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Movement parameters that distinguish between voluntary movements and levodopa-induced dyskinesia in Parkinson's disease

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Abstract

It is well known that long-term use of levodopa by patients with Parkinson's disease causes dyskinesia. Several methods have been proposed for the automatic, unsupervised detection and classification of levodopa induced dyskinesia. Recently, we have demonstrated that neural networks are highly successful to detect dyskinesia and to distinguish dyskinesia from voluntary movements. The aim of this study was to use the trained neural networks to extract parameters, which are important to distinguish between dyskinesia and voluntary movements.

Thirteen patients were continuously monitored in a home-like situation performing in about 35 daily life tasks for a period of approximately 2.5 h. Behavior of the patients was measured using triaxial accelerometers, which were placed at six different positions of the body. A neural network was trained to assess the severity of dyskinesia. The neural network was able to assess the severity of dyskinesia and could distinguish dyskinesia from voluntary movements in daily life. For the trunk and the leg, the important parameters appeared to be the percentage of time that the trunk or leg was moving and the standard deviation of the segment velocity of the less dyskinetic leg. For the arm, the combination of the percentage of time, that the wrist was moving, and the percentage of time, that a patient was sitting, explained the largest part of the variance of the output. Dyskinesia differs from voluntary movements in the fact that

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dyskinetic movements tend to have lower frequencies than voluntary movements and in the fact that movements of different body segments are not well coordinated in dyskinesia.

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1. Introduction

After several years of levodopa medication, many patients with Parkinson's disease suffer from levodopa-induced dyskinesia (LID) (Horstink, Zijlmans, Pasman, Berger, & van't Hof, 1990; Marsden, 1994; Nutt, 1990; Nutt, Carter, & Woodward, 1995). To alleviate or reduce these dyskinesias, several pharmacological and surgical treatments have been introduced (Brochie, 1998; Fraix et al., 2000; Manson, Schrag, & Lees, 2000b). The benefits of these interventions have been evaluated using self-report by the patient or by using semi-quantitative rating scales during consults (Damier et al., 1999; Goetz, 1999; Widner & Defer, 1999). However, self-assessment can be unreliable and motor behavior of patients during a consult is not always representative for the behavior in daily life (Goetz, Stebbins, Blasucci, & Grobman, 1997; Golbe & Pae, 1988; Vitale et al., 2001). For these reasons, an ambulatory assessment of LID would be highly useful (Brown & Manson, 1999).

Recently, several investigators successfully used an ambulatory accelerometry to monitor (abnormal) activities of patients (Busmann, Reuvenkamp, Veltink, & Martens, 1998; Dunnewold et al., 1998; Veltink, Bussmann, de Vries, Martens, & van Lummel, 1996). Accelerometry was also used for assessing the severity of dyskinesia in several other studies (Burkhard, Shale, Langston, & Tetrud, 1999; Hoff, Plas, Wagemans, & Hilten, 2001a; Keijsers, Horstink, van Hilten, Hoff, & Gielen, 2000; Keijsers, Horstink, & Gielen, 2003; Manson et al., 2000a). The main challenge in automatically assessing LID is to distinguish between dyskinesias and voluntary movements. This requires information about the specific movement features, which distinguish voluntary movements from dyskinesia. Most studies focused mainly on the frequency and/or amplitude of the accelerometer signals to detect LID and to assess the severity of LID (Burkhard et al., 1999; Hoff et al., 2001a; Manson et al., 2000a). However, some studies reported that there is a large overlap in the frequency range of voluntary movements and dyskinesias (Hoff et al., 2001a; Keijsers et al., 2000, 2003), which suggests that frequency components alone will not be able to provide a complete distinction between LID and voluntary movements. This may explain why Hoff et al. (2001a) were successful to detect dyskinesia when subjects abstained from any voluntary movements, but could not successfully assess the severity of LID for patients who made voluntary movements. In the study of Manson et al. (2000a), the authors did succeed to distinguish between LID and voluntary movements by using the accelerations in the 1–3 Hz frequency domain. However, all patients in the study of Manson et al. (2000a) suffered from severe dyskinesias and it is not clear whether the same analysis would also be successful to detect mild

dyskinesias. Another explanation for the different results in the studies by Hoff et al. (2001a) and by Manson et al. (2000a) might be related to the fact that these studies tested patients in different sets of tasks and that the set of tasks (like in most other studies, Keijsers et al., 2000) was a very limited set of daily life activities in a laboratory setting.

In order to study the effect of task conditions in a group of patients with varying degrees of dyskinesia, Keijsers et al. (2003) monitored patients while performing a large variety of daily life tasks in a natural environment for a long period of time. In that study, a neural network was used to analyze the data and to assess the severity of LID. The neural network was highly successful in detecting and assessing the severity of dyskinesia and revealed considerable improvement upon that of previous studies. The neural network correctly classified dyskinesia or the absence of dyskinesia in 15-min intervals in 93.7%, 99.7% and 97.0% of the time for the arm, trunk and leg, respectively.

The excellent performance of the neural network raises the question whether it would be possible to obtain insight in the various parameters, which allow the detection of LID and the distinction between LID and voluntary movements. This is important for two reasons. The first reason is that acceptance of a new technique will be easier if physicians, who will use the technique, do understand why it is successful. In our case, this requires that physicians will be able to match their own criteria for the detection and rating of dyskinesia with the criteria provided by the neural network. The other reason is that insight in the movement parameters, which underlie pathological behavior, might be valuable for understanding normal motor behavior. For example, several studies have shown that angular velocities in elbow and shoulder are highly correlated in normal aiming movements of the hand (Gielen, Vrijenhoek, Flash, & Neggers, 1997; Soechting, Lacquaniti, & Terzuolo, 1986). This has been interpreted as evidence for the existence of specific muscle synergies in human motor control. It would be interesting to investigate whether and to what extent muscle synergies are also observed in LID.

In our previous study (Keijsers et al., 2003), we reported the performance of neural networks in detecting and assessing dyskinesia and the performance of neural networks to distinguish dyskinesia from voluntary movements. In this study, we will focus on the architecture of the trained neural network to extract the relevant parameters that are used by the neural networks for a proper detection and rating of dyskinesia. In summary, the purpose of this study was to analyze the behavior of the optimal neural networks in the detection and rating of dyskinesia and to describe the relevant movement parameters and their relation to the severity of LID.

2. Methods

Thirteen patients with Parkinson's disease (8 male and 5 female) with a mean age of 61 years (range between 48 and 71) participated in this study. They had experienced symptoms of Parkinson's disease for between 10 and 21 years (mean 15 years). The patients were on levodopa medication for about fifteen years and all patients

suffered from LID. During the test, seven patients showed a severity of dyskinesia varying between absence of dyskinesia and mild dyskinesia (rating between 0 and 1 on the AIMS scale (Guy, 1976)). The other six patients showed a severity of dyskinesia varying between absence of dyskinesia to moderate dyskinesia (rating between 0 and 3 on the AIMS scale). All patients gave informed consent. The study was approved by the Medical Ethical Committee of the University Medical Center of the University of Nijmegen.

The study started between noon and one o'clock. The patients were continuously monitored for a period of approximately 2.5 h. During this period, the patients took their regular medication at their usual time. However, when dyskinesia did not occur halfway through the testing period, extra levodopa was taken to induce dyskinesia. The registration took place in a natural home-like setting in the occupational therapy department of the University Medical Center. During the 2.5 h monitoring session, the patients performed about 35 functional daily-life activities, like walking, putting on a coat, making coffee, preparing lunch, eating, taking off their shoes, reading a newspaper, drinking coffee, and washing hands. The order of the activities was randomized between subjects by a dedicated computer program. Subjects were allowed to carry out the activities in their own way and at their own pace. They were free to take a rest between activities at any time.

2.1. Data acquisition

The movements and postures were automatically measured using accelerometers and a portable data recorder. Six sets of three orthogonal accelerometers (ADXL-202, Analog Devices, USA) were used, which were placed at six different positions of the body. These six positions were at both upper arms (just below the shoulder), at both upper legs (halfway between the hip and the knee), at the wrist of the most dyskinetic side, and at the trunk (top of the sternum) (see Fig. 1). The accelerometer signals were digitally stored on a recorder (Vitaport 3, TEMEC instruments, Kerkrade, The Netherlands) that was attached to a belt around the patient's waist. The accelerometer signals were sampled at a frequency of 256 Hz, low-pass filtered using a moving averaging window over four samples and digitally stored at a sample frequency of 64 Hz.

Thus far, the most reliable method to assess the severity of LID in daily life is to have the performance rated by experienced physicians. Therefore, the behavior of the patients was videotaped. The videotapes were used to rate the severity of LID on the modified AIMS-scale (Guy, 1976) off-line by two experienced physicians, independently. A five-point scale was used for the rating with a value between 0 (no dyskinesia) and 4 (extreme dyskinesia). Rating was done for each of the four limbs and for the trunk, separately. Data in a hypokinetic off-period without LID was excluded from further analysis.

Each start and end of an activity was stored on the data recorder using a radiographic system. A receiver was connected to the data recorder, and a sender was attached to a portable computer. When the patient started an activity, the experimenter pressed a key on the portable computer indicating the task that was

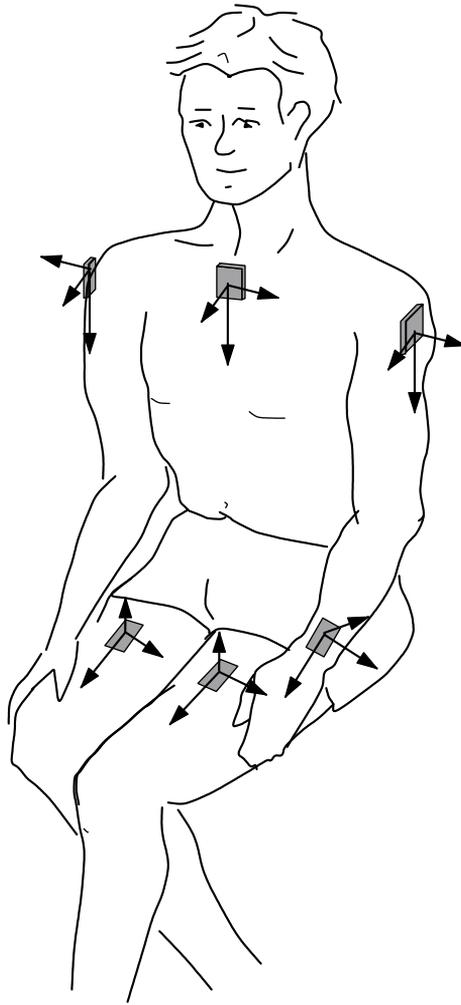


Fig. 1. Schematic overview of the position of accelerometers on the body. The directions for measurement of acceleration by each set of accelerometers are indicated by arrows.

started. The computer immediately transmitted a code to the receiver and the code was written on a separate channel of the data recorder worn by the patient. Simultaneously with recording onset and offset, an LED attached to the receiver was switched on and off. This switching LED informed the physicians to start or to end the video rating of LID.

Since tasks had a different duration and since the severity of LID could fluctuate during an activity, we divided each task in subsequent time intervals of 1-min, since a time resolution of 1-min is clinically relevant and sufficient. Each 1-min interval was evaluated separately, i.e. the severity of LID was video rated by the physicians and the accelerometer characteristics were calculated for all subsequent 1-min intervals.

3. Data analysis

For each 1-min interval signal, several variables were calculated from the accelerometer signals (to be described in detail later) before being presented to the neural network. The neural network was trained using these variables as input and the rating scores given by the physicians as output. Since the training of the neural network has been described in detail elsewhere (Keijsers et al., 2003), we will focus on the main aspects of the neural network architecture and training procedure.

3.1. Preprocessing accelerometer signals

Each accelerometer signal was filtered by a second-order low-pass digital Butterworth filter with a 3-dB cut-off frequency of 8 Hz. Each accelerometer measures a contribution of gravity, related to the orientation of the accelerometer relative to gravity, and a contribution related to linear acceleration of the accelerometer. These components cannot be distinguished from each other. However, any movement will affect the sum of both components and thus any change in the accelerometer signal will reflect movement of the accelerometer. For this reason, the derivative of the accelerometer signal was used as a measure of the amount of movement made by the subject. At each of the six body segments we attached three accelerometers orthogonal to each other. This allows us to measure movement of body segments in all directions. To calculate the frequency and amplitude of body segment movements, we took the square root of the sum of squares of the derivatives of the three accelerometer signals from that body segment (see Eq. (1)). The result will be referred to as “segment velocity”.

$$\text{segment velocity} = \sqrt{\sum_{i=1:3} (ds_i/dt)^2}, \quad (1)$$

where s_i refers to the signal from the i th accelerometer.

For each of the body segments, the segment velocity was used to compute several input variables for a series of subsequent 1-min intervals. The variables and their descriptions are shown in Table 1 and were calculated by a dedicated computer program. The first nine variables were calculated for each of the six different body segments. The variables \bar{V} segment, $SD(V)$ segment, $\%V_\theta$ segment and \bar{V}_θ segment represent the mean velocity of a segment, the standard deviation relative to the mean velocity, the percentage of time a segment is moving, and the mean velocity when a segment moves, respectively. The variables $\bar{V}_{<3\text{Hz}}$ segment, $\bar{V}_{>3\text{Hz}}$ segment, $\bar{V}_{<3\text{Hz}}/\bar{V}_{>3\text{Hz}}$ segment represent the mean segment velocity for frequencies below and above 3 Hz, and their ratio, respectively. These variables were used because it has been suggested before that dyskinesia differs from voluntary movements in the frequency content of the movements (Keijsers et al., 2000; Manson et al., 2000a; Hoff et al., 2001a). Based on the results from these studies, we took the signal power for frequencies in the range between 1 and 3 Hz ($P_{1-3\text{Hz}}$ segment) and above 3 Hz ($P_{>3\text{Hz}}$ segment) as input parameters.

Table 1
Definition of the input variables to the neural network

Symbol	Description
\bar{V} segment	Mean segment velocity
$\bar{V}_{<3\text{ Hz}}$ segment	The mean segment velocity for frequencies below 3 Hz
$\bar{V}_{>3\text{ Hz}}$ segment	The mean segment velocity for frequencies above 3 Hz
$\bar{V}_{<3\text{ Hz}}/\bar{V}_{>3\text{ Hz}}$ segment	The ratio between $\bar{V}_{<3\text{ Hz}}$ segment and $\bar{V}_{>3\text{ Hz}}$ segment
$\text{SD}(V)$ segment	The standard deviation of the segment velocity
$\%V_0$ segment	Percentage of time that a segment was moving. A segment was considered as moving when the low-pass filtered segment velocity was above a threshold of about 0.05 m/s
\bar{V}_0 segment	The mean segment velocity when the segment was considered to be moving, i.e. when V segment $>$ V_0 segment
$P_{1-3\text{ Hz}}$ segment	Power for frequencies in the range between 1 and 3 Hz
$P_{>3\text{ Hz}}$ segment	Power for frequencies above 3 Hz
$\bar{\rho}_{\text{segment}-\text{segment}}$	The mean value of the normalized cross-correlation between the segment velocities of different segments
$\max(\rho_{\text{segment}-\text{segment}})$	The maximum value of the normalized cross-correlation between the segment velocities of different segments
$\%$ Sitting	The percentage of time that a patient was sitting
$\%$ Upright	The percentage of time that a patients body was upright

The variables were calculated for each 1-min interval. The segment could be the most dyskinetic leg (mleg), the less dyskinetic leg (lleg), the most dyskinetic arm (marm), the less dyskinetic arm (larm) and the trunk (trunk). For detailed explanation of the variables, see text.

The cross-correlation between accelerometer signals from different body segments gives an indication of the covariation of movements of these segments. A high cross-correlation indicates that movements of the two limb segments covary, whereas a value near zero indicates that movements of the two limbs are uncorrelated. For this study, we calculated the mean normalized cross-correlation between the velocity of two segments ($\bar{\rho}_{\text{segment}-\text{segment}}$) and the maximum of the normalized cross-correlation ($\max(\rho_{\text{segment}-\text{segment}})$) defined as

$$\bar{\rho}_{\text{segment1}-\text{segment2}} = \frac{1}{T} \int_0^T \frac{1}{2T} \int_{-T}^T v_{s1}(t)v_{s2}(t-\tau) dt d\tau, \quad (2)$$

$$\max(\rho_{\text{segment1}-\text{segment2}}) = \max\left(\frac{1}{2T} \int_{-T}^T v_{s1}(t)v_{s2}(t-\tau) dt\right), \quad (3)$$

respectively, where v_{s1} and v_{s2} represent the segment velocity and T refers to the duration of the signals in time.

The percentage of the time a patient was sitting ($\%$ sitting) or when the patient was standing or walking ($\%$ upright) were also used as variables. These variables were calculated by using the accelerometer signals of the trunk and the leg in a similar way as done by Veltink et al. (1996).

The first nine variables were calculated for each of the six segments, which gave 54 different variables. Other variables were the mean value of the auto- and cross-correlations between movements of the six body segments ($n = 21$). The maximum value

of the cross-correlation between movements of the six body segments gave another 15 variables. The percentage of time, while the patient is sitting or while the patient was standing or walking, added another two variables, which brings the total number of variables to 92. All these variables were presented as input variables to the neural network.

3.2. *Neural network*

The neural network used in this study was a multilayer perceptron (MLP) with an input layer, one hidden layer, and an output layer. Each unit is connected to all units in the next layer. As input variables, we used the variables derived from the accelerometer signals (see Table 1). The number of units in the hidden layer is crucial for the ability of the network to generalize. Generalization is the ability to give a proper classification for a new input pattern, which the network has not encountered before. There was one output unit for each body segment, the value of which reflects the severity of LID of that body segment. This segment could be the most dyskinetic arm, the trunk, or the most dyskinetic leg. The output of the units in the hidden layer was given by a hyperbolic tangent sigmoid transfer function that gives a value between -1 and $+1$. The output of the unit in the output layer was given by a linear transfer function and had a value in the range between 0 and 4 reflecting the AIMS score.

Neural networks need a set of data, which provide examples how sets of input values are related to the output (training-set). The neural network uses these examples to adjust the weights between units in subsequent layers in order to minimize the error between the desired network output and the neural network output for each example. Fig. 2 shows a schematic overview of the data preprocessing and the subsequent neural network approach in assessing the severity of dyskinesia. The lower panel of Fig. 2 shows a neural network with an input layer with six units, a hidden layer with three units and an output layer with one unit. After training, the network was tested using data, which had not been used in the training process (test-set). The neural network was trained using backpropagation. For a good review of neural networks, see Hertz, Krogh, and Palmer (1991).

3.3. *Evaluating the neural network*

The performance of the network was evaluated using the mean square error (MSE) between the neural network output and the score given by the physicians. Since physicians could disagree in their rating, the mean value of the scores of the two physicians was used for training and testing the neural network. The physicians never had a difference in score larger than 1. In addition, the percentage of correctly classified signals by the neural network was used as a second criterion to evaluate the performance of the network. Because physicians rate dyskinesia by integers in the range between zero and four, the neural network classification was seen as correct when the difference between the neural network output and the score given by the physicians was smaller than 0.5. In other words, a classification was seen as correct

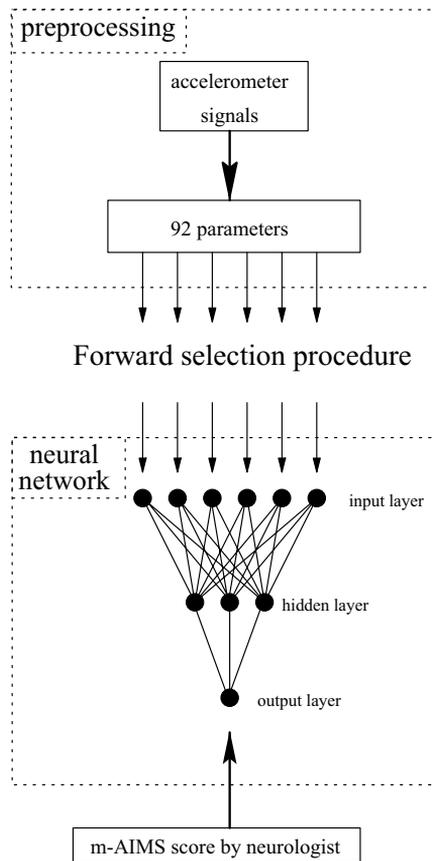


Fig. 2. Schematic overview of the data preprocessing and the subsequent neural network approach in assessing the severity of dyskinesia. The neural network maps the parameters of the accelerometer signal (input) to the rating by the neurologist (output) by adjusting the connection between units in subsequent layers.

when the rounded neural network output was exactly the same as that by the physicians.

3.4. Finding the optimal neural network

The severity of dyskinesia may be different for the different body parts, which is why the severity of dyskinesia has been rated for each body part separately. Furthermore, it is most likely that different parameters are required to detect dyskinesia for different body parts. For these reasons, different neural networks were trained for each body part (trunk, most affected leg and most affected arm). The complexity of a network depends on the number of units in the hidden layer and the number of input parameters. A complex network will result in a good performance on a

training set but can give a poor performance on a test-set as a result of overfitting of the data-set, i.e. the network has a poor generalization performance. For this reason, neural networks with various numbers of hidden units and various numbers of input parameters were trained to assess the severity of the most dyskinetic leg, the most dyskinetic arm, and the trunk. For each number of hidden units the procedure of forward selection (van der Laar, Heskens, & Gielen, 1999) was used to find the most valuable input variables to the neural network to assess the severity of LID. Forward selection means that we started with an empty set of variables, and add, one after another, the variable which causes the largest reduction of the MSE between the neural network output and the score given by the physicians. After each step, we look for the next most important variable, and so forth. This procedure provides insight into the variables which are used by the neural network and which characterize its performance. An advantage of this procedure is that it only adds parameters that add to a better performance.

The optimal neural network was the network with the best generalization performance. The generalization performance of the network was tested by training the network with 80% of the data-set and testing the network with the remaining 20% of the data. This was done 50 times for different randomly selected sets of training and test-sets. The optimal architecture of the network was seen as the network, which gave on average the smallest MSE between the neural network output and the physician's rating on the test-set for the 50 randomly selected sets.

4. Results

In a previous study (Keijsers et al., 2003), we have presented the results of a neural network approach for the detection and rating of dyskinesia in patients with Parkinson's Disease. The performance of the neural network was considerably better than that of previous studies. The main results of that approach are shown in Table 2. Columns 2 and 3 show the MSE for movements of the arm, trunk, and leg between the rating given by the physicians and the rating by the neural network. Considering that dyskinesia is rated on an integer scale between zero (normal subjects) and four (severe dyskinesia), the MSE of 0.17, 0.14 and 0.15 for the arm, trunk and leg, respectively, is quite small. Any differences between the rating by the neural network

Table 2

The MSE between the predicted rating by the neural network and the rating given by the clinicians (columns 2 and 3) for the arm, trunk and leg

Segment	MSE (1-min interval)		Percentage of correct performance
	Training-set	Test-set	
Arm	0.17 ± 0.01	0.19 ± 0.02	90.6
Trunk	0.14 ± 0.01	0.14 ± 0.02	97.5
Leg	0.15 ± 0.01	0.18 ± 0.03	93.4

Moreover, the last column gives the percentage of correctly predicted ratings in 15-min interval for the arm, trunk and leg on the test set.

and that by the physicians were smaller than one, indicating that in the worst case the rating by the neural network was in a class next to that given by the physicians. The fourth column shows the percentage of correctly classified data for 15-min intervals, indicating that the neural network somehow learned to detect and to classify the large majority of dyskinesias. More detailed information about these results can be found in Keijsers et al. (2003).

Each body segment (trunk, most affected leg and most affected arm) was trained with a different neural network architecture. The optimal neural network is defined as the neural network that gave the smallest mean square error on the test-set. This architecture was found by using the forward selection procedure for neural networks with various numbers of hidden units. Since dyskinesia usually lasts longer than 1 min, the accuracy of detecting dyskinesia in 15-min intervals is better than in periods of 1 min. However, since the network was trained on 1-min intervals, we will mainly analyze the results of 1-min interval periods. Therefore, the performance for 1-min intervals shown in Figs. 3, 5, and 9 is slightly less than reported in column 4 of Table 2, which refers to the performance on 15-min intervals.

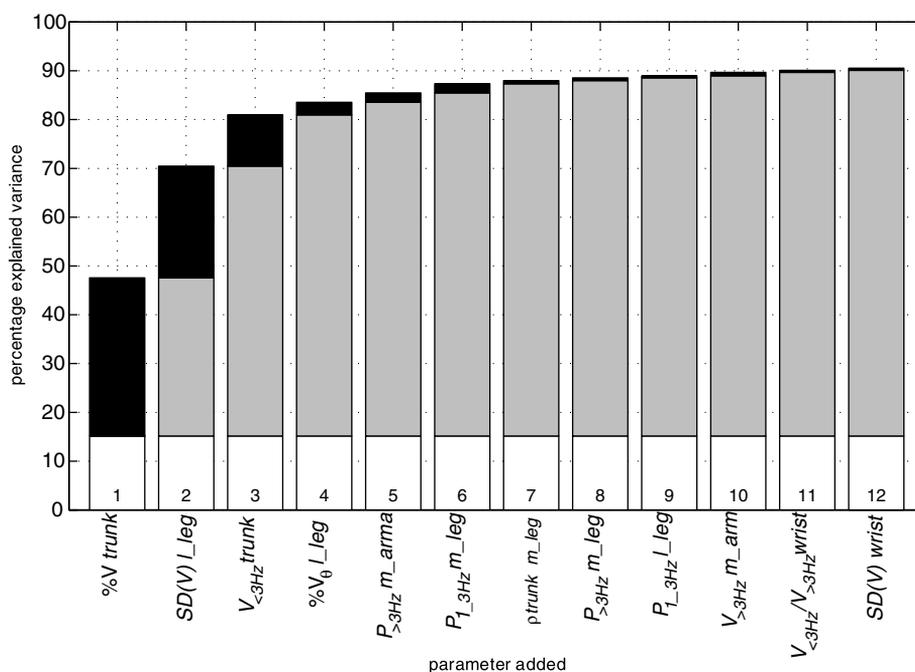


Fig. 3. Most important parameters (see Table 1 for definition of parameters) for assessing the severity of dyskinesia for the trunk. Parameters added at each stage of the forward selection procedure and the percentage of the variance explained (total bars). The white part of the bars shows the percentage of variance due to the difference in rating by the physicians (integer values) and the neural network output (continuous value). The black part of each bar shows the performance due to including this parameter.

4.1. Assessing the severity of dyskinesia for the trunk

For the trunk, the best performing neural network had one hidden unit and required 12 input parameters to reach a correct classification performance of over 97%. The optimal neural network had one hidden unit, indicating that a linear classification was sufficient to assess the severity of dyskinesia for the trunk. Fig. 3 shows the most important parameters, which contribute to the correct classification of dyskinesia for the trunk, in order of their contribution in explaining dyskinesia. Each bar indicates the performance on 1-min intervals that is obtained by including a parameter in the neural network analysis. Since physicians give an integer rating of 0, 1, 2, 3 or 4, while the neural network gives a continuous output between zero and four, there will hardly ever be a perfect match. The white segment of each bar shows the error due to this difference in rating output. The black part of the bar for each parameter indicates the increase of performance due to inclusion of that parameter.

The most important parameter for the classification of movements appears to be the percentage of time that the trunk is moving in a 1-min interval ($\%V_{\theta}$ trunk). This parameter adds 32.4% to the correct performance of the neural network. Parameter $\%V_{\theta}$ trunk appeared to have the largest correlation with the neural network output (0.61), which explains why this parameter appears as the most important parameter to rate dyskinesia. The second most important parameter is the standard deviation of the velocity of the less affected leg ($SD(V)$ l leg), which adds another 22.9% to the performance. The third parameter in order is the power of the velocity signals in the range below 3 Hz ($\overline{V}_{<3\text{ Hz}}$ trunk), which adds an extra 10.5% to the performance. The contribution of the other nine parameters becomes gradually smaller, but is significant and explains an extra 9.6% to the correct performance of the neural network.

The three most valuable parameters together explain 81% of the variance (see Fig. 3). The role of the three most valuable parameters can be appreciated by the data shown in Fig. 4. Fig. 4A shows that patients moving the trunk for a large fraction of time ($\%V_{\theta}$ trunk) and having a small value of the standard deviation of the segment velocity of the less affected leg ($SD(V)$ l leg), are most likely to have dyskinesia. Fig. 4B shows the relation between the second ($SD(V)$ l leg) and third ($\overline{V}_{<3\text{ Hz}}$ trunk) most important parameters at the one hand and the dyskinesia rating by the neural network at the other hand. This figure shows that patients tend to suffer more from dyskinesia when the trunk movements with frequency components below 3 Hz ($\overline{V}_{<3\text{ Hz}}$ trunk) are large relative to the standard deviation of the segment velocity of the leg ($SD(V)$ l leg).

4.2. Assessing the severity of dyskinesia for the arm

The optimal neural network for rating the severity of dyskinesia for the arm was a neural network with two hidden units and six input parameters. The order of the most important parameters and their contribution to the performance is shown in Fig. 5A. The three most important parameters were $\overline{V}_{<3\text{ Hz}}/\overline{V}_{<3\text{ Hz}}$ m leg, $\bar{\rho}_{\text{wrist-trunk}}$ and $\%V_{\theta}$ m leg, adding 23.1%, 18.0% and 7.5% to the correct performance of the neural network for rating 1-min intervals. The other three parameters, added in the for-

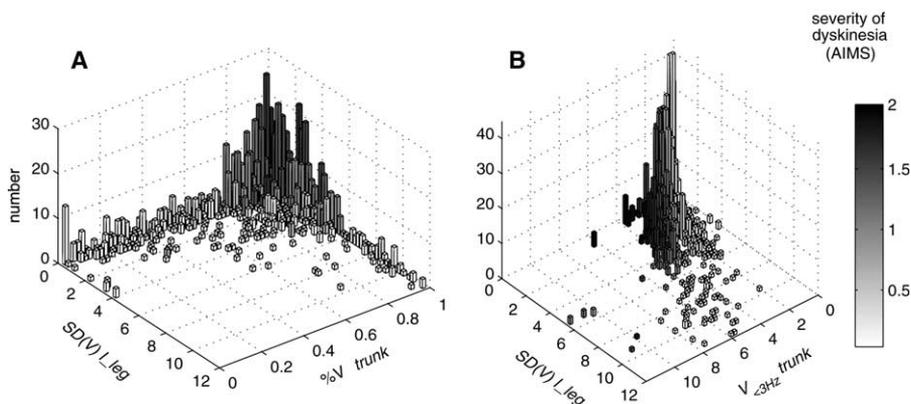


Fig. 4. The relation between the three most valuable parameters and the rating by the neural network for the trunk. The gray scale indicates the severity of dyskinesia given by the neural network (see gray scale bar on the right). The height of the bar indicates the number of 1-min intervals. Panel A shows the severity of dyskinesia as a function of the two most valuable parameters, percentage of time that the trunk is moving ($\%V_0$ trunk) and the standard deviation of the segment velocity of the less affected leg ($SD(V)$ l leg), respectively. Panel B shows the severity of dyskinesia as a function of the second and third most valuable parameter, $SD(V)$ l leg and the power of the segment velocity signal in the range below 3 Hz ($\overline{V}_{<3\text{Hz}}$ trunk), respectively.

ward selection procedure, provided an increase in the performance of the neural network by another 11.6%.

Since the neural network has two hidden units, the relation between the input parameters and the network output is non-linear and not easy to appreciate. Both hidden units contribute in their own way to the severity of dyskinesia. The order of the most important parameters for each hidden unit is shown in panel B and C of Fig. 5. The most important parameters for hidden unit 1 appeared to be the ratio between low and high frequencies of the most affected leg ($\overline{V}_{<3\text{Hz}}/\overline{V}_{<3\text{Hz}}$ mleg) and the cross correlation between wrist and trunk ($\bar{\rho}_{\text{wrist-trunk}}$). For hidden unit 2 the two most important parameters appeared to be parameters of the most affected leg ($\%V_0$ mleg and $\overline{V}_{<3\text{Hz}}/\overline{V}_{<3\text{Hz}}$ mleg).

Hidden unit 1 appeared to be most sensitive to variations in input parameters and was able to detect and rate mild dyskinesias. The output of hidden unit 1 depends on the parameters $\overline{V}_{<3\text{Hz}}/\overline{V}_{<3\text{Hz}}$ mleg, $\bar{\rho}_{\text{wrist-trunk}}$, $\% \text{ sitting}$, $\%V_0$ wrist and $\bar{\rho}_{\text{wrist-larm}}$ (see Fig. 5A). Fig. 6 shows the relation between the two most important parameters ($\overline{V}_{<3\text{Hz}}/\overline{V}_{<3\text{Hz}}$ mleg and $\bar{\rho}_{\text{wrist-trunk}}$, panel A) and the relation between both cross-correlation parameters ($\bar{\rho}_{\text{wrist-trunk}}$ and $\bar{\rho}_{\text{wrist-larm}}$, panel B) for assessing dyskinesia. Hidden unit 1 will contribute to a rating of dyskinesia for the arm mainly when the movements of the most affected leg are predominantly at lower, rather than at higher frequencies (large value for parameter $\overline{V}_{<3\text{Hz}}/\overline{V}_{<3\text{Hz}}$ mleg), and for relatively larger cross-correlation values between wrist and trunk ($\bar{\rho}_{\text{wrist-trunk}}$) (see Fig. 6A). A larger cross-correlation value between movements of the wrist and the trunk ($\bar{\rho}_{\text{wrist-trunk}}$) than between movements of the wrist and least affected arm ($\bar{\rho}_{\text{wrist-larm}}$) resulted in

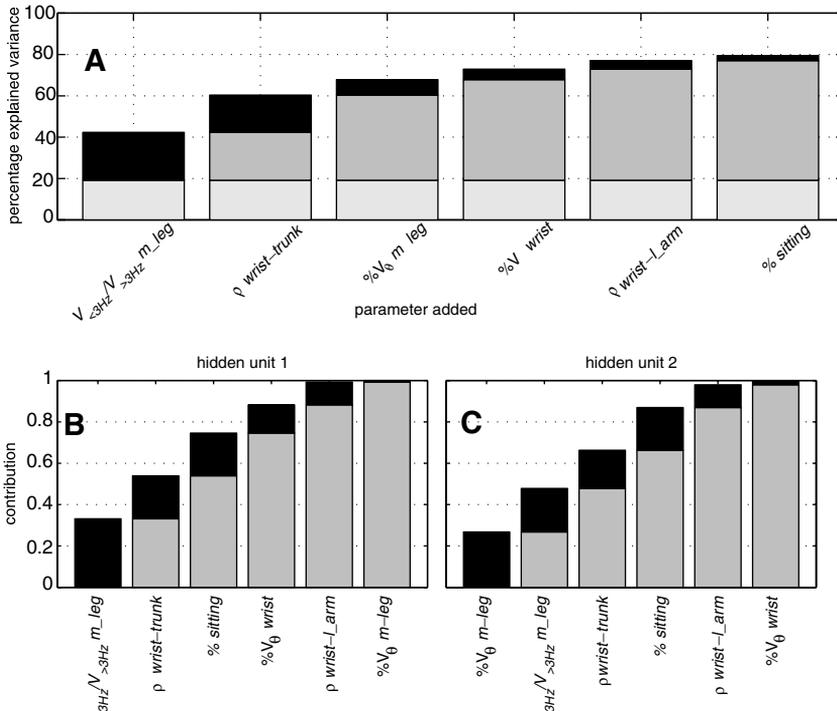


Fig. 5. (Panel A) The six most important parameters (see Table 1 for definition of parameters) for assessing the severity of dyskinesia for the arm as found using forward selection, and the percentage of the variance explained (total bars). The white part of the bar shows the percentage of variance due to the difference in rating by the physicians (integer values) and the neural network output (continuous value). Black part of the bars shows the percentage of variance explained by including the parameter. (Panels B and C) The contribution of the input parameters to the output of the two hidden units of the optimal neural network for the arm (total bars). The contribution was determined using the forward selection procedure. The most important parameter is the first selected parameter. The black part of each bar indicates the increase of performance due to including the parameter.

a higher probability that hidden unit 1 will contribute to a rating of dyskinesia (see Fig. 6B).

Fig. 7 shows the probability that hidden unit 1 contributes to a rating of dyskinesia, as a function of the percentage of time that the wrist was moving for patients who were sitting (black bars, % sitting was larger than 0.95) or for patients who were standing or walking (i.e. when % sitting was smaller than 0.05, gray bars). Hidden unit 1 mainly contributes to a rating of dyskinesia when patients are moving their wrist for a large fraction of time. Moreover, the probability, that a patient, who is moving the wrist for a long time, shows dyskinesia, is larger for a patient who is sitting than for a patient who is standing or walking.

The output of hidden unit 2 depends mainly on the percentage of the time that the most affected leg is moving ($\%V_0 \text{ mleg}$). It contributed to the rating of movements as

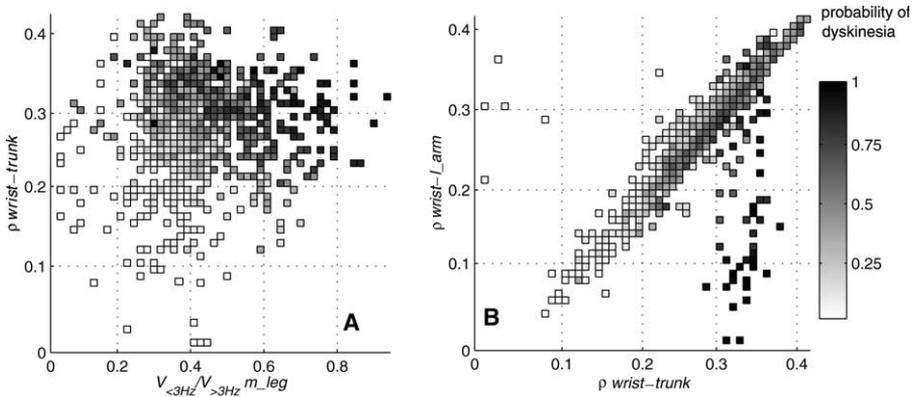


Fig. 6. The probability that hidden unit 1 contributes to a rating of dyskinesia of the arm. Panel A shows the relation between the two most important parameters ($\bar{V}_{<3\text{Hz}}/\bar{V}_{>3\text{Hz}}$ mleg and $\bar{\rho}_{\text{wrist-trunk}}$) and the output of hidden unit 1. Panel B shows the relation between the two cross-correlation parameters ($\bar{\rho}_{\text{wrist-trunk}}$ and $\bar{\rho}_{\text{wrist-larm}}$) and the output of hidden unit 1. The gray scale indicates the probability that hidden unit 1 contributes to a rating of dyskinesia (black, dyskinesia; white, no dyskinesia).

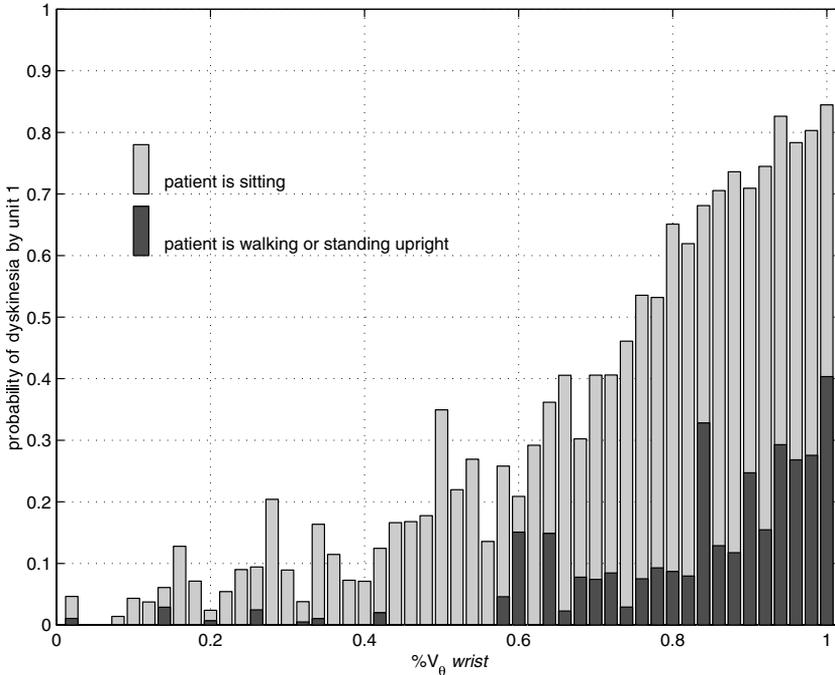


Fig. 7. The probability that hidden unit 1 contributes to a rating of dyskinesia as a function of the percentage of time that the wrist was moving for patients who were sitting (gray bars) and for patients standing upright or walking (black bars) (0, no dyskinesia, 1, dyskinesia).

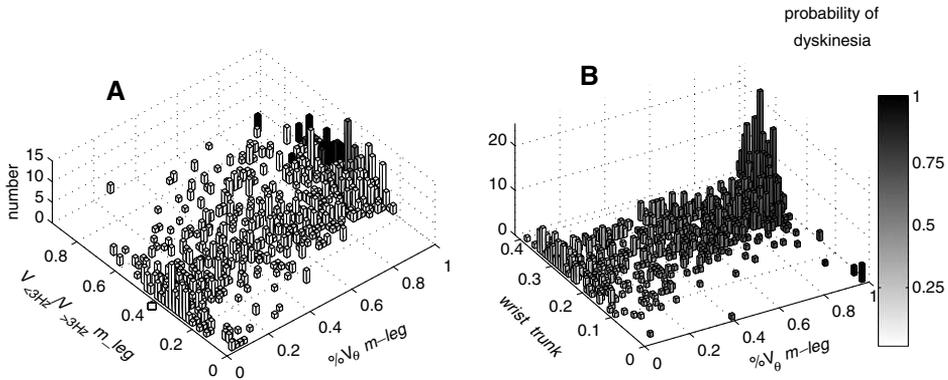


Fig. 8. The relation between the three most valuable parameters and the output of hidden unit 2 of the network for assessing the severity of dyskinesia for the arm. The gray scale indicates the probability that hidden unit 2 contributes to a rating of dyskinesia (see gray scale bar on the right). Panel A shows the probability that unit 2 contributes to a rating of dyskinesia as a function of the two most valuable parameters of hidden unit 2 ($\%V_0$ mleg and $\bar{V}_{<3\text{ Hz}}/\bar{V}_{<3\text{ Hz}}$ mleg). Panel B shows the probability that unit 2 contributes to a rating of dyskinesia as a function of the most important parameter ($\%V_0$ mleg) and third valuable parameter ($\bar{\rho}_{\text{wrist-trunk}}$) of hidden unit 2.

normal (absence of dyskinesia) in 91% of the 1-min intervals and contributed to rating movements as dyskinesia when the most affected leg was moving for at least 88% of the time. This is illustrated in Fig. 8, which shows the role of the second ($\bar{V}_{<3\text{ Hz}}/\bar{V}_{<3\text{ Hz}}$ mleg) and the third ($\bar{\rho}_{\text{wrist-trunk}}$) most important parameter in rating dyskinesia. When the most affected leg is moving in at least 88% of the time, hidden unit 2 contributes to a rating of dyskinesia when these movements are predominantly at lower, rather than at higher frequencies (large value for parameter $\bar{V}_{<3\text{ Hz}}/\bar{V}_{<3\text{ Hz}}$ mleg) (see Fig. 8A), and when the movements between wrist and trunk are uncoordinated (small value for parameter $\bar{\rho}_{\text{wrist-trunk}}$) (see Fig. 8B). Hidden unit 2 appeared to contribute to a rating of dyskinesia when patients suffer from severe dyskinesia in the arm. This became obvious from the fact that the physicians rated a score of 2 or more for the arm in 71% of the 1-min intervals that were rated dyskinetic by hidden unit 2.

4.3. Assessing the severity of dyskinesia for the leg

The optimal neural network for rating the severity of dyskinesia for the leg was a neural network with three hidden units and seven input parameters. Fig. 9A shows the order of the most important parameters and their contribution to the correct classification of dyskinesia for the leg. The parameters $SD(V)$ lleg and $\%V_0$ mleg were the most important parameters and explained together 72.1% of the performance for rating 1-min intervals. The other five parameters added in the forward selection procedure, provided an increase of 13.4% to the performance.

The neural network for the leg used three hidden units. The various parameters play a different role for each of the hidden units. The order of the most important

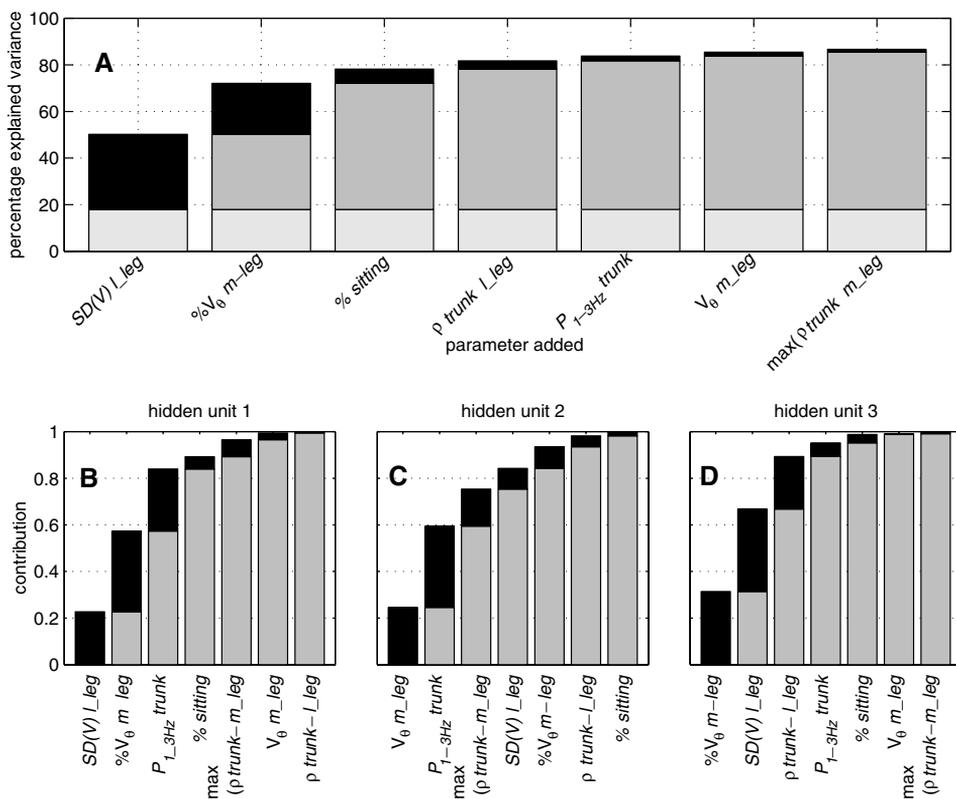


Fig. 9. (Panel A) Most important parameters (see Table 1 for definition of parameters) for assessing the severity of dyskinesia for the leg. Parameters added at each stage of the forward selection and the percentage of the variance explained. The white part of the bar shows the percentage of variance due to the difference in rating by the physicians (integer values) and the neural network output (continuous value). Black part of the bars shows the percentage of variance explained by including the parameter. (Panels B, C and D) The contribution of the input parameters to the output of the three hidden units of the optimal neural network for the leg (total bars). The contribution was determined using the forward selection procedure. The most important parameter is the first selected parameter. The black part of each bar indicates the increase of performance due to including the parameter.

parameters for each hidden unit is shown in panels B, C and D of Fig. 9. Hidden unit 1 appeared to be most sensitive to variations in the input parameters and played a role in the rating of mild dyskinesias. The most valuable parameters of hidden unit 1 were the parameters selected in the early stages of the forward selection procedure (parameters SD(V) l leg and %V_θ m leg and P_{1-3Hz} trunk). Fig. 10 shows the probability, that hidden unit 1 contributes to a rating of dyskinesia as a function of the two most valuable parameters (SD(V) l leg and %V_θ m leg, panel A) and as a function of the first and third most important parameters (SD(V) l leg and P_{1-3Hz} trunk, panel B). Hidden unit 1 contributes to a rating of dyskinesia when the standard deviation of the less dyskinetic leg has a small value and when the most dyskinetic leg is moving

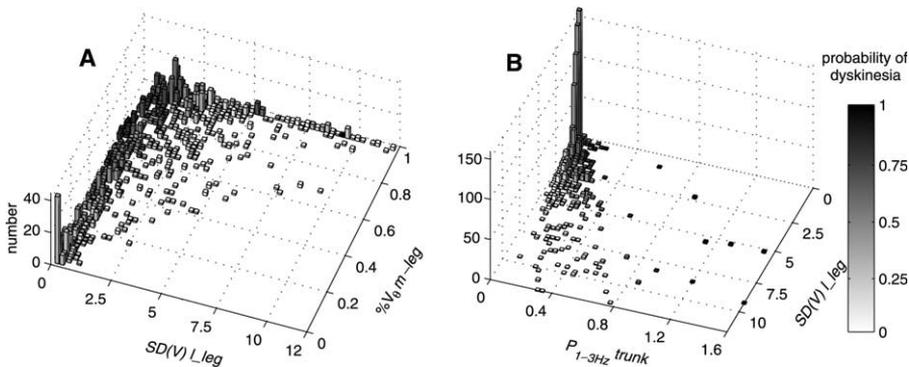


Fig. 10. The relation between the three most valuable parameters and the output of hidden unit 1 of the network for assessing the severity of dyskinesia for the leg. The gray scale indicates the probability that hidden unit 1 contributes to a rating of dyskinesia (see gray scale bar on the right; black, dyskinesia; white, no dyskinesia). Panel A shows the probability that hidden unit 1 contributes to a rating of dyskinesia as a function of the two most valuable parameters ($SD(V)_{lleg}$ and $\%V_0 mleg$). Panel B shows the probability that hidden unit 1 contributes to a rating of dyskinesia as a function of the most important parameter ($SD(V)_{lleg}$) and third valuable parameter ($P_{1-3Hz} trunk$).

for a large fraction of time (see Fig. 10A). In addition, the probability that hidden unit 1 contributes to a rating of dyskinesia increases for a higher power for frequencies in the range between 1 and 3 Hz of the trunk (see Fig. 10B). The contribution of the parameter % sitting is that the probability of rating dyskinesia by the neural network increases for patients who are mainly sitting.

Hidden unit 2 played a role in rating dyskinesia in a special case. The most valuable parameters of hidden unit 2 were the parameters selected in the later stage of the forward selection procedure ($\bar{V}_\theta mleg$, $P_{1-3Hz} trunk$ and $\max(\rho_{mleg-trunk})$, see Fig. 9). Hidden unit 2 contributes to a rating of dyskinesia in only 7.6% of the 1-min intervals. The most valuable parameters for hidden unit 2 appeared to be the parameters $\bar{V}_\theta mleg$ and $P_{1-3Hz} trunk$ and to a lesser extent the parameters $\max(\rho_{mleg-trunk})$, $SD(V)_{lleg}$ and $\%V_0 mleg$. Hidden unit 2 contributes to a rating of dyskinesia when the mean velocity of the dyskinetic leg during moving is relatively small and when the power for frequencies in the range between 1 and 3 Hz of the trunk is large.

Hidden unit 3 reveals a behavior similar to that by hidden unit 2 of the neural network for the arm. It contributes to the rating of dyskinesia only when a patient suffers from severe dyskinesia in the leg. Hidden unit 3 rated dyskinesia in 8% of the 1-min intervals and parameter $\%V_0 mleg$ was the most important parameter. The other important parameters ($SD(V)_{lleg}$ and $\bar{\rho}_{lleg-trunk}$) played only a role when the most affected leg was moving in at least 91% of the time. Hidden unit 3 appeared to contribute to a rating of dyskinesia when the leg was moving in at least 91 percent of the time, when the standard deviation of velocities of the less affected leg ($SD(V)_{lleg}$) was small. The probability that hidden unit 3 contributes to a rating of dyskinesia increases when the cross-correlation between the less affected leg and the trunk ($\bar{\rho}_{lleg-trunk}$) is relatively small for the large number of movements.

5. Discussion

In a previous study (Keijsers et al., 2003), we have presented the results of a neural network approach for the detection and rating of dyskinesia in patients with Parkinson's disease. The neural network correctly classified dyskinesia or the absence of dyskinesia in 15-min intervals in 93.7%, 99.7% and 97.0% for the arm, the trunk, and the leg. In the present study, we focused on the role of the important parameters to assess the severity of dyskinesia and on how they contribute to a better understanding of movement characteristics in dyskinetic patients with Parkinson's disease.

A major advantage of using neural networks for the detection and rating of LID with the forward selection procedure to find the most relevant parameters is that this procedure searches for the most relevant parameters without any prior information and restriction. Our results showed that the most important parameters ($\bar{V}_{<3\text{ Hz}}/\bar{V}_{<3\text{ Hz}}$ mleg, $\%V_{\theta}$ trunk and $\text{SD}(V)$ lleg for arm, trunk and leg, respectively) were the best parameters for all segments, whatever the search algorithm. We also found that sometimes one parameter could be replaced by another parameter without large consequences for the performance of the neural network. This was usually related to the fact that parameters were highly correlated. For example, parameter $P_{<3\text{ Hz}}$ segment gave almost the same performance as parameter $\bar{V}_{<3\text{ Hz}}$ segment. We conclude that the selected parameters give a good representation of the important relevant parameters, which play a role in the assessment of the severity of dyskinesia.

For both the trunk and the leg the percentage of time that this segment was moving ($\%V_{\theta}$ trunk and $\%V_{\theta}$ mleg, respectively) and the standard deviation of the segment velocity of the less dyskinetic leg ($\text{SD}(V)$ lleg) gave the best performance. The importance of the percentage of time that a segment is moving is obvious, since a small percentage indicates few movements and probably no dyskinesia, while a large percentage indicates many movements and thus a higher probability that the subject might suffer from dyskinesia. Parameter $\text{SD}(V)$ lleg appeared to play an important role to detect whether a patient is walking or not. In general, dyskinesia is characterized by large values of $\%V_{\theta}$ segment and small values of $\text{SD}(V)$ lleg (see Figs. 3, 7, 8, 10). During walking, the percentage of time that a segment is moving is large like in dyskinesia. But in contrast to dyskinesia, parameter $\text{SD}(V)$ lleg showed large values for patients with normal walking behavior. The leg and to a lesser extent the trunk, are segments that are mainly involved in displacement of the whole body. The neural network is able to detect normal displacement (walking) by using parameters $\%V_{\theta}$ segment and $\text{SD}(V)$ lleg. This might explain the importance of these two parameters and the good performance of assessing the severity of dyskinesia for the trunk and leg using these two parameters. For the arm, the parameter combination $\%V_{\theta}$ wrist and $\%$ sitting appeared to be the parameter combination which explained the largest part (70.6%) of the variance of the output of the most sensitive hidden unit (hidden unit 1). The role of parameter $\%$ sitting can be compared with the role of parameter $\text{SD}(V)$ lleg. During sitting, subjects usually do not voluntarily move their arms continuously. Thus a large percentage of time that the wrist is moving when a patient is sitting implies a higher probability that a patient suffers from dyskinesia.

Previous studies in assessing dyskinesia focussed mainly on parameters in the frequency domain (Hoff et al., 2001a; Manson et al., 2000a). The results of these studies showed that dyskinetic movements were represented in the lower frequency bands (between 1 and 4 Hz, refs). In the present study, parameters $\bar{V}_{<3\text{Hz}}$ trunk, $\bar{V}_{<3\text{Hz}}/\bar{V}_{<3\text{Hz}}$ mleg and $P_{1-3\text{Hz}}$ trunk showed relatively larger values for patients suffering from dyskinesia (see Figs. 4, 6, 8, and 10). Therefore, these results support the results of previous studies that dyskinesia is most dominant for movements in the lower frequency range. Moreover, dyskinesia occurs in frequencies significantly lower than the frequency domain of tremor, which is found above 3 Hz (Dubinsky, 1995; Hoff, Wagemans, & Hilten, 2001b). Therefore, dyskinesia can easily be distinguished from tremor.

The cross-correlation parameter played an important role in assessing the severity of dyskinesia but its role is somewhat complicated. The role of the cross-correlation parameter was related to motor activity of the segments and the correlation of the segment velocity between the segments. Subjects showing small values of the mean cross-correlation (below 0.2) or large mean cross-correlation values (above 0.38) were not suffering from dyskinesia (see Fig. 6) while patients showing mean cross-correlation values between 0.2 and 0.38 will have a larger probability that they were dyskinetic. Values of the mean cross-correlation below 0.2 are usually a result of little motor activity, while values of the mean cross-correlation above 0.38 are a result of a large number of well correlated voluntary movements. The large mean value of the cross-correlation corresponds to the observation by Soechting et al. (1986), that joint velocities in elbow and shoulder covary during reaching and pointing movements to targets in 3D space. When the mean cross-correlation has a value between 0.2 and 0.38, parameter $\bar{V}_{<3\text{Hz}}/\bar{V}_{<3\text{Hz}}$ mleg appears to be an important parameter to indicate whether a subject is dyskinetic. Patients with mean cross-correlation values between 0.2 and 0.38 are most likely dyskinetic, when movements are predominantly at lower, rather than at higher frequencies (see Fig. 6). The hidden unit, which contributed mainly to a rating of dyskinesia for severe dyskinesia (hidden unit 2 for the arm and hidden unit 3 for the leg), rated dyskinesia when the cross-correlation parameter has a relatively small value in conditions when there are a lot of movements ($\%V_{\theta}$ large, see Fig. 8). The role of the cross-correlation suggests that movements of body segments are not well coordinated in dyskinesia, which was also found in our previous study (Keijsers et al., 2000).

The neural network for assessing the severity of dyskinesia for the arm used two cross-correlation parameters, namely $\bar{\rho}_{\text{wrist-trunk}}$ and $\bar{\rho}_{\text{wrist-larm}}$. When parameter $\bar{\rho}_{\text{wrist-trunk}}$ has a value between 0.2 and 0.38 and when parameter $\bar{\rho}_{\text{wrist-larm}}$ was smaller than parameter $\bar{\rho}_{\text{wrist-trunk}}$, the probability that hidden unit 1 will rate dyskinesia increases (see Fig. 6B). This means that it is most likely that subjects move voluntarily when wrist movements covary equally with movements of the trunk and of the less affected arm.

The neural networks for assessing the severity of dyskinesia for the arm and the leg used two and three units in the hidden layer, respectively. The neural network of both segments had one hidden unit (hidden unit 1 for leg and arm) that played a role in assessing mild dyskinesia using general characteristics of dyskinesia as described

above. The other hidden units of the neural network were involved in detecting severe dyskinesia. Hidden unit 2 of the arm and hidden unit 3 of the leg were hidden units that rated only dyskinesia when a patient suffered from severe dyskinesia. For both segments, the hidden unit rated dyskinesia when the most dyskinetic leg was moving ($\%V_{\theta}$ mleg) in at least 90% of the time while the other parameters did not imply stereotyped voluntary movements. The leg is a segment that is involved in voluntary movements mainly during displacements of the whole body like walking. Therefore, a lot of movement in the leg means either dyskinesia or displacement of the whole body. A distinction of the latter is made by a large value of parameter $SD(V)$ lleg and a relatively large value of the cross-correlation parameter.

For assessing the severity of dyskinesia of the leg and trunk, the neural network used mainly parameters of the trunk and leg (see Figs. 3 and 9). However, for assessing the severity of dyskinesia of the arm, parameters of the most dyskinetic leg ($\bar{V}_{<3\text{ Hz}}/\bar{V}_{<3\text{ Hz}}$ mleg and $\%V_{\theta}$ mleg) were important (see Fig. 5). Especially for severe dyskinesia, the rating was mainly based on the percentage of time that the most dyskinetic leg was moving (hidden unit 2). Presumably, severe dyskinesia in the leg implies at least mild dyskinesia in the arm, which was also described by Marconi et al. (1994). The advantage of using parameters of the leg instead of the arm is that the leg is less involved in voluntary movements than the arm except for walking. In case the leg is voluntarily moving, other parameters ($\bar{V}_{<3\text{ Hz}}/\bar{V}_{<3\text{ Hz}}$ mleg and $\bar{\rho}_{\text{wrist-trunk}}$) indicate that the patient may be moving voluntarily. Apparently, the neural network used parameters of the most affected leg to rate dyskinesia for the arm, based on the assumption that severe dyskinesia for the leg will imply at least mild dyskinesia for the arm (Marconi et al., 1994).

In our previous paper (Keijsers et al., 2003), we reported that neural networks could successfully detect dyskinesia and distinguish dyskinesia from voluntary movements. In this study, we have analyzed the optimal neural networks to find the important parameters that can detect and explain the severity of dyskinesia. The analysis showed that the percentage of time that a segment was moving is the most important parameter to detect dyskinesia. Other movement parameters are important, but in a different way for different limb segments. For the trunk and the leg, the standard deviation of the segment velocity of the less dyskinetic leg is important too. For the arm the combination of the percentage of time, that the wrist was moving, had to be combined with the percentage of time, that a patient was sitting. In addition, dyskinesia differs from voluntary movements in the fact that dyskinetic movements tend to have lower frequencies than voluntary movements and in the fact that movements of different body segments are not well coordinated in dyskinesia.

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