MEASURING THE TACTILE SENSE

CORTICAL MECHANISMS AND CLINICAL APPLICATIONS OF TACTILE DIRECTION DISCRIMINATION

UNIVERSITY OF GOTHENBURG

LINDA C LUNDBLAD

Department of Clinical Neurophysiology

Institute of Neuroscience and Physiology

Sahlgrenska Academy

University of Gothenburg

Sweden

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Cover illustration: “TDD the cat way”. The cat “Vips” performs frictional TDD on my right index finger. Photograph by Johan Kling.

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ABSTRACT

Most of the studies aiming to investigate the human tactile sense are done on the glabrous skin. Still, there is a need for a quantitative method for evaluating nervous function of the hairy skin. Tactile direction discrimination, the ability to determine the direction of movement across the skin provides a clinical method to quantify tactile function of the hairy skin in humans. The method is easy-to-use, rapid, and inexpensive but has not been compared to vibration detection which is considered as the standard method for psychophysical examination of peripheral neuropathy. The peripheral neural mechanisms for tactile direction discrimination have been extensively studied, as well as the ascending pathways in the spinal cord. Nevertheless, the supraspinal mechanisms are imperfectly known. In this study we have compared the clinical test for tactile direction discrimination with vibration detection in a group of patients with diabetic neuropathy. We have also thoroughly studied the cortical processing of tactile direction discrimination. The results are presented in four separate papers.

The results showed that the clinical test for tactile direction discrimination had similar sensitivity as vibration detection in detecting patients with diabetic neuropathy. The cortical network for tactile direction discrimination involved the primary somatosensory cortex, the opercular parietal area 1 of the secondary somatosensory cortex, and dorsolateral prefrontal cortex as well as anterior insular cortex.

In conclusion, the clinical test for tactile direction discrimination provides a quantitative clinical test that is sensitive in detecting peripheral nervous lesions. The test seems well-suited for following patients with disturbances in the peripheral and central nervous systems. The neurophysiological mechanisms underlying tactile direction discrimination are well studied from the peripheral afferents in the skin, through the spinal cord and to information processing in the brain.

Keywords: AIC, diabetic neuropathy, DLPFC, fMRI, hairy skin, psychophysics, QST testing, somatosensory cortex, tactile direction discrimination

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POPULÄRVETENSKAPLIG SAMMANFATTNING

ENKEL METOD FÖR MÄTNING AV HUDKÄNSEL

Människans sinnen kan drabbas av nedsättningar av olika slag och måste då kunna utvärderas i olika (bl. a medicinska) sammanhang. Synen utvärderas vanligtvis med ett syntest då man läser på en syntavla, hörseln utvärderas med ett hörseltest då man får lyssna på olika ljud med olika frekvens och intensitet, men hur ska man utvärdera känseln? Huden är vårt största känselorgan och man kan undersöka många olika dimensioner av hudkänseln, såsom förmågan att uppleva temperatur eller förmågan att lokalisera beröring. Man måste komma ihåg att vår känsel är olika på olika hudytor som till exempel på fingrarna eller på ryggen.

I denna avhandling har en metod för att kvantifiera den behårade hudens förmåga att bedöma ett föremåls riktning över huden utvärderats. Denna metod som kallas för taktilt riktningskänseltest har visat sig vara ett bra verktyg för att diagnostisera diabetes neuropati i ett tidigt stadium och metoden används i klinisk rutin på avdelningen för Klinisk Neurofysiologi vid Sahlgrenska Universitetssjukhuset i Göteborg. I avhandlingen jämfördes två metoder, taktilt riktningskänseltest och vibrationsdetektion för diagnostisering av diabetes neuropati hos en grupp av patienter med diabetes mellitus typ 1. Det visade sig att testet för taktil riktningskänsel detekterade något fler patienter än vibrationsdetektion och därmed tycks testet för taktil riktningskänsel vara åtminstone lika känsligt som vibrationsdetektion för att upptäcka nervskador. Den främsta fördelen med taktilt riktningskänseltest är att testet är avsevärt mycket billigare än vibrationsdetektion.

Genom funktionell magnetresonansavbildning (fMRI) studerades hur de från huden inkommande signalerna från taktil riktningskänsel bearbetas i hjärnan. Resultaten visade att taktil riktningskänsel bearbetas i ett kortikalt nätverk som består av somatosensorisk kortex, dorsolateral prefrontal kortex och insulär kortex.

Taktilt riktningskänseltest är ett kliniskt test för undersökning av den behårade hudens funktion som kan användas för bedömning av hudkänsel och för att följa förlopp både i det perifera och i det centrala nervsystemet. Taktilt riktningskänseltest är ett test som inte kräver sofistikerad utrustning och är lätt att utföra. Fynden från studierna av hur taktil riktningskänsel bearbetas i hjärnan illustrerar att lesioner i flera olika delar av hjärnan kan påverka vår hudkänsel.

LIST OF PUBLICATIONS

This thesis is based on the following papers, which are referred to in the text by their roman numerals.

I. Löken LS, **Lundblad LC**, Elam M, Olausson HW. Tactile direction discrimination and vibration detection in diabetic neuropathy. *Acta Neurol Scand*. 2010 May; 121(5):302-8. Epub 2009 Oct 5.

II. Backlund Wasling H, **Lundblad L**, Löken L, Wessberg J, Wiklund K, Norrsell U, Olausson H. Cortical processing of lateral skin stretch stimulation in humans. *Exp Brain Res*. 2008 Sep; 190(2): 117-24. Epub 2008 Jun 24.

III. **Lundblad LC**, Olausson HW, Malmeström C, Backlund Wasling H. Processing in prefrontal cortex underlies tactile direction discrimination: an fMRI study of a patient with a traumatic spinal cord lesion. *Neuroscience Letters*. 2010 Oct 15;483(3):197-200. Epub Aug 11.

IV. **Lundblad LC**, Olausson HW, Hermansson A-K, Backlund Wasling H. Cortical processing of tactile direction discrimination based on spatiotemporal cues in man. *Manuscript*

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ABBREVIATIONS

AIC	Anterior insular cortex
BA	Brodmann area
BOLD	Blood oxygenation level dependent
CNS	Central nervous system
CV	Conduction velocity
DLPFC	Dorsolateral prefrontal cortex
EMG	Electromyography
fMRI	Functional magnetic resonance imaging
FWE	Family-wise error
GLM	General linear model
IC	Insular cortex
MR	Magnetic resonance
MRI	Magnetic resonance imaging
OP	Opercular parietal area
PC	Pacinian corpuscle
QST	Quantitative sensory testing
R.A.	Male patient with dorsal column lesion in Paper III
RA	Rapidly adapting afferents
ROI	Region of interest
RPA	Response profile area
SA1	Slowly adapting type 1 afferents
SA2	Slowly adapting type 2 afferents
S1	Primary somatosensory cortex
S2	Secondary somatosensory cortex
SD	Standard deviation
SEP	Sensory evoked potential
TDD	Tactile direction discrimination
TE	Echo time
TR	Repetition time
T2*	T2 star

INTRODUCTION

The skin is the body's largest and one of its most important sensory organs. It is a highly complex organ supplied by receptors which mediate tactile, thermal, painful, and affective touch, as well as itch. The first sense to be developed in an embryo is touch, and the first sites on the human body to develop touch sensibility are the ones that have the largest representation in the primary somatosensory cortex (Montagu, 1984). Touch or the cutaneous sense can be divided into discriminative and affective functions. The discriminative functions register spatial and temporal occurrences on the skin such as when you sense a fly walking on your forehead. The affective functions register pain and positive emotional experiences of affiliative touch such as when you get stepped on a toe and your toe starts to hurt, and then the culprit turns around and comforts you by giving you a gentle stroke along your arm. There are several different skin receptors that mediate different aspects of touch and those signals travel in different types of nerve fibres. We have two main types of skin. On the palms of the hand and on the sole on the foot we have glabrous skin and on the rest of the body we have hairy skin. The glabrous and hairy skin serve different functions that are reflected in differences in their innervations. Various sensory inputs are processed in the spinal cord and in various brain areas that makes us aware of how we should respond to the stimulation.

We have studied tactile direction discrimination (TDD), the ability to determine the direction of movements across the skin, which is used as a method to quantify tactile sensibility. Most of the studies aiming to investigate the tactile sense are done on the glabrous skin that only covers a small part of the body. Still, there is a need for a quantitative method to evaluate nervous function of the hairy skin. In the present study, the clinical TDD test (**Paper I**) and the cortical processing of TDD was investigated (**Paper II-IV**). Functional magnetic resonance imaging (fMRI) was used to study the cortical processing of TDD based on skin stretch information in healthy subjects (**Paper II**), and in a patient with a unilateral disturbance in TDD following a spinal cord lesion (**Paper III**). fMRI was also used to study the cortical processing of TDD based on spatiotemporal information in healthy subjects (**Paper IV**). The study of the clinical TDD test demonstrated that the TDD test is at least as sensitive as vibration detection to reveal diabetic neuropathy. The fMRI studies demonstrated that the secondary somatosensory cortex (S2), anterior insular cortex (AIC) and dorsolateral prefrontal cortex (DLPFC) are important for the processing of TDD based on skin stretch information. A similar cortical network was demonstrated for the processing of TDD based on

spatiotemporal information, which in addition included the primary somatosensory cortex (S1) and posterior insular cortex (IC).

TACTILE DIRECTION DISCRIMINATION, TDD

There are several clinical methods for examination of touch and tactile function. The standard test of sensory nerve function at a clinical neurophysiology department is probably examination of nerve conduction, i.e., neurography. In addition to neurography, it is common to use quantitative sensory testing (QST) such as thermal detection and vibration detection. All of these methods demand special and expensive equipment and skilled personnel. Another quantitative clinically used test for tactile function is the clinical TDD test. TDD as a quantitative clinical test was developed at the Department of Physiology, University of Gothenburg, about 15 years ago (Olausson *et al.*, 1997). The test is easy-to-use and inexpensive. It is normally easy for people to tell the direction of a moving tactile stimulus on the hairy skin of the body. After moving the stimulus only a very short distance, the subject will be able to discriminate the relevant direction. The clinical TDD test is used to detect peripheral nerve damage and has been shown to be a useful test to discover diabetic neuropathy in an early stage (Norrsell *et al.*, 2001b).

The underlying peripheral mechanisms of TDD have been extensively studied over the past 150 years (Weber, 1846; Aubert & Kammler, 1858; Hall & Donaldson, 1885; Ahringsmann & Buch, 1926; de Cillis, 1944; Loomis & Collins, 1978; Gould *et al.*, 1979; Essick & Whitsel, 1985b; Whitsel *et al.*, 1986; Gardner & Palmer, 1989; Olausson & Norrsell, 1993; Olausson *et al.*, 2000). TDD is mainly signalled by two different types of peripheral afferents i.e. slowly adapting type 1 and 2 afferents (SA1 and SA2) (Gould *et al.*, 1979; Norrsell & Olausson, 1992, 1994). Our knowledge, however, about information processing of TDD on the supraspinal level is limited. Earlier studies have shown that the information from TDD is dependent on an intact dorsal column (Foerster, 1936; Wall & Noordenbos, 1977) and that the information from TDD is dependent on the contralateral hemisphere (Norrsell, 1973; Olausson *et al.*, 2001; Backlund *et al.*, 2005). Increased knowledge about the supraspinal processing will improve our ability to understand sensory consequences of restricted brain lesions. TDD has also been shown to play an important role in basic motor function. Studies of the relationship between TDD and postural control have

demonstrated that directional sensibility may aid postural stability at least as much as vision (Norrsell *et al.*, 2001a; Backlund Wasling *et al.*, 2005).

Peripheral mechanisms underlying tactile direction discrimination

Almost a century ago, Tshlenow (1928) observed that healthy subjects easily could tell the direction of a skin pull even if there was no movement over the skin. The skin pulls were done through pinching the skin between the examiners fingers, and pulled in either of four directions. He called this capacity "cinesthésie cutanée" and recommended it as a useful method for detecting peripheral and central disorders of the nervous system. Halpern (1947) confirmed the finding by describing patients with various spinal cord disorders that had intact touch sensibility but were unable to tell the direction of skin pulls.

Gould, Vierck and Luck (1979) used an air-stream stimulus to determine thresholds for TDD on the forearm skin. They concluded that TDD may depend on two types of peripheral signalling. One consists of information about friction induced changes in lateral skin stretch and the other of spatiotemporal information, i.e. information about the sequential order of activation of adjacent mechanoreceptors.

The spatiotemporal aspects of TDD have been analysed carefully by Essick, Whitsel and co-workers. They characterized the dependence of TDD on stimulus velocity and stimulation distance for different body areas (Dreyer *et al.*, 1978; Whitsel, 1979; Essick & Whitsel, 1985b, a; Essick *et al.*, 1988b; Essick *et al.*, 1989; Essick *et al.*, 1991; Essick *et al.*, 1992). Dreyer et al. (1978) showed that the TDD capacity increases with transverse length and is optimal for velocities between 3 and 25 cm/s. Essick and co-workers found that the optimal velocity for TDD increased, whereas the accuracy of TDD decreased, with distance proximally along the upper limb. The authors' explanation was that TDD is maximal at an optimal temporal frequency of stimulation of adjacent receptors, regardless the test site. "Due to differences in cutaneous innervation density, this optimal temporal frequency is necessarily achieved by different stimulus velocities at skin sites differing in cutaneous innervations density" (Essick *et al.*, 1991, p.21).

Srinivasan et al. (1990) investigated the capacity of human subjects to discriminate the direction of skin stretch mediated by a glass plate pressed to the skin applied on one fingertip. The findings were in agreement with Gould et al. (1979), and showed that the

subject easily could tell the direction of skin stretch even if there was no movement over the skin surface. Actually, the ability of the subjects to discriminate directions of skin stretch was almost the same whether or not movement over the skin was present.

Olausson and Norrsell (1993) used a blunt metal tip moving on the forearm and determined that TDD depended on contact load and distance of movement. When the subject extended the arm the accuracy of TDD decreased through diminishing the cutaneous distensibility. The authors also pointed out that velocity of the stimulus' motion is important for TDD. However, there seems to be "speed limits", within which changes of the velocity are less influential.

Tactile direction discrimination in patients with peripheral nerve lesions

TDD testing has been advantageously used for detecting sensory disturbances due to post-operative injuries in the perioral region (Walter & Gregg, 1979; Frost *et al.*, 1982; Bailey & Bays, 1984; Zaytoun *et al.*, 1986; Nishioka *et al.*, 1987; Essick *et al.*, 1988a; Essick *et al.*, 1989; Ghali & Epker, 1989; Essick *et al.*, 1990; Essick *et al.*, 1992; Naples *et al.*, 1994; Essick *et al.*, 2002). TDD has been found to be more sensitive than detection of light touch, two-point discrimination and thermal detection for detecting post-operative sensory disturbances in the mandibular nerve (Frost *et al.*, 1982; Bailey & Bays, 1984; Nishioka *et al.*, 1987) and has been recommended as a standard test for sensory disturbances in the perioral region (Ghali & Epker, 1989; Essick *et al.*, 1992).

Olausson et al. (1997) constructed a quantitative test for TDD that took into account the importance of friction, the degree of static skin tension determined by the position of the external limb, the stimulation distance and the stimulation area. They determined normal values for different body parts in healthy subjects of different ages and compared the normal values with values from measurement of patients with symptoms indicating sensory neuropathy. The TDD test was found to be as sensitive as electrophysiological measurements of nerve conduction velocity (i.e. neurography) in detecting sensory neuropathy. In a study of patients with diabetic neuropathy Norrsell et al. (2001b) compared five different procedures used to diagnose sensory neuropathy. Among TDD, neurological examination, neurography, temperature sensibility and monofilament testing, TDD had the highest sensitivity and specificity and was suggested as an easy-to-use, fast and inexpensive clinical tool to detect and follow the development of neuropathic damage to sensory nerves. The TDD test initiated

by Olausson and co-workers was used in the first part of this thesis (**Paper I**) when a group of patients with diabetic neuropathy were examined and is also currently a part of the routine clinical sensory examination at the department of Clinical Neurophysiology at Sahlgrenska University Hospital in Gothenburg.

Tactile direction discrimination in patients with spinal cord lesions

Foerster (1936) showed that TDD depends on an intact dorsal column. He described that patients with dorsal column lesions had preserved touch sensibility but were unable to tell the direction of an object's movement across the skin. He concluded that the TDD task was dependent on the integration of temporal and spatial information, carried in the dorsal columns. Foerster's findings were confirmed by Wall and Noordenbos (1977) who showed that patients with lesions in the dorsal columns did not lose what the authors regarded as the classical primary capacities of cutaneous sensibility (von Frey hair detection, localization of a point stimulus, vibration detection or two-point discrimination), but lost an ability to carry out tasks where they must simultaneously analyze spatial and temporal characteristics of the stimulus. They concluded from a clinical point of view, that TDD and figure writing on the skin surface (graphesthesia) seem to be the most useful and simple test to detect a dorsal column lesion. Vierck (1974) showed that monkeys with dorsal column lesions could differentiate between stationary and moving stimuli but were severely impaired in their ability to detect direction of movement. Nathan et al. (1986) concluded in their review of sensory effects of spinal cord lesions that a lesion to the posterior columns causes only a slight disturbance in the ability to detect tactile and pressure stimuli, whereas TDD is disturbed. Further, in another study of patients with spinal cord lesions, Hankey and Edis (1989) described 11 patients with spastic paraparesis that had impaired TDD and preserved perceptions of light touch, pain, temperature, vibration and joint position. They proposed that TDD is a sensitive sign of posterior column function which can be usefully incorporated into the clinical sensory examination in the evaluation of spinal cord disorders.

Tactile direction discrimination in patients with brain lesions

Sperry and co-workers (1969) used TDD in examinations of patients with "split-brain" symptoms following forebrain commisurotomy. Their patients could verbally report the presence of a tactile stimulus on the left hand but could not tell the direction of a line drawn

on the palm of the same hand. Norrsell (1973) examined four right-handed commissurotomized patients and reported disturbed TDD, for verbal readouts, on the patients' entire left body half. Thermal and touch perception tested with verbal readouts were normal on both body halves in all patients. Backlund et al. (2005) examined four patients who had undergone hemispherectomy due to brain lesions early in life, with monofilament detection and TDD. On the non-paretic side all results were normal but on the paretic side the TDD results were severely disturbed while the touch detection was quite normal. They concluded that TDD was dependent on processing in the hemisphere contralateral to the stimulation.

In a large study of neurological patients (n = 558) with peripheral or central nervous lesions, Bender et al. (1982) compared the test results for directional sensibility (i.e. TDD), graphesthesia, directional dermatokinesthesia, tactile point localization, two-point discrimination, detection of joint movement, determination of the direction of joint movement, stereognosis, pain perception, deep pressure sensation, thermal sensations and vibration sensation. They found that TDD and graphesthesia were the most useful tests and proposed them to be included in the clinical sensory examination, since both provide distinct information of somatic sensibility. They also suggested that TDD constitutes the basis for graphesthesia, since the tests often gave similar results and that TDD perhaps should be preferred since it is easier to perform in a standardized way compared to graphesthesia.

Tactile direction discrimination and postural control

Backlund Wasling and co-workers have studied how TDD influences postural control. They found that TDD is important for motor control. Non-supportive tactile contact between the forearm or fingertip skin and spatially fixed tactile objects or an air-stream stimulus reduced postural sway comparable to the effect of vision (Norrsell *et al.*, 2001a; Backlund Wasling *et al.*, 2005).

Thresholds for tactile direction discrimination

Gould, Vierck and Luck (1979) used an air-stream stimulus to determine thresholds for TDD on the forearm skin. The thresholds ranged from 9 to 17 mm. However, the same subjects

were able to tell the direction of a < 1mm skin stretch caused by a probe glued to the skin. In another study of TDD based on spatiotemporal information Norrsell and Olausson (1994) used a well controlled air-stream stimulus on the forearm skin. The thresholds for TDD were 4-8 mm. They found a positive correlation between stimulation distance and TDD, whereas there was no correlation between accuracy and contact load of the air-stream. Backlund Wasling et al. (2005) applied an air-stream stimulus on the hairy skin of the distal forearm and on the glabrous skin on the tip of the index finger. The authors reported that the subjects were able to discriminate movements of ≤ 2 mm on the fingertip and ≥ 8 mm on the forearm. Olausson et al (1998) have determined the thresholds for TDD for a skin pull stimulus that provided information about friction induced changes in lateral skin stretch. The subjects were able to determine the movement direction of a pin glued to the skin with an excursion of less than 0.13 mm. Experiments performed during local skin anaesthesia showed that stretch sensitive receptors located more than 15 mm in front and behind the moving skin correctly signalled the direction of the skin pulls.

Electrophysiological studies of the skin innervation

Electrophysiological studies on the innervation of the human hairy skin have rarely been performed in contrast to the tactile afferents in the glabrous skin of the human hand that have been analyzed extensively (Johansson & Vallbo, 1983; Vallbo & Johansson, 1984). In microneurographic studies Vallbo et al. (1995) have identified five types of mechanoreceptive units in the forearm of the hairy skin. Two of the unit types were slowly adapting, i.e slowly adapting type 1, SA1, (Merkel) afferents and slowly adapting type 2, SA2, (Ruffini) afferents and three units were rapidly adapting, RA, i.e. hair, field and Pacinian-type (PC) units. All the mechanoreceptors possess large diameter myelinated afferents (Aβ fibres) (Aminoff, 1998). RA units with small receptive fields (hair and field units) seem to be common on the dorsum of the hand (Edin & Abbs, 1991) and have also been found on the thigh (Edin, 2001). Vallbo and co-workers, and Olausson and co-workers, however, did not find any RA units with small receptive fields on the forearm. They found field units (RA) with large receptive fields but they were quite rare (Vallbo *et al.*, 1995; Olausson *et al.*, 2000). The receptive fields of SA1 afferents (Merkel) seem to be similar in size in different regions of hairy skin (Edin & Abbs, 1991; Vallbo *et al.*, 1995; Olausson *et al.*, 2000). SA2 afferents (Ruffini) are sensitive to skin stretch and have been identified in the forearm, the thigh and in the face (Nordin & Hagbarth, 1989; Vallbo *et al.*, 1995; Olausson *et al.*, 2000; Edin, 2001). Vallbo et al. (1995) suggested

that the skin of the forearm probably is more representative of the hairy skin covering the main part of the extremities and the trunk, whereas the face and the dorsum of the hands may be regarded as specialized sensory regions with some unique innervation features. Edin (2001) on the other hand suggested that each skin area in humans has its own unique characteristics.

Olausson and co-workers suggested that SA1 afferents and field units have the capacity to signal spatiotemporal information since they respond to probe movements within spatially well-defined receptive fields. The contribution from the field afferents is probably minor, since they innervate the skin less densely and have large, irregular, receptive fields (Vallbo *et al.*, 1995; Olausson *et al.*, 2000). The SA2 afferents are spontaneously active and have been reported to decrease their firing rate when a probe that causes friction approaches the receptor (unloading of the receptor) and increase their firing rate when the probe moves away from the receptor (stretching of the receptor). Hence, SA2 units may signal friction induced changes in skin stretch. A single SA2 unit may signal if a probe is moving towards or away from the receptor, but not the direction of probe movement *per se.* On the other hand the response from a population of SA2 units should be able to provide information for direction discrimination from a stimulus that induces changes in skin stretch by friction (Olausson *et al.*, 2000).

The hairy skin is also innervated by low-threshold mechanoreceptive C-afferents, proposed to signal pleasant touch (Vallbo *et al.*, 1993; Vallbo *et al.*, 1999; Olausson *et al.*, 2002). These C tactile afferents are unlikely to be involved in spatial discrimination of mechanical stimuli partly due to their unique receptor response properties. The C tactile afferents are easily fatigued when subjected to repetitive stimuli, they respond poorly to rapid moving stimuli and have highly non-uniform receptive fields (Wessberg *et al.*, 2003).

Electrophysiological studies of the somatosensory cortex

Studies of the underlying peripheral mechanisms for TDD have also inspired to electrophysiological analyses of neural activity in the cortex of monkeys. Studies of moving stimuli across both the glabrous and hairy skin with recordings in both S1 and S2 have been undertaken (Werner & Whitsel, 1968; Whitsel *et al.*, 1969; Whitsel *et al.*, 1972; Hyvarinen & Poranen, 1978; Costanzo & Gardner, 1980; Essick & Whitsel, 1985b, a; Warren *et al.*, 1986). They all report that the neurons in S1 fire more vigorously for movements in certain

directions. This directional preference did not seem to depend on asymmetries in patterns of skin stretching since it was observed for low-friction stimuli such as a rolling wheel with surface gratings (Warren *et al.*, 1986). In addition, neurons with cutaneous receptive fields that are direction selective have been found in the parietal association cortex in monkeys (Sakata *et al.*, 1973; Mountcastle *et al.*, 1975; Hyvarinen & Poranen, 1978). Whitsel et al. (1969) reported that there are neurons in S2 that respond more vigorously to tactile motion compared to stationary stimulation. The authors also pointed out that neurons in S2 often have bilateral receptive fields, in contrast to neurons in S1 that have contralateral receptive fields. Hyvärinen and Poranen (1978) described that they found neurons in S1 that were not activated by skin stretch in different directions but by spatiotemporal movement along the skin.

OBJECTIVE

The ability to determine the direction of an object's motion across the skin seems to be an important component of somatosensory function. The peripheral mechanisms of tactile direction discrimination, TDD, in human hairy skin have been extensively explored in our laboratory with psychophysical and electrophysiological methodology. Along with studies of the peripheral mechanisms we have also studied the cerebral processing of TDD in hemispherectomized patients as well as the coupling between TDD and postural control. The clinical TDD test is a routine method at the Department of Clinical Neurophysiology at Sahlgrenska University Hospital, Gothenburg. It is not clear, however, how useful the TDD test is in comparison to the often recommended test of vibration detection. Our knowledge about TDD processing at the supraspinal level is still limited, and such knowledge would improve the clinical value of the TDD test.

Specific aims

This thesis aspired to answer the following questions:

1. How does the clinical TDD test compare to vibration detection in detecting diabetic neuropathy? (**Paper I**)

2. What are the cortical patterns of fMRI activity during TDD based on skin stretch information in healthy subjects? (**Paper II**)

3. What are the cortical patterns of fMRI activity during TDD based on skin stretch information in a patient with a dorsal column lesion? (**Paper III**)

4. What are the cortical patterns of fMRI activity during TDD based on spatiotemporal information in healthy subjects? (**Paper IV**)

METHODOLOGICAL CONSIDERATIONS

In **Paper I** the clinical TDD test was compared with vibration detection in a group of patients with diabetes mellitus type 1. In **Paper II** and **III** the cortical processing of TDD based on skin stretch cues was studied with fMRI in a group of healthy subjects and in a patient, R.A., with a unilateral disturbance in skin stretch TDD following a spinal cord lesion. **Paper IV** investigated the cortical processing of TDD based on spatiotemporal cues in a group of healthy subjects.

The studies were approved by the local ethics committee of the medical faculty, University of Gothenburg, Sweden and were performed according to the Declaration of Helsinki. The declaration emphasizes the subject's right to terminate his or her participation at any time without stating any reason. Signed informed consent was obtained from each subject. Reimbursement was provided at SEK 200 per hour to the healthy subjects, and the patients were provided reimbursement for their travel costs to and from the laboratory.

PAPER I

Patients

We investigated 43 patients with type 1 diabetic neuropathy. The patients were evaluated in two steps before inclusion in the study. In the first evaluation the patients were examined by a senior consultant in internal medicine. The examination included assessment of symptoms of numbness, dysesthesia, allodynia, paresthesia, and spontaneous pain, as well as tendon reflexes, perception of touch, pinprick, vibration, temperature, and joint movements. The inclusion criteria were body mass index less than 30 kg/m2, duration of type 1 diabetes > 5 years, glycosylated haemoglobin (HbA1c) < 12% and clinical signs and symptoms indicating neuropathy. In the second evaluation the patients were examined with electrodiagnostics (i.e., neurography), temperature detection and heart rate variability. To be included in the study the patients needed to have at least one pathological test result in the second evaluation. Exclusion criteria were neuropathy or signs of nerve dysfunction unrelated to type 1 diabetes, amputation or wounds in the lower limbs that hindered neurological or neurophysiological examination, unstable glucose control as clinically judged, and pharmacological treatment unrelated to diabetes that may influence nerve function.

Clinical method for tactile direction discrimination

The clinical quantitative test of TDD has been used at the Department of Clinical Neurophysiology, Sahlgrenska University Hospital for about ten years (Olausson *et al.*, 1997). The clinical TDD test was performed with a hand-held stimulator (Fig. 1) with a contact surface that consisted of a halfcylinder (diameter 4 mm, length 15 mm) covered by fine woven fabric (Leukoplast, Hamburg, Germany). The stimulation was made on the dorsum of the foot, halfway between the toes and ankle with a vertical load of 16 g. The stimulator was moved with a speed 1 cm/s. We used a two-alternative forced-choice method (Sekuler *et al.*, 1973), and the stimulator was moved over a predetermined distance in either proximal or distal direction in a pseudorandom order (Durup, 1967). We marked the stimulation area with parallel lines at 3 mm intervals with a rubber stamp and the stimuli were distributed randomly over this 100 mm marked area (Fig. 2). The participants were instructed to have their eyes closed and verbally report the direction "up" or "down" of the movement. The test started with motion over a distance of 18 mm and varied between 3, 6, 18, 32, 56 and 100 mm dependent on the answers from the participant. If three correct responses were delivered in a sequence the stimulation distance was shortened, and if a response was incorrect the following stimulation distance was lengthened. The recording was made according to a protocol (Fig. 3) where answers were marked in a way to provide a response profile area, RPA, in the end, which expressed the proficiency of the TDD test.

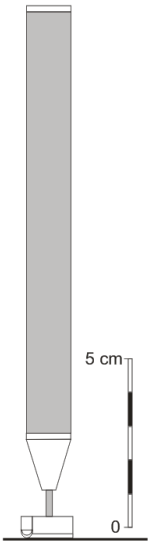

Figure 1. Hand-held stimulator for tactile direction discrimination.

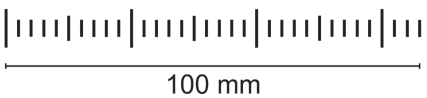

Figure 2. A 100 mm distance was marked with a rubber stamp on the skin. The distance between the parallel lines are 3 mm.

In a subgroup of nine randomly chosen patients we re-examined the TDD test, to study the reproducibility of the test.

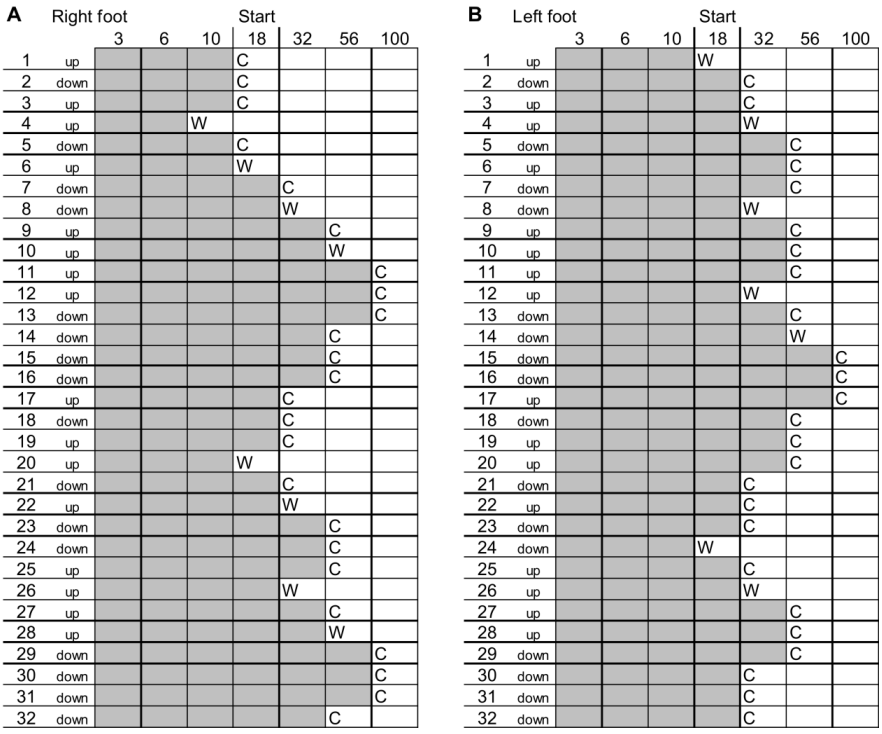

Figure 3. Protocol for the clinical tactile direction discrimination (TDD) test. (A, B) Abnormal TDD test results from a patient (no 1006, cf. Fig 3, paper I) with diabetic neuropathy. Test results for 32 trials on the dorsum of the right (A) and left (B) foot. Available stimulation distances were 3, 6, 10, 18, 32, 56 or 100 mm. Up refers to stimulations in proximal direction, down to stimulations in distal direction. C, correct response; W, wrong response. Shaded boxes indicate the response profile areas (RPAs) which were 143 for the right foot and 146 for the left foot. Abnormal TDD = RPA value > 74.

Clinical method for vibration detection

In addition to the clinical TDD test, thresholds for vibration detection were measured bilaterally on the dorsum of the feet, over the first metatarsal with a vibrameter (Medoc TSA 2001, Ramat Yishai, Israel). Vibration detection is widely used as a clinical tool and has been recommended as a standard method for quantitative testing of diabetic neuropathy (Olaleye *et al.*, 2001; Perkins *et al.*, 2001; Dimitrakoudis & Bril, 2002). The threshold amplitude was determined using a constant probe pressure of 1.2 N at a vibration frequency of 100 Hz. The amplitude was automatically increased from 0 until the patient reported a sensation by pressing a button. The vibration stimuli were repeated six times on each foot.

Statistical considerations

In **Paper I** all statistical calculations were done with SPSS (12.0.1 for Windows, SPSS Inc, Chicago, IL, USA). Test result ≥ 2 standard deviation (SD) outside mean values in healthy subjects were considered abnormal. We calculated z-scores as

(measured value – reference value)/SD

The sensitivity was calculated by dividing the number of patients assessed as abnormal in each test with the total number of patients included in the test:

(n abnormal patients)/(n tested patients)

To see if there was any significant difference between TDD test and vibration detection in detecting diabetic neuropathy we did a one sided two sample z-test by the following equation

$$z = \frac{p_1 - p_2}{\sqrt{p(1-p)(1/n_1 + 1/n_2)}}, \qquad \text{where} \qquad p = \frac{n_1 p_1 + n_2 p_2}{n_1 + n_2}$$

where p_1 and p_2 are the proportions of the two samples, and n_1 and n_2 are the samples for the two types of tests.

PAPER II-IV

Functional magnetic resonance imaging, fMRI

fMRI has over the past two decades become one of the most important tools in neuroscientific research to study the operational organization of the human brain during cognitive, perceptual, sensory and motor tasks. This non-invasive technique, which uses the oxygenation level of the blood in the brain as an intrinsic contrast, is based on magnetic resonance imaging, MRI. fMRI uses a standard MR scanner with scanning protocols sensitive for changes in blood oxygenation level. The underlying signal in MRI comes from hydrogen atoms in water in the body. When you put a person inside the powerful magnetic field of the MR scanner, the hydrogen nuclei, which are slightly magnetic, give rise to a small net magnetization. This net magnetization starts to rotate in the magnetic field and its dynamics can be manipulated by exposing it to radio frequency pulses in resonance with the rotation. The measured MR signals are small currents induced in pick up coils by the rotating magnetization by means of magnetic induction. Since tissues have different local magnetic environment, the temporal dynamics of the hydrogen and thus the MR signal differs and give

rise to contrasts in the produced images. Commonly the MRI technique is used to produce detailed images of the human body, but is also used to study for example blood flow by measuring physiological changes over time (Buxton, 2002).

The far most commonly used method to study neural activity in fMRI is the blood oxygenation level dependant (BOLD) contrast (Ogawa *et al.*, 1990; Ogawa *et al.*, 1992). The physiological changes during brain activation are complex, but one main factor that affects the MR signal is the concentration of oxygen in the blood. The physical basis of BOLD contrast is oxygenation-dependent magnetic susceptibility of haemoglobin (Bandettini & Ungerleider, 2001; Arthurs & Boniface, 2002). When neurons are activated, localized increases in blood flow increase blood oxygenation. The oxygen is carried by the haemoglobin that contains ferromagnetic iron atoms. In oxygenated haemoglobin the iron is shielded by the oxygen whereas it is unshielded in deoxygenated haemoglobin. The effect of the unshielded iron is an increase in the magnetic susceptibility of the blood, which leads to a decreased T2* MR signal. However, during neural activity, the arterial blood flow, with the oxygenated haemoglobin, increases more than the oxygen consumption. This results in a relatively lower concentration of deoxyhaemoglobin and a slight increase in the T2* MR signal (Bandettini & Ungerleider, 2001; Buxton, 2002). The functional scans are collected using a BOLD protocol with a T2*-weighted gradient echo, echo-planar imaging sequence (TR, 3.5; TE 51 ms; flip angle, 90˚ in this thesis). The BOLD signal is delayed and reaches a plateau about 6 seconds after onset of neural activity (Logothetis *et al.*, 2001). The haemodynamic response is considered to adequately reflect the neural activity down to a few millimetres scale (Kim *et al.*, 2004) and the signal changes of the BOLD response are only a few percent. Electrophysiological recordings of local field potentials in monkeys have been found to yield a better estimate of the haemodynamic response than multi-unit responses, suggesting that the BOLD contrast reflects the synaptic input and intracortical processing of a given area rather than its spiking output (Logothetis *et al.*, 2001; Goense & Logothetis, 2008). However, the relationship between neural activity and cerebral haemodynamics is still not thoroughly understood. Thus, when interpreting fMRI it is important to emphasize that absence of fMRI activation should be interpreted with caution and does not exclude stimulus-related neural activity in the examined region (Davis *et al.*, 1998; Disbrow *et al.*, 1998).

Since the fMRI signal is noisy and the signal changes to the neural activity are small, preprocessing and statistical analysis of the data is necessary to pull out the effects. To get enough statistical power, the stimuli have to be repeated a number of times during continuous

scanning. The stimuli are commonly presented in blocks of about 10-30 seconds alternating with blocks of rest (baseline) and a typical length of an fMRI time series can be ten minutes. In connection with the functional images a high resolution anatomical image is usually acquired during the experiment for anatomical identification of activated areas in the brain.

fMRI software

The fMRI analysis is done with one of several software packages available, some commercial and others freely available. The data preprocessing and analysis procedures are similar for the different packages. In this thesis, two packages were used: one developed at Montreal Neurological Institute, McGill University, Montreal (FMRISTAT, available at http://packages.bic.mni.mcgill.ca/ and http://www.math.mcgill.ca/keith/fmristat/) (**Paper II** and **III**) and one from Functional Imaging Laboratory, University College London, London (SPM8, available at http://www.fil.ion.ucl.ac.uk/spm/) (**Paper IV**).

Preprocessing of fMRI data

Standard preprocessing steps were applied to the data which include realignment, unwarping (only in **Paper IV**), spatial normalization and smoothing. Even if the subjects were well supported in order to avoid movements during scanning, small movements are unavoidable. In the realignment an algorithm aligns each volume to a reference volume in the time series, but though the realignment is merely a spatial co-registration, movement-related signal changes may still persist. To further reduce the so called "susceptibility-by-movement" interaction caused by the brain having different shape at different time points, we did unwarping to get an unwarped (to some true geometry) version of the time series. Since every brain differs in size and shape the brains are normalized to a standard anatomical space and put into the same coordinate system. This procedure allows the user to be able to compare results and perform group analyses. Finally the images are smoothed with a Gaussian kernel; typically with a filter width double the voxel (a volumetric pixel) size. Spatial smoothing is used to provide a degree of spatial integration. In this thesis we used a Gaussian full width at half maximum filter of 6 mm (**Paper II** and **III**) and 8 mm (**Paper IV**).

General linear model, GLM

The most common method used to analyze BOLD fMRI is within the framework of the general linear model, GLM. GLM is a powerful technique for analyzing BOLD data to estimate the strength and significance of activations (Buxton, 2002). The aim of the GLM is to explain the variation of the time course, in terms of a linear combination of explanatory variables and noise. The model is described by the following equation

$$Y_i = X_{ij}\beta_j + \varepsilon_i$$

where Y_i is the acquired time series data, X_{ij} the set of model functions (regressors), β_i the amplitudes (parameters) to be estimated and ε_i the residuals. Index *i* denotes the number of volumes in the time series and index *j* the number of explanatory variables or model functions. A fixed effect model was used to generalize the patient's activations (**Paper III**) and a random effect model to generalize healthy subject activation to the group level (**Paper II** and **IV**). The resulting activation maps were thresholded at $P < 0.05$ (**Paper II** and **III**) and at $P < 0.05$ family-wise error (FWE) (**Paper IV**). Directed searches were performed in several areas (**Paper II** and **III**). The threshold t values for directed searches were calculated within these regions of interests (ROIs) by taking into account the volume, the spatial smoothing and the degrees of freedom (cf. http://www.math.mcgill.ca/keith/fmristat/). A ROI analysis was performed in **Paper IV** using PickAtlas (Maldjian *et al.*, 2003).

Subjects

Paper II

In the first fMRI study we investigated 16 healthy subjects. Eight of the subjects (5 females/3 males), aged 21-31 years (mean, 25 years) was instructed to discriminate the direction of tangential skin pulls. Another 8 subjects (4 females/4 males), aged 23-27 years (mean, 25 years) were passive recipients of skin pulls. All 16 subjects were right handed according to a modified handedness inventory (Varney & Benton, 1975).

Paper III

In the second fMRI study we investigated a patient, R.A., with a traumatic spinal cord lesion. The patient is a right-handed previously neurologically healthy male who, at the age of 45 years, underwent surgery for a colon adenoma. During the epidural anaesthesia procedure, the anaesthesiologist accidently caused a spinal cord lesion with the syringe needle. An MR examination two weeks after the injury revealed a 12 mm long and 2 mm wide lesion (Fig. 4) at the level of Th XI-XII dorsolaterally to the right of the centre of the medulla. One month after surgery a neurophysiological examination was performed. The examination showed normal EMG, and normal neurography. Sensory evoked potentials (SEPs) for tibial nerve and dermatome (L4, L5 and S1) stimulations were within the normal range (within 2 SD, of locally determined normal values). However, the tibial SEP latencies for the unaffected (left) foot (N1=39.1 ms) were slightly shorter than for the affected (right) foot (N1= 43.0 ms). There were no consistent side differences for the dermatome SEPs. A second expanded neurophysiological examination seven months after the injury revealed that R.A.'s perception threshold for vibration on the affected foot was significantly elevated (> 2 SD above in-house normal values) and three times higher than on the unaffected foot.

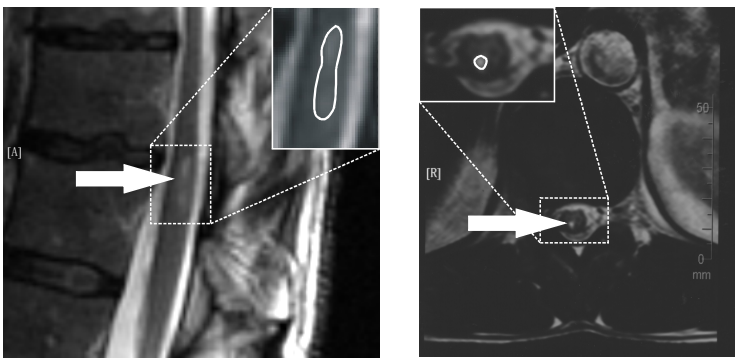

Figure 4. MR images of the patient R.A.s spinal cord lesion. The dotted square surrounds the lesion that is magnified and marked in the solid line square.

A. Projections in the sagittal plane. [A] = anterior.

B. Projection in the transverse plane. [R] = right.

Paper IV

In the third fMRI study 16 healthy subjects (8 females/8 males), aged 23-32 years (mean, 25.5 years) were investigated. All subjects were right handed according to a modified handedness inventory (Varney & Benton, 1975).

Experimental paradigms and setup

Paper II

In **Paper II** we investigated the cortical processing of skin stretch stimulations (i.e., skin stretch TDD). fMRI was performed using a 1.5 T Siemens Vision scanner (Siemens Medical System, Erlangen, Germany). Eight of the subjects were instructed to discriminate the direction (proximal or distal) of tangential skin pulls ("task experiment"). Another 8 subjects were passive recipients of skin pulls ("no task experiment"). The subjects were instructed to keep their eyes closed during scanning. All skin pull stimulations were delivered by means of a non-magnetic custom-built hydraulic system on the right lower leg (Fig. 5).

Task experiment

The subjects received long (2 mm) or short (0.8 mm) skin pulls either in distal or proximal direction, according to a modified pseudorandom protocol (Durup, 1967) and the testing was made with a two-alternative forced-choice procedure (Sekuler *et al.*, 1973). The subjects were instructed to indicate in which direction (proximal or distal) the skin was pulled by extending or flexing their left index finger. Each functional scan contained eight blocks of skin pull stimulations and eight blocks of rest. Each block consisted of a task instruction (3.5 s, one volume acquisition) followed by three identical skin pulls (10.5 s, three volumes acquisitions); after each skin pull the probe was moved back to its initial, resting position. Following the three skin pulls the subject was instructed to respond (3.5 s). Following the response was a rest block consisted of rest instruction (3.5 s) and rest (10.5 s) after the subject was instructed to extend or flex the left index finger as he/she liked (3.5 s). Instructions were given verbally through a loudspeaker. We performed six functional scans in each subject.

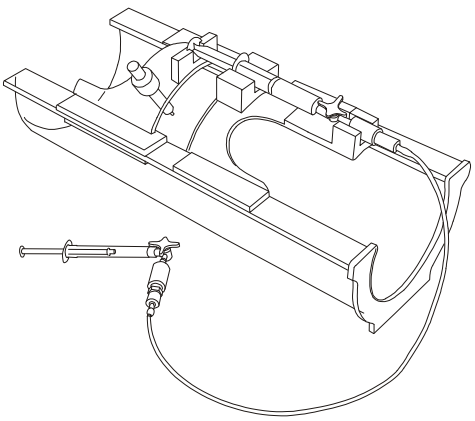

Figure 5. MR compatible, custom-built hydraulic system for skin pull stimulations.

One day prior to the scanning the subjects participated in an introductory experiment during which behavioral data were collected in the same way as during fMRI.

No task experiment

The subjects received skin pulls of one length (2 mm) in either proximal or distal direction. Each functional scan consisted of 20 blocks of skin pull stimulations and 20 blocks of rest. We performed three functional scans in each subject where a block consisted of three identical skin pulls (10.5 s) and rest (10.5 s).

Paper III

In the second fMRI study we investigated cortical processing of TDD based on skin pull stimulations (i.e., skin stretch TDD) further by examining a patient (R.A.) with a traumatic spinal cord lesion. MRI was performed using a 1.5 T Phillips Intera scanner (Eindhoven, Netherlands). R.A. was examined with basically the method used for task experiments with healthy subjects in **Paper II**. The differences were that only long (2 mm) skin pulls were applied, and that R.A. had his eyes opened, fixated a point on a screen and indicated the stimulus direction by pressing a button. All skin pull stimulations were delivered by means of a non-magnetic custom-built hydraulic system on the right and left lower leg (Fig. 4). Each functional scan contained 16 blocks of skin pull stimulations and 16 blocks of rest. We performed three functional scans on each of the patient's legs (on different days). The stimulation block consisted of three identical skin pulls (10.5 s) and after each skin pull the probe was moved back to its initial, resting position. Following the three skin pulls the fixation cross changed into arrows so the patient could indicate in which direction the stimulation was done by pressing on one of two buttons on a response pad with the left thumb (3.5 s). Following the stimulation there was a rest block (10.5 s). Before the first scanning session R.A. participated in an introductory experiment where behavioral data were collected in the same way as during fMRI.

Single subject fMRI data from seven healthy subjects, previously examined with a similar protocol (**Paper II** task experiment), were revisited using directed searches with respect to areas uniquely activated by TDD on R.A.'s unaffected but not on his affected leg.

Paper IV

In the third fMRI study we investigated the cortical processing of TDD based on spatiotemporal cues (rolling a wheel on the right thigh) in a group of 16 healthy subjects. MRI was performed using a 1.5 T Phillips Intera scanner (Eindhoven, Netherlands). The subjects

were instructed to determine the initial distal or proximal movement direction of the stimulus. The setup and paradigm was similar to the one in **Paper III**. The low friction stimulations were delivered by means of a wheel (diameter 2 cm, width 1.5 cm and weight 20g, Fig. 6) on the right thigh. The wheel was rolled manually, 35 mm in distal or proximal direction and back to the initial position. The stimulation load was constant during the whole experiment and the same as the weight of the stimulator (20 g). Subjects indicated movement direction by pushing with their left thumb on one of two buttons on a fibre optic response pad.

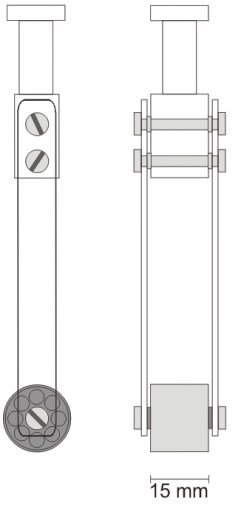

Figure 6. MR compatible stimulator for spatiotemporal tactile direction discrimination.

RESULTS AND DISCUSSION

PAPER I

Tactile direction discrimination

Twenty-six of the 43 patients had RPA values > 2 SD above the reference value (12 unilateral and 14 bilateral). The mean RPA from the clinical TDD testing in the 43 patients was 70 (SD 38, Z-score 1.8), which shows that they had severe difficulties in judging the direction of the movement. Nevertheless all patients reported a touch sensation during the TDD testing. The TDD test had a sensitivity of 0.60, i.e., detected abnormality in 60% of the patients diagnosed with mild diabetic neuropathy. Through the inclusion evaluation we were able to classify 16 of the 43 patients into an electrodiagnostically positive group, where they had abnormal neurography in at least both sural nerves or one sural and one peroneal nerve. Eleven patients of the electrodiagnostically positive group had abnormal values of the TDD test (3 unilateral and 8 bilateral) with a mean RPA of 87 (SD 36, Z-score 3.3). In this electrodiagnostically positive group the sensitivity for the TDD test was 0.69.

The clinical TDD test has a good reproducibility shown by the high degree of linear correlation (r = 0.87) from the test-retest examinations of nine patients. The mean RPA was 84 day one, and 76 day two. For vibration detection and heart rate variability, mediocre or good reproducibility has been reported in diabetic patients (Valensi *et al.*, 1993).

Vibration detection

Twenty of the 43 patients had abnormal vibration detection (8 unilateral and 12 bilateral). The mean amplitude for vibration detection was 11.7 μm (SD 9.6, Z-score 2.2). Vibration detection had a sensitivity of 0.46 in the patient group. Nine patients of the electrodiagnostically positive group had abnormal vibration detection (4 unilateral and 5 bilateral) with a mean vibration detection threshold of 15.9 μm (SD 11.7, Z-score 3.2). In the electrodiagnostically positive group the sensitivity was 0.56.

Tactile direction discrimination and vibration detection

All patients had clinical signs and symptoms indicating neuropathy, and abnormal test results in at least one of neurography, heart rate variability and temperature detection. Among these,

26 patients had abnormal test results from the TDD test and 17 had normal TDD test results. Twenty of the 43 patients had abnormal vibration detection and 23 had normal vibration detection. This shows that normal results from the TDD test or normal vibration detection does not exclude diabetic neuropathy. Diabetic neuropathy can engage thin nerve fibres, thick nerve fibres or both. We have microneurography data showing that TDD is signalled mainly by SA1 and SA2 receptors with Aβ (myelinated) afferents (Olausson *et al.*, 2000). Vibration detection is mainly signalled by PC receptors with Aβ afferents (Aminoff, 1998). Therefore, the clinical TDD test and vibration detection will be normal in patients with a pure thin fibre diabetic neuropathy, which might explain that the abnormality was undetected in some patients.

In the patient group the TDD test in combination with temperature detection, i.e. cold and warm sensation detected neuropathy in as much as 38 out of 43 patients. The TDD test alone detected 26 patients and temperature detection 32 patients. Twenty-four of the patients had abnormal nerve conduction or response amplitude in at least one of the tested nerves, and it seems most likely that more patients would have abnormal neurography results if F-waves and additional sensory and motor nerves had been examined. F-waves were not examined to limit the examination time. The TDD test-results were more similar to sural amplitude than to conduction velocity (CV). CV reflects degree of myelination whereas amplitude reflects number of functioning afferents suggesting that the TDD test is especially sensitive to reduction of number of nerve fibres. As mentioned above, TDD is mainly signalled by SA1 and SA2 afferents and is partly dependent on skin stretch information, and it seems possible that a reduction of number of nerve fibres reduces the ability of the CNS to interpret direction specific changes in patterns of skin stretch.

The study showed that testing for TDD was equally sensitive as testing for vibration detection in detecting diabetic neuropathy in this group of patients with mild diabetic neuropathy. The TDD test had a higher sensitivity (0.60) than vibration detection, (0.46). However, the statistical test of the two proportions did not show any significant difference between the TDD test and vibration detection ($P = 0.14$). Vibration detection involves reaction time as well as subjective criterion of what is to be considered as vibration and not static pressure. These factors are likely to produce response variability that is unrelated to peripheral nervous function. Vibration detection also requires sophisticated and expensive equipment in comparison to the TDD test which is easy-to-use, rapid and inexpensive.

PAPER II

Psychophysics

The psychophysical data from the introductory experiment on the day before scanning showed that subjects were 86% ± 16% (mean and SD) correct in determining the direction of the skin pulls. During scanning subjects were 92% ± 11% correct. As mentioned before, these results are in agreement with previous studies showing that healthy subjects can determine the direction of skin pulls as short as 0.13 mm on the hairy skin (Gould *et al.*, 1979; Olausson *et al.*, 1998). There was no significant difference between the results obtained before or during scanning, nor for results for long and short skin pulls ($P > 0.05$, Student's t-test). Therefore only long skin pull stimulations were used in the no task experiment.

fMRI

The study consisted of two experiments; a task experiment where subjects were instructed to focus on and respond to the direction of the stimulus; and a no task experiment where they were passive recipients of the skin pulling. Both task and no task experiments showed cortical activations in the S2 area for all subjects. In the task experiment a closer examination of S2 on a single subject level showed that all the seven subjects had the highest peak of activation in the contralateral left hemisphere in the superficial and caudal part belonging to the opercular parietal (OP) area 1. In the no task experiment, on a single subject level, the most prominent activation was either in OP1 or in OP4.

There was no significant S1 activation in the task experiment, either on a group level or for individual subjects. In the no task experiment one subject had a contralateral S1 activation. The lack of observable S1 activation needs to be interpreted with caution since the absence of a BOLD response does not logically exclude all covert stimulus related neural activity. Nevertheless, it is possible that neurons in S1 mainly process spatiotemporal information (Hyvarinen & Poranen, 1978; Gardner *et al.*, 1992; Essick & Whitsel, 1993; Bremmer *et al.*, 2001; Hagen *et al.*, 2002) whereas neurons in S2 process both spatiotemporal information and information about skin stretch.

The S2 region is frequently activated in studies with moving tactile stimuli (Burton *et al.*, 1999; Bodegard *et al.*, 2000; Disbrow *et al.*, 2000; Downar *et al.*, 2000; Bremmer *et al.*, 2001; Olausson *et al.*, 2001; Olausson *et al.*, 2002). OP1 corresponds best to S2 in the

monkey (Eickhoff *et al.*, 2006) and is regarded as a somatosensory "perceptive" area strongly interconnected with the inferior parietal cortex (Disbrow *et al.*, 2003; Eickhoff *et al.*, 2010).

All subjects in both the task and no task experiment had significant peak activations in the ipsilateral (right) S2. The functional significance of this activation is unclear. Epileptic, therapeutically commissurotomized, or hemispherectomized patients, however, have been found to possess disconnected or single hemispheres contralateral to stimulation that are sufficient for apparently normal direction discrimination.

A contrast between the two groups, task vs. no task did not show any significant activation. However, a cluster of voxels in the contralateral left prefrontal cortex (i.e. DLPFC, Brodmann area, BA9) was close to being significantly activated. This area processes decision-relevant information about tactile stimulation (Pleger *et al.*, 2006), and may thus be involved in the tactile decision making involved in the task experiment. This area was also found to be activated by spatiotemporal TDD in **Paper IV**.

PAPER III

Psychophysics

In the introductory, psychophysical experiment, before scanning the patient R.A. was 94% correct in determining the direction of the skin pulls on the unaffected (left) leg. During fMRI R.A. was 95% correct on his unaffected leg. The results were within the range of healthy subjects in **Paper II**. Before scanning R.A was 56% correct (chance level 50%) on the affected (right) leg, or almost 2 SD worse than mean results for healthy subjects (cf. **Paper II**). During scanning he was 63% correct (significantly above chance level $P < 0.05$ binomial distribution, n=48) which was almost 3 SD worse than the mean results from the healthy subjects.

fMRI

We studied the cortical processing of TDD based on skin stretch cues on the patient R.A.'s both legs. TDD for the affected as well as the unaffected leg during fMRI showed activations in the contralateral OP1 area of S2 irrespective of TDD performance. The location of the S2 OP1 peak was in the range of the *x*, *y* and *z* coordinates in healthy subjects (**Paper II**). The S2

OP1 activation for the patient's affected leg could indicate that the patients did not have a complete dorsal column lesion and that some information ascends in the lesioned dorsal column. Another possibility is that the S2 OP1 activation from the patient's affected leg originates from signalling in afferents that cross over on the segmental level, travel through the anterior spinothalamic tract and up to S2 (Stevens *et al.*, 1993). Thus, the S2 OP1 activation for the affected leg may represent a more general aspect of tactile processing as R.A. reported perceiving the stimulus on the paretic side but failed to report its movement direction.

TDD for R.A.s unaffected (left) leg evoked cortical activations in several additional areas that included ipsilateral S2 OP1, bilateral DLPFC (BA9), bilateral AIC and right visual cortex. TDD for R.A.s affected leg also activated several cortical areas that in addition to contralateral S2 OP1 also included ipsilateral S2 OP1. However, DLPFC and AIC were only activated for the unaffected leg.

Revisiting healthy subjects' individual fMRI data for the task experiment (**Paper II**) revealed that 7 subjects out of 7 had cortical activations in DLPFC and 7 subjects out of 7 had cortical activations in AIC. A revisit of healthy subject's individual fMRI data for the no task experiment (**Paper II**) revealed that 1 subject out of 8 had cortical activation in DLPFC and 4 subjects out of 8 had cortical activations in AIC.

The DLPFC has been reported to be involved in sensory decision making (Heekeren *et al.*, 2006) and also to correlate to the accuracy of perceptual decisions (Pleger *et al.*, 2006). We found activation in the DLPFC for TDD on the patient's unaffected leg where he was able to perceive the difference in movement direction. Further, we found activation of the DLPFC in healthy subjects during TDD but not during skin pull stimulation *per se*. We therefore suggest that DLPFC is involved in tactile decision making based on proper tactile input.

AIC has been reported to be involved in stimulus attention (Li Hegner *et al.*, 2007; Albanese *et al.*, 2009; Craig, 2009). In the no task experiment (**Paper II**), where the subjects were instructed to concentrate on the skin pull stimulation without any explicit instructions to focus on the direction of the stimulus, 4 subjects out of 8 had an AIC activation. R.A. had AIC activation for the unaffected but not the affected leg. Thus it seems likely that AIC activation represents stimulus attention.

TDD based on skin stretch cues did not evoke any S1 activation neither for R.A. nor for the healthy subjects (**Paper II**, task experiment).

PAPER IV

Psychophysics

The psychophysical data collected during fMRI revealed that the subjects were on average 98% ± 2% (mean and SD) correct in determining the direction of the initial stimulus movement of 35 mm. These results are consistent with previous studies of spatiotemporal TDD that showed a minimal stimulation distance for accurate direction discrimination of 8 mm (Norrsell & Olausson, 1994; Backlund Wasling *et al.*, 2005).

fMRI

The spatiotemporal TDD stimuli evoked cortical activations in several areas including contralateral left medial S1, bilateral posterior IC, bilateral S2 OP1 and bilateral AIC. An ROI analysis revealed bilateral activations in DLPFC. Spatiotemporal TDD evoked activations in S1 and posterior IC, in contrast to skin stretch TDD. Observations from electrophysiological studies in monkeys showed that directional sensitive neurons in S1 were not activated by skin stretch but rather by spatiotemporal movement along the skin surface (Hyvarinen & Poranen, 1978). Our research group has previously shown through microneurography studies, that spatiotemporal TDD is mainly signalled by SA1 afferents (Olausson *et al.*, 2000) and that skin stretch TDD mainly is signalled by SA2 afferents (Norrsell & Olausson, 1994; Olausson *et al.*, 1998; Olausson *et al.*, 2000). It is also noteworthy that microstimulation of SA2 afferents does not generate a percept in contrast to microstimulation of SA1 afferents (Ochoa & Torebjork, 1983; Schady & Torebjork, 1983; Vallbo & Johansson, 1984; Macefield *et al.*, 1990). This may indicate that these two afferent types have different CNS projections.

The activation of posterior IC may reflect an activation of peripheral C tactile afferents, which respond well to slow movements over their receptive field (Löken *et al.*, 2009) and have projections to the posterior IC (Olausson *et al.*, 2002; Björnsdotter *et al.*, 2009).

The present study of spatiotemporal TDD suggests that the cortical processing is similar to that of skin stretch TDD and includes S2 OP1, AIC and DLPFC. In addition, spatiotemporal TDD activated S1 and posterior IC.

GENERAL DISCUSSION

Tactile direction discrimination, TDD, i.e. the ability to tell the direction of an object's movement across the skin, is used as a clinical method to quantify tactile function of hairy skin, i.e. the clinical TDD test. TDD is signalled by two types of peripheral afferents and use parallel processing of skin stretch information and spatiotemporal information, signalled by large diameter myelinated afferents. Skin stretch TDD is mainly signalled by SA2 (Ruffini) afferents. Spatiotemporal TDD is mainly signalled by SA1 (Merkel) afferents and field (RA) units (Vallbo *et al.*, 1995; Olausson *et al.*, 2000). TDD has been found to depend upon an intact dorsal column, since patients with dorsal column lesions loose the TDD capacity (Foerster, 1936; Wall & Noordenbos, 1977; Hankey & Edis, 1989). TDD is dependent upon processing in the contralateral hemisphere since hemispherectomized patients have severely disturbed TDD on their paretic body half (Olausson *et al.*, 2001; Backlund *et al.*, 2005) and commissurotomized "split-brain" patients can only verbally report the TDD on their right body half (Norrsell, 1973).

In these studies we have investigated clinical applications and cortical mechanisms of TDD. The clinical TDD test was evaluated with regard to reproducibility and compared to vibration detection to see how effectively the two methods discovered diabetic neuropathy in a group of patients with type 1 diabetes. The results showed that the clinical TDD test had similar sensitivity as vibration detection in detecting diabetic neuropathy, and the test-retest showed that the TDD test had high reproducibility between different examination days. The clinical TDD test does not require any expensive equipment, in contrast to vibration detection. The TDD test is also a rapid test to both perform and learn.

Twenty-six of the 43 patients had abnormal results from the TDD test which means that the TDD test solely, is not sufficient to diagnose diabetic neuropathy. This problem is not particular for the TDD test as for example vibration detection diagnosed 20, temperature detection diagnosed 33 and neurography diagnosed 23 of the 43 patients. This indicates need for a combination of tests to be able to diagnose patients with diabetic neuropathy. Diabetic neuropathy can involve only thin-fibres (unmyelinated), motor fibres (myelinated), sensory fibres (combination of unmyelinated and myelinated) or combinations of these. Therefore, in order to diagnose you need to combine tests that investigate all fibre-types. Neurography is the most common test for examination of large myelinated sensory and motor fibres at a clinical neurophysiology department, but these tests do not examine the most distally located

nerve receptors. A combination of the clinical TDD test, examining Aβ-fibres, and temperature detection (cold and warmth sensation), examining Aδ-fibres (thinly myelinated), and C-fibres (unmyelinated) detected 38 of the 43 patients in this study. Therefore, the TDD test together with temperature detection seems to be a preferable combination, for diagnosing diabetic neuropathy.

Knowing that TDD is signalled by parallel processing of skin stretch information and spatiotemporal information, we have studied the cortical mechanisms of both types of stimuli with fMRI. Skin stretch TDD activated a cortical network consisting of S2 OP1, DLPFC and AIC. Spatiotemporal TDD activated a similar network, and in addition S1 and posterior IC. Skin stretch TDD was first evaluated in a group of healthy subjects (**Paper II**), divided into two subgroups (i.e. task and no task experiment). The main finding from the task and no task experiment was a contralateral activation of S2, mainly in OP1. When R.A. performed the same skin stretch TDD task during fMRI, surprisingly, we found S2 OP1 activation from stimulation on both legs, despite his inability to discriminate the direction of the skin pull stimulations on his affected, right leg. There were differences, however, between the activation patterns following stimulation of R.A.'s unaffected and affected legs. Ipsilateral S2 OP1, bilateral DLPFC and bilateral AIC were activated from the unaffected leg, but not from the affected leg. A revisit to the healthy subjects' individual data in the task experiment in **Paper II** also revealed activations of AIC and DLPFC for skin stretch TDD.

The S2 OP1 activation from R.A.'s affected leg seems to represent a general aspect of tactile processing and not just the skin stretch TDD task since R.A. reported perceiving the stimulus on his affected side, but failed to report its movement direction.

DLPFC has been reported to be involved in working memory, (Curtis & D'Esposito, 2003) sensory decision making (Heekeren *et al.*, 2006), and the accuracy of perceptual decisions (Pleger *et al.*, 2006). We saw DLPFC activation when we contrasted results from task experiment with those from the no task experiment. This indicates that DLPFC is activated when subjects are evaluating the direction of a tactile stimulus but not during skin stretch stimulations alone. DLPFC was activated during skin stretch TDD on R.A.'s unaffected leg, but not on his affected leg where he was unable to tell the direction of skin pulls. Activation of DLPFC was also seen during spatiotemporal TDD. It seems like the DLPFC activation mainly reflects the sensory decision processing when based on proper tactile input. The TDD paradigm contains a memory task since the subjects have to remember

in which direction the stimulus is moved and had to indicate this a few seconds later. Our results, however, did not involve additional prefrontal and cingulate areas often seen activated by working memory operations (Budson & Price, 2005; Bledowski *et al.*, 2010). Although, it may also be argued that it may not be meaningful to separate DLPFC activation related to working memory from perceptual decision making since the TDD task involves both components (Bledowski *et al.*, 2010).

The TDD task demands the subject to attend to the stimulus and then indicate in which direction the stimulus was moved. We found activation in AIC when stimulating R.A.'s unaffected leg and in the healthy subjects in the task experiment (skin stretch TDD). In the no task experiment 4 subjects out of 8 showed AIC activation. In addition AIC activation was found in the study of spatiotemporal TDD. These findings, together with earlier studies (Li Hegner *et al.*, 2007; Albanese *et al.*, 2009; Craig, 2009) suggest that the AIC activation represents stimulus attention.

In contrast to skin stretch TDD, spatiotemporal TDD showed a contralateral S1 activation. Activation of S1 has earlier been reported for studies of tactile spatiotemporal information (Bremmer *et al.*, 2001). Further, in an electrophysiological study in monkeys it was shown that directional sensitive neurons in S1 were not activated by skin stretch, but rather by spatiotemporal movements along the skin surface (Hyvarinen & Poranen, 1978). The results from our studies of skin stretch and spatiotemporal TDD is in concordance with those earlier observations suggesting that there is a difference in cortical processing between skin stretch and spatiotemporal TDD. Further, to the best of our knowledge there are no studies available that indicate SA2 afferent projections to S1.

Most of the activations in the TDD studies are bilateral, despite the fact that earlier studies of hemispherectomized patients and commissurotomized ("split-brain") patients have show that the contralateral hemisphere is sufficient for TDD (Norrsell, 1973; Backlund *et al.*, 2005). The importance's of the ipsilateral activations are ambiguous. The ipsilateral activations can reflect a redundant function or else the examined patients in the above mentioned studies had congenital lesions and therefore their "healthy" hemisphere could have been subjected to plastic changes. Further, the frictional TDD test made on these patients was a simplified version of the clinical TDD test and possibly less able to detect subtle changes in TDD capacity.

The clinical TDD test is inexpensive, rapid and easy-to-learn, and has good reproducibility. The need for a simple test might be limited in specialized university hospitals where you can find a department of clinical neurophysiology that already has specialized equipment. However, in smaller hospitals and district health care centres it could very well provide an effective method to be used both for diagnosis and to follow the process of sensibility disorders in for example patients with mild diabetic neuropathy, in contrast to other methods as for example von Frey testing.

The clinical TDD test provides a sensitive clinical test for detection and following patients with disturbances in the peripheral and central nervous systems. Patients with poor TDD test results of the hairy skin (e.g. stroke patients) might benefit less from balance aids or bandages for joint stabilization. Many supportive bandages are not constructed to give mechanical support, but scrape against the skin as the limb and joint are moved to provide additional proprioceptive information through cutaneous afferents (Barrett *et al.*, 1991; Callaghan *et al.*, 2002).

With the TDD test we have developed a method for quantification of sensibility of hairy skin. The information processing has been thoroughly studied all the way from the peripheral afferents in the skin and up to the brain areas. The clinical TDD test does not require any sophisticated equipment and is easy to use.

Considering the distributed cortical network engaged by TDD, it is important for clinicians to consider that patients with lesions outside S1 can have sensibility disturbances, which might easily be detected through a TDD test where other tests fail.

CONCLUDING REMARKS

The main findings from this thesis are:

I. The clinical TDD test is equally sensitive as vibration detection for the detection of diabetic neuropathy.

II. The cortical network for skin stretch TDD processing and spatiotemporal TDD processing includes S2 OP1, DLPFC and AIC.

III. The cortical processing of skin stretch TDD and spatiotemporal TDD is similar, although the network for spatiotemporal TDD also includes S1 and posterior IC.

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