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ORIGINAL ARTICLE

# Changes in recruitment of motor cortex excitation and inhibition in patients with drug-induced tardive syndromes

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Tardive syndrome;
Transcranial magnetic stimulation;
Transcallosal inhibition

**Summary**
*Objectives.* — It has recently been suggested that drug-induced tardive syndromes (TS) might be due to maladaptive plasticity, which increases motor excitability in cerebral cortex and basal ganglia. In order to test this hypothesis, we performed the first measurements of cortical excitability in TS.
*Methods.* — Motor cortex excitability was examined using transcranial magnetic stimulation (TMS) in 22 TS patients and compared with that in 20 age and sex-matched healthy individuals. Resting and active motor threshold (RMT, AMT) and input—output curves (I/O curves) assessed corticospinal excitability. The duration of the contralateral silent period (cSP) at a range of stimulation intensities and ipsilateral silent period (iSP) were used as measures of inhibition.
*Results.* — There were no significant differences in RMT and AMT between patients and controls, although the input—output curves were significantly steeper in patients. The cSP (at different stimulus intensities) and iSP were both longer in the patients compared to the control group. However, most of this difference could be accounted for by increased recruitment of motor evoked potentials (MEPs) in patients.

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*Conclusion.* — TS is characterized by hyperexcitability of corticospinal output that might contribute to the lack of selectivity in muscle recruitment and contribute to excess involuntary movement. The findings are opposite to those in naturally-occurring hyperkinesia such as Sydenham's and Huntington's chorea, suggesting a fundamental difference in the pathophysiology.


## Introduction

Tardive syndrome (TS) is defined as a group of disorders caused by exposure to a dopamine receptor antagonist within 6 months of the onset of symptoms and persisting for at least 1 month after stopping the offending drug [5]. The occurrence of TD is estimated to be 2%—5% annually, [3,6,27], and the condition occurs in 15%—30% of those who receive long-term treatment with antipsychotic drugs (APD). The occurrence of TD can also depend on whether the APD is typical (also known as first generation) or atypical (also known as second generation), [27] with a 32.4% occurrence with typical APD and a 13.1% occurrence with atypical APD [11]. According to the diagnostic and statistical manual of mental disorders, 5th edition (DSM V) [1], the spectrum of TS includes involuntary movements of the tongue, jaw, trunk, or extremities, and may be choreiform, athetoid, or stereotypic in nature. Based on the phenomenology, tardive syndromes can be subtyped as: tardive dyskinesia, tardive stereotypy, tardive dystonia, tardive tremor, tardive akathisia, tardive myoclonus and tardive Tourettism [2].

TS has been commonly attributed to hypersensitivity or upregulation of dopamine receptors, particularly the D2 subtype, following chronic blockade. A more recent hypothesis relates to synaptic plasticity. Synapses have the ability to increase or decrease the effectiveness of transmission through distinct mechanisms mediated by increases in intracellular calcium. It has been proposed that hypersensitization of D2 receptors and a direct drug action on N-methyl-D-aspartate (NMDA) receptors could provoke maladaptive plasticity in cortex and basal ganglia. This would lead to reduced selectivity of motor commands and aberrant motor learning [23].

The present experiments used transcranial magnetic stimulation (TMS) methods to probe the excitability of motor cortex circuits in order to obtain further evidence of the pathophysiological changes in TS. In physiological terms, reduced selectivity of motor commands equates to less control over access of excitatory inputs to corticospinal neurons. Given that a TMS pulse activates synaptic inputs to corticospinal neurons, we predicted that if this were the case, a TMS pulse would generate a larger response in TS than in healthy participants. Reduced selectivity could also result from changes in the excitability of inhibitory circuits. We therefore evaluated these by measuring the duration of the contralateral and ipsilateral silent periods, which follow the muscle twitch evoked by TMS, and which are thought to be due in part to activation of GABAergic connections within motor cortex [28]. We did not measure intracortical plasticity directly by means of paired-pulse TMS paradigm, since some of the medications such as amantadine (which has actions on NMDA receptors) or propranolol [15] that the TS patients were taking at the present time may interact with these assessments.

## Methods

Twenty-two patients with drug-induced tardive syndromes (12 males and 8 females, mean age 41.15 ± 16.8 years; range, 21—62 years) as defined according to the diagnostic and statistical manual of mental disorders (DSM V) [1], were recruited from the outpatient clinic of Aswan University Hospital. Depending on the previous antipsychotic drugs that they received they were classified into 3 groups: 5 patients had received 1st generation antipsychotic (haloperidol 50 mg/2—4 weeks or zuclopenthixol (Clopexol Depo™) 200 mg/3—4 weeks), 4 patients had received 2nd generation antipsychotic (risperidone or aripiprazole 4—6 mg/day) and 13 patients had received both 1st + 2nd generation antipsychotic drugs. The previous duration of treatment ranged from to 12—30 months. All patients stopped antipsychotic treatment after developing tardive syndromes. The average duration of TS was 18.3 ± 30.8 months ranging from 1 month to 120 months. At the time of study, patients were receiving a variety of medications including amantadine, benzotropine, propranolol and biperiden ''anticholinergics'', but with little effect on TS. The duration of current medical treatment was 6.06 ± 8.8 months ranging from 2 weeks to 36 months. Exclusion criteria: patients who had history of metabolic disorders (diabetes mellitus, renal or liver impairment) or had history of seizure, severe dementia or any neurological disorders were excluded. Patients with magnetic or any other implanted device, or patients with intracranial lesion on neuroimaging were also excluded.

None of the patients suffered from any other clinically relevant disorders. Each patient was assessed with the abnormal involuntary movement scale (AIMS) [7]. The AIMS test has a total of twelve items rating involuntary movements of various areas of the patient's body. These items are rated on a five-point scale of severity from 0—4. The scale is rated from 0 (none), 1 (minimal), 2 (mild), 3 (moderate), 4 (severe). Two of the 12 items refer to dental care. The remaining 10 items refer to body movements themselves.

The mean patients' AIMS score was 12.4 ± 2.9 ranging from 5 to 17 points.

Previously diagnosed psychiatric disorders (according to DSM V) were: 13 patients had schizophrenia, 9 had mood disorders. Tardive syndromes included: tardive dyskinesia (oro-buccal-lingual) in 10 patients, and tardive tremors, bradykinesia and rigidity in 12 patients. Details of demographic data of the patients are illustrated in Table 1.

Twenty age- and sex-matched healthy volunteers (12 males and 8 females; mean age, 40.8 ± 19.8 years; range, 20—69 years) represented the control population for assessment of cortical excitability. Controls were asked not to take drugs that affect motor cortex excitability (dopaminergic, tranquillizer, antidepressant, or antiepileptic) for at least one week before the study; the same exclusion criteria were used as for the patients. Education levels were the same in patients (mean 10.5 yrs) and controls (10.3 years).

**Table 1** Demographic and clinical data of studied groups.

| | |
|---|---|
| Demographic and clinical parameters | $n = 22$, mean ± SD |
| Age (years) | 41.45 ± 14.6 |
| Sex male/female | 15/7 |
| Duration of tardive syndromes (months) | 14.9 ± 19.8 |
| Duration of treatment of tardive syndromes (months) | 6.7 ± 8.6 |
| Background psychiatric illness Mood disorder/schizophrenia | 9/13 |
| Offending antipsychotic | 5 patients received 1st generation antipsychotic drugs, 4 patients received 2nd generation antipsychotic drugs, and 13 patients received both 1st and 2nd generation antipsychotic drugs |
| Current treatment with little effect on tardive syndromes (TS) | Amantadine, benzotropine and biperiden, propranolol, sodium valproate |
| Types of tardive syndromes | Tardive dyskinesia: classical oro—buccal—lingual (OBL) dyskinesia and to choreic movements in other body parts (10 patients). Tardive tremor: kinetic, postural and resting tremor, usually with high amplitude, frequency of 3—5 Hz, in the absence of parkinsonian (12 patients) signs |
| Abnormal involuntary movement scale (AIMS) | 12.7 ± 3.3 |
| Overall severity | 2.7 ± 0.7 |
| Incapacitation | 2.4 ± 0.7 |
| Awareness | 2.5 ± 0.9 |

The study was approved by the Institutional Ethical Committee of Aswan University Hospital, and subjects gave their informed consent according to the Declaration of Helsinki.

## Experimental setup and design

Subjects sat in a comfortable chair. Electromyographic (EMG) recordings (Nihon Kohden 9400, Japan) from the first dorsal interosseous muscle of right hand were acquired with silver—silver chloride surface electrodes, using a muscle belly—tendon setup, using a 3-cm-diameter ground electrode placed on the wrist. The EMG parameters included a bandpass of 20 to 1000 Hz and a recording time window of 200 ms. TMS was performed with a 90-mm figure-of eight coil connected to Magstim (UK) super rapid magnetic stimulator. RMT, AMT, I/O, cSP and iSP were evaluated as previously reported by Khedr et al. [8—10]. Any trials in which there was detectable pre-stimulus EMG activity were discarded from the analysis on the basis that this indicated that the participants were not completely relaxed. Motor thresholds were determined after localization of the motor ''hot spot'' for the first dorsal interosseous muscle in each hemisphere. The EMG signals were monitored and recorded for 20 ms before stimulation. Resting motor threshold (RMT) was measured at complete rest; active motor threshold (AMT), while subjects made a mild contraction of approximately 10% maximum. Both RMT and AMT were expressed as a percentage of the maximal stimulator output (equal to 100%).

Input—output curve was evaluated at rest by increasing the intensity of stimulation in steps of 10% from 110% to 150% of RMT. At each intensity, five trials were collected, with inter-trial intervals of 5 seconds, and averaged.

The contralateral cortical silent period (cSP) of each hemisphere was evoked with stimuli of 130% RMT during isometric 50% maximum voluntary contraction of the contralateral first dorsal interosseous muscle. Contraction started 5 s before TMS. Ten stimuli were delivered not closer than once every 15 s to avoid fatigue. The EMG traces were rectified and averaged. The length of the cortical silent period (ms) was determined visually from the end of the MEP to the recurrence of at least 50% of EMG background activity.

Ipsilateral silent period (iSP) was assessed in the same way, except that the subject contracted the ipsilateral first dorsal interosseous muscle, and the stimulation intensity was 150% RMT. If RMT was above 65% of maximum stimulator output, then maximum intensity was used. The onset and the offset of iSP were defined as the points where the EMG trace fell persistently below and where it returned persistently to the base line. The iSP duration was calculated as the time of offset of iSP minus the onset of iSP (ms).

## Statistical analysis

One- or two-way analysis of variance (SPSS version 16) was used to compare measures between patients and controls. Means ± standard deviation (SD) were used to represent data. The level of significance was set at $P < 0.05$. A two factor repeated measures analysis of variance (ANOVA) with ''groups'' (patients versus control) and ''intensity'' as main factors was conducted for the I/O and cSP curves. When

necessary, a Greenhouse—Geisser correction was applied to correct for non-sphericity. Post-hoc unpaired *t*-tests were carried out for specific comparisons of data from the two groups. Non-parametric Spearman correlation between the AIMS score and different parameters of cortical excitability was also performed. The subgroup analysis (medication, previous psychiatric condition and type of involuntary movement) used one or two-way ANOVA to compare measures of thresholds, I/O curve, and silent periods between groups.

## Results

### Motor thresholds

There were no significant differences in either RMT or AMT between patients and controls (Table 2).

### Input-output (I/O) curve

A two-way repeated measures analysis of variance with main factors of ''TMS intensity'' (110, 120, 130,140, and 150% of RMT) and ''group'' (patients and controls) showed a significant intensity × group interaction [F = 3.6, df = 1.6 (65), and *P* = 0.03]. This was attributable to significantly higher amplitudes of MEP at 130, 140, and 150% of RMT (Table 2 and Fig. 1a).

### cSP at different TMS intensities

A two-way repeated measures analysis of variance with main factors of ''TMS intensity'' (110, 120, 130,140, and 150% of RMT) and ''group'' (patients and controls) showed no significant group × intensity interaction [F = 0.89, df = 2.6 (104), and *P* = 0.43]. However; there was a significant main effect of group, meaning that at all intensities studied, the cSP was longer in the patients than the controls specially at stimulus intensities (110, 120, 130, and 140% of rMT) (Table 2 and Fig. 1b).

### iSP

The iSP was significantly longer in patients in comparison to controls (*P* = 0.0001) (Table 2 and Fig. 2).

### Correlations

The clinical severity was assessed for each patient using the AIMS score. There was no significant correlation between the score and any of the parameters of cortical excitability.

### Subgroup analyses

Analyses regarding medication, previous psychiatric condition and type of involuntary movement are presented in Tables 3A, B and C. There were no significant differences between neurophysiological results (rMT, aMT, I/O curve, iSP and cSP) in any of the subgroup analysis.

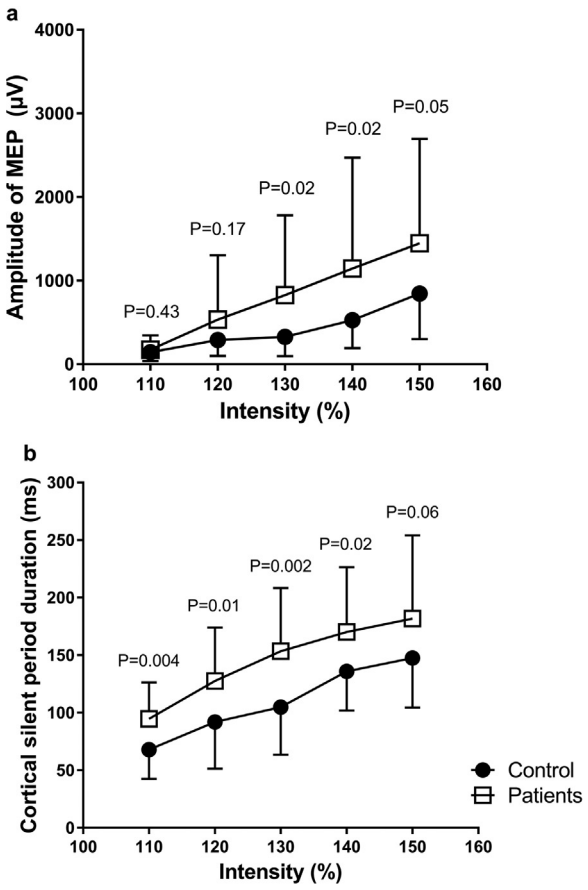


**Figure 1** a: amplitude of MEP in input/output curve (μV) at different intensities (110, 120, 130, 140, 150% of resting motor threshold, RMT). There were significantly higher amplitudes in patients compared to controls (at 110, 120, 130, 140% of RMT) and a significant interaction between the curves (*P* = 0.03); b: duration of the contralateral silent period at different intensities (130, 140, 150% of resting motor threshold). There was significantly longer CSP duration in patients (at 110, 120, 130, and 140% of RMT).

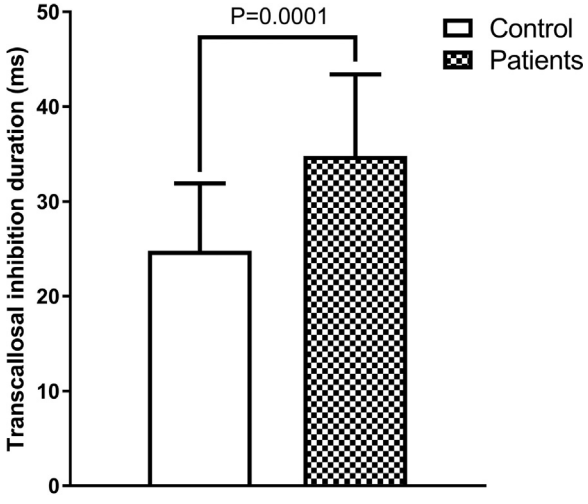


**Figure 2** Ipsilateral silent period duration (iSP). The iSP duration was longer in patients than in controls (*P* = 0.0001).

**Table 2** Cortical excitability parameters of patients and controls.

| | Patients, $n = 22$, mean ± SD | Controls, $n = 20$, mean ± SD | *P*-value | Repeated measure analysis (time × groups) |
|---|---|---|---|---|
| Age (years) | 41.5 ± 14.6 | 40.8 ± 19.8 | 0.91 | |
| rMT (%) | 42.2 ± 5.8 | 42.6 ± 6.2 | 0.83 | |
| aMT (%) | 36.0 ± 5.4 | 34.9 ± 5.7 | 0.52 | |
| I/O curve (μV) | | | | F = 3.6, df = 1.6 (65), and *P* = 0.03 |
| 110% | 172.1 ± 172.2 | 143.9 ± 106.9 | 0.43 | |
| 120% | 532.9 ± 771.3 | 288.9 ± 190.7 | 0.17 | |
| 130% | 824.9 ± 957.1 | 326.5 ± 230.9 | 0.02 | |
| 140% | 1143.9 ± 1327.8 | 526.8 ± 335.7 | 0.02 | |
| 150% | 1445.6 ± 1250.7 | 843.3 ± 545.1 | 0.05 | |
| cSP (ms) | | | | F = 0.89, df = 2.6 (104), and *P* = 0.43 |
| 110% | 94.7 ± 31.7 | 67.9 ± 25.3 | 0.004 | |
| 120% | 127.7 ± 46.4 | 91.9 ± 40.7 | 0.01 | |
| 130% | 153.4 ± 55.0 | 104.9 ± 41.5 | 0.002 | |
| 140% | 170.1 ± 56.4 | 135.9 ± 34.1 | 0.02 | |
| 150% | 181.8 ± 72.3 | 147.6 ± 43.1 | 0.06 | |
| iSP (ms) | 34.8 ± 8.6 | 24.8 ± 7.1 | 0.0001 | |

rMT: resting motor threshold; aMT: active motor threshold; CSP: cortical silent period; iSP: ipsilateral silent period; I/O: input/output curve.

**Table 3A** Cortical excitability parameters according to the type of antipsychotic drugs.

| Parameters of cortical excitability | 1st generation (5 patients) | 2nd generation (4 patients) | 1st + 2nd generation (13 patients) | One-way ANOVA between groups (*P*-value) | Two-way ANOVA (intensity × groups) |
|---|---|---|---|---|---|
| rMT (%) | 39.8 ± 6.4 | 43.3 ± 2.2 | 42.8 ± 6.4 | 0.59 | |
| aMT (%) | 33.8 ± 7.5 | 37.00 ± 2.2 | 36.5 ± 5.3 | 0.60 | |
| I/O curve (μV) | | | | | F = 0.75, df = 3.0 (29), *P* = 0.72 |
| 110% | 123.9 ± 63.4 | 94.4 ± 45.2 | 214.6 ± 140.3 | 0.14 | |
| 120% | 306.1 ± 278.3 | 134.4 ± 111.8 | 742.9 ± 943.4 | 0.30 | |
| 130% | 524.2 ± 492.9 | 359.9 ± 423.5 | 1083.7 ± 1137.9 | 0.31 | |
| 140% | 924 ± 1164.9 | 564.2 ± 649.9 | 1406.9 ± 1223.7 | 0.40 | |
| 150% | 1257.8 ± 1267.6 | 987.7 ± 828.7 | 1658.8 ± 1533.6 | 0.60 | |
| cSP (ms) | | | | | F = 2.1, df = 3.9 (37), *P* = 0.09 |
| 110% | 115.1 ± 35.6 | 76.5 ± 37.2 | 92.5 ± 26.5 | 0.18 | |
| 120% | 143.7 ± 58.4 | 96.7 ± 45.7 | 131.2 ± 45.1 | 0.30 | |
| 130% | 148.7 ± 49.0 | 104.7 ± 49.7 | 170.2 ± 52.7 | 0.10 | |
| 140% | 163.4 ± 47.8 | 126.6 ± 47.8 | 186.1 ± 57.4 | 0.14 | |
| 150% | 177.5 ± 50.0 | 123.5 ± 76.6 | 201.6 ± 72.7 | 0.16 | |
| iSP (ms) | 37.3 ± 10.6 | 26.1 ± 9.6 | 36.5 ± 6.2 | 0.07 | |

rMT: resting motor threshold; aMT: active motor threshold; CSP: cortical silent period; iSP: ipsilateral silent period; I/O: input/output curve.

## Discussion

The main finding of this study was that despite similar thresholds, MEPs were larger in patients than the healthy control group. There was also a significant prolongation of both the iSP and cSP (at 110, 120, 130, 140% of rMT). The results are opposite to those described in early Sydenham chorea reported by Khedr et al. [8].

### Motor thresholds

These TMS measures probe a range of physiological functions in motor cortex. MT is the minimum TMS intensity required to evoke an EMG response and is thought to reflect axonal membrane excitability, since it is increased following medication with voltage-gated sodium channel blockers [21], but unaffected by drugs which modulate GABAergic or

**Table 3B** Cortical excitability parameters according to the type of psychiatric illness.

| | Schizophrenia (13 patients) | Mood disorders (9 patients) | One-way ANOVA between groups (*P*-value) | Two-way ANOVA (intensity × groups) |
|---|---|---|---|---|
| rMT (%) | 42.9 ± 3.4 | 41.7 ± 7.1 | 0.60 | |
| aMT (%) | 36.2 ± 3.6 | 35.8 ± 6.5 | 0.86 | |
| I/O curve (μV) | | | | F = 0.49, df = 1.7 (34), *P* = 0.58 |
| 110% | 209.3 ± 125.7 | 146.4 ± 119.8 | 0.25 | |
| 120% | 544.3 ± 464.4 | 525.2 ± 947.2 | 0.95 | |
| 130% | 817.9 ± 819.4 | 829.8 ± 1074.9 | 0.97 | |
| 140% | 1117.3 ± 1069.3 | 1122.9 ± 1208.4 | 0.91 | |
| 150% | 1387.3 ± 1079.2 | 1485.9 ± 1566.8 | 0.87 | |
| cSP (ms) | | | | F = 1.8, df = 4.4, *P* = 0.141 |
| 110% | 89.5 ± 35.1 | 98.3 ± 30.1 | 0.343 | |
| 120% | 119.9 ± 51.9 | 133.1 ± 43.5 | 0.287 | |
| 130% | 148.0 ± 59.7 | 151.8 ± 53.7 | 0.124 | |
| 140% | 159.5 ± 52.1 | 177.4 ± 60.1 | 0.079 | |
| 150% | 164.3 ± 68.3 | 194.0 ± 75.1 | 0.022 | |
| iSP (ms) | 34.0 ± 10.7 | 35.3 ± 7.3 | 0.158 | |

rMT: resting motor threshold; aMT: active motor threshold; CSP: cortical silent period; iSP: ipsilateral silent period; I/O: input/output curve.

**Table 3C** Cortical excitability parameters according to the type of tardive symptoms.

| | Tardive dyskinesia (10 patients) | Tardive tremors (12 patients) | One-way ANOVA between groups (*P*-value) | Two-way ANOVA (intensity × groups) |
|---|---|---|---|---|
| rMT (%) | 40.9 ± 4.4 | 43.3 ± 6.8 | 0.33 | |
| aMT (%) | 35.2 ± 5.6 | 36.6 ± 5.6 | 0.53 | |
| I/O curve (μV) | | | | F = 2.1, df = 1.6 (32), *P* = 0.14 |
| 110% | 139.8 ± 67.6 | 199.1 ± 152.9 | 0.24 | |
| 120% | 269.8 ± 249.8 | 752.4 ± 984.6 | 0.12 | |
| 130% | 485.1 ± 664.2 | 1108.2 ± 1093.4 | 0.17 | |
| 140% | 687.4 ± 772.9 | 1524.4 ± 1277.5 | 0.07 | |
| 150% | 951.6 ± 962.9 | 1857.3 ± 1522.5 | 0.10 | |
| cSP (ms) | | | | F = 0.69, df = 1.7 (33), *P* = 0.48 |
| 110% | 88.9 ± 40.0 | 99.5 ± 23.6 | 0.47 | |
| 120% | 111.2 ± 50.4 | 141.5 ± 39.8 | 0.14 | |
| 130% | 140.0 ± 57.5 | 164.5 ± 52.7 | 0.31 | |
| 140% | 150.1 ± 59.3 | 186.7 ± 50.2 | 0.13 | |
| 150% | 171.6 ± 85.1 | 190.5 ± 62.3 | 0.56 | |
| iSP (ms) | 34.1 ± 11.1 | 35.3 ± 6.4 | 0.76 | |

rMT: resting motor threshold; aMT; I/O: input-output curve; active motor threshold; cSP: contralateral silent period; iSP: ipsilateral silent period.

glutamatergic transmission [21,22]. The fact that MT was normal in patients suggests that TS is not due to a long-term effect of antipsychotic drugs on the excitability of axonal membranes.

## Input—output relationship

The I/O curve measures how the amplitude of the MEP varies with TMS intensity. Because the MEP is produced by activity in corticospinal fibers that excite spinal motoneurons, the I/O curve gives an indication of how easily a TMS pulse can evoke corticospinal activity. Interestingly, TMS itself does not stimulate corticospinal neurons directly; instead, it activates neurons that have synaptic inputs to corticospinal neurons. Thus, the I/O curve gives information about the excitability of inputs to corticospinal output neurons. As we argued in the Introduction section, it has been proposed that TS results from a disorder of synaptic plasticity that

reduces the selectivity of motor commands. The fact that we observed increased I/O curves in TS is compatible with this idea, since it would predict increased access of synaptic inputs to corticospinal output.

Note that the increased I/O curve is unlikely to be a direct effect of antipsychotic drugs since all patients had stopped treatment few weeks (2—3 weeks) before assessment. It therefore seems likely that antipsychotic treatment in some individuals causes a long-term change in synaptic mechanisms that does not reverse after stopping treatment. The patients' current medications are not known to have effects on I/O slope [29]. The changes are also unlikely to be a direct result of long-term changes in the excitability of dopamine receptors in TS since dopaminergic drugs have been reported to have no effect on corticospinal excitability, at least in single dose studies in healthy adults [29].

## Silent periods

The cSP and iSP are both thought to involve activity in GABAb receptor-mediated systems [22,25]. Interestingly, the cSP duration at lower stimulus intensities (110% and 120% of MT) could reflect activation of GABAa receptors, whereas the longer cSP at higher stimulus intensities (140% of MT) may reflect the activation of GABAb receptors [17]. Thus, the tendency for both cSP and iSP to be longer in patients might suggest that these GABAergic connections are more excitable in patients.

However, several groups have noted that the duration of the cSP depends on the amplitude of the MEP [16,24]. In the present case, patients have a larger MEP for a given intensity of stimulation than the control group. Thus, it could be that the longer cSP, is a secondary consequence of the larger MEPs. Examination of the I/O slope and the cSP-intensity relationship suggest that this is a likely possibility. If we assume that the EMG activity in patients and controls is comparable (i.e. that the compound muscle action potential to supramaximal peripheral nerve stimulation is the same in each group) then the MEP evoked at 150% intensity in controls is approximately equal in size to the MEP evoked by 130% intensity in patients. Looking at the cSP-intensity relationship shows that the duration of the cSP at 130%, is 140 ms in patients which is similar to that measured in controls at 150%, consistent with the notion that the changes in cSP are secondary to differences in MEP amplitude in patients and controls.

There is no data on the relationship between iSP duration and MEP amplitude. However, the iSP is produced by activation of pyramidal neurons in layer III of cortex. If these have an increased excitability similar to that of the corticospinal neurons of layer V that produce the MEP, then this may account for the longer iSP.

Another possibility is that the changes in cSP and iSP are related to the underlying psychiatric condition of the patients. However, in many cases these are the opposite to what we observed although the literature suggests a complex interaction between pathology and drug treatment. For example, Wobrock et al. [26] reported that patients with limited exposure to drugs have longer cSP, whereas Liu et al. [13] found treatment resistant patients to have shorter cSP. The effect of drug treatment is also unclear. Clozapine and quetiapine increase cSP [12,19], whereas the atypical neuroleptic olanzapine and the classical neuroleptic haloperidol do not alter cSP duration in healthy subjects [4]. Note that since we did not measure the maximum compound muscle action potential the possibilities of drug-induced changes at the level of neuromuscular junction or spinal motoneuron cannot be excluded.

## Comparison with other movement disorders

There is a large literature on responses to TMS in patients with movement disorders. We will focus the discussion here on corticospinal excitability since this was the major abnormality that we observed in TS. In general, excitability has been reported to be reduced in Parkinson's disease [20], whereas in other pathological hyperkinesias such as Huntington's disease or Sydenham's chorea, it is reduced [8,21] or normal in Huntington's disease: [18]. Dystonia is usually reported to have abnormal excitability [14]. In the hyperkinetic disorders, reduced excitability is sometimes seen as a possible compensatory mechanism that tries to reduce the over-excitability of basal ganglia output. Since this does not occur in drug-induced disorders, (even though there has been plenty of time for long-term changes to happen), it points to a rather different pathophysiology. The ''natural'' conditions might have more specific pathology in basal ganglia, whereas the drug-induced deficit could be much more widespread.

To the best of our knowledge, this is the first study to describe abnormalities of cortical excitability using TMS in subjects with tardive syndrome. These preliminary findings indicate that corticospinal output is hyperexcitable in individuals with TS. If so, then one potential avenue for treatment might be to induce long-term depression (LTD) using forms of rTMS or tDCS to reduce excitability. Further work on the physiological characterization of the TS population is needed with increased sample size and classification into different subtypes of TS. Drug-induced changes at the level of neuromuscular junction or spinal motoneuron should also be examined in further studies.

## Disclosure of interest

The authors declare that they have no competing interest.

## References

[1] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington, VA: American Psychiatric Association; 2013 [712 p.].

[2] Bhidayasiri R, Boonyawairoj S. Spectrum of tardive syndromes: clinical recognition and management. Postgrad Med J 2011;87:132—41.

[3] Correll CU, Leucht S, Kane JM. Lower risk for tardive dyskinesia associated with second-generation antipsychotics: a systematic review of 1-year studies. Am J Psychiatry 2004;161:414—25.

[4] Daskalakis ZJ, Christensen BK, Chen R, Fitzgerald PB, Zipursky RB, Kapur S. Effect of antipsychotics on cortical inhibition using transcranial magnetic stimulation. Psychopharmacology (Berl) 2003;170:255—62.

[5] Fernandez HH, Friedman JH. Classification and treatment of tardive syndromes. Neurologist 2003;9:16—27.
[6] Gebhardt S, Hartling F, Hanke M, Mittendorf M, Theisen FM, Wolf-Ostermann K, et al. Prevalence of movement disorders in adolescent patients with schizophrenia and in relationship to predominantly atypical antipsychotic treatment. Eur Child Adolesc Psychiatry 2006;15:371—82.
[7] Guy W. ECDEU Assessment Manual for Psychopharmacology: revised (DHEW publication number ADM 76-338). Rockville, MD: US Department of Health, Education and Welfare, Public Health Service, Alcohol, Drug Abuse and Mental Health Administration, NIMH Psychopharmacology Research Branch, Division of Extramural Research Programs; 1976. p. 534—7.
[8] Khedr EM, Ahmed MA, Ali AM, Badry R, Rothwell JC. Changes in motor cortical excitability in patients with Sydenham's chorea. Mov Disord 2015;30:259—62.
[9] Khedr EM, Gabra RH, Noaman M, Abo Elfetoh N, Farghaly HS. Cortical excitability in tramadol dependent patients: a transcranial magnetic stimulation study. Drug Alcohol Depend 2016;169:110—6.
[10] Khedr EM, Elbeh KA, Elserogy Y, Khalifa HE, Ahmed MA, Hafez MH, et al. Motor cortical excitability in obsessive-compulsive disorder: transcranial magnetic stimulation study. Neurophysiol Clin 2016;46:135—43.
[11] Kim J, Macmaster E, Schwartz TL. Tardive dyskinesia in patients treated with atypical antipsychotics: case series and brief review of etiologic and treatment considerations. Drugs Context 2014;3:212259.
[12] Langguth B, Eichhammer P, Spranz C, Landgrebe M, Frick U, Sand P, et al. Modulation of human motor cortex excitability by quetiapine. Psychopharmacology (Berl) 2008;196:623—9.
[13] Liu SK, Fitzgerald PB, Daigle M, Chen R, Daskalakis ZJ. The relationship between cortical inhibition, antipsychotic treatment, and the symptoms of schizophrenia. Biol Psychiatry 2009;65:503—9.
[14] Lozeron P, Poujois A, Richard A, Masmoudi S, Meppiel E, Woimant F, et al. Contribution of TMS and rTMS in the understanding of the pathophysiology and in the treatment of dystonia. Front Neural Circuits 2016;10:90.
[15] Nitsche MA, Grundey J, Liebetanz D, Lang N, Tergau F, Paulus W. Catecholaminergic consolidation of motor cortical neuroplasticity in humans. Cereb Cortex 2004;14:1240—5.
[16] Orth M, Rothwell JC. The cortical silent period: intrinsic variability and relation to the waveform of the transcranial magnetic stimulation pulse. Clin Neurophysiol 2004;115:1076—82.
[17] Paulus W, Classen J, Cohen LG, Large CH, Di Lazzaro V, Nitsche M, et al. State of the art: pharmacologic effects on cortical excitability measures tested by transcranial magnetic stimulation. Brain Stimul 2008;1:151—63.
[18] Philpott AL, Cummins TDR, Bailey NW, Churchyard A, Fitzgerald PB, Georgiou-Karistianis N. Cortical inhibitory deficits in premanifest and early Huntington's disease. Behav Brain Res 2016;296:311—7.
[19] Radhu N, de Jesus DR, Ravindran LN, Zanjani A, Fitzgerald PB, Daskalakis ZJ. A meta-analysis of cortical inhibition and excitability using transcranial magnetic stimulation in psychiatric disorders. Clin Neurophysiol 2013;124:1309—20.
[20] Rothwell JC, Edwards MJ. Parkinson's disease. Handb Clin Neurol 2013;116:535—42.
[21] Schippling S, Schneider SA, Bhatia KP, Münchau A, Rothwell JC, Tabrizi SJ, et al. Abnormal motor cortex excitability in preclinical and very early Huntington's disease. Biol Psychiatry 2009;65:959—65.
[22] Siebner HR, Dressnandt J, Auer C, Conrad B. Continuous intrathecal baclofen infusions induced a marked increase of the transcranially evoked silent period in a patient with generalized dystonia. Muscle Nerve 1998;21:1209—12.
[23] Teo JT, Edwards MJ, Bhatia K. Tardive dyskinesia is caused by maladaptive synaptic plasticity: a hypothesis. Mov Disord 2012;27:1205—15.
[24] Werhahn KJ, Behrang-Nia M, Bott MC, Klimpe S. Does the recruitment of excitation and inhibition in the motor cortex differ? J Clin Neurophysiol 2007;24:419—23.
[25] Werhahn KJ, Kunesch E, Noachtar S, Benecke R, Classen J. Differential effects on motorcortical inhibition induced by blockade of GABA uptake in humans. J Physiol 1999;517:591—7.
[26] Wobrock T, Schneider-Axmann T, Retz W, Rösler M, Kadovic D, Falkai P, et al. Motor circuit abnormalities in first-episode schizophrenia assessed with transcranial magnetic stimulation. Pharmacopsychiatry 2009;42:194—201.
[27] Yassa R, Jones BD. Complications of tardive dyskinesia: a review. Psychosomatics 1985;26:305—13.
[28] Ziemann U, Netz J, Szelenyi A, Homberg V. Spinal and supraspinal mechanisms contribute to the silent period in the contracting soleus muscle after transcranial magnetic stimulation of human motor cortex. Neurosci Lett 1993;156:167—71.
[29] Ziemann U, Reis J, Schwenkreis P, Rosanova M, Strafella A, Badawy R, et al. TMS and drugs revisited 2014. Clin Neurophysiol 2015;126:1847—68.