seemed normal in younger subjects, so the slowing in painful stimuli processing may be considered a symptom of the stage immediately preceding the clinical diagnosis of HD. This is also confirmed by the clear LEPs abnormalities observed in the early HD patients. The neurophysiological abnormalities we observed would be caused by structural changes in the presymptomatic brain, which seem to predict HD clinical onset [2]. How LEPs abnormalities may be correlated with specific clinical symptoms is actually unclear. Moreover, the possible lower frequency of chronic pain syndromes in pre- and manifest HD people seems worthy of extensive evaluation and comparison to general population. This question would have relevance in the HD management, even in a very early stage, as the impairment in nociceptive stimuli processing seems to be associated with reduced functional capacities. LEPs are a reliable tool to assess the functional state of nociceptive pathways, but they do not always reflect subjective pain perception [10], because compensatory phenomena may occur in the early damaged brain [29] and mask subtle sensory changes. Moreover, LEPs abnormalities may concur with a slight attention deficit possibly present in the presymptomatic HD carriers. There is actually little evidence of cognitive decline before HD clinical appearance [2, 30], and, in addition, cognitive factors influence LEPs amplitudes more than latencies [31]. However, we did not perform a careful cognitive evaluation in our HD and PHD series, given that the MMSE provided only for the exclusion of severe dementia, so the possible correlation between LEPs abnormalities and subtle cognitive impairment deserves further studies.

The ability to recognize others' negative emotions and especially disgust facial expression is impaired in early HD and in the presymptomatic phase [32], so a deficit in processing negative stimuli may be caused by HD pathological changes. However, in a recent study by Baez et al. [12], empathy for pain, which is processed in some cortical areas involved in LEPs generation, as the insula and anterior cingulate [23, 33], was normal in HD relatives and compromised in patients with manifest disease, though some behavioral and cognitive responses may be preserved even in the presence of subtle anatomical and functional brain changes [29].

Other neurophysiological patterns as event-related cognitive potentials (Mismatch Negativity and P300) showed abnormalities in presymptomatic subjects [34]. Surprisingly, the same authors did not confirm the same abnormalities in patients with manifest HD, attributing this apparent puzzling result to possible compensatory upgrading of excitatory circuits occurring in the course of neurodegeneration [34]. In this sense, LEPs abnormal pattern seems to be a more robust indicator of pathological changes progressively occurring in HD brain.

Main Study Limitations. The limited number of presymptomatic HD patients and the lack of a prospective design are major flaws of the present study, together with the absence

of a morphometric assessment of cortical areas possibly generating LEPs and of a complete clinical examination, including cognitive and emotional aspects. However, data in manifest HD seem to confirm that LEPs abnormalities may be a feature of early preclinical phase, marking the progression of HD severity and disability.

5. Conclusions

Data of the present study seem to suggest that the functional state of nociceptive pathways as assessed by LEPs may be a potential biomarker of disease onset and progression. This is not surprising, given the importance of pain in human life and the influence of basal ganglia on cortical areas devoted to nociceptive stimuli processing. As a matter of fact, this study may indicate the opportunity of more extensive and possibly longitudinal LEPs studies, integrating further clinical and anatomical examination. The assessment of pain symptoms in premanifest and manifest HD may also open a new scenario in terms of subtle disturbances of pain processing, which may have a role in the global burden of the disease.

Competing Interests

The authors declare that they have no competing interests.

Acknowledgments

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Research Article

Orofacial Pain during Mastication in People with Dementia: Reliability Testing of the Orofacial Pain Scale for Non-Verbal Individuals

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Objectives. The aim of this study was to establish the reliability of the "chewing" subscale of the OPS-NVI, a novel tool designed to estimate presence and severity of orofacial pain in nonverbal patients. *Methods*. The OPS-NVI consists of 16 items for observed behavior, classified into four categories and a subjective estimate of pain. Two observers used the OPS-NVI for 237 video clips of people with dementia in Dutch nursing homes during their meal to observe their behavior and to estimate the intensity of orofacial pain. Six weeks later, the same observers rated the video clips a second time. *Results*. Bottom and ceiling effects for some items were found. This resulted in exclusion of these items from the statistical analyses. The categories which included the remaining items ($n = 6$) showed reliability varying between fair-to-good and excellent (interobserver reliability, ICC: 0.40–0.47; intraobserver reliability, ICC: 0.40–0.92). *Conclusions*. The "chewing" subscale of the OPS-NVI showed a fair-to-good to excellent interobserver and intraobserver reliability in this dementia population. This study contributes to the validation process of the OPS-NVI as a whole and stresses the need for further assessment of the reliability of the OPS-NVI with subjects that might already show signs of orofacial pain.

1. Introduction

Statistics Netherlands predicts that the percentage of elderly people (i.e., 60 years of age or older) will rise from 15% at present to 25% by 2040 [1]. This is not just a national Dutch phenomenon. Globally, the United Nations predict proportions of elderly rising to approximately 20%, thus doubling the percentage of people over 60, and even more so in more developed regions where life expectancy is higher (up to 40% regionally) [2].

One of the major challenges with an ageing population is dementia, of which a prevalence up to 7% in people over 60 is reported [3]. Many of these individuals' functions deteriorate to such a level that self-care is no longer possible. Although in some cases the care for people with dementia is supported by their families, others eventually come to live in a nursing home. Many people's functions continue to deteriorate until verbal communication is no longer possible [4]. The progressive decline in communicative abilities may hamper pain assessment in people with dementia, especially when it comes to orofacial pain [5]. In 2011, Lobbezoo et al. [5] emphasized that the existing diagnostic tools for establishing the intensity of pain in nonverbal elderly people with dementia are not appropriate for the assessment of dental or orofacial pain. In

the same article, it was noted that there is a lack of research dealing with the assessment of orofacial pain in nonverbal people with dementia. The same is true for the literature on management of orofacial pain in this group [5, 6].

During the international and interdisciplinary process towards the development the Pain Assessment in Impaired Cognition metatool [4], the importance of developing a specific orofacial pain assessment tool was noted. Unfortunately, even though the recently developed Orofacial Mobilization-Observation-Behavior-Intensity-Dementia Pain Scale was proposed as a tool to assess the intensity of orofacial pain in individuals with dementia, it proved to be unreliable [7]. This led to the development of the "Orofacial Pain Scale for Non-Verbal Individuals" (OPS-NVI) [4, 8, 9]. This instrument is meant to assess the presence of possibly pain-related nonverbal communication, such as facial expressions, body movements, and vocal expressions. The patient's behavior is monitored during four types of activities, namely, "resting," "drinking," "chewing," and "oral care," and the intensity of the possible orofacial pain is scored as well. For the OPS-NVI, a reliability and validity assessment has yet to be performed. The present study therefore focuses on testing the reliability of the "chewing" subscale of the OPS-NVI by the assessment of video recordings of older people with dementia during their meal.

2. Material and Methods

2.1. Study Sample. For this study, video clips were used. These clips were part of the data set recorded in relation to the STA-OP!-protocol [10]. The video clips were recorded at various nursing homes throughout the Netherlands and consisted of audiovisual material of residents of these homes recorded during mealtime. Participating nursing homes met the following criteria:

(i) Management was willing to give permission for at least one psychogeriatric unit to participate.

(ii) No major organizational changes or building activities were planned or performed in the study period.

For the residents to be preselected for enrollment, the inclusion criteria were

(i) presence of moderate to severe cognitive impairment according to the Global Deterioration Scale (GDS), that is, a score of 5, 6, or 7 [11],

(ii) absence of chronic psychiatric diagnoses other than a dementia-associated diagnosis.

Both criteria were assessed by elderly care physicians who are part of the staff of Dutch nursing homes.

Informed proxy consent for the videotaping and use of the videotapes in the STA-OP!-study and related studies was obtained from family and/or caregivers for every included resident. The Medical Ethics Review Committee of the VU University Medical Center Amsterdam approved the protocol (registration number 2009/119).

After preselection, in order to be enrolled into the study, an additional inclusion criterion was the presence of "clinically significant symptoms of pain" and/or "difficult behavior," defined as

(i) Cohen-Mansfield Agitation Inventory (CMAI) [12] score ≥44;

(ii) Neuropsychiatric Inventory-Nursing Home Version (NPI-NH) [13] score ≥4 on every respective item; or

(iii) indication of clinically relevant pain according to the Minimum Data Set of the Resident Assessment Instrument pain scale (MDS-RAI) (MDS-RAI pain scale ≥2) [14].

The degree of cognitive deterioration was measured according to the MDS-Cognitive Performance Scale (CPS) [15]. The CPS is a seven-category index, ranging from cognitively intact to very severely impaired. The index is categorized by combining the three severe categories as "severe" cognitive deterioration, the middle two categories as "moderate" deterioration, and the remaining two categories as "normal" cognitive performance or only mild deterioration. The CPS scale has shown excellent agreement with the Mini-Mental State Examination (MMSE) in the identification of cognitive impairment in research [16]. The CPS score's mean and standard deviation are shown in Table 1.

Comorbidity was assessed with the MDS-RAI comorbidity list, which contains the following groups of diseases: endocrine diseases, visual impairments, cardiovascular diseases, psychiatric disorders, pulmonary diseases, diseases of musculoskeletal system, neurological diseases (without Alzheimer disease or other types of dementia), infection in the last 7 days, and other [14]. Information on comorbidity is included in Table 1.

2.2. Procedure. The OPS-NVI consists of four subscales wherein different activities are assessed, namely, "resting" (I), "drinking" (II), "chewing" (III), and "oral care" (IV). Each subscale contains a total of 16 items of observed behavior that are classified into four categories, namely, "facial activities" (1), "body movements" (2), "vocalizations" (3), and "specific behavior"(4). All categories and items therein are identical for each subscale. For this study, only the "chewing" subscale was used. The items of observed behavior are shown in the following.

Items for Observed Behavior of the "Chewing" Subscale of the OPS-NVI

(1) Facial Activities

(Q1) Frowning: lowering and drawing brows together.

(Q2) Narrowing or closing eyes: narrowed eyes with tension around the eyes, not just blinking.

(Q3) Raising upper lip: upper lip raised, nose may be wrinkled.

(Q4) Opened mouth: the lips are parted and jaw is dropped.

(Q5) Tightened lips: lips are pressed together and appear more narrow.

Table 1: Descriptive and demographic data of subjects ($N = 153$).

	Mean	SD	N	Percentage
Age	83.3	7.1		
Male	81.1	7.6		
Female	84.1	6.7		
CPS score	4.4	1.3		
Comorbidity				
Endocrine[a]			46	30.1
Vision impairment[b]			25	16.3
Heart/cardiovascular disease[c]			86	56.2
Psychiatric/mood[d]			22	14.4
Lung disease[e]			22	14.4
Diseases of musculoskeletal system[f]			42	27.5
Neurological diseases[g]			38	24.8
Infection in the last 7 days[h]			6	3.9
Other[i]			21	13.7

SD: standard deviation.
CPS: Cognitive Performance Scale.
a = diabetes mellitus, hypothyroidism, and/or hyperthyroidism.
b = cataract, diabetic retinopathy, glaucoma, and/or macular degeneration.
c = arteriosclerotic disease, heart rhythm disorders, heart failure, hypertension, hypotension, peripheral vascular disease, and other.
d = anxiety disorder, depression, manic depression, and schizophrenia.
e = asthma, emphysema/COPD.
f = rheumatic diseases, hip fracture, amputation, osteoporosis, and pathologic bone fracture.
g = aphasia, cerebral palsy, stroke, hemiplegia/hemiparesis, paraplegia, multiple sclerosis, Parkinson disease, seizures, transient ischemic attack, traumatic brain injury, and quadriplegia.
h = pneumonia, respiratory tract infection, and urinary tract infection.
i = allergies, anemia, cancer, and renal failure.

(2) Body Movements

(Q6) Resisting care: resisting care, being uncooperative.

(Q7) Guarding: protecting affected area, holding body part, avoiding touch, and moving away.

(Q8) Rubbing: tugging or massaging affected area.

(Q9) Restlessness: fidgeting, wringing hands, and rocking back and forth.

(3) Vocalizations

(Q10) Using offensive words: cursing, sweating, or using foul language.

(Q11) Using pain-related words: using pain words, like "ouch," "ow," or "that hurts."

(Q12) Screaming/shouting: using a loud voice to express sounds/words.

(Q13) Groaning: making deep, inarticulate sounds.

(4) Specific Behavior

(Q14) Restricting jaw movement: making smaller jaw movements than possible.

(Q15) Refusing prosthetics: removing prosthetics again and again.

(Q16) Drooling: flowing of saliva outside the mouth.

To complete the OPS-NVI for the purpose of this study, an adaptation of the standard instructions of the OPS-NVI was given to the observers:

(1) Observe the behavior of the client while chewing:

(a) Observe the activity for 3 minutes *or* for the length of the activity. Segments where no activity is shown can be skipped.

(2) For each item, tick off the appropriate box:

(a) Y = Yes, I saw this behavior.
(b) N = No, I did not see this behavior.
(c) N/A = Not Applicable; it was not possible to score this behavior, because the client was not able to perform this behavior (not: not visible. In that case, tick off "No").

(3) Rate the *estimated* pain intensity with a number between 0 and 10:

(a) 0 is no pain and 10 is pain as bad as it possibly could be.
(b) Rate what *you think* is the experienced pain intensity.

For this study, a total of 321 video clips were collected. Of these, 84 were not used. This was because in 83 cases, no or hardly any masticatory movement was detected, while one clip was removed from the data set because, in retrospect, the person had a possible alcohol-related dementia diagnosis, which did not meet the inclusion criteria as described in the STA-OP!-protocol. This yielded a total of 237 video clips to be observed, with a total of 153 subjects. From these, 69 subjects featured in only one video clip, whereas 84 featured in two clips. The subjects that were filmed twice were recorded with a 3-month interval (12-13 weeks) in between both recordings [10]. There were 109 women and 44 men, with a mean age of 83.3 (SD: 7.1; range: 63.8–102.4), as shown in Table 1.

The video clips featured residents during their mealtime. The clips were recorded with audiovisual recording equipment (JVC brand, type Everio G Series nr. GZ-MG575, Yokohama, Japan). The camera was placed in such a way that the resident's face was shown, nearly all masticatory movements were clearly visible, and vocalizations were clearly heard over the course of the clip. If the resident moved during the recording, the camera position was adjusted accordingly. The duration of the clips varied between 3 and 5 minutes.

2.3. Reliability Assessment. Two observers, both sixth year dental students at the Academic Centre for Dentistry Amsterdam (ACTA), were given a training by an experienced user of the OPS-NVI and were instructed to individually observe the behavior of the participants and estimate the pain intensity

Table 2: Proportion of positive observations of the OPS-NVI items by observer and assessment (N = 237 video clips).

	Observer 1 Assessment 1		Observer 1 Assessment 2		Observer 2 Assessment 1		Observer 2 Assessment 2	
	Count Yes	Percentage %	Count Yes	Percentage %	Count Yes	Percentage %	Count Yes	Percentage %
(1) Facial activities								
(Q1) Frowning	135	57.0	137	57.8	143	60.3	135	57.0
(Q2) Narrowing or closing eyes	118	49.8	108	45.6	153	64.6	167	70.5
(Q3) Raising upper lip	65	27.4	54	22.8	124	52.3	117	49.4
(Q4) Opened mouth*	237	100.0	237	100.0	237	100.0	237	100.0
(Q5) Tightened lips	143	60.3	138	58.2	175	73.8	189	79.8
(2) Body movements								
(Q6) Resisting care*	1	0.4	1	0.4	1	0.4	0	0.0
(Q7) Guarding*	0	0.0	0	0.0	3	1.3	2	0.8
(Q8) Rubbing*	0	0.0	0	0.0	6	2.5	6	2.5
(Q9) Restlessness	7	2.9	6	2.5	12	5.1	4	1.6
(3) Vocalizations								
(Q10) Using offensive words*	0	0.0	0	0.0	1	0.4	1	0.4
(Q11) Using pain-related words*	0	0.0	0	0.0	0	0.0	1	0.4
(Q12) Screaming/shouting*	2	0.8	3	1.3	2	0.8	2	0.8
(Q13) Groaning*	2	0.8	2	0.8	2	0.8	5	2.1
(4) Specific behavior								
(Q14) Restricting jaw movement	36	15.2	41	17.3	29	12.2	34	14.3
(Q15) Refusing prosthetics*	0	0.0	0	0.0	1	0.4	0	0.0
(Q16) Drooling*	1	0.4	1	0.4	0	0.0	0	0.0

*Excluded from further data analysis.

with the OPS-NVI for every clip ($t0$), followed by a period of 6 weeks of no observation. After this period, the observers were instructed to complete the OPS-NVI again for every clip ($t1$).

2.4. Statistical Analysis. To establish the reliability of the "chewing" subscale of the OPS-NVI, the interobserver and intraobserver reliability were assessed by analyzing the test-retest reliability for individual items of the instrument. The sum scores of the items per category and the interobserver and intraobserver reliability of the estimated pain score were also analyzed. For all interobserver reliability analyses, the $t0$-measurements of both observers were used.

In cases where the database showed a bottom or ceiling effect for an item, meaning that the item was scored in less than 5% or more than 95% of the cases, it was decided that the item was excluded from the statistical analyses. Thus, items with a Yes or No count <12 were excluded.

The interobserver and intraobserver reliability of the item scores were analyzed using Intraclass Correlation Coefficients (ICCs). The interobserver and intraobserver reliability of the sum scores of the included items per category and of the estimated pain scores were also estimated by ICC. ICCs < 0.4 were considered poor, ICCs between 0.4 and 0.75 fair-to-good, and ICCs > 0.75 excellent [17]. The confidence interval was calculated with a 95% confidence level. The percentage agreement for the item scores was also determined.

Probability levels of $p < 0.05$ were defined as statistically significant. All statistical analyses were performed using the SPSS software package version 20.0 (IBM, Armonk, NY, USA, 2011).

3. Results

As shown in Table 2, a total of ten items were excluded from the statistical analyses, because there was hardly any variability in observed behavior. As a result, the category "vocalizations" was not used in the further analyses. For most cases, excluded items were scored "No," with the exception of (Q4), which was excluded from the analyses because in all cases subjects opened their mouths as part of their chewing activities.

Table 3 shows the intraobserver and interobserver reliability and percentage agreement per included item. The table clearly shows a discrepancy between the different observations: the intraobserver reliability of observer 1 ranges from fair-to-good to excellent, while the intraobserver reliability and interobserver reliability of observer 2 range from poor to fair-to-good.

In Table 4, where intraobserver and interobserver reliability per category as well as pain intensity estimations are shown, a similar discrepancy between the two intraobserver reliabilities is noted. However, the reliability per category seems to be slightly higher than the reliability per item.

Table 3: Intraobserver and interobserver reliability per item.

Item	Intraobserver Observer 1			Intraobserver Observer 2			Interobserver Over assessments 1		
	ICC	Agreement (in %)	95% CI	ICC	Agreement (in %)	95% CI	ICC	Agreement (in %)	95% CI
(Q1) Frowning	0.64	82.3	0.56–0.71	0.48	74.7	0.38–0.57	0.50	75.5	0.40–0.59
(Q2) Narrowing or closing eyes	0.68	84.0	0.61–0.74	0.31	69.6	0.19–0.42	0.25	62.4	0.13–0.37
(Q3) Raising upper lip	0.61	85.2	0.52–0.68	0.35	67.5	0.24–0.49	0.30	64.1	0.15–0.43
(Q5) Tightened lips	0.80	90.3	0.75–0.84	0.29	74.7	0.17–0.40	0.35	70.5	0.23–0.46
(Q9) Restlessness	0.92	99.6	0.90–0.94	0.49	96.6	0.38–0.58	0.40	95.4	0.29–0.50
(Q14) Restricting jaw movement	0.77	93.7	0.71–0.81	0.40	86.1	0.29–0.50	0.41	86.1	0.30–0.51

ICC = Intraclass Correlation Coefficient.
CI = confidence interval.

Table 4: Intraobserver and interobserver reliability for the category sum scores as well as for the estimated pain intensity scale.

Category	Intraobserver Observer 1		Intraobserver Observer 2		Interobserver Over assessments 1	
	ICC	95% CI	ICC	95% CI	ICC	95% CI
Facial activities	0.76	0.70–0.81	0.49	0.38–0.58	0.41	0.25–0.54
Body movements	0.92	0.90–0.94	0.49	0.38–0.58	0.40	0.29–0.50
Vocalizations*	N/A	N/A	N/A	N/A	N/A	N/A
Specific behavior	0.77	0.71–0.82	0.40	0.29–0.50	0.41	0.30–0.51
Pain intensity	0.81	0.76–0.85	0.58	0.49–0.66	0.47	0.36–0.56

ICC = Intraclass Correlation Coefficient.
CI = confidence interval.
* All items from the category "vocalizations" were excluded from statistical analysis.

4. Discussion

The aim of this study was to assess interobserver and intraobserver reliability of the "chewing" subscale of the OPS-NVI, with patient and environment standardized through video recordings. When analyzing the video clips, the two observers reported clear bottom and ceiling effects, meaning that there were a considerable number of cases in which an item was observed in less than 5% or more than 95% of the cases. This might be due to the fact that although there was preselection for "clinically significant symptoms of pain" and/or "difficult behavior," as defined by the STA-OP!-protocol inclusion criteria [10], there was no specific selection of cases with probable orofacial pain. Therefore, it was decided that all items that were considered noncontributing to orofacial pain for this population were excluded. While the category "facial activities" only lost a single item (namely, "opened mouth," which was excluded because this behavior is always present while eating), the category "vocalizations" was completely excluded, and of the categories "body movements" and "specific behavior" only one item was maintained. These results suggest that the "chewing" subscale of the OPS-NVI might be reduced to the remaining 6 items, which would facilitate its use in daily practice.

The discrepancies in the intraobserver reliability between the two observers, as shown in Tables 3 and 4, could be explained as follows. The instructions to the observers were to first score the presence of different items of behavior, regardless of whether the observer thought it was related to orofacial pain. Looking at, for example, the first category, namely, "facial activities" ((Q1) to (Q5)), it indicates behavior that can also be present during masticatory movement without pain. This complicates the observations considerably. Within this context, when observing this behavior, the different observers apparently showed a different sensitivity for the more subtle facial movements, which show that the scoring of the OPS-NVI items is based on a subjective interpretation of observed behavior. To improve the reliability, a different set of instructions, for example, pictures of frowning and nonfrowning individuals that guide the decision to (not) score this specific item, could be developed.

From 84 people, two video fragments were available, because the clips were recorded as part of the STA-OP!-protocol and were therefore obtained at baseline and after 3 months [10]. It could be argued that this could have created observer bias within this study; that is, the pain score could have been based on recollection of previous film clips featuring the same person rather than on independent observations. This could have led to an overestimation of reliability. However, the time between both recordings was relatively long. Taking this into account, along with the fluctuating nature of most painful conditions, it was therefore decided that even though a person featured twice in the database, both clips could be considered as independent of each other.

4.1. Strengths and Limitations. A strength of the present study is the large number of video clips ($n = 237$) included in the sample, which contributed greatly to the power of the study. Furthermore, not only did using video clips provide an efficient way to collect a lot of data in a short period of time, but also it offered the possibility of assessing the intraobserver reliability, which would otherwise have been impossible.

A limitation might be that observing video clips is not the same as real-life observation. Although most clips were at most 5 minutes long, it is still a limited period of time. This may have resulted in the observed bottom and ceiling effects. Life observation over a longer period, that is, during the course of the entire meal, may have yielded a more accurate estimate of the presence of orofacial pain during mastication. However, longer observations create the risk of making the OPS-NVI more impractical to use and more difficult to implement on a large scale. This study could also have benefited from additional observers, since clear discrepancies between the ICC scores of observer 1 and observer 2, the former ranging from fair-to-good to excellent and the latter from poor to fair-to-good. The lack of a control group with subjects matched for age but without cognitive decline is also a potential limitation: in this study, establishing the presence and intensity of orofacial pain in the included subject is confounded not only by the use of a novel tool, but also by the fact that the subject suffers from severe cognitive decline. By including a control group, the latter will no longer be a confounding factor. It is therefore suggested that future studies into the reliability and validity of the OPS-NVI include a control group.

4.2. Implications. This study was performed to contribute to the reliability assessment of the "chewing" part of the OPS-NVI and also to its development as a whole. In the process of assessing the interobserver and intraobserver reliability, it was found that a total of ten items could be excluded from this subscale of the OPS-NVI, which makes it more concise and easier to use. Additional reliability assessments are required for the other subscales of the OPS-NVI (namely, resting, drinking, and oral hygiene). Following this, validity of the tool will also need to be assessed.

4.3. Conclusion. The Orofacial Pain Scale for Non-Verbal Individuals (OPS-NVI) is developed to improve the recognition of the presence and intensity of orofacial pain. In this study, it was used to assess pain in older people with dementia during their meal, for which the "chewing" subscale of the OPS-NVI was used. The categories within the "chewing" subscale of the OPS-NVI have a fair-to-good to excellent interobserver and intraobserver reliability. The outcomes stress the need for further assessment of the reliability of the OPS-NVI in subjects with more severe orofacial pain.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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