



**Title:** Investigation of sensory abnormalities in patients suffering from Parkinson's disease.

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Maria Skallerup Andersen

**Supervisors:**

Parisa Gazerani, Pharm D, PhD, Associate Professor, Center for Sensory- Motor Interaction, Dept. of Health Science and Technology, Faculty of Medicine, Aalborg University, Aalborg, Denmark

Ali Karshenas, MD, Chief physician in Neurology, Neurological department, Outpatient Clinic for Parkinson's disease, Aalborg University Hospital, Denmark

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## Abstract

**Background/Aims:** Parkinson's disease (PD) is a chronic and progressive neurodegenerative disease, which affect 1% of the population. The disorders is characterized as a neurodegenerative disease, which affects the basal ganglia and is known by loss of dopamine-containing neurons in substantia nigra pars compacta. PD affects both motor and sensory, but the aim of this study was to investigate whether PD patients have an altered sensory and pain perception in response to non-painful and painful stimuli and further investigate whether the PD medication taken by the PD patients can have an effect on the responsiveness to the perception of touch and pain.

**Methods:** Twelve PD patients (9 male and 3 female) and twelve healthy controls (8 male and 4 female) were studied. Sensory perception was investigated in both forearms, lower back and both hands by four tests; brush test, pinprick test, cold pressure test (CPT) and pressure pain threshold (PPT) test. In all tests, the PD patients and healthy controls rated the pain intensity on VAS. Mini mental state examination (MMSE) was used to check the cognitive function in both PD patients and healthy controls and McGill Pain Questionnaire was used to locate the pain area in PD patients with pain. The PD medication was studied in relation to the effect on sensory disturbances.

**Results:** There were a significant difference in right ( $P=0.021$ ) and left forearms ( $P=0.025$ ) and lower back ( $P=0.002$ ) between PD patients and healthy subjects in the brush test. PD patients had increased pain intensity in the pinprick test; mean was calculated of each pinprick stimulus (8mN, 16mN, 32mN, 64mN, 128mN, 256mN and 512mN) and there were a significant difference between each stimulus ( $P<0.001$ ). There were no significant difference between PD patients and healthy controls in the right forearm and left forearm, but a significant difference in lower back ( $P<0.001$ ) in the pinprick test. CPT showed at significant result in tolerance time ( $P=0.016$ ). There were a significant difference between PD patients and healthy controls in PPT before ( $P=0.011$ ) and after ( $P=0.050$ ) the CPT, but there was no significant difference in non-dominant hand and lower back. There was no difference showed in sensory test in relation to PD medication.

**Conclusion:** We found that PD patients had altered perception of touch and pain. PD patients had increased pain intensity to non-painful and painful stimuli. The sensory disturbance was independent of PD medication.

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## 1. Parkinson's disease

PD is a chronic and progressive neurodegenerative disease (Beiske, Loge et al. 2009; Ceravolo, Cossu et al. 2013), which affect 1% of the population. Although PD may occur in younger men and women, but it is more frequent in older populations (>60 year) (Huether 2010; Shaikh and Verma 2011). PD is characterized as a primary neurodegenerative disorder that affects the basal ganglia (Ford 2010) and is characterized by loss of



dopaminergic neurons in substantia nigra pars compacta (Huether 2010). The basal ganglia, which is an important structure in PD, is normally divided into three parts: the caudate nucleus, putamen and globus pallidus, where putamen and the caudate nucleus together are termed striatum. In addition, the basal ganglia is divided into two functional parts: subthalamic nucleus and substantia nigra, where substantia nigra further can be divided into two areas; the pigmented pars compacta and the pale pars reticulata (Chesselet and Delfs 1996; Per Brodal 2010). Substantia nigra is located in mesencephalon and consists of dopaminergic neurons. It is the area in the brain, that controls coordination of involuntary muscle movements and is particularly important for start-up/initiation of the muscle movements (Kathryn L. McCane 2010). In PD, a dysfunction occurs in the basal ganglia network due to destruction of dopaminergic pigmented neurons in the substantia nigra pars compacta, which gives rise to significant reduced dopaminergic deficit in striatum especially in the putamen part (Kathryn L. McCane 2010). This dysfunction in the basal ganglia is believed to lead to the loss of dopaminergic terminals in striatum (Wasner and Deuschl 2012), which is best known for planning and modulation of muscles movements and it is involved in a number of cognitive processes. Since the dopaminergic terminals are lost from striatum, it may give rise to disturbance in motor pathways, which may result in decreased muscle coordination and movements in PD patients. What we do know is that, PD affects the basal ganglia and motor neurons, as the disease progresses. However, PD also affects sensory neurons and can induce pain and cognitive impairment in affected patients (Beiske, Loge et al. 2009; Ford 2010). Following a loss of 75% of the pigmented nigral and striatal dopaminergic neurons symptoms such as resting tremor, bradykinesia, rigidity, loss of facial expression, akinesia and posturale abnormalities may occur (Huether 2010; Berardelli, Conte et al. 2012). These symptoms can cause significant loss of functional abilities and decrease quality of life for the affected individuals (Ceravolo, Cossu et al. 2013).

### 1.1. Sensory system and nociceptive processes in Parkinson patients

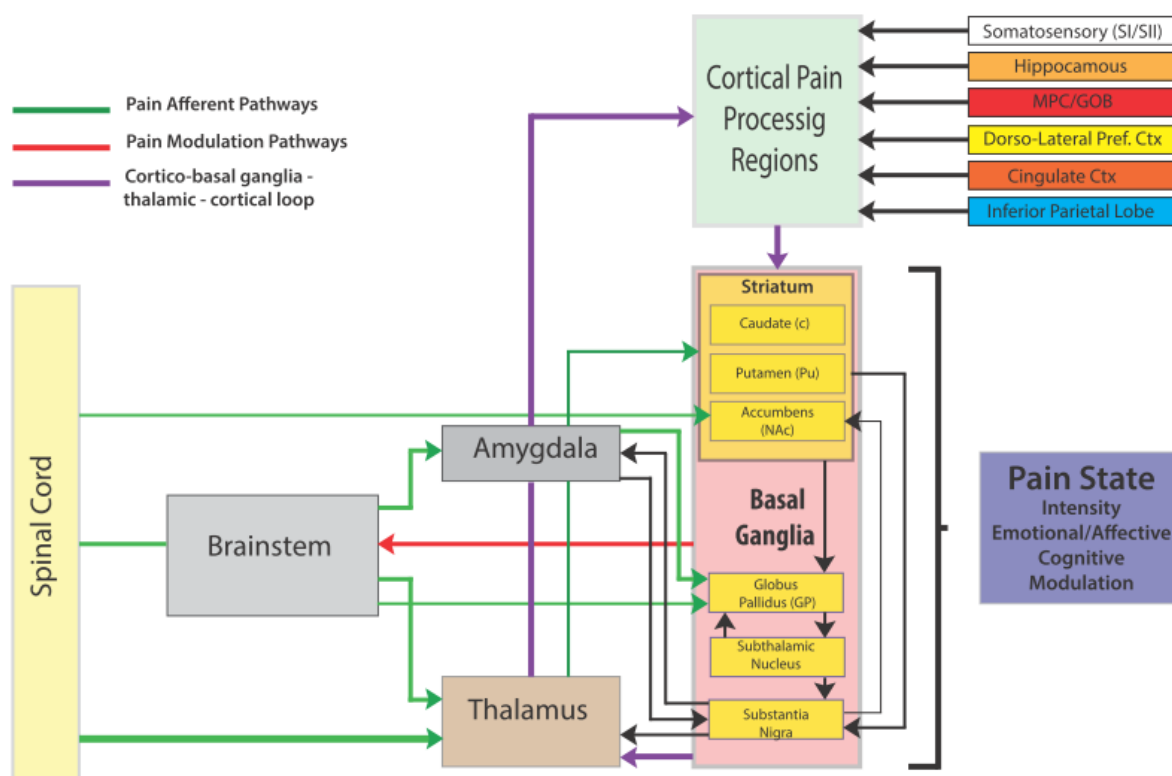
Over the years, major research has been focused on the motor impairments in PD, which has contributed to the development of symptomatic treatments for PD's patients (Peavy, Salmon et al. 2001; Chaudhuri, Prieto-Jurcynska et al. 2010; Bridges, Van Lancker Sidtis et al. 2013). However, an unexplored area in PD is the impairment of the sensory system, followed by sensory disturbances including pain. Research in PD has shown that patients have sensory impairment and reduced quality of life, mainly due to daily chronic pain (Skogar, Fall et al. 2012; Giorelli, Bagnoli et al. 2014).

Several studies have suggested, that pain associated with PD might involve the basal ganglia, which are thought to be involved in nociceptive processes (Chudler and Dong 1995; Lim, Farrell et al. 2008). Several studies suggest that an abnormal basal ganglia function in PD can modulate pain directly, either by increasing



or reducing the spread of nociceptive signals or indirectly by changes in affective and cognitive processes related to pain perception (Brefel-Courbon, Payoux et al. 2005; Truini, Frontoni et al. 2013). Psychological pain perception is the result of a complex balance between affective impairment and cognitive impaired functions and thus it is thought to be associated with changes in pain tolerance (Benedetti, Vighetti et al. 1999). In addition, the basal ganglia receives direct and indirect afferent input from medulla spinalis and truncus encephalicus. Moreover, the basal ganglia receives connection from the intralaminar nuclei in thalamus, and the majority of these inputs are received in striatum and a small part is sent to globus pallidus and substantia nigra (Chudler and Dong 1995; Borsook, Upadhyay et al. 2010). Striatum also receives excitatory connections, such as glutamate from both the motor part and the limbic part of cortex and from associated area (**figure 1**) (Per Brodal 2010).

Novel research has shown that medulla spinalis transmits pain pathways directly to globus pallidus, through the pain sensing system spino-basal ganglia and indirect projecting pain pathways from medulla spinalis to thalamus and further to striatum, through pain sensing system spino-thalamic-basal ganglia (**figure 1**) (Borsook, Upadhyay et al. 2010). Moreover, medulla spinalis transmits afferent input to thalamus, which is transmitted to cortical pain processing regions, whereupon cortical-basal ganglia-thalamic-cortical loop is initiated (**figure1**). These processes are believed to play a role in pain processes and cause chronic pain in PD patients (Borsook, Upadhyay et al. 2010). In addition, Nolano, Provitiera et. al. (2008) investigated the nerve conduction velocity in PD patients, which showed a normal response (Nolano, Provitiera et al. 2008). Over the past decade it has been gradually revealed that sensory perception in PD patients has been altered (Gerdelat-Mas, Simonetta-Moreau et al. 2007; Lim, Farrell et al. 2008; Zambito Marsala, Tinazzi et al. 2011), in relation to the basal ganglia that may have influence on modulations and impairment of nociceptive processes in PD patients and leading to pain and sensory impairment.



**Figure 1: Basal ganglia and pain system.** This figure illustrates the structure in the central nervous system that is involved in the pain system. Pain afferent pathways (green line) and pain modulation pathways (red line) illustrate the inputs from the spinal cord, the brainstem and thalamus that are received in the basal ganglia and thalamus also send input direct to cortical pain processing regions. The cortical area initiates a cortical loop, which is shown by purple line. The figure is modified from (Borsook, Upadhyay et al. 2010)

## 1.2. Pain in Parkinson patients

Studies have reported a prevalence of 43% of PD patients who suffer from pain (Chaudhuri, Prieto-Jurcynska et al. 2010; Ford 2010), while other studies report a prevalence of 60-80% in these patients (Lee, Walker et al. 2006; Defazio, Berardelli et al. 2008; Beiske, Loge et al. 2009). It is well-known that pain and sensory symptoms are often more frequent and severe in younger patients (Waseem and Gwinn-Hardy 2001). Two different reviews have focused on the different types of pain, that affect PD patients e.g.; musculoskeletal pain, radicular-neuropathic pain, dystonic pain, central neuropathic pain and akathisia (Ford 2010; Ha and Jankovic 2012). Around 53% of the patients experienced only one type of pain, 24% reported two types of pain and 5% three types of pain (Beiske, Loge et al. 2009). The most frequent pain in PD patients are



musculoskeletal pain and dystonic pain, whereas only a small percentage of the patients experience radicular-neuropathic pain and central neuropathic pain (Beiske, Loge et al. 2009). Some patients experience musculoskeletal pain symptoms such as aching, cramping (Ford 2010), frozen shoulder and back pain (Williams and Lees 2009; Farnikova, Krobot et al. 2012), whereas patients with dystonia pain experience persistent muscular contractions in different extremity and/or in facial- and pharyngeal musculature (Ford 2010; Albanese, Asmus et al. 2011). These contractions cause sustained twisting movements or abnormal posture, which very often is painful for the affected patients (Albanese, Asmus et al. 2011; Phukan, Albanese et al. 2011).

The pain in PD can occur through two different pathways: neuropathic or nociceptive pain. Neuropathic pain is a result of abnormal nociceptive information and processing, where nociceptive pain is closely related to motor symptoms, such as muscle contractions, muscle cramps and painful dystonia. (Brefel-Courbon, Payoux et al. 2005; Brefel-Courbon, Ory-Magne et al. 2013). Parkinson patients often suffer from nociceptive pain, which is due to musculoskeletal pain and dystonia pain (Beiske, Loge et al. 2009; Wasner and Deuschl 2012). Neuropathic pain is associated with radicular-neuropathic pain and central neuropathic pain, which together account for some of the pain that PD patients have to endure on a daily basis (Beiske, Loge et al. 2009; Wasner and Deuschl 2012). Pain related to PD is general thought to involve central mechanisms, however the peripheral nervous system is also affected (Ha and Jankovic 2012).

### 1.3. Peripheral nerves that possibly can be affected in Parkinson disease

Normally, peripheral nociceptors respond to potentially harmful stimuli, such as thermal, mechanical or chemical stimuli (Garland 2012). Upon activation of afferent nociceptive fibers, the signals are transmitted to the dorsal root ganglia and from there into the dorsal horn, and thereafter to the cerebral cortex through afferent neurons. The signal is transmitted by excitatory neurotransmitters such as glutamate and substance P. These neurotransmitters are thought to be involved in nociceptive processing and therefore believed to be important components of pain transmission, since these substances transmit signals from the peripheral tissues, which are injured (Dickenson, Chapman et al. 1997). Pain transmission activates a number of peptide receptors and excitatory amino acid receptors, in which the amino acid receptors consist of three different receptors: the  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA), the metabotropic and the N-methyl-D-aspartate receptor (NMDA) receptors and the metabotropic glutamate receptor (mGluR).

To assess pain and sensory function in Parkinson patients, several tests can be applied (Hara, Hirayama et al. 2013) have been performed in an effort to assess the function of A $\delta$ -fibers and C-fibers. Rolke et. Al. (2006)





used the PPT test and pinprick test to assess the functioning of the nociceptive fibers and a brushing test to investigate tactile A $\beta$ -fiber. Other studies have investigated whether there are altered sensory perception by activation of A $\beta$ -fibers and C-fibers, which are tested by the brush and pinprick tests, respectively (Rolke, Magerl et al. 2006; Liljencrantz, Bjornsdotter et al. 2013). Another test investigating, the loss of sensory patterns is the CPT which is also used to test nociceptive fibers (Rolke, Magerl et al. 2006). These fibers become activated when cold receptors are affected e.g. when the body temperature in the regional site drops below the normal (approximately 32 °C) (Dubin and Patapoutian 2010; Per Brodal 2010). Sensory disturbances can occur because of injuries to the nerves or disorders in the nervous system in form of changed tactile and sensory perception, which among other things can cause clinical symptoms, such as allodynia (non-noxious stimuli) (Gottrup, Nielsen et al. 1998) and hyperalgesia (increased pain response to painful stimuli) (Svensson, Baad-Hansen et al. 2011).

#### 1.4. Sensory impairment in Parkinson patients

Recent research has shown that there is a consensus that PD patients have altered somatosensory perception compared to healthy subjects (Hara, Hirayama et al. 2013; Tykocki, Kornakiewicz et al. 2013), and in addition, several studies have found changes in pain threshold in Parkinson patients compared with healthy subjects (Brefel-Courbon, Payoux et al. 2005; Vela, Cano-de-la-Cuerda et al. 2012). Another study showed that there was a statistically significant difference between the groups, as PD patients showed a lower threshold in Cold pain threshold. Furthermore, the same study has shown that there was a significant difference between the groups in a mechanical test, PPT (Vela, Cano-de-la-Cuerda et al. 2012). However, there is still uncertainties about this alteration in sensory perception as some studies have not been able to demonstrate a significant change (Zambito Marsala, Tinazzi et al. 2011). It remains to be determined whether PD patients suffer from sensory disturbances in terms of hyposensitivity or hypersensitivity in response to application of a painful stimulus.

In addition, it is still not clear whether sensory impairment is different in PD patients who suffer from a long-term spontaneous chronic pain, who also often have a poor quality of life, in comparison with those who do not have pain on a daily basis for a long term. It is also a question whether different PD medications have a possible effect on the perception of pain and peripheral sensory input. PD patients can actually be divided into two large groups of with and without pain and then the sensory tests can be conducted to see the differences between these two patient groups. The responses can also be compared with age and sex matched healthy individuals. The test can elucidate the responses of touch, pressure and temperature in the subjects.

## 2. Aims and hypothesis

The aims of the present study were 1) to investigate whether PD patients have an altered sensory perception that might lead to an increased pain perception in response to noxious stimuli when they are compared with age and sex matched healthy subjects and 2) to examine whether different medications taken by PD patients can have an effect on responsiveness to the sensory tests applied and pain perception in PD patients. It is hypothesized that some alteration in pain and sensory perception will be detected in mechanical and thermal perception in PD patients versus healthy controls and that the PD patients with pain are more affected. In addition, it is proposed that the most common class of drug that can induce or exacerbate the sensory impairment are levodopa preparation and dopamine agonists.

## 3. Methods

### 3.1. Subjects

A total number of twelve (9 male and 3 female) PD patients between 60 and 80 years ( $68.67 \pm 5.5$ ) were recruited through the chief physician, Ali Karshenas, from Neurological Department, Aalborg University Hospital. Patients were of Caucasian descent, either with PD's related pain or without pain. The study was conducted in cooperation with the Neurological Department, Aalborg University Hospital. Patients >60 years who had been diagnosed  $\leq 5$  years and with no central or peripheral disorders, were included. Patients with pain (except pain which was not related to PD), on painkillers, psychical disorders such as schizophrenia and dementia, mental retardation, memory impairment or a mini mental status examination score (MMSE) <24 (**appendix I**) and other disorders of the central nervous system or polyneuropathy were excluded from the study. The patients did not take alcohol, caffeinated drinks or smoked 24h before the experiments. The tests took place in Neurological outpatient clinic at Aalborg University Hospital and took around 60 minutes per patient.

The PD group was compared to a control group consisting of twelve healthy volunteers (8 male and 4 female) between 60 and 80 years ( $67.5 \pm 5.39$ ) of Caucasian descent and were recruited through public notices posted at Aalborg University Hospital and social media. Having pain or taking any painkiller was among exclusion criteria for healthy volunteers. The experiments took place in Neurological outpatient clinic, Aalborg University Hospital and the subjects were asked to attend one session at around 1h.

Written informed consent was obtained from all PD patients and healthy volunteers before the conduction the experiments. The Ethical Committee of Region Nordjylland approved the study protocol (case number N-20130073) (**Appendix B and F**) and the experiments were performed in accordance with the Declaration of Helsinki.



### 3.2. Study design

The study consisted of PD patients and healthy subjects who were divided into two groups: Parkinson's patients (with pain and without pain) and healthy subjects group, who were age and sex matched with the patients' group. The study consisted of one session at 1h. First, all patients were screened by Ali Karshenas, chief physician at Neurological department, Aalborg University Hospital and in cooperation with him the written consent was obtained. Subsequently, a journal including history and information from all participants was prepared and a mental test was taken before the participants were finally included. To include PD patients and healthy subjects a MMSE and a clock face test were applied and a score <24 was the exclusion criteria. This test was used to assess the cognitive function and investigate cognitive disturbances to ensure that the participants understood the visual analog scale (VAS) and the sensory tests and the pain tests. McGill pain questionnaire (**appendix J**) was used for Parkinson's patients with pain before the thermal and mechanical tests. In the experimental session, the stimuli were given on both forearms in a supine position, the dominating hand and on the lumbar part (**figure 4**) in order to see the location of the stimulated areas. To assess the sensitivity and pain threshold to non-painful and painful stimuli a VAS was applied after all the mechanical tests and during/after the thermal test. The VAS was used in the way that the participants indicated a number from 0-10; in which 0 was "no pain" and 10 was the "worst possible pain". All these tests were performed in accordance with the approved protocol (**appendix B**). Since the Parkinson's medications might have an impact on perception of touch and pain in Parkinson's patients, the medications taken by patients were recorded to avoid any bias.

### 2.3. Sensory- and pain tests

#### 3.3.1. Dynamic Mechanical Allodynia by brush

To assess dynamic mechanical allodynia, a brush test was performed. Parkinson's patients and healthy subjects were seated with both forearms lying on the table in a supine position. A standardized brush (Somedic, Sweden) was used. Subjects were asked to keep the eyes closed during the test. The hand-held brush was moved across the skin for five times (interstimulus interval 3-5 s) with a speed of 1-2 cm/s and with an angle of approximately 45°. Each stroke was 5 cm in length over the skin and was repeated three times for each forearm, after which the subjects were asked to rate the pain intensity on a VAS. The brush was applied alternately from right to left forearm and each stroke was performed from distal to proximal direction. This test was also performed in the lumbar part, on the left side opposite the vertebrae lumbales LIII, applying the same procedure, while the healthy volunteers and the patients rested on their stomach on a couch.

This test was performed to assess the function of A $\beta$ -fibers in Parkinson's patients (in comparison with controls) and investigate sensory perception, which may lead to pain, such as allodynia. The brush test was performed on the forearm and the lumbar part, since these sites are among the regions where the PD patients frequently complain of irritation and pain.

### 3.3.2. Mechanical Pain Sensitivity by Pinprick

In order to measure the mechanical pain sensitivity, seven pinprick stimulators were applied one by one with one prick at a time in a random order. The hand-held pinprick stimulator (from German company) consists of seven weighted flat needles (8mN, 16mN, 32mN, 64mN, 128mN, 256mN and 512mN) with a contact area of 0.2mm<sup>2</sup>. This test was performed in the middle of both forearms in a supine position, while the subjects were seated with both forearms lying on the table. The patients and the healthy subjects were asked to keep the eyes closed during the stimulations with the weighted needles. Each stimulations with weighted needles were repeated three times (interstimulus interval 2-4 s) with an angle of approximately 90° for each forearms. Stimulators were applied alternately from right to left forearms and only one forearm at a time were stimulated with seven weighted needles. During the pinprick test, the patients and the healthy subjects were asked to rate the pain intensity of each stimuli on a VAS.

The seven pinprick stimulators were also applied on the lumbar part (around vertebrae lumbales LIII on the left side), with the same procedure as the forearm. The subjects were asked to rate the pain intensity after each stimulus on a VAS.

This test was designed to assess the function of A $\delta$ -fibers and C-fibers by PD patients (in comparison with controls) to see whether the patients had altered perception and sensitivity to painful stimuli and to test the patients for hypoalgesia and hyperalgesia. These areas were selected because of some Parkinson's patients frequently complain of pain in the lower back and forearm.

### 3.3.3. Pressure Pain Threshold

A hand-held pressure algometer (Somedic, Sweden) was applied. The algometer had a circular sensor tip covered with a rubber material with an area on 1cm<sup>2</sup>. The pressure rate was set for 30kPa/s. The digital display on the pressure algometer showed the force in numbers (kPa/s) when the subjects press to stop key, which was the first time they felt that the pressure turned to pain.

To assess the PPT the pain intensity was measured on the middle of both forearms and around LIII on the left side of the lower back. The pressure algometer was used in two ways; first, it was used to measure the pain intensity in both forearms, in which the subjects were seated with their forearms lying on the desk in a supine

position. The subjects were instructed to use a handheld button, when the pain threshold reached or they felt the pressure to be uncomfortable, after which the subjects were asked to rate their pain intensity on a VAS. This test was performed three times on each forearm with a resting period on 60 s in between of each test. The pressure algometer was used with the same procedure on the lower back, however, the algometer was only used at one place on the back (left side of vertebrae lumbales LIII).

The purpose of this test was to investigate mechanical sensitivity of the nociceptive fibers: A $\delta$ -fibers and C-fibers and to compare the results from healthy volunteers and PD patients to see if there was difference in pain threshold when the nociceptive fibers were activated.

#### 3.3.4. Cold pressor test

The thermal pain intensity and pain tolerance in subjects were assessed by means of a CPT. First, the dominant hand was immersed in a bucket of 9 liters water (30°C) for 2 minutes, after which the temperature of the upper side of the hand was measured with an infrared thermometer. Subsequently, the CPT was carried out and the hand was immersed in a bucket of 9 liters of ice water (5°C) for maximum of 2 minutes. The hand was covered in ice water few cm above the wrist. Subjects were instructed to withdraw their hand when it was uncomfortable or painful. Subjective pain intensity was rated on a VAS during and after the experiment. Three measurements were made at 30 sec., 60 sec., and at the termination of the test (tolerance time), the patients were asked to rate the pain intensity after each measurements. The subjects were informed that there was a limited maximum possible tolerance time at 2 minutes, after which they were asked to remove the hand from the ice water, and then the tolerance time was noted and the final pain intensity was measured on a VAS.

After the CPT, the hand temperature was measured again with an infrared thermometer. This measurement was not carried out in the same place as before the dominated hand was immersed in ice water, but in the area where the subjects felt the greatest pain after the experiment with ice water. The CPT tested mechanical sensitivity of the nociceptive fibers: A $\delta$ -fibers and C-fibers. The A $\delta$ -fibers become activated when the skin touch the cold water, in which the C-fibers become activated when pain occur in the subjects because of the cold water (Svensson, Baad-Hansen et al. 2011) and then both type of fibers become activated. This test was performed to compare Parkinson patients with healthy subjects and to investigate if there was a different in pain intensity and pain tolerance between this two groups.

This CPT was followed by a PPT test. The aim was to investigate whether there was altered perception of pain after the subjects were being exposed to the cold water. The dominate hand was exposed to the pressure

algometer before and after the CPT and the subjects were asked to rate their pain intensity after each impact of the pressure algometer and the force of the pressure from each subject was recorded. The purpose was to examine the function of A $\delta$ -fibers and C-fibers and to examine if there was altered perception in Parkinson patients compared to healthy subjects.

### 3.4. Statistical Analysis

All data were first analyzed for normality. Histogram, Q-Q plot and boxplots were created to check the normality. Whenever the data were distributed normally, parametric tests were applied for statistical comparison. Otherwise, non-parametric tests were applied. A Mann-Whitney test was used to calculate the median and to determine the difference between healthy subjects and PD patients in the presented test. Furthermore, Kruskal-Wallis test was applied to show the median of each stimulators in the pinprick test and to show which area that is most affected by the current stimulator. Friedman test was used to show how the mean of pain intensity for all stimulators was rated and finally, a multiple linear regression analysis was applied to show the correlation between healthy subjects' and PD patients' average for each stimulator in each area. All statistical test were used to investigate whether there was changed perception of touch, pain and pressure in PD patients compared to healthy subjects.

The results are presented as the median and interquartile range (IQR, 25<sup>th</sup>-75<sup>th</sup>) and the significance level are accept if the P-value is <0.05. All calculations were performed in word excel 2013 and all statistical calculations and graph were performed by using the SPSS version 18.0 to windows and SigmaPlot 12.0 to windows.

## 4. Results

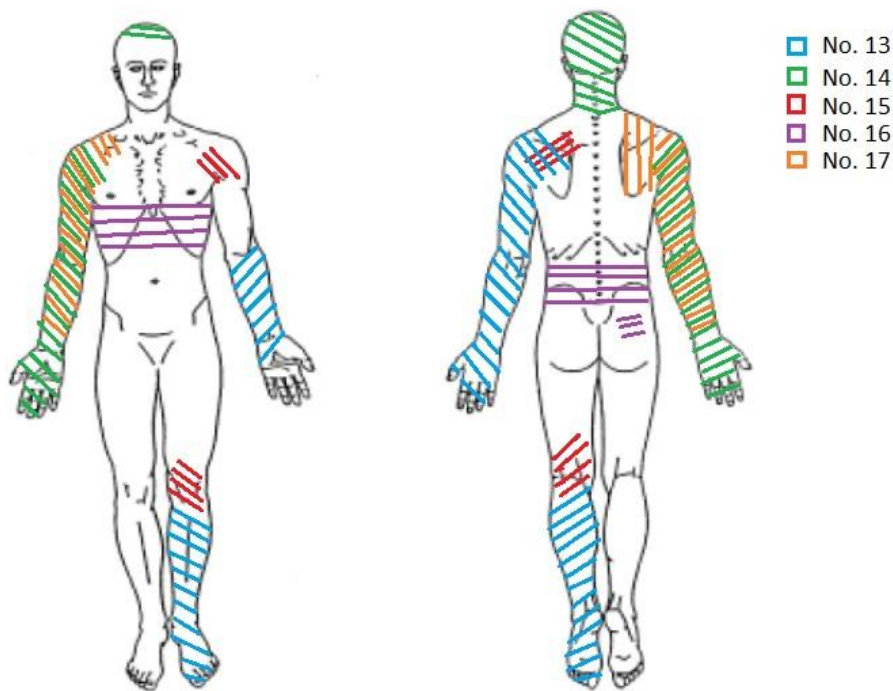
### 4.1. Subjects

Twelve PD patients (9 men and 3 women) with an age of 68.7 (64.23 to 72.00) years, who have been diagnosed with PD for  $\leq 5$  years and had a MMSE score on  $\geq 24$  and an acceptable performance of the clock face test were included (**Appendix I**). Twelve healthy subjects (8 men and 4 women) were included with a mean age of 67.5 (64.25 to 72.00) years and a MMSE score between 24 and 30 and an acceptable clock face test (**Appendix I**). A test of normality was performed to check whether the healthy subjects and PD patients were normal distributed in sex and age, but the test showed that the distribution was not normal, however, the distribution of sex and age were very close matched, since there was not a statistics significant different (p-value for sex; 0,660 and age; 0,311). The PD patients and healthy subjects had a mean MMSE score on



26.83 and 28.17 (27.00 to 28.75), respectively. There was no statistics significant different between the two groups, since the p-value was 0.060.

Five PD patients (41.7%) out of twelve had chronic pain and completed McGill pain Questionnaire (**Appendix J**) to get an overview of how their pain(s) were localized. All patients had chronic pain in upper part of the body and 60% had chronic pain in lower part of the body (**figure 2**). The performance status (WHO) showed that healthy subjects had normal function, since they had a WHO on 0. The PD patients had a WHO status between 0 and 2, which means that 58.33% had decreased function in the daily. It was also observed that 41.67% had left-Parkinson and 58.33% had right-Parkinson. Furthermore, all patients got PD medication and 33.33% received one preparation and 66.66% got >1 PD preparation. The two most frequently taken preparations in these twelve PD patients were Sifrol (33.33%) and Sinemet (66.66%) and 50% received another preparation in addition to Sifrol and Sinemet and 16.67% received not these two preparations, for more information (**table 1 and 2**). The majority of PD patients got heart medication. Some of the Parkinson medications can cause heart problems as a side effect. Few healthy subjects were taken medication (**table 1 and 2**).



**Figure 2: The pain location in 5 PD patients.** The figure present how the 5 PD patients outlined their pain at McGill pain Questionnaire and patient no. 13, 14, 15 and 16 had pain more than one place and patient no. 17 only had pain at one place, but over a wider area. The figure is modified from McGill pain Questionnaire. For more information about the patients in **appendix L**.



**Table 1.** The table shows the different medications the subjects get. The PD medication got a letter and other medications got a number. The healthy subject's numbers and PD patient's number are shown in the table below and with a medication letter and number to give an overview over which medication the subjects are taken. For more detailed table look at **appendix M**.

PD medication	Mechanism of action	Side effects (most common)
Sifrol <sup>A</sup>	Anti-parkinson agent <sup>D</sup> .	E.g. nausea, hypotension, dizziness
Sinemet <sup>B</sup>	Ani-parkinson agent <sup>A</sup> .	E.g. dyskinesia, palpitations, nausea, dizziness
Madopar Quick <sup>C</sup>	Ani-parkinson agent <sup>A</sup> .	E.g. nausea, vomiting, diarrhea, ECG changes, orthostatic hypotension
Selegilin "Mylan" <sup>D</sup>	Ani-parkinson agent <sup>C</sup> .	E.g. dyskinesia, orthostatic hypotension, nausea, dizziness
Stalevo <sup>E</sup>	Ani-parkinson agent <sup>A</sup> .	E.g. dyskinesia, nausea, fatigue, dystonia, orthostatic hypotension
Rivastigmin <sup>F</sup>	cholinesterase inhibitor - dementia	E.g. Weight loss, nausea, diarrhea, dizziness, abdominal pain
Requip depot <sup>G</sup>	Anti-parkinson agent <sup>D</sup> .	Vomiting, nausea, dyskinesia
Madopar <sup>H</sup>	Anti-parkinson agent <sup>A</sup> .	E.g. nausea, vomiting, diarrhea, ECG changes, orthostatic hypotension
Eldepryl <sup>I</sup>	Ani-parkinson agent <sup>C</sup> .	E.g. dyskinesia, nausea, vomiting, orthostatic hypotension, diarrhea
Requip <sup>J</sup>	Anti-parkinson agent <sup>D</sup> .	Vomiting, nausea, dyskinesia
Azilect <sup>K</sup>	Anti-parkinson agent <sup>C</sup> .	E.g. dyskinesia, headache, weight loss, nausea, agina pectoris, orthostatic hypotension
<b>Other medication (association with the heart)</b>		
Ramipril <sup>1</sup>	Antihypertensives	E.g. fatigue, diarrhea, nausea
Norvasc <sup>2</sup>	Antihypertensives	E.g. fatigue, abdominal pain
Nifedipin <sup>3</sup>	Antihypertensives	E.g. headache, vasodilatation
Corodil <sup>4</sup>	Antihypertensives	E.g. nausea
Cordarone <sup>5</sup>	antiarrhythmic	E.g. muscle weakness
Metoprolol <sup>6</sup>	Antiarrhythmic	E.g. fatigue, hypotension
Asasantin <sup>7</sup>	Anti-platelet agent	E.g. abdominal pain, nausea
Simvastatin <sup>8</sup>	Statinderivate	Only rare side effects
Hjertemagnyl <sup>9</sup>	Thromboprophylaxis	E.g. abdominal pain, bleeding diathesis
Marevan <sup>10</sup>	Anticoagulant	bleeding diathesis
Centyl <sup>11</sup>	Diuretic	E.g. nausea, fatigue
Diural <sup>12</sup>	Loop diuretic	Dehydration, electrolyte disorders
Ancozan <sup>13</sup>	Antihypertensives	Hypotension
Furix <sup>18</sup>	Loop diuretic	Dehydration, electrolyte disorders
Fem-mono-retand <sup>16</sup>	vasodilator effect	E.g. tachycardia, hypotension
<b>Other medication</b>		
Tolterodin <sup>14</sup>	difficulty urinating	Dry mouth
Metformin <sup>15</sup>	Antidiabetic	Nausea
Kaleorid <sup>17</sup>	potassium deficiency	Hyperkalaemia
Folimet <sup>19</sup>	B-vitamin	Only rare side effects
Methotrexate <sup>20</sup>	Folic acid antagonist	Nausea
Euthyrox <sup>21</sup>	Thyroid hormon	Only rare side effects
Eltroxin <sup>22</sup>	Thyroid hormon	Only rare side effects
Zolpidem <sup>23</sup>	Insomnia	E.g. nausea, diarrhea
Gabapentin <sup>24</sup>	Antiepileptic	E.g. fatigue

**Tabel 2:** Shows the subjects number and which medication they receiver. The number are other medication and the letter are PD medication. Look at the table above to see the different medication typs.

Subjects No.	Medication
5	10,22
7	1,12
8	8
10	8
13	1,2,5,10,12,17,A,B
14	7,8,13,14,B,C
15	13,15,B
16	B,D
17	1,3,8,9,C,E
18	A
19	19,20,B,F
20	8,9,A
21	4,6,10,16,17,18,21,23,24,B,G
22	8,13,H
23	B,I
24	B,J,K

#### 4.2. Brush stimulation

To investigate the sensitivity of PD patients, a brush test was performed. The results showed that 58.33% of PD patients had brush allodynia, since healthy subjects rated pain intensity <1 and the major part of PD patients rated the pain intensity >1 and few <1. All subjects' data were compared with the Mann-Whitney test. The median of both groups were calculated for all three location and the mean rank showed that the PD patients were more sensitive for the brush than the healthy subjects were (**table 3**). The brush test showed that there was a significant different between healthy subjects and PD patients in all three location, for more information (**table 3**). To get a better overview of where the subjects were stimulated with a brush (**figure 2**).

**Table 3: Shows the difference between healthy subjects and PD patients in the brush test.** Mean rank present the difference between the two groups, which shows that the patients felt uncomfortable during the brush test and there was a significant difference between these two groups perception of sensory stimuli (non-painful stimuli).

Location	Median from both groups	The difference between (healthy/PD) in rated VAS score	P-value
Right forearm	0.00 (0.00 to 1.00)	9.83/15.17	<b>0.021*</b>
Left forearm	0.00 (0.00 to 1.00)	9.92/15.08	<b>0.025*</b>
Lower back	0.00 (0.00 to 0.83)	9.00/16.00	<b>0.002*</b>

Values are medians with 25th and 75th centiles.

Mean rank and P-value: Mann-Whitney test.

VAS= Visual Analog Scale, PD= Parkinson disease

The star (\*) indicate that the result was statistics significant.

#### 4.3. The effect of pinprick stimulators

The results from the mechanical pain sensitivity test revealed that there was a statistics significant difference in the perception of painful stimulus. First, an average for all seven stimuli were calculated from three area in each subjects and then the Mann-Whitney test was used to calculate whether there was a difference between the two groups. There was a statistics significant difference between healthy subjects and PD patients by stimulation of the lower back, since the p-value was  $<0.05$  (**table 4**), however there was no statistics significant difference by pinprick stimulation of right and left forearm, since, the p-value was 0.769 and 0.838, respectively (**table 4**). Then, the average of each stimulus were calculated for all healthy subjects and all PD patients and Mann-Whitney revealed that PD patients had rated the pain intensity higher than healthy subjects had (**table 4**). The perception of pain was significantly increased in PD patients, since the p-value for all seven stimulators were  $<0.001$ . Kruskal Wallis test was performed to investigate whether there was an area that was more sensitive than other was. The test revealed that there was not much difference in terms of how the two groups were more sensitive, the healthy subjects were a little bit more sensitive on the right forearm, where PD patients rated lower back higher, there was not a significant difference between these two groups (**table 4**). The test was also used to calculate the median for all seven stimuli in both groups, the median shows that there was a difference between these two groups, since PD patients rated the pain intensity to  $\geq 1$  and the healthy subjects rated the pain intensity to  $\leq 1$  (**table 4**). This result indicated that PD patients have hyperalgesia, since the pain intensity was rated higher in healthy subjects. **Figure 4** shows the area the subjects were stimulated with needle and the location of hyperalgesia. Friedman test made it also clear that the higher the stimulus was the higher was the pain intensity rated, for a better visual view look at



the three graph, which shows three exponential curve from healthy subjects and PD patients. The three curves also showed a clear difference between healthy and patients by stimulation of right forearm, left forearm and lower back, **(figure 3)**. A merged curve are shown in **appendix R**, which gives a clear picture of the statistics significant difference between these two groups, the p-value from Freidman test are shown in **table 4**.

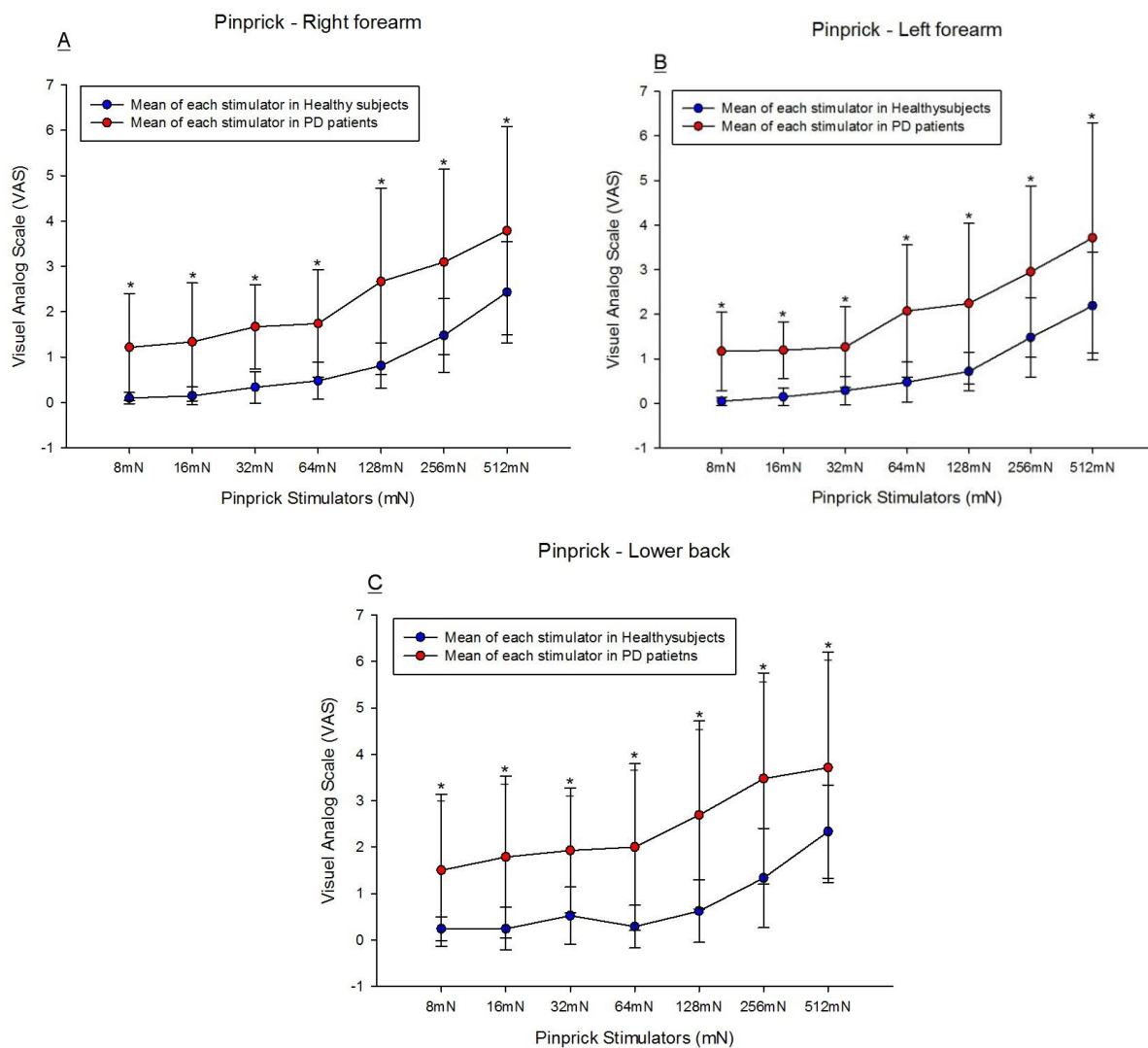
**Table 4: Shows the result from the pinprick test.** The present result shows that PD patients rated the pain intensity significantly higher than healthy subjects did in the pinprick test. The mean of each stimulator in PD patients were calculated and compared with healthy subjects, which shows a significant difference between these two groups. The table shows where the subjects were most sensitive to the different stimulators. Friedman test shows that the rated pain intensity of all stimulators (mN) were significantly different. Below in the table, the mean of all stimulators were calculated for each area in PD patients and compared with healthy subjects.

Pinprick stimulators (mN)	The median of rated pain intensity by (healthy/PD)/(both groups)	The difference between (healthy/PD) in rated pain intensity	pain intensity from both groups	The most painful area (healthy/PD)	P-value
8mN	<b>0.00</b> (0.00 to 0.00)/ <b>1.00</b> (1.00 to 2.00) <sup>A</sup>	20.08/52.92 <sup>C</sup>	1.08 <sup>B</sup>	LB /LB <sup>A</sup>	<b>&lt;0.001</b> <sup>*C</sup>
16mN	<b>0.00</b> (0.00 to 0.00)/ <b>1.00</b> (1.00 to 2.33) <sup>A</sup>	19.49/53.51 <sup>C</sup>	1.92 <sup>B</sup>	RF and LF/LB <sup>A</sup>	<b>&lt;0.001</b> <sup>*C</sup>
32mN	<b>0.00</b> (0.00 to 0.25)/ <b>1.67</b> (1.00 to 2.67) <sup>A</sup>	20.61/52.39 <sup>C</sup>	3.17 <sup>B</sup>	LB/LB <sup>A</sup>	<b>&lt;0.001</b> <sup>*C</sup>
64mN	<b>0.00</b> (0.00 to 0.33)/ <b>2.00</b> (1.00 to 3.25) <sup>A</sup>	20.51/52.49 <sup>C</sup>	3.83 <sup>B</sup>	RF/LF <sup>A</sup>	<b>&lt;0.001</b> <sup>*C</sup>
128mN	<b>0.17</b> (0.00 to 0.67)/ <b>2.67</b> (1.42 to 3.58) <sup>A</sup>	20.39/52.61 <sup>C</sup>	5.00 <sup>B</sup>	LF/RF <sup>A</sup>	<b>&lt;0.001</b> <sup>*C</sup>
256mN	<b>0.50</b> (0.33 to 1.00)/ <b>3.67</b> (2.00 to 5.00) <sup>A</sup>	21.33/51.67 <sup>C</sup>	6.00 <sup>B</sup>	RF/LB <sup>A</sup>	<b>&lt;0.001</b> <sup>*C</sup>
512mN	<b>1.00</b> (0.67 to 1.92)/ <b>4.00</b> (2.42 to 6.83) <sup>A</sup>	23.07/49.93 <sup>C</sup>	7.00 <sup>B</sup>	LB/RF <sup>A</sup>	<b>&lt;0.001</b> <sup>*C</sup>
All stimulators (mN)	-	-	-	-	<b>&lt;0.001</b> <sup>*B</sup>
Right forearm	<b>0.29</b> (0.00 to 1.00) <sup>C</sup>	-	-	12.92/12.08 <sup>C</sup>	0.769 <sup>C</sup>
Left forearm	<b>0.29</b> (0.01 to 1.00) <sup>C</sup>	-	-	12.21/12.79 <sup>C</sup>	0.838 <sup>C</sup>
Lower back	<b>1.10</b> (0.25 to 2.43) <sup>C</sup>	-	-	7.00/18.00 <sup>C</sup>	<b>&lt;0.001</b> <sup>*C</sup>

<sup>A</sup>= Kruskal Wallis test, <sup>B</sup>= Friedman test, <sup>C</sup>= Mann-Whitney

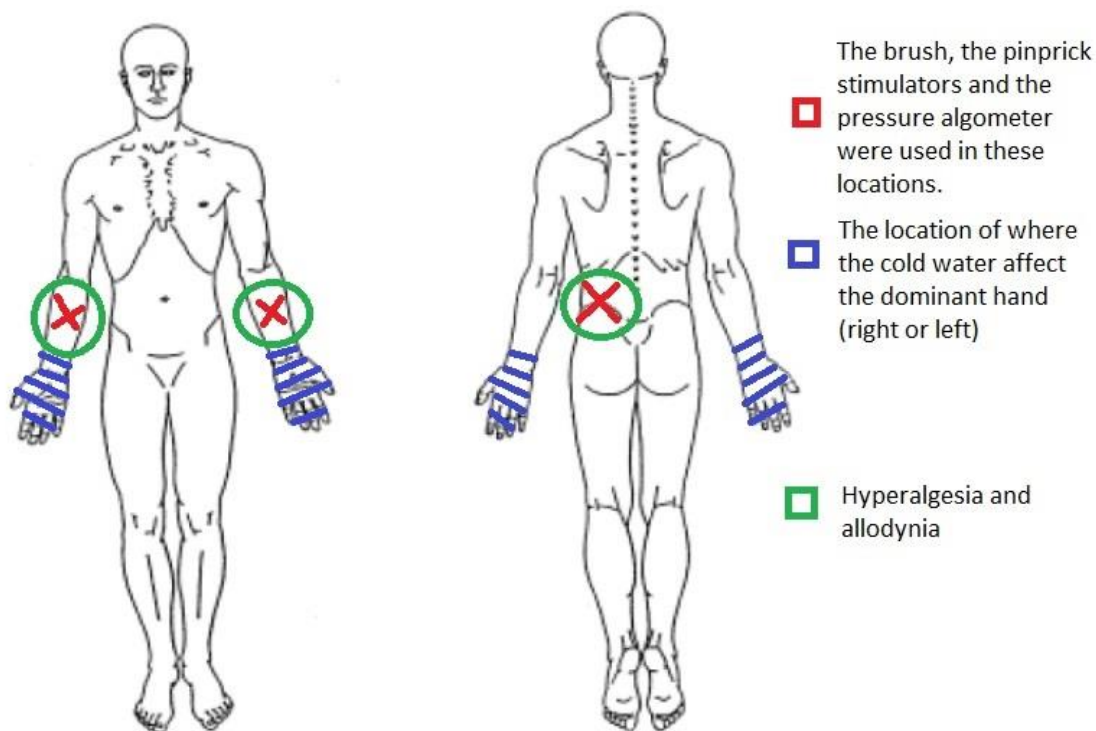
Values are medians with 25th and 75th centiles. Mean rank and P-value: Mann-Whitney test. RF =right forearm, LF= left forearm, LB=lower back, PD=Parkinson disease

The star (\*) indicate that the result was statistically significant



**Figure 3: The three graph shows the different between healthy subjects and PD patients in each area.** Each point is the average of each stimulator in all three graph. The error bars are shown in mean  $\pm$  SD and shows the wide spread of all subjects and gives a broad picture of how each stimulus is perceived. Graph A shows the different between these two groups in the right forearm. Graph B shows the different between healthy subjects and PD patients in the left forearm and graph C shows also the different between healthy subjects and PD patients in the lower back. It is especially seen in PD patients that they had rated the pain intensity spreads than healthy subjects, since e.g. 8 mN was rated from approximately 0 to just over 3 in VAS, in which healthy subjects had rated 8 mN from 0 to just under 0.5. A merge graph of all subjects are shown in **appendix R**, this graph present a significant different between healthy subjects and PD patients. The two graph present an exponential curve, in which it is clear that the pain intensity was rated higher as the weight increased. PD= Parkinson disease, SD= standard deviation, VAS=visual analog scale.

The star (\*) indicate that the result was statistics significant between the healthy subjects and PD patients in this stimulus.



**Figure 4:** The figure shows the four stimulated area on the body. The red cross in the figure shows the area where the subjects were stimulated with a brush, pinprick stimulators and the pressure algometer. The red cross also shows the area in which the patients develop allodynia and hyperalgesia due to the stimulation with a brush and from the pinprick stimulators, respectively. The blue line shows where healthy subjects and PD patients were stimulated with cold water. Finally, the green circle shows the area in which the patients were hypersensitive to the stimulation with a brush and the pinprick stimulators. The figure are modified from McGill pain Questionnaire

#### 4.4. Stimulation with pressure algometer

To investigate if there was a difference between healthy subjects and PD patients by evoked-pain stimulation with a pressure algometer, a Mann-Whitney test was performed and showed that there was a difference between these two groups. There was no doubt that the PD patients had rated the pain intensity higher than healthy subjects had and it was also clear that healthy subjects could tolerate a higher pressure than PD patients (**table 5**). However, there was only statistics significant difference between healthy subjects and PD patients by pressure before and after the cold water test, since the p-value was 0.011 and 0.050, respectively (**table 5**). **Figure 4** shows all three stimulated area on the body.

**Table 5: The pain intensity and the pressure from the algometer in healthy subjects and PD patients.** The present result shows the press from the algometer in ka/p and the rated pain intensity from the subjects. Mean rank from press shows that healthy obtain the highest press and the PD patients rated the highest pain intensity by press from the algometer. The p-value shows that there is a difference between healthy and PD patients in how much pain they can tolerated.

Location and time	Press (ka/p) from the algometer	Rated pain intensity (VAS)	Difference between (healthy/PD) in force	Difference between (healthy/PD) in pain intensity	P-value (press/VAS)
Pre cold water dominant hand	<b>406.67</b> (306.83 to 546.75)	<b>4.33</b> (4.00 to 5.67)	16.17/8.83	11.13/13.88	<b>0.011*</b> /0.337
Post cold water dominant hand	<b>503.83</b> (349.75 to 646.08)	<b>5.00</b> (4.00 to 6.75)	15.33/9.67	10.75/14.25	<b>0.050*</b> /0.223
Non-dominant hand	<b>468.17</b> (296.50 to 633.33)	<b>5.00</b> (4.00 to 6.50)	15.17/9.83	10.33/14.67	0.065/0.129
Lower back	<b>501.58</b> (340.58 to 748.00)	<b>3.67</b> (4.33 to 6.33)	14.83/10.17	10.38/14.63	0.106/0.140

Values are medians with 25th and 75th centiles. Mean rank and P-value: Mann-Whitney test. PD= Parkinson disease, VAS=visual Analog Scale

The star (\*) indicate that the result was statistics significant.

#### 4.5. Stimulation with cold water

A CPT was performed to investigate whether there was difference between healthy subjects and PD patients in perception of pain, a Mann-Whitney test was used to calculate the result. All healthy subjects and nine PD patients completed 30 seconds or more in the cold water. The test showed a difference in pain intensity between these two groups, but the difference was not statistics significant **table 6**. Furthermore, the difference between the rated pain intensity in these two groups by 60 seconds was not significant, since the p- value was 0.183 **table 6**. Only nine healthy subjects and five PD patients completed the test by 60 seconds in 5°C cold water. The median of the tolerance by all subjects were 6.00 (5.25 to 8.00) and the result showed that the pain intensity was rated higher in PD patients compared with healthy subjects, however, the result



was not statistics significant, since the p-value was 0.078 **table 6**. The Mann-Whitney revealed that there was a statistics significant impact by PD patients, since the p-value was <0.005 **table 6** and it was clear that healthy subjects had a higher tolerance time compared with PD patients, **table 6**. There was no significant difference between the groups in temperature before and after stimulation with cold water **table 6**. The location of the stimulation with cold water is shown in **figure 4**. When performing of the cold water test it was observed that the PD patients started to shake significantly more than they did before the test. The 30° water did not affect the PD patients.

**Tabel 6: Shows the result from the cold water test.** The present table shows the difference between healthy and PD patients in the cold water test. The tolerance time was significant different from the healthy subjects result, the result revealed that PD patients had the dominate hand in the cold water for less than the healthy subjects.

Duration and temperature	Median (healthy subjects and PD patients)	Difference in pain intensity (healthy/PD)	P-value
30 seconds	<b>5.00</b> (4.00 to 7.00)	9.46/13.06	0.183
60 seconds	<b>5.00</b> (5.00 to 7.25)	6.83/8.70	0.402
Tolerance	<b>6.00</b> (5.25 to 8.00)	10.00/15.00	0.078
Tolerance time	<b>65.00</b> (37.00 to 112.50)	15.96/9.04	<b>0.016*</b>
Temperature –before	<b>27.90</b> (25.23 to 30.00)	14.17/10.83	0.248
Temperature - after	<b>18.40</b> (17.25 to 20.18)	12.63/12.38	0.931

Values are medians with 25th and 75th centiles. Mean rank and P-value: Mann-Whitney test. PD= Parkinson disease.

The star (\*) indicate that the result was statistics significant.

## 5. Discussion

The current study investigated the sensory perception characteristics in PD patients compared with the healthy controls. There are only few studies available on sensory tests in PD patients with conflicting results (Tinazzi, Del Vesco et al. 2008; Brefel-Courbon, Ory-Magne et al. 2013). Twenty-four subjects completed four sensory tests and results revealed that PD patients suffered from allodynia to brush, hyperalgesia to prick stimulation in the back and in both forearms. PPT test revealed that the PD patients had lower threshold in the dominant hand both before and after the CPT, but were not different in the non-dominant hand and back. PD patients had also shorter tolerance time to CPT. We also found differences between PD patients with pain



and without pain. Below, the obtained results, their importance and potential implications of findings are discussed.

### 5.1. Spontaneous pain in PD

In the current study, 12 Parkinson patients were included, 5 of them had PD related pain (41.7% of the patients had chronic pain), which is in accordance with Chaudhuri et. Al.'s (2010) results, who found that approximately 40.0-45.9% of PD patients suffer from Parkinson related pain. Patients in the present study had musculoskeletal pain and dystonia pain and few presented symptoms of the central pain, i.e. neuropathic pain. Musculoskeletal pain and dystonia pain are the two most frequently pain types (**see section 1.2. Pain in Parkinson patients**) and the locations where the patients marked their pain, were also in agreement with frequently presented of these types of pain (Ford 2010; Ha and Jankovic 2012). The PD patients with pain also reported their pain descriptors on the McGill Pain questionnaire with symptoms described as muscle contraction, stiffness/tight, tiring/exhausting, and pinching, aching and muscle tenderness (Ford 2010; Fil, Cano-de-la-Cuerda et al. 2013).

PD patients suffer primary from motor problems, which often affect the extremities and the face and result in inner restlessness. A study (Tinazzi, Del Vesco et al. 2006) investigated the association between pain and motor complications in PD patients with pain and without pain and showed a significant association of pain with motor problems. This suggests that pain may occur because of motor complications. An abnormal function in the motor system is often associated with decreased quality of life, because it leads to loss of daily function. As the disease progresses, it is necessary to increase the administration of PD medication with higher doses. A study (Gerdelat-Mas, Simonetta-Moreau et al. 2007) has investigated whether the PD medications have a sensory impact on PD patients and showed that levodopa normalized the altered perception to different stimuli. Possibly, regulation by the PD medications would reduce pain due to muscles stiffness and change the perception of external stimuli in these patients to lower extent. In the event that patients are inactive because of PD, it could be a possibility to perform a training program for the individual patient, which helps to strengthen the muscles and softens the patients and enhance functionality. This will probably increase the quality of life. Nevertheless, this area needs further investigation.

### 5.2. Allodynia

In the current study, we demonstrated that PD patients had an altered perception in response to the light touch compared to healthy subjects. Our results showed that PD patients without pain had the highest pain intensity on VAS in comparison with PD patients with pain. This might indicate that the patients without pain



were more sensitive to a non-painful stimulus than the PD patients with pain, but both were allodynic in comparison with healthy controls. Based on our knowledge, allodynia has not been tested in PD patients before. The three investigated areas were selected based on the five types of pain that PD patients often suffer from, which frequently affect the extremities and the back. Our results showed that 58.33% of PD patients had discomfort to the non-painful stimuli by brush (allodynia). It is not well known that what causes the perception of allodynia in PD patients. However, animal studies have shed light on some possible mechanisms that might be involved in development of allodynia in PD. A recent study has investigated dynamic mechanical allodynia in a rat model of PD. The rats received an injection of 6-hydroxy dopamine bilaterally to produce a lesion in the nigrostriatal dopaminergic pathways. This study showed significant dynamic mechanical allodynia in the orofacial area, in response to tactile stimulus. When rats received a dopamine 2 receptor agonist, Bromocriptine (Parlodel), which is a PD medication, the dynamic mechanical allodynia was dramatically reversed compared with control rats who were treated with saline (Wisam Dieb 2013). This study demonstrated that a lesion in the nigrostriatal pathways could result in dynamic mechanical allodynia. The authors speculated that degeneration of dopamine containing neurons in substantia nigra pars compacta might be the main underlying mechanism for development of dynamic mechanical allodynia in rats and most likely in humans. Possibly, the neuronal loss of dopaminergic neurons results in an abnormal basal ganglia function and this abnormality might modulate the perception of the tactile and nociceptive information from medulla spinalis, truncus encephalicus and thalamus. Furthermore, it was also speculated that the possible abnormal function in the nigrostriatal pathways result in central sensitization and presence of allodynia in PD.

Previous studies have shown that central nervous system disorders can cause altered perception of touch and pain (Bowsher 2005). Brush stimulation, activates primary sensory neurons encoding signals for low intensity (A $\beta$ -fibers), which under normal condition should be perceived as sensation of touch (Woolf 2011). However, under pathological conditions, central sensitization might occur, which is defined as increased response to e.g. light touch (Schaible 2007; Woolf 2011). Our observation suggests that the PD patients had central sensitization, which leads to increased synaptic ascending transmission and a decrease in the descending inhibition. Normally, the A $\beta$ -fibers become activated by touch to a light stimulus such as brushing, but when allodynia occurs, it is proposed that the signals from myelinated A $\beta$ -fibers intersect to unmyelinated C-fibers, which causes pain in response to a non-painful stimulus (Woolf 2011). Furthermore, spontaneous pain in PD patients occurs due to an abnormal function that has developed in the dorsal horn neurons in the spinal cord. Transduction might be affected in PD patients, however, a study (Nolano, Provitera et al. 2008) has investigated the conduction velocity and it seems that this parameter appears to be normal in PD patients. The release of neurotransmitters, such as substance P excites the second order

neurons in the spinal cord, but the excitation might become increased in PD patients and the second order neurons might transmit information about pain instead of perception of touch. Furthermore, PD patients with pain and without pain perceived the non-painful stimulus differently. This might suggest that different stages of central sensitization may occur during this progressive disorder and the PD patients without pain might have further increased release of neurotransmitters to non-painful stimulus due to the fact that the neurons are hyperactive and causes increased release of neurotransmitters, which causes an enhanced excitation in the second order neuron. Descending neurons, especially interneurons have been known to have an impact on the ascending neurons in the spinal cord. Normally, the interneuron releases inhibitory neurotransmitters, but when enhanced excitation occurs in the sensory neurons, it might suggest that pain inhibit pain, which possibly explains a loss of inhibitory interneurons' activity because of an irritation of the neurons. This may explain modulation of pain in both groups of PD patients. This novel observation might contribute to future investigations and extend the literature of alloynic conditions in PD patients. Future research would eventually contribute to improvement of the current PD treatment, and development of new treatments for PD patients, which is necessary because currently only symptomatic treatment are available.

### 5.3. Hyperalgesia

The results indicated that PD patients had increased pain intensity in response to an already painful stimulus (pinprick). The rating of pain on the VAS in PD patients was between 3 and 7, where healthy controls only indicated an average of 1 on the VAS. PD patients with pain rated the pain intensity higher than PD patients without pain, which was opposite to what was seen for allodynia. Normally, the prick from the needles is an uncomfortable stimulation, but the PD patients revealed increased responses to a painful stimulus (hyperalgesia). This may indicate that PD patients have an altered central sensitivity in their nervous system. We investigated the stimulus-dependent-response in PD patients, which showed increased pain intensity to noxious stimuli; the larger the weight was, the higher the responses were. However, the stimulus-dependent-response revealed that the PD patients felt higher pain by larger stimulation compared with healthy controls. Nevertheless, the presented study also investigated the location of the most sensitive area to pinprick test. The results revealed a higher tendency in lower back, followed by the right forearm and the lowest pain intensity was in left forearm. However, the result did not show a significant difference between the test areas in the right and left forearms. The author could not find similar studies that have investigated the mechanical pain sensitivity in PD patients by use of pinprick stimulation and there would be no point for comparison with other findings in relation to this test.

The hypersensitivity to pinprick stimuli in PD patients is believed to occur because of an induction or presence of the state of central sensitization that leads to increased ascending synaptic transmission and reduction in



descending inhibition in the somatosensory pathways. Under this condition, a central amplification of signals arises and causes increased pain response to noxious stimuli (Sandkuhler 2009; Woolf 2011). As discussed in the section of allodynia, the altered perception of pain and touch is thought to occur in the dorsal horn due to possibly the disturbances in the release of neurotransmitters, which may make the PD patients more sensitive to noxious stimuli. Nevertheless, other alteration may be occur in PD patients with pain, since the perception of painful stimuli also is changed. It is speculated that the second order neurons increase responsiveness to a given stimuli following a primary sensory neuron is being hyperactive. Furthermore, the pain afferent pathways carry information about noxious stimuli to the brain both directly and indirectly. A part of the noxious stimuli are received in the basal ganglia and some of the stimuli are sent directly to the cortical pain processing regions from thalamus, which initiates the cortical-basal ganglia-thalamic-cortical loop and this cortical loop is thought to be stimulated further with information about pain from e.g. pinprick stimuli. When pain is perceived and processed via cortical area and the basal ganglia, the modulation of pain is sent through descending pathway (pain modulation pathways) (Borsook, Upadhyay et al. 2010). It is speculated that the PD patients were affected on both pathways and that the interaction between afferent and efferent neurons in the spinal cord has an impact on central sensitization, which possibly reflects on responsiveness of PD patients to noxious stimulus.

It is not clear but disturbances in the basal ganglia could increase the pain perception to non-painful stimulus in PD patients without pain, with enhanced activation of A $\beta$ -fibers and C-fibers in these patients, whereas PD patients with pain had already had increased nociceptive activation compared with PD patients without pain. This study helps to support that the PD patients have altered pain perception. In the longer term, increased knowledge on impaired sensory function in PD may lead to a better diagnostic, stratification of PD patients, and development of PD medication to help PD patients more efficiently overcoming sensory disturbances along with motor dysfunction.

#### **5.4. Conditioned Pain Modulation: function of descending inhibitory pain pathways**

It was observed that PD patients rated higher pain intensity than healthy subjects did in response to cold stimulation by immersion of hand in ice-water, however, the difference between these two groups were not significant. All twelve healthy subjects completed the test, but only 9 PD patients within 30 sec. 9 healthy subjects and 5 PD patients completed test by 60 sec. The drop out and even numbers per group for comparison might have caused insufficient power for statistical analysis. There was a significant difference in tolerance time between healthy controls and PD patients, where PD patients had shorter tolerance time than healthy controls. The result revealed a difference between PD patients with pain that withdrew their hand several minutes before PD patients without pain. The PPT test showed a significant difference in

pressure pain threshold before and after the CPT. The PD patients were more sensitive than healthy controls, however, a difference between the PD patients with pain and without pain was not observed. The PPT is believed to test the deep pain sensitivity transmitted by A $\delta$ -fibers and C-fibers (Svensson, Baad-Hansen et al. 2011). Our results indicate that these nociceptive fibers were activated in PD patients and in healthy controls, but the perception of pain occur faster in PD patients. We could indirectly investigate pain sensitivity transmitted by A $\delta$ -fibers and C-fibers. The PD patients complained of discomfort the first few seconds, after which the pain was initiated. This indicated that the activation of A $\delta$ -fibers were initiated in the beginning of the test and further an activation of C-fibers occurred, when the PD patients felt an uncomfortable pain by performing the CPT (Svensson, Baad-Hansen et al. 2011). The CPT test, however showed a significant difference between PD patients and healthy controls, where the PD patients had higher PPT values before the cold test compared with PPTs after the test. PD patients were more sensitive after the CPT that might be due to central sensitization present in these patients. There is no similar study that investigated the PPT before and after the CPT in PD patients. It was speculated that the CPT affected the PPT after the cold test, the PD patients had tendency to rate higher thresholds, but it was not statistically significant. Furthermore, it was also considered whether the evoked pain from the CPT test might affect the perception of the PPT test, a tendency to increased threshold would have been seen.

Vela et. Al.'s (2012) investigated the PPT in PD patients with and without administration of PD medications in comparison with healthy control groups and found a significant difference in all four investigated areas (frontal bone, C5-C6 joint, the second metacarpal and the tibialis anterior muscle). We did not find a significant difference in PPT values between the right and left forearm in PD patients and healthy controls, but found a tendency that the PD patients had lower pressure in the lower back and the non-dominant hand. Due to the lack of data available for other studies on CPT in PD patients, comparison of results obtained here with other similar studies is not possible.

This area needs future investigation to clarify the underlying mechanism, such as the functionality of the descending inhibitory pain pathways and the tolerance to cold water stimulation. Our findings support that the PD patients have altered perception in deep pain sensitivity.

### 5.5. The effect of PD medication on sensory and pain perception

In the current study, all PD patients received their medication as usual, which included four groups of dopaminergic drugs: Levodopa preparation, Catechol-O-Methyl transferase (COMT-inhibitors), Monoamine oxidase inhibitors (MOA-B-inhibitors) and dopamine agonists. The most common medications were from the group of levodopa preparation and dopamine agonists, such as Sinemet and Sifrol. Sinemet is a combination



preparation of Levodopa and Carbidopa (Thamir M. Alshammari 2014), Levodopa is absorbed in the brain and converted to dopamine, in which Carbidopa enhances the effects of Levodopa and reduces the side effects such as heart rhythm disturbances. Whereas Sifrol is a dopamine agonist (pramipexol). Dopamine agonists are often given as an adjunct to other PD medications and pramipexol works by direct stimulation of dopamine receptors. This group of PD medication is also associated with cardiovascular side effects similar to levodopa preparations (Jankovic and Stacy 2007). In the present study, based on the ethical considerations, the patients stayed on their medications in the course of the study, therefore this could have an effect on the results. The PD patients in the current study reported lower threshold and higher pain intensity in the brush test, the pinprick test, PPT test and the CPT test compared to healthy controls. Christine Brefel-Courbon et. al. (2005) have shown that PD patients without dopaminergic drug had lower nociceptive threshold compared with a control group, but there was shown that by administration of dopaminergic drugs PD patients have similar findings to the normal range. Some patients in the current study took medication every two hours, which means that they had just taken PD medication before the experiment was initiated, whereas other PD patients had been taking medication in the morning or several hours before the sensory tests. However, the PD patients rated nevertheless the pain intensity higher than healthy subjects in general, which means an overall hyper responsiveness in PD patients compared with controls regardless of the type or time of medication. Gerdelat-Mas et. Al. (2007) investigated the effect of levodopa in PD patients in comparison with healthy controls. This study was in agreement with our observations, since they reported that PD patients had lower pain threshold than the control group, even though that the levodopa increased the pain threshold in PD patients.

Taken together data supports that an altered perception in PD patients with pain and without pain. We know that the patient's nervous system is affected, but future research is needed to study both ascending and descending pathways. Perhaps, an increased dosage of certain types of PD medication could reduce the sensory perception, but if we increase the dosage possibly, the motor problems will increase, because of the higher amount of dopaminergic drug that further increases the release of dopamine in PD patients. Dopaminergic drug directly stimulates the receptors in neurons that normally would be stimulated by dopaminergic neurotransmitters. It was speculated whether the increased amount of dopaminergic drug might be able to excessively stimulate the dopaminergic neurons, which may lead to increased spontaneous pain in PD. To increase the quality of life we need some revisions in the PD medication and maybe we need administration of painkillers to reduce the pain in some PD patients. Another suggestion could be training, which strengthens the muscles and smoothen the patients. Perhaps that could reduce the pain and strengthening the motor skills in these patients, which also increases the functionality and quality of life.

## 6. Limitation and future perspective

The current study had a limitation in the recruitments of PD patients, because the number of recruited PD patients are low. The statistical power of these test would likely increase in recruitment of a higher numbers of PD patients. A high statistical power results in higher validation, which support our findings better. The current study wanted to recruits thirty PD patients and thirty healthy controls, but it was not possible. It could be interesting to continue, this study in relation to increase the recruitment of PD patients and healthy controls, because it could be interesting to investigate a bigger population and investigate if the results have changed and an increased statistical power.

## 7. Conclusion

In conclusion, we found that PD patients had increased pain intensity compared with healthy controls and the PD patients felt discomfort to the non-painful and painful stimuli by brush and pinprick, respectively. This indicates that PD patients had developed allodynia by light touch and hyperalgesia by painful stimulation. We found that the PD patients had decreased pressure pain threshold compared with healthy controls before and after the Cold pressor test. The cold pressor test indicates that the PD patients had increased pain intensity and shorter tolerance time compared with healthy controls. We also found a tendency that a difference occurs between PD patients with pain and without pain. Medication did not altered the sensory disturbances, which indicates that the sensory disturbances in PD patients are independent of PD medication. The current study demonstrated sensory disturbance in PD patients compared with healthy controls.

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