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Defective Inhibition and Inter-Regional Phase Synchronization in Pianists With Musician's Dystonia: An EEG Study

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Key words: music performance; focal dystonia; inhibition; phase synchronization; EEG

INTRODUCTION

Music performance at a professional level is probably one of the most demanding tasks for the human central nervous system. It involves the precise execution of very fast and, in many instances, extremely complex physical movements under continuous auditory feedback in an unyielding context of social rewards and punishment.

The basis for the musician's skill is the appropriate retrieval of these highly complex memorized motor programs. In this context, motor programs have to be activated only if necessary. In many musical situations, it is necessary to inhibit motor programs. For instance, a typical scenario relevant for a pianist is the sight-reading of a violin sonata. The accompanying pianist is required to react to the timing of the violinist's entry and tempo variations by rapidly adjusting his or her timing and tempo, thereby activating and inhibiting motor programs. In general, a characteristic feature of accomplished musicianship is the appropriate activation (ACT) and inhibition (INH) of motor memory traces under constrained timing conditions.

Musician's dystonia (MD), a form of focal task-specific dystonia (FTSD), is characterized by a degradation of these motor memory traces. MD is a movement disorder, which occurs while a musician is playing the instrument and is marked by the painless loss of voluntary motor control of extensively trained movements [Altenmüller, 2003].

In affected musicians, deficient inhibition of motor programs can be demonstrated on several levels [for a review, see Lim et al., 2001]: (i) On a "micro-level," involuntary cramping of single fingers can be interpreted as the defective inhibition of inappropriate motor subroutines [Wilson et al., 1993]. (ii) On a "macro-level," the central-nervous preparatory sets of movements seem to be disinhibited. This has been reported, for instance, in data of the Bereitschaftspotential (BP) [Deuschl et al., 1995; Yazawa et al.,

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TABLE I. Patients with musician's dystonia

Patient	Age (years)	Sex	Year of manifestation	Affected digits of the right hand	Therapy	Accumulated practice time (h)	mSD-IOI
Dyst_01	50	M	1989	D3 > D4,5	None	47,866	21.83
Dyst_02	27	M	2000	D3,4	None	33,488	18.08
Dyst_03	41	M	1994	D4	None	76,622	18.32
Dyst_04	38	M	1992	D3,4,5	Botulinum toxin (2 years after last injection)	25,700	14.15
Dyst_05	34	M	1998	D3	None	24,934	32.12
Dyst_06	35	F	1993	D1,2	None	13,104	15.65
Dyst_07	29	M	2002	D4,5	None	35,594	16
Dyst_08	30	M	2000	D3	None	15,000	15.92
Dyst_09	34	M	1999	D3	Botulinum toxin (6 months after last injection)	20,202	–

The last column shows the mean standard deviation of the interonset intervals (mSD-IOI) of all scales, previously reported to be a precise indicator of the motor impairment in pianists with focal dystonia (see Performance Analysis section). For healthy pianists, this measure was between 8.5 and 16.5.

1999] and the contingent negative variation (CNV) [Lim et al., 2001, 2004].

In a previous study [Hummel et al., 2002], deficient inhibition of simple motor patterns was demonstrated in six patients with FTSD using TMS and EEG-alpha oscillatory activity. To the best of our knowledge, one relevant question remained unaddressed: Does FTSD also affect the inhibition of long-term overlearned motor programs? Consequently, the aim of the present study was to investigate with multichannel EEG the neural correlates associated with the ACT and INH of a pianistic long-term overlearned motor program in pianists with MD.

Within the primary sensorimotor cortex of humans, oscillatory activity in the alpha (8–13 Hz) and beta (13–30 Hz) frequency bands is modulated during the preparation and performance of movements [Cassim et al., 2001; Salmelin et al., 1995]. Furthermore, functional coupling between brain regions has been demonstrated to mediate sensorimotor integration [Gerloff et al., 1998b; Hummel and Gerloff, 2005].

Accordingly, to clarify the aforementioned question, the study of (i) the standard slow shift of movement-related cortical potentials (MRCPs) was complemented with (ii) the spectral power of the oscillations and (iii) the phase coupling between brain regions, in a paradigm mimicking the unyielding time constraints of professional musicianship.

So far, there have been no studies of phase synchronization in patients with FTSD. However, in patients with other diseases in which deficient inhibition plays a role in the pathogenesis, such as Tourette's syndrome, attention deficit hyperactivity disorder, or Parkinson's disease, cortical inter-regional synchronization has been associated with defective corticocortical interactions [Barry et al., 2002; Serrien et al., 2005; Silberstein et al., 2005].

In the present study, the specific motor program had to be executed or *inhibited*, this last condition referring to the motor program being *suppressed*. Our main hypotheses were as follows. First, the sensorimotor integration required for fine motor control would be modulated at the cortical level by local oscillatory activity and functional coupling among cortical regions. Second, under pathophysiological conditions with deficient inhibitory circuits (as in FTSD), we speculated that this type of inhibitory control should be disturbed. Third, the defective inhibition should be manifested in differences in focal spectral power and inter-regional functional coupling for pianists with MD and healthy pianists.

MATERIALS AND METHODS

Participants

Nine healthy pianists (eight males, age range 26–47 years, mean 36.5 years) and nine pianists with MD (eight males, age range 27–50 years, mean 35.3 years) participated in this study. In all patients, the right hand was affected. Further information on the patients is given in Table I. All participants were professional pianists (accumulated practice time over 10,000 h). Eight of the nine participants in each group were right-handed, according to the Edinburgh inventory [Oldfield, 1971]. All subjects gave informed consent to participation in the study, which had received approval of the Ethics Committee of the University of Music and Drama, Hanover.

Experimental Design

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

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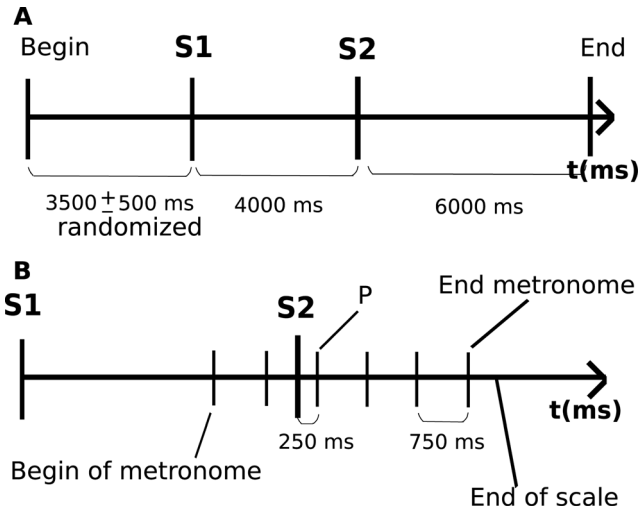

Figure 1.

Scheme of the experimental paradigm. (**A**) Time course of the presentation of the first visual cue (S1) and second visual cue (S2). (**B**) Time evolution of the metronome-like auditory cues and motor performance. The first metronome beat appeared at 1,250 ms prior to S2. Pianists had to begin to play the C-major scales at the third metronome beat (~250 ms).

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. In a modified Go/NoGo-study, the task was to play upward C-major scales over two octaves. Scales were played as semiquavers, and the tempo was standardized at 80 beats/min for a quarter note (=one key stroke every 187.5 ms) and paced by metronome-like auditory cues. Scales were played using the conventional C-major fingering: 1,2,3,1,2,3,4,1,2,3,1,2,3,4,5 (The fingers 1–5 refer to thumb, index, middle, ring, and little finger, respectively). The specifications of the Go/NoGo-study were as follows: A first visual cue (S1) indicated that participants should be prepared to start playing soon. The metronome was started 2,750 ms after S1. Participants were instructed to play the first note of any scale coinciding with the third metronome beat. Two hundred and fifty milliseconds before the third metronome beat, a second visual cue (S2) was presented indicating that the participant should either execute (Go, green ellipse) or not execute (NoGo, red ellipse) the motor sequence (see Fig. 1). The selection of 250 ms after S2 for playing the first note was based on previous studies of De Jong et al. [1990] and Logan et al. [1984], which have shown that the stop-signal reaction time, measuring the inhibition of an initiated response, is between 200 and 250 ms.

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It is important to note that the associations between the green/red ellipses and Go/NoGo cues were easily learned by all participants because of their familiarity with the universal color code of traffic lights: green to go and red to stop. Because the timing of the entrance of the musicians and the tempo were indicated by the metronome-like auditory cues, we chose a visual stimulus as Go/NoGo cue to avoid interference with the auditory modality.

EEG and EMG Recordings and Preprocessing

Continuous EEG was recorded from 22 electrodes placed over the scalp according to the extended 10–20 system referenced to linked earlobe mastoids. Additionally, a right vertical electrooculogram was recorded to monitor blinks and eye movements. Impedance was kept under 5 kΩ. Data were sampled at 500 Hz; the upper cutoff was 100 Hz, and the time constant was set to DC (DC amplifiers and software by NeuroScan, Herndon, VA). One bipolar EMG channel was recorded from surface electrodes positioned over the right flexor pollicis longus muscle, located 6 cm apart from each other. The bandpass filters for EMG were set to 5 Hz (highpass) and 100 Hz (lowpass). Visual trigger stimuli, key strokes, 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 the visualization and filtering of the EEG signals. After rejecting segments of data with artefacts such as blinks, eye movements, and muscle activity as determined by visual inspection, we applied a notch filter at 50 Hz (49–51 Hz) to eliminate power-line noise. Trials that included errors, such as a response following a NoGo target or a miss on a Go cue, were not included in the analysis. The data epochs representing single experimental trials time-locked to the onset of the second visual (S2) cue were extracted from −5,000 to 1,000 ms, resulting in approximately n = 100 artifact free epochs per condition (Go/NoGo) and participant.

Data Analysis

We performed the following three analyses: (i) standard time averaging technique to analyze the slow shift of MRCPs; wavelet based time–frequency representations (TFR) to analyze (ii) the spectral power of the oscillatory contents and (iii) the spatiotemporal dynamics of the functional coupling.

The functional interaction between brain regions is believed to be best characterized by transient phase relationships between the oscillatory activities of underlying neuronal populations, termed as phase synchronization [Sauseng et al., 2005; Tass et al., 1998; Varela et al., 2001]. Consequently, the analysis (iii) was done with phase synchronization approaches. More specifically, it was performed by means of the synchronization cluster analysis (SCA) [Allefeld and Kurths, 2004].

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MRCPs were derived by averaging the raw trials about the Go/NoGo signal (S2) for each subject and condition, and the result was baseline-corrected. The baseline was computed from 4,500 to 4,000 ms prior to S2 (500–0 ms before S1).

For the synchronization analysis, a modified version of the nearest-neighbor Hjorth Laplacian algorithm computed by Taylor's series expansion [Lagerlund et al., 1995] was applied, to avoid the spurious increase in correlations introduced by the common reference [Nunez et al. 1997].

A complex Morlet wavelet was used to extract time–frequency complex phases $\phi_{ik}(t,f)$, at an electrode i and epoch k, and amplitudes of the EEG signal $x(t)$. The frequency domain was sampled from 2 to 40 Hz with a 1 Hz interval between each frequency.

We studied changes in the spectral content of the oscillatory activity by means of the wavelet-based TFR of the energy [Tallon-Baudry et al., 1997]. After removing the baseline level, we normalized the TFR energy with the standard deviation of the baseline period (between −4,500 and −4,000 ms prior to S2). The normalization procedure reduced the effects of intersubject and interelectrode variability.

Oscillatory activity in the alpha (8–13 Hz) and beta (13–30 Hz) band was analyzed, based upon its sensitivity to movement-related changes in cortical oscillatory activity in humans [Gerloff et al., 1998b; Pfurtscheller et al., 1997; Salmelin et al., 1995; Tiihonen et al., 1989].

The assessment of phase synchronization between the multichannel EEG signals was done by means of the SCA [Allefeld and Kurths, 2004; Allefeld et al., 2005], a method that provides information about both the global synchronization strength and the topographical details of the synchronization in event-related brain responses. The SCA has been successfully applied to EEG data in language and music processing paradigms [Allefeld et al., 2005; Herrojo et al., in press). Following this approach, we computed the following measure:

$$\overline{R}_{iC} = \left| \frac{1}{n} \sum_{k} \exp(i(\phi_{ik} - \Phi_k)) \right| \quad (1)$$

where n is the number of epochs, ϕ_{ik} is the complex phase at an electrode i and epoch k, and Φ_k is the phase of the synchronized cluster that characterizes in each epoch the dynamics of the array as a whole and which is the result of a circular weighted mean of the individual oscillator phases. The index $\overline{R}_{iC}$ estimates the phase locking between each individual oscillator of the whole ensemble and the synchronized cluster. This index is nearly 0 when there is no phase synchrony and approaches 1 for strong phase synchronization.

For each frequency, the index $\overline{R}_{iC}$ [Eq. (1)] was averaged across the electrodes of the sensorimotor and prefrontal cortex to obtain the *cluster strength* $\overline{R}_C$ in these regions.

The investigation of the phase synchronization focused on the theta (4–8 Hz) and alpha (8–13 Hz) frequency bands, due to the relevance of these slow oscillations in mediating long-range cortical functional coupling [von Stein and Sarnthein, 2000].

In the beta (13–30 Hz) band, we did not observe between-condition or between-group changes in the measures of phase synchronization, which could be due to the specific task. Consequently, this band was left out of the present manuscript.

EMG Analysis

The raw EMG signal was rectified and smoothed via the root mean square (RMS) algorithm over a window of 10 ms. For ensemble average EMG curves, we first normalized the amplitude of the smoothed rectified trials to the mean value within each epoch, [−5 s, 5 s], and then averaged it across trials. The *amplitude mean value* in the analysis interval and the *EMG peak* were selected as EMG activity parameters. The analysis interval for Go trials was 250–2,875 ms, coinciding with the time the pianists had to play; for NoGo trials, the selected time window was 0–350 ms to detect whether pianists initiated a movement around 250 ms in spite of the NoGo signal.

Performance Analysis

The temporary unevenness of interonset intervals (IOI, time between note onsets of two subsequent notes) was previously reported to be a precise indicator of pianists' motor control and its impairment in pianists with focal dystonia [Jabusch et al., 2004]. For each participant, temporary unevenness was analyzed by calculating the mean standard deviation of IOI (mSD-IOI) of all scales. Motor performance was compared with the EEG measures to look for correlations between the degree of motor impairment in pianists with MD and the EEG response.

Statistical Analysis

To assess the statistical differences in the spectral power and phase synchronization indices, we first averaged for each subject and condition the indices across the electrodes in the regions of interests (ROIs) defined for each case (described below). Next, for each time–frequency point, the averaged indices were analyzed by means of synchronized permutations of a 2 × 2 (Group × Condition) design [Good, 2005]. Synchronized permutations are based on the nonparametric pairwise 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 permutations provide a clear separation of main effects and interactions. Here, it was necessary to use a nonparametric test, because the distributions cannot be assumed to be Gaussian.

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TABLE II. Behavioral data of healthy pianists (Cont) and patients with musician's dystonia (Dyst)

Participant	Total number of scales during Go	Number of scales missed	Number of scales with early onset	Number of scales with wrong notes	mSD-IOI	Number of trials during NoGo	Number of trials with onset of a note in spite of NoGo
Cont_01	101	0	0	0	16.51	97	13
Cont_02	101	0	0	0	10.05	97	42
Cont_03	101	1	0	0	11.35	99	2
Cont_04	101	1	0	0	14.97	97	13
Cont_05	101	0	0	0	8.97	97	1
Cont_06	82	0	0	0	11.74	117	2
Cont_07	99	0	0	0	15.78	100	1
Cont_08	101	0	0	0	12.72	97	5
Cont_09	97	4	0	0	12.76	100	14
Dyst_01	101	2	0	0	21.83	101	23
Dyst_02	101	0	0	0	18.08	101	6
Dyst_03	101	2	0	0	18.32	101	39
Dyst_04	97	0	0	0	14.15	101	15
Dyst_05	97	0	0	0	32.12	101	11
Dyst_06	101	2	0	0	15.65	101	2
Dyst_07	101	0	0	0	16	99	3
Dyst_08	101	1	0	0	15.92	97	3

Scales missed refers to scales not played during Go. Early onset occurred when the first note of the scale was played before the Go/NoGo signal. The performance analysis of the last patient could not be completed because of lost MIDI data.

With the synchronized permutations approach, the mean spectral power was analyzed between 0 and 900 ms (to avoid windowing effects, since the epochs were extracted up to 1,000 ms) in the alpha (8–13 Hz) and beta (13–30 Hz) bands separately. Similarly, in the same time window and in the separate theta (4–8 Hz) and alpha (8–13 Hz) bands, the index of phase synchronization between cluster and electrode, $\overline{R}_{iC}$, averaged across the corresponding ROIs was analyzed. The statistical differences of the grand-averages of MRCP waveforms were also analyzed by means of a 2 × 2 (Group × Condition) design of synchronized permutations. In this case, selected electrode sites were pooled to three topographical ROIs (see below), and in each one the synchronized permutations were computed.

Differences were considered significant if $P < 0.05$. Significance levels for multiple 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 and physiological knowledge [Gerloff et al., 1998b; Hummel et al., 2002]. For the analysis of the spectral power and MRCP waveforms, we chose electrodes that cover the lateral premotor cortex, the SM1 bilaterally (left: FC3, C3, CP3; right: FC4, C4, CP4), and the mesial frontocentral cortex including the SMA (FCz, Cz, CPz). For these topographic analyses, the threshold value after the Bonferroni-correction was thus 0.017. In the case of the phase synchronization analysis, we included additionally the prefrontal electrodes (F3, Fz, F4) due to the role of the prefrontal cortex in top–down processing [Sauseng et al., 2005; von Stein and Sarnthein, 2000]. We hypothesized that the prefrontal electrodes could be functionally coupled to the EEG channels in the sensorimotor cortex for the Go/NoGo decision making [Shibata et al., 1997, 1998].

The univariate analyses of the statistical differences between conditions or between groups were performed with the use of a nonparametric pairwise permutation test [Good, 2005]. As previously stated, for multiple comparisons of same data pool significance levels, we used the Bonferroni-correction. Between-group differences in the behavioral and electromyographic data were also analyzed using a nonparametric pairwise permutation test.

RESULTS

Behavioral Data

The number of NoGo trials that included errors (for instance, a motor response following the NoGo cue) was not statistically different between pianists with MD (8.5; 2.0–39) and healthy pianists (5.0; 1.0–42; permutation test across subjects, $P > 0.05$). In the Go condition, the missed scales, namely a scale not played, did not differ statistically between pianists with MD (0.67; 0–4) and healthy pianists (0.87; 0–2) either. As expected, the mSD-IOI, previously described for quantification of motor impairment in pianists with MD [Jabusch et al., 2004], differed between both groups (pianists with MD: 17.2 ms; 14.2–32.1; healthy pianists: 12.7 ms; 9.0–16.5; $P < 0.01$). Further information on the behavioral data is provided in Table II.

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EMG Data

In Go trials, the amplitude mean value over the interval 250–2,875 ms differed significantly between healthy pia-

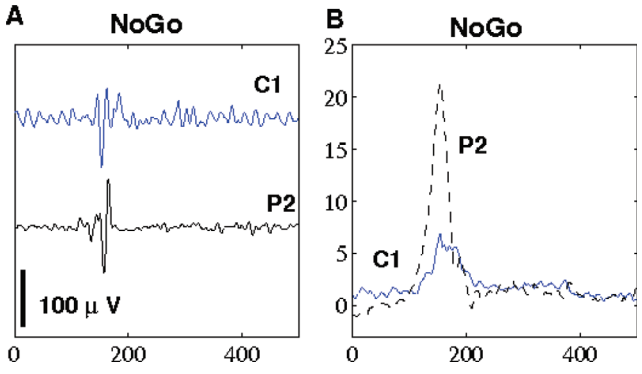

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Figure 2.

EMG, right flexor pollicis longus muscle of the right hand. (**A**) Raw data of a single NoGo trial are given for a control (C1) and a patient (P2). Bursts of EMG activity can be observed before 200 ms in spite of the NoGo signal. (**B**) Rectified and smoothed EMG activity in the NoGo condition for the same patient (P2, dashed line) and healthy pianist (C1, bold line) as in (**A**). Peaks of EMG activity averaged across trials can be observed despite the NoGo signal.

nists (20 μV; 12–36 μV) and pianists with MD (30 μV; 21–50 μV; $P < 0.05$, permutation test across subjects), due to higher EMG amplitude in patients. The EMG peak, indicating the maximum value in the amplitude curves, did not differ statistically between healthy pianists (59 μV; 38–79 μV) and pianists with MD (78 μV; 54–125 μV; $P > 0.05$). As indicated before (see Table II), in the NoGo condition, participants initiated movements of the thumb in some trials in spite of the NoGo signal. Interestingly, the number of NoGo trials in which bursts of EMG activity were observed was higher than the number of trials in which the first key of the MIDI piano was actually played (Table II). This result confirmed that inhibition in our paradigm demanded active suppression of the motor program.

Bursts of raw EMG activity in a NoGo trial are depicted in Figure 2A for one patient and one healthy pianist. As in Go trials, the mean-rectified and RMS-smoothed value of the EMG signal was computed (Fig. 2B). The EMG peak was found significantly higher in pianists with MD (14 μV; 5.2–50 μV) than in healthy ones (5.5 μV; 3.1–16 μV). Contrary to the Go trials, the amplitude mean value in both groups was not statistically different (healthy pianists: 3.3 μV; 1.1–10 μV; patients: 5.7 μV; 2.4–20 μV; $P > 0.05$).

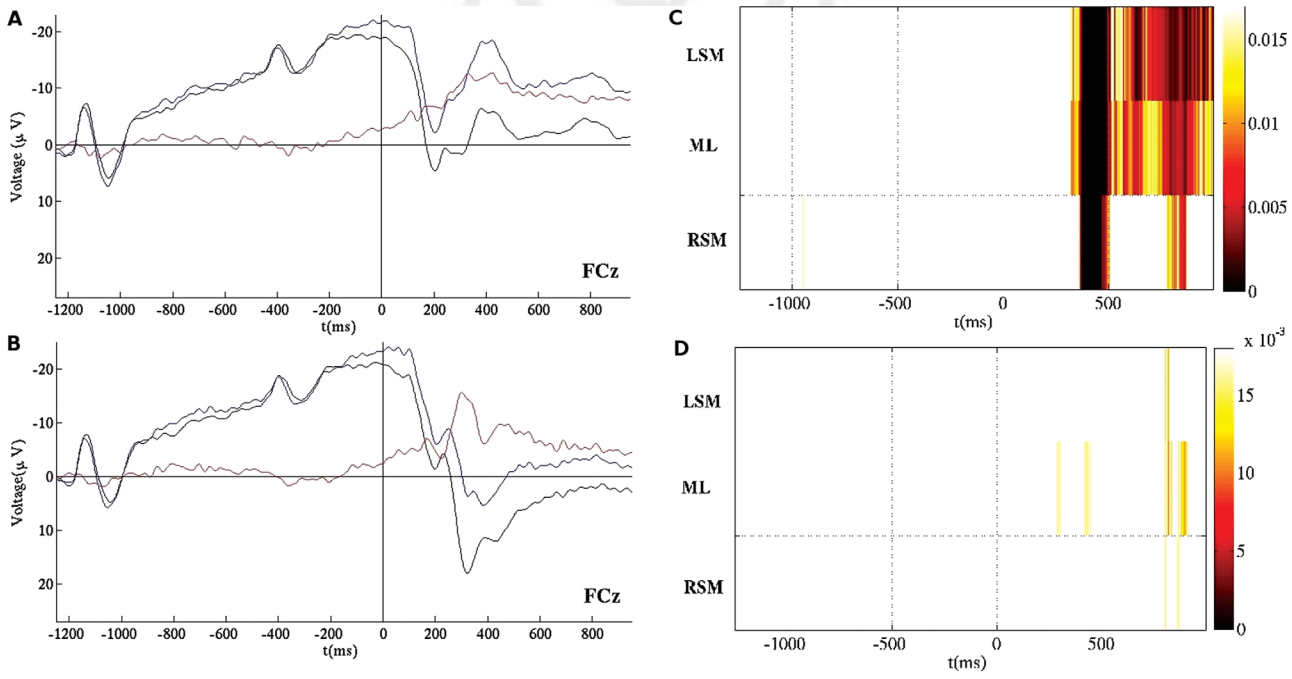

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Figure 3.

Movement-related cortical potentials (MRCPs) analysis. (**A**) Grand average of the MRCPs for Go trials in pianists with MD (blue line), healthy pianists (black line) and difference (MD minus healthy, red line). (**B**) Same as in (**A**) but for NoGo trials. (**C**) Latency periods, in which the main effect of Group for the MRCPs is statistically significant ($P < 0.017$, Bonferroni-corrected), calculated with respect to synchronized permutation test in three ROIs. The *P* values are presented for three different areas of electrodes: LSM (left sensorimotor cortex), ML (midline), RSM (right sensorimotor cortex). (**D**) Time windows, in which the main effect of Condition for the MRCPs is statistically significant ($P < 0.017$), calculated with respect to a synchronized permutations test in three ROIs. The stronger significant effect was found in the ML electrodes.

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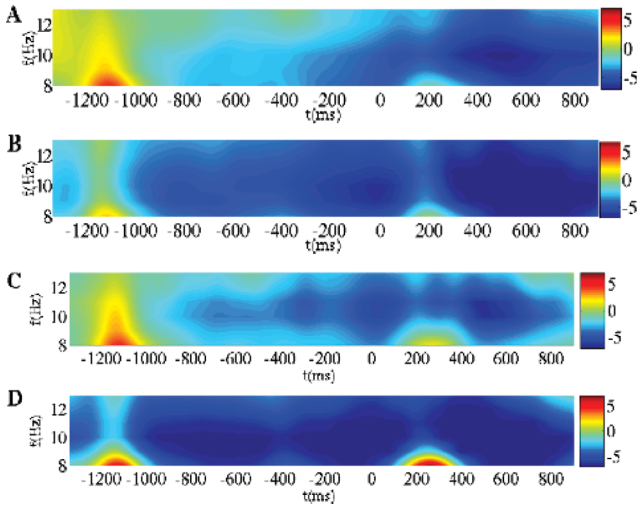

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Figure 4.

Time course of spectral power of total alpha (8–13 Hz) oscillatory activity averaged across the electrodes over the sensorimotor areas during ACT for pianists with MD (**A**) and healthy pianists (**B**). Similar measure during INH for pianists with MD (**C**) and healthy pianists (**D**). In all cases, we observed a decrease relative to baseline in the alpha spectral power, which is sustained after S2. Healthy pianists showed a stronger decrease in the alpha oscillatory activity than pianists with MD.

Movement-Related Cortical Potentials

F3 In Figure 3A,B, the grand-average MRCP waveforms for pianists with MD and healthy pianists are depicted at electrode FCz for Go and NoGo conditions. Both groups showed similar premovement activity over the sensorimotor cortex, characterized by the slow negative MRCP termed as CNV. In our paradigm, the CNV reflected the maintenance of a motor response in readiness [Haider et al., 1981]. In both conditions, the premovement negativity returned to baseline levels. During ACT, we observed a postmovement negative peak more pronounced in pianists with MD, whereas the NoGo condition was characterized by a positive shift post-S2. The positive peak after S2, which could be related to the inhibition of the motor pattern, had larger amplitude across sensorimotor areas in healthy pianists than in pianists with MD. The synchronized permutations yielded a significant ($P < 0.017$) main effect of Group in the three ROIs of the sensorimotor cortex (Fig. 3C), which was more prominent in the time window 370–500 ms. This result indicated that in pianists with MD, the MRCPs after the Go/NoGo cue were less positive over all ROIs in the sensorimotor cortex. A significant main effect of Condition was found in the frontocentral regions around ~280 ms, ~ 430 ms, and >800 ms (Fig. 3D). The first latency corresponded with the positive peak after S2 in the NoGo condition, possibly related to the relaxation after motor preparation. The second latency referred to the negative peak after the onset of playing in the Go condition. No significant interaction of the factors Group × Condition was found.

An univariate permutation test across subjects in the NoGo condition yielded a significant between-group difference ($P < 0.017$) in the post-S2 positive peak at the midline electrodes within the latency period 270–308 ms, suggesting that the weaker inhibition for the patients group was localized in the mesial frontocentral cortex.

Spectral Power Analysis

The spectral power in the alpha band (8–13 Hz) averaged across the sensorimotor regions for each group separately is presented in Figure 4. In both groups, we F4 observed a decrease relative to the baseline in the amplitude of the alpha oscillations after the beginning of the metronome beat in the Go and NoGo conditions. No significant main effects or interaction of the factors Group or Condition were found.

Figure 5 shows the time–frequency maps of the beta F5 band (13–30 Hz) spectral power averaged across the electrodes over sensorimotor regions in the INH condition. As in the alpha frequency range, we observed for both groups a reduction, relative to the baseline, in the power of the beta oscillations following the beginning of the metronome (not shown). After the NoGo cue, the decrease in beta oscillations attenuated slowly, returning to baseline levels. An increase of 650–900 ms in the power of beta oscillations manifested itself, which was weaker for pianists with MD than for healthy controls. This general picture was con-

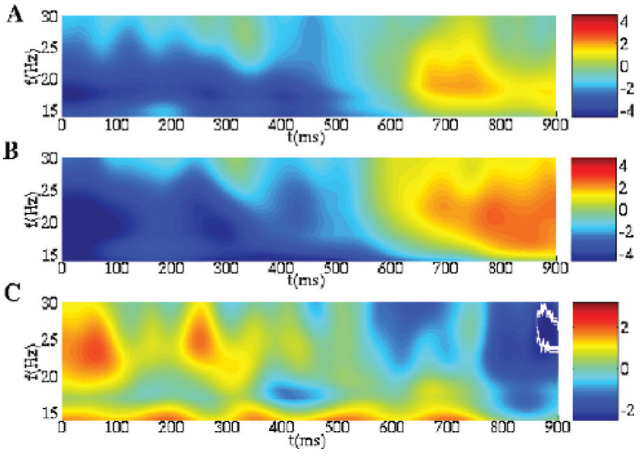

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Figure 5.

Beta spectral power. TFR energy averaged across electrodes in sensorimotor areas in the 13–30 Hz range and after S2 for pianists with MD (**A**), for healthy pianists (**B**), and between-group difference (**C**, A–B). The white contour denotes the region in which the between-group difference is significant at 0.003 level (Bonferroni-corrected) according to the permutation test.

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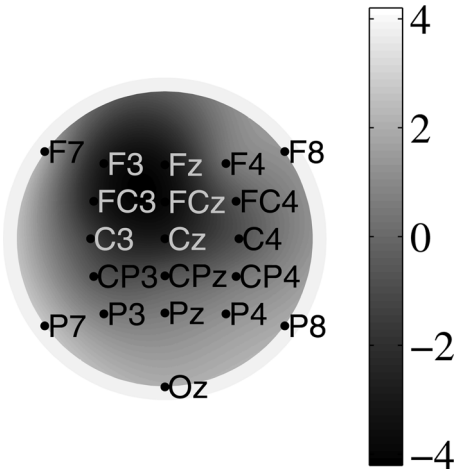

Figure 6.

Topographical map of the 23–30 Hz difference (MD minus healthy) spectral power averaged in the time window 860–900 ms. The beta activity is less positive in pianists with MD than in healthy pianists, an effect which is maximal over the left premotor and sensorimotor cortex (FC3, C3), mesial frontocentral cortex (FCz, Cz), and prefrontal regions (F3, Fz).

firmed in all individual pianists with MD and healthy pianists.

The synchronized permutations did not reveal a significant main effect of Group, but of Condition, in the time–frequency window 700–900 ms and at 16–26 Hz ($P < 0.003$, Bonferroni-corrected). This result indicated that, independently of the Group, Go and NoGo trials differed at the late stage. Further, in the 20–30 Hz frequency range and with the time spans of 550–650 ms and 790–900 ms, cortical oscillatory activity differed between musicians with and without MD depending on the task condition (significant interaction of the factors Group × Condition, $P < 0.003$).

The univariate permutation test across subjects in the NoGo condition revealed a significantly smaller ($P < 0.003$) spectral power increase of the beta oscillations between 23 and 30 Hz and at a latency of 850–900 ms for pianists with MD compared with healthy pianists. The increase in the TFR energy of beta oscillations for pianists with MD was weaker than for healthy pianists (see Fig. 6) over the left premotor and sensorimotor cortex (FC3, C3) and mesial frontocentral cortex (FCz, Cz) and extended to prefrontal regions (F3, Fz).

Synchronization Cluster Analysis

NoGo trials were associated with a robust increase in the degree of global synchronization $\overline{R}_C$ in the theta and lower alpha band (7–8 Hz) with a time span of 200–400 ms, thence coinciding with the latency when the participants were required to begin playing (Fig. 7A,B). This increase was more enhanced for healthy pianists than for pianists with MD (Fig. 7C). Interestingly, we found no changes in phase synchronization after the Go signal in any of the groups or in the between-group difference (results not shown).

We found a significant main effect of the factor Condition in the theta band (5–8 Hz) with a latency period of 120–470 ms and in the alpha band (8–13 Hz) between 220 and 450 ms. This indicated that, independently of Group, the global phase synchronization was different for Go and NoGo trials, or more specifically, it was higher during INH, because during ACT no changes were observed. A significant interaction of the factors Group × Condition was found in the theta band (6-8 Hz), with the same latency as in the main effect Condition and also in the alpha band (8–9 Hz) between 170 and 320 ms. The significant interaction reflected that the phase synchronization effects differed between musicians with and without MD depending on the task conditions around the time when playing had to be activated or inhibited (~250 ms). No main effect of factor Group was found.

To test our main hypothesis, whether the functional coupling during INH is impaired for pianists with MD compared with healthy pianists, we computed a univariate permutation test across subjects (Fig. 7C). A significant effect ($P < 0.005$, Bonferroni-corrected) was found between 230 and 330 ms and at 7–8 Hz, due to lower global synchronization for pianists with MD than for healthy pianists.

The topography of the phase synchronization index, averaged over the time window 230–330 ms and frequency range 7–8 Hz, is illustrated in Figure 8. Note that in pianists with MD the synchronized cluster consisted only of electrodes FCz and Fz (Fig. 8A), whereas in healthy pianists the synchronized structure included also the electrode Cz and the contralateral sensorimotor regions (Fig. 8B). Compared with healthy pianists, in pianists with MD (Fig. 8C), we observed a pronounced decrease in the phase synchronization between the supplementary motor cortex (Cz) and left premotor and sensorimotor electrodes (FC3, C3, CP3).

DISCUSSION

Inhibition

Our study focused on the execution and inhibition of long-term overlearned motor programs, due to its relevance in real playing conditions. Our assumption was that in the nonretrieval condition, motor memory traces, strongly activated after the first metronome beat, needed to be suppressed after S2 [Hummel et al., 2002].

A number of studies have supported the hypothesis that FTSD is associated with impaired inhibitory function at multiple levels of the central nervous system [Chen et al., 1995, Yazawa et al., 1999; Siebner et al., 1999]. At the behavioral level, electromyographic [Cohen and Hallett,

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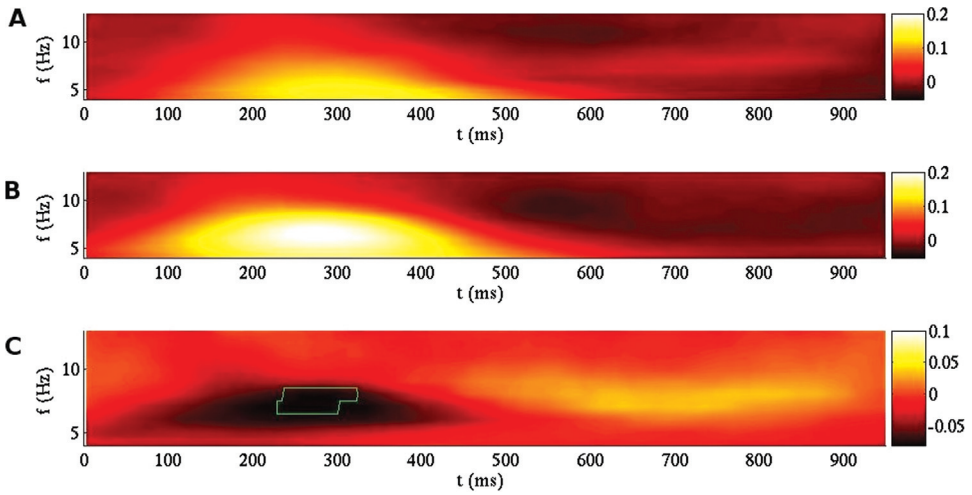

Figure 7.

Synchronization cluster analysis during INH. The time–frequency plots of the cluster strength, $\overline{R}_C$, averaged for the INH condition across electrodes over sensorimotor and prefrontal areas, are presented in the frequency range 4–13 Hz for pianists with MD (**A**), for healthy pianists (**B**), and for the between-group difference (**C**, A–B). A pointwise paired permutation test between groups yielded significant differences ($P < 0.005$) between 230 and 330 ms and at 7–8 Hz, due to higher global synchronization for healthy pianists than for pianists with MD in this time–frequency window. This region is indicated by the green contour.

1988; Stinear and Byblow, 2004] and kinematic [Odergren et al., 1996; Serrien et al., 2000] studies of FTSD have demonstrated the presence of cocontraction of the forearm and hand musculature, resulting in excessive and uncontrolled force output and, more generally, impaired sensorimotor integration.

Evidence from studies of neurophysiological function and TMS further supports deficient corticocortical and intracortical inhibition in focal hand dystonia [Gerloff et al., 1998a; Hummel et al., 2002; Ziemann et al., 1996].

In the present study, we aimed at studying a task that is closer to naturalistic piano performance. Accordingly, we imposed higher temporal constraints on the task, we used a larger sample of patients suffering from MD, and we had healthy musicians as controls.

In this setting, (i) the role of the interelectrode functional coupling in the sensorimotor integration of inhibitory processes turned out to be the most relevant physiological marker. This outcome could be related to the specific task and to the high temporal constraints. Our study further showed that in pianists with MD, the nonretrieval of the motor program was associated with (ii) a weaker positive shift after-S2 over cortical sensorimotor areas and (iii) a weaker increase in local beta oscillations at around 850 ms over the left and mesial sensorimotor and prefrontal (F3, Fz) cortex.

Finally, the EMG peak in NoGo trials was found to be significantly higher in pianists with MD than in healthy pianists. Our findings, thus, offer evidence that patients with MD, as compared to healthy pianists, have a signifi-

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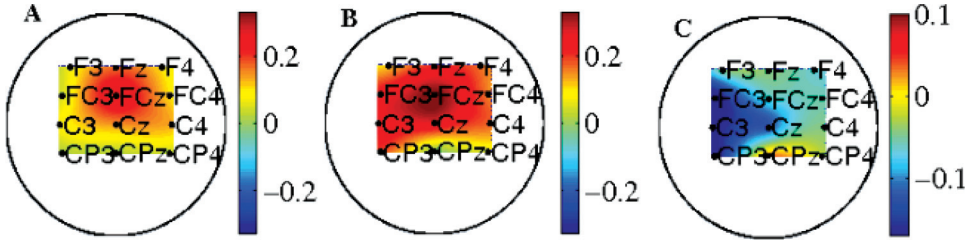

Figure 8.

Topographical distribution of the synchronization strength between each electrode and cluster, averaged over the time window 230–330 ms and frequency range 7–8 Hz, for pianists with MD (**A**), for healthy pianists (**B**), and for the between-group difference (**C**, A–B). A pronounced decrease in the phase synchronization between the supplementary motor cortex (Cz) and left premotor and sensorimotor electrodes (FC3, C3, CP3) was observed for pianists with MD compared with healthy pianists.

cantly higher innervation input of the flexor pollicis longus during NoGo trials. This outcome supports the main hypothesis of deficient inhibition in pianists with MD.

Movement-Related Cortical Potentials

Similar premovement activity over the sensorimotor cortex, as reflected in the CNV, was observed in both healthy pianists and those with MD. Previous studies reported in musicians with MD higher amplitude and laterality in the CNV prior to motor tasks [Ikeda et al., 1996; Lim et al., 2004]. Our data show a trend to higher amplitudes in the late phase of the MRCP prior to S2, albeit nonsignificant. This discrepancy can be ascribed to the different design of our study. Furthermore, in the study of Lim et al. [2004], the patients were more strongly affected by FTSD as compared with those in the present investigation.

The post-S2 resolution of the negative slow MRCPs showed a main effect of Condition and Group over the sensorimotor cortex, with a topographic maximum at the midline electrodes.

Moreover, in NoGo trials, the between-group positive shift in the MRCPs was significantly different over the midline regions with a latency of 270–308 ms. This outcome further stressed the relevance of the mesial frontocentral cortex during INH.

Nevertheless, some alternative interpretations of this finding merit consideration. First, no significant interaction of the factors Group × Condition was found. Therefore, the group differences in the univariate permutation test must be taken cautiously. Second, the latency of 270–308 ms is shortly after the time of the withheld movement during the NoGo trial. This result could indicate that the positive shift in the MRCPs around this latency reflects the relaxation of the mesial frontocentral once the movement has been successfully suppressed, rather than actively inhibited. Note, however, that the role of these brain regions in the Go and NoGo trials is consistent across the multivariate tests.

Our data, thus, emphasize the role of the mesial frontocentral cortex, including the region of the SMA, in the activation and deactivation of motor programs. Recent studies relating the SMA activation to MRCP amplitude changes have emphasized the role of frontocentral midline electrodes (Fcz and Cz) for various motor behaviors [MacKinnon et al., 1996; Marsden et al., 1996]. Regarding inhibitory processes, new findings show that the SMA mediates inhibition of motor plans [Sumner et al., 2007].

Increases of Beta Spectral Power After Offset of Motor Imagery

Research in motor tasks reported over sensorimotor areas decrease of task-related alpha power associated with ACT [Gerloff et al., 1998b; Hummel et al., 2002], whereas during INH task-related alpha power increase was found [Hummel et al., 2002]. However, the main empirical evidence of the increases in alpha oscillations has been provided over brain areas that are not task-relevant [for a review, see Klimesch et al., 2007].

In our study, the reduction of the power of alpha oscillations persisting after both Go and NoGo cues may indicate that the sensorimotor areas were task-relevant not only during ACT, but also during INH in terms of motor imagery. Nevertheless, this outcome may be specific to our paradigm, due to the higher time pressure, which would have activated strongly the motor programs and had made the inhibition of motor traces more difficult.

An unexpected between-group difference was the weaker late increase in beta spectral power for pianists with MD, after the nonretrieval of the motor program. The significant difference was localized over the left premotor, sensorimotor, and mesial frontocentral cortex and extended to prefrontal regions (F3, Fz).

Beta event-related synchronization (ERS) has been found after movement execution [Müller et al., 2003; Pfurtscheller et al., 1997] and movement imagination [Kühn et al., 2006; Pfurtscheller et al., 2005]. It appears within the first 1,000 ms after movement or motor imagery offset [Müller-Putz et al., 2007], which is in strong agreement with the latencies in our experiment (~700–900 ms). Nevertheless, despite the evidence that cortical deactivation or inhibition of the motor cortex is coincident with increases in beta oscillations [Pfurtscheller et al., 1997; Salmelin et al., 1995], the precise functional role of the bursts of beta oscillations is still poorly understood. According to Pfurtscheller et al. [2005] and Müller-Putz et al. [2007], the beta ERS has to do with the activation/deactivation of the sensorimotor cortex circuitry and the resetting process of motor cortex control systems to make the network control system ready for further motor actions. At the subcortical level, a Go/NoGo study recording local field potentials from the region of subthalamic nuclei [Kühn et al., 2004] reported that when movement was inhibited, the subcortical beta event-related desynchronization (ERD) was terminated and reversed into an ERS.

In the present study, the beta rebound, which followed the period of suppression of beta band spectral power in the NoGo condition, could not be related to movement-offset, but rather could support the role of motor imagery in our paradigm. Prior to the Go/NoGo signal, participants rehearse mentally the motor program, which in the NoGo condition has to be deactivated after S2. Thus, in our paradigm, this deactivation refers to the offset of motor imagery.

In light of the findings of Pfurtscheller et al. [2005] and Müller-Putz et al. [2007], our data would suggest that the resetting mechanisms that prepare the cortical networks for the execution of upcoming motor patterns in pianists with MD are less efficient than those of healthy pianists. Still, we believe that the question of the functional role of the increase of beta oscillatory activity has not yet been fully answered.

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Phase Synchrony Analysis

Our data reflect the binding between synchronized activity of distant sensorimotor cortical regions, characterized mainly by *short-range* connections between neighboring electrodes within the contralateral sensorimotor cortex and within/or with the SMA.

So far, functional coupling has not been compared during INH and ACT in patients with FTSD. EEG research in diseases in which deficient inhibition plays a role in the pathogenesis has proven that the measure of the synchronization between cortical brain regions delivers relevant results. For instance, inter-regional cortical synchronization correlates with the defective corticocortical interactions in patients with Tourette's syndrome [Serrien et al., 2005], attention deficit hyperactivity disorder [Barry et al., 2002], or Parkinson's disease [Silberstein et al., 2005].

Importantly, the work of Serrien et al. [2005] demonstrated in a Go/NoGo paradigm enhanced coherence during INH as compared with ACT. Previous literature also reported stronger task-related coherence for NoGo than for Go conditions [Shibata et al., 1997, 1998], results which our data support: The inter-regional functional coupling during ACT is weaker than that during INH in both groups.

It remains unknown whether the higher demand in phase synchronization observed during NoGo trials is due to active motor inhibition per se or to the stronger challenge that may represent the NoGo condition. Here, we consider that the patterns of increased functional coupling observed during INH around the time of playing (~250 ms), which were absent during ACT, may indicate that the NoGo cue does not merely imply disregarding the motor execution; rather, it may be a manifestation of some active processes required for the nonretrieval of the motor program.

In pianists with MD, as compared with healthy pianists, weaker functional connectivity underlying the nonretrieval of motor programs was found around ~250 ms between the supplementary motor cortex (Cz) and left premotor and sensorimotor electrodes (FC3, C3). This outcome reflected their impaired motor INH.

The SMA is thought to play an important role in the functional control of movement in that it has direct projections to the primary motor cortex and the spinal chord [Matsuzaka et al., 1992]. Recent data has proven the suppressive influence of SMA on the primary motor cortex (M1) in motor imagery, thus reflecting the inhibitory function of the forward connection between the SMA and M1 [Kasess et al., 2008]. Hence, our results could be interpreted as a deficient *higher order* motor functioning in pianists with MD: The phase coupling between the SMA and the left premotor and sensorimotor cortex, which is required for the nonretrieval of the motor program, is weaker in pianists with MD. Consequently, these data can be regarded as an electrophysiological correlate of the impaired inhibition in pianists with MD. We believe that assessing functional interactions between brain regions in patients with deficient inhibitory circuitry, such as is the case in dystonias [Abbruzzese et al., 2001; Hummel et al., 2002; Ridding et al., 1995; Tinazzi et al., 2000], could be a key issue, since these measures reveal the deficits of patients in engaging the network connectivity used by healthy controls.

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