Alla cortese attenzione della commissione scientifica della Fondazione NEURECA Onlus – Milano

Roma 17 ottobre 2009

Rendiconto finale sull’attività di ricerca svolta


Il manoscritto reca nei ringraziamenti la dicitura “A.F. is partially funded by NEURECA onlus – Milan.”.

Lo studio è stato selezionato come comunicazione orale presso il prossimo congresso della Società Italiana di Neurologia (Padova, novembre p.v.)

È stata conclusa l’analisi della seconda parte del progetto, volta ad indagare l’effetto della modulazione estrinseca dell’asimmetria sullo schema del passo nei pazienti con malattia di Parkinson. Tale sottoprogetto, anch’esso svolto in collaborazione con i colleghi dell’Università di Kiel (Germania), si è avvalso dell’uso del paradigma sperimentale “spli-belt” (treadmil con doppio nastro con velocità differente per ciascun arto inferiore).

I risultati di questo ultimo (già illustrati con il precedente rendiconto) sono oggetto di un manoscritto in procinto di essere sottomesso presso un giornale scientifico.
internazionale. Si allega in allegato B il poster recentemente presentato presso la LIMPE di Genova.

Infine, i dati cinematici registrati durante le analisi del cammino sono stati analizzati in collaborazione con l’”Institute of Neuroinformatics” di Zurigo, Svizzera (Jan Bartussek) e il Max-Planck Institut fuer Physik komplexer Systeme, Dresden, (Elena Shchekinova) con l'intento di elaborare un modello matematico che “predica” l'inizio del singolo episodio di freezing e colga le differenze intrinseche fra festinazione senza freezing e destinazione con successivo freezing. I risultati sono esposti in allegato C.

I risultati dei suddetti progetti sono oggetto di presentazioni orali nel corso di lecture su invito in Italia e all’estero (allegati D e E). In ogni presentazione sarà riconosciuto a Neureca il ruolo di finanziatore del progetto.

Infine, fra le possibilità offertemi dalla borsa NEURECA, c’è stata anche la possibilità di collaborare con colleghi stranieri a progetti paralleli. Pertanto, un recente manoscritto in corso di stampa presso Molecular Psychiatry (Fasano and Petrovic, “Insights into Pathophysiology of Punding Reveal Possible Treatment Strategies”) (allegato F) recherà il ringraziamento a NEURECA come promotore di parte del progetto.

A chiusura di questo anno con NEURECA, colgo l’occasione per ringraziare ancora una volta la commissione scientifica tutta per la fiducia accordatami e la Sig.ra Linda Toscano per l’assidua assistenza.

Con cordialità ed affetto.

Dott. Alfonso Fasano
ALLEGATO A
From: brain@medschl.cam.ac.uk
To: alfonso.fasano@rm.unicatt.it
CC:
Subject: Brain - Decision on Manuscript ID BRAIN-2009-01066

Body:

Modulation of Gait Coordination by Subthalamic Stimulation Improves Freezing Of Gait

Dear Dr Fasano

We are writing to let you know the editorial decision on your manuscript. On the basis of the referees' reports and our own assessments, we do not feel that the present version is suitable for publication but would be willing to receive a revised manuscript.

The referees' comments are attached and we hope these will guide you in reworking the manuscript. There is certainly enthusiasm for your manuscript, but there are a number of issues that must be successfully dealt with. The phase coordination index may not have been calculated correctly, and, in any event needs a clearer explanation. Treadmill walking is not the same as free field walking, and this issue needs more discussion; how do the results here really illuminate FOG in real conditions. There are many other points that need clarification.

You should pay careful attention to each of the points raised before resubmitting. It is likely that your revised paper will be returned to one or more referees. Sometimes we invite an expert who was not part of the initial review process to comment on a revision. This may mean that criticisms not mentioned as part of the initial review, and matters arising from the revisions themselves, are identified at this stage in the editorial process. It is important to remember that factors other than the referees criticisms and recommendations may also be considered in reaching a decision. This offer of resubmission is designed to provide an opportunity for you to address issues raised by the expert referees, and our editorial comments. It does not necessarily guarantee eventual acceptance and it would be unusual for us to request a second major revision.

If you do plan to resubmit, the revised manuscript must be received within 6 weeks. The due date is 04-Oct-2009. Please contact the editorial office if you anticipate not being in a position to meet this deadline so that an extension can be negotiated since Manuscript Central will not accept a revision after this interval and your paper would then be treated as a new submission.

To revise your manuscript, log on to http://mc.manuscriptcentral.com/brain and enter your Author Centre, where you will find your manuscript title listed under "Manuscripts with Decisions." Under "Actions," click on "Create a Revision." Your manuscript number has been appended to denote a revision.

You will be unable to make your revisions on the originally submitted version of the manuscript. Instead, revise your manuscript using a word processing program and save it on your computer. Please also highlight the changes to your manuscript within the document by using the track changes mode in MS Word or by using coloured text.

Please note that you should also resubmit the figures.

Once the revised manuscript is prepared, you can upload it and submit it through your Author Centre. Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

When submitting your revised manuscript, you will be able to respond to the comments made by the referees in the space provided. You can use this space to document any changes you make to the original manuscript. In order to expedite the processing of the revised manuscript, please be as specific as possible in your response to the referees. It would be most helpful if you could restate each of the points made by the referees, followed by your response to them.

Thank you for submitting your manuscript to Brain and we look forward to receiving your
This study examined the role of leg asymmetry and gait disturbance in Parkinson’s disease and its role in Freezing of Gait (FOG). Stable PD subjects who had undergone Deep Brain Stimulation of subthalamic nuclei were divided into clinical groups consisting of those which experienced FOG and those that did not experience FOG. A 3 dimensional motion analysis system was used to document gait parameters and testing was carried out on a treadmill; the belt speed set at ground speed measures for previous “on” and “off” gait conditions. Conditions included “on” and “off” DBS stimulation and a 50% reduction in voltage for the better leg and a 50% reduction in voltage for the worse leg. It was found that the number of FOG episodes and their duration would decrease when the better leg voltage was reduced by 50% compared to the worse leg voltage reduction. This was found only in the FOG prone group. It was concluded that leg asymmetry was a major risk factor for FOG and adjustments to leg asymmetry could lead to significant benefits in FOG reduction.

This is an interesting and clever paper which attempts to provide further insights into the mechanism of gait freezing in Parkinson’s disease. However there are a number of methodological issues which makes interpretation of the results difficult and the conclusion uncertain. These issues are outlined below.

1. It is unclear how long subjects walked on the treadmill for each condition.
2. It is unclear whether recordings, or later analysis, were made for the whole period while on the treadmill or only for select periods.
3. During analysis a total of 40 second recording was used. How was this selected from a bigger sample and why was the selection made.
4. Where within the 40 second period of analysis were background gait parameters measured particularly in relation to a FOG episode. The cadence rates are quite high for the FOG prone group suggesting the measures occurred close to or during FOG episodes.
5. FOG was not defined in the context of underlying mechanisms which include firstly the sudden stop and secondly the difficulty in subsequent gait initiation. These two mechanisms need to be assessed separately not simultaneously as they may well be associated with difference control mechanisms. How was this issue addressed?
6. Why was a treadmill used and not normal land walking? Treadmill mediated brain control mechanisms may be completely different to land based control mechanisms. This issue was not addressed or discussed.
7. The reduction in FOG episodes was associated with an increase in stride length of the better leg. Why were not the decrease FOG episodes due to the bigger stride length rather than improved leg coordination? (see. Chee et al BRAIN Volume 132, Number 8 August 2009.
8. The authors need to explain why a decrease in DBS stimulation voltage improved stride length. One would have expected that this would reduce the stride length. Was this due to side effects from DBS stimulation, the tread mill paradigm or some other reason?
9. There is an obvious sequence effect in the raw data. This issue was not investigated nor its contribution to FOG episodes and stimulation effects.
10. The conclusion is not applicable to land based walking as this was not tested. The conclusion is only applicable to treadmill walking.
Referee: 2
Comments to the Author
Fasano et al, have studied the effect of reduction of STN-DBS amplitude in one side and its effect on gait in general and on freezing of gait in particular. They report for the first time, that reducing stimulation parameters of the better leg can improve gait and decrease FOGs. This is a nicely planned study which is based on solid theoretical background that asymmetry in legs movement is an important contributing factor for the development of FOG.

Comments:
1. In an interventional study that is planned to assess FOG using a treadmill can influence the results. Treadmill has been shown to act as an external cueing device mainly through pacing (Frenkel et al.,) and as such is not giving the full picture. I think this limitation should be discussed in the discussion part.
2. I could not find any information about IRB approval neither what type of consent form the patients signed and if they knew that FOG is assessed. Please provide this information and take into an account that FOG is highly variable and can be influenced by what the patients were told.
3. Abstract: "by the Phase Coordination Index (PCI) quantifying the phase between both legs" The terminology is not accurate may be 'quantifying the ability to generate anti phase stepping' is a better one.
4. Abstract: Not readily apparent what the first statement in the conclusions is based on.
5. Page 9: The authors do not describe correctly the calculation of $\phi$.

$\phi = (\text{time for the shorter stride time/time for the longer stride time}) \times 360^\circ$

Stride and step are confused. Please double check if you have followed exactly the methods described in the paper in Exp Brain Res paper (Plotnik et al., 2007) and please better define the $\phi$.
6. In figure 4 the $\phi$ is difficult to understand. What is a phase of 360 degrees? Did patients jump on both legs together? Please make sure you have used the right definition.
7. In general the PCI values are very high while the use of a treadmill should have caused the PCI to improve. Please look again at your calculations to make sure there are no calculation changes.
8. There are several ways to assess FOGs. If FOG was one of the most important outcomes if not the primary one (this is not clear what was the primary outcome, PCI?) I would expect more detailed assessment including the most frequent situations where FOG occurs: turning and step initiation. It is not clear from this paper which type of FOGs were observed and if patients were challenged by those common tasks. If so, I think it is extremely important to give this information because of its clinical implications.
9. In regards to clinical assessment:
   a. The FOG-Q that was used was the 6 items short version with a maximum of 24 points and not 64 as mentioned in the text and the table. This can be seen by the mean among the two groups.
   b. When defining FOG+ and FOG- I would like to know their scores on item #3 of the FOG-Q, which gives also the subjective assessment of the patient. Please add to the table
   c. It is not clear how FOGs were times and calculated. What was the course they walked and how start hesitation and turning hesitations were scored and timed. During the 40 seconds walk, did patients had stops and turns? Please add this information to the method and results section and if possible discuss the effect of BSR on the different FOG sub-types.
   d. I would like to know the subjective impression of the stimulation manipulations on the patients' subjective impression. Did they notice any clinical effect of the BSR and the WSR?
   e. Based on the results one would suspect that the DBS parameters were changed in those patients who participate in the study. This is especially important considering the growing amount of data that FOG is probably the most significant risk factor for falls in PD. I would like the authors to give that information and if those changes truly had a clinical benefit. How many patients were left with the new stimulation parameters after the study was ended?
   f. It is not clear exactly how the FOG duration was calculated. An example on the figure would help. Be more specific in the Method section about this issue.
   g. It is very surprising that so many patients experienced FOG during simple walking in "open runway". Please explain why or how or may be the definition is different for FOG and festination was considered FOG.
10. If patients were also tested on ground level and not on treadmill, I think it would be appropriate to give those gait parameters and it is especially important in regards to CV which is directly influenced by the treadmill. Table 4.
11. It is not clear how gait speed was changed while walking on the treadmill? Please explain.
12. The Discussion is good. I would add other potential explanations for the improvement in BSR. For example the fact that the patient felt unusual feeling and that it worked as a cue \ motor-cognitive trick. It does not explain the PCI data but the clinical improvement. The whole concept of worsening the better side should be given more thought and be discussed.
13. Small issues:
a. Table 1 the amp. On ch2 is misplaced

Referee: 3
Comments to the Author
This manuscript describes the effects of asymmetric stimulation of the STN in 13 subjects with freezing of gait (FOG) and 9 subjects without FOG. Bilateral STN stimulation reduced FOG in the 13 subjects with FOG. However, the most striking improvement was produced by reducing the stimulation voltage in the STN contralateral to less affected leg. The effect was accompanied by an improvement in the phase coordination index. Changing the stimulation parameters in the subjects without FOG had no effect on gait parameters. It is concluded that “failure of gait coordination plays a causative role in FOG.”
This manuscript adds further evidence to the hypothesis that FOG is related to an impaired coordination of the legs during locomotion.
There are a couple other observation that might strengthen their argument.
First, it seems that increasing the gait asymmetry in the subjects without FOG might induce FOG. Did the stimulation in the subjects without FOG ever worsen the PCI in these subjects to the range seen in the subjects with FOG? Being able to induce FOG in subjects that previously had not had FOG would strengthen their argument that gait asymmetry is “causative.” As it is, altering gait asymmetry (PCI) only increases or decreases FOG in subjects who exhibit the phenomenon.
Secondly, did the authors try adjusting gait symmetry for the DBS off condition; that is using 50% or 100% stimulation on one side only?
A few more mundane questions;
Was the 11 meter walk used to classify subjects as having FOG just straight ahead or did it contain the various challenging conditions used by Snijders et al to precipitate FOG?
It would seem that the gait analysis would be very influenced by the FOG episodes. What were the exact methods of deciding when FOG was occurring to decide what portion of the treadmill locomotion to exclude from the analysis of gait parameters?
Figure 1 appears to be incompletely labeled. Is the light tracing from the 5th metatarsal on one foot and the dark tracing on the calcaneus on the other foot?

Date Sent: 26-Aug-2009
ALLEGATO B
INTRODUZIONE e OBIETTIVI

La marcia nella malattia di Parkinson (MP) è caratterizzata dalla riduzione della lunghezza del passo (1). La nota asimmetria motoria della MP si ripercuote anche nelle prestazioni motorie degli arti inferiori conferendo alla marcia anche caratteristiche asimmetriche (2). L’interazione fra ipocinesia e asimmetria del cammino nella MP e il contributo relativo di ciascun arto inferiore nella patogenesi del disturbo della marcia non sono stati mai indagati.

In un precedente lavoro abbiamo dimostrato che la modulazione dell’asimmetria tramite elettrodi subtalamici è in grado di migliorare il disturbo della marcia non sono mai indagati.

Il cammino è stato analizzato su treadmill programabile a doppio nastro (Woodway, Germania) nelle seguenti condizioni:  

PAZIENTI e METODI

• 10 pazienti con MP in med off  
• Età: 60,5 ± 8,8 anni  
• Durata di malattia: 12,2 ± 5,7 anni  
• Arto inferiore più lento: 5 Dx/ 5 Sn

I pazienti sono stati sottoposti a gait analysis dopo una sospensione di almeno 12 ore della terapia dopaminergica (med off). La registrazione è stata effettuata con sistema opto-cinetico di cattura del movimento a velocità di campionamento di 240 Hz (Qualisys, Svezia). Un software dedito e Matlab sono stati utilizzati per calcolare i parametri standard del cammino e il phase coordination index (PCI) per quantificare la coordinazione fra i due arti inferiori.

La velocità del nastro (Veln) è stata mantenuta costante per tutta la durata della fase di addestramento con lo scopo di assicurare una deambulazione sicura e confortevole. 

L’asimmetria della marcia predispone alla riduzione della lunghezza del passo perché l’arto meno affetto si adatta al più affetto per preservare una quota di simmetria.

L’uso del treadmill a doppio nastro (split-belt) è in grado di modulare efficacemente l’asimmetria degli arti inferiori durante la marcia.

CONCLUSIONI

L’asimmetria della marcia predispone alla riduzione della lunghezza del passo perché l’arto meno affetto si adatta al più affetto per preservare una quota di simmetria. 

RINGRAZIAMENTI

NEURECA onlus – Milano finanzia parte del progetto.

BIBLIOGRAFIA


CONCLUSIONI

L’uso del treadmill a doppio nastro (split-belt) è in grado di modulare efficacemente l’asimmetria degli arti inferiori durante la marcia.

RISULTATI: effetto sui parametri standard

RISULTATI: effetto sulla coordinazione
ALLEGATO C
0.1 Data Acquisition

The feet marker recordings from the total of 20 individuals are analyzed. We use a comparative study of healthy patient and patients suffering PD under different conditions. For 11 PD patients who suffer freezing of gait (FG) episodes and for 8 PD patients without (FG) the effect of stimulation is discussed in terms of comparative analysis of power spectrum and bilateral phase difference for feet marker recordings.

As in the first part of "Preliminary results" the labeling of figures and is according to the column number in the Excel file. Figures contain labels such as Wolles stim on 18,39 presents analysis of 18 and 39 marker sets for patient Wolles with stimulation on conditions. Figures labeled fftWolles0001.eps and DiffWolles0001.eps contain power spectrum decomposition and phase analysis results for data file Wolles0001.xls.

0.2 Spectral analysis

The data for each marker set are analyzed using Fast Fourier transform. We use a smoothed time sequence obtained from the original set by centering it around its mean and filtering high frequency content. In terms of spectral properties the effects of stimulation can be classified according to the following list:

- increase of main frequency under the applied stimulation; simultaneously, the secondary frequency peak gets magnified;
- frequency shift towards the lower frequency during stimulation;
- sharpening of the frequency distribution: dissappearance of the frequency components that lie within the narrow band of the main frequency;

In the following paragraphs we provide examples of each type of phenomenon listed.

0.2.1 Frequency increase under applied stimulation

The effect of frequency increase is observed for patients who does not suffer freezing of gait episodes as well as for patients with FG. Example of power spectrum is shown in figures (1-2) for data with stimulation on and off, correspondingly. First of all, the band of frequencies around main frequency becomes narrow when the stimulation is applied. Apart from sharpening of the frequency content around main frequency the secondary frequency appears as a distinct sharp peak at 2.2Hz. In the second set of data obtained from another patient the frequency remains the same after the stimulation is applied (see figures (3-4)). However, the secondary frequency component becomes larger during stimulation. Main frequency values are presented in table (1) for 5 PD patients and for 6 PD+FG patients with stimulation on and off conditions.

0.2.2 Frequency shift towards lower frequency

Unlike the effect of frequency increase, the transition towards the lower frequency under stimulation conditions is not a common feature. It is observed in
0.2. SPECTRAL ANALYSIS

Figure 1: Power spectrum for different set of markers obtained with FFT. The left and right side are indicated by distinct colors. Data are presented for PD patient without freezing of gait during stimulation protocol.

Figure 2: Power spectrum for different set of markers obtained with FFT. Data are for PD patient without freezing of gait and with no stimulation.
Figure 3: Power spectrum for different set of markers obtained with FFT. Data are given PD patient without freezing of gait during stimulation. The secondary peak is as large in amplitude as the first one and corresponds to the secondary frequency 1.82 Hz.

Figure 4: Power spectrum for different set of markers obtained with FFT. Data are for PD patient with no stimulation applied.
0.2. SPECTRAL ANALYSIS

Figure 5: Power spectrum for different set of markers obtained with FFT. Data are given for PD patient without stimulation applied.

Figure 6: Power spectrum for different set of markers obtained with FFT. Data are for PD patient during stimulation on.
<table>
<thead>
<tr>
<th>Patient name</th>
<th>Stimulation on</th>
<th>Stimulation off</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burger (PD patient)</td>
<td>1.2</td>
<td>0.75</td>
</tr>
<tr>
<td>Carl (PD patient)</td>
<td>0.82</td>
<td>0.82</td>
</tr>
<tr>
<td>Schmidt (PD patient)</td>
<td>0.79</td>
<td>0.79</td>
</tr>
<tr>
<td>Trude (PD+FG)</td>
<td>0.73</td>
<td>0.53</td>
</tr>
<tr>
<td>Rieschel (PD+FG)</td>
<td>0.95</td>
<td>0.82</td>
</tr>
<tr>
<td>Lorenz (PD patient)</td>
<td>0.98</td>
<td>0.95</td>
</tr>
<tr>
<td>Wegner (PD+FG)</td>
<td>0.89</td>
<td>0.72</td>
</tr>
<tr>
<td>Bruntrup (PD+FG)</td>
<td>0.92</td>
<td>0.8</td>
</tr>
<tr>
<td>Broish (PD+FG)</td>
<td>1.4</td>
<td>0.98</td>
</tr>
<tr>
<td>Fischer (PD+FG)</td>
<td>1.15</td>
<td>0.65</td>
</tr>
<tr>
<td>Kohilhaas (PD patient)</td>
<td>1</td>
<td>0.98</td>
</tr>
</tbody>
</table>

Table 1: Main frequency obtained from FFT for PD patients with and without stimulation protocol applied.

<table>
<thead>
<tr>
<th>Patient name</th>
<th>Stimulation on</th>
<th>Stimulation off</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenz (PD patient+FG))</td>
<td>1.1</td>
<td>1.35</td>
</tr>
<tr>
<td>Wolles (PD patient + FG)</td>
<td>0.72</td>
<td>1.3</td>
</tr>
<tr>
<td>Berding (PD patient)</td>
<td>1</td>
<td>1.17</td>
</tr>
<tr>
<td>Holscher (PD patient + FG)</td>
<td>0.81</td>
<td>1.25</td>
</tr>
<tr>
<td>Ostwald (PD patient)</td>
<td>1</td>
<td>1.25</td>
</tr>
</tbody>
</table>

Table 2: Main frequency obtained from FFT for PD patients, PD patients + FG. The protocol with stimulation on and off is used.

2 PD patients and in 3 PD+FG patients. In table (2) we list main frequency values calculated from FFT. In all the cases stimulation protocol leads to a shift of frequency towards a lower value. An example of corresponding changes in power spectrum for PD+FG patient is presented in figures (5-6). Due to stimulation applied the main peak is shifted to the left. In addition, the interval between main and secondary peaks is narrowed down.

### 0.3 Bilateral phase variation

In this section we present results of temporal analysis of phase behavior for data from healthy, PD patients with and without freezing episodes.

The plan of this section can be simplified in several steps. First, our numerical procedure is introduced and discussed. Second, the results of numerical calculations are presented for patients under different conditions with and without stimulation. We will show the typical features of phase difference variation taken for distinct groups of markers. Third, the intervals of locking of phase will be introduced and simple procedure to detect these intervals is detailed. We present the diagram with list of markers for each patient where the locking phenomenon is detected. Later, we discuss the typical variation of phase that occurs during freezing of gait episode. Other effects of stimulation such as gradual decrease of distribution width are specified as well. At last, we list the main
observations that follow from the numerical analysis.

We focus our observations on discussing mainly the effect of stimulation on bilateral phase behavior.

0.3.1 Brief introduction to numerical procedure

In the "Freezing of Gait: Preliminary results" the phase calculations are introduced to measure the phase difference between left and right marker groups at discreet times (at the extreme extension positions). These extreme positions correspond to maxima of marker traces. We do comparative analysis for 3 individuals and show that the mean bilateral phase difference for a healthy control patient is larger than for PD and PD+FG patients. Also the bilateral phase variance is found to be the largest for PD+FG patients.

Here we introduce an additional notion that can well describe the bilateral phase behavior. This notion is in terms of definition of continuous phase which is calculated not at discreet times but over the whole time segment at every time point. The calculations of continuous phase of time series carried out from the Hilbert transform \[2\]. Figure (7) shows two marker positions versus time in the top panel and their instantaneous phases obtained from the Hilbert transform. The insets show the corresponding variations over period corresponding to few cycles. One more example of instantaneous phase variation is shown in figure (8). Here the positions and phases are given for different set of markers for the same patient. The main feature is that the phases of marker positions exhibit non–monotonic growth with time, phase temporal behavior is different for each marker set.

0.3.2 Phase difference variation and distributions

The instantaneous phase is a measure that lets to observe variations between phases of left and right side continuously throughout the whole interval of observation. In figure (9) the phase difference variation is shown for a healthy control for different groups of markers. Here we used the recordings smoothed and centered around its mean. The phase difference \(|\phi_{\text{left}} - \phi_{\text{right}}|\) vary around \(\pi\) due to the fact that two sides move in an antiphase. We show the quantity \(|\phi_{\text{left}} - \phi_{\text{right}} + \pi|\) that is fluctuating in a characteristic periodic–like pattern around zero value. Each period of fluctuation corresponds to a single cycle of legs movement. In the right column the distribution of phase difference is shown for every marker group. The distributions are close to uniform or bimodal with two distinct maxima at extreme points of corresponding phase difference variation.

In figure (10) bilateral phase variation and distributions are shown for PD patient with FG episodes. In the marker group 18,39 one can observe clustering of distribution to a unimodal pattern and to a narrow distribution with single peak for marker group 11,32. The phase difference variation can be compared with the healthy control in figure (9) for the same marker sets. Large periodic variations around zero can be observed for 11,32 markers in figure (9) does not occur for PD patient. Instead the phase difference oscillate only within a narrow interval around zero and does not show periodic–like pattern.

In the next subsection we discuss episodes of phase clustering or "locking" and provide several examples of data sets for which it occurs. In particular,
Figure 7: Marker positions (top) and instantaneous phases (bottom) for left and right side. The inset show variation of instantaneous phase over a few cycles.

Figure 8: Marker positions and instantaneous phases for left and right side as in figure (7) but for different marker sets. The insets show variation of instantaneous phase over a few cycles.
Table 3: List of PD patients for whom phase difference "locking" is observed. For each patient we list marker names where the "locking" occurs.

<table>
<thead>
<tr>
<th>Patient name</th>
<th>Marker name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scaap (PD+FG)</td>
<td>08,29,11,32,14,35,15,36,17,38,18,39,20,41,21,42</td>
</tr>
<tr>
<td>Lenz (PD+FG))</td>
<td>14,35,17,38</td>
</tr>
<tr>
<td>Fischer (PD+FG)</td>
<td>06,24,05,23,08,29</td>
</tr>
<tr>
<td>Wolles (PD+FG)</td>
<td>11,32</td>
</tr>
<tr>
<td>Wolles</td>
<td>08,29,18,39</td>
</tr>
<tr>
<td>Bruntrup (PD+FG)</td>
<td>15,36</td>
</tr>
<tr>
<td>Bruntrup</td>
<td>05,23,15,33</td>
</tr>
<tr>
<td>Trude (PD+FG)</td>
<td>08,29,11,32</td>
</tr>
<tr>
<td>Broish (PD+FG)</td>
<td>09,30,12,33,14,35</td>
</tr>
<tr>
<td>Broish</td>
<td>12,33,14,35,20,41</td>
</tr>
<tr>
<td>Holscher (PD+FG)</td>
<td>11,32</td>
</tr>
<tr>
<td>Holscher</td>
<td>11,32,14,35</td>
</tr>
<tr>
<td>Nix (PD+FG)</td>
<td>11,32,12,33</td>
</tr>
<tr>
<td>Burger (PD)</td>
<td>08,29,11,32</td>
</tr>
</tbody>
</table>

0.3.3 Episodes of locking

In figures (11-12) we present data for two PD patients with FG episodes under different conditions: with and without stimulation applied. In both cases the application of stimulation improves the consistency of phase variation by increasing the amplitude of phase variation and changing the pattern to more periodic-like. The results of stimulation can be easily observed in the distribution plot. The singulary peaked and narrow distribution broadens and converges to bimodal for the data with stimulation on. From the analysis of data from different PD patients it is noticed that "locking" phenomenon occurs not always for all the groups of markers. Most of the cases it can be observed in one or two distinct marker sets (see table (3) with the list of markers that feature phase difference "locking" behavior). We give an example in figure (13) where such locking really happens for all the marker sets.

0.3.4 Effect of stimulation: decrease of width distribution

The temporal behavior of phase difference in most of the subjects studied shows regular oscillations with consistent amplitude and frequency over the whole interval of \( t = 20 \text{ s} \). The period of each oscillation is the length of a single leg movement cycle. In most of the subjects studied so far the application of stimulation regularizes the temporal behavior of phase difference (see figure (12)). One example demonstrates an interesting feature that might be a consequence of applied stimulation. It is shown in figure (14) that the amplitude of oscillations...
Figure 9: Phase difference variation for healthy individual. Data are presented for different marker groups. The variation is shown for the phase difference centered around its mean $|\phi_{left} - \phi_{right} - \phi_{mean}|$, $\phi_{mean} = \pi$. (Left column) Bilateral phase difference versus time. (Right column) Distribution of phase difference is shown for different marker groups.
Figure 10: Temporal variation and distribution of phase difference are shown in the left and right columns correspondingly. The results are presented for PD patient with FG.
Figure 11: Episode of locking of phase difference taken from PD patient + FG. It is characterized by a clustering of distribution from a bimodal to a unimodal pattern. Locking of phase difference is presented for a single marker group. (a) Temporal variation of phase difference for data without stimulation. (b) The distribution of phase difference for the same set of data. (c) Temporal variation of phase difference with stimulation on. (d) The distribution of phase difference for the data in (c).
Figure 12: Episode of locking of phase difference taken from PD + FG patient. The effect of stimulation is shown in the top two panels. (a) Temporal variation of phase difference for data with stimulation. The temporal dependence shows periodic oscillations about center 0. (b) The distribution of phase difference for the same set of data. (c) Temporal variation of phase difference without stimulation. The temporal dependence is irregular. It shows time intervals where phase difference collapses to $\pi$ (in the plot to 0). (d) The distribution of phase difference for the data in (c). The phase distribution shifts to bimodal unlike in the lower right panel where distribution clusters to a unimodal pattern (no stimulation applied). Locking of phase difference is presented for a single marker group.
Figure 13: Temporal variation and distribution of phase difference are shown in the left and right columns correspondingly. The results are presented for PD patient with FG.
0.3. BILATERAL PHASE VARIATION

Figure 14: Bilateral phase difference centered at zero and distribution of phase difference for different marker groups. Data are obtained for PD patient with FG.
Figure 15: (Left column) Bilateral phase difference measured during two subsequent time intervals: first half of stimulation $t = [1, 10]$ and the second half of stimulation $t = [10, 20]$. (Right column) The bilateral phase distribution for two time intervals. The distribution shows bimodal feature and the width between two peaks indicated by double arrow. The width is narrowed during the second half of the stimulation interval. (Data are shown for the patient suffering freezing of gait episodes).
tions is not constant over the interval of stimulation $t = 20s$. Instead it tends to decrease gradually. We plot the bilateral phase difference and its distribution observed for two subsequent intervals of time in figure (15). The amplitude of oscillations is larger and the width of distribution is broader during the first half of stimulation interval than during its second half.

0.4 Analysis of phase difference during onset of freezing of gait

Among the results for PD+FG patients we pick up two data sets that showed two distinct features: broad frequency spread around peak frequency and atypical variation of bilateral phase difference. Specifically, the temporal behavior of phase difference exhibits large amplitude oscillations with the frequency of oscillations much smaller than the main frequency $\approx 1Hz$. The evidence of large spread of energy across a broad range of frequencies around the leading frequency has been observed during freezing of gait in [3]. From our spectral and phase analysis we distinguish two data sets Trude and Rieschel with featured behavior. An example of this behavior is presented in figure (16). Two time intervals are indicated with stimulation off and on. At about $t = 9.8s$ the large amplitude variations are set on. The period of each oscillation is longer than the natural one before the onset of freezing. In the next set of intervals the data are shown for the same patient with the stimulation applied. Variations are qualitatively different and their temporal behavior is structured towards normal (typical) behavior.

0.4.1 Discussion

Our main observations from the comparative study of temporal variation of phase for healthy control and PD patients are finalized into several points:

- bilateral phase difference between left and right side shows regular variations about its mean value $\pi$ for healthy individual;
- the shape and form of these variations depend on the particular marker set: it can vary within $[-\pi/2; \pi/2]$ interval or within smaller range depending on the group of markers analyzed;
- the phase difference variation features irregular behavior that is accompanied by decrease of amplitude of variations for PD patients with FG; the distribution of phase difference clusters to very narrow unimodal pattern;
- clustering or "locking" occurs mostly for PD+FG patients, only one subject among 8 PD patients who does not suffer FG showed similar clustering;
- the clustering of distribution to atypical pattern can occur either for a few number of markers or for the whole set of feet markers simultaneously.

The effect of stimulation on phase difference behavior can be summarized as follows:
Figure 16: (Top panels) Phase difference and distribution measured for PD patient during onset of freezing of gait episode. (Bottom panels) The same quantities are measured for recordings with stimulation on. Stimulation structures the temporal behavior as well as the amplitude of variations.
• stimulation improves behavior of phase variation from irregular one to (normal) periodic–like; phase distribution pattern either resumes bimodal shape or exhibits broadening to almost uniform distribution that is typical for a healthy subject;

• stimulation can affect the width between maxima in bimodal distribution;

• our analysis shows one example when the width of bimodal distribution gradually varies during the interval of stimulation.
Bibliography


ALLEGATO D
Dear Colleagues and Friends,

Since 10 years, Deep Brain Stimulation has become an important treatment modality offered jointly by the Departments of Neurosurgery and Neurology in Kiel. Parallel to clinical treatment, scientific high level research broadens the indications and optimizes results.

During these 10 years the Neurocenter in Kiel has grown into one of the biggest centres for Deep Brain Stimulation in Germany with more than 70 new patients operated every year. The experiences of various international groups, growth of knowledge, current state of treatment and expanding prospects in national and international discussion will be the subject of this symposium, both for movement disorders and pain and its neurosurgical treatment. It is our great pleasure to invite you all to actively participate in this symposium to discuss present results and future trends in an international atmosphere.

We really look forward to welcome you in Kiel in November 2009.

H. Maximilian Mehdorn

G. Deuschl

Preface

Information & Deadlines

Besides expert lecture, oral and poster presentations are encouraged

Structured abstracts are encouraged with a maximum of 250 words in the following fields:
- Deep Brain Stimulation
- Movement Disorders
- Pain, neurosurgical treatment
- Psychiatric Disorders and DBS

The deadline for Abstract submission is: 30.09.2009
Please Email the abstracts to: devulderm@nch.uni-kiel.de

Registration

Early Registration is highly recommended, preferably until mid-october. Please register per Email to: devulderm@nch.uni-kiel.de

Congress fee: € 30,-

Accommodation

If needed, please ask for a hotel list when you send your Email to: devulderm@nch.uni-kiel.de

CME Credit: 22 points at the Ärztekammer Schleswig-Holstein.
**Thursday, 05.11.2009**  
**Get together**  
18:00 Opening of the Symposium and Get together

**Friday, 06.11.2009**  
**Scientific sessions (preliminary)**  
08:00 Reception  
08:30-10:30 **Session 1: The historical and physiological fundamentals of DBS**  
08:30-08:55 D. Müller: The historical background of DBS in Germany  
08:55-09:20 P. Tass: Rhythms in the CNS and DBS  
09:20-09:45 G. Nikkhah: Transplantation in Huntington’s disease  
09:45-10:10 P. Krack: Cognition, emotion and DBS  
10:10-10:30 NN: The motor system and DBS

Coffee Break

11:00-12:30 **Session 2: New solutions for long-standing treatment problems**  
11:00-11:30 A. Fasano: Gait problems  
11:30-12:00 M. Pinsker: TBD  
12:00-12:30 P. Limousin: Speech problems

Lunch

13:30-15.00 **Session 3: New developments in the neurobiology of DBS**  
13:30-13:50 J. Herzog: Pathophysiology of intention tremor  
13:50-14:10 M. Schüpbach: Impulsivity and quality of life  
14:10-14:30 M. Hariz: DBS in Neurology and Psychiatry: The pendulum of history  
14:30-15:00 V. Sturm: Neurorecovery

Coffee Break

**15:30-17:30 Session 4: Treatment results 1**  
15:30-15:45 J. Krauss: Multifocal stimulation  
15:45-16:00 S. Nanta-Aree: DBS in Thailand  
16:00-16:15 T. Schläfper: Psychiatry and DBS  
16:15-16:30 D. Servello/P. Porta: Methodological and ethical aspects with DBS in refractory Tourette’s Syndrome: a personal experience  
16:30-16:45 B. Nuttin: DBS for Psychiatric disorders  
16:45-17:00 J. Mehrkens: DBS in Tourette  
17:00-17:15 B. Sun: DBS for addiction and anorexia  
17:15-17:30 J. Voges: DBS for the treatment of severe alcohol addiction

**17:30 -18:30 Session 5: Treatment results 2**  
17:30-17:45 J. Krauss: DBS and pain  
17:45-18:00 A. Franzini: Cluster headaches  
18:00-18:15 G. Broggi: Headaches  
18:15-18:30 S. Chabardes: Experience in PPN-DBS

19:00 Dinner

**Saturday, 07.11.2009**  
**Parkinson Awareness Day**

**09:00-11:00 Session 5: New Technologies**  
09:00-09:40 W. Hamel: DBS in narcosis  
09:40-10:20 F. Alesch: Place of ablative procedures in view of DBS  
10:20-11:00 B. Leplow: Psychology in Parkinson’s disease

Coffee Break

**11:30-13:00 New technical and biological developments**  
11:30-11:50 M. Decré: Emerging technological innovations  
11:50-12:10 T. Denison: Innovations in DBS Technologies

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**Scientific Program / Contact**

12:10-12:30 J. Vesper: DBS for Huntington’s disease  
12:30-12:45 W. Hamel: Early genes in DBS  
12:45-13:00 P. Almqvist: Genetotechnology (Future)

Parallel sessions:  
**10.00-14:00 Parkinson Panel**  
German Parkinson Association  
Questions and Answers to the Experts

14:30 Late Lunch and Farewell

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Via Fax to 0049-(0)431-597-4918
Via E-mail to devulderm@nch.uni-kiel.de

10 Years Deep Brain Stimulation in Kiel
Present and Future
3rd International Symposium
in Kiel, 05. - 07.11.2009

I will attend the Symposium:

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I will attend dinner on friday, 06.11.2009, 19:00

Yes ............ No ............

Abstract registration

Besides expert lecture, oral and poster presentations (max. 15 minutes) are encouraged. The deadline for abstract submission is the 30.09.2009. Please e-mail the abstracts (max. 250 words) to:

devulderm@nch.uni-kiel.de

Required information:

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ALLEGATO E
Corso di aggiornamento sulla Malattia di Parkinson
La Malattia di Parkinson: storia naturale e trattamento dei sintomi neurologici e psichiatrici
Problemi internistici nella Malattia di Parkinson

ROMA
Mercoledì, 28 ottobre 2009
Martedì, 10 novembre 2009
Policlinico Universitario “A. Gemelli” – UCSC
Largo Agostino Gemelli, 8

PROGRAMMA

1^ Giornata - 28 ottobre 2009
La Malattia di Parkinson:
storia naturale e trattamento dei sintomi neurologici e psichiatrici

Moderatori: R. Bernabei; P. Tonali

15.30 Registrazione dei partecipanti
16.00 Storia Naturale della Malattia di Parkinson (G. Loria)
16.25 Diagnosi differenziale (G. Fabbrini)
16.50 Scelte terapeutiche nelle fasi non complicate (A.R. Bentivoglio)
17.15 Complicanze psichiatriche (M. Pomponi)
17.40 Disturbi assiali e rischio di cadute (A. Fasano)
18.05 Discussione
18.30 Presentazione di Casi clinici (A.R. Bentivoglio, G. Fabbrini)
19.00 Discussione dei Casi Clinici
19.30 Verifica di apprendimento con questionario

2^ Giornata - 10 novembre 2009
Problemi internistici nella Malattia di Parkinson

Moderatori: R. Bernabei; P. Tonali

15.30 Registrazione dei partecipanti
16.00 Disautonomia cardiovascolare: diagnosi (D. Brisinda)
16.25 Gestione dei disturbi pressori (Zuccalà)
16.50 Stipsi (G. Brisinda, G. Maria)
17.15 Epatotossicità da farmaci (M. Pompili)
17.40 Prevenzione e trattamento dell’osteoporosi e del dolore osteoartica (F. Pagano)
18.05 Discussione
18.30 Presentazione di Casi clinici (R. Fenici, R. Manna)
19.00 Discussione dei Casi Clinici
19.30 Verifica di apprendimento con questionario
Razionale dell’evento formativo.

La malattia di Parkinson è una malattia neurodegenerativa che colpisce il sistema nervoso centrale. La nozione che il circuito dopaminergico nigro-striatale sia il principale bersaglio dei processi degenerativi è confermata, tuttavia alcune ricerche dell’ultima decade hanno gettato una nuova luce sul coinvolgimento molto più ampio di strutture monoaminergiche centrali e su nuclei coinvolti nel controllo delle funzioni vegetative, del controllo dell’umore e del comportamento. Dunque la malattia di Parkinson è molto più complessa che la degenerazione di un insieme di circuiti che regolano il movimento volontario: coinvolge anche gli organi viscerali.

Sintomi disautonomici quali stipsi ed ipotensione ortostatica possono precedere di anni l’esordio dei sintomi motori; inoltre, nelle forme avanzate la gestione dei sintomi non motori costituisce una vera sfida che coinvolge diverse figure che prendono in carico l’individuo con malattia di Parkinson: neurologo, cardiologo, internista e geriatra. Quest’ultimo, il geriatra, spesso è l’unico referente del paziente anziano con malattia di Parkinson e, d’altra parte, anche il neurologo ha spesso la necessità di gestire sintomi non neurologici in prima persona.

Da questa premessa deriva l’obiettivo di questo corso: realizzare una osmosi di esperienze fra diverse figure professionali utili alla gestione dei sintomi motori e non motori nei pazienti con malattia di Parkinson.

Sono stati invitati come relatori, discussori e moderatori, clinici con anni di esperienza nella gestione clinica di pazienti complessi. Il taglio delle relazioni sarà prevalentemente pratico. In ognuna delle due giornate verrà lasciato spazio alla discussione di casi clinici.

Il corso è rivolto a neurologi, geriatri, internisti interessati alla malattia di Parkinson.
## Detailed Status Information

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### Abstract
Punding is a stereotyped behavior characterized by an intense fascination with a complex, excessive, non-goal oriented, repetitive activity. Men tend to repetitively tinker with technical equipment such as radio sets, clocks, watches and car engines, the parts of which may be analyzed, arranged, sorted, and cataloged but rarely put back together. Women, in contrast, incessantly sort through their handbags, tidy continuously, brush their hair, or polish their nails. Punders are normally aware of the inapposite and obtuse nature of the behavior; however, despite the consequent self-injury, they do not stop such behavior. The most common causes of punding are dopaminergic replacement therapy in patients affected by Parkinson’s disease (PD) and cocaine and amphetamine use in addicts. The vast majority of information about punding comes from PD cases. A critical review of these cases shows that almost all afflicted patients (90%) were on treatment with drugs acting mainly on dopamine receptors D1 and D2, whereas only three cases were reported in association with selective D2 and D3 agonists. Epidemiological considerations and available data from animal models suggest that punding, drug-induced stereotypies, addiction, and dyskinesias all share a common pathophysiological process. Punding may be related to plastic changes in the ventral and dorsal striatal structures, including the nucleus accumbens, and linked to psychomotor stimulation and reward mechanisms. Possible management guidelines are proposed.

### Keywords
- Addiction, cocaine, dopamine dysregulation syndrome, dopamine, Impulse Control Disorders, Parkinson's disease, Punding

### Conflict of Interest Statement
The authors have declared there is NO conflict of interest to disclose