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Reward enhances tic suppression in children within months of tic disorder onset

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ABSTRACT

Tic disorders are childhood onset neuropsychiatric disorders characterized by motor and/or vocal tics. Research has demonstrated that children with chronic tics (including Tourette syndrome and Chronic Tic Disorder: TS/CTD) can suppress tics, particularly when an immediate, contingent reward is given for successful tic suppression. As a diagnosis of TS/CTD requires tics to be present for at least one year, children in these tic suppression studies had been living with tics for quite some time. Thus, it is unclear whether the ability to inhibit tics is learned over time or present at tic onset. Resolving that issue would inform theories of how tics develop and how behavior therapy for tics works. We investigated tic suppression in school-age children as close to the time of tic onset as possible, and no later than six months after onset. Children were asked to suppress their tics both in the presence and absence of a contingent reward. Results demonstrated that these children, like children with TS/CTD, have some capacity to suppress tics, and that immediate reward enhances that capacity. These findings demonstrate that the modulating effect of reward on inhibitory control of tics is present within months of tic onset, before tics have become chronic.

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1. Introduction

Tic disorders (including Tourette syndrome and Chronic Tic Disorder: TS/CTD) are complex childhood-onset neuropsychiatric disorders of the central nervous system characterized by the presence of motor and/or vocal tics. Tics are movements or noises, often brief and repeated many times a day in a stereotyped fashion, that may look intentional but serve no useful purpose (Black, 2010). Common tics include forceful eye blinking, nose twitching, head jerking, sniffing, and throat clearing. The average age of tic onset in TS/CTD is ~6 years old (Leckman et al., 1998, 2006), and tics must be present for at least a year to diagnose TS/CTD. Though historically thought to be rare disorders, careful epidemiologic studies show that TS and CTD affect at least 2–6% of all children (Hornsey et al., 2001; Robertson, 2008; Cubo et al., 2011). Many more children have tics for less than a year, with point prevalence estimates of about 20% of school-aged children (Kurlan et al.,

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2001; Snider et al., 2002; Khalifa and von Knorring, 2003; Cubo et al., 2011). Therefore, within the first year after tic onset, some children experience marked improvement or become asymptomatic, while others develop a chronic disorder that can substantially impair their quality of life (Cavanna et al., 2008; Eddy et al., 2011a, 2011b).

Tics are distinguished from other abnormal movements in several ways, one of which is that there is usually some degree of voluntary control (Robertson et al., 1999; Black, 2010; Leckman et al., in press). Specifically, many adults and children with TS/CTD can suppress tics, at least briefly, and often attempt to suppress tics, especially in certain environmental contexts such as social gatherings or school. Because of this partial voluntary control, TS/CTD has been thought to involve faulty inhibitory control processes (Mink, 2001). In addition, tics are often described as being preceded by a "premonitory urge," defined as a feeling of discomfort (e.g., a sensation like itch or pressure, or a sense that one must tic). This premonitory urge is temporarily relieved by the performance of a tic (Leckman et al., 2006). Thus, tics may reflect deficient inhibitory control over the motor response to this urge.

The issue of inhibitory control in TS/CTD is actually quite complex, as there is debate over whether certain domains of inhibitory control are in fact affected. For example, some electrophysiological studies (using transcranial magnetic stimulation) have found reduced cortical inhibition in the primary motor cortex in TS/CTD (Ziemann et al., 1997; Gilbert et al., 2004), suggesting altered motor inhibition. However, other studies have shown that differences in cortical excitability may be more related to comorbid attention deficit hyperactivity disorder (ADHD) symptoms than to tics (Gilbert et al., 2005; Orth and Rothwell, 2009). Similarly, although behavioral studies in children and adults with TS/CTD have demonstrated impairments in response inhibition, selective attention, and cognitive flexibility (Bornstein et al., 1991; Channon et al., 2003, 2009; Watkins et al., 2005), some have argued that these impairments are driven by comorbid conditions, including ADHD and obsessive-compulsive disorder (OCD) (Ozonoff et al., 1998; Denckla, 2006). Further, some studies have even shown evidence for enhanced executive function in TS/CTD (Mueller et al., 2006; Jackson et al., 2007). Neuroimaging data are also somewhat inconsistent (for a review, see Greene et al., 2013). There is some evidence for atypical and immature task control systems in the brain in TS/CTD (Church et al., 2009a, 2009b; Wang et al., 2011) as well as atypical activation of frontostriatal regions posited to support inhibitory control (Aron et al., 2014) in TS/CTD (Hershey et al., 2004a; Marsh et al., 2007; Baym et al., 2008; Raz et al., 2009). However, the directions of specific effects were inconsistent among the fMRI studies, and others have not been able to replicate differences between TS/CTD and controls with similar study designs (Hershey et al., 2004b; Debes et al., 2011). EEG and fMRI studies specifically investigating tic suppression have shown increased activation in frontostriatal regions that support inhibitory control during active tic suppression in children and adults with TS/CTD (Peterson et al., 1998; Hong et al., 2013). Thus, while studies of inhibitory control per se in TS/CTD may be inconsistent, a relationship between tic suppression and inhibitory control mechanisms likely exists.

The ability to suppress tics has been measured using a standardized tic suppression paradigm (Woods and Himle, 2004). In this task, children are seated in front of a "tic detector" (described below) and asked to suppress or not to suppress their tics under varying conditions. Studies using this task have demonstrated that children with TS/CTD can suppress tics in response to a simple verbal request, though suppression is inconsistent and varies among individuals (Meidinger et al., 2005; Conelea and Woods, 2008). By contrast, when immediate rewards are given for brief periods of successful tic suppression, children with TS/CTD can robustly and reliably reduce tic rate (Woods and Himle, 2004; Himle and Woods, 2005; Himle et al., 2007, 2008; Woods et al., 2008; Specht et al., 2013). Further, rewards delivered specifically when tics were suppressed led to better tic suppression than rewards given without a temporal link to tic behavior (Himle et al., 2008). In other words, contextual variables that were not immediately linked to tic behavior (i.e., a verbal request to suppress tics, or non-contingent reward) had less impact on tics than contingent rewards. Thus, the presence of a reward that is specifically contingent upon tic behavior may create an environmental context for more consistent tic suppression in TS/CTD.

Since a diagnosis of TS/CTD requires tics to be present for a minimum of one year, the children in the cited tic suppression studies had been living with tics for at least a year and usually much longer. Years of experience with tics usually brings years of experience attempting to suppress tics, and some argue that this experience enhances inhibitory control in TS/CTD (Jackson et al., 2011). Thus, it is unclear whether inhibitory control over tics is present at the onset of the tic disorder or develops with experience. In the present study, we investigated children whose tics began within the previous six months. Surprisingly little is known from controlled studies about children with recent-onset tics. Anecdotally, many of these children display little awareness of their tics, and few of them have experienced the social pressure to inhibit their tics that children with TS/CTD have experienced. Children with recent-onset tics have, at most, a few months' experience suppressing tics, and the extent to which they can suppress tics has not been reported.

The present study tested whether children with recent-onset tics are capable of suppressing their tics and if so, whether an environmental contingency (namely, reward) modifies this ability. Given evidence that reward can enhance inhibitory control in children without tics (Padmanabhan et al., 2011; Geier and Luna, 2012), we hypothesized that children with recent-onset tics would be able to suppress tics successfully when rewarded for doing so, even though they have little to no experience suppressing tics.

2. Methods

2.1. Participants

Children with recent-onset tics (DSM-IV-TR Transient Tic Disorder) were recruited for this study via clinicians in

Table 1
Participant information; data listed as "mean (SD); range" where appropriate.

N	21
Male/female	14/7
Age	8.14 (2.79); 5.0–14.5
IQ	109.3 (15.1); 83–127
Months since tic onset	3.51 (1.45); 0.82–5.98
YGTSS	
Total tic score	16.6 (6.9); 7–29
Motor tic score	10.2 (4.9); 0–17
Vocal tic score	6.3 (5.2); 0–15
YGTSS impairment rating	8.5 (9.0); 0–30
PUTS[a]	12.8 (5.2); 9–29
DCI	33.4 (14.8); 14–60
CY-BOCS	7.7 (6.6); 0–20
ADHD rating	16.0 (9.6); 0–36
SRS	50.5 (8.8); 36–67
SES (Barratt)	51.3 (11.5); 28.5–66
No. on psychoactive medication	2[b]
No. with ADHD (current or past)	11[c]
No. with OCD (current or past)	6
No. with other anxiety disorder (current or past)	8 (4 specific phobia, 2 separation anxiety disorder, 1 agoraphobia, 2 social phobia, 1 generalized anxiety disorder, 1 avoidant disorder)
No. with other K-SADS diagnosis	7 (1 oppositional defiant disorder, 1 depressive disorder not otherwise specified, 7 enuresis, 1 encopresis)
No. with no non-tic K-SADS diagnosis	1

[a] *N* = 17, as the PUTS was incomplete for four children.
[b] Two additional children took occasional diphenhydramine and one additional child took occasional chlorpheniramine for seasonal rhinitis.
[c] Five additional children were diagnosed with ADHD Not Otherwise Specified

the Washington University School of Medicine Movement Disorders Center, faculty and fellows from child neurology and child psychiatry, local pediatricians, and flyers posted in the Washington University community. Participants had tics at the time of the study visit, but no tics prior to six months before the visit. Multiple sources of information were used to determine the best estimate of tic onset date, including queries to parent and child regarding tic onset during diagnostic interviews, careful discussion with the parent and child, and in some cases, reviewing home videos or talking to current and past teachers. Repetitive behaviors that were diagnostically ambiguous (e.g., knuckle popping, rhythmic foot tapping, repeatedly poking a sibling) were not considered for dating tic onset. Since historical information was imperfect, children were also allowed to enroll if they had a single possible tic that had disappeared at least a year prior to the current episode, which was true for 2 of the children enrolled (ages 8.5 and 14.3 years). Of 28 children recruited, 5 were determined ineligible during screening due to tics for more than 6 months prior to the visit, 1 was not interested after screening, and 1 dropped after screening for personal reasons. Thus, 21 children (14 male, 7 female) with recent-onset tics, ages 5–14 years (mean = 8.14, SD = 2.79), all right-handed, participated in the study. Exclusion criteria included a neurological disorder other than tics or migraine, known structural brain disease, mental retardation, autism, psychosis, mania, current major depression, severe systemic illness, or non-proficiency with the English language. A parent/guardian gave informed consent for each child, and children assented to participation. Subjects were compensated for their participation. The Washington University Human Research Protection Office (IRB) approved the study. Table 1 summarizes demographic and clinical information and Supplemental Table S1 provides individual participant information.

2.2. Clinical assessment

Parents and children were interviewed separately by two trained raters to assess psychiatric comorbidity using the Kiddie-Schedule for Affective Disorders and Schizophrenia: K-SADS (Kaufman et al., 1997). Over the course of the study, three raters participated, all of whom had masters-level credentials in counseling or social work, several years' previous experience in psychiatric diagnostic interviewing, and additional training with author KJB on psychiatric diagnosis in TS. A psychiatric rater, with at least 10 years' experience, reviewed information from the parent and child interviews. Final diagnoses were determined by clinical judgment from all available information according to the K-SADS instructions. Author KJB was the arbiter for any diagnostic questions. Author KJB also examined all children for TS/CTD, ADHD, and OCD (The Tourette Syndrome Association International Consortium for Genetics, 1999), assessed current symptom severity with the Yale Global Tic Severity Scale [YGTSS; total tic score range 0–50, impairment score range 0–50, higher scores indicate greater severity (Leckman et al., 1989)], Children's Yale-Brown Obsessive Compulsive Scale [CYBOCS; range 0–40, higher scores indicate greater severity (Scahill et al., 1997)], and ADHD Rating Scale [range 0–54, higher scores indicate greater severity (Barkley, 1998)], and assessed typical historical features of TS with the Diagnostic Confidence Index [DCI; range 0–100, higher scores indicate more "typical" TS (Robertson et al., 1999)]. Parents also completed the YGTSS tic symptom checklist, the Child Behavior Checklist [CBCL (Achenbach and Ruffle,

2000)], the Social Responsiveness Scale [SRS (Constantino et al., 2003)], the Barratt Simplified Measure of Social Status to assess socioeconomic status (SES) (Barratt, 2012), and the PedsQoL to assess quality of life (Varni et al., 1999). Children completed the Premonitory Urge for Tics Scale [PUTS; range 9–36, higher scores indicate more premonitory symptoms (Woods et al., 2005)] with parental help if needed. The K-BIT II (Kaufman and Kaufman, 2004) was used to estimate IQ. We also recorded handedness, history of maternal smoking or other problems during pregnancy, history of birth complications, and pertinent family history.

These data were collected as part of a study that included neuroimaging and psychometrics. The current manuscript reports the tic suppression data.

2.3. Tic suppression paradigm

We implemented a tic suppression paradigm following the procedures of Woods and Himle (2004) and Himle et al. (2008). Participants completed two 5-min sessions under each of four conditions: Baseline, Verbal Instruction, Differential Reinforcement of Zero-rate Ticcing (Differential Reinforcement of Other behavior: DRO), and Noncontingent Reinforcement (NCR). Each condition is described below. During each session, participants were seated in a room facing a token dispenser box (Med Associates, Inc. Part #ENV-703) with a camera on top and a microphone clipped to their clothing near their larynx. The children were told that the box was a "tic detector" that watches and counts tics using a motion sensor (camera: Linksys wireless camera WVC80N) and sound sensor (microphone: Radio Shack wireless microphone Catalog #32-1257). The token dispenser dispensed a reward token (poker chip) into a tray when an experimenter in the next room pressed a dispense button. Unbeknownst to the child, the live video and audio feeds were viewed and heard on a laptop computer in the adjacent room, which also recorded the audio and video using CamStudio (http://camstudio.org/). During each session, the door was closed so the child was in the room alone (with the exception of one young child who was uncomfortable without his mother in the room with him). The consenting parent was informed that the child would be videotaped and watched during the task, but the child was not told this information. This choice was consistent with previous studies (e.g., Woods and Himle, 2004; Himle et al., 2008) and alleviates concerns that awareness of observation may increase tic suppression. The experimenter used a custom computer program on the laptop (Tic Timer™) to record the timing of each tic observed. The Tic Timer™ program tracked non-overlapping 10 s periods during which no tic was observed ("tic-free intervals"), and in the DRO condition this information indicated when a token was to be dispensed.

Prior to each session, the experimenter gave the child specific instructions (Supplementary Materials S3) and ensured comprehension by asking the child to explain the instructions. In the Baseline condition, children were told that the tic detector would watch and count their tics, but that they were free to tic as little or as much as they needed. A tic list was made listing each tic identified during the initial evaluation or observed during the first tic suppression Baseline condition. Before the Verbal Instruction condition, the child was asked to do his/her best to suppress the movements and/or sounds on the tic list. The tic list was also reviewed when necessary prior to each DRO and NCR condition. In the DRO condition, they were told to do their best to suppress these tics, and that they would receive a token for every 10 s that a tic was not detected. Thus, the reward was contingent upon the ability to suppress tics. In the NCR condition, children were told to do their best to suppress their tics, but that they would receive tokens regardless of their tic behavior. The tokens were dispensed at the same time points as they were dispensed during their first DRO session (e.g., if tokens were dispensed at 1:23, 2:05 and 4:37 during the first DRO session, then tokens were only dispensed at those times during both NCR sessions, regardless of the child's current behavior). Children were told that at the end of the day, they would be able to exchange tokens for money, about three cents ($0.03 USD) for each token. The first four sessions followed the same order for all participants: Baseline, Verbal Instruction, DRO, NCR; this order was necessary because we wanted the first Baseline to be as natural as possible, we wanted to exclude past rewards from the first Verbal Instruction condition, and the NCR had to follow a DRO condition since the NCR condition's reward timing was yoked to the first DRO session. However, to account for order effects, a second set of four sessions was completed in which the condition order was counterbalanced across participants. All children received between $2 and $4 depending on the number of tokens dispensed.

2.4. Tic ratings

During the tic suppression paradigm ("live"), a neuropsychiatrist with movement disorders fellowship training (KJB) pressed a button on the Tic Timer™ program every time he observed a tic. After the first Baseline session, only tics on the tic list described in the previous paragraph were counted. The "live" tic recording was needed to provide appropriate rewards, but the experimenter was perforce not blind to the session condition or to the purpose of the study. Therefore, the video recordings were subsequently relabeled and presented in randomized order to a movement disorders trained pediatric neurologist (ARV) who was blind to each session's condition and to the purpose of the study. She was given the tic list for each child and recorded the time of each tic in each session using a modified version of the Tic Timer™ program from which all clues had been removed that could unblind the rater.

To measure inter-rater reliability, we calculated the intra-class correlation coefficient (ICC) using a two-way mixed effects model assessing consistency. The single rater ICC for tic-free intervals was .72 and for tic frequency was 0.75, indicating good reliability across the two raters.

2.5. Data management and analyses

Study data were managed using REDCap [Research Electronic Data Capture] electronic data capture tools hosted at Washington University (Harris et al., 2009). Data analyses were conducted on the 20 participants scored by the blind rater (video from one child was lost) and on the 21

participants scored live by the unblinded rater. Here, we report results from the blind ratings (i.e., the rater who was blind to each session's condition and to the purpose of the study). Results from the unblinded rater appear in Supplemental Materials (S4). There were two dependent measures for all analyses: (1) number of non-overlapping 10 s tic-free intervals during the session, divided by the session duration ("tic-free intervals"; possible range 0–6 per minute), and (2) tic frequency in tics per minute (number of tics observed in each session, divided by the session duration). As described above, the four task conditions were administered in two sets, with sessions always in the same order for the first set (Baseline, Verbal Instruction, DRO, NCR), but with session order counterbalanced for the second set. To test for an order effect, a repeated-measures ANOVA was conducted with Set (first set of sessions, second set of sessions) and Condition (Baseline, Verbal Instruction, DRO, NCR) as within-subjects factors. As there was no significant main effect of Set and no interactions with Set, we collapsed across Set for all subsequent analyses (see Section 3.2). One-way repeated measures ANOVAs were conducted to test for main effects of Condition, and paired *t* tests were then conducted to compare specific conditions. Pearson's *r* was used to test for correlations between the effects of interest and demographic and clinical variables.

3. Results

3.1. Baseline tic severity, impact, and awareness of tics

Tic severity was relatively mild in this sample (YGTSS Tic scores, Table 1), and for most children, tics caused little or no distress and little or no impairment in school, social life, or family life (YGTSS Impairment scores, Table 1). Although unfortunately we did not prospectively record subjective awareness of tics in every child, there is evidence that several children were unaware of tics at study entry. The DCI includes an item to reflect whether the child ever intentionally suppressed tics, and this was scored "no" for 12 of the 21 children. The PUTS was not completed in two children because when asked about urges or sensations before tics (e.g., "before you raise your eyebrows like this"), the child said "I don't do that" or "who cares" (or words of similar effect). For two additional children, one item on the PUTS was incomplete (one by accident and the other because the child did not know the meaning of the words "wound up"). Several children reported that they were not aware of any tics, even when the examiner mimicked specific observed tics after the extensive clinical evaluation.

3.2. Testing for order effects

As stated previously, here we report the results from the blind rater ($n = 20$). As two children only completed one set of sessions due to fatigue or limited cooperation, the Set × Condition ANOVA to test for an order effect was run on the 18 children who completed both sets. There was no significant main effect of Set, $F(1,17) = 2.1$, $p = .68$, or interaction of Set × Condition, $F(3,51) = 1.26$, $p = .3$, indicating no significant order effect. Therefore, subsequent analyses were performed on the data from all 20 participants collapsed across Set.

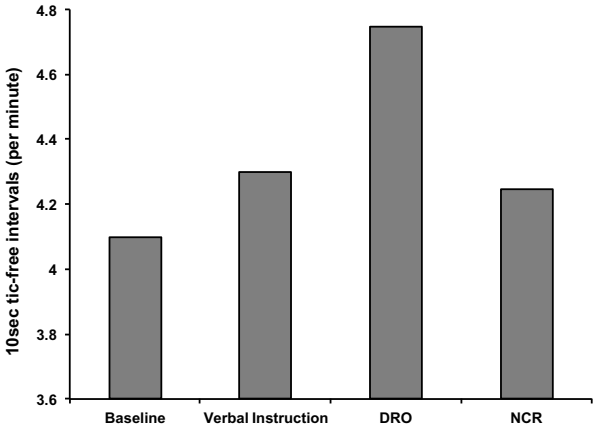

Fig. 1. Mean number of 10 s tic-free intervals per minute during each task condition.

3.3. Tic-free intervals

Fig. 1 displays the mean number of 10 s tic-free intervals for each condition (blind ratings) and Supplemental Table S2 provides individual participant data. The one-way ANOVA on tic-free intervals demonstrated a significant main effect of Condition, $F(3,57) = 4.01$, $p = .012$. Post hoc paired *t* tests confirmed expected significant effects; namely, there were significantly more tic-free intervals in the DRO condition ($M = 5.03$, $SD = 0.93$) than in the Baseline condition ($M = 4.35$, $SD = 0.96$), $t(19) = 2.93$, $p = .009$, in the Verbal Instruction condition ($M = 4.54$, $SD = 1.02$), $t(19) = 3.82$, $p = .001$, and in the NCR condition ($M = 4.55$, $SD = 1.44$), $t(19) = 2.44$, $p = .025$. All but three children exhibited suppression (i.e., received more rewards) during the DRO condition compared to the baseline condition (see Supplemental Table S2). There was more individual variability in suppression in the other conditions, as 12 of the 20 children exhibited suppression during the Verbal Instruction condition and 13 of the 20 children exhibited suppression during the NCR condition.

3.4. Tic frequency

Fig. 2 displays the mean tic frequency for each condition (blind ratings). The one-way ANOVA on tic frequency did not reveal a significant main effect of condition, $F(3,57) = 1.94$, $p = .13$. However, the mean results followed the expected pattern across conditions. Specifically, tic frequency was lower for the DRO condition ($M = 2.67$, $SD = 3.12$) than the Baseline condition ($M = 4.37$, $SD = 2.95$), $t(19) = 2.35$, $p = .03$, and the Verbal Instruction condition ($M = 3.41$, $SD = 3.06$), $t(19) = 2.36$, $p = .029$. Tic frequency was also lower in the DRO condition than in the NCR condition ($M = 4.01$, $SD = 5.62$), $t(19) = 1.76$, $p = .092$. Single subject data showed that 15 children showed reduced tic frequency in the DRO condition compared to Baseline, 14 showed reduced tic frequency in the Verbal Instruction

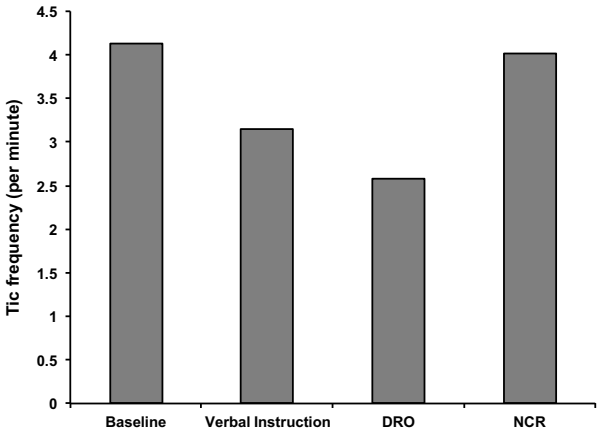

Fig. 2. Mean number of tics per minute (tic frequency) during each task condition.

condition, and 13 show reduced tic frequency in the NCR condition (see Supplemental Table S2).

3.5. Relationships of tic suppression with age, ADHD symptoms, and time since tic onset

Our sample included children younger than in the previous studies of tic suppression. Therefore, we tested whether there was a relationship between the ability to suppress tics and age. The ability to suppress tics was measured as the difference in tic-free intervals and tic frequency between the Baseline condition and each suppression condition (Verbal Instruction, DRO, NCR). Pearson's *r* correlations revealed no significant relationship between these difference measures and age (all *p*'s > .1). Inspection of the individual subject data patterns showed that the two youngest children in the sample did not exhibit successful tic suppression, suggesting that younger children may have greater difficulty suppressing tics. However, several other children across the age range also did not exhibit suppression in certain conditions. Further, when we split the sample into children younger than 8 years old and children 8 years old and older, there was no significant difference in the degree of suppression between the younger and older children ($p > .1$).

We also considered whether ADHD symptoms would relate to the ability to suppress tics, as we had hypothesized that children with more severe ADHD may have more difficulty suppressing tics. We found that the ADHD Rating Scale (ARS) score was most strongly correlated with Baseline vs. NCR tic frequency, $r(18) = .465$, $p = .039$ (this correlation was the only one that met statistical significance), Baseline vs. NCR tic-free intervals, $r(18) = -.417$, $p = .07$, Baseline vs. Verbal Instruction tic-free intervals, $r(18) = -.427$, $p = .06$, and Baseline vs. Verbal Instruction tic frequency, $r(18) = .413$, $p = .07$. However, the direction of these correlations was opposite to the predicted direction, indicating that, if anything, children with more ADHD symptoms suppressed their tics to a greater extent. No other correlations had $p < .1$.

Finally, in this sample, children's tics began on average 3.5 months prior to the study visit, but that duration varied from less than 1 month to 6 months. Therefore, we tested for a relationship between time since tic onset and the ability to suppress tics, but found no significant correlations (all *p*'s > .1).

4. Discussion

4.1. Children with recent-onset tics are capable of suppressing their tics

The present study examined a common, yet rarely studied, population: children with recent-onset tics. We investigated whether or not children with recent-onset tics are capable of suppressing their tics, and whether that ability is modulated by reward. Compared to the Baseline condition (when not instructed to suppress tics), these children had more tic-free periods when asked to suppress tics with and without non-contingent rewards, and even more tic-free periods when immediately rewarded for suppressing tics. This ability to suppress tics was not related to the child's age or the number of months since tic onset. Thus, children with recent-onset tics can in fact suppress their tics, and are most successful when an immediate, contingent reward is delivered for tic suppression. These findings extend the results from children with TS/CTD – who generally have substantial experience suppressing tics – to children who have only had tics for a few months, with generally modest tic severity and in some cases no awareness of the tics. The largest sample of children previously studied using this tic suppression paradigm was 13 children with TS/CTD. Therefore the present experiment is also the largest study to date using the tic suppression paradigm in children.

4.2. Reward enhances inhibitory control over tics within months of tic onset

In typical development, there is an interesting relationship between inhibitory control and reward processes. Inhibitory control clearly matures over the course of development, reflected by behavior (Tipper et al., 1989; Levin et al., 1991; Ridderinkhof et al., 1999; Williams et al., 1999; Luna et al., 2004) and brain development (Luna et al., 2001; Bunge et al., 2002; Rubia et al., 2006; Velanova et al., 2008). However, only recently have studies investigated the interplay between inhibitory control and reward, demonstrating that reward can indeed modulate inhibitory control. Specifically, the presence of a reward enhanced response inhibition task performance in children, adolescents, and adults (Padmanabhan et al., 2011; Geier and Luna, 2012). Most interestingly, children and adolescents were capable of adult-level task performance when motivated by a reward. Thus, the presence of an immediate reward enabled optimal, "mature" inhibitory control.

The children previously studied in tic suppression tasks had TS/CTD, and therefore had been living with tics for at least one year, but usually much longer. Children with TS/CTD often attempt to suppress tics in social settings. Therefore, these children not only have ample practice suppressing tics, but it is also likely that they have experienced repeated reinforcement when successful. The social

rewards (or avoidance of social punishment) incurred when inhibiting tics in social situations provides a strong motivation to alter behavior. That is, the social incentive to inhibit tics may motivate children with TS/CTD to exert as much inhibitory control over their tics as possible. Thus, one might expect that in children with TS/CTD, the ability to suppress tics in a rewarding context has been learned over years of experience. In fact, it has been argued that such experience enhances inhibitory control broadly in TS/CTD (Jackson et al., 2011). However, our results demonstrate that children with recent-onset tics can successfully suppress their tics when rewarded for doing so, suggesting that this ability is present at tic disorder onset. These children do not have the experience living with and attempting to suppress tics that children with TS/CTD often do. Thus, the modulating effect of reward on inhibitory control is in place early on, at least for many of these children, consistent with the findings in typical development. However, it is important to note that previous studies in TS/CTD reported 60–80% reductions in tic rates (Woods and Himle, 2004; Himle and Woods, 2005; Himle et al., 2008; Woods et al., 2008; Specht et al., 2013), whereas we found a mean reduction in tic frequency close to 40%. Thus, the degree of suppression in the present study was not as strong as the degree of suppression reported in TS/CTD. It is possible that the ability to suppress tics when rewarded improves over time with tics even though it is present early on, supporting the importance of environmental consequences and/or practice in tic suppression. Future longitudinal work can directly examine improvement in the ability to suppress tics over years of experience with tics beginning when children first manifest tics.

4.3. The brain mechanisms underlying rewarded tic suppression are unknown

There are a limited number of studies investigating the underlying neural circuitry of tic suppression in TS/CTD (Peterson et al., 1998; Kawohl et al., 2009; Hong et al., 2013). Only the EEG study of Hong et al. included children, and found prefrontal-sensorimotor cortex interactions during tic suppression. There are no studies investigating the neural correlates of tic suppression in a reward context. Even in typical development, studies investigating the interplay between inhibitory control and reward mechanisms in the brain are scarce. An fMRI study focusing on adolescence found delayed and heightened activity in the ventral striatum in adolescents compared to adults during reward trials on an inhibitory control task (Geier et al., 2010). Another study that implemented similar methods investigated children, adolescents, and adults, and demonstrated that brain regions supporting inhibitory control and reward processing were recruited in all age groups (Padmanabhan et al., 2011). However, the magnitude of responses showed varying developmental trajectories. Thus, the authors posited that the neural circuitry underlying reward and inhibitory control is in place by childhood, but continues to undergo developmental changes that influence behavior.

Given our results, and the previous results in children with TS/CTD, it would be interesting to understand the relationship between the underlying inhibitory control mechanisms and the underlying reward mechanisms in children with tics. Since tic suppression is enhanced when a reward is provided compared to when the child is simply asked to suppress his/her tics, it seems that engaging reward processing mechanisms leads to enhanced inhibitory control. This suggestion leads to a number of questions: Does the underlying reward circuitry interact with the mechanisms underlying inhibitory control to achieve better performance? Or are inhibitory control mechanisms bypassed when reward processes are engaged? Future work studying tic suppression both with and without reward using neuroimaging methods would help elucidate these questions. Further, future work examining children with recent-onset tics can investigate whether or not the mechanisms involved in tic suppression at tic disorder onset change over time as a child lives with tics for years or as tics improve into late adolescence.

4.4. Comorbid conditions and medications

This study included children with conditions commonly comorbid with tic disorders and children currently taking psychoactive medications. Only two children in our sample were taking psychoactive medications (both for ADHD), yet a majority of the children had a comorbid condition. This is not surprising, since about 60% of patients with TS/CTD have ADHD, 30% have OCD, and only 10–15% have no comorbidities (Freeman et al., 2000). In our sample, 52% had ADHD (the number was 76% when including ADHD NOS), 29% had OCD, and 4.7% had no comorbidities at all. Therefore, our sample is quite representative of clinical tic disorders samples, and our results are more generalizable to children who first present with tics than if we had excluded comorbid conditions. As more than half of our subjects had ADHD, we did consider whether increased severity of ADHD symptoms would adversely affect the children's ability to suppress tics. Children with ADHD are expected to have difficulty staying on task for a period of time, especially when seated alone in a room for a total of 40 min. In fact, there is some evidence that attentional deficits are associated with worse tic suppression (Himle and Woods, 2005; Woods et al., 2008). However, the correlations between ADHD severity and tic suppression in the present study leaned opposite the predicted direction. Thus, even children with recent-onset tics who have ADHD can suppress tics when provided with an immediate reward.

4.5. Limitations

There are some limitations of this study that should be noted. First, determining the date of tic onset is difficult, as there is no clinical gold standard for doing so. We used clinical approaches with multiple sources of information (see Section 2) to narrow in on a date for each child to the best of our ability. For some children, the exact date was clear (e.g., emergency room visit the day tics were first noticed). For others, the date was less clear, so we used all available information to determine a best estimate date (e.g., a teacher first noticed a tic in August and a parent recalled

the same tic at a birthday party in mid-June, but the tics were never noticed prior to June by parent, child, or the teacher from the previous year). Second, there is the possibility that children in this study had a history of prior tics that were unnoticed. To address this issue to the best of our ability, the parent completed the YGTSS tic symptom checklist, we reviewed each child's history carefully with the child and parent (including with the semi-structured K-SADS interviews), we educated parents about possible tics (e.g., frequent blinking that the parent could have overlooked may be a tic), and we determined an onset date for any tics observed at screening but not reported by the parent or child. This thorough process successfully identified previous, unrecognized tics in 7 children originally thought to have recent onset. However, there is still the possibility that other past tics may have gone completely unnoticed, which is an inevitable limitation of studying this population. A third limitation is the absence of a specific measure of tic awareness. Some of the measures we administered (DCI, PUTS) included questions about phenomena related to tic awareness, and anecdotally several children reported no awareness of their tics. However, a prospective measure of tic awareness would have been beneficial. A final limitation of our study is the potential for a biased sample, as it included (1) children whose parents, family, physician, or teachers actually noticed their tics, and (2) children whose parents were willing to participate in a somewhat time-consuming research study. In fact, half of our sample was recruited from clinical sources, whereas population studies find that most children with Transient Tic Disorder have not come to clinical attention (Khalifa and von Knorring, 2005). Thus, it is possible that we captured only those children with more severe tics. On the other hand, many of these children had only mild tics at screening. We speculate that our advertising the study in the community and to pediatricians facilitated detection of milder cases. We believe this sample includes the full range of severity, but only a future study with random population sampling can completely rule out selection bias.

4.6. Implications

We are not aware of any previous data on tic suppression in children with recent-onset tics. In fact, the only studies on this population have focused on epidemiology and clinical characteristics (Shapiro et al., 1988; Carter et al., 1994; Bruun and Budman, 1997; Peterson et al., 2001). Understanding this early stage of a tic disorder is important for clarifying characteristics and behaviors that are intrinsic to the disorder versus those that develop with years of having tics.

The observation that children with recent-onset tics can suppress their tics, and that tic suppression can be improved with consistent timely rewards, can be seen as hopeful since behavior therapy for TS/CTD – e.g., Cognitive Behavioral Intervention for Tics (CBIT) – depends upon the modulation of tic frequency by environmental contingencies (Piacentini et al., 2010). Even though CBIT encourages awareness of premonitory sensations, our results suggest that CBIT may still have possible benefit as a first line of therapy even if premonitory sensations are not reported, as some children in our study reported no premonitory sensations and some were unaware of their tics entirely, yet they still were able to suppress tics when rewarded. Further, the observation that children suppressed tics better with immediate rewards than with the presumed intangible and delayed social reward in the Verbal Instruction condition suggests the intriguing hypothesis that therapeutic instruction in tic inhibition (e.g., with competing responses as in CBIT or exposure with response prevention (Verdellen et al., 2004)) augmented with immediate reward may enhance outcomes or benefit TS/CTD patients who do not improve with these strategies alone. In the recent-onset tic population, early intervention with behavior therapy may provide substantial clinical benefit in the short term or even reduce future morbidity. On the other hand, since as many as 20% of children have tics at some point, while only 2–6% of all children go on to a diagnosis of TS/CTD, intervention may be superfluous for many children with Transient Tic Disorder (revised to Provisional Tic Disorder in DSM5). Thus the ability to predict which children will go on to have a chronic disorder could revolutionize treatment approaches and clinical care. Furthermore, parents of a child with recent-onset tics want to know prognosis. Yet few studies have prospectively addressed outcome. In the present study, children with recent onset tics were generally capable of suppressing their tics, yet there was individual variability in tic suppression. Does this ability to suppress tics at tic disorder onset predict symptom progression? We are currently collecting longitudinal follow-up data from these children in order to answer this very question.

Conflict of interest statement

No conflicts of interest to report.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.dcn.2014.08.005.

References

Achenbach, T.M., Ruffle, T.M., 2000. The Child Behavior Checklist and related forms for assessing behavioral/emotional problems and competencies. Pediatr. Rev. 21, 265–271.

Aron, A.R., Robbins, T.W., Poldrack, R.A., 2014. Inhibition and the right inferior frontal cortex: one decade on. Trends Cogn. Sci. 18, 177–185.

Barkley, R.A., 1998. Attention Deficit/Hyperacticity Disorder: A Handbook for Diagnosis and Treatment, 2nd edition. Guilford Press, New York.

Barratt, W., 2012. The Barratt Simplified Measure of Social Status (BSMSS). [online]. Available at: http://socialclassoncampus.blogspot.com/2012/2006/barratt-simplified-measure-of-social.html

Baym, C.L., Corbett, B.A., Wright, S.B., Bunge, S.A., 2008. Neural correlates of tic severity and cognitive control in children with Tourette syndrome. Brain 131, 165–179.

Black, K.J., 2010. Tics. In: Kompoliti, K., Metman, L.V. (Eds.), Encyclopedia of Movement Disorders. Elsevier (Academic Press), Oxford, pp. 231–236.

Bornstein, R.A., Baker, G.B., Bazylewich, T., Douglass, A.B., 1991. Tourette syndrome and neuropsychological performance. Acta Psychiatr. Scand. 84, 212–216.

Bruun, R.D., Budman, C.L., 1997. The course and prognosis of Tourette syndrome. Neurol. Clin. 15, 291–298.

Bunge, S.A., Dudukovic, N.M., Thomason, M.E., Vaidya, C.J., Gabrieli, J.D., 2002. Immature frontal lobe contributions to cognitive control in children: evidence from fMRI. Neuron 33, 301–311.

Carter, A.S., Pauls, D.L., Leckman, J.F., Cohen, D.J., 1994. A prospective longitudinal study of Gilles de la Tourette's syndrome. J. Am. Acad. Child Adolesc. Psychiatry 33, 377–385.

Cavanna, A.E., Schrag, A., Morley, D., Orth, M., Robertson, M.M., Joyce, E., Critchley, H.D., Selai, C., 2008. The Gilles de la Tourette syndrome-quality of life scale (GTS-QOL): development and validation. Neurology 71, 1410–1416.

Channon, S., Pratt, P., Robertson, M.M., 2003. Executive function, memory, and learning in Tourette's syndrome. Neuropsychology 17, 247–254.

Channon, S., Drury, H., Martinos, M., Robertson, M.M., Orth, M., Crawford, S., 2009. Tourette's syndrome (TS): inhibitory performance in adults with uncomplicated TS. Neuropsychology 23, 359–366.

Church, J.A., Wenger, K.K., Dosenbach, N.U., Miezin, F.M., Petersen, S.E., Schlaggar, B.L., 2009a. Task control signals in pediatric Tourette syndrome show evidence of immature and anomalous functional activity. Front. Hum. Neurosci. 3, 38.

Church, J.A., Fair, D.A., Dosenbach, N.U., Cohen, A.L., Miezin, F.M., Petersen, S.E., Schlaggar, B.L., 2009b. Control networks in paediatric Tourette syndrome show immature and anomalous patterns of functional connectivity. Brain 132, 225–238.

Conelea, C.A., Woods, D.W., 2008. The influence of contextual factors on tic expression in Tourette's syndrome: a review. J. Psychosom. Res. 65, 487–496.

Constantino, J.N., Davis, S.A., Todd, R.D., Schindler, M.K., Gross, M.M., Brophy, S.L., Metzger, L.M., Shoushtari, C.S., Splinter, R., Reich, W., 2003. Validation of a brief quantitative measure of autistic traits: comparison of the social responsiveness scale with the autism diagnostic interview-revised. J. Autism Dev. Disord. 33, 427–433.

Cubo, E., Gabriel y Galan, J.M., Villaverde, V.A., Velasco, S.S., Benito, V.D., Macarron, J.V., Guevara, J.C., Louis, E.D., Benito-Leon, J., 2011. Prevalence of tics in schoolchildren in central Spain: a population-based study. Pediatr. Neurol. 45, 100–108.

Debes, N.M., Hansen, A., Skov, L., Larsson, H., 2011. A functional magnetic resonance imaging study of a large clinical cohort of children with Tourette syndrome. J. Child Neurol. 26, 560–569.

Denckla, M.B., 2006. Attention deficit hyperactivity disorder: the childhood co-morbidity that most influences the disability burden in Tourette syndrome. In: Walkup, J.T., Mink, J.W., Hollenbeck, P.J. (Eds.), Advances in Neurology: Tourette Syndrome. Lippincott Williams & Wilkins, Philadelphia, PA, pp. 17–21.

Eddy, C.M., Rizzo, R., Gulisano, M., Agodi, A., Barchitta, M., Cali, P., Robertson, M.M., Cavanna, A.E., 2011a. Quality of life in young people with Tourette syndrome: a controlled study. J. Neurol. 258, 291–301.

Eddy, C.M., Cavanna, A.E., Gulisano, M., Agodi, A., Barchitta, M., Cali, P., Robertson, M.M., Rizzo, R., 2011b. Clinical correlates of quality of life in Tourette syndrome. Mov. Disord. 26, 735–738.

Freeman, R.D., Fast, D.K., Burd, L., Kerbeshian, J., Robertson, M.M., Sandor, P., 2000. An international perspective on Tourette syndrome: selected findings from 3,500 individuals in 22 countries. Dev. Med. Child Neurol. 42, 436–447.

Geier, C.F., Luna, B., 2012. Developmental effects of incentives on response inhibition. Child Dev. 83, 1262–1274.

Geier, C.F., Terwilliger, R., Teslovich, T., Velanova, K., Luna, B., 2010. Immaturities in reward processing and its influence on inhibitory control in adolescence. Cereb. Cortex 20, 1613–1629.

Gilbert, D.L., Sallee, F.R., Zhang, J., Lipps, T.D., Wassermann, E.M., 2005. Transcranial magnetic stimulation-evoked cortical inhibition: a consistent marker of attention-deficit/hyperactivity disorder scores in tourette syndrome. Biol. Psychiatry 57, 1597–1600.

Gilbert, D.L., Bansal, A.S., Sethuraman, G., Sallee, F.R., Zhang, J., Lipps, T.D., Wassermann, E.M., 2004. Association of cortical disinhibition with tic, ADHD, and OCD severity in Tourette syndrome. Mov. Disord. 19, 416–425.

Greene, D.J., Black, K.J., Schlaggar, B.L., 2013. Neurobiology and functional anatomy of tic disorders. In: Martino, D., Leckman, J.L. (Eds.), Tourette Syndrome. Oxford University Press, New York, NY, pp. 238–275.

Harris, P.A., Taylor, R., Thielke, R., Payne, J., Gonzalez, N., Conde, J.G., 2009. Research electronic data capture (REDCap) – a metadata-driven methodology and workflow process for providing translational research informatics support. J. Biomed. Inform. 42, 377–381.

Hershey, T., Black, K.J., Hartlein, J.M., Barch, D.M., Braver, T.S., Carl, J.L., Perlmutter, J.S., 2004a. Cognitive-pharmacologic functional magnetic resonance imaging in tourette syndrome: a pilot study. Biol. Psychiatry 55, 916–925.

Hershey, T., Black, K.J., Hartlein, J., Braver, T.S., Barch, D.M., Carl, J.L., Perlmutter, J.S., 2004b. Dopaminergic modulation of response inhibition: an fMRI study. Brain Res. Cogn. Brain Res. 20, 438–448.

Himle, M.B., Woods, D.W., 2005. An experimental evaluation of tic suppression and the tic rebound effect. Behav. Res. Ther. 43, 1443–1451.

Himle, M.B., Woods, D.W., Bunaciu, L., 2008. Evaluating the role of contingency in differentially reinforced tic suppression. J. Appl. Behav. Anal. 41, 285–289.

Himle, M.B., Woods, D.W., Conelea, C.A., Bauer, C.C., Rice, K.A., 2007. Investigating the effects of tic suppression on premonitory urge ratings in children and adolescents with Tourette's syndrome. Behav. Res. Ther. 45, 2964–2976.

Hong, H.J., Sohn, H., Cha, M., Kim, S., Oh, J., Chu, M.K., Namkoong, K., Jeong, J., 2013. Increased frontomotor oscillations during tic suppression in children with Tourette syndrome. J. Child Neurol. 28, 615–624.

Hornsey, H., Banerjee, S., Zeitlin, H., Robertson, M., 2001. The prevalence of Tourette syndrome in 13–14-year-olds in mainstream schools. J. Child Psychol. Psychiatry 42, 1035–1039.

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, 357–364.

Jackson, S.R., Parkinson, A., Jung, J., Ryan, S.E., Morgan, P.S., Hollis, C., Jackson, G.M., 2011. Compensatory neural reorganization in Tourette syndrome. Curr. Biol. 21, 580–585.

Kaufman, A., Kaufman, N.L., 2004. Kaufman Brief Intelligence Test, 2nd edition. AGS Publishing, Circle Pines, MN.

Kaufman, J., Birmaher, B., Brent, D., Rao, U., Flynn, C., Moreci, P., Williamson, D., Ryan, N., 1997. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. J. Am. Acad. Child Adolesc. Psychiatry 36, 980–988.

Kawohl, W., Bruhl, A., Krowatschek, G., Ketteler, D., Herwig, U., 2009. Functional magnetic resonance imaging of tics and tic suppression in Gilles de la Tourette syndrome. World J. Biol. Psychiatry 10, 567–570.

Khalifa, N., von Knorring, A.-L., 2003. Prevalence of tic disorders and Tourette syndrome in a Swedish school population. Dev. Med. Child Neurol. 45, 315–319.

Khalifa, N., von Knorring, A.-L., 2005. Tourette syndrome and other tic disorders in a total population of children: clinical assessment and background. Acta Paediatr. 94, 1608–1614.

Kurlan, R., McDermott, M.P., Deeley, C., Como, P.G., Brower, C., Eapen, S., Andresen, E.M., Miller, B., 2001. Prevalence of tics in schoolchildren and association with placement in special education. Neurology 57, 1383–1388.

Leckman, J.F., King, R.A., Bloch, M.H., 2014. Clinical features of Tourette syndrome and tic disorders. J. Obsess.-Compul. Related Disorders, http://dx.doi.org/10.1016/j.jocrd.2014.03.004 (in press).

Leckman, J.F., Bloch, M.H., King, R.A., Scahill, L., 2006. Phenomenology of tics and natural history of tic disorders. Adv. Neurol. 99, 1–16.

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, 566–573.
Leckman, J.F., Zhang, H., Vitale, A., Lahnin, F., Lynch, K., Bondi, C., Kim, Y.S., Peterson, B.S., 1998. Course of tic severity in Tourette syndrome: the first two decades. Pediatrics 102, 14–19.
Levin, H.S., Culhane, K.A., Hartmann, J., Evankovich, K., Mattson, A.J., Harward, H., Ringholz, G., Ewing-Cobbs, L., Fletcher, J.M., 1991. Developmental changes in performance on tests of purported frontal lobe functioning. Dev. Neuropsychol. 7, 377–395.
Luna, B., Garver, K.E., Urban, T.A., Lazar, N.A., Sweeney, J.A., 2004. Maturation of cognitive processes from late childhood to adulthood. Child Dev. 75, 1357–1372.
Luna, B., Thulborn, K.R., Munoz, D.P., Merriam, E.P., Garver, K.E., Minshew, N.J., Keshavan, M.S., Genovese, C.R., Eddy, W.F., Sweeney, J.A., 2001. Maturation of widely distributed brain function subserves cognitive development. Neuroimage 13, 786–793.
Marsh, R., Zhu, H., Wang, Z., Skudlarski, P., Peterson, B.S., 2007. A developmental fMRI study of self-regulatory control in Tourette's syndrome. Am. J. Psychiatry 164, 955–966.
Meidinger, A.L., Miltenberger, R.G., Himle, M., Omvig, M., Trainor, C., Crosby, R., 2005. An investigation of tic suppression and the rebound effect in Tourette's disorder. Behav. Modif. 29, 716–745.
Mink, J.W., 2001. Neurobiology of basal ganglia circuits in Tourette syndrome: faulty inhibition of unwanted motor patterns? In: Cohen, D.J., Jankovic, J., Goetz, C.G. (Eds.), Advances in Neurology: Tourette Syndrome. Lippincott Williams & Wilkins, Philadelphia, pp. 113–122.
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, 570–573.
Orth, M., Rothwell, J.C., 2009. Motor cortex excitability and comorbidity in Gilles de la Tourette syndrome. J. Neurol. Neurosurg. Psychiatr. 80, 29–34.
Ozonoff, S., Strayer, D.L., McMahon, W.M., Filloux, F., 1998. Inhibitory deficits in Tourette syndrome: a function of comorbidity and symptom severity. J. Child Psychol. Psychiatry 39, 1109–1118.
Padmanabhan, A., Geier, C.F., Ordaz, S.J., Teslovich, T., Luna, B., 2011. Developmental changes in brain function underlying the influence of reward processing on inhibitory control. Dev. Cogn. Neurosci. 1, 517–529.
Peterson, B.S., Pine, D.S., Cohen, P., Brook, J.S., 2001. Prospective, longitudinal study of tic, obsessive-compulsive, and attention-deficit/hyperactivity disorders in an epidemiological sample. J. Am. Acad. Child Adolesc. Psychiatry 40, 685–695.
Peterson, B.S., Skudlarski, P., Anderson, A.W., Zhang, H., Gatenby, J.C., Lacadie, C.M., Leckman, J.F., Gore, J.C., 1998. A functional magnetic resonance imaging study of tic suppression in Tourette syndrome. Arch. Gen. Psychiatry 55, 326–333.
Piacentini, J., Woods, D.W., Scahill, L., Wilhelm, S., Peterson, A.L., Chang, S., Ginsburg, G.S., Deckersbach, T., Dziura, J., Levi-Pearl, S., Walkup, J.T., 2010. Behavior therapy for children with Tourette disorder: a randomized controlled trial. JAMA 303, 1929–1937.
Raz, A., Zhu, H., Yu, S., Bansal, R., Wang, Z., Alexander, G.M., Royal, J.M., Peterson, B.S., 2009. Neural substrates of self-regulatory control in children and adults with Tourette syndrome. Can. J. Psychiatry 54, 579–588.
Ridderinkhof, K.R., Band, G.P.H., Gordon, D.L., 1999. A study of adaptive behavior: effects of age and irrelevent information on the ability to inhibit one's actions. Acta Psychol. (Amst.) 101, 315–337.
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, 461–472.
Robertson, M.M., Banerjee, S., Kurlan, R., Cohen, D.J., Leckman, J.F., McMahon, W., Pauls, D.L., Sandor, P., van de Wetering, B.J., 1999. The Tourette syndrome diagnostic confidence index: development and clinical associations. Neurology 53, 2108–2112.
Rubia, K., Smith, A.B., Woolley, J., Nosarti, C., Heyman, I., Taylor, E., Brammer, M., 2006. Progressive increase of frontostriatal brain activation from childhood to adulthood during event-related tasks of cognitive control. Hum. Brain Mapp. 27, 973–993.
Scahill, L., Riddle, M.A., McSwiggin-Hardin, M., Ort, S.I., King, R.A., Goodman, W.K., Cicchetti, D., Leckman, J.F., 1997. Children's Yale-Brown Obsessive Compulsive Scale: reliability and validity. J. Am. Acad. Child Adolesc. Psychiatry 36, 844–852.
Shapiro, A.K., Shapiro, E., Young, J.G., Feinberg, T.E., 1988. Gilles de la Tourette Syndrome, 2nd edition. Raven Press, New York.
Snider, L.A., Seligman, L.D., Ketchen, B.R., Levitt, S.J., Bates, L.R., Garvey, M.A., Swedo, S.E., 2002. Tics and problem behaviors in schoolchildren: prevalence, characterization, and associations. Pediatrics 110, 331–336.
Specht, M.W., Woods, D.W., Nicotra, C.M., Kelly, L.M., Ricketts, E.J., Conelea, C.A., Grados, M.A., Ostrander, R.S., Walkup, J.T., 2013. Effects of tic suppression: ability to suppress, rebound, negative reinforcement, and habituation to the premonitory urge. Behav. Res. Ther. 51, 24–30.
The Tourette Syndrome Association International Consortium for Genetics, 1999. A complete genome screen in sib pairs affected by Gilles de la Tourette syndrome. Am. J. Hum. Genet. 65, 1428–1436.
Tipper, S.P., Bourque, T.A., Anderson, S.H., Brehaut, J.C., 1989. Mechanisms of attention: a developmental study. J. Exp. Child Psychol. 48, 353–378.
Varni, J.W., Seid, M., Rode, C.A., 1999. The PedsQL: measurement model for the pediatric quality of life inventory. Med. Care 37, 126–139.
Velanova, K., Wheeler, M.E., Luna, B., 2008. Maturational changes in anterior cingulate and frontoparietal recruitment support the development of error processing and inhibitory control. Cereb. Cortex 18, 2505–2522.
Verdellen, C.W., Keijsers, G.P., Cath, D.C., Hoogduin, C.A., 2004. Exposure with response prevention versus habit reversal in Tourettes's syndrome: a controlled study. Behav. Res. Ther. 42, 501–511.
Wang, Z., Maia, T.V., Marsh, R., Colibazzi, T., Gerber, A., Peterson, B.S., 2011. The neural circuits that generate tics in Tourette's syndrome. Am. J. Psychiatry 168, 1326–1337.
Watkins, L.H., Sahakian, B.J., Robertson, M.M., Veale, D.M., Rogers, R.D., Pickard, K.M., Aitken, M.R., Robbins, T.W., 2005. Executive function in Tourette's syndrome and obsessive-compulsive disorder. Psychol. Med. 35, 571–582.
Williams, B.R., Ponesse, J.S., Schachar, R.J., Logan, G.D., Tannock, R., 1999. Development of inhibitory control across the life span. Dev. Psychol. 35, 205–213.
Woods, D.W., Himle, M.B., 2004. Creating tic suppression: comparing the effects of verbal instruction to differential reinforcement. J. Appl. Behav. Anal. 37, 417–420.
Woods, D.W., Piacentini, J., Himle, M.B., Chang, S., 2005. Premonitory Urge for Tics Scale (PUTS): initial psychometric results and examination of the premonitory urge phenomenon in youths with Tic disorders. J. Dev. Behav. Pediatr. 26, 397–403.
Woods, D.W., Himle, M.B., Miltenberger, R.G., Carr, J.E., Osmon, D.C., Karsten, A.M., Jostad, C., Bosch, A., 2008. Durability, negative impact, and neuropsychological predictors of tic suppression in children with chronic tic disorder. J. Abnorm. Child Psychol. 36, 237–245.
Ziemann, U., Paulus, W., Rothenberger, A., 1997. Decreased motor inhibition in Tourette's disorder: evidence from transcranial magnetic stimulation. Am. J. Psychiatry 154, 1277–1284.