

Running head: Imitation inhibition in Tourette children

Imitation inhibition in children with Tourette syndrome

**Valerie Cathérine Brandt^{1,2*}, Agnes Moczydlowski³, Melanie Jonas⁴, Kai Boelmans⁵, Tobias
Bäumer¹, Marcel Brass⁶, Alexander Münchau¹**

¹ Department of Paediatric and Adult Movement Disorders and Neuropsychiatry, Institute of Neurogenetics, University of Lübeck, Lübeck, Germany

² Department of Psychology, University of Southampton, Southampton, UK

³ Department of Neurology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

⁴ Department of Human Resources, Health and Social Affairs, Fachhochschule des Mittelstands - University of Applied Sciences, Köln, Germany

⁵ Department of Neurology, Julius-Maximilians-University, Würzburg, Germany

⁶ Department of Experimental Psychology, Ghent University, Henri Dunantlaan 2, 9000 Ghent, Belgium

Word count (exc. abstract, figures/tables and references): 3987

***Requests for reprints should be addressed to:**

Valerie Brandt

¹ Department of Paediatric and Adult Movement Disorders and Neuropsychiatry,

Institute of Neurogenetics, University of Lübeck,
Maria-Goeppert-Str. 1, 23562 Lübeck, Germany

valerie.brandt@neuro.uni-luebeck.de

Tel: +49-451-2903-422

Fax: +49-451-2903-423

²Institute of Psychology

Building 44, Highfield Campus

University of Southampton

SO17 1BJ Southampton, UK

E-mail: V.C.Brandt@soton.ac.uk

Abstract

Objective: Echopraxia, i.e. the open and automatic imitation of other peoples' actions, is common in patients with Gilles de la Tourette syndrome, autism spectrum disorder, and also those with frontal lobe lesions. While systematic reaction time tasks have confirmed increased automatic imitation in the latter two groups, adult patients with Tourette syndrome appear to compensate for automatic imitation tendencies by an overall slowing in response times. However, whether children with Tourette syndrome are already able to inhibit automatic imitation tendencies has not been investigated.

Method: Fifteen children with Tourette syndrome and 15 healthy children (aged 7-12 years) performed an imitation inhibition paradigm. Participants were asked to respond to an auditory cue by lifting their index finger or their little finger. Participants were simultaneously presented with either compatible or incompatible visual stimuli.

Results: Overall responses in children with Tourette syndrome were slower than in healthy children. Although responses were faster in compatible than in incompatible trials in both groups, this "interference effect" was smaller in children with Tourette syndrome.

Conclusions: Children with Tourette syndrome have a smaller interference effect than healthy children, indicating an enhanced ability to behaviourally control automatic imitation tendencies at the cost of reacting slower. The results suggest that children with Tourette syndrome already employ different or additional inhibition strategies compared to healthy children.

Keywords: imitation; inhibition; Tourette syndrome; tic; mirror neuron system; echopraxia

Theoretical Background

Gilles de la Tourette syndrome (GTS) is a common developmental neuropsychiatric disorder characterized by multiple motor and phonic tics. A recent meta-analysis estimates the population prevalence of GTS to be 0.3-0.9% in children (Scharf et al., 2015). First symptoms typically occur around the age of 5-7 years (Robertson, 2011), peak around the age of 10 years (Schlander, Schwarz, Rothenberger, & Roessner, 2011) but subside in 59-85% of patients when entering adulthood (Hassan & Cavanna, 2012; Pappert, Goetz, Louis, Blasucci, & Leurgans, 2003). Overall, GTS is 3–4:1 times more likely to occur in males than in females (Centers for Disease & Prevention, 2009; Robertson, 2008).

Echophenomena are a common feature of GTS (Finis et al., 2012; Ganos, Ogrzal, Schnitzler, & Munchau, 2012) and occur in approximately 50% of patients (Finis et al., 2012; Muller et al., 1997; Robertson, Trimble, & Lees, 1988). Echopraxia refers to the tendency to automatically imitate observed behaviour such as gestures and facial movements, echolalia refers to the tendency to imitate vocal expressions. GTS is not the only disorder displaying imitation over and above the normal range. Echopraxia has been reported in patients with frontal lesions (De Renzi, Cavalleri, & Facchini, 1996; Lhermitte, Pillon, & Serdaru, 1986) and patients with an autism spectrum disorder (ASD; Williams, Whiten, & Singh, 2004) but very little research exists on this phenomenon.

A general tendency to imitate might be based on the human mirror neuron system (MNS), a cortical circuit encompassing the inferior frontal gyrus, the inferior parietal lobe, the superior temporal lobe, and the premotor cortex (for meta-analysis and review see Iacoboni & Dapretto, 2006; Molenberghs, Cunnington, & Mattingley, 2012; Rizzolatti, Cattaneo, Fabbri-Destro, & Rozzi, 2014). First discovered in Macaque monkeys (Gallese, Fadiga, Fogassi, & Rizzolatti, 1996;

Rizzolatti, Fadiga, Gallese, & Fogassi, 1996), mirror neurons (or mirror areas in humans, respectively) are active both during the execution of own movements and the observation of the same movements executed by others (di Pellegrino, Fadiga, Fogassi, Gallese, & Rizzolatti, 1992; Gallese et al., 1996; Rizzolatti et al., 1996). One of the most compelling questions in motor learning and social development is how and when MNS functions develop in normally and abnormally developing children (for a review see Vanderwert, Fox, & Ferrari, 2013).

The imitation inhibition paradigm is a paradigm that can systematically and sensitively assess dysfunctions of imitation tendencies by requiring motor responses that are either compatible or incompatible with a visual stimulus displaying a movement (Brass, Bekkering, Wohlschläger, & Prinz, 2000). Research in ASD patients and patients with frontal lesions showed that both groups have difficulties inhibiting imitative tendencies compared with healthy controls, i.e. they showed an increased number of errors when the movement that had to be executed was incompatible with the movements shown on the screen (Brass, Derrfuss, Matthes-von Cramon, & von Cramon, 2003; Spengler, Bird, & Brass, 2010). Unlike ASD patients and patients with frontal lesions, adult GTS patients do not show an increased interference effect compared with healthy controls (Jonas et al., 2010). However, their response pattern points to a compensatory mechanism, whereby adult GTS patients exert increased top-down control over their movements in settings where motor responses are required to observed biological movements rather than, for instance, moving objects (Ganos et al., 2012; Jonas et al., 2010).

If GTS patients develop a compensatory mechanism as a response to the increased tendency to imitate movements, it is of interest to investigate whether this compensation might not yet occur in childhood. The present study employed the imitation inhibition paradigm described above in children with GTS and healthy children aged 7-12 years. Clinical observations suggest that

children with GTS at this age show echopractic behaviour. We hypothesized that the assumed compensatory mechanisms might not have (fully) developed at this age. Therefore, we expected that children with GTS would show increased interference in response to biological movements compared to healthy children.

Methods and Materials

Participants

Data of 15 children with GTS (7-12 years, mean 9.13+/-1.81 years; 11 male) were compared with data of 15 neurologically and psychiatrically healthy, age-matched controls (7-12 years, mean 9.87+/-1.77 years; 8 male). The inclusion criterion for the GTS group was fulfilment of DSM-5 diagnostic criteria for GTS. Anxiety, OCD and ADHD as co-morbidities were not grounds for exclusion but we attempted to only recruit children with “pure” GTS. Exclusion criteria for the healthy groups were tics, another movement disorder, OCD, and ADHD.

None of the GTS patients had clinically relevant psychiatric comorbidities according to DSM-5 diagnostic criteria (American Psychiatric Association, 2013). Two patients were taking medication for their tics at the time of study (tiapride/aripiprazole). Children with GTS were diagnosed in a GTS consultation hour (GTS diagnosis, OCD, ADHD, as well as anxiety disorders, depression and oppositional defiant disorder where indicated, according to DSM-5) in the outpatient Department of the Neurology Department of Hamburg University Medical Center.

Healthy children were partly non-symptomatic siblings of children diagnosed with GTS (n = 1) and were partly recruited via bulletin boards. All healthy children were pre-screened together with their parents by a clinician administering a number of clinical questionnaires (see below). Three children had to be rejected for the healthy control group because they had motor tics.

Additionally, all children were filmed during the task and videos of the healthy controls were later reviewed for tics. Parents gave their written informed consent to the participation of their children in the study, as well as all videos taken during the study. The study followed the provisions of the Declaration of Helsinki and was approved and confirmed by the local Ethics Committee.

Measures

Tic severity was measured with the Yale Global Tic Severity Scale (YGTSS; Leckman et al., 1989). The YGTSS is a clinician-rated tic scale and has been shown to have high internal consistency, stability and convergent as well as discriminant validity (Storch et al., 2005). ADHD was assessed based on the DSM-IV ADHD diagnostic checklist (ADHD-DC; Rösler, Retz-Junginger, Retz, & Stieglitz, 2008), a checklist assessing ADHD symptoms according to the DSM-IV with good inter-rater reliability and convergent validity (Schmidt & Petermann, 2008). The scale is applicable to DSM-5 criteria but does not contain symptom severity ratings. Obsessive-compulsive disorder (OCD) was assessed using the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS; Goodman et al., 1989; Uher, Heyman, Turner, & Shafran, 2008). The CY-BOCS contains an OCD symptom checklist and a structured clinical interview with very good convergent validity and good discriminant validity (Gallant et al., 2008), as well as good reliability (Lopez-Pina et al., 2015). Cognitive skills were assessed by 6 subtests (vocabulary, block design, picture completion, letter-number sequencing and coding) of the fourth German version of the “Wechsler Intelligence Scale For Children” (WISC-IV; German: HAWIK-IV; Wechsler, 2004), which has been shown to have very good reliability (Petermann & Petermann, 2008) and validity (Hagmann-von Arx, Grob, Petermann, & Daseking, 2012). School degree (number of years) of the parents was assessed as an indicator of socio-economic status.

Experimental Stimuli and Procedure

Experiment 1

A simple imitation paradigm was used as previously described (Biermann-Ruben et al., 2008; Jonas et al., 2010) to test whether participants showed the expected facilitation in responding to biological as compared to non-biological movements. Participants were placed in front of the monitor at a distance of 60cm. The index and little finger were placed on a custom-made opto-electronic device recording up and down movements of the fingers (Biermann-Ruben et al., 2008; Jonas et al., 2007).

Participants were presented with stimuli displaying a left hand on a white background and were asked to respond with their right hand. This creates a “mirror-fashion” imitation situation (Koski, Iacoboni, Dubeau, Woods, & Mazziotta, 2003), which is preferred over an “anatomically correct” imitation (Koski et al., 2003). Two red dots marked the fingernails of the index and the little finger and a white fixation cross was fixed in the middle of the screen. Participants were then presented with biological and non-biological picture stimuli: (i) raising and lowering of the index or little finger including a red dot marking the fingernail (finger & dot movement), (ii) only the red dot moving up and down while fingers remained static (dot movement; see Figure 1).

Participants were asked to simply imitate the movement on the screen as quickly as possible, irrespective of whether it was a finger- or a dot movement. All participants completed 72 trials of this simple imitation task.

Experiment 2

Prior to the start of the main imitation inhibition task, participants were trained (40 trials)

to lift their index finger or their little finger in response to a high-pitched or a low-pitched auditory cue respectively. Finger to auditory cue assignment was pseudo-randomized across participants.

Participants were then instructed to watch the presented movement stimuli closely but only to react in response to an auditory cue, not the movement on the screen. All participants were filmed throughout the experiment to ensure that they were watching the stimuli. Movements displayed on the screen were either biological or non-biological ('Type of Movement'), and compatible or incompatible with the movement instructed by the cue ('Compatibility'). Cues were presented either at the beginning 'onset presentation' or after the completion of the movement stimulus 'offset presentation' ('Presentation Mode'). All participants completed 20 practice trials before starting the main task, consisting of 200 trials.

Data Analysis

RT was defined as the time between the presentation of an auditory cue and the onset of the movement. Only correct responses as well as RTs slower than 100ms and faster than 2000ms were included in the RT analysis. Linear mixed models were used to analyse RT data. This analytic approach accounts for the non-independence between nested observations (multiple observations per participant), while making use of all data points per participant (Aarts, Verhage, Veenliet, Dolan, & van der Sluis, 2014). Errors (omissions, false responses and multiple responses) were analysed separately, using repeated measures ANOVA.

Experiment 1

Regarding the simple imitation task, the variables 'Type of Movement' (biological, non-biological) and 'Group' (GTS, healthy) and their interaction were included as fixed effects factors

in a linear mixed model.

Experiment 2

Regarding the imitation inhibition task, the variables ‘Type of Movement’ (biological, non-biological), ‘Compatibility’ (compatible, incompatible), ‘Presentation Mode’ (onset, offset presentation), ‘Group’ (GTS, healthy) and their interactions were included as fixed effects factors in a linear mixed model. Confidence intervals (CI) are reported as a measure of effect size.

Correlations between tic-related questionnaire scores and median RTs as well as interference variables were performed using Pearson’s r . Additionally, a difference variable was created reflecting the size of the RT interference effect by subtracting RTs in the compatible condition from RTs in the incompatible condition and was then correlated with age using Pearson’s r . Due to the limited validity of cross-sectional study designs regarding developmental questions, this analysis was exploratory. We were interested in whether the interference effect would become smaller with increasing age in children with GTS (reflecting compensatory mechanisms). Results were considered significant if $p < 0.05$.

Results

Clinical Assessment

Table 1 shows clinical and WISC-IV scores and demographical data. According to CY-BOCS cut-off criteria, one child with GTS scored in the clinical range for OCD but did not have clinically significant OCD according to DSM criteria. There were no differences in any of the WISC-IV sub-scales between the groups, all $p \geq .1$, $d \leq .59$. All children had normal or corrected to normal vision. Information about parents’ school degrees was collected for all children with

GTS and 14 healthy controls. Mean YGTSS motor score was 10.93 +/-5.38 (range = 0 – 17), vocal tic score was 5.73 +/- 4.96 (range = 0 - 15). All patients showed suggestibility of tics on the behavioural level when screened for the study. Seven patients reported echophenomena according to the YGTSS and DCI: 4 patients reported echopraxia, 4 reported echolalia, 3 palilalia.

Behavioural Data

Experiment 1

Table 1 shows RT and error data. In the simple imitation task, the main effect of Group was not significant $F(1,28) = 3.33, p = .08, CI_{lower} = -.234, CI_{upper} = 13.55$, however, GTS patients tended to respond slower than healthy controls. There was a main effect of Type of Movement, $F(1,1225) = 7.26, p = .007, CI_{lower} = -.44.55, CI_{upper} = -7.00$, all participants responded faster to biological movements than to non-biological movements as expected. There was no interaction between Type of Movement and Group $F(1,1225) = .04, p = .84$.

Error rates did not differ significantly between GTS patients and healthy controls $t(28) = .89, p < .38, d = .34$. Total error rate was 9%.

Experiment 2

In the imitation inhibition task, children with GTS responded significantly slower than healthy controls [Group], $F(28) = 7.95, p = .009, CI_{lower} = 48.54, CI_{upper} = 306.73$, all participants showed faster responses in compatible compared with incompatible trials [Compatibility], $F(1,3997) = 91.74, p < .001, CI_{lower} = 66.33, CI_{upper} = 100.47$, and all children responded slower with onset than with offset presentation [Presentation Mode] $F(1,3997) = 7.52, p < .001, CI_{lower} = 19.37, CI_{upper} = 53.49$. Furthermore, there was a significant interaction Compatibility x Group,

$F(1,3997) = 13.70, p < .001, CI_{lower} = 48.54, CI_{upper} = .306.73$ (Figure 2).

Post-hoc t -tests showed that children with GTS had a smaller interference effect on average (60ms) than children without GTS (119ms) $t(28) = 2.07, p = .048, d = .76$ (see Figure 3a). Twelve out of the 15 children with GTS (80%) had an interference effect smaller than 119ms.

Non-significant effects on RT were found for Type of Movement $F(1,3990) = .68, p = .41$ and all remaining two- and three-way interactions involving the factors Type of Movement, Compatibility, Presentation Mode and Group: all $p \geq .1$.

Regarding error rates, the groups did not differ, $t(28) = 0.14, p = .89, d = .06$. Overall error rate was 11%. A 2 x 2 ANOVA showed that both groups made more errors in response to incompatible than to compatible trials [Compatibility], $F(1,28) = 22.48, p < .001, \eta^2 = .45$. There was no significant interaction Compatibility x Group $F(1,28) = .28, p = .6, \eta^2 = .01$ (see Figure 3b).

Median RT and error rate were unrelated across participants, $r = .07, p = .72$, suggesting that there was no speed-accuracy trade-off.

Correlations between RT tasks and sample characteristics

Age was significantly negatively correlated with RT, $r = -.59, p = .001$, and errors, $r = -.43, p = .017$. There was a substantial correlation between the RT interference measure and age in healthy children, $r = .55, p = .036$ suggesting that younger healthy children had a larger interference effect than older children. There was no such correlation between the RT interference measure and age in children with GTS, $r = .009, p = .975$.

The YGTSS motor score in children with GTS was neither substantially correlated with median RT, $r = -.08, p = .79$, nor with sum of errors, $r = .02, p = .94$. When accounting for the

effect of age, there were no significant partial correlations between the WISC-IV sub-scales and RT or number of errors in either group, all $r \leq .44$, all $p \geq .1$.

Discussion

The present study investigated the influence of compatible and incompatible visual movement stimuli on motor responses in children with and without GTS. All children exhibited interference effects, i.e. they made more errors and RTs were longer in incompatible than in compatible trials. However, the interference effect in RTs was larger in children without GTS than in children with GTS, while the interference effect in errors was comparable between the groups.

This is an unexpected finding. Typically, patients with echopraxia show larger interference effects compared with healthy controls. Previous studies using similar imitation inhibition paradigms in ASD patients and patients with frontal lesions suggest that both groups experience an enhanced interference effect in error rates, indicating a decreased ability to inhibit the tendency to imitate movements (Brass et al., 2003; Spengler et al., 2010). This effect was not found in adult GTS patients, who showed RTs and error rates similar to healthy participants. Adult GTS patients' pattern of RTs suggested that they exert increased inhibitory control when presented specifically with biological movement stimuli compared to healthy controls by responding slower overall (Jonas et al., 2010). RT slowing is often interpreted as exerting greater effort and might reflect a compensatory mechanism for an increased tendency to imitate actions in adult GTS patients (Finis et al., 2012).

The smaller interference effect in RTs in children with GTS, combined with slower overall response times, indicates that they might also exert higher "default" or "tonic" inhibition (Draper et al., 2014). It is important to note that children with GTS did not show a deficit in inhibitory

control during the task. Normal error rates and increased reaction times combined with a decreased interference effect in a group that typically shows echopractic behaviour may indicate compensation for an increased tendency to imitate actions. The results are in line with previous studies showing that motor cortex excitability is reduced in adolescents with GTS prior to voluntary movements compared to healthy adolescents (S. R. Jackson et al., 2013). Draper and colleagues (2014) also found that higher GABA levels in the SMA are associated with better control over motor cortex excitability in GTS patients and have therefore proposed that increased tonic (GABAergic) inhibition in the SMA may counter-act excessive excitatory inputs to motor areas (Draper et al., 2014).

Interestingly, the data also point to some differences in imitation inhibition between children and adults in general. In the simple imitation task (Experiment 1), specific facilitation of imitative responses to biological stimuli compared with non-biological stimuli was present in both GTS and healthy children, whereas this effect disappeared in the complex task (Experiment 2). In adults, modulation in response times to biological stimuli can be found in both tasks (Jonas et al., 2010).

Assuming that imitation of (biological) stimuli is mediated by areas of the human MNS, the difference between children and adults might be due to the natural development of the MNS and its functions. The recently proposed associative sequence learning model (ASL; e.g., (Cook, Bird, Catmur, Press, & Heyes, 2014; Heyes, 2010) states that humans are not born with a pre-set mirror neuron system but rather that such a system develops during sensorimotor learning in ontogeny. Sensory and motor neurons coding similar actions become linked through their correlated activation, for instance, when children observe themselves in a mirror or are imitated by others. Recent evidence that functional connectivity of the rostral inferior parietal area in the

MNS correlated with age in healthy participants aged 7-26 years further corroborates the notion of a developing system throughout adolescence and early adulthood (Wang et al., 2017).

While there is neurophysiological evidence in adults indicating that imitative tendencies might be controlled by a dedicated mechanism that is distinct from mechanisms controlling responses to other types of stimuli (Cross, Torrisi, Reynolds Losin, & Iacoboni, 2013), it has not yet been studied whether children do already recruit different control mechanisms for different stimuli. When a task requires children to inhibit incorrect responses elicited by *any* incompatible stimulus, as in Experiment 2, they might rely on general cognitive control mechanisms which might obstruct specific effects of biological stimuli on responses. Healthy children showed larger RT differences between compatible and incompatible conditions compared with healthy adults (45 vs. 119ms) overall, supporting the assumption that children might generally experience greater difficulties inhibiting incorrect, prepotent responses triggered by incompatible visual movement stimuli. This could be due to the development of the prefrontal cortex (Diamond, 2002), which appears to play an important role in imitation inhibition (Brass, Ruby, & Spengler, 2009). A substantial positive correlation between the interference effect and age in healthy children in this study provides limited further corroboration of this assumption by showing that the interference effect becomes smaller during adolescence. The same correlation was not found in children with GTS. This may suggest that GTS patients recruit a different, or additional inhibitory system, that may normally compensate for increased motor excitability associated with the disorder (Draper et al., 2014). However, whether imitation inhibition shares the same neural correlates in GTS patients and healthy controls should be investigated in a further study, for instance by using the task in combination with functional magnetic resonance imaging. With regard to the task presented in this study, children with tics appear to possess a behavioural advantage over healthy children. This

result further corroborates previous research, showing superior inhibition in young GTS patients in a task-switching paradigm (G. M. Jackson, Mueller, Hambleton, & Hollis, 2007; Mueller, Jackson, Dhalla, Datsopoulos, & Hollis, 2006).

Overall, the WISC-IV sub-scales were unrelated to the behavioural results. Hence, the results presented here are unlikely to be based on general differences in cognitive ability between children with and without GTS. One question that remains open is why children with GTS show a behavioural advantage compared to healthy children but adult GTS patients do not appear to have the same advantage compared to healthy adults. There are two possible explanations for this finding. On the one hand, it is possible that, while all adults have developed equally successful inhibition strategies and reach a behavioural ceiling, children with GTS apply a more effective strategy than healthy children do by heightening their default threshold for movement inhibition. On the other hand, it is possible that children with tics who can very successfully inhibit unwanted movements belong to the approximately 75% of GTS patients that are tic-free in adulthood (Hassan & Cavanna, 2012; Pappert et al., 2003) and therefore drop out of the adult GTS sample. This would be in accordance with the finding that 80% of the children investigated in the presented study tested below the mean interference effect displayed by healthy children, while the remaining 20% of children with GTS tested above the healthy mean. It is possible that GTS patients who develop appropriate compensatory mechanisms have a higher likelihood of being tic-free in adulthood. To our knowledge, there is only one study predicting symptom severity in children with GTS from a behavioural task, showing that poorer fine motor skills as assessed by the purdue pegboard task predict worse tic outcome 7 years later (Bloch, Sukhodolsky, Leckman, & Schultz, 2006). The authors attribute this finding to abnormal basal ganglia development (Bloch, Leckman, Zhu, & Peterson, 2005). Increased cortical control may compensate for an imbalance in the basal

ganglia (Kataoka et al., 2010). However, this is only speculative at this point.

Limitations

One limitation of the present study is its cross-sectional design, which does not permit conclusions as to when patients with GTS might develop slowing in response to interfering stimuli. In order to represent developmental changes in inhibitory mechanisms and strategies, a longitudinal design spanning a larger age range in a preferably larger and younger sample should be adopted. Regarding the validity of the present results the homogeneity of the clinical sample of children with “pure” GTS and without current psychiatric comorbidities can be regarded both an advantage and a disadvantage of our study. Selecting a homogenous group assured minimal influence of potential confounders on behavioural data. At the same time, our findings may not be generalizable to children with comorbid disorders such as OCD or ADHD, both of which are very common in patients with GTS (Robertson, 2011). It can be difficult to rely on children- or parent-report when it comes to echophenomena. Although children were screened for suggestibility of tics, this is not strictly classified as an echophenomenon. A formalized task of whether the child shows any echophenomena would have been preferable but would not have been feasible given the time constraints when studying children.

Conclusions

Children with GTS have a smaller interference effect than children without tics. This is an unexpected finding with regard to the observation that GTS patients frequently exhibit echopraxia and that other patient groups who also experience echopraxia typically show an increased interference effect compared with healthy controls. The data point to compensatory mechanisms

that appear to be already present at the age range of 7-12.

References

- Aarts, E., Verhage, M., Veenliet, J. V., Dolan, C. V., & van der Sluis, S. (2014). A solution to dependency: using multilevel analysis to accommodate nested data. *Nat Neurosci*, *17*(4), 491-496. doi:10.1038/nn.3648
- American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders: DSM-V* (5 ed.). Washington, DC.
- Biermann-Ruben, K., Jonas, M., Kessler, K., Siebner, H. R., Baumer, T., Schnitzler, A., & Munchau, A. (2008). Observing repetitive finger movements modulates response times of auditorily cued finger movements. *Brain Cogn*, *68*(1), 107-113. doi:10.1016/j.bandc.2008.03.005
- Bloch, M. H., Leckman, J. F., Zhu, H., & Peterson, B. S. (2005). Caudate volumes in childhood predict symptom severity in adults with Tourette syndrome. *Neurology*, *65*(8), 1253-1258. doi:65/8/1253 [pii] 10.1212/01.wnl.0000180957.98702.69
- Bloch, M. H., Sukhodolsky, D. G., Leckman, J. F., & Schultz, R. T. (2006). Fine-motor skill deficits in childhood predict adulthood tic severity and global psychosocial functioning in Tourette's syndrome. *J Child Psychol Psychiatry*, *47*(6), 551-559. doi:10.1111/j.1469-7610.2005.01561.x
- Brass, M., Bekkering, H., Wohlschlagel, A., & Prinz, W. (2000). Compatibility between observed and executed finger movements: comparing symbolic, spatial, and imitative cues. *Brain Cogn*, *44*(2), 124-143. doi:10.1006/brcg.2000.1225
- Brass, M., Derrfuss, J., Matthes-von Cramon, G., & von Cramon, D. Y. (2003). Imitative response tendencies in patients with frontal brain lesions. *Neuropsychology*, *17*(2), 265-271.
- Brass, M., Ruby, P., & Spengler, S. (2009). Inhibition of imitative behaviour and social cognition. *Philos Trans R Soc Lond B Biol Sci*, *364*(1528), 2359-2367. doi:10.1098/rstb.2009.0066
- Centers for Disease, C., & Prevention. (2009). Prevalence of diagnosed Tourette syndrome in persons aged 6-17 years - United States, 2007. *Morb Mortal Wkly Rep*, *58*(21), 581-585.
- Cook, R., Bird, G., Catmur, C., Press, C., & Heyes, C. (2014). Mirror neurons: from origin to function. *Behav Brain Sci*, *37*(2), 177-192. doi:10.1017/S0140525X13000903

- Cross, K. A., Torrisi, S., Reynolds Losin, E. A., & Iacoboni, M. (2013). Controlling automatic imitative tendencies: interactions between mirror neuron and cognitive control systems. *Neuroimage*, *83*, 493-504. doi:10.1016/j.neuroimage.2013.06.060
- De Renzi, E., Cavalleri, F., & Facchini, S. (1996). Imitation and utilisation behaviour. *J Neurol Neurosurg Psychiatry*, *61*(4), 396-400.
- di Pellegrino, G., Fadiga, L., Fogassi, L., Gallese, V., & Rizzolatti, G. (1992). Understanding motor events: a neurophysiological study. *Exp Brain Res*, *91*(1), 176-180.
- Diamond, A. (2002). Normal development of prefrontal cortex from birth to young adulthood: Cognitive functions, anatomy, and biochemistry. *Principles of frontal lobe function*. New York: Oxford University Press.
- Draper, A., Stephenson, M. C., Jackson, G. M., Pepes, S., Morgan, P. S., Morris, P. G., & Jackson, S. R. (2014). Increased GABA contributes to enhanced control over motor excitability in Tourette syndrome. *Curr Biol*, *24*(19), 2343-2347. doi:10.1016/j.cub.2014.08.038
- Finis, J., Moczydlowski, A., Pollok, B., Biermann-Ruben, K., Thomalla, G., Heil, M., . . . Munchau, A. (2012). Echoes from childhood-imitation in Gilles de la Tourette Syndrome. *Mov Disord*, *27*(4), 562-565. doi:10.1002/mds.24913
- Gallant, J., Storch, E. A., Merlo, L. J., Ricketts, E. D., Geffken, G. R., Goodman, W. K., & Murphy, T. K. (2008). Convergent and discriminant validity of the Children's Yale-Brown Obsessive Compulsive Scale-Symptom Checklist. *J Anxiety Disord*, *22*(8), 1369-1376. doi:10.1016/j.janxdis.2008.01.017
- Gallese, V., Fadiga, L., Fogassi, L., & Rizzolatti, G. (1996). Action recognition in the premotor cortex. *Brain*, *119* (Pt 2), 593-609.
- Ganos, C., Ogrzal, T., Schnitzler, A., & Munchau, A. (2012). The pathophysiology of echopraxia/echolalia: relevance to Gilles de la Tourette syndrome. *Mov Disord*, *27*(10), 1222-1229. doi:10.1002/mds.25103
- Goodman, W. K., Price, L. H., Rasmussen, S. A., Mazure, C., Fleischmann, R. L., Hill, C. L., . . . Charney, D. S. (1989). The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. *Arch Gen Psychiatry*, *46*(11), 1006-1011.
- Hagmann-von Arx, P., Grob, A., Petermann, F., & Daseking, M. (2012). [Concurrent validity of the HAWIK-IV and the Intelligence and Development Scales (IDS)]. *Z Kinder*

- Jugendpsychiatr Psychother*, 40(1), 41-50. doi:10.1024/1422-4917/a000148
- Hassan, N., & Cavanna, A. E. (2012). The prognosis of Tourette syndrome: implications for clinical practice. *Funct Neurol*, 27(1), 23-27.
- Heyes, C. (2010). Where do mirror neurons come from? *Neurosci Biobehav Rev*, 34(4), 575-583. doi:10.1016/j.neubiorev.2009.11.007
- Iacoboni, M., & Dapretto, M. (2006). The mirror neuron system and the consequences of its dysfunction. *Nat Rev Neurosci*, 7(12), 942-951. doi:10.1038/nrn2024
- Jackson, G. M., Mueller, S. C., Hambleton, K., & Hollis, C. P. (2007). Enhanced cognitive control in Tourette Syndrome during task uncertainty. *Exp Brain Res*, 182(3), 357-364. doi:10.1007/s00221-007-0999-8
- Jackson, S. R., Parkinson, A., Manfredi, V., Millon, G., Hollis, C., & Jackson, G. M. (2013). Motor excitability is reduced prior to voluntary movements in children and adolescents with Tourette syndrome. *J Neuropsychol*, 7(1), 29-44. doi:10.1111/j.1748-6653.2012.02033.x
- Jonas, M., Biermann-Ruben, K., Kessler, K., Lange, R., Baumer, T., Siebner, H. R., . . . Munchau, A. (2007). Observation of a finger or an object movement primes imitative responses differentially. *Exp Brain Res*, 177(2), 255-265. doi:10.1007/s00221-006-0660-y
- Jonas, M., Thomalla, G., Biermann-Ruben, K., Siebner, H. R., Muller-Vahl, K., Baumer, T., . . . Munchau, A. (2010). Imitation in patients with Gilles de la Tourette syndrome - a behavioral study. *Mov Disord*, 25(8), 991-999. doi:10.1002/mds.22994
- Kataoka, Y., Kalanithi, P. S., Grantz, H., Schwartz, M. L., Saper, C., Leckman, J. F., & Vaccarino, F. M. (2010). Decreased number of parvalbumin and cholinergic interneurons in the striatum of individuals with Tourette syndrome. *J Comp Neurol*, 518(3), 277-291. doi:10.1002/cne.22206
- Koski, L., Iacoboni, M., Dubeau, M. C., Woods, R. P., & Mazziotta, J. C. (2003). Modulation of cortical activity during different imitative behaviors. *J Neurophysiol*, 89(1), 460-471. doi:10.1152/jn.00248.2002
- Leckman, J. F., Riddle, M. A., Hardin, M. T., Ort, S. I., Swartz, K. L., Stevenson, J., & Cohen, D. J. (1989). The Yale Global Tic Severity Scale: initial testing of a clinician-rated scale of tic severity. *J Am Acad Child Adolesc Psychiatry*, 28(4), 566-573. doi:S0890-

8567(09)65477-0 [pii]

10.1097/00004583-198907000-00015

- Lhermitte, F., Pillon, B., & Serdaru, M. (1986). Human autonomy and the frontal lobes. Part I: Imitation and utilization behavior: a neuropsychological study of 75 patients. *Ann Neurol*, *19*(4), 326-334. doi:10.1002/ana.410190404
- Lopez-Pina, J. A., Sanchez-Meca, J., Lopez-Lopez, J. A., Marin-Martinez, F., Nunez-Nunez, R. M., Rosa-Alcazar, A. I., . . . Ferrer-Requena, J. (2015). Reliability generalization study of the Yale-Brown Obsessive-Compulsive Scale for children and adolescents. *J Pers Assess*, *97*(1), 42-54. doi:10.1080/00223891.2014.930470
- Molenberghs, P., Cunnington, R., & Mattingley, J. B. (2012). Brain regions with mirror properties: a meta-analysis of 125 human fMRI studies. *Neurosci Biobehav Rev*, *36*(1), 341-349. doi:10.1016/j.neubiorev.2011.07.004
- Mueller, S. C., Jackson, G. M., Dhalla, R., Datsopoulos, S., & Hollis, C. P. (2006). Enhanced cognitive control in young people with Tourette's syndrome. *Curr Biol*, *16*(6), 570-573. doi:S0960-9822(06)01136-5 [pii]
- 10.1016/j.cub.2006.01.064
- Muller, N., Putz, A., Kathmann, N., Lehle, R., Gunther, W., & Straube, A. (1997). Characteristics of obsessive-compulsive symptoms in Tourette's syndrome, obsessive-compulsive disorder, and Parkinson's disease. *Psychiatry Res*, *70*(2), 105-114.
- Pappert, E. J., Goetz, C. G., Louis, E. D., Blasucci, L., & Leurgans, S. (2003). Objective assessments of longitudinal outcome in Gilles de la Tourette's syndrome. *Neurology*, *61*(7), 936-940.
- Petermann, F., & Petermann, U. (2008). *Manual HAWIK-IV*. Huber: Hogrefe.
- Rizzolatti, G., Cattaneo, L., Fabbri-Destro, M., & Rozzi, S. (2014). Cortical mechanisms underlying the organization of goal-directed actions and mirror neuron-based action understanding. *Physiol Rev*, *94*(2), 655-706. doi:10.1152/physrev.00009.2013
- Rizzolatti, G., Fadiga, L., Gallese, V., & Fogassi, L. (1996). Premotor cortex and the recognition of motor actions. *Brain Res Cogn Brain Res*, *3*(2), 131-141.
- Robertson, M. M. (2008). The prevalence and epidemiology of Gilles de la Tourette syndrome. Part 1: the epidemiological and prevalence studies. *J Psychosom Res*, *65*(5), 461-472. doi:10.1016/j.jpsychores.2008.03.006

- Robertson, M. M. (2011). Gilles de la Tourette syndrome: the complexities of phenotype and treatment. *Br J Hosp Med (Lond)*, 72(2), 100-107.
- Robertson, M. M., Trimble, M. R., & Lees, A. J. (1988). The psychopathology of the Gilles de la Tourette syndrome. A phenomenological analysis. *Br J Psychiatry*, 152, 383-390.
- Rösler, M., Retz-Junginger, P., Retz, W., & Stieglitz, R.-D. (2008). *Homburger ADHS-Skalen für Erwachsene (HASE). Manual*. Göttingen: Hogrefe.
- Scharf, J. M., Miller, L. L., Gauvin, C. A., Alabiso, J., Mathews, C. A., & Ben-Shlomo, Y. (2015). Population prevalence of Tourette syndrome: a systematic review and meta-analysis. *Mov Disord*, 30(2), 221-228. doi:10.1002/mds.26089
- Schlender, M., Schwarz, O., Rothenberger, A., & Roessner, V. (2011). Tic disorders: administrative prevalence and co-occurrence with attention-deficit/hyperactivity disorder in a German community sample. *Eur Psychiatry*, 26(6), 370-374. doi:S0924-9338(09)00181-3 [pii]
10.1016/j.eurpsy.2009.10.003
- Schmidt, S., & Petermann, F. (2008). Testbesprechung. *Zeitschrift für Psychiatrie, Psychologie und Psychotherapie*, 56(2), 155-159.
- Spengler, S., Bird, G., & Brass, M. (2010). Hyperimitation of actions is related to reduced understanding of others' minds in autism spectrum conditions. *Biol Psychiatry*, 68(12), 1148-1155. doi:10.1016/j.biopsych.2010.09.017
- Storch, E. A., Murphy, T. K., Geffken, G. R., Sajid, M., Allen, P., Roberti, J. W., & Goodman, W. K. (2005). Reliability and validity of the Yale Global Tic Severity Scale. *Psychol Assess*, 17(4), 486-491. doi:10.1037/1040-3590.17.4.486
- Uher, R., Heyman, I., Turner, C. M., & Shafran, R. (2008). Self-, parent-report and interview measures of obsessive-compulsive disorder in children and adolescents. *J Anxiety Disord*, 22(6), 979-990. doi:10.1016/j.janxdis.2007.10.001
- Vanderwert, R. E., Fox, N. A., & Ferrari, P. F. (2013). The mirror mechanism and mu rhythm in social development. *Neurosci Lett*, 540, 15-20. doi:10.1016/j.neulet.2012.10.006
- Wang, M., Zhang, J., Dong, G., Zhang, H., Lu, H., & Du, X. (2017). Development of rostral inferior parietal lobule area functional connectivity from late childhood to early adulthood. *Int J Dev Neurosci*, 59, 31-36. doi:10.1016/j.ijdevneu.2017.03.001
- Wechsler, D. (2004). *The Wechsler intelligence scale for children—fourth edition* (Vol. 4).

London: Pearson Assessment.

Williams, J. H., Whiten, A., & Singh, T. (2004). A systematic review of action imitation in autistic spectrum disorder. *J Autism Dev Disord*, 34(3), 285-299.

Tables

Table 1. Demographical data, WISC-IV and clinical scores of GTS patients and healthy controls

	GTS	Healthy controls	Effect size Cohen's <i>d</i>
Age: <i>Mean</i> (<i>SD</i> ; male:female)	9.13 (1.81; 11:4)	9.87 (1.77; 8:7)	
SES: <i>Mean</i>	11.7	12.5	<i>d</i> = -.57
WISC-IV scales: <i>Mean</i> (<i>SD</i>)			
Similarities	11.43 (1.6)	12 (2.48)	<i>d</i> = -.29
Vocabulary	10.71 (2.4)	11.92 (2.57)	<i>d</i> = -.51
Block design	10.79 (3.24)	12.54 (2.88)	<i>d</i> = -.59
Picture completion	10.86 (3.33)	12.38 (1.98)	<i>d</i> = -.57
Letter-number sequencing	10.79 (2.52)	11.62 (2.1)	<i>d</i> = -.37
Coding	9.79 (1.97)	10.69 (2.9)	<i>d</i> = -.38
YGTSS	16.7 (8)	0	<i>d</i> = 3.19***
CY-BOCS	2 (5.9)	0	<i>d</i> = -.52
ADHD-CL	2.43 (2.89)	0.4 (1.55)	<i>d</i> = .94

Data of Gilles de la Tourette syndrome (GTS) patients are displayed on the left, those of healthy controls in the middle column. The upper rows show age (*Mean*, 1 *SD*), male to female ratio (male:female) and socioeconomic status (SES) as number of school years of the parent with the

higher education. The middle rows display means \pm SD scores of six sub-scales of the Wechsler Intelligence Scale for Children IV (WISC-IV). Differences between the groups were tested with independent *t*-tests, with effect sizes displayed in the right-most column (***p* < .001). The lower rows show scores (*Mean, SD*) of the Yale Global Tic Severity Scale (YGTSS), the Child Yale-Brown Obsessive Compulsive Scale (CY-BOCS) and the Attention Deficit Hyperactivity Disorder Checklist (ADHD-CL).

Table 2. Error and reaction time data in the imitation inhibition paradigm

	GTS		Healthy children	
Errors: <i>M</i> (<i>SD</i> ; sum)	22 (19; 335)		21 (17; 321)	
Reaction time: <i>M</i> (<i>SD</i>)				
	Onset	Offset	Onset	Offset
	Finger			
Compatible	925 (223)	882 (144)	735 (181)	683 (160)
Incompatible	992 (196)	960 (179)	845 (202)	808 (230)
	Dot			
Compatible	960 (202)	902 (222)	722 (162)	689 (141)
Incompatible	977 (225)	943(192)	842 (178)	798 (218)

Errors (*M*, *SD* and sum) as well as reaction time (*M*, *SD* in ms) for 15 children with Gilles de la Tourette syndrome (GTS) and 15 healthy children. Data for compatible and incompatible trials, for onset and offset presentation mode and for the little and index finger are shown separately.

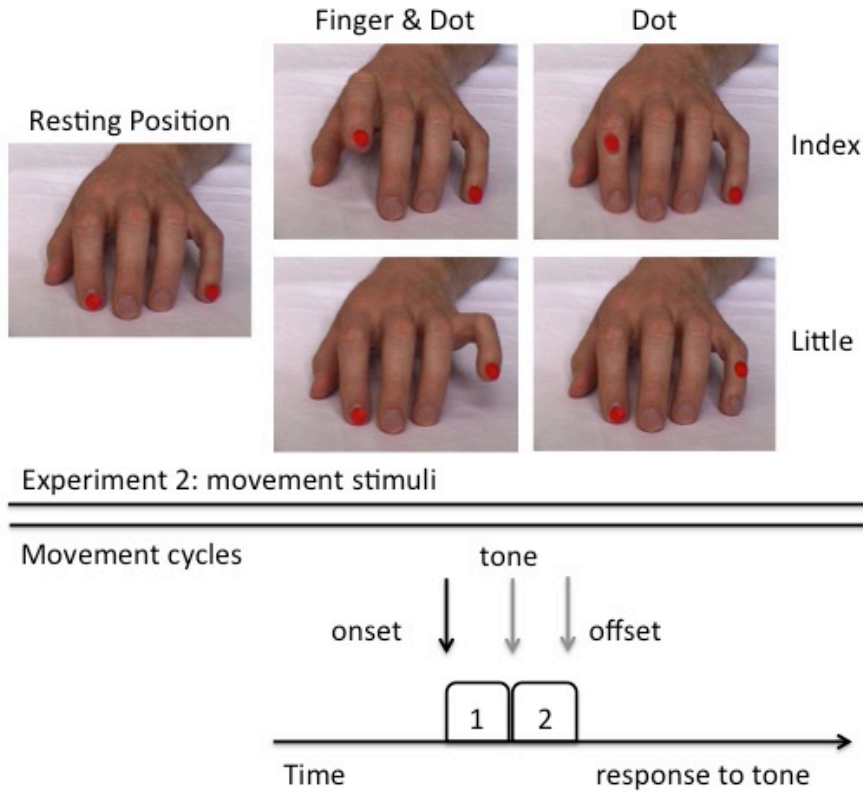


Figure 1. Displayed are movement stimuli and movement cycles used in the experiment.

Upper panel: pictures show the resting position (leftmost frame) and conditions “finger & dot movement” vs. “dot movement” for index and little finger respectively (presented in colour during the experiment).

Lower panel: one arc represents one movement (up and down) of one or two cycles presented in the experiment.

Exemplary condition plotted in black: two cycles with tone presentation at the onset of the movement. In grey: tone presentation at the offset of one or two movements. Modelled after (Jonas et al., 2010).

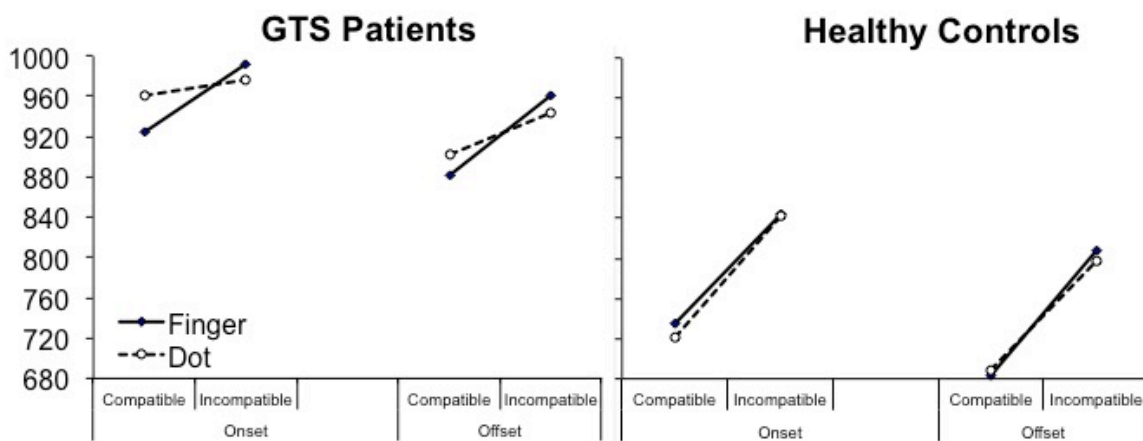


Figure 2. Displayed are mean reaction times for the interaction terms “type of movement” x “compatibility” in experiment 2, separately for onset and offset presentation mode.

Left panel: data of 15 children with GTS. Right panel: data of 15 healthy children. All children reacted faster in compatible than in incompatible trials. This interference effect was smaller in children with GTS. As expected, all children reacted faster in offset trials than in onset trials.

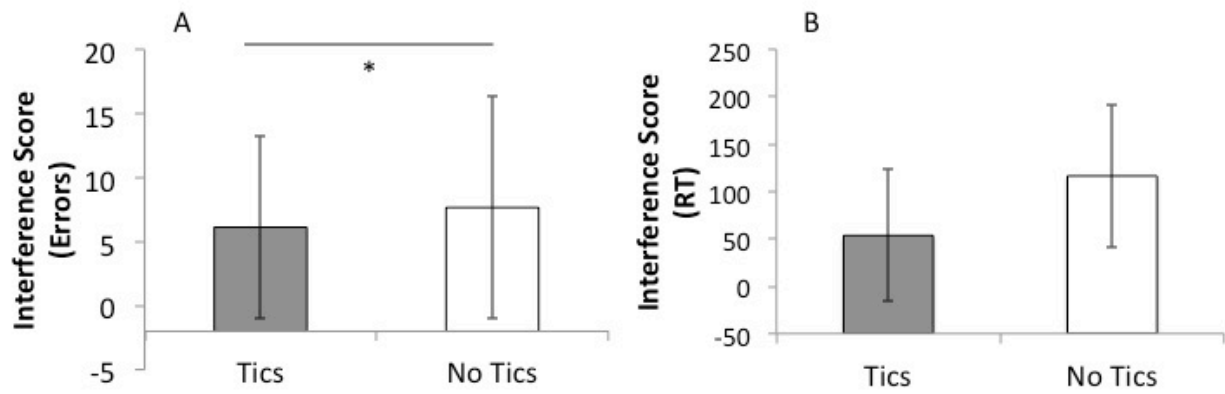


Figure 3. A: displayed are mean interference effects (incongruent trials – congruent trials) +/- 1 standard deviation (SD) of reaction times (RT) for children with and without tics

B: displayed are mean interference effects +/- 1 SD of errors for children with and without tics