Evidence for a developmental delay in brain maturation in Tourette syndrome: a multicentre mega-analysis of TMS data

MRC International Tic Research Partnership

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We report a multi-centre mega-analysis examining how motor cortex excitability develops across childhood, adolescence, and adulthood in Tourette syndrome (TS).

We pooled resting motor threshold (RMT) data collected using TMS from **415 participants** (229 with TS; 186 neurotypical controls; CS) collected at **11 international research centres**. Individuals ranged in age from 8-48 years, (mean age: CS = 20 ± 7.9 years, TS = 18.7 ± 7.2 years). The groups did not differ in age or in the proportion of males and females in each group. These data allowed us to ask a fundamental question:

Does the maturation of motor excitability follow a different developmental trajectory in individuals with TS?

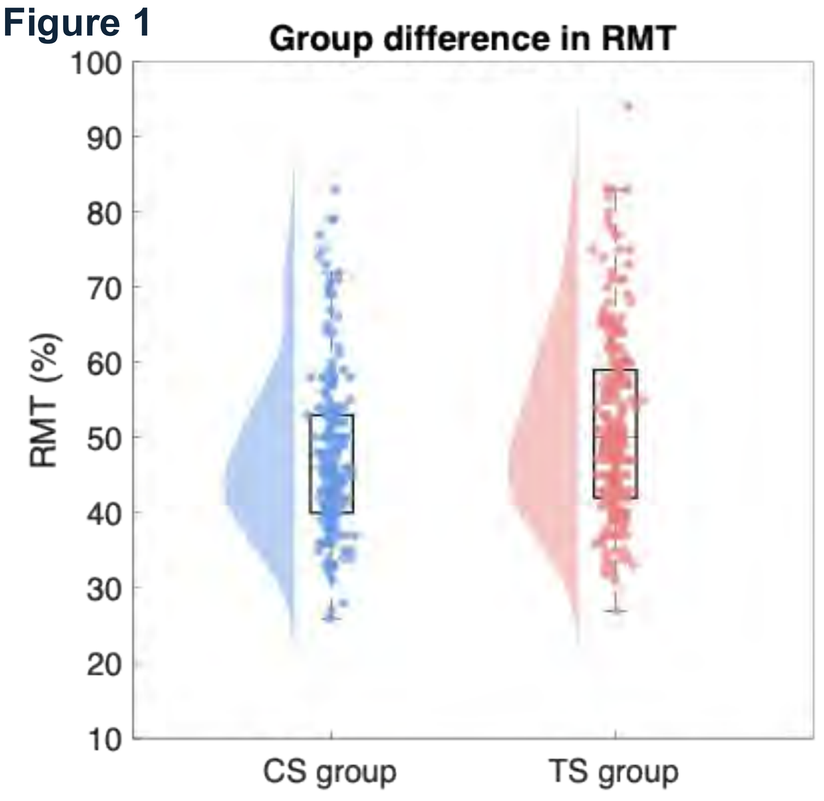
Key Findings

Preliminary multiple regression analysis demonstrated that RMT values were predicted by Age, Group, and the Age x Group interaction ($F = 24.0$, $R^2 = 0.15$, $p < 0.001$)

- **Age**: $\beta = -1.0$, $t = -4.5$, $p < 0.001$
- **Group**: $\beta = -9.3$, $t = -3.14$, $p < 0.002$
- **Group x Age** = 0.32, $t = 2.24$, $p < 0.03$

Group RMT (% mean stimulator output; MSO) are displayed in Figure 1 and Table 1.

Figure 1



1 Children and adolescents with TS show higher RMT than controls

Although previous studies have been inconsistent, our large sample confirms that RMT is significantly elevated in TS — but crucially, this difference is driven by differences in the **rate at which RMT decreases** with age across adolescence, and the **age at which RMT plateaus** in adulthood.

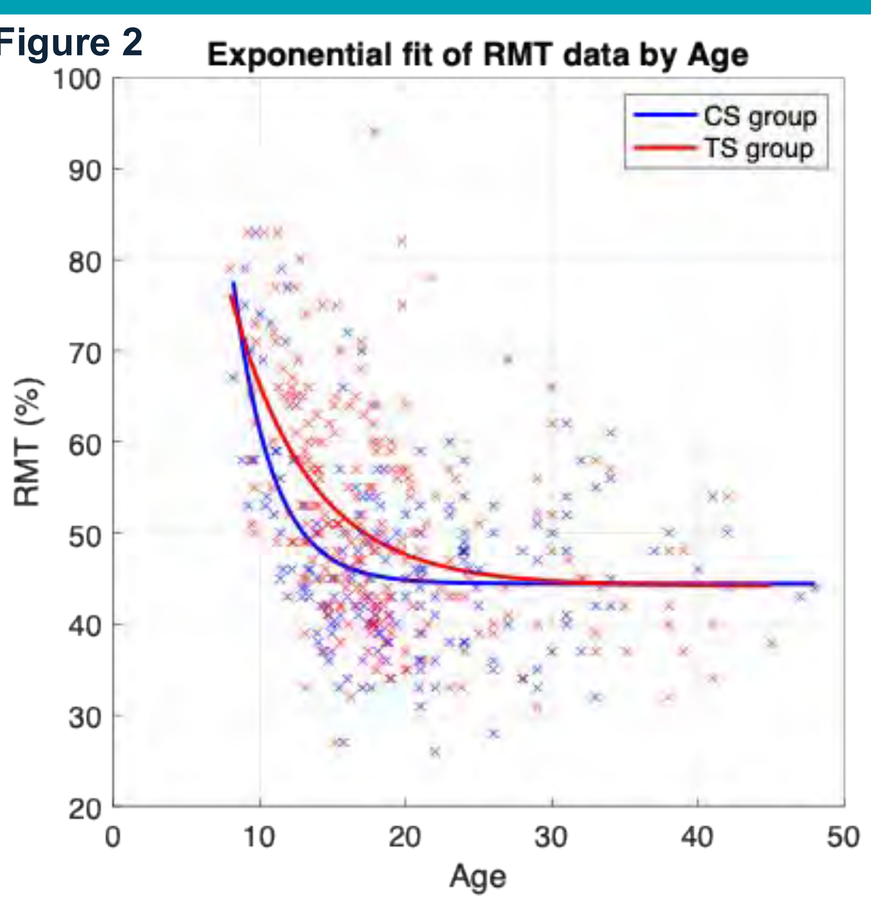
2 Adults with TS do *not* differ from neurotypical adults

Once individuals reach adulthood, RMT levels converge. This suggests that motor cortex excitability ultimately normalises.

Table 1 **Resting motor threshold** (%MSO; mean±SD)

	Children and Adolescents	Adults
CS	47.8 ± 10.9 %	45.2 ± 8.5 %
TS	51.6 ± 12.1 % t(413) = -3.32, p = 0.001	44.5 ± 8.6 % t(190) = 0.4, p = 0.7

Figure 2



3 The developmental trajectory is delayed in TS

- Neurotypical individuals reach adult-like RMT levels by **~12.4 years**.
- Individuals with TS do not reach this level until **~24.8 years**.

This represents a **~12-year developmental delay** in the maturation of motor excitability (asymptote difference = 12.4 years, $p = 0.008$; Difference in rate of decrease in RMT (k) = 0.19, $p = 0.004$)

4 Tic severity does not predict RMT

YGTSS motor and phonic scores were not associated with RMT, suggesting that RMT reflects underlying neurodevelopment rather than symptom severity.

What this means

Our findings support the idea that TS involves a delay in the maturation of motor control networks, rather than a fixed abnormality. This aligns with the clinical course of TS, where many young people experience improvement in tics during adolescence as control networks develop.

Why it matters

Understanding the developmental trajectory of cortical excitability in TS may help:

- Explain why some individuals improve with age while others do not
- Identify biomarkers of atypical neurodevelopment
- Guide neuromodulation-based interventions targeting motor control circuits

This work represents the largest analysis of motor excitability in TS to date and highlights the importance of developmental neuroscience in understanding tic disorders.