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Der neuronale Prozess der Fehlerüberwachung bei gesunden Pianisten und Pianisten mit Musikerdystonie

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EEG oscillatory patterns are associated with error prediction during music performance and are altered in musician's dystonia

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ABSTRACT

Skilled performance requires the ability to monitor ongoing behavior, detect errors *in advance* and modify the performance accordingly. The acquisition of fast predictive mechanisms might be possible due to the extensive training characterizing expertise performance. Recent EEG studies on piano performance reported a negative event-related potential (ERP) triggered in the ACC 70 ms before performance errors (pitch errors due to incorrect keypress). This ERP component, termed pre-error related negativity (pre-ERN), was assumed to reflect processes of error detection in advance. However, some questions remained to be addressed: (i) Does the electrophysiological marker *prior to errors* reflect an error signal itself or is it related instead to the implementation of control mechanisms? (ii) Does the posterior frontomedial cortex (pFMC, including ACC) interact with other brain regions to implement control adjustments following motor prediction of an upcoming error? (iii) Can we gain insight into the electrophysiological correlates of error prediction and control by assessing the local neuronal synchronization and phase interaction among neuronal populations? (iv) Finally, are error detection and control mechanisms defective in pianists with musician's dystonia (MD), a focal task-specific dystonia resulting from dysfunction of the basal ganglia–thalamic–frontal circuits? Consequently, we investigated the EEG oscillatory and phase synchronization correlates of error detection and control during piano performances in healthy pianists and in a group of pianists with MD. In healthy pianists, the main outcomes were increased pre-error theta and beta band oscillations over the pFMC and 13–15 Hz phase synchronization, between the pFMC and the right lateral prefrontal cortex, which predicted corrective mechanisms. In MD patients, the pattern of phase synchronization appeared in a different frequency band (6–8 Hz) and correlated with the severity of the disorder. The present findings shed new light on the neural mechanisms, which might implement motor prediction by means of forward control processes, as they function in healthy pianists and in their altered form in patients with MD.

Introduction

Playing tennis and performing a piece of music from memory are examples of complex multimodal tasks which rely on predictive mechanisms acquired through extensive training. These sensory-motor tasks depend on time-based sequential behaviors and, as such, require accurate preparation in advance of the events planned for production (Pfordresher and Palmer, 2006). Moreover, skilled performance demands the perfect tuning of the action-monitoring system to the extent that potential errors, which might otherwise interact with the goals, must be predicted in advance (Bernstein, 1967; Wolpert et al., 1995).

Computational models of motor control propose that *internal forward models* might be available through the efference copy of the motor command, which is used to predict the outcome of the action based on the current state of the system (Latash, 2008; Desmurget and Grafton, 2000; Wolpert et al., 1995). The incoming information (reafference) is compared with the predicted outcome and, in case of a mismatch, rapid adjustments are initiated to modify the anticipated outcome. Thus forward models might rely also on sensory and proprioceptive feedback, yet they can still generate rapid movements and predictions (*dual models*, Desmurget and Grafton, 2000). This current view does away with the traditional separation between feedback (based only on sensory input) and feedforward (based only on predictions from the motor command) models of motor control.

Here we propose that overlearned sensorimotor tasks present an ideal paradigm for the study of brain activity associated with the implementation of error detection via forward models during action control. In the present study, we expected to detect electrophysiological correlates associated with *error prediction and corrective adjustments*

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triggered prior to errors. Within this framework, we specifically focused on skilled pianists. The central questions were as follows:

Study 1 Can we identify in healthy pianists oscillatory brain states associated with (i) predictive mechanisms of error detection or (ii) implementation of control prior to overt errors? Does the posterior frontomedial cortex (pFMC) interact with the lateral prefrontal cortex (lPFC) to implement control adjustments following motor prediction of an upcoming error (Ridderinkhof et al., 2004)? To this end, we investigated action-monitoring during piano performance in healthy pianists.

Study 2 (iii) Are error detection and correction mechanisms dysfunctional in performers with musician's dystonia (MD), a focal task-specific dystonia (FTSD), as the result of the irregular cortico-basal ganglia-thalamic-cortical circuitry and impaired sensorimotor processing in this disorder (see subsequent discussion; Meunier and Hallett, 2007)? For this purpose we further studied action-monitoring in a group of pianists with MD during the performance of memorized music pieces with the *unaffected hand*, and compared the results with an age-matched group of healthy pianists. We expected generic changes in the electrophysiological correlates of error-monitoring in MD pianists despite the unilateral symptoms based on the abnormal *bilateral* sensory and motor processing reported in this group (Ridding et al., 1995; Molloy et al., 2005).

Medial prefrontal cortex (mPFC) and particularly the posterior frontomedial cortex (pFMC; including the ACC) have been broadly implicated in action-monitoring, whereas lateral prefrontal brain regions (lPFC) have been proposed to implement performance adjustments in a variety of tasks (Miller, 2000; Wittfoth et al., 2009; Cavanagh et al., 2009). Thus, both brain structures seem to interact during goal-directed behavior (Botvinick et al., 2001; Ridderinkhof et al., 2004). Recently, Cavanagh et al. (2009) demonstrated that the mechanism by which the pFMC and lPFC might interact in action-monitoring and cognitive control is the adjustment of the phases of neural oscillations in both brain regions.

The vast majority of the previous studies of the action-monitoring system used reaction time conflict-tasks which elicit error-related brain activity after the commission of the error. A seminal finding in the context of action-monitoring was an error-related negativity (ERN/Ne: Falkenstein et al., 1990; Gehring et al., 1993) in the event-related potentials (ERP), which peaks roughly 80 ms after error commission. Errors in these tasks are produced due to the wrong response selection from the activation of two competing responses. Therefore, the ERN has been hypothesized to reflect either error-detection processes (Holroyd and Coles, 2002) or conflict monitoring (Cohen et al., 2000; Botvinick et al., 2001). In paradigms with repetitive monotonous tasks, such as speeded reaction-time tasks, erroneous outcomes have been shown to originate partly in attentional deficits (Ridderinkhof et al., 2003; Eichele et al., 2008; Weissman et al., 2006; Mazaheri et al., 2009; O'Connell et al., 2009). This is reflected in the markers of brain activity which precede errors as shown in the mentioned paradigms: an error-preceding positivity over the anterior cingulate cortex (ACC), decreases in prefrontal cortex activation, increases in the default-mode activation, and enhanced prestimulus alpha oscillations across occipital brain regions (Ridderinkhof, 2003; Eichele et al., 2008; Weissman et al., 2006; Mazaheri et al., 2009; O'Connell et al., 2009).

In the context of piano performance, two recent electrophysiological studies found that around 70 ms prior to performance errors a negative component — termed pre-ERN and resembling the post-response ERN — was elicited in the event-related potentials (ERP; Herrojo Ruiz et al., 2009a; Maidhof et al., 2009). *Performance errors* (hereafter termed *errors*) in these settings consisted of playing an incorrect key (note) on the piano. Further, the pre-ERN was generated by the rostral ACC (Herrojo Ruiz et al., 2009a). Interestingly, here it was reported that the loudness of errors decreased in comparison with the loudness of the corresponding correct notes at the same position in the score. This finding was interpreted as a behavioral correlate of a corrective control mechanism triggered in order to cancel the sensory consequences of erroneous outcomes. Some questions remained to be addressed, particularly whether the electrophysiological marker *prior to* performance errors reflects an error signal itself or is related instead to the implementation of performance adjustments. To investigate the latter, one could look at other brain regions that possibly interact with the pFMC for that purpose.

Furthermore, ERP analyses do not offer any information about oscillatory neuronal synchronization within and between cortical regions; there is, however, widespread evidence that neuronal synchronization, both local and global, acts as a flexible mechanism for interaction between different regions within a network during attentional control and motor performance (Fries, 2005; Varela et al., 2001; Gerloff et al., 1998; Serrien and Brown, 2002). Therefore, we aimed here at studying the neural synchronization associated with performance errors. To study neural synchronization among different brain regions we measured the phase synchronization between pairs of EEG signals, whereas for the analysis of the local synchronization we focused on the amplitude of the oscillations at each electrode region.

The patterns of neural oscillatory activity associated so far with error evaluation are an increase in theta oscillatory activity in the pFMC as well as increased theta phase coupling between the pFMC and the lPFC following errors; in correct trials with high conflict, the additional suppression of beta oscillations is found prior to response selection (Luu et al., 2004; Cavanagh et al., 2009; Cohen et al., 2008).

For a more complete understanding of the action-monitoring system, the *reinforcement learning theory* – which provides an account of the ERN based on phasic dopaminergic activity induced by the basal ganglia (BG) – is of special interest (Holroyd and Coles, 2002; Schultz, 2002). This theory assumes that the integration of prefrontal and motor cortico-striato-thalamo-cortical circuits provides the motor ACC regions with contextual information to enable their function in performance monitoring (Ullsperger and von Cramon, 2006). Evidence in support of the reinforcement learning theory comes from reports of direct activation in the BG during action-monitoring (Brown et al., 2006; Münte et al., 2007; Kühn et al., 2008; Wittfoth et al., 2009). Further evidence is provided by data on altered error-related brain activity in patients with BG disorders due to anomalous dopaminergic modulations (Huntington's disease: Ito and Kitagawa, 2006; Parkinson's Disease [PD]: Beste et al., 2006, 2009) or hyperactive striatocortical dynamics (Tourette Syndrom: Johannes et al., 2002). Such data have not been studied in patients with dystonia, also a condition marked by dysfunction of the basal ganglia–thalamic–frontal circuit (Naumann et al., 1998; Preibisch et al., 2001). In musician's dystonia (MD), as in other types of focal task-specific dystonias (FTSD), there is support for a reduced pallidal inhibition of the thalamus, which results in the overactivity of medial and prefrontal cortical areas (Berardelli et al., 1998). This could lead to altered error signals projected from the internal globus pallidus, an output nucleus in the BG, to the pFMC. In addition, abnormal bilateral cortical sensorimotor processing has been reported in FTSD despite unilateral symptoms (Ridding et al., 1995; Molloy et al., 2003). Consequently, MD represents an interesting model to investigate possible abnormalities in error-detection and evaluation in this patient group during the performance of complex overlearned musical sequences.

Materials and methods

Participants in study 1

The data of the 18 healthy pianists from Herrojo Ruiz et al. (2009a) were reanalyzed for the investigation of the oscillatory and

synchronization properties of the brain activity associated with error processing.

Participants in study 2

We conducted a new experiment with MD pianists and healthy controls with matching age. Eight healthy pianists (five males, age range 26–44 years, mean 35 years, SD 7 years) and six pianists with MD (four males, age range 28–52 years, mean 40 years, SD 10 years) participated in this study. All participants were professional pianists, were right-handed, and reported normal hearing. All participants gave informed consent to participation in the study, which had received approval by the local Ethics Committee of Hanover. Patients with MD affecting the *left hand* were recruited from the database of our outpatient movement disorders clinic, which contains the data of more than 400 musician patients who have been carefully examined and diagnosed by a neurologist with specific competence in movement disorders. The clinical course was compatible with primary dystonia, with no clinical features to suggest secondary dystonia. No patient was affected by dystonia at rest. Further information on the patients is given in Table 1.

Assessment of motor control in study 2

Motor control at the piano was assessed by a MIDI-based scale analysis, because it has been demonstrated that scale playing is affected early in pianists during the onset of MD (Jabusch et al., 2004). Scales were performed with the left and right hands on a digital piano. Sequences of 10 to 15 C major scales were played over two octaves in inward (radial) and outward (ulnar) direction. Scales were played using the conventional C major fingering: 1,2,3,1,2,3,4,1,2,3,1,2,3,4,5 (fingers 1–5 refer to thumb, index, middle, ring, and little finger, respectively). The tempo was standardized and paced by a metronome (120 beats per minute, four notes per beat: one note every 125 ms). The temporary unevenness of inter-onset intervals (IOI, time between note onsets of two subsequent notes) has been evaluated as a valid, reliable and precise indicator of the degree of pianists' motor control and its dysfunction in pianists with musician's dystonia (Jabusch et al., 2004). For each participant, temporary unevenness was analyzed for both hands and for both playing directions by calculating the mean standard deviations of IOI (mSD-IOI) of all scales for the respective playing direction. For further analyses, we selected for each hand and participant the maximum value of the mSD-IOI results for the inward and outward playing. In the following sections, the result of this procedure will be referred to as Max-mSD-IOI. This procedure allowed us to include all patients in the same analysis irrespective of the playing direction affected by MD.

In MD pianists, motor performance of the affected left hand (Max-mSD-IOI-L) was compared with the different measures of the EEG analysis to look for correlations between the degree of motor impairment and the neurophysiological signal.

Stimulus materials in studies 1 and 2

The stimuli were six sequences extracted from the right-hand parts of Preludes V, VI and X of *The Well Tempered Clavier* (Part 1) by J. S. Bach and the *Piano Sonata No. 52 in E Flat Major* by J. Haydn. These pieces were chosen because their parts for the right hand contain mostly one voice consisting of notes of the *same* value (duration), sixteenth-notes, which made our stimulus material homogeneous. The number of notes per sequence was around 200. Accordingly, the stimulus material consisted of approximately 1200 notes. The tempo for each piece was selected so that the ideal IOI was 125 ms (8 tones per second) in all cases. The performance tempo was fast in order to induce error production in the pianists. Most pieces were familiar to all pianists. However, they were instructed to rehearse and memorize them before the experimental session. During the rehearsing sessions, the given tempi were paced by a metronome. More details of the stimuli can be obtained in Fig. 1 and in Herrojo Ruiz et al. (2009a).

Experimental design in studies 1 and 2

Participants were seated at a digital piano (Wersi Digital Piano CT2) in a light-dimmed room. They sat comfortably in an arm-chair with the left forearm resting on the left armrest of the chair. The right forearm was supported by a movable armrest attached to a sled-type device that allowed effortless movements of the right hand along the keyboard of the piano. The keyboard and the right hand of the participant were covered with a board to prevent participants from visually tracking hand and finger movements. Instructions were displayed on a TV monitor (angle 4°) located above the piano. Before the experiment, we tested whether each pianist was able to perform all musical sequences according to the score and in the desired tempo. They were instructed to perform the pieces each time from beginning to end without stopping to correct errors. Playing the correct notes and maintaining accurate timing were stressed. Pianists were unaware of our interest in investigating error-monitoring processes.

The experimental design consisted of one condition comprising 60 trials (around 12,000 notes). The 60 trials were randomly selected out of the 6 stimulus materials. The task was to play the musical stimuli 1–6 from memory without the music score, while listening to the auditory feedback of the notes played. The specifications of each trial were as follows: The pianists pressed the left pedal when they were ready for a trial. After a silent time interval of 500 ± 500 ms randomized, the first two bars of the music score were presented visually on the monitor for 4000 ms to indicate which of the 6 sequences had to be played. To control for the timing in each piece, we used a synchronization–continuation paradigm. After 2500 ms of the visual cue, the metronome started and paced the tempo corresponding to the piece for 1500 ms and then faded out. After the last metronome beat, the visual cue vanished. Participants were instructed not to play while the music score was displayed on the screen, but to start playing after a green ellipse appeared on the monitor (100 ms after the vanishing of metronome and visual cue with the score).

Table 1
Patients with musician's dystonia.

Patient	Age (years)	Sex	Year of manifestation	Affected digits of the left hand	Therapy	Accumulated practice time (h)	Max-mSD-IOI-L/ Max-mSD-IOI-R (ms)
Dyst_01	29	F	2004	D2	None	37,595	20/11
Dyst_02	39	M	1996	D2, 4	Botulinum toxin (6 months after last injection)	27,922	14/12
Dyst_03	40	M	1996	D2	None	36,135	21/21
Dyst_04	49	M	1995	D3	Botulinum toxin (7 years after last injection)	62,962	21/12
Dyst_05	51	M	2004	D4, 5>D1, 2, 3	None	92,892	23/10
Dyst_06	52	F	1992	D2	Botulinum toxin (9 years after last injection)	26,645	21/9

The last column shows the maximum values of the mean standard deviation of the IOI (Max-mSD-IOI) of all scales, for the affected left (L) and unaffected right hand (R). The maximum value in each participant and hand was selected between the mSD-IOI of the inward and outward playing directions. Further explanations are given in the text.

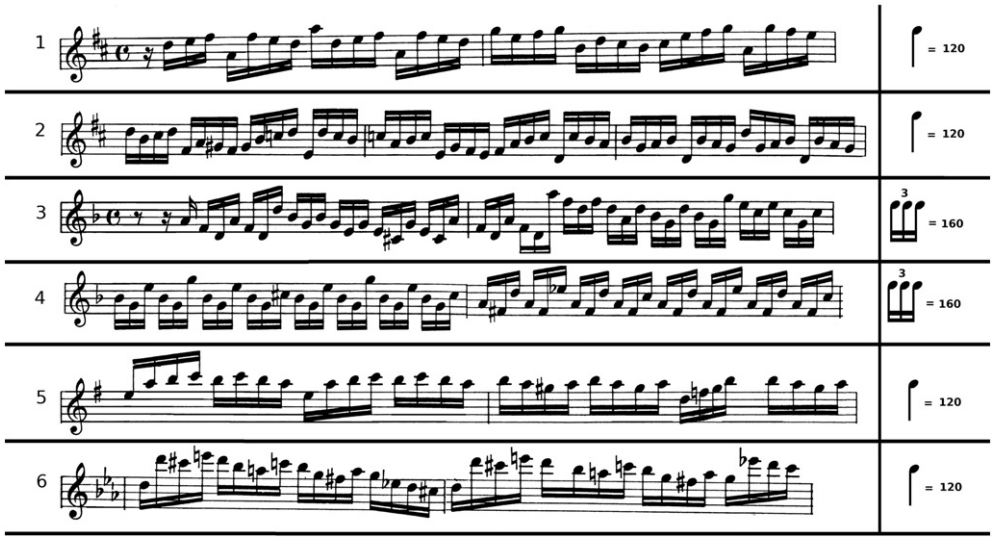

Fig. 1. Examples of musical stimuli. The opening bars of the six musical sequences are illustrated. Pieces 1 and 2 were adapted from the Prelude V of the *Well Tempered Clavier* (Part 1) by J. S. Bach; pieces 3 and 4 were adapted from the Prelude VI; piece 5 from the Prelude X. The sixth sequence was adapted from the *Piano Sonata No. 52 in E Flat Major* by J. Haydn. The tempi which were given in the experiment are indicated: 120 for quarter notes and 160 for the triplets of eighth notes. In all cases, the inter-onset interval (IOI) was 125 ms.

EEG recordings and pre-processing in studies 1 and 2

Continuous EEG signals were recorded from 35 electrodes placed on the scalp according to the extended 10–20 system referenced to linked mastoids. Additionally, electrooculogram was recorded to monitor blinks and eye movements. Impedance was kept below 5 kΩ. Data were sampled at 500 Hz; the upper cutoff was 100 Hz (software by NeuroScan Inc., Herndon, Va., USA). Visual trigger stimuli, note onsets, and metronome beats were automatically documented with markers in the continuous EEG file. Performance was additionally recorded as MIDI (music instruments digital interface) files using a standard MIDI sequencer program. We used the EEGLAB Matlab® Toolbox (Delorme and Makeig, 2004) for visualization and filtering purposes. A high-pass filter at 0.5 Hz was applied to remove linear trends and a notch filter at 50 Hz (49–51 Hz) to eliminate power-line noise. The EEG data were cleaned of artifacts such as blinks and eye movements by means of wavelet-enhanced independent component analysis (wICA; Castellanos and Makarov, 2006), after first computing the ICA components with the FastICA algorithm (Hyvärinen and Oja, 2000). The data epochs representing single experimental trials time-locked to the onset of the isolated errors (see *Data analysis*) and isolated correct notes were extracted from −500 ms to 500 ms, resulting in approximately $n = 50$–120 artifact-free epochs for errors and $n = 500$ artifact-free epochs for correct notes per participant. More details can be found in Herrojo Ruiz et al. (2009a).

Data analysis in studies 1 and 2

To analyze the MIDI performance, we used the error detection algorithm developed in MatLab® for Herrojo Ruiz et al. (2009a). Like Finney and Palmer (Finney and Palmer 2003), we removed all performance errors which systematically appeared in at least 7 out of 10 trials of a type and which could be related to an error in reading the notation at the time of learning the music sequences. In addition, when several consecutive errors were identified, they were also excluded. Furthermore, only isolated errors which were preceded and followed by three correct notes were considered in the analysis of the brain responses (see Herrojo Ruiz et al., 2009a for more details). This criterion ensured that there would be no overlap of brain responses triggered by consecutive errors. Similarly, only isolated correct notes based on the previous description were selected. With this selection, we obtained an appropriate "correct" control condition unaffected by changes in timing or neural processing from neighboring error notes. Additional details of the constraints imposed can be found in Herrojo Ruiz et al. (2009a). MIDI-based performance parameters such as IOI values or key velocities – an indirect measure of loudness – were additionally analyzed as behavioral data. The term *loudness* will hereafter be used referring to key velocity.

Two main analysis of the EEG signal were performed: (i) the wavelet-based spectral power of the oscillatory contents (Tallon-Baudry et al., 1997), in order to study the *local* synchronization at each recorded position; and (ii) the bivariate phase synchronization (Lachaux et al., 1999; Pereda et al., 2005), with the aim of investigating the dynamical *interaction* between oscillatory populations of different recorded regions.

For that purpose, we computed the wavelet-based time–frequency representations (TFR) of the EEG signals corresponding to the brain responses triggered by actions leading to performance errors and to correct notes.

A complex Morlet wavelet was used to extract time–frequency complex phases $\varphi_{ik}(t,f)$, at an electrode i and epoch k, and amplitudes $A_{ik}(t,f) = |Wx_{ik}(t,f)|$ of the EEG signal $x(t)$. The constant η characterizes the family of wavelet functions in use and defines the constant relation between the center frequency and the bandwidth $\eta = f/\sigma_f$. We selected a value $\eta = 7$ which provides a good compromise between high frequency resolution ($\sigma_f = f/\eta$) at low frequencies and high time resolution ($\sigma_t = \eta/4\pi f$) at high frequencies: for example, $\sigma_t = 55$ ms and $\sigma_f = 1.4$ Hz at 10 Hz; $\sigma_t = 28$ ms and $\sigma_f = 2.8$ Hz at 20 Hz. The frequency domain was sampled from 4 to 60 Hz with a 1 Hz interval between each frequency.

To study changes in the spectral power, we used the wavelet energy, which was computed as the average across epochs of the squared norm of the complex wavelet transform:

$$E_{xi}(t,f) = \sum_{k=1}^{n} |Wx_{ik}(t,f)|^2 \quad (1)$$

where n is the number of epochs. After removing the baseline level (from 300 to 150 ms prior to note onset), we normalized the wavelet energy with the standard deviation of that baseline period and expressed it as a percentage of power change.

For the bivariate phase synchronization analysis, the strength of the phase coupling between two electrodes *i* and *j*, at time *t* and with a center frequency *f* was computed as

$$\overline{R}_{ij} = \left| \frac{1}{n} \sum_{k=1}^{n} exp\left(i\left(\phi_{jk} - \phi_{ik}\right)\right) \right|. \quad (2)$$

This index approaches 0 (1) for no (strict) phase relationship between the considered electrode pair across the epochs. When averaged across pairs of electrodes, the index $\overline{R}_{ij}$ represents a measure of global synchronization strength ($\overline{R}$). For this analysis, before computing the wavelet-coefficients, the raw EEG trials were first transformed with a modified version of the nearest-neighbor Hjorth Laplacian algorithm computed by Taylor's series expansion (Lagerlund et al., 1995). This algorithm eliminates the spurious increase in correlations introduced by the common reference, providing a reference-free, spatially enhanced signal representation (Nunez et al., 1997). Furthermore, the Laplacian algorithm emphasizes local activities and diminishes the representation of distal activities, thus reducing the volume conduction effects. The bivariate synchronization index was normalized by subtracting the baseline level from 300 to 150 ms prior to the note onset.

The investigation of the pairwise phase synchronization focused on the electrodes F_3–FC_z and F_4–FC_z, as a measure of the synchronization between areas located over the lPFC and pFMC. Our selection was based on the proposed theory of the prefrontal cortex function which postulates that the pFMC interacts with the lPFC in a dynamic loop during goal-oriented behavior (Ridderinkhof et al., 2004; Cavanagh et al., 2009). To confirm that the outcomes of this analysis were not the result of volume conduction, the bivariate synchronization index was additionally calculated between C_3–FC_z and C_4–FC_z: these pairs have a similar distance as pairs F_3–FC_z and F_4–FC_z, but a more posterior location; however, there are no a priori hypotheses that posit a role of these brain regions in cognitive control.

Oscillatory and synchronization activities in three frequency ranges were analyzed (i) in the theta band (4–8 Hz), based upon its modulation of the ERN (Trujillo and Allen, 2007; Cavanagh et al., 2009; Luu et al., 2004); (ii) in the alpha band (8–13 Hz), specifically over occipital electrode regions, as an indicator of attention-deficits and precursor of forthcoming mistakes in monotonous tasks (Mazaheri et al., 2009; O'Connell et al., 2009); (iii) and in the beta band (13–30 Hz), due to its sensitivity to motor errors (Koelewijn et al., 2008).

Statistical analysis. Study 1

To assess in the indices of spectral power or phase synchronization the statistical differences between conditions (errors minus correct notes), we averaged for each participant and event type (error, correct note) the indices across the electrodes in the regions of interest (ROIs) defined for each case (described later). Next, in each time–frequency point, the averaged indices were analyzed by means of a nonparametric pairwise permutation test across participants (Good, 2005) by computing 5000 permutations. The test statistic was the difference (errors minus correct notes) of sample means of each measure. This difference quantity reflects neural activity associated with the processing of the erroneous action relative to the correct note.

Statistical analysis. Study 2

In each group the indices of the spectral power and phase synchronization were averaged across the electrodes in the ROIs (see subsequent discussion). Next, these indices were analyzed with a two-factor (group × event type) design through the use of synchronized rearrangements (Pesarin, 2001; also Good, 2005). Each of the factors had two levels: patients and healthy controls for factor group; errors and correct notes for factor event type. Synchronized rearrangements are based on the nonparametric permutation test (Good, 2005) and are recommended to obtain exact tests of hypotheses when multiple factors are involved. They are generated, for instance, by exchanging elements between rows in one column and duplicating these exchanges in all other columns. Thus, synchronized rearrangements provide a clear separation of main effects and interactions. A total number of 5000 synchronized rearrangements was performed. In addition, we were specifically interested in the between-groups differences in the contrasted (error minus correct) TFR maps, which would reflect a different error processing between groups. Consequently, as a post-hoc analysis, we selected as test statistic the difference between pianists with MD and healthy controls in the contrasted TFR maps (MD minus healthy pianists: errors minus correct notes) of the averaged indices under study. For this purpose, a nonparametric pairwise permutation test across participants between groups was performed. In sum, in Study 2, main effects group or event type and the interaction between these two factors are reported; as well as the post-hoc statistical difference between contrasted conditions and groups (patients minus healthy controls: errors minus correct).

Statistical analysis. Studies 1 and 2

The permutation tests were computed at each time point from −200 to 500 ms around keypresses to obtain running *p*-values (Herrojo Ruiz et al., 2009a). Differences were considered significant if $p<0.05$. Significance levels for multiple frequency comparisons of same data pool were obtained by a Bonferroni-correction of the 0.05 level.

The regions of interest were selected on the basis of a priori anatomical knowledge and physiological evidence from action-monitoring studies (Carter et al., 1998; Dehaene et al., 1994; Mazaheri et al., 2009). For the analysis of the spectral power, we selected the electrodes that cover the mesial prefrontal cortex, anterior cingulate cortex and extend to the posterior cingulate cortex (F_z, FC_z, C_z, and CP_z). These electrodes constituted one single group for the averaged indices of spectral power. However, for the investigation of alpha-band spectral power prior to note onset, we additionally analyzed the electrodes over parietal-occipital regions (PO7, PO_z, PO8, O1, and O2). As indicated earlier in the Materials and methods section, in the phase synchronization analysis we specifically selected the pairs of electrodes F_3–FC_z and F_4–FC_z, representing the lPFC and pFMC, and the additional pairs C_3–FC_z and C_4–FC_z as controls.

Statistical effects in the behavioral data were assessed by pairwise permutation tests across subjects with the difference of means as test statistic.

Results

Study 1: normal participants

The details of the behavioral data for the group of 18 healthy participants can be found in Table 2. An average of 80 (SD 30) isolated errors were available for the analysis. From this number, 88% were purely *motor errors*, in which pianists pressed the neighboring key on the MIDI-keyboard. The remaining 12% of isolated errors were confined within the diatonic scale and mostly reflected similarity-based confusions among elements that have similar structure (such as diatonically related pitches from the key of the musical sequence; see Finney and Palmer [2003] for more details). Motor errors might arise from motor noise or a wrong motor command, whereas diatonic errors seem to be driven by retrieval or planning failures (Finney and Palmer, 2003). We expected the detection in advance of the errors by forward models in both cases (see Supplementary Table 1). Therefore, and also because we needed the largest number of trials possible for

Table 2
Performance data in the 18 healthy pianists of study 1. Performance errors (termed errors) are defined as playing an incorrect key (note) on the piano. Isolated errors were preceded and followed by three correct notes.

	Mean (SD)
Percentage of total performance errors	3% (2%)
Percentage of isolated errors	0.7% (0.3%)
Number of total performance errors	400 (300)
Number of isolated errors	80 (30)
Number of repeated isolated errors	30 (10)
IOI of all correct notes (ms)	121 (8)
Mean IOI of three notes before isolated errors ([$n-1$, $n-2$, $n-3$]; ms)	200 (50) 120 (10) 130 (10)
Mean IOI of three notes after isolated errors ([$n+1$, $n+2$, $n+3$]; ms)	160 (30) 130 (10) 130 (10)
Overall loudness: correct	75 (6)
Overall loudness: errors	68 (6)
DiffLoudness (Corr − Err) at same position on the score	7 (4)

the EEG analysis, we did not analyze further these types of error separately.

Unless otherwise stated, the statistical results presented subsequently were assessed by permutation tests across subjects with the difference of means as test statistic. The main findings were a reduced loudness (MIDI velocity) of the isolated errors as compared with the loudness of the corresponding correct notes at the same position in the score ($p=0.008$). For this computation, an average of 40 (SD 10) trials was available. In addition, there was a pre- and post-error slowing reflected in the difference IOI between the current error (n) and the previous ($n-1$, IOI ~200 ms) and subsequent ($n+1$, ~160 ms) correct notes. These values differed significantly from the mean IOI of all notes in the performance (pre-IOI vs mean IOI of all notes: $p=0.001$; post-IOI vs mean IOI of all notes: $p=0.001$). Further details of the performance data are provided in Supplementary Table 1 (e.g. repeated isolated errors).

Oscillatory activity in the posterior frontomedial cortex

The statistical analysis by permutation tests focused on the 4–30 Hz frequency range. Panels A–J in Fig. 2 display the TFR and topographical maps of the grand-averaged spectral power for errors, correct notes and their difference, in the theta and beta frequency bands, respectively (TFR in full frequency range 4–60 Hz is provided in Supplementary Fig. 1. The permutation test was run between 4 and 30 Hz, due to the lack of oscillatory modulations above 30 Hz). The processing of errors elicited strong bursts of theta and beta oscillations before and after the note onset, whereas the processing of correct notes led to the opposite effect: a decrease in theta and beta oscillations (panels A, B, E and F in Fig. 2). Theta band power differences between error and correct trials were statistically significant at 5–6 Hz after note onset up to 200 ms ($p=0.0018$, significant at the 0.002 level, Bonferroni-correction in the 4–30 Hz range; Fig. 2C). This effect was localized at electrodes FC_z, over the pFMC, and F_4, over the right lPFC (Fig. 2D). An additional significant effect was found in the beta frequency band from −120 to −70 ms at 14–17 Hz and from 100 to 200 ms at 14–18 Hz ($p=0.001$; Figs. 2G–I). This effect reflected the increase of beta oscillations associated with the detection and resolution of errors compared with correct notes. The topography of this oscillatory activity was localized at the F_z, FC_z and F_4 electrodes, in a similar fashion to the theta band effects, but additionally there was an effect localized at the mesial centroparietal electrodes CP_z and P_z, which could be indicative of two different scalp foci of the beta activity (Figs. 2H–J). Of particular interest for the investigations of the error detection mechanisms was the early increase in 14–17 Hz oscillations around 100 ms prior to errors. To examine the possible relationship between this outcome and the error detection and correction mechanisms, we calculated the nonparametric Spearman correlation index between the single-subject pre-error difference (error minus correct) in beta power – averaged between 150 and 0 ms to account for single-subject variability – and the difference (correct minus error) in loudness. We observed a significant *positive* correlation between these two measures (Spearman $\rho=0.60$, $p=0.03$). This result associated increased pre-error beta oscillations with a larger reduction of the loudness of errors relative to correct notes and, thus, with a larger correction effect. Interestingly, although the theta spectral power did not differ significantly between errors and correct notes before note onset, we observed in all participants a broad pattern of bursts of oscillations starting 100 ms before errors. The theta-band spectral power prior to errors correlated positively with the reduction in loudness of errors ($\rho=0.54$, $p=0.04$). Similar correlation analyses between the pre-onset theta or beta band spectral power and behavioral data such as the pre and post-error slowing revealed no significant correlations.

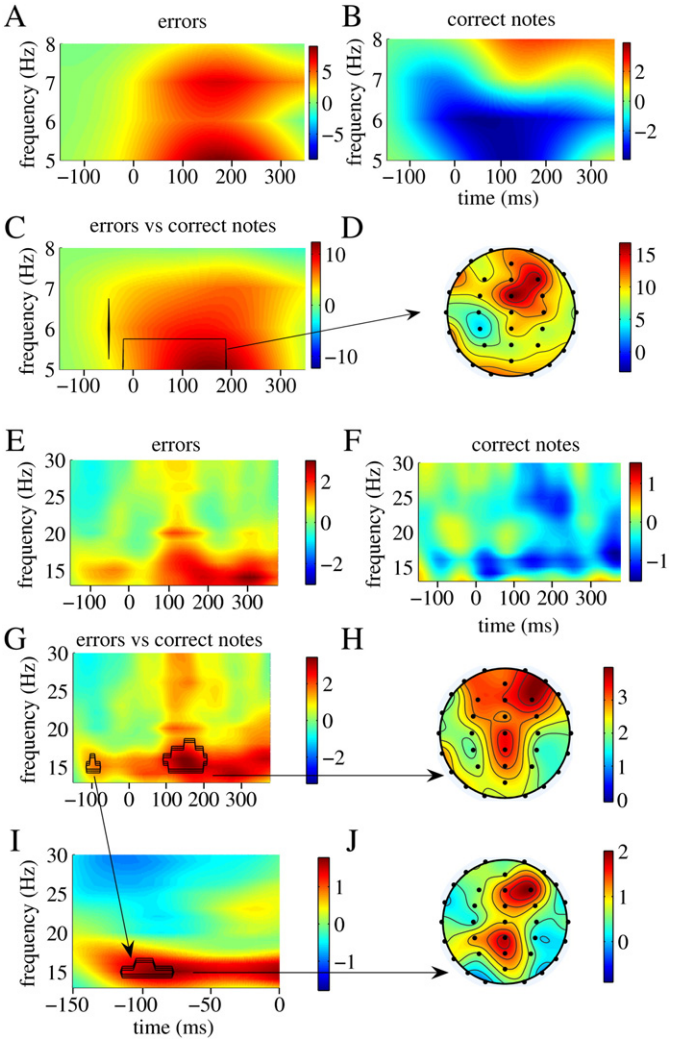

Fig. 2. Study 1. Spectral power. Theta band (4–7 Hz) spectral power for errors (A), correct notes (B) and the difference (errors minus correct notes, C) in the large group of 18 healthy pianists. Significant between-event type differences in the pre- and post-note event period are denoted by the black contour ($p=0.001$, significant at the 0.002 level, Bonferroni-correction in the full 4–30 Hz range). The contrasted topography of the significant effect is depicted in panel D. Beta band (13–30 Hz) spectral power for errors (E), correct notes (F) and the difference (errors minus correct notes, G, I) in the large group of 18 healthy pianists. Significant between-event type differences in the pre- and post-note event period are denoted by the black contour ($p=0.001$, significant at the 0.002 level, Bonferroni-correction in the full 4–30 Hz range). The spatial distribution of the significant between-conditions differences is depicted in panels H, J.

Neither were significant correlations found between theta or beta band power following note onset and the behavioral data.

Following O'Connell et al. (2009) and Mazaheri et al. (2009), we additionally performed a "short-term" analysis of pre-onset parietal–occipital alpha band oscillatory activity to investigate whether there was a progressive increase in this activity prior to errors, as compared with the activity prior to correct notes. This could indicate a lapse of attention leading to the overt error. Short-term epochs of 400 ms prior to note onset were explored, because the constraints imposed on the selection of isolated errors and correct notes guaranteed that three notes before (and after) targets had correct timing and pitch. Thus, at least for 375 ms (3 IOIs) before note onset there was no interference of prior error processing. Furthermore, for this analysis, the wavelet energy was not normalized with the activity of a baseline interval (Eq. (1)) because of the difficulty in selecting a baseline interval that would not potentially overlap with a hypothetical progressive increase of alpha oscillatory activity towards the onset of errors (see Mazaheri et al., 2009).

The results demonstrated no enhancement of alpha activity during the 400 ms interval prior to errors, as compared with the alpha activity before correct notes (Supplementary Fig. 2A–B, no significant differences). In addition, the temporal average of the alpha oscillatory activity from 400 to 0 ms before errors and correct notes did not differ either (Supp. Fig. 2C, no significant differences).

Phase synchronization analysis

The statistical analysis by permutation tests focused on the 4–30 Hz frequency range. The lower beta (13–15 Hz) phase coupling index between FC_z and F_4 increased robustly from 100 to 0 ms before overt errors as compared with the same index before correct notes ($p = 0.001$, significant at the 0.002 level, Bonferroni-correction in the 4–30Hz range; Fig. 3A). In the theta frequency range we observed additional enhancement of FC_z–F_4 phase coupling prior to errors, although this effect was non-significant ($p > 0.05$ in this frequency range; non-significant after Bonferroni-correction). Similar statistical tests were run at 4–30 Hz on the pairs F_3–FC_z, C_4–FC_z and C_3–FC_z but no significant effects were found. Post-hoc analyses of the pairs FC_z–CP_z and FC_z–P_z were performed due to the enhanced error-preceding beta band oscillations in these electrode regions observed in Fig. 2J. There were no significant effects either (Supplementary Fig. 3). These findings give evidence for an increased right-lateralized phase interaction between FC_z and F_4 preceding errors, which could be related to the mechanisms of error detection and correction by forward models. To investigate the latter, we assessed the modulations by the FC_z–F_4 phase coupling of the corrective mechanisms with a Spearman correlation analysis between the beta phase coupling and the decrease in loudness of errors. The phase synchronization index, averaged in the time–frequency windows of −100 to 0 ms and 13–15 Hz, correlated positively and significantly with the reduction in the loudness of errors (Spearman $\rho = 0.62$, $p = 0.001$; Fig. 3B). Such a positive correlation suggests that in participants with a higher pre-error FC_z–F_4 phase coupling there was a better corrective mechanism that resulted in a larger reduction of the loudness of errors. In addition, larger pre-error beta phase coupling between FCz and F4 was associated with shorter pre-error slowing (IOI between positions n and $n-1$; Spearman $\rho = -0.72$, $p = 0.04$). Similar analyses for other electrode pairs revealed no significant correlations.

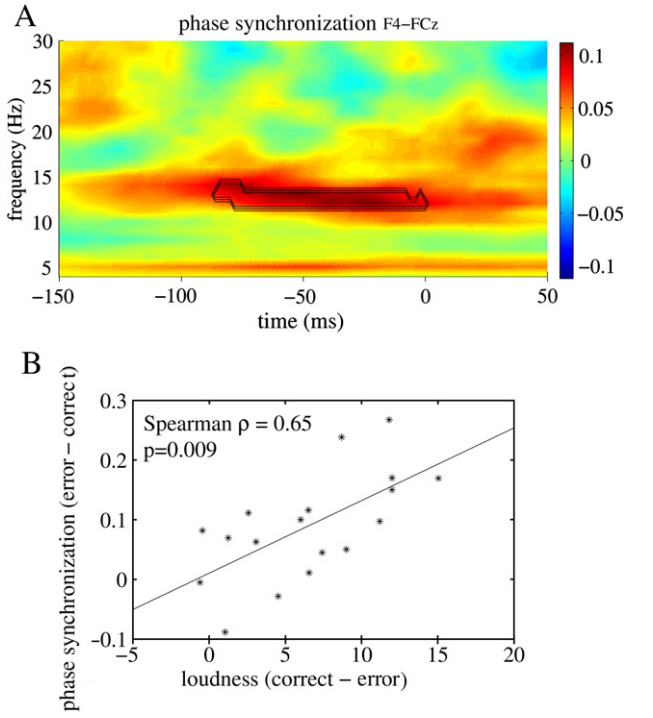

Fig. 3. Study 1. Phase synchronization. (A) Difference between erroneous and correct trials in the grand-averaged phase synchronization index between channels F_4 and FC_z, corrected with the baseline level from −300 to −150 ms. An increase in the index of bivariate phase synchronization can be observed starting 100 ms prior to the note onset and due to a larger phase coupling index for error trials. Significant differences are marked by the black contour ($p = 0.001$, significant at the 0.002 level, Bonferroni-correction in the 4–30 Hz range). (B) Scatter plot showing the correlation between individual difference in loudness (correct minus error) and the difference (errors minus correct notes) in the index of beta phase synchronization between F_4 and FC_z (mean over 100 ms before note onset and at 13–15 Hz). The significant negative Spearman correlation suggests that a larger pre-error beta phase synchronization was associated with better corrective mechanisms.

Study 2: patients with MD vs healthy controls

Performance analysis

Information on the patients is given in Table 1. Unless otherwise stated, the statistical results presented subsequently were assessed by permutation tests across subjects (within a group or between groups) with the difference of means as test statistic. The accumulated practice time of healthy pianists was between 25,000 and 78,110 h (mean 44147 h). There was no significant difference between the accumulated practice time in healthy and MD pianists ($p = 0.83$). The last column in Table 1 shows the maximum values of the mean standard deviation of the IOI (Max-mSD-IOI) of all scales for the affected left (L) and unaffected right hand (R). The maximum value in each participant and hand was selected between the mSD-IOI of the inward and outward playing directions. This parameter was here selected as a reliable and precise indicator of the degree of pianists' motor control and its dysfunction in pianists with MD (see Materials and methods section). In healthy pianists, the Max-mSD-IOI was between 8 and 12 ms. As expected, the Max-mSD-IOI in the affected *left hand* differed significantly between both groups: $p = 0.00001$, pianists with MD, mean 20 ms (SD 3 ms); healthy pianists, mean 11 ms (SD 1 ms). Similarly, in the patient group, the Max-mSD-IOI differed between the affected left and non-affected right hand: $p = 0.013$ (permutation test for paired samples [hands]), right hand, mean 13 ms (SD 4 ms). The Max-mSD-IOI in the unaffected hand was similar in both groups ($p = 0.76$; non-significant). These results confirm that the pianists with MD suffered from focal motor impairment in the left hand.

Results of the behavioral data corresponding to the performance of the musical stimuli used in the EEG study are presented as the mean and standard deviation in Table 3 for healthy and MD participants. Healthy pianists made an average of 80 (SD 40) isolated errors, and the pianists with MD 70 (SD 30). Both groups committed an average of 30 (SD 20) repeated isolated errors, which was too small a number to enable an additional analysis of the brain responses to errors repeated on consecutive trials. The values of the mean IOI of all correct

Table 3
Performance data in healthy and MD pianists expressed as mean (SD). Performance errors (termed errors) are defined as playing an incorrect key (note) on the piano. Isolated errors were preceded and followed by three correct notes. Note that MD pianists played with their unaffected hand.

	Healthy pianists	MD pianists
Percentage of total performance errors	3% (3%)	3% (3%)
Percentage of isolated errors	0.7% (0.4%)	0.7% (0.4%)
Number of total performance errors	400 (300)	500 (300)
Number of isolated errors	80 (40)	70 (30)
Percentage of repeated isolated errors	40% (20%)	40% (10%)
Number of repeated isolated errors	30 (20)	30 (20)
IOI of all correct notes (ms)	114 (6)	123 (8)
Mean IOI of three notes before isolated errors ($[n-1, n-2, n-3]$; ms)	150 (10) 113 (5) 111 (3)	155(10) 120 (5) 123(6)
Mean IOI of three notes after isolated errors ($[n+1, n+2, n+3]$; ms)	140(30) 112(5) 117(6)	160 (30) 122(7) 127(5)
Overall loudness: correct	74 (9)	76 (6)
Overall loudness: errors	61 (8)	61 (6)
DiffLoudness (Corr − Err) at same position on the score	12 (5)	16 (3)

These data correspond to the performance of the sequences extracted from the right-hand parts of Preludes V, VI and X of the Well Tempered Clavier (Part 1) by J. S. Bach and the Piano Sonata No. 52 in E Flat Major by J. Haydn.

notes and its SD provide an indication of how the pianists adjusted to the given tempi (ideal IOI of 125 ms). The mean IOI was not significantly different between both groups, although there was a trend toward significance ($p=0.06$; healthy pianists were faster on average). This result is interesting in that it seems as if the pianists with MD performed with a better timing. As in Herrojo Ruiz et al. (2009a) and in Table 3, there was, in both groups, a pre- and post-error slowing (~150 ms) in the IOI between the current error and the neighboring note. These values differed significantly from the mean IOI of all notes in the performance ($p=0.001$ in all cases), but did not differ significantly between MD pianists and healthy pianists ($p=0.42$). Interestingly, the slowing (larger IOI) occurred only between the current error (n) and the previous correct note (n-1) in the case of pre-error slowing; and between the current error and the subsequent correct note ($n+1$) in the case of post-error slowing. The IOI of second and third previous/subsequent notes was similar to the mean IOI within each group. This result indicates that the IOI did not change gradually several notes before errors, due to, for instance, lapses (Weissman et al., 2006; Mazaheri et al., 2009; O'Connell et al., 2009). Nor did the overt error affect the IOI of several upcoming notes.

The overall loudness (mean MIDI key velocity) of correct notes did not differ significantly between healthy pianists and MD pianists either ($p=0.34$). Additionally, in both groups the loudness of errors was significantly reduced compared with the loudness of correct notes at the same position in the score: The decrease in loudness was 12 (SD 5) in controls ($p=0.04$), and 16 (SD 3) in pianists with MD ($p=0.001$). For this computation there was an average of 40 (SD 10) trials available for both groups. Interestingly, the reduction of the loudness of errors was similar in both groups ($p=0.15$), which indicates that in all pianists – irrespective of the presence or absence of MD – a corrective response had already been initiated by the time the participants pressed the erroneous key.

In summary, none of the behavioral data for the performance of the music stimuli differed significantly between groups ($p>0.05$ in all cases).

Oscillatory activity

In Figs. 4A-C, the TFR maps of the spectral power contrasted between error and correct trials are presented in the range 4–30 Hz for each group separately and for the difference between MD and healthy pianists. In panels A and B we can observe pre- and post-error enhancement of theta and beta oscillations in both groups. The two-factor analysis group × event type, assessed by means of synchronized rearrangements, revealed a main effect for event type at 16–20 Hz and in two temporal intervals: from −100 to −50 ms and later from 200 to 350 ms ($p=0.001$, significant after Bonferroni-correction in the 4–30 Hz range). This result indicated that, independently of the group, error and correct trials differed in these time–frequency regions. Note that these windows resemble the beta band spectral power results from study 1. No significant main effect for group was found. However, a strong significant interaction at 13–18 Hz was obtained between −50 and 50 ms around keystroke and from 70 to 270 ms following keystroke ($p=0.001$). Thus, the lower beta band spectral power differed between error and correct trials in a different degree for MD pianists than for healthy pianists.

To test further the specific between-groups statistical difference in the contrasted TFR maps (Fig. 4C), we performed a post-hoc analysis with the difference between patients and controls in the means for error minus correct trials as test statistic. This analysis revealed that the post-error beta power enhancement was significantly more pronounced in the patient group than in the control group, as was the beta power increase around note onset ($p=0.001$). The later effect appeared between 100 and 250 ms and at 13–17 Hz, whereas the earlier effect was observed from −20 to 50 ms and at 13–16 Hz. Because the temporal resolution of the Morlet wavelet selected is of 37 ms at ~15 Hz, it cannot be guaranteed that the earlier effect at −20 ms was robust in the pre-onset interval and will hereafter be referred to as effect *at note onset*. The enhanced beta activity was localized at electrodes over the pFMC. No significant between-groups difference was found in the theta frequency range ($p>0.12$ in this range). We additionally evaluated, in analogy to study 1, whether the Spearman correlation between beta/theta spectral power prior to note onset and the decrease in loudness was consistent in the patient group and, moreover, whether it depended on the degree of the motor impairment in MD. Note that, although the differences between groups were primarily localized at the post-keystroke interval, there was – as in study 1 – a robust pattern of beta and theta oscillations preceding-errors in each group (Panels A and B). Therefore, we selected in the patient data the broader $[-100, 0]$ ms and $[100, 300]$ ms time windows for the Spearman correlation analyses in the pre- and post-note intervals, respectively. In this group there was a negative correlation between the post-onset difference (error minus correct) beta power and the decrease in loudness of errors ($\rho=-0.77, p=0.01$). Moreover, the values of beta activity following errors correlated positively with the Max-mSD-IOI-L parameter ($\rho=0.49$, $p=0.03$, post-error period), but not with pre- or post-error slowing values. Finally, indexes of pre-error theta or beta power were not associated with the behavioral data in patients.

In summary, beta band oscillations of error and correct trials were robustly and significantly different independently of the group (main effect event type). However, when patients were compared with healthy pianists, more beta oscillations were elicited over the pFMC in patients at the onset and resolution of errors. In addition, in MD pianists, the larger values of beta power in the post-error interval were directly related to the severity of the movement disorder, as assessed by the Max-mSD-IOI-L parameter of motor control, and were associated with reduced correction mechanisms (smaller loudness reduction).

Phase synchronization analysis

We investigated whether the phase interaction in 4–30 Hz between the pair FC_z and F_4 prior to error commission was also present in pianists with MD, and furthermore, whether this effect would be different from the values of the healthy population. Figs. 4D–F display the TFR maps of the difference (error minus correct trials) in the grand-averaged FC_z–F_4 phase coupling in patients (D), healthy pianists (E) and patients minus controls (F). In both groups we observed a robust increase in phase coupling before

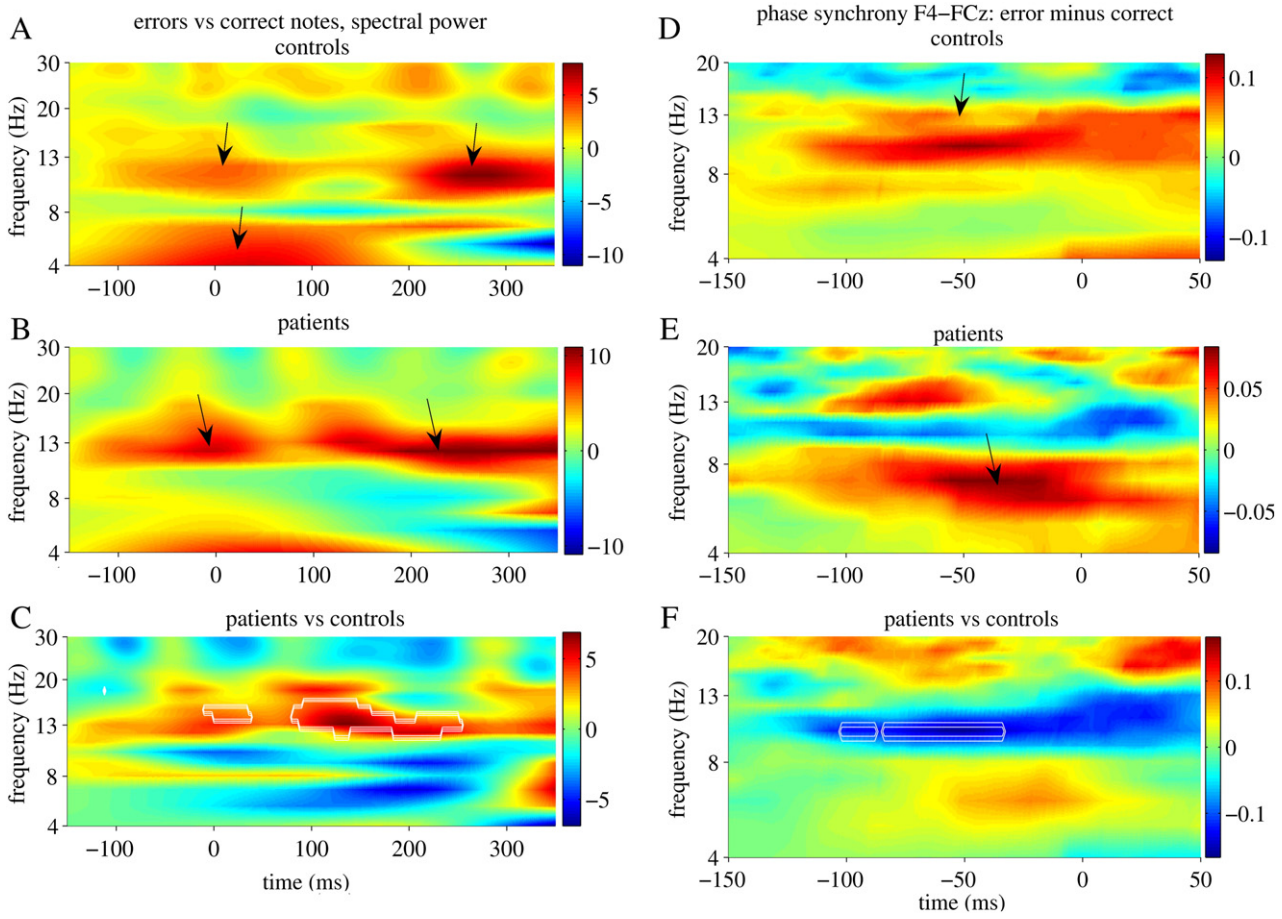

Fig. 4. Study 2. Spectral power and phase synchronization. A–C: Time–frequency representations of errors minus correct notes within 4–30 Hz in healthy pianists (A), MD pianists (B) and MD minus healthy pianists (C). In each case, the error minus correct difference between the TFR maps of the spectral power is depicted from −150 to 350 ms. Arrows indicate loci of maximum oscillatory burst. Pre- and post-error enhancement in beta and theta power was observed in both groups. (C) The results of the post-hoc permutation test for the difference between groups of the contrasted spectral power (error minus correct: patients vs controls) are denoted by the white contour ($p<0.002$, Bonferroni-correction in the 4–30 Hz range). In MD pianists compared to healthy pianists, larger between event-types spectral power was obtained in the beta band and both at note onset and following errors. D–F: Difference between error and correct trials in the grand-averaged phase synchronization index between channels F_4 and FC_z for the control group (D), the patient group (E) and the difference between patients and controls (F). The index of phase coupling increased prior to error commission in the lower beta/upper alpha frequency range in controls (black arrow); and mainly in the theta band in the patient group (black arrow). The white contour in F indicates the between-groups significant effect revealed by the permutation test in the 4–30 Hz range ($p<0.002$, Bonferroni-correction in the 4–30 Hz range). The difference between MD and healthy pianists in the pre-error index of phase coupling was mainly due to the lack of phase synchronization in the upper alpha/lower beta range in MD patients. See Results section for results of the two-factor analysis.

errors (Figs. 4D and E). The two-factor analysis revealed no significant main effects for event type or group ($p>0.08$ throughout the TFR maps; non-significant at the 0.002 level, Bonferroni-correction in 4–30 Hz). However, there was a significant interaction at 11–13 Hz and between −100 and 30 ms, reflecting a between-groups difference in the degree of phase synchronization when comparing errors to correct trials ($p=0.001$). A post-hoc permutation test with the means of the difference between groups in the error minus correct indices provided a significant result similar to the interaction effect: the contrasted phase synchronization index was weaker in MD than in healthy pianists from 100 to 30 ms prior to note onset and at 10–11 Hz ($p<0.002$, white contour in Fig. 4F). Finally, we performed two additional post-hoc permutation tests, one in each group separately, to investigate the difference between the phase synchronization index of errors and correct notes. This final analysis was motivated by the seemingly different frequency ranges in which the enhancement of phase synchronization before errors relative to correct notes appeared in each group in panels D and E in Fig. 4. Whereas in healthy pianists the significant difference effect was localized in the lower beta band (13–15 Hz) and extended to the 10–12 Hz range ($p=0.0012$), in MD pianists the F_4–FC_z phase coupling was predominantly mediated by theta band oscillations (6–8 Hz; $p=0.001$). In addition, we also observed in the patient group a pre-error increase in beta band phase coupling, which was however non-significant ($p>0.05$). These outcomes indicate that the phase adjustment of the oscillatory populations underlying F_4 and FC_z was mediated by different frequencies in each group. Moreover, in the patient group, the pre-onset 6–8 Hz phase coupling index of errors minus correct notes correlated negatively with the severity of the disorder (Max-mSD-IOI-L; Spearman $\rho=-0.83$, $p=0.01$; Fig. 4C) and positively with the reduction in loudness ($\rho=0.531$, $p=0.063$), although the latter reflected only a trend toward significance. This finding suggests that, in MD pianists, there was a trend toward significance in the relation between the pre-error 6–8 Hz phase coupling and better corrective mechanisms. Furthermore, the pre-error interaction between lPFC and pFMC in MD pianists, mediated by the 6–8 Hz phase coupling, was associated with a weaker severity of the focal dystonia. Pre- and post-error slowing values were not associated with the neurophysiological data in MD pianists.

Similar analyses performed in electrode pairs F_3–FC_z, C_3–FC_z and C_4–FC_z, which have a similar distance as pairs and F_4–FC_z; and also for pairs FC_z–CP_z and Fc_z–P_z, revealed no significant effects in neither of both groups or in the group difference.

Discussion

The present study has revealed several novel electrophysiological markers of error-monitoring processes in *healthy participants* during the execution of a complex overlearned sensory-motor task. First, strong bursts of beta and theta band oscillations were elicited prior to errors at electrodes placed over the pFMC (F_z, FC_z), as early as 120 ms in the case of the beta band activity. The effect in the theta band, however, reached significance only shortly before note onset. In addition, there were positive correlations between the indices of pre-error beta and theta activity and the reduction in loudness of wrong notes. The results indicate an association between larger beta and theta band oscillations prior to errors and a larger correction effect at keystroke. Second, after overt errors, the spectral power in the theta and beta frequency ranges was enhanced at mesial electrodes. Third, the beta band phase synchronization between F_4 and FC_z increased 100 ms before errors; this measurement correlated positively with the reduction in loudness of errors and negatively with the pre-error slowing (IOI with previous note). Thus, the degree of increased pre-error bivariate synchronization between this pair of electrodes – with F_4 representing the lPFC and FC_z representing the pFMC – was associated with more efficient correction mechanisms and a shorter pre-error slowing.

In patients with MD, beta and theta band activity could be observed prior to and following errors, which confirmed the oscillatory patterns reported in study 1. The index of F_4–FC_z phase synchronization showed robust increases prior to wrong notes, which were mostly localized in the theta band. A comparison between the patients and the control group revealed the following outcomes: (i) an enhanced beta band spectral power at note onset and following errors in MD pianists, and (ii) a shift to a lower frequency range (theta band) in the index of phase synchronization between electrodes F_4–FC_z. Moreover, in the patient group, larger values of post-error beta power followed weaker correction mechanisms and were related to the degree of motor impairment in the affected hand. Finally, the pre-onset difference between error and correct trials in the theta phase synchronization index correlated negatively with the severity of the disorder and showed a trend toward significance in its correlation with the reduction in loudness.

Motor prediction mechanisms during action control

We propose that the following neural processes might implement motor prediction and control during the performance of an over-learned sensory-motor task: (a) The monitored *error signal* is indexed by the pre-error beta and theta oscillations over the pFMC, which probably indicate the reduced probability of obtaining rewards (Ridderinkhof et al., 2004); (b) the *control signal of a forward* – which indicates the need for a behavioral adjustment – might be conveyed from the pFMC to the lPFC and reflected here in the pre-error interaction between FCz and F4 through beta band phase synchronization. In our paradigm, a corrective response, which was possibly triggered to cancel the undesired sensory effects of the wrong movement, might have led to an observed decrease in the loudness of errors and to the pre-error slowing (~150–160 ms). Post-error behavioral adjustments were reflected in the post-error slowing (IOI to next note ~140–160 ms). Processes such as conscious error recognition, attentional resource allocation or evaluation of the error were previously suggested to be signaled by the error positivity (P_e: Falkenstein et al., 1990, Nieuwenhuis et al., 2001; Van Veen and Carter, 2002; Herrojo Ruiz et al., 2009a). These processes might be manifested here in the increased theta and beta spectral power from 100 to 200 ms after errors.

Optimization in performance might be achieved by the interaction between the action-monitoring and the cognitive control systems (Botvinick et al., 2001; Ridderinkhof et al., 2004). According to this view, the action-monitoring system supervises ongoing performance and signals the need for adjustments, which are in turn implemented by the cognitive control system. Most of the previous investigations have located the neural activity associated with action-monitoring processes in the pFMC, whereas the control system is ascribed to the lPFC (Eichele et al., 2008; Botvinick et al., 2001; Ridderinkhof et al., 2004; Ullsperger and von Cramon, 2004; Kerns et al., 2004). This proposed theory is supported by evidence for a relation between post-error behavioral adjustments and (a) activity in the lPFC (Kerns et al., 2004; Cavanagh et al., 2009) and also (b) increased theta band phase synchronization between electrodes located over the lPFC and pFMC (Cavanagh et al., 2009). Our results are in line with this model, in which the pFMC monitors ongoing performance to detect unfavorable upcoming actions and interacts with the lPFC, so that this brain region can implement the behavioral adjustments. The present findings are of particular relevance because, to the best of our knowledge, for the first time the predictive error-detection and control mechanisms have been documented in patterns of neural oscillatory activity and phase synchronization between brain regions observed around 100 ms *before* errors were committed. As was emphasized in the introduction, such fast predictive mechanisms are required for the optimal execution of pre-programmed temporal and spatial movement patterns which characterize piano performance (Catalan et al., 1998) as well as other highly trained sensory-motor tasks such as tennis playing or typewriting. One possible approach to explain the accuracy of fast movements is to rely on a dual model which uses both internal forward information in terms of a motor plan and sensory feedback loops to make corrections at the end of the trajectory (Meyer et al., 1988; Milner, 1992; Plamondon and Alimi, 1997). Another approach, based on the equilibrium-point theory (Feldman, 2010), proposes that the final referent position of a finger (or hand) during fast movements is established before movement offset. This earlier ending of control processes enables the neural systems to predict upcoming deviations (i.e. errors) from that reference position.

Generally, most researchers believe that hypothetical internal models of motor prediction are broadly distributed by the structures of the central nervous system, from which the cerebellum and the BG have attracted increasing attention (Latash, 2008; Seidler et al., 2004). In this view, the cerebellum and/or the BG possibly monitor the current motor command and the unfolding of the movement. The monitoring processes enable the prediction of an upcoming error. In our study the projection of this information to the pFMC might have been reflected in the cortical patterns of oscillatory activity, which then likely signaled the predicted error warning. Finally, the interaction between the mPFC and lPFC is mediated by beta band phase synchronization and predicts successful cognitive control.

In contrast to the present paradigm, in which pianists retrieved memorized music pieces and engaged the motivational limbic system to a large extent, a vast number of previous investigations of performance-monitoring were based on repetitive and nonarousing tasks (for instance, reaction time conflict-tasks such as Flanker/Stroop task or continuous temporal expectancy tasks). The difficulty in maintaining an adequate level of attention in these paradigms generates suboptimal brain states which eventually lead to the commission of errors (Ridderinkhof et al., 2003; Mazaheri et al., 2009; Eichele et al., 2008; O'Connell et al., 2009; Weissman et al., 2006). To our knowledge, the main differences between our paradigm and the nonarousing tasks in previous studies are as follows: First, due to the low variability of stimulus types, (e.g., in the flanker task, stimulus "flanker" arrows point left or right and target arrow points left or right), these tasks are repetitive and after a while participants might

reduce their effort or attention. Second, music performance becomes *automated* after intensive rehearsal and thus does not require attention to be directed toward the details of the movement (Davidson, 2009). These two aspects were demonstrated in that in our study there was no increase in occipital alpha oscillations several notes prior to performance errors (Supplementary Fig. 2). Thus, whereas attention plays a key role in stimulus-driven tasks which demand a response according to the stimulus (e.g., reaction-time conflict tasks, continuous temporal expectancy tasks), this might not be the case in memorized music performance. Overall, the present data support that complex overlearned sensory-motor tasks constitute an optimal framework for the study of motor prediction by forward models.

One potential limitation of our study is that we did not record EMG activity concurrently with the EEG activity and MIDI signal. This measure would allow us to relate the electrophysiological correlates to the movement onset. Thus, we could investigate whether the oscillatory and synchronization patterns reported in this study precede both movement onset and key press, or if they are triggered after movement onset. Similar future studies should take this issue into account.

Beta oscillatory dynamics in error-monitoring

The patterns of oscillatory activity and phase synchronization were mainly localized over the pFMC and right lPFC in the theta and lower beta frequency bands. The latter effect is a novel finding which gives evidence for a role of beta oscillations in action-monitoring. Importantly, because the temporal resolution provided by the family of wavelet functions was ~30 ms in the lower beta band (15–20 Hz), the oscillatory and synchronization effects observed around 100–120 ms before note onset cannot be due to spurious backwards oscillatory activity.

Multiple accounts of the pFMC oscillatory activity have reported neural oscillations in the theta range, reflecting conflict or error-detection immediately after wrong responses and later error evaluation (Trujillo and Allen, 2007; Luu et al., 2003; Cohen et al., 2008; Luu et al., 2004), findings which are in agreement with our data. Thus, the role of the theta band oscillations in error-monitoring is confirmed by our study. Furthermore, pre-error theta and beta oscillations were associated in our paradigm with better corrective adjustments, so that our tentative interpretation of the data is that oscillations in both frequency ranges triggered at the pFMC preceding errors might signalize an upcoming failure or reduced probability of receiving rewards (Ridderinkhof et al., 2004).

Whereas previous data have shown that an increased theta phase synchronization between the pFMC and the lPFC reflects the interaction between these brain regions to implement cognitive control in reaction-time conflict tasks (Cavanagh et al., 2009), our findings point to an interaction between these two brain systems rather mediated by beta phase synchronization, which predicts successful cognitive control. This novel outcome might demonstrate that the neural assemblies across the pFMC and lPFC – which exhibited enhanced local beta oscillatory activity – interacted by means of phase entrainment in the same beta frequency range.

Theta oscillations are robust neural correlates of attention and working memory tasks (Kahana, 2006) and of conflict and error-detection in routinely executed repetitive tasks (Trujillo and Allen, 2007; Luu et al., 2003; Cohen et al., 2008; Luu et al., 2004). However, the precise functional role of the bursts of beta oscillations is still under debate (Müller-Putz et al., 2007; Engel and Fries, 2010). Most of the previous evidence for increased beta oscillations is limited to motor tasks (Pfurtscheller et al., 1997, 2005; Kühn et al., 2006; Müller et al., 2003), although more recent investigations on new aspects of motor processing posit additional hypotheses regarding the role of beta oscillations, such as an engagement during action-monitoring (Gilbertson et al., 2005; Androulidakis et al., 2006; Koelewijn et al., 2008). Koelewijn et al. (2008) demonstrated increased beta band oscillations over the motor cortex following incorrect actions as compared with correct actions. The stronger beta oscillations after erroneous outcomes were interpreted as an electrophysiological marker of response inhibition, which typically follows error detection (Ridderinkhof et al., 2004), and could have been influenced by the outcome of error-monitoring processes in the ACC. Thus, although a direct comparison between this work and our data is difficult because of the focus on different tasks and brain regions, the increased beta oscillations *following* performance errors in our paradigm could be interpreted in a similar fashion: as an indication of response inhibition after erroneous outcomes. Response inhibition is in this context can therefore be envisioned as a mechanism of control relevant for reinforcement learning in the cortico-striato-thalamo-cortical circuits, and might enhance learning from errors (Ridderinkhof et al., 2004; Cohen and Frank, 2009). It is important to note, however, that we did not observe different beta oscillations in response to errors or correct notes over the left primary motor cortex (contralateral to the movement; see Fig. 2). Therefore, this interpretation should be used with care. The lack of observed differences over the primary motor cortex also indicates that the findings reported in the beta band cannot be simply related to a different motor output during the production of errors compared with correct notes, which would be primarily observed in that cortical region.

Regarding the increased beta oscillatory activity *preceding* errors, which was associated with better corrective mechanisms, the first tentative interpretation would be to associate it with inhibitory mechanisms prior to error commission. Although the link between beta band activity and inhibition has been primarily demonstrated over the primary and supplementary motor cortex (Pfurtscheller et al., 1997, 2005; Kühn et al., 2006), we suggest that this link could also be observed in other neural structures within the monitoring system (such as the pFMC and lPFC), to signal the need to inhibit an upcoming action. Interestingly, another study confirmed a benefit of beta oscillations for corrective movements (Androulidakis et al., 2006). Thus, although there is no unifying hypothesis for the role of beta oscillations in error-monitoring yet (Engel and Fries, 2010), our findings might advocate a specific role of beta band oscillations and phase synchronization in motor prediction, corrective adjustments and evaluation of errors during skilled motor behavior. Further investigations of the brain mechanisms in error-monitoring during skilled performance might reveal new insights into the possible role of beta oscillations in this context.

Action-monitoring in focal dystonia

The highly influential account of the ERN within the context of the reinforcement theory suggests that this component is modulated by dopamine (Holroyd and Coles, 2002; Schultz, 2002). According to this view, the basal ganglia (BG) evaluate ongoing events and generate predictions of failure or success. In association with future failures, the phasic decreases in the dopaminergic activity lead to a larger ERN in the ACC. A direct prediction follows from the reinforcement learning theory, namely, a different error processing in BG disorders characterized by dopaminergic alterations, such as Huntington's disease and Parkinson's disease (Ito and Kitagawa, 2006; Beste et al., 2006, 2009). The main findings in both disorders have been a decreased ERN and later P_e suggesting impaired performance, conflict monitoring, and abnormal conscious error evaluation. On the contrary, in Tourette Syndrom, which is related to hyperactive basal-ganglia thalamocortical pathways, an enhanced ERN has been reported (Johannes et al., 2002). We studied error detection and evaluation mechanisms in an overlearned sensory-motor task in pianists with focal task-specific dystonia (FTSD), a condition also considered to result from BG dysfunction (Naumann et al., 1998;

Preibisch et al., 2001). In particular, there is support for an impaired center–surround inhibition within the basal ganglia–thalamic circuit, which results in the overactivity of medial and prefrontal cortical areas (Berardelli et al., 1998). In FTSD, this phenomenon can be observed, for instance, in the excessive activation of sensorimotor cortical areas during skilled movements of the affected hand (Peller et al., 2006). Our main hypothesis was that the degraded neural activity observed at all levels in the cortico-basal ganglia-thalamocortical loops in FTSD might interact with the error-monitoring processes associated with the BG (Holroyd and Coles, 2002; see also Lardeux et al., 2009, and Arkadir et al., 2004, for evidence from animal studies). This interaction could, consequently, result in abnormal cortical oscillatory patterns associated with error processing.

An important aspect of our paradigm is that it required participants to perform with the unaffected hand and they therefore were able to produce an *optimal behavioral output*. The selection of the unaffected hand was motivated by evidence from studies on FHD which revealed that despite unilateral symptoms, physiologic measures show abnormal bilateral activations mainly in the primary somatosensory cortex, but also in the motor cortex. This phenomenon might reflect a genetic predisposition in FHD and has been termed "endophenotype" (Meunier and Hallett, 2007). Specifically, abnormal bilateral cortical processing of somatosensory inputs, impaired finger sensory perception irrespective of the site of the dystonia, bilateral plastic changes in S1, and bilateral changes in intracortical inhibition in the motor cortex have been found in FHD (Ridding et al., 1995; Molloy et al. 2003; Garraux et al., 2004).

The outcomes rendered a first insight into the neural mechanisms of action-monitoring in this patient group. When comparing the group of MD pianists with an age-matched sample of healthy pianists, the most relevant outcomes were as follows: (i) in both groups the loudness of errors was similarly reduced, indicating equivalent efficient forward corrective mechanisms; (ii) MD pianists showed larger beta oscillatory activity at note onset and following errors, and a pre-error phase synchronization between F_4 and FC_z in a different frequency range (6–8 Hz) from that of healthy controls (~13 Hz). In addition, in MD pianists increased post-error beta power was associated with smaller corrective mechanisms and related to the severity of the disorder. Interestingly, also in this group, the pre-error 6–8 Hz phase synchronization index between F_4 and FC_z correlated highly with the degree of motor impairment in the affected hand and there was a trend toward significance in its correlation with predictive mechanisms. The latter result, though non-strictly significant, suggests a link between the specific electrophysiological marker of motor control by forward models in patients and the severity of their disorder. Future investigations with larger sample size should look further into this link.

Our results add to the existing literature on error-monitoring in BG disorders by suggesting that in patients with focal dystonia, the generalized degraded neural activity at all levels of the central nervous system is manifested in specific neural correlates of the executive functions that monitor an overlearned sensory-motor performance. More specifically, pianists with MD might have an enhanced evaluation of errors as reflected in the larger oscillatory activity following errors. This result might be related to the reduced pallidal inhibition of the thalamus in this patients (Berardelli et al., 1998), which might convey enhanced error-related information from the BG to medial and frontal cortical areas; or to the altered central sensory processing – key to action-monitoring – in patients with FTSD (Hallett, 1998; Peller et al., 2006). Furthermore, in control processes by forward models, the interaction between electrodes representing the pFMC and lPFC seems to be mediated in MD patients by theta phase synchronization, a lower frequency range from that in healthy pianists. Thus, the coordination between brain regions and the corresponding large-scale integration – assessed here by the phase synchronization – seems to be altered in MD, even in tasks performed by the healthy non-affected hand. This result is in line with a previous study of cortical function in MD in an overlearned motor task (Herrojo Ruiz et al., 2009b): in MD pianists an altered inter-regional phase synchronization was detected in the upper theta/lower alpha (7–8 Hz) bands between the neuronal assemblies required to inhibit motor memory traces. Thus, both studies suggest a possible predominance of theta band oscillations to mediate cortical phase interactions among electrode regions. Interestingly, pathological theta oscillations have been reported in the internal segment of the globus pallidus (GPi) in patients with dystonia undergoing deep brain stimulation, both at rest (Silberstein et al., 2003) and prior to stimulus-presentation in a reaction-time conflict task (Herrojo Ruiz et al. in preparation). Future studies are required in the area of error-monitoring in dystonia to validate the specific patterns of error-related brain activity in this condition.

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Error monitoring is altered in musician's dystonia: evidence from ERP-based studies

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Musician's dystonia (MD) is a task-specific movement disorder characterized by a loss of voluntary motor control in highly trained movements like piano playing. Its underlying pathophysiology is defined by deficient functioning of neural pathways at different levels of the central nervous system. However, a few studies have examined the brain responses associated with executive functions such as error monitoring in MD. We recorded the electroencephalogram (EEG) in professional pianists during the performance of memorized music sequences at fast tempi. Event-related potentials (ERPs) locked to pitch errors were investigated in MD and a control group. In MD patients, significantly larger error-related brain responses before and following errors were observed as compared with healthy pianists. Our results suggest that in MD, the generalized degraded neural activity at all levels of the central nervous system is manifested in specific neural correlates of the executive functions that monitor an overlearned sensorimotor performance.

Keywords: error monitoring; dystonia; music performance

Introduction

Musician's dystonia (MD) is a focal task-specific dystonia (FTSD), which is defined by involuntary and dysfunctional movement patterns when playing a musical instrument. It affects one out of a 100 professional musicians and is therefore the most common of all dystonias in a specific population.[1] As underlying pathology, external triggering factors, such as overuse and biomechanical constraints, seem to contribute importantly. Furthermore, recent studies have shown that impaired sensorimotor integration and decreased inhibition on all levels of the sensorimotor pathways play important roles in its manifestation.[2–4] Deficient inhibition also leads to hyperactive basal ganglia pathways.[5,6]

It has been shown that disabilities involving basal-ganglia dysfunction such as Gilles de la Tourette syndrome (TS), obsessive-compulsive disorder (OCD), and Parkinson's disease (PD) can result in different modulation of event-related potentials (ERPs). Therefore, the goal of our study was to further investigate the pathology of musicians' dystonia by means of evoked potentials in an ecological design involving frontal executive functions and error monitoring in professional pianists suffering from dystonia.[7–10]

With respect to error monitoring in general, recent electroencephalogram (EEG) studies have shown several error-specific ERP components. The most relevant are the so-called error-related negativity (ERN or Ne) and the error-related positivity (Pe).[11,12] An ERN is characterized by its negative deflection of voltage between 50 and 100 ms after the actual error commitment, regardless of the type of task error.[11,12] The most recent evidence demonstrates that the posterior cingulate cortex is the generator of the ERN and that it is functionally related to the dorsal anterior cingulate cortex.[13] Evidence suggests that the ERN mainly reflects earlier stages of error detection, although its amplitude may be influenced by the affective or emotional significance of the error.[14–16] Another specific error-related component is the Pe, the maximum of which is usually

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at parietal scalp electrodes between 200 and 500 ms after an incorrect action. It has been suggested that the Pe is influenced by the subjective error perception.[17,18]

Playing the piano at a professional level is exceptionally well suited to study error monitoring because it is an extremely demanding task, requiring the highest spatio-temporal precision of complex movements under the unyielding control of the auditory system. Because in classical reproductive music "correct" notes have to be played and wrong notes have to be avoided, piano playing has recently been used in several EEG studies to investigate error-monitoring processes.[19–22] A very interesting and novel finding in this context was an early ERP component termed pre-ERN.[20,21] The pre-ERN shows maximum negative deflection at about 70–30 ms before note onset. Its neural generator was localized in the rostral ACC.[20] The pre-ERN was interpreted as a neural correlate of error prediction signals in overlearned performance.

The objective of this study was to take advantage of the expertise of highly trained classical pianists and compare electrophysiological correlates of error monitoring in pianists with MD and healthy pianists. Our hypothesis was that deficient inhibition and disturbed basal ganglia loops would be reflected in altered error-related brain potentials.

Materials and methods

Participants

Twelve professional pianists took part in the study, six of whom were MD patients (four males; age range, 28–52 years; mean, 40 years; SD, 10 years) and six were healthy control subjects (four males; age range, 26–44 years; mean, 35 years; SD, 7 years). All patients were right handed according to the Edinburgh Handedness Scale and reported normal hearing. Informed consent was obtained from each participant.[23] The study received approval by the local ethics committee of Hannover and the patient data are presented in Table 1.

Before participating in the study, all patients were examined by a movement disorders specialist (E.A., the senior author) to confirm the diagnosis of MD, based on a neurological examination and visual inspection while they played the piano. In all patients, solely the left hand was affected. Secondary dystonia and genetic forms of dystonia were excluded by a laboratory test and clinical examinations. In all participants, motor control at the piano was assessed by musical instruments digital interface (MIDI)-based scale analysis previously reported as a valid tool for this purpose.[24]

Stimulus material

The musical stimuli consisted of six sequences taken from the right-hand parts of Preludes V, VI, and X of *The Well-Tempered Clavier* (Part 1) by Johann Sebastian Bach and the Piano Sonata No. 52 in E Flat Major by Joseph Haydn, described previously by Herrojo Ruiz *et al.*[20] We chose these pieces because they consist mainly of 16th notes and therefore provide homogeneous stimulus material of the same duration. The tempo for each piece was chosen so that the interonset interval (IOI; time between two consecutive onset keypresses) was 125 ms, which resulted in fast tempi even for

Table 1. MD and healthy pianists did not differ in the accumulated practice time

Patient	Sex	Age	Affected digits of the left hand (in descending degree of impairment)	Year of MD manifestation	Last therapy	Accumulated practice time (h)
Pat_1	Female	52	2	1992	Botox (9 years since last injection)	26,645
Pat_2	Male	51	4, 5, 1, 2, 3	2004	–	92,892
Pat_3	Male	49	3	1995	Botox (7 years since last injection)	62,962
Pat_4	Male	40	2	1996	–	36,135
Pat_5	Male	39	2, 4	1996	Botox (6 months after last injection)	27,922
Pat_6	Female	29	2	2004	–	37,595

professional musicians. This was necessary in order to induce a higher error-production rate. All participants were instructed to learn and rehearse the sequences using a metronome, though. The score of the pieces is depicted in Figure 1.

Experimental design

The experiment was carried out in a dimly lit and acoustically shielded room, where participants sat comfortably in front of a digital piano (Wersi Digital Piano CT2) in an armchair, with their left forearms resting on the armrest. For artifact reduction interfering with the EEG recording, participants were told to also let their right forearm rest on a movable armrest attached to a sled-type device, which had been constructed specifically for that purpose. In order to prevent pianists from tracking their finger movement with their eyes, the surface of the keyboard was covered with a black board, which still made effortless playing possible.

Before the experimental session we checked that every participant was able to perform the pieces from memory and according to the score at the desired tempi. Every pianist was instructed to perform the score from beginning to the end without stopping to correct errors, but they were unaware of our interest in error-specific data.

The experimental session consisted of 10 trials per type of sequence, which were presented randomly. The 60 sequences they played in total amounted to 40 min of continuous performance.

EEG recording and preprocessing

Continuous EEG signals were recorded from 35 electrodes placed on the scalp according to the extended 0–20 system, linked mastoids as references. To monitor blinks and eye movements, we additionally recorded a transversal electrooculogram. EEG signals were digitized at a sampling frequency of 500 Hz and impedance was kept below 5 kΩ. The upper cutoff was 100 Hz (software by NeuroScan Inc., Herndon, VA). Note onsets, visual trigger stimuli, and metronome beats were automatically recorded with markers within the continuous EEG file. Performance was recorded as a MIDI file using a standard MIDI sequencer program.

For filtering and processing the continuous EEG files, we used the EEGLAB MATLAB® Toolbox v. 7.2.11.22bb.[25] After data acquisition, we applied a 0.5–35 Hz band-pass finite impulse response (FIR) filter to remove linear trends and muscle artifacts. We then performed a wavelet-enhanced independent component analysis (wICA)[26] after first computing the ICA components with the FastICA algorithm[27] to clean data from artifacts, such as blinks and eye movements. The use of ICA for artifact removal has been reported to constitute a loss of neural activity since the rejected components usually contain not only artifacts, but also neuronal

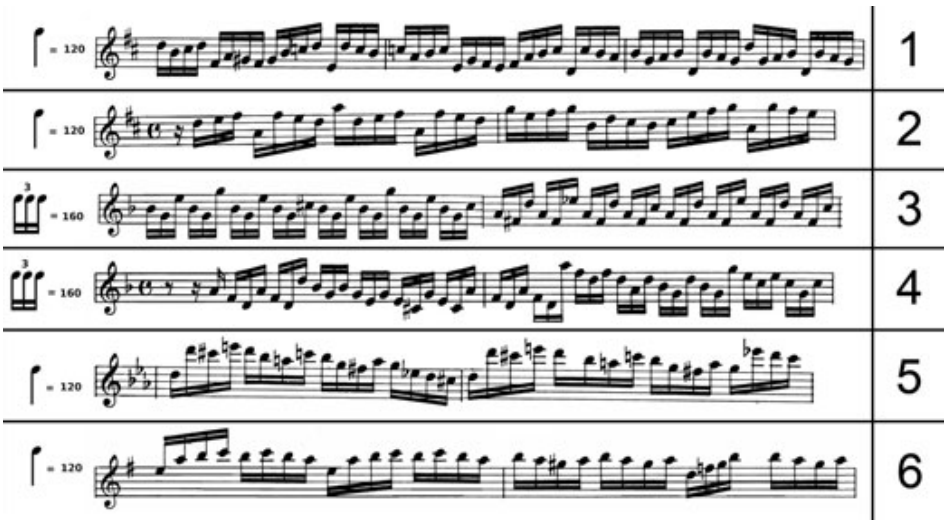

Figure 1. **Examples of musical stimuli. The first bars of the six musical sequences are illustrated. Pieces 1 and 2 were taken from Prelude V of *The Well Tempered Clavier* (Part 1) by Johann Sebastian Bach. Pieces 3 and 4 were adapted from Prelude VI and piece 6 from Prelude X. The fifth sequence was adapted from the Piano Sonata No. 52 in E Flat Major by Joseph Haydn. The tempi as were given in the experiment are indicated: metronome 120 for quarter note and 160 for triplet of eighth notes. In all cases, the IOI was 125 milliseconds.**

activity. wICA solves this problem by using wavelet thresholding, which filters out the artifacts by their specific time–frequency properties.[20] Any artifacts that could still reside in the epoched EEG file were manually subtracted. Data were epoched into two conditions representing correct and erroneous notes with a time window time-locked from 300 ms before note onset to 500 ms after note onset. The baseline was set from 300 to 150 ms before the actual keystroke.

Data analysis

Errors were defined as wrong pitches. Correct notes were defined as keypresses correct in pitch and timing, according to the given tempi. To discriminate errors from correct notes, we used an algorithm developed in MATLAB that compared each MIDI performance with its template in pitch.[20] Only incorrect or correct notes that were preceded or followed by three correct notes entered the analysis. Additional criteria for accepting a correct or erroneous note as events for further analysis were as follows: First, the time interval between keypress and key release was not accepted above 150 ms in order to avoid overlapping of auditory processing from two simultaneous notes. Second, in correct pitch notes, we set a strict timing criterion to make sure that there were no deviations in timing, which could lead to neural processing related to timing monitoring. Specifically, the IOI of correct pitch notes was accepted when in the range of 120–130 milliseconds. In pitch errors, the timing criterion was set for the range of 100–300 milliseconds. We did not set a stricter timing criterion for pitch errors because performance errors typically lead to slowing in the next event (post-error slowing) and can also be associated with pre-error slowing or speeding phenomena.[11,12,20] All errors that appeared in at least seven out of 10 trials of each type, which therefore could be related to learning errors, were removed from the analysis.

Statistical analysis

Analysis of the behavioral data was performed by means of nonparametric permutation tests.[28] For statistical assessment of the ERPs, the waveforms were first averaged across trials in each subject and condition (error, correct) and in five medial scalp electrodes (Fz, FCz, Cz, CPz, Pz). Before investigating the between-group differences, we first conducted a two-sample *t*-test (errors versus correct notes) in the patient and control groups separately. The analysis focused on two different relevant time windows that were based on visual inspection: (i) the pre-ERN time window (70–20 ms prior to note onset) and (ii) the Pe time window (230–270 ms after note onset).

Based on the findings from previous studies, only anterior or posterior electrodes were selected for the analysis of the pre-ERN or Pe.[20,21] Because the topographic maximum for the ERN is acknowledged to spread across all medial electrodes, we used all medial electrodes to compute the statistics.[29]

The between-group statistics were computed using two-way analyses of variance (ANOVAs) with the factors group (patients versus controls) and condition (erroneous versus correct notes). Multiple comparisons were corrected by controlling the false discovery rate (FDR) at level $q = 0.05$.[30]

Results

Performance analysis

MD and healthy pianists did not differ in the accumulated practice time ($P = 0.83$; Table 1 in MD; healthy pianists had an accumulated practice time between 25,000 and 78,110 h; mean, 44,147 h) or in average age ($P = 0.077$). As a reliable parameter for the assessment of motor control dysfunction, we investigated the mean standard deviation of the IOI (mSD-IOI) in both groups based on a scale analysis procedure previously described.[24] As expected, this value differed significantly between groups in the affected left hand ($P = 0.000001$; mean mSD-IOI, 20 ms [SD, 3 ms] in patients, 11 ms [SD, 1 ms] in healthy pianists). Both groups did not differ in the average of isolated errors ($P = 0.72$; 80 [SD, 40] in healthy pianists, 70 [SD, 30] in MD). Furthermore, we observed a reduced loudness (MIDI velocity) in incorrect notes compared to correct notes in both groups ($P = 0.001$ in MD, $P = 0.04$ in healthy pianists), although there was no difference between groups ($P > 0.05$). Additionally, pre- and posterror slowing ($\sim$150 ms) was found in both groups in the IOI between incorrect note and the neighboring event note, which differed significantly from the mean IOI in the performance ($P = 0.001$). Again, no difference between groups was found.

ERP analysis

A graphical overview of the ERP components can be found in Figure 4. Control subjects and patients

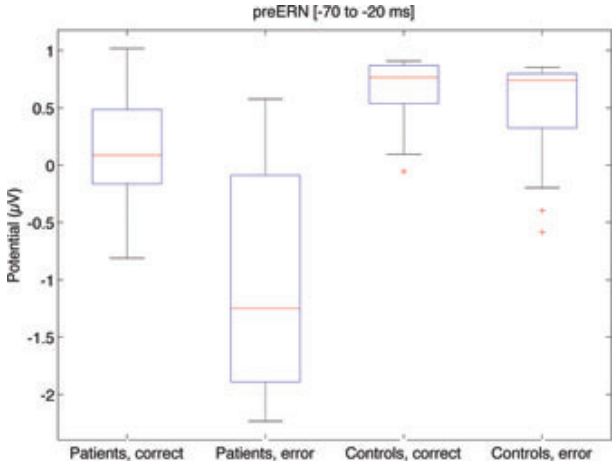

Figure 2. pre-ERN component overview. This box-plot graph was calculated for the pre-ERN time interval ranging from 70 to 20 ms before note onset. Patients and controls showed larger negative deflections for erroneous keypresses compared to correct keypresses.

showed larger negative oscillations in the pre-ERN time interval (70–20 ms before note onset) for incorrect notes (Fig. 2). Later, a positive amplitude modulation was observed between 230 and 270 ms when comparing incorrect to correct notes (Fig. 3). This could be related to the Pe. An ERN component, which would typically peak at around 50–100 ms after keypress, could not be observed.

Within-group ERP analysis

In the control group, we found a significant difference between errors and correct notes for the pre-ERN ($P = 0.0003$) as well as for the Pe ($P = 0.02$). Similarly, in the patient group we found significant differences between errors and correct notes for the pre-ERN ($P < 0.0001$) and the Pe ($P < 0.0001$). These results confirmed the presence of pre-ERN and Pe in both experimental groups.

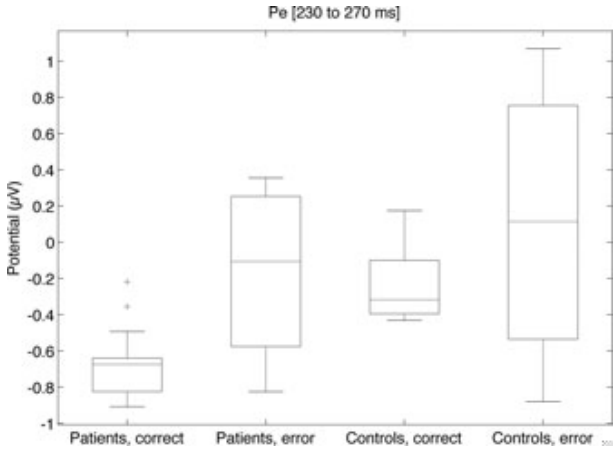

Figure 3. Pe component overview. This box-plot graph was calculated for the Pe time interval ranging from 220 to 270 ms after note onset. As compared to correct notes, the positive deflection is larger for erroneous keypresses in both groups.

Between-group data analysis

We found significant effects (i) in the pre-ERN time window for the factors group ($P < 0.0001$) and condition ($P = 0.0002$), as well as for their interaction ($P < 0.0001$). Contrasts revealed that the main effect for factor condition resulted from larger negative deflections of the pre-ERN in the patient group than in the control group. (ii) In the Pe time window, we obtained significant main effects for the factors group ($P = 0.0002$) and condition ($P < 0.0001$). Error minus correct contrasts revealed that the Pe in the control group was characterized by smaller positive amplitude deflections than in the patient group. Therefore, both groups differed in the pre-ERN and Pe components due to larger pre-ERN and Pe deflections in the MD group.

Discussion

The current study investigated the error-related potentials in professional pianists suffering from dystonia and in a healthy group. When comparing correct and erroneous notes, we could show two specific error-related potentials within each group, that is, pre-ERN and Pe. Both components were significant within each group. These results are in line with the previous studies that used a similar experimental paradigm, and therefore confirm the pre-ERN and Pe as key ERP components reflecting error-monitoring processes during piano performance.[20,21]

As it has been suggested, the pre-ERN might reflect a predictive error signal triggered by an internal forward model or by a reward estimation system, which anticipates the lack of reward. In both cases, the pre-ERN can be interpreted as a neural signal reflecting the mismatch between a planned keypress and the predicted erroneous outcome.[20–22] Furthermore, its neural generator lies in the rostral ACC, a region associated with detecting motivational errors.[31,32] Interestingly, our between-group analysis depicted a larger pre-ERN in MD patients. This could be the result of higher motivational modulation of the predictive error signal in MD: patients might place greater importance on pressing

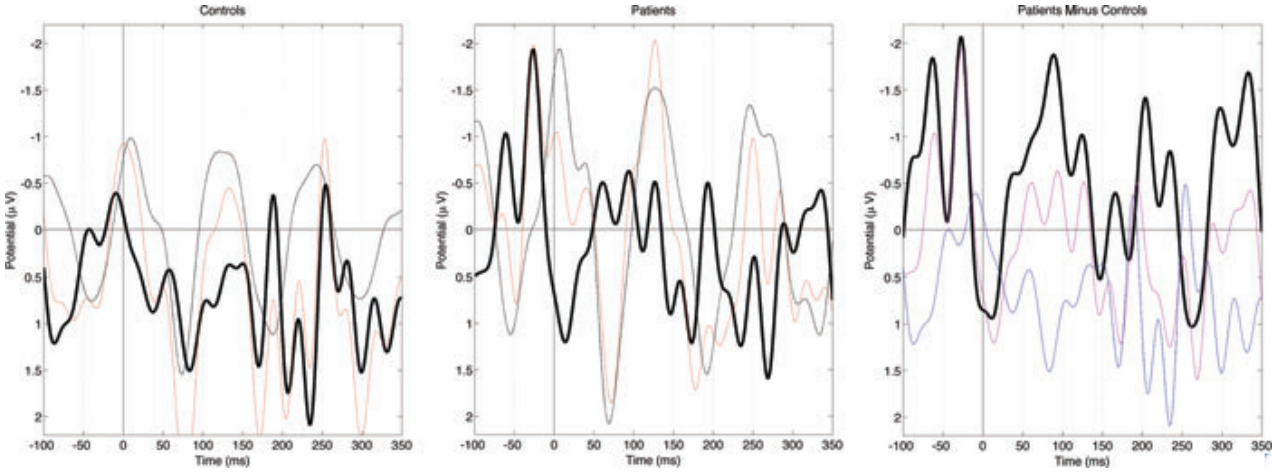

Figure 4. Grand-averaged EEG overview. The grand-averaged EEG files across patients and healthy controls are illustrated at electrode position Fz. The bold line in controls and patients represents the difference between incorrect (red line, dashed) and correct (black line, solid) notes. In the group comparison (Patients Minus Controls), differences from patients (violet, dashed line) and controls (blue line, solid) were subtracted again, resulting in the between-group difference (bold line).

the right note. Therefore, it is plausible to assume that the mismatch between the predicted error and the planned correct event is more enhanced.

In fact, findings of recent studies in which the relation between psychological factors and the development of MD has been examined could support the thesis of a higher motivational impact of errors on MD patients. Not only do MD patients tend to have a more distinct sense of perfectionism, it is also assumed that MD is accompanied by higher levels of anxiety and neuroticism.[33,34] Thus, the abnormal cortico-thalamic neural activity found in MD may influence limbic loops, resulting in both altered motor and affective processing.[35]

These results converge with the second outcome of our study: a larger Pe following errors in pianists with MD than in healthy pianists. This ERP has been suggested to signal conscious error recognition as well as evaluation, and it might even reflect response strategy adaptation.[18,36,37] Enhanced Pe amplitudes have also been found in children suffering from OCD.[38] The authors conclude that the emotional impact of an error might be reflected by the Pe such that the greater the emotional significance of the error, the higher the Pe.

If taken into consideration that the Pe in this paradigm also seems to be generated by rostral ACC areas and that the rostral ACC is associated with affective processing, a higher Pe in MD patients may suggest enhanced conscious and emotional error evaluation.[10,17,20,39]

Other studies have shown that patients with dystonia suffer from higher intensity of obsessive-compulsive symptoms.[40,41] Cavallaro and Bihari concluded that OCD and FD might indeed share a common pathologic background indicating basal-ganglia dysfunction.[42,43]

There is also support for a reduced pallidal inhibition of the thalamus in dystonia, which results in the over-activity of medial and prefrontal cortical areas.[44] In MD, this could be expressed by an excessive activation of sensorimotor cortical areas during skilled movements of the affected hand. In addition, it could be speculated that the phenomenon of enhanced pallidal disinhibition of the thalamus in dystonia leads to altered error signals projected from the output of the basal ganglia to the posterior frontomedial cortex.[44]

Further studies have shown evidence for hyperactive basal-ganglia signaling in FTSD.[5] It has been hypothesized that the integration of prefrontal and motor fronto-thalamico-striato-cortical circuits provides contextual information to the motor ACC to enable their function in performance monitoring.[45]

We did not observe an ERN component in our experiment in both healthy pianists and patients. Most studies focusing on the ERN use flanker or Stroop tasks that participants are not trained for, whereas the pianists in our study were all professionally trained pianists and the performance was overlearned. Their experience provided them with a fast-functioning, internal self-monitoring system

during the memorized performance, which enables an earlier detection of the errors. In contrast, participants in speeded choice reaction tasks are not trained for the task and, in addition, no planning in terms of a memory representation of the task is possible. These key differences in the population and in the task can account for the lack of ERN in the present study as well as in related piano performance studies.[20,21]

This study provides evidence to support the idea that the degraded neural activity in the basal-ganglia-thalamocortical loops might interact with error-monitoring processes associated with the basal ganglia, which results in altered error-monitoring mechanisms in focal dystonia.[22]

Notwithstanding the altered ERP patterns observed during error monitoring in MD, at the behavioral level no differences in performance between patients (performing with the healthy hand) and healthy pianists were observed. This outcome suggests that it is necessary to look further into the interaction between behavior and brain activity during action monitoring in MD. Only then can the implications of the reported altered error-related ERPs in MD be better understood.

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Conflicts of interest

The authors declare no conflicts of interest.

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2. Zusammenfassung

2.1 Einleitung

Die Dystonie ist eine neurologische Bewegungsstörung aus dem Kreis der extrapyramidalmotorischen Erkrankungen. Unter dem Oberbegriff der Dystonie werden mehrere phänomenologisch und ätiologisch heterogene Krankheitsbilder zusammengefasst, deren Leitsymptom sich in unwillkürlichen und repetitiven Muskelkontraktionen, myoklonischen Zuckungen und auch in dystonem Tremor äußern kann.

Fahn und Bressmann zufolge werden die Dystonien nach Erkrankungsbeginn, Verteilungstyp und Ätiologie klassifiziert (Tab. 1).[1]

Tabelle 1: Klassifikation der Dystonien (mod. nach Fahn 1998, Bressman 2004)

I. - nach Alter bei Erkrankungsbeginn
- früh (< 26 Jahre) - spät (> 26 Jahre)
II. - nach Verteilungstyp
a) fokal (nur einzelne Körperregionen betreffend) - Augenlider (Blepharospasmus) - Mund (Ansatzdystonie, oromandibuläre Dystonie) - Larynx (spasmodische Dystonie) - zervikale Dystonie (Torticollis, Laterocollis, Antecollis) - Extremitätendystonie (Schreibkrampf, Musikerkrampf, Sportlerdystonien)
b) segmental (zusammenhängende Körperregionen betreffend) - kranial: zwei oder mehrere Anteile des Kopfes, des Gesichts bzw. der Halsmuskulatur - axial: Hals- und Rumpfmuskulatur - brachial: Muskeln eines oder beider Arme und des Rumpfes - krural: Muskeln eines oder beider Beine mit bzw. ohne Beteiligung des Rumpfes
c) multifokal (zwei oder mehrere nicht zusammenhängende Körperregionen betreffend) - Hemidystonie: gleichseitige Arm- und Beinmuskulatur
d) generalisiert (Bein, Rumpf und mindestens ein weiteres Segment betreffend)
III. - nach der Ätiologie
a) primäre Dystonien (ohne äußere Einwirkung oder degenerative Ursache) - sporadische Formen (bspw. idiopathische Torsionsdystonie) - erbliche Formen (DYT1-, DYT6-, DYT7-, DYT13-Gene)

b) sekundäre Dystonien

- psychogene Ursachen
- erworben (z.B. medikamenteninduziert, traumatisch, durch Überbelastung und maladaptive Plastizität, Overuse-Syndrom)
- Assoziation mit hereditär oder sporadisch auftretenden neurodegenerativen Erkrankungen (z.B. Morbus Wilson, Dopa-responsive Segawa-Dystonie)
- Assoziation mit metabolischen Störungen (z.B. Homozystinurie)

Die Musikerdystonie ist definiert als eine neurologische Erkrankung aus der Gruppe der fokalen, tätigkeitsspezifischen Dystonien, die bei professionellen Musikern auftritt. Charakteristischerweise leiden Patienten beim Spielen eines Instruments unter rezidivierenden, unwillkürlichen Muskelkrämpfen mit nachfolgendem Verlust der feinmotorischen Kontrolle. Diese Störungen können sowohl die obere Extremitätenmuskulatur als Handdystonie wie auch die orofaziale Muskulatur, z.B. bei Bläsern, als Ansatzdystonie betreffen. Typischerweise ist die Musikerdystonie schmerzlos, obwohl von einigen Patienten über Muskelschmerzen nach prolongiertem Krampf berichtet wurde. Diese Unterscheidung ist wichtig für die Klassifikation der Musikerdystonie als nicht-sekundär, wie z.B. als Folge einer lange anhaltenden Schmerzsymptomatik.[2]

Epidemiologie

Die Musikerdystonie tritt laut neuesten Erkenntnissen bei ca. einem von 100 professionellen Musikern auf - im Gegensatz dazu beträgt die Prävalenz der Dystonie in der Allgemeinbevölkerung nur zwischen 29,5 pro 100 000 in den USA und 6.1 pro 100 000 in Japan.[3] Dass 65% aller Berufsmusiker infolge ihrer Erkrankung ernsthafte berufliche Einbußen erleiden müssen und sogar 29% aller Patienten zu einer Aufgabe jeglicher musikalischen Tätigkeit gezwungen sind, zeigt die soziale und ökonomische Relevanz der Erkrankung auf.[4]

Pathophysiologie

Die Pathophysiologie der Musikerdystonie, wenn auch noch nicht vollständig geklärt, ist wahrscheinlich multifaktoriell. Neben genetischen Merkmalen konnten psychologische Triggerfaktoren nachgewiesen werden; auch wurden Veränderungen in neuronalen Prozessen beobachtet.

Etwa 10 bis 20 % aller unter einer Art von fokaler Dystonie leidenden Patienten weisen eine familiäre Disposition auf.[5]
Obwohl noch kein spezifisches, für die Entstehung der Musikerdystonie verantwortliches Gen identifiziert wurde, konnte bei einigen an fokaler Dystonie leidenden Patienten eine GAG-Deletion auf dem DYT1-Gen nachgewiesen werden.[6]
Auch wenn die Musikerdystonie als eindeutige neurologische Erkrankung definiert wird[7], konnten gewisse psychologische Triggerfaktoren identifiziert werden, welche die Entstehung der Erkrankung begünstigten; namentlich Angsstörungen, spezifische und soziale Phobien und eine erhöhte Neigung zum Perfektionismus.[8-9]

In letzter Zeit wird verstärkt angenommen, dass die Musikerdystonie damit einen gewissen Bezug zu veränderten basalganglionären neuronalen Schleifen besitzt und somit als auf Dysfunktion der Basalganglien beruhende Erkrankung zu definieren ist.[10-11]
Studien über deren Ätiologie auf neuronaler Ebene zeigten Abnormalitäten auf mehreren Ebenen des zentralen Nervensystems: Einerseits eine reduzierte Fähigkeit zur Inhibition im motorischen System auf kortikaler, subkortikaler und spinaler Ebene, andererseits eine beeinträchtigte sensorische Wahrnehmung und Integration sensorisch-motorischer Signale.

Das zentrale Inhibitionsdefizit äußert sich bei der Musikerdystonie einerseits in einer fehlerhaften lateralen Inhibition motorischer Efferenzen[12] mit unwillkürlicher Antagonistenaktivierung[13] als auch in einer Fusion rezeptiver Felder somatomotorischer Rindenareale[14]. Als für die defizitäre Hemmung hauptverantwortlichen Ort werden die Basalganglien favorisiert[15], jedoch konnte das Inhibitionsdefizit auch auf spinaler[16] sowie kortikaler[17] Ebene nachgewiesen werden.

Klinische Observationen führten zu der Annahme, dass eine abnormale Verarbeitung sensorisch-motorischer Reize eine Ursache für fokale Dystonien sein könnte. Dies äußert sich darin, dass eine Modulation der afferenten Information zu einer Verbesserung der Symptomatik führen kann. Dieser Effekt wird allgemein als „sensory trick"-Phänomen bezeichnet und ist bei der Handdystonie auch als „Handschuheffekt"[2], bei unter Torticollis leidenden Patienten auch als sog. „geste antagoniste" bekannt.[18] Dass eine durch repetitive motorische Aktivität ausgelöste Desorganisation somatosensorisch repräsentativer Areale zu einer der fokalen Dystonie analogen Symptomatik führen kann, wurde in einer an Affen durchgeführten Studie aufgezeigt.[19] Auf diesen Befund stützen sich auch Ergebnisse weiterer Studien, die den Zusammenhang zwischen sog. „Overuse" und dem Auftreten einer Dystonie untersuchten.[20]
Ein Grund für jene Beeinträchtigungen der sensorisch-motorischen Integration liegt neben der Dedifferenzierung sensorisch-motorischer Felder möglicherweise in einer maladaptiven neuronalen Plastizität, wie sie auch im sensorischen Thalamus bzw. im Putamen beschrieben wurden.[21-22]

Die Elektroenzephalographie in der Forschung und die Fehlerüberwachung

Unter den bildgebenden Modalitäten kommt der Elektroenzephalographie seit Beginn der neurophysiologischen Forschung ein besonders großer Anteil zu. Mit ihrer Hilfe konnte bisher eine Vielzahl spezifischer sogenannter ereigniskorrelierter Potentiale identifiziert werden.
Als ereigniskorreliertes Potential (engl. *event related potential* oder ERP) werden im EEG aufgezeichnete Wellenformen bezeichnet, die einen Zusammenhang mit einer bestimmten kognitiven Komponente (z.B. Sprachverarbeitung) oder einem Sinneseindruck (z.B. die Weitergabe auditiver Informationen) aufweisen. Besonderes Interesse gilt seit einiger Zeit der Erforschung derjenigen ERPs, die spezifisch mit der Fehlerüberwachung (engl. *error monitoring*) assoziiert sind.

Eines der wichtigsten spezifischen fehlerassoziierten ERPs stellt die sogenannte fehlerbezogene Negativität (error related negativity, ERN) dar. Die ERN tritt typischerweise zwischen 50 und 100 ms nach Begehen eines Fehlers auf und wird mit einer ersten Stufe der Fehlerverarbeitung in Verbindung gebracht.[23]

Ein weiteres wichtiges Potential stellt die fehlerbezogene Positivität (*error related positivity*, Pe) dar, welche ca. 200 bis 500 ms nach fehlerhafter Handlung auftritt und mit der subjektiven Wahrnehmung des Fehlers assoziiert wird.[24]

Eine sensationelle Entdeckung bot ein erst kürzlich gefundenes, im musikalischen Kontext wichtiges Potential, nämlich die sogenannte *pre-error related negativity* (preERN). Es konnte gezeigt werden, dass bereits 70-30 ms vor Begehen des eigentlichen Fehlers ein spezifisches neuronales Korrelat im rostralen Anteil des anterioren Gyrus cinguli entsteht. Dieses Gehirnareal wird mit Fehler- und Konfliktevaluation in Verbindung gebracht.[25] Möglicherweise stellt die preERN einen ersten Schritt zur Fehlerwahrnehmung und auch -korrektur dar.[26-28]

Die vorliegende Arbeit besteht aus zwei Projekten, aus denen zwei englischsprachige Publikationen entstanden. Thema des ersten Projekts war die Identifikation und neurophysiologische Interpretation oben genannter ereigniskorrelierter Potentiale bei gesunden Pianisten und Pianisten mit Musikerdystonie, die im Zusammenhang mit der Fehlerüberwachung stehen. Das zweite Projekt umfasste die weitere klinische Interpretation der während des ersten Projekts gesammelten Daten auch hinsichtlich psychologischer Komponenten, die bei der Ätiologie der Musikerdystonie eine Rolle spielen.

Alle Projekte wurden am Institut für Musikphysiologie und Musikermedizin (IMMM) der Hochschule für Musik, Theater und Medien in Hannover unter der Leitung von Prof. Dr. med. E. Altenmüller durchgeführt.

2.2 Ergebnisse und Diskussion

Im folgenden Abschnitt der Zusammenfassung werden zu jedem der beiden Projekte Methodik, Ergebnisse, Diskussion und Eigenanteil des Promovenden angeführt.

Projekt 1 benutzte unter anderem EEG-Daten einer Vorstudie (Ref. Nr. 26); der Experimentalaufbau jener Studie glich im Wesentlichen dem unten beschriebenen, welcher für die Gewinnung neuer Daten benutzt wurde. Für die Ergänzung von Projekt 1 und die Durchführung von Projekt 2 wurde ein neues Experiment mit sechs gesunden professionellen Pianisten sowie sechs unter Musikerdystonie leidenden Pianisten durchgeführt. Der Experimentalaufbau soll hier kurz beschrieben werden.

Alle Teilnehmer der Studie waren rechtshändig, während die dystone Symptomatik bei den Patienten nur in der linken Hand auftrat. Diese Unterscheidung war wichtig, da Patienten somit in der Lage waren, ein optimales Spielverhalten ohne Krämpfe an den Tag zu legen und für die Krankheit spezifische Veränderungen im EEG somit leichter - und artefaktfreier - beobachtet werden konnten.
Vor Beginn der Studie wurden alle Teilnehmer gebeten, den rechtshändigen Part der ersten Takte sechs ausgewählter klassischer und bekannter Musikstücke auswendig zu lernen.
Die Montage des EEGs erfolgte nach dem erweiterten 10-20-System, welches gegen die Processi mastoidei beider Schläfenbeine referenziert wurde. Zusätzlich wurde ein Elektrookulogramm aufgezeichnet, um okuläre Artefakte wie Augenblinzeln später leichter identifizieren und entfernen zu können.
Am Tag des Experiments saßen alle Teilnehmer in einem abgedunkelten Raum vor einem Keyboard und einem Monitor. Auf dem Monitor wurden die ersten Takte der nach dem Zufallsprinzip ausgewählten Musikstücke (Stimulus) präsentiert, gefolgt von Metronomschlägen, die die Teilnehmer auf das gewünschte Tempo einstimmen sollten. Das Tempo wurde vergleichsweise hoch gewählt, um eine höhere Rate an Fehlern zu provozieren. Die Aufzeichnung der Noten und Gehirnströme wurde nach ca. 200 Noten abgebrochen und der Teilnehmer darüber informiert, bevor der nächste Stimulus folgte. Insgesamt bekamen die Teilnehmer 60 derartige Stimuli präsentiert, sodass pro Experiment insgesamt 12000 Noten inklusive dazugehöriger EEG-Signale gesammelt werden konnten.
Auf einem entfernten Computer wurden alle EEG- und MIDI-Signale (Noten) aufgezeichnet und einander zugeordnet, sodass unter Verwendung eines eigens geschriebenen Algorithmus für die Analyse infrage kommende Zeitperioden leichter identifiziert werden konnten. Dadurch konnten 50-100 für die weitere Verarbeitung gültige Fehler und 500 korrekte Ereignisse pro Teilnehmer erzielt werden.
Artefakte motorischen Ursprungs oder aufgrund Augenblinzelns wurden unter Verwendung der EEGLAB-Toolbox für MATLAB® manuell entfernt.[29]
Die Verhaltensdaten der Studie wurden mit Hilfe nonparametrischer Permutationstests analysiert. Beide Gruppen unterschieden sich nicht hinsichtlich der Anzahl von Fehlern, jedoch konnte bei beiden Gruppen eine nach dem Begehen von Fehlern aufgetretene reduzierte Lautstärke bzw. Anschlagstärke sowie Verlangsamung nachgewiesen werden. Diese Ergebnisse sind im Einklang mit vorherigen ähnlichen Studien zu erwarten gewesen.[26]

Projekt 1:

Die in unserem Institut vorher durchgeführte Studie (s. Referenz Nr. 26) warf Fragen auf, welche in diesem Projekt weiter beleuchtet werden sollten: Zum einen sollte beforscht werden, ob die gefundene preERN ein elektrophysiologischer Marker per se, d.h. ein eigentliches Fehlersignal, ist, oder ob die preERN stattdessen im Zusammenhang mit anderen Kontrollmechanismen steht. Auch sollte untersucht werden, ob der Prozess der Fehlerüberwachung bei Patienten mit fokaler Dystonie unterschiedlich zu dem Gesunder ist.
Zur Beantwortung dieser Fragen wurden die EEG-Daten mit Hilfe der sogenannten Zeit-Frequenz-Analyse analysiert. Im Gegensatz zur weiter verbreiteten Amplitudenanalyse zieht jene noch die Frequenz der EEG-Signale (im Sinne der bekannten EEG-Frequenzbänder) mit in die Analyse der Daten mit ein; es werden also Aktivierungen oder Deaktivierungen bestimmter Frequenzbänder im Verhältnis zu einer bestimmten Zeit dargestellt.

Bei gesunden Pianisten zeigte sich eine vor Fehlerereignis erhöhte Oszillation im Beta- und Thetafrequenzband über dem posterioren frontomedialen Cortex sowie eine Phasensynchronisation bei 13-15 Hz zwischen dem posterioren frontomedialen Cortex sowie dem rechten lateralen präfrontalen Cortex. Letztgenannte Phasensynchronisation sagte einen Korrekturmechanismus voraus, während die vestärkten Oszillationen im Beta-Frequenzband möglicherweise auf die Schwierigkeit der Korrektur bzw. Unterdrückung des kommenden Fehlers hinweisen. Bei unter fokaler Dystonie leidenden Patienten trat die Phasensynchronisation in einem anderen Frequenzband, nämlich von 6-8 Hz, auf und korrelierte negativ mit dem Grad der Beeinträchtigung.
Etwa 100 bis 200 ms nach Fehlerereignis zeigten sich außerdem erhöhte Oszillationen im Theta- und Beta-Frequenzband, was der Pe oder *error related positivity* entspricht. Interessanterweise korrelierten die Beta-Frequenzband-Oszillationen positiv mit der Abschwächung der Anschlagstärke (bzw. Lautstärke) der den Fehler folgenden Noten. Daraus kann man schließen, dass bewusstere und im Kontext des Spielens „schlimmere“ Fehler eine verstärkte Fehlerantwort zur Folge haben.
Diese neu gewonnenen Erkenntnisse zeigen, dass neuronale Prozesse, welche die Motorik im Voraus kontrollieren und anpassen, sowohl bei gesunden Pianisten als auch bei unter fokaler Dystonie leidenden Patienten existieren, bei letzteren jedoch in abgewandelter Form.

Der Promovend war an der Durchführung und Auswertung der Studie maßgeblich beteiligt. Er montierte das EEG und überwachte die Aufzeichnung der Daten. Weiterhin bereinigte er die Daten von Artefakten, analysierte die Verhaltensdaten und war am Schreiben sowie Revidieren der Publikation beteiligt.
Publikation: Ruiz MH, **Strübing F**, Jabusch HC, Altenmüller E: „EEG oscillatory patterns are associated with error prediction during music performance and are altered in musician‘s dystonia.“, *Neuroimage*, 2011 Apr 15; 55(4):1791-803

Projekt 2:

Ziel des Projekts war die weitere Erforschung oben genannter spezifischer ereigniskorrelierter Potentiale hinsichtlich ihrer Bedeutung für den Hergang der Fehlerüberwachung sowie ihren

Entstehungsort. Eine weitere Fragestellung war, ob sich der Prozess des Fehlerüberwachung bei Pianisten mit Musikerdystonie von dem gesunder Pianisten unterschied. Dieser Vergleich bot sich insbesondere an, da die Musikerdystonie - wie in der Einleitung erwähnt - zu den basalganglionären Störungen gerechnet wird und basalganglionäre Verschaltungen einen starken Einfluss auf die Fehlerüberwachung haben.[10-11]

Für die Analyse der ereigniskorrelierten Potentiale wurde für alle Wellenformen in fünf medial gelegenen Elektroden (Fz, FCz, Cz, CPz, Pz) ein Durchschnittswert pro Proband und Kondition (Fehler, korrekte Note) gebildet. Die so ermittelten Werte wurden einem separaten t-Test pro Gruppe unterzogen, um das Vorhandensein der ereigniskorrelierten Potentiale in jeder Gruppe zu bestätigen. Im Anschluss daran wurde auf statistische Unterschiede zwischen den Gruppen mit Hilfe der zweifaktoriellen Varianzanalyse (engl. Analysis of variance, ANOVA) untersucht.
Innerhalb jeder Gruppe (gesunde Pianisten, Dystoniker) konnte sowohl das Vorhandensein der preERN als auch der Pe nachgewiesen werden. Zwischen den Gruppen ergaben sich Unterschiede in der Amplitude der ERPs, und zwar war sowohl die negative Amplitude der preERN als auch die positive Amplitude der Pe höher bei Patienten mit Musikerdystonie.

Zur Deutung der gefundenen Phänomene mussten die vergrößerten Amplituden der preERN und der Pe separat betrachtet und in Zusammenhang mit ähnlichen Beobachtungen in anderen Experimenten gestellt werden. Der Entstehungsort der preERN (namentlich der rostrale Anteil des anterioren Gyrus cinguli) wurde vorher als Ort der motivationalen Erkennung und Bewertung eines Fehlers beschrieben[25], während von der preERN per se geglaubt wird, dass sie die Diskrepanz zwischen geplanter Aktion und fehlerhafter Ausführung darstellt. Eine höhere Amplitude der preERN kann also bedeuten, dass der Patient dem Fehler eine größere motivationale Bedeutung zuordnet, was mit der Erkenntnis, dass unter Musikerdystonie leidende Patienten eine stärkere Neigung zu Psychopathologien wie Angststörungen, erhöhten Neurotizismus oder Perfektionismus aufweisen, in Einklang gebracht werden kann.[8-9]

Einen weiteren Hinweis für die Verknüpfung der fokalen Dystonie mit eben genannten psychologischen Faktoren liefert die Interpretation der höheren Pe-Amplitude. Solche erhöhten Potentiale konnten auch bei unter Zwangsstörungen (*obsessive compulsive disorder*, OCD) leidenden Kindern gefunden werden.[30] Eine erhöhte Neigung zu Symptomen einer Zwangsstörung konnte wiederum auch Patienten mit fokaler Dystonie nachgewiesen werden.[31-32] Manche Autoren behaupten somit, dass fokale Dystonie und Zwangsstörungen einen gemeinsamen pathophysiologischen Hintergrund haben könnten.[33-34] Unser Experiment erhärtet diesen Verdacht.

Die zusammenfassende Erkenntnis der Studie war, dass die unterschiedliche neuronale Aktivität bei Patienten mit fokaler Dystonie eine veränderte Fehlerüberwachung zur Folge hat, und psychologische Effekte bei der Ätiologie der fokalen Dystonie unter Umständen eine Rolle spielen.

Der Promovend war für die gesamte Konzeption und Durchführung der Studie verantwortlich. Er analysierte die gewonnenen Daten anhand selbst programmierter Algorithmen, wertete die Statistiken aus und ist Erstautor einer aus den gewonnenen Daten entstandenen englischsprachigen Publikation.
Publikation: **Strübing F**, Ruiz MH, Jabusch HC, Altenmüller E: „Error monitoring is altered in musician‘s dystonia: evidence from an ERP-study“ *Annals of the New York Academy of Sciences, 2012 Apr; 1252:192-9*

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2.4 Kurzzusammenfassung

Die Musikerdystonie ist eine neurologische Krankheit aus dem Formenkreis der fokalen Dystonien, welche durch unwillkürliche Bewegungen und Verkrampfungen beim Spielen eines Instruments charakterisiert ist. Obwohl deren Pathophysiologie wissenschaftlich noch nicht vollständig bekannt ist, deuten neuere Erkenntnisse auf eine Dysfunktion und Dysregulation neuronaler Verschaltungen auf mehreren Ebenen des ZNS hin.

Zu deren weiteren Erforschung wurden an unserem Institut experimentelle Studien durchgeführt, welche die neuronalen Prozesse der Fehlerverarbeitung in einer Gruppe gesunder sowie einer unter Musikerdystonie leidenden Gruppe professioneller Pianisten per Elektroenzephalographie untersuchten. Bei Gegenüberstellung der Ergebnisse zeigten sich signifikante Unterschiede in der Reaktion auf Fehler sowohl vor als auch nach deren Begehen, die auf einen Zusammenhang der Musikerdystonie mit anderen basalganglionären Erkrankungen hinweisen. Auch ließ sich schlussfolgern, dass psychologische Effekte wie erhöhte Ängstlichkeit und Neurotizismus bei der Ätiologie der Musikerdystonie eine Rolle spielen könnten.

Langfristiges Ziel ist es, durch weitere Studien die Pathophysiologie der Musikerdystonie auf neuronaler Ebene besser zu verstehen, um den Patienten durch die Entwicklung neuer Therapieansätze bessere Rehabilitationsmöglichkeiten zur Verfügung stellen zu können.

4. Danksagung

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5. Erklärung nach § 2 Abs. 2 Nrn. 6 und 7

Ich erkläre, dass ich die der Medizinischen Hochschule Hannover zur Promotion eingereichte Dissertation mit dem Titel „Der neuronale Prozess der Fehlerüberwachung bei gesunden Pianisten und Pianisten mit Musikerdystonie“ im Institut für Musikphysiologie und Musikermedizin unter Betreuung von Prof. Dr. E. Altenmüller ohne sonstige Hilfe durchgeführt und bei der Abfassung der Dissertation keine anderen als die dort aufgeführten Hilfsmittel benutzt habe.
Die Gelegenheit zum vorliegenden Promotionsverfahren ist mir nicht kommerziell vermittelt worden.
Insbesondere habe ich keine Organisation eingeschaltet, die gegen Entgelt Betreuerinnen und Betreuer für die Anfertigung von Dissertationen sucht oder die mir obliegenden Pflichten hinsichtlich der Prüfungsleistungen für mich ganz oder teilweise erledigt.
Ich habe diese Dissertation bisher an keiner in- oder ausländischen Hochschule zur Promotion eingereicht. Weiterhin versichere ich, dass ich den beantragten Titel bisher noch nicht erworben habe.
Ergebnisse der Dissertation wurden in den Fachzeitschriften „Neuroimage“ und „Annals of the New York Academy of Sciences“ veröffentlicht.

Hannover, den