Dissociation of Habit-Learning in Parkinson’s and Cerebellar Disease

K. Witt, A. Nuhsman, and G. Deuschl

Abstract

Damage to the medial-temporal region is known to result in declarative (explicit) memory deficits but nondeclarative (implicit) memory is largely unaffected by such lesions. Earlier studies have shown that some forms of implicit learning depend on cerebellar circuits but remain preserved following affections of the basal ganglia circuits. It is unknown which forms of implicit learning persist in patients with cerebellar pathology but are affected after basal ganglia lesions. Therefore, we determined if a test sensitive for habit-learning (probabilistic classification task) resulted in normal values for patients with cerebellar disease but resulted in affected results in patients with Parkinson’s disease (PD). To this end, 23 patients with PD, 16 patients with familial or idiopathic cerebellar degeneration (CD), and 20 controls were tested for habit-learning. There was no impairment of patients with CD for the early learning period but there was abnormal learning in the PD group. For a later learning period, the patients with the PD showed improved performance. We conclude that the probabilistic learning task is an implicit, nonmotor learning task which is sensitive for basal ganglia pathology but remains unaffected in the case of cerebellar pathology. Such a test may be of special interest for the detection and possible neurobehavioral treatment of cognitive and motor deficits.

INTRODUCTION

Cerebellar pathology of various etiologies causes motor impairments. In addition, some studies have found deficits in cognitive planning (Schmahmann & Sherman, 1997; Grafman et al., 1992), executive functions (Appollonio et al., 1994), and paired association learning (Drepper, Timmann, Kolb, & Diener, 1999). Other studies, however, could not confirm these findings (Gomez Beldarrain, Garcia-Monco, Quintana, Llorens, & Rodeno, 1997; Daum et al., 1993). The role of the cerebellum in explicit (declarative) learning and memory is still a matter of debate, but profound impairment in implicit (nondeclarative) learning has been demonstrated (Daum, Schugens, Breitenstein, Topka, & Spieker, 1996; Pascual-Leone et al., 1993; Topka, Valls-Sole, Massaquoi, & Hallett, 1993; Sanes, Dimitrov, & Hallett, 1990). Patients with cerebellar dysfunction failed to learn the serial reaction time task, which is sensitive for testing modality-specific memory for skill-based procedures (Pascual-Leone et al., 1993). These patients are impaired in motor learning (Sanes et al., 1990) and in classical conditioning (Topka et al., 1993) (e.g., eye-blink conditioning with the electrically elicited blink reflex). A similar, though milder, deficit in performing the serial reaction time task has been reported for patients with Parkinson’s disease (PD) (Ferraro, Balota, & Connor, 1993), but classical conditioning is unaffected in PD (Sommer, Grafman, Clark, & Hallett, 1999; Daum, Schugens, Breitenstein, Topka, & Spieker, 1996). It has been concluded that basal ganglia and cerebellum are part of implicit learning and memory systems in humans (Salmon & Butters, 1995). However, these results demonstrate that some forms of implicit learning such as classical conditioning depend on cerebellar circuits but persist following affections of the basal ganglia circuits. It remains unknown if there are forms of implicit learning which are preserved in cerebellar pathology but are affected following basal ganglia disturbances.

Knowlton, Squire, and Gluck (1994) could demonstrate normal implicit learning in amnesic patients in a probabilistic classification task without a relevant motor component. In this computer task (weather prediction task), subjects learn associations between a stimulus (four cards appearing alone or in sets of two or three cards) and the correct response (predicting “rain” or “sunshine”). The probabilistic structure of the task is not obvious and therefore difficult to memorize in a declarative manner. Nondemented patients with PD and patients with Huntington’s disease (HD) showed no learning effects in this task (Knowlton, Mangels, & Squire, 1996; Knowlton & Squire, 1996). Learning deficits in these patients cannot be explained by limited motor function. The authors concluded that this probabilistic discrimination paradigm describes a specific...
class of nondeclarative learning abilities in human subjects. This might be a form of habit-learning as it shows a graded learning pattern similar to stimulus–response habit-learning in animal studies and it is known that diseases affecting the basal ganglia (PD and HD) in humans display specific impairments (Knowlton et al., 1996; Knowlton & Squire, 1996). This is of special interest because it might indicate a specific basic

### Table 1. Clinical Data of the Patients and the Controls

<table>
<thead>
<tr>
<th></th>
<th>Parkinsonian Patients</th>
<th>Cerebellar Patients</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SEM)</td>
<td>Mean (SEM)</td>
<td>Mean (SEM)</td>
</tr>
<tr>
<td>n</td>
<td>23</td>
<td>16</td>
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<tr>
<td>Female</td>
<td>11</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Male</td>
<td>12</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>Age</td>
<td>60.35 (7.64)</td>
<td>53.38 (14.71)</td>
<td>59.81 (7.58)</td>
</tr>
<tr>
<td>Years of education</td>
<td>9.91 (1.83)</td>
<td>9.95 (1.0)</td>
<td>9.47 (1.21)</td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>106.59 (17.60)</td>
<td>101.16 (6.40)</td>
<td>101.59 (5.11)</td>
</tr>
<tr>
<td>Hoehn and Yahr</td>
<td>2.3 (0.76)</td>
<td></td>
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</tr>
<tr>
<td>UPDRS (III) scores</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Drug on</td>
<td>17.83 (7.63)</td>
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<td></td>
</tr>
<tr>
<td>Drug off</td>
<td>35.75 (12.25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebellar rating scale</td>
<td>17.75 (4.95)</td>
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</table>

IQ = estimated IQ using a formula by Wilson et al. (1978); UPDRS = Unified Parkinson’s Disease Rating Scale; Cerebellar Rating Scale = a clinical rating scale for cerebellar function assessing standing balance impairment, gait ataxia, upper and lower limb ataxia, muscle tone, tremor, dysarthria, and ocular movement impairment (Deuschl, Toro, Zeffiro, Massaquoi, & Hallett, 1996).

### Table 2. Background Neuropsychological Evaluation of Patients and Control Subjects

<table>
<thead>
<tr>
<th></th>
<th>Parkinson Patients (n = 23)</th>
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<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
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<tr>
<td>WIP IQ</td>
<td>108.22 (24.76)</td>
<td>106.25 (13.52)</td>
<td>110.90 (12.63)</td>
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<tr>
<td>Information</td>
<td>111.87 (14.71)</td>
<td>106.56 (13.87)</td>
<td>106.67 (11.22)</td>
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<td>108.86 (12.09)</td>
<td>105.62 (9.99)</td>
</tr>
<tr>
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<td>111.34 (14.36)</td>
<td>102.25 (16.35)</td>
<td>103.62 (14.59)</td>
</tr>
<tr>
<td>Block design</td>
<td>95.60 (24.76)*</td>
<td>97.63 (18.78)*</td>
<td>114.10 (15.22)</td>
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<tr>
<td>MMSE</td>
<td>28.17 (1.2)</td>
<td>27.9 (1.86)</td>
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<tr>
<td>Verbal IQ</td>
<td>109.35 (13.78)</td>
<td>106.19 (18.76)</td>
<td>105.10 (11.40)</td>
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**Digit span**

<table>
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<tr>
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<th>Control Group (n = 20)</th>
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<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Forward</td>
<td>6.78 (1.20)</td>
<td>5.63 (1.15)</td>
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<tr>
<td>Backward</td>
<td>5.09 (1.38)</td>
<td>3.63 (0.96)*</td>
<td>5.57 (0.98)</td>
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</table>

**WCST**

<table>
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<th>Control Group (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Numbers of categories correctly sorted</td>
<td>4.35 (1.37)*</td>
<td>4.93 (1.29)*</td>
<td>5.55 (0.60)</td>
</tr>
<tr>
<td>Number of errors</td>
<td>11.17 (1.45)*</td>
<td>9.00 (4.13)*</td>
<td>4.75 (1.45)</td>
</tr>
</tbody>
</table>

WIP = Wechsler Intelligence Scale; MMSE = Mini-Mental State Examination, verbal IQ from a vocabulary test, WCST = Wisconsin Card Sorting Test.

*Significant difference to the control subjects at the level of p < .05 (t test).
deficit of cognitive performance. The question has never been addressed as to whether these abnormalities are specific for basal ganglia abnormalities or whether they might reflect concurrent functional affection of the cerebellum. Indeed, there is considerable evidence that the cerebellum plays an important role in certain types of nondeclarative learning, but little is known about the involvement of the cerebellum in specific habit-learning. Therefore, we tested 16 patients with cerebellar degenerations (CDs) on a task (weather prediction task) sensitive to a specific form of habit-learning in humans and compared them with 23 patients with PD and 20 normal age-matched controls (for descriptive statistics, see Table 1). A standard neuropsychological test battery was applied to assess general intelligence, working memory, and executive functions.

RESULTS
There is no significant difference between patients and control subjects regarding age, sex, years of education, and estimated premorbid IQ. The results of the neuropsychological test battery are summarized in Table 2. Both PD and CD patients were impaired in the subtest Block Design of the Wechsler Intelligence Scale. A paired t test showed that the number of categories correctly sorted was significantly lower in the patients groups compared to the controls groups (t test, p < .05). Significantly lower scores were also obtained by the CD group in the digit backwards test.

Figure 1 displays the weather task performance in the early phase (Trials 1–50). All groups started at chance performance on the first block of 10 trials. For the first 50 trials, cerebellar patients and control subjects performed similarly, increasing the correct predictions made by chance to a level of about 63% correct responses in Trials 41 to 50. A two-way ANOVA comparing the CD group with the controls across five blocks of 10 trials (early learning period) revealed no group effect or Group × Trial Block interaction. Comparing the PD group with the controls, a two-way ANOVA revealed a significant effect of the PD group (F = 6.43, p = .015). There is also a significant difference comparing the CD group with the PD group (F = 4.75, p = .036). Both the control and the CD group performed significantly better than chance performance in Trials 31–40 [controls: t(3,3), p = .001; CD group: t(2.84), p = .006] and in Trials 41–50 [controls: t(2.9), p = .005; CD group: t(1.3), p = .05]. Performance on Trials 51–100 was better for the control subjects than the PD group but failed statistic significance (p > .05). In the last learning phase (Trials 101–150), there was no significant difference between the PD and the CD groups (Figure 1).

DISCUSSION
The probabilistic classification task has been shown to be an implicit-learning task because amnesic patients perform equally as well as normal subjects (Knowlton et al., 1994), and therefore, explicit-learning circuits do not play a major role in the early learning phase of the
task. The present study has demonstrated, for the first time, that intact cerebellar circuits are not essential to performing this test and we have confirmed that patients with PD have a significant deficit of this kind of implicit learning. This task seems to be the first implicit-learning test which displays abnormal results in PD but normal results in patients with cerebellar pathology and which does not depend on the motor performance of the subjects. Therefore, it is well suited for assessing patients with movement disorders.

The implicit-learning systems are divided into priming, which is considered to be dependent mainly on cortical areas and conditioning, as well as on skills-learning and habit-learning, which are considered to be dependent mainly on subcortical structures. The role of the brainstem and the cerebellar structures in classical conditioning has been extensively studied in humans (Doyon et al., 1997; Deuschl et al., 1996; Solomon, Stowe, & Pendlebury, 1989) and animals with various lesions (Yeo, Hardiman, & Glickstein, 1984, 1985). Diseases affecting the basal ganglia do not influence classical conditioning (Daum et al., 1996). The role of subcortical structures in skill-learning remains less clear. Patients with HD and PD are impaired in learning sequence-specific facts in the serial reaction time task (Ferraro et al., 1995) and are impaired in motor skill learning in the pursuit rotor task (Heindel, Salmon, Shultz, Walicke, & Butters, 1989). Patients with cerebellar pathology also demonstrate impaired performance in these tasks (Pascual-Leone et al., 1993). Furthermore, they show abnormal adaptation learning (Sanes et al., 1990), which is considered to be a form of skill-learning.

All these skill-like procedures have a significant motor component that sets specific constraints on the interpretation of the results. The impaired execution of movements in cerebellar disease may influence the results in the pursuit rotor task. Furthermore, cerebellar input to the basal ganglia and prefrontal cortical areas (Middleton & Strick, 1994) may be impaired in cerebellar disorders. For that reason, the sequence structure of the serial reaction time task, which is considered to be a function of the frontal cortex, might explain the learning deficit in patients with cerebellar diseases. In contrast, the probabilistic classification task presented here has no significant motor component which could confound the results in our patients handicapped by akinetic or cerebellar symptoms.

Factors other than cerebellar pathology might explain the results of this study. Firstly, learning in the early phase may be mediated through the working memory. However, not only the PD, but also the CD, group in our study showed significant impairment in the reverse digit span, a test sensitive for working memory capacity (Lezak, 1995). Furthermore, Knowlton et al. (1994) have posed this issue in an earlier study in amnesic patients known to have a spared working memory. After a break of 5 min following the first 50 trials, retaining knowl-

edge of cue–outcome associations in working memory was interrupted. In the following 20 trials, the amnesic patients showed significant saving of stimulus–response habits compared to the performance of control subjects. If working memory played a major role in the probabilistic classification task, the performance of the amnesic patients after a break and the CD group in our study showing significantly impaired working memory capacity should have demonstrated defective probabilistic classification learning. Another possible confounder of our findings would be the dependence of the task upon frontal lobe functions. Our CD and PD patients performed comparably in the Wisconsin Card Sorting Test, a test sensitive for disturbances in executive function. Knowlton et al. (1996) found normal classification learning in patients with frontal lesions, but only 10 patients with frontal lesions were tested. Additionally, the frontal cortex does not seem to be critical in acquiring perceptual skills (Daum et al., 1995) (e.g., mirror reading) and motor skills (Doyon et al., 1997, 1998) (e.g., the serial reaction time task). Finally, there was no difference in the overall score of the general intelligence test (Wechsler Intelligence Scale) between the three groups of our study. In the subtest Block Design, the PD and the CD groups performed significantly lower compared to the control group. This task has a motor and a large visuospatial component. Visuospatial deficits are present in Parkinson patients (Boller et al., 1984) and patients with cerebellar dysfunction (Schmahmann & Sherman, 1998). In addition, both patient groups showed motor impairment, which may explain why the patients performed worse than the control subjects. Generally, subnormal intelligence or any specific declarative learning deficit excluding the working memory could not be observed in the examined groups. Thus, additional deficits of the explicit-learning system cannot explain the results. In summary, probabilistic classification learning is independent of working memory, executive functions, and declarative learning. This favors the concept of an independent habit-learning system located at the basal ganglia and is against the view that all neuropsychological deficits of PD are due to limited processing resources or the result of a frontal dysfunction (Brown & Marsden, 1990). Our findings are in accordance with the hypothesis of Mishkin, Malamut, and Bechelavier (1984) that the basal ganglia are the “head ganglia” of the habit system. Further studies in man have confirmed this hypothesis although these investigations could not separate neostriatal from frontal functions (Saint-Cyr, Taylor, & Lang, 1988; Butters, Wolfe, Martone, Granholm, & Germak, 1985).

The paradigm used in this article has been recently explored with functional MRI in normal subjects (Polack, Prabhakaran, Seger, & Gabrieli, 1999). Compared to a perceptual-motor control task, the bifrontal cortices, the right caudate nucleus, and the occipital cortex
were active during probabilistic classification. Interestingly, Poldrack et al. also found significant cerebellar activation during probabilistic classification, although this was not mentioned explicitly in their publication. This finding is still unexplained and simply does not match our results, but implicit- and explicit-learning systems may work in parallel (Squire & Zola, 1996) and therefore complement each other. The cerebellar activation may reflect such explicit learning. Another possibility would be that the cerebellum is active during this task, but this activation is not necessary for normal performance. Other explanations cannot be excluded.

Another observation of our study was that the PD patients performed better during extended learning sessions. Knowlton et al. (1994) observed that control subjects were able to outrank the amnesic patients beyond the 50th trial. They found that controls could verbalize knowledge about a successful strategy in the later learning stage, indicating that they had become aware of the stimulus–response patterns. Therefore, declarative learning may improve learning in the later trials. The PD patients in this study who had normal intelligence may also demonstrate declarative learning effects in the later learning phase. Unfortunately, this explanation remains hypothetical because this study was not addressed to answer this question and the achieved declarative knowledge has not been formally tested. Further studies should focus on this question.

For medically applied cognitive neuroscience, the results of our study may be of considerable interest because implicit learning strategies are assumed to underlie adaptation of motor and cognitive behavior. It is well known that basal ganglia disease, compared to cerebellar disease, produces different motor and cognitive deficits in daily life. The compensation of these deficits may be specifically impaired because of different deficiencies in implicit learning. As far as we are concerned, there is currently no data available to demonstrate the clinical impact of abnormal habit-learning abilities. Further studies are necessary to investigate the implications of such implicit-learning deficit on everyday life and thus to improve rehabilitation strategies.

METHODS
Subjects
Twenty-three Parkinson patients (PD group), 16 patients with familiar or idiopathic cerebellar degeneration (CD group), and 20 healthy controls were included in this study. PD was diagnosed according to the brain-bank criteria (Hughes, Daniel, Kilford, & Lees, 1992); especially the presence of an asymmetric akinetic syndrome and a positive therapeutic response to levodopa was required. Four patients received a levodopa monotherapy. In addition to a levodopa therapy, 15 patients were given a D2-agonist, 2 patients received a D2-agonist monotherapy, 4 patients an NMDA-antagonist, 3 a COMT-inhibitor, 3 patients took anticholinergics, and 2 took antidepressants. PD patients were scored by the motor examination of the Unified Parkinson’s Disease Rating Scale (UPDRS). The diagnosis of CD was based on clinical, neurophysiological, and radiological evidence. Four patients showed genetic mutations (two SCA 1 and two SCA 2) with a family history of cerebellar symptoms. Three of the patients were diagnosed as having olivo-pontocerebellar atrophy (OPCA) and nine as having cerebellar cortical atrophy. The diagnosis of CD was based on clinical examination and cerebral MRI. The latter was performed to exclude other diseases such as multiple sclerosis. Blood was examined to exclude toxic cerebellar atrophy (e.g., alcoholism). Cerebellar signs and symptoms were rated according to a cerebellar rating scale (Deuschl et al., 1996). Each patient with CD underwent a magnetic resonance imaging of the brain. The scans were assessed for the presence or absence of cerebellar atrophy and/or brainstem atrophy. Table 1 shows the descriptive variables of the patients and controls (sex, age, education, disease duration, Hoehn and Yahr scale, cerebellar rating scale, estimated IQ using a formula of Wilson et al., 1978). The control subjects were normal subjects who showed no signs or symptoms of cerebral neurologic diseases. Exclusion criteria were a Mini-Mental Status Examination (Folstein, Folstein, & McHugh, 1975) score <26 and cerebral diseases other than PD or CD. All participants were examined by a clinical neurologist. All subjects signed informed consent forms. The protocol was approved by the local ethical committee of Kiel University.

Neuropsychological Status
All subjects were assessed with a standard neuropsychological test battery including the Mini-Mental Status (Folstein et al., 1975), digit span presented forward and backwards to investigate immediate recall and working memory (Lezak, 1995), a German translation of the short form of the Wechsler Intelligence Scale (Dahl, 1972), and the ‘‘Mehrfach–Wahl–Wortschatz-Test B’’ (MWT-B)—a multiple choice vocabulary test which has been demonstrated to correlate with the ‘‘premorbid’’ general intelligence test (Lehrl, Triebig, & Fischer, 1995). The subtests of the Wechsler Intelligence Scale were Information, Similarities, Picture Completion, and Block Design.

Probabilistic Classification Task
The probabilistic classification task (weather prediction task) was introduced by Knowlton et al. (1994). The task is presented on a personal computer. The display shows one of four cards, alone, or in combination with one or two other cards bearing geometric symbols (beams,
diamonds, squares, and triangles). The subject is asked to decide which of the combination of cards indicates “rain” or “sunshine.” The cards had the overall probability of 75%, 57%, 43%, and 25% for the outcome “rain” and the complementary likelihood for the outcome “sunshine.” At the beginning, the distribution of these probabilities was randomly distributed but fixed for the ongoing test procedure. The probability for each combination was determined by the constant occurrence and the outcome probability of each card on display (see Table 3). The sequence of the cue combination was randomized. The probabilistic element of the task was identified by the feedback. These associations are difficult to memorize since there is no absolute association between single cards and the outcome and the conscious recollection of the associations fails, at least in the early phase of the test.

Patients and controls were seated comfortably at a distance of 60 cm in front of the computer screen. The participants were told that they would become the weather forecaster predicting “sunshine” or “rain” with the help of the cards. They were told that at first they would be guessing, but that they would later improve automatically. They were instructed to “solve the task by intuition.” To predict “sunshine,” they had to press a 3 cm response button on the right side of the computer labeled with a sunshine symbol; for predicting “rain,” they had to press a similar button on the left labeled with a rain icon. Feedback for correct prediction was provided by a short-pitched tone (900 Hz, 500 msec) and a smiling face appearing next to the correct icon sunshine or rain for 2 sec. Incorrect responses elicited a long tone (900 Hz, 2000 msec) and a frowning face appearing next to the hint for the correct icon for 2 sec. Immediately after this feedback, the next set of cues appeared. After 5 sec without response, the subject was called upon to react. After 50 and 100 trials, a short break (45 sec) was inserted. In the ongoing test procedure, all single trials were excluded from the analysis, which had a cue pattern of equal probabilities for both outcomes (50%, Patterns 6 and 9 in Table 3) because these patterns cannot indicate classification learning. Ignoring these trials, the task included a total of 150 trials.

To assess chance performance of the weather task, 20 runs of alternating predictions “sunshine” and “rain” were carried out. Thus, chance performance could be compared between the control and patient group.

Data Analysis

The first 50 responses were analyzed in blocks of 10 trials each. The next 100 trials were divided in two blocks of 50 trials. A response was rated to be correct if the “rain” or “sunshine” decision of the subject corresponded to an outcome probability above 50%, respectively (see Table 3). An increasing number of correct responses reflect the ability to learn the complex probabilistic associations.

A two-way analysis of variance was used for statistical analysis comparing the group results in the weather task. Independent sample t tests were performed to compare differences between the groups and chance performance (20 runs of random predictions) as well as the neuropsychological background data. Bonferroni corrections were used for multiple comparisons.

Acknowledgments

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Reprint requests should be sent to Prof. Dr. G. Deuschl, Department of Neurology, Christian Albrecht University Kiel, Germany Niemannsweg 147, 24105 Kiel, or via email: g.deuschl@neurologic.uni-kiel.edu.

REFERENCES


