Zu den Auswirkungen taktiler Berührung bei Parkinson-Patienten

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Zusammenfassung
Hintergrund: Tactile Touch als Behandlungsmethode ist im Großen und Ganzen wissenschaftlich unerforscht. Patientinnen und Patienten nutzen in hohem Maße komplementär- und alternativmedizinische Behandlungsformen (CAM) außerhalb des pharmazeutischen Bereichs, insbesondere Patienten mit chronischen Erkrankungen. Die Darstellung und Auswertung der eigenen Linderungserfahrungen der Patientinnen und Patienten mit unterschiedlichen Behandlungsformen ist eine wichtige Aufgabe für das moderne Gesundheitswesen. Die Suche nach humoralen Substraten, die körperliche Stresserfahrungen widerspiegeln, ist ein Bereich, der wissenschaftliche Neugier weckt. Krankheiten, die das Gehirn betreffen, scheinen mit modernen Bildgebungs- und Labortechniken gründlich untersucht zu werden, aber es bleibt Unsicherheit, wie sich degenerative Prozesse auf hormonelle Sekretionsmuster auswirken, die durch Drüsen vermittelt werden, die sich im oder in der Nähe des zentralen Nervensystems befinden. Eine erhöhte Cortisolkonzentration wird häufig als Biomarker für Stress verwendet. Dieses Hormon wird ausgeschüttet und ist im Speichel messbar, und es gibt viele Hinweise auf seine Nützlichkeit als nicht-invasiver Test der Hypothalamus-Hypophysen-Achse (HPA)-Funktion, zu der es gehört.
Ziele: Es fehlt viel Wissen über die Auswirkungen komplementärer Behandlungsformen auf nicht-motorische Symptome bei Morbus Parkinson (PD). Basierend auf Patientenberichten wissen wir, dass Symptome wie chronische Schmerzen, Schlafstörungen und ein negativer Einfluss auf die Stimmung die gesundheitsbezogene Lebensqualität (HRQoL) beeinträchtigen. Ziel dieser Arbeit ist es, die kurz- und langfristigen Auswirkungen von zwei verschiedenen Formen komplementärer Behandlungen, Tactile Touch (TT) und Rest To Music (RTM), bei Parkinson-Patienten mit chronischen Schmerzen zu beschreiben, zu vergleichen und zu bewerten. Chronische Schmerzen sind definiert als das Auftreten von Schmerzen im Zusammenhang mit Parkinson an drei Tagen oder mehr pro Woche während mindestens drei Monaten vor der Aufnahme in die Studie. Endpunkte sind der Einfluss von TT und RTM auf nicht-motorische Symptome wie subjektive Schmerzerfahrungen und Schlafstörungen sowie die Auswirkungen von Interventionen auf die HRQoL. Weitere Ziele sind die Beschreibung der Funktion der HPA-Achse bei Parkinson mit und ohne Langzeitschmerzen und die Untersuchung der Auswirkungen von Interventionen auf die Cortisolkonzentration im Speichel als Surrogatmarker für Stress.
Methoden: Fünfundvierzig Patienten mit stabiler und gut definierter Parkinson-Erkrankung seit mehr als zwei Jahren und chronischen Schmerzen während mindestens drei Monaten wurden aus routinemäßigen Arztbesuchen an Standorten in Südschweden rekrutiert. Sie wurden blind randomisiert in TT (n=29) oder RTM (n=16) eingeteilt. Während der 34-wöchigen Studie wurde während der 34-wöchigen Studie viermal innerhalb von 24 Stunden (um 8 Uhr, 13 Uhr, 20 Uhr und 8 Uhr am nächsten Morgen) Cortisol im Speichel in einem Wattestäbchen entnommen. Darüber hinaus wurden bei zwei Gelegenheiten, beim ersten und beim achten Mal, Proben unmittelbar vor, unmittelbar nach und 30 Minuten nach dem Ende der Interventionen entnommen. Die Cortisolkonzentrationen wurden zur gleichen Zeit und im selben Labor mit einer gut etablierten radioimmunologischen Technik (Cortisol RIA I125) analysiert. Visuelle Analogskalen (VAS), Fragebögen zur Schmerzbeurteilung (Patient Evaluation Analysis, PEA), die Parkinson Disease Sleep Scale (PDSS) und die SF-36 (Swe.ver.1) zur Bewertung der HRQoL wurden während der Interventions- und Nachbeobachtungsperioden wiederholt verwendet. Um den Schweregrad der Parkinson-Krankheit zu messen, wurden die Unified Parkinson Disease Rating Scale I-IV (UPDRS I-IV) und die Hoehn&Yahr-Skala (H&Y) verwendet, und um die Medikations- und Medikamentenlisten der Teilnehmer zu verfolgen wurden während der Studie mehrfach abgeschlossen.

Ergebnisse: Die wichtigsten Ergebnisse der Studie sind: 1. Das tägliche Muster der Cortisolsekretion deutet auf eine normale HPA-Achsenfunktion bei Parkinson mit und ohne chronische Parkinson-bedingte Schmerzen hin; 2. Es werden signifikant erhöhte morgendliche Cortisolkonzentrationen im Vergleich zu denen in einer gesunden Referenzgruppe aus demselben Bereich festgestellt, die nach Alter und Geschlecht abgeglichen sind. 3. Es werden keine Auswirkungen auf die täglichen Cortisolkonzentrationen im Speichel beobachtet, die auf den Schweregrad der Parkinson zurückzuführen sind, der mit der Unified Parkinson Disease Rating Scale (UPDRS I-IV) gemessen wird. 4. Signifikant verringerte Cortisolkonzentrationen im Speichel werden nach Intervention mit TT und in geringerem Maße nach RTM gefunden, keine signifikanten Unterschiede zwischen den Gruppen; 5. Parkinson-bedingte Schmerzen gehen bei einem Drittel der Teilnehmer der Diagnose der Parkinson-Krankheit voraus und bei der Hälfte der Patienten sind sie während der gesamten Wachzeit vorhanden. 6. Polypharmazie ist weit verbreitet; Einem Viertel aller Teilnehmer werden Analgetika verschrieben, von denen Paracetamol am häufigsten vorkommt. Nur 1/3 berichten von einer Schmerzlinderung mit Analgetika. Fast alle (9/10) verwenden Medikamente gegen Angstzustände/Schlaflosigkeit und einer von fünf verwendet Antidepressiva; 7. Verschiedene Schmerzparameter werden in der kurzfristigen Nachsorge bei TT und RTM positiv beeinflusst. Eine signifikante Abnahme der Schmerzerfahrung (VAS) wird in der TT-Gruppe, aber nicht in der RTM-Gruppe in Woche 3 registriert. Insgesamt gab es eine signifikante Abnahme der Schmerzen, gemessen mit der VAS-Skala, sowohl bei TT als auch bei RTM vom Screening bis zur letzten Nachuntersuchung in Woche 34; 8. Der Schlaf, gemessen an der Parkinson-Schlafskala (PDSS), verbessert sich innerhalb der TT-Gruppe nach den ersten Behandlungen signifikant; Unterschiede zwischen den Gruppen erreichen keine Signifikanz auf dem Niveau von 0,05; und 9. Die HRQoL verbessert sich im Vergleich zu einer schwedischen gesunden Referenzpopulation (SF-36, Swe ver.) in beiden Gruppen, aber normale Werte der HRQoL werden nur in der kurzfristigen Nachbeobachtung in der TT-Gruppe erreicht.
Diskussion: CAM-Behandlungen mit TT und RTM haben in mehrfacher Hinsicht positive Effekte, insbesondere in der kurzfristigen Nachsorge. Es ist schwieriger, signifikante Unterschiede zwischen zwei Gruppen zu finden, wenn die positiven Effekte "innerhalb der Gruppe" in vielen Bereichen erheblich sind. Absolute Effekte werden durch relative Effekte ersetzt, da die Kontrollgruppe aktiv ist. Es fehlt an Langzeitwirkungen. Nur sehr wenige veröffentlichte CAM-Studien im Allgemeinen und insbesondere bei Parkinson werden mit einer so langen Nachbeobachtungszeit durchgeführt wie in der Parkitouch-Studie. Die Berücksichtigung weiterer Behandlungsarme, einschließlich "überhaupt keine Behandlung", und die Verwendung wiederkehrender kurzer Behandlungsperioden, um die nachgewiesenen kurzfristigen Effekte zu erleichtern, sollten in zukünftigen Studien berücksichtigt werden.
Schlussfolgerungen: Die Funktion der HPA-Achse bei Parkinson mit und ohne chronische Schmerzen scheint intakt zu sein. Es zeigt sich ein erhöhtes morgendliches Speichelcortisol. Parkinson mit chronischen Parkinson-bedingten Schmerzen hat negative Auswirkungen auf die HRQoL. Es werden Vorteile beider Behandlungsformen mit TT und RTM aufgezeigt, und zwar in unterschiedlicher Hinsicht in Bezug auf Schmerzen, Schlaf und HRQoL. Die positiven Kurzzeiteffekte in beiden Gruppen sind bei TT im Vergleich zu RTM nicht signifikant besser. Die Langzeitwirkungen sind spärlich.

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On the effects of Tactile Touch in Parkinson´s Disease patients

"THE PARKITOUCH STUDY"

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To my beloved family
Gerd, Martin, Magnus and Annika

“To Touch is to give life”
- Michelangelo, 1475 -1564.

“Music for wellbeing”

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ABSTRACT

Background

Tactile Touch as a treatment modality is, in broad terms, scientifically unexplored. Patients use Complementary and Alternative Medicine (CAM) forms of treatment outside the area of pharmaceuticals to a great extent, particularly patients suffering from chronic diseases. Delineating and evaluating patients' own experiences of alleviation using different treatment forms are important tasks for modern health services.

The search for humoral substrates that reflect bodily experiences of stress is an area that is attracting scientific curiosity. Diseases affecting the brain appear to be thoroughly investigated using modern imaging and laboratory techniques, but uncertainty remains concerning how degenerative processes affect hormonal secretion patterns mediated by glands located in or near the central nervous system.

An elevated cortisol concentration is commonly used as a biomarker of stress. This hormone is secreted and is measurable in saliva, and there is much evidence concerning its usefulness as a non invasive test of the Hypothalamic-Pituitary-Axis (HPA) function, of which it is a part.

Aims

Much knowledge is lacking with respect to the effects of complementary treatment forms on non motor symptoms in Parkinson´s Disease (PD). Based on patients' reports, we know that symptoms such as chronic pain, disruption of sleep and a negative impact on mood affect Health Related Quality of Life (HRQoL). This thesis aims to describe, compare and evaluate short- and long-term effects of two different forms of complementary treatments, Tactile Touch (TT) and Rest To Music (RTM) in PD patients with chronic pain. Chronic pain is defined as the occurrence of pain related to PD for three days or more per week during at least three months prior to inclusion in the study. Outcome measures are the impact of TT and RTM on non motor symptoms such as subjective pain experiences and disturbed sleeping pattern, as well as the effects of interventions on HRQoL. Other aims are to describe the HPA-axis function in PD with and without longstanding pain and to study the effects of interventions on salivary cortisol concentrations as a surrogate marker for stress.

Methods

Forty-five patients with stable and well defined PD for more than two years and with chronic pain during at least three months were recruited from routine health care visits at sites in Southern Sweden. They were blindly randomized to TT (n=29) or RTM (n=16). Salivary cortisol was sampled in a cotton swab four times during 24 hours (at 8am, 1pm, 8pm and 8am the next morning) at five occasions during the 34-week-long study. In addition, samples were taken immediately before, immediately after, and 30´after the end of the interventions at two occasions, at the first and at the eighth occasion. The cortisol concentrations were analyzed at the same time and at the same laboratory with a well established radioimmunological technique (Cortisol RIA ^{I125}). Visual Analogue Scales (*VAS*), Questionnaires for pain evaluation *(Patient Evaluation Analysis, PEA),* the Parkinson Disease Sleep Scale (*PDSS*), and the *SF-36 (Swe.ver.1)* for evaluation of HRQoL were repeatedly used during the intervention and follow-

up periods. To measure severity of PD, the Unified Parkinson Disease Rating Scale I – IV, (*UPDRS I-IV*) and the Hoehn&Yahr (*H&Y*) scales were used, and to follow participants' medications, *drug lists* were completed at several occasions during the study.

Results

The main findings of the study are:
1. The diurnal pattern of cortisol secretion indicates a normal HPA-axis function in PD with and without chronic PD-related pain.

2. Significantly elevated morning cortisol concentrations, compared to those in a healthy reference group from the same area matched by age and gender, are detected.

3. No effects on diurnal salivary cortisol concentrations are seen that are due to the severity of PD measured by the Unified Parkinson Disease Rating Scale (UPDRS I-IV).

4. Significantly decreased salivary cortisol concentrations are found after intervention with TT and to a lesser extent after RTM, no significant differences between groups.

5. PD-related pain precedes the diagnosis of PD in one third of the participants and in half of the patients it is present during all their waking hours.

6. Polypharmacy is common; One quarter of all participants are prescribed analgesics of which paracetamol is the most common. Only 1/3 report pain relief with analgesics. Almost all (9/10), use medication for anxiety/insomnia and one of five use antidepressants.

7. Different pain parameters are positively affected in the short term follow up in TT and RTM. A significant decrease in pain experience (VAS) is registered in the TT-group but not in the RTM-group at week 3. In total there was a significant decrease in pain measured by the VAS scale in both TT and RTM from screening to the last follow-up, at week 34.

8. Sleep, measured by the Parkinson Disease Sleep Scale (PDSS) improves significantly within the TT group after the initial treatments; differences between groups do not reach significance at the 0.05 level.

9. HRQoL , compared to a Swedish healthy reference population (SF-36,Swe ver.) improves in both groups but normal values of HRQoL are only achieved in the short-term follow-up in the TT group.

Discussion

CAM treatments with TT and RTM have positive effects in several respects, especially in the short-term follow-up. It is more difficult to find significant differences between two groups

when the positive “within group” effects are substantial in many areas. Absolute effects are replaced by relative effects, as the control group is active. There is a lack of longstanding effects. Very few published CAM studies in general, and especially in PD, are performed with a follow-up time as long as in the Parkitouch study. Consideration of more treatment arms, including "no treatment at all," and the use of recurrent brief treatment periods to facilitate the demonstrated short-term effects should be taken into account in future studies.

Conclusions

The HPA-axis function in PD with and without chronic pain seems to be intact. Increased morning salivary cortisol is shown. PD with chronic PD-related pain has negative effects on HRQoL. Benefits from both treatment forms with TT and RTM are shown and in different respects concerning pain, sleep and HRQoL. The positive short term effects in both groups are not significantly better in TT compared to RTM. Long-term effects are sparse.

Svensk sammanfattning

Bakgrund

Taktil beröring är en behandlingsform som fortfarande har stora outforskade områden. Komplementärmedicinska behandlingsformer (*eng. CAM- therapies*) som tillägg till de farmakologiska används i hög utsträckning av våra patienter, inte minst av dem som lider av kroniska sjukdomar. Det är en viktig uppgift för modern sjukvård att utvärdera patienternas egna symptomupplevelser avgränsade till effekten av dessa behandlingsformer.
Humorala substansers funktion som surrogatmarkörer för stress är fortfarande delvis okända. Sjukdomar som drabbar centrala nervsystemet kan tyckas grundligt utforskade med modern bild och laboratorieteknik men det finns fortfarande bristande kunskap om hur dessa degenerativa processer påverkar till exempel hormonell sekretion medierad från körtlar belägna i eller nära det centrala nervsystemet.
Förhöjda kortisolkoncentrationer används ofta som biomarkör för stress. Detta hormon utsöndras och är mätbart även i saliv och det finns flera vetenskapliga arbeten som stödjer användbarheten av fritt kortisol i saliv som icke-invasiv testmarkör av det hypothalamo-hypofysära systemet (*eng. HPA-axis*) i vilket det ingår.
Det saknas mycket kunskap avseende komplementärmedicinska behandlingars effekter vid s.k. icke motoriska symptom vid Parkinsons sjukdom (*eng. Parkinson´s Disease, PD*). Vi känner till från patienter och tidigare studier, att symptom som t.ex. långvarig smärta, sömnfragmentering och humörsänkningar kan ha ett negativt inflytande på den hälsorelaterade livskvaliten *(eng. Health Related Quality of Life, HRQoL*).

Syften

Denna avhandling är ägnad att beskriva smärt-, sömn och livskvalitetskarakteristika hos en grupp PD patienter med långvarig smärta. Den är också ägnad att beskriva HPA-axelns funktion hos PD patienter med *(PD-P)* och utan smärta *(PD-noP)* samt att jämföra och utvärdera kort- och långtidseffekter av två olika former av komplementärmedicinska behandlingar, taktil helkroppsberöring (*eng. Tactile Touch, TT*) och kontrollgruppen, vila till musik (*eng. Rest To Music, RTM*) vid PD-P.
Resultatmått är den hypotalamiska–hypofysära–adrenokortikala (HPA) axelns funktion hos PD patienter med respektive utan långvarig smärta samt studier av salivkortisolförändringar i direkt samband med respektive långtidseffekter av TT och RTM där cortisolkoncentrationer i saliv utgör surrogatmarkör för stress.
Andra resultatmått utgörs av kort och långtidseffekter av TT respektive RTM på icke motoriska symptom såsom subjektiva smärtupplevelser och sömnmönster men också behandlingseffekter på HRQoL.

Metoder

45 patienter med stabil och väldefinierad PD under mer än två års tid och samtidig långvarig smärta rekryteras från öppenvårdsmottagningar i södra Sverige. Långvarig smärta definieras i

denna studie som parkinsonrelaterad smärta under tre eller fler dagar per vecka under minst tre månader före inklusion. Deltagarna randomiseras blint till behandling med TT (n=29) eller RTM (n=16). Salivkortisolprover tas vid fyra tillfällen per dygn (kl.8, 13, 20 och kl.8 påföljande morgon) vid fem tillfällen under den 34 veckor långa studien. Dessutom tas salivkortisolprover på deltagarna omedelbart före, omedelbart efter samt 30 minuter efter avslutad behandling vid två olika tillfällen, dels vid första och dels i samband med den åttonde behandlingen. Saliven samlas upp i en bomullstuss (Salivette^{TM}) och samtliga cortisolprover analyseras samtidigt och vid samma laboratorium med en väletablerad radioimmunologisk metodik (Cortisol RIA$^{I\ 125®}$). Vid upprepade tillfällen under interventions- och uppföljningsperioderna används följande mätverktyg: Mätning av smärtupplevelse; Visuell Analog Skala (VAS) samt ett smärtfrågeformulär, PEA (*eng*. *PEA, patient evaluation analysis*) och med en Pain-O-Meter (POM). För sömnskattning används PDSS (eng. *Parkinson Disease Sleep Scale, PDSS).* SF-36 (swe. ver.1) används för utvärdering av den hälsorelaterade livskvaliteten och för värdering av sjukdomens svårighetsgrad används UPDRS I-IV,(*eng. Unified Parkinson Disease Rating Scale, I – IV*) samt Hoehn & Yahr skalan, (*H&Y*). För uppföljning av deltagarnas läkemedelskonsumtion används särskilda läkemedelslistor. (Mätinstrument i de svenska versioner som används, se Appendix).

Resultat

De huvudsakliga fynden utgjordes av:

1. Dygnsutsöndringen av kortisol indikerar att en normal funktion av HPA axeln hos PD med och utan långvarig PD relaterad smärta föreligger.
2. Signifikant förhöjda koncentrationer av morgonkortisol jämfört med en frisk referensgrupp från samma geografiska område, matchat för ålder och kön konstateras.
3. Inga effekter ses på dygnsutsöndringen av salivkortisol som beror på svårighetsgraden av PD mätt med UPDRS (I-IV).
4. Signifikant sänkta nivåer av salivkortisolkoncentrationer efter interventioner med TT och i mindre utsträckning efter interventioner med RTM ses, utan signifikanta skillnader mellan grupperna.
5. PD relaterad smärta föregår diagnosen PD hos en tredjedel av deltagarna och var närvarande under alla vakna timmar hos hälften av den undersökta gruppen vid studiestart.
6. Polyfarmaci är vanligt förekommande; En fjärdedel av samtliga deltagare hade förskrivits smärtlindrande, paracetamol är det vanligaste smärtlindrande läkemedlet. Endast 1/3 rapporterar smärtlindring av analgetika. Nästan samtliga (9/10) använder läkemedel mot ångest/insomningsbesvär och 1/5 använder antidepressiva i PD-P (TT och RTM).
5. Inga kvarstående långtidseffekter avseende HPA axelfunktionen i form av förändrade dygnprofiler av salivkortisolutsöndring ses under uppföljningsperioden.
6. Inga långtidseffekter avseende dygnskortisolkoncentrationerna kan påvisas beroende på sjukdomens svårighetgrad mätt med UPDRS I-IV.
8. Olika smärtparametrar påverkas i det korta perspektivet positivt i både TT och RTM, signifikant minskad smärtupplevelse registreras inom TT gruppen under interventionsperioden.

Totalt sett uppmättes en signifikant minskad smärta från screening till sista uppföljningen i hela gruppen, utan signifikant skillnad mellan TT och RTM.
8. Sömnkvaliteter, mätt med PDSS, förbättras signifikant inom TT gruppen jämfört med RTM efter de inledande behandlingarna.
9: HRQoL, jämfört med en frisk svensk ålders och könsmatchad referenspopulation (SF-36, sve.ver.1) förbättrades i båda grupperna, men normala nivåer nåddes endast i det korta perspektivet i TT-gruppen.

Diskussion

Vi har i Parkitouchstudien visat att patienter med PD och långvarig smärta har en kraftigt sänkt livskvalitet. Studien är en av få publicerade komplementär- medicinska studier med denna långa uppföljningstid. Salivkortisol är en användbar metod för insamling av information om HPA-axelns funktion och förändringar i samband med interventioner. Minskad utsöndring av salivkortisol ses i det korta perspektivet i synnerhet efter TT men även efter RTM, en aktiv kontrollgrupp, som sannolikt uttryck för ett minskat stresspåslag. Svårigheterna att finna signifikanta skillnader mellan grupper till förmån för den ena behandlingen framför den andra ökar när effekter påvisas i båda undersökta grupper. Evidens saknas i denna studie för kvarstående långtidseffekter. Att beakta behovet av ytterligare behandlingsarmar såsom ” ingen behandling alls” och att facilitera de uppnådda korttidseffekterna med återkommande korta behandlingsperioder bör övervägas i framtida studier.

Konklusion

Den endokrina funktionen avseende HPA axeln är intakt hos PD patienter med eller utan långvarig smärta. Förhöjda morgonkortisolnivåer påvisas jämfört med friska kontroller. PD med kronisk PD relaterad smärta har negativa effekter på livskvaliteten. Patienter upplever positiva effekter av såväl TT som RTM i avseenden som berör smärta, sömn och livskvalitet. Det är inte statistiskt signifikant bättre effekt av TT jämfört med RTM, båda behandlingarna har positiva korttidseffekter. Kvarstående långtidseffekter är få.

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II. Törnhage C-J., **Skogar Ö.**, Borg A., Larsson B., Robertson L., Andersson L., Andersson L., Backstrom P., Fall P-A., Hallgren G., Bringer B., Carlsson M., Lennartsson U., Sandbjörk H., Lökk J. "Short and Long-term Effects of Tactile Touch on Salivary Cortisol Concentrations in Parkinson's Disease". *BMC Complementary and Alternative Medicine, submitted, under re-review.*

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IV. **Skogar Ö.**, Borg A., Larsson B, Robertsson L., Andersson L., Backstrom P., Fall P-A., Hallgren G., Bringer B., Carlsson M., Lennartsson U., Sandbjork H., Lökk J., Törnhage C-J. "Effects of Tactile Touch on pain, sleep and health related quality of life in Parkinson's disease with chronic pain": A randomized,controlled and prospective study. *European Journal of Integrative Medicine. 2013;5(2): 14152.http: //dx.doi.org/ 10.1016/j.eujim . 2012.10.005.*

CONTENTS

LIST OF ABBREVIATIONS

AADC	Amino acid decarboxylase inhibitor
ACTH	Adrenocorticotropic hormone
AMTA	American Massage Therapy Association
AT	Aroma Therapy
AUC	Area Under Curve
BBB	Blood Brain Barrier
BPI	Brief Pain Inventory
CAM	Complementary and Alternative Medicine
CAR	Cortisol Arousal Reaction
CDS	Continuous Dopaminergic Stimulation
CRF	Case report form
CRH	Corticotropin releasing hormone
DA	Dopamine
DBS	Deep Brain Stimulation
DLB	Lewy Body Dementia
H&Y	Hoehn and Yahr scale
HPA	Hypothalamo-Pituitary-Adrenal axis
HRQoL	Health Related Quality of Life
MRI	Magnetic Resonance Imaging
fMRI	functional Magnetic Resonance Imaging
MS	Motor Symptoms
MT	Massage Therapy
MuT	Music Therapy
MW-U	Mann–Whitney U test
NMS	Non Motor Symptoms
NREM	Non-rapid eye movement
NRS	Numerical Rating Scale
PD	Parkinson´s Disease
PD-P	Parkinson´s Disease with chronic pain
PD-nonP	Parkinson´s Disease without pain
PEA	Patient Evaluation Analysis
PDSS	Parkinson's Disease Sleep Scale
POM	Pain-O-Meter, includes POM^{phys} and POM^{emo} emotional and physical word descriptors
PTSD	Posttraumatic stress disorder
REM	Rapid eye movement
RLS	Restless legs syndrome

RSBD	REM sleep behavior disease
RTM	Rest To Music
SD	Standard deviation
SF-36	Short Form Health Survey (36), Swedish version 1.0
SPECT	Single-photon emission computed tomography
SRBD	Sleep related breathing disorder
STN-DBS	Subthalamic nucleus – deep brain stimulation
TCA	Traditional Chinese acupuncture
TCM	Traditional Chinese medicine
TMB	Tetramethylbenzidine
TT	Tactile Touch
UPDRS	Unified Parkinson Disease Rating Scale
VAS	Visual Analogue Scale
VAS^{MAX}	VAS maximal pain (indicated during the defined days, see methods).
WDS	Word Descriptors

1 INTRODUCTION

1.1 PROLOGUE

Complementary and Alternative Medicine Therapies (CAM- therapies) have been used for a very long time. Traditional Chinese medicine (TCM), which encompasses many different practices, is rooted in the ancient philosophy of Taoism and dates back more than 5000 years. Its approach is based on the ancient Chinese perception of humans as microcosmos of the larger, surrounding universe, interconnected with nature and subject to its forces.

Prana is the Sanskrit word for "vital life". Prana is the notion of a vital, life-sustaining force of living beings and vital energy, comparable to the Chinese notion of Qi. Prana is a central concept in Hinduism, particularly in Ayurveda and Yoga, where it is believed to flow through a network of fine, subtle channels called nadis (Narayanananda 1974).

In Egypt, foot and hand massage is depicted on a wall painting on the physician's tomb in Saqqara, dating back to 2330 B.C. (Calvert 2002)

Today TCM is practiced side by side with Western medicine in many of China's hospitals and clinics. It is also commonly used in the Western world (Cassidy 1998). TCM practitioners use a variety of therapies in an effort to promote health and treat disease. Chinese herbal medicine and acupuncture are the therapies that are used most frequently. Chinese massage, mind-body therapies such as qi gong, tai chi, and dietary therapy are other forms of commonly used TCM.

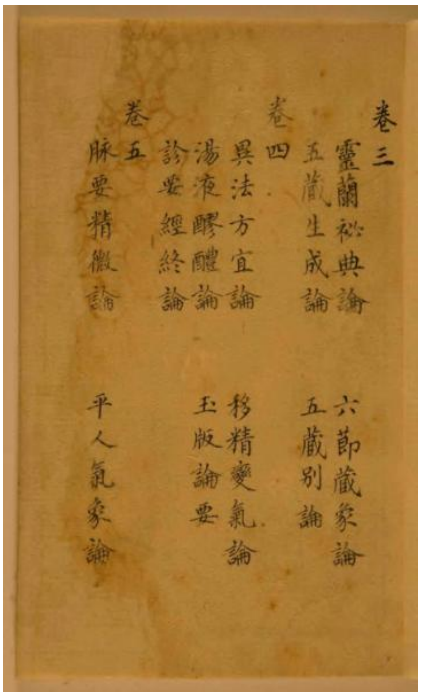

卷三
靈蘭秘典論
五藏生成論
卷四
異法方宜論
湯液醪醴論
診要經終論
卷五
脉要精微論
六節藏象論
五藏別論
移精變氣論
玉版論要
平人氣象論

Fig. 1: The Su Wen of the Huangdi Neijing:
The ancient Chinese medical text that has been treated as the fundamental doctrinal source for Chinese medicine for **more** than two millennia. It is comparable in importance to the Hippocratic Corpus in Greek medicine or the works of Galen in Islamic and medieval European medicine. The work is composed of two texts each of eighty-one chapters or treatises in a question-and-answer format between the mythical Huangdi (Yellow Emperor) and six of his equally legendary ministers. (Wang 1115 CE - 1234 CE)

The Cochrane Collaboration defines CAM as:
"*A broad domain of healing resources that encompasses all health systems, modalities, and practices and their accompanying theories and beliefs, other than those intrinsic to the politically dominant health system of a particular society or culture in a given historical period. CAM includes all such practices and ideas self-defined by their users as preventing or treating illness or promoting health and well-being. Boundaries within CAM and between the CAM domain and that of the dominant system are not always sharp or fixed".*
Thus among other medicinal therapies CAM includes: Physiotherapy, Homeopathy, Acupuncture, Anthroposophic medicine, Naturopathy, Traditional Herbal Chinese Medicine and bodily treatments including Osteopathy, Chiropractic, and Shiatsu (Vickers and Zollman 1999).

Expressed in another way, CAM can be said to be a group of diverse medical and health care systems, practices, and products that are not generally considered part of conventional medicine. Complementary medicine is used together with conventional medicine, and alternative medicine is used in place of conventional medicine.

1.1.1 Patterns of CAM consumption in the World, in Europe and in Sweden

The prevalence of CAM use by the general population is substantial (Harris et al. 2012). Based on data from 15 countries, the 12-month prevalence of visits to CAM practitioners ranges from 1.8% to 48.7%. Adults use CAM more frequently than children. National estimates of CAM use are highest in East Asian countries. In Anglo-Saxon countries four of 10 adults have used some type of CAM (Hunt et al. 2010). These figures are comparable and consistent with those presented in corresponding reviews a decade ago. In the Scandinavian countries CAM is used to almost the same degree (Hanssen et al. 2005). In a telephone survey in 2000 with complete answers from 1000 participants in Stockholm County, 57% reported ever having used massage therapy. One third of responders had used naprapathy and one out of four had used acupuncture. The CAM therapies were most often used by those aged 30 -59 years and more often by women with higher education. Many individuals used both CAM and conventional health services.

1.1.2 A brief background to the Parkitouch Study

"In 2001, four women met at the home of Gittan Larsson in Lidkoping, Sweden..Gittan Larsson and Laila Robertsson had initiated the meeting, which included Ulla-Britt Lotun, chairman of the local Parkinson Association in Jonkoping, and myself, at that time chairman of the local Parkinson Association of Skaraborg. The main reason for the meeting was that Laila had performed tactile touch on patients with Parkinson´s disease and pain and the patients reported good results. Laila and Gittan worked together with a treatment technique they had developed over time. The concept included nice-smelling oils and quiet, peaceful and enjoyable music."
/ Astrid Borg, RN, secretary of the "Parkitouch Study Group".

The following section includes background knowledge concerning Parkinson´s Disease (PD), its treatment options, motor (MS) and non motor symptoms (NMS). Methods for measuring pain and sleep are described, and interpretations of stress as a phenomenon in chronic disease and its potential physiological markers such as the hypothalamo-pituitary-adrenal (HPA) axis are included. In addition, historical, physiological and psychological knowledge and experiments using different forms of therapies are described. The history of CAM, its spread, and current knowledge about its effects in different trials are described in the hope of helping readers achieve a better understanding of the results of this thesis, the "Parkitouch study".

1.2 A: PARKINSON´S DISEASE

1.2.1 Clinical Parkinson´s Disease

Parkinson's disease (PD), also known as Parkinson disease, Parkinson's, idiopathic parkinsonism, primary parkinsonism and paralysis agitans, is a degenerative disorder of the central nervous system. The disease is named after the English physician James Parkinson, who published the first detailed description in "*An Essay on the Shaking Palsy"* in 1817. PD usually affects people over the age of 50. Early symptoms of PD are subtle and occur gradually. The progression rate of the disease varies; for some patients the disease progresses more quickly than for others. The shaking, or tremor, which affects the majority of PD patients, may begin to interfere with daily activities, as do slowness and stiffness. Other symptoms may include depression, anxiety and sleep disruptions. The diagnosis is based on medical history and a thorough neurological examination. The disease can be difficult to diagnose accurately at the time of the first symptoms due to many differential diagnoses in the spectrum of movement disorders.
The clinical diagnosis of PD is based on the identification of combinations of the cardinal motor signs of bradykinesia, rigidity, tremor, and postural instability. Three levels of diagnostic confidence are differentiated: definite, probable and possible. The

diagnoses of possible and probable PD are based on clinical criteria alone. Neuropathological confirmation is required to diagnose definite PD in patients with a history of clinical diagnosis of possible or probable PD. Currently, only about 75% of clinical diagnoses of PD are confirmed at autopsy, largely because the cardinal signs also occur in conditions other than PD; they are then termed "extrapyramidal signs," "parkinsonian features," or "parkinsonism" (Gelb et al. 1999).

Tremor
The characteristic tremor of PD is a 3 to 6-Hz distal resting tremor, but patients with PD may have a resting tremor, an action tremor, or both, and the character of the tremor may change during the course of the illness. The proportion of patients with PD who have tremor ranges from 79 to 90% in clinical series (Hoehn and Yahr 1967).

Rigidity
The frequency with which rigidity occurs in PD has been reported explicitly in only a few series, with values ranging from 89 to 99%. (Hughes et al. 1992). Rigidity is, however, not specific to PD. Indeed, even patients with uncomplicated essential tremor may demonstrate cog wheeling.

Bradykinesia
Bradykinesia is present in 77 to 98% of patients with PD (Martin et al. 1973). It can also occur as a result of normal aging, depression, and Alzheimer's disease, as well as in the group of PD-associated diseases, usually called Parkinson +.

Asymmetric Onset
Symptoms begin unilaterally in most patients with PD. In two series of patients with pathologically proven PD, symptoms began asymmetrically in 72 to 75% of patients (Colosimo et al. 1995).

Postural Instability
Although many authors consider postural instability to be a cardinal feature of PD, it usually does not occur early in the disease. Postural instability has limited diagnostic specificity because it can result from a variety of problems in afferent and efferent pathways, central processing, and even musculoskeletal mechanical function. For the Parkinson+ groups this symptom can be of early onset in the disease.

1.2.2 Supportive diagnostic tests

No single investigation or laboratory analysis can diagnose PD. The aim of most investigations is to exclude other diagnoses. Computerized Tomography (CT) or Magnetic Resonance Tomography (MRI) is used for exclusion of structural lesions and tumors. Ultrasound of ecogenecity of the midbrain is under development, but has not yet been fully evaluated. Single-photon emission computed tomography (SPECT) can be used with DaT-scan (Dopamine-Transporters, injection with ioflupane- iodine^{123}).

This technique is of two kinds. *Pre-synaptic SPECT* can differentiate between PD and Essential Tremor (ET) and can also be helpful in discriminating between Lewy Body Dementia (DLB) and Alzheimer´s Disease (AD). The sensitivity of DaT-scan is low when used to discriminate between PD and atypical parkinsonism. *Post-synaptic SPECT* is less predictive after treatment with dopaminergic pharmacotherapy. Analysis of tau, phospho-tau, neurofilaments and beta amyloid in liquor may be helpful for support in determining the progress of other diseases. Studies of the value of analysis of alpha-synuclein in liquor are in progress, as well as gene expression profiling tests.

1.2.3 Non Motor Symptoms in Parkinson´s Disease (NMS)

Although still considered a paradigmatic movement disorder, PD is associated with a broad spectrum of NMS. While overall NMS become increasingly prevalent with advancing disease, many of them can also antedate the first occurrence of motor signs. In recent years much attention has been focused on NMS in the clinical science concerning PD. In table 1 the most common NMS are listed based on a summary of reviews in this field (Bernal-Pacheco et al. 2012).

Neuropsychiatric dysfunction	**Sleep disorders**	**Autonomic dysfunction**	**Sensory symptoms and pain**
Mood disorders	*Sleep fragmentation and insomnia*	Orthostatic hypotension	Olfactory dysfunction
Apathy and anhedonia	RBD[1]	Urogenital dysfunction	Abnormal sensations
Frontal executive dysfunction	PLMS/RLS[2]	Constipation	*Pain*
Dementia and psychosis	Excessive daytime somnolence		

Table 1: Most common NMS symptoms in PD.
[1] = REM Sleep Behavior Disorder, [2] = Periodic Limb Movements of Sleep / Restless Legs Syndrome.

NMS vary among PD patients but also with the current state of PD, wearing-off and the so called *on or off-states*, in advanced PD. An increase in NMS symptoms of between 10 and 30% from the on to the off-state has been shown, but also in the opposite direction for symptoms due to hyperstimulation, hallucinosis, sweating, etc. (Witjas et al. 2002).

1.2.4 General pain and pain in PD

1.2.4.1 Definitions and prevalence

"Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". (The International Association for the Study of Pain (IASP)).
Pain is one of the most common reasons for physician consultations in the Western world (Cole 2010) and the most common in the United States. It is a major symptom in many medical conditions, and can interfere to a great extent with a person's quality of life and general functioning. Psychological factors such as social support, hypnotic suggestion, excitement or distraction can significantly modulate the intensity or unpleasantness of pain.
Pain that has lasted for a long time is commonly called chronic or persistent pain. In medicine, the distinction between *acute* and *chronic* pain has traditionally been determined by an arbitrary interval of time since onset; the two most commonly used markers are three and six months, respectively, although some theorists and researchers have placed the transition from acute to chronic pain at 12 months after debut. Sometimes three different intervals are used; *acute* for pain that lasts less than 30 days, *chronic* for pain of more than six months duration, and *sub acute* for pain that lasts from one to six months. A popular, and probably the most appealing alternative definition of *chronic pain* that includes no arbitrarily fixed time durations is "pain that extends beyond the expected period of healing."
Unlike chronic pain, acute and transient pain is a part of the body's defense. Chronic pain can occur anywhere in the body. It can range from being mild and annoying to being so severe that it has a great negative impact on activities of daily life.

1.2.4.2 An historical recapitulation of the experience of pain

The *biomedical* input of pain science dominates our modern medical culture and has its origin in the reductionism of the 16th century. The ideas stem from the French philosopher and mathematician Rene Descartes. In short, the theories describe how complex systems are not more than the sum of their components. The soul was thought to be placed outside the body, and the philosophical ideas of cartesianism were created in this medieval doctrine. In modern times the *biopsychosocial model* has been introduced (Engel 1977). In this model the soul is a genuine part of the body, with dialectical cooperation between body, soul and society. The causal relationships can be targeted in different directions.
In fact, the Visual Analogue Scale (VAS) was first introduced in the second half of the 1960s and was originally used to measure *degree of depression*, and not only to measure pain intensity (Rolfsson 2009).

1.2.4.3 General prevalence of pain

Chronic pain is more common in older adults, but it is not a part of normal aging. Recent systematic reviews of moderate-to-severe non-cancer chronic pain reveal that this type of pain is common. Almost one out of five persons experiences pain, and there is a significant impact on patient-perceived health status, everyday activities including financial pursuits, and personal relationships. An association with depressive symptoms is also common. The majority of patients rely on drugs for pain control, and NSAIDs are the most frequent choice. Despite this, a large proportion of patients experience inadequate pain control (Reid et al. 2011). In corresponding studies from the Netherlands (Bekkering et al. 2011) it was found that four out of ten patients reported not receiving treatment for pain, and eight out of ten considered that their pain was inadequately treated. All studies reported a detrimental effect of chronic pain on quality of life, activities of daily living and mental health.

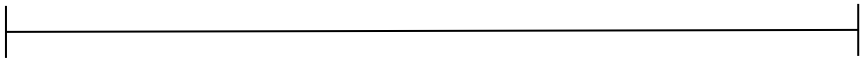
1.2.5 The measure of pain

1.2.5.1 http://archneur.jamanetwork.com/article.aspx?volume=56&issue=1&page=33 - ref-nsa7701-20*Examples of pain scales*

A **pain scale** measures the patient´s pain *intensity* or other features of pain. Pain scales are most often based on self-reports, but observational (behavioral) or physiological data may be an alternative among children and dyscognitive patients. Self-reports are considered primary and should be obtained if possible.

One-dimensional scales

These forms have the advantages of being quick and easily handled, and are preferable for acute pain. They do not measure the quality, duration, localization or impact on quality of life.
VAS = Visual Analogue Scale; pain is measured by a mark made by the patient on a 100 mm straight line (recommended) (Huskinson 1983).



No pain Pain as bad as it could possibly be

The following are examples of other one-dimensional scales that are important to know about but which are not used in this study. **Face scales:** Patients who do not understand the other scales (due to dyscognition, etc.) choose the expression on a face best correlated to his or her own experience of pain.**VDS** = Verbal Descriptor Scale: pain is described with words from no pain to worst pain. **NRS** = Numerical Rating Scale: pain evaluation ranging from 1 to 10. **CPOT** = Critical-Care Pain Observation Tool:

developed for patients who cannot communicate verbally and combines signs of pain in the face with motor responses. The instrument is used among intensive care unit patients.

1.2.5.2 The complexity of measuring pain

Based on the IASP definition of pain (see above, definition of pain) that emphasizes the subjective content of pain, it is easy to consider this entity as a *construct,* a label, comparable to depression, anxiety, etc., and not mix in activation of nociceptors. From this point of view it is similar to an *operationalization* or categorization of pain into measurable variables. By developing descriptive words in connection with the scale, this results in semiquantitative data with high resolution.

1.2.5.3 Reliability and validity and statistical data type of the VAS scale.

Testing-retesting is a method for considering the *reliability* of a method. Different studies have shown different results concerning the reliability of the VAS scale. (Jensen 2003). Concerning the *validity* of VAS there are also some contradictory results. To decide whether we are measuring what we intend to measure, different pain evaluation instruments are compared with one another. Scientists often indicate that non parametric statistical methods are to be preferred, as the VAS scale data are of an ordinal type**.** However, parametric methods are often used just as if measures of pain are continuous, quantitative data, even though statisticians often argue that pain as a "construct" does not measure anything about magnitude and distance and that non parametric studies have shown that pain represents ordinal data (Lund et al. 2005)
A non parametric test that is often used when analyzing data from VAS-scales is the Wilcoxon rank test, a method for comparing related samples. In a report from the SBU (the Swedish Council on Health Technology Assessment) (ref.http://www.sbu.se) it is also stated that parametric methods should be avoided when analyzing data on pain.

1.2.5.4 Multi-dimensional scales

These scales measure the combined effects of the physical, mental and social impacts of pain. They provide a more detailed picture of pain experiences. The scales are more difficult to deal with for patients with dyscognitive problems. Examples are:
the **POM** = Pain-O-Meter, which includes POM^{phys} and POM^{emo} ; physical and emotional word descriptors translated to numbers indicating different strengths of pain experience. See, Measures: *Pain, (Papers III and IV) The measurements of pain.*
Other instruments of importance, although not used in our study, are the Brief Pain Inventory (BPI), which includes questions on life situation, pain history, intensity and

localization, and treatment of pain, and the McGill Pain Questionnaire (MPQ), which includes measurements of sensory, emotional and cognitive dimensions of pain.

1.2.6 Parkinsonian pain

James Parkinson described this phenomenon in 1817 in his original work "An essay on the shaking palsy". *"…the writer of these lines was called to a female about forty years of age, complaining of great pain in both the arms, extending from the shoulder to the finger ends. She stated, that she …was not benefited by any of the medicines which had been employed… leaving both the arms and hands in a very weakened and trembling state."* (From J. Parkinson, An essay on the shaking palsy.1817).
The primary aim of this thesis was to study the effects of TT and RTM on chronic pain in PD.
Based on our own studies in this field, RN Mrs Astrid Borg and Mr. Anders Borgman, Board Chairman and members of the Swedish "Parkinsonstiftelsen", presented the results of a Swedish survey among members of the Swedish Parkinson Association more than a decade ago (A.Borgman 2002). Almost 1000 members of the association responded to the survey and the results are summarized below.

Question	**Yes (%) (females /males)**	**No (%) (females/males)**	**Total (n) (females /males)**
Components of pain in PD?	66.6 (74.5/61.9)	33.4 (25.5/38.1)	947 / (630/317)

Type of pain	**% agreement among respondents**
cramping	46
dull	40
numbness	24
tingling	17
burning	16
stabbing	16

Table 2: Co-existence of pain and type of pain in PD. A Swedish survey.

In this survey the participants were asked to describe the modality of their pain experience. To our knowledge this has not been done before from the perspective of Swedish patients. The information from these surveys was analyzed and the involved

professionals (doctors, nurses) and patients developed the "Patient Evaluation Analysis" (PEA). The Parkitouch Study group used the PEA in the present work (see Appendix IV).
B. Ford et al. categorized the modalities of pain in PD into five categories (Ford 1998). Several years later Beiske and coworkers (Beiske et al. 2009) examined 176 home-living PD patients; musculoskeletal pain was reported by 70%, dystonic pain by 40%, radicular-neuropathic pain by 20% and central neuropathic pain by 10%. Twenty-five percent experienced pain from more than one modality. Similar descriptions of the characteristics of PD- related pain have been observed in other studies; muscular stiffness is common and the fluctuations due to on or off-states of advanced PD are apparent.
In 2008 a French study (Negre-Pages et al. 2008) was published comprising 450 PD patients. Sixty-two percent reported chronic pain (pain that lasted for more than 3 months) and 60% of this group experienced chronic pain *related to PD.* In this category, pain was considered to be *directly related* to PD if it could not be attributed to any other health problem according to medical history, clinical examination, laboratory tests, or imaging results, or *indirectly* related to PD if another disease caused pain (e.g. osteoarthritis) but PD aggravated pain intensity because of rigidity, abnormal posture, or movements. Patients reporting more than one pain described their most severe pain first.
PD was the sole cause of pain in more than 100 patients and indirectly aggravated pain of another origin in over 60 patients. Parkinsonian patients with "PD-pain" were younger at PD onset, had more motor complications, and more severe depressive symptoms than those without pain or with "non-PD pain". "PD-pain" was more intense, but less frequently reported to doctors. PD-related chronic pain was considered as one of the common NMS in PD, often preceding the motor symptoms of the disease; this was also confirmed by the findings in our study (paper III).

1.2.6.1 Treatments for chronic pain

Brief summaries of treatment suggestions for chronic pain often include exercising, but also getting enough sleep may help reduce chronic pain. Usage of over-the-counter pain medicine such as paracetamol (acetaminophen), aspirin, or ibuprofen may also help. Complementary therapies such as massage and yoga are often used.

1.2.7 Sleep in Parkinson´s Disease

The dopaminergic system has an important influence on the maintenance of normal sleep, and sleep disturbances have a negative impact on HRQoL (Rye and Jankovic 2002). Studies of sleep architecture show alterations in different stages of sleep depth in PD. (Chaudhuri et al. 2002)

Normal sleep has two distinct states: non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. NREM sleep was previously divided into four stages, but it has been reduced to three stages since 2007 (update by the American Academy of Sleep Medicine, AASM). Stage 1, mostly in the beginning of sleep; α-waves are replaced by δ-waves in the EEG. Stage 2, in which no eye movements are recognized; so-called sleep spindles and K-complexes occur in the EEG. Stage 3, slow-wave sleep (SWS), where less vivid dreaming is common as are parasomnias. During REM sleep, rapid eye movements occur, breathing becomes irregular, blood pressure rises, and there is loss of muscle tone (paralysis). However, the brain is highly active, and the electrical activity recorded in the brain by EEG during REM sleep is similar to that recorded during wakefulness. REM sleep is usually associated with more vivid dreaming and accounts for 20%-25% of the total sleep period.

The links between certain primary sleep disorders, PD and PD-related complications have not been clarified (Peeraully et al. 2012). As examples, studies using polysomnography have hypothezised the existence of connections between the reduced amount of sleep spindles seen in PD with mild cognitive impairment (MCI-PD) and impairments of memory (Latreille et al. 2013). Sleep-related breathing disorders (SRBDs) such as the sleep apnea syndrome (SAS) may also coexist with PD. With the same techniques supplemented with registrations of respiratory rates/saturation, sleep apnea was registered in half of a group PD patients but without the oxygen desaturation profile normally found in these conditions (Schulte and Winkelmann 2011).

Thus sleep problems in PD are multifactorial and are interwoven with the causes mentioned above. The degree to which sleep disorder is a primary NMS in PD is still unclear and separation of the components is not easily achievable. Mechanisms of sleep disturbances in PD also include pain, rigidity and bradykinesia hindering turning in bed. Nocturia and possible effects of concomitant antiparkinson medication are examples of factors adding to the normal aging processes that interact with sleep patterns.

Dopaminergic medications are known to have sleep-inducing properties, and reduction of episodes with sudden daytime sleepiness in PD have been shown with reduction or discontinuation of these agents (Hauser et al. 2000).

Changes in the brainstem occur in the course of PD, affecting neurotransmitters that play roles in arousal and wakefulness. There is evidence of involvement of orexinergic (Greek for appetite), also called *hypocretin* neurons. These are present in the posterior part of the lateral hypothalamus and represent dopaminergic neurons of the ventral tegmental area (Haq et al. 2010)

Lewy bodies are found in brainstem nuclei in both parkinsonism and in REM sleep behavior disorder (RSBD) (Thorpy 2004). RSBD is characterized by vigorous movements during sleep and can be a forerunner or a sequela of PD. It is a unique parasomnia that is also characterized by dream enactment behavior during REM sleep (Postuma et al. 2012).

In a person with RSBD, the paralysis that normally occurs during REM sleep is incomplete or absent, allowing the person to "act out" his or her dreams. The dreams are often vivid, intense, and violent. Dream-enacting behaviors include talking, yelling, punching, kicking, sitting, jumping out of bed, arm flailing and grabbing.

This condition also increases with age, independent of PD, promoting the neurodegenerative basis for some aspects of sleep disruption in PD. This is also supported by the fact that the likelihood of sleep disturbances in PD is directly related to the severity of the disease as indicated by motor symptoms, the overall effects of daily living, and the dosages of antiparkinson drugs (Kumar et al. 2002).
Another more specific disorder with a negative impact on sleep quality in PD is Restless Legs Syndrome (RLS). However, to date a direct pathologic link between the two diseases remains elusive. More PD patients suffer from akathisia, and the sensory symptoms can be due to augmentation, or unmasking, of RLS-like symptoms. No genome wide associations have so far been shown to overlap between PD and RLS.

1.2.8 Later stages of PD

As the disease progresses, new symptoms may occur. After five to ten years of levodopa therapy, dyskinesias and so called "on-off" symptomatology are frequently a part of the disease. These phenomena are often very disabling and are suggested to be an effect of the progressively diminishing numbers of dopaminergic neurons that act on the given dopamine substitution.

1.2.9 Pharmacotherapy in Parkinson´s disease

1.2.9.1 Levodopa

Levodopa is one of the most commonly used drugs in PD and its effects are primarily in the nigro striatal pathways. It has the following pharmacological background:
The history of L- 3, 4- dihydroxy- phenylanaline dates back to the original experiments in the 1950s by the Swedish Nobel prize winner Arvid Carlsson, who showed the concentration-dependent inversion of reserpine-induced paralysis in rats caused by this substrate (Carlsson 2001)

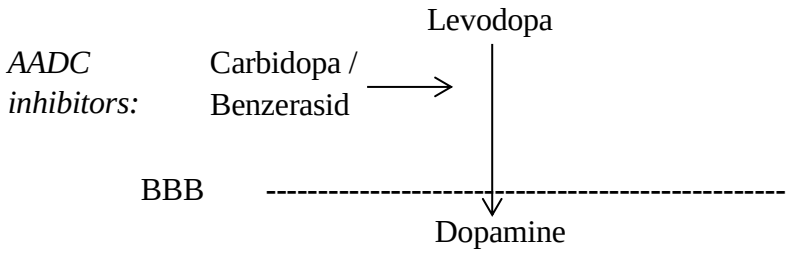


Fig. 2: Peripheral actions of Amino acid decarboxylation inhibitors (AADC).

Tyrosine Hydroxylase is the rate-limiting step and levodopa is a precursor (prodrug).

By adding the peripheral AADC, carbidopa or benzerasid, the response in striatum is increased and side effects such as nausea are diminished due to the absence of peripheral dopamine (DA). Most patients with idiopathic PD (over 90%) respond to levodopa (Rajput et al. 1990)

1.2.9.2 Examples of other pharmacological treatments in PD

Dopamine agonists act directly on the postsynaptic receptors.
MAO-B inhibitors (Mono Amino Oxidase- inhibitors) and COMT-inhibitors (Catechol-O-methyl Transferase) act as enzyme inhibitors of the breakdown process of dopamine. Amantadine probably acts as a NMDA receptor antagonist. It is today mostly used as an antidyskineticum.The oldest known antiparkinson medications, the anticholinergics are today most often avoided, especially in the treatment of elderly due to its severe side effects such as confusion etc. Some PD patients with severe dystonia or tremor can be helped with these drugs.

1.2.10 Advanced therapies in Parkinson´s Disease

Since the mid 1990 high frequency electric stimulation of deep brain structures (DBS) has replaced earlier neurosurgical lesional therapies. The brain damage is limited in this way and can be adjusted in relation to symptoms and progress of the disease. STN-DBS is, however, sometimes complicated by psychiatric side effects and an apparently altered energy homeostasis in a considerable number of patients. STN stimulation could possibly act as an internal stressor of the limbic system (Benabid et al. 2009). Reconstructive surgery with transplantation of dopamine-producing cells is still experimental in nature. Continuous dopaminergic stimulation (CDS) with pump technique and administration of the drug directly into the duodenum is a concept that has shown obvious benefits compared to intermittent oral administration of levodopa in late PD (Nyholm 2012). Apomorphine can also be administered as a continuous infusion through a pump and is another alternative in the advanced therapy arsenal for PD (Clarke et al. 2009). All of these methods have their challenges and their benefits, but these lie outside the scope of this thesis.

1.2.11 Hypothesis of chronic stress and Health Related Quality of Life (HRQoL) in Parkinson´s Disease

PD has great influence on the lives of affected patients as measured by HRQoL. This is an area that still requires further research. The most effective treatments for both early- and advanced-stage disease need to be determined, as clear evidence is lacking regarding the drugs of choice for each stage and regarding what other efforts are of most value for patients and their families. Clearly, given the impact that advanced-stage PD has on the HRQoL of patients, finding the most effective treatments to improve life

circumstances should be of prime concern. In paper III we compared the overall HRQoL in PD patients with chronic pain with that of healthy controls from the same country. The combined chronic stress of the burden of PD itself, along with the recurrent, sometimes continuous, ongoing pain, had a strong negative impact on HRQoL, as shown in the paper.

1.3 B: CAM THERAPIES

1.3.1 Complementary therapies related to the Parkitouch Study

1.3.1.1 Touch

A human being is by nature a social being, and communication is vital to his/her existence. The importance of verbal communication is well known while, on the other hand, nonverbal communication related to touch is not always on a conscious level. Touch has sometimes been claimed to communicate the hedonic values of emotion, either positive or negative, or merely to amplify the intensity of emotional displays from the face and voice.
The rules for haptic behavior – how, when and where to touch objects or people – are established early in life. It is considered one of the earliest but also one of the most social interventions in life. By establishing the integrity of things and persons, social order is made possible.

Touch in invertebrates

Touch, one of the most fundamental means of contact with the world, is also the simplest and most straightforward of the sensory systems. In living organisms sensory systems are involved in survival and thus play essential roles. Touch serves many functions in nonhuman primates and invertebrates. As an example in one of the most diverse of all animals, the nematode species, multidendritic nociceptors in the head respond to harsh touch throughout their receptive field but respond to gentle touch only at the tip of the nose (Field 1995).

Touch in vertebrates

The genetic basis for effects of touch has been investigated by designing experiments with maternal separation in rats (Schanberg et al. 2003). Changes were seen in the activity of the enzyme ornithine decarboxylase (ODC) in rat pups taken away from their mothers, and the animals switched to a survival mode. The activity of this enzyme is a well-documented index of cell differentiation and replication. The time to return of tissue levels of ODC in the heart and brain of the pups after reuniting them with their mother was about two hours. Decreased growth hormone (GH) secretion, slowing of insulin catabolism and increase of corticosterone secretion were seen in the experiments with maternal separation. Heavy stroking in these experiments had a normalizing effect on serum GH. Experiments with β-endorphine, an opiate receptor

agonist injected in the brain cisterns of rat, mimicked the effects of maternal separation on ODC-levels, contributing to the hypothesis in these studies that β-endorphine is a central mediator of the touch deprivation syndrome.

Touch among mammals

Most of us have watched monkeys in animal parks or in wild life and have been amused by their behavior. Their sitting close together, itching and touching each other is behavior that must play an essential role in the socialization processes. Contact comfort does not entirely disappear with age. Other forms of physical contact with other members, not only their mother, become common when the monkeys get older.

Fig.3: Touch among mammals.

In a series of controversial experiments conducted in the 1960s, the powerful effects of love and the lack of physical contacts were demonstrated (Harlow et al. 1964). By showing the devastating effects of deprivation on young rhesus monkeys, Harlow revealed the importance of a mother's love for healthy childhood development. Harlow removed young monkeys from their natural mothers a few hours after birth and left them to be "raised" by mother surrogates. The experiment demonstrated that the baby monkeys spent significantly more time with their cloth mother than with their wire mother. These data make it obvious that contact comfort is a variable of overwhelming importance in the development of affectional response, whereas lactation is a variable of negligible importance.

1.3.1.2 Massage / Touch therapy in preterm and term infants

Most preterm infants are positively affected by massage therapy, as shown for instance by better weight gain and better performance of developmental tasks (Barnard and Bee

1983).In a study performed 25 years ago, an increase in gastrointestinal food absorption hormones such as gastrin and insulin was demonstrated when stimulating the inside of the mouth in newborns (Uvnäs-Moberg et al. 1987). There is a long tradition in different parts of the world, especially in Africa and Asia, of practicing infant massage. It is often performed with oil following the daily bath or prior to sleep time. In the 1990s massage therapy schools were established in the United States to teach parents infant massage. Inspiration emerged from books published by Amelia Aucket in1982 and later by Vimala Schneider Mc Clure (Amelia 1982; McClure 2001), two massage therapists who trained in India. Infant massage therapy groups reported that infants with different kinds of special needs, such as preterm infants and infants with cerebral palsy appeared to benefit more from infant massage.

1.3.1.3 Communication of emotion via touch

In adulthood touch continues to have a central role when, for example, flirting, expressing power, soothing, and playing. Becoming ill and suffering from chronic disease causes a profound change in life´s circumstances. Emotions are deeply involved in these changes. Facial and vocal displays of emotions have received much attention (Stack 2007), while communication of emotion by touch has been explored to a lesser extent.

As is the case with facial expressions and vocal displays, touch communicates specific positive as well as negative emotions to the refined way in which individuals communicate with one another. An analysis of the tactile system as a communicator reveals tremendous complexity. Touch can vary in its action, i.e. in the specific movements used, such as rubbing, intensity, degree of pressure used, abruptness, acceleration and deceleration, temperature, location and duration (Hertenstein et al. 2006).

A number of studies have shown that touch can fail to have positive effects and may even have negative effects. Communicating by means of touch can make subjects feel anxious and generally uncomfortable. Touch can carry an inherent ambiguity; it can impose a greater level of intimacy than the recipient desires, it can communicate symbols of the recipient´s lower status, etc. However, touch usually has a fairly clear intentionality.

The coding of tactile communication

Message sent by the initiator ⟶ decoding by recipient ⟶ conclusion by recipent

The interpretation relies almost entirely on the subjective conclusion reached by the recipient, and the intended message may vary from the message that is decoded. Among persons using touch frequently, gestures are interpreted as pleasant and satisfying more often than is the case among persons who are unaccustomed to touch.

The use of touch in situations with recipients who are suspicious, filled with fear, or who do not want to be touched is, of course, not recommended.
That physical contact from a caregiver can encourage calmness and diminish anxiety in a patient overwhelmed by panic is widely accepted. It has been shown that physical contact combined with verbal contact more often results in responses with positive changes in facial expression than if verbal contact alone is made with a person with a serious physical illness. The situation is often interpreted as if the physical contact does something to the body and facilitates recovery (Bradley et al. 2001; Jourard 1964).
Hospitalized female psychiatric patients, and volunteers as controls, were examined concerning their attitudes toward body contact. The degree of depression, anxiety and anger influenced the need for touch/body contact, and the action of touch provided feelings of being loved, protected and comforted (Farrah 1971; Hollender 1970).
The degree of family support seems to be another dimension of the need for touch. Less need for touch has been shown in families with good support (Pattison 1973).
It is known that feelings of anger, fear, disgust, love, gratitude and sympathy are able to be decoded in this way at greater than chance levels.
A recent study comprising over 200 younger people of both genders showed a very high degree of ability to decode different underlying emotions just by touching an unacquainted partner without visual contact (Hertenstein et al. 2006). The specific types of touch used included squeezing, stroking, rubbing, pushing, pulling, pressing, patting, trembling, poking, hitting, scratching, massaging, tickling, slapping, lifting, picking, hugging , finger interlocking, swinging and tossing. Both the intensity and duration were registered. In this study happiness and sadness were decoded at significant levels independent of gender (male-male, male-female, female-female or female-male). The emotions of anger, gratitude and love were decoded on average at the highest rates (78%, 74% and 68%, respectively) between encoder-decoder groups.

Connections with psychotherapy
In addition to having similar effects, the structure of Touch therapies is similar to that of psychotherapy. Both forms of therapy routinely rely on repeated, private, interpersonal contact between two persons. Treatment protocols are often similar in Touch studies, compared to those used in short-term psychotherapy, with effects on the trait of anxiety and on depression outcomes, with twice weekly meetings over a span of five weeks being the most common (Moyer et al. 2011).

1.3.2 Therapeutic Touch in modern literature

In our modern society there are many indications that we have lost parts of the physical proximity that is important for us as a species (Bunkan, 1993). The body may exhibit malnutrition, but it can also have emotional deficiencies. "The hunger of skin" is an expression used by behavioral scientists. We live in a culture of low-level touch, and the effects of this on society are interesting to reflect upon. We know the costs of traffic accidents but we do not know the costs of lack of touch. If the negative effects of stress, exhaustion, depression and sickness absences could decrease, a lot of costs would be saved both for the individual and for society (Beijbom, 1996).

Several trials with a scientific approach have been performed in this area in recent times.

Following Dolores Krieger's introduction of Touch Therapies in 1974 (Krieger, 1975) there have been some scientific approaches well worth reflection. However, the studies often suffer from the absence of operational definitions, random assignments of groups, Hawthorne effects, etc. A study of the concept of Therapeutic Touch used by "healers" from that time makes it apparent that those methods can hardly be compared with the mode of application of Tactile Touch (TT) used in our studies.

A common nomenclature was" *Non-Contact Therapeutic Touch*"(NCTT), a kind of "energy therapy" in which practitioners' claimed that they promoted healing and reduced pain and anxiety. This was performed by placing their hands on, or near, a patient and claiming that the therapist was able to detect and manipulate the patient's energy field.

In table 3A below, some of the earlier studies on Therapeutic Touch and Massage Therapy (MT) are summarized and some more recent studies are presented in table 3B.

Author/year	N	Design	Variables and population	Intervention	Instruments	Outcome
Krieger 1974	64	Quasi-exper. Pre Post Test	Hemoglobin in hospitalized adults	TT / Routine care	Hemoglobin monitor	Significant increase in TT group
Heidt 1979	90	Experimental Pre Post	Anxiety in adult hospitalized cardiovascular patients	TT / CasualTouch /No Touch	STAI Questionnare	Significant decrease in TT group
Randolph 1979	60	Experimental Pre Post	Physiologic response to stressful stimuli in college students	Modified TT/ Modified TT mimic	GSR, EMG, temperature probe	No significant differences
Quinn 1982	60	Experimental Pre Post	Anxiety in adult hospitalized cardiovascular patients	NCTT/ MTT	STAI Questionnare	Significant decrease in TT group
Fedoruk 1984	17	Quasi-Exper. Repeated Measures	Response to stress in neonates	NCTT / MTT	ABIP Description of state.TcPO	Significant differences in APIB
Connell-Meehan 1985	108	Experimental Pre Post Test	Pain in postoperative adults	NCTT/ MTT/ medication	Visual Analogue Scale	No significant differences
Parkes 1985	60	Experimental Pre Post Test	Anxiety in gerontological hospitalized patients	NCTT/ MTT Adapted MTT	STAI Questionnare	No significant differences
Keller 1986	60	Experimental Pre Post Test	Tension Headache Pain in adults	NCTT/ MTT	McGill Melzack Pain Questionnare	Significant decrease in TT group

Table 3A: Research on Therapeutic Touch (TT), 1974 – 1986.

Author/year	N	Design	Variables and population	Intervention	Instruments	Outcome
Cronfalk 2008	22	interviews	Degree of satisfaction among palliative cancer patients	Soft tissue massage	BMT	Increased satisfaction. Counteracting vulnerability
Henricson 2008	44	RCT	Anxiety levels Intensive Care patients	TT / standard treatment	Motor Activity Assessment Scale	Anxiety decreased. Stabilization of circulatory parameters
Rosemary 2010	40	RCT	Stress reactivity in healthy newborn infants	TT-only/ Auditory, TT, visual, and vestibular, or no stimulation	Cortisol in saliva. Infant Behavioral State	Increase of stress reactivity in TT alone. Decrease of stress reactivity in multisensory stimulation group.
Jensen 2012	95	RCT	Healthy subjects	Moderate pressure massage/ control	Oxytocin, ACTH, betaendorfin	Increase in oxytocin, decrease in ACTH, betaendorfin
Morhenn 2012	22	RCT	Change in anxiety Massage therapists	Swedish massage / control	DASS	Decrease in subjective anxiety in MT

Table 3B: Modern research on TT and MT in the 2000s (examples).

Explanations of terminology used in tables 3A and 3B: *Quasi-experimental= specifically lack the element of random assignment to treatment or control. Casual touch = taking pulse, etc., MTT= Mock Therapeutic Touch,mimics TT, NMTT= Non Contact Tactile Touch, STAI= self evaluation questionnaire of subjective perceived feelings of anxiety, ABIP= endpoint infant state of anxiety, an instrument used in premature neonates, TcPO= transcutaneous pO_2, Modified TT= Therapeutic Touch, hands placed on fixed parts of the body. BMT= in-depth interviews. DASS = Depression, Anxiety and Stress Scale. RCT = Randomized Controlled Trial.*

1.3.3 Touch, hormonal and neuronal effects

In the literature the effects of "Touch" on pain sometimes are discussed in terms of alterations in concentration of the nine amino acid peptide *oxytocin*, secreted from the posterior lobe of the hypophyseal gland. The word oxytocin is derived from the Greek ὠκυτοκίνη, *ōkytokínē*, meaning "quick birth", after its uterine-contracting properties. Oxytocin is a mammalian hormone that also acts as a neuromodulator via oxytocinreceptors in hypothalamus, amygdala and other defined places in the brain. It is best known for its role in sexual reproduction, in particular during and after childbirth, facilitating breastfeeding. The behavioral effects of oxytocin are thought to reflect release from centrally projecting oxytocin neurons.
Professor Kerstin Uvnäs Moberg at the Swedish University of Agricultural Sciences introduced the theory of the secretion of oxytocin during massage therapy. Professor Uvnäs claims that only oxytocin can reduce aggression and increase social interaction and that it acts through intracerebral mechanisms with influences on oxytocin sensitive neurons. In a recent study significantly increased oxytocin concentrations were found when comparing moderate pressure massage of the upper back for 15 minutes with a control group that only received rest (Morhenn, 2012). In another recent study (five weeks long, 45 minutes per session) with Swedish massage therapy increased concentrations of oxytocin in plasma was found in the twice weekly massage group but not in the group that received massage once weekly. (Rapaport M.H., 2012)
Lenita Lindgren at Norrlands University Hospital in Umeå (Nus) has recently completed a dissertation concerning the intracerebral effects of tactile touch (Lindgren et al. 2012). Using functional Magnetic Resonance Imaging (fMRI) the hypothesis of eliciting specific responses in brain areas coding for pleasant sensations was studied. The fMRI results revealed that Touch Massage stimulation most strongly activated the pregenual anterior cingulate cortex (pgACC), the same area that has previously been shown to be activated by both opioid analgesia and placebo.

1.4 MUSIC THERAPY (M_UT):

Music is a universal art form that exists in every culture in the world. Music may also be a means through which people are able to cope with emotional conflicts and increase self-awareness. Music can induce changes in heart and respiratory rates. The neural pathways by which musical stimuli might exert their emotional and physical effects have been in focus in recent decades.

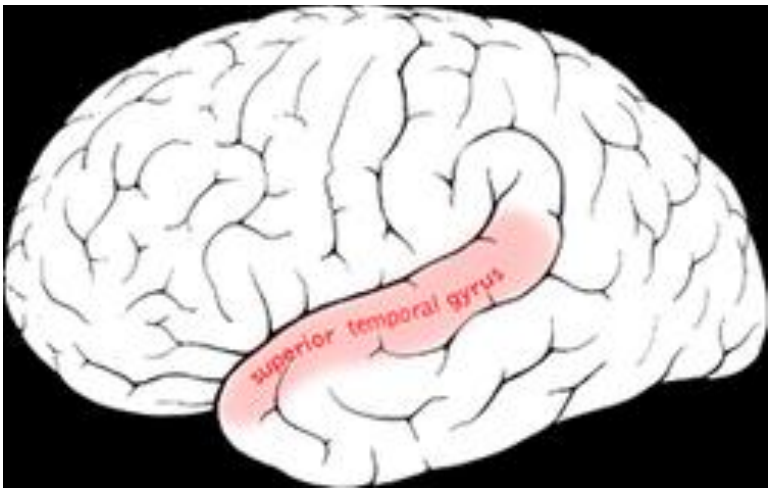


Fig.4: The *superior temporal gyrus contains the primary auditory cortex, which is responsible for processing sounds. Some areas of the superior temporal gyrus are specialized for processing combinations of frequencies, and other areas are specialized for processing changes in amplitude or frequency. The superior temporal gyrus also includes Wernicke's area, which (in most people) is located in the left hemisphere. It is the major area involved in the comprehension of language.*

Neuroimaging studies have shown the activation of specific pathways in several brain areas associated with emotional behaviors, such as the insular and cingulate cortex, hypothalamus, hippocampus, amygdala and prefrontal cortex (Boso et al. 2006) Among biochemical mediators likely to play a role in the perceptual and emotional processing of music in the brain, dopamine plays an important role. It has been shown to be released from the ventral striatum and from the ventral tegmental area in subjects listening to pleasant music (Menon and Levitin 2005)

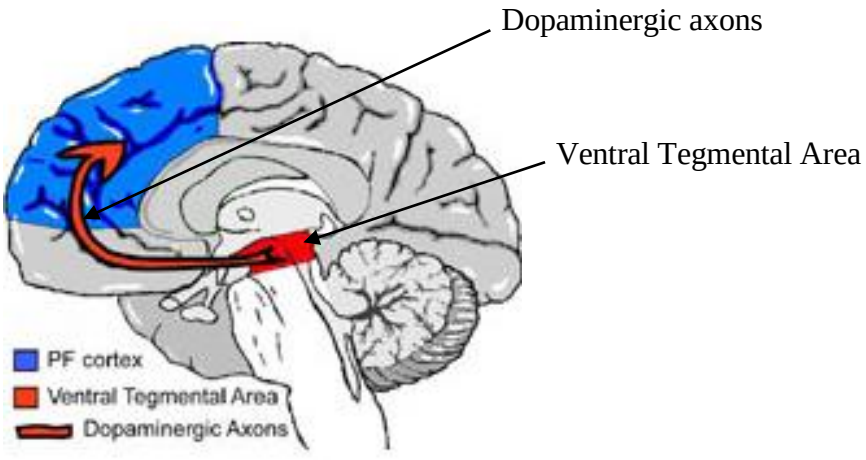


Fig. 5: The ventral tegmental area is involved in DA release in MuT.

Studies also indicate that MuT could be useful in the clinical management of numerous neurological and psychiatric disorders. The usefulness of MuT in motor, affective and behavioral functions of PD has been shown, and it has been suggested that MuT is a novel potential tool in rehabilitation programs involving PD patients (Pacchetti et al. 2000).
Our studies included the concept of MuT in that both the TT and the RTM groups were exposed to smooth, quiet music; **"**Music for well-being II – Letting go of stress", with identification number C6607, Fönix Musik, Sweden.

1.4.1 MuT and pain

Listening to music may reduce pain intensity levels and opioid requirements, but the magnitude of these benefits is small, and its clinical importance is therefore unclear. In studies that have evaluated mean pain intensity there have been considerable variations in the effect of music, indicating statistical heterogeneity. Studies that permitted patients to select the music on their own did not reveal a benefit from music as compared to those who did not select their own music. In this review only studies evaluating acute pain intensity up to 24 hours after surgery pointed toward reduced pain intensity levels and opioid requirements (Cepeda et al. 2006).
Soft slow music has, however, been shown to be effective in reducing depression and improving sleep quality (Chan et al. 2010), findings of utmost importance in understanding the couplings between depression, sleep and experiences of pain, and also in realizing the probable augmentation effects when added to Touch Therapies.

1.5 AROMA THERAPY (AT)

AT is the therapeutic use of essential oils from herbs, flowers, and other plants. As our studies included the use of specific oils, **"**Fibro oil" from Crearome AB, Gamleby, Sweden, mixed with Virgin oil comprising one third of the total volume, it is of interest to include current knowledge in the area of AT. In an overview of 10 relevant articles, Lee and co-authors concluded that the methodological quality in the studies was poor and that there was no convincing evidence regarding any of the studied conditions (Lee et al. 2012).

1.5.1 AT and pain

Two trials with the aim of examining the effects of aromatherapy for pain management in labor on maternal and perinatal morbidity were analyzed several years ago (Smith et al. 2011).
The trials found no difference between groups (AT / controls) for the primary outcomes of pain intensity or for the use of pharmacological pain relief. It is obvious when studying other articles and reviews in this field that most studies indicate positive effects in quelling anxiety, but the methodology is often lacking in quality and the evidence concerning effects is not convincing (Lee et al. 2012).
However, caregivers have used complementary therapies for many years in order to relieve anxiety, promote comfort, and reduce or alleviate pain. Anecdotal evidence and findings from numerous smaller studies provide support for the use of AT and other complementary therapies to manage chronic pain or for use as adjuncts in the treatment regimen. It is naturally of interest to study combined effects of treatments with impact on several senses simultaneously (Snyder and Wieland 2003).

1.6 MASSAGE THERAPIES (MT)

However, although sometimes confusing, massage therapies and Touch therapies often are divided.
The word derives from the French word massage [massa:sj]"friction of kneading", or from the Arabic massa meaning "to touch, feel or handle" or from the Latin massa meaning "mass, dough". The corresponding Greek verb is μάσσω (massō) "to handle, touch, to work with the hands, to knead dough". In contrast, the ancient Greek word for massage was "anatripsis", and the Latin word was "frictio".
The American Massage Therapy Association defines massage as "*manual soft tissue manipulation that includes holding, causing movement and/or applying pressure to the body. The practitioner applies manual techniques, and may apply adjunctive therapies with the intention of positively affecting the health and well-being of the client*" (AMTA, 1999).
MT is the manipulating of superficial and deeper layers of muscle and connective tissue using various techniques to enhance function, and "aid in the healing process", and to promote relaxation and well-being.
Per Henrik Ling (1776 - 1839) developed Swedish massage, the basis of many modern forms of MT. Ling was not trained in medicine, but he applied his ideas and techniques to the treatment of disease. This met with opposition from the Swedish medical community. However, Ling gained support from influential clients and was eventually able to teach his system to physicians who then adopted his techniques. Later in the 19th century the Dutch physician Johann Mezger was successful in reintroducing massage to

the scientific community, codifying some of its elements with terms that are still in use today (Fritz 2009).
In modern practice, MT is not a single technique. It is a broad heading for a range of approaches that share common characteristics. There is considerable variation in duration, and in the types of touch and strokes administered. Massage therapists and recipients may subscribe to different explanatory mechanisms. The outcomes being pursued may also vary widely, with one recipient hoping to obtain relief from a backache and another receiving MT to reduce emotional tension.
The most practical definition of MT is "*the manual manipulation of soft tissue intended to promote health and well-being"*.

1.6.1 Postulated physiological, neurological and psychological effects of MT

The interpersonal touch in the form of tissue manipulation is postulated to trigger certain physiological responses, and much of the research concerning MT is focused on measurable physiological parameters obtained in "positive directions" by the MT.
For short-term effects *the gate control theory* is most often referred to. This was first described almost 50 years ago (Melzack and Wall 1965).
In short, competing stimuli, such as pressure or cold, travelling along nerve fibers with faster velocity than the fibers with which pain is mediated, reduce the transmission of pain stimuli to the brain, effectively "closing the gate" (Moyer 2004) .
CT (C tactile) afferents are a distinct type of unmyelinated, low-threshold mechanoreceptive units existing in the hairy but not glabrous skin of humans and other mammals. Evidence from patients lacking myelinated tactile afferents indicates that signaling in these fibers activates the insular cortex (Olausson et al. 2010). Recent studies in mice have supplemented the knowledge in this field with the detection of unmyelinated sensory neurons that exclusively innervate hairy skin and that have large terminal nerve- arborizations that resemble the receptive fields of C-tactile afferents in humans. These findings probably explain the pleasant sensations produced by stroking the skin. (Vrontou et al. 2013).
MT may also provide *a shift in the autonomic nervous system* from a state of sympathetic response to a parasympathetic state of response. A body faced with threat or challenge is associated with an increase in stress hormones, increased cardiovascular activity and feelings of tension. The pressure applied during MT may stimulate vagal activity (Field and Diego 2008). In this way MT may promote reductions in anxiety, depression and pain, consistent with a state of calmness.
Several condition-specific benefits are shown with MT; increased immune system responses in HIV-positive individuals have been demonstrated (Diego et al. 2001). Increased levels of serotonin have been shown in some studies; others have suggested stimulation of endorphine release into the bloodstream with MT.

The breakdown of subcutaneous adhesions and the prevention of fibrosis have also been discussed (Donnelly 2002). The relationship between sleep deprivation and pain sensations is interesting. We know that substance P increases and somatostatin decreases in the absence of deep sleep. Both these substances have been linked to pain experience (Callahan 2001). In the present “Parkitouch study”, among other outcome measures, effects of TT and RTM on sleep were studied.

1.7 C: STRESS AND ASSOCIATED TERMS

The Merriam-Webster encyclopedia® defines the term *stress* as a *"physical, chemical, or emotional factor that causes bodily or mental tension and may be a factor in disease causation"*. The result of stress can be explained as bodily or mental tension resulting from factors that tend to alter an existing equilibrium.

The findings of Hans Seyle
Hans Seyle (1907-1982), a Hungarian endocrinologist, conducted a great deal of important scientific work on the hypothetical non-specific response of an organism to stressors. While he did not recognize all of the many aspects of glucocorticoids, Seyle was aware of their role in the stress response and demonstrated the existence of biological stress. He discovered and documented that stress differs from other physical responses in that "stress is stressful" whether one receives good or bad news, whether the impulse is positive or negative. One of the systems whereby the body copes with stress, the hypothalamic-pituitary-adrenal (HPA) system, was also first described by Seyle. He also pointed out an "alarm state", a "resistance state", and an "exhaustion state", largely referring to glandular states.

1.7.1 Physiological responses

The well known role of stress in humans is as a method of reacting to difficult and possibly dangerous situations. The "fight or flight" response when a person perceives a threat helps the body exert energy to fight or to run away in order “to live another day”. This response is noticeable when the adrenal glands release *epinephrine*, causing the blood vessels to constrict and the heart rate to increase. In addition, *cortisol* is released under stress and its purpose is to increase the level of *glucose* in the blood. Glucose is the main energy source for human cells and the purpose of its increase during times of stress is to have energy readily available for overactive cells. The release of these substances is intended to be temporary. If someone is under stress for long periods of

time (“chronic stress”) this is hypothesized to result in adverse health effects later on, such as hypertension and increased risk of cardiovascular disease, see 1.7.2 below.

1.7.2 Chronic stress

This expression does not have an official scientific explanation; it is mainly used as a concept expressing the *effects* of sustained stress. Chronic stress can be rooted in prolonged psychological stressors. It can be described by using an epidemiological study as an example. When looking at the health effects of social discrimination in African Americans, markedly higher hypertension levels were found that were attributed to higher levels of perceived social discrimination (Blascovich et al. 2001; James et al. 1984).
Another important term in this context is *exhaustion*, which is not used in current literature but which is expressed in the experiences of PD patients with chronic pain. Exhaustion is described as a state of being depleted or emptied, a loss of strength and vitality. In scientific literature the term is often used interchangeably with *fatigue*, described as weariness or exhaustion from labor, exertion or stress. In biophysiological terms fatigue can be described as the temporary loss of power to respond that is induced in a sensory receptor or motor end organ by continued stimulation.
The connections between exhaustion, depression, anxiety and diurnal concentrations of cortisol were thoroughly described in a thesis by Sara Lindeberg in 2011. One of the main conclusions was that exhaustion - as a unique condition in chronic stress - is probably associated with specific HPA dysregulation, involving flattened diurnal cortisol rhythm and hypocortisolism (Lindeberg 2011).

1.8 D: HPA-AXIS FUNCTION

1.8.1 Relations between different forms of stress and HPA-axis function

One of the major contributors to the allostatic load of an organism (i.e. an organism burdened by cumulative stress) resulting in wear and tear on the organism is the exposure of cortisol as one of the catabolic agents together with other substances such as stress peptides (corticitropin releasing factor,CRF) and pro-inflammatory cytokines (IL-1, TNFα). As described, cortisol secretion plays an important role in these processes, regulated by the hypothalamic–pituitary–adrenal (HPA) axis.

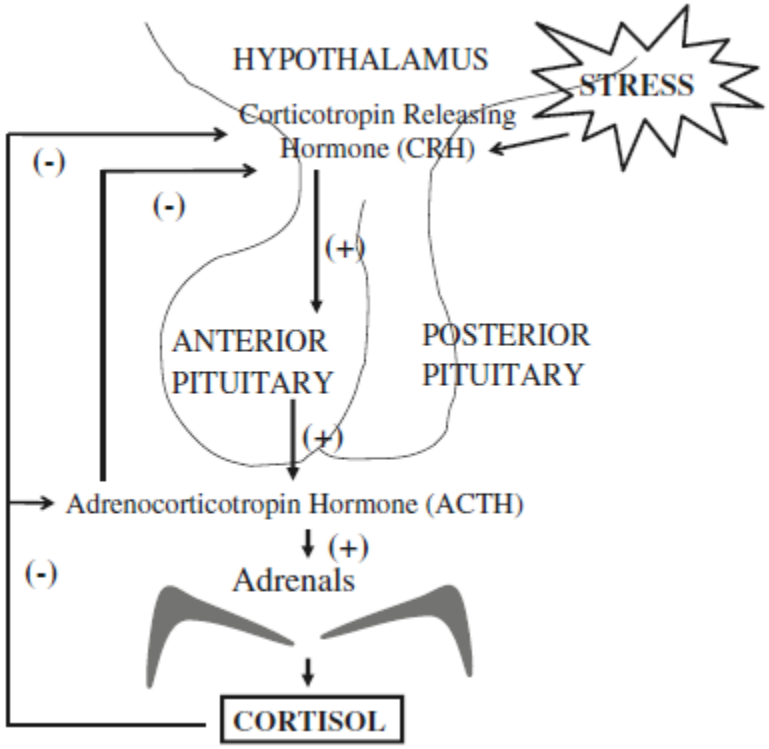


Fig.6: Physiology of the hypothalamic–pituitary–adrenal (HPA) axis (Source: File:Basic HPA Axis.jpeg. wikipedia.org)

The HPA axis involves the release of CRH from the paraventricular nucleus of the hypothalamus, causing the secretion of adrenocorticotropic hormone (ACTH) from the anterior pituitary gland, which in turn leads to the release of glucocorticoids from the adrenal cortex. Cortisol is described as an "active" glucocorticoid as it has direct impact on the metabolism of glucose, protein and fats as well as being a regulator of the immune system.

In the literature, several studies have focused on stress exposure and acute effects on the HPA axis.
A model study of the acute effects shortly after intervention with an "emotional freedom technique" (EFT) was recently presented. Significantly decreased salivary cortisol concentrations were shown in the active groups that received EFT and these mirrored the observed improvement in psychological distress. Anxiety and depression scores also improved (Church et al. 2012).

Salivary cortisol and posttraumatic stress reactions have been studied (Aardal-Eriksson et al. 2001), and condensed data from five studies showed increased free salivary cortisol and ACTH responses in all age and gender groups when participants were exposed to psychosocial laboratory stress tests (Trier Social Stress Test, TSST). The patterns in young and elderly adults suggested a decrease in the heightened hypothalamic drive with age (Kudielka et al. 2004). In another study of parents of mentally ill adult children with severe psychiatric illness, multiple samples of cortisol in the saliva of the parents were analyzed in order to reflect the psychological impact on the parents (Barker et al. 2012). On days after elevated stress, a hypoactivation pattern of diurnal cortisol suggestive of chronic stress was evident for parents of individuals with a serious mental illness. These findings, along with others, led to the hypothesis of "hypocortisolism," referring to low levels of circulating cortisol in persons living with chronic stress conditions.

The HPA axis can be described as a major stress response system that is critical for survival and adaptation. The so-called " preservative cognition hypothesis", which in brief is a theory of how repetitive, intrusive thoughts may amplify, maintain or reactivate physiological responses to stressors, was described in one of the few studies that examined rumination as a contributor to prolonged activation of cortisol secretion. The recall of a stressor served to reactivate the physiological stress response later in time. The effects were mirrored by an increased salivary cortisol concentration reflecting an activation of the HPA-axis function when participants were reminded of uncomfortable experiences several weeks earlier. These effects are also important to take into consideration when HPA-axis function is studied in PD patients with chronic relapsing pain. It is very probable that earlier unpleasant experiences within the groups studied in this thesis are corresponding "triggers" of the HPA-axis function.
As mentioned, there are several examples of studies where acute stress-relieving interventions have had an impact on the HPA axis function. In a study from 2006 where massage therapy was used in migraine treatment, there was a decrease in salivary cortisol concentration from 6.2 to 3.9 nmol/l after the first session, and from 6.2 to 3.4 after the sixth intervention. Unfortunately, no registrations of cortisol concentrations in the untreated control group, also suffering from migraine, were performed (Lawler and Cameron 2006).
The degree of depression may play a role in both pain sensitivity measured by the Pain-O-meter instrument (POM) and salivary cortisol concentration. This was shown in a study where 88 patients with major depression and 41 healthy controls were compared concerning effects of pain stimuli and cortisol/amylase concentrations in saliva.

Subjects wore coils connected to a stimulator on the wrist. The device provided electrical current to the motor and sensory fibers of the median nerve in incremental steps until the threshold stimulus for toleration was reached. POM scores in this study were rated significantly higher in the group with major depression than in the control group (Tanaka et al. 2012). However, in this study there were significantly elevated levels of salivary amylase in depressed female participants compared to controls, but no differences were seen in salivary cortisol levels between major depressive patients and controls before and after painful stimulation.

1.8.2 Challenges with HPA-axis function as a physiological mirror of changes in stress

There are numerous environmental and genetic factors that can increase an individual's exposure to cortisol. To date, population-based studies have been hampered in exploring a neuroendocrine link between chronic stress and concentration of cortisol in plasma, urine or saliva. This is due to lack of incorporation of reliable measures of chronic cortisol exposure that would permit quantification of the metabolic burden imposed by cortisol production. Golden et al. point out that one of the major problems in selecting and interpreting cortisol measurements in epidemiological studies is that most existing measures reflect cortisol exposure over a very short duration of time, often only as single measurements of morning cortisol concentration. Interpretations of the results are not reliable for quantifying the allostatic load imposed by chronic cortisol exposure over time (Golden et al. 2011). Another problem discussed by Golden is the need to be aware of the test-retest reliability of cortisol procedures, which vary widely, and only a few can be useful for epidemiological studies. In addition, certain measurements of HPA-axis tone, such as overnight and 24-h urine free cortisol, laboratory-based stress tests, and measurements of CRH and ACTH, respectively, are cumbersome for use in population-based studies. In particular, CRH and ACTH are labile and require immediate laboratory processing to avoid sample degradation, and they are pulsatile, so that a one-time measurement is unlikely to reflect diurnal activity. Golden concludes that sampling multiple salivary cortisol measures across the diurnal curve (with awakening cortisol) has similar between-visit reliability as dexamethasone-suppressed salivary cortisol concentrations and adrenal gland volumes as measures of HPA-axis tone.

The correlations between chronic stress and the HPA-axis function have been further problematized by Morris et al in a meta-analysis of 47 studies with respect to effects on the HPA axis of exposure to traumatic stress and development of posttraumatic stress disorder (PTSD).The daily cortisol output was lower for PTSD compared to trauma-exposed individuals without PTSD and no-trauma controls. The HPA effect size was moderated by the time since index event, thus suggesting the HPA feedback function to be a marker of trauma-exposure rather than vulnerability for PTSD. (Morris et al. 2012).

1.8.2.1 Relations between antiparkinson therapies, HPA-axis function and other neuronal systems

A synergistic relationship is thought to exist between HPA-axis activity and dopamine neurotransmission, but this is not fully understood (van Schijndel et al. 2011).

1.8.2.1.1 Levodopa

Data indicate that the major effects observed after administration of exogenous levodopa are not due to a direct action of the compound on dopamine receptors, or to extrastriatal release of dopamine, but to conversion of levodopa to dopamine by serotonergic terminals and probably intrastriatal cells. Consideration of interactions between other neuronal systems than the dopaminergic system is of great interest. Serotonergic neurons also appear to play an important role in the action of levodopa in the later stages of Parkinson's disease (Lopez et al. 2001).
Questions about the impact of levodopa on the HPA function were raised and discussed as early as in the 1970s. In one study 1 g of levodopa was given to 14 male volunteers and concentration levels of plasma growth hormone were measured. The increase in growth hormone in plasma correlated well with the absorption of the drug. Changes in prolactin concentration corresponded to a decrease in the circulating hormone. However, no correlations between basal levels of growth hormone and prolactin and the magnitude of the changes were seen.
Following nighttime administration of levodopa, RLS patients have been shown to manifest a more pronounced inhibition of prolactin release and an increase in growth hormone secretion. Prolactin plasma levels have been shown to significantly correlate to the periodic limb movement index on a polysomnogram and could possibly reflect enhanced circadian variations in dopaminergic function and support an increased sensitivity at night of dopamine receptors in patients with RLS (Garcia-Borreguero et al. 2004).
Administering levodopa and testing for insulin-tolerance have been shown to result in normal increments of plasma cortisol following induction of hypoglycemia, but no consistent cortisol response after L-dopa administration (Vizner et al. 1983).
Other studies have also confirmed the lack of effect on cortisol concentration and the HPA-axis function after levodopa administration or by dopamine agonists (Charlett et al. 1998).
In one study, however, a decreased concentration 30 minutes after intake of 200 mg levodopa (Muller et al. 2007) was shown. The methodology in this study included the complete withdrawal for 12 hours of the ordinary antiparkinson therapy in form of levodopa, which per se must be considered a stressor.

1.8.2.1.2 Other examples of antiparkinson therapies and HPA-axis function

Although Charlett et al did not show any effects on the HPA axis of

levodopa/dopamine- agonists, their study revealed significant reduction in plasma cortisol concentration (around 80%) by selegeline, a MAO-B inhibitor used in the arsenal of antiparkinson drugs (Charlett et al. 1998).

1.8.2.1.3 Advanced therapies in PD and HPA-axis function

As earlier described, one of the treatments for PD in later phases of the disease is deep brain stimulation of the subthalamic nucleus (STN-DBS). In patients with advanced PD this has been clearly shown to improve quality of life and reduce the amount of oral antiparkinson medication. Considering anatomical and functional connections of the STN with the HP system, a study has recently (Seifried et al. 2012) been performed to investigate HPA functioning in PD patients with STN-DBS. Chronic application of high-frequency electrical stimuli in the STN in this study was not found to be associated with HP dysfunction in patients with advanced PD. The diurnal variability of peripheral cortisol secretion as an important element in the endogenous biological clock remained intact.

1.8.3 Relations between MT treatments and effects on the HPA axis, an overview

Physiological effects of MT on the HPA axis measured by cortisol in plasma/urine or saliva have been observed in different studies (Moraska et al. 2010).It was found that a single treatment with MT resulted in reductions in cortisol concentration and heart rate. These findings were consistently noted when analyzing 25 articles relevant to both massage therapy and stress. The data concerning effects of multiple treatments were insufficient in order to draw definitive conclusions regarding the effects of MT on urinary cortisol.

Table 4 shows a review of the results concerning HPA-axis function after different forms of MT. In some studies single and multiple treatment effects were registered, analysis of urinary cortisol was used for multiple treatment effects, and most studies used salivary cortisol sampling for short-term effects. Plasma cortisol was analyzed in only one study. The median number of participants in these studies was 28, and only one study had more than 50 participants. In 9 /14 studies ≥ 80% were females.

First author	Year	Participants /conditions	n/% female	Mean age (y)	Study design	Massage duration (min)	Massage regimen	Time of sampling	Results cortisol
Field	1996	Medical staff	n=50/80%	26	RCT	15	2/Wx5W	Pre-post 1st and 10th massage	Single treatment (S) 1st ↓b 10th ↔
Ironson	1996	HIC positive and negative gay men	n=19/0%	33	Within subjects	45	5/Wx1M	Pre-post 1st massage, 1st versus last day	Single treatment (S) 1st ↓a Multiple treatment (U) ↓a
Field	1997	Sexual abuse victims	n=20/100%	35	RCT	30	2/Wx1M	Pre-post 1st and 8th massage	Single treatment (S)1st ↔ 8th ↓a
Field	1998	Burn patients	n=28/14%	NR	RCT	20	5/Wx1W	Pre-post 1st and 5th massage	Single treatment (S) 1st: ↓b 5th ↓a
Field	1998	Bulimia	n=24/100%	16-21	RCT	30	2/Wx5W	Pre-post 1st and 10th massage 1st versus last day	Single treatment (S) 1st ↓a 10th ↔ Multiple treatment (U) ↓a
Leivadi	1999	University dance students	n=30/100%	20	RCT	30	2/Wx5W	Pre-post 1st and 10th massage	Single treatment (S) 1st ↓b 10th ↓a
Hernandez-Reif	2000	Hypertension	n=30/70%	52	RCT	30	2/Wx5W	Pre-post 1st and 10th massage 1st versus last day	Single treatment (S) 1st ↓a 10th ↓b ↓a Multiple treatment (U)

Abbreviations: N= number of subjects; Y = years; NR Not Reported; RCT; Randomized Controlled Study; W = week; M= month; P= plasma sampling; S=saliva sampling; U= urine sampling: ↓= significant decrease; ↑= significant increase; ↔= no significant change; [a] = p< 0.05; [b] =p<0.001

First author	Year	Participants /conditions	n/ % female	Mean age (y)	Study design	Massage duration (min)	Massage regimen	Time of sampling	Results cortisol
Hart	2001	Anorexia nervosa	n=19/100%	26	RCT	30	2/Wx5W	Pre-post 1st and 10th massage 1st versus last day	Single treatment (S) 1st ↓a 10th ↔ Multiple treatment (U) ↔
Hernandez-Reif	2001	Low back pain	n=24/54%	40	RCT	30	2/Wx5W	1st versus last day	Multiple treatment (U) ↔
Hernandez-Reif	2002	***Parkinson´s disease***	n=16/50%	58	RCT	30	2/Wx5W	1st versus last day	Multiple treatment (U) ↔
Taylor	2003	Post-operative cancer	n=105/100%	NR	RCT	45	1 dayx3 days	Pre 1st and 3rd massage	Multiple treatment (U) ↔
Andersson	2004	Type II diabetes	n=11/100%	58	Within subjects	60	1/Wx10W	1W pre, 1Wpost, 12W post	Multiple treatment (P) (1 W pst) ↓a (12 W post) ↔
Hernandez-Reif	2004	Post-surgery breast cancer	n=34/100%	53	RCT	30	3/Wx5W	1st versus last day	Multiple treatment (U) ↔
Bost	2006	Nurses/healthy	n=48/100%	42	RCT	15	1/Wx5W	Baseline, W1,3,5	Multiple treatment (U) ↔
Lawler	2006	Migraine	n=44/91%	41	RCT	45	1/Wx6W	Pre-post 1st and 6th massage	Single treatment (S) 1st ↓b 6th ↓b

Table 4: Studies of Massage Therapy effects on HPA-axis function, 1996 - 2006.

Comments: In Field´s study from 2006 on medical staff, chair massage (sitting position) was administered; in Andersson´s interventions from 2004 on patients with diabetes type II, whole body Tactile massage was administered. In Hart´s study from 2001on patients with anorexia nervosa, there were group differences at baseline for salivary and urinary cortisol, and in Lawler´s study from 2006 on migraine patients, salivary cortisol was not measured in the control group.

1.8.4 The Cortisol Arousal Reaction (CAR)

The CAR is considered a reliable measure of the acute reagibility of the HPA axis (Schmidt-Reinwald et al. 1999). Determination of the CAR typically requires self-collection of saliva samples within the domestic setting at regular intervals post-awakening for between 30 and 60 min (e.g. 0, 15, 30 and 45 min post-awakening), and the peak of secretion characteristically occurs between 30 and 45 min post-awakening (Fries et al. 2009).

An approximate 10-min time lag between awakening and the start of the cortisol rise has been shown (Smyth et al. 2013).

Subjects who described themselves as chronically (i.e. for at least six months) stressed due to work overload showed an enhanced morning cortisol response (Schulz 1998). Results showed that the morning cortisol response was of similar magnitude as that following injection of 1 μg /kg h-CRH or exposure to a brief psychosocial stressor test (TSST).

Influences on the CAR by CAM therapies has only been described in a small pilot study with traditional Chinese acupuncture (TCA) consisting of 18 adult volunteers, all with a high degree of self-reported stress (Huang et al. 2012) The small cohort was split into three arms: one with intervention with TCA, one attentional group without TCA, and one control group. The CAR showed an average increase during the intervention for both the TCA and attention groups, interpreted by the study group as normalization of the CAR and a lower state of stress, although significant differences could not be shown between the groups. The conclusion reached in this study was that measuring the increase in morning cortisol (CAR) could be a useful outcome measure for monitoring the effects of treatment on perceived stress. The CAR reaction after intervention with TT and RTM was not specifically analyzed in our study. However, it is of great importance to be aware of this phenomenon when analyzing HPA-effects of interventions administered with short time lags after awakening.

2 HYPOTHESIS AND AIMS

2.1 GENERAL AIMS

- To describe and analyze the subjective experiences of pain, sleep patterns, health-related quality of life (HRQoL) and the function of the hypothalamic-pituitary-adrenal (HPA) axis in a population of patients with stable, well-treated Parkinson´s disease (PD).
- To describe the subjective experiences of Complementary and Alternative Medicine (CAM) and the specific effects of Tactile Touch (TT) in PD patients with chronic pain.

2.2 SPECIFIC AIMS AND HYPOTHESIS

2.2.1 Paper I

Hypothesis: PD patients have an abnormal diurnal cortisol secretion curve with decreased cortisol variability (Hartmann et al. 1997).
The primary aim of this paper was to analyze diurnal salivary cortisol concentrations in patients with and without chronic pain and to correlate these with age, gender, body mass index (BMI), duration of PD and pain.
The secondary aim was to compare the HPA-axis function in PD patients with chronic pain with a healthy sex and age- matched reference group from the same area.

2.2.2 Paper II

Hypothesis: Single and multi-repeated TT decreases the HPA-axis activity and salivary cortisol concentrations by reducing the degree of stress.
The primary aim was to analyze and compare the basal diurnal and total secretion of salivary cortisol in short and long-term aspects of interventions with TT and RTM.
The secondary aim was to study associations between salivary cortisol, clinical characteristics and interventions.

2.2.3 Paper III

Hypothesis: PD with chronic pain affects patients differently in different respects and the experiences of pain affect sleep patterns and HRQoL in a negative way.
The primary aim was to evaluate and describe PD patients' subjective experiences of chronic pain, sleeping patterns and HRQoL.
The secondary aim was to analyze the time point for onset of pain in relation to the time point for PD diagnosis, and to describe experiences of treatments and differences between genders.

2.2.4 Paper IV

Hypothesis: TT decreases the degree of stress and results in diminished pain, normalized sleep patterns and HRQoL.
The primary aim was to compare the short and long-term effects of TT and RTM in patients with PD with chronic pain.
The secondary aim was to describe the within-group effects regarding aspects of pain experiences, sleep patterns and changes in HRQoL.

3 METHODS

3.1 CONSORT FLOW

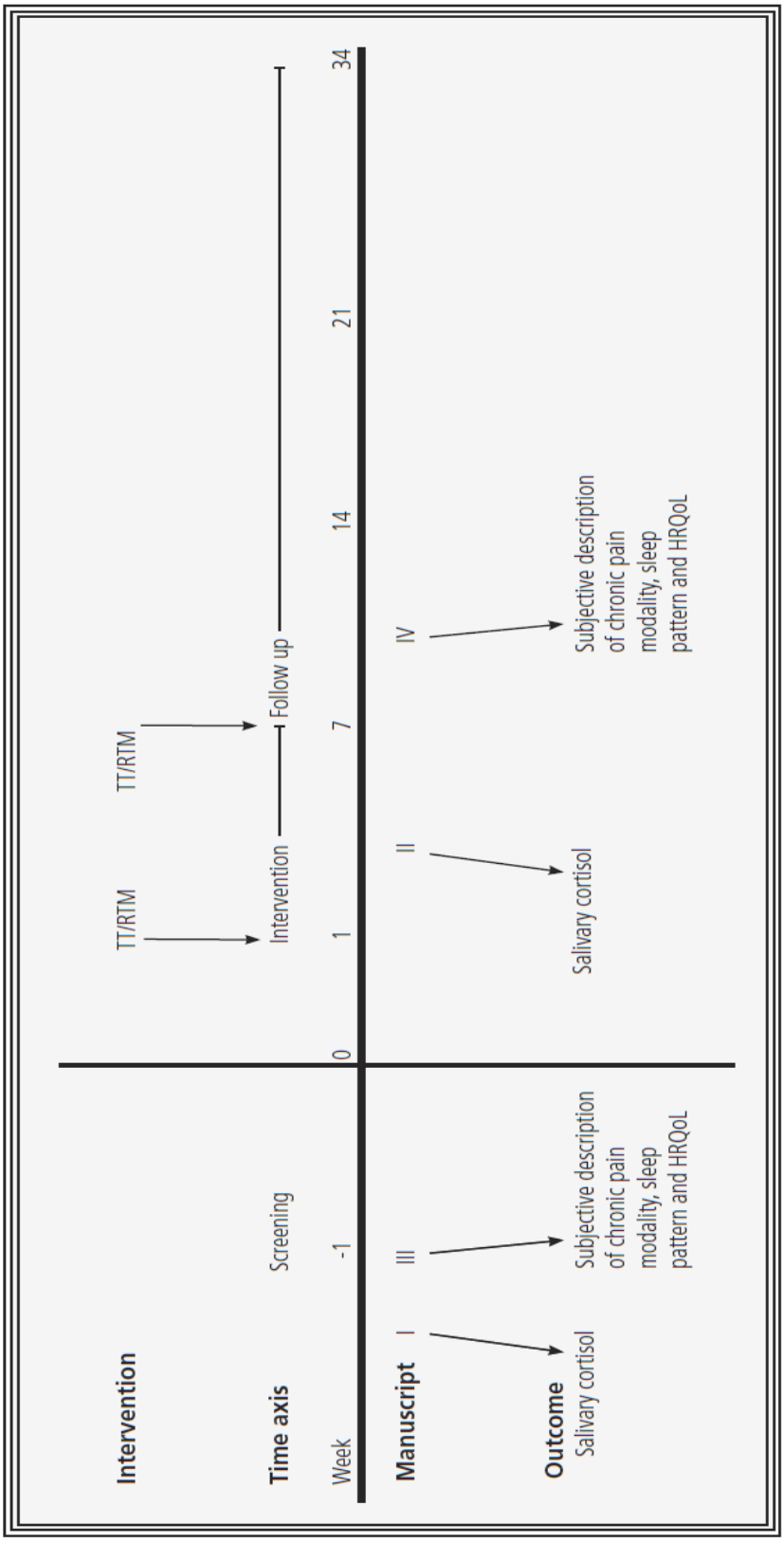


Fig 7: Consort Flow scheme for the Parkitouch study, manuscripts / relation to time axis.

3.2 THE TACTILE TOUCH CONCEPT

The CAM-method studied in this thesis is called "Tactile Touch"*. A short description of the technique and the content of this concept are described in *Appendix I.* Soft music (Music for well-being II - letting go of stress" LC6607 Fönix Musik, Sweden), and a fragrant lavender aroma, **"**Fibro oil®" (Crearome AB, Gamleby, Sweden), mixed with Virgin oil comprising one third of the total volume, filled the room. The room temperature was approximately 22-24° C. There were lighted candles, a draped massage table and a chair in the room.

** In this thesis, as the active control, "Rest To Music", includes all parts of the concept except the tactile component, the collective name used is Tactile Touch when described in broader perspectives than comparisons between the two groups TT and RTM.*

3.2.1 Rest to Music

As several of the external conditions described above may appear as a form of therapy on their own, we chose a control group that experienced the same concept except for the tactile touch component. The physical contact between the therapist and the recipient was the only difference between the two groups; for a description see *Appendix II*.

3.3 PARTICIPANTS AND PROCEDURES

row	Samples	Total	Main measures used	Papers
1	PD-patients with chronic pain TT group	29	Basal characteristics Salivary cortisol samples, VAS^{max}-scale, UPDRS I-IV, H&Y, POM, PEA, PDSS, SF36, Pharmacotherapy	I - IV
2	PD-patients with chronic pain RTM group	15	Basal characteristics Salivary cortisol samples VAS^{max}-scale, UPDRS I-IV, H&Y, POM, PEA PDSS, SF36, Pharmacotherapy	I - IV
3	PD –patients without pain	16	Basal characteristics, Salivary cortisol samples, UPDRS I-IV, H&Y Drug list	I
4	Reference group[1]	608	Basal characteristics Salivary cortisol samples	I

Table 5: Participants in the Parkitouch study group (rows 1 and 2), control group without chronic pain (row 3), and reference group (row 4) [1]= from Larsson et al. 2009.

Data collection was cross-sectional and prospective. The general procedure in the study was as follows: Patients in regular outpatient clinics were contacted about participating in the study. Written information about the purpose and procedures was given to the patients. The participants gave their written informed consent to take part.
Questionnaires and tubes for collecting saliva were distributed to the participants. Questionnaires were completed in the waiting room or at home. They were collected by the research staff at the predetermined time points
To minimize stress salivary sampling was performed at home with detailed written instructions; time points for wake up, sampling and intake of medicine were registered in a special protocol. Saliva was sampled at four time points daily; in the early morning at 8am, at 1pm, at 8pm and at 8 am the next morning. Samples were placed in their fridges before sending the collected samples to the laboratory.This procedure was performed at five occasions: at baseline, and at three, eight, 21 and 34 weeks after randomization.

3.3.1 Samples from participants with PD and no history of chronic pain (PD-noP)

Sampling from these 16 participants, eight females and eight males, followed the same procedures as for the participants in the Parkitouch study.
Verbal information was given to patients at a visit or by telephone, and was thereafter followed by written information on the purpose of the study. Written informed consent was obtained from the patients. Salivary cortisol tubes along with a schedule for the exact time points for sampling (see above) were then given to the patients.The detailed instructions were the same as for the PD-P: Participants were instructed to have no intake of food within 30 minutes of sampling and that the swab was to be chewed for two minutes and then placed into the plastic tube. They were also told not to brush their teeth immediately before sampling to avoid possible blood contamination.

3.3.2 Samples associated with interventions (PD-P)

Salivary cortisol samples were also measured at two additional different time points, immediately before, immediately after and thirty minutes after the end of interventions number one and eight in the TT and the RTM groups.The same procedures were followed as described above, samples were collected at the place for intervention.

3.3.3 Samples referred to from the reference group

Information about these samples comes from the study by Charlotte Larsson et al (Larsson, 2009). The same device along with both verbal and written instructions for usage was employed. Saliva was collected at 8am and 10pm with a maximum deviation of 30 minutes, participants abstained from food, drinks, snuff, smoking, brushing of the

teeth and exertion before the sampling. The sampling was performed in the same municipality. The analysis of cortisol in saliva used the same laboratory and the same method as among our participants; radioimmunoassay from Orion Diagnostica (Spectria^{TM} Cortisol^{I125}). The preparation, freezing procedures and method of analysis were identical to ours.

3.4 MEASURES

3.4.1 Cortisol sampling scheme

Comparison			**First v Eighth**	**First v Eighth**	**Screening**	**Screening**	**Screening**	**Screening**	
Time axis (Week)		wk -1	wk 0	wk 5	wk 7	wk 14	wk 21	wk 34	
		Screening	First Intervention	Eighth Intervention	Follow up				Statistical methods used[3]
Outcome		Cortisol Diurnal	Cortisol Before, 0 min, 30 min	Cortisol Before, 0 min, 30 min	Cortisol Diurnal	Cortisol Diurnal	Cortisol Diurnal	Cortisol Diurnal	
PD without chronic pain (PD-no-pain)	n=16	X							
PD with chronic pain (PD-pain)	n=44 TT,[1]n=29 / RTM[2],n=15	X	X	X	X	X	X	X	

Table 6: Cortisol sampling scheme, an overview. *Notes: [1]=TT = Tactile Touch, [2]=RTM = Rest To Music. [3]= Kruskal Wallis one way analysis, Mann-Whitney U-test used to compare TT and RTM. Friedman´s ANOVA used to compare diurnal cortisol rhythm and total cortisol secretion during the five study time points.Added to these tests were Spearman rank order corr.test used to analyze association between cortisol and clinical characteristics.Wilcoxon matched-pairs signed rank test analysed the individual diurnal cortisol rhythm.*

3.4.2 Salivary cortisol, Papers I and II.

The measurement of salivary cortisol

Previously, cortisol was measured solely by sampling blood or urine. During recent decades techniques for collecting and measuring cortisol concentrations in saliva have been developed for adults. (Aardal-Eriksson 2002, Kirschbaum 1994).

An advantage over urinary cortisol is that serial samples can be collected to discern real-time levels - time-of-day differences or pre-post-stress levels. Urinary cortisol provides a measure of total secretion over a time period, 12 or 24 hours.

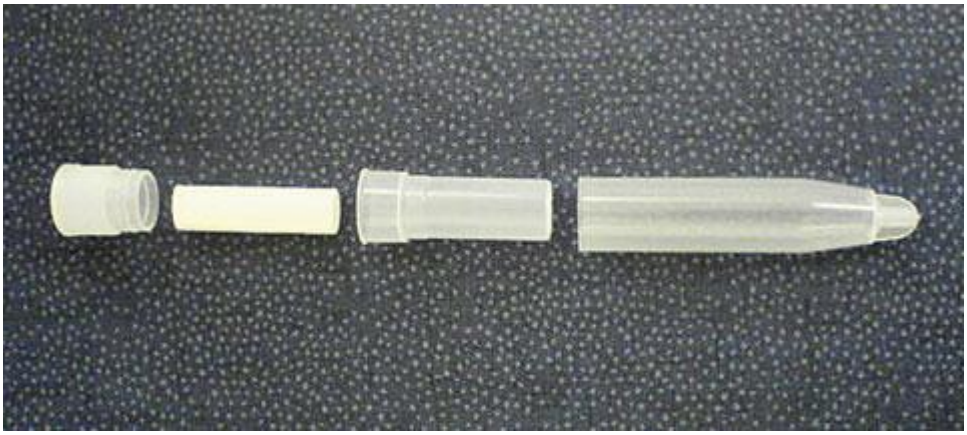


Fig. 8: Equipment for collection of salivary cortisol; cotton-based Salivette ™.

Salivary cortisol is highly correlated with the active free fraction of cortisol in serum (Kirschbaum & Hellhammer 1994). Cortisol, which is a small, neutral, lipophilic molecule, enters the saliva through passive diffusion through the salivary gland epithelium (Quissel 1993).

The salivary cortisol concentration is not influenced by salivary flow rate or protein content (Aardal-Eriksson 2002, Kirschbaum 1994, Umeda et al 1981).

Measurement of salivary cortisol has the advantage of being easy to perform in large studies in the free-living state. It has several other advantages including being non-invasive, pain-free, and that it allows for timed sample collections in the free-living state without the need for medical personal. It is stable at room temperature for at least one week and thus can be mailed back to the investigator for measurement of the free or the physiologically active form of cortisol. It has a strong correlation to free cortisol measured in plasma and serum. Salivary cortisol concentrations are also stable following repeated cycles of freezing and thawing, and cortisol levels in centrifuged saliva samples may be stored at ^{0}C for 3 months or at -20 - -80 ^{0}C for at least one year. Because cortisol measured in saliva is free and not bound, it is not subject to variation by factors such as oral contraceptives that affect cortisol binding globulin (CBG), the primary transport protein for serum cortisol (Golden et al. 2011).

In 2007 Granger et al. showed that a small methodological problem in field studies of salivary cortisol might be blood contamination due to minor wounds in the oral mucosa, since cortisol is present in roughly 50 times higher concentrations in serum than in saliva (Kivlighan et al 2004).

Limitations to consider in using salivary cortisol measurements to assess HPA-axis tone include contamination of the salivary cortisol collection device by over-the-

counter hydrocortisone creams and ointments, salivary blood, consumption of low pH substances (which can artificially raise cortisol levels), non-compliance with the recommended sample collection time, insufficient saliva collection, and the effect of smoking (current smoking is associated with higher levels than non-smoking and former smoking). Additionally, several medications (e.g. oral, nasal, topical, and ophthalmic corticosteroids; alpha, beta, and cholinergic receptor antagonists) have the potential to impact salivary cortisol levels; however, few behaviorally oriented studies have comprehensively documented medication use or focused on the impact of various medication classes on salivary cortisol levels (Golden et al. 2011)

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3.4.2.1 Salivary cortisol compared to serum cortisol

In a study by T. Deutschbein and others (Deutschbein et al. 2009) it was elegantly shown that measurement of cortisol in saliva is a sensitive method with a very good correlation to serum cortisol in different tests.
From comparisons in children with recurrent abdominal pain (RAP), Törnhage has shown high correlations between salivary and serum cortisol, see fig.9:

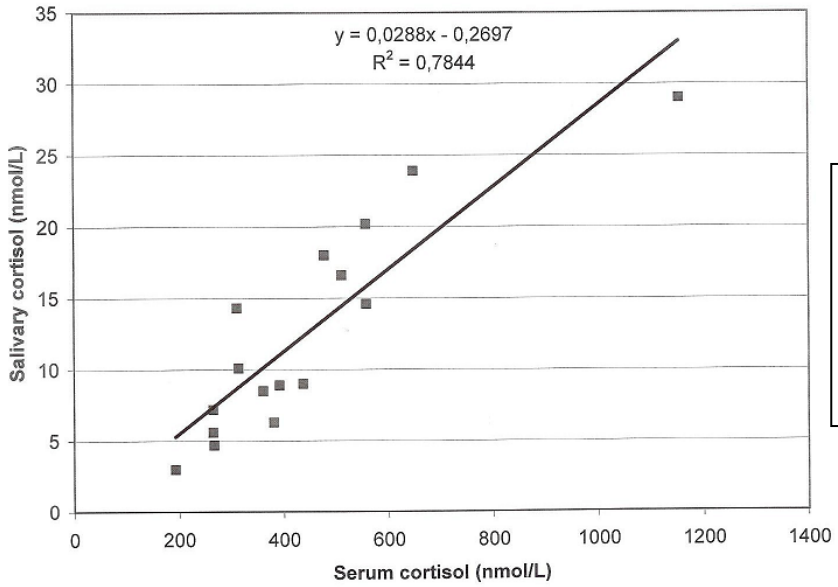


Fig. 9: Correlation between salivary and serum cortisol in 16 children with RAP. (Törnhage, 2008, unpublished data)

3.4.2.2 Salivary cortisol in this thesis

Saliva was collected using a commercial Salivette plastic test tube (fig.8), consisting of an absorbent cotton roll, a plastic roll retainer and a centrifuge tube. The following written and oral instructions were given to the participants: "Mark the tubes with the adhesive test strip and complete the sampling referral with the same marked adhesive test strip. Remove the swab from the tube and place it under your tongue. Chew for two minutes but avoid chewing directly on the swab. Continue until the swab is wet. Return the wet swab to the tube, replace the cap and put the tube into the refrigerator. When all samples are taken, mail them within 48 hours to be sure that the laboratory receives them within three days after sampling".
Salivary cortisol in *paper I* was collected during one day (24 hours) before screening (baseline).
In paper II, salivary cortisol was collected during a 24-hour period at five occasions: at baseline, at weeks three, eight, 21 and 34. In addition, salivary cortisol was measured at

two occasions immediately before, immediately after and 30 min after the end of the interventions in the TT group and the RTM group, respectively. These samples were collected by the study staff, placed in the refrigerator, and thereafter mailed to the laboratory.
The Case Report Form (CRF) contained a protocol to ensure that notes were made concerning date, time point of the day, time point of awakening, time point of intake of antiparkinson medication, time point for food intake before/after salivary cortisol sampling.
When salivary cortisol was sampled before/after intervention, the samples were taken in an *upright position* and at the same time point of the day at both occasions. For the individual participants, interventions started in most cases before10 am.
Upon arrival at the laboratory, not later than three days after sampling, the samples were brought to room temperature. The Salivette tubes were then centrifuged at 1711G for 15 minutes at 20^0 C and then frozen at minus 80^0 C until assayed simultaneously. A commercial RIA-based technique for salivary cortisol was used (Spectria ^{TM} Cortisol $^{I\ 125}$, Landskrona, Sweden).
All analyses were performed at the Unilabs, Skaraborgs Hospital in Sweden. The technique has been developed specifically for the measurement of salivary cortisol and the test is carried out as follows:
Cortisol in standards and samples (the study samples) are added to a 96-well microtitrate plate, pre-coated with monoclonal anticortisol antibodies. During incubation, the tests compete with cortisol linked to horseradish peroxidase for the antibody binding sites, and the unbound components are washed away. Tetramethylbenzidine (TMB) is added, and the bound cortisol peroxidase catalyzes a reaction of the TMB, generating a blue color. The reaction is stopped by adding sulfuric acid, generating a yellow color. Optical density is then measured at 450 nm. The amount of bound cortisol in the study sample is inversely related to the amount of cortisol peroxidase.

The cortisol concentrations in all of the salivary samples collected in our study ranged from about just over 1 nmol/l to 60 nmol/l; only one participant had extremely high values (174.6 nmol/l, 22.3 nmol/l, 14.6 nmol/l and 110 nmol/l the next morning).
The numerical values were used in data analysis, even for concentrations outside the highest detection rate; however, in the final data analysis the values above 100 nmol/l were excluded.
The median cortisol concentration was calculated for the time of day and was used as the main dependent variable in papers I and II, i.e. early morning values at 8am, noon values at 1pm and evening values at 8 pm.
The cortisol arousal reaction (CAR) is important to consider when analyzing data for morning cortisol concentrations. In 11 of our participants the time interval from awakening to the exact time point for sampling was less than 60 minutes and in 10 of these it was less than 45 minutes, with a high risk for an arousal effect. We recognized an arousal reaction in only one of these 10 patients.

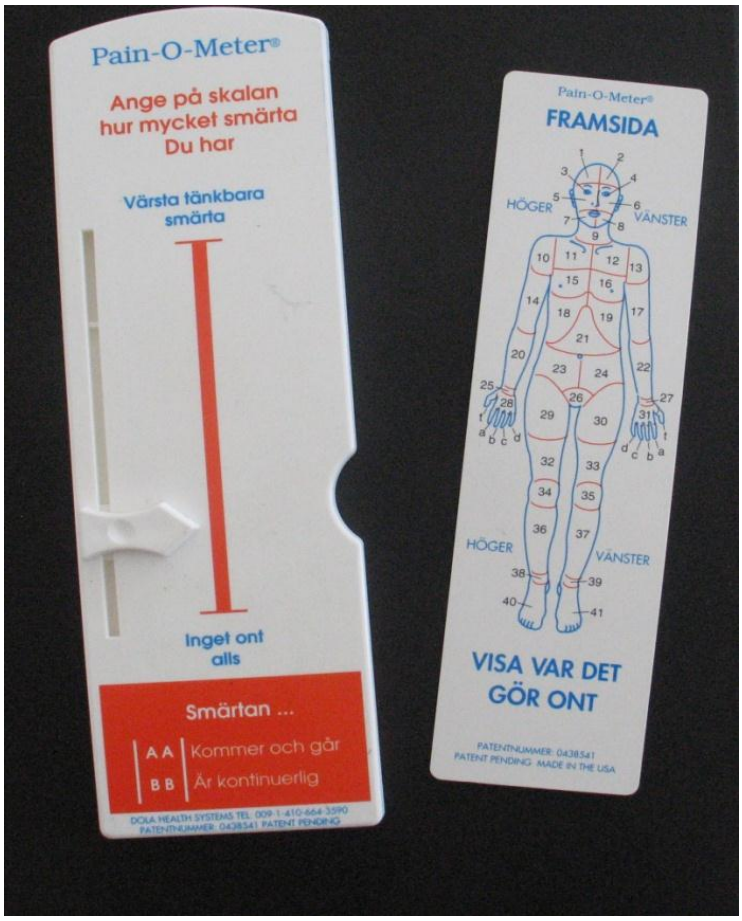
3.4.3 Pain, Papers III and IV

3.4.3.1 The measurements of pain

The participants completed different questionnaires about pain. In *papers III and IV* analyses were based on theVAS-scales, the Patient Evaluation of Pain (PEA), and the Pain-O-Meter (POM) scales, *(see Appendices III, IV and VI*).
Defintion of pain is described in other parts of this thesis. *PD-related pain* is a challenge to differ from pain from other origin. However, earlier descriptions have showed that experience of muscle cramps and relations to intake of antiparkinson drugs are of importance. B.Ford and later Negre-Pages et al have categorized PD related pain (Ford, 1998; Negre-Pages et al. 2008). Polyneuropathi was an exclusion criterion in our study. All the participants studied in *papers III and IV* had suffered from chronic pain for three days or more per week during at least three months prior to inclusion.
Before screening and randomization participants received oral and written information about pain registration. At several occasions during the study the participants were asked to put a cross on a 10-cm horizontal line with the text "no pain at all" to the left and "worst imaginable pain" to the right. This was started at 5 am, which was explained in the written text at the top of the paper. Participants were asked to mark every time they suffered from pain and / or when the pain changed markedly. Just below the line participants were asked to describe how long they had experienced pain during the previous 24-hour period. They were also asked to mark at what time point of the day they had marked their cross on the line.
In *paper III* the answers were analyzed together with responses on the Patient Evaluation of Pain (PEA). This questionnaire was the result of investigations of the prevalence and expressions of pain in Parkinson´s Disease by Astrid Borg, RN, and Anders Borgman, founder of the Swedish Parkinson Foundation in 1995. It was first published in Parkinsonjournalen, no.4, 1999, the official Journal of the Swedish Parkinson Association. This in turn was the result of a questionnaire which was sent to 1800 individuals in 1998, with 947 responses, in which the prevalence of pain in PD was evaluated.
The Patient Evaluation of Pain *(PEA)* was completed at one timepoint (baseline) in paper III and at another two time points during the study described in *paper IV* ; at week 21 and at week 34.
After questions concerning duration of pain, time point for diagnosis of PD and time correlations, participants are asked to describe more in detail the distribution of pain, changes in distribution, factors that worsen and relieve their pain, their own hypothesis about the origin of their pain, and their own use of different therapies for pain, both pharmacological and non pharmacological. On the final page (p.3) the respondent is asked to translate the descriptive words for the pain into numbers that are placed in a grid for different time points of the day. At the same time the respondent is asked to mark where the current pain is located on diagrams of the front and the back of the body. *(Appendix V).*
The questionnaire was completed either at home before a visit or at the time point for the visit, in an area with a minimum of disturbance.

The Pain-O-Meter *(POM) (*Gaston-Johansson 1996) was used in *paper III* with the intention of completing the pain analysis, as well as at several occasions during the study described in *paper IV:* at screening, at week three and eight immediately before and after intervention , at week 11 after the interventions were completed, and during follow-up at weeks 14, 21 and 34.
The Pain-O-Meter is a hands-on tool made of plastic; see *Appendix VI* and the pictures below:

Fig. 10A: The Pain-O-Meter, front.



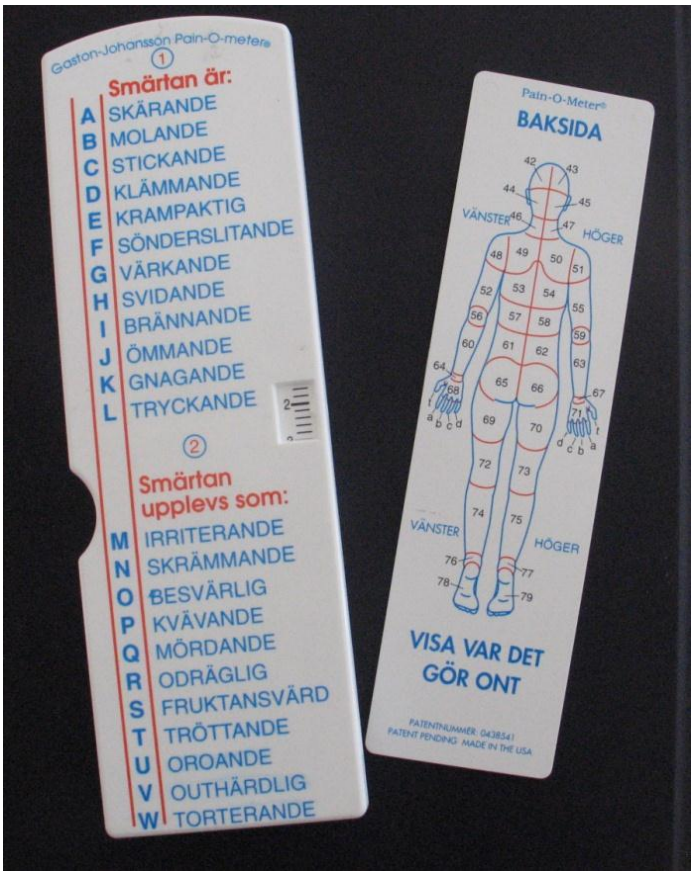


Fig. 10B: The Pain-O-Meter, back.

Fig.10A+B: The Pain-O-meter (Swedish): Intensity, character and body localizations of pain are registered.

The front is an ordinary VAS scale with a continuous line from "no pain at all" to “worst imaginable pain". By placing the moveable marker situated to the left of the line at the experienced level of pain at that moment, the study staff can scan the figure(0 - 100 mm). This was completed by choosing "Pain is recurrent" or "Pain is continuous". On the back of the instrument the participant was asked to describe the pain in ***physical*** words: cramping, dull, splitting, burning, tearing, sore, shocking, radiating, aching, crushing, sharp, stabbing, tearing, hurting or pressing. As a second choice participants were asked to describe the ***sensory*** words and to choose among the following: nagging, agonizing, annoying, killing, tiring, sickening, terrifying, miserable, torturing, unbearable or troublesome. These 15 (12 in the Swedish version) sensory and 11 affective word descriptors (WDS) are assigned intensity values with a range from one to five. A pain intensity score is provided for the sensory and the affective WDSs. Information about pain location and duration can also be registered on the POM, see Fig.10A and B.

3.4.4 Pharmacotherapy, Papers I - IV

A drug list was filled in during the Parkitouch study *(see first page of appendix IV).* Participants were asked to register the amount and timepoint of medication. They started the list with their Parkinson medication and the exact time point for intake. All medications were registered according to name and amount. The drug schedule started at 5am and could be registered each hour until 4 am the next morning. Nonprescription medication was also registered.
The drug list was completed at screening, and at weeks three, eight, 10, 14, 21 and 34.

3.4.4.1 Levodopa equipotent doses

Insufficient knowledge about the possible impact of antiparkinson pharmacotherapy on HPA-axis function, as well as the need for manageable comparisons of the antiparkinson therapy load between groups, led to the use of formulas to translate doses of other antiparkinson compounds such as dopamine agonists, MAO-B inhibitors and entacapone, to levodopa equivalent doses (Tomlinson et al. 2010).

3.4.5 Parkinson´s Disease Sleep Scale (PDSS), Papers III and IV

In clinical practice, scales such as the Epsworth Sleepiness Scale (ESS) and the Pittsburgh Sleep Quality Index (PSQI) have been widely used, but reports have shown a poor sensitivity for sudden onset of sleep, not uncommon in PD. This is not the case with the PDSS, which is an instrument to quantify sleep problems in PD. It consists of a visual analogue scale (VAS) for each of 15 features commonly associated with sleep

disturbance in PD. The answers are based on the participant's experience during the past week and the patient was asked to place a cross at the appropriate point on a 10-cm line *where 0 represents worst and 10 represents the best*.
Examples of questions concern: how the overall quality of sleep has been, difficulties in staying asleep, awakenings to urinate during the night, the coexistence of restless legs, distressing dreams, numbness or tingling in arms or legs as factors causing the person to wake up. Other questions in the PDSS involve experiences of sleepiness when waking up in the mornings and the sudden onset of sleep during the day *(see Appendix VII).*
The PDSS was completed at screening and twice during the intervention period and at four occasions during the follow-up, the last registration at week 34.

3.4.6 Unified Parkinson Disease Rating Scale (UPDRS), Papers I-IV

The severity of PD is mirrored by the UPDRS, parts I - IV. This scale was developed as an effort to incorporate elements from earlier existing scales to provide a comprehensive instrument for capturing multiple aspects of PD-related disability and impairment. The scale itself has four components *(see Appendix VIII).* It is widely used for both clinical and scientific purposes. *Part I* addresses mental dysfunction and mood; *part II* assesses motor disability - activities of daily living, and *part III* addresses motor impairment. *Part IV* assesses treatment-related motor and non-motor complications. Of all available clinical scales in PD, the UPDRS is currently the most commonly used.

3.4.7 The Hoehn and Yahr scale (H&Y), Papers I - IV

Strengths of the HY scale include its wide utilization and acceptance. Progressively higher stages correlate with neuroimaging studies of dopaminergic loss, and strong correlations exist between the HY scale and some standardized scales of motor impairment, disability, and quality of life. Weaknesses include the scale's mixing of impairment and disability and its non-linearity. *(Appendix IX)*

4 DATA ANALYSIS

The hypothesis concerning the distribution of a material is usually based on earlier experiences and studies. It is, of course, of utmost importance to discuss the distribution of the data material before the start of a study, and consequently how the results are to be managed and processed statistically. In the "Parkitouch study" the samples were small and there was most often no evidence for a normal distribution of the samples. Therefore *non parametric tests* were used for statistical processing. Without equidistances between observations, i.e. *ordinal* and *nominal* data, as was often the case in this study, *median* values with specifications of percentiles was the most correct method for describing position. It was also more robust in terms of the impact of extreme values than is the case for *mean* values. Most often the 10^{th} / 90^{th} percentiles were chosen to catch most of the spread and to avoid outliers.
Salivary cortisol concentration is an example of *quote data*, the data is always > 0.The diurnal cortisol concentration secretion varies between individuals and we cannot expect a normal distribution of concentrations or secretion rates of cortisol in saliva. This fact is generally accepted among scientists and statisticians.
Consideration of what methods of analysis should be used for data concerning different modalities of pain and sleep experiences is worth reflection. Most psychological tests such as the VAS provide more information than simple rank ordering, but equality of units cannot be ensured. The data thus lie somewhere between ordinal and interval values.
In the case of data concerning health-related quality of life (HRQoL) in paper IV we had to take into account that the official recorded analyses of quality of life (SF-36) in the reference population were presented in terms of *means* and *standard deviations* in official reference materials. The corresponding methods were used in paper IV.

4.1 POWER OF THE STUDY

The power of a statistical test is the probability that the test will reject the null hypothesis when the null hypothesis is false (i.e. the probability of not committing a Type II error, or making a false negative decision). Power analysis is used to calculate the minimum sample size required to be reasonably likely to detect a true effect of a given size. Power analysis can also be used to calculate the minimum effect size that is likely to be detected in a study using a given sample size.
The power calculated for in this thesis is based on the analysis of salivary cortisol:
Before study start we controlled for the power concerning the analyses of salivary cortisol concentration. In order to have a 20% difference in cortisol concentration between groups, **a total of** 40 patients were needed to have 80% power (significance level of 0.05).

4.2 STATISTICAL METHOD FOR PAIRED ORDINAL DATA

In recent years Elisabeth Svensson, Professor of Biostatistics at the Örebro University, has introduced a statistical method (Svensson, 1998) especially developed to analyze changes in a data material consisting of categorical data, i.e. without information concerning magnitude and distances between categories. Thanks to the special ranking technique with coupled pairs it is possible to describe and analyze the group-related changes separately from the individual changes, see paper IV. The change can apply to a treatment effect or to other changes over time, and the pattern of change attributable to the group can be distinguished from an individual heterogenecity in the pattern of change, see Fig.11.

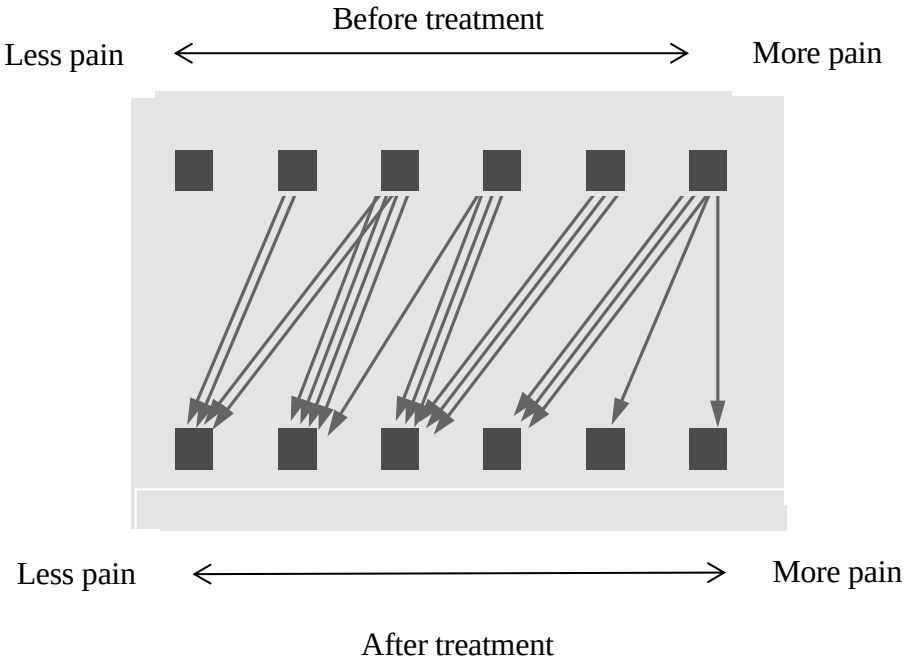
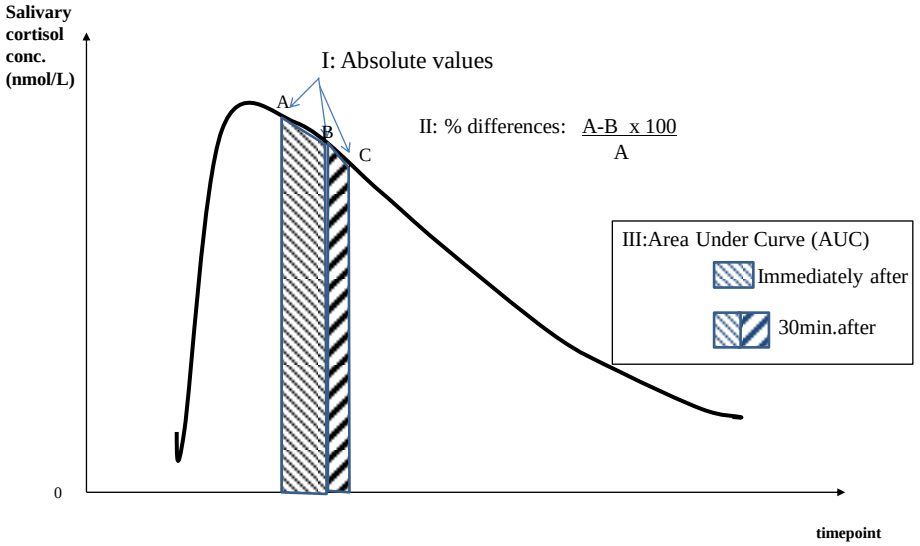


Fig.11: Illustration of systematic change in position towards categories with less pain on scales with ordinal categories. This method was used to describe physical and emotional word descriptors for pain in paper IV (POM^{VAS}, POM^{PHYS} and POM^{EMO} , respectively)

4.3 DATA ANALYSIS OF SHORT-TERM EFFECTS OF INTERVENTION

To measure the effects of interventions with TT and RTM and to compare differences between types of interventions, salivary cortisol concentrations were measured immediately before, immediately after, and 30 minutes after TT and RTM, respectively, at two different time points: at the first and at the eighth intervention. Cortisol concentrations were compared with each paricipant's *corresponding concentrations at the same time point as the interventional time point at screening*, i.e. the diurnal concentration curve before treatment start. The slope of the curves were compared: between the first intervention and screening and between the eighth intervention and screening.



Explanations: A: Immediately before intervention, B: Immediately after intervention, C: 30 minutes after intervention. III: see fig.13 A and B for details.

Fig. 12: Short-term effects, an illustration of different forms of presentation

Each participant presented his/her own diurnal secretion curve at screening. Time points for interventions were plotted for each patient and the linear curve represented the basis for the corresponding linear slopes at the first (before, immediately after and 30 minutes after intervention) and at the eighth intervention.
The differences were compared in three ways; I: Absolute values of salivary cortisol concentrations at each time point, II: differences between values in %, and III: differences between the AUCs.

4.4 THE CONCEPT OF AREA UNDER THE CURVE (AUC)

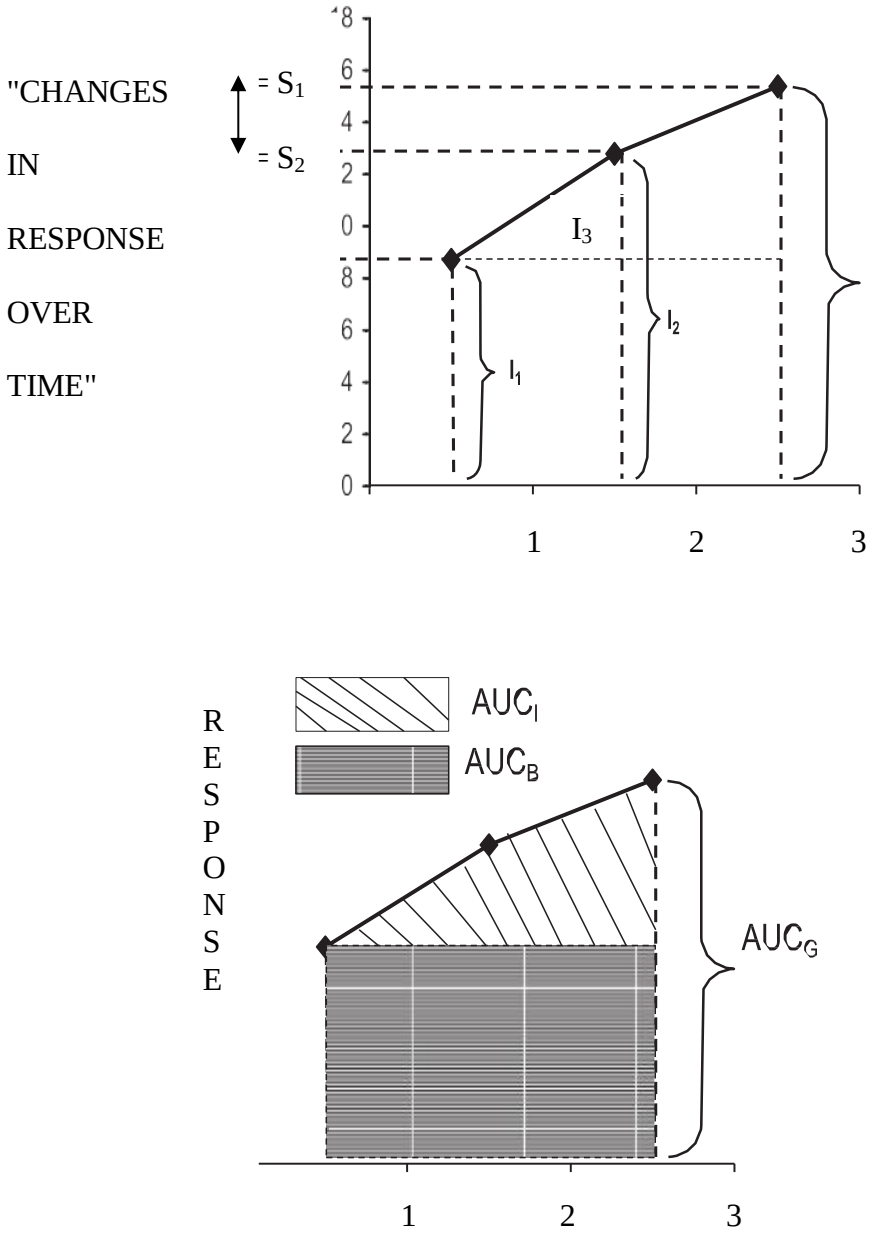


Fig.13 A+B: *Explanations*: I_1, I_2 *and* I_3 *,(Intensity,) represent the magnitude of response and* S_1 *and* S_2 *,(Sensitivity,)changes in response over time (Fig.13A).* AUC_i *,* AUC_B *and* AUC_G *illustrate the three forms of AUC (Fig. 13B)*

AUC_G is the total area under the curve of all measurements. It takes into account both sensitivity (the difference between the single measurements from each other) and intensity (the distance of these measures from baseline). AUC_I is calculated with reference to the *baseline measurement* and it ignores the distance from zero for all measurements and emphasizes the changes over time. With endocrinological data, AUC_G is assumed to be a measure that is related more to *total hormonal output*, whereas AUC_I is a parameter that emphasizes the *changes over time* and is related more to the sensitivity of the system.

4.5 SPECIFIED STATISTICAL NON PARAMETRIC METHODS USED IN THE THESIS

4.5.1 The Bonferroni effect

As we increase the number of hypotheses in a test, we also increase the likelihood of witnessing a rare event, and therefore the chance to reject the null hypotheses when it is true (Type I error). Bonferroni correction is the most naive way to address this issue. As several test procedures were performed in paper IV, this method was used.

4.5.2 Fischer´s test and the Chi-square test

Comparisons between qualitative, categorical variables with respect to proportions (presence of different symptoms or characteristics) were done by means of the chi-square test or Fisher's test in papers III and IV.

4.5.3 Friedman´s ANOVA

This test was used to compare differences within group over time; the diurnal cortisol rhythm and total cortisol secretion during the five study time points in paper II.

4.5.4 Kruskal-Wallis one-way analysis of variance

This test was used to compare the cortisol concentrations at the same timepoint in the two independent groups TT and RTM in paper II. It was also used in paper IV.

4.5.5 Logistic regression analysis

Maximal pain above 7 (VAS > 7) was used as the outcome in a logistic regression model to explore factors with possible influence on pain. The model was used in paper III.

4.5.6 The Mann-Whitney U test and the Wilcoxon rank sum test

These non parametric tests were used in papers I to IV to compare the independent variables of ordinal data type between different categories of the small samples.

4.5.7 The Spearman rank order correlation test (Spearman´s rho)

This test was used to analyze associations between cortisol concentration and clinical characteristics in papers I and II and between ordinal data in paper IV.

4.5.8 The Wilcoxon signed-rank test

For situations involving either matched items or repeated measurements of the same item, the nonparametric **Wilcoxon signed-ranks test for the median difference** can be used.This test was used to compare the PD-P and PD-noP groups of median cortisol levels with the reference group in paper I. Wilcoxon´s matched-pairs signed ranks test was used to analyse the individual diurnal rhythm of cortisol secretion at the five time points presented in paper II.

5 ETHICAL CONSIDERATIONS

All studies were approved before study start by the Ethics Committees at the University of Gothenburg (Ö 762-03) and the University of Linkoping (D 03-673), Sweden.
Written and verbal information about the study was given to all participants. The voluntary nature of participation and the possibility to terminate participation at any time was explained to each person and written informed consent was obtained from all participants.
Travel expenses were reimbursed for massage therapists as well as for patients. The massage therapists got paid for their contributions in accordance with normal fees for treatment.
The identities of the participants were coded and the results were only presented on a group level to avoid identification.
There were few elements of risk in the study, but because of the possible discomfort and risk of falling when lying down and turning over on the massage table,participants over 80 years of age were excluded from the study.
Another potentially disturbing element of the study was saliva sampling; saliva sampling is a non-invasive method that is well used and well described in literature. It is preferable to invasive methods due to its non-stressfulness. The sampling and storage of biological samples is a potential source of disturbance regarding personal integrity. To ensure the integrity of the participants, the storage and use of the biological samples was in accord with the Act (2002:297) on Biobanks in Health Care.
The questionnaires could be considered to disturb the integrity of the participants: All questionnaires, or similar questionnaires, have been used previously. They were stored in Case Report Forms (CRFs), one for each participant, and kept in a locked area.
The commitment for participating in the study was not to alter or increase the intake of antiparkinson medication during the intervention and follow-up. The natural progress of PD often results in changes in drug therapy. As occasional extra daily intake of levodopa (Madopark Quick Mite®) 50 mg was permitted during the study, this regime turned out to be well tolerated and accepted. None of the participants were on "advanced antiparkinson therapy, such as apomorphine, Duodopa®, or Deep Brain Stimulation (DBS) therapy.
In summary, the advantage of increased knowledge about stress, health consequences and other effects of TT and RTM, relevant to all PD patients in Sweden as well as in other countries, should reasonably compensate for the disturbances induced by saliva samples, questionnaires and limitations of changes in pharmacotherapy.

6 RESULTS AND DISCUSSION

The main results of the Parkitouch study are presented along with a corresponding discussion of each paper. The participant flow diagram below (Fig.14) displays the progress of all participants throughout the trial.

6.1 FLOW CHART

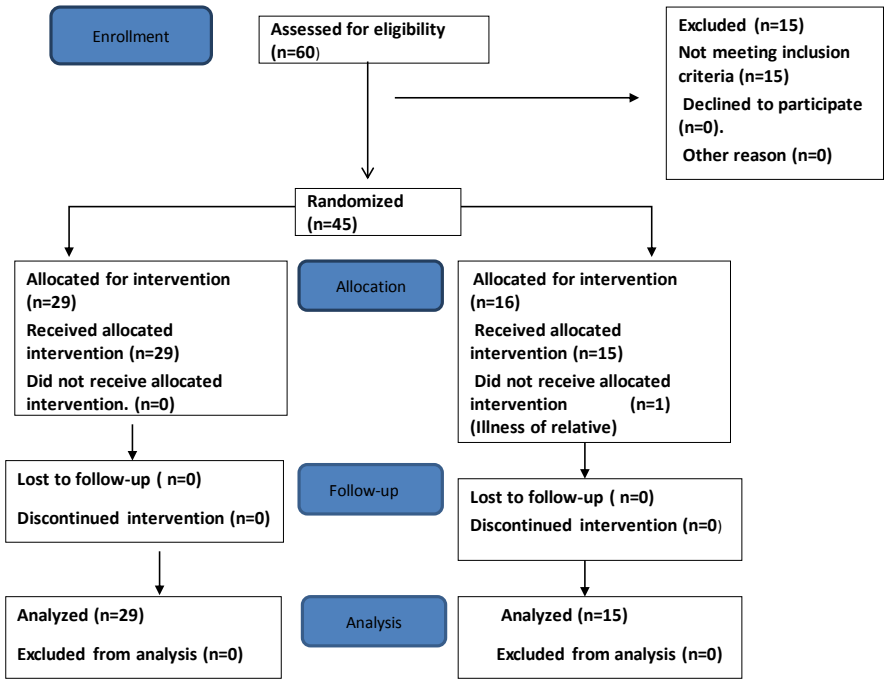


Fig. 14: Consort Flow Diagram for the Parkitouch Study.

6.2 BASAL CHARACTERISTICS AT SCREENING

6.2.1 Participants in the Parkitouch study

Gender	**Age[1,2] (y)**	**Duration of pain (y)**	**UPDRS[4] (III) score**	**UPDRS (I-IV) score**	**H&Y[3,5] score**
Females (n=28)	66.7/ 66.5 (60/73)	6.5/4 (1/13)	23.3/23 (10/37)	36.3/36 (19/60)	2 (0/3)
Males (n=16)	62.8/64.5 (54/69)	4.8/4 (2/10)	20.4/16.5 (12/36)	34.5/32.5 (24/49)	1.5 (0/3)
Total	65.3/66 (59/73)	5.8/4.0 (1.4/12)	22.2/20 (10/36)	36.3/35.5 (21/60)	2 (0/3)

Table 7A: Basal clinical characteristics of the Parkitouch study group.

Notes: Values are given as mean/median[1], 10/90th percentiles[2], median[3], Unified Parkinson´s Disease Rating Scale[4], Hoehn & Yahr scale[5].

Group	Sex	Number	Age [1]	Weight [2]	BMI [2]	UPDRS III [1,2]
PD (PD-P+PD-NoP)	male	24	50-78	84.1	26.8	20.1 (8-37)
	female	35	60-79	68.4	25.5	22.0 (3-57)
Reference[a]	male	303	50-74	_	26.9	_
	female	305	50-74	_	26.8	_

Table 7B: Characteristics of the PD population (PD-P and PD-no-P) and the [a]healthy reference population according to the study by Larsson et al. 2009.

Notes: Values are given as range [1] and mean [2].

6.2.2 Paper I

6.2.2.1 Results

6.2.2.1.1 PD with chronic pain and PD without pain.

In this paper the individual diurnal secretion profiles of two groups of PD patients were studied; 44 patients (28/16; females/males) with chronic pain (PD-P) and 16 (8/8; females/males) patients without chronic PD pain (PD no-P). Mean age in the PD-P group was 65 years, and in the PD no-P group it was 73 years. Severity of disease measured by total UPDRS score was a mean of 36.3 in the PD-P and 27.8 in the PD no-P group. BMI was a mean of 25.9 in the PD-P group and 26.3 in the PD no-P group. Levodopa therapy was a mean of 500 mg in the PD-P group and 528 mg in the PD no-P group. No significant differences between groups were found in any of these comparisons. The individual diurnal variations of salivary cortisol for the two PD groups are shown in fig.14.

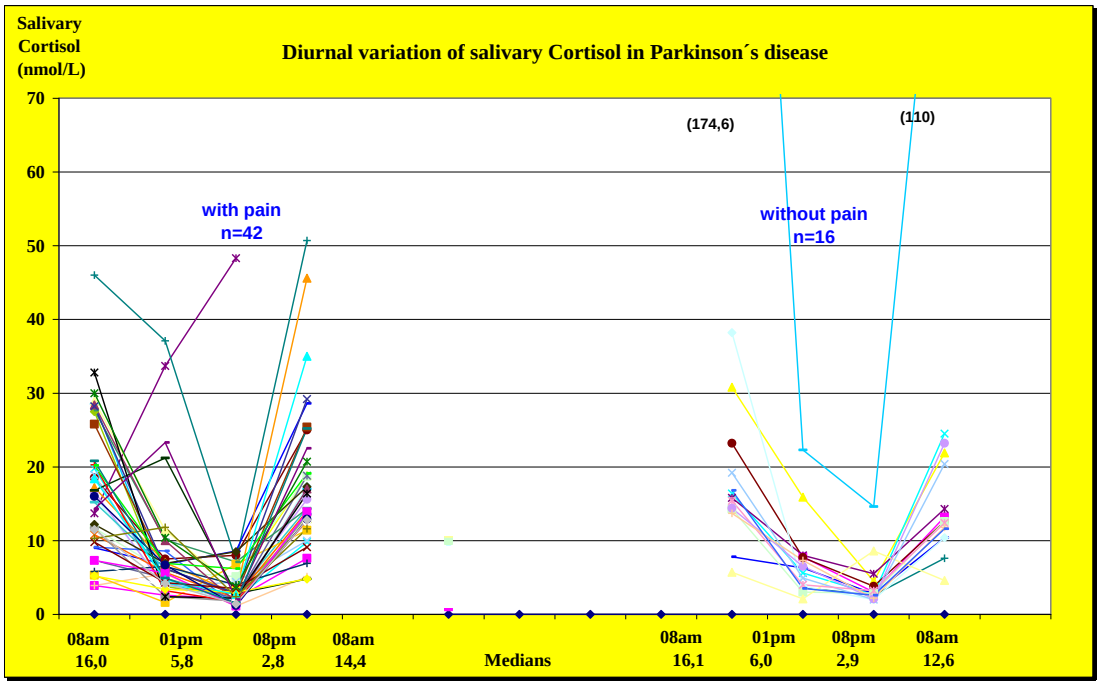


Fig.14: The individual diurnal variation of salivary cortisol in PD with and without chronic pain. There were no significant differences between groups.

Time intervals between awakening and sampling in the morning: Of 10 patients with a time lag from awakening to sampling of less than 45 minutes, a cortisol arousal reaction with an increase in salivary cortisol of 2.5 nmol/L was noted in only one patient. There were no statistically significant differences in salivary cortisol concentrations between the two groups. One patient in the PD no-P group had extremely high values (174.6, 22.3, 14.6, and 110 nmol/L). No difference in cortisol concentration between participants taking their levodopa medication within one hour either side of salivary sampling was seen.
No significant correlations between BMI, motor dysfunction, measured as UPDRS III ≤20 compared with >20, gait (UPDRS III, item 30), acute pain (maximum VAS at screening), chronic pain, or cortisol concentrations were identified.
Patients in both PD groups (n=59) generally showed a similar 24-hour rhythm of cortisol secretion, see Fig.14 and 15.

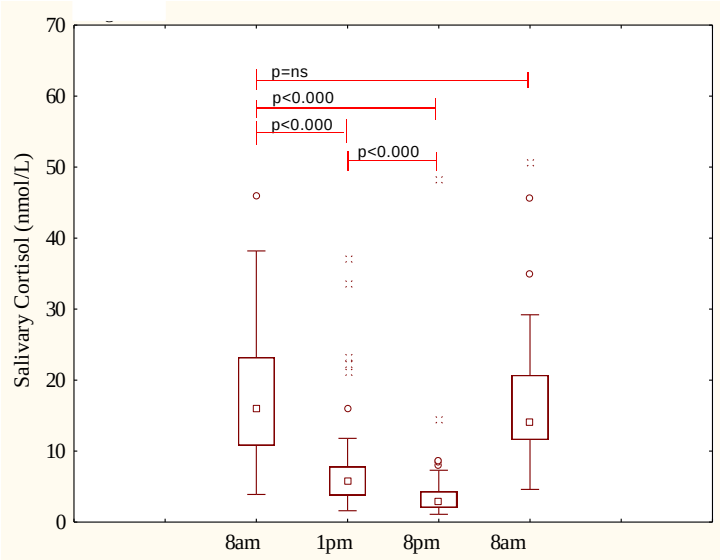


Fig.15: Diurnal salivary cortisol concentrations (nmol/L) in all 59 patients with Parkinson's disease. Statistical analyses between paired time points. *Method*: *Spearman´s rank correlation test.*

6.2.2.1.2 PD-P and PD no-P compared to a healthy reference group

The diurnal salivary cortisol secretions of these 59 patients with a diagnosis of PD for more than two years with or without chronic pain were also compared with a reference group of gender-, BMI-, and age-matched healthy individuals from the same catchment area, with analyses performed at the same laboratory. Time points for sampling differed by only two hours in the evening between the PD-P and PD no-P groups and the reference group (8pm and10pm, respectively). The linear equation for the cortisol trend curve that was calculated to estimate AUC was y = 23.56–1.02x versus y=17.84–0.69x for the PD and the reference group, respectively. The adjusted salivary cortisol concentration at 8 pm in the reference group was 4.0nmol/L compared with 3.2 nmol/L in the PD group, and this difference was not statistically significant.

Morning cortisol concentrations were higher in the PD group compared with those in the reference group, see table 8.

Group	**Sex (N)**	**Day 1**					**Day 2**
		8am		**1pm**	**8pm**		**8am**
		Geom. Mean **Median (10/90th perc)**	**p value**[a]	**Geom. Mean** **Median (10/90th perc)**	**Geom. Mean** **Median (10/90th perc)**	**p-value**[a]	**Geom. Mean** **Median with (10/90th perc)**
PD-P	Male (16)	12.5 14.8 (5.2-20.3)	0.215	5.6 5.6 (3.2-11.8)	2. 3 2.6 (1.1-5.1)	0.016*	15.1 14.2 (5.1-35)
	Female (27)[2]	15.6 17.9 (5.8-30)	0.021*	6.4 6.2 (2.6-21.2)	3.4 2.9 (1.6-8.5)	0.614	15.1 15.4 (7.6-28.6)
PD-no P	Male (8)	20.5 15.4 (5.7-174.6)	0.128	6.4 6.5 (2.1-22.3)	4.2 3.1 (2.2-14.6)	0.779	16.9 12.9 (4.6-110)
	Female (8)	17.5 16.8 (7.8-38.2)	0.091	5.3 5.6 (3.5-8.0)	2.8 2.6(2-5.5)	0.035*	13.0 12.1 (7.6-23.2)
Reference	Male (303)	12.1[1]	-	-	3.9[b]	-	-
	Female (305)	12.5[1]	-	-	4.1[b]	-	-

Table 8: Comparisons of salivary cortisol concentrations (nmol/L) in PD patients with (PD-P) and without chronic PD-related pain (PD no-P) and the reference group.

Notes: Values are given as geometric means [(1)]. PD=Parkinson´s Disease, PD no-P=PD without chronic pain. P-value refers to test of the corresponding reference population [(a)]. [2] =27 females in the PD-P group due to missing data from patient no. 12.
**statistically significant at the 5% level. (Statistical method: Mann-Whitney U-test).*

The total cortisol secretion during the day (8am–8pm, AUC_0–AUC_G) was significantly increased in PD patients, at 112.8 nmolh versus 81.1 nmolh in the reference group.
(*P*= 0.001). The decrease in the salivary cortisol secretion rate during the day (8am–8 pm, negative AUCi) in the PD and reference groups was -73.7 nmolh versus -49.9 nmolh. This difference was statistically significant (*P* = 0.001).

6.2.2.2 Discussion

The aim of Paper I was to study basal characteristics of the HPA axis in PD with and without chronic pain. Availability of recent results from a healthy reference population, matched by age, gender and BMI, with diurnal salivary cortisol analyzed in the same laboratory, and with essentially the same time points for sampling and routines as in our study, made it possible to compare them with the results from our study.
Previous data in this field (Hartmann et al. 1997) have revealed that patients with Alzheimer's Disease (n=12) as well as PD (n=12) in age groups comparable to those of our patients secret significantly more cortisol in 24 h than normal volunteers (n=10). *Plasma cortisol* sampling in this study was done *every 15 minutes* starting at 8am for 24 hours. Patients with AD and PD had higher masses of cortisol secreted per burst and the difference was explained as related to an elevated pulsatile cortisol production rate. In another study serum cortisol was significantly elevated among parkinsonian patients with gait deficits compared to controls (Charlett et al. 1998). In this study significantly decreased plasma concentrations of cortisol were seen in patients treated with the MAO-B inhibitor selegiline. Seven participants in our study were prescribed MAO-B inhibitors. Our analysis did not show any significant differences in cortisol concentration between the group for which these drugs were prescribed and the group without these drugs. Nor were differences seen between the group with > 500mg of levodopa and those with less than 500 mg of levodopa per day.
Our study showed that PD patients with mild to severe PD have a normal diurnal cortisol rhythm, higher morning cortisol concentrations and increased cortisol secretions during the day (8am–8pm) compared with the healthy reference group. We did not find any gender differences, in contrast to findings in the reference population (Larsson et al. 2009). Our results at 8am were highly correlated between day 1 and day

2, which indicates a good reliability of the procedures. Salivary cortisol has been shown to correlate very well with cortisol in plasma (Aardal and Holm 1995, Vining et al. 1983).
We did not find any differences in HPA-axis function between PD-P and PD no-P patients, which was not in accord with results from another study (Turner-Cobb et al. 2010) in which patients with chronic pain syndrome had a significantly lower overall mean diurnal salivary cortisol concentration compared to a healthy control group.
Our results showed a significant increase in secretion rate and total cortisol secretion. There is potential evidence for a well functioning adrenal and hypothalamic-pituitary-adrenal axis, independent of age, gender and severity of PD. The increased concentration of cortisol in the morning supports the hypothesis that this neurodegenerative disorder itself does not interfere with hypothalamic pituitary-adrenal axis function. This was also reported by Seifried et al. in 2012 in severe PD treated with Deep Brain Stimulation (DBS).

6.2.3 Paper II

6.2.3.1 Results

The aim of this study was to analyze the basal diurnal and acute secretion of salivary cortisol related to the short and long-term effects of TT on the hypothalamic-pituitary-adrenal (HPA) axis in PD. The control group received RTM, i.e. the TT concept except for the components of whole body Touch.

		Age [1]	[2]	**BMI**[2]	**H&Y** [2,3]	**UPDRS (I-IV),**[2,4]
"Tactile Touch "	Males (n=10)	50-78	86.5 (68.1/103.4)	26.6 (24.1/37.4)	1.5 (1.0/2.5)	31.5 (24.1/46.4)
	Females (n=19)	60-79	64.7 (54.8/95.0)	25.0 (20.2/35.9)	2.5 (1.5/3.1)	39.0 (27.5/61.2)
"Rest to Music "	Males (n=6)	50-74	88.6 (62.0/102.0)	27.0 (23.6/31.5)	3.0 (1.5/3.0)	42.5 (32.0/57.0)
	Females (n=9)	50-74	70.8 (44.5/92.4)	24.2 (17.8/31.2)	2.0 (1.0/4.0)	39.0 (21.0/78.0)

Table 9: Characteristics of the two PD populations.

Notes: Values are given as range[1] and medians/10th and 90th percentiles[2]. The Hoehen and Yahr[3] Unified Parkinson´s Disease Rating Scale[4] . There were no statistical differences between the groups or the sexes.

6.2.3.1.1 Long-term effects on diurnal secretion rhythm

The median cortisol concentrations for all participants were 16.0, 5.8, 2.8, and 14.0 nmol/L respectively, at baseline, reproduced four times during the study: at screening, and at weeks 8, 21 and 34, without significant differences.
Cortisol concentrations decreased significantly after TT intervention but no change in long-term diurnal salivary cortisol rhythm or in total secretion patterns was found. No significant differences between the TT group and the control group were seen.
Cortisol concentrations at baseline and during the follow-up period were independent of age, gender, weight, Body Mass Index, duration or severity of PD, and the levodopa dose. The total diurnal cortisol secretion was lower during the day (8am-8pm) versus the night (8pm-8am) at baseline.

AUC
Cortisol (nmolh/L)

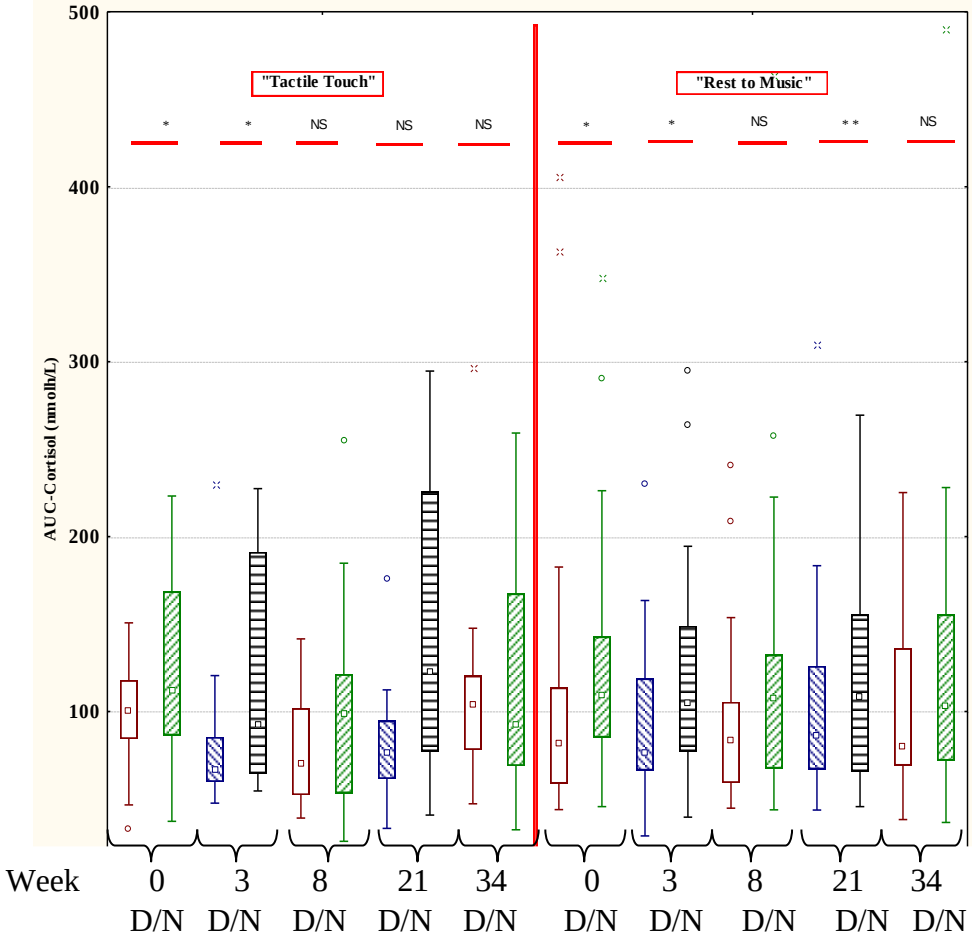


Fig.16: Total diurnal salivary cortisol secretion. Comparison between day (D) (8am-8pm) and night (N) (8pm-8am) in the two groups. * = $p < 0.05$, ** = $p < 0.01$.

6.2.3.1.2 Short-term effects on HPA-axis function

TT was performed with a mean duration of 52 minutes per session (range 40 -79 minutes), and a total of 10 massages during a period of eight weeks. At the first and eighth intervention, TT / RTM was given 133 (10-293) (mean; range) and 109 (10-272) minutes, respectively, after intake of the morning PD medication. Salivary cortisol was sampled immediately before, immediately after and 30 minutes after the end of the intervention.

6.2.3.1.2.1 AFTER *FIRST* INTERVENTION

There was a significant decrease in salivary cortisol concentration in the TT group, but not in total secretion (AUC), immediately after the interventions. In contrast, 30 min after the interventions, salivary cortisol concentrations were significantly decreased in both TT and RTM. The total cortisol secretion (AUC) was not changed in any group.

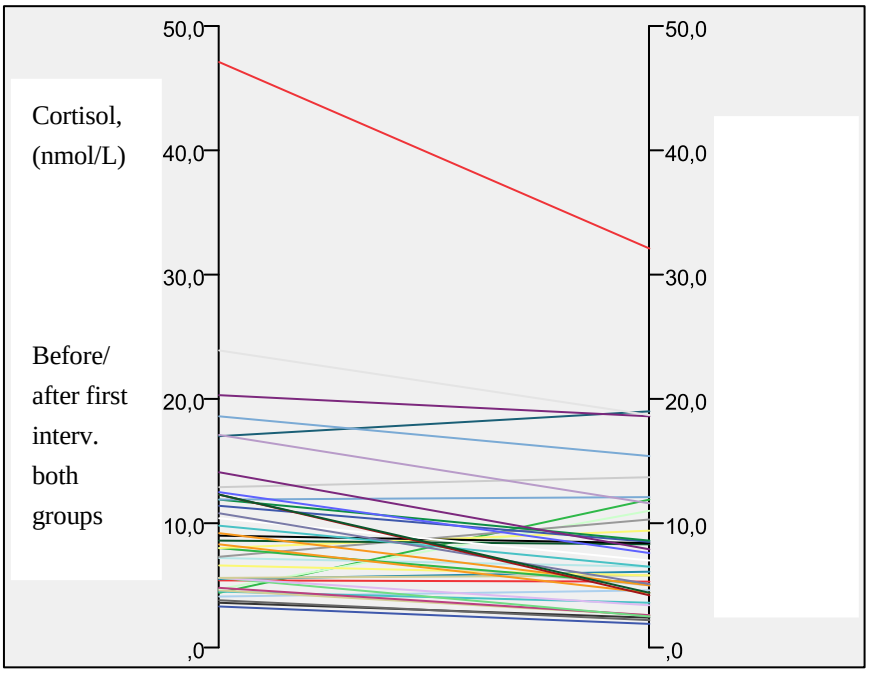


Fig.17: Changes in salivary cortisol concentrations at the individual level; both groups, immediately before/immediately after the first intervention.

	Group	AUC scr[1] Median (10^{th} and 90^{th} perc)	AUC interv[2] Median (10^{th} and 90^{th} perc)	p-value[3]
First intervention	RTM	875 (292-1641)	582 (255-1939)	0.158
	TT	918 (337-1752)	662 (267-1366)	0.076

Table 10: Area Under Curve (AUC) for short-term effects, immediately before to 30 min after interventions.

Notes: [1] =AUC estimated according to individual intervention time for start and duration in minutes+ 30 min. based on linear equation for daily AUC at screening.

[2] *AUC according to intervention duration and salivary concentration at start and 30 min after start.*
[3] *AUC interv compared to AUC scr., Wilcoxon test for paired data.*

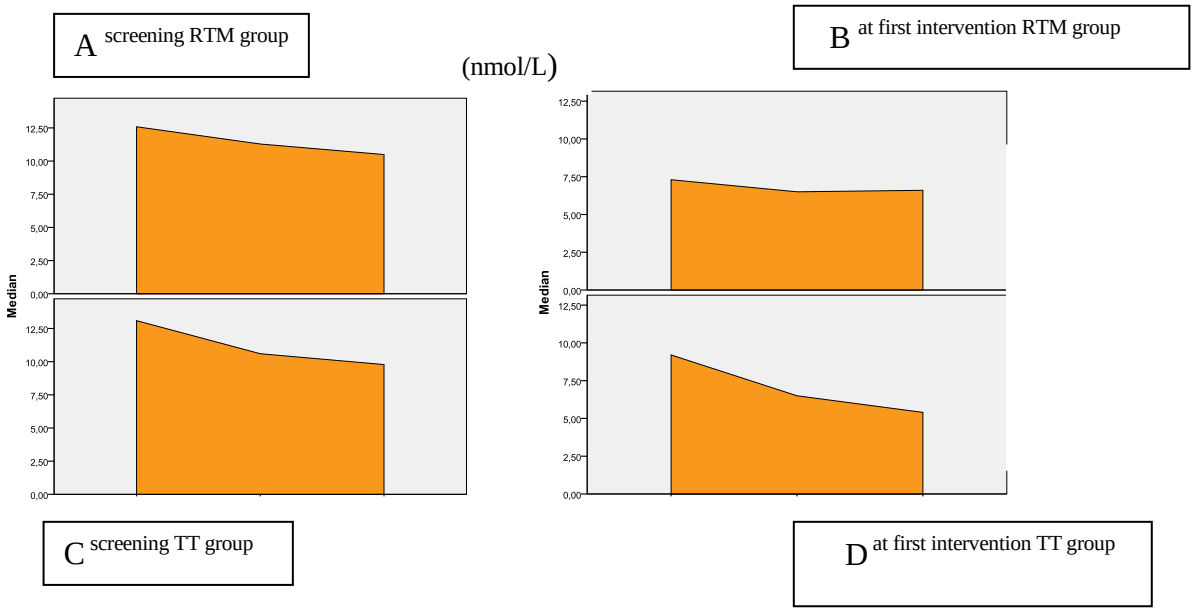


Fig. 18A-D: Changes in AUC defined by time points for each individual at screening are visualized in A and C.
B and D represent the change in AUC during interventions with RTM and TT from immediately before to 30 minutes after the first intervention.

Percentile difference in Cortisol	**RTM**	**TT**
Before - after 0`	26.8 (-41.0/+42.4)	27.7 (-2.2/+55.4)
Before- after 30`	45.8 (-4.5/+71.5)	33.3 (-12.9/+60.7)

Delta Cortisol (nmol/L)	**RTM**	**TT**
Before - after 0`	1.8 (-3.0/+5.5)	1.9 (-2.0/+6.2)
Before- after 30`	2.4 (-0.3/+17.1)	3.4 (-2.2/+6.5)

Table 11: Percentile changes and delta cortisol values in cortisol concentration. Values are given as median and 10/90 percentiles. *Note: There were no statistical differences between groups*

6.2.3.1.2.2 AFTER *EIGHTH* INTERVENTION

Salivary cortisol concentrations were significantly decreased immediately and 30 min. after intervention in both groups. The total salivary cortisol secretions (AUC) were significantly decreased immediately after intervention in both groups but remained decreased only in the TT group.

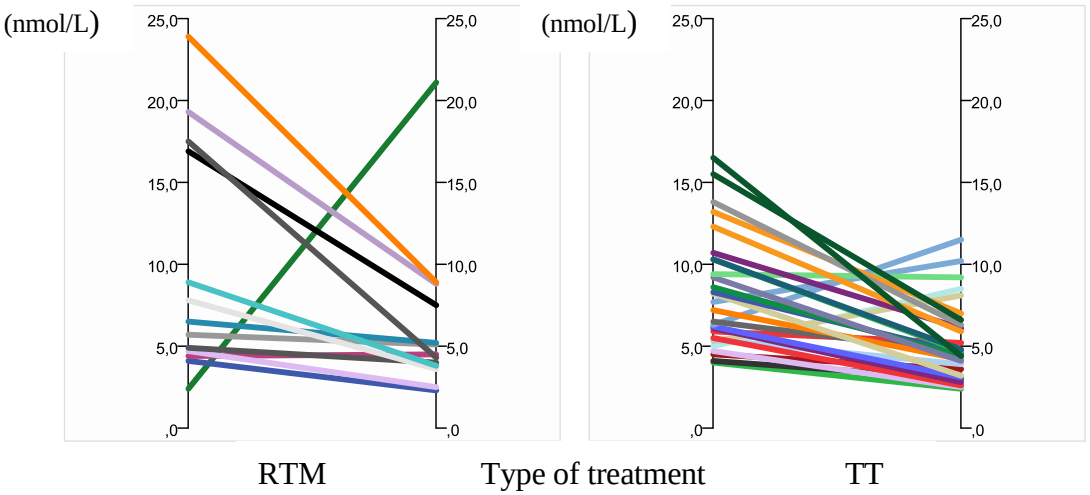


Fig. 19: Individual changes in salivary cortisol concentrations immediately before to 30 min after the 8 Th intervention, at week 5.

	Group	AUC scr[1]	AUC interv[2]	p-value[3]
Eighth intervention	RTM	870 (315-1686)	562 (262-1614)	0.087
	TT	883 (373-1783)	491 (303-854)	0.004*

Table 12: Area Under Curve (AUC) for short-term effects immediately before to 30 min after the eighth intervention at week 5. Values are given as medians (10th and 90th percentiles)

Notes: [1] *AUC estimated according to individual intervention time for start and duration in minutes+ 30 min. based on linear equation for daily AUC at screening.*
[2] *AUC according to intervention duration and salivary concentration at start and 30 min after intervention.*
[3] *AUC interv compared to AUC scr., Wilcoxon test for paired data.*
*Statistically significant difference

Each individual constituted his or her *own control* at the corresponding time points at the first and at the 8 th interventions and the corresponding time points at screening (Fig.20 A and C). In this way, an individual adjustment to the normal slope of the cortisol secretion without treatment was individually compared to the effects of RTM and TT (Fig.20 B and D).

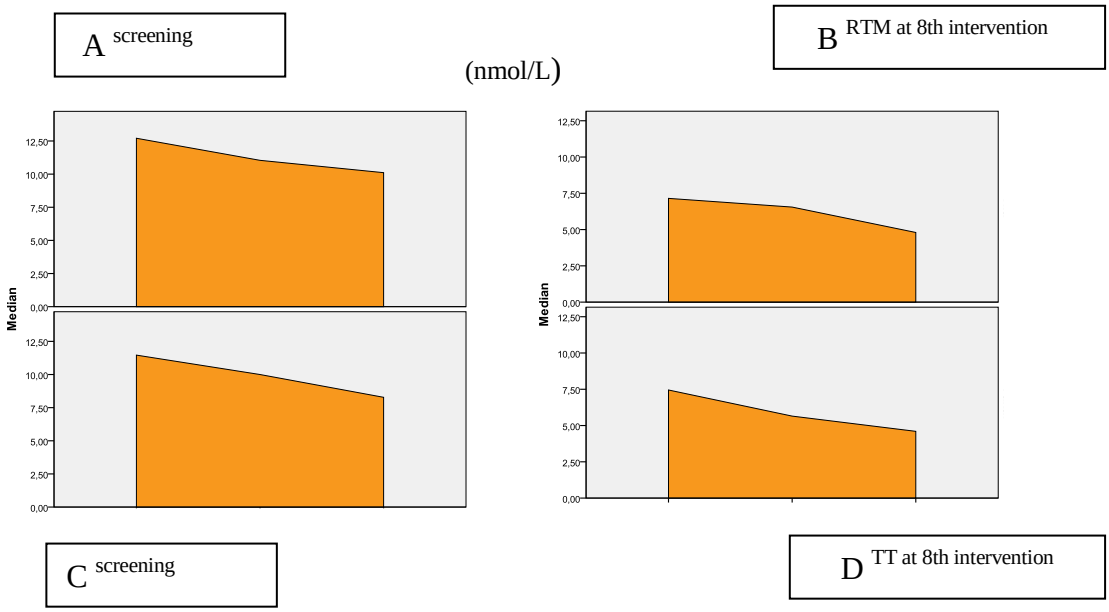


Fig. 20 A+C: A and C represent the change in AUC for each individual at screening at corresponding time points when the interventions were performed with RTM / TT from immediately before to 30 minutes after the 8 th intervention. These changes are visualized in **Fig.20 B+D**. *(A= individuals who received RTM, B= Individuals who received TT).*
No differences between groups in *delta* cortisol values or *percentile changes* after TT and RTM were seen after the eighth intervention, see table 11.

6.2.3.2 Discussion

We found that the diurnal salivary cortisol rhythm is normal in PD. Salivary cortisol concentrations were significantly reduced after the TT intervention, and to a less significant degree after RTM, but with no significant differences between the groups and no sustained long-term effect.
We did not find any associations between salivary cortisol concentration and clinical and/or pharmacological characteristics.
This study did not reject the 0-hypothesis that there were no differences between TT and RTM reflected by the HPA-axis function. Both TT and RTM resulted in an immediate decrease in cortisol concentrations, which further strengthens the effects of the TT-concept as a stress alleviator. However, no long-term effects were shown.
Previous studies in this field have shown different results, but no studies have had this long-term follow-up design. Previous studies with MT of comparable duration and frequencies are shown in table 5. In two studies with short duration (less than one month) Field et al. showed a decrease in plasma cortisol after 2 / 5 interventions with MT per week, respectively, and in a study by Ironson et al. comprising 5 treatments per week during one month significant reductions in urinary cortisol were demonstrated. Hernandez-Reif, Lawler and Leivadi et al. have shown similar results, but all of the studies must be considered as having short-term-effect designs, for details see table 6.
Our study is unique as it was performed with two similar groups; the effects of the TT-concept were compared with a control group that received the same conditions except for the touch component.
Most studies lack detailed information about the time point for sampling, the time lag between awakening and sampling (CAR reaction), and drug intake. In our study only small changes with extra levodopa doses were permitted during the study, thus optimizing the control of data quality. External circumstances are often poorly described in earlier studies.
Cortisol in saliva as well as in plasma reflects immediate effects on the HPA axis, and only cortisol in urine or in hair reflects effects over a very long time. The combination of different sampling sources can be an alternative for future studies in this field.
The lack of significant differences between groups is probably an effect of the fact that the RTM group itself comprised multiple stress-alleviating components. The Music Therapy (MuT), the Aroma Therapy (AT), the pleasant circumstances with the attention of the study staff, etc., all contributed to the short-term effects of RTM.
Another challenge in this study was that the blinded randomization process resulted in skewness between groups. When theoretically doubling identical outcome measures from RTM, differences between groups increased and became significant between groups in some qualitative outcome measures, but not in salivary cortisol outcome measures (Type II error).

6.2.4 Paper III

The aim of this paper was to describe the situation for PD patients with chronic pain according to experiences of pain, sleep and HRQoL variables.

6.2.4.1 Results

6.2.4.1.1 Baseline characteristics

The severity of PD expressed by the UPDRS score for females and males was a median of 23.3 (10/37) and 20.4 (12/36), respectively; 10/90 percentiles for females and males, respectively, and a total of 22.2 ; (10/37) for the whole group. Only one patient described sustained depression (one week or more), 19 patients had experienced short (single days) periods of sadness or guilt and 22 patients had no experience of depressive mood (UPDRS, part 1, q.3, *see Appendix VIII*)
Duration of disease, duration and intensity of pain and pharmacological treatments are shown in table 13.

Gender (n)	**Duration of disease** ≤5 / >5 (years)	**Duration** [1] **of pain/day** ≤10h / >10h	**VAS** [2] ≤ 5/ > 5	**Levodopa** [3,4] **treatment** (mg)	**Analgesics** (n)	**Antidepress.** (n)	**Anxiolytics/ sedatives** (n)
Females (28)	11/16 [5]	20/8	13/14 [5]	634/562 (300/1140)	9	6	23
Males (16)	9/7	9/7	9/7	768/758 (350/1205)	3	2	16

Table 13: Baseline characteristics of the study group.

Notes: [1] *= maximal duration (less or more than 10 hours) of pain per day,* [2] *= Visual Analogue Scale , maximal pain (less or more than 5 cm on the VAS-scale) day 1 – 5* [3] *= values are given as mean/median;(10/90 percentiles), ,* [4] *= LED levodopa equipotent doses,* [5] *= 1 missing data.*

6.2.4.1.2 Evaluation of pain and pain description

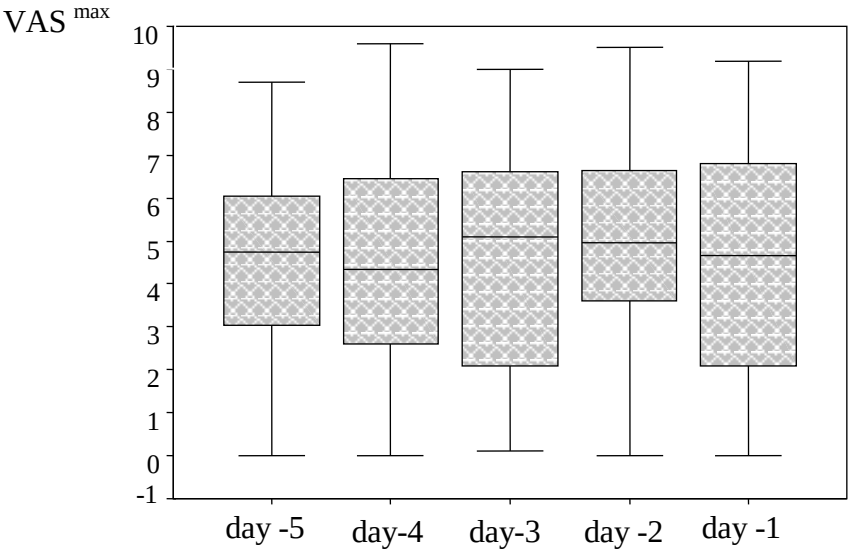


Fig.21A

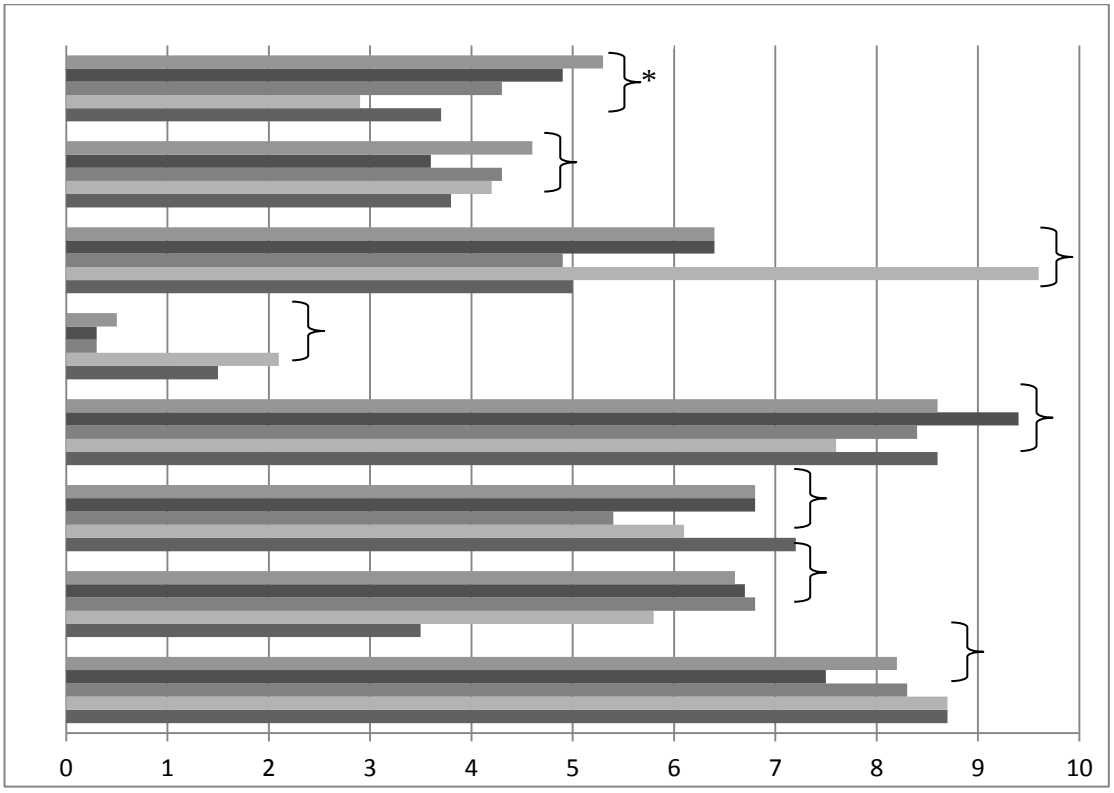


Fig.21B

Fig. 21A + B: A: Registration of maximal pain (VAS ^{max}) each day for five days prior to investigation, all groups (n=44). B: * =Individual daily variability of pain in eight randomly selected participants (VAS ^{max} day-5 to -1).

More females than males described pain as migrating and troublesome, and more males described it as irritating. Thirty-nine percent described the pain as migrating. The body distribution of pain was heterogeneous but significantly more males than females experienced pain from the front of the lower extremities (p-value = 0.014 / 0.019; left/right, respectively). Otherwise no gender differences were shown.
When asked for their thoughts about pain *origin*, 68% specified the muscles and 27% thought that the pain originated in the nervous system. One third of the participants stated more than one source for the pain.
Detailed descriptions of the type of pain experiences were obtained with the instruments POM and PEA, see fig.22 and table 14 below.

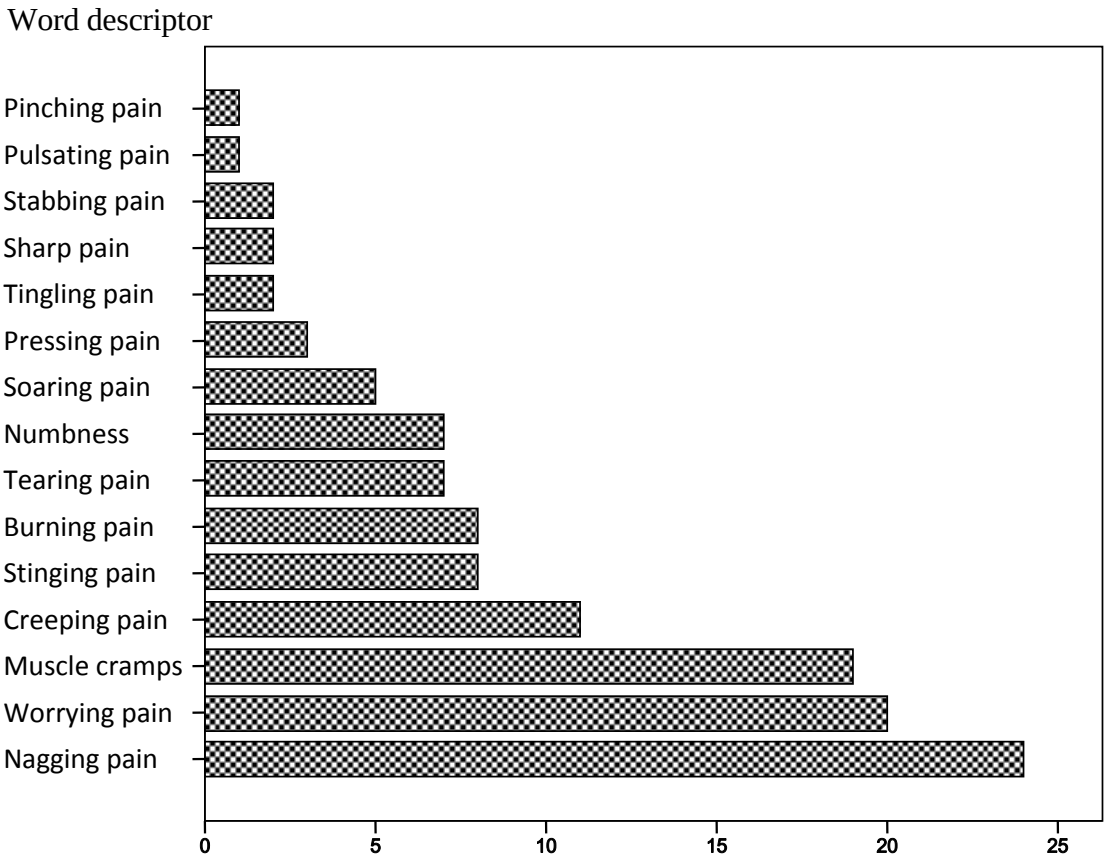


Fig. 22: Different types of pain reported by the participants. (n): *Instrument: The Pain-O-meter.*

Gender	Pain characteristics						
	Migrating	**Irritating**	**Worrying**	**Trouble-some**	**Tiring**	**Suffocating**	**Tingling**[1]
Females (28)	13*	5*	3	20*	20	1	15/44
Males (16)	4*	9*	5	5*	9	0	29/44

Table 14: Subjective descriptions of pain characteristics. *Notes:* * *= p-value ≤0.01, between gender.*
[1] *= symptoms of akathisia, often described as Restless Legs Syndrome (RLS). Questionnare used: The PEA.*

Taking a bath was by far the most common CAM therapy experienced previously; more than half of the participants in the Parkitouch study had done so. Acupuncture, rest, TNS and ultrasound had been used by one patient each.

6.2.4.1.3 Evaluation of sleep

The PDSS-scale contains 15 questions, and answers are registered on a continuous scale from 0 = worst to 10= best; *for questions see Appendix VII*. Fig. 23 illustrates the spread of answers for each item.

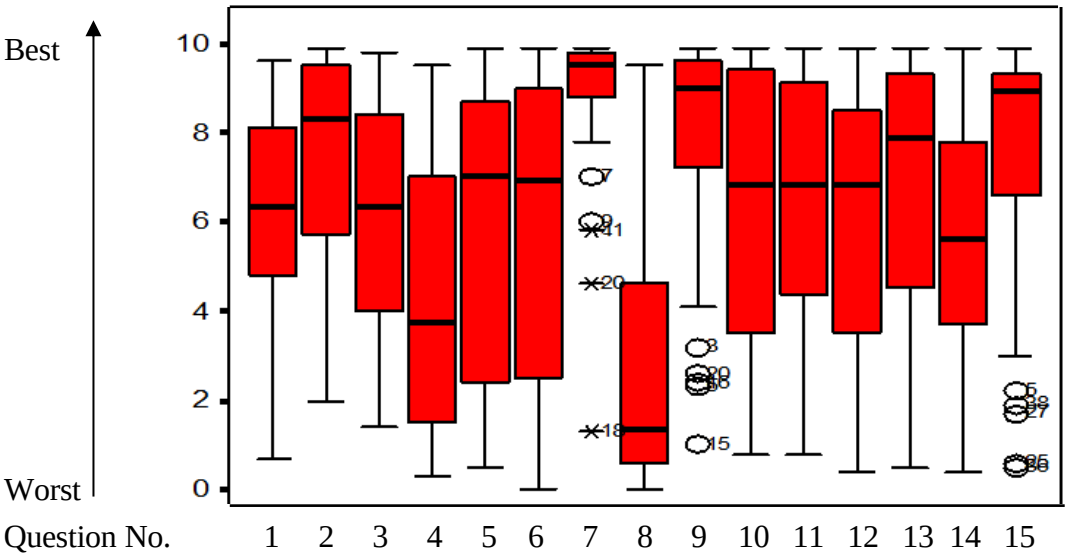


Fig.23: PDSS; distribution of answers**.** ***Note:*** *(medians; 25/75% percentiles; range)*

As illustrated in fig.23, the answers to questions seven and eight deviate from one another**.** Very few patients suffered from nightly hallucinations (q.7) but a majority suffered from nocturia (q.8).

6.2.4.1.4 HRQoL. Comparisons between the PD group, the stroke reference group and healthy individuals

To highlight the HRQoL in PD patients with chronic PD-related pain, a comparison with 107 Swedish patients six months after an acute ischemicstroke is presented in Fig.24.

The PD group scored lower in most items compared to even the oldest persons (75+) in the healthy reference group ($N^{total\ 45\ -\ 75+}$ = 3100)

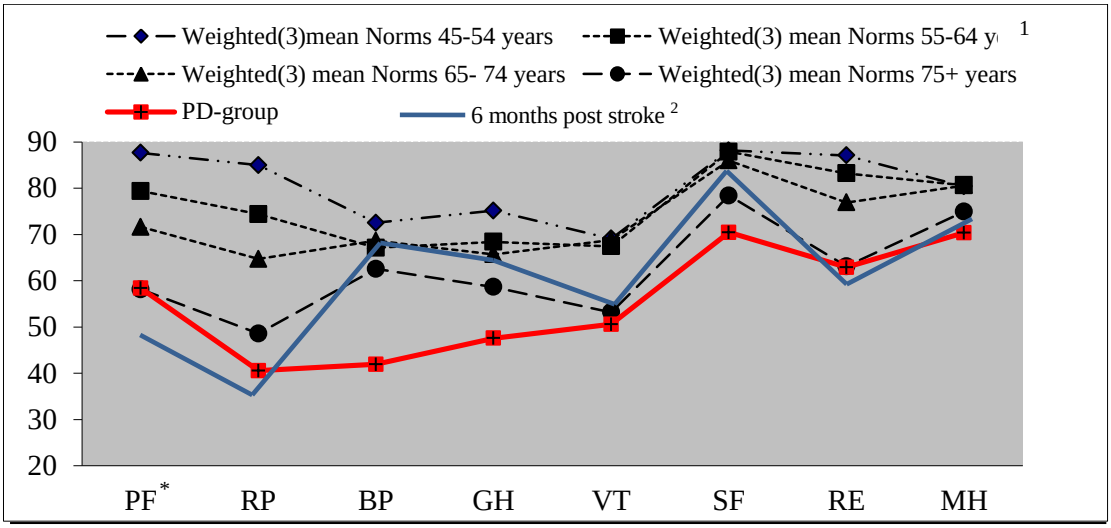


Fig.24: Health-Related Quality of Life (HRQoL) in the PD group compared to a healthy Swedish age-matched reference group and a group of Swedish stroke patients.

Notes: Abbreviations: * = PF = Physical Functioning, RP = Role Physical, BP = Bodily Pain, GH = General Health, VT = Vitality, SF = Social Functioning, RE = Role Emotional, MH = Mental Health. [1] = presented within age groups of a healthy Swedish reference population; weighted according to age distribution within PD-group ; 64% / 36%, (females/males). [2] = data from 107 Swedish patients 6 months after an ischemic stroke, (Sprigg et al. 2011).

6.2.4.2 Discussion

In this paper there was a more in-depth description of PD patients' experiences of chronic pain and sleep. Inclusion criteria were PD-related pain for at least three days per week during the last three months. Patients´ own thoughts about the origin of their pain, its duration, fluctuations, migrational nature, and verbal expressions combined with their own comments about effects of earlier therapy emphasized the individual variability and the strict subjective qualities of pain. The visual impression of each individual´s own pain scheme for five consecutive days was that the intensity of pain as expressed by the VAS-scale was relatively constant for each day. This is shown in Fig. 21 B in a condensed form based on eight randomly chosen individuals. Earlier studies have shown the impact of PD on sleep patterns, but little has been described concerning PD patients with chronic pain.
The availability of complementary treatment forms in ordinary healthcare surroundings – most often combined with a structured training programme - might have influenced the frequent use of the bath as a CAM treatment form in this study. As different forms of financial subsidies are common in the Swedish healthcare system, the economic impact of patients´ choices of preferred treatments cannot be neglected. In this situation it is even more important to evaluate the patient-experienced effects of each form of CAM therapy offered. Interestingly, only one participant reported an earlier experience of massage therapy.

Health-Related Quality of Life (HRQoL) refers to the health dimension of QoL, taking into account aspects of physical health, emotional status and mental status. Individuals with PD who are depressed, have more advanced disease, and have high levels of disability are most likely to experience poor HRQoL, (Soh et al. 2011).
It is well known that gait impairments and demographic factors contribute to a negative HRQoL in PD. Our study shows that non-depressed, moderately severe PD, expressed by the UPDRS score, has severe negative effects on HRQoL when concomitant chronic pain is present.
A comparison of the impact on HRQoL in 107 Swedish patients six months after an ischemic stroke is presented in fig 24. In this study, the same instrument, SF-36, was used. (Sprigg et al. 2011). Mean age in the stroke group was 73.2 years, the male/female ratio was 56/44, and this corresponded well to our group. In five out of eight items in the SF-36 our study group scored worse HRQoL. In summary, this comparison visualizes the heavy burden suffered by PD patients with chronic pain.

6.2.5 Paper IV

The aim of this paper was to compare the effects of Tactile Touch (TT) with Rest to Music (RTM) in PD patients with chronic pain on pain, sleep and HRQoL parameters, and to describe effects within groups.

6.2.5.1 Results

6.2.5.1.1 Effects on pain

Effects on pain experiences constitute one of the main outcome measures in the Parkitouch study. As time aspects are of major interest, the results are divided into short- and long-term effects.

6.2.5.1.1.1 SHORT-TERM EFFECTS ON PAIN

Pain $^{max/5d}$, measured during five consecutive days before intervention, resulted in a trend in favor of TT compared to RTM. No significant differences between groups were seen from screening to week 3.
The change in POM^{VAS} before/after intervention at week 3 was statistically significant in the TT-group *(p-value=0.001). (Method: Mann-Whitney U-test).* This effect was not seen in the RTM group *(p-value= 0.398).* No significant differences between groups were seen.
The effects of TT and RTM from screening until after the seventh intervention, POM^{VAS}, are presented in fig. 25.

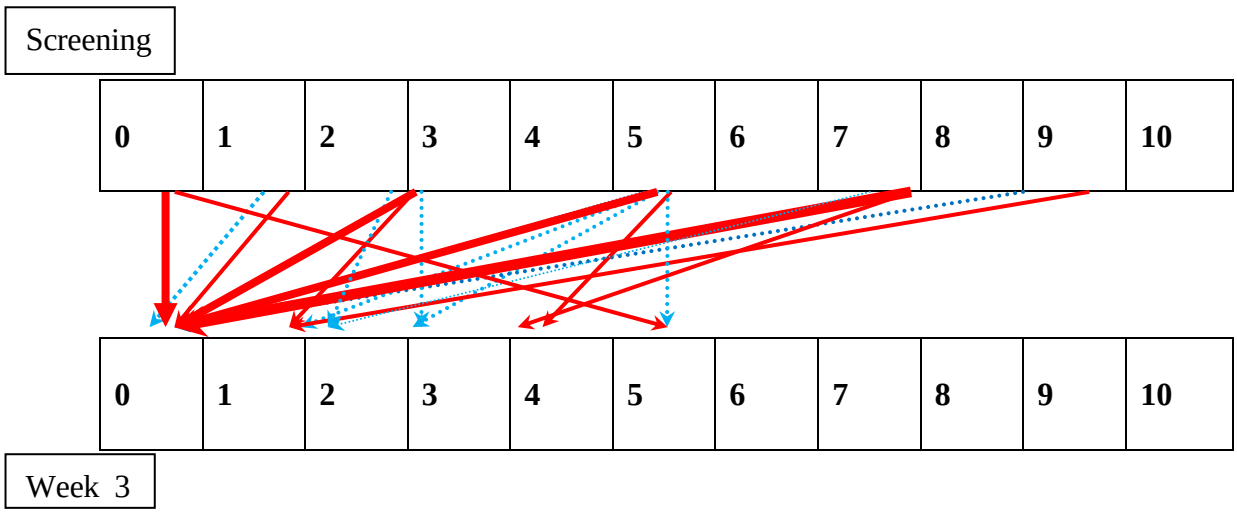


Fig. 25: Visual Analogue Scale (VAS; 0-10): TT →1 pt., ➡ 2- 3 pts., ➡ 4-5 pts.
RTM 1 pt., ⇢ 2- 3 pts., ⇢ ⇢ ⇢

Affective word descriptors:

POM^{phys}: The decrease in the physical affective word descriptors before and after intervention at week 3 was significant within the TT-group *(p-value = 0.027)* but not within the RTM-group. No significant differences were seen between groups *(p-value= 0.086).*

POM^{emo}: The decrease in the emotional affective word descriptors was also most substantial before/ after the intervention at week three. Within the TT-group there was a significant change *(p-value= 0.03)* that was not identified within the RTM group. No significant differences between groups were seen *(p-value=0.178).*

6.2.5.1.1.2 Long-term effects; pain

In total, there was a significant decrease in pain in both TT and RTM *(p-value <0.05)* from screening to the last follow-up, but no statistically significant differences between groups were seen.

The Pain-O-meter was used at seven occasions during the study. The results of the sensory and affective word descriptors (WDS) from screening to the final visit at week 34 *for the TT group* are presented in tables 15A + B. The change from stronger to milder word descriptors was not obvious in the RTM group .

Cross table (TT-group)	At screening							
		Mild → **POM^{emo}** → Strong						n=
		0	1	2	3	4	5	
At week 34	5							0
	4							0
	3	1			2			3
	2			1				1
	1							0
	0				5		2	7
	n=	1	0	1	7	0	2	11

Cross table (TT-group)	At screening Mild → **POM^{phys}** → Strong						N=
		0	1	2	3	4	5	
At week 34	5							0
	4			2				2
	3							0
	2				2		1	3
	1	1				1		2
	0	1		1	2		1	5
	N=	2	0	3	4	1	2	12

Tables 15 A+B: Long-term effects in terms of word descriptors (WDS) with the Pain-O-meter, from screening to the final visit at week 34.
*Notes: **Pain**^{emo} (15A) expressed in number of patients switching from one strength of emotional pain expression to another from screening to week 34 in the TT-group.) The corresponding shift for **Pain**^{phys} (15B).*

A decrease from migrating to non migrating pain was also seen from screening to the last follow-up at week 34, by 22% in the TT-group and 7 % in the RTM group, but the difference was not significant (*p-value=0.38*). *Method: Chi-Square test*.

6.2.5.1.2 Effects on sleep

6.2.5.1.2.1 SHORT-TERM EFFECTS ON SLEEP

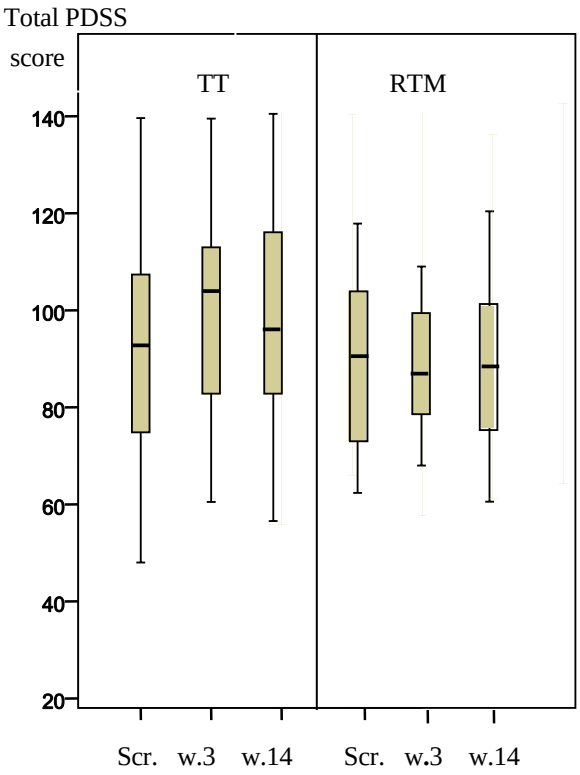


Fig.26: Short-term effects on sleep parameters, TT / RTM, respectively.
Notes: PDSS $^{total\ score}$ *, maximal symptoms = 0, no symptom per item = 10, 15 items, maximal score 150. See Appendix VII, PDSS,Swe.ver. for details.*

A significant increase in PDSS $^{total\ score}$ was seen within the TT-group from screening to week 3, *(p-value=0.016);* this was not seen within the RTM-group *(p-value=0.778),* see fig.26. *Method: Mann-Whitney U-test.* There were no significant differences between groups *(p-value=0.082).*
A significant decrease in early awakenings and vivid dreams was seen in the TT group from screening to week 3 *(p-values=0.001 / 0.009, respectively).* There were no significant differences between groups (*p-value 0.06).*

PDSS [total score] at screening compared to follow-up at weeks 21 and 34 is shown in fig.27.

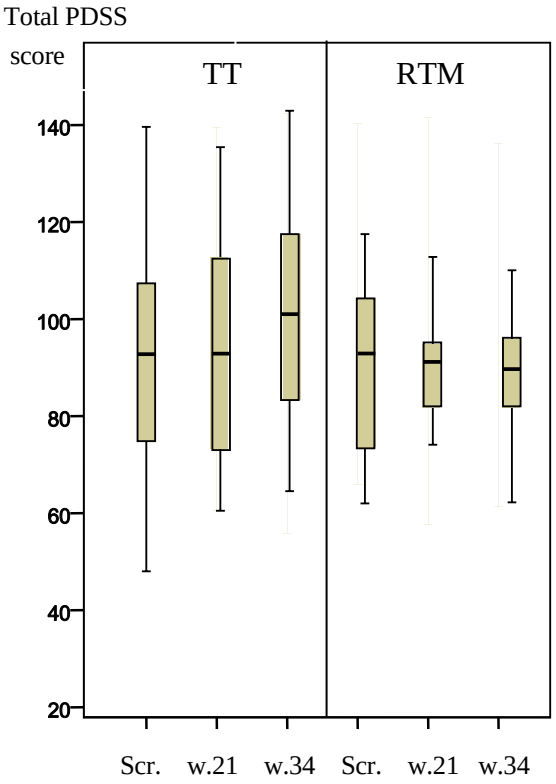


Fig. 27: PDSS [total score] at screening, weeks 21 and 34; TT / RTM, respectively. There were no significant differences between groups. *(Method: Mann-Whitney U-test).*

Analyses with the PEA-instrument did not show any significant differences between groups, but the *within-group* effects were pronounced.

	Group	***Screening***	***Week21***	***Week34***	***p-value[1]***
Awakenings at night (no.)	RTM	3 (2-4)	1.5 (1-2)	2 (1-3)	0.001
	TT	2 (1-3)	1 (1-2)	1 (1-2)	<0.001
Sleep without disruption (hours)	RTM	2 (1-2)	2 (2-3)	2 (1-3)	0.070
	TT	2 (2-3)	3 (2-3)	2 (2-3)	0.027

Table 16: Changes in reported awakenings at night: median;(10/90perc.).[1] = Comparison between screening and *week 21* within the groups. *Statistical method: Wilcoxon Rank test.*

6.2.5.1.3 Short and long-term effects on HRQoL

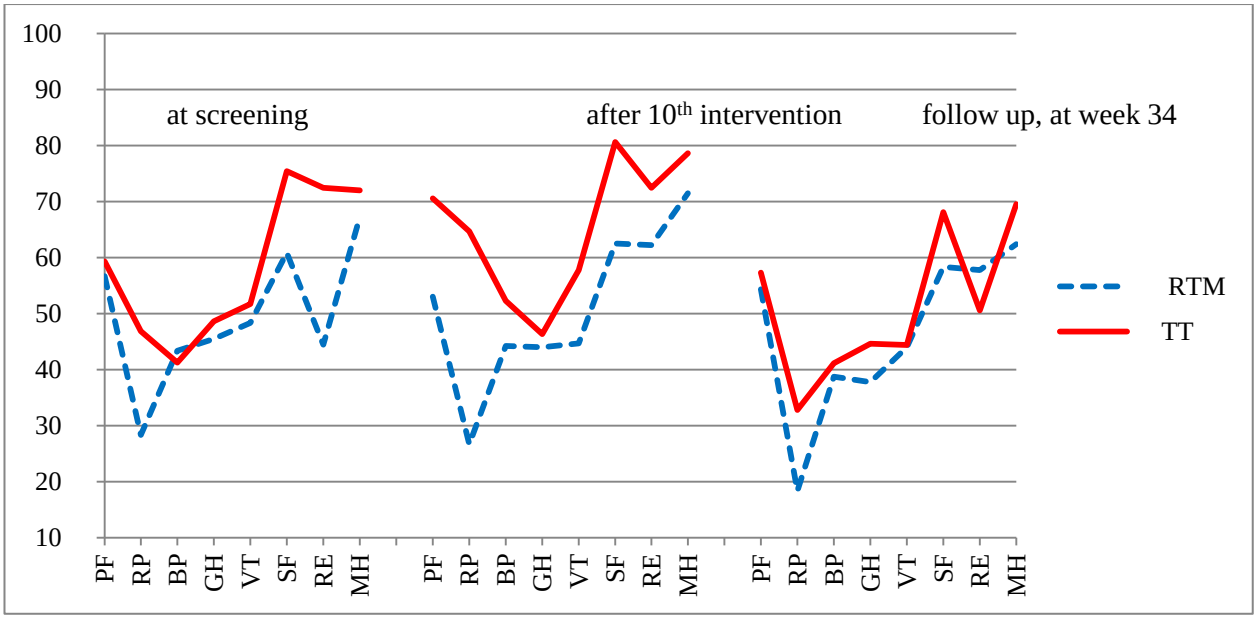


Fig.28: Mean values of HRQoL at screening, after ten interventions, and at follow-up at week 34, TT / RTM (SF-36,Swe.ver.1)

The mean results are shown in Fig.28**.** The study population had, in general, a low HRQoL compared to a Swedish age-matched population as described in paper III. Mental health (MH), Role-Emotional (RE) and Vitality (VT) were almost in concordance with the oldest individuals in the healthy reference population. However, except for Bodily Pain (BP), Role-Physical (RP) and General Health (GH) were scored low by the study groups, see fig.24, page 74.

Participants on antidepressants scored worse than those not on antidepressants in items concerning RP, Mental Health (MH) and Social Functioning (SF), both at screening and during follow-up. There were no significant differences between groups. Those with total scores on the UPDRS I – IV of more than 47 points scored worse in RP and SF but not in MH at screening and during follow-up. In the short-term follow-up from screening to week 8 (10th interv.) there was a significant increase in HRQoL for items RP and SF in the TT group (RP /SF; p-values: 0.006/ 0.012, respectively).

6.2.5.2 Discussion

One of the main hypotheses of the Parkitouch study was that TT could relieve some of the symptoms and problems with pain and sleep, and increase HRQoL in PD patients suffering from chronic PD-related pain and that these effects would persist over a longer follow-up period.

We could doubtless prove that the treatments confirmed this hypothesis in the short-term follow-up, but only in few aspects in long time follow-up.

We also hypothesized that it would be significantly better to add the tactile component to the "active control group", Rest to Music (RTM).

We were aware of the risk of attaching too much importance to a lone significant result among a mass of non-significant results. Therefore we used the Bonferroni method to compensate for this.

This resulted in a lack of significant differences between TT and RTM.

More patients in the RTM group had previously experienced earlier CAM therapies. The limiting effects of this fact on interpreting the study results are difficult to assess. It could be that expectations of positive effects of RTM were already increased at the start. If so, this could interfere with the early positive effects also seen in the RTM group.

However, in this paper we could show that patients with PD and chronic pain benefit from CAM therapy with both TT and RTM in the short-term perspective. The Pain-O-Meter (POM^{emo} and the POM^{phys}) results revealed significantly better within-group effects in the TT group compared to the RTM group from screening to week 8, and also from before to after intervention in the TT-group at week 8. Fig.25 visualizes the POM^{VAS} effects before / after intervention at week 3, revealing altered / diminished pain experiences.

We could not see any long-term effects in the parameters measured after 34 weeks of follow-up. However, POM^{phys} and POM^{emo}, as demonstrated in tables 15A+B, showed a shift in the expressions of pain experiences in the TT-group that is notable.

TT was significantly better than RTM alone in some aspects of sleep in the short term. The frequency of troublesome dreams at night decreased significantly more in TT than in RTM.

The total PDSS score was significantly better within the TT group from screening to week 8, but not in the RTM group and not in a comparison of the two groups. We hypothesized that this could be a question of low statistical strength (Type II error). Over time there were some missing data. Only patients with data collected at both occasions could be analyzed.

For instance $PDSS^{total\ score}$ for the entire period had n= 24 in the TT group and n= 14 in the RTM group. On the other hand, we consider it a strength of the study that when the different parameters of sleep were analyzed there were the same tendencies in favor of TT.

When *theoretically* doubling identical outcome measures from RTM (n=28),

differences between groups became significantly better in favor of TT in the following outcome measures: PDSS $^{\text{total score}}$ from screening to week three and also to week10. Anxiety, restlessness, troublesome dreams, twitching in bed and early awakenings from screening to week 3.

However, as randomization was computerized and blinded, no influence on the distribution of patients in the TT / RTM groups was possible.

We could not show any remaining effects on sleep at the last follow-up (week 34), but the Patient Evaluation Analysis (PEA) at screening and week 21 showed a decrease of one nightly awakening every second night in both the TT and the RTM groups. Participants in the TT group reported an increase in coherent undisturbed sleep from two to three hours from screening to week 21.

Regarding HRQoL, there was an increase in HRQoL in both the TT and the RTM groups in almost all items as measured with the SF-36. TT resulted in an increase in the items Physical Role (RP) and Social Functioning (SF) in HRQoL after eight weeks of the study. RP was still significantly better in the TT group than in the RTM group when adjusted for the Bonferroni effect (p-value = 0.048).

Differences in long-term effects between groups could not be shown.

The challenges involved when comparing two "active" groups have been clearly pointed out in the literature, as mentioned earlier. Effects can be expected in both treatment arms. The terms *relative* results and *absolute* results have been introduced, with *absolute* referring to comparisons with "no treatment at all" or "wait-list" conditions.

7 GENERAL DISCUSSION

7.1 AUTHORITY, GLOBAL AND SCIENTIFIC REFLECTIONS OF CAM THERAPIES

Today, in 2013, there are 21 regulated health care professions in Sweden that require a license to practice, and these are issued by the National Board of Health and Welfare. Physiotherapists, Naprapaths and Chiropractors belong to this group, while massage therapists do not.

Swedish regulations and general guidelines (SOSFS 2010: 659) regulate the legal aspects of the "management system for systematic quality work".

As mentioned in the Introduction of this thesis, CAM therapies are widely utilized; in Anglo- Saxon countries 4 of 10 adults have used some type of CAM (Hunt et al. 2010), and in a telephone survey in 2000 with complete responses from 1000 participants in Stockholm County, 57% had ever used massage therapy (Hanssen et al. 2005). Adult women with high education levels seem to be best represented in this pattern of consumption.

The area of Complementary and Alternative therapies has been a continuous source of discussion. The challenging title of the Swedish Council on Health Technology Assessment´s (SBU) report back in 1998 was:

"Can alternative methods keep their promises?"

Critics argue that Complementary Medicine sells false hope to the sick and suffering at a high price. Common objections to the complementary approaches involve the competence of the performers; the risk of misdiagnosing, thereby delaying effects of conventional treatment. On the other hand, many people experience relief from their suffering with these methods and are willing to pay for them.

As has been carefully described in this thesis, many studies have shown positive effects of CAM therapies.

- Improvement in sensorimotor functions and compensation for their losses in old age through passive sensory stimulation, so-called tactile coactivation, has been shown (Kalisch et al. 2008).
- Positive effects on immune function following massage therapy have been shown in HIV adolescents (Diego et al. 2001)
- Reduced anxiety by means of MT has been shown (Field et al. 1996), including a decrease in anxious behavior, heart rate, and salivary as well as urinary cortisol concentration, suggesting lower stress.
- Facilitation of growth, reduced pain, and increased alertness have also been shown (Field 1998).

Some recently published Swedish theses in this area should be mentioned, all of great interest and with different approaches:
"The effect of massage for women with breast cancer", by Annika Billhult, University of Gothenburg (2007), showed decreased nausea, lowered blood pressure, and effects on natural killer cells with light pressure effleurage massage during chemotherapy.
"Being in safe hands: the experiences of soft tissue massage as a complement in palliative care. Intervention studies concerning patients, relatives and nursing staff", by Berit Seiger Cronfalk, Karolinska Institute, Stockholm (2008), showed, among other things, that palliative care patients receiving soft tissue massage experienced feelings of getting a respite from illness and worrying concerns.
"A pathway for pleasant touch", by Line Sofie Löken, University of Gothenburg (2009), investigated the mechanisms underlying pleasant touch. C tactile (CT) non myelinated afferent fibers were found and these CT afferents were shown to project somatotopically to the posterior insular cortex.
"Exploring integrative medicine for back and neck pain: On the integration of manual and complementary therapies in Swedish primary care", by Tobias Sundberg, Karolinska Institute, Stockholm (2010), found trends toward increased HRQoL in the group of patients who were treated with Swedish massage therapy, manipulative therapy/naprapathy, shiatsu, acupuncture or qigong compared to the control group who received "conventional care" mainly consisting of pain management advice (stay active) and analgesics.
"Migraine and Stress: An Internet administered Multimodal Behavioral Treatment Intervention", by Kerstin Hedborg, Uppsala University (2011), did not show an effect of hand massage on migraine headache frequency, but other parts of the Multi modal Behavioral Therapy program proved effective in decreasing migraine headache.
"Emotional and physiological responses to touch massage", by Lenita Lindgren, University of Umeå (2012), included four different touch stimulations in the design of the study, human touch with movement (TM), human stationary touch, and rubber glove with or without movement. The control group rested in a sitting position. TM was rated as the significantly most pleasant touch stimulation. Participants in this study were young, healthy individuals and the MT-technique was hand and foot massage for 80 minutes per session (20 min. per hand; 20 min. per foot). Participants were their own controls. Cortisol in saliva and insulin levels, which were measured before, immediately after and one hour after intervention, decreased significantly after a single intervention.

The fMRI results revealed that human moving touch most strongly activated the pregenual anterior cingulate cortex. TM reduced the stress response as indicated by decreased heart rate and decreased activity in the sympathetic nervous system, followed by a compensatory decrease in parasympathetic nervous activity.

8 LIMITATIONS AND STRENGHTS

8.1 LIMITATIONS

One of the main approaches of this study was to study the effects of TT in a well defined population of PD patients with PD-related pain. As the prevalence of this condition is limited, the recruiting process was slow. Several of the participants lived outside the city and sometimes transportation issues precluded implementation. This resulted in relatively few participants despite the best of recruitment efforts. The computerized draw resulted in a relative bias with 29 (19/10; females/males) to be treated with TT and 16 (10/6) to be treated with RTM. One of the latter patients withdrew from participation after randomization.

Measurement methods focused on certain non motor symptoms of PD. Measures of pain experiences as a complex of non wellbeing were supplemented with validated scales for sleep disturbances, quality of life and severity of disease. The latter included questions about mood and depression, but as longstanding pain is closely linked to depressed mood, this area of intervention could have been more extensively studied.

The age range of our participants was 50 to 79 years and thus did not include the oldest PD patients. The relative difficulties for elderly PD patients with balance problems and stiffness to turn over on the gurney was a limiting factor. Trips to the treatment sessions were also a limiting factor in this regard.

Dyscognition is a major problem among PD patients with longstanding disease. This was an exclusion criterion in the study. Sampling of salivary cortisol required the ability to understand aspects of the procedure such as avoiding food intake, smoking and brushing the teeth before sampling as well as carefully and acurately recording time points for awakening, intake of antiparkinson medication, etc.

Two active treatments were compared in the Parkitouch study, TT and RTM. As both treatments had positive effects on outcome measures, it was difficult to demonstrate significant differences between groups. The within-group effects were substantial and were described in the papers. Comparison with a group with "*no treatment at all*" would have been preferable in some respects, but as using salivary cortisol as a surrogate marker for stress is a very sensitive method, it would have been difficult to interpret the results from such a group.

A range of choices must be decided upon before start of a study like this. Of what importance is choosing one's own music? Listeners have reported more intense emotions to self-chosen music than to randomly selected music (Liljeström et al. 2012). However, in our study we chose to have all other parameters constant and only compare the effects with or without tactile stimulation.

8.2 STRENGTHS

To compensate for not having a "no treatment at all" group, all measurement analyses were performed at screening before the first intervention.This was our "*own control point*", similar to the *basal preinterventional state.* This time point in our study was used to compare the real/absolute therapy-induced effect of the first and 8 th interventions, and in our opinion this methodology must be included as one of the strengths of the study.

The impressive compliance among participants is noteworthy. Follow-up rates were 100% and 93%, TT/RTM, There are no previously published studies that have analyzed diurnal cortisol rhythm and/or multiple salivary cortisol samples even during a passive non-interventional follow-up period of this length.

The data collection procedures were extensive and accurate and the protocols were carefully completed.

The exact time points for awakening and sampling made it possible to control for CAR reactions.

Missing data were few in number. Only 7 / 7 salivary cortisol samples before and after interventions were missed, and these were equally divided between the two groups. During the follow-up period only 20 samples were missing, corresponding to 3 % of all samples, (20/700).

All samples were analyzed at the same time point and at the same laboratory. The same laboratory had previously analyzed the cortisol samples from the reference group (paper I).

The supplementary analyses of the AUC are a particular strength when cortisol secretion rates are studied.

Competing treatments of a complementary nature were not allowed during the study, and not all studies of this type emphasize the importance of this fact.

The pharmacological treatments were fully controlled; 42 of 44 patients were treated with levodopa with no significant differences between the two groups, even when we integrated all anti-PD drugs and recalculated the total dopaminergic load using formulas for equipotent doses.

The pharmacological treatment for PD was essentially unchanged, and only single extra doses of anti-PD treatment were taken during the study.

9 CLINICAL IMPLICATIONS AND FUTURE RESEARCH

9.1 THE INTERNATIONAL PERSPECTIVE

The huge consumption of CAM therapies has been discussed above. In 2005 the rising use of CAM therapies in the U.S. during the 1990s was surveyed by the National Institute of Health (NIH) (*Book*: Prevalence, Cost, and Patterns of CAM Use, 2005). An estimated 30 to 62% of adults in the U.S. used CAM during that time. One of the conclusions was that the lack of consensus concerning the definition of CAM had led to inconsistencies among the reports of various surveys of CAM prevalence and patterns of use. The total expenditures for CAM therapies in 1997 were conservatively estimated at 27 billion US dollars. The NIH recommended that public and private agencies should sponsor quantitative and qualitative research to examine the social and cultural dimensions of illness experiences, health care-seeking processes and preferences. How often users of CAM, including patients and providers, adhere to treatment instructions and guidelines, and the effects of CAM on wellness and disease prevention, were other recommended areas for research, as well as systematic evaluations of adverse events associated with CAM therapies, and interactions between CAM and conventional treatments.

A search in the Cochrane database for the concept "*tactile touch*" in systematic reviews during the 2000s resulted in only three relevant matches. "*Massage therapies"* resulted in about 40 matches. This can be compared with search words such as "smoke", "hypertension" and "stroke", which resulted in 140 - 350 relevant review matches.

9.2 THE NATIONAL PERSPECTIVE

In a 10-year-old study of the resource use in a Swedish PD population the mean total annual cost for PD in the sample was estimated at approximately EUR 13,800 per patient. The cost distribution per person, per year for direct healthcare costs/nonmedical costs/lost production costs was EUR 3,200 / EUR 4.800 / EUR 5,800, respectively (Hagell et al. 2002).

Not much is known about the extent to which CAM therapies contribute to this resource utilization among PD patients.

What do Swedish authorities consider to be evidence-based medicine in this field? Using the above-mentioned approach, with key words as "Complementary and Alternative Medicine"," massage therapy", "massage" and "tactile" in a Swedish database - (the Swedish Council on Health Technology Assessment, (SBU), only a few relevant results were found. Touch Massage for Dementia, a Swedish report from 2002 (SBU Alert, 2002) concluded that there was little scientific evidence concerning the effects of soft massage on demented patients and that scientific evidence was absent concerning its costs and cost-effectiveness.

In another report, "Treatment of Insomnia in Adults" (SBU report, 2010), those conclusions were repeated; there is insufficient evidence for assessing the effect of alternative and complementary methods for the treatment of insomnia. "Available studies are scarce and of poor quality".

In conclusion, CAM therapies are widely used by the population and several Swedish theses have dealt with the topic during the past decade, as described above. Nevertheless, there is an obvious lack of broad scientific studies of good quality, based on coherent variables, in both the Swedish and the international literature.

The Parkitouch study has added some new knowledge to this huge and somewhat heterogeneous field.

Detailed analyses of methodological challenges and efforts to make comparisons possible in terms of data sampling, interventional preconditions, measurements, and external circumstances in the field of CAM research are main issues for the future.

10 MAIN CONCLUSIONS

10.1 AT BASELINE, BEFORE INTERVENTIONS

- PD patients with mild to severe PD, with and without chronic PD-related pain, have a normal diurnal cortisol rhythm, higher morning cortisol concentrations and increased cortisol secretions during the day (8 am–8 pm) compared with healthy age-matched and gender-matched individuals.

- PD patients' diurnal cortisol concentration is unrelated to age, duration of disease, gender, severity of motor dysfunction, coexistence of chronic pain, doses of pharmacological antiparkinson therapies expressed in levodopa equivalents, or BMI. The findings were confirmed repeatedly during the 34-week-long study.

- A considerable proportion of PD patients with chronic PD-related pain have pain onset many years before diagnosis.

- A severe impact on sleep with disrupted sleep patterns is seen among PD patients with chronic pain.

- HRQoL in PD patients with chronic pain is significantly lower than in a healthy reference population matched for age and gender.

10.2 AFTER SINGLE AND MULTIPLE INTERVENTIONS

- Short-term effects of CAM with TT and RTM result in a significant decrease in salivary cortisol concentration and total secretion of cortisol during the day in both groups, but with no significant differences between groups.

- After repeated interventions with TT and RTM, salivary cortisol concentrations significantly decreased immediately and 30 min. after intervention. The total salivary cortisol secretions (AUC) also significantly decreased immediately after intervention in both groups, but with sustained effect only in the TT group,

- There were no recognizable long-term (34 weeks) effects of the interventions on the hypothalamic-pituitary-adrenal axis in terms of diurnal cortisol rhythm and total cortisol secretion.

- Health-related quality of life increased in both the TT and RTM groups in almost all items measured with the SF-36 (Swedish ver.1).

- Positive effects regarding pain were shown in both TT and RTM, most pronounced during the first 21 weeks of the study.

- No longstanding effects of TT and RTM were seen at the follow-up after 34 weeks.

11 EPILOGUE

The background, implementation, data collection and processing of this thesis were permeated by a deep-seated search for the truth, and a search for a way to advance the scientific basis for continuing the work that is needed in this field. At the same time, the emotionally controlled aspects of human beings be considered. This is summarized in the following quotations.

"Without touching a child dies, the human heart is aching and the soul withers" (Phyllis 1990)

"*I am a"parkinsonian". Captured in my own skin. Tight. Stiff. Splinter chaos. My inner pulse is gone and gone is the inner music of me, my rhythm. What has happened? What is happening inside my body? Where is control? Where is balance? My own will is at times paralyzed. The impulses must come from outside. Thoughts and action are incompatible. The powerlessness haunts me, everything within me stops. The impulses are absent. Help! Levodopa is not enough!"* (Sunvisson 2003)

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14 APPENDIX

14.1 *APPENDIX I:* SHORT DESCRIPTION OF THE TACTILE TOUCH CONCEPT (TT)

The method "*Tactile touch"* - a structured touch on the skin according to tactile methods.
Tactile touch means stroking with intention, using soft and encompassing hands on the skin. The strokes are given with respect, empathy and sensitivity for the special needs of the individual.
When performing *Tactile touch*, the **start** and **finish** are important. **Start** means that the therapist first places both hands on the body part to be massaged and briefly waits before beginning the strokes. **Finish** means the hands linger a short period before going on to the next body part. Except for the **start** and **finish**, the therapist's hands maintain a steady flow from one stroke to another using a pressure that is comfortable for the receiver. It is this sequence of strokes, rhythm, flow and moderate pressure on the skin, developed through prior experience massaging Parkinson patients, which characterizes tactile touch.
The therapist: Conveys an attitude of dignity, respectfulness and caring for the individual's integrity.
Room: Located in the hospital, approximately 22-24° C, lighted candles, a draped massage table and a chair.
Draping: With the exception of underwear, the recipient removes all their clothing, including jewellery, eye glasses and hair clips. A light blanket and pillows are used as desired by the receiver. Only the part to be stroked is uncovered.
The receiver: Is encouraged to close their eyes and avoid conversation not related to the massage.
Music: "Music for well being II" from "Fönix Music Wellness" is played at a sound level desired by the recipient.
Oil: Sufficient oil is used to facilitate this smooth flow of the hands. The entire *Tactile touch* is done with cold-pressed vegetable oil. The oil used in this study was "Fibro Olja" from Creacome AB and is a blend of sesame, rape, thistle, shea butter, arnica, olive and borage oils as well as Vitamin E and essential oils from ginger, lavender, rosemary and rose absolue.
On larger surface areas, i.e. back, thighs, chest, upper arm, etc, the entire palmer surface of the hands, including finger pads, is gently molded on and around the body part being massaged, following the contours of that body part. This type of stroking can be divided into two main categories:
1. Long strokes moving up or down the length of the body part. The fingers generally point toward the midline of the client's body. Referred to as **effleurage**.
2. Strokes moving across the width of the body part. Referred to as **wringing**.
Where a more specific touch is desired, i.e. face, hands, feet and around the knees or elbows, the following strokes are used:

1. **Petrasage -**where the finger pads perform small, gentle circles.
2. **Spreading –** where the palmer surface of the fingers or thumb stroke from the midline to the sides of the body part.

For the first visit, the therapist describes a full body massage and the recipient's questions are answered.

Experience has shown that most Parkinson patients prefer to start the massage lying face down (prone) on the table. The therapist always asks the recipient if it feels OK to start the massage.

Sequence for *Tactile touch*

1. Back of legs
2. The back
3. Back of the head

The recipient turns over

4. Abdomen
5. Chest
6. Face, ears
7. Front of head
8. Right arm, then right hand
9. Left arm, then left hand
10. Left leg, then left foot
11. Right leg, then right foot

All strokes are performed twice.

Tactile touch is ended by the therapist holding onto both feet outside the cover then gently releasing the feet.

The therapist now releases contact with the recipient, who is invited to lie still for a moment before water, which always is nearby, is offered.

The therapist thanks the recipient for the privilege of massaging and assists them off the table and with dressing, if the recipient so desires.

Each session is concluded with a discussion of what the recipient has felt and experienced.

14.2 *APPENDIX II* : SHORT DESCRIPTION OF REST TO MUSIC (RTM)

(Swedish version)

Metodbeskrivning av vila till musik. 2003 11 26

Under åtta veckor behandlas kontrollpatienten vid tio besök varav två planeras till ordinarie besök hos sjuksköterska. Tio minuters samtal med sjuksköterska före och efter behandlingen för information och utvärdering av denna. Musikstunden pågår fyrtio minuter.

Lokal:
Ett enskilt rum per patient anordnas på sjukhuset.

Tid:
Besöket skall i möjligaste mån ske ½ - 1 timma efter medicinintag.

Musik:
Samma musik som spelas under beröringsmassagen.

Patienten välkomnas i ett varmt rum, rek värme ca 22 – 24 grader, med levande ljus och en färdigbäddad brits. Under samtalet sitter patienten i en stol i rummet. Ett lugnt bemötande av sjuksköterskan för att patienten skall slappna av. Patienten lägger sig sedan i ett vilsamt läge på britsen som är bäddad med liggunderlag, bomullslakan och kudde. Ett täcke läggs över kroppen. Vid behov placeras en kudde där patienten så önskar. Musiken spelar på den ljudnivå patienten finner lämplig. Efter fyrtio minuter avslutas vilostunden då vatten erbjuds. Viktigt är att dokumentation förs huruvida patienten dricker vatten eller inte efter behandlingen. Patienten allmäntillstånd och skattning följer patientschemat.

Viktigt att du bokar för om patienten tar vatten eller inte efter behandlingen.
ja nej

Vilken ljudnivå föredrog patienten? (uppskattas subjektivt)

ingen svag medel stark

14.3 *APPENDIX III*: REGISTRATION OF PAIN, FIVE CONSECUTIVE DAYS PRIOR TO VISITS

(Swedish verison)

Skattning av smärta studiev Kod nr:

Ange på skalan hur mycket smärta Du har. Sätt ett **kryss** på linjen **varje gång du har ont eller smärtan ändrar sig påtagligt Börja räkna dygnet från kl 06.** Gör detta **under 5 dagar närmast före sjuksköterskebesöket.**

Datum

Inte ont alls ◄——————————————————► värsta tänkbara smärta

Hur stor del av dygnet i timmar hade du värk……..

Datum

Inte ont alls ◄——————————————————► värsta tänkbara smärta

Klockslag när värsta smärtan startade….

Hur stor del av dygnet i timmar hade du värk……..

Datum

Inte ont alls ◄——————————————————► värsta tänkbara smärta

Klockslag när värsta smärtan startade …

Hur stor del av dygnet i timmar hade du värk……..

Datum

Inte ont alls ◄——————————————————► värsta tänkbara smärta

Klockslag när värsta smärtan startade …

Hur stor del av dygnet i timmar hade du värk……..

Datum

Inte ont alls ◄——————————————————► värsta tänkbara smärta

Klockslag när värsta smärtan startade …

Hur stor del av dygnet i timmar hade du värk……..

14.4 *APPENDIX IV:* PATIENT EVALUATION ANALYSIS

(Swedish version)

Frågeformulär om smärta

Namn ..... Adress .....
Personnummer ..... Postnr .....
Ort .....

För att kunna kartlägga förekomsten av smärta hos personer med Parkinsons sjukdom, ber vi Dig vänligen besvara nedanstående frågor. Kryssa för Ja eller Nej.
Vi vill gärna ha Ditt svar inom 10 dagar: senast .....

Har Du problem med smärta?
❑ Ja
❑ Nej - Om nej, besvara endast sista frågan om nattsömn (kursiverad stil)!

Har Du nyligen fått problem med smärta? (smärtan kom för några timmar, dagar, eller veckor sedan)
❑ Ja
❑ Nej

Har smärtan pågått i mer än 3 månader?
❑ Ja
❑ Nej

Har Du inslag av smärta dagligen?
❑ Ja
❑ Nej - Om nej, kryssa för en av följande tre frågor:

- ❑ Har Du inslag av smärta minst tre gånger/vecka?
- ❑ Har Du inslag av smärta en gång/vecka?
- ❑ Har Du inslag av smärta mindre än en gång/vecka

Nattsömn:
Har Du smärta som inte påverkar Din nattsömn?
❑ Ja
❑ Nej

Påverkar smärtan Din nattsömn?
❑ Ja
❑ Nej

Har Du störd nattsömn utan smärta?
❑ Ja
❑ Nej

Tack för Din medverkan!
Vänliga hälsningar
Neurologmott.

.....
Tel.
.....

SCH MA FÖR MÄRTANALYS VID PARKINSONS SJUKDOM

Namn		Personnr	
Adress	Postnr/Ort		
Tel.nr	E-mail		
Diagnosår	Behandlande läkare		
Yrke	Arbetar Ja ☐ Nej ☐ Arbetssituation 25% ☐ 50% ☐ 75% ☐		
Aktuellt datum	Blodtryck Stående:	Blodtryck Liggande:	Vikt:
Jag är allergisk mot		Blodvärde	

Kod

Smärtprojekt 2004-6
Ett forskningsprojekt i samarbete mellan Skaraborgs sjukhus (SKAS) och Ryhovs sjukhus, Jönköpings län rörande beröringsmassage/vila till musik till Parkinsonpatienter med smärt- med/utan samtidig sömnproblematik.

När sker normalt intaget av mediciner och i vilken mängd? Börja med dina parkinsonmediciner. Notera de **verkliga tiderna** för dina intag och sätt sedan in dem här nedan.

OBS! Alla intag av medicin, även icke receptbelagd (exempelvis Alvedon, Treo, Naturläkemedel, Tedrycker etc.) skall noteras.

Mediciner	Styrka	Ggr	05	06	07	08	09	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	01	02	03	04

Servicetelefon: 0200-22 10 40 * Kont 0911–919 4[illegible] * Fax: 0911-23 00 20 * E-post: parkinson@bre[illegible]nd.net * Or[illegible] 898801-1311 * Gåvogiro 90 11 18-0

Svenska Parkinsonstiftelsen

1. Hur länge har du haft smärta? _____ år _____ mån _____ dagar

2. Hur många gånger vaknar du på natten? _____ ggr

3. Hur ofta gör du nattliga toalettbesök? _____ ggr

4. Hur många timmar sover du sammanhängande?
   ☐ mindre än 2 timmar ☐ 2-3 timmar
   ☐ 3-4 timmar ☐ 4-5 timmar
   ☐ Mer än 5 tim.

5. Besväras du av rastlösa ben, myrkrypningar? ☐ Ja När på dygnet:_____ ☐ Nej

6. Hur började smärtan/-orna ☐ Plötsligt ☐ Långsamt ☐ Minns ej

7. Anser du att smärtorna började före din Parkinson? ☐ Ja ☐ Nej ☐ Minns ej

8. Smärtorna började i samband med annat - vad? _____

9. Var började smärtan/-orna? _____

10. Smärtan ges acceptabel lindring av ☐ Smärtstillande medicin ☐ Parkinsonmedicin
    Vilken? _____

11. Smärtan lindras av ☐ Annat
    Vad? _____

12. Smärtan förvärras av:
    ☐ Lyft ☐ Gång ☐ Sittande
    ☐ Liggande/vila ☐ Beröring ☐ Kyla
    ☐ Väderomslag ☐ Värme ☐ Belastning
    ☐ Annan rörelse ☐ Tryck ☐ Stående
    ☐ Kläder på det smärtande området ☐ Inget bestämt
    Annat vad? _____

13. Upplever du att smärtan "vandrar runt" i kroppen? ☐ Ja ☐ Nej ☐ Vet ej

Vid Ja, markera tider och smärttyp på kropps-schablonen på baksidan.

14. Varifrån tror du din smärta kommer?

☐ Nervsystemet (hjärna, ryggmärg, nerver) ☐ Psyket (oro, ångest, depression)
☐ Hjärta och/eller lungor (andning, cirkulation) ☐ Muskler, skellett, bindväv
☐ Hud, underhud ☐ Njurar, urinvägar ☐ Körtlar, lymfsystem, blod
☐ Könsorgan ☐ Mage/ Tarm ☐ Vet ej

SMÄRT-ANALYS

15. Upplever du att smärtan ökar vid stressituationer? ☐ Ja ☐ Nej ☐ Kan ej avgöra

16. Beskriv hur smärtan upplevs: ☐ Irriterande ☐ Oroande ☐ Besvärlig ☐ Kvävande ☐ Tröttande

17. Får du/ har du fått annan behandling än mediciner mot smärta?

☐ Akupunktur ☐ Zonterapi ☐ Styrketräning ☐ Stödjande samtal
☐ Tens (olika ställen) ☐ Stretching ☐ Kortisonsprutor ☐ Klassisk massage
☐ Bad ☐ Beröringsmassage

☐ Annat vad? _____ _____

18. Av vem/ vilka får du/ har du fått behandling för din smärta?

☐ Läkare ☐ Sjuksköterska ☐ Sjukgymnast ☐ Arbetsterapeut
☐ Kiropraktor ☐ Naprapat ☐ Homeopat

☐ Massör (Vilken typ av massage)? _____

☐ Annan (ange av vem/ vilka)? _____ _____

19. Vilka mediciner har prövats tidigare?

1. mot Parkinson _____ _____
2. mot oro _____ _____
3. mot depression _____ _____
4. mot värk _____ _____
5. mot sömnproblem _____ _____

20. Vad tror du skulle kunna hjälpa dig? _____ _____

21. Beskriv dina andra symtom (på Parkinsons sjukdom mm.) _____ _____

22. Har du dagliga smärtinslag? ☐ Ja ☐ Nej

23. Hur lång är varje smärtattack? ☐ Kommer och går ☐ Finns hela tiden ☐ Mindre än en timma ☐ Timmar ☐ Dagar ☐ Veckor

24. Är smärtan ☐ Ytlig (t ex i huden) ☐ Djup (t ex muskelkramp) ☐ Diffus (olika ställen) ☐ Utstrålande ☐ Både och

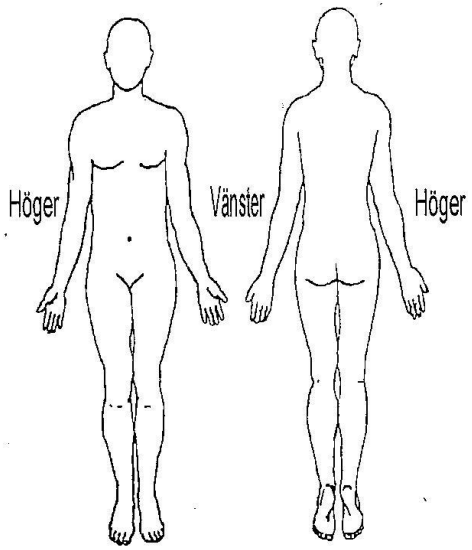
	Typ av smärta	M	Fm	Em	Kv	N
1	Muskelkramp					
2	Domning					
3	Krypningar					
4	Ilningar					
5	Värkande					
6	Tryckande					
7	Brännande					
8	Molande					
9	Klämmande					
12	Pulserande					
13	Skärande					
14	Stickande					
15	Huggande					

Ange; med en siffra 1-5, **hur besvärande respektive smärta är under** *ett genomsnittligt dygn.*

Lindrig smärta	= 1
Måttliga besvär	= 2
Svår smärta	= 3
Mycket svår smärta	= 4
Outhärdligt	= 5
Ingen smärta	= 0

Förkortningarna i tabellen till vänster står för: **morgon** (05-08), **förmiddag** (08-12), **eftermiddag** (12-16), **kväll** (16–22) och **natt** (22-05).

Smärt-analysen fylls i när man önskar en dokumenterad utvärdering av sin aktuella situation. Svaret ger den behandlande läkaren ett säkrare underlag för justering.
En förändring/justering av medicineringen, följs alltid upp med en ny smärt-analys t.ex. efter 14 dagar.
Genom att jämföra svaren med varandra; det första mot det andra, kan man snabbt utvärdera om insatt åtgärd gett förväntat resultat.



Ringa in, alternativt markera med en pil, de platser där smärta/ smärtor förekommer.

Använd siffrorna (1-15) i tabellen till vänster för att **ange typ/ typer av smärta.**

Ange även om **samma smärta ändrar placering** under dygnet.

14.5 APPENDIX V: INSTRUCTIONS: COLLECTION PROCEDURES FOR SALIVARY CORTISOL.

(Swedish version)

Parkitouch ***Salivprovtagning***

		Modell	Modell
Provtagn 1	***Screening***	***A***	
" 2	***V 0***		***B***
" 3	***v 3***	***A***	
" 4	***v5***		***B***
" 5	***v7***	***A***	
" 6	***v21***	***A***	
" 7	***v34***	***A***	

Kom ihåg!

I sbm provtagningen skall ***ett protokoll fyllas i för varje gång.***

Det är ***viktigt*** att ***bomullstussen är ordentligt fuktig- blöt.***

A-Dygnskurva
Proverna- dygnskurva *-tas dagen före besöket* hos parkinsonssk för att
1/kunna upprepas om det skulle blivit fel
2/tas med till system- för att vi skall veta att de tagits
3/system skickar proverna till kemlab-***bockar av på listan***

Fyll i protokoll
1/ Kodnr _____
2/Datum (år,mån,dag) _____
3/Vaknade kl (tim, min) _____
4/Tog min Parkinsonmedicin senast kl (tim,min) _____
5/ Ätit—före efter provtagningen (ringa in)
6/ salivprov tas (0800) ange exakt tid (tim,min) _____
(1300) _____
(2000) _____
nästa dag (0800) _____

B-massage
Alla prover tas i ***upprest läge*** och vid ***samma tidpunkt för varje enskild individ*** (v0 och v5).
Första provet *tas kl 09-10.(dvs inga massager efter kl 1000 när vi tar salivkortisol samtidigt)*

Ex		
Omedelbart före	0900	1000
Omedelbart efter	1000	1100
30 min efter massagen	1030	1130

Fyll i protokoll som A men tider enl ovan.
Prover tagna hos massören sätts i kylskåpet och skickas nästa vardag (senast torsdag förmiddag) till kemlab, Skövde i frankerat kuvert med ifyllda remisser (3 st). Klistra på motsvarande etikett på provröret.

Provtagningsremiss Fylls i ***"Parkitouch" studien***
Kodnr
Datum
Klockslag

Alla ***märkta (etiketter) prover*** (3-4st) skickas in i samma frankerade kuvert tillsammans med ifyllda provtagningsremisser (3-4 st).

Carl-Johan Törnhage 2004 07 06
A:\Parkitouch salivkortisolprovtagningprotokoll.doc04-07-15

"Parkitouch"-studien

Salivkortisol protokoll

Fyll i protokoll för varje provtagningsomgång.

(dygnskurva eller massage/vila till musik)

1/ Kodnr ----------

2/Datum (år,mån,dag) ----------

3/Vaknade kl (tim, min) ----------

4/Tog min Parkinsonmedicin senast kl (tim,min) ----------

5/ Ätit—före efter provtagningen (ringa in)

6/ salivprov tas

Dygnskurva	(0800)	ange exakt tid (tim,min)	----------
	(1300)		----------
	(2000)		----------
nästa dag	(0800)		----------

Massage-vila till musik

Omedelbart före	ange exakt tid (tim,min)	----------
Omedelbart efter		----------
30 min efter avslut		----------

C-J Tömhage 2004 07 14

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Studie "Parkitouch"
Kodnr_____

Instruktioner för sjuksköterska.

Första besök-screening (dag –7-0 / vecka -1)
Vikt-_____, kortisol, smärtanalys, SF36, UPDRS I-IV, PDSS, VAS, POM, LK-grund och vb.
beräknat datum_____/ verkligt datum_____

Andra besök (dag 21-27/ vecka 3)
Vikt_____, kortisol, SF36, PDSS, VAS, POM före och efter massage, LK grund och vb

beräknat datum_____/ verkligt datum_____

Tredje besök (dag 49-55/ vecka 7)
Vikt_____, kortisol, SF36, UPDRS I-IV, PDSS, VAS, POM före och efter massage, LK-grund och vb.

beräknat datum_____/ verkligt datum_____

Fjärde besök (dag 70-76/ vecka 10)
Vikt_____, SF36, UPDRS I-II och IV, PDSS, VAS, POM, LK grund och vb

beräknat datum_____/ verkligt datum_____

Femte besök (dag 98-104/ vecka 14)
Vikt_____, SF 36, PDSS, VAS, POM, LK grund och vb

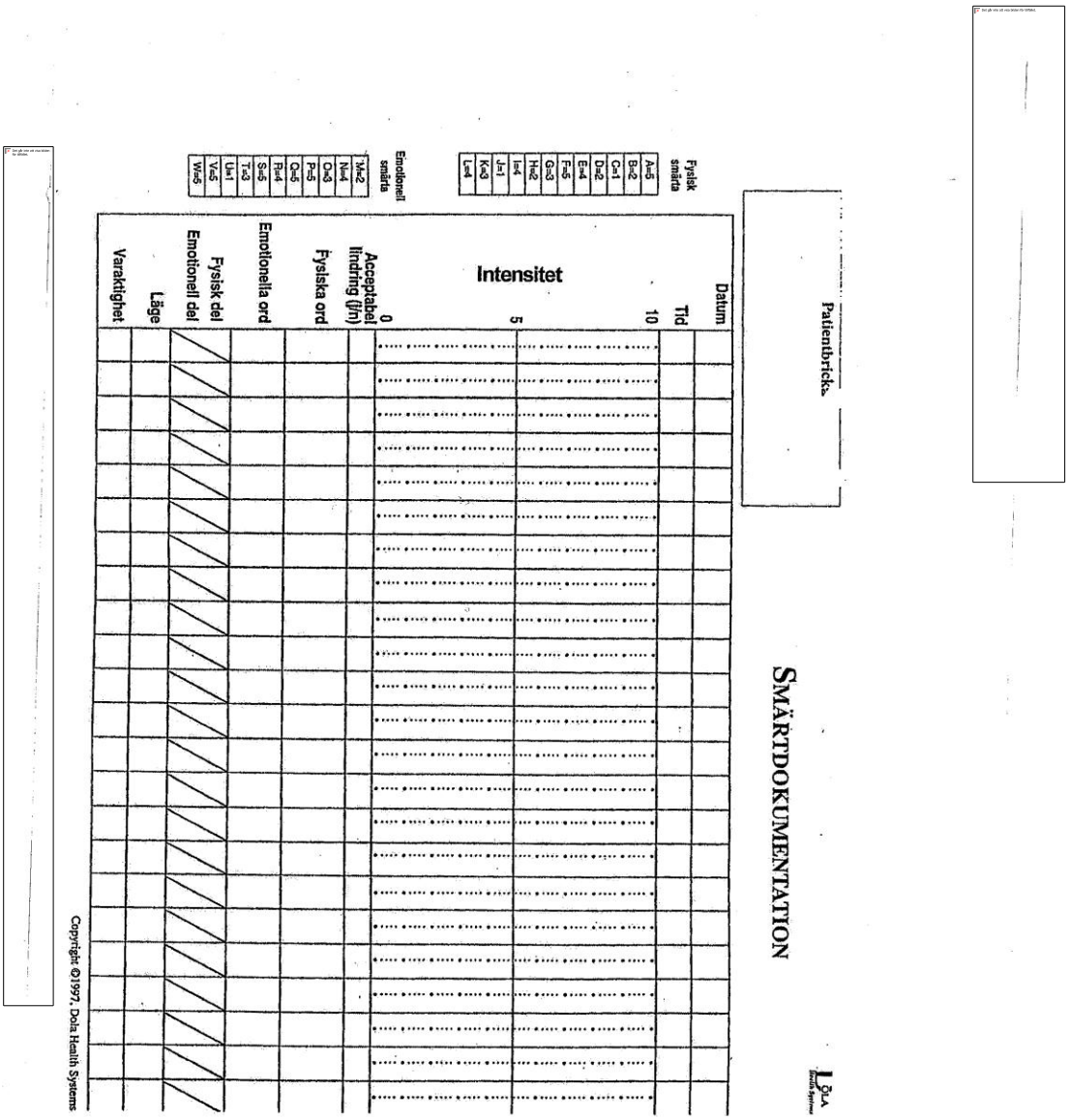
beräknat datum_____/ verkligt datum_____

Sjätte besök (vecka 21)
Vikt_____, kortisol, smärtanalys, SF36, UPDRS I-IV, PDSS, VAS, POM, LK gund och vb
beräknat datum_____/ verkligt datum_____

Sjunde besök (vecka 34)
Vikt_____, kortisol, smärtanalys, SF36, UPDRS I-IV, PDSS, VAS, POM, LK gund och vb
beräknat datum_____/ verkligt datum_____

14.6 APPENDIX VI: THE PAIN-O-METER PROTOCOL

(Swedish ver.)



14.6.1 Descriptve words: Physical descriptive word, POM^{phys}

(Swedish ver.)

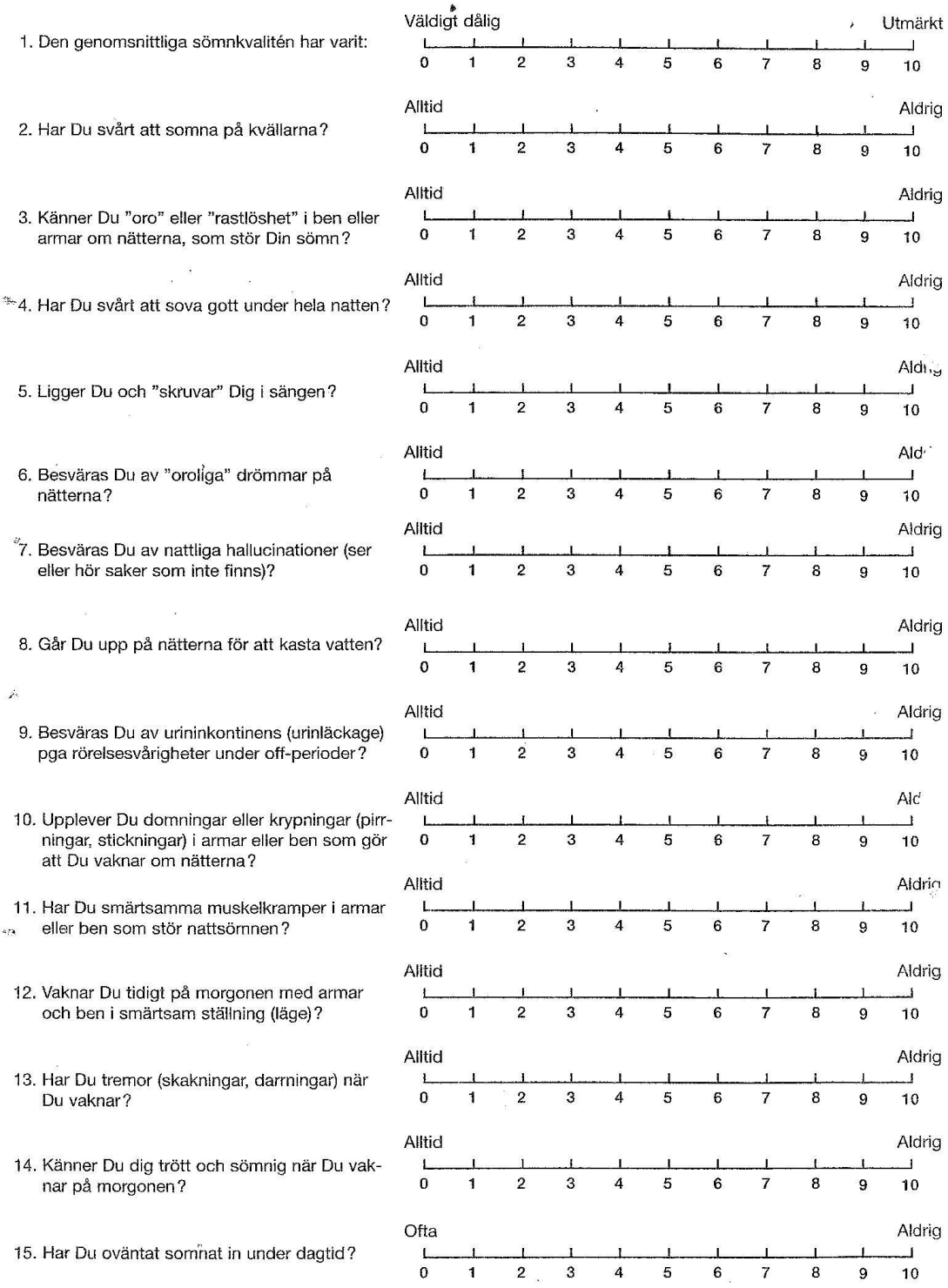
A= skärande
B= molande
C= stickande
D= klämmande
E= krampaktig
F= sönderslitande
G= värkande
H= svidande
I= brännande
J= ömmande
K= gnagande
L= tryckande

14.6.2 Descriptive words: Emotional descriptive words, POM^{emo}

M= irriterande
N= skrämmande
O= besvärlig
P= kvävande
Q= mördande
R= odräglig
S= fruktansvärd
T= tröttande
U= oroande
V= outhärdlig
W= torterande

14.7 *APPPENDIX VII* THE PARKINSON DISEASE SLEEP SCALE (PDSS)

PARKINSON SÖMNSKALA (PDSS) (Swedish ver.)



14.8 APPENDIX VIII THE UNIFIED PARKINSON DISEASE RATING SCALE (I - IV), UPDRS (I-IV). (SWEDISH VER.)

Stationsbricka Patient-ID

	Besöksnr:	Datum & klockslag	Senaste dos kl.				
	1				:		
	2				:		
	3				:		
	4				:		
	5				:		
Del	Nr	Text	1	2	3	4	5
I		**TANKEFÖRMÅGA, BETEENDE och SINNESSTÄMNING**					
	1	**Intellektuell påverkan**					
		0=Ingen.					
		1=Mild. Ständig glömska med partiell hågkomst av händelser och inga andra problem					
		2=Måttlig minnesstörning med desorientering och måttliga svårigheter att hantera komplexa problem. Lätt men definitiv störning av funktionen i hemmet med behov av påstötning ibland.					
		3=Svår minnesstörning med desorientering i tid och ofta i rummet. Stora svårigheter att lösa problem.					
		4=Svår minnesstörning med orientering endast till person. Oförmögen att göra bedömningar eller lösa problem. Kräver mycket hjälp med personlig skötsel. Kan inte lämnas ensam överhuvudtaget.					
	2	**Tankestörning (p.g.a. demens eller läkemedelspåverkan)**					
		0=Ingen.					
		1=Livliga drömmar.					
		2="Benigna" hallucinationer med bevarad insikt					
		3=Enstaka till ofta förekommande hallucinationer eller vanföreställningar. Ingen insikt. Kan störa dagliga aktiviteter.					
		4=Kontinuerliga hallucinationer, vanföreställningar eller fluorid psykos. Oförmögen att klara sig själv.					
	3	**Depression**					
		0=Föreligger ej.					
		1=Perioder av nedstämdhet eller skuldkänslor mer uttalade än normalt, men som aldrig kvarstår i dagar eller veckor.					
		2=Ihållande depression (1 vecka eller mer)					
		3=Ihållande depression med vegetativa symtom (sömnlöshet, anorexi, viktnedgång, apati)					
		4=Ihållande depression med vegetativa symtom och suicidtankar eller planer)					
	4	**Motivation/initiativförmåga**					
		0=Normal					
		1=Mindre initiativrik än vanligt, mer passiv.					
		2=Förlust av initiativförmåga eller ointresse i elektiva (icke-rutin) aktiviteter					
		3=Förlust av initiativförmåga eller ointresse i dagliga (rutin) aktiviteter.	Summa del I				
		4=Tillbakadragen, total förlust av motivation.					

II		AKTIVITETER I DAGLIGA LIVET (UNDER DEN SENASTE VECKAN)					
	5	**Tal**					
		0=Normalt					
		1=Mild påverkan. Ingasvårigheter med förståligheten					
		2=Måttligt påverkat. Blir ibland ombedd att upprepa meningar.					
		3=Svårt påverkat. Blir ofta ombedd att upprepa meningar.					
		4=Obegripligt större delen av tiden.					
	6	**Salivation**					
		0=Normal.					
		1=Lätt med definitivt överskott av saliven i munnen, kan dregla nattetid.					
		2=Måttligt överskott av saliv, kan dregla minimalt.					
		3=Uttalat överskott av saliv med en del dregling.					
		4=Uttalad dregling, krävs handuk eller servett hela tiden.					
	7	**Sväljning**					
		0=Normal					
		1=Sätter sällan i halsen					
		2=Sätter i halsen ibland.					
		3=Kvrävs mjuk föda.					
		4=Krävs sond eller gastrostomig					
	8	**Handstil**					
		0=Normal					
		1=Något förlångsammad eller liten.					
		2=Måttligt förlångsammad eller liten. Alla ord är läsliga					
		3=Mycket påverkad. Alla ord är inte läsliga.					
		4=Majoriteten av orden är inte läsliga.					
	9	**Skära mat och använda bestick**					
		0=Normalt					
		1=Något förlångsammat och klumpigt. Behöver ingen hjälp.					
		2=Kan skära den mesta maten, men klumpigt och långsamt. Behöver viss hjälp.					
		3=Maten måste skäras upp av någon annan. Kan fortfarande äta själv långsamt.					
		4=Måste matas.					
	10	**Påklädning**					
		0=Normalt.					
		1=Något förlångsammat. Behöver ingen hjälp.					
		2=Behöver hjälp ibland med att knäppa knappar och att få in armen i ärmar.					
		3=Behöver mycket hjälp, men kan göra en del själv.					
		4=Hjälplös.					

11	**Hygien**	
	0=Normal	
	1=Något förlångsammad. Behöver ingen hjälp.	
	2=Behöver hjälp att duscha eller bada eller mycket långsam med sin personliga hygien.	
	3=Behöver hjälp att tvätta sig, borsta tänder, kamma håret och gå på toaletten.	
	4=KAD eller andra mekaniska hjälpmedel.	
12	**Vända sig i sängen och räta till sängkläderna**	
	0=Normalt.	
	1=Något långsamt och klumpigt, men behöver inte hjälp.	
	2=Kan vända sig själv eller rätta till lakanen men med stor svårighet.	
	3=Kan påbörja, men inte vända sig eller rätta till sängkläderna själv.	
	4=Hjälplös.	
13	**Fall (utan relation till "freezing")**	
	0=Inga.	
	1=Faller någon sällsynt gång.	
	2=Faller ibland, mindre än en gång om dagen.	
	3=Faller i genomsnitt en gång om dagen.	
	4=Faller mer än en gång om dagen.	
14	**"Freezing" vid gång**	
	0=Ingen.	
	1=Sällsynt "freezing" vid gång; kan ha hesitation vid igångsättning.	
	2=Ibland "freezing" vid gång.	
	3=Frekvent "freezing". Ibland fall på grund av "freezing".	
	4=Ofta fall på grund av "freezing".	
15	**Gång**	
	0=Normal.	
	1=Lätta svårigheter. Medrörelser kan saknas eller kan tendera att släpa fot.	
	2=Måttliga svårigheter, men kräver föga eller ingen hjälp.	
	3=Svår gångstörning, kräver hjälp.	
	4=Kan inte gå alls, inte ens med hjälp.	
16	**Tremor (tremorsymtom i någon del av kroppen)**	
	0=Saknas.	
	1=Lätt och sällan förekommande.	
	2=Måttlig. Besvärande för patienten.	
	3=Uttalad. Stör många aktiviteter.	
	4=Svår. Stör de flesta aktiviteter.	
17	**Sensoriska besvär relaterade till parkinsonism**	
	0=Inga.	
	1=Har ibland domningar, stickningar eller lätt värk.	
	2=Har ofta domningar, stickningar eller värk, inte plågsamt.	**Summa del II**
	3=Ofta smärtsamma förnimmelser.	
	4=Fruktansvärd smärta.	

III		MOTORISK UNDERSÖKNING						
	18	**Tal**						
		0=Normalt.						
		1=Lätt försämring av uttryck, uttal och/eller röstvolym.						
		2=Monotont, sluddrigt men förståeligt, måttligt stört tal.						
		3=Uttalad talstörning, svårt att förstå.						
		4=Obegripligt.						
	19	**Mimik**						
		0=Normal.						
		1=Minimal hypomimi, skulle kunna vara normalt "poker-ansikete".						
		2=Lätt men definitivt onormal minskning av ansiktsmimik.						
		3=Måttlig hypomimi; läpparna ibland åtskilda.						
		4=Maskansikte eller fixerat ansiktsuttryck med svår eller fullständig förlust av mimiskt uttryck; läpparna åtskilda 6 mm eller mer.						
	20	**Vilotremor**						**Ansik**
		0=Saknas.						**Hö han**
		1=Lätt och intermittent.						**Vä hand**
		2=Liten amplitud och konstant. Alternativt måttlig amplitud och intermittent.						**Hö fot**
								Vä fot
		3=Måttlig amplitud och mer eller mindre konstant.						
		4=Stor amplitud och mer eller mindre konstant.						
	21	**Aktionstremor eller postural tremor i händerna**						**Hö**
		0=Saknas.						**Vä**
		1=Lätt, syns vid rörelser.						
		2=Måttlig amplitud, syns vid rörelser.						
		3=Måttlig amplitud, syns både posturalt och vid rörelser.						
		4=Stor amplitud, försvårar ätande.						
	22	**Rigiditet (Bedöms med passiva rörelser i stora leder med patienten avslappad i sittande. Kugghjulsfenomen skall ej beaktas).**						**Nacke**
		0=Ingen rigiditet.						**Hö arm**
		1=Lätt rigiditet eller endast vid aktivering med spegelrörelser eller andra rörelser.						**Vä a**
		2=Lätt till måttlig rigiditet.						**Hö be**
		3=Uttalad rigiditet, men det fulla rörelseomfånget kan lätt tas ut.						**Vä ben**
		4=Uttalad rigiditet, rörelseomfånget kan med svårighet tas ut.						
	23	**Fingerknackning (Patienten knackar snabbt med pekfingret mot tummen flera gånger i följd med största möjliga amplitud, varje hand för sig).**						**Hö**
								Vä
		0=Normalt.						
		1=Lätt förlångsamning och/eller minskad amplitud.						
		2=Måttligt inskränkt förmåga. Definitiv och snabb uttröttning. Kan ha enstaka avbrott i rörelsen.						
		3=Uttalat inskränkt förmåga. Ofta svårighet att starta rörelsen eller avbrott i pågående rörelse.						
		4=Kan knappt utföra momentet.						

24	**Handrörelser (Patienten knyter och öppnar handen snabbt flera gånger i följd med största möjliga amplitud, varje hand för sig).**						Hö Vä
	0=Normalt.						
	1=Lätt förlångsamning och/eller minskad amplitud.						
	2=Måttligt inskränkt förmåga. Definitivt och snabb uttröttning. Kan ha enstaka avbrott i rörelsen.						
	3=Uttalat inskränkt förmåga. Ofta svårighet att starta rörelsen eller avbrott i pågående rörelse.						
	4=Kan knappt utföra momentet.						
25	**Snabbt alternerande handrörelser (Pronations- supinationsrörelser i händerna, vertikalt eller horisontalt med så stor amplitud som möjligt, varje handerna för sig).**						Hö Vä
	0=Normalt.						
	1=Lätt förlångsamning och/ellerminskad amplitud.						
	2=Måttligt inskränkt förmåga. Definitiv och snabb uttröttning. Kan ha enstaka avbrott i rörelsen.						
	3=Uttalat inskränkt förmåga. Ofta svårighet att starta rörelsen eller avbrott i pågående rörelse.						
	4=Kan knappt utföra momentet.						
26	**Benrörlighet (Patienten knackar med hälen i golvet flera gånger i snabb följd. Hela foten skall lyftas från golvet. Amplitud cirka 7-8 cm).**						Hö Vä
	0=Normalt.						
	1=Lätt förlångsamning och/eller minskad amplitud.						
	2=Måttligt inskränkt förmåga. Definitiv och snabb uttröttning. Kan ha enstaka avbrott i rörelsen.						
	3=Uttalat inskränkt förmåga. Ofta svårighet att starta rörelsen eller avbrott i pågående rörelse.						
	4=Kan knappt utföra momentet.						
27	**Uppresning från stol (Patienten försöker resa sig från en rakryggad trä- eller metallstol. Armarna i kors över bröstet).**						
	0=Normalt.						
	1=Långsam eller behöver mer än ett försök.						
	2=Lyfter sig upp med hjälp av armstöden.						
	3=Tenderar att falla tillbaka och kan behöva försöka mer än en gång, men kan komma upp utan hjälp.						
	4=Oförmögen att resa sig upp utan hjälp.						
28	**Hållning.**						
	0=Normalt upprätt.						
	1=Inte helt rak, lätt böjd hållning. Skulle kunna vara normalt hos äldre person.						
	2=Måttligt böjd hållning, definitivt inte normal. Kan vara lätt lutande i sidled.						
	3=Kraftigt böjd hållning med kyfos. Kan vara måttligt lutande i sidled.						
	4=Uttalad flexion med hållning som är extremt avvikande från det normala.						

29	**Postural stabilitet (Reaktion på plötslig rubbning av jämvikten bakåt genom att man drar patienten bakåt vid skuldrorna. Patienten står upprätt med öppna ögon och fötterna lätt isär. Patienten är förberedd och får göra flera försök).**	
	0=Normal.	
	1=Retropulsion (går bakåt) men klarar att återfå balansen utan hjälp.	
	2=Avsaknad av postural respons. Hade fallit om inte undersökaren fångat upp patienten.	
	3=Mycket instabil. Tenderar att spontant förlora balansen.	
	4=Oförmögen att stå utan stöd.	
30	**Gång.**	
	0=Normal.	
	1=Går långsamt, kan hasa med fötterna eller gå med små steg men utan festination eller propulsion.	
	2=Går med svårighet, men behöver ingen eller föga hjälp. Kan ha lite festination, korta steg eller propulsion.	
	3=Svår gångstörning, kräver hjälp.	
	4=Kan inte gå alls, inte ens med hjälp.	
31	**Kroppsbradykinesi och hypokinesi (Kombinerad bedömning av förlångsamning, hesitation, minskade medrörelser i armar och allmän rörelsefattigdom).**	
	0=Ingen.	
	1=Minimal förlångsamning som ger rörelserna en speciell karaktär, skulle kunna vara normalt för vissa personer. Möjligen minskad amplitud.	
	2=Lätta grader av förlångsamning och rörelsefattigdom som definitivt är onormal. Alternativt något minskad rörelseamplitud.	
	3=Måttlig förlångsamning, rörelsefattigdom eller liten rörelseamplitud.	**Summa del III**
	4=Uttalad förlångsamning, rörelsefattigdom eller liten rörelseamplitud.	
IV	**BEHANDLINGSKOMPLIKATIONER (Senaste veckan)**	
32	**A DYSKINESIER**	
	Duration: Hur stor del av dagens vakna tid föreligger dyskinesier? (Anamnestiska upplysningar.)	
	0=Ingen.	
	1=1-25 % av dagen.	
	2=26-50 % av dagen.	
	3=51-75 % av dagen.	
	4=76-100 % av dagen.	
33	**Handikapp: Hur handikappande är dyskinesierna? (Anamnestiska upplysningar; kan modifieras av undersökningen på mottagningen).**	
	0=Ej handikappande.	
	1=Lätt handikappande.	
	2=Måttligt handikappande.	
	3=Svårt handikappande.	
	4=Fullständigt handikappande.	

34	**Smärtsamma dyskinesier: Hur smärtsamma är dyskinesierna?**	
	0=Inga smärtsamma dyskinesier.	
	1=Lätt smärta.	
	2=Måttlig smärta.	
	3=Uttalad smärta.	
	4=Svår smärta.	
35	**Förekomst av tidig morgondystoni (Anamnestisk upplysning).**	
	0=Nej.	
	1=Ja.	
	B KLINISKA FLUKTUATIONER	
36	**Är några off-perioder förutsägbara i tiden i förhållande till medicinintag?**	
	0=Nej.	
	1=Ja.	
37	**Är några off-perioder oförutsägbara i tiden i förhållande till medicinintag?**	
	0=Nej.	
	1=Ja.	
38	**Kommer någon av off-perioderna plötsligt, d v s på några sekunder?**	
	0=Nej.	
	1=Ja.	
39	**Hur stor del av dagen är patienten i genomsnitt "off"?**	
	0=Ingen del.	
	1=1-25 % av dagen.	
	2=26-50 % av dagen.	
	3=51-75 % av dagen.	
	4=76-100 % av dagen.	
	C ANDRA KOMPLIKATIONER	
40	**Har patienten aptitlöshet, illamående, kräkningar?**	
	0=Nej.	
	1=Ja.	
41	**Har patienten någon sömnstörning, t ex sömnlöshet eller hypersomni?**	
	0=Nej.	
	1=Ja.	
42	**Har patienten symtomgivande ortostatism?**	
	0=Nej.	
	1=Ja.	

Summa del IV

14.9 APPENDIX IX THE HOEHN & YAHR SCALE

(Swedish ver.)

Modifierad stadieindelning enligt Hoehn & Yahr

STADIUM

1 = unilateral sjukdom.
1,5 = Unilateral plus axial påverkan.
2 = Bilateral sjukdom, utan balansstörning.
2,5 = lätt bilateral sjkudom men klarar postural stabilitet.
3= lätt till nåttlig bilateral sjukdom;
någon postural instabilitet, fysiskt oberoende.
4 = svår sjukdom; kan ännu gå och stå utan hjälp.
5 = rullstolsburen eller sängliggande utan assistans.

Paper I

Diurnal salivary cortisol concentrations in Parkinson's disease: increased total secretion and morning cortisol concentrations

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Abstract

Background:

Parkinson's disease (PD) is a chronic neurodegenerative disorder. There is limited knowledge about the function of the hypothalamic-pituitary-adrenal axis in PD. The primary aim of this prospective study was to analyze diurnal salivary cortisol concentrations in patients with PD and correlate these with age, gender, body mass index (BMI), duration of PD, and pain. The secondary aim was to compare the results with a healthy reference group.

Methods:

Fifty-nine PD patients, 35 women and 24 men, aged 50–79 years, were recruited. The reference group comprised healthy individuals matched for age, gender, BMI, and time point for sampling. Salivary cortisol was collected at 8 am, 1 pm, and 8 pm, and 8 am the next day using cotton-based Salivette® tubes and analyzed using Spectria® Cortisol I^{125}. A visual analog scale was used for estimation of pain.

Results:

The median cortisol concentration was 16.0 (5.8–30.2) nmol/L at 8 am, 5.8 (3.0–16.4) at 1 pm, 2.8 (1.6–8.0) at 8 pm, and 14.0 (7.5–28.7) at 8 am the next day. Total secretion and rate of cortisol secretion during the day (8 am–8 pm) and the concentration of cortisol on the next morning were lower (12.5 nmol/L) in the reference group. No significant correlations with age, gender, BMI, duration of PD, Hoehn and Yahr score,

Unified Parkinson's Disease Rating Scale III score, gait, pain, or cortisol concentrations were found.

Conclusion:

The neurodegenerative changes in PD does not seem to interfere with the hypothalamic-pituitary-adrenal axis. Salivary cortisol concentrations in PD patients were increased in the morning compared with the reference group, and were not influenced by motor dysfunction, duration of disease, or coexistence of chronic or acute pain.

Keywords: cortisol, hypothalamic-pituitary-adrenal axis, Parkinson's disease

Introduction

Parkinson's disease (PD) is a chronic progressive neurodegenerative disorder accompanied by autonomic dysfunction and alterations in a number of regulatory mechanisms, including loss of circadian rhythms in dopaminergic systems and fluctuations in the kinetics of drugs used in treatment of the disease. [1]
Pain in PD is common. Our own investigations [2] reveal an incidence of pain of about 60%. Other studies in this area reveal incidence rates of 40%–80%. [3-7] The pathogenesis of pain in PD is probably complex. Degeneration of descending dopaminergic pain-inhibiting fibers from the midbrain is probably one of the central pathways. Dystonia, a motor symptom of PD, is a common explanation for pain. Direct effects of levodopa on pain sensation support the hypothesis of an influence of the regulating mechanisms of autonomic and inhibitory modulation of pain input in dopamine-dependent centers.[8]
Typically, signs of PD are hypokinesia, rigidity, and tremor, also referred to as the motor symptoms of the disease. Nonmotor signs, such as mood changes and pain, are frequent. [9] The pathogenesis of the nonmotor symptoms is not fully understood, and concomitant endocrine dysfunctions have been suggested. There have been few studies in PD on endocrinopathy, such as hypothyreosis and cortisol deficiency. Munhoz et al showed that the secretion of thyroid and cortisol hormones is changed in PD, possibly caused by disturbances in the hypothalamic-pituitary-adrenal axis.[10] A recent study by Aziz et al analyzed thyroid-stimulating hormone, free thyroxine, prolactin, and growth hormone, but not cortisol, in PD patients.[11]
Influences of aging and stress on the glucocorticoid system may result in reduction of hormone production capacity, impaired neuronal adaptive responses to environmental challenges, and increased vulnerability to stress-induced loss of hippocampal neurons.[12] Aging is hypothesized to alter the function of the hypothalamic-pituitary-adrenal axis in both men and women. Increasing cortisol concentrations, especially

nocturnal concentrations, [13] have been described. Some studies have indicated that there are gender differences. [13-16] One study showed significantly higher evening cortisol concentrations with increasing age, regardless of gender, while in the mornings this pattern was seen only in men. Diurnal cortisol variations were lower in older women but not in men. [17]

Studies of plasma cortisol in PD have shown variable results. Higher cortisol concentrations have been reported in untreated PD patients without dementia compared with healthy controls,[18-19] and also compared with age-matched and gender-matched patients with Alzheimer's disease. However, another study found decreased plasma cortisol concentrations in untreated PD patients compared with healthy controls, suggesting that this may be a consequence of hypothalamic/hypophyseal disturbance. Further, a previous study showed higher plasma cortisol concentrations in the evening and during the night in PD patients.[18] One study reported higher concentrations of adrenocorticotrophic hormone in a subgroup of PD patients (both demented and nondemented) found to be dexamethasone nonsuppressors, suggesting higher concentrations of corticotrophin-releasing hormone.[20] This surprisingly high incidence of dexamethasone non-suppression in patients with PD could indicate a possible central pathologic disturbance of neurotransmitter function. However, levodopa medication and dopamine alone exert no influence on corticotrophin-releasing hormone, and the effects of other PD medications (such as dopamine agonists) on cortisol concentrations have not been studied.

In one study, acute levodopa intake has been shown to induce lower plasma cortisol levels in patients on long-term treatment for PD who were depleted of antiparkinsonian medication for 12 hours.[21] We believe that description of the diurnal salivary cortisol concentration curve in patients with chronic neurodegenerative diseases, such as PD, could be of great interest for future studies of pharmacological and nonpharmacological interventions, with the aim of reducing stress-related symptoms and lifelong suffering.

The primary aim of this study was to measure salivary cortisol concentrations in a well-defined group of PD patients, with and without chronic PD-related pain, with regard to age, duration of disease, body mass index (BMI), motor function (Unified Parkinson's Disease Rating Scale [UPDRS] III, gait) and influence of concomitant pain. The secondary aim was to compare the salivary cortisol concentrations in these PD patients with those in a healthy reference group, matched by age, gender, and BMI.

Methods and materials

Patients

Patients with stable and well-defined PD [22] for more than two years, who were aged 40–80 years, with chronic pain (PD-P) or without chronic pain (PD no-P), were recruited from the outpatient departments of three medium-sized city hospitals in southern Sweden. The study was approved by the ethics committees at the University of Gothenburg and the University of Linkoping.

A period of two years since receiving the diagnosis of PD was chosen to decrease the risk of recruiting patients with an incorrect diagnosis, given that a number of other disorders can mimic PD. The individual course of PD is variable, and in our study the range of disease duration was 2–27 years (median 5–6 years). Stable PD was defined as

lack of severe fluctuations of the disease (on-off symptomatology) in terms of need for frequent extra doses of antiparkinsonian medication and absence of dementia. Exclusion criteria were severe fluctuations in PD, concurrent epilepsy, active malignancy, polyneuropathy, or other serious disease of somatic or psychiatric origin that could interfere with the study. Patients with severe abnormalities of blood parameters, electrolytes, liver or renal parameters, including bilirubin >20 mmol/L, serum creatinine >130 mmol/L, SR >30 mm, fasting plasma glucose >6.7 mmol/L, were excluded. Patients on corticosteroids (oral, nasal, or inhalation), insulin, antiepileptic drugs, or medication for dementia, and those participating in other therapeutic or pharmacological studies were also excluded.
Chronic pain was defined as the occurrence of PD-related pain on at least three days per week during the three months prior to recruitment. A reference population consisting of healthy individuals, matched by gender, age, and BMI, were recruited from another project,[17] and consisted of 1700 healthy men and women aged 30–80 (mean 48) years. These individuals were recruited from the same catchment area as our patients, and their cortisol levels were analyzed using the same method and in the same laboratory. Demographic and clinical characteristics of the population with PD and the reference group are presented in Table 1.

Table 1: *Characteristics of the PD population and the healthy reference group. Values are given as means[1] and range[2].*

GROUP	SEX	NUMBER	AGE[2]	WEIGHT[1]	BMI[1]	UPDRS III[1,2]
PD	Male	24	50-78	84,1	26,8	20,1 (8-37)
	Female	35	60-79	68,4	25,5	22,0 (3-57)
Reference[1]	Male	303	50-74	-	26,9	-
	Female	305	50-74	-	26,8	-

Methods

Motor function was assessed by the UPDRS.[23] Duration and severity of pain was measured using a visual analog scale (VAS)[24] for five consecutive days before sampling. Maximal pain during each of these five days was registered in our protocol. Collection of salivary cortisol samples for both groups was done in the community using a technique which has been well described elsewhere.[25-29] To summarize, patients were instructed to have no intake of food within 30 minutes of sampling. Samples were taken at four time points, ie, at 8 am, 1 pm, and 8 pm, and then at 8 am the next morning. Cotton-based neutral Salivette® tubes (Landskrona, Sweden) were used. A swab was chewed for two minutes and then placed in a sterile plastic tube. This was then put in the patient's refrigerator at home. The tubes for each patient were collected and sent by post to the laboratory within three days. The Salivette tubes were then centrifuged at 1711 G for 15 minutes at 20°C, and then frozen at −80°C until assayed. A commercial radioimmunoassay-based technique for measurement of salivary cortisol was used (Spectria™ Cortisol I^{125}, Landskrona, Sweden). Total cortisol secretion during the day (8 am–8 pm) and during the night (8 pm–8 am) was calculated using the formula for area under the curve from the zero level (AUC_0–AUC_G), and the increase in cortisol secretion from the baseline level during the same time interval (AUCi) was calculated according to the method reported by Pruessner et al [30] and Fekedulegn et al.[31] The latter author has shown significant associations ($r > 0.7$; $P = 0.001$) between AUC_G and cortisol concentrations. All analyses of saliva from the same person were performed at the same time to minimize interassay variance.

Statistical analysis

STATISTICA version 8.0 (Statsoft Inc, Tulsa, OK) and SPSS version 18.0 (SPSS Inc, Chicago, IL) were used for the statistical evaluations. Nonparametric, Mann–Whitney U, and Wilcoxon paired signed-rank tests were used. The Spearman's rank correlation test was also used. The Wilcoxon signed-rank test for one sample was used when comparing median salivary cortisol levels in PD patients with the median in the reference population.

Results

Fifty-nine patients, consisting 24 men and 35 women aged 50–79 years of age (median 66.5/67.5 years for men/women) were recruited for this study. The PD-P group comprised 43 patients (16 men and 27 women aged 50–77 years [median 63/66 years for men/women]), and the PD no-P group comprised eight men and eight women (median 70/75 years for men/women). Age at onset of PD was 40–74 years (median 60.0) and duration of PD was 2–27 years, with a median of 5.0/6.0 years for men/women, respectively. Most patients (96%) were over 55 years of age at the start of the study. No patient was younger than 64 years in the PD no-P group compared with 18 of 43 (42%) patients in the PD-P group.

Time of awakening in the PD-P and PD no-P groups did not differ significantly, and varied from 4.35 am to 8.00 am on the two days when sampling took place. Time points for sampling varied in relation to specified time points, ie, 8 am (±30 minutes), 1

pm (−60/+30 minutes) and 8 pm (−95/+75 minutes). Time intervals between awakening and sampling in the morning were 0–220 minutes and 5–187 minutes in the PD-P group and PD no-P group, respectively, and in 10 patients was less than 45 minutes. A cortisol arousal reaction with an increase in salivary cortisol of 2.5 nmol/L was noted in only one patient.

Maximal pain in the PD patients during the five days prior to inclusion were calculated on the VAS scale as the median (10/90 percentiles), with a value of 6.2 (2.8/9.1) and minimal pain of 3.0 (0.0/6.5). Motor function as estimated by UPDRS III scores was 3–57, corresponding to mild to severe PD (see Table 1).

Basal salivary cortisol

Salivary cortisol concentrations varied over a 24-hour period, as shown in Figures 1A and 1B. Individual salivary cortisol values in the PD-P and PD no-P patients are shown in Figure 1A. There were no statistically significant differences in salivary cortisol concentrations between the two groups. One patient in the PD no-P group had extremely high values (174.6, 22.3, 14.6, and 110 nmol/L).

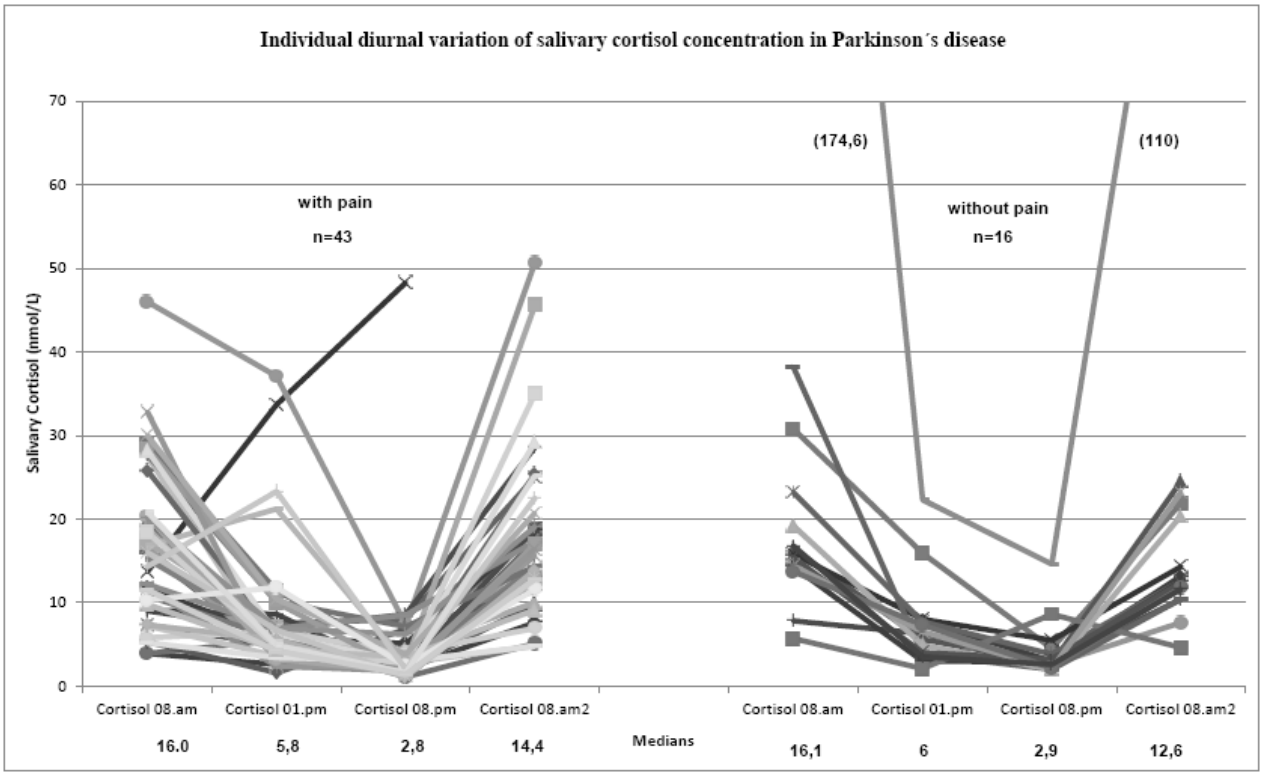

Figure 1A: Individual diurnal salivary cortisol concentrations (nmol/L) in Parkinson's disease with and without chronic pain.

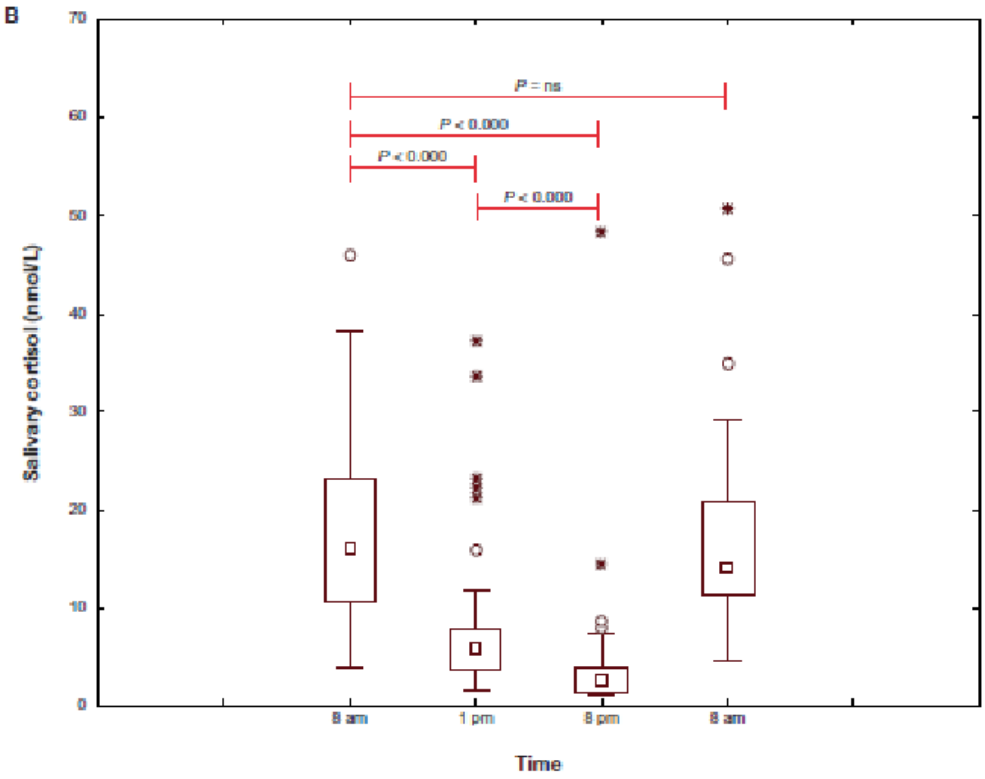

Figure 1 B: Diurnal salivary cortisol concentrations (nmol/L) in all 59 patients with Parkinson's disease. Statistical analysis, between paired time points.

Salivary cortisol concentrations at 8 am, 1 pm, 8 pm, and 8 am, along with delta values, are shown in Tables 2A and 2B. Morning cortisol concentrations were higher in the PD group compared with the reference group, and the concentration was not dependent on time interval between awakening and time point of salivary sampling. There was also no difference in cortisol concentration between participants taking their levodopa medication within one hour either side of salivary sampling. The linear equation for the cortisol trend curve calculated to estimate AUC was y = 23.56–1.02x versus y = 17.84–0.69x for the PD and reference groups, respectively.

Group	Sex N	Day 1					Day 2
		8am		1pm	8pm		8am
		Geom. Mean Median with (10th and 90th perc)	p-value[a]	Geom. Mean Median with (10th and 90th perc)	Geom. Mean Median with (10th and 90th perc)	p-value[a]	Geom. Mean Median with (10th and 90th perc)
PD-P	Male 16	12.5 14.8(5.2-20.3)	0.215	5.6 5.6(3.2-11.8)	2. 3 2.6(1.1-5.1)	0.016*	15.1 14.2(5.1-35)
	Female 27	15.6 17.9(5.8-30)	0.021*	6.4 6.2(2.6-21.2)	3.4 2.9(1.6-8.5)	0.614	15.1 15.4(7.6-28.6)
PD-no P	Male 8	20.5 15.4(5.7-174.6)	0.128	6.4 6.5(2.1-22.3)	4.2 3.1(2.2-14.6)	0.779	16.9 12.9(4.6-110)
	Female 8	17.5 16.8(7.8-38.2)	0.091	5.3 5.6(3.5-8.0)	2.8 2.6(2-5.5)	0.035*	13.0 12.1(7.6-23.2)
Reference	Male 303	12.1[1]	-	-	3.9[b]	-	-
	Female 305	12.5[1]	-	-	4.1[b]	-	-

Values are given as geometric mean *(1)*.
PD=parkinson´s disease, PD no-P=PD without pain
Testing median of the corresponding reference population (a)
Values were estimated according to equations of lines between 8am and 10pm (b*)*
*statistically significant at 5%-level.

Table 2A:Comparisons of salivary cortisol concentrations (nmol/L) in PD patients with (PD-P) and without chronic PD-related pain (PD no-P) and the reference group

Group	Sex N				
		Delta 8am-1pm	**Delta 1pm-8pm**	**Delta 8am-8pm**	
		G. mean **Median**	**G. mean** **Median**	**G. mean** **Median**	**p-value**[a]
PD-P	Male 16	6.9 9.2	3.3 3.0	10.2 12.2	0.049*
	Female 27	9.2 11.7	3.0 3.3	12.2 15.0	0.052
PD-no P	Male 8	14.1 8.9	2.2 3.4	16.3 12.3	0.128
	Female 8	12.2 11.2	2.5 3	14.7 14.2	0.043*
Reference	Male 303	-	-	8.2[1]	-
	Female 305	-	-	8.4[1]	-

Values are given as geometric mean *(1).*
PD=parkinson´s disease, PD no-P=PD without pain
Testing median of the corresponding reference population (a)
*statistically significant at 5%-level.

Table 2B:

Differences in salivary cortisol concentrations between paired time points, delta cortisol (nmol/L)

Total cortisol secretion and secretion rate

Total cortisol secretion during the day (8 am–8 pm, AUC_0–AUC_G) was significantly increased in PD patients, at 112.8 nmolh versus 81.1 nmolh in the reference group ($P < 0.001$). The corresponding value for 8 pm–8 am in PD patients was 109.8 nmolh. The decrease in the salivary cortisol secretion rate during the day (8 am–8 pm, negative AUCi) in the PD and reference groups was −73.7 nmolh versus −49.9 nmolh. This difference was statistically significant ($P = 0.001$). The increase in salivary cortisol secretion rate during the night (8 pm–8 am, AUCi) was 72.6 nmolh, and similar to the day time value.

Somatic status and symptom correlations with cortisol

There was a highly significant correlation (r = 0.44; $P < 0.01$) between values at 8 am on day 1 and 8 am on day 2. There were also significant correlations between cortisol concentrations at 1 pm and for all other time points (r values 0.28–0.42; P 0.001–0.034). No significant correlations between BMI, motor dysfunction, measured as UPDRS III ≤ 20 compared with >20, gait (UPDRS III, item 30), acute pain (maximum VAS at screening), chronic pain, and cortisol concentrations were identified.

Discussion

In this study, we compared salivary cortisol concentrations in a group of patients with a diagnosis of PD for more than two years with those in a reference group of gender-, BMI-, and age-matched healthy individuals.[17] There were two groups of PD patients, ie, those with and those without PD-related pain.

The cortisol concentrations in this study were unrelated to age. This is in disagreement with the hypothesis that aging alters the function of the hypothalamic-pituitary-adrenal axis in both men and women. Increasing cortisol concentrations, especially at night, have been described previously.[13, 16] Even in our reference group, significantly higher evening cortisol concentrations were found with increasing age, regardless of gender, while in the mornings this pattern was seen only in men.[17]

We found no gender differences in cortisol rhythm and/or amplitude in our PD patients. This is in contrast with findings in our reference group, where differences were found for cortisol concentrations in the morning, and the diurnal variations in cortisol were lower in older women but not in men. Other studies have also indicated gender differences.[13-16]

For estimation of total secretion and the secretion rate of cortisol, we analyzed AUC_0–AUC_G for cortisol during the daytime (8 am–8 pm) according to the recommendations of Fekedulegn et al.[31] The results were significantly higher in the PD group than in the reference group. The corresponding value for nocturnal AUC_G (8 pm–8 am) was similar. The decreasing secretion rate (negative AUCi) was significantly higher in the PD group. Our results showing a significant increase in secretion rate and total cortisol secretion are potential evidence for a well functioning adrenal and hypothalamic-pituitary-adrenal axis, as reported by Fekedulegn et al.[31]

The excellent correlation between salivary cortisol levels and plasma total and free biologically active cortisol levels in healthy men and women was reported as early as 1983 by Vining et al,[32] and this was confirmed in a subsequent study.[33] This method has been the “gold standard” for estimating stress in psycho-biologic-endocrine research for a number of years.[34] A recent report by Törnhage described the usefulness of salivary cortisol for assessing the hypothalamic-pituitary-adrenal axis.[27] These observations make it appropriate and convenient to use salivary cortisol sampling at home as a pain-free, simple, repeatable, and useful method for assessment of the hypothalamic-pituitary-adrenal axis.

Cortisol as a reflector of chronic stress in chronic disease has not undergone adequate investigation, although some studies have been performed. PD has several potentially

stressful nonmotor symptoms, such as pain, mood change, and autonomic dysfunction, all of which could result in changes in cortisol secretion.

The time point for sampling in the evening differed between the PD and reference groups. Sampling occurred about two hours later in the reference group. We believe that the consequences of this are trivial, because we know that the negative slope is minimal between 8 pm and 10 pm.[35] We also estimated the linear equation for salivary cortisol in both groups. When we adjusted for the time difference, the salivary cortisol concentration at 8 pm in the reference group was 4.0 nmol/L compared with 3.2 nmol/L in the PD group, and this difference was not statistically significant.

The fact that the time point for awakening corresponds to sleep duration is important. A previous study found a positive correlation between sleep duration and cortisol concentration.[35] The time interval from awakening in the morning to the exact time point of sampling is also important because of the cortisol arousal reaction. In our study, we registered the exact time for sampling in all patients in order to control for both the cortisol arousal reaction and food intake. For most patients in our study, the exact time points for sampling were in accordance with those stipulated and stated for the reference group (±30 minutes). In 11 patients, the time interval was less than 60 minutes. In seven of these 11 patients, the interval was 30–45 minutes, with a high risk for an arousal effect. There was a cortisol arousal reaction in only one of 59 participants.

We found that patients in both PD groups generally showed a similar 24-hour rhythm of cortisol secretion. However, morning cortisol concentrations were higher in the PD group compared with those in the reference group. This is in disagreement with the findings of Hartmann et al, who reported normal morning plasma cortisol but increased concentrations in the evening and at night.[18]

Our hypothesis that chronic neurodegenerative disease, using PD as an example, could change hypothalamic-pituitary-adrenal axis function was not confirmed. However, we found no correlation between duration of disease and cortisol concentrations. Some patients in our study showed very high morning salivary cortisol concentrations on both days. Function of the hypothalamic-pituitary-adrenal axis seems to be optimal, even at this age and after many years of disease. This, in turn, could indicate a normal-functioning hypothalamic-pituitary-adrenal axis in individuals with PD, thereby not supporting the hypothesis of earlier studies by Rabey et al [20] and Bellomo et al [36] concerning pathophysiological changes at the hypothalamic-hypophyseal-adrenal level.

There were marked differences in motor function of the patients according to UPDRS III scores. We predicted that motor dysfunction would be a severe stress factor resulting in increased cortisol concentration, but this was not confirmed. We found no correlation between gait problems, defined by UPDRS III item 30, and salivary cortisol concentration. This is in disagreement with Charlett et al who found a positive correlation between gait problems and plasma cortisol concentrations.[19] The reason for this difference is not obvious.

In this study, there was no correlation between BMI and cortisol concentrations in either the PD group or the reference group. In contrast, a study by Travison et al found a negative correlation between BMI and morning cortisol.[37]

The hypothalamic-pituitary-adrenal axis seems to be preserved in patients with PD. Effects of acute or chronic pain were not seen in our study, in contrast with the findings by Heim et al.[38] The "glucocorticoid cascade hypothesis," as described by McEwen,[12] ie, an acquired or primary decrease in hippocampal glucocorticoid receptor numbers leads to a reduction in central feedback sensitivity that results in basal glucocorticoid hypersecretion, is partially confirmed in our study. Possibly, the night-time lack of antiparkinsonian dopaminergic substitution contributes to the elevated cortisol concentration in the morning. The limitation of our study is the relatively small numbers of PD patients (n = 59), although this number compares well with those used in earlier studies in this field.[19,20]

Conclusion

PD patients with mild to severe PD have a normal diurnal cortisol rhythm, and higher morning cortisol concentrations and increased cortisol secretions during the day (8 am–8 pm) compared with healthy age-matched and gender-matched individuals. PD patients seem to have a normal cortisol arousal reaction and hypothalamic-pituitary-adrenal axis function, and their cortisol concentration is unrelated to age, duration of disease, gender, severity of motor dysfunction, and BMI, supporting the hypothesis that this neurodegenerative disorder itself does not interfere with hypothalamic-pituitary-adrenal axis function.

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Footnotes

Disclosure

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported in this paper.

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Paper II

Short and long-term effects of Tactile massage on salivary cortisol concentrations in Parkinson's disease.

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Running header: Effects of Tactile massage on Salivary Cortisol concentrations

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Abstract

Background

Parkinson's disease (PD) is a chronic neurodegenerative disorder with limited knowledge about the normal function and effects of non-pharmacologic therapies on the hypothalamic-pituitary-adrenal (HPA) axis. The aim of the study was to analyse the basal diurnal and total
secretion of salivary cortisol in short and long-term aspects of "Tactile massage" (TT) on the hypothalamic-pituitary-adrenal (HPA) axis in PD.

Methods

Design: Prospective, Controlled and Randomized Multicenter Trial.

Setting and interventions: 45 women and men, aged 50-79 years, were recruited. 29 of them were blindly randomized to Tactile massage (TT) and sixteen of them to the control group, Rest to Music (RTM). Ten interventions were given during eight weeks after randomization,
followed by a 26 week follow up. Salivary cortisol was collected at 8am, 1pm, 8pm and 8am the next day, at five occasions. At the first and eighth interventions it was collected immediately before and after intervention.

Main outcome measures: The primary aim was to assess and compare cortisol concentrations before, during and immediately after the interventions with TT and RTM and also during the follow-up period. The secondary aim was to assess the impact of age, gender, Body Mass Index (BMI), duration and severity of PD, effects of interventional time-point of the day and
levodopa doses on cortisol concentration.

Results

The median cortisol concentrations for all participants were 16.0, 5.8, 2.8, and 14.0 nmol/L respectively at baseline, reproduced four times without significant differences. Cortisol concentrations decreased significantly after TT intervention but no change in diurnal salivary

cortisol pattern was found. The acute findings of decreased salivary cortisol concentrations are in agreement with previous studies. However, there was no significant difference between the TT and control groups. There were no significant correlations between cortisol concentrations and age, gender, BMI, time-point for intervention, time interval between anti-parkinson pharmacy intake and sampling, levodopa doses, duration or severity of PD.

Conclusions

Diurnal salivary cortisol rhythm is normal in PD. Salivary cortisol concentrations were significantly reduced after the TT intervention and to a less significant degree after RTM, however with no significant differences between the groups and no sustained long term effect. No associations were seen between salivary cortisol concentration and clinical and/or pharmacological characteristics.

Trial registration: Clin. Trials.gov. No. NCT 01734876 and FoU Sweden 108881

Key words Circadian Rhythm; Complementary Therapies; Cortisol; Massage; Parkinson Disease; Stress;

Background

Why studying the HPA-axis in PD?

Parkinson's disease (PD) is a chronic progressive neurodegenerative disorder accompanied by autonomic dysfunction and alterations in different regulatory mechanisms [1]. Typically, signs of PD are hypokinesia, rigidity and tremor. Non-motor (NM) signs such as mood changes, pain and autonomic dysfunctions are frequent [2, 3, 4]. Many PD patients have sleep disorders, apathy, tiredness, anorexia and instability (hypotension). These symptoms can mimic a decreased adrenal cortisol activity.

Health related quality of life (HRQoL) is poor in people with PD compared to other disabled populations [5]. As the disease progresses, motor and non-motor complications aggravates, consequently making patients´ adherence to medication still more important. A complicated dosing or titration schedule is a part of daily life in PD [6]. In addition to pharmacological treatment there are also non-pharmacological approaches aimed at alleviating symptoms of PD. Complementary and alternative methods (CAM) are commonly used in PD patients [7]. Acute and chronic stress seems to raise the hypothalamic-pituitary axis function in terms of elevated concentrations of cortisol [8, 9, 10]. Several studies have shown salivary cortisol concentration to be an excellent mirror of hypothalamic-pituitary axis function [11] with fast reactions to changes in the surroundings [12].We hypothesized this to be a natural biomarker for stress in our study. In a previous study by our group, we found that median morning
salivary cortisol concentrations and total cortisol secretion during the day were higher in PD than in an age and sex matched healthy reference group [8]. In a previous study by Hartmann, (13), total serum cortisol was analysed each 15min for 24 hours. They found higher diurnal cortisol secretion in PD compared to a healthy reference group. This study was very intensive in a hospital situation and analysed not the free biologic active form of cortisol. Could these results be a consequence of stress in the sampling situation?
Other later studies have shown that the free biologic active cortisol increase much more than the total cortisol in situations of stress, intensive care and so on. (12). Literature findings in 2003, when this study began were sparse. There was no other

similar study which had analysed the diurnal cortisol secretion in PD during and after interventions and during a long follow up period.

To confirm or reject the previous findings, we have performed this study in a group of healthy patients with well defined PD for more than 2 years of duration. They had pharmacy only for PD and the disease was not as severe as they needed deep brain subthalamic nerve stimulation, continuous release of L-dopa in their duodenal bulb (Duo-Dopa) or Apomorphine injections.

What is the primary causal factor in HPA-axis dysregulation? Consequences of aging, stress or PD itself?

In a previous study, we have compared the HPA-axis function in PD patients with *and* without chronic pain (8). Chronic pain was defined as significant *PD related pain* for more than three times/week during at least three months before inclusion.
We have compared salivary cortisol in an age and sex-matched healthy reference group. These analysis has been performed identically in the same laboratory as our analysis. We found *higher* morning cortisol in **both PD groups** compared to the reference group. There was **no significant difference** between PD with and without chronic pain (8). In a 76 years old female, the diurnal cortisol curve was very prominent with very high morning cortisol concentrations in agreement with a well functioning circadian rhythm.

In summary, the HPA-axis seems to be up-graduated in PD patient without other disorders (somatic, psychiatric). The chronic pain=stress resulted in no difference. We have found *no* correlation between salivary cortisol concentration (HPA axis function) and **age**, sex, BMI, and adjusted daily dose of L-Dopa and time point-interval between taken medicines within one hour either side of salivary sampling (8). Therefore**, PD itself** seems to **results** in HPA-axis dysregulation.

Massage therapy

The Greek physician Hippocrates´ (460-377 B.C) advocated rubbing as a treatment for stiffness and massage was the primary form of care for stiffness until the pharmaceutical revolution of the 1940s. Massage therapy has received empirical support for facilitating growth, reducing pain, increasing alertness, diminishing depression and enhancing immune
function [14].
In agreement with these historical experiences, massage therapists in our region also experienced excellent effects on relaxation, reduced pain, increased motor function and improved sleep in PD patients. Stress tolerance is low in this type of patients, Health Related Quality of Life (HRQoL) is known to be worse than in age and sex-matched healthy persons
as well as in patients with other chronic disorders such as stroke. [15, 16]

As an attempt to study the effects of this non-pharmacological approach on hypothalamic-pituitary-adrenal axis function and some of the associated non-motor (NMS) symptoms such as pain and sleep disturbances " The Parkitouch study ", was initiated with the intention to report effects of TT on salivary cortisol concentrations.

Methods

Subjects

Patients with stable and well defined PD for more than two years who fulfilled the established clinical criteria for diagnosis and with chronic pain were recruited from the outpatient departments of three medium-sized city hospitals in southern Sweden. Chronic pain was defined as the occurrence of PD related pain for three days or more per week during at least three months prior to inclusion. Exclusion criteria were severe

fluctuations in PD, concurrent existence of epilepsy, active malignancy, polyneuropathy or other serious disease of somatic or psychiatric origin that could interfere with the study.
Patients with severe abnormalities of blood parameters, electrolytes, liver or renal parameters such as bilirubin >20 mmol/L, s/creatinin >130 mmol/L, sedimentation rate >30 mm, p/glucose > 6.7 mmol/L (fasting) were also excluded. Participation in other studies was not allowed.

Pharamacological treatment.
They had only medicine for PD and chronic pain, mainly non-steroid anti-inflammatory drugs (NSAID). We have adjusted for the total L-DOPA equivalent dose for their dopamine agonists .

Unified Parkinson Disease related Scale (UPDRS) questionnaire I-IV were used to classify the participants in different groups in relation to, cognition, mood, performance, motor function, activity of daily living and adverse reaction of their medicine.

Procedures

To optimize our study design, we have analysed salivary cortisol in their home to minimize stress, at exact time points according to detailed written instructions for sampling and caring of the samples in their fridges before sending the collected samples to the laboratory. All samples, five diurnal curves and six samples from two interventions (n=26) from each person, were analysed at the same time point to minimize the intra-inter-assay coefficient of variance (CV).

Study design, recruitment and randomization
The study was controlled, prospective and the participants were randomized by computer to either Tactile Touch (TT), or the control group (RTM) by lottery procedure. We had no adjustment with block strategy in randomization. All patients gave their written informed consent. An independent member of the " Parkitouch Study Group" was responsible for communicating the blinded, computerized randomization course.

Patients visited the outpatient clinic of the respective hospitals during the 34-week study period (Fig 1.) Two interventions per week were performed during the first three weeks and thereafter one intervention per week. The 10th intervention was performed eight weeks after randomization, followed by a 26 week follow up.

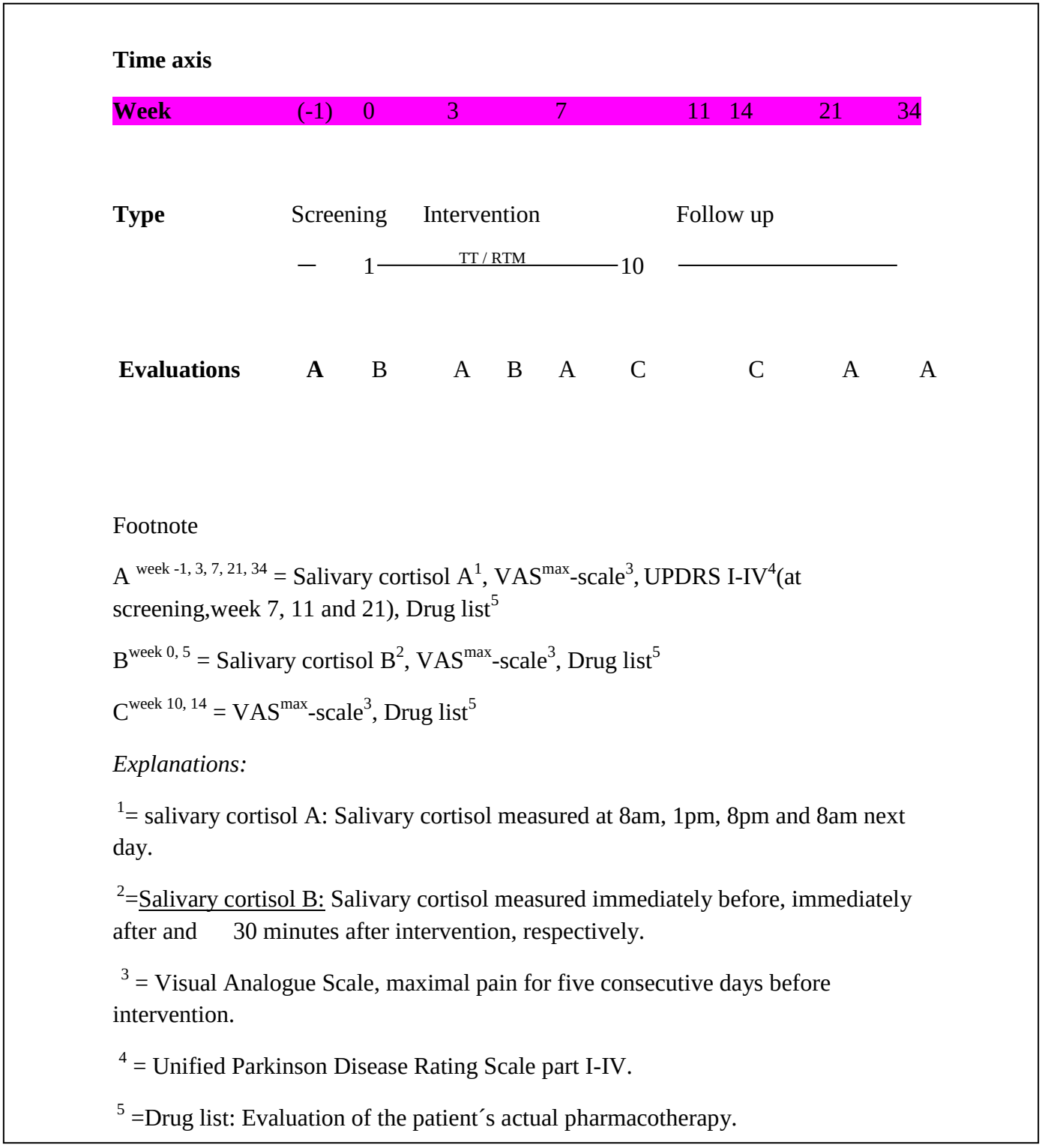

Fig.1: Time axis, the Parkitouch Study, TT/RTM groups.

Study intervention

All sessions were predetermined to be *performed during 9am to 12am.*
During TT, a specific oil was used, "Fibro oil" from Crearome AB, Gamleby, Sweden, mixed with Virgin oil comprising one third of the total volume. TT was performed following detailed instructions, written in 2003 by licensed massage therapists Laila Robertson and Birgitta Larsson, co-authors. They certified the competence of the participating local massage therapists.
Patients randomized to RTM had the same external conditions. RTM was given in the same locals as TT, it prolonged for the same time as TT at both sessions and the other circumstances were identical to TT excluding the specific massage. The music was identical in both groups: "Music for well-being II – Letting go of stress", LC6607 Fönix Musik, Sweden. The participants could regulate the sound level to a convenient level.

Collection of salivary cortisol samples

All time points for sampling were registered exactly in a protocol.
For both groups, collection of salivary samples was done using a well described technique 17]. In short, a cotton-based neutral swab was used, teeth should not be brushed and no food should be eaten within 30 min before sampling. Thereafter, a neutral swab was chewed for 2 min and later the swab was placed in a plastic double lumen tube. Thereafter, the tube was
placed in a refrigerator at home until it was sent for further analysis within three days. In the lab it was centrifuged at 3,000 rpm for 10 min at room temperature followed by freezing at –20 to –80 ° C until assayed. All samples were analysed at the same time. Time points for sampling were 8am, 1pm, 8pm and 8am next day and before, immediately and 30

minutes after intervention was finished, respectively. A commercial RIA-based technique for salivary cortisol was used (Spectria Cortisol I^{125} TM , Landskrona, Sweden).

Measures

The total secretions of cortisol during day, 8am-8pm, and during night, 8pm-8am, were calculated using the formula for Area under curve (AUC) from the zero level (AUC0=AUCG), according to investigations of Preussner [18] and Fekedulegn [19]. All analysis of saliva from the same individual (n=26) were performed simultaneously. Salivary cortisol during days was measured at baseline, at three, eight, 21 and 34 weeks after randomization. In addition, the immediate effects; just before, immediately after and 30' after the intervention was finished, were measured at the first and the eighth interventions.

Statistical analysis

STATISTICA version 8.0 and 10.0 (STATsoft Inc. Tulsa, OK, USA) and SPSS version 18.0 (SPSS Inc, Chicago, IL, USA) were used for the statistical evaluations. Non-parametric tests were used to adjust for the skewness in the subjects. Mann-Whitney U test and Kruskal-Wallis one-way analysis of variance were used to compare the two groups. Friedman´s ANOVA were used to compare the diurnal cortisol rhythm and total cortisol secretion during the five study time points. Wilcoxon´s matched-pairs signed ranks test analysed the individual diurnal rhythm and Spearman rank order correlation test to analyse association between cortisol and clinical characteristics. All tests were two-sided and statistical significance was assumed at $p < 0.05$.

Power: In order to have a 20% difference in cortisol concentration (AUC) between groups, a total of 40 patients were needed to have 90% power with a significance level of 0.05.

Ethics

The study was approved by the Ethics Committees at the University of Gothenburg (Ö 76203) and the University of Linkoping (D 03-673), Sweden.

Results

Our study included 45 participants randomized to TT (n=29) or RTM (n=16). One participant in the RTM group were excluded immediately after randomization because of disease in the family. Clinical and demographic characteristics at baseline were similar between groups
(Table 1).

Group	Sex	Age[1]	Weight[2]	BMI[2]	H&Y [2,3]	UPDRS (I-IV) [2,4]
"Tactile Touch "	Male (n=10)	50-78	86.5 (68.1/103.4)	26.6 (24.1/37.4)	1.5 (1.0/2.5)	31.5 (24.1/46.4)
	Female (n=19)	60-79	64.7 (54.8/95.0)	25.0 (20.2/35.9)	2.5 (1.5/3.1)	39.0 (27.5/61.2)
"Rest to Music "	Male (n=6)	50-74	88.6 (62.0/102.0)	27.0 (23.6/31.5)	3.0 (1.5/3.0)	42.5 (32.0/57.0)
	Female (n=9)	50-74	70.8 (44.5/92.4)	24.2 (17.8/31.2)	2.0 (1.0/4.0)	39.0 (21.0/78.0)

Table 1: Clinical and demographic characteristics of the two PD populations at baseline.

Values are given as range[1] and medians/10th and 90th percentiles[2]. Hoehn and Yahr[3] , Unified Parkinson´s Disease Rating Scale[4] .
There were no statistical differences between the groups or gender. (Statistical method: Mann-Whitney U-test).

Follow-up rates were 100% and 93%, respectively. The natural diurnal negative slope of cortisol concentrations between 8am and 1pm was estimated to 2.0 nmol/h. Comparisons between TT and RTM groups at the time points for awakening, sampling, interventions and cortisol concentrations, delta cortisol , percentile changes of cortisol concentration and total cortisol secretion during and within 30 min after intervention (Area Under Curve; AUC) are shown in Table 2.

	RTM (n=14)		TT (n=28)	
Age (year)	62.5	(54-73)	66.0	(61-73)
Gender (M/F)	6/8		10/18	
Time of wakening				
first /	04.30-07.30		02.00-07.30	
eighth intervention	04.30-08.00		04.00-08.00	
Time of sampling				
first /	07.20-15.35		08.00-15.49	
eighth intervention	08.00-15.12		07.51-15.15	
Time interval after	90-585		110-543	
wakening (min)	55-578		40[§]-555	
Cortisol (nmol/L) (median/10/90%)				
Before first /	7.0	(4.5/23.9)	9.2	(4.1/17.0)
eighth intervention	7.2	(4.1/23.9)	7.5	(4.5/13.8)
After 0`	6.3	(2.6/18.7)	6.8	(2.5/15.4)
	6.6	(2.5/11.0)	5.7	(3.5/9.8)
After 30`	6.6	(2.4/8.3)	5.6	(2.6/13.2)
	4.8	(2.5/21.1)	4.6	(2.6/9.2)
Delta Cortisol (nmol/L)				
Before - after 0`				
first /	1.8	(-3.0/+5.5)	1.9	(-2.0/+6.2)
eighth intervention	2.6	(-2.5/+17.1)	1.7	(-2.0/+5.4)
Before- after 30`				
first /	2.4	(-0.3/+17.1)	3.4	(-2.2/+6.5)
eighth intervention	3.6	(-0.1/+13.2)	3.1	(-2.8/+7.5)

Table 2: Baseline variables and cortisol concentrations at first and eighth intervention split by arms.

Footnote:
TT= Tactile Touch, RTM= Rest to Music. AUC_G=area under curve from ground level
Statistical methods used; Mann-Whitney-U, Chi-2-test, Median test and Kruskal-Wallis test. There were no statistical differences between groups.Eight time intervals < 60 min. at 8th intervention and once at first intervention. [§] This patient had concentrations, 7.7, 9.7, and 10.2 nmol/L, excluding a cortisol arousal reaction (CAR)

Pharmacological Treatment

No significant differences between the two groups were seen even when we integrated other forms of anti-PD drugs and recalculated the total dopaminergic load using formulas from literature [20]. Forty-two of forty-four patients were treated with levodopa with a total dose
of 625 mg/day in median after recalculation. The pharmacological treatment was essentially unchanged and only single extra doses of anti-PD treatment were taken during the study.

Massage

The TT was performed for each individual patient by the same therapist for a mean duration of 52 minutes per session (range 40 –79 minutes), with a total of 10 massages during a period of eight weeks. At the first and eighth intervention, TT / RTM was given 133; (10-293) and
109; (10-272) minutes after intake of the morning PD medication.

All interventions were performed before 12am, excluded three participants from each type of intervention at both sessions. There was no statistical difference in salivary cortisol response between early or late interventions.

Salivary cortisol
Basal, short and long-term effects of intervention on cortisol concentrations are shown in Fig 2. and Table 2-3. At baseline, there was no significant difference between the groups. Salivary
cortisol concentrations at baseline before the first intervention and at week three, after the sixth intervention, were not significantly different between groups, as shown in Table 3. Acomparison of the two groups regarding the total diurnal secretion of cortisol (AUC) showed no differences between groups (not visualized).

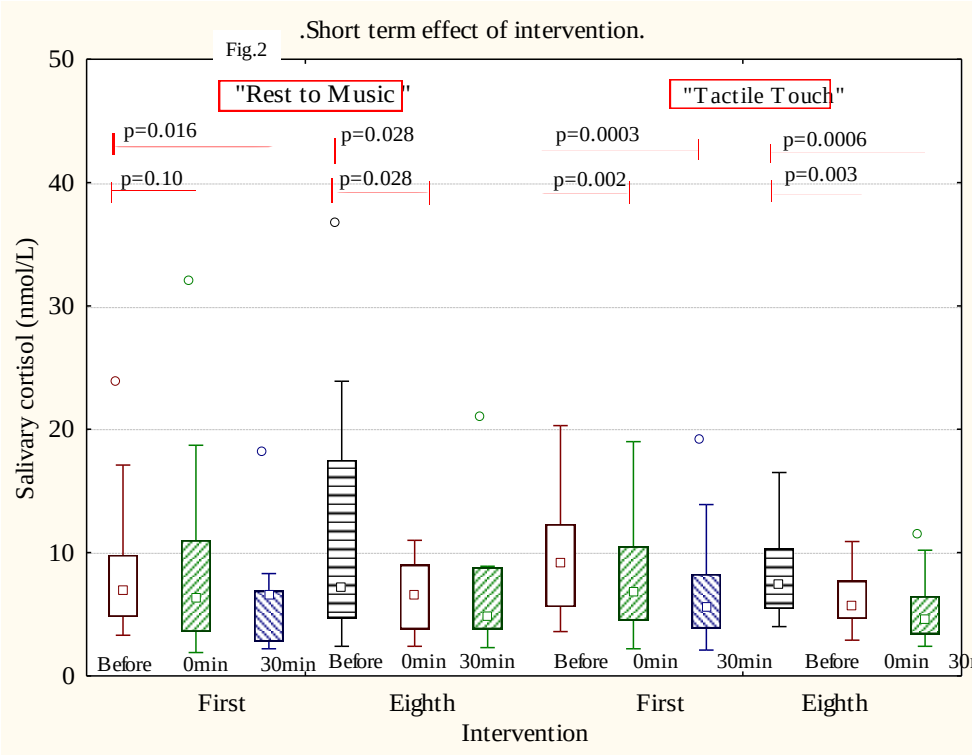

Fig 2: Short term effects of intervention.

WEEK	"Tactile Touch"				"Rest To Music"				p-values[1]
	8am	1pm	8pm	8am	8am	1pm	8pm	8am	
0	14.3(5.8-28.9)	4.9(2.4-23.3)	2.8(1.6-7.1)	14.0(6.9-35.0)	18.5(3.9-28.5)	6.2(3.7-10.0)	2.8(1.1-8.5)	17.0(7.6-28.6)	ns
3	13.4(6.2-26.7)	6.3(3.1-10.1)	2.6(1.2-6.1)	14.1(6.7-29.5)	15.9(8.8-18.8)	3.9(3.0-10.5)	1.9(1.4-7.8)	12.4(8.1-34.0)	ns
8	12.1(6.6-37.3)	4.9(2.9-14.3)	2.5(1.5-4.8)	14.0(7.6-34.9)	11.6(6.9-28.0)	5.1(2.7-10.3)	2.6(1.1-7.6)	12.6(5.6-28.2)	ns
21	12.2(5.6-25.4)	6.2(3.5-18.4)	3.1(1.2-7.9)	13.2(6.5-26.9)	12.5(6.4-19.5)	6.0(3.5-8.0)	2.6(1.4-9.8)	14.3(6.2-42.0)	ns
34	13.2(6.3-35.9)	7.3(3.5-16.8)	2.6(1.4-11.3)	15.1(5.7-32.0)	14.5(6.4-30.0)	6.4(3.2-11.0)	3.5(1.3-9.4)	13.4(7.0-40.9)	ns
p-values[2]	ns	ns	ns	ns	ns	ns	ns	ns	

Table 3: Diurnal salivary cortisol concentrations (nmol/L) during and after interventions.

Results are given as median and 10^{th}- 90^{th} percentiles. The statistical methods used were Kruskal-Wallis[1] comparing the two groups and Friedman´s ANOVA [2] comparing the longitudinal process. ns=non-significant difference.

Effects of intervention

Short-term effects

In Table 4A+B differences in total cortisol secretion, at screening (AUCscreening.) and during the separate interventions (AUCintervention.), are shown.

After first intervention;

There was a significant decrease in salivary cortisol concentration in the TT group but not in total secretion (AUC) immediately after intervention. In contrast, 30 min after intervention, salivary cortisol concentrations were significantly decreased in both TT and RTM but the total cortisol secretion (AUC) was not changed in any group, (Fig. 2 and Table 4A+B).

After eighth intervention;

Salivary cortisol concentrations were significantly decreased immediately and 30 min. after intervention in both groups (Fig. 2). The total salivary cortisol secretions (AUC) were significantly decreased immediately after intervention in both groups but remained decreased only in the TT group, (Table 4A+B).

	Group	*AUC screening*[1]	*AUC intervention*[2]	p-value[3]
First intervention	RTM	553 (175-1118)	350 (143-1271)	0.249
	TT	571 (219-1226)	456 (189-954)	0.153
Eighth intervention	RTM	563 (188-1117)	338 (173-1030)	0.035*
	TT	525 (242-1215)	352 (221-656)	0.003*

Table 4A Area under the Curve (AUC) for short-term effects, before to *0 minutes* after intervention.

	Group	*AUC screening*[1]	*AUC intervention*[2]	p-value[3]
First intervention	RTM	875 (292-1641)	582 (255-1939)	0.158
	TT	918 (337-1752)	662 (267-1366)	0.076
Eighth intervention	RTM	870 (315-1686)	562 (262-1614)	0.087
	TT	883 (373-1783)	491 (303-854)	0.004*

Table 4B Area under the Curve (AUC) for short-term effects, before to *30 minutes* after intervention.

[1] AUC estimated according to individual intervention time for start and duration in minutes based on linear equation for daily AUC at screening. Median (10^{th} and 90^{th} perc)

[2] AUC according to intervention duration and salivary concentration at start, 0 min after and 30 min after. Median (10^{th} and 90^{th} perc)

[3] AUC intervention compared to AUC screening, Wilcoxon´s test for paired data.

*Statistically significant difference.

We found no differences between groups in delta cortisol values and percentile changes after TT and RTM as shown in Table 2. The immediate effects of intervention were not correlated to interventional time point of the day (morning/afternoon), age, gender, BMI or duration of disease.

Long-term effects

The diurnal cortisol concentrations are shown in Table 3. We compared the diurnal cortisol curve at baseline and during the study period (wk 3, 8, 21 and 34). We found no change in diurnal rhythm or absolute cortisol concentrations during 26 weeks follow up. At baseline and after three weeks of the intervention period, the total cortisol secretion was higher during
night (8pm-8am) than day (8am-8pm) in both the TT and the control group. The total cortisol secretion during the day was not significantly different between the TT and RTM groups.

Associations between salivary cortisol, clinical characteristics and intervention.

No associations were seen between salivary cortisol concentration and age, gender, weight,
BMI, severity or duration of disease, interventional time point of the day, time point of or
dose of levodopa intake .

Discussion

In this study we found an immediate effect (short term effect) on the hypothalamic-pituitary axis with a significant decrease in cortisol concentration at both first and eighth time points after TT. However, there were no significant differences between the TT and the RTM groups
at these time points when comparing the decrease in cortisol concentration.
Nor were differences seen in cortisol concentrations between the groups due to the interventional time point of the day. The delta cortisol and absolute values for salivary cortisol concentrations were similar in the two groups. The percentile decrease after intervention was more than 20 % in both groups, which was in agreement with results from another study in cancer patients receiving massage [21]. To our surprise, we found no
significant correlations with cortisol concentration and age, gender, weight, BMI and disease duration. Our results further suggest that the diurnal pattern of cortisol secretion, i.e. the sensitivity of hypothalamic-pituitary axis function, was normal at baseline before intervention and was unchanged during the interventions and up to 26 weeks after the last treatment session.

Comparison of previous studies in this field

A recently published finding from the "Parkitouch" -study was significantly increased morning salivary cortisol concentration compared to an age and sex-matched healthy group[8]. In 2002, Hernandez-Reif et al [22] performed a pilot study on massage in PD patients, and to our knowledge this is the first study of massage effects on the hypothalamic-pituitary-adrenal axis function in PD. They found no differences in urine cortisol secretion after the first and last interventions. However, in 2005 Field et al [23] showed changes in cortisol concentrations in saliva after massage therapy. This finding is in agreement with our results. A review article of massage therapy combined with analysis of cortisol in urine, saliva or plasma in healthy and sick adults by Moraska et al. summarises the current knowledge until 2008 [24]. In eight studies, salivary cortisol was analysed at the first and/or sixth to 10th intervention. In 89 %, salivary cortisol concentration decreased after the first intervention. In four out of eight studies salivary cortisol also decreased after the last treatment. This is in agreement with our results. Only one study has shown a significant decrease in urine cortisol after multiple treatments. No study has analysed diurnal or multiple salivary cortisol samples during intervention. During the passive non-interventional follow-up period there is no previously published study that has analysed diurnal cortisol rhythm and/or multiple salivary cortisol samples.

Non motor symptoms.

We have *not* included a self reported mood questionnaire. Even a specific, sensitive questionnaire for depression and anxiety is missing. However, our nurses or massage therapists have met each person, 10-16 times, at these interventions. *Nobody* seemed to be depressed, very anxiety or reported signs of depression in their UPDRS I questionnaire.
We have instead used *specific questionnaires, Parkinson´s Disease Sleeping Scale (PDSS) and SF36 swedish version 1.0* to compare sleep pattern and Heath Related Quality of Life (HRQoL).We found disturbed sleep and a low HRQoL, even lower

than in patient who had had a major stroke six months earlier. These facts are recently published (25).

Interacting factors

Personal care and kind treating are naturally of great value in all patient care. The placebo effect is also of essential importance as described by Wormnes et al [26]. The TT method also includes listening to tranquil and peaceful music. The volume was adjusted by the individual participants to a pleasant level to avoid stress-discomfort. In the
pleasantly warm room some smells of plants (aroma) were present but it was not a specific aromatherapy. To minimize and eliminate confounders because of these conditions, the control group (RTM) was adapted to be identical in detail to the TT group, except for the specific moderate tactile massage of the skin. The intention was to study the unique effect of this specific TT method and reduce the numbers of independent variables, therefore we performed the study with two "active" groups where only the presence of tactile touch differed.

Limitation of this study

Relatively few patients were included. The oldest PD patients were excluded due to difficulties in carrying out the extensive program, and the risk of falling or balance problems in conjunction with the interventions on the massage table. However, compared with previous studies of combined massage therapy and analysis of cortisol, our study is the second largest
of nine controlled studies [24]. Distribution of participants between TT and RTM was somewhat distorted. However, as randomization was performed with a computerized lottery technique and blinded, we had no influence on the distribution of patients to the respective group. As the RTM group was quite small it could be possible that the spread of results within
this group hides significant differences between TT and RTM. (Type II error). A hypothetic comparison between the TT and RTM group with similar number of participants in each group (n=28) was therefore performed using identical cortisol results as for the first 14 RTM-participants. This theoretical model resulted in a significant difference between some factors representing pain and sleep but not the

cortisol concentrations after interventions with the TT-method compared to the RTM-method (control). The study included no arm with a group given no intervention at all.

We have *not* included a specific self reported mood questionnaires after interventions but used a parkinson disease specific UPDRS I questionnaire. Even a specific, sensitive questionnaire for depression and anxiety is missing.

Conclusion

Diurnal cortisol rhythm was normal in PD. The short-term effects of the intervention resulted in a significant decrease in salivary cortisol concentration and total secretion of cortisol during the day in both the TT and the control RTM groups, however with no significant difference between groups. The effects on the hypothalamic-pituitary-adrenal axis were dependent on the time point for intervention (first or eighth). A tendency towards more pronounced decrease in cortisol concentration was seen when TT was added to the treatment. Cortisol concentrations at baseline and during the follow up period were independent of age, gender, weight, Body Mass Index and the levodopa dose. The total diurnal cortisol secretion was lower during day (8am-8pm) versus night (8pm-8am) at baseline. There was no recognizable long-term effect of the interventions on the hypothalamic-pituitary-adrenal axis in terms of diurnal cortisol rhythm and total cortisol secretion.

List of abbreviations

AUC = Area Under Curve
BMI = Body Mass Index
CAM = Complementary and Alternative Methods
CAR = Cortisol Arousal Reaction
HRQoL = Health Related Quality of Life
HPA-axis = Hypothalamic-Ppituitary-Adrenal axis
PD = Parkinson´s disease
RTM = Rest to Music
SF-36 = The Short Form (36) Health Survey
TT = Tactile massage

Competing Interests

None of the authors has any competing interests regarding this study.

Authors contributions

CJT, OS, AB, PAF, GH, MC, UL and HS were responsible for the study conception, data collection and design. BL, LR, LA, LA and PB performed the intervention. CJT and OS performed the data analysis. CJT, OS, PAF, GH and JL were responsible for drafting the manuscript.

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collection, analysis or interpretation of data; nor in the writing of the manuscript.

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Paper III

Parkinson's disease patients' subjective descriptions of characteristics of chronic pain, sleeping patterns and health-related quality of life

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Abstract

Objective

Nonmotor symptoms are common in Parkinson's disease (PD). Health-related quality of life (HRQoL) is negatively affected by different factors, of which pain and sleep disturbances are important contributors. This study was performed to evaluate and describe subjective experiences of pain, sleeping patterns, and HRQoL in a cohort of PD patients with chronic pain.

Methods

A total of 45 participants with established PD for more than 2 years, and PD-related pain for the preceding three months, were recruited from three sites in Sweden. Data regarding time point for onset, duration and degree of pain parameters, body localization of pain, external influences, and treatments were obtained. HRQoL was evaluated with the Short Form-36® Health Survey, and sleeping patterns were registered with the Parkinson's disease Sleep Scale, both completed along with a questionnaire.

Results

In one-third of participants, pain preceded the PD diagnosis. Median pain score measured with a visual analog scale was 6.6 and 5.9 (for females and males, respectively) the week before the study. In almost half of the participants, pain was present during all their waking hours. Significantly more females described their pain as troublesome, while more males described their pain as irritating. Feelings of numbness and creeping sensations at night were strongly associated with the maximal visual analog scale scores. Polypharmacy was common; 89% used medication for anxiety/insomnia, and 18% used antidepressants. Only one-third of patients who reported pain relief with analgesics had these prescribed on their drug lists. Sleep was characterized by frequent awakenings. Urinary urgency and restless legs were frequently reported as troublesome. Patients rated HRQoL as significantly worse in all items compared with a healthy reference population matched for age and sex.

Conclusions

Experiences of chronic PD-related pain are complex; there is substantial sleep fragmentation and negative impact on HRQoL.

Keywords: data reporting, pain, Parkinson disease, sleep fragmentation

Introduction

Pain in Parkinson's disease (PD) was described in 1817 by James Parkinson in "An essay on the shaking palsy."[1] Since that time, the symptom has occasionally been discussed in the literature. Ford [2] categorized five modalities of pain in PD: musculoskeletal, radicular-neuropathic, dystonic, central pain and akathisia. Beiske et al found musculoskeletal and dystonic pain to be most common type of pain, and they estimated that the overall prevalence of chronic pain was over 80%.[3]

Muscular stiffness is common, and fluctuations due to "on" or "off " states in chronic PD-related pain are well described in the literature.[4,5] Pain is an early nonmotor symptom in PD,[6] and often precedes the start of anti-PD medication.[7]

The reported prevalence of pain in PD varies in different studies. In 2008, Negre-Pages et al[8] estimated the prevalence of chronic pain in PD to be 62%. Ten years earlier The Swedish Parkinson Association reported on a survey of nonmotor symptoms comprising almost 1000 PD respondents.[9] They found that chronic pain was more common among females than males (54% and 45%, respectively). However, pain is also common in the general population, and there is a lack of studies on chronic noncancer pain. In a recent review article, the prevalence of moderate to severe, noncancer chronic pain was estimated to be 19% among adults.[10]

The origin of pain in PD is still obscure. Pathways other than those secondary to rigidity, tremor, or any other motor manifestations of the disease, are probable. The basal ganglia process somatosensory information in different ways. Increased subjective pain sensitivity with lower electrical- and heat-pain thresholds have been reported in PD patients.[11] PD-related disorders such as multiple system atrophy show almost the same prevalence of pain as PD.[12]

Nocturnal symptoms with sleep disturbance are well known in PD.[13,14] Sleep is disrupted in the majority of patients,[15] and more than two-thirds of patients with PD are affected.[16] As with PD-related pain, the origin of sleep disturbance is partially caused by the neurodegenerative process but also most probably due to the interaction with chronic pain. Sleep fragmentation and pain are common in PD, and negatively affect health-related quality of life (HRQoL).[17,18]

Previous descriptions of the diurnal recurrence and the migrational nature of pain are scarce, as are patients' self-reported experiences, restrictions in their movements, experienced interference with sleep, and their views regarding causal factors and consequences in daily life.

An increased understanding of PD-related pain and its impact on everyday life, as well as the interactions with sleep disturbances, is essential for all caregivers caring for patients with this disease. Thus we decided to describe these variables in a group of outpatients with established PD and chronic PD-related pain.

Methods

Patient population

Patients with stable and well-defined PD for more than 2 years, who fulfilled the clinical criteria for diagnosis according to the United Kingdom Parkinson's Disease Society brain bank criteria,19 and with chronic PD-related pain, were included. They were recruited during routine care visits at the outpatient departments of three medium-sized city hospitals in southern Sweden. Anamnestic reports of chronic pain from patients resulted in a more detailed analysis by the clinician. If inclusion and exclusion criteria were met, the patients were surveyed about their interest in participating in the study. Patients were asked to sign an informed consent. The study followed the tenets of the Declaration of Helsinki.

Chronic pain was defined as the occurrence of pain related to PD for three days or more per week during at least three months immediately prior to inclusion in the study. The pain was considered to be related to the disease when associated with fluctuations of the motor symptoms, cramps, or other pain sensation not explained by coexisting physical or mental problems. Exclusion criteria were musculoskeletal pain, such as the coexistence of arthrosis, tension headache, or neck ache, not associated with PD. Severe fluctuations in PD, concurrent existence of epilepsy, active malignancy, polyneuropathy, or other serious disease of somatic or psychiatric origin that could interfere with the study were exclusion criteria as well.

To avoid possible other coexistent chronic or acute diseases that might have concurrent influence on sensory systems, neuropathies, etcetera, patients with severe abnormalities in blood parameters, electrolytes, liver or renal parameters, such as bilirubin > 20 mmol/L, serum creatinine > 130 mmol/L, sedimentation rate > 30 mm, glucose 1-phosphate > 6.7 mmol/L (fasting), were also excluded. Participation in other studies was not allowed.

Patients' evaluations of their pain, sleep and HRQoL

Before the study was started all patients received careful instructions about how to complete the self-reporting pain scales, and were assessed as being competent to complete their own forms. The week prior to their clinical visit, patients completed a 0–10 cm visual analog scale (VAS),20 marking maximal pain and duration of pain for each day, for five consecutive days. At the assessment visit, patients filled out a four-

page “pain evaluation analysis” questionnaire, comprised of multiple-choice questions, body contours, and short free-text questions about different aspects of pain. Pain was also evaluated using the Pain-O-Meter (POM),21 which comprised a 10 cm VAS (POM^{vas}), and a list of 15 sensory and 11 affective word descriptors with an assigned intensity value ranging from 1–5. A pain intensity score was calculated for the sensory, and for the affective components of pain. Experiences of sleep were evaluated using the Parkinson’s Disease Sleep Scale (PDSS).22 HRQoL was evaluated with the Short Form (36) Health Survey (SF-36®) (Swe.ver.1; Quality Metric Inc, Lincoln, RI).[23]

All medications were carefully registered and supervised by the study staff. At each site, a specialist trained in movement disorders completed the Unified Parkinson’s Disease Rating Scale (UPDRS) version 3.0, parts 1–4,24 and the modified Hoehn and Yahr scale.25

Statistical analyses

Comparisons between categorical variables with respect to proportions (presence of different symptoms or characteristics) were done by means of chi-square test or Fisher’s test.

When comparing variables of ordinal data type between different categories, the Mann–Whitney U test was used, and median with percentiles were presented.

Maximal pain above 7 (VAS ≥ 7) was used as the outcome in a logistic regression model, to explore factors with possible influence on pain.

The different domains of HRQoL levels in the study group were compared to mean levels in the Swedish norm population by means of a one sample *t*-test. As means of HRQoL in the norm population were presented as age- and sex-specific, and means within the study group were calculated as age-specific but not sex-specific, before comparisons we calculated weighted means based on norm data, and weighted by sex distribution in the study group, in order to exclude the sex effect.

Data were analyzed with STATISTICA© versions 8.0 and 10.0 (Statsoft Inc, Tulsa, OK) and SPSS© version 18.0 (IBM, Armonk, NJ).

Ethics

The study was approved by the Ethics Committees at the University of Gothenburg (Ö 762-03), and the University of Linkoping (D 03-673), Sweden.

Results

Our study included a convenience sample of 45 participants, 16 men and 29 women, who were 50–77 years of age. There were nine patients from Linkoping University Hospital, one of whom chose not to complete the study for personal reasons; 16 patients from Ryhov County Hospital; and 20 patients from Skaraborg County Hospital. Clinical characteristics of the PD population, severity of disease and pharmacological treatments are seen in Table 1.

Table 1: Basal characteristics of the study population, duration of pain, severity of PD and pharmacological treatment.

Gender	**Age[1,2] (y)**	**Duration of pain (y)**	**UPDRS[4] (III) score**	**UPDRS (I-IV) score**	**H&Y[3,5] score**	**Levodopa[6] Treatment (mg)**	**Antidepress. (n)**	**Anxiolytics / sedatives (n)**
Females (n=28)	66.7/ 66.5 (60/73)	6.5/4 (1/13)	23.3/23 (10/37)	36.3/36 (19/60)	2 (0/3)	634/562 (300/1140)	6	23
Males (n=16)	62.8/64.5 (54/69)	4.8/4 (2/10)	20.4/16.5 (12/36)	34.5/32.5 (24/49)	1.5 (0/3)	768/758 (350/1205)	2	16
Total	65.3/66 (59/73)	5.8/4.0 (1.4/12)	22.2/20 (10/36)	36.3/35.5 (21/60)	2 (0/3)	682/650 (300/1205)	8	39

Notes:Values are given as mean/median[1], 10/90th percentiles[2], median[3] , Unified Parkinson´s Disease Rating Scale[4], Hoehn & Yahr scale[5], LED levodopa equivalent doses [6],according to reference [36].

Results of basal analyses of pain parameters, the degree and duration of pain compared to time point for PD diagnosis, and the patients' descriptions of pain are shown in Table 2.

Table 2: Basal characteristics, onset, duration and expression of pain.

Gender	Duration[1] of disease ≤5 / >5	Pain before/ after PD diagnos	Duration[2] of pain/day ≤10h / >10h	VAS[3] ≤ 5/ > 5	Pain expressions by participants						
					migrating	irritating	worrying	trouble-some	tiring	suffocating	RLS[4]
Females (28)	11/16[5]	10/17[5]	20/8	13/14[5]	13[a]	5[a]	3	20[a]	20	1	5[a]
Males (16)	9/7	6/10	9/7	9/7	4[a]	9[a]	5	5[a]	9	0	10[a]

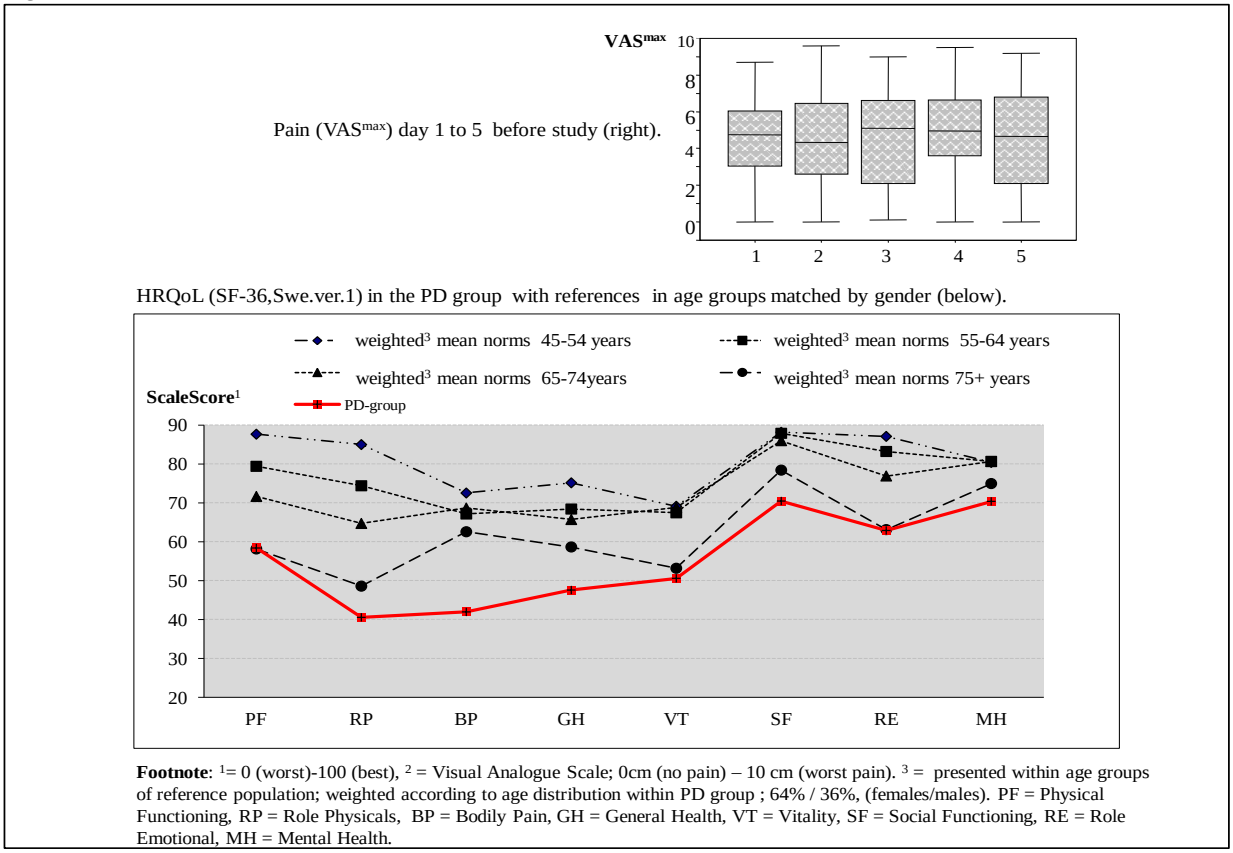
Notes: Less or more than 5 years[1], maximal duration [2](less or more than 10 hours) of pain day 1 -5 , Visual Analogue Scale [3] maximal pain (less or more than 5 cm) day 1 – 5, Restless Legs Syndrome [4] (yes/ no), 1 missing data [5], [a] = statistical significant differences between gender, p-value ≤0.05.

Pain onset and characteristics of pain

Thirty-five percent of the patients experienced chronic pain before the time point of PD diagnosis, and in 45%, the onset of pain occurred within 5 years from diagnosis.

Maximal pain on the five consecutive days (VAS^{max}) before assessment of the entire group is presented in Figure 1. The median score of the VAS^{max} during the 5 days for all patients, was 5.0 (5.2 and 4.8 for females and males, respectively), in comparison with a median score of 3.3 (2.8 and 3.9 for females and males, respectively) at baseline, estimated by the POM^{VAS}.

Fig. 1



Footnote: [1]= 0 (worst)-100 (best), [2] = Visual Analogue Scale; 0cm (no pain) – 10 cm (worst pain). [3] = presented within age groups of reference population; weighted according to age distribution within PD group ; 64% / 36%, (females/males). PF = Physical Functioning, RP = Role Physicals, BP = Bodily Pain, GH = General Health, VT = Vitality, SF = Social Functioning, RE = Role Emotional, MH = Mental Health.

Figure 1
Pain (VAS^{max}) and HRQoL (SF-36®, Swe.ver.1) in the study group.

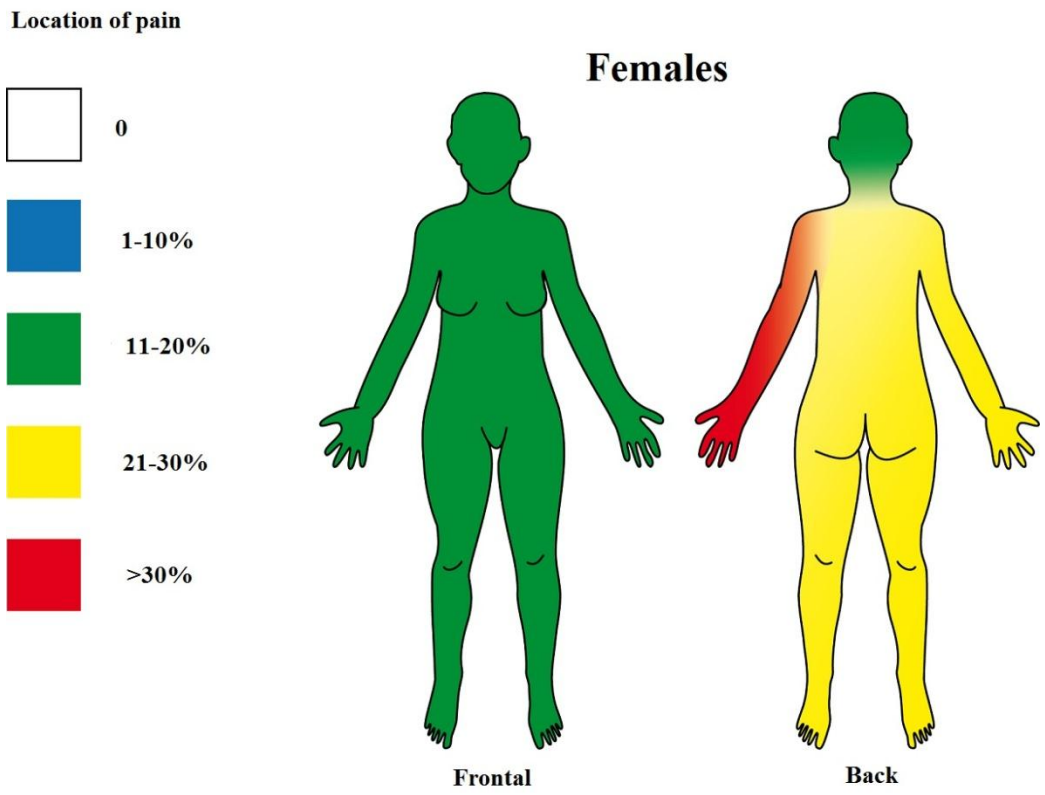
The individual descriptions of pain characteristics differed between sexes but this was not influenced by age or disease duration (Table 2).

Dystonic cramps were seen in twelve females and eight males, all of whom experienced benefits regarding pain from anti Parkinson therapy. Three females and two males suffered from dystonic cramps for more than half of the day.

Significantly more patients with a long duration of PD (≥5 years) described their pain symptoms as troublesome compared with those with a short (<5 years) duration (74% versus 26%, respectively; $P = 0.006$).

Descriptive terms such as “tiring” and “worrying” increased with disease duration, but not significantly. We did not find any association between the descriptive terms and disease severity as expressed by the UPDRS parts 1–4 scores.

Thirty-four percent of the patients suffered from restless legs, which was significantly more common in males than in females (62.5% versus 17.9%, [$P = 0.003$]). Figure 2 shows, in percentage of participants, a summary of localizations of chronic pain and the differences between sexes. More males than females experienced pain from the front of the lower extremities (P-values = 0.014 and 0.019, for left and right, respectively).



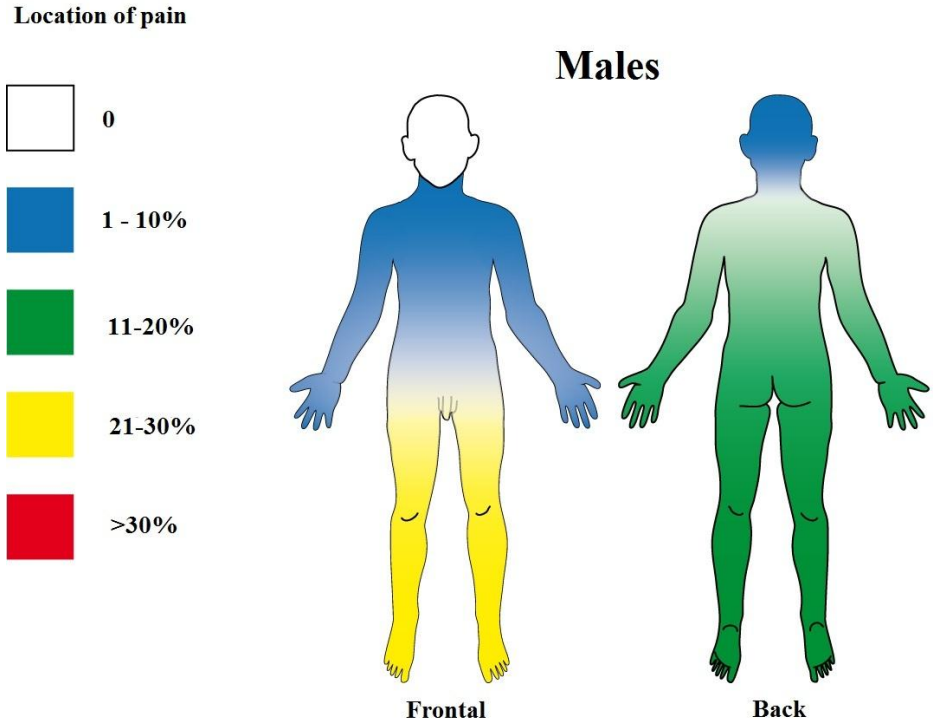


Figure 2
Visualization of the localization of chronic pain and differences between sexes.

Duration and fluctuation of chronic pain

More males than females experienced pain from the front of the lower extremities (*P*-values = 0.014 and 0.019, for the left and right, respectively). Duration of pain was 6.7/5.5; (2/14) years for females, and 5.7/4.5; (2/12) years for males. Almost the whole study population (90%) suffered from daily pain attacks, with no differences between sexes. One third (36%) of the patients registered pain all their waking hours, and only one out of six (16%) reported less than 1 hour of pain per day.

Pharmacological treatment

We could not find any significant correlations between the amount of levodopa and the intensity of pain that was reported (not shown). About half of the patients confirmed pain relief from anti-PD medication. Although 67% of participants indicated relief of pain from analgesics, these drugs were documented in the drug lists of only 27% of those patients. Paracetamol and nonsteroidal anti-inflammatory drugs were the most commonly used analgesics (10/44 and 6/44, respectively). Anxiolytics and medication for insomnia were very commonly prescribed (Table 1). The majority (4/6) of participants who were prescribed antidepressants had a long duration of PD.

Patients' experiences of nonpharmacological treatments and their thoughts concerning pain relief and pain origin

There was a tendency for more females than males to have tried treatments other than pharmacotherapy, for pain. Taking a bath was most common (n = 18), and four females and four males worked out to alleviate pain. Acupuncture (4), rest (4), active movements (3), and cooling the aching area (3), were other reported examples of self-treatments. Massage, transcutaneous nerve stimulation, and sonography were practiced by one patient each. Approximately three out of four patients had an opinion about which nonpharmacological therapy could be useful for relief of pain. No associations were seen with regard to age or sex.

Almost all patients had an opinion about the origin of pain; most patients (71%) thought that the pain originated from the musculoskeletal system, and 28% said it came from the nervous system. Individual patients indicated that the pain originated from the kidneys, the skin, or that the origin was mental. One fourth of the patients (26%) indicated more than one origin, and three (6%) had no idea of the origin.

There were some restrictions due to chronic pain, where the most common conditions that had a negative impact on pain were "physical strain" (50%), "cold" (29%), and " walking" (29%). A "sitting position" increased the sensation of pain (48%), more so in patients with severe PD.

Sleep and nightly pain characteristics

The length of unfractioned sleep during the night was 3–4 hours (median) for both sexes. Females woke up two times per night, and males two to three times per night. These values corresponded well to the responses of the item " difficulty staying asleep," plotted to in median three to four on the VAS scale in the PDSS questionnaire (worst = 0, best = 10). Females arose a median of twice nightly to urinate, while males arose once. Three females reported distressing pain at night. Nightly muscle cramps, numbness, and burning pain were reported by ten, five, and two patients, respectively. The sex distributions were equal.

Impact on health-related quality of life (HRQoL)

HRQoL was significantly lower in the study group compared with mean levels in a reference population, matched for age and sex (*P*-value <0.001) for all items except Emotional Role (*P*-value = 0.021).

Even when compared with a reference group over 75 years of age (ie, older than the study group), there was a statistically significant lower HRQoL within the study group with respect to bodily pain, general health, and social functioning (*P*-value = <0.001, <0.001, and 0.037, respectively).

Correlations between maximal pain ($VAS^{max} \geq 7$) and factors with possible influence on pain were analyzed by logistic regression. There was significant positive correlations between VAS^{max} and POM-VAS^{emon} (*P*-value = 0.03, odds-ratio (OR) = 2.33), the PDSS item "numbness and creeping sensation" (*P*-value = 0.03, OR 1.33). Age, sex, PD duration, POM-VAS, ^{phys}UPDRS I-IV, UPDRS depression, PDSS total and PDSS unexpected day sleep were also analyzed, but there were no significant correlations.

Discussion

In this study we have analyzed different aspects of chronic PD-related pain and sleeping patterns, focusing on the patients' own experiences, as well as on the impact on quality of life. In contrast, previous studies in this area have categorized PD-related pain into classical subgroups (musculoskeletal, radicular-neuropathic, dystonic, central pain and akathisia).[2]

Pain

Characteristics of onset of pain

As chronic pain in the general population without PD is common and increases with age, we attempted to exclude chronic pain due to concomitant diseases unrelated to PD.[3,26] The oldest PD patients were excluded from the study. The time point for onset of pain in PD differs with respect to age at onset of the disease.[8] In recent studies focusing on early premotor symptoms of PD, pain has been identified as one of ten risk indicators for disease.[27] In agreement with other studies, approximately one-third of the participants experienced pain as an early phenomenon.[5]

Location of pain and type of pain

We found sex differences in the relative locations of pain as described in Figure 2. Results from earlier studies in this field have been contradictory; Marinkovic et al28 found the most affected parts of the body to be upper and lower limbs in about 70% of the studied population. In another study neck and paraspinal cramps were predominant.[29] Our findings showed topographical dominance for lower extremities in males compared with females.

Dystonic cramps in the extremities are a common phenomenon in PD.3 Prominent dystonia affecting the feet and toes is not uncommon, and in special cases paroxysmal exercise-induced dystonia of the feet has been described as having preceded the onset of more classical PD symptoms.[30] These observations are in agreement with our results.

Pharmacological aspects

One-third of our patients reported pain relief in connection with intake of anti-PD medication. High concentrations of striatal dopamine (hyperdopaminergic state) are associated with the “on” phase, and can contribute to the development of some sensory symptoms, such as peak-dose akathisia, although this symptom is usually associated with a hypodopaminergic state.[4] A temporal relation between onset of pain symptoms and medication intake may reveal an association of pain with wearing “off ” periods, such as in early morning dystonia.[29] Adjusting anti-PD medication can be more effective than the administration of analgesics in these cases.

Intraventricular or striatal microinjections of the dopamine agonist apomorphine have been shown to result in a dose-dependent decrease in nociceptive responses, supporting the theory of dopamine as a pain modulator. Mood and anxiety disorders have also been associated with an increased likelihood of developing chronic pain symptoms. This reciprocal relationship may be partially due to shared dysfunctions in central dopamine signaling, which plays a role in these disorders, as well as in pain processing.[31]

Patients' subjective opinions regarding pain treatment

Our study reveals a variety of measures are employed to attain pain relief. About 30% of the patients were prescribed analgesics, most frequently paracetamol and nonsteroidal anti-inflammatory drugs. Surprisingly, many patients took anxiolytics, sedatives and/or antidepressants on a daily basis. The outcome of using analgesics in PD and related disorders has not been reported in any controlled trial, and systematic reports are also lacking.[32] Hence, pain is probably underreported and many neurologists might consider it difficult to treat pain associated with PD and PD-related disorders.

Sleep

Undisturbed sleep was rare in our study. This is consistent with the findings by van Hilten et al,[33] who found more severely disturbed sleep maintenance in the PD group than healthy controls, and that nocturia, pain, stiffness, and problems with turning over in bed were the main causes of frequent awakening in PD patients. Difficulties in remaining asleep were revealed by both the PDSS and the pain evaluation analysis scales in our study. Numbness and "creeping" sensations at night were strongly associated with the maximal VAS scores, which strengthens our assumption that pain is an important cause of sleep disruptions in PD. Frequent awakenings to urinate, and early awakenings with painful posturing of arms and/or legs, were common.

Sleep disturbances can occur at any stage of PD, but they gradually worsen as the disease progresses.[16] Excessive daytime sleepiness and daytime sleep attacks are common features in PD, and are only partially an effect of the type and dosage of anti-PD drug treatment. Sleepwalking and sleep talking, nightmares, sleep terrors, and panic attacks are common,[13] and most certainly contributes to a low HRQoL in this patient group. Painful leg cramps, back pain, limb/facial dystonia, and difficulty in turning over in bed are also common symptoms verified in our study.

Nonpharmacological aspects of sleep treatment

A majority of the study population used sedatives and/or anxiolytics (Table 1). There is a lack of scientific studies of complementary therapies addressing treatment of sleep disturbances. Tactile massage has shown positive effects in relation to pain, sleep, relaxation, energy, and mood in healthy adults in one Swedish study from 2009.[34] Further studies are warranted in this field, as many PD patients currently are using different complementary and alternative medical therapies.[35]

HRQoL

HRQoL decreases with increased age in healthy people.[23] Even when compared to a reference population of the oldest ages, the study patients' HRQoL was

significantly lower in several items, indicating the powerful negative impact of PD symptoms.

Most obvious regarding HRQoL was the importance of sleep interruption, fidgeting in bed, nightmares, painful muscle cramps whilst sleeping, and urinating during the night.

We compared the results of HRQoL in our PD patients with the results of a group of patients (N = 104) with the same country of origin and the same age, who were suffering from sequelae of ischemic stroke.[36] The same instrument, SF-36, was used for both groups. Our study group had lower scores in six out of nine HRQoL items. Major negative differences in the PD group were in the items relating to general health and bodily pain. Both items closely associated to our research questions.

Limitations of the study

Relatively few patients were included. Diff iculties in separating PD-related pain from pain of non-PD origin was harder among the oldest PD patients, who therefore were underrepresented.

Conclusion

Our study has confirmed that chronic PD-related pain is complex in nature. A considerable proportion of the patients had onset of pain many years before diagnosis of PD. Patients with PD-related pain had high scores on the VAS scales. Individual descriptions of pain and experiences with nonpharmacological therapies varied between sexes. A severe impact on sleep with disrupted sleep patterns was seen. Concomitant pharmacotherapy with anxiolytics, analgesics, and antidepressant was common, with significant differences in prescriptions between the sexes. HRQoL in PD patients with chronic pain was significantly lower than in an age-matched healthy reference population. Future studies should address pain-reducing therapies, both pharmacological and nonpharmacological.

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Authors' contributions

CJT, OS, GH, PAF, MC, HS, UL, BB were responsible for the study conception, data collection, and design. OS performed the data analysis. OS was responsible for drafting the manuscript, with support from CJT and JL.

Disclosure

The authors declare no conflicts of interests in this work.

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Paper IV

"Effects of Tactile Touch on Pain, Sleep and Health Related Quality of Life in Parkinson´s Disease with Chronic Pain"
A Randomized, Controlled and Prospective study

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Abstract

Introduction: Parkinson´s Disease (PD) is often associated with chronic PD related pain.
Complementary medicine are widely used but randomized, controlled and prospective studies
of the effects are sparse.
Aims of the study: To compare the effects of Tactile Touch (TT) with Rest to Music (RTM) in PD patients with chronic pain and to describe effects within groups.
Patients and Methods: A 34 week controlled randomized and prospective trial compared the effects of TT with RTM in 45 (29 TT and 16 RTM) patients with PD and chronic pain. The whole body tactile stimulation method was performed for each individual patient by the same therapist for 10 times during the first eight weeks. The RTM group received the same therapy except for the tactile stimulation. Pharmacotherapy was kept unchanged. Participants were assessed at pre- and post-intervention for pain, sleep patterns and Health Related Quality of Life (HRQoL).
Results: Differences between TT and RTM groups were few. Total PDSS significantly improved within the TT but not in the RTM-group. No significant differences between groups were seen in pain parameters, although significant improvements were seen within the TT-group after the intervention period. There were significant improvements within both groups in HRQoL and between groups in the items Physical Role and Social Functioning four weeks after screening.
Conclusions: No significant differences between the TT and RTM groups were seen. Only in single aspects did patients with PD and chronic pain have more benefit more from CAM therapy with TT in combination with RTM.
Key words Pain; Parkinson's disease; Quality of Life; Rest; Sleep; Touch.

Introduction

Parkinson´s disease (PD) is a chronic neurodegenerative disease with typical features for diagnosis. Bradykinesia expressed as slowness of initiation of voluntary movements with progressive reduction in speed and amplitude of repetitive actions, muscular rigidity, 4-6 Hz rest tremor and postural instability are typical [1]. Recent research has found beneficial effects of non-conventional therapies in prevention and deceleration of the progression of Parkinson´s disease [2].
Pain in PD is common and was described by James Parkinson in his classical work "An essay on the shaking palsy" from 1817 [3]. His descriptions told us something about the chronic character of the disease; terms such as "rheumatic pain to the fingers ends" and "rheumatic affection of the deltoid muscle" were used to describe the common component of pain in the disease. During the past decade more focus has been directed towards the frequent presence of Non-Motor Symptoms (NMS) in PD and the challenges involved in their treatment. In a recent study by Kleiner-Fisman, pain is ranked as the major troublesome NMS in PD [4]. The prevalence of PD related pain is estimated at 30 - 40% [5,6]. It is complex regarding pathogenesis, types and locations [7]. From our own projects at three different sites in Sweden, with more than 200 PD

patients (mean age 68 years), a prevalence of chronic pain of 48 - 66% was found, and 36 - 61 % experienced negative effects on sleep [8].

The origin of pain in PD is not quite clear but changes in the central sensory discriminative systems of the basal ganglia, influences on modulations of nociceptive information and sensory gating to higher motor areas as well as lowering of pain thresholds in PD are described [9,10].

Dystonic and muscular cramps in feet, neck, back or stomach are common [11] and sometimes represent an early symptom of the "off-state" in PD. The impact of chronic pain on sleeping patterns as well as on Health Related Quality of Life (HRQoL) is an important field for exploration.

Problems with sleep initiation, maintenance and early arousal are common in PD with an estimated prevalence of 74-98% [12]. Fragmentation of sleep is the most common manifestation and is three times more common than in healthy controls [13]. Nocturia, which affects up to 80% of PD patients [12], and inability to turn over or get out of bed [14], also contribute to disruption of sleep. About 40% of patients with PD consume sleeping pills, significantly more often than in elderly people or patients with other chronic illness [15]. Although the correlations between daytime sleepiness and fatigue are not quite clear, evidence suggests that significant night-time sleep disturbance contributes to excessive daytime sleepiness [16]. Specific effects on sleep in PD are well known [15].The interactions between chronic pain and nightly awakenings are not well studied. Several studies have recognized negative consequences of disturbed sleep, both in patients and their spouses, on HRQoL [17,18,19].

In the absence of definite cures for chronic pain, sleeping disorders and other NMS in the symptom complex of PD, there is an obvious need to maximize symptom relief. A wide range of complementary medicine (CAM) therapies are available and often used by the patients [20], who report positive effects. *Massage therapy* is older than recorded time, and rubbing was one of the primary forms of medicine until the pharmaceutical revolution of the 1940s [21]. However, Tactile Touch (a superficial touch technique) and a majority of other CAM therapies still remain to be evaluated [22] and limitations of studies that have been performed are multiple [23,24].

Comparisons of two groups of active treatments are discussed by Moyer CA et al in a meta analysis of massage therapy research [25, 26]. *Absolute efficacy* is best addressed when treated patients are compared with *untreated* participants and *relative efficacy* is typically investigated by comparison of two treatments.

In the present study the effects on pain, sleep and HRQoL were investigated using the concept of a repetitive whole body tactile stimulation therapy, ”Tactile Touch” (TT), and compared it to an active control group, “Rest To Music” (RTM) alone, in a 34-week follow-up design.

Materials and Methods

Patients with stable and well defined PD who had fulfilled the clinical criteria for diagnosis according to the UK Parkinson’s Disease Society Brain Bank Criteria [1] for more than two years and who had chronic PD related pain were recruited. Chronic pain was defined as the occurrence of PD related pain for three days or more per week during at least three months prior to inclusion in the study.

Exclusion criteria were: severe fluctuations in PD, concurrent existence of active epilepsy, active malignancy, poly-neuropathy or other serious disease of somatic or psychiatric origin that could interfere with the study. Patients with severe abnormalities in blood parameters, electrolytes, liver or renal parameters such as bilirubin >20 mmol/L, s/creatinin >130 mmol/L, sedimentation rate >30 mm, p/glucose > 6.7 mmol/L (fasting) were excluded.

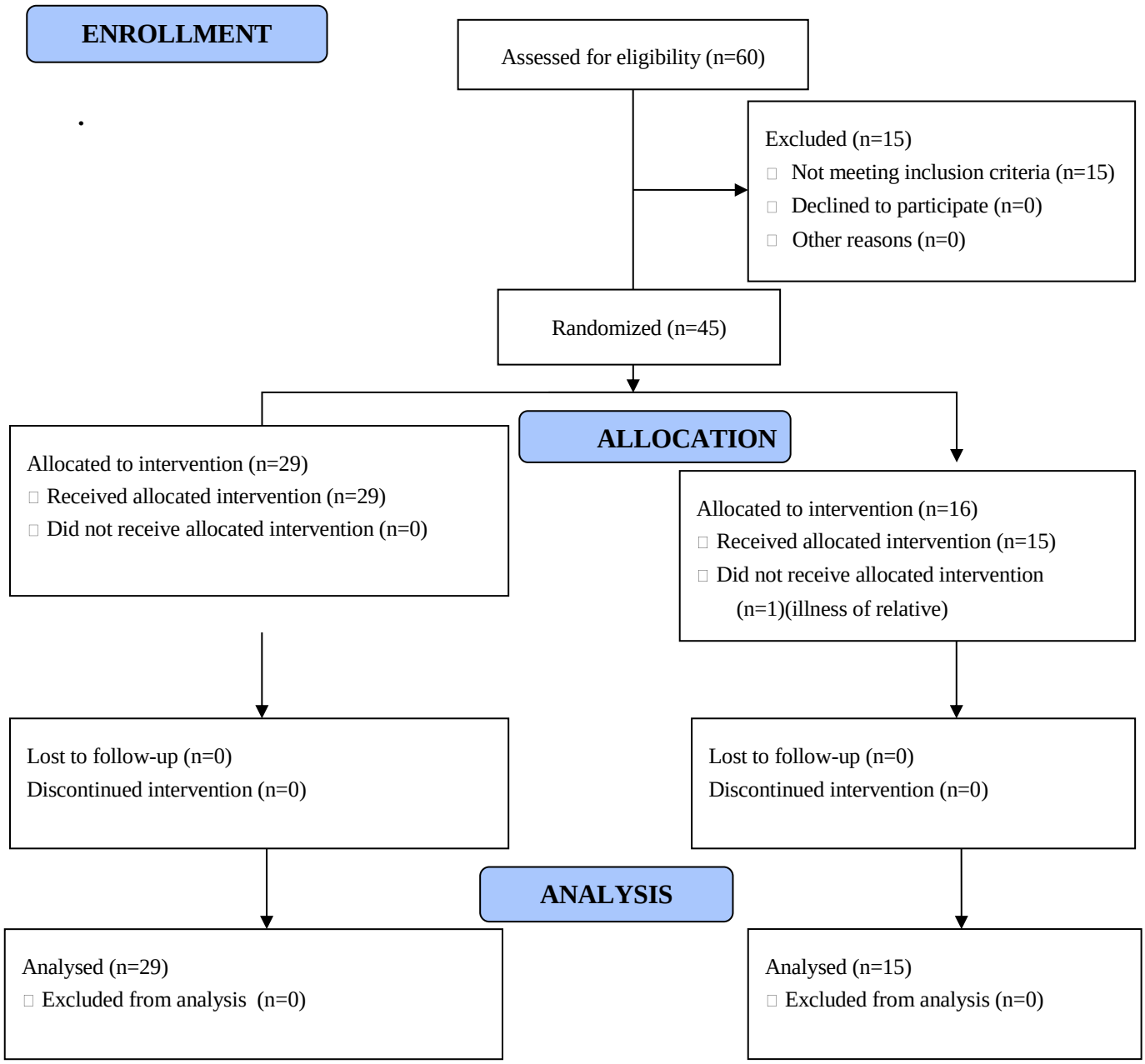
Participation in other studies or receiving other CAM treatments simultaneously was not allowed.

Study design, recruitment and randomization

The study was controlled, prospective and randomized. Participants were recruited from routine health care visits at outpatient departments of three medium-sized city hospitals in Southern Sweden.

All patients gave their written informed consent and were informed that they would either be randomized to TT or RTM. An independent member of our study group was responsible for communicating the computerized randomization course using a lottery random number generator. No blocking or stratification procedures were used. Patients were not asked for their own opinions or expectations concerning the two treatment forms before or during the interventions. Patients were not allowed to modify their antiparkinson medication during the study. A Consort Flow diagram is shown in **Fig.1.**

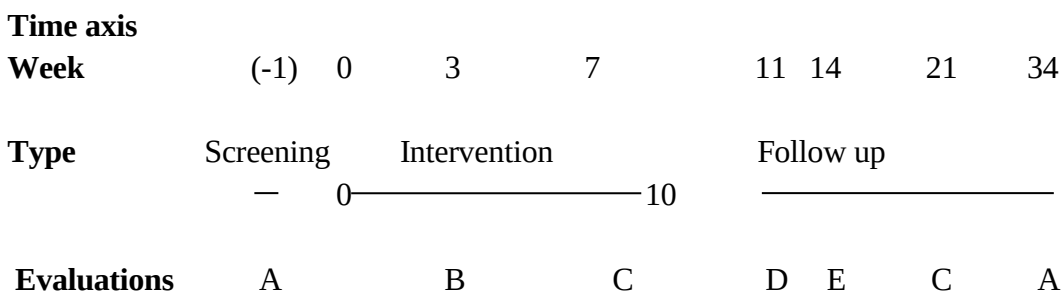
Fig1. CONSORT Flow Diagram



Data collection and analysis

Patients visited the outpatient clinics of their respective hospitals 16 times during the 34-week study period. Two interventions per week were performed during the first three weeks and thereafter one intervention per week. The 10th intervention was performed eight weeks after randomization. The time schedule with assessment types and protocols is shown in **Fig.2**.

Fig.2: Time schedule with assessment types.



Footnote

A week -1,w.34 = VAS^{max}-scale[1], PEA[2], UPDRS I-IV[3], POM vas,emo,phys4, PDSS[5], SF36[6], Drug list[7]

B week3 = VAS^{max}-scale[1], POM vas,emo,phys/before and after 4, PDSS[5], SF36[6], Drug list[7]

C week8and w. 21 = VAS^{max}-scale[1], UPDRS I-IV[3], POM^{vas,emo,phys4}, PDSS[5], SF36[6], Drug list[7], PEA[2](at week 21)

D week11 = VAS^{max}-scale[1], UPDRS (parts I, II, IV)[3], POM^{vas,emo,phys4}, PDSS[5], SF36[6], Drug list[7]

E week14 = VAS^{max}-scale[1], POM^{vas,emo,phys4}, PDSS[5], SF36[6], Drug list[7]

Explanations:

[1] = Visual Analogue Scale, maximal pain for five consecutive days before intervention.

[2] = Patient Evaluation of Pain.

[3] = Unified Parkinson Disease Rating Scale part I-IV.

[4] = Pain-O-Meter.

[5] = Parkinson's Disease Sleep Scale.

[6] = Short Form Health Survey, Swedish ver. 1.

[7] = List of the study participants pharmacological treatment.

All medications were carefully registered in drug lists and supervised on repeated occasions during the study. At each study site a trained specialist in movement disorders completed the Unified Parkinson´s Disease Rating Scale (UPDRS), parts I-IV, version 3.0 [27] and the modified Hoehn and Yahr scale [28].

Each patient was furnished with his/her own evaluation forms, SF-36, Swedish version 1.0 [29], and on three occasions completed a self-report "Patient Evaluation Analysis" (PEA). This included short, free-text responses and multiple choice questions with different aspects of pain experiences, effects of other treatments, both pharmacological and complementary, their own thoughts on the nature of experienced pain, physical and emotional restraints, and temporal and anatomical aspects. Study participants filled in a VAS-scale (0 - 10 cm) [30] marking the maximal pain for each day during five consecutive days before intervention and follow-up (**Fig2**). Instructions about methods for self-reporting pain scales were given by professionals in the study group before and during the study. The Pain-O-Meter [31] completed the self-reports and was used on seven occasions during the intervention and follow-up. POM^{VAS}, a 10 cm visual analogue scale with a moveable marker for reporting pain was completed with an affective word descriptor (WDS). A list of 11 sensory and 12 affective words was transformed to figures; POM^{emo}, grading emotional words for pain ranging from worrying (=1) to terrific (= 5), and physical expressions of pain, POM^{phys}, ranging from soaring, (=1) to tearing, (=5).

For collection of data and prior to data analysis, data were transformed electronically to Microsoft Office Access©2007.

Intervention

TT and RTM

The whole body tactile stimulation method was performed for each individual patient by the same therapist at the same time of the day, mostly in the mornings. RTM was performed under the same circumstances except for the tactile stimulation. The room was kept at a comfortable temperature (22^0 /72^0 - 24^0/75^0 ; Celsius/ Fahrenheit). The interventions lasted for about one hour (mean; range: 52; 40 – 79 min.). Ten interventions were given during a period of eight weeks. During TT, a specific oil was used, **"**Fibro oil®" (Crearome AB, Gamleby, Sweden), mixed with Virgin oil comprising one third of the total volume. A lavender aroma filled the room during the sessions in both groups. The music was identical for TT and RTM**: "**Music for well-being II – Letting go of stress", LC6607 Fönix Music®, Sweden. All patients were asked to indicate the most comfortable volume before the intervention.

TT was performed following detailed instructions, written in 2003, by licensed massage therapists Mrs. Laila Robertson and Mrs. Birgitta Larsson; a short description is added in the **appendix**. They certified the competence of the other five participating local massage therapists.

Statistics

Descriptive statistics were generated and STATISTICA versions 8.0 and 10.0 (Statsoft Inc., Tulsa, OK) and SPSS version 18.0 (SPSS Inc., Chicago, IL) were used for the statistical evaluations. As the majority of the analyzed variables were of the ordinal data type we used medians with percentiles and used nonparametric tests for comparisons. The Mann–Whitney U test, the Kruskal-Wallis test, the Chi-Square test, the Wilcoxon paired signed-rank test and Spearman's rank correlation test were used. For the results of the SF 36 questionnaire, evaluations of validity, reliability and item

correlations were performed by the Quality Metric Health Outcomes$^{TM\ Scoring}$ Software 4.0, and the results were statistically analyzed by the MW-U test and Repeated measures ANOVA, where appropriate. The Bonferroni corrections for multiple testing were used. A power analysis was performed in which a total of 40 patients was calculated to have 80% power to detect a significant ($p< 0.05$) difference between two groups.

Ethics

The study was approved by the Ethics Committees at the University of Gothenburg (Ö 762-03) and the University of Linkoping (D 03-673), Sweden.

Results

Our study included 45 participants randomized to TT (n=29) or RTM (n=16). Follow-up rates were 100% and 93%, respectively. Clinical and demographic characteristics at baseline were similar in both groups as shown in **Table 1**. Patients' own experiences from other non-pharmacological interventions differed between groups as shown in **Table 2**.

	Sex (n)	**Age[a]**	**BMI[b]**	**H&Y[b,c]**	**UPDRS (I-IV)[b,d]**
"Tactile Touch "	Male (10) Female (19)	50-78 60-79	26.6 (24.1/37.4) 25.0 (20.2/35.9)	1.5 (1.0/2.5) 2.5 (1.5/3.0)	31.5 (24.1/46.4) 39.0 (27.5/61.2)
"Rest to Music "	Male (6) Female (9)	50-74 50-74	27.0 (23.6/31.5) 24.2 (17.8/31.2)	3.0 (1.5/3.0) 2.0 (1.0/4.0)	42.5 (32.0/57.0) 39.0 (21.0/78.0)

Table 1. Clinical and demographic characteristics of the two PD populations.

[a] =Values are given as range , [b]= medians/10th and 90th percentiles, [c] = Hoehn and Yahr (0-4), [d] = Unified Parkinson´s Disease Rating Scale (0-147points). There were no statistical differences between groups or gender, statistical method; Mann-Whitney U-test.

Pharmacological Treatment

Forty-two of forty-four patients were treated with levodopa in a total dose of (median, mean, range) 500; 534; 25–1200 mg/day. Additive treatments with dopamine agonists were recalculated using formulas for levodopa equivalent doses [32.33]. There were no

significant differences between the groups. The pharmacological treatment for PD was essentially unchanged and only single extra doses of anti-PD treatment were taken during the study.
The time span between intake of anti-PD medication in the morning and the time point for TT / RTM was controlled at the first and eighth interventions; (mean; range. 121; (10-293) minutes). Analgesics and antidepressants were more commonly used among females, but without significant differences between groups or genders, see **Table 2**. Two of three patients reported pain relief with analgesics and half of the patients reported pain relief with anti-Parkinson medication. Paracetamol was the most frequently used analgesic.

Type of intervention	Gender (n)	Analgesics	Antidepressants(SSRI,SNRI and tricyclics)	Medication for insomnia	Antiepileptics[b]	Anxiolytics	Experience of former non pharmacological therapies	Missing
TT (n=29)	Females (19)	6	5	4	1	17	6	4
	Males (10)	1	1	0	0	10	2	2
RTM (n=16)	Females (9)	3	1	3	0	6	7	2
	Males (6)	2	1	1	0	6	2	2
p-value[a]		0.72	0.52	0.44	0.26	0.66	0.19	0.036*	0.46

Table 2 Concomitant therapy.

[a]p-value between TT / RTM. [b] = indication for use was not epilepsy. *Statistically significant difference ($p < 0.05$).

Pain at screening, effects on pain after interventions

Maximal pain on the five consecutive days before screening ($Pain^{max/5d}$) was: (**median**; (quartile percentiles)) **6.5**; (3.8 / 7.7) for the TT group and **6.6**; (4.5 / 7.4) for the RTM group; comparative data at different time points of the study are shown in **Fig. 3**.

The Pain-O-Meter was used before/after intervention at week 3. No significant differences between groups were seen regarding (POM^{vas}) (p-value 0.174), $POM^{emo\ before}$/ $POM^{emo\ after}$ (p-value 0.178), or $POM^{phys\ before}$ / $POM^{phys\ after}$ (p-value 0.086).

Fig.3

Comparative effects of TT and RTM on pain

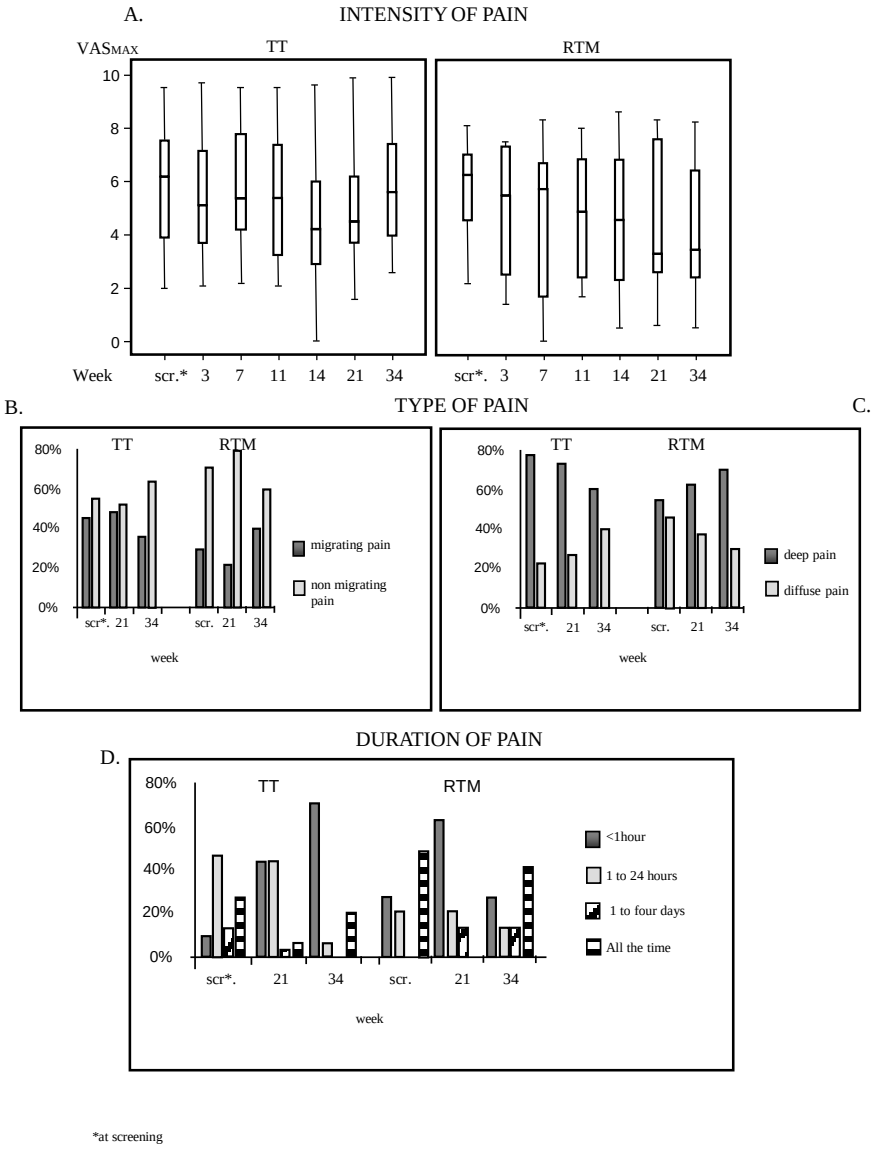


Fig. 3: Comparative Effects of Tactile Touch / Rest To Music on pain.

Footnote:
Comparative Effects of Tactile Touch / Rest To Music on pain.
A: Maximal pain (max of max) for five consecutive days before intervention and follow-up.
B: Switch from migrating to non-migrating pain (NS between groups)
C: Switch from deep pain to diffuse pain (NS between groups).
D: Duration of pain attacks (NS between groups)
[1]= B – D percentage of answers at screening and follow-up at week 21 and week 34.

Sleep patterns: Differences between groups were not significant. The results with distributions are shown in **Table 3.** The total scores for PDSS covered 24 patients in the TT group and 14 in the RTM group. A trend, but not a statistically significant difference, was seen between groups (p-value = 0.082) concerning PDSS total scores from screening to week 3.

Timepoint PDSS item	TT [1]	RTM [1]	p-value [2]
PDSS3 tot.scr	95.3;(75.2/111.5)	92.9(73.0/103.9)	0.056
PDSS tot. w.3	104.8;(84.8/115.8)	86.9(78.6/99.4)	
PDSS tot w.7	104.8;(85.8/119.4)	92.9;(81.4/103.5)	
PDSS totw.21	94.6;(74.0/114.6)	91.4;(82.0/95.2)	
PDSS totw.34	104.3;(82.2/121.1)	89.6;(81.7/95.8)	
Quality of sleep scr	6.3;(4.8/7.8)	6.7;(4.0/8.3)	0.289
Quality of sleep w.3	6.7;(6.0/7.9)	7.9;(5.4/3.7)	
Quality of sleep w.7	7.0;(4.6/7.9)	5.8(3.2/7.5)	
Quality of sleep w.21	6.6;(4.5/8.2)	5.1;(2.8/7.0)	
Quality of sleep w.34	7.1;(5.2/8.6)	6.0;(3.2/7.2)	
No. early awakenings scr	7.2;(4.3/8.9)	4.5;(2.0/7.7)	0.035*
No. early awakenings w.3	8.6;(6.3/9.2)	4.6;(2.6/8.2)	
No. early awakenings w.7	8.1;(4.9/9.2)	4.4;(2.5/8.0)	
No. early awakenings w.21	8.3;(5.7/9.2)	4.4;(2.5/7.4)	
No. early awakenings w.34	8.2;(5.6/9.4)	5.7;(2.0/9.2)	
Troblesome drems.scr	6.4;(2.2/9.1)	7.4;(3.3/8.0)	0.021*
Troblesome drems.w.3	8.0;(4.8/9.3)	6.2;(3.3/7.5)	
Troblesome drems.w.7	7.6;(4.0/9.2)	7.0;(5.0/8.5)	
Troblesome drems.w.21	7.0;(3.3/9.4)	7.2;(3.4/8.5)	
Troblesome drems.w.34	8.0;(5.5/9.0)	7.5;(5.0/8.5)	
Restlessness at nighttime.scr	6.3;(3.2/8.9)	6.8;(5.0/8.4)	0.171
Restlessness at nighttime.w.3	7.9;(6.2/8.8)	7.9;(4.8/8.5)	
Restlessness at nighttime.w.7	7.9;(5.2/9.0)	7.0;(5.3/8.0)	
Restlessness at nighttime.w.21	7.1;(4.6/9.0)	8.0;(5.2/8.9)	
Restlessness at nighttime.w.34	8.0;(6.2/8.7)	7.0;(4.5/8.5)	
Unvoluntary nightly movements.scr	7.0;(2.4/8.8)	7.0;(2.0/8.7)	0.053
Unvoluntary nightly movements.w.3	7.0;(4.4/9.0)	5.0;(2.0/7.3)	
Unvoluntary nightly movements.w.7	8.0;(5.1/9.0)	5.4;(2.0/7.2)	
Unvoluntary nightly movements.w.21	7.2;(4.3/8.3)	5.5;(4.0/7.8)	
Unvoluntary nightly movementsw.34	8.0;(4.5/9.1)	6.6;(3.0/8.0)	

Table 3: Sleep patterns, total PDSS scores and individual items. Change between groups.

[1]=Type of treatment; TT= Tactile Touch, RTM= Rest To Music; median ;(25/75 percentiles). [2] =Comparison of change from screening to week 3 between groups. [3] PDSS=Parkinson´s Disease Sleep Scale; visual analogue scale, 0= worst, 10=best.

Long-term effects (to follow-up at week 34).
No statistically significant differences between the two groups were seen regarding pain, sleep or HRQoL parameters.

Short term effects *within* groups
The TT group had a more prominent decrease of $pain^{max/5d.}$ in the short term follow up (after 6 and 10 interventions, respectively) compared to the RTM group, Fig **3.**
Regarding the results of the Pain-O-Meter (POM^{vas}), there were significant within group effects from screening to week 3 after intervention: (TT^{scr} / RTM^{scr} (**median**; quartile percentiles) = **2.8**; 0.3 / 5.5 **/ 4.0**; 1.8 / 5.2, TT^{after} / RTM^{after} = **0.0**; 0.0 / 1.0 / **0.4**; 0.0/ 2.0 .P-values 0.007 / 0.016, respectively.
In the TT group the emotional and physical expressions of pain ($POM^{emo\ before}$/ $POM^{emo\ after,}$ $POM^{phys\ before}$ / $POM^{phys\ after}$) from screening to week 3 reduced significantly (**median**; quartile percentiles): **3.0**; 0.0 / 3.5 / **0**; 0.0 / 3.0 and **2.0**; 0.0 / 3.0 / **0**; 0.0/ 2.0. P-values = 0.03 / 0.027 respectively. This was however not observed in the RTM group ($POM^{emo\ before}$/ $POM^{emo\ after}$ and $POM^{phys\ before}$ / $POM^{phys\ after}$): **3.0**; 0.0/ 3.0 / **3.0**; 0.0/ 3.0 and **2.0**; /0.0/ 2.0 / **2.0**; 1.0/ 2.0. (P-values 0.178/ 0.414, respectively).
Using methods for comparing paired ordinal data [32] for POM^{emo} and POM^{phys}, the effects of pain expressions from screening to week 3 are illustrated in **Fig. 4**.

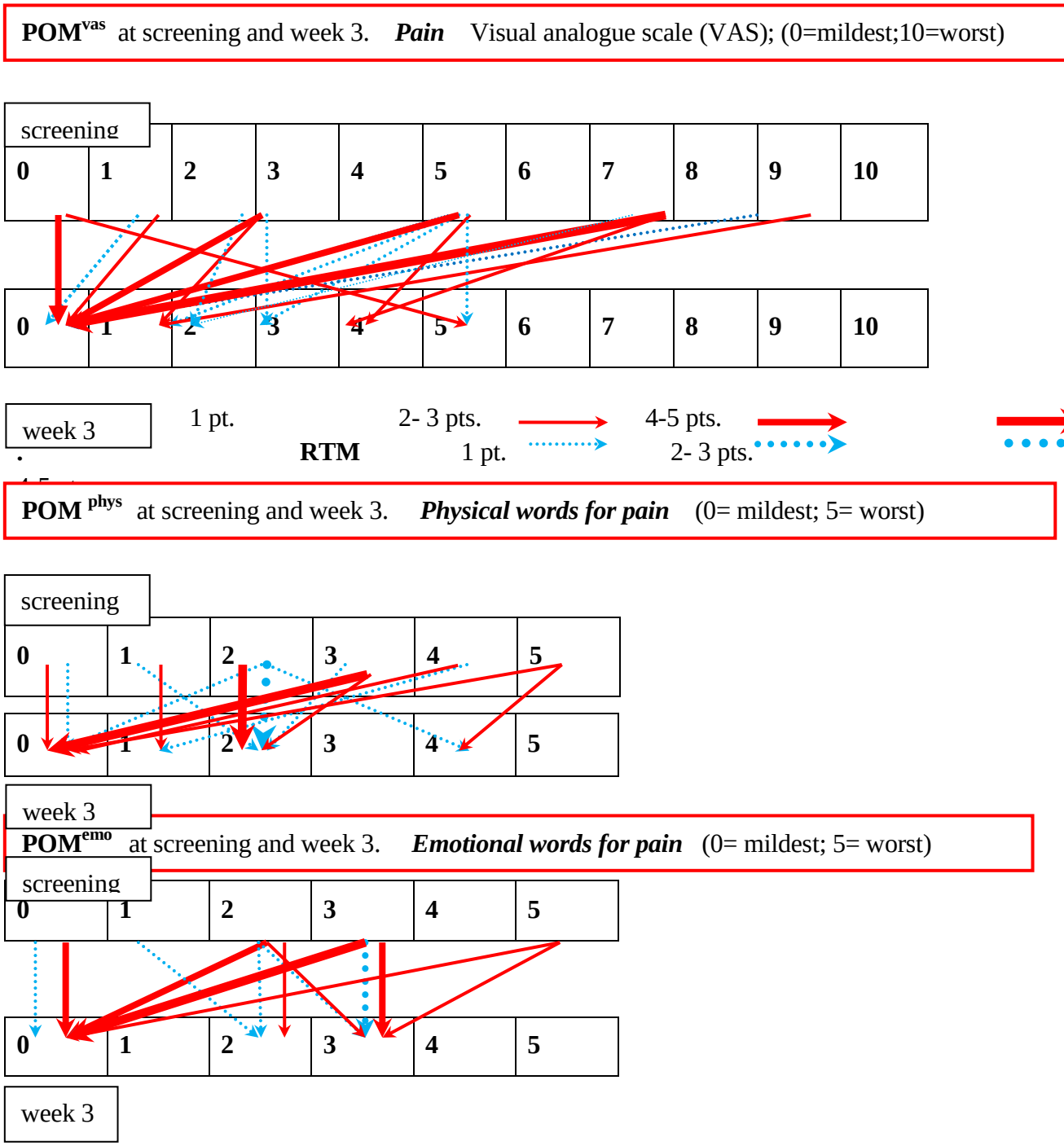


Fig. 4: Improvements within groups (TT/RTM), for paired ordinal data of POM^{vas}, POM^{phys} and POM^{emo} from screening to week 3 after six interventions.

Within the TT group there was significant improvement in the frequency of early awakenings (p-value = 0.015) from screening to week 3, even when we adjusted for the risks with multiple comparisons, which was not seen in the RTM group. The total PDSS scores were significantly better (p-value 0.016) within the TT group from screening to week 3, without similar effects within the RTM-group (p-value 0.78), although the difference between groups did not reach significance.

Long-term effects within groups (to follow-up at weeks 11, 21 and 34)
In total (both groups) ,there was a significant decrease between maximal pain during five days before screening ($pain^{max/5d.scr.}$) and maximal pain during five days before the

last follow-up at week 34 ($pain^{max/5d.week34}$), (**median**; quartile percentiles): **6.6**; 4.5/ 7.4 / **4.8**; 3.0/ 7.0. (P-value = 0.05).
At screening 41% of TT participants and 23% of RTM participants suffered from restless legs. A transient non-significant effect was seen in the TT group at week 21 (from 41 to 34%).
Both TT and RTM had positive effects on pain in the time window from screening to week 21. An important finding was that the duration of pain decreased in both groups, especially for those reporting pain "all the time" at screening. At the final follow-up at week 34 these positive effects could partially be identified in the TT group. A minor non-significant switch from deep to diffuse pain was seen in both groups (**Fig.4).**
After 11 weeks the PDSS total scores were still significantly improved within the TT group.
Participants in the TT group reported an increase in undisturbed sleep from two to three hours from screening to week 21. No effects were seen on daytime tiredness, difficulties in falling asleep or the frequency of nightly urination, painful cramps or nightly numbness. In the Patient Evaluation Analysis (PEA) at screening and week 21 the participants registered a decrease of one nightly awakening every second night in both the TT and the RTM groups.
Significant effects on *HRQoL* were seen within both groups (p-values were 0.006 / 0.012, RP / SF respectively).
The mean results with distributions are shown in **Fig 5.** As mean values are presented for the reference population, this parametric presentation was chosen. The study population in general had a low HRQoL compared to a Swedish age-matched population (N= 3100), 45 - > 75 years of age. Mental health (MH), Role- Emotional (RE) and Vitality (VT) are almost in accord with the reference population. However, the study groups scored low on Role- Physical (RP) and General Health (GH).
Participants on antidepressants scored worse than those without antidepressants on items concerning RP, Mental Health (MH) and Social Functioning (SF) at screening and during follow-up. For total scores on UPDRS I – IV, more than 47 scored worse in RP and SF but not in MH at screening and during follow up.
HRQoL: From screening to week 8 there were significant differences between groups in the item RP (physical role), and also when adjusted for the Bonferroni effect (p-value = 0.048). A trend towards a better outcome for SF (social function) in favor of the TT group compared to the RTM group was seen, for details see **Fig. 5**.

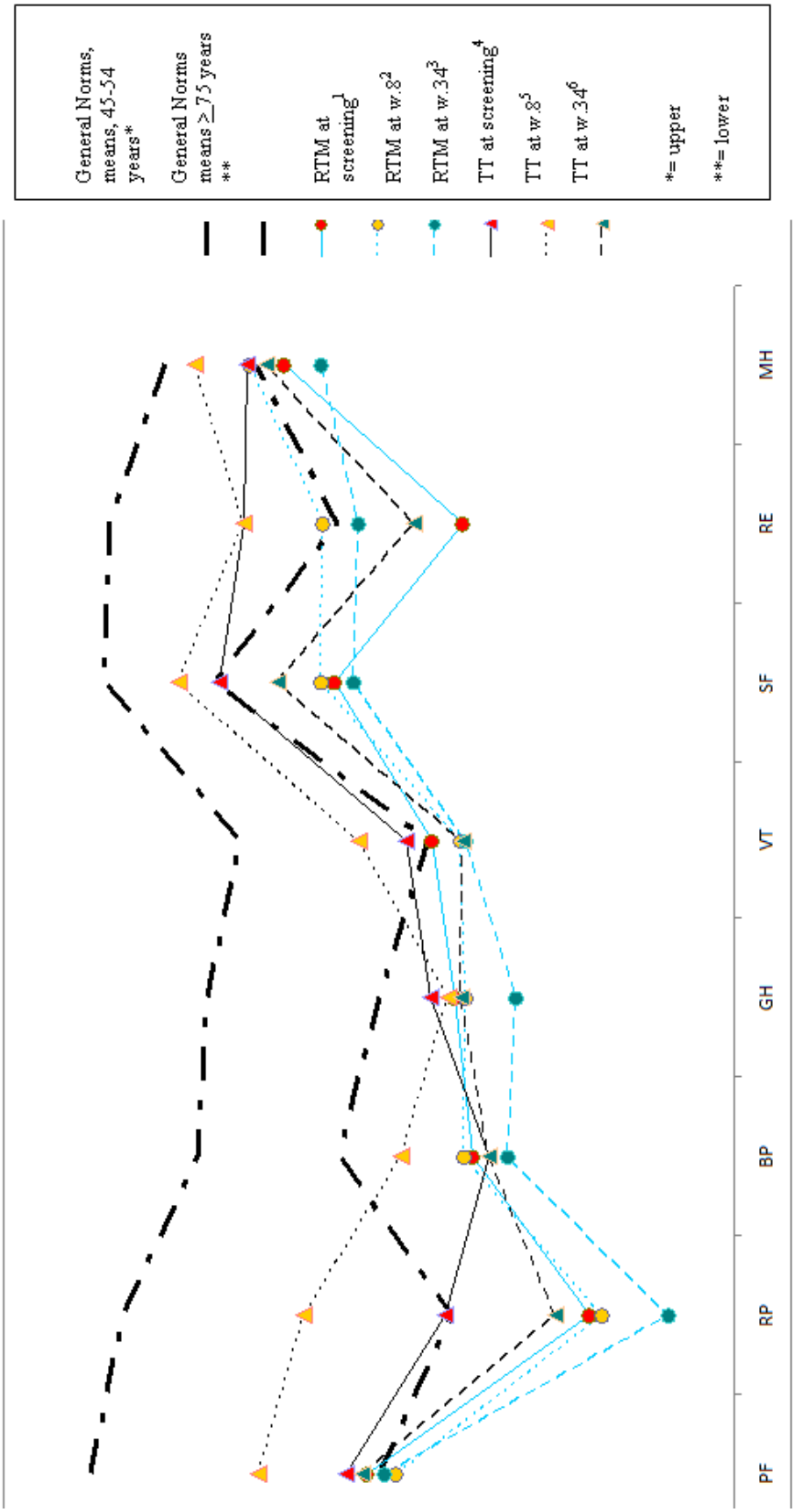


Fig 5: Effects on SF-36 parameters of TT/RTM during intervention and after 34 weeks followup compared to General Norms of Swedish population, 45 - > 75 years of age.

Legends to figure:

Fig 5:SF-36 (Swedish ver.1). Mean values during intervention and follow up. Comparison to an age-matched Swedish reference group.

PF = Physical Functioning, RP = Role-Physical, BP = Bodily Pain, GH = General Health, VT = Vitality, SF = Social Functioning, RE = Role-Emotional, MH = Mental Health

Standard Deviations (SD):

SD^{1} (PF; RP; BP; GH; VT; SF; RE; ME ,respectively) = 22.0; 41.0; 14.5; 13.8; 19.2; 26.7; 44.8; 21.2.

SD^{2} (PF; RP; BP; GH; VT; SF; RE; ME ,respectively) = 17.3; 29.1; 19.4; 13.5; 15.1; 18.3; 45.2; 15.0.

SD^{3} (PF; RP; BP; GH; VT; SF; RE; ME ,respectively) = 16.6; 32.0; 20.0; 15.5; 15.1; 16.1; 44.5; 17.5.

SD^{4} (PF; RP; BP; GH; VT; SF; RE; ME ,respectively) = 20.4; 37.5; 16.4; 17.5; 20.2; 22.0; 32.2; 18.9.

SD^{5} (PF; RP; BP; GH; VT; SF; RE; ME ,respectively) = 20.2; 29.5; 14.4; 16.1; 18.5; 18.2; 36.8; 17.4.

SD^{6} (PF; RP; BP; GH; VT; SF; RE; ME ,respectively) = 23.6; 38.4; 16.0; 15.9; 19.8; 21.3; 40.5; 16.9.

Discussion

CAM therapies are frequently used in chronic illness. Caregivers and patients are in urgent need of safe, evidence based therapies to relieve symptoms with known negative impact on HrQoL. Although some studies on the effects of massage therapy, and even some reviews, have been published there are conflicting results. However, to our knowledge our study is the only RCT on PD patients with chronic pain that has contributed knowledge concerning massage therapy.

In this study no significant benefits favoring TT over RTM were found. As mentioned above, Moyer and Wampold [25, 26] emphasize the challenges involved when comparing two "active" groups. Effects can be expected in both treatment arms, which makes it more difficult to prove differences between groups. The terms *relative* and *absolute* results are introduced, *absolute* referring to comparisons with "no treatment at all" or "wait-list" conditions. As the authors stress that this has not been made sufficiently explicit in MT research, the results are presented with a subanalysis of between group results and within group results. The **only** difference between our groups was the tactile touch component.

Differences between groups regarding different aspects of pain were, however, not significant. The positive effects shown in both groups were most pronounced during the first 21 weeks of the study and the group reporting pain “all the time” at screening experienced positive effects of TT and of RTM. It was only in the TT group that this

effect partially remained at the final follow-up at week 34. This and the more salient shift from deep to diffuse pain in the TT group is quite probably an indication of a more prominent effect of TT, although this is not a statistically significant difference between groups.

Our study confirms the importance of breaking vicious circles. Positive effects on sleep are important results of CAM therapies in PD, where this problem is prominent. A marked trend in favor of TT contra RTM was seen, and *within* the TT group a significant positive effect on sleep was seen. Nighttime restlessness and early awakenings favored TT when assessing the first eight weeks. Fewer awakenings, prolonged undisturbed sleep, less troublesome dreams and less involuntary nightly movements are all important findings that have not been well-studied before.

HRQoL was measured repeatedly during the study using the SF-36, Swedish version 1. This has been evaluated in 8000 healthy Swedish persons (mean age 42.7, range 15-93 years) [29]. Our results were in line with and confirmed the results from other studies showing that idiopathic PD has a major negative impact on HRQoL [35]. During the study, a significant increase in HRQoL was seen in physical roles (RP) in favor of TT compared to RTM. Only a trend was seen in social function (SF) in favor of TT after adjustments for multiple comparison effects. SF and RP are important parts of everyday life. When chronic disease is expressed in PD symptoms with concomitant chronic pain, situations like climbing stairs and carrying bags of food, as well as the impact on family life and on meeting relatives and friends, are probable targets for positive effects of repetitive CAM therapy. The study was performed to investigate differences between TT and RTM. However, as significant improvements *within* the TT and the RTM groups were seen in all items of HRQoL except emotional role (RE), it is of importance to consider the relative effects when interpreting the apparently negative results when comparing *between* group effects.

Massage therapy effects in other studies

Despite the importance of well-being derived from touch, and a continuously growing literature in this field, there is a need for more empirical research on this topic. Mueller-Oerling published a paper in 2004 on 32 depressed patients who received slow-stroke massage or relaxation-perception [36]. They found stronger effects in the massage group in some modalities such as depression and restlessness.

In a review article by Essic et al in 2010 [37] the question was raised as to whether the body surface can be mapped affectively in a meaningful manner and whether pleasantness-to-touch can be viewed as a one-dimensional construct. Materials, sites of the body, velocities, forces and the subject's sex were studied. Olausson et al have shown the existence of a distinct type of unmyelinated, low-threshold mechanoreceptive unit existing in the hairy but not the glabrous skin of humans and other mammals, so called CT-afferents [38]. The group hypothesizes that these CT afferents have a particular potential to elicit pleasant subjective experience alongside hormonal and autonomic responses during gentle touch between individuals.

Rest to Music

Music (MT) as CAM therapy is well known. The use of music as an adjuvant to the control of pain, especially during medical procedures, is described in a review article by Bernatzky [39]. In PD, Pacchetti et al studied another form of MT; the effects of choral singing, voice exercise, rhythmic and free body movements [40]. They found a significant overall effect on bradykinesia as measured by the UPDRS. Our study did not show any significant improvements in UPDRS (I-IV) in the RTM or the TT group. Effects of Rest to Music in PD have not been well studied before.

The combined use of peaceful music and a mild lavender fragrance in the room during intervention was the same in both the TT and the RTM groups. To avoid bias in terms of differences in aroma in the room, the "Fibro oil" used by the massage therapist during tactile touch was diluted one to three with fragrance-free oil. The effects of the presence of the massage therapist in the room during TT were part of the concept studied. As the welcoming and closing procedures were also identical in both groups and performed by the same therapists, the differences in the study are confined to the tactile touch component.

Other aspects

Prospective randomized trials in CAM basic care, as in our study, are rare, and the optimization of basic care is still a matter of dispute. Significant differences between TT and RTM were hard to prove in this study.

As the concept of RTM and TT also includes pleasant aromas and music in the room, it is of importance to comment on the possible effects of aroma therapy (AT) and music therapy (MT) in general. Fellowes et al found short-term benefits for psychological well-being, with the effect on anxiety supported by limited evidence when studying eight RCTs (357 patients) with AT [41]. Evidence was contradictory as to whether AT enhanced the effects of massage.

MT has helped improve and, at times, restore many functions, including motor capacities in PD [39].

The majority of participants in this study expressed a wish to continue the interventions. Effects over time are still not clear; the intervention period was short in comparison to the follow up period. Our hypothesis is that sensitization of CT-fibers, hormonal and behavioral effects and effects on pain inhibition need a still more powerful and extended period of intervention with TT. Our results show positive effects in both TT and RTM, and the only difference between groups was the tactile stimulus .Stronger effects were seen in few aspects in the TT group. The studied population was large enough to meet power criteria.

Limitations of the study

Relatively few patients were included. The oldest PD patients were excluded due to difficulties in carrying out the extensive program, and the risk of falling or balance problems in conjunction with the interventions on the massage table. Distribution of participants between TT and RTM, which was determined by a lottery random number generator, became somewhat distorted. When theoretically doubling identical outcome measures from RTM (N=28 in each group), differences between groups increased and became significant between groups in more outcome measures (Type II error). However, as randomization was computerized and blinded, no influence on the

distribution of patients in the TT / RTM groups was possible. Only one significant difference between groups was seen at screening. More patients in the RTM group had experience from earlier CAM therapies. The limiting effects of this fact on interpreting the study results are difficult to assess. It could be that expectations of positive effects of RTM were already increased at the start. If so, this could interfere with the early positive effects also seen in the RTM group.

Conclusions
No significant differences between the TT and RTM groups were seen. The short-term positive "within group" effects were prominent. Only in single aspects did patients with PD and chronic pain have more benefit more from CAM therapy with TT in combination with RTM compared to only RTM. There was an increase in both the TT and RTM groups in almost all items in HRQoL measured with the SF-36. No effects at the follow-up after 34 weeks were seen. The methods were safe and well tolerated by the participants.

Authors: All research was done by the authors.

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Conflict of interest
None

Acknowledgments
Authors´ contributions
CJT, OS, GH, PAF, MC, HS, UL, BB were responsible for the study conception, data collection and design. OS, CJT and Salmir Nasic, statistician, performed the data analysis. OS, JL and CJT were responsible for drafting the manuscript.

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Legends to Tables and Figures.

Fig. 1: CONSORT Flow diagram
Fig. 2: Time schedule with assessment types.
Fig. 3: Comparative Effects of Tactile Touch / Rest To Music on pain.
Footnote:
Comparative Effects of Tactile Touch / Rest To Music on pain.
A: Maximal pain (max of max) for five consecutive days before intervention and follow-up.
B: Switch from migrating to non-migrating pain (NS between groups)
C: Switch from deep pain to diffuse pain (NS between groups).
D: Duration of pain attacks (NS between groups)
[1]= B – D percentage of answers at screening and follow-up at week 21 and week 34.

Fig. 4: Improvements within groups (TT/RTM), for paired ordinal data of POM^{vas} , POM^{phys} and POM^{emo} from screening to week 3 after six interventions.

Fig 5: SF-36 (Swedish ver.1). Mean values during intervention and follow-up. Comparison with an age-matched Swedish reference group.
Foot note:
PF = Physical Functioning, RP = Role-Physical, BP = Bodily Pain, GH = General Health, VT = Vitality, SF = Social Functioning, RE = Role-Emotional, MH = Mental Health
Standard Deviations (SD)
SD^1 (PF; RP; BP; GH; VT; SF; RE; ME) = 22.0; 41.0; 14.5; 13.8; 19.2; 26.7; 44.8; 21.2, respectively.
SD^2 (PF; RP; BP; GH; VT; SF; RE; ME) = 17.3; 29.1; 19.4; 13.5; 15.1; 18.3; 45.2; 15.0, respectively.

SD [3](PF; RP; BP; GH; VT; SF; RE; ME) = 16.6; 32.0; 20.0; 15.5; 15.1; 16.1; 44.5; 17.5, respectively.
SD [4] (PF; RP; BP; GH; VT; SF; RE; ME) = 20.4; 37.5; 16.4; 17.5; 20.2; 22.0; 32.2; 18.9, respectively.
SD [5] (PF; RP; BP; GH; VT; SF; RE; ME) = 20.2; 29.5; 14.4; 16.1; 18.5; 18.2; 36.8; 17.4, respectively.
SD [6] (PF; RP; BP; GH; VT; SF; RE; ME) = 23.6; 38.4; 16.0; 15.9; 19.8; 21.3; 40.5; 16.9, respectively.

Table 1: Clinical and demographic **c**haracteristics of the two PD populations.
Table 2: Concomitant therapy.
Table 3: Sleep patterns, total PDSS scores and individual items. Change between groups.