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Response inhibition in youth undergoing intensive treatment for obsessive compulsive disorder

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ABSTRACT

Response Inhibition (RI) is the ability to suppress behaviors that are inappropriate for a given context. Obsessive-compulsive disorder (OCD) has been associated with impaired RI in adults as measured by the Stop Signal Task (SST). Conflicting results have been found in terms of the relationship between OCD severity and SST performance, and no studies to date have examined the relationship between SST and response to OCD treatment. Also relatively unknown is whether RI performance in OCD is associated with developmental or gender differences. This naturalistic study examined the relationship between SST performance, OCD severity, and OCD treatment response in a pediatric sample undergoing intensive treatment involving exposure and response prevention and medication management (n = 36). The SST and Children's Yale-Brown Obsessive Compulsive Scale (CYBOCS) were administered at admission and program discharge. OCD severity was not significantly related to stop signal reaction time (SSRT) in the whole sample and among subgroups divided by age and gender. Baseline SSRT and SSRT change did not predict CYBOCS change across treatment in the whole sample, but exploratory analyses indicated both were significant predictors among female adolescents. Results suggest there may be developmental gender differences in the relationship between RI and clinical improvement in pediatric OCD.

1. Introduction

Response Inhibition (RI) is the ability to suppress behaviors that are inappropriate for a given context (Bari & Robbins, 2013). A large body of literature supports the division of the RI construct into action restraint (not initiating an action) and action cancellation (inhibition of a prepotent response or already initiated action; Chambers et al., 2009), particularly because distinct neural systems underlie each process (see Bari & Robbins, 2013 for review). Obsessive-compulsive disorder (OCD) is characterized by failure to inhibit compulsive motor behaviors, leading researchers to suspect OCD-related dysfunction in neural systems underlying RI, particularly those involved in action cancellation (Stern & Taylor, 2014). Numerous studies have shown an association between OCD and impaired RI, including deficits on behavioral indices of RI performance (e.g., Bannon et al., 2002; Chamberlain et al., 2006; McLaughlin et al., 2016a; Penades et al., 2007) and hypoactivation of RI circuit nodes during action cancellation (right inferior frontal gyrus, pre-supplementary motor area; de Wit et al., 2012; Page et al., 2009; Roth et al., 2007). A recent fMRI meta-analysis of inhibitory control and error monitoring in OCD confirmed impaired task performance in patients versus healthy controls, including slowed inhibitory reaction time and more inhibitory control errors (Norman et al., 2019).

Studies assessing RI in OCD frequently use the stop signal task (SST) to measure action cancellation (Schachar et al., 2007; Sebastian et al., 2013). Behavioral performance on the SST is used to calculate stop signal reaction time (SSRT), an index of RI that reflects the processing time required to inhibit a prepotent motor response. Research in adults and older adolescents generally shows slowed SSRT compared to healthy controls in those with lifetime (McLaughlin et al., 2016b) and current OCD (Boisseau et al., 2012; Chamberlain et al., 2006; de Wit et al., 2012; Fan et al., 2016; Lei et al., 2015; Morein-Zamir et al., 2010; Penades et al., 2007; Sohn et al., 2014) and their first-degree relatives

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(Chamberlain, 2007; Menzies et al., 2007), though results are not completely consistent, with two studies showing no differences (Fan et al., 2017; Kalanthroff et al., 2017). Research in children has failed to find SST performance differences when comparing youth with OCD to typically developing controls (Gooskens et al., 2019; Hybel et al., 2017; Rubia et al., 2010) and children with autism spectrum disorder (Gooskens et al., 2019) and anxiety disorders (Hybel et al., 2017). Based on this pattern of results, researchers have speculated that problems with RI in OCD may only emerge later in development (Gooskens et al., 2019).

Research in typically developing people suggests that there are extensive developmental differences in RI between adults and children, including age-related differences in accuracy and reaction time on RI tasks that are thought to reflect the prolonged maturation of the fronto-striatal network (Booth et al., 2003). Whether this developmental trajectory is altered in OCD is somewhat unclear. In pediatric OCD samples, there are a few studies supporting RI deficits (e.g., Rubia et al., 2010; Woolley et al., 2008), though findings seem to differ depending on the specific task used to measure RI. For example, a recent meta-analysis of neuropsychological functioning in pediatric OCD found RI to be comparable to controls (Abramovitch et al., 2015). However, the meta-analysis was based on 6 studies that do not separate action restraint and cancellation (e.g., Stroop) or use tasks that measure meaningfully different functions, like attention (e.g., continuous performance task). As adult research generally supports a specific RI deficit in action cancellation, it is possible that a parallel specific deficit is present in pediatric OCD but has been obscured by combining data from tasks measuring different RI processes.

The relationship between SSRT and OCD severity is somewhat unclear. Several adult studies found impaired SSRT in OCD vs. control groups without finding a significant correlation between SSRT and overall OCD severity, leading to suggestions that RI deficits are an abnormal trait marker or endophenotype of OCD (de Wit et al., 2012; McLaughlin et al., 2016a). A study in children did find SSRT to be significantly and positively correlated with OCD severity (Mancini et al., 2018). In the only study that considered distinctive symptom presentations in analyses (obsessions vs. compulsions), SSRT was shown to be significantly and positively correlated with compulsion severity only (Berlin & Lee, 2018), suggesting that RI deficits in OCD may be uniquely linked to compulsions.

RI may be particularly relevant to OCD treatment involving exposure and response prevention (ERP), the gold-standard psychotherapy for pediatric OCD (Freeman et al., 2014). The ability to inhibit compulsions during exposure to anxiogenic cues is required for extinction learning to occur (Benito et al., 2018). Thus, the inability to inhibit compulsions or other avoidance behaviors is likely to negatively impact ERP outcome. However, little is known about the role of RI in treatment response. Medication status seems to have no effect on SSRT in adults with OCD, although in a cross-sectional study, medicated patients showed significantly greater SSRT variability vs. unmedicated patients and controls (Kalanthroff et al., 2017). Reasons for increased variance in medicated patients were not clear, though authors speculated that it may reflect the variable effects of medication on anxiety (given that elevated anxiety is linked to poorer response inhibition; Pessoa et al., 2012). To our knowledge, no prior research has longitudinally examined whether changes in OCD severity co-occur with changes in SSRT or whether SSRT is impacted by pharmacological or cognitive-behavioral treatments for OCD (or their combination).

It is also possible that RI performance and its relationship to treatment outcome in pediatric OCD differs across developmental groups, or between males and females. Successful RI relies on brain regions that show gender-related activation differences and ovarian steroid influences, including prefrontal cortex, anterior cingulate cortex, and inferior frontal gyrus (Amin et al., 2006; Bannbers et al., 2013; Roberts et al., 2008). Importantly, there are also known developmental gender differences in the neural circuitry underlying RI (Rubia et al., 2013). While several adult SST studies found no gender difference in inhibitory performance (Evans & Hampson, 2015; Li et al., 2006, 2009), gender differences may emerge when development is considered. For example, Rubia et al. (2013) found that gender differences on SST may be stronger in adolescence and normalize in mid-adulthood. In their sample, faster SSRT (i.e., better inhibitory control) in females was shown in adolescents, but performance was equivalent between male and female genders in adults. Functional imaging during the SST revealed gender-dimorphic activation patterns during RI that were driven by differences in the functional maturation of inhibitory networks. Specifically, females showed increased activation in left frontal and striatal areas vs. males, and these activations were more age-correlated in females than males. Males showed enhanced right inferior parietal activation vs. females, and this activation was also more age-correlated in males. It is possible that these gender-dimorphic functional maturation findings have relevance to RI performance in youth with OCD. To our knowledge, there are no studies examining the relationship between gender differences or gender by age interactions on SST performance in OCD. There is some indication that female adults with OCD may have more diminished performance on an acoustic prepulse inhibition task (Ahmari et al., 2012; Steinman et al., 2016), suggesting that gender differences may be relevant to inhibition processes in OCD.

In the current study, we assessed RI performance longitudinally using the SST in a sample of youth undergoing intensive treatment for OCD involving ERP and medication management. This was a naturalistic, exploratory study which sought to assess relationships between OCD severity and SSRT over a period in which we expect to see OCD symptoms change. In other words, our goal was not to test the effect of a specific intervention on SSRT but rather to see if SSRT performance has a meaningful relationship with OCD symptom change. Accordingly, study aims were to examine: Aim 1) the relationship between baseline SSRT and baseline OCD severity; Aim 2) the relationship between baseline SSRT and treatment outcome; and Aim 3) the relationship between change in SSRT and change in OCD severity over the course of treatment. In addition, given the sparse literature examining gender differences and RI, we aimed to explore age by gender mean differences in SSRT and OCD severity, at baseline and across treatment (Aim 4a), as well as assess whether the relationships in the first three aims differed by age and gender (Aim 4b).

2. Methods

Participants were 36 youth admitted to an intensive treatment program for OCD focused on ERP plus as-needed medication management, the standard treatment components for this level of care. As part of program admission, all youth underwent a diagnostic evaluation by a psychologist and psychiatrist with extensive training and experience in the diagnosis and treatment of pediatric OCD. Diagnosis was determined based upon clinical interviews with the child and caretakers, medical record review, and measures designed to assess the presence and severity of OCD. Eligibility criteria for the current study were 1) parent consent and youth assent to participate in research, 2) diagnosis of OCD based on DSM 5 criteria (American Psychiatric Association, 2013), as indicated in the medical record for the admission assessment, and 4) available and complete Children's Yale-Brown Obsessive Compulsive Scale (Scahill et al., 1997) total OCD severity score and Stop Signal Task from both admission and discharge.

The sample was 50% female (n = 18). Gender status was obtained from the medical record. Participants had a mean age of 12.3 years (SD = 2.58). The majority of participants (n = 29, 80%) identified as white; two participants (5%) identified as Native American, two as multiracial, and six (16%) did not report race/ethnicity. The majority (n = 31, 86%) of the sample had at least one comorbid psychiatric diagnosis at the time of the admission evaluation. Specific diagnoses included attention deficit hyperactivity disorder (ADHD, n = 16), non-OCD anxiety disorders (n = 15), mood disorders (n = 12), tic disorders (n = 8); other body-

focused repetitive behavior disorders (i.e., hair pulling disorder, skin picking disorder; n = 2), autism spectrum disorder (n = 5), and oppositional defiant disorder (n = 3).

Admission to intensive care for OCD typically necessitates that the child experience inadequate response to treatment at a lower level of care. At the time of admission, 26 (72%) youth were taking at least one psychotropic medication. The most frequent classes of prescribed medication were selective serotonin reuptake inhibitors (SSRI; n = 22, 61%) followed by antipsychotics (n = 5; 14%) and benzodiazepines (n = 5; 14%). Other medications included alpha 2 agonists (n = 4), mood stabilizers (n = 3), anxiolytics (n = 2), stimulants (n = 2), SNRIs (n = 2), and N-acetylcysteine (NAC; n = 2). A total of 16 (44%) were on more than one psychotropic medication at the time of admission.

Treatment involved ERP delivered in a milieu setting, individual sessions focused on exposure implementation in home or community settings, medication management, group therapy, and family therapy. Youth participated in treatment 5 days per week for 4 hours per day. Mean length of stay was 39.9 days (SD = 21.9, range = 13–126). Medication changes were made during the course of treatment as needed under the direction of each child's program psychiatrist. Due to the naturalistic nature of this study, only admission and discharge medication status were available for research purposes, precluding examination of medication changes and timing that occurred during the course of care. At the time of discharge, 35 out of 36 youth were taking at least one psychotropic medication. The most frequent classes at discharge were SSRIs (n = 31) followed by alpha 2 agonists (n = 10), stimulants (n = 9), antipsychotics (n = 8), benzodiazepines (n = 4), mood stabilizers (n = 3), N-acetylcysteine (n = 4), and SNRI (n = 2). A total of 23 (64%) were on more than one psychotropic medication at the time of discharge.

2.1. Measures

2.1.1. Children's Yale-Brown obsessive compulsive scale (CYBOCS; Scahill et al., 1997)

The CYBOCS is a clinician-administered interview measuring OCD severity in youth. The CYBOCS consists of a symptom checklist of common obsessions and compulsions, which are used to inform severity scale ratings. The severity scale measures OCD severity over the past week and consists of 10-items. Item ratings are summed to yield a total score (range = 0–40); total scores were available for all included participants. Separate subscales of obsession and compulsion severity (each with range = 0–20) were available for 31 participants (scores were unavailable for 5 participants because they were inadvertently not recorded by the administering clinician). Higher scores represent greater symptom severity.

2.1.2. Stop-signal task (SST; Logan et al., 1984)

A computerized version of the SST task adapted from (Aron et al., 2003) and used in prior research in adult OCD (McLaughlin et al., 2016a) was used to assess inhibition of prepotent motor responses. Total task time (after practice trials where participants were trained to 50% accuracy on "stop" trials) was approximately 13 min. During task trials (two blocks of 128 trials per block), participants watched a computer screen displaying arrows pointing either right or left (each 50% of trials, randomized). Youth were instructed to press a button corresponding to the arrow direction as quickly and accurately as possible. In a random 25% of trials, an audible stop-signal was heard after the arrow presentation. Participants were instructed to inhibit the button press on these "stop" trials. Inter-stimulus interval and stop-signal delay were varied according to participant performance, such that participants were able to successfully inhibit responses on 50% of stop trials. SST behavioral data were used to calculate mean reaction time and stop-signal reaction time (SSRT; processing time required to inhibit prepotent response). SSRT was estimated by subtracting average time between stimulus onset and tone from median no-signal reaction time. During data analysis, participants with more than 10% errors on "go" trials were removed. Participants who had less than 35% or more than 65% accuracy on the "stop" trials were also removed from the analysis.

2.2. Procedures

This study was approved by the Institutional Review Board at Lifespan/Rhode Island Hospital. Parental consent and youth assent were obtained upon program admission from research staff who were not involved in clinical care. Data were collected at two time points: 1) admission, defined as the first week of treatment, and 2) discharge, defined as the last week of treatment. The CYBOCS was completed by the participant's treating psychologist. Participant electronic medical records for admission and discharge were examined for the following variables: age, gender, psychiatric diagnostic status, medication status, and CYBOCS total score. The SST was administered by trained research staff during a study visit that typically occurred before the start of that day's treatment. All SST administration occurred in a private testing room.

2.3. Data analytic plan

2.3.1. Covariate identification

We identified potentially important model covariates a priori, based on theory and prior literature demonstrating a relationship with SSRT. Comorbidity status was not included as a covariate (e.g., ADHD, mood disorder) because doing so may obscure important sources of shared underlying pathology across OCD and those disorders. Moreover, SSRT was not significantly related to any comorbidities ($ps > .05$). For each covariate of interest, we determined whether it would be included in final modeling by first examining the relationship of each with baseline SSRT using Pearson's correlations. For models under Aim 2, the role of stimulant initiation during treatment (yes/no) was also considered, based on the likelihood that initiation of a stimulant would improve RI independent of treatment specifically for OCD (i.e., ERP, SSRI use); children with ADHD have shown shorter SSRT following initiation of a stimulant (e.g., Rosch et al., 2016). ANOVA was used to examine whether SSRT change over treatment was different by stimulant initiation group (yes/no).

2.3.2. Analyses

Analyses for primary aims (1–3) used a Bonferroni correction ($p < .017$). Exploratory analyses (aim 4) did not correct for multiple comparisons given the importance of avoiding type II error in analyses for which hypothesis generation is the major goal. Aim 1. Pearson's correlation was used to examine the relationship between baseline CYBOCS and baseline SSRT. Aim 2. Hierarchical regression was used to determine whether baseline SSRT predicts change in OCD severity across treatment (i.e., change in CYBOCS score from admission to discharge), entering covariates into step 1 and admission SSRT into Step 2. Aim 3. Hierarchical regression was used to determine whether change in SSRT across treatment (i.e., change in SSRT from admission to discharge) relates to change in OCD severity across treatment, entering covariates into into Step 1, initiation of stimulant during treatment into Step 2, and change in SSRT into Step 3. Exploratory Aim 4a. Independent sample t-tests were used to test for mean differences in SSRT and CYBOCS, at baseline and across treatment, between children and adolescents as well as between males and females. Age was split into a dichotomous variable for these analyses, with children defined as ≤12 years and adolescents defined as 13–17 years. This dichotomous approach was modeled after prior research suggesting adolescent specific sex differences in SSRT (Rubia et al., 2013). One-way ANOVA was used to test for mean differences in SSRT and CYBOCS at baseline and across treatment, between male children, female children, male adolescents, and female adolescents. Exploratory Aim 4b. Analyses from Aims 1, 2, and 3 were re-run within subgroups split by age (children and adolescents), gender (males and females), as well as age by gender groupings (male children, female

children, male adolescents, and female adolescents).

3. Results

Mean SSRT and CYBOCS scores across treatment are presented in Table 1, including mean scores for sample divisions by age and gender.

3.1. Covariates

Age was not significantly correlated with baseline SSRT ($r = -0.18$, $p = .28$). Age was unrelated to OCD severity at baseline ($r = -0.06$, $p = .74$). SSRT changed significantly between admission and discharge, $F(1, 34) = 5.62$, $p = .02$, *partial* $\eta^2 = 0.14$, but there was not a significant interaction effect of stimulant initiation on SSRT change, $F(1, 34) = 2.03$, $p = .16$, *partial* $\eta^2 = 0.06$. Go Reaction Time on the SST was not significantly correlated with SSRT at baseline ($r = -0.08$, $p = .62$) or post-treatment ($r = 0.03$, $p = .85$), nor was change in Go Reaction Time significantly correlated with change in SSRT ($r = -0.10$, $p = .53$).

3.2. Primary aims

Aim 1. There was not a significant correlation between SSRT and global OCD severity (CYBOCS total score) at baseline ($r = -0.175$, $p = .308$). There was not a significant correlation between SSRT and obsession severity ($r = -0.11$, $p = .54$) or between SSRT and compulsion severity ($r = -0.17$, $p = .37$) at baseline.

Aim 2. Given the nonsignificant correlation between SSRT and baseline OCD severity, baseline CYBOCS score was not included in step 1 of Aims 2 and 3 hierarchical regressions. Similarly, based on the lack of a significant interaction effect of stimulant initiation on SSRT change, stimulant initiation was not entered in Step 2 of the hierarchical regression exploring whether change in SSRT predicted change in OCD severity. Consequently, analysis reduced to simple linear regression. SSRT at admission did not predict a significant amount of the variance in total CYBOCS change, $F(1, 35) = 0.82$, $p = .37$, $R^2 = -0.02$. Similar results were found when CYBOCS subscales were examined separately. SSRT at admission did not predict a significant amount of the variance in obsession severity change $F(1, 30) = 0.04$, $p = .84$, $R^2 = 0.00$, or in compulsion severity change $F(1, 30) = 2.43$, $p = .13$, $R^2 = -0.08$.

Aim 3. CYBOCS scores significantly improved from pre- (mean = 27.67, SD = 4.45) to post-treatment (mean = 17.44, SD = 5.06; t = 12.06, $p < .000$, $g = 2.10$). SSRT change did not predict a significant amount of the variance in total CYBOCS change $F(1, 35) = 0.38$, $p = .54$, $R^2 = -0.01$, in obsession severity change $F(1, 30) = 0.21$, $p = .65$, $R^2 = 0.00$, or in compulsion severity change $F(1, 30) = 1.95$, $p = .17$, $R^2 = -0.06$.

3.3. Exploratory analyses

Aim 4a. There were no significant differences between children and adolescents in mean SSRT at baseline ($t(34) = 0.34$, $p = .74$, $\eta^2 = 0.003$) or CYBOCS total scores at baseline ($t(34) = -0.35$, $p = .73$, $\eta^2 = 0.003$) and across treatment ($t(34) = 0.97$, $p = .34$, $\eta^2 = 0.027$). There were no significant differences between females and males in baseline mean SSRT ($t(34) = 1.45$, $p = .16$, $\eta^2 = 0.058$) or CYBOCS total scores ($t(34) = -0.30$, $p = .77$, $\eta^2 = 0.003$). Similarly, there were no gender differences observed for change in mean SSRT ($t(34) = 0.09$, $p = .93$, $\eta^2 = 0.000$) and change in CYBOCS total scores ($t(34) = 0.67$, $p = .51$, $\eta^2 = 0.013$) across treatment. Incidence of comorbidities did not differ across genders (see Table 2). In terms of the age by gender groupings, we found no significant differences between male children (n = 12), female children (n = 7), male adolescents (n = 6), and female adolescents (n = 11) in mean SSRT at baseline ($F(3, 35) = 0.71$, $p = .55$, $\eta^2 = 0.062$) or across treatment ($F(3, 35) = 0.91$, $p = .45$, $\eta^2 = 0.078$). There were also no significant differences between these groups in mean CYBOCS total at baseline ($F(3, 35) = 0.48$, $p = .70$, $\eta^2 = 0.043$) or across treatment ($F(3, 35) = 0.40$, $p = .76$, $\eta^2 = 0.036$).

Aim 4b analyses explored whether relationships between CYBOCS and SSRT in the first three aims differed by age and gender.

Age. *Aim 1.* Admission SSRT was unrelated to admission CYBOCS in adolescents ($r = -0.15$, $p = .56$) and children ($r = -0.20$, $p = .41$). *Aim 2.* Simple linear regressions showed that in adolescents, baseline SSRT did not predict CYBOCS change $F(1, 16) = 3.81$, $p = .07$, $R^2 = -0.20$. This was also the case in children $F(1, 18) = 0.02$, $p = .89$, $R^2 = 0.00$. *Aim 3.* Similarly, SSRT change did not predict CYBOCS change in adolescents, $F(1, 16) = 2.16$, $p = .16$, $R^2 = -0.13$, or in children $F(1, 18) = 0.07$, $p = .80$, $R^2 = 0.00$.

Gender. *Aim 1.* Paralleling the full sample, admission SSRT was not significantly related to admission CYBOCS for females ($r = -0.30$, $p = .23$) and males ($r = -0.06$, $p = .82$), although the effect was larger for

Table 1
Descriptive scores and regression outcomes organized by age and gender sample divisions.

	Child	Adolescent	Combined Ages
Female Gender			
Baseline SSRT M(SD)	227.73 (59.60)	221.00(56.99)	223.61 (56.35)
Baseline CYBOCS M(SD)	26.57 (2.23)	28.73 (5.55)	27.89 (4.59)
SSRTΔ M(SD)	30.13 (52.67)	12.68 (40.97)	19.46 (45.20)
CYBOCSΔ M(SD)	10.14 (3.63)	9.27 (4.58)	9.61 (4.15)
SSRT-CYBOCS (R^2)	-.09	-.10	-.09
SSRT-CYBOCS Δ (R^2)	-.41	-.64[a]	-.53[a]
SSRT Δ -CYBOCS Δ (R^2)	-.28	-.63[a]	-.40[a]
Male Gender			
Baseline SSRT M(SD)	250.77 (79.61)	260.56 (46.06)	254.03 (68.90)
Baseline CYBOCS M(SD)	27.92 (4.64)	26.50 (4.23)	27.44 (4.44)
SSRTΔ M(SD)	38.47 (85.06)	-12.71 (72.23)	21.41 (82.66)
CYBOCSΔ M(SD)	11.58 (7.54)	9.33 (3.98)	10.83 (6.53)
SSRT-CYBOCS (R^2)	-.05	.48	.00
SSRT-CYBOCS Δ (R^2)	.00	.17	.01
SSRT Δ -CYBOCS Δ (R^2)	.00	.02	.01
Combined Genders			
Baseline SSRT M(SD)	242.28 (72.03)	234.96 (55.43)	238.82 (63.92)
Baseline CYBOCS M(SD)	27.42 (3.91)	27.94 (5.11)	27.67 (4.45)
SSRTΔ M(SD)	35.40 (73.24)	3.72 (53.25)	20.44 (65.66)
CYBOCSΔ M(SD)	11.05 (6.29)	9.29 (4.25)	10.22 (5.43)
SSRT-CYBOCS (R^2)	-.04	-.02	-.02
SSRT-CYBOCS Δ (R^2)	.00	-.20	.00
SSRT Δ -CYBOCS Δ (R^2)	.00	-.13	.00

Abbreviations: SSRT = Stop Signal Reaction Time; CYBOCS = Children's Yale-Brown Obsessive Compulsive Scale.
Note: male children (n = 12), female children (n = 7), male adolescents (n = 6), and female adolescents (n = 11); lower baseline SSRT indicates better performance, lower baseline CYBOCS indicates less severe symptoms, lower SSRT Δ indicates less improvement across treatment, lower CYBOCS Δ indicates less improvement across treatment.
[a] Slope significantly different from zero ($p < .05$).

Table 2
Incidence of OCD comorbidities by gender.

Comorbidity	Total Males	Total Females	c^2	df	*p*
ADHD	10	6	1.80	1	.18
BFRBs	4	6	.56	1	.46
Mood	5	7	.50	1	.48
ODD	2	1	.36	1	.55
ASD	4	1	2.09	1	.15
Other Anxiety	5	10	2.86	1	.09
Any Comorbidity	15	16	.23	1	.63

SSRT = Stop Signal Reaction Time; CYBOCS = Children's Yale-Brown Obsessive Compulsive Scale; ADHD = Attention Deficit Hyperactivity Disorder; BFRBs = Body Focused Repetitive Behavior disorders (i.e., tic disorders, hair pulling disorder, skin picking disorder); ODD = Oppositional Defiant Disorder; ASD = Autism Spectrum Disorder.

females (where the negative correlation suggests shorter/better SSRT relates to higher/worse CYBOCS). *Aim 2.* Simple linear regressions showed that in females, baseline SSRT significantly predicted CYBOCS change $F(1, 17) = 18.12$, $p = .00$, $R^2 = -0.53$. This was not the case in males, $F(1, 17) = 0.14$, $p = .72$, $R^2 = 0.01$. *Aim 3.* Similarly, in females, SSRT change significantly predicted CYBOCS change, $F(1, 17) = 10.82$, $p = .01$, $R^2 = -0.40$. This relationship was not present in males, $F(1, 17) = 0.09$, $p = .76$, $R^2 = 0.01$.

Age by Gender. *Aim 1.* Admission SSRT was also not significantly correlated with CYBOCS within age by gender subgroups: female adolescents ($r = -0.32$, $p = .34$), male adolescents ($r = 0.69$, $p = .13$), female children ($r = -0.30$, $p = .51$) and male children ($r = -0.23$, $p = .48$). Notably, the size and direction of these observed correlations differed, with male adolescents showing a positive correlation with a large effect size (where the positive correlation suggests longer/worse SSRT relates to higher/worse CYBOCS). *Aim 2.* The above findings in females seem to be driven by female adolescents specifically. In female adolescents (n = 11), baseline SSRT predicted a significant amount of the variance of CYBOCS change, $F(1, 10) = 15.96$, $p = .003$, $R^2 = -0.64$. In female children (n = 7), baseline SSRT did not predict a significant amount of the variance of CYBOCS change, $F(1, 6) = 3.48$, $p = .12$, $R^2 = -0.41$. In male adolescents, baseline SSRT did not predict CYBOCS change, $F(1, 5) = 0.84$, $p = .41$, $R^2 = 0.17$; this was the same for male children, $F(1, 11) = 0.04$, $p = .85$, $R^2 = 0.00$. Plotted data (Fig. 1) suggest that, in female adolescents, faster baseline SSRT (i.e., better response inhibition) is associated with more CYBOCS change. *Aim 3.* Also in female adolescents, SSRT change predicted a significant amount of the variance in CYBOCS change, $F(1, 10) = 15.07$, $p = .00$, $R^2 = .-63$ (Fig. 2). There was also no relationship between SSRT change and CYBOCS change in female children, $F(1, 11) = 1.91$, $p = .23$, $R^2 = -0.28$. In male adolescents, change in SSRT did not predict change in CYBOCS, $F(1, 5) = 0.08$, $p = .79$, $R^2 = 0.02$; this was the same for male children, $F(1, 11) = 0.00$, $p = .99$, $R^2 = 0.00$. Plotted data (Fig. 2) suggest that, in female adolescents, larger SSRT change (i.e., toward better response inhibition) is associated with less CYBOCS change.

4. Discussion

Response inhibition is thought to be a core deficit in OCD. However, little is known about the role of RI in treatment response, including whether RI changes alongside treatment-related reductions in OCD severity. While one study has explored the effect of medication status on SSRT in a cross-sectional sample of adults with OCD (Kalanthroff et al., 2017), no prior research has explored potential treatment effects in a longitudinal sample. In the current naturalistic, exploratory study (not designed as a fully powered test of RI), we administered the SST longitudinally to explore whether SST-measured RI is predictive of clinical change in a sample of youth with OCD undergoing standard-of-care intensive treatment involving a combination of ERP and medication management. Based on prior research showing developmental gender differences on SST (Rubia et al., 2013), we also sought to explore whether relationships between SSRT and OCD severity differed by age and gender.

In this sample, OCD severity was not significantly related to SSRT in the whole sample and among subgroups divided by age and gender (Aim 1). This finding is consistent with prior research in adults (Chamberlain et al., 2007; Kalanthroff et al., 2017; McLaughlin et al., 2016a) but inconsistent with a study in children showing a significant positive correlation between SSRT and CYBOCS scores (Mancini et al., 2018). Notably, although significance was not met in our age by gender subgroups (Aim 4b), we only observed a positive correlation between SSRT and CYBOCS scores among adolescent males ($r = 0.69$). It is therefore possible that group level findings across studies obscure potentially meaningful differences in the SSRT-CYBOCS relationship that emerge differentially in development across genders. It is also possible that methodological differences explain this inconsistency. The Mancini et al. (2018) sample was comprised of outpatients with OCD, Tourette Syndrome, or both diagnoses, which led to a wider range of CYBOCS scores than we observed in our intensive treatment sample.

More recent adult research suggests that SST performance may be more specifically related to compulsion severity (Berlin & Lee, 2018), but we did not observe this relationship. This may relate to the relatively small sample used in the present study. For example, we observed a medium-sized effect suggesting greater improvement in compulsions among those with better baseline SSRT; this non-significant relationship might have reached significance in a larger sample. The relationship between OCD severity and measures of RI should be assessed further in future research with larger pediatric samples and better representation across age by gender subgroupings to clarify these mixed findings.

Aims 2 and 3 of this study focused on the relationship between SSRT and clinical outcomes. Results reveal a potential relationship between SSRT and OCD treatment outcome that is influenced by developmental

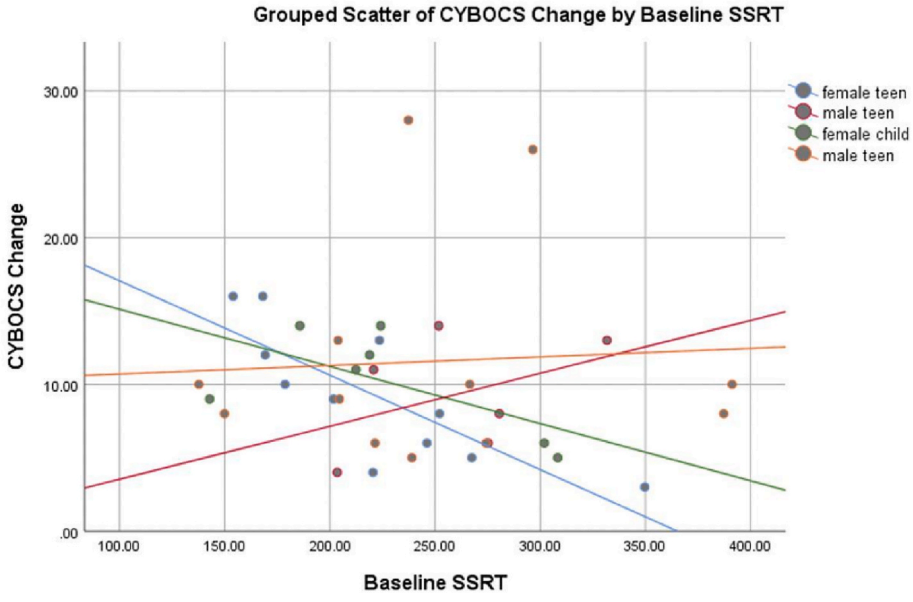

Fig. 1. Plot depicting relationship between baseline SSRT and CYBOCS change across treatment for participants in age-gender groupings.

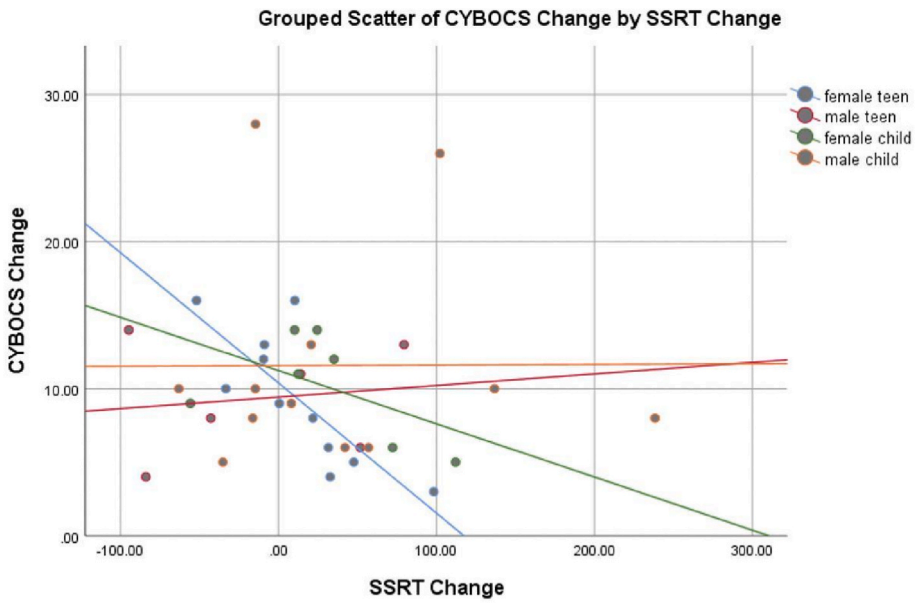

Fig. 2. Plot depicting relationship bewteen change in SSRT and CYBOCS change across treatment for participants in age-gender groupings.

gender differences. When associations between SSRT and OCD severity were tested in the whole sample and in subgroups divided by age, no significant relationships were found: both baseline SSRT and SSRT change did not predict CYBOCS change across treatment. However, when the sample was subgrouped based on gender, we found that baseline SSRT and SSRT change both significantly predicted CYBOCS change in females only. These findings appear to be driven by female adolescents specifically, as neither relationship reached significance for female children. The direction of these relationships suggests that better RI at baseline was associated with greater improvement in OCD symptoms across treatment, which is consistent with the theorized mechanism of ERP (i.e., that recruitment of RI is helpful for inhibiting rituals during exposure). Interestingly, females who experienced greater improvement in RI across treatment exhibited *less* symptom improvement during that time. Although seemingly discrepant, this pattern of results would be consistent with the idea that RI may act as an ERP moderator but is not a mechanism through which ERP produces clinical improvement. It could also be that RI is generally helpful during exposure but that newly acquired RI skills are more difficult to recruit in this context (i.e. under emotional conditions). Future studies should seek to understand the reasons for this interesting finding.

Our findings suggest that there may be gender-related differences in the relationship between RI and clinical improvement among those with OCD, especially at certain developmental windows. Prior research has shown that sex and gender interact with developmental processes to influence executive functioning deficits in neurodevelopmental disorders (Grissom & Reyes, 2018). Biological mechanisms that potentially contribute to these developmental sex/gender differences include neurochemistry, genotype by sex interactions, synaptic pruning, microglial function, and cortical maturation and complexity. There is evidence that hormones can influence the function of RI circuits (Amin et al., 2006; Roberts et al., 2008). Among females, performance differences on various indices of RI have been shown depending on hormonal status (Amin et al., 2006; Bannbers et al., 2012, 2013; Mansouri et al., 2016). Further exploration of developmental sex and gender differences in OCD is warranted, as this might reveal novel treatment targets.

We did not observe a significant relationship between age and baseline SSRT, although this may relate to the relatively small sample used in this study. The direction of the relationship was consistent with prior research showing that SST-measured RI improves over childhood (Dupuis et al., 2018) and reflects developmental maturation of fronto-striatal networks (Booth et al., 2003). However, the specific developmental processes that lead to these age-related differences in task performance have yet to be delineated. For example, it is unclear if children recruit the same circuitry to engage RI as adults but do so suboptimally, or if youth use different strategies that recruit distinct circuitry (Garnaat et al., 2018). It is also possible that interactions between particular neurodevelopmental disorders, development, and sex and gender drive differences in the strategy and circuitry that underlie behavioral performance on tasks like the SST, and that these differences are obscured when we focus on an endpoint metric like SSRT. In other words, by examining only the "destination" (e.g., SSRT), we may be missing differences in the "journey" taken to get there. Indeed, prior research indicates that males and females can engage different brain areas to achieve the same end performance result on an inhibitory control task (e.g., females engage more frontal areas and males more parietal areas; Christakou et al., 2009). This may help to explain some discrepant findings in the present study; for example, we found that better RI at baseline relates to greater symptom improvement for female adolescents but observed a large non-significant effect suggesting that it could relate to *less* symptom improvement for male adolescents. Future research that administers the SST alongside methods such as neuroimaging will be useful in understanding whether there are developmental sex/gender differences in the neural mechanisms underlying RI improvement over the longitudinal course of OCD.

Several study limitations warrant mention. First, a control group of youth not affected by OCD was not included, reflecting our primary interest in investigating relationships between RI and OCD treatment outcome. This precludes us from drawing firm conclusions about whether this sample showed globally impaired RI. Our sample's SSRT performance at baseline ($m = 253$, $SD = 56$) is comparable to means reported for healthy controls in some studies (e.g., $m = 258$, $SD = 53$; van Rooij et al., 2015) but higher than others (e.g., $m = 209$, $SD = 90$; Brennan et al., 2016), although minor task construction or administration differences make it difficult to understand if similarities/differences in raw SSRT values across studies are meaningful.

Second, this study was conducted in a natural clinical setting with non-standardized treatment components (e.g., heterogeneous medication regimens), variable "dose of therapy" in terms of lengths of stay and prior therapy history, and non-masked raters of OCD severity. The nature of our study precluded us from gathering rigorous data about changes in medication type and dose throughout the course of care,

making it difficult to explore medication effects more specifically. We were also unable to examine whether circumstances surrounding length of stay impacted possible change in RI (e.g., whether the patient discharged because of improvement, discontinuation of insurance coverage, or left against medical advice). The intensive level of care inherently tends to serve patients with more severe, complex, or refractory cases of OCD who are not medication naive. Although our sample's CYBOCS mean is similar to those in the outpatient Pediatric OCD Treatment Studies (POTS I: CYBOCS mean = 24.6, SD = 4.1, (Pediatric OCD Treatment Study Team, 2004); POTS II: CYBOCS mean = 26.3, SD = 5.0; Franklin et al., 2011)), we cannot assume that results generalize to youth in other treatment settings. It is possible that RI and OCD symptoms may have different relationships over the course of a first or different treatment experience.

Third, there was a high preponderance of ADHD, and some patients initiated stimulant medication during their course of treatment. Research has shown that greater ADHD traits are associated with longer SSRT and gender affects at younger ages (e.g., Crosbie et al., 2013 found longer SSRT scores in girls with ADHD traits vs. male counterparts at age 6, but there was no significant gender effect at age 18). As part of covariate identification, we examined ADHD status and did not find a significant difference in baseline SSRT or SSRT change in youth with vs. without ADHD. Unfortunately, our small sample size and lack of a continuous measure of ADHD severity precluded more thorough investigation of ADHD-related effects on our results. Although we did not find stimulant medication initiation to significantly contribute to SSRT change, it is important to note that stimulant medication can independently improve RI performance on the SSRT (Boonstra et al., 2005; Rosch et al., 2016). More tightly controlled research outside of the clinical context will be needed to further clarify how ADHD status and stimulant medications contribute to RI performance in individuals with OCD, both at baseline and longitudinally across treatment.

Fourth, we used only one task to measure RI, with the intent of focusing specifically on action cancellation. Although SSRT was not related to CYBOCS change, it is possible that other facets of RI not captured by the SST or SSRT index have more relevance to the ERP context, such as the specific ability to inhibit compulsions during an affect-laden task like exposure. Preliminary research indicates that ritual inhibition during exposure is related to OCD improvement (Benito et al., 2012; McLaughlin et al., 2016a), suggesting that other measurable RI constructs may possibly predict ERP outcomes. Other limitations regarding the SST include variable time between pre- and post-treatment measures (given the link to program discharge) and the possibility of task practice effects.

Finally, there was no measure of pubertal status. Instead, age was used as a proxy to classify participants as children or adolescents. Formal measurement of pubertal and hormonal status will be important in future research assessing developmental sex differences in OCD.

An interesting direction for future research would be more rigorous, mechanistic examination of the relationship between RI and response prevention (inhibition of compulsions during exposures), including the extent to which this relationship may differ depending on compulsion topography. Given the nature of RI as measured by the SST (i.e., inhibition of a motor response), we speculate that SST-measured RI could be most relevant for motor compulsions vs. mental compulsions. More broadly, examining how indices of neurocognitive functioning relate to specific behaviors linked to mechanisms of change in ERP (extinction/inhibitory learning) may help identify viable targets for ERP augmentation.

In conclusion, this first longitudinal examination of SST-measured RI in the intensive OCD treatment context suggests that pediatric OCD severity and response to treatment are not generally related to RI. However, SST-measured RI was predictive of treatment outcome among female adolescents, indicating that there may be developmental sex differences among youth with OCD that contribute to different "paths to wellness." Researchers should continue to examine neurocognitive processes in pediatric OCD through this developmental sex differences lens, as it may reveal novel ways to target and personalize treatment for this chronic and debilitating condition.

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Author Statement

Conelea: Conceptualization, methodology, writing (original draft and review/editing).

Morris: Data analysis, data visualization, writing (original draft).

McLaughlin: Conceptualization, methodology, writing (original draft and review/editing).

Mamaril: Project coordination support

Benito: Conceptualization, methodology, writing (original draft and review/editing), data analysis, Case: Supervision.

Garcia: Supervision.

Declaration of competing interest

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Data availability

The data that has been used is confidential.

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