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Quantitative EEG analysis during motor function and music perception in Tourette's syndrome

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Abstract Gilles de la Tourette's syndrome (TS) is a neurobehavioral disorder of childhood onset that is characterized by motor and vocal tics and associated behavioral disturbances including obsessive-compulsive symptoms. We performed 30 channel quantitative electroencephalograms (EEGs) on 13 Tourette patients and 26 controls and studied both resting and manumotor/music perception activation conditions. Resting EEGs did not show any differences between patients and controls, as known from the literature. However, during simple and complex hand movements, as well as music perception tasks, there were subtle differences predominantly in alpha frequency. They suggested reduced brain activation during motor tasks in frontal and central regions, and on music perception in temporal and parietal regions, respectively. These findings may add evidence to the functional neuroanatomy of Tourette syndrome, affecting more areas than disturbed motor circuits.

Key words QEEG · Tourette's syndrome · Cortical activation · Motor dysfunction · Cognitive dysfunction

Introduction

Gilles de la Tourette Syndrome (TS) is a complex neurological disorder of childhood onset characterized by multiple motor and vocal tics and associated behavioral disturbances including obsessive – compulsive symptoms (Müller et al. 1988). It appears to have an organic basis as suggested by positron emission tomography (PET) and single photon emission computed tomography (SPECT) studies (Braun et al. 1993; George et al. 1992; Malison et al. 1995; Moriarty et al. 1995), epidemiological evidence (Apter et al. 1993), neuropsychological findings (Yazgan et al. 1995), presence of autoantibodies (Toren et al. 1994), and prenatal/early environmental as well as genetic (Curtis et al. 1992; Editorial 1993; Remschmidt and Hebebrand 1993; Müller et al. 1994) influences.

Routine and quantitative electroencephalographic (EEG) analysis (Neufeld et al. 1990; Verma et al. 1986), as well as investigation of the premotor potential (Obeso et al. 1982), yielded inconclusive findings. Because TS is unambiguously a disorder of motor function, we used 30-channel EEG mapping and motor activation paradigms involving simple and complex movements of the right dominant hand to study patients with TS. This methodology has been shown to reveal even subtle signs of motor brain dysfunction in schizophrenic (Günther et al. 1993 a, b) and mild to moderate Alzheimer patients (Günther et al. 1993 c). Additionally, magnetic resonance imaging (MRI) findings yielded an altered corpus callosum morphology in these patients, suggesting that circuits other than motor circuits may be affected also (Peterson et al. 1994). Because this notion was supported also by a recent MRI study linking basal volume asymmetry to neuropsychological dysfunction in various psychomotor and word perception tasks in TS patients (Yazgan et al. 1995), we included motor and music perception tasks in the EEG investigation of TS patients, similar to previous studies in other psychiatric populations (Günther et al. 1993 a–c).

Patients and methods

The subjects were 13 TS patients (for a minimum of 2 weeks unmedicated with psychoactive drugs), 11 male and 2 females, aged 36.4 years (range 18–65 years, SD 11.33 years). Their symptomatology was assessed using the Tourettes Syndrome Global scale (Harcherik et al. 1984; average 31.3, SD 14.4) and the Yale Global Tic Severity scale (Leckman et al. 1989; average 50.2, SD 19.8), indicating moderate to severe symptoms. Control subjects were 26 persons (22 males and 4 females), average age 35.2 years (range 20–67 years, SD 11.18 years). On *t*-test statistical screening no differences were found between controls and patients concerning age

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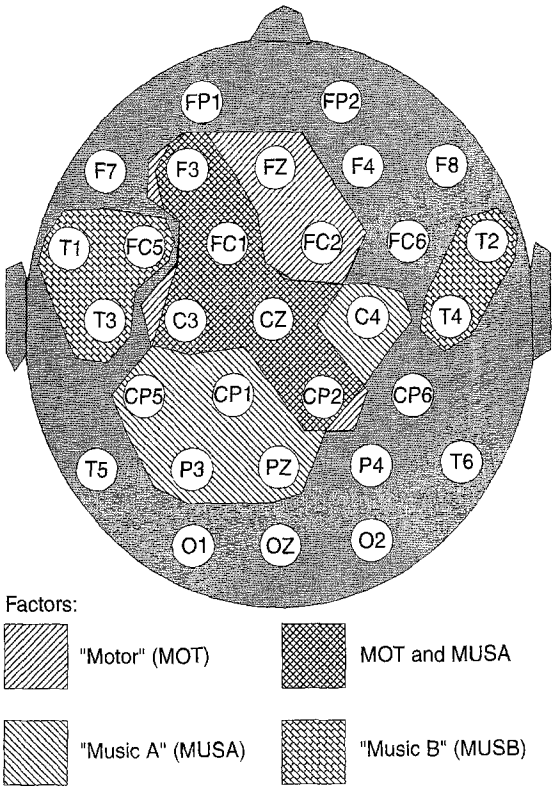


Fig. 1 Electrode placements, 10/20 system. Indicated also are the electrodes which constitute the motor and music factors (TS, n = 13; CNT, n = 26). TS Tourette's syndrome, CNT Control persons

and gender; pairwise matching was not performed in order not to further reduce sample size. Thirty-channell EEG mapping (Brain Star, Schwind, Erlangen, Germany; low pass filter 30 cps, time constant 0.3 s, digitalization rate 128 cps, 12-bit resolution per data point, reference linked ears) was performed during resting, simple (flexion on the thumb against the index finger), and complex movements of the dominant hand (flexion of thumb against the index finger twice, the middle finger once, the ring finger three times, and the little finger twice; the sequence is then reversed) and simple (keyboard-generated rumba rhythm) and complex music perception conditions (Mozart "Jagdquartett" KV 458, beginning of the first movement) delivered binaurally by earphones. A resting period separated each activation condition, thus yielding four resting and four challenge periods of analysis. The 30 electrode placements according to the 10/20 system are shown in Fig. 1; two channels were used for vertical and horizontal electro-oculography (EOG).

Careful off-line artifact exclusion using both the raw EEG data and the EOG was performed by an EEG expert who was blind to the diagnosis. We preferred this clinical artifact exclusion to mathematical procedures, which would have been possible also (e.g., by regression analyses; Anderer et al. 1992). As artifact-free continuous EEG periods as possible (minimum 12 s, which was available in all clinical and control subjects, average 14.6, 14.2, 14.8, 15.2, 14.6, 15.0, 15.0, and 14.5 s for resting 1, hand simple, resting 2, hand complex, resting 3, music simple, resting 4, and music complex, respectively; no fast Fourier transform (FFT) analyses of subperiods performed) were submitted to FFT and absolute power values (in square microvolts) in the frequency bands delta (0.5–4.5), theta (5.0–7.5), alpha (8.0–13.5), beta 1 (14.0–20.5), and beta 2 (21.0–30.0 cps) used for further off-line multivariate analysis. Results for these EEG power data are presented in this paper, whereas EEG microstate and topography analysis are reported separately (Stevens et al., in preparation).

Results

At first, series of MANOVAs (SPSS/PC; Norusis 1985) were performed in 30 electrode (not considering EOG data) positions implicating two "between" factors (diagnosis), and five frequency bands as well as eight resting/task conditions as "within" factors. No significant differences (main effects) in resting/activated EEG were found in accordance with the literature (Neufeld et al. 1990). However, several significant (including tendency, i.e., $P < 0.1$ on two-sided testing) diagnosis/task interactions (exact F-values from 2.457 to 1.688, P from 0.036 to 0.094) were obtained in *alpha* frequency band in the electrodes F3, Fz, FC1, FC2, C3, C7, CP5, CP1, and CP2 (i.e., predominantly left-hemispheric frontal-central areas; cf. Fig. 1) for resting/motor conditions and electrodes F3, T1, FC5, FC1, T2, T3, C3, Cz, C4, T4, CP1, CP2, CP5, P3, and Pz (exact F-values from 2.988 to 1.674, P from 0.022 to 0.095), thus involving bilateral temporoparietal areas (cf. Fig. 1). The precondition of normal distribution was established for this frequency band performing 480 Kolmogorov-Smirnov tests (Clauss and Ebner 1974), none (!) of them being significant, indicating no statistically relevant deviations from normal distribution.

Because it is reduction of alpha power, which is most widely accepted as the EEG variable indicating brain activation, and because only one significant diagnosis/task interaction was obtained in delta, theta, and beta 1 frequency bands each and none in beta 2, these 15 significant diagnosis/task interactions in alpha were examined further.

Taking into account the high intercorrelation of the power values in electrodes involved in these interactions in the alpha band, we reduced the amount of data by applying factor analyses (principal component analysis, varimax rotation, exit eigenwerte above 1). By this procedure we empirically derived aside from the motor factor (electrodes F3, Fz, FC1, FC2, C3, C7, CP5, CP1, and CP2) two music factors: music A (electrodes F3, FC1, C3, Cz, C4, CP5, CP1, CP2, P3, Pz) and music B (electrodes T1, T2, T3, T4, CP5), explaining between 91.4 and 92.8% of the variance, respectively (Table 1). Results of changes in power sum scores for these electrodes (motor and music A/B factor scores) are displayed in Fig. 2.

As can be seen from Fig. 2, there are opposite effects on power in alpha, summed up over the motor and the two music factor scores in TS patients and controls. Whereas control persons decrease their alpha power both during simple motor and music stimulation, this is not (motor and music A) or only minimally (music B) the case in TS patients. They show, additionally, in contrast to normals after music stimulation, an increase in alpha in the subsequent resting condition, both for music A and B factor scores.

In order to assess how this "differential activation" is suitable to distinguish between patients and controls, two discriminant analyses were performed using the difference scores from resting 1-simple motor-resting 2 for the

Table 1 Factor-loading coefficients on the first two factors of a principal component analysis in simple and complex music conditions and the preceding resting conditions, respectively. Displayed are only factor loadings greater than 0.6. Note a similar factor structure for both simple and complex music perception, when both patients and controls were included in the analysis

Resting 3
Rotated factor matrix:

	Factor 1	Factor 2
PZ	0.92749	
P3	0.91676	
CP2	0.90940	
CP1	0.90636	
CP5	0.82092	
CZ	0.79959	
C4	0.79081	
C3	0.76248	
FC1	0.69329	0.68136
T1		0.89035
T2		0.87813
FC5		0.78443
F3	0.61746	0.74188
T4	0.60462	0.72936
T3	0.61931	0.70893

Percent of (explained) variance: 91.4

Resting 4
Rotated factor matrix:

	Factor 1	Factor 2
PZ	0.92631	
CP1	0.91440	
CP2	0.91403	
P3	0.90431	
CZ	0.85140	
C4	0.82529	
CP5	0.81892	
C3	0.81165	
FC1	0.78787	
F3	0.72600	0.62118
T1		0.92119
T2		0.85745
FC5		0.81674
T4		0.74619
T3	0.62233	0.71850

Percent of (explained) variance: 91.8

Music simple
Rotated factor matrix:

	Factor 1	Factor 2
PZ	0.94106	
P3	0.93164	
CP1	0.92836	
CP2	0.92362	
CZ	0.88574	
C4	0.86509	
CP5	0.83557	
C3	0.83148	
FC1	0.82337	
F3	0.76678	
T1		0.93345
FC5		0.86165
T2		0.84652
T3		0.77261
T4		0.74462

Percent of (explained) variance: 92.8

Music complex
Rotated factor matrix:

	Factor 1	Factor 2
PZ	0.94322	
CP1	0.93823	
CP2	0.93489	
P3	0.91946	
CZ	0.90459	
C4	0.86971	
FC1	0.84239	
C3	0.83653	
CP5	0.80490	
F3	0.75742	
T1		0.88583
FC5		0.87223
T2		0.85837
T3		0.77388
T4		0.75320

Percent of (explained) variance: 91.1

motor, and resting 3-simple music-resting 4 for the music A/B factors, respectively. It should be noted here that due to "differential sequential cerebral activation" (see Günther et al. 1994), the resting power values before the complex motor and music condition are already significantly different, which prevents further analysis of possibly differential cortical activation on these tasks in both groups (i.e., complex motor and music tasks were not used in the discriminant analyses). Thus, only nine variables (three for each factor) remained for both a simultaneous and a stepwise (selection criterion minimize Wilk's lambda) discriminant analysis. Figure 3 shows the results of the direct (Fig. 3 a) and stepwise (Fig. 3 b) discriminant analyses.

As can be seen from Fig. 3, in both discriminant analyses more than 4/5 (82.1% simultaneous and 84.6% stepwise) of all persons were classified correctly. It seems especially notable that only three variables were used in the stepwise method, which, however, yielded a lower sensitivity (3 false negatives) as compared with the simultaneous analysis using nine variables (one false negative).

Discussion

Thirty-channel EEG mapping findings during complex manumotor and music perception conditions suggest that signs of disturbed brain function in TS may not be restricted to motor circuits. Other complex cortical functions may also be involved as indicated by EEG changes elicited through complex music perception. However, before discussing these findings further, several methodological limitations of our study have to be pointed out:

1. Although there have been considerable efforts to exclude artifact-contaminated periods from further analysis including monitoring vertical and horizontal EOG in two

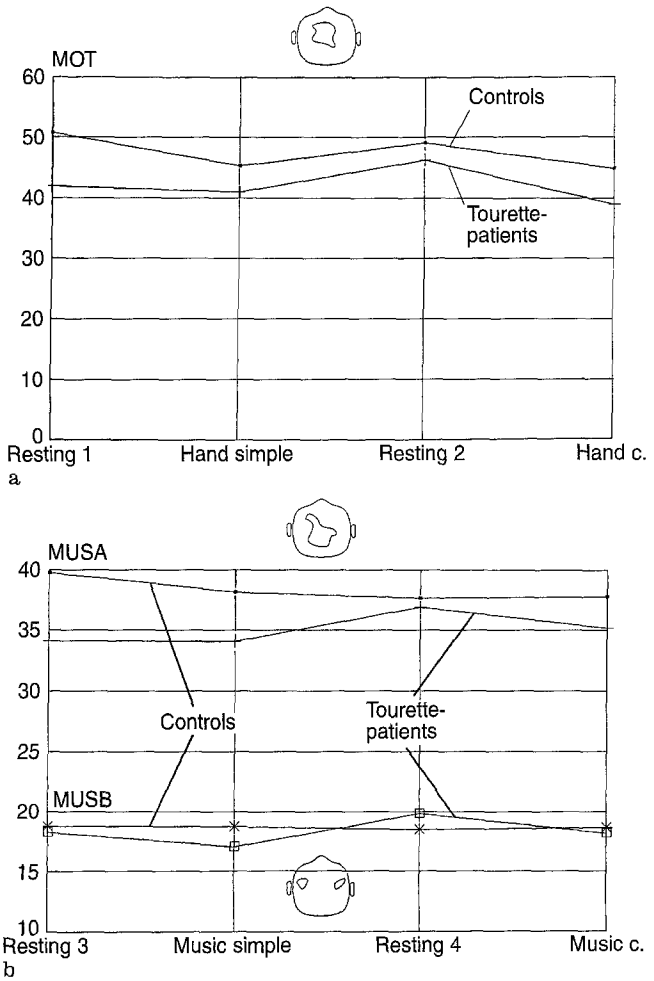
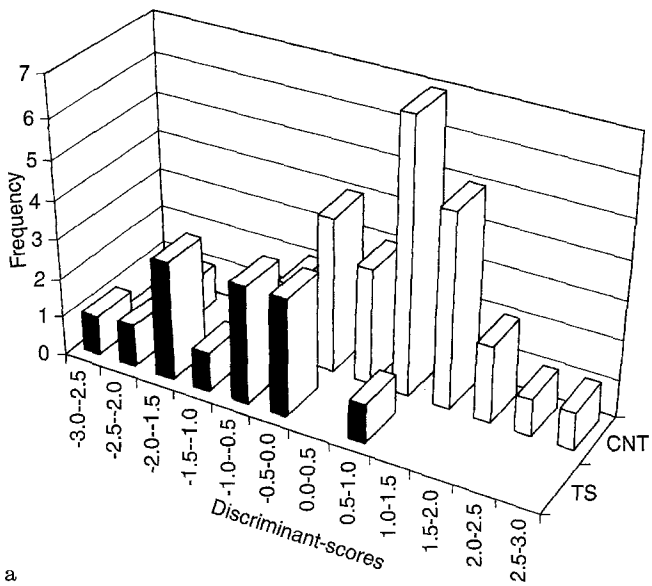


Fig. 2 **a** A Changes in alpha power (motor factor) in TS (n = 13) vs CNT (n = 26, c. = complex). **b** Changes in alpha power (music A, and B factors in TS) (n = 13) vs controls (n = 26; c. = complex). Note a decrease in alpha power in controls in music A factor on simple music, which is not seen in TS. Note an increase in alpha power from music simple to resting for TS in both music factors, which is not seen in normal persons. A decrease for both music factors is found in patients for complex music, which again is not present in control persons

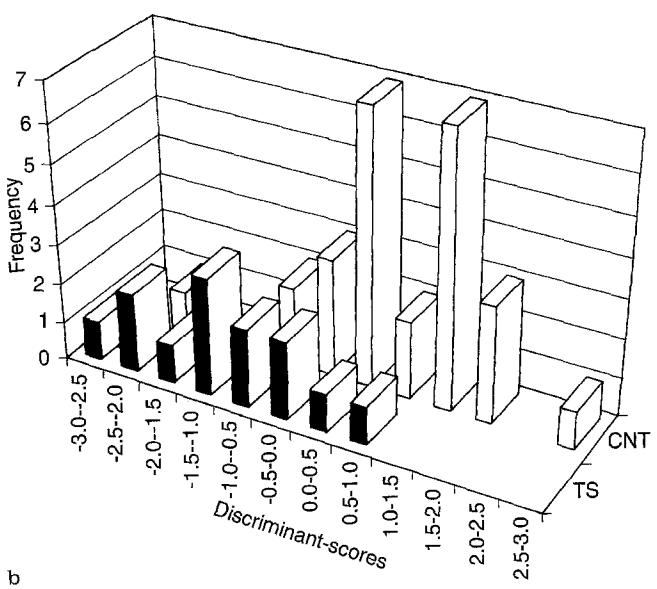
separate channels for (blind) expert off-line evaluation, this is not *entirely* possible, and may have influenced the findings. However, artifact contamination may be less important in alpha frequency band, in which our subtle differences between TS and control persons emerge under challenge conditions.

2. Although our statistical evaluation attempted to minimize differential effects of sequential brain activation, there might still be a major difference between different clinical and control samples, which we study prospectively involving additional clinical groups (schizophrenic and demented patients, detoxified chronic alcoholics; first results in Günther et al. 1994). Additionally, because factorial analyses were performed for patient and control groups together for statistical reasons (sample size), it is not possible to rule out the possibility of different topographic patterns in both groups, which must be checked



Actual Group	No. of Cases	Predicted Group Membership	
CNT	26	20 (76,9%)	6 (23,1%)
TS	13	1 (7,7%)	12 (92,3%)

Percent of correctly classified cases: 82,05%



Actual Group	No. of Cases	Predicted Group Membership	
CNT	26	23 (88,5%)	3 (11,5%)
TS	13	3 (23,1%)	10 (76,9%)

Percent of correctly classified cases: 84,62%

Fig. 3 **a** Results of a discriminant analysis of 13 TS and 26 control persons The simultaneous method using only simple motor and music tasks as related to both preceding and subsequent resting conditions yields a correct classification of 82.05%. **b** Results of a discriminant analysis of 13 TS and 26 control persons. The stepwise method using only simple motor and music tasks as related to both preceding and subsequent resting conditions yields a correct classification of 84.62%

in a cross validation study for TS patients). The EEG findings for normal persons are reported separately, especially those for music tasks, which indicate distinct separation of areas involved in simple (rhythm) (midline frontal-central-parietal areas) vs complex (Mozart; bitemporal areas) perception (Günther et al., in preparation). However, with a classical EEG method, be it qualitative or quantitative, it is not possible to establish exact topographic relations to brain function, nor can the question be answered precisely as to whether or not more deeply located cerebral structures contribute to a given electrical field distribution on the skull.

3. There may be deviant coupling of EEG parameters to underlying brain function as, for example, reflected by glucose uptake measured with PET in various clinical groups was already suggested for schizophrenic vs normal persons (Günther et al. 1993a; Alper et al. 1994). Thus, our QEEG results must be considered preliminary and heuristical in nature, warranting further study using more established neuroimaging methods. However, several results using these methods have been reported already and seem to be consistent with some of our findings.

George and colleogues (1992) used 99Tc-HMPAO and SPECT in 20 unmedicated TS patients under resting conditions and found elevated right frontal/visual cortex activity in these patients as compared with eight control persons. The authors suggested activation/challenge procedures in order to further analyze brain dysfunction in TS (which we used).

Using 18FDG and PET, Braun and coworkers (1993) investigated 16 medication-free TS patients and 16 healthy controls. They reported decreased (normalized) metabolic rates in paralimbic and ventral prefrontal cortices, particularly in orbitofrontal, inferior insular, and parahippocampal regions for patients, which were associated with concomitant bilateral increases in metabolic activity in supplementary motor, lateral premotor, and Rolandic cortices. The authors speculated that an altered relationship between limbic-related regions for the cortex and striatum and cortical regions involved in the initiation of movement may contribute to the pathogenesis of TS disorder.

Furthermore, during the process of researching this paper, two SPECT studies were reported which may add further support to our results. Moriarty et al. (1995) found a wide range of abnormal perfusion areas in TS patients using SPECT with 99Tc-HMPAO as tracer, with no characteristic pattern for behavioral subgroups. Malison et al. (1995) applied (^{3}H) mazindol, a marker of striatal dopamine transporters and SPECT, to five TS patients and five control persons. They observed a 37% increased binding in TS patients and speculated on a dysregulation of presynaptic dopamine function in this condition, involving more than motor circuits. Thus, with the necessary precautions outlined above for our QEEG findings in TS vs normal persons, there seems to be the following consistency of our findings with these recent PET and SPECT result: If we consider the absence of alpha blockage both on voluntary motor and music perception tasks as sign of reduced brain reactivity, EEG also finds both primary and supplementary motor brain region to be dysfunctional in TS patients, as well as limbic-related bilateral temporal regions.

Furthermore, our EEG results appear consistent with MRI findings on corpus callosum size reductions in TS, which were also speculatively linked by the authors to aberrant cortial connectivity and/or altered functional lateralization suggesting that "a pathoetiologic process diffusely affecting the TS CNS should be sought" (Peterson et al. 1994, p. 96). This notion is further supported by recent MRI basal ganglia asymmetry findings linked to motor and verbal perception dysfunction in TS (Yazgan et al. 1995) and a report on enhanced stress responsitivity of TS patients, suggesting as another altered brain function an abnormal hypothalamic-pituitary-adrenal axis reactivity (Chappell et al. 1994).

Finally, results of our motor and music perception tasks seem consistent with the growing evidence that abnormal motor behavior to both external and internal stimuli may be present in the pathophysiology of TS (Cohen and Leckman 1992; Eapen et al. 1994). Despite its limitations, EEG methodology using quantitative evaluation and suitable functional challenge paradigms may contribute to the understanding of the biological basis for Tourettes syndrome and new therapeutic attempts (Iancu et al. 1995).

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